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

Maryland Rosenfeld Franklin, Thomas Dailey and Wilbur R. Leopold; Labcorp Early Development Laboratories Inc., Ann Arbor, Michigan

## 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 1x10$^7$ 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 (Table 1).
- Mice were randomized into treatment groups (Tables 1 and 2) when the mean tumor volume in each group was ~200mm$^3$. 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 (220kV, 13.0mA) was applied using a 10x10mm collimator and delivered to a total daily dose of 8Gy or 2.5Gy in 2 equally weighted beams. The average calculated dose rate at the beam isocenter was 2.4Gy/min for 8Gy and 2.5Gy/min for 2.5Gy 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.

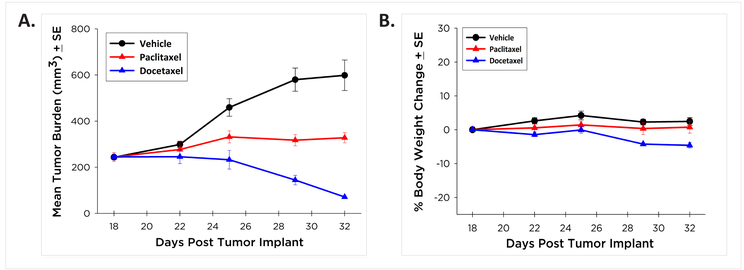


**Figure 1. Anti-tumor activity of paclitaxel and docetaxel in HCC70 SC tumor xenografts.** (A) Tumor volume measurements over time. (B) Body weight changes over time.

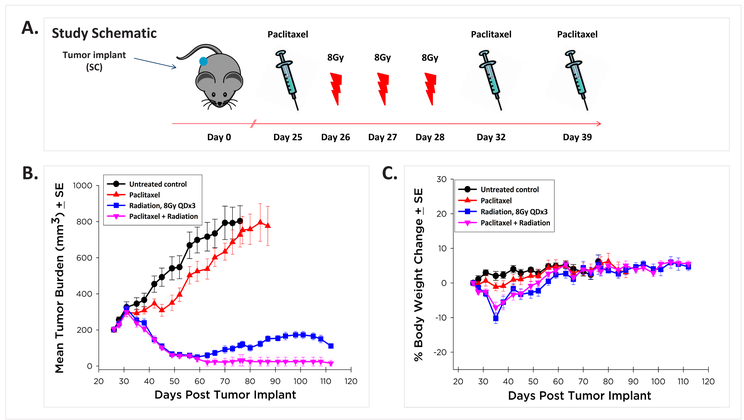


**Figure 2. Hypofractionated radiation combination.** (A) Study schematic. (B) Tumor volume measurements over time. (C) Body weight changes over time.

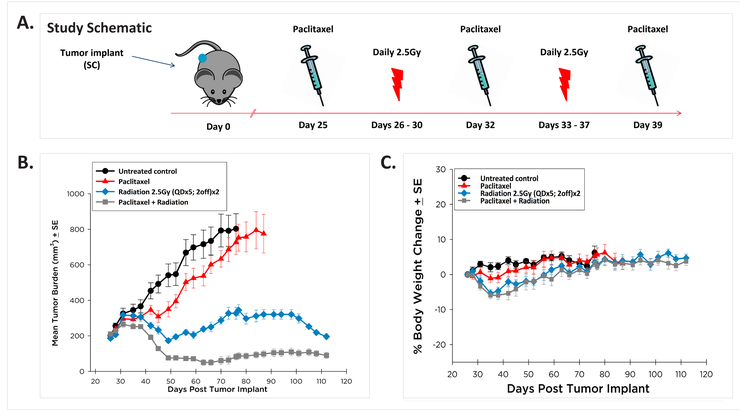


**Figure 3. Fractionated radiation combination.** (A) Study schematic. (B) Tumor volume measurements over time. (C) Body weight changes over time.

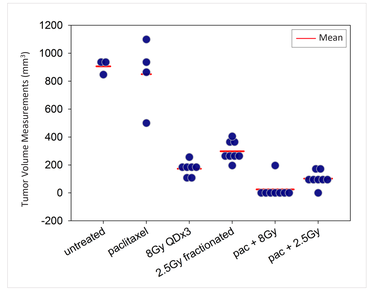


**Figure 4. Tumor volume measurements on study d100.**

**Table 1. Study Design: Effects of Paclitaxel and Docetaxel on HCC70 Growth *In Vivo***

| 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 |

**Table 2. Study Design: Effects of Paclitaxel, Radiation or the Combination on HCC70 Growth *In Vivo***

| 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 |

**Table 3. Endpoint Analysis**

| Group | Treatment Related Weight Change | Median % ΔT/ΔC (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.

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