Protocol Synopsis

Title: BGOG-ov5: Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynaecological cancers

Study Phase: 2

Indication: treatment of subjects with recurrent epithelial ovarian, primary peritoneal or fallopian tube cancers, endometrial carcinoma or cervical carcinoma

Primary Objective: To evaluate occurrence of grade 4 neutropenia during weekly paclitaxel/ carboplatin with prophylactic G-CSF, 36 patients will be included in each cohort of ovarian, endometrial and cervical carcinoma and compared with historical data as published earlier

Secondary Objective(s):

- To evaluate per cohort (ovarian, endometrial, cervical carcinoma) the occurrence of grade 4 neutropenia.
- To evaluate other toxicity than neutropenia (bone marrow, peripheral neuropathy, alopecia, ..) and dose reductions or delay.
- Determine the progression free survival according to the RECIST-criteria (Eisenhauer et al) of the combination of weekly paclitaxel/carboplatin
- To evaluate the response rate and overall survival.

Study Design:

This is a phase 2, multicenter study examining the occurrence of grade 4 neutropenia during weekly paclitaxel/ carboplatin with prophylactic G-CSF in the treatment of with recurrent epithelial ovarian, primary peritoneal or fallopian tube cancers, endometrial carcinoma or cervical carcinoma.

108 subjects will be included in the trial:

- 36 subjects in ovarian, fallopian tube or peritoneal carcinoma cohort
- 36 subjects in endometrial carcinoma cohort
- 36 subjects in the cervical cohort

Subjects will receive Paclitaxel 60 mg/m² followed by Carboplatin AUC 2.7 intravenously weekly during 18 weeks. Filgastrim (Neupogen®) 30 Mio U (0,600 mg/ml) will be given to all patients on day 5 of each course in patients weighing less than 60 kg and filgastrim (Neupogen®) 48 Mio U 0,5 ml(0,960 mg/ml) to patients of 60 kg or more. Subjects who develop disease progression will discontinue therapy. Subjects who have no evidence of disease progression after completion of study therapy will be followed until disease progression, withdrawal of informed consent, or death.

Subjects will be evaluated by CT/MRI scan after 9 cycles of chemotherapy (week 10), after 18 cycles of chemotherapy, then every 6 months for the next 2 years and then if clinically indicated.

Sample Size: 108

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria

Ovarian, fallopian tube or peritoneal carcinoma cohort.

- Female subjects more than 18 years of age
- Histologically confirmed diagnosis of invasive epithelial ovarian, fallopian tube, or peritoneal carcinoma (serous, mucinous, endometrioid, clear cell, or carcinosarcomas are eligible).
- All patients with at least 1 earlier platin treatment can be included but should be platin refractory (RECIST or GCIG (RECIST or CA125) progression during platin defined as progression within 28 days after the last dose of platin) or resistant (RECIST or GCIG

(RECIST or CA125) progression within 6 months after last dose of platin therapy). Earlier weekly or dose-dense regimens with paclitaxel and carboplatin are not allowed. Consolidation after the last platin dose with non-platinum containing chemotherapy or molecular targeted drugs is allowed

- Performance status must be ECOG 0-2.
- Adequate organ function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)	≤2.5 X ULN
Calculated creatinine clearance (Cl_{CR}) (Cockroft)	≥30 mL/min

- Measurable disease by RECIST version 1.1 or CA125 progression according to the GCIG definition (Vergote et al) .
- Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up

Endometrial carcinoma cohort.

- Female subjects more than 18 years of age
- Histologically confirmed diagnosis of endometrial carcinoma (endometrioid, adenoacanthoma, adenosquamous, serous, clear cell carcinoma or carcinosarcomas are eligible).
- Recurrent or advanced endometrial carcinoma can be included. Earlier platin therapy is allowed. But earlier weekly or dose-dense regimens with paclitaxel and carboplatin are not allowed.
- Performance status must be ECOG 0-2.
- Adequate organ function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)	≤2.5 X ULN
Calculated creatinine clearance (Cl_{CR}) (Cockroft)	≥30 mL/min

- Measurable disease by RECIST version 1.1. Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up

Cervical carcinoma cohort.

- Female subjects more than 18 years of age

- Histologically confirmed diagnosis of cervical carcinoma (adenocarcinoma or squamous carcinomas are eligible).
- Recurrent or advanced endometrial carcinoma can be included. Earlier platin (including concomitant with radiotherapy) therapy is allowed. But earlier weekly or dose-dense regimens with paclitaxel and carboplatin are not allowed.
- Performance status must be ECOG 0-2.
- Adequate organ function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)	≤2.5 X ULN
Calculated creatinine clearance (Cl_{CR}) (Cockroft)	≥30 mL/min

- Measurable disease by RECIST version 1.1. Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up

Key Exclusion Criteria

Subjects will not be eligible for inclusion in the study if any of the following criteria apply:

- Other histologies than those mentioned above such as non-epithelial ovarian carcinomas, neuro-endocrine tumors, sarcomas, metastases from other primary tumors, ...
- Earlier weekly or dose-dense paclitaxel and carboplatin regimen.
- Any unstable or serious condition e.g. uncontrolled infection requiring systemic therapy.
- Prior other malignancies treated primarily or for recurrence within 3 years prior to inclusion in this study, except for completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma of the skin or cervix of the uterus.
- Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures
- Metastatic disease to the brain or leptomeninges.
- Treatment with any of the following anti-cancer therapies:
    - radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of study chemotherapy.
    - chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs similar or related to Paclitaxel, Carboplatin or G-CSF.

Procedures:

- Physical examination, including vital signs
- Laboratory assessments (hematology, chemistry)
- CT/MRI of chest/abdomen/pelvis

Sponsor: BGOG