

#5194. Focal Radiation Enhances Paclitaxel Therapy in a Mouse Model of Triple Negative Breast Cancer

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Introduction and Background

- ▶ Triple negative breast cancer (TNBC) accounts for 15-20% of all breast cancers in the United States.
- ▶ Patients with TNBC have poorer prognosis and therapeutic intervention is more challenging due to insensitivity to hormonal and anti-HER2 therapies.
- ▶ Therapeutic options for TNBC can include chemotherapy and/or radiation (RT) treatment.
- ▶ Clinical trials evaluating shorter, hypofractionated doses of radiation are being conducted in patients with breast cancer.
- ▶ This study evaluated preclinical activity of paclitaxel in combination with either lower dose, more frequent radiation or higher dose, less frequent radiation.

Materials and Methods

- ▶ Female NSG (Jackson Laboratory) mice were implanted subcutaneously with 1×10^7 HCC70 cells in 50% matrigel in the right low axilla region. HCC70 is a human, triple negative breast cancer cell line (ATCC).
- ▶ A preliminary study evaluated whether paclitaxel or docetaxel would be more useful in combination with focal radiation (see Table 1).
- ▶ Mice were randomized into treatment groups (see Tables 1 and 2) when the mean tumor volume in each group was $\sim 200 \text{ mm}^3$. Tumor volumes and body weights were measured twice weekly for the duration of each study.
- ▶ Docetaxel (Selleckchem) was formulated in saline. Paclitaxel (Selleckchem) was formulated in a vehicle of 10% EtOH, 10% Cremophor and 80% saline (0.9% sodium chloride). Paclitaxel was formulated immediately prior to each dose.
- ▶ 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 60kV and 0.5mA 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 (220 kV, 13.0 mA) was applied using a 10x10 mm collimator and delivered to a total daily dose of 8 Gy or 2.5 Gy in 2 equally weighted beams. The average calculated dose rate at the beam isocenter was 2.4 Gy/min for 8 Gy and 2.5 Gy/min for 2.5 Gy treatments. For daily treatments, the same treatment plan was applied and adjusted for changes in animal positioning or target alteration over time.
- ▶ All treatment plans were optimized and designed to minimize normal tissue toxicity and produce a homogeneous distribution in the target. Dose distribution maps, dose volume histograms and normal tissue interactions were all taken into account during the treatment planning process.

Tables 1 and 2 – Outline of Study Designs

Group	# of Animals	Drug	Route/ Dose (mg/kg)	Schedule
1	6	Vehicle	IV/ NA	Q7Dx3
2	6	Paclitaxel	IV/ 15	Q7Dx3
3	6	Docetaxel	IV/ 15	Q7Dx3

Group #	# of Animals	IV Paclitaxel Dose (mg/kg)	Paclitaxel Schedule	Radiation Dose (Gy)	Radiation Schedule
1	8	None	---	None	---
2	8	15	Q7Dx3	None	---
3	8	None	---	8	QDx3
4	8	None	---	2.5	(QDx5; 2off)x2
5	8	15	Q7Dx3	8	QDx3
6	8	15	Q7Dx3	2.5	(QDx5; 2off)x2

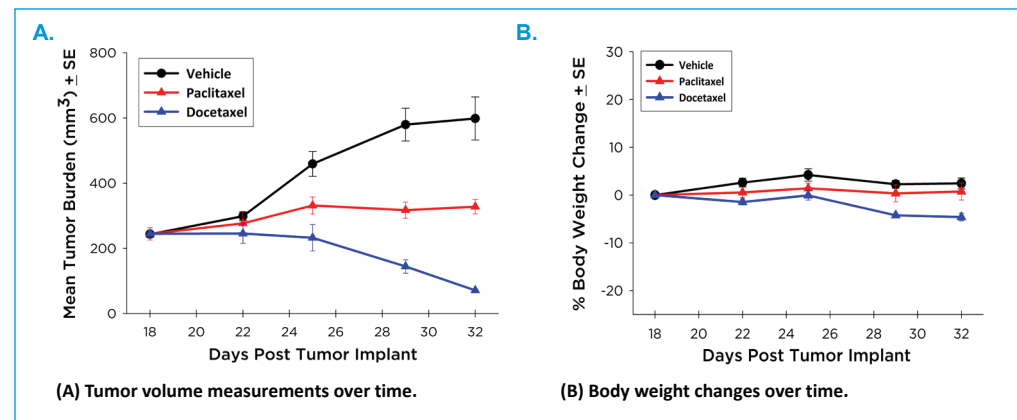


Figure 1. Anti-tumor Activity of Paclitaxel and Docetaxel in HCC70 SC Tumor Xenografts.

