

## Tumor Grade & Pre-Operative Therapy Impact the Establishment of Soft Tissue Sarcoma Patient-Derived Orthotopic Xenografts (PDOX): UCLA Sarcoma Program Prospective Clinical Trial

Tara A. Russell<sup>1,2</sup>, Irimina Elliott<sup>2</sup>, Mark A. Eckardt<sup>3</sup>, Takashi Murakami<sup>4,5</sup>, Arun S. Singh<sup>6</sup>, Tasuku Kiyuna<sup>4,5</sup>, Kentaro Igarashi<sup>4,5</sup>, Kei Kawaguchi<sup>4,5</sup>, Yunfeng Li<sup>7</sup>, Joseph Crompton<sup>2</sup>, Sarah M. Dry<sup>7</sup>, Noah Federman<sup>8</sup>, Bartosz Chmielowski<sup>6</sup>, Elizabeth Shurrell<sup>2</sup>, Robert M. Hoffman<sup>4,5</sup>, Fritz C. Eilber<sup>2</sup>

1. Veterans Affairs Los Angeles Health Services Research & Development Center of Innovation, Los Angeles, CA
2. Division of Surgical Oncology, Jonsson Comprehensive Cancer Center Sarcoma Program, University of California, Los Angeles, CA
3. Department of Surgery, Yale School of Medicine, New Haven, CT
4. AntiCancer Inc., San Diego, CA
5. Department of Surgery, University of California, San Diego, CA
6. Department of Medicine, Jonsson Comprehensive Cancer Center Sarcoma Program, University of California, Los Angeles, CA
7. Department of Pathology, Jonsson Comprehensive Cancer Center Sarcoma Program, University of California, Los Angeles, CA
8. Department of Pediatrics, Jonsson Comprehensive Cancer Center Sarcoma Program, University of California, Los Angeles, CA

**Objective:** Given the diverse and often aggressive nature of soft tissue sarcomas (STS), there is a need for more precise therapy. Information obtained from the surgical specimen and propagated through murine models can provide a platform for personalized therapy. The aims of this trial were to determine the feasibility of establishing STS PDOX models in the clinical setting & identifying factors associated with PDOX establishment.

**Methods:** From 5/2015-5/2016 all 107 patients with biopsy-proven or potential STS offered enrollment signed pre-operative consent. FCE obtained tumor in the OR which was transported immediately for surgical orthotopic implantation (SOI) in nude mice. Once a PDOX reached 500mm<sup>3</sup> and was passaged, it was considered established. PDOX with no growth at 6 months were classified as failed. No low grade STS established. To date, 65 high-grade (HG)-STS PDOX completed surveillance and were analyzed for factors contributing to establishment.

**Results:** Of the 65 HG-STs, 29 (47%) successfully established thus far (Table 1). Median establishment time was 44 days. Take-rates were similar by gender, presentation, location & histology, but varied by pre-operative therapy (preop-tx). Untreated patients (no preop-tx) had the highest take rate, 62%. On univariate analysis, preop chemotherapy (CT) and radiation (XRT) both impacted the likelihood of xenograft establishment (OR 0.29 with CT, OR 0.13 with XRT, p<0.05 for both). On multivariate analysis, only preop XRT significantly impacted likelihood of establishment (OR 0.12, p=0.007).

**Conclusion:** In the largest PDOX study to date, we demonstrate a 62% establishment rate in untreated high-grade STS tumors, with median establishment time of 44 days. Preop therapy, most notably with XRT, significantly decreased the ability to establish a PDOX. Physicians and/or patients considering utilizing PDOX for personalized therapy in HG-STs, should obtain tumor for xenografting prior to therapy.

