

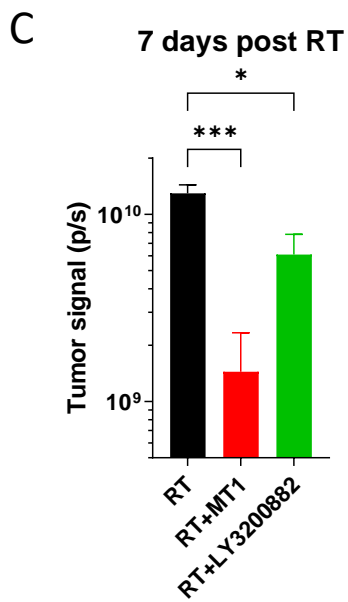
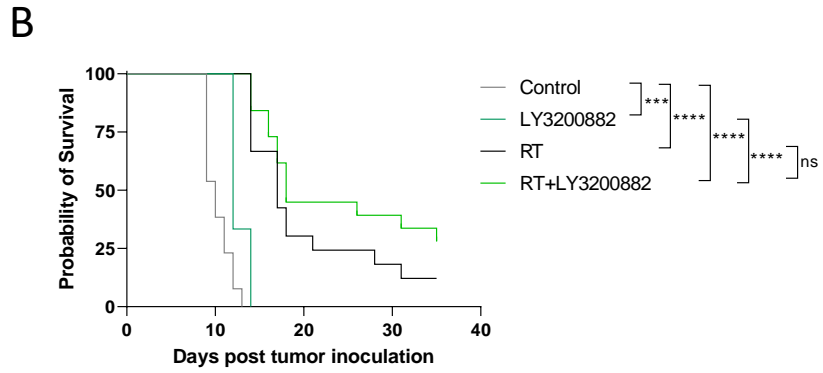
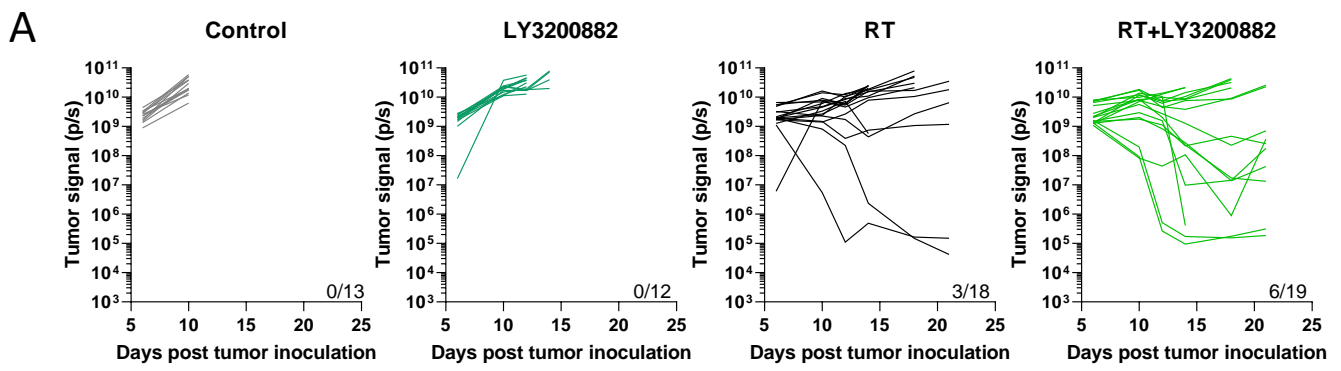
1 **Supplementary Figure 1: TGFβR1 inhibition improves radiotherapy efficacy against head and**
2 **neck orthotopic tumors. (A)** Quantification of the bioluminescent signal from individual
3 tumors was performed at different time points post treatment in mice treated with the
4 TGFβR1 inhibitor LY3200882, RT or RT+ LY3200882 7 days after TC1/Luc inoculation (n = 12-
5 19 mice/group from 2 independent experiments). **(B)** Kaplan-Meier survival curves. **(C)** Tumor
6 signals were quantified by bioluminescence *in vivo* imaging 7 days post radiotherapy for each
7 indicated group. For all panels: *: p<0.05; ***: p<0.001; ****: p<0.0001; ns: non-significant (**B**
8 log-rank test, **C** one-way ANOVA with Tukey's multiple comparison test).

