NICE advice

Ovarian cancer (advanced): bevacizumab 7.5 mg/kg in combination with paclitaxel and carboplatin for first-line treatment

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in October 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

One large (n=1528), open-label, randomised controlled trial (RCT; ICON7) that assessed the efficacy and safety of bevacizumab 7.5 mg/kg for treating ovarian cancer was identified; quality of life outcomes from this study were also reported separately (Stark et al. 2013). ICON7 found that interim analysis of overall survival data showed no benefit for adding bevacizumab to standard chemotherapy compared with standard chemotherapy alone, except in a subgroup deemed at high risk for progression. In this subgroup median results for progression-free survival after a median follow-up of 19 months were 10.5 months with standard chemotherapy and 15.9 months with standard chemotherapy plus bevacizumab. Adding bevacizumab to standard chemotherapy resulted in a small but clinically relevant reduction in quality of life.

Regulatory status: Off-label for treating advanced ovarian cancer at the 7.5 mg/kg dose.

Effectiveness • Adding bevacizumab to standard chemotherapy increased progression-free survival by a median of around 1 to 2 months. • Greater benefit was shown in a subgroup deemed at high risk for progression. • Interim analysis of overall survival data showed no benefit for adding bevacizumab to standard chemotherapy compared with standard chemotherapy alone, except in a subgroup deemed at high risk for progression. Data for overall survival benefit are due to be published at the end of 2013.	**Safety** • Adverse effects occurred more commonly in the bevacizumab group in ICON7 and included bleeding, gastrointestinal perforation, thrombotic events, complications of wound healing and hypertension. • Bevacizumab can be associated with necrotising fasciitis.
Patient factors • Additional hospital visits with continued cycles of bevacizumab. • Small but clinically relevant reduction in quality of life with bevacizumab compared with standard chemotherapy.	**Resource implications** • Bevacizumab 100 mg/4 ml costs £242.66. • Bevacizumab 400 mg/16 ml costs £924.40. • Drug-only cost per cycle for a woman weighing 53.4 kg to 66.6 kg would be £1167.06. • Additional costs of hospital visits for IV administration of bevacizumab.

Key points

Bevacizumab (Avastin, Roche) at a recommended dose of 15 mg/kg, in combination with paclitaxel and carboplatin, is licensed for the front-line treatment of adults with advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer. NICE assessed bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (NICE technology appraisal guidance 284) at the licensed dose of 15 mg/kg and did not recommend it.

Bevacizumab at a dose of 7.5 mg/kg is not the recommended licensed dose for first-line treatment of advanced ovarian cancer and so its use is off-label.

This evidence summary is based on 1 open-label, multicentre RCT which studied the efficacy of bevacizumab 7.5 mg/kg in addition to standard chemotherapy for treating ovarian cancer in 1528 women (ICON7, Perren et al. 2011); quality of life outcomes from this study were also reported separately (Stark et al. 2013)

Women were randomised to receive standard chemotherapy (paclitaxel and carboplatin given every 3 weeks for 6 cycles) or the same regimen plus bevacizumab 7.5 mg/kg given every 3 weeks for 5 or 6 cycles and then bevacizumab continued on its own for 12 additional cycles or until progression of disease.

After a median follow-up of 19 months, median progression-free survival was 19 months in the bevacizumab group compared with 17.3 months in the standard chemotherapy group. The ICON7 authors also reported results from a pre-planned subgroup of 465 women with advanced ovarian cancer whom they termed at 'high risk for progression' (women had either FIGO stage III disease and >1.0 cm of residual disease after debulking surgery or FIGO stage IV disease). For the subgroup at 'high risk for progression', median progression-free survival was15.9 months in the bevacizumab group compared with 10.5 months in the standard chemotherapy group.

An updated analysis of progression-free survival was performed after a median follow-up of 28 months. This found that median progression-free survival was 19.8 months in the bevacizumab group compared with 17.4 months in the standard chemotherapy group. For the subgroup at 'high risk for progression', median progression-free survival was16.0 months in the bevacizumab group compared with 10.5 months in the standard chemotherapy group.

Further results for overall survival are still awaited, but no statistically significant difference was found after a median of either 19 or 28 months' follow-up. However, in the subgroup at 'high risk for progression', after a median follow-up of 28 months, interim analysis showed that median overall survival was 36.6 months with bevacizumab compared with 28.8 months with standard chemotherapy alone. These results are preliminary and should be interpreted with caution. The trial was in women with all stages of ovarian cancer (FIGO stage I to IV), including a proportion of women with FIGO stage I and II (18%) who are not representative of the advanced ovarian cancer population.

The manufacturers of bevacizumab (Avastin, Roche) advise that unless the final intention-to-treat overall survival data from ICON7 shows a significant overall survival benefit for the 7.5 mg/kg dose

then it is unlikely that a licence will be applied for (Roche: personal communication, September 2013).

Stark et al. (2013) found that in women whose disease had not yet progressed, mean global quality of life at 54 weeks was statistically significantly lower in the bevacizumab group compared with the standard chemotherapy group (69.7 points compared with 76.1 points respectively). This statistically significant ($p<0.0001$) difference of 6.4 points was small but considered clinically relevant. A higher proportion had a clinically significant improvement in health-related quality of life of at least 10 points in the standard chemotherapy group (66%) compared with the bevacizumab group (56%) between baseline and 54 weeks. This was measured using the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.

The ICON7 trial reported recognised adverse events of bevacizumab including mucocutaneous bleeding, bleeding within the central nervous system (CNS) grade 3 or more, gastrointestinal perforation grade 3 or more, thrombotic events, complications of wound healing and hypertension. These adverse events occurred more frequently in the bevacizumab group compared with the standard chemotherapy group.

The manufacturer of bevacizumab (Avastin, Roche) warned about the risk of necrotising fasciitis associated with bevacizumab in May 2013 in information sent to healthcare professionals about the safety of medicines.

The summary of product characteristics lists adverse reactions that may be associated with bevacizumab treatment. These include gastrointestinal perforations, fistulae, wound healing complications, hypertension, posterior reversible encephalopathy syndrome, proteinuria, arterial and venous thromboembolism, haemorrhage, pulmonary haemorrhage or haemoptysis, congestive heart failure, neutropenia and infections, hypersensitivity or infusion reactions, osteonecrosis of the jaw, eye disorders, and ovarian failure.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

Overview for healthcare professionals

Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). It is useful in treating certain types of cancer because it stops the growth of new blood vessels, preventing the cancer cells from growing.

