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

# One Wales Medicines Assessment Group Recommendation: Bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression (OW01)

**February 2024**

## ONE WALES INTERIM DECISION

**Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression**

**Date of original advice: June 2019**
**Date of review: December 2023**

**The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.**

Bevacizumab 7.5 mg/kg dose in combination with carboplatin and paclitaxel can be made available within NHS Wales for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression. High risk is defined as: International Federation of Gynaecology and Obstetrics [FIGO] stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

Bevacizumab 7.5mg/kg dose is not licensed to treat this indication and is therefore ‘off-label’. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

The risks and benefits of the off-label use of bevacizumab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

**Clinician responsibility**
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

**Health board responsibility**
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

**One Wales advice promotes consistency of access across NHS Wales.**

**Starting and stopping criteria for bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk for progression**

Prescribers should note that front-line treatment with bevacizumab is available for patients with stage III and IV homologous recombination deficiency (HRD)-positive disease who are eligible to receive olaparib plus bevacizumab maintenance therapy in line with the National Institute for Health and Care Excellence (NICE) guidance TA946 and should refer to this for full eligibility criteria[1].

These criteria are adapted from the NHS England National Cancer Drugs Fund List[2].

**Starting criteria:**
Patients with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer with sufficient performance status to undergo treatment with carboplatin, paclitaxel and bevacizumab in one of the following groups:

- patients with FIGO stage III disease debulked but residual disease more than 1 cm
- patients with FIGO stage III disease and unsuitable for debulking surgery
- patients with FIGO stage IV disease
- patients with FIGO stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction.

Patients who satisfy the eligibility criteria will be prescribed bevacizumab following consultation with the patient and/or carer taking into account potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

Bevacizumab is prescribed at a dose of 7.5 mg/kg every three weeks up to a maximum of 18 cycles. Bevacizumab should be given with the:

- first or second cycle of chemotherapy following primary debulking surgery
- first or second cycle of chemotherapy for those patients with inoperable stage IV disease or inoperable stage III disease or who are unable to undergo surgery due to increased risk during COVID19
- first or second cycle of chemotherapy following interval debulking surgery performed after three to four cycles of non-bevacizumab-containing neoadjuvant chemotherapy
- first or second cycle of neoadjuvant chemotherapy.

**Stopping criteria:**

- radiological or clinical evidence of disease progression
- toxicity
- patient request
- after 18 cycles of bevacizumab.

**References:**


1. National Institute for Health and Care Excellence. Technology Appraisal TA946. January 2024. Available at: https://www.nice.org.uk/guidance/ta946. Accessed January 2024.
2. NHS England. National Cancer Drugs Fund. February 2024. Available at: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/. Accessed February 2024.

**This is a summary of new evidence available and patient outcome data collected, to inform the review.**

**Bevacizumab at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel for the front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer at high risk of progression.**

**This report was prepared by the All Wales Therapeutics and Toxicology Centre in November 2023. It summarises any new evidence available and patient outcome data collected since the last review in September 2022.**

**Background**: Ovarian cancer is the leading cause of death from gynaecological cancer in the UK. Cancer survival statistics for Wales show that outcome for women with ovarian cancer is generally poor with an overall five-year survival rate for women diagnosed between 2014-2018 of 46.2%; women with advanced ovarian cancer (FIGO stage III or IV) have a five-year survival rate of 28.1% and 10.8%, respectively. Bevacizumab 7.5 mg/kg dose is on the Cancer Drugs Fund in England for patients with FIGO stage III debulked but residual disease more than 1.0 cm or stage IV disease, or stage III disease at presentation and requiring neoadjuvant chemotherapy due to low likelihood of optimal primary surgical cytoreduction. A cohort of patients was identified in Wales based on data from individual patient funding request panels. Clinicians in Wales considered there to be an unmet need and based on these two factors this medicine was considered suitable for assessment via the One Wales Medicines process.

**Current One Wales decision:** Supported

**Licence status:** Off-label use for this licensed medicine.

**Guidelines:** There have been no relevant updates to existing guidelines identified.

**Licensed alternative medicines or Health Technology Assessment advice for alternative medicines:** As mentioned in the last report, a review of TA693: Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer is currently underway.

**Effectiveness:** A repeat literature search conducted by AWTTC identified one retrospective cohort study which analysed the clinical effectiveness of bevacizumab pertinent to the recommendation and one meta-analysis investigating quality of life (QOL) in ovarian cancer patients treated with bevacizumab.

