NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA284; Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced and/or metastatic ovarian cancer, and TA285; Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer

These guidelines were issued in May 2013.

The review date for TA284 is April 2016 and for TA285 it is June 2016.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

TA284

To appraise the clinical and cost effectiveness of bevacizumab within its licensed indication in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer.

TA285

To appraise the clinical and cost effectiveness of bevacizumab within its licensed indication for the treatment of platinum-sensitive or partially platinum-sensitive recurrent advanced ovarian cancer (including fallopian tube and primary peritoneal cancer).

3. Current guidance

TA284

1.1 Bevacizumab in combination with paclitaxel and carboplatin is not recommended for first-line treatment of advanced ovarian cancer (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV epithelial ovarian, fallopian tube or primary peritoneal cancer).

1.2 People currently receiving bevacizumab for first-line treatment of advanced ovarian cancer should be able to continue treatment until they and their clinicians consider it appropriate to stop.

Please note that NICE can only issue guidance on any drug within the terms of its marketing authorisation. Consequently, bevacizumab for first-line treatment of advanced ovarian cancer has only been appraised at its licensed dose of 15 mg/kg body weight.

TA285

1.1 Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.

1.2 People currently receiving bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer should be able to continue treatment until they and their clinician consider it appropriate to stop.

4. Rationale[1]

TA284 - Since the publication of TA284, additional data have been reported from 2 of the trials considered as part of the original appraisal: GOG-0218 and ICON7.

The results from GOG-0218 (Randall 2013) represent an exploratory subgroup analysis of people with stage IV disease; confirmatory studies are required to strengthen Randall et al.'s conclusion that bevacizumab is more effective in people with stage IV disease. In addition, this analysis may not address the uncertainty in the survival benefit of bevacizumab.Considering these limitations, and the high incremental cost effectiveness ratio (ICER) for bevacizumab in the overall patient population, this exploratory subgroup analysis does not warrant a review of the guidance.

The ICON7 trial investigated an unlicensed dose of bevacizumab; the committee is unable to issue guidance on a technology used outside the terms of its marketing authorisation.

TA285 - Since the publication of TA285 final survival data from the OCEANS clinical trial have been published, which show no significant benefit in favour of bevacizumab. Results from an additional randomised phase III trial (GOG-0213) have also been reported. These data may lead to an extension to the marketing authorisation for bevacizumab for treating ovarian cancer but this is unlikely to improve the cost effectiveness of bevacizumab.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

6. New evidence

The search strategy from the original ERG reports was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2012 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Roche are considering the feasibility of a patient access scheme for this indication if a review were to be scheduled. No final decision has been reached.

TA284 (bevacizumab for the first-line treatment of ovarian cancer)

Since the publication of TA284, additional data have been reported from 2 of the trials considered as part of the original appraisal (GOG-0218 and ICON7).

Additional subgroup data now available from the GOG-0218 trial

- In TA284, the committee concluded that bevacizumab was clinically effective in the overall patient population (although the survival benefit was uncertain), but agreed that the range of ICERs obtained from the cost-effectiveness model of bevacizumab plus paclitaxel and carboplatin (£128,000 to £161,000 per QALY gained) were outside the range normally considered as a cost-effective use of NHS resources. The uncertainty in the survival benefit of bevacizumab plus carboplatin and paclitaxel in this indication was because of the uncertainty related to the extent to which patients received bevacizumab after progression in GOG-0218, and the impact of this (paragraph 4.7 final guidance).

- In its submission for TA284, the company suggested that bevacizumab provides greater benefit for people with advanced ovarian cancer who have a poor prognosis, but the committee noted that subgroup data from GOG-0218 did not appear to support this conclusion (paragraph 4.11 final guidance).

- Additional, exploratory, subgroup data have now been reported from GOG-0218 (Randall 2013). These data show more favourable results for first-line bevacizumab with carboplatin and paclitaxel in people with FIGO stage IV disease. However, the authors acknowledged that a study specifically designed to test this hypothesis is required to know this conclusively. In addition, it is unclear whether the new subgroup data will address the uncertainty in the survival benefit associated with bevacizumab (related to the extent to which patients received bevacizumab after progression and the impact of this).