Regulatory status of bevacizumab

Bevacizumab (at a recommended dose of 15 mg/kg body weight), in combination with paclitaxel and carboplatin, is licensed for the front-line treatment of adults with advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.

Bevacizumab (at a recommended dose of 15 mg/kg body weight), in combination with carboplatin and gemcitabine, is licensed for treating adults with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Bevacizumab is also licensed at various doses (including 7.5 mg/kg) for metastatic colorectal cancer, metastatic breast cancer, non-small-cell lung cancer and renal cell cancer.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using bevacizumab outside its authorised indications.

Evidence statements

- One phase III, open-label, randomised controlled trial (ICON7) was identified. It assessed the effect of bevacizumab 7.5 mg/kg on survival in 1528 women with all stages of ovarian cancer and good physical ability.
- Quality of life data obtained from 890 of these women 54 weeks after starting treatment was also reported separately (Stark et al. 2013).
- The women received either standard chemotherapy (paclitaxel and carboplatin given every 3 weeks for 6 cycles) or the same regimen plus bevacizumab 7.5 mg/kg given every 3 weeks for 5 or 6 cycles and then bevacizumab continued on its own for 12 additional cycles or until progression of disease.
- After a median follow-up of 19 months, median progression-free survival was 19 months in the bevacizumab group compared with 17.3 months in the standard chemotherapy group. The ICON 7 authors also reported results from a pre-planned subgroup of 465 women with advanced ovarian cancer whom they termed at 'high risk for progression' (women had either FIGO stage III disease and >1.0 cm of residual disease after debulking surgery or FIGO stage IV disease). For the subgroup at 'high risk for progression', median progression-free survival was15.9 months in the bevacizumab group compared with 10.5 months in the standard chemotherapy group.
- An updated analysis performed after a median follow-up of 28 months showed an improvement in median progression-free survival of 2.4 months in the bevacizumab group compared with the standard chemotherapy group. For the subgroup of women termed at 'high risk for progression', an improvement of 5.5 months with bevacizumab was shown.
- Full results for overall survival are still awaited but no statistically significant difference was found after a median of either 19 or 28 months' follow-up.
- In the subgroup at 'high risk for progression', after a median follow-up of 28 months, interim analysis showed that median overall survival was 36.6 months with bevacizumab compared with 28.8 months with standard chemotherapy alone. However, these results are preliminary and should be interpreted with caution.
- Health-related quality of life, assessed by Stark et al. (2013), found that mean global quality of life at 54 weeks was statistically significantly lower in the bevacizumab group compared with the standard chemotherapy group (69.7 points compared with 76.1 points respectively). This statistically significant ($p<0.0001$) difference of 6.4 points was small but clinically relevant.

- A higher proportion of women on standard chemotherapy had a clinically significant improvement (an improvement of at least 10 points) in global quality of life after 54 weeks compared with those on bevacizumab (66% compared with 56% respectively).
- Further analyses of subscales showed clinically small but statistically significant reduced quality of life for women in the bevacizumab group for role functioning, financial worries, attitudes to disease or treatment, hormonal symptoms and rash (all $p<0.01$).
- The ICON7 trial reported recognised adverse events of bevacizumab including mucocutaneous bleeding, bleeding within the central nervous system (CNS) grade 3 or more, gastrointestinal perforation grade 3 or more, thrombotic events, complications of wound healing and hypertension. These adverse events occurred more frequently in the bevacizumab group compared with the standard chemotherapy group.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the Evidence review section.

Efficacy

One open-label, randomised controlled trial (ICON7) was identified that assessed the efficacy of bevacizumab 7.5 mg/kg for treating ovarian cancer. Quality of life results were also reported separately (Stark et al. 2013).

ICON7 was a multicentre trial including 1528 women who had undergone surgery for epithelial ovarian, fallopian tube or primary peritoneal cancer. The majority of women (94%) had good physical ability as measured by the Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and the rest were ambulatory for more than 50% of the time and did not require nursing care, with an ECOG performance status of 2. Women who had all stages of ovarian cancer were recruited. The trial reported overall results, but also results for a pre-specified subgroup of women with advanced ovarian cancer who had FIGO stage III disease and more than 1.0 cm of residual disease after debulking surgery or who had FIGO stage IV disease. They termed these 465 women at 'high risk for progression'.

Women were randomised to either standard chemotherapy with paclitaxel and carboplatin every 3 weeks for 6 cycles (the standard chemotherapy group), or the same regimen plus bevacizumab 7.5 mg/kg every 3 weeks for 5 or 6 cycles, followed by bevacizumab on its own for an additional 12 cycles or until disease progression or unacceptable toxicity occurred (the bevacizumab group).

Allocation to treatment was concealed by central randomisation using an interactive telephone or web-based system.

In the primary analysis, median progression-free survival in the intention-to-treat population estimated after a median follow-up of 19 months showed an improvement of 1.7 months for the bevacizumab group compared with the standard chemotherapy group (19.0 months compared with 17.3 months respectively). The Kaplan-Meier curves for progression-free survival crossed over demonstrating non-proportional hazards. A test for non-proportional hazards confirmed this ($p<0.0001$). The conventional hazard ratio is not meaningful when calculated using data that demonstrates non-proportional hazards. To better estimate the effect of bevacizumab on progression-free survival, restricted mean values were estimated. Using all data up to 36 months after randomisation, an improvement in restricted mean progression-free survival of 1.5 months was found for bevacizumab compared with standard chemotherapy (21.8 months compared with 20.3 months respectively).

An updated analysis after a median follow-up of 28 months was performed. This showed an improvement in median progression-free survival of 2.4 months for the bevacizumab group compared with the standard chemotherapy group (19.8 months compared with 17.4 months respectively). Restricted mean values for progression-free survival, estimated using data up to 36 months and up to 42 months after randomisation, showed an improvement of 1.9 months and 1.7 months respectively for bevacizumab compared with standard chemotherapy.

In women at 'high risk for progression', after a median follow-up of 19 months median progression-free survival was improved by 5.4 months with bevacizumab compared with standard chemotherapy (15.9 months compared with 10.5 months respectively). In this same subgroup of women, the restricted mean values for progression-free survival, estimated using data up to 36 months after randomisation, showed an improvement of 3.4 months for bevacizumab compared with standard chemotherapy (16.5 months compared with 13.1 months respectively).

In the updated analysis in women at 'high risk for progression', after a median follow-up of 28 months median progression-free survival was improved by 5.5 months with bevacizumab compared with standard chemotherapy (16.0 months compared with10.5 months respectively). In the same subgroup of women, restricted mean values for progression-free survival, estimated using data up to 36 months and up to 42 months after randomisation, showed an improvement of 3.5 months and 3.6 months respectively for bevacizumab compared with standard chemotherapy.