|                                 |                         | Sample<br>n = 65 |              | Take-Rate by<br>Individual Factors |         | Univariate Logistic<br>Regression |         | Multivariate Logistic<br>Regression^ |         |
|---------------------------------|-------------------------|------------------|--------------|------------------------------------|---------|-----------------------------------|---------|--------------------------------------|---------|
|                                 |                         | n                | %            | % (n)                              | p-value | OR (SE)                           | p-value | OR (SE)                              | p-value |
| <b>Gender</b>                   | Female                  | 30               | 46.2%        | 46.7% (14)                         | 0.758   | 1.17 (0.584)                      | 0.758   |                                      |         |
|                                 | Male                    | 35               | 53.8%        | 42.9% (15)                         |         | Ref                               |         |                                      |         |
| <b>Grade</b>                    | Low grade               | 0                | 0.0%         | 0                                  |         |                                   |         |                                      |         |
|                                 | High grade              | 65               | 100.0%       | 44.6% (29)                         |         |                                   |         |                                      |         |
| <b>Presentation</b>             | Primary                 | 40               | 61.5%        | 45.0% (18)                         | 0.937   | 1.041 (0.534)                     | 0.937   |                                      |         |
|                                 | Recurrent or Metastatic | 25               | 38.5%        | 44.0% (11)                         |         | Ref                               |         |                                      |         |
| <b>Location</b>                 | Trunk                   | 37               | 56.9%        | 35.1% (13)                         | 0.077   | Ref                               |         |                                      |         |
|                                 | Extremity               | 28               | 43.1%        | 57.1% (16)                         |         | 2.462 (1.266)                     |         | 0.080                                |         |
| <b>Subtype</b>                  | Leiomyosarcoma          | 13               | 20.0%        | 46.2% (6)                          | 0.901   | 1.524 (1.059)                     | 0.545   |                                      |         |
|                                 | Liposarcoma             | 12               | 18.5%        | 58.3% (7)                          | 0.290   | 2.489 (1.789)                     | 0.205   |                                      |         |
|                                 | NOS/Spindle Cell/UPS    | 15               | 23.1%        | 46.7% (7)                          | 0.855   | 1.556 (1.033)                     | 0.506   |                                      |         |
|                                 | Other                   | 25               | 38.5%        | 36.0% (9)                          | 0.269   | Ref                               |         |                                      |         |
| <b>Pre-operative CT</b>         | Yes                     | 20               | 30.8%        | 25.0% (5)                          | 0.034*  | 0.292 (0.174)                     | 0.039*  | 1.055 (0.817)                        | 0.945   |
|                                 | No                      | 45               | 69.2%        | 53.3% (24)                         |         | Ref                               |         |                                      |         |
| <b>Pre-operative XRT</b>        | Yes                     | 20               | 30.8%        | 15.0% (3)                          | 0.001*  | 0.129 (0.090)                     | 0.003*  | 0.121 (0.100)                        | 0.011*  |
|                                 | No                      | 45               | 69.2%        | 57.8% (26)                         |         | Ref                               |         |                                      |         |
| <b>Pre-operative Therapy</b>    | None                    | 39               | 60.0%        | 61.5% (24)                         | 0.001*  | 6.720 (4.010)                     | <0.001* |                                      |         |
|                                 | CT alone                | 6                | 9.2%         | 33.3% (2)                          | 0.560   | 0.593 (0.536)                     | 0.563   |                                      |         |
|                                 | XRT alone               | 6                | 9.2%         | 0% (0)                             | 0.021*  | --                                |         |                                      |         |
|                                 | CT + XRT                | 14               | 21.5%        | 21.4% (3)                          | 0.049*  | 0.262 (0.186)                     | 0.059   |                                      |         |
| <b>Xenograftability</b>         | Success                 | 29               | 44.6%        |                                    |         |                                   |         |                                      |         |
|                                 | Failure                 | 36               | 55.4%        |                                    |         |                                   |         |                                      |         |
|                                 |                         | <b>Median</b>    | <b>Range</b> |                                    |         |                                   |         |                                      |         |
| <b>Age</b>                      |                         | 59               | 16-91        |                                    |         | 1.00 (0.041)                      | 0.990   | 1.026 (0.018)                        | 0.138   |
| <b>Size (cm)</b>                |                         | 7.5              | 0.9-35.5     |                                    |         | 0.990 (0.042)                     | 0.812   | 1.027 (0.050)                        | 0.590   |
| <b>Time to Establish (days)</b> |                         | 44               | 9-184        |                                    |         |                                   |         |                                      |         |

\* significant at p<0.05, CT: chemotherapy, XRT: radiation therapy, NOS: not otherwise specified  
^ Multivariate logistic regression model included the following factors: age, size, neoadjuvant chemotherapy, neoadjuvant radiation. Pseudo R-squared 0.1564, likelihood ratio chi squared 13.98 (p=0.007)