**Supplemental Figure 1.** Immunohistochemistry and H&E staining of WRJ388 tumors from the control group and the experimental group. The whole lung was dissected from nude mice with subcutaneous WRJ388 tumors. 5-µm-thick formalin-fixed paraffin-embedded mouse tumor lung sections were used for H&E or TTF-1 IHC analyses. These samples were blinded and analyzed by a lung cancer pathologist (G. Sica). Reds squares and black arrows indicated the location of lung adenocarcinoma metastasis in H&E slides at 2x or 10x magnification, respectively.
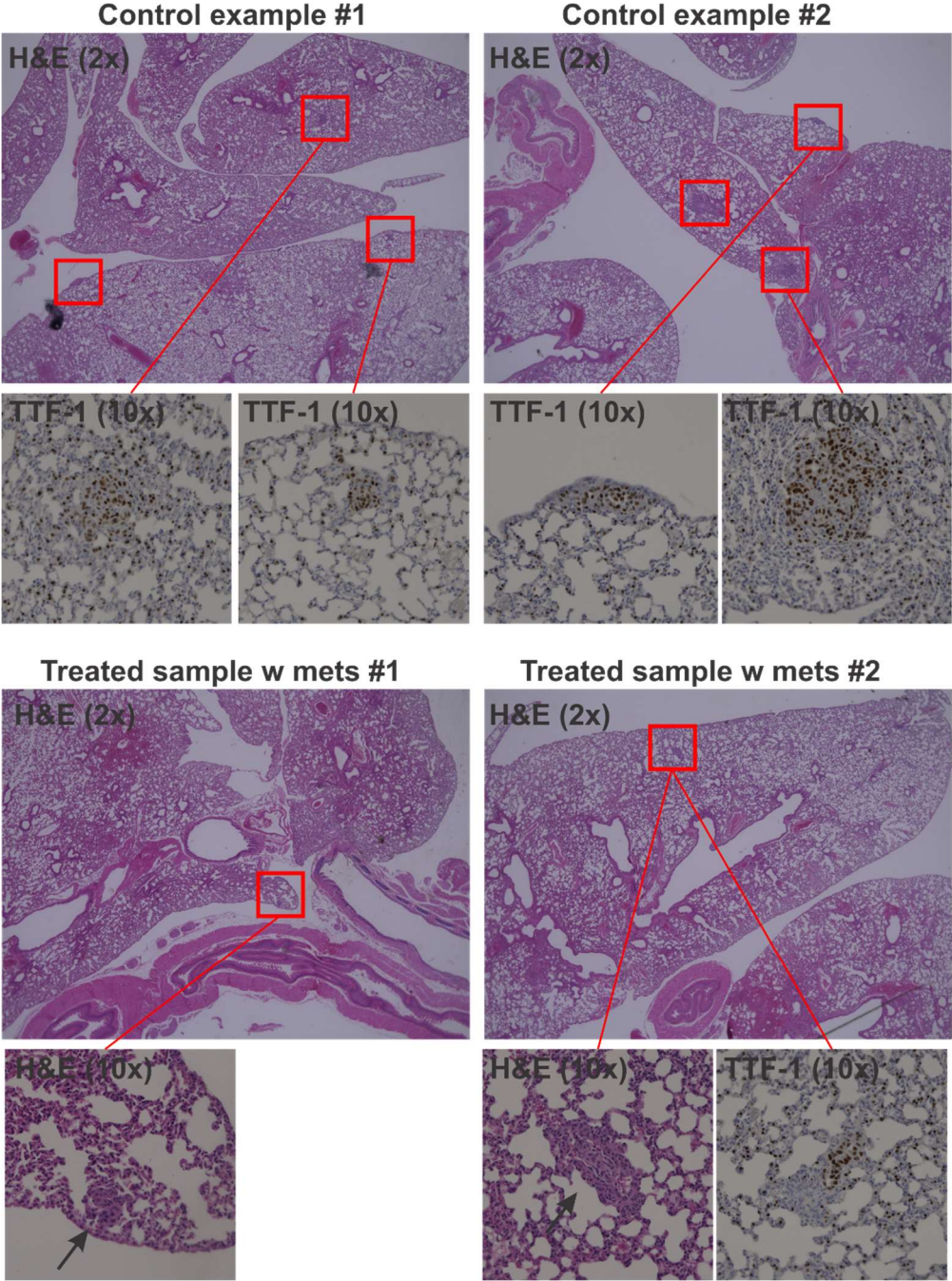
**Supplemental Figure 2.** Leflunomide dose-response in WRJ388 cells isolated from a leflunomide-resistant subcutaneous tumor. Leflunomide treatment significantly attenuated the growth of WRJ388 cells *in vivo* initially, but tumor growth resumed in the treated mice from day 22-24 (Figure 6B), and tumor number 9 (Figure 6D, bottom row) had the most significant growth. Cancer cells were isolated from this tumor and treated with leflunomide using SRB assay similar to the ones described in Figure 5B to determine leflunomide dose-response at Days 2 and 4.