Further subgroup analysis of the group at 'high risk for progression' was performed. These analyses were reported in the NICE technology appraisal guidance on bevacizumab in combination with

paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer. After 28 months, women with stage III suboptimally debulked disease had an improvement in progression-free survival of 6.8 months on bevacizumab compared with those on standard chemotherapy (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.52 to 0.87), but no statistically significant difference was reported for stage III women with optimally debulked cancer (difference of 1.6 months favouring bevacizumab) or stage IV cancer (difference of 3.4 months favouring bevacizumab). Only the hazard ratio is provided for the subgroup of women with inoperable stage III or IV cancer, which showed a statistically significant improvement in progression-free survival with bevacizumab (HR 0.66, 95% CI 0.48 to 0.91; p=0.011).

The protocol-specified final overall survival analysis for ICON7 is expected at the end of 2013. An interim overall survival analysis was conducted in the subgroup who were at 'high-risk for progression': approximately 47% of women in the standard chemotherapy group and 34% in the bevacizumab group had died. This showed a statistically significant increase in the median overall survival of 7.8 months in the bevacizumab group (36.6 months compared with 28.8 months). However, these results are preliminary and should be interpreted with caution.

Health-related quality of life was measured using the European Organisation for the Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30) with a translated scale from 0 (worst) to 100 (best). All questionnaires were requested in the Stark et al. (2013) study from the ICON7 trial. At baseline 684 (90%) of women in the standard chemotherapy group and 691 (90%) of those in the bevacizumab group had completed quality of lifequestionnaires. At week 54, 388 (51%) women in the standard chemotherapy group and 502 (66%) women in the bevacizumab group provided quality of life data. It is unclear what impact this may have had on the results.

The mean global quality of life score was higher in the standard chemotherapy group (76.1, standard deviation [SD] 18.2) at 54 weeks compared with the bevacizumab group (69.7, SD 19.1), with a difference of 6.4 points (95% CI 3.7 to 9.0, p<0.0001).

The number of women whose global quality of life improved by at least 10 points between baseline and 54 weeks was higher in the standard chemotherapy group at 66% (221 of 333) compared with 56% (250 of 444) in the bevacizumab group (odds ratio 0.58, 95% CI 0.42 to 0.80, p=0.001).

Analyses of subscales of the QLQ-C30 and the additional QLQ-OV28 questionnaire showed small but statistically significant lower quality of life for women in the bevacizumab group for role functioning, financial worries, attitudes to disease or treatment, hormonal symptoms and rash (all p<0.01).

The reason for the small reduction in quality of life in the bevacizumab group remains unclear, and was not shown to be due to resolution timing of ascites, abdominal wall wound healing, or life disruption with continued chemotherapy.

Table 1 Summary of the primary analyses from the ICON7 trial and the Stark et al. (2013) quality of life report

	Standard chemotherapy (paclitaxel and carboplatin)	Standard chemotherapy + bevacizumab	Analysis
ICON7: a phase III trial of bevacizumab in ovarian cancer. Results after a median follow-up of 19 months			
Regimen	Paclitaxel (175 mg/m^2) and carboplatin (area under the curve, 5 or 6) every 3 weeks for 6 cycles	Paclitaxel (175 mg/m^2) and carboplatin (area under the curve, 5 or 6) every 3 weeks for 6 cycles with concurrent IV bevacizumab (7.5 mg/kg) for 5 or 6 cycles and continued as sole therapy for 12 additional cycles or until disease progression	
Randomised	n=764	n=764	
Efficacy	n=764	n=764	
Progression-free survival: percentage of women who had disease progression or died	51.3% (392/764)	48.0% (367/764)	
Progression-free survival: median number of months	17.3	19.0	HR 0.81, 95% CI 0.70 to 0.94, p=0.004[a]

Overall survival: percentage of women who died	17.0% (130/764)	14.5% (111/764)	HR 0.81, 95% CI 0.63 to 1.04, p=0.098[a]
Progression-free survival in women at high risk for progression: percentage of women who had disease progression or died	67.5% (158/234)	74.9% (173/231)	
Progression-free survival in women at high risk for progression: median number of months	10.5	15.9	HR 0.68, 95% CI 0.55 to 0.85), p<0.001[a]
Overall survival in women at high risk for progression[b]: percentage of women who died	46.6% (109/234)	34.2% (79/231)	
Overall survival in women at high risk for progression[b]: median number of months	28.8	36.6	HR 0.64, 95% CI 0.48 to 0.85), p=0.002[a]

Quality of life	n=727/764 (at baseline) Mean global quality of life score: Baseline 55.7 18 weeks 71.1 54 weeks 74.5 76 weeks 73.7	n=724/764(at baseline) Mean global quality of life score: Baseline 53.6 18 weeks 66.9 54 weeks 69.5 76 weeks 72.6	Quality of life differences between bevacizumab and standard chemotherapy were statistically significant at 18 and 54 week time points only (p<0.01)
Safety: percentage of women that had any adverse event	Grade 1 or 2: 44% (331/753) Grade 3 or 4: 54% (410/753) Grade 5: 1% (9/753)	Grade 1 or 2: 34% (254/745) Grade 3 or 4: 65% (483/745) Grade 5: 1% (8/745)	p value not reported
Adverse events: mucocutaneous bleeding	Grade 1 or 2: 7% (55/753) Grade ≥3: 0% (0/753)	Grade 1 or 2: 36% (271/745) Grade ≥3: 1% (5/745)	p value not reported
Adverse events: bleeding within the central nervous system (CNS) grade ≥3	0% (0/753)	<1% (2/745)	p value not reported
Adverse events: gastrointestinal perforation grade ≥3	<1% (3/753)	1% (10/745)	p value not reported

Adverse events: hypertension	Grade 1: 4% (31/753) Grade 2: 2% (14/753) Grade ≥3: <1% (2/753)	Grade 1: 8% (57/745) Grade 2: 12% (90/745) Grade ≥3: 6% (46/745)	p value not reported
Adverse events: any thrombotic event	Grade 1 or 2: 3% (22/753) Grade ≥3: 3% (23/753)	Grade 1 or 2: 4% (29/745) Grade ≥3: 7% (51/745)	p value not reported
Complication of wound healing	Grade 1 or 2: 2% (13/753) Grade ≥3: <1% (3/753)	Grade 1 or 2: 4% (27/745) Grade ≥3: 1% (10/745)	
Stark et al. (2013): **quality of life outcomes from ICON7**			
Randomised	n=764	n=764	
Number of women with data at week 18	n=662 (87%)	n=693 (91%)	
Number of women with data at week 54	n=388 (51%)	n=502 (66%)	
Mean global quality of life score at baseline	58.6 (SD 20.6)	55.1 (SD 20.8)	
Mean global quality of life score at week 18 (end of chemotherapy)	64.4 (SD 20.3)	59.2 (SD 19.4)	Difference favoured standard chemotherapy group −5.1 (95% CI −7.4 to −2.9), p<0.0001

Mean global quality of life score at week 54 (end of continuation bevacizumab)	76.1 (SD 18.2)	69.7 (SD 19.1)	Difference favoured standard chemotherapy group -6.4 (95% CI -9.0 to -3.7), p<0.0001

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; IV: intravenous; n, number of women; p, p value; RR, relative risk; SD, standard deviation.

