

Supplemental Table 1. Median survival (days) of B16F10 tumor-bearing mice post-treatment with TRT, single ICI, dual ICI, or TRT + dual ICI.

| Treatment group | Experiment | N | Days till palpable | Survival from injection, days median (min-max) | Survival from treatment, days median (min-max) | Adjusted p-value**** (compare to #1 Control) | Adjusted p-value**** (compare to #8) | Adjusted p-value**** (compare to #9) |
|----------------------|------------|---------|--------------------|------------------------------------------------|------------------------------------------------|----------------------------------------------|--------------------------------------|--------------------------------------|
| 1. Control* | 1, 2, 3 | 6, 4, 4 | 8, 7, 8 | 14 (14-15) | 7 (6-8) | --- | <0.001 | <0.001 |
| 2. CTLA-4** | 2 | 8 | 7 | 15.5 (15-18) | 7.5 (7-10) | 0.97 | <0.001 | <0.001 |
| 3. PD-1*** | 2 | 8 | 7 | 15.5 (14-18) | 7.5 (6-10) | 0.99 | <0.001 | <0.001 |
| 4. PD-L1 | 3 | 8 | 7 | 15.5 (14-17) | 7.5 (6-9) | >0.99 | <0.001 | <0.001 |
| 5. PD-1+CTLA4 | 3 | 8 | 7 | 17.5 (17-20) | 9.5 (9-12) | <0.001 | <0.001 | <0.001 |
| 6. PD-L1 + CTLA4 | 1 | 8 | 9 | 18 (17-19) | 9 (8-10) | <0.001 | 0.29 | <0.001 |
| 7. Lu-177 | 1, 4 | 6, 6 | 7, 8 | 19 (17-22) | 12 (9-14) | <0.001 | 0.002 | <0.001 |
| 8. Lu177+PD-1+CTLA4 | 3 | 8 | 7 | 22 (21-23) | 15 (14-16) | <0.001 | --- | 0.20 |
| 9. Lu177+PD-L1+CTLA4 | 1 | 8 | 8 | 23 (21-24) | 15 (13-16) | <0.001 | 0.22 | --- |

*Describe treatment group details here, including that the radiation dose of ¹⁷⁷Lu-LLP2A is below the maximum tolerated dose (MTD) in tumor bearing mice.

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*** etc

**** linear mixed effects regression model with log(survival days from treatment) as outcome, with random experiment effects, days from injection to palpation as a covariate, and treatment group as the covariate of interest. Multiple comparisons in each column adjusted using Dunnett's test.

All treatment groups significantly improved over control (P < 0.005)

All immunotherapy groups not significantly different except PD-L1 vs PD-L1 + CTLA-4 (P=0.0082)

