BAY 1895344, A NOVEL ATR INHIBITOR, DEMONSTRATES IN VIVO ACTIVITY AGAINST ATRX ALTERED UTERINE LEIOMYOSARCOMA

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Objectives

Uterine leiomyosarcoma (uLMS) is a rare, aggressive gynecologic malignancy. Up to 51% of uLMS harbor somatic mutations in ATRX, a tumor suppressor in the transcription regulation pathway, which increase sensitivity to ATR inhibitors. We sought to investigate the in vivo activity of a novel ATR inhibitor, BAY 1895344, against ATRX altered uLMS.

Methods

ATRX altered PDX models LEY11 and LEY 16 were grafted into female CB-17/SCID mice and triaged to treatment with control or BAY1895344 (10 or 20 mg/kg daily). Treatments were given via oral gavage twice daily for three days weekly and tumor measurements and weights obtained twice weekly. ATR and DAXX expression were determined by Western blotting and RTPCR. Tumor volume differences were calculated with a two-way ANOVA, and p-value <0.05 was considered statistically significant. OS was compared via a Kaplan-Meier survival curve.

Results

Tumor growth inhibition was significantly greater in the BAY1895344 groups in both LEY 11 (n=12) and LEY 16 (n=13) (p=0.0003 and p = 0.006, respectively). Median overall survival was significantly longer in both LEY 11 (12.5 vs. 42 days, p < 0.001) and LEY 16 (32 vs. 60 days, p < 0.001). There was no significant toxicity. ATRX was overexpressed in LEY 11 (Avg dCt 10.09 vs. 6.56) as well as DAXX (Avg dCt 8.97 vs. 6.46).

Conclusions

BAY1895344 demonstrates promising in vivo activity against a PDX model of uLMS that harbors ATRX mutations, with no significant toxicity. Phase I trials of BAY1895344 are currently ongoing, and its clinical use in uLMS warrants further investigation.

COMPARATIVE GENOMIC ANALYSIS OF OVARIAN CLEAR CELL CARCINOMA PATIENTS WITH AND WITHOUT A SECOND PRIMARY MALIGNANCY

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Objectives

Previous study showed that patients with Ovarian clear cell carcinoma (OCCC) are at increased risk for developing secondary malignancy (SM). Objectives: To identify and compare germline and somatic mutations in patients with OCCC only, and patients with OCCC and a SM by whole exome sequencing (WES) analysis. To compare somatic mutations in primary and SM tissue from the same patient by WES and deep targeted sequencing.

Methods

DNA was extracted from patient tumour(s) and peripheral blood samples, sequenced to identify somatic and germline mutations, copy-number variants and rearrangements in the exome. Exome sequencing was performed using the Agilent SureSelect Human All Exon (V7) panel covering 49.7 Mb across all genes annotated by RefSeq, CCDS, and GENCODE.
**Results** Ten patients with OCCC were selected: Five had SM and 5 patients had OCCC only. We did not uncover any pathogenic or likely-pathogenic germline variants in this cohort, as annotated by ClinVar. Consistent with previous reports in OCCC, we uncovered recurrent, oncogenic mutations in PIK3CA and loss-of-function mutations in ARID1A in 8 OCCCs. One of the two OCCCs without these mutations had somatic mutations of RRAS2 (encoding downstream target of PIK3CA pathway) and loss-of-function mutation in ARID4B, consistent with the more frequent oncogenic mechanisms in OCCC. In the SM, none of the somatic mutations were shared with the primary OCCCs.

**Conclusions** In this pilot study, SM did not share somatic mutation with OCCC. Larger cohort and deeper molecular analysis can be used to further understand potential common pathway contributing to development of SM in patients with OCCC.

**Abstract EP09/#709 Figure 1**

**Abstract EP09/#709 Figure 2**

**EP009/#709 LIPOLYSIS-STIMULATED LIPOPROTEIN RECEPTOR – ANTIBODY-DRUG CONJUGATES (LSR-ADC) DEMONSTRATES POTENT ANTITUMOR ACTIVITY TO EPITHELIAL OVARIAN CANCER**

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**Objectives** Epithelial ovarian cancer (EOC) is the leading cause of cancer-related deaths among women, thus new treatment option is urgently required. Lipolysis-stimulated lipoprotein receptor (LSR) is widely expressed in EOC and associated with poor prognosis. In this study, we developed antibody-drug conjugate (ADC) targeting LSR as a new therapy for EOC.

**Methods** We developed novel anti-LSR monoclonal antibodies (mAbs) and LSR-ADC by conjugating monomethyl auristatin E (MMAE) as a payload. Then, we evaluated the expression of LSR in EOC cell lines and antitumor effect of LSR-ADC in vitro and in vivo xenograft models.

**Results** We evaluated the strong expression of LSR in EOC cell lines (NOVC7C and OVCAR3) and the strong binding affinity of LSR-ADC to these LSR-positive cell lines. Moreover, we demonstrated the rapid internalization of LSR-ADC into tumor cells and trafficked to lysosome. In vitro, LSR-ADC showed a potent antitumor effect against NOVC7C and OVCAR3. Moreover, in the OVCAR3 xenograft model (figure 1A), and patient-derived xenograft (PDX) models of LSR-positive EOC (figure 1B), LSR-ADC significantly inhibited tumor growth.

LSR-ADC also suppresses omental/bowel metastasis in OVCAR3-Luc xenografts (figure 2) and improved median survival.

**Conclusions** LSR-ADC showed significant antitumor activity against LSR-positive EOC cell lines and LSR-positive EOC tissues. Our preclinical data demonstrated that LSR-ADC is a novel therapy for patients with LSR-positive EOC.

**EP010/#645 TRANSCRIPTOMIC ANALYSIS OF PROGESTERONE RESISTANCE IN ENDOMETRIAL CANCER CELLS**

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**Objectives** To identify differentially expressed genes (DEGs) and signaling pathways in progesterone-resistant endometrial cancer (EC) cells.