Abstracts

Objectives UpRi is a first-in-class NaPi2b ADC with a novel scaffold-linker-payload that enables high drug-to-antibody ratio and controlled bystander effect. NaPi2b is a sodium-dependent phosphate transporter broadly expressed in high-grade serous ovarian cancer (HGSOC), with limited expression in normal tissues. Emerging UpRi data suggests a relationship between high NaPi2b expression and clinical activity. To determine if archival material would be sufficient to classify biomarker status, we evaluated NaPi2b expression in paired freshly biopsied and archive material from the Phase 1b study.

Methods Two sample sets were evaluated for NaPi2b expression using an IHC assay. The first set (18 pairs) was procured from tissue banks, representing synchronous sampling of primary and metastatic lesions to establish a reference NaPi2b heterogeneity rate. The second set were matched metachronous samples (56 pairs) from the Phase 1b study, sampled prior to UpRi administration. Expression was shown as a tumor proportion score (TPS ≥75). Concordance rates and Kappa values were calculated.

Results Synchronous primary and metastatic lesions from an archival tumor bank showed a concordance rate of 72%. When fresh biopsy samples from a clinical study cohort were compared to archival tissue from the same patient, 76% of NaPi2b high tumors in archival tissue were also high in fresh samples, regardless of the elapsed time between archival and fresh tissue samples.

Conclusions UpRi is being evaluated in clinical trials, requiring either fresh or archival tissue for NaPi2b expression assessment. The high expression concordance rate seen suggests that NaPi2b remains consistent throughout chemotherapy treatment, supporting use of archival tissue for analysis.

EP018/#324 THE EFFICACY AND MOLECULAR MECHANISMS OF MDR-REVERSAL AGENTS (STONEY 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 IC50 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. 21–140825, the Czech Ministry of Education, Youth and Sports: INTER-ACTION, project no. LTAUSA19032, and the National Institutes of Health (NIH), U.S.A. grant R01 CA103314.

Abstract 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.
Methods Female C57BL/6 mice were divided into 5 groups: Normal, Tumor, Model, RG-L or RG-H group. Cell-derived xenograft model was established for mice in all groups in advance except Normal group. On D1–7, mice were administered by gavage once in the morning: Normal group, Tumor group and Model group were given distilled water, RG-L group and RG-H group were given RG solution at the doses of 100 mg·kg⁻¹ or 200 mg·kg⁻¹ respectively. On D5–7, mice were also administered by gavage once every afternoon: Normal and Tumor group was given distilled water, Model group, RG-L Group and RG-H group were given Niraparib solution 80 mg·kg⁻¹. Samples were collected on D8.

Results With the increase of concentration, the effect of RG on protecting the hematopoietic function of bone marrow might improve (figures 1 and 2). The mechanisms of RG ameliorating myelosuppression were that it protected the differentiation ability, promoted the repair of DNA double-stand breaks and improved the cell cycle transition of bone marrow nucleated cells (figure 3). There was no evidence suggesting that RG worsened the efficacy of Niraparib (figure 4).

Conclusions 1. RG may have the advantage of relieving myelosuppression induced by Niraparib. High concentration of RG may be more effective. 2. RG may be a safe agent which does not negatively affect the efficacy of Niraparib.