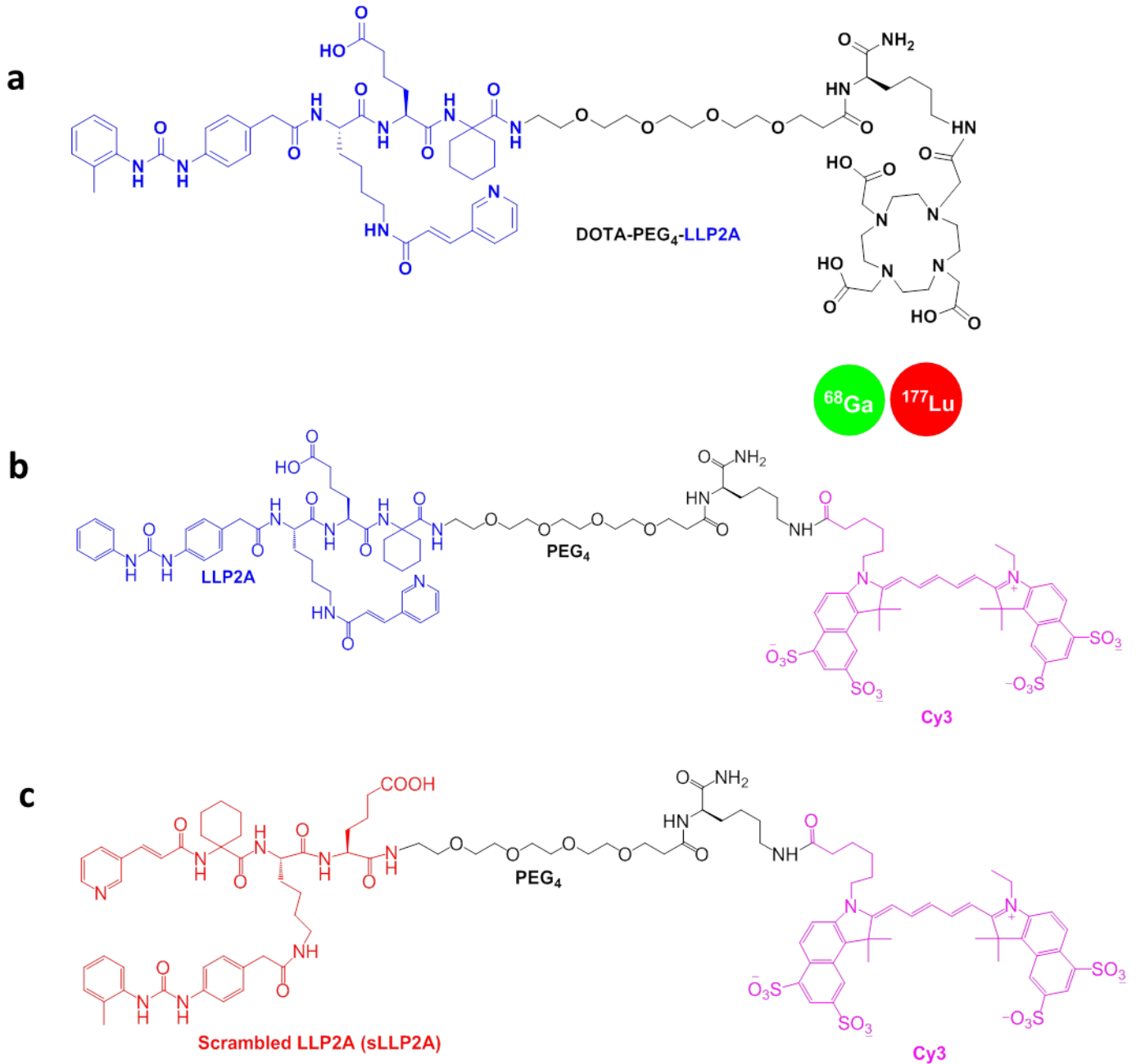
¹⁷⁷Lu-LLP2A + immunotherapy significantly improved over ¹⁷⁷Lu-LLP2A (P < 0.001)

¹⁷⁷Lu-LLP2A + immunotherapy significantly improved over dual immunotherapy (P<0.0005)

