Sensitivity of Syngeneic Tumor Models to Focal Radiation

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Abstract #A208

Introduction and Background

- Use of image-guided focal irradiation is a mainstay of human cancer treatment.
- Image guidance allows for highly conformal treatment plans that minimize normal tissue toxicity and systemic response.

With the advent of image-guided small animal irradiators such as the Small Animal Radiation Research Platform (SARRP) (Xtrac Inc., Sunnyvale, CA), targeted focal irradiation can now be utilized in a broad range of preclinical oncology models.

Of particular interest is the possibility of focal irradiation to broaden the efficacy and response duration of immunotherapy.

- We identified a base-line response of several syngeneic mouse models to focal irradiation therapy.

Materials & Methods

- Image-guided irradiation was performed under 1-2% isoflurane anesthesia on the Small Animal Radiation Research Platform (SARRP) (Xtrac Inc., Sunnyvale, CA). Following placement on the treatment bed, animals were imaged with an open field at 60kV and 0.5mA for a planning CBCT. The resultant CBCT was then loaded into the treatment planning software (Mтурpir, Xtrac Life Sciences) and a treatment plan applied and optimized for each target.

- Treatment was delivered at 220kV and 13.0mA using an appropriately sized collimator to the total indicated dose (in Gray; Gy) in 2 equally weighted beams. For daily treatments, the same treatment plan was applied and adjusted for changes in animal positioning or target alternation over time.

- Subcutaneous (SC) mouse tumor models tested were A20 (B cell lymphoma; Balb/C mice) and CT26.WT (colon carcinoma; Balb/C mice) and tumor growth changes were tracked over time by caliper measurements.

- Orthotopic mouse tumor models tested were 4T1-Luc2 (mammary carcinoma; Balb/C mice) implanted in the mammary fat pad and GL261-Luc2 (glioblastoma, albino C57BL/6 mice) implanted in the brain.

- For the A20, CT26.WT and 4T1-Luc2 models, a single dose of focal irradiation was delivered specifically to the tumor at the time of study staging (see Fig 1A).

- For the GL261-Luc2 model, mice were injected with Carprofen at 5mg/kg and anesthetized using 2% isoflurane and then secured in a stereotaxic frame (ASI Instruments, Inc.). Mice were implanted with 1.00E+06 cells per 10µl. The burr hole was sealed with bone wax and the incision was closed with a stainless steel steel stitch. Wound sites were treated with 100 days post implant. A single dose of focal irradiation was delivered to the brain on the day of study staging and tumor burden was tracked by bioluminescence imaging (BLI) over time. BLI was performed using an IVIS Spectrum (Caliper Life Sciences, Hopkinton, MA).

Fig. 1 – Small Animal Radiation Research Platform

- SC flank with a 200Gy focal irradiation
- Orthotopic brain tumor with 7.5Gy focal irradiation

Results & Conclusions

- Targeted delivery of focal irradiation overcomes radiation-induced side effects widely seen with whole body irradiation, and provides a more clinically translatable approach to preclinical testing.

- The tumor models tested showed dose-dependent anti-tumor activity following a single dose of focal irradiation to the tumor. In the A20 and the CT26.WT models there was a few a few days a more that tumor free survival following radiation treatment. These mice were rechallenged with tumor implantation on the contralateral (left) flank and no tumors grew out suggesting a memory immune response was elicited.

- Combination of radiation and anti-PD-1 therapy provided improved benefit over single agent therapies in the GL261-Luc2 model.

- Changes in immune cell populations were determined by flow cytometry.

Additional syngeneic models are being tested and further combination studies with I/O agents are ongoing.