ARIES: A PHASE 2, OPEN-LABEL STUDY TO EVALUATE MODULATION OF CA125 EXPRESSION BY HTERT IN A130

To investigate the possible inter-relationship between Ca125 secretion and telomerase activity, and the possible modulation of this signaling pathway in the modulation of hTERT 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, wortmannin, 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 BBIR 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.

**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. Preclinical 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 (≥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.

**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 BBIR 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.