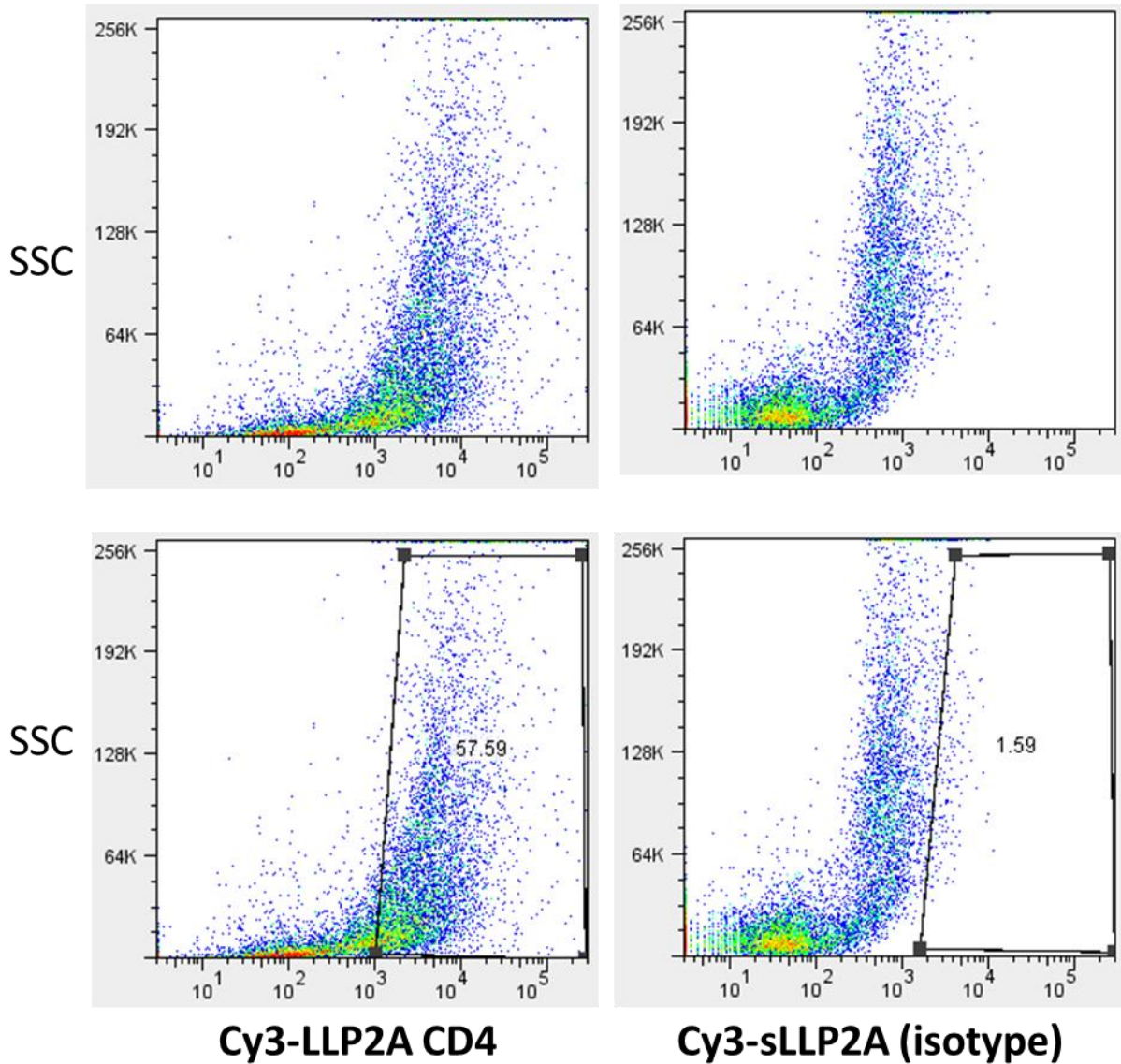
Supplemental Table 2. Uptake (%ID/g) of ¹⁷⁷Lu-LLP2A in tissues and organs for ICR normal mice from 1 h to 7 day post-injection

