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2019 ASCO Annual Meeting Proceedings

55th Annual Meeting
May 31-June 4, 2019
McCormick Place
Chicago, IL

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55th
Annual Meeting of the American Society of Clinical Oncology
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Chicago, Illinois

2019 Annual Meeting Proceedings

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TPS5605 **Poster Session (Board #422b), Sat, 1:15 PM-4:15 PM**

EUDARIO/ENGOTov-48: A European multicenter randomised phase II trial on the combination of the HSP90 inhibitor ganetespib with carboplatin followed by maintenance treatment with niraparib (+/- ganetespib) compared to platinum-based combination-chemotherapy followed by niraparib in relapsed platinum-sensitive ovarian cancer patients. *First Author: Nicole Concin, Medical University of Innsbruck, Innsbruck, Austria*

Background: Carboplatin (C) mainly acts by forming interstrand crosslinks (ICL) within the DNA double helix, which can only be removed by the Fanconi Anemia (FA) pathway. HSP90 inhibitors destabilise a number of HSP90 client proteins, such as those governing the FA DNA repair pathway and the G2/M checkpoint (e.g. Chk1 and Wee1). Kramer et al. (Cell Death Differ, 2017) showed that the HSP90 inhibitor Ganetespib (G) virtually eliminates a functional FA DNA repair complex, therewith preventing the repair of DNA ICL in vitro and vivo. In parallel, G abrogated Chk1 and Wee1 expression and circumvented a G2/M arrest. Consequently, cells with unrepaired DNA damage rushed into mitosis, which resulted in massive tumour cell death. Furthermore, HSP90 inhibition has been shown to reduce the amount of BRCA1 in the cell therewith broadening sensitivity towards PARPi and preventing acquired PARP resistance. Our trial approach is tested in ovarian carcinomas with a mutant p53 background. EUDARIO (EUDRACT 017-004058-40) is funded by the European Commission (FP7 project GAN-NET53). **Methods:** Eligible patients have relapsed platinum-sensitive ovarian cancer, no limits in prior lines, high-grade (but clear cell) histology or carcinosarcoma, disease measurable or evaluable according to RECIST 1.1. Patients are randomised into 3 treatment arms (1:1:1), a) control arm: C+Gemcitabine or C+Paclitaxel (q3w, 6 cycles, investigator`s choice) followed by Niraparib, b+c) 2 experimental arms: C (AUC5, d1) + G (150mg/m^2, d1) q3w 6 cycles followed by either Niraparib alone (arm b) or by Niraparib+G (arm c; G at 100mg/m^2 weekly, limited to 9 months). Niraparib (200/300mg/day) is given in case of SD, PR or CR after platinum-based treatment until disease progression. The main analysis will combine both experimental arms b+c and jointly compare them against arm a using log-rank test. Primary endpoint is PFS, secondary endpoints are PFS2, TFST, TSST, safety, ORR, PRO, OS. The first patient was dosed in January 2019. Clinical trial information: NCT03783949.

TPS5606 **Poster Session (Board #423a), Sat, 1:15 PM-4:15 PM**

Phase Ib clinical investigation of intraperitoneal ipilimumab and nivolumab in patients with peritoneal carcinomatosis due to gynecologic malignancy. *First Author: Emily Hinchcliff, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The peritoneal cavity is a frequent site of metastasis and recurrence for gynecologic malignancy, including approximately 80% of epithelial ovarian cancer (EOC) that presents with peritoneal involvement. These observations have led to the use of intraperitoneal (IP) route of administration for traditional cytotoxic chemotherapy. IP immunotherapy is a recognized but under explored area of clinical investigation with many potential advantages. Indeed, IP administered antibodies in both animals and human subjects are associated with absent or much lower peripheral blood concentrations. In addition to higher local and lower systemic exposure, other theoretical advantages include preferential binding to intraperitoneal and intratumoral immune cells, and absorption through the draining lymphatics of the peritoneal cavity. These pelvic and peri-aortic lymph nodes represent the most relevant lymphoid organs and as such may be the ideal site for T cell activation and trafficking back to the peritoneal tumor. **Methods:** The trial (NCT03508570) is a single-institution phase Ib trial to determine the recommended phase II dosing (RP2D) of IP administration of nivolumab in combination with ipilimumab. For the purpose of dose finding, the assessment period for dose limiting toxicity (DLT) is 12 weeks. The trial starts with a safety lead-in to confirm the safety of IP nivolumab before combining it with ipilimumab. A maximum sample size of 12 will be used to find the RP2D for nivolumab, up to 24 patients for the combination, and a planned expansion will be carried out such that at least 12 EOC patients are treated at RP2D of the intraperitoneal combination strategy. The secondary objectives are to describe the pharmacokinetics and toxicities, and to estimate the clinical benefit rate for the expansion cohort. Translational objectives include description of immunologic and biologic changes in serial blood and IP fluid collections as well as pre and on-treatment biopsies. Eligibility criteria include recurrent or progressive biopsy-confirmed platinum resistant EOC or other gynecologic cancer with measurable peritoneal disease, and no exposure to prior treatment with checkpoint inhibition. Enrollment began in January of 2019 with 3 subjects enrolled to date. Accrual update will be provided at the annual meeting. Clinical trial information: NCT03508570.