[a] p value obtained using the unadjusted log-rank test.

[b] No overall survival analyses were performed for the subgroup at high risk for progression after a median follow-up of 19 months and so data presented are interim analyses performed after a median follow-up of 28 months.

Safety

The manufacturer of bevacizumab (Avastin, Roche) warned about the risk of necrotising fasciitis associated with bevacizumab in May 2013 in information sent to healthcare professionals about the safety of medicines.

The summary of product characteristics (SPC) lists adverse reactions that may be associated with bevacizumab treatment. These include gastrointestinal perforations, fistulae, wound healing complications, hypertension, posterior reversible encephalopathy syndrome, proteinuria, arterial and venous thromboembolism, haemorrhage, pulmonary haemorrhage or haemoptysis, congestive heart failure, neutropenia and infections, hypersensitivity or infusion reactions, osteonecrosis of the jaw, eye disorders, and ovarian failure.

The safety and efficacy of bevacizumab has not been studied in children, or in people with renal or hepatic impairment. It is contraindicated in people with hypersensitivity to the active substance, Chinese hamster ovary (CHO) cell products, or other recombinant human or humanised antibodies. Bevacizumab is also contraindicated in pregnancy. The SPC advises that women of childbearing potential should use effective contraception during and up to 6 months after treatment and breastfeeding should be avoided during and for at least 6 months after treatment.

Adverse drug reactions have been reported with sunitinib, platinum- or taxane-based therapies and epithelial growth factor receptor (EGFR) monoclonal antibodies when used in combination with bevacizumab.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

The ICON7 trial reported recognised adverse events of bevacizumab including mucocutaneous bleeding (n=276 [37%] with bevacizumab compared with n=55 [7%] with standard chemotherapy respectively), bleeding within the CNS grade 3 or more (n=2 [<1%] compared with n=0 respectively), gastrointestinal perforation grade 3 or more (n=10 [1%] compared with n=3 [<1%] respectively), any thrombotic event (n=80 [11%] compared with n=55 [7%] respectively), complications of wound healing (n=37 [5%] compared with n=16 [2%] respectively) and hypertension (n=193 [26%] compared with n=47 [6%] respectively).

Cost effectiveness and cost

No studies on the cost effectiveness of bevacizumab 7.5 mg/kg for advanced ovarian cancer were identified.

For women whose weight is in the range of 53.4 kg to 66.6 kg, the 'drug-only' cost of bevacizumab at a dose of 7.5 mg/kg would be £1167.06 per cycle at the current (July 2013) price listed in MIMS. The suggested regimen would be in combination with paclitaxel and carboplatin for 6 cycles and then up to an additional 12 cycles or until disease progression. This would equate to between £7002.36 (for the first 6 cycles) and £21,007.08 (for the first 6 cycles plus an additional 12 cycles). This does not include the cost of administration by intravenous infusion in hospital. This additional cost would be greater during the extended treatment phase when standard chemotherapy has finished.

Relevance to NICE guidance programmes

The use of bevacizumab at a dose of 7.5 mg/kg is not appropriate to be appraised by the NICE technology appraisal programme because it is off-label. It is not currently planned for any other NICE work programme.

NICE has issued a clinical guideline on Ovarian cancer: the recognition and initial management of ovarian cancer (NICE clinical guideline 122).

NICE has issued the following 2 technology appraisals on the licensed use of bevacizumab at a dose of 15 mg/kg in ovarian cancer:

- Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (NICE technology appraisal guidance 284). It does not recommend bevacizumab 15 mg/kg for this indication but people already receiving it in this way can continue treatment until they and their clinician consider it appropriate to stop.
- Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer (NICE technology appraisal guidance 285). It does not recommend bevacizumab 15 mg/kg for this indication but people already receiving it in this way can continue treatment until they and their clinician consider it appropriate to stop.

NICE guidance also exists for the following licensed indications for bevacizumab in which it is not recommended:

- Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (NICE technology appraisal guidance 263)
- Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal guidance 118) (NICE technology appraisal guidance 242)
- Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (NICE technology appraisal guidance 214)
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (NICE technology appraisal guidance 212)
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (NICE technology appraisal guidance 118).

Intervention and alternatives

Bevacizumab is a humanised monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) angiogenesis. This reduces vascularisation of tumours, thereby inhibiting tumour growth. It is used in combination with chemotherapy, given through intravenous infusion.

Condition

Cancer research UK indicates ovarian cancer is the fifth most common cancer in women in the UK, and epithelial ovarian cancer accounts for almost 90% of cases. Most cases occur after the menopause, and 10% are caused by an inherited faulty gene. There is no accurate and reliable screening test as yet and early symptoms are absent or vague, including lower abdominal pain or bloating, urinary frequency or urgency, dyspareunia and postmenopausal bleeding. Advanced symptoms include loss of appetite, nausea, vomiting, fatigue and shortness of breath. Ovarian cancer: the recognition and initial management of ovarian cancer (NICE clinical guideline 122) reports the 5-year survival rate for women with ovarian cancer as being less than 35% because most women present with advanced disease.

Alternative treatment options

The NICE clinical guideline on ovarian cancer recommends that low-risk FIGO stage 1 disease (confined to the ovaries, grade 1 or 2, stage 1a or 1b) is treated surgically. It also recommends that adjuvant chemotherapy is offered to women with high-risk stage 1 disease (grade 3 or stage 1c) or to those who have had suboptimal surgical staging. According to Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (NICE technology appraisal guidance 284), chemotherapy with paclitaxel and carboplatin is the current standard clinical practice in the NHS in England and Wales for first-line treatment of advanced ovarian cancer (FIGO stages II–IV) after debulking surgery. It states that 3 cycles of chemotherapy may be given before surgery for some patients expected to have residual disease left after surgery.

