**Purpose:** Adenoid cystic carcinoma (ACC) is a salivary gland malignancy that can require relatively high doses of radiation to achieve local control. Given distant recurrences are common and metastases can grow slowly, local treatments are often pursued. Here, we investigate the ability of hypofractionated radiotherapy (RT) to affect local responses when given in combination with the PD-1 inhibitor pembrolizumab (pembro) in a prospective phase II trial. We hypothesized the combination of pembro and RT would serve as effective local treatment, even at relatively modest radiation doses.

**Materials and Methods:** We enrolled patients with recurrent or metastatic ACC with evidence of progressive disease over the last year, >1 measurable non-CNS lesion, and 1-5 lesions appropriate for RT prescribed to a dose of 30Gy/5. Twenty patients were randomized to receive pembro alone (200mg IV q3 weeks) or pembro with RT started within seven days of cycle 1, day 1 (10 patients each arm). The primary endpoint was objective response rate outside the RT field by RECIST 1.1. In this exploratory analysis, local responses of irradiated lesions were assessed using centralized imaging review. The product of the longest two perpendicular dimensions of all irradiated lesions were determined at each restaging scan on study as well as at two sequential time points >1 month apart prior to study treatment and at two longest two perpendicular dimensions of all irradiated lesions were assessed using centralized imaging review. The product of the longest two perpendicular dimensions of all irradiated lesions were determined at each restaging scan on study as well as at two sequential time points >1 month apart prior to study treatment to determine best overall response (BOR).

**Results:** Nine of the 10 patients who received RT had measurable irradiated lesions. Among these nine patients, 11 lesions were treated: nine intrathoracic lesions and two liver lesions. All the lesions increased in size prior to study entry, with an average of 35.8% (range 2.9-84.1%) tumour growth. Following RT, all but one irradiated lesion decreased in size compared to baseline, although one patient experienced initial growth of an irradiated liver lesion (283%) before subsequent response. The mean BOR in the cohort was -47.4% (range: -3.9% to -85.7%) and five of nine patients had a BOR >50%. The median time to BOR was 4.9 months (range: 2.3-10.0 months). With a median follow-up of 5.5 months prior to withdrawal / censure (range: 2.8-12.9), eight of nine patients demonstrated an ongoing response of the irradiated lesion.

**Conclusions:** Preclinical studies suggest immune activation may enhance the local effects of RT. Here, we observed significant local responses within the RT field in growing ACC lesions treated with the combination of hypofractionated radiation to a dose of 30Gy and pembro administered on a phase II study. We also observed a potential case of pseudoprogression within the RT field, a phenomenon that has been previously linked to immune checkpoint inhibitors. Ongoing translational studies are investigating immunologic correlates associated with these responses. NCT03087019

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**TARGETING AURORA KINASE TO ENHANCE THE CURATIVE POTENTIAL OF RADIOThERAPY IN HPV RELATED CANCERS**

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**Purpose:** Cervical cancer is caused by human papilloma virus (HPV), a sexually transmitted environmental agent. Approximately 40% of cervical cancer patients treated with radio(chemo)therapy (RTCT) develop recurrence that can be difficult to treat. New approaches for overcoming treatment failures are needed. Alisertib is a clinically approved, oral selective inhibitor of Aurora kinase A (AurkA), which causes G2/M cell cycle arrest and apoptosis. High E7 oncogene expressing tumours and/or those carrying the ARID1A mutation are found in several disease sites, including cervix, and are more sensitive to AurkA inhibition. Our goal is to identify a clinically relevant treatment strategy, using AurkA as a therapeutic target in patients, to advance curative combination treatments with RTCT for HPVE7 related cancers. We hypothesize Alisertib influences the sensitivity to RT to improve primary tumour response and reduce lymph nodal disease compared to RT or drug alone. The aims are: 1) to determine the efficacy of fractionated RT combination with Alisertib in HPVE7/ARID1A expressing orthotopic cervical PDXs on tumour growth delay response; and 2) to determine the effect on metastases development in response to AurkA inhibition with RT treatment.

**Materials and Methods:** HPVE7 expression profiles of the cervix PDX models were determined by qRT-PCR. An orthotopic patient derived cervix cancer xenograft was treated with RT (30Gy/2Gy/day) with or without Alisertib (30mg/kg/day) given concurrently with RT daily (3wks). Expression of anti-apoptotic and DNA damage response proteins was evaluated by western blot at the end of treatment. Tumour growth delay and lymph node metastasis was/will be assessed.

**Results:** The PDX HPV subtypes reflect the patients clinical HPV status at diagnosis. In an E7 expressing PDX model, RT combined with Alisertib treatment shows prolonged tumour growth delay compared with RT alone. Reduced lymph node metastasis was observed with Alisertib alone compared to control. These studies are still in progress. Tumours analysed at end of treatment suggest that AurkA inhibition resulted in the loss of RT-induced anti-apoptotic expression and γ-H2AX phosphorylation was enhanced by the combined treatment relative to RT alone. This suggests that Alisertib may reduce repair of DNA damage induced by RT treatment, which is consistent with its expected action on AurkA. Further investigation is ongoing to assess mechanisms underlying the RT induced effects with Alisertib on tumour response.

**Conclusions:** Alisertib may enhance the curative potential of RT in patients with high E7 expressing cancers, and/or ARID1A mutations, which impacts on the sensitivity to treatment response. This study presents a promising approach to treating aggressive HPV cancers and may apply to other HPV-related cancers where RT plays a curative role and supports successful translation of new radiation-drug combinations to the clinic.

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**EFFECT OF MAGNETIC FIELD DURING RADIOThERAPY ON DOUBLE-STRAND DNA BREAKS AND CELL PROLIFERATION ON PROSTATE, CERVICAL, AND BREAST CANCER CELLS**

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**Introduction:** MR-guided radiotherapy (RT) using MR-Linacs is an emerging technology. It allows for real-time tracking of targets and organs-at-risk to deliver RT with high precision. However, the biological effect of a strong magnetic field on cancer cells during RT is not well known, with conflicting data reported in literature. In this study, the effects of a magnetic field during RT on resulting DNA double-strand breaks (DSBs) and cell viability were investigated.

**Materials and Methods:** Human cancer cells from prostate (PC3), cervix (HeLa), and breast (MCF-7, MB 231, T47D) were cultured used DMEM media with 10% FBS. A Varian LINAC (Palo Alto, CA, USA) 6 MV beam was used to deliver RT to a 96 well plate. The plate was mounted in a custom 0.21 T magnetic solenoid coil with the magnetic field oriented parallel to the RT beam. DSBs were assessed via γ-H2AX assay: cells were fixed 24-hours post-2Gy