Final survival data now available for ICON7 trial

- In TA284, an interim survival analysis of patients in ICON7 (conducted when approximately 25% of patients had died) was presented. The final overall

survival (OS) analysis is now available based on a data cut off on 31 March 2013 and a median follow up of 48.9 months (Oza 2015). However, there are a number of disadvantages associated with the ICON7 trial which the committee acknowledge during TA284:

- investigated an unlicensed dose of bevacizumab (7.5 mg/kg) and a treatment duration that differed from the marketing authorisation
- included patients who were not part of the scope (stage I and II cancer)
- was open-label in design.

Although the unlicensed dose of bevacizumab is the dose most commonly used in the NHS for advanced ovarian cancer, the committee is unable to issue guidance on a technology used outside the terms of its marketing authorisation and the results of ICON7 were considered only as supporting evidence in TA284.

- The final OS analysis from ICON7 (Oza 2015) showed that, in the overall study population, bevacizumab plus chemotherapy did not increase OS compared with chemotherapy alone.
- It should also be noted that the updated PFS analysis from ICON7 showed that the difference between treatment groups was no longer statistically significant for the overall population (Oza 2015); this contradicts the findings of the interim PFS analysis which was considered as part of the supporting evidence in TA284 (in which the difference was statistically significant).

Cancer Drugs Fund

Bevacizumab in combination with paclitaxel and carboplatin is currently available on the Cancer Drugs Fund, at the unlicensed dose of 7.5mg/kg, for the first-line treatment of stage III or IV advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

TA285 (bevacizumab for treating platinum-sensitive or partially platinum-sensitive recurrent advanced ovarian cancer)

Since the publication of TA285, results from an additional randomised phase III trial (GOG-0213) have been reported. Final survival data are also available from the OCEANs trial which, as in the interim analyses, show no significant benefit in favour of bevacizumab.

Results from a new clinical trial available: GOG-0213

- The GOG-0213 trial was a phase III randomised controlled clinical trial of combination chemotherapy given with or without bevacizumab in people with recurrent ovarian, peritoneal primary and fallopian tube cancer after primary cytoreductive surgery (second line treatment in the advanced setting). This was followed by secondary cytoreductive surgery and further combination chemotherapy given with or without bevacizumab (maintenance treatment).

All patients had platinum-sensitive disease. The chemotherapy combinations (given alone or with bevacizumab) were carboplatin with paclitaxel and carboplatin with gemcitabine. Roche have suggested that the results of this trial could lead to an extension to the marketing authorisation for bevacizumab, to include:

- [redacted]
- [redacted]

Final survival data now available for clinical trial: OCEANS

- During TA285, the committee concluded that the OCEANS trial showed that bevacizumab did not have a beneficial effect on OS (based on an interim analysis). The final survival analysis also showed no significant difference between treatment arms for OS (Aghajanian 2015), and therefore these results may not change the estimates of clinical and cost effectiveness for bevacizumab.

Cancer Drugs Fund

- Bevacizumab in combination with carboplatin and gemcitabine chemotherapy for recurrent platinum sensitive ovarian cancer was delisted from the Cancer Drugs Fund in March 2015.

8. Adoption and Impact

No submission was received from the Adoption and Impact team.

9. Equality issues

No issues relating to equality considerations were raised in the submissions or the Committee meetings for either TA284 or TA285.

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Ovarian cancer (2016) NICE pathway.

Ovarian cancer (2012) NICE quality standard 18.

Ovarian cancer (2011) NICE guideline CG122.
Surveillance proposal: do not update. Review decision due: March 2016.

Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy (2016) NICE technology appraisal guidance 381.
Review date: 2 years after publication or when SOLO-2 data is available.

Bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer (terminated appraisal) (2015) NICE technology appraisal guidance 353.

Ovarian cancer (advanced): bevacizumab 7.5 mg/kg in combination with paclitaxel and carboplatin for first-line treatment (2013) NICE evidence summary of unlicensed or off-label medicines 21.

Trabectedin for the treatment of relapsed ovarian cancer (2011) NICE technology appraisal guidance 222.
Review: to be combined with the review of TA91.

Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer (2005) NICE technology appraisal guidance 91. Note: replaced TA28, TA45 and parts of TA55.
Review date: February 2008. Review decision: to be reviewed (along with TA222).

Guidance on the use of paclitaxel in the treatment of ovarian cancer (2003) NICE technology appraisal guidance 55.

In progress

Cediranib for treating platinum-sensitive fallopian tube or primary peritoneal ovarian cancer. [ID790] NICE technology appraisal guidance. Publication expected April 2017.