Evidence review: efficacy

During the development of this evidence summary, a search was carried out for published studies using bevacizumab 7.5 mg/kg in combination with paclitaxel and carboplatin for treating ovarian cancer. One open-label randomised controlled trial (RCT) that assessed the efficacy of bevacizumab 7.5 mg/kg for treating ovarian cancer (ICON7) was identified, with the quality of life results also reported separately (Stark et al. 2013). They form the evidence base for this summary. Other RCTs such as Burger et al. (2011) and economic analyses were excluded because they assessed the licensed 15 mg/kg dose of bevacizumab.

ICON7 was a multicentre, randomised, open-label controlled phase III trial that recruited 1528 women who had undergone surgery for epithelial ovarian, fallopian tube or primary peritoneal cancer and who had adequate coagulation values and bone marrow, liver and renal function with no plans for further surgery before disease progression. Women were eligible for the

trial if they had either high-risk, early-stage disease (International Federation of Gynaecology and Obstetrics [FIGO] stage I or IIA and clear-cell or grade 3 tumours – maximum 10% of trial population) or advanced disease (FIGO stage IIB to IV). In addition, women needed to have a reasonable level of daily function as measured on the Eastern Cooperative Oncology Group (ECOG) performance status (scale of 0–4 with 0 indicating normal activity and 4 indicating bedridden and possibly needing hospitalisation). To be eligible for the trial, women had to have an ECOG performance status of between 0 and 2. Most women (94%) had a good performance status of 0 or 1. The median age of participants was 57 years. A total of 90% of the women had epithelial ovarian cancer; 9% had high-risk, early-stage disease; 30% were at high risk for progression; 21% had FIGO stage III, IIIA or IIIB disease; 70% had FIGO stage IIIC or IV disease; 69% had serious histological type; and 26% had more than 1.0 cm of residual disease after debulking surgery.

Women were randomised centrally on a 1:1 basis using an interactive phone or web-based system, therefore allocation to treatment was concealed. Randomisation was stratified according to Gynaecological Cancer Intergroup (GCIG) group, the intended time of initiation of post-surgical chemotherapy (4 weeks or less, or more than 4 weeks), cancer stage and residual disease to ensure the groups were well matched in terms of these baseline characteristics.

The trial treatment period lasted up to 54 weeks and women were randomised to 1 of 2 treatment arms:

- The standard chemotherapy group (n=764): paclitaxel 175 mg/m^2 of body surface area and carboplatin at a target area under the curve of 5 or 6 mg/ml per minute every 3 weeks for 6 cycles.
- The bevacizumab group (n=764): the same regimen as the standard chemotherapy group plus bevacizumab 7.5 mg/kg every 3 weeks for 5 or 6 cycles, followed by continued treatment with bevacizumab alone for an additional 12 cycles or until disease progression (cycle 1 of bevacizumab was omitted to avoid delayed wound healing if chemotherapy was started within 4 weeks of surgery).

More than 90% of women in each group received 6 cycles of chemotherapy and 62% of the women in the bevacizumab group had 18 cycles. A total of 5% of women (n=48 in standard chemotherapy group and n=27 in the bevacizumab group) received additional chemotherapy or bevacizumab before disease progression.

The primary outcome was progression-free survival (calculated from the date of randomisation until the date of disease progression or death, whichever occurred first). Analysis of efficacy for

progression-free survival was performed on the intention-to-treat population (all women who had been randomly assigned to treatment) using an un-stratified log-rank test.

Women were assessed for disease progression using the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines, using a combination of clinical assessment, computerised tomography (CT) scan, magnetic resonance imaging (MRI) scan and cancer antigen 125 (CA-125) levels.

Secondary outcomes included overall survival, biological progression-free survival, response to therapy, toxicity and quality of life.

Pre-planned analyses included a log-rank test that stratified for factors used for randomisation, and interaction analyses to explore the difference in the relative size of treatment effects in subgroups according to baseline characteristics, high risk for progression, and stratification factors.

After submission of the primary progression-free survival analysis, regulatory authorities requested an overall survival analysis with at least 365 deaths and an update on progression-free survival using the same data set. Results for both the primary and updated analysis are presented below.

Progression-free survival

Primary analysis: intention-to-treat population

In the primary analysis (data cut-off February 2010), after a median follow-up of 19 months, an improvement in median progression-free survival of 1.7 months was seen in the bevacizumab group compared with the standard chemotherapy group (19 months compared with 17.3 months respectively). The estimated hazard ratio (HR) for progression or death in the bevacizumab group was 0.81 (95% confidence interval [CI] 0.70 to 0.94, p=0.004). The Kaplan-Meier curves for progression-free survival crossed over demonstrating non-proportional hazards. A test for non-proportional hazards confirmed this (p<0.0001). The conventional hazard ratio is not meaningful when calculated using data that demonstrates non-proportional hazards. To better estimate the effect of bevacizumab on progression-free survival, restricted mean values were estimated. Using all data obtained up to 36 months after randomisation, an improvement in restricted mean progression-free survival of 1.5 months was estimated for the bevacizumab group compared with the standard chemotherapy group (21.8 months compared with 20.3 months respectively).

Primary analysis: subgroup at high risk for progression

The trial reported on a pre-specified subgroup of the women with advanced ovarian cancer who had FIGO stage III and more than 1.0 cm of residual disease after debulking surgery or who had FIGO stage IV disease. They termed these women at 'high risk for progression' (n=465). No other subgroup analyses were presented.

In the primary analysis for this subgroup of women, after a median follow-up period of 19 months, median progression-free survival improved by 5.4 months in the bevacizumab group compared with the standard chemotherapy group (15.9 months compared with10.5 months respectively; HR 0.68, 95% CI 0.55 to 0.85, p<0.001). However, the number of women who had disease progression or who died was similar in both groups (bevacizumab: n=173 [74.9%] compared with standard chemotherapy: n=158 [67.5%]).

Restricted mean progression-free survival estimated using data up to 36 months after randomisation showed an improvement of 3.4 months in the bevacizumab group compared with the standard chemotherapy group (16.5 months compared with 13.1 months respectively; no p value reported).

Updated analysis: intention-to-treat population

An updated analysis was performed (data cut-off November 2010) after a median follow-up period of 28 months. This showed an improvement in median progression-free survival of 2.4 months in the bevacizumab group compared with the standard chemotherapy group (19.8 months compared with 17.4 months respectively; HR 0.87, 95% CI 0.77 to 0.99, p=0.04). However, a similar number of women in each group had either disease progression or died (bevacizumab: n=470 [61.5%] compared with standard chemotherapy: n=464 [60.7%]).