Day 2 IC50=56.68 $R^2$=0.94
Day 4 IC50=28.67 $R^2$=0.94

Cell Growth (%) vs Leflunomide (uM)
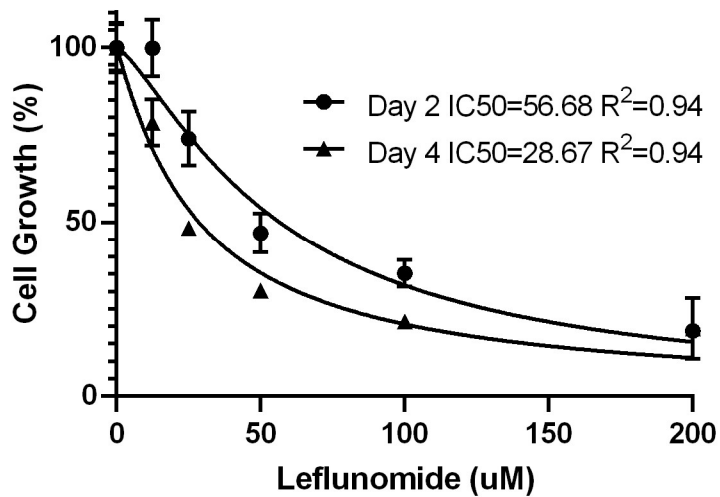
**Supplemental Table 1.  Leflunomide treatment of HeLa xenograft**

**Table 1A. Log (tumor volume) across experiment groups at different time points**

| Days | Group | Mean (Std.Err) | p-value | Adjusted  P-value* |
|------|-------|----------------|---------|---------------------|
| 0 | control | 4.879 (0.131) | 0.115 | 0.575 |
| 0 | treatment | 4.571 (0.131) | . | |
| 3 | control | 5.12 (0.12) | <.001 | <0.005 |
| 3 | treatment | 4.44 (0.12) | . | |
| 6 | control | 5.361 (0.113) | <.001 | <0.005 |
| 6 | treatment | 4.309 (0.113) | . | |
| 12 | control | 5.844 (0.115) | <.001 | <0.005 |
| 12 | treatment | 4.048 (0.115) | . | |
| 21 | control | 6.567 (0.152) | <.001 | <0.005 |
| 21 | treatment | 3.656 (0.152) | . | |

*p-value is adjusted for the multiple comparisons by Bonferroni method.

**Table 1B. Xenograft growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Growth Rate - Treatment | -0.044 (0.008) | <.001 |
| Growth Rate - Control | 0.08 (0.008) | . |

**Table 1C. Analysis of final tumor weight**

| Level | N | Mean | Median | ANOVA P-value | Kruskal-Wallis P-value |
|-------|---|------|--------|---------------|------------------------|
| Control | 9 | 0.38 | **0.22** | 0.004 | <0.001 |
| Treatment | 9 | 0.02 | 0.01 | | |

**Table 1D. Animal weight across experiment groups at different time points**

| Days | Group | Mean (Std.Err) | p-value | Adjusted  P-value* |
|------|-------|----------------|---------|---------------------|
| 0 | control | 20.814 (0.499) | 0.327 | 0.999 |
| 0 | treatment | 20.101 (0.499) | . | |
| 3 | control | 21.026 (0.485) | 0.239 | 0.999 |
| 3 | treatment | 20.186 (0.485) | . | |
| 6 | control | 21.237 (0.478) | 0.172 | 0.86 |
| 6 | treatment | 20.272 (0.478) | . | |
| 12 | control | 21.661 (0.48) | 0.092 | 0.46 |
| 12 | treatment | 20.442 (0.48) | . | |
| 21 | control | 22.366 (0.534) | 0.045 | 0.225 |
| 21 | treatment | 20.727 (0.534) | . | |

*p-value is adjusted for the multiple comparisons by Bonferroni method.

