#A208. Sensitivity of Syngeneic Tumor Models to Focal Radiation

Sarah Krueger, Kevin Guley, Chris Bull, Sumi Urs, Alden Wong, Dan Saims, Scott Wise and Maryland Rosenfeld Franklin
Labcorp Early Development Laboratories Inc., Ann Arbor, Michigan

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; Xstrahl Inc., Suwanee, GA), targeted focal irradiation can now be utilized in a broad range of preclinical oncology models.
- Of particular interest is the possible use of focal irradiation to broaden the efficacy and response duration of immuno-oncology therapy.
- Here we identified base-line response of several syngeneic mouse models to focal irradiation therapy.

Materials and Methods

- Image-guided irradiation was performed under 1-2% isoflurane anesthesia on the Small Animal Radiation Research Platform (SARRP; Xstrahl Inc., Suwanee, GA). Following placement on the treatment bed, animals were imaged with an open field at 60 kV and 0.5 mA for a planning CBCT. The resultant CT was then loaded into the treatment planning software (Muriplan, Xstrahl Life Sciences) and a treatment plan applied and optimized for each target.
- Treatment was delivered at 220 kV and 13.0 mA 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 alteration 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-luc (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 (Figure 1A).
- For the GL261-luc model, mice were injected with Carprofen at 5 mg/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 10 µL. The burr hole was sealed with bone wax and the incision was closed with a stainless steel wound clip. Wound clips were removed 7-10 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).

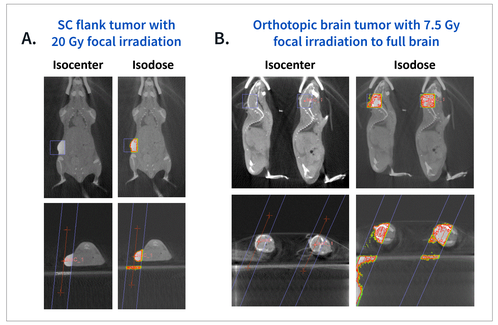

Figure 1. Small animal radiation research platform. Following placement onto the treatment bed, a CBCT is performed for treatment planning. The resultant CT is then loaded into the treatment planning software and a treatment plan is optimized for each target. In 1A and 1B treatments were delivered using a 10x10 collimator and the total indicated dose (in Gray; Gy) was administered in 2 equally weighted beams. The isodose figures shown on the right hand panels of 1A and 1B show homogeneity of the delivered dose with limited/no scatter.

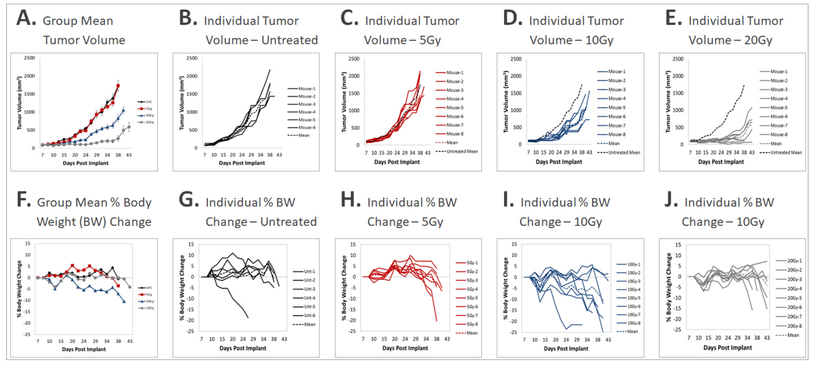

Figure 2. Sensitivity of 4T1-Luc2 mammary tumor model.

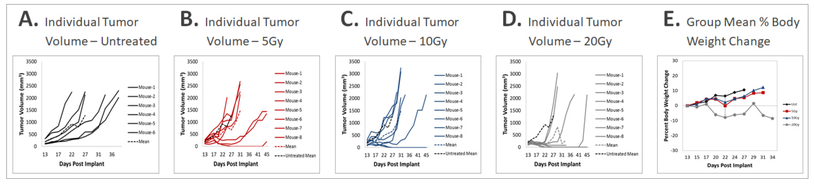

Figure 3. Sensitivity of A20 B cell lymphoma model. 2 mice at 10 Gy and 2 mice at 20 Gy showed complete tumor regressions, these mice were rechallenged with A20 tumor on the left flank; no tumor growth was observed, suggesting a memory immune response was generated.

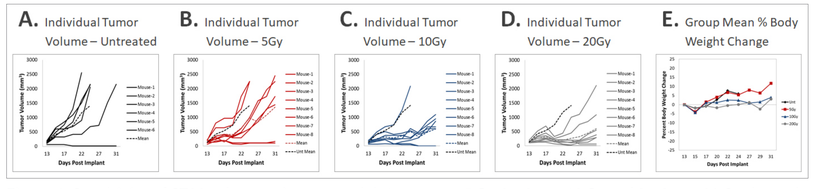

Figure 4. Sensitivity of CT26 colon carcinoma model. 1 mouse at 5 Gy, 2 mice at 10 Gy and 2 mice at 20 Gy showed complete tumor regressions, these mice were rechallenged with CT26 tumor on the left flank; no tumor growth was observed, suggesting a memory immune response was generated.

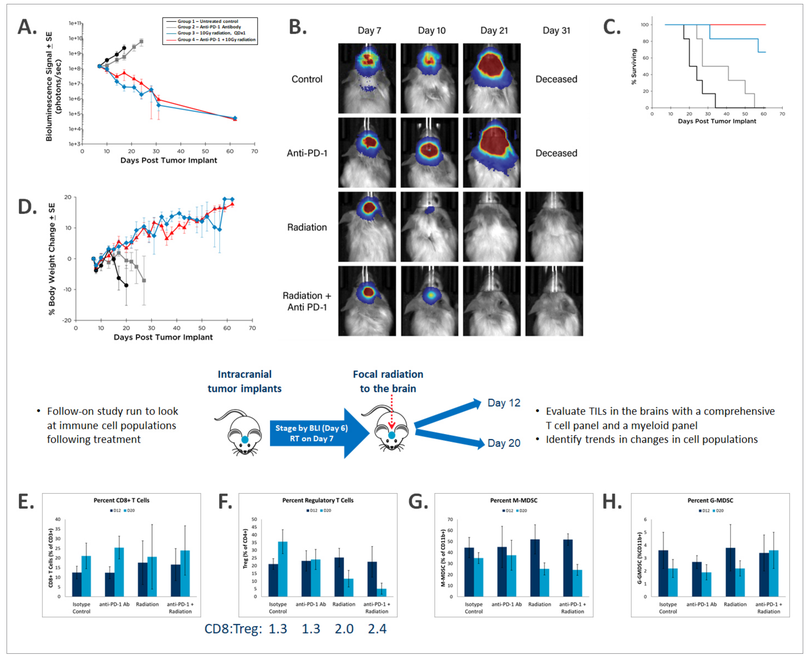

Figure 5. Anti-PD-1 antibody in combination with focal radiation in the murine GL261-luc intracranial tumor model. Mice received no treatment (black lines), 10 mg/kg anti-PD-1 antibody (gray lines), single dose of 10 Gy focal irradiation (blue lines) or the combination (red lines). Tumor burden was tracked over time (A, B) along with overall survival (C) and body weight changes (D). Single agents increased life-span vs. control. The combination resulted in 100% survival.

Results and Conclusions

- Targeted delivery of focal irradiation overcomes radiation-induced side effects widely seen with whole-body cabinet irradiators, 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 models there were a few mice that became tumor-free survivors 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-luc 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.

Presented at AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference 2017

labcorp Drug Development