In the updated analysis, restricted mean progression-free survival using data up to 36 months after randomisation showed an improvement of 1.9 months using bevacizumab compared with standard chemotherapy (22.5 months compared with 20.6 months respectively). Restricted mean progression-free survival was also estimated using data up to 42 months after randomisation, which showed a similar improvement of 1.7 months on bevacizumab compared with standard chemotherapy (24.1 months compared with 22.4 months respectively). No statistical tests were reported for these comparisons.

Updated analysis: subgroup at high risk for progression

In the updated analysis, after a median follow-up period of 28 months, median progression-free survival improved by 5.5 months on bevacizumab compared with standard chemotherapy for the subgroup of women at 'high risk for progression' (16.0 months compared with 10.5 months respectively; HR 0.73, 95% CI 0.60 to 0.93, p=0.002). However, the number of women who had disease progression or who died was similar in both groups (bevacizumab: n=190 [82.3%] compared with standard chemotherapy: n=196 [83.8%]).

Updated analysis of restricted mean progression-free survival using data up to 36 months after randomisation for this subgroup of women, showed an improvement of 3.5 months in the bevacizumab group compared with the standard chemotherapy group (17.6 months compared with 14.1 months respectively; no p value reported). A similar level of improvement in restricted mean progression-free survival of 3.6 months was observed using data up to 42 months after randomisation (18.1 months compared with 14.5 months respectively; no p value reported).

Further subgroup analysis was provided in a manufacturer's submission reported in the NICE technology appraisal on bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (NICE technology appraisal guidance 284). After an average of 28 months, women with stage III suboptimally debulked disease had a median improvement in progression-free survival of 6.8 months using bevacizumab compared with standard chemotherapy (16.9 months [n=140] compared with 10.1 months [n=154] respectively; HR 0.67, 95% CI 0.52 to 0.87, p value not reported). No statistically significant difference between treatment groups was observed for women with stage III optimally debulked cancer: median increase in progression-free survival of 1.6 months on bevacizumab compared with standard chemotherapy (19.3 months [n=383] compared with 17.7 months [n=368] respectively; HR 0.89, 95% CI 0.74 to 1.07). In addition, no statistically significant difference between treatment groups was observed for women with stage IV cancer: median increase in progression-free survival of 3.4 months on bevacizumab compared with standard chemotherapy (13.5 months [n=104] compared with 10.1 months [n=97] respectively; HR 0.74, 95% CI 0.55 to 1.01).

In the supplementary appendix of ICON7, only the hazard ratio was reported for the subgroup of women with inoperable stage III or IV disease, which showed a statistically significant improvement for those receiving bevacizumab (HR 0.66, 95% CI 0.48 to 0.91, p<0.011).

Overall survival

Primary analysis: intention-to-treat population

In the primary analysis, after a median follow-up of 19 months 241 deaths had occurred (111/764 in the bevacizumab group and 130/764 in the standard chemotherapy group): 231 (96%) were disease related, 5 treatment related and 5 due to other causes. There was no statistically significant difference between the 2 treatment groups for overall survival (HR 0.81, 95% CI 0.63 to 1.04, p=0.098). These results are interim results and should be interpreted with caution.

Updated analysis: intention-to-treat population

In the updated analysis, after a median follow-up of 28 months 378 deaths had occurred (178/764 in the bevacizumab group and 200/764 in the standard chemotherapy group). There was no statistically significant difference between the 2 treatment groups for overall survival (HR 0.85, 95% CI 0.69 to 1.04, p=0.11). However, only half of the pre-specified number of deaths (n=715) that was needed for an 80% power to detect a 23% increase in median overall survival had occurred at this time and so the results of these analyses should be interpreted with caution. The complete overall survival results are expected to be published at the end of 2013.

Updated analysis: subgroup at high risk for progression

Results for the subgroup at 'high risk for progression' (which was defined as women with FIGO stage III and >1.0 cm residual disease after debulking or women with FIGO stage IV) showed a statistically significant improvement in overall survival for the bevacizumab group after a median follow-up of 28 months. There were 79 deaths out of 231 women in the bevacizumab group compared with 109 deaths out of 234 women in the standard chemotherapy group. After a median follow up of 28 months, median survival still favoured bevacizumab with an improvement of 7.8 months compared with standard chemotherapy (36.6 months compared with 28.8 months respectively; HR 0.64, 95% CI 0.48 to 0.85, p=0.002). However, in the NICE technology appraisal on bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (NICE technology appraisal guidance 284) it was noted that, 'taking into account the shape of the Kaplan–Meier curve from the interim analysis of the high-risk patients, it is likely that the mean overall survival benefit would be much less than the median'. In addition, only half of the pre-specified number of deaths (n=715) that would be needed for an 80% power to detect a 23% increase in median overall survival had occurred at this time and so the results of these analyses should be interpreted with caution.

Quality of life

Health-related quality of life was measured using the European Organisation for the Research and Treatment of Cancer (EORTC) quality-of-life questionnaire ovarian cancer module (QLQ-OV28) and QLQ-C30 questionnaires. The OV28 contains 28 questions that assess symptoms, chemotherapy side effects, peripheral neuropathy, body image, attitude to disease and treatment, and sexual functioning. The QLQ-C30 contains 30 questions grouped into global health status, 5 function scales and 9 symptom scales.

Participants in the trial completed quality of life questionnaires on their own before the administration of treatment or medical consultation at baseline, before each chemotherapy cycle, then every 6 weeks for the rest of year 1 and every 3 months in year 2 unless women had disease progression. Data are due to be collected at 3 years for all those women who are still alive. The primary outcome was comparison of mean global quality of life in the standard chemotherapy and bevacizumab groups at 54 weeks using the EORTC-QLQ-C30 global quality of life scale on a translated scale from 0 (worst) to 100 (best).

The final results from the analysis of these questionnaires are due at the end of 2013. Preliminary results showed statistically significantly higher mean global quality of life score in the standard chemotherapy group compared with the bevacizumab group at 18 weeks (71.1 [n=594] compared with 66.9 [n=678] respectively, $p<0.01$) and 54 weeks (74.5 [n=454] compared with 69.5 [n=562] respectively, $p<0.01$). A quality of life difference of more than 10 points was defined as clinically significant by the study authors and these results fell short of this threshold. There was no statistically significant difference at 76 weeks (standard chemotherapy: 73.7 and bevacizumab: 72.6).