TPS5607 **Poster Session (Board #423b), Sat, 1:15 PM-4:15 PM**

A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer. *First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT. Pembrolizumab (PEMBRO) is a monoclonal antibody targeting programmed cell death receptor 1 (PD-1). Preliminary analyses of a phase 1b/2 study of LEN + PEMBRO showed promising antitumor activity and a manageable safety profile in advanced endometrial cancer (EC). **Methods:** A multicenter, randomized, open-label, phase 3 study (KEYNOTE-775/E7080-G000-309; clinicaltrials.gov NCT03517449) will evaluate efficacy and safety of LEN + PEMBRO vs treatment of physician's choice (TPC) in patients with advanced EC. Patients must be aged $\geq$ 18 years, have advanced EC that progressed after 1 prior platinum-based therapy, have measurable disease per RECIST v1.1, and an Eastern Cooperative Oncology Group performance status $\leq$ 1. Patients must have mismatch repair (MMR) status confirmed by central laboratory via immunohistochemistry on archived or fresh tumor biopsy. ~780 patients (~120 MMR-deficient; ~660 MMR-proficient) will be randomized to receive LEN 20 mg orally once daily and PEMBRO 200 mg intravenously (IV) every 3 weeks (Q3W) or TPC. Patients will be randomized first according to MMR status; MMR-proficient patients will be further stratified by ECOG PS, geographic region, and prior history of pelvic radiation. TPC is either doxorubicin 60 mg/m^2 by IV Q3W or paclitaxel 80 mg/m^2 by 1-hour IV infusion weekly (3 weeks on/1 week off). The dual primary endpoints are progression-free survival (PFS; per RECIST v1.1 by blinded independent central review) and overall survival (OS). The PFS analysis will occur at the planned interim analysis (~363 OS events in MMR-proficient patients; ~524 PFS events), and the study will have 99% power to detect a hazard ratio (HR) of 0.55 with a 1-sided 0.0005 significance level. A final OS analysis will occur at 518 OS events, when the study will have 90% power to detect a HR of 0.75 with a 1-sided 0.0245 significance level. Secondary endpoints include objective response rate, health-related quality of life, safety and tolerability, and pharmacokinetics. Clinical trial information: NCT03517449.

TPS5608 **Poster Session (Board #424a), Sat, 1:15 PM-4:15 PM**

AtTEnd/ENGOT-en7: A multicenter phase III double-blind randomized controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer. *First Author: Nicoletta Colombo, University of Milan-Bicocca and Istituto Europeo di Oncologia, Milan, Italy*

Background: Prognosis of advanced/recurrent endometrial cancer (EC) is poor with median survival of 12-15 months for patients with measurable disease. Treatment options are limited, with primary management being chemotherapy with carboplatin and paclitaxel. EC is known to be one of the tumor types with highest mutational load. Ultra- and hyper-mutated EC, which harbor POLE and mismatch repair gene defects respectively, have shown peri-tumoral T cell infiltration and high expression of PD-1 and PD-L1 proteins, suggesting that immune regulation may enhance specific T cell responses and result in improved anti-tumour immunity. Preliminary data in EC patients have shown tumour control activity of the PD-L1 targeting agent atezolizumab. **Methods:** 550 patients with newly diagnosed, advanced stage III/IV or recurrent EC will be accrued during a period of 24 months with a 1:2 randomization ratio into two arms: i. control group receiving standard chemotherapy plus placebo IV every 21 days up to 6/8 cycles followed by placebo until progression; ii. experimental group receiving standard chemotherapy plus 1200 mg atezolizumab IV every 21 days up to 6/8 cycles followed by atezolizumab until progression. Standard chemotherapy will consist of 175 mg/m^2 paclitaxel plus AUC5/6 carboplatin. Stratification factors are: histology, disease stage, microsatellite status, country of experimental site. The study is planned to demonstrate a survival increase and is equally powered for PFS. Secondary endpoints include ORR, duration of response, PFS2, quality of life, adverse events and compliance. The study is sponsored by MaNGO group and will involve sites from ENGOT and GCIG networks across Europe, Japan, Australia and New Zealand. Currently, the trial is open in Italy and in Switzerland where a total of 6 patients have been enrolled. Clinical trial information: NCT03603184.