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer (including reviews of TA 91 & TA 222) [ID468] NICE technology appraisal guidance. Publication expected April 2016.

Suspended/terminated

Vintafolide in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of folate receptor positive, platinum resistant ovarian cancer [ID564] NICE technology appraisal guidance. Publication date to be confirmed.
Status: the manufacturer has withdrawn its application for a conditional marketing authorisation.

Pazopanib for the maintenance treatment of epithelial ovarian, fallopian and peritoneal cancer in patients whose disease has not progressed after first line therapy [ID545] NICE technology appraisal guidance. Publication date to be confirmed.
Status: the manufacturer is not pursuing an application for marketing authorisation

Details of changes to the indications of the technology

Indication and price considered in original appraisals	Proposed indication (for this appraisal) and current price
Indication TA284 Bevacizumab in combination with carboplatin and paclitaxel has a UK marketing authorisation for 'the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer'. The licensed dose is 15 mg/kg body weight given once every 3 weeks in addition to carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of bevacizumab as single agent until disease progression, or for a maximum of 15 months, or until unacceptable toxicity is reached, whichever occurs earlier. TA285 Bevacizumab in combination with carboplatin and gemcitabine has a marketing authorisation for 'treatment of adult patients 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'. The licensed dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles, followed by continued use of bevacizumab as single agent until disease progression. **Price** Bevacizumab is available in 100 mg and 400 mg vials at net prices of £242.66 and £924.40 respectively (excluding VAT; 'British national formulary' edition 65).	**Indication** TA284: No current changes. Source: SPC (October 2015) TA285: [redacted]Source: letter from Roche to NICE (20 January 2016) **Price** No current changes Source: BNF (January 2016) Roche are considering the feasibility of a patient access scheme for this indication if a re-review were to be scheduled. No final decision has been reached. Source: letter from Roche to NICE (20 January 2016)

Details of new products

Drug (company)	Details (phase of development, expected launch date)
Paclitaxel encapsulated in XR-17 (Oasima)	Phase 3 clinical trials UK launch expected [redacted]
Paclitaxel poliglumex (Novartis)	Phase 3 clinical trials UK launch expected [redacted]
Cositecan (BioNumerik)	Phase 3 clinical trials UK launch expected [redacted]
Binimetinib (Pierre Fabre)	Phase 3 clinical trials UK launch expected [redacted]
Niraparib (Merck)	Phase 3 clinical trials UK launch expected [redacted]
Olaparib (AstraZeneca)	Phase 3 clinical trials UK launch expected [redacted]
Trebananib (Amgen)	Phase 3 clinical trials Development discontinued
Nintedanib (Merck)	Phase 3 clinical trials UK launch expected [redacted]
Rucaparib (Clovis)	Phase 2 clinical trials UK launch expected [redacted]
Avelumab (Merck and Pfizer)	Phase 3 clinical trials UK launch expected [redacted]
Cabozantinib (Exelixis)	Phase 2 clinical trials UK launch expected [redacted]
Camptothecin (Cerulean)	Phase 2 clinical trials UK launch expected [redacted]
ENMD-2076 (CASI)	Phase 2 clinical trials UK launch expected [redacted]

Fosbretabulin (Oxigene)	Phase 2 clinical trials UK launch expected [redacted]
Motolimod (VentiRx)	Phase 2 clinical trials UK launch expected [redacted]

Registered and unpublished trials

TA284

Trial name and registration number	Details
A Phase III Clinical Trial of Bevacizumab With IV Versus IP Chemotherapy in Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma NCT00951496 GOG-0252	Purpose: bevacizumab and intravenous chemotherapy compared with bevacizumab and intraperitoneal chemotherapy in stage II-III ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer Methods: randomized, open label Status: ongoing, not recruiting Enrollment: 1500 Start date: July 2009 Expected completion: March 2016
A phase III randomised trial investigating the combination of dose-fractionated chemotherapy and bevacizumab compared to either strategy alone for the first-line treatment of women with newly diagnosed high-risk stage III-IV epithelial ovarian, fallopian tube or primary peritoneal cancer ISRCTN10356387 ICON8b	Status: ongoing Enrollment: 2655 Start date: August 2015 Expected completion: May 2022
A GCIG Intergroup Multicenter Phase III Trial of Open Label Carboplatin and Paclitaxel +/- Bevacizumab Compared With Oxaliplatin and Capecitabine +/- Bevacizumab as First Line Chemotherapy in Patients With Mucinous Epithelial Ovarian or Fallopian Tube Cancer (MEOC) NCT01081262 GOG-0241	Status: ongoing, not recruiting Enrollment: 332 Start date: October 2010 Expected completion: July 2020