The Stark et al. (2013) study changed the definition for clinical significance of difference in quality of life in March 2011 after the publication of a review (Cocks et al. 2011). For the QLQ-C30, a small clinically important difference was defined as 4 to 7 points and a moderate difference was 10 to 15 points. For the QLQ-OV28, no evidence of a clinically relevant effect size was found and so a difference of 0.3 standard deviations was used. There were discrepancies between the number of questionnaire responses reported in the study by Stark et al. (2013) and the ICON7 trial, which may have affected the accuracy of the results.

After 18 weeks, a small clinically important difference in the mean global quality of life score of 5.1 points was seen favouring standard chemotherapy compared with bevacizumab (64.4 compared with 59.2 respectively; 95% CI 2.9 to 7.4, $p<0.0001$). Mean global quality of life at 54 weeks in women whose disease had not yet progressed also showed a small clinically important

increase for women in the standard chemotherapy group by an average of 6.4 points compared with those in the bevacizumab group (76.1 compared with 69.7 respectively; 95% CI 3.7 to 9.0, p<0.0001). The number of women whose global quality of life score improved by at least 10 points between baseline and 54 weeks was also higher in the standard chemotherapy group compared with the bevacizumab group (66% [221/333] compared with 56% [250/444]; odds ratio [OR] 0.58, 95% CI 0.42 to 0.80, p=0.001).

Exploratory analysis of subscales showed clinically small but statistically significant reductions in quality of life for women in the bevacizumab group for role functioning, financial worries, attitudes to disease or treatment, hormonal symptoms and rash (all p<0.01).

There are no data available yet for quality of life after disease progression.

The reason for the small reduction in quality of life in the bevacizumab group remains unclear, and was not shown to be due to resolution timing of ascites, abdominal wall wound healing, or life disruption with continued chemotherapy.

Evidence review: safety

Precautions for use

The manufacturer of bevacizumab (Avastin, Roche) warned about the risk of necrotising fasciitis associated with bevacizumab in May 2013 in information sent to healthcare professionals about the safety of medicines. The summary of product characteristics (SPC) lists adverse reactions that may be associated with bevacizumab treatment. These include gastrointestinal perforations, fistulae, wound healing complications, hypertension, posterior reversible encephalopathy syndrome, proteinuria, arterial and venous thromboembolism, haemorrhage, pulmonary haemorrhage or haemoptysis, congestive heart failure, neutropenia and infections, hypersensitivity or infusion reactions, osteonecrosis of the jaw, eye disorders, and ovarian failure.

The safety and efficacy of bevacizumab has not been studied in children, or in people with renal or hepatic impairment. It is contraindicated in people with hypersensitivity to the active substance, Chinese hamster ovary (CHO) cell products, or other recombinant human or humanised antibodies. Bevacizumab is also contraindicated in pregnancy. The SPC advises that women of childbearing potential should use effective contraception during and up to 6 months after treatment and breastfeeding should be avoided during and for at least 6 months after treatment.

Adverse drug reactions have been reported with sunitinib, platinum- or taxane-based therapies and epithelial growth factor receptor (EGFR) monoclonal antibodies when used in combination with bevacizumab.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Adverse events reported in the randomised controlled trial

The ICON7 trial reported 5 deaths that were related to treatment or to treatment and disease. One occurred in the standard chemotherapy group due to central nervous system (CNS) ischaemia. Four occurred in the standard chemotherapy plus bevacizumab group. These were due to gastrointestinal perforation, intracerebral haemorrhage, recurrent bowel perforation and ovarian cancer, and neutropenic sepsis and ovarian cancer.

Adverse events were common in both groups. Any adverse events of grade 1 or 2 were reported in 44% of women in the standard chemotherapy group and 34% of those in the bevacizumab group. Grade 3 or higher adverse events were reported in 56% of women in the standard chemotherapy group and 66% of those in the bevacizumab group.

Adverse events occurred more frequently in women receiving bevacizumab including:-

- bleeding other than mucocutaneous tumour-associated, or within the CNS, grade 1 or 2 (standard chemotherapy n=39 [5%] compared with bevacizumab n=55 [7%])
- mucocutaneous bleeding grade 1 or 2 (standard chemotherapy n=55 [7%] compared with bevacizumab n=271 [36%]) and grade 3 or higher (standard chemotherapy n=0 compared with bevacizumab n=5 [1%])
- bleeding within the CNS grade 3 or higher (standard chemotherapy n=0 compared with bevacizumab n=2 [<1%])
- abscess and fistula grade 1 or 2 (standard chemotherapy n=3 [<1%] compared with bevacizumab n=7 [1%])
- gastrointestinal perforation grade 3 or higher (standard chemotherapy n=3 [<1%] compared with bevacizumab n=10 [1%])

- any thromboembolic event grade 1 or 2 (standard chemotherapy n=22 [3%] compared with bevacizumab n=29 [4%]) and grade 3 or higher (standard chemotherapy n=23 [3%] compared with bevacizumab n=51 [7%])
- complications of wound healing grade 1 or 2 (standard chemotherapy n=13 [2%] compared with bevacizumab n=27 [4%]) and grade 3 or higher (standard chemotherapy n=3 [<1%] compared with bevacizumab n=10 [1%])
- hypertension grade 1 (standard chemotherapy n=31 [4%] compared with bevacizumab n=57 [8%]), grade 2 (standard chemotherapy n=14 [2%] compared with bevacizumab n=90 [12%]) and grade 3 or higher (standard chemotherapy n=2 [<1%] compared with bevacizumab n=46 [6%]).

Evidence review: economic issues

Cost effectiveness

No studies on the cost effectiveness of bevacizumab 7.5 mg/kg for advanced ovarian cancer were identified.

Cost

MIMS (July 2013) lists the price for bevacizumab at 25 mg/ml solution for intravenous infusion in the following vials:

- bevacizumab 100 mg/4 ml: £242.66
- bevacizumab 400 mg/16 ml: £924.40.

For women whose weight is in the range of 53.4 kg to 66.6 kg, the 'drug-only' cost of bevacizumab at a dose of 7.5 mg/kg would be £1167.06 per cycle. This assumes that a 16 ml vial can treat a woman who weighs up to 53.3 kg, but for those weighing between 53.4 kg and 66.6 kg a 16 ml and a 4 ml vial would be needed in combination (assuming wastage). The suggested regimen would be bevacizumab in combination with paclitaxel and carboplatin for 6 cycles and then on its own for up to an additional 12 cycles or until disease progression (up to 18 cycles in total). This would equate to between £7002.36 (for the first 6 cycles) and £21,007.08 (for the first 6 cycles plus an additional 12 cycles). This does not include the cost of administration by intravenous infusion in hospital. This additional cost would be greater during the extended treatment phase when standard chemotherapy has finished.

