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Titolo:	Studio di fase III aperto, in cieco per lo sponsor, randomizzato, controllato, multicentrico, su trastuzumab deruxtecan (T-DXd) più Rilvegostomig o pembrolizumab vs chemioterapia più pembrolizumab come terapia di prima linea per il carcinoma endometriale primario avanzato o ricorrente esprimente HER2 (IHC 3+/2+), con capacità di riparazione degli errori (pMMR). (DESTINY Endometrial01)
Patologia:	Carcinoma endometriale
Tipo di studio:	Interventistico farmacologico
Tipologia:	Profit
Fase:	III
Principali criteri di inclusione:	1. Histologically confirmed diagnosis of epithelial endometrial carcinoma. All histologies are allowed except for sarcomas (carcinosarcomas are allowed). 2. Following surgery or diagnostic biopsy, participant must have primary advanced disease (Stage III/IV) or first recurrent EC, and meet at least one of the following criteria: a) Primary Stage III (per FIGO 2023) disease with measurable disease at baseline per RECIST 1.1 based on the investigator's assessment. b) Primary Stage IV (per FIGO 2023) disease regardless of presence of measurable disease at baseline. c) First recurrent disease regardless of presence of measurable disease at baseline. 3.. Endometrial cancer with HER2 IHC expression of 3+ or 2+ by prospective central testing. 4. Endometrial cancer that is determined pMMR by prospective central IHC testing. 5. Provision of adequate formalin fixed and paraffin embedded (FFPE) tumor tissue sample of a tumor lesion that was not previously irradiated for central HER2, MMR, and PD-L1 IHC testing and valid central test results for randomization/stratification. 6. Prior therapy: a) Naïve to first-line systemic anticancer therapy. Participants may have received one prior line of adjuvant/neoadjuvant chemotherapy with curative intent (chemotherapy or chemoradiation) if disease recurrence or progression occurred ≥ 6 months after last dose of chemotherapy. Prior trastuzumab in the adjuvant/neoadjuvant setting is allowed. b) No prior exposure to ADCs or ICIs including (but not limited to) anti-PD-1/PD- L1/PD-L2 and anti-CTLA-4 antibodies and therapeutic anticancer

	vaccines. c) Participants may have received prior radiation therapy for the treatment of EC. Prior radiation therapy may have included pelvic radiation therapy, extended field pelvic/para-aortic radiation therapy, and/or intravaginal brachytherapy. Adequate treatment washout period is required. 7. Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1. 8. Minimum life expectancy of 12 weeks. 9. LVEF ≥ 50% within 28 days before randomization.
Principali criteri di esclusione:	1. Uncontrolled intercurrent illness including, but not limited to ongoing or active known infection, serious chronic gastrointestinal conditions associated with diarrhea (e.g., active inflammatory bowel disease) and active non-infectious skin disease (including any grade rash, urticarial, dermatitis, ulceration, or psoriasis) requiring systemic treatment. 2. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Participants with clinically inactive brain metastases may be included in the study. Participants with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study randomization. 3. Participants with a medical history of myocardial infarction (MI) within 6 months before randomization, or symptomatic congestive heart failure (CHF) (NYHA Class II to IV), clinically significant arrhythmia, or cardiomyopathy of any etiology. Participants with troponin levels above upper limit of normal (ULN) at screening (as defined by the manufacturer), should have a cardiologic consultation before enrollment to rule out MI. 4. Corrected QT interval (QTcF) prolongation to > 470 msec based on average of the screening triplicate 12-lead ECG. 5. History of (non-infectious) ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening. 6. Lung criteria: a) Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (e.g., pulmonary emboli within 3 months of the study enrollment, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion etc.). b) Any autoimmune, connective tissue or inflammatory disorders (including rheumatoid arthritis, Sjogren's and sarcoidosis) where there is documented, or a suspicion of pulmonary involvement at the time of screening. Full details of the disorder should be recorded in the eCRF for participants who are included in the

	study. c) Prior pneumonectomy (complete). 7. Active or prior documented autoimmune or inflammatory disorders requiring chronic treatment with steroids or other immunosuppressive treatment. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed. Participants with vitiligo are eligible. 8. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals. 9. Active primary immunodeficiency/active infectious disease(s): 10. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. 11. Known allergy or hypersensitivity to T-DXd, rilvegostomig or any of their excipients. 12. History of severe hypersensitivity reactions to other mAbs, pembrolizumab, carboplatin, paclitaxel and/or their excipients. 13. Pregnant or breastfeeding female participants, or participants who are planning to become pregnant. 14. Multiple primary malignancies within 3 years, except for: • Adequately resected non-melanoma skin cancer • Curatively treated in-situ disease • Other solid tumors curatively treated 15. A pleural effusion, ascites or pericardial effusion that requires drainage, peritoneal shunt, or Cell-free and Concentrated Ascites Reinfusion Therapy (CART). Prior/Concomitant Therapy 16. Any concurrent anticancer treatment without an adequate washout period prior to the first dose of study intervention. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., HRT) is allowed. 17. Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 4 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.
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