DYNAMIC CHANGES OF PERIPHERAL REGULATORY T CELLS DURING PARP INHIBITOR MAINTENANCE THERAPY IN PATIENTS WITH OVARIAN CANCER

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Objectives Poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors (PARPi) are becoming the standard of care for ovarian cancer. However, it has been reported that poly(ADP-ribosyl)ation of FoxP3 negatively regulates suppressive function of regulatory T cells (Treg). Most of the studies on PARPi have focused on the tumor itself and synthetic lethality. The immunological effect, particularly the effect on Treg cells, has been overlooked. In the current study, we investigated the dynamic changes of immune properties of peripheral Treg cells during PARPi maintenance therapy and explored their clinical implications.

Methods We analyzed serial peripheral blood mononuclear cells (PBMCs) from PARPi-treated patients (n=46) with ovarian cancer using multicolor flow cytometry. The PBMCs were collected at the time points included pre-treatment as well as 1, 3, and 6 months after the initiation of treatment. Olaparib or niraparib was used as maintenance therapy.

Results First, the percentages FoxP3+CD4+ regulatory T cells (Treg cells) did not change significantly after initiation, but only the % of resting Treg cells (CD45RA+FoxP3low) increased 3 months after initiation. Second, we analyzed expression of immune checkpoints and properties of Treg cells. We found that the PD-1 and CTLA-4 expression on Treg cells significantly decreased after 3 months and TIGIT and CCR8 decreased after 6 months.

Conclusions Long-term PARPi treatment regulated suppressive function of Treg cells, but since PARPi-induced changes in Treg cells and their clinical implications has not yet been fully elucidated, further research is warranted.
Abstracts

**EP018/#324** THE Efficacy and Molecular Mechanisms of MDR-Reversal Agents (Stony Brook Taxanes) in Resistant Ovarian Carcinoma Models

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**Objectives** Taxane resistance is a serious problem in the successful treatment of ovarian carcinoma. New generations of taxane analogs (Stony Brook taxanes; SB-Ts) seem to be effective against resistant solid tumors. Our aim was to estimate in vitro and in vivo efficacy of SB-Ts in comparison to paclitaxel and discover underlying changes of gene expression profile connected with the treatment of taxanes.

**Methods** NCI/ADR-RES and SKOV-3/PCT-RES human ovarian cancer cell lines were used as multidrug-resistant model. The efficacy of taxanes was compared via assessment of IC_{50} values. Flow cytometry was used for analysis of cell cycle changes. In vivo efficacy of taxanes was measured after intraperitoneal application of paclitaxel alone (10 mg/kg) or combined with SB-Ts (1–5 mg/kg) twice a week in resistant ovarian cell line-derived xenograft (CDX) models. Gene expression profiles were followed by quantitative real-time PCR in CDX tumors.

**Results** In vitro experiments revealed the third generation SB-Ts – SB-T-121605 and SB-T-121606 as the most effective. In vivo, both SB-Ts effectively suppressed tumor growth at low doses (<3 mg/kg) in combination with paclitaxel, limiting their adverse effects. Treatment of SB-Ts also led to significant deregulation of many genes involved in resistance.

**Conclusions** SB-T-121605 and SB-T-121606 are promising candidates for further studies, aimed at development of novel therapeutics for therapy of resistant ovarian tumors. Supported by projects of the Czech Science Foundation no. 21-14082S, the Czech Ministry of Education, Youth and Sports: INTERACTION, project no. LTAUSA19632, and the National Institutes of Health (NIH), U.S.A. grant R01 CA103314.

**EP019/#212** The prophylactic effects of red ginseng on niraparib-induced myelosuppression

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**Objectives** Myelosuppression is one of the evident side effects of Niraparib. The aim of this study was to investigate the prophylactic effect of the red ginseng (RG) on Niraparib-induced myelosuppression.

**Abstract EP019/#212 Figure 1 and 2**