A.O. Ordine Mauriziano Torino

Titolo:	Studo di fase III, randomizzato e in aperto, che confronta AZD5335 con mirvetuximab soravtansive in pazienti con tumore epiteliale di alto grado, resistente al platino, che presentano un'elevata espessione di FRα, e confronta AZD5335 con la chemioterapia a scelta dello sperimentatore in pazienti con bassa espressione di FRα (TREVI-OC-01, ENGOT-OV93).
Patologia:	Carcinoma ovarico platino resistente
Tipo di studio:	Interventistico farmacologico
Tipologia:	Profit
Fase:	III
Principali criteri di inclusione:	1. Participants must be females ≥ 18 years of age (or the legal age of consent in the jurisdiction where the clinical trial is conducted) at the time of signing the informed consent form. 2. Participants with confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer. 3. Participants must have platinum-resistant disease: (a) Participants who have only had one prior line of platinum-based therapy must have received at least 4 cycles of platinum, must have had a response (CR or PR) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum. (b) Participants who have received 2 or 3 lines of platinum therapy must have progressed ≤ 6 months after the date of the last dose of platinum. Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression. Note: Participants who are platinum-refractory during front-line treatment are excluded (see Section 5.2 [Exclusion Criteria]). 4. Participants must have radiologically progressed on or after their most recent line of therapy. 5. Participants must have received at least one, but no more than 3, prior systemic lines of anti-cancer therapy, and must be those for whom single-agent therapy is appropriate as the next line of treatment: a. Adjuvant ± neoadjuvant considered one line of therapy. b. Prior treatment with bevacizumab is required if the participant is eligible per approved label and SoC institutional guidelines, except in cases of documented contraindication, precaution or intolerance. c. Maintenance therapy (eg, bevacizumab, PARPi) will be considered as part of the preceding line of therapy (ie, not counted as a line of therapy).

	d. Therapy changed due to toxicity in the absence of progression will be considered as part of the same line (ie, not counted independently). e. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance. 6. Participants with documented BRCA mutation (germline and/or somatic) must have received prior PARPi if the participant is eligible per approved label and standard-of-care institutional guidelines, except in cases of documented contraindication, precaution or intolerance. 7. Participants must have an ECOG Performance Status of 0 or 1 with no deterioration over the previous 2 weeks prior to baseline at screening and prior to randomisation. 8. Minimum life expectancy of 12 weeks at screening. 9. Provision at Screening 1 of an FFPE tumour tissue sample for central testing of FRα expression. 10. Participant's tumour must have at least ≥ 25% of viable tumour cells with ≥ 1+ membrane staining intensity via central testing with the VENTANA FOLR1 (FOLR1-2.1) IUO IHC assay. 11. At least one measurable lesion not previously irradiated that qualifies as a RECIST 1.1 TL at baseline that can be accurately measured as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with CT (preferable) or MRI and is suitable for accurate repeated measurements. 12. Participants must have adequate organ and bone marrow function
Principali criteri di esclusione:	1. Participants with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumours containing any of the above histologies, or low-grade or borderline ovarian tumour. 2. Primary platinum-refractory disease, defined as disease that did not respond to or has progressed ≤ 3 months after the last dose of first line platinum-containing chemotherapy. Medical Conditions 3. Participants with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular oedema, macular degeneration, presence of papilledema, and/or monocular vision. 4. As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including active bleeding diseases, history of allogenic organ transplant) which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol. 5. Current signs, symptoms, or clinical investigations consistent with bowel obstruction, including sub-occlusive disease.

	6. History of another primary malignancy except for malignancy treated with curative intent and with no known active disease for at least 2 years prior to screening of study intervention and of low potential risk for recurrence. Exceptions include adequately treated non-melanoma skin cancer or lentigo maligna and curatively treated carcinoma in situ without evidence of disease and localised non-invasive primary disease under surveillance. 7. Persistent toxicities (CTCAE Grade ≥ 2) caused by previous anti-cancer therapy, excluding alopecia. Participants with irreversible toxicity that is not reasonably expected to be exacerbated by study intervention in the opinion of the investigator may be included (eg, hearing loss). Note: Participants with chronic, stable Grade ≤ 2 toxicities (with no worsening to Grade > 2 for 3 months prior to randomisation and managed with standard treatment) from previous anti-cancer therapy, such as peripheral neuropathy, fatigue, and endocrinopathies may be included. 8. Spinal cord compression or brain metastases unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of study intervention, or a history of leptomeningeal carcinoma. A minimum of 28 days must have elapsed between the end of whole brain radiotherapy and study enrolment 9. Participant has non-infectious ILD/pneumonitis or has a history of non-infectious ILD/pneumonitis that required oral or IV steroids or supplemental oxygen, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening. 10. Participant meets one or more of the following cardiovascular criteria: • Uncontrolled hypertension (refractory to medical intervention) • Mean resting QTcF > 470 ms, obtained from triplicate ECGs performed at screening. • Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives. • History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted based on investigator judgement with cardiologist consultation recommended. • Acute coronary syndrome/acute myocardial infarction, unstable angina pectoris, coronary intervention procedure with percutaneous coronary intervention, or coronary artery bypass grafting within 6 months of screening.

	• History of brain perfusion problems (eg, carotid stenosis) or stroke, or transient ischemic attack in the last 6 months prior to screening. • Other cardiovascular comorbidites including symptomatic heart failure (as defined by New York Heart Association class ≥ 2), prior or current cardiomyopathy, or severe uncorrected valvular heart disease. Prior/Concomitant Therapy 14. Prior treatment with any FRα-targeted therapy, including MIRV, or any TOP1i ADC. 11. Prior exposure to nitrosourea, mitomycin C, chloroquine, or hydroxychloroquine without adequate treatment washout period before randomisation 12. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, targeted therapy, biologic therapy, tumour embolisation, or monoclonal antibodies) without adequate washout period prior to the first dose of study intervention 13. Any concurrent anti-cancer treatment without an adequate washout period 14. Any investigational agents or study interventions from a previous clinical study without an adequate washout period 15. Palliative radiotherapy with a limited field of radiation within 14 days, or with wide field of radiation or to more than 30% of the bone marrow within 28 days, prior to the first dose of study intervention.
Struttura:	SCDU Ginecologia e Ostetricia
Contatto:	Prof.ssa Annamaria Ferrero annamaria.ferrero@unito.it aferrero.studiclinici@gmail.com