ENGOT-cx13/AGO/FERMATA

Leading group: AGO

Clinical Trial Study: FERMATA Trial: An international randomized double-blind clinical trial of BCD-100 plus platinum-based chemotherapy with and without Bevacizumab versus placebo plus platinum-based chemotherapy with and without Bevacizumab as first-line treatment of subjects with advanced cervical cancer

Planned number of patients: 316

Participating groups: A-AGO, BGOG, CEEGOG, NSGO, PGOG, TRSGO

ARMS and INTERVENTIONS

Arm	Intervention/treatment
Experimental: BCD-100 BCD-100 3 mg/kg Q3W	Biological: BCD-100 Anti-PD-1 monoclonal antibody, IV infusion Biological: Bevacizumab IV infusion Drug: Paclitaxel IV infusion Drug: Cisplatin (or Carboplatin) IV infusion
Placebo Comparator: Placebo	Biological: Bevacizumab IV infusion Drug: Paclitaxel IV infusion Drug: Cisplatin (or Carboplatin) IV infusion Other: Placebo Placebo

Outcome Measures

Primary Outcome Measures:

1 Overall Survival (OS) [Time Frame: 3 years] The time from the date of randomization until death

Secondary Outcome Measures:

1 Progression-Free Survival (PFS) per RECIST 1.1 [Time Frame: 3 years] The time from the date of randomization until progression of disease according to RECIST 1.1 criteria or death

2 Progression-Free Survival (PFS) per iRECIST [Time Frame: 3 years] The time from the date of randomization until progression of disease according to iRECIS criteria or death
3 Overall Response Rate per (ORR) RECIST 1.1 [Time Frame: 1 year] The percentage of the participants who have a Complete Response or a Partial Response as assessed by a blind independent central reviewer per RECIST 1.1
4 Overall Response Rate (ORR) per iRECIST [Time Frame: 1 year] The percentage of the participants who have a Complete Response or a Partial Response as assessed by a blind independent central reviewer per iRECIST
5 Disease Control Rate (DCR) [Time Frame: 1 year] The percentage of the participants who have a Complete Response, a Partial Response or a Stable Disease as assessed by a blind independent central reviewer
6 Time to Response (TTR) [Time Frame: 1 year] TTR will be calculated from the randomization date
7 Duration of Response (DOR) [Time Frame: 1 year] DOR will be calculated from the moment of registration of response till event (progression or death)

Eligibility Criteria

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	Female
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1 Signing an IRB/EC-approved informed consent
2 Females ≥ 18 years of age on day of signing informed consent
3 Histologically confirmed squamous carcinoma of the cervix
4 Progressing thru or recurrent disease treated for curative intent or primary metastatic cervical cancer stage FIGO IVB
5 Agreement to newly obtained core or excisional biopsy of a tumor lesion not previously irradiated for determination of PD-L1 status prior to randomization (using archival biopsy material is only acceptable in subjects in whom obtaining a new sample is contraindicated)
6 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7 For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use a contraceptive method with a failure rate of < 1% per year from the moment of signing informed consent, during the treatment period and at least 6 months after administration of the last dose of study drug. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries, fallopian tubes, and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include but are not limited to bilateral tubal ligation and/or occlusion, male sterilization, and intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) is not acceptable method of contraception.

Exclusion Criteria:

1 Indications for potentially curative treatment (surgery or radiation therapy)
2 Prior systemic treatment for recurrent, secondarily progressive or initially metastatic disease
3 Previous use of chemotherapy other than initial treatment for curative intent (e.g. chemotherapy used concurrently with radiation therapy, neoadjuvant or consolidation chemotherapy cycles before radiotherapy or 2 chemotherapy cycles after completion of chemoradiotherapy are allowed)
4 Contraindications to cisplatin, carboplatin, paclitaxel, or bevacizumab
5 Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with known brain metastases may participate provided that the brain metastases have been previously treated with radiotherapy or surgery only and are radiographically stable
6 Concomitant diseases or conditions which pose a risk of AE development during study treatment:
a uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg;
b stable angina functional class III-IV;
c unstable angina or myocardial infarction less than 6 months prior to randomization;
d NYHA Grade III-IV congestive heart failure;
e serious cardiac arrhythmia requiring medication (subjects with asymptomatic atrial fibrillation can be enrolled if controlled ventricular rate);
f atopic asthma, Stage III-IV COPD, angioedema;
g severe respiratory failure;
h any other diseases which pose unacceptable risk of AE development during study treatment in Investigator's opinion.
7 Active or known or suspected autoimmune disease (subjects with Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, or skin disorders (vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll).
8 Condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days prior to randomization.
9 History of (non-infectious) pneumonitis that required corticosteroids or current pneumonitis
10 Neutrophils <1500/mcl or platelets <100 000/mcl or hemoglobin <90 g/l.
11 Creatinine ≥ 1.5 x UNL.
12 Bilirubin ≥ 1.5 x UNL (excluding Gilbert's syndrome if bilirubin < 50 µmol/l) or AST/ALT ≥ 3 x UNL (excluding subjects with liver metastases if AST/ALT < 5 x UNL) or alkaline phosphatase ≥ 2.5 x UNL.
13 Chemotherapy or radiation therapy less than 28 days prior to randomization.
14 Major surgery procedure less than 28 days prior to randomization.
15 Previous use of PD-1/PD-L1/PD-L2 agent or another agent directed to stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX 40, CD137).
16 Previous use of VEGF/VEGFR inhibitors, including bevacizumab, ramucirumab, aflibercept and tyrosine kinase inhibitors.
17 Prior invasive malignancy with any evidence of disease within the last 3 years. Subjects with non-melanoma skin cancer or carcinoma in situ (e.g. breast cancer) who have undergone potentially curative therapy are not excluded.
18 Pre-existing clinically significant (≥ grade 2) peripheral neuropathy or hearing impairment
19 Any conditions or circumstances that limit subject's ability to comply with protocol

requirements

20 Active hepatitis B, active hepatitis C or history of positive HIV.

21 Active infection requiring therapy or systemic antibiotics use less than 14 days prior to enrollment. Severe infections within 28 days prior to first study drug administration.

22 Administration of a live vaccine within 28 days prior to enrollment

23 Current using of another investigational device or drug study, or less than 30 days since ending of using of another investigational device or drug study

24 Life expectancy less than 12 weeks

25 Significant adverse events (AE) of previous therapy excluding chronic and/or irreversible events which cannot affect study drug safety evaluation (e.g. alopecia)

26 Known hypersensitivity or allergy to paclitaxel, cisplatin, carboplatin, bevacizumab, BCD-100 or any of their excipients. Known hypersensitivity or allergy to drugs derived from Chinese hamster (CHO) ovary cells or history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

27 Pregnancy or breast-feeding