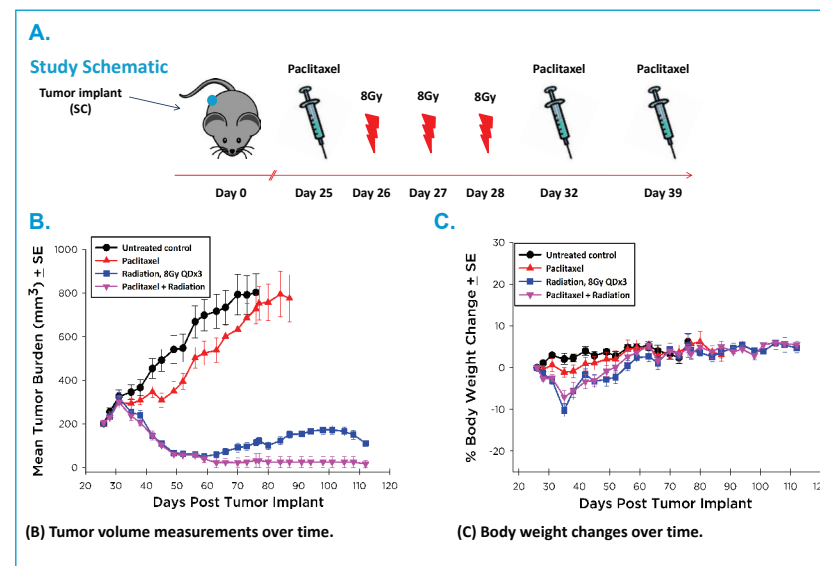


Figure 2. Hypofractionated Radiation Combination.

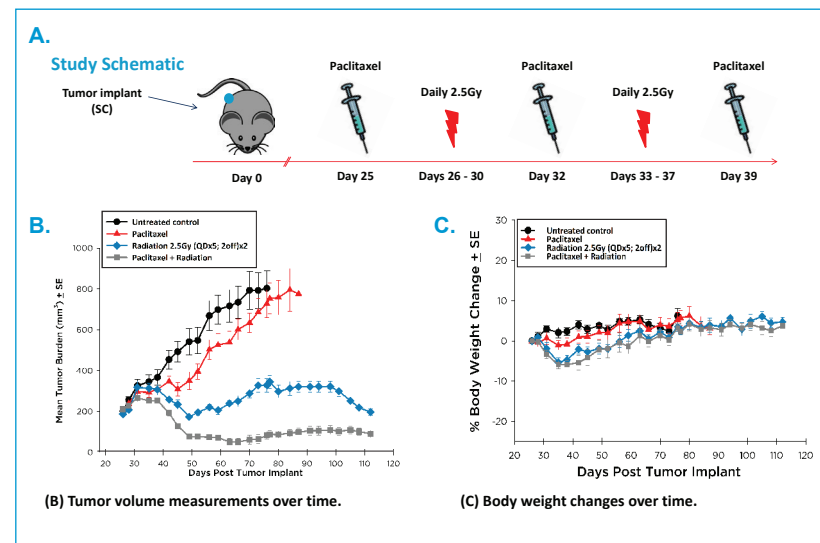


Figure 3. Fractionated Radiation Combination.

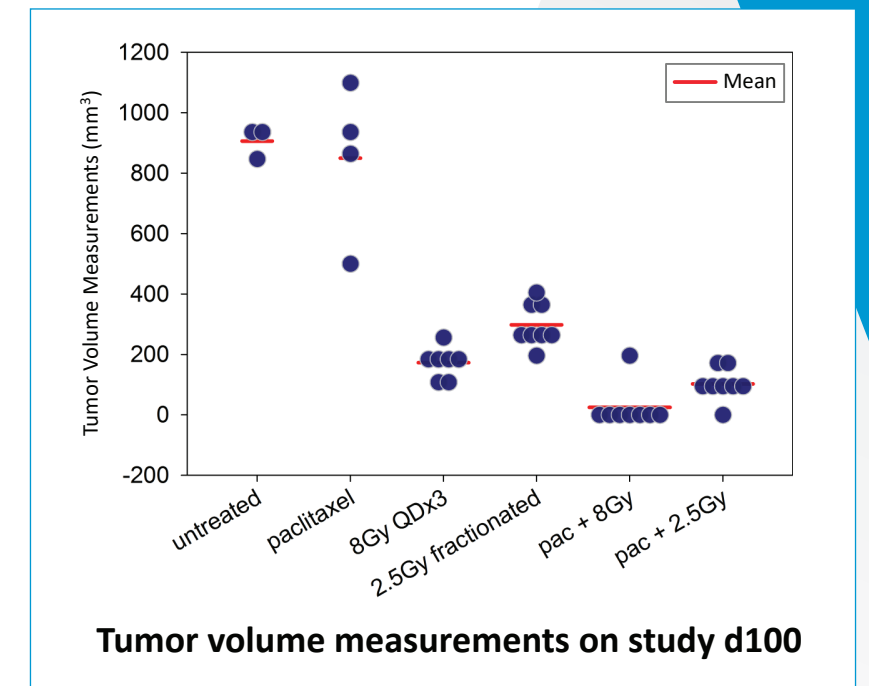


Figure 4. Tumor Volume.

Table 3. Endpoint analysis

Group #	Treatment Related Weight Change	Median % $\Delta T/\Delta C$ (day 63)	% Regression (day 63)	% Complete Response	% Partial Response	% Tumor Free Survivors
1	4.8	100	0	0	0	0
2	4.4	72.2	0	0	0	0
3	-10.2	NA	62	25	75	0
4	-5.4	12	0	0	0	0
5	-7.1	NA	94	87.5	0	87.5
6	-5.9	NA	99	37.5	50	12.5

Results and Conclusions

- ▶ Hypofractionated radiation dosing resulted in an increased therapeutic response over fractionated dosing with 62% regression and all mice demonstrating either complete or partial response.
- ▶ Addition of paclitaxel to either radiation regimen increased efficacy over single agent radiation based on mean tumor volume on d100, the increased incidence of tumor regressions and 12.5–87.5% tumor-free survivors observed.
- ▶ The therapeutic advantage of hypofractionated radiation comes at the cost of lower tolerability.