Indication	As 1st line treatment for patients with stage III or IV ovarian, fallopian tube or primary peritoneal carcinoma. NB: Neither a dose of 7.5mg/kg bevacizumab nor its use in the neoadjuvant setting, nor its use in stage IIIA disease is licensed in ovarian cancer, this use of bevacizumab must be within the treating Trust's governance framework.
Treatment Intent	Palliative / neo-adjuvant / adjuvant
Frequency and number of cycles	Repeat every 21 days Induction 6 cycles of bevacizumab, paclitaxel & carboplatin, followed by 12 cycles of maintenance bevacizumab monotherapy, to complete a total number of 18 cycles. For neo-adjuvant patients omit bevacizumab in the cycle prior to interval debulking surgery.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • DTPA should be used to measure GFR prior to cycle 1. C+G may be used to estimate CrCl if there is a delay in obtaining DTPA result. • Monitor CA125 and dipstick urine for proteinuria and test BP each cycle. Report to consultant if BP >/= 140/90. Reference should be made to KMCC guidelines for bevacizumab induced hypertension https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/guidelines-for-the-management-of-sact-induced-adverse-reactions/ See table 1 for guidance on proteinuria. • Monitor U+Es, LFTs and FBC ~~at~~ on day 1, 8 and 15 of each cycle. If CrCl falls by >25% repeat EDTA. ○ **Day 1** If neuts >/= 1.0 and PLT >/=75 proceed with treatment. If parameters not met delay until recovery. If haematological recovery occurs within 7 days, no dose modification is required. If haematological recovery occurs beyond 7 days, dose review of carboplatin and paclitaxel is recommended based on day 22 blood count (or subsequent FBC if lower). It is recommended that G-CSF prophylaxis is used in preference to dose reduction where appropriate to maintain planned dose intensity. ○ **Day 8 & Day 15** if neuts >/=0.5 and PLT >/=50 with no sign of fever, infection or bleeding give paclitaxel. ○ If neuts <0.5 or PLT <50 omit that dose. Omitted doses will not be replaced. • **Hepatic impairment:** ○ Bevacizumab: no dose recommendations. ○ Carboplatin: No dose adjustment required. ○ Paclitaxel: If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction, not recommended in severe hepatic impairment. • **Renal impairment:** ○ Bevacizumab: no dose recommendations. ○ Carboplatin: stop if CrCl<30ml/min. ○ Paclitaxel: no dose reduction necessary. • **Infusion-related reactions:** If the infusion related reaction can be attributed to a particular agent, treat as follows:

- **Bevacizumab:** If a patient experiences a mild infusion-related reaction, give the next infusion over 60 - 90 minutes +/- chlorphenamine cover. If this is tolerated, reduce the infusion time for the next doses in a step-wise fashion to a minimum of 30 minutes, and maintain that infusion time for all remaining doses.
- **Paclitaxel:** Patients developing hypersensitivity reactions to Paclitaxel may be re-challenged with full dose Paclitaxel following prophylactic medication (e.g. famotidine 40mg po given 4 hours prior to treatment plus Hydrocortisone 100mg iv and chlorphenamine 10mg iv 30 minutes prior to treatment), then give paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible). If patients experience no hypersensitivity reactions after the first two doses of paclitaxel, remove pre-medication with dexamethasone and chlorphenamine from dose 3 onwards.
- **Carboplatin:** Mild/moderate reactions (grade 1-2): If symptoms resolve after treatment with hydrocortisone and chlorphenamine, the infusion may be restarted at 50% rate for 30 mins, then, if no further reaction, increase to 100% rate.
- If symptoms do not resolve after treatment with hydrocortisone and chlorphenamine, do not restart the infusion. At consultant's discretion, patients may be rechallenged at a later date with additional prophylaxis. In the event of further reaction (grade 1-3), stop infusion and consider alternative treatment.
- Severe (grade 3): Do not restart infusion. Consider alternative treatment.
- Anaphylaxis (grade 4): Follow anaphylaxis protocol. Discontinue permanently and consider alternative treatment.

- **Dose Modification:**
  - **Bevacizumab:** Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended. If chemotherapy is delayed, bevacizumab should also be delayed. In the event chemotherapy is permanently discontinued continue with bevacizumab only.
  - **Paclitaxel:** Dose reduce Paclitaxel by 20% in the event of >/= grade 2 neuropathy and consider a delay until recovery to </= grade 1.
  - Consider omitting paclitaxel in event of recurrent >/= grade 3 neuropathy OR recurrent or persistent >/= grade 2 neuropathy following a dose reduction.
  - If doses delayed or omitted due to neutropenia, consider use of G-CSF.
  - If more than one paclitaxel dose is omitted in the same cycle or at least one dose is omitted from two consecutive cycles, the dose of both carboplatin and paclitaxel should be reduced.
    1st Dose reduction carboplatin AUC 4 (based on starting dose of AUC 5) and paclitaxel 60mg/m^2
    2nd Dose reduction carboplatin AUC3.5 (based on starting dose of AUC 5) and paclitaxel 45mg/^{2}
  - Dose reduction of **carboplatin** and **paclitaxel** should be considered if any other grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia).
- **Bevacizumab specific monitoring and guidance:**
  - **For neo-adjuvant patients omit bevacizumab in the cycle prior to interval debulking surgery.**
  - Bevacizumab may adversely affect wound healing. Do not give bevacizumab if patient has undergone major surgery within the last 28 days. Treatment should be stopped at least 28 days prior to elective surgery.
  - Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation with bevacizumab. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. It is recommended

