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ARIES: A PHASE 2, OPEN-LABEL STUDY TO EVALUATE RUCAPARIB (PARP INHIBITOR) IN COMBINATION WITH NIVOLUMAB (ANTI-PD-1 ANTIBODY) IN PATIENTS WITH OVARIAN OR UROTHELIAL CANCER (UC)

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Objectives In the US and EU, rucaparib is approved for recurrent ovarian cancer (rOC) associated with or without homologous recombination deficiency (HRD; ie, *BRCA* mutation or high genomic loss of heterozygosity [LOH]); nivolumab is approved for recurrent, locally advanced/metastatic UC. Pre-clinical data suggest that PARP inhibition may work synergistically with PD-L1 blockade by stimulating the tumor microenvironment to enhance immune-mediated antitumor activity. ARIES (NCT03824704) is evaluating rucaparib plus nivolumab for rOC (Cohorts A1/A2) or locally advanced, unresectable/metastatic UC (Cohort B).

Methods Cohort A is enrolling 2 groups of patients (A1 and A2) with platinum-sensitive rOC who have received ≤ 2 prior treatments. The first group (Cohort A1) includes wild-type *BRCA* and high genomic LOH ($\geq 16\%$) rOC; the second exploratory group (Cohort A2) includes *BRCA*-mutated rOC. Cohort B is enrolling UC patients regardless of HRD or PD-L1 status who are cisplatin-ineligible and declined carboplatin-based therapy or progressed following 1 line of platinum-based therapy. Patients in Cohorts A1 and B must have measurable disease (RECIST v1.1). Tumor sample is mandatory for tumor *BRCA*/LOH status assessment. Prior PARP or immune checkpoint inhibitor treatment is exclusionary. Patients are receiving rucaparib (600 mg PO BID) and nivolumab (480 mg IV Q4W). The primary endpoints are investigator-assessed objective response rate (RECIST v1.1; Cohorts A1 and B) and the effect of rucaparib on the immune microenvironment (Cohort A2).

Results Approximately 140 patients are being enrolled in the US. **Conclusions** ARIES is assessing the efficacy of rucaparib plus nivolumab in patients with rOC or locally advanced, unresectable/metastatic UC.

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MODULATION OF CA125 EXPRESSION BY HTERT IN OVARIAN CANCER: POSSIBLE IMPLICATION OF PI3K/AKT/MTOR SIGNALING PATHWAY

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Objectives To investigate the possible inter-relationship between Ca125 secretion and telomerase activity, and the possible

implication of the PI3K/Akt/mTOR pathway in this modulation.

Methods Ovarian cancer cell lines OVCAR-3, SK-OV-3 and IGROV-1 were treated with three different telomerase inhibitors, BIBR-1532, Costunolide and MST-312, one activator, LPS, and various inhibitors of the PI3K/Akt/mTOR pathway, PI828, wortmanin, GSK692690 and rapamycin. Ca125 expression was quantified by Q-PCR and its secretion by ELISA.

Results The three telomerase inhibitors decreased the Ca125 mRNA expression and protein secretion by the three cell lines. The same pattern was obtained when cells were treated with hTERT siRNA. The activation of hTERT lead to an increase in Ca125 expression and secretion, and to an increase in cell migration and motility. Interestingly, inhibition of PI3K/Akt/mTOR signaling pathway by PI828, wortmanin, GSK692690 and rapamycin lead to a decrease in Ca125 concentration suggesting the involvement of this pathway in Ca125 regulation. Moreover, an additive effect was shown when costunolide and BIBR 1532 were combined with the previous inhibitors. A decrease in telomerase expression and activity was obtained after gene silencing of Ca125 by the three cell lines, along with a decrease in PI3k, Akt and mTOR gene expression, which may explain the possible implication of this signaling pathway in the modulation of hTERT by Ca125.

Conclusions Both inhibition of telomerase and PI3K/Akt/mTOR signaling pathway decreased the Ca125 secretion, while inhibition of Ca125 decreased hTERT expression and activity suggesting a mutual modulation and a substantial role of Ca125 in cancer initiation and progression.

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PATIENTS WITH OVARIAN CLEAR CELL CARCINOMA ARE AT HIGH RISK OF SECONDARY MALIGNANCY

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Objectives Ovarian clear cell carcinoma (OCCC) has unique clinical and molecular features compared to other epithelial ovarian cancer histologies. Our objective was to describe the incidence of secondary malignancies (SM) in patients with OCCC.

Methods Retrospective cohort study of patients with pure OCCC at two tertiary academic centres in Toronto, Canada between 1995–2017. Demographic and histopathologic details were obtained from chart review and confirmed with a provincial cancer registry.

Results Of 209 patients with OCCC, 53 developed a SM (25.4%), of whom 7 developed 2 SM. SM included: breast (13), skin (10), gastrointestinal tract (9), other gynecologic malignancies (8), thyroid (6), lymphoma (5), head and neck (4), urologic (3) and lung malignancies.

Thirty-five SM occurred before index OCCC (median 9.4 years before), 21 after OCCC (median 5.8 years after), and 4 were diagnosed concurrently.