| % ID/g | 1 hr | 2 hr | 4 hr | 12 hr | 24 hr | 48 hr | 5 days | 7 days |
|-----------------|---------------|--------------|--------------|--------------|-------------|-------------|-------------|-------------|
| Blood | 1.14 ± 0.29 | 0.38 ± 0.04 | 0.37 ± 0.04 | 0.11 ± 0.02 | 0.03 ± 0.01 | 0.03 ± 0.01 | 0.01 ± 0.00 | 0.02 ± 0.01 |
| Lungs | 4.73 ± 0.35 | 3.99 ± 0.51 | 2.61 ± 0.08 | 1.21 ± 0.30 | 0.48 ± 0.17 | 0.32 ± 0.12 | 0.47 ± 0.81 | 0.03 ± 0.03 |
| Liver | 2.04 ± 0.38 | 1.11 ± 0.43 | 1.16 ± 0.28 | 1.58 ± 0.55 | 0.91 ± 0.59 | 0.76 ± 0.19 | 0.47 ± 0.26 | 0.36 ± 0.19 |
| Spleen | 27.45 ± 10.71 | 22.26 ± 8.53 | 15.19 ± 4.01 | 11.86 ± 3.65 | 5.96 ± 1.51 | 4.20 ± 1.64 | 5.23 ± 2.01 | 2.07 ± 2.04 |
| Kidney | 3.59 ± 0.73 | 1.96 ± 0.49 | 2.40 ± 0.20 | 2.18 ± 0.32 | 1.11 ± 0.14 | 0.62 ± 0.14 | 0.27 ± 0.06 | 0.11 ± 0.05 |
| Bladder | 10.05 ± 7.51 | 1.74 ± 1.32 | 6.99 ± 10.14 | 1.41 ± 1.01 | 0.55 ± 0.20 | 0.33 ± 0.13 | 0.16 ± 0.10 | 0.09 ± 0.08 |
| Gallbladder | 13.52 ± 9.70 | 0.92 ± 1.15 | 0.80 ± 0.72 | 2.91 ± 2.53 | 4.14 ± 3.32 | 1.04 ± 1.44 | 0.17 ± 0.34 | 0.26 ± 0.27 |
| Muscle | 1.41 ± 0.36 | 1.13 ± 0.36 | 1.21 ± 0.52 | 0.49 ± 0.22 | 0.20 ± 0.02 | 0.14 ± 0.04 | 0.11 ± 0.06 | 0.34 ± 0.31 |
| Fat | 0.67 ± 0.37 | 0.39 ± 0.26 | 0.43 ± 0.23 | 0.19 ± 0.04 | 0.09 ± 0.05 | 0.05 ± 0.02 | 0.03 ± 0.03 | 0.22 ± 0.46 |
| Heart | 0.83 ± 0.19 | 0.30 ± 0.24 | 0.44 ± 0.13 | 0.20 ± 0.07 | 0.09 ± 0.01 | 0.06 ± 0.01 | 0.03 ± 0.01 | 0.14 ± 0.28 |
| Brain | 0.08 ± 0.02 | 0.16 ± 0.23 | 0.03 ± 0.00 | 0.02 ± 0.01 | 0.01 ± 0.00 | 0.02 ± 0.02 | 0.00 ± 0.00 | 0.01 ± 0.01 |
| Bone+Marrow | 6.92 ± 2.45 | 3.91 ± 1.44 | 3.45 ± 0.74 | 3.78 ± 0.76 | 1.65 ± 0.58 | 1.35 ± 0.25 | 0.93 ± 0.15 | 0.97 ± 0.84 |
| Adrenals | 1.74 ± 1.10 | 0.45 ± 0.38 | 0.61 ± 0.09 | 0.97 ± 0.50 | 0.31 ± 0.11 | 0.23 ± 0.17 | 0.11 ± 0.09 | 0.04 ± 0.04 |
| Thyroid | 1.61 ± 0.30 | 1.80 ± 1.33 | 1.45 ± 1.09 | 0.56 ± 0.21 | 0.26 ± 0.10 | 0.25 ± 0.19 | 0.06 ± 0.02 | 0.03 ± 0.04 |
| Pancreas | 0.84 ± 0.17 | 1.56 ± 1.95 | 0.50 ± 0.11 | 0.57 ± 0.32 | 0.17 ± 0.06 | 0.13 ± 0.11 | 0.06 ± 0.04 | 0.38 ± 0.80 |
| Thymus | 5.03 ± 1.41 | 3.37 ± 3.71 | 3.73 ± 0.92 | 4.40 ± 0.57 | 1.45 ± 0.23 | 0.91 ± 0.60 | 0.74 ± 0.37 | 0.18 ± 0.17 |
| Stomach | 0.66 ± 0.08 | 1.55 ± 2.17 | 0.62 ± 0.05 | 0.47 ± 0.07 | 0.17 ± 0.03 | 0.07 ± 0.03 | 0.05 ± 0.02 | 0.02 ± 0.02 |
| Small Intestine | 3.94 ± 0.67 | 2.34 ± 0.92 | 2.01 ± 0.21 | 1.37 ± 0.16 | 0.68 ± 0.20 | 0.35 ± 0.11 | 0.21 ± 0.08 | 0.07 ± 0.04 |
| ULI | 3.62 ± 1.28 | 2.48 ± 1.14 | 2.15 ± 0.45 | 1.51 ± 0.09 | 0.76 ± 0.40 | 0.33 ± 0.07 | 0.18 ± 0.08 | 0.07 ± 0.04 |
| LLI | 2.18 ± 0.47 | 1.19 ± 0.32 | 1.46 ± 0.22 | 1.17 ± 0.21 | 0.50 ± 0.14 | 0.22 ± 0.04 | 0.13 ± 0.04 | 0.04 ± 0.01 |