The retrospective cohort study by Ethier et al (2023) reported survival outcomes in 282 patients who received 7.5 mg/kg bevacizumab in addition to front-line chemotherapy treatment for ovarian cancer between March 2016 and October 2019 in Ontario, Canada. Mean age was 64 years old, 37% had stage III and 58% stage IV disease (remainder unknown). Patients received a mean of 7 cycles of chemotherapy and 10 cycles of bevacizumab. Reasons why the number of cycles given was lower than the recommended 18 cycles could not be derived from the dataset. Median overall survival in this real-world cohort treated

with front-line bevacizumab was shorter than in pivotal clinical trials (29 months compared to 39 months in the high-risk subgroup in ICON7 and 43 months in GOG-218). To determine the effect of bevacizumab on survival, a before and after bevacizumab approval analysis was performed in a larger cohort of patients (n = 761) with stage IV disease and serous subtype who received front-line chemotherapy. Survival was not significantly different in the PRE and POST groups (HR 0.92, 0.75–1.12, p = 0.382). However, as uptake of bevacizumab treatment was low at only 23% the study lacked power to detect differences between groups and to provide any meaningful comparison with the pivotal studies. Debulking status was not available for this dataset, so a comparative effectiveness analysis could not be performed in stage III disease. The median OS for patients with stage III disease in the bevacizumab-treated cohort was 37 months, shorter than observed in clinical trials. However, for those patients who underwent primary surgery the median OS was 43 months, similar to the median OS (40 months) of stage III suboptimally debulked patients in ICON7.

The meta-analysis conducted by Wu et al (2023) included four RCTs comparing the QOL of bevacizumab plus chemotherapy versus chemotherapy in ovarian cancer patients and found that the extended survival associated with bevacizumab is not accompanied by a significant deterioration in QOL. However, one study was open label and a second was not powered for the secondary QOL endpoint. There was also significant heterogeneity between the studies included. Two trials were conducted in the frontline setting (ICON7 and GOG-218), and the other two were conducted in the recurrent setting (AURELIA and GOG-213). The dosages of bevacizumab were 7.5-15 mg/kg, and most trials administered a dosage of 15 mg/kg every 3 weeks. This is higher than the dose currently recommended by One Wales. Therefore, the generalisability of these results to the population under consideration is relatively low.

**Safety:** No new relevant safety analyses identified in the repeat literature search.

**Cost effectiveness:** No relevant cost-effectiveness analyses identified in the repeat literature search.

**Budget impact:** Twenty-five patients from the south-east Wales area who were negative for BRCA mutations or homologous recombination deficiency (HRD) started bevacizumab treatment (7.5mg/kg) between June 2022 and May 2023. Patients with BRCA mutations or HRD were not included in the outcomes report because they are eligible for treatment under NICE TA693 guidance.

No patient numbers for south-west or north Wales have been received. The estimated eligible population reported in the original evidence status report from 2019 was 30 patients per year in Wales, not accounting for population growth. The south-east Wales area services around 1.5 million people in Wales, around 50% of the population of Wales, meaning true patient numbers could be higher than the estimated annual uptake.

In the original estimates all patients were assumed to receive 18 cycles of bevacizumab, however 14 of the 25 confirmed patients had a median of 10.5 cycles (range 5-15), indicating lower usage. This indicates that overall usage is comparable to the original estimates. Bevacizumab continues to be available at a discounted price.

**Impact on health and social care services:** Minimal.

**Patient outcome data:** Outcome data was provided for 37 patients receiving treatment for two years from July 2019, the median treatment duration was 10 months (range 0-31 months). The median number of cycles given was 14, and the interquartile range for the number of cycles given was 7-18 cycles. This is slightly lower than quoted in the ICON7 study, however the ICON7 study reported on all patients, not just the high-risk group. [confidential data removed] and all other patients who received 18 cycles stopped at 18 cycles. These results are similar to those in the real-world study by Bertelli et al where the median treatment duration was 8 months (range 0-34 months).

Of the 25 eligible patients who started treatment between June 2022 and May 2023, [confidential data removed] patients have completed 18 cycles and seven patients are still receiving treatment (median 10 cycles, range 7-15 cycles). Fourteen patients have stopped treatment due to disease progression (median 10.5 cycles, range 5-15 cycles).

Data have also been provided for eight patients who were already on treatment in June 2022. Of these, five patients completed 18 cycles with [confidential data removed] of these five patients continuing beyond 18 cycles with IPFR funding due to continued response (median 32 cycles, range 31-37 cycles). [confidential data removed] patients stopped treatment due to disease progression (median 16 cycles, range 13-16 cycles).

It would be unadvisable to draw meaningful comparisons between these data and outcomes reported in published clinical evidence without further analyses on all available outcome data since bevacizumab was made available in Wales for this cohort of patients in 2019. AWTTC is hoping to work with clinicians to progress this further.

**Evaluation of evidence**

No significant new evidence has been published which challenges the current One Wales advice. The outcome data show some patients have had a prolonged response to bevacizumab treatment. AWTTC recommends continuing access in Wales to low dose bevacizumab for the treatment of advanced ovarian cancer.

**Next review date:** 12 months

**References**: A full reference list is available on request

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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