**Table 1E. Animal weight growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Growth Rate - Treatment | 0.028 (0.018) | 0.099 |
| Growth Rate - Control | 0.071 (0.018) | . |

**Supplemental Table 2.  Leflunomide treatment of H460-xenografts**

**Table 2A. Log (tumor volume) across experiment groups at different time points**

| Day | Group | Mean (Std.Err) | p-value | Adjusted  P-value* |
|-----|-------|----------------|---------|--------------------|
| 0 | Control | 4.126 (0.2) | 0.669 | 0.999 |
| 0 | Treatment | 4.003 (0.2) | . | . |
| 4 | Control | 4.824 (0.194) | 0.266 | 0.999 |
| 4 | Treatment | 4.508 (0.194) | . | . |
| 9 | Control | 5.696 (0.191) | 0.054 | 0.324 |
| 9 | Treatment | 5.139 (0.191) | . | . |
| 14 | Control | 6.568 (0.191) | 0.009 | 0.054 |
| 14 | Treatment | 5.769 (0.191) | . | . |
| 18 | Control | 7.266 (0.194) | 0.002 | 0.012 |
| 18 | Treatment | 6.274 (0.194) | . | . |
| 23 | Control | 8.138 (0.201) | <.001 | <0.006 |
| 23 | Treatment | 6.905 (0.201) | . | . |

*p-value is adjusted for the multiple comparisons by Bonferroni method.

**Table 2B. Xenograft growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Growth Rate - Treatment | 0.126 (0.005) | <.001 |
| Growth Rate - Control | 0.174 (0.005) | . |

**Table 2C. Analysis of final tumor weight**

| Level | N | Mean | Median | ANOVA P-value | Kruskal-Wallis P-value |
|-------|---|------|--------|---------------|------------------------|
| Control | 10 | 2.78 | 3.05 | <.001 | 0.004 |
| Treatment | 10 | 1.00 | **0.88** | | |

**Table 2D. Animal weight across experiment groups at different time points**

| Day | Group | Mean (Std.Err) | p-value | Adjusted  P-value* |
|-----|-------|----------------|---------|--------------------|
| 0 | Control | 18.723 (0.403) | 0.372 | 0.999 |
| 0 | Treatment | 19.245 (0.403) | . | . |
| 4 | Control | 18.966 (0.391) | 0.676 | 0.999 |
| 4 | Treatment | 19.201 (0.391) | . | . |
| 9 | Control | 19.271 (0.383) | 0.822 | 0.999 |
| 9 | Treatment | 19.147 (0.383) | . | . |
| 14 | Control | 19.575 (0.384) | 0.386 | 0.999 |
| 14 | Treatment | 19.093 (0.384) | . | . |
| 18 | Control | 19.819 (0.39) | 0.181 | 0.999 |
| 18 | Treatment | 19.05 (0.39) | . | . |
| 23 | Control | 20.123 (0.406) | 0.065 | 0.39 |
| 23 | Treatment | 18.996 (0.406) | . | . |

*p-value is adjusted for the multiple comparisons by Bonferroni method.

**Table 2E. Animal weight growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Growth Rate - Treatment | -0.011 (0.011) | <.001 |
| Growth Rate - Control | 0.061 (0.011) | . |

**Supplemental Table 3.  Leflunomide treatment of LKB1-mutant PDX**

**Table 3A. Log (tumor volume) across experiment groups at different time points**

| Days | Group | Estimated Mean (Std.Err)* | p-value | Adjusted  P-value** |
|------|-------|---------------------------|---------|---------------------|
| 0 | Control | 5.305 (0.109) | 0.927 | 0.9990 |
| 0 | Treated | 5.32 (0.109) | | |
| 7 | Control | 5.749 (0.105) | 0.063 | 0.3155 |
| 7 | Treated | 5.428 (0.105) | | |
| 14 | Control | 6.192 (0.104) | 0.002 | 0.0104 |
| 14 | Treated | 5.536 (0.104) | | |
| 21 | Control | 6.636 (0.104) | <.001 | 0.0008 |
| 21 | Treated | 5.644 (0.105) | | |
| 28 | Control | 7.079 (0.107) | <.001 | 0.0001 |
| 28 | Treated | 5.753 (0.108) | | |

*the estimation is based on the linear mixed-effect model assuming a linear growth of tumor volume.
**This p-value is adjusted for multiple comparisons by Bonferroni method.