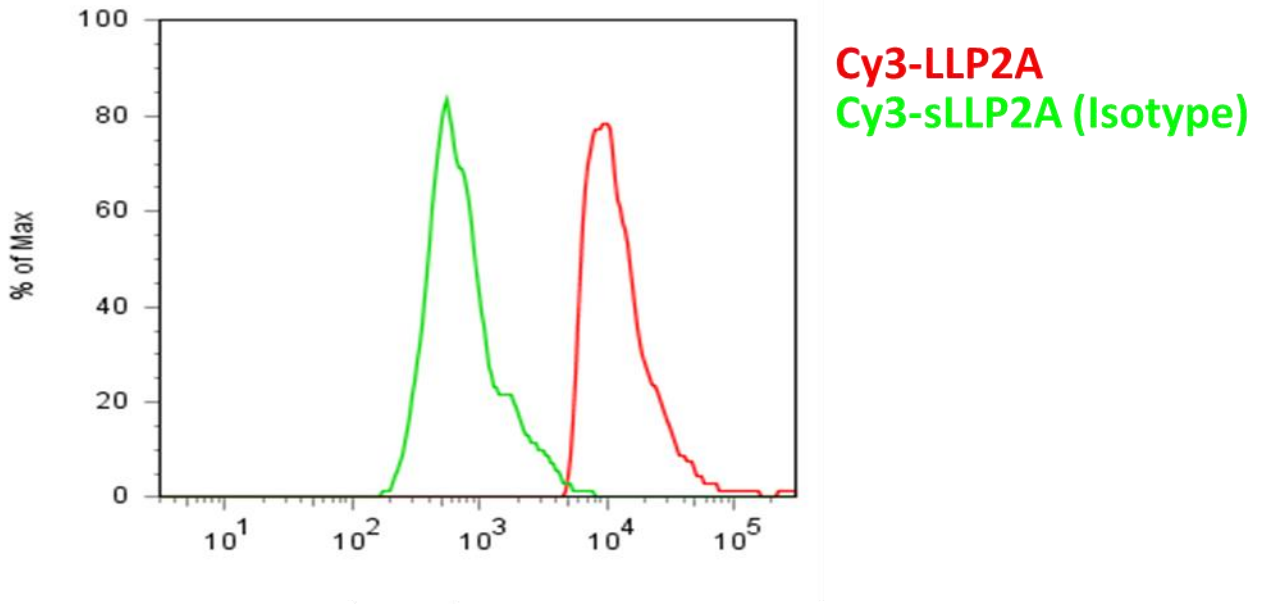
Supplemental Fig 1. Chemical structure of A) LLP2A B) Cy3-LLP2A and C) Cy3-sLLP2A.



Supplemental Fig. 2. Cy3-LLP2A and Cy3-sLLP2A distribution in live cells with Side Scatter (SSC) X-axis and Cy3 signal y-axis. Cy3-sLLP2A (Isotype control) was used to determine as control. Only 1.5 % (n=12) of the isotype Cy3-LLP2A were untaken in live cells via flow cytometry whereas 60.1 % (n=12) of Cy3-LLP2A was untaken in live cells from the collected tumor.



Supplemental Fig. 3. The histogram of Cy3-LLP2A and Cy3-scambled LLP2A in collected B16F10 tumor cells (gate live cells). There is no correlation between Cy3-LLP2A and Cy3-sLLP2A localization in B16F10 tumor cells.



Supplemental Fig. 4. Representative contour plot of immune cell markers from collected B16F10 tumor 4 h after injection of Cy3-LLP2A.