	an OGD is undertaken in patients at high risk of variceal bleeding and that all sizes of varices be assessed and treated as per local standard of care prior to treatment. ○ Patients may be at increased risk for the development of fistulae when treated with bevacizumab. ○ Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with bevacizumab. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. ○ Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially, as cases of osteonecrosis of the jaw have been reported. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible. ○ Any suspected thrombosis and/or haemorrhage d/w consultant. ○ Patients with a history of arterial thromboembolism, diabetes or >65 years old should be treated with caution. Patients with thromboembolic reactions </= Grade 3 need to be closely monitored. ○ Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism or (refer to SPC for management). • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ **Bevacizumab:** Caution when used with drugs known to cause bleeding, concurrent use may increase risk. ○ **Paclitaxel** Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole, erythromycin, fluoxetine, clopidogrel, cimetidine, ritonavir and nelfinavir); toxicity may be increased. CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) may reduce efficacy. ○ **Carboplatin** Caution with other nephrotoxic drugs.
References	KMCC protocol V1 Gynae NOG decision regarding dose capping.

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Bevacizumab induced proteinuria

1+ or 2+ on dipstick (0.3 – 2.9g/L)	**3+ on dipstick (3 - 19g/L):**	**4+ on dipstick (>/=20g/L)**
Continue with bevacizumab. No additional evaluation required	May have dose of bevacizumab as scheduled, but will need 24-hour urine collection to measure protein a few days before next cycle due. If 24hr protein result < 2g, continue with bevacizumab. With continued proteinuria monitoring via 24-hour urine before each dose. If the 24-hour protein level falls to < 1g/24hr, return to dipstick analysis. If >/=2g, withhold bevacizumab until repeat 24-hour urine collection shows < 2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24-hour urine.	**Withhold bevacizumab**. 24-hour urine collection required. Follow 24-hour urine monitoring and guidance as for 3+ on dipstick.

Cycle 1 to 6: Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1	Dexamethasone	8mg (may be reduced to 4mg in subsequent doses)	IV	Bolus	
	Chlorphenamine	10mg	IV	Slow bolus	Over 3 min through the side of a fast running Sodium Chloride 0.9% intravenous infusion.
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	Please ensure pre-meds are given 30 mins prior to paclitaxel				
	PACLITAXEL	**80mg/m²**	IV	1 hr	In 250ml Sodium Chloride 0.9% (non-PVC bag and non-PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%
	CARBOPLATIN	**AUC 5** **Dose =(GFR + 25) x AUC** (dose capped at 790mg on epx system)	IV	30 mins	Glucose 5% 500ml In clinical practice the dose is usually capped at either 700mg OR for a maximum calculated dose of GFR 125ml/min
	BEVACIZUMAB	**7.5mg/kg**	IV	15mins*	In a total of 100mls sodium chloride 0.9% Flush the line with sodium chloride 0.9% for injection at the end of the infusion.
	If a patient experiences a mild infusion-related reaction, give the next infusion over 60 - 90 minutes +/- chlorphenamine cover. If this is tolerated, reduce the infusion time for the next doses in a stepwise fashion to a minimum of 30 minutes, and maintain that infusion time for all remaining doses. *unlicensed rate of infusion				
Day 8 and 15	Dexamethasone	8mg (may be reduced to 4mg in subsequent doses)	IV	Bolus	
	Chlorphenamine	10mg	IV	Slow bolus	Over 3 min through the side of a fast running Sodium Chloride 0.9% intravenous infusion.
	Metoclopramide	20mg	IV	Bolus	
	Please ensure pre-meds are given 30 mins prior to paclitaxel				
	PACLITAXEL	**80mg/m²**	IV	1 hr	In 250ml Sodium Chloride 0.9% (non-PVC bag and non-PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%

TTO cycle 1 to 6

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	6mg	PO	OM for 3 days after day 1
Day 1, 8 & 15	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. (Maximum of 30mg per day including 10 mg pre-chemo dose) Do not take for more than 5 days continuously.
Day 8 & 15	Dexamethasone	4mg	PO	OM for 2 days after day 8 and Day 15

Cycle 7 to 18 repeat every 21 days: NB alternatively, eligible patients may continue on to olaparib and bevacizumab 15mg/kg following 1st line induction.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**BEVACIZUMAB**	**7.5mg/kg**	IV	15mins*	In a total of 100mls sodium chloride 0.9% Flush line with sodium chloride 0.9%
	If a patient experiences a mild infusion-related reaction, give the next infusion over 60 - 90 minutes +/- chlorphenamine cover. If this is tolerated, reduce the infusion time for the next doses in a step-wise fashion to a minimum of 30 minutes, and maintain that infusion time for all remaining doses. *unlicensed rate of infusion				