**Table 3B. PDX growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Growth Rate - Treatment | 0.015 (0.002) | <.001 |
| Growth Rate - Control | 0.063 (0.002) | . |

**Table 3C. Analysis of final PDX tumor weight**

| Level | N | Mean (SD) | Median | ANOVA P-value | Kruskal-Wallis P-value |
|-------|---|-----------|--------|---------------|------------------------|
| Control | 5 | 1.42 (1.27) | 0.89 | 0.093 | **0.009** |
| Treatment | 5 | 0.32 (0.16) | 0.30 | | |

**Table 3D. Animal weight across experiment groups at different time points**

| Days | Group | Mean (Std.Err) | p-value | Adjusted  P-value* |
|------|-------|----------------|---------|--------------------|
| 0 | Control | 24.047 (0.512) | 0.010 | 0.051 |
| 0 | Treated | 26.468 (0.512) | | |
| 7 | Control | 24.307 (0.505) | 0.020 | 0.099 |
| 7 | Treated | 26.377 (0.505) | | |
| 14 | Control | 24.567 (0.502) | 0.042 | 0.209 |
| 14 | Treated | 26.286 (0.502) | | |
| 21 | Control | 24.828 (0.503) | 0.091 | 0.455 |
| 21 | Treated | 26.194 (0.504) | | |
| 28 | Control | 25.088 (0.508) | 0.196 | 0.982 |
| 28 | Treated | 26.103 (0.51) | | |

The estimation is based on the linear mixed-effect model assuming a linear growth of tumor volume. *p-value is adjusted for the multiple comparisons by Bonferroni method.

**Table 3E. Animal weight growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Growth Rate - Treatment | -0.013 (0.007) | <.001 |
| Growth Rate - Control | 0.037 (0.007) | . |

**Supplemental Table 4.  Univariate Association with Leflunomide treatment in GEMM**

| Covariate | Statistics | Level | Group | | Parametric P-value* | Non-Parametric P-value** |
| | | | Cont N=10 | Trt N=10 | | |
| --- | --- | --- | --- | --- | --- | --- |
| Percentage Change of BLI from Day0 | N | | 10 | 10 | **0.006** | **0.003** |
| | Mean | | 129.08 | 32.36 | | |
| | Median | | 89.59 | 18.2 | | |
| | Min | | 55.69 | 5.92 | | |
| | Max | | 330.98 | 76.86 | | |
| | Std Dev | | 92.74 | 28.76 | | |
| Percentage Change of Animal Weight from Day0 | N | | 10 | 10 | 0.151 | 0.096 |
| | Mean | | -0.13 | -0.05 | | |
| | Median | | -0.09 | -0.02 | | |
| | Min | | -0.34 | -0.34 | | |
| | Max | | 0 | 0.07 | | |
| | Std Dev | | 0.11 | 0.11 | | |
| Lung Weight(g) at Day 44 | N | | 10 | 10 | **0.021** | **0.023** |
| | Mean | | 0.51 | 0.38 | | |
| | Median | | 0.51 | 0.36 | | |
| | Min | | 0.34 | 0.27 | | |
| | Max | | 0.78 | 0.63 | | |
| | Std Dev | | 0.14 | 0.1 | | |

*  The parametric p-value is calculated by ANOVA.
** The non-parametric p-value is calculated by the Kruskal-Wallis test.