Current drug usage

Bevacizumab is currently available in England through the national cancer drugs fund list at a dose of 7.5 mg/kg for first-line treatment of advanced (stage IIIc/IV) ovarian cancer, suboptimally debulked either at primary or delayed primary (interval) surgery (including peritoneal and fallopian tube cancer) or unsuitable for debulking surgery. The latest figures from NHS England show that 116 notifications were received in the first quarter of 2013/14 for use of bevacizumab 7.5 mg/kg. Each notification represents 1 patient being registered to start a full course of treatment. The definition of advanced ovarian cancer for the indication on the national cancer drugs fund list includes people with stage IIIC/IV ovarian cancer. This differs from the definition of advanced ovarian cancer in the NICE technology appraisal guidance on bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer, which defines advanced ovarian cancer as those with stage IIIB, IIIC and IV disease.

Evidence strengths and limitations

It is not clear from the interim reporting on overall survival for the ICON7 trial which women with advanced ovarian cancer could benefit from bevacizumab.

The scope of this evidence summary is for advanced ovarian cancer, the definition of which is described in the NICE technology appraisal on bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer (NICE technology appraisal guidance 284) as International Federation of Gynaecology and Obstetrics (FIGO) stages IIIB, IIIC and IV. ICON7 enrolled women with all stages of ovarian cancer, and separate analysis of women with only stages IIIB, IIIC and IV was not reported. Instead, a subgroup labelled those 'at high risk for progression', defined as FIGO stage IV disease or FIGO stage III disease and more than 1.0 cm of residual disease after debulking surgery, was reported. It is not clear if the results would be the same if women with FIGO stage III disease and less than 1.0 cm of residual disease were also included in this 'high risk subgroup'. Further subgroup analyses according to baseline characteristics and stratification factors were pre-planned but were not reported in full in the ICON7 trial. Additional data from the manufacturer's submission were presented in the NICE technology appraisal on bevacizumab. This reported that a subgroup of women with stage III suboptimally debulked ovarian cancer may have the most benefit from bevacizumab in terms of progression-free survival, with limited benefit for 2 other subgroups (that is, women with optimally debulked stage III disease and those with stage IV disease). However, the results for the subgroup of women with inoperable stage III and stage IV ovarian cancer were reported to a limited extent in the supplementary appendix of the ICON7 paper. In terms of overall survival, the only subgroup analysis reported so far is for women at 'high risk for progression'.

The current results of the Stark et al. (2013) quality of life study includes women with all stages of ovarian cancer before progression, and so this may not accurately represent quality of life for women with advanced ovarian cancer. There was a discrepancy in the number of quality of life questionnaires that Stark et al. (2013) was able to obtain compared with the number reported in the ICON7 trial. It is unclear why this occurred and what effect it may have had on the underlying results. Stark et al. (2013) reported that there was no difference in quality of life depending on stage of disease but no data were provided.

The ICON7 trial was of a reasonable size (n=1528) but there were some limitations to the open-label design that allowed clinicians and patients to know they were receiving bevacizumab. Therefore, there may have been some systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation (performance bias) in favour of bevacizumab.

Randomisation was appropriate and achieved comparable groups across disease stage, grade, histology and Eastern Cooperative Oncology Group (ECOG) performance status, although 96% of the women were Caucasian and it is unclear whether the results would be applicable to women of different ethnicity. Allocation to treatment was appropriately concealed by central randomisation using an interactive telephone or web-based system.

The vast majority of women recruited to ICON7 (94%) scored 0 or 1 for the ECOG performance status score meaning they were asymptomatic or symptomatic but completely ambulatory. They also had adequate coagulation values, and bone marrow, liver and renal function. It is not clear whether similar results would be found in women who have higher care needs or poorer organ function. It is also not clear whether those with higher care needs would be able to tolerate the raised frequency of adverse effects found to be associated with bevacizumab over standard chemotherapy.

Summary for patients

A summary written for patients is available on the NICE website.

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

Project team

Bazian Ltd

Medicines and Prescribing Centre, NICE

Peer reviewers and contributors

Lizzie Amis, Senior Public Involvement Adviser, Public Involvement Programme, NICE

Expert advisers

Dr Sarah Blagden, Consultant/Senior Lecturer in Medical Oncology, Director of Phase I Cancer Trials, Imperial College London

Roche reviewed the evidence summary and provided additional technical information.

Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- Broad internet search: ***allintitle: ovarian bevacizumab OR avastin filetype:pdf***
- Trip Database

MEDLINE (via Ovid)

1. exp Ovarian Neoplasms/
2. (ovar$ and (cancer or neoplasm or tumour or tumor)).mp.
3. 1 or 2
4. (bevacizumab or avastin or R435 or RG435 or rhuMAbVEGF).mp.
5. 3 and 4

Embase (via Ovid)

1. exp Ovarian Neoplasms/
2. (ovar$ and (cancer or neoplasm or tumour or tumor)).ti.
3. 1 or 2

4. (bevacizumab or avastin or R435 or RG435 or rhuMAbVEGF).ti.
5. bevacizumab/
6. 4 or 5
7. 3 and 6

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Ovarian Neoplasms] explode all trees

#2 (over* and [cancer or neoplasm or tumour or tumor]):ti, ab

#3 #1 or #2

#4 (bevacizumab or avastin or R435 or RG435 or rhuMAbVEGF):ti,ab

#5 #3 and #4

CRD HTA, DARE and EED database

1. MeSH DESCRIPTOR Ovarian Neoplasms EXPLODE ALL TREES
2. (bevacizumab or avastin):ti
3. #1 AND #2

Grey literature and ongoing trials

- NICE Evidence
- Health Canada – Clinical Trials Search
- metaRegister of Controlled Trials (mRCT)
- ClinicalTrials.gov

Manufacturers' websites

Roche

Evidence selection

The focus of the literature search was on use of bevacizumab 7.5 mg/kg for ovarian cancer. The search returned 194 articles, which was reduced to 44 during the first sift. This eliminated all non-randomised controlled trial (RCT) studies but included any ongoing trials if the dosage was unclear.

From the 44 sifted results, studies that looked at the licensed dose of bevacizumab 15 mg/kg were excluded. One phase III RCT was identified as the best available evidence that examined the effectiveness of bevacizumab 7.5mg/kg in ovarian cancer. An adjunct to this trial measured quality of life outcomes. Other sources were used for background information and context.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

> This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

Contact NICE

National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

www.nice.org.uk; nice@nice.org.uk; 0845 003 7780

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