Trial name and registration number	Details
A Phase III Trial of Every-3-Weeks Paclitaxel Versus Dose Dense Weekly Paclitaxel in Combination With Carboplatin With or Without Concurrent and Consolidation Bevacizumab (NSC #704865) in the Treatment of Primary Stage II, III or IV Epithelial Ovarian, Peritoneal or Fallopian Tube Cancer NCT01167712 GOG-0262	Purpose: is giving paclitaxel with combination chemotherapy once every three weeks more effective than giving paclitaxel once a week? Methods: non-randomized, parallel assignment, open label Status: ongoing, not recruiting Enrollment: 773 Start date: September 2010 Expected completion: December 2015
A Prospective Randomised Phase III Trial to Evaluate Optimal Treatment Duration of First-line Bevacizumab in Combination With Carboplatin and Paclitaxel in Patients With Primary Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer NCT01462890 BOOST	Purpose: is the early and continuous addition of bevacizumab for up to 30 months to the standard chemotherapy more effective than the early and continuous addition of bevacizumab for up to 15 months? Status: ongoing, not recruiting Enrollment: 800 Start date: November 2011 Expected completion: November 2021

TA285

Trial name and registration number	Details
A Phase III Randomized Controlled Clinical Trial of Carboplatin and Paclitaxel (or Gemcitabine) Alone or in Combination With Bevacizumab (NSC #704865) Followed by Bevacizumab and Secondary Cytoreductive Surgery in Platinum-Sensitive, Recurrent Ovarian, Peritoneal Primary and Fallopian Tube Cancer NCT00565851 GOG-0213	Status: recruiting Enrollment: 1038 Start date: December 2007 Expected completion: March 2019

Trial name and registration number	Details
A Prospective Randomized Phase III Trial of Carboplatin/Gemcitabine/Bevacizumab vs. Carboplatin/Pegylated Liposomal Doxorubicin/Bevacizumab in Patients With Platinum-sensitive Recurrent Ovarian Cancer NCT01837251 AGO-OVAR 2.21	Methods: randomized, parallel assignment, open label Status: ongoing, not recruiting Enrollment: 682 Start date: May 2013 Expected completion: November 2019
Multicenter Phase III Randomized Study With Second Line Chemotherapy Plus or Minus Bevacizumab in Patients With Platinum Sensitive Epithelial Ovarian Cancer Recurrence After a Bevacizumab/Chemotherapy First Line NCT01802749 MITO-16	Status: recruiting Enrollment: 400 Start date: November 2013 Expected completion: July 2017

Relevant services covered by NHS England specialised commissioning

NHS England (2013) NHS standard contract for cancer: chemotherapy (adult)

NHS England (1 Feb 2016) National Cancer Drugs Fund List v6.1

> The first line treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Additional information

European Society of Medical Oncology (2013) Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Scottish Medicines Consortium (2015) Bevacizumab (Avastin) - 806/12. 2nd resubmission

> **Bevacizumab (Avastin)** is accepted for restricted use within NHS Scotland.
>
> **Indication under review**: In combination with carboplatin and paclitaxel, for the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

SMC restriction: In patients with FIGO stage IV disease

Scottish Medicines Consortium (2013) Bevacizumab (Avastin) - 853/13

Bevacizumab (Avastin) is not recommended for use within NHS Scotland.

Indication under review: Bevacizumab, in combination with carboplatin and gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelian ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Scottish Intercollegiate Guidelines Network (2013) Management of epithelial ovarian cancer. SIGN 135

References

Aghajanian C, Goff B, Nycum LR et al. (2015) Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecologic Oncology* 139 (1): 10-16.

Coleman RL, Brady MF, Herzog TJ et al. (2015) A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinumsensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). *Gynecologic Oncology* 137: 3-4.

Oza AM, Cook AD, Pfisterer J et al. (2015) Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncology* 16 (8): 928-936.

Randall L, Burger R, Nguyen H et al. (2013) Outcome differences in patients with advanced epithelial ovarian, primary peritoneal and fallopian tube cancers treated with and without bevacizumab. *Gynecologic Oncology* 130 (1): e33-e34.