**Supplemental Table 5. Leflunomide treatment of WRJ388 subcutaneous tumor**

**Table 5A. Log (tumor volume) across experiment groups at different time points**

| Days | Group | Mean (Std.Err) | p-value | Adjusted P-value* |
|------|-------|----------------|---------|-------------------|
| 0 | Control | 5.003 (0.087) | 0.808 | 0.999 |
| 0 | Treatment | 5.034 (0.092) | | |
| 2 | Control | 5.182 (0.085) | 0.462 | 0.999 |
| 2 | Treatment | 5.09 (0.089) | | |
| 4 | Control | 5.361 (0.083) | 0.089 | 0.999 |
| 4 | Treatment | 5.145 (0.087) | | |
| 7 | Control | 5.63 (0.08) | 0.003 | 0.040 |
| 7 | Treatment | 5.229 (0.085) | | |
| 9 | Control | 5.81 (0.079) | <.001 | 0.004 |
| 9 | Treatment | 5.285 (0.084) | | |
| 11 | Control | 5.989 (0.079) | <.001 | <.001 |
| 11 | Treatment | 5.34 (0.083) | | |
| 13 | Control | 6.168 (0.078) | <.001 | <.001 |
| 13 | Treatment | 5.396 (0.083) | | |
| 15 | Control | 6.348 (0.079) | <.001 | <.001 |
| 15 | Treatment | 5.452 (0.083) | | |
| 17 | Control | 6.527 (0.08) | <.001 | <.001 |
| 17 | Treatment | 5.507 (0.084) | | |
| 19 | Control | 6.706 (0.081) | <.001 | <.001 |
| 19 | Treatment | 5.563 (0.085) | | |
| 21 | Control | 6.886 (0.082) | <.001 | <.001 |
| 21 | Treatment | 5.619 (0.087) | | |
| 23 | Control | 7.065 (0.084) | <.001 | <.001 |
| 23 | Treatment | 5.675 (0.089) | | |
| 24 | Control | 7.155 (0.085) | <.001 | <.001 |
| 24 | Treatment | 5.702 (0.09) | | |

*p-value is adjusted for the multiple comparisons by Bonferroni method.

**Table 5B. Xenograft growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Growth Rate - Treatment | 0.028 (0.003) | <.001 |
| Growth Rate - Control | 0.09 (0.003) | |

**Table 5C. Analysis of final tumor weight (g)**

| Group | Mean (Std.Err) | p-value |
|-------|----------------|---------|
| Treatment | 0.0218(0.0954) | 0.0002 |
| Control | 0.794 (0.3094) | |

**Table 5D. Animal weight across experiment groups at different time points**

| Days | Group | Mean (Std.Err) | p-value | Adjusted p-value* |
|------|-------|----------------|---------|-------------------|
| 0 | Control | 20.015 (0.337) | 0.447 | 0.999 |
| 0 | Treatment | 19.633 (0.356) | | |
| 2 | Control | 20.014 (0.329) | 0.556 | 0.999 |
| 2 | Treatment | 19.727 (0.347) | | |

| | | | | |
|---|---|---|---|---|
| 4 | Control | 20.013 (0.323) | 0.686 | 0.999 |
| 4 | Treatment | 19.82 (0.34) | | |
| 7 | Control | 20.011 (0.315) | 0.913 | 0.999 |
| 7 | Treatment | 19.96 (0.332) | | |
| 9 | Control | 20.01 (0.311) | 0.924 | 0.999 |
| 9 | Treatment | 20.054 (0.328) | | |
| 11 | Control | 20.009 (0.309) | 0.763 | 0.999 |
| 11 | Treatment | 20.147 (0.326) | | |
| 13 | Control | 20.008 (0.309) | 0.611 | 0.999 |
| 13 | Treatment | 20.241 (0.326) | | |
| 15 | Control | 20.007 (0.31) | 0.478 | 0.999 |
| 15 | Treatment | 20.334 (0.327) | | |
| 17 | Control | 20.006 (0.312) | 0.366 | 0.999 |
| 17 | Treatment | 20.428 (0.329) | | |
| 19 | Control | 20.005 (0.316) | 0.277 | 0.999 |
| 19 | Treatment | 20.521 (0.333) | | |
| 21 | Control | 20.004 (0.321) | 0.209 | 0.999 |
| 21 | Treatment | 20.615 (0.339) | | |
| 23 | Control | 20.003 (0.328) | 0.157 | 0.999 |
| 23 | Treatment | 20.708 (0.346) | | |
| 24 | Control | 20.003 (0.332) | 0.137 | 0.999 |
| 24 | Treatment | 20.755 (0.35) | | |

*p-value is adjusted for the multiple comparisons by Bonferroni method.

**Table 5E. Animal weight growth rate across two experiment groups**

| Group | Mean (Std.Err) | p-value |
|---|---|---|
| Growth Rate - Treatment | 0.047 (0.011) | 0.003 |
| Growth Rate - Control | -0.001 (0.011) | |

**Table 5F. The BLI signals ($1 \times 10^5$) in the lung for both experiment groups**

| Statistics | Control (N=10) | Treatment (N=9) | Parametric p-value* |
|---|---|---|---|
| N | 10 | 9 | **0.008** |
| Mean | 97.58 | 6.58 | |
| Median | 68.23 | 5.88 | |
| Min | 9.01 | 1.09 | |
| Max | 249.8 | 20.76 | |

*The parametric p-value is calculated by ANOVA (two-sample t-test for two-group comparison)