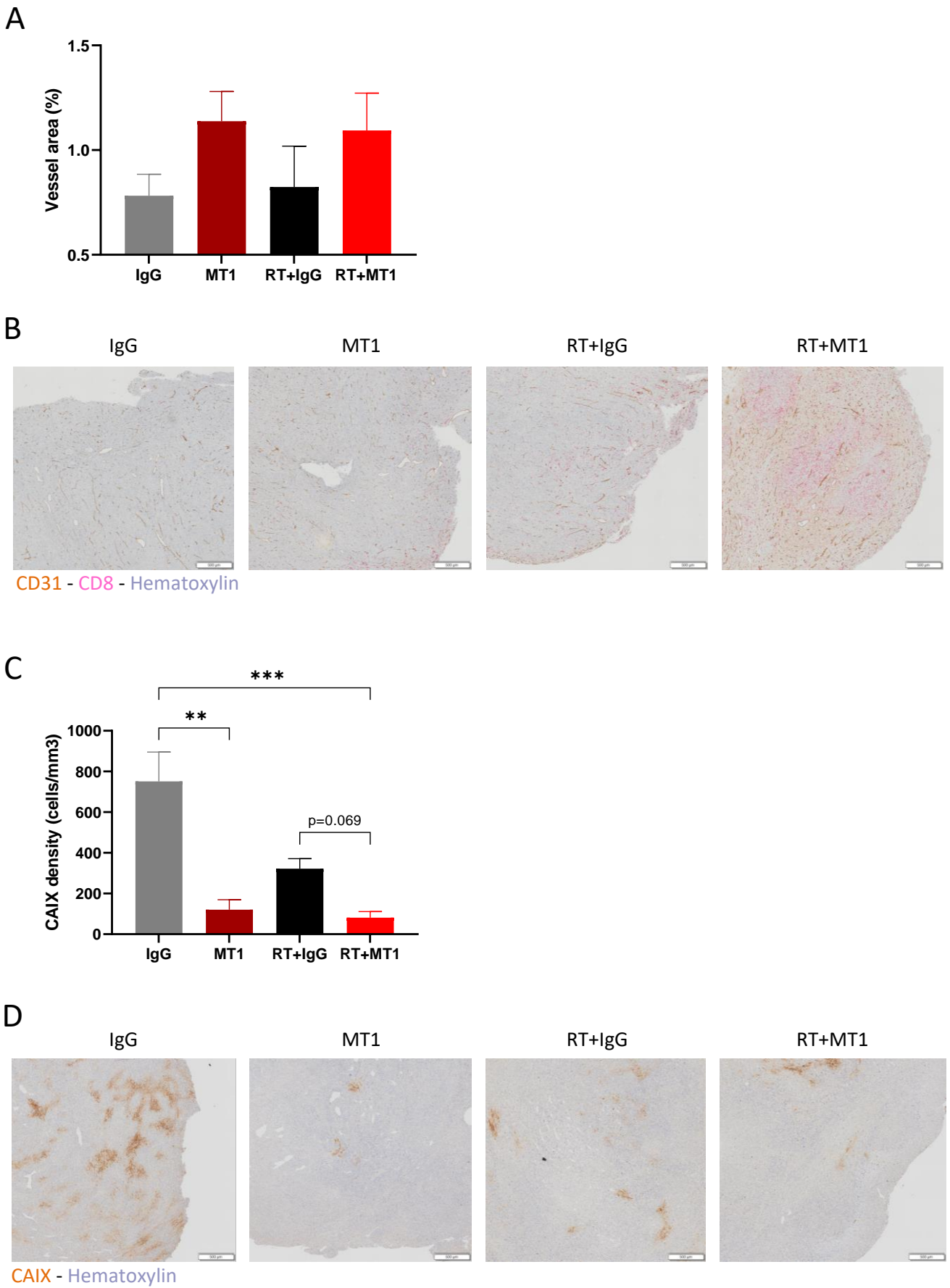
9 **Supplementary Figure 2: Combination of RT and MT1 modulates tumor vascularization and**
10 **hypoxia. (A)** Histogram representing the percent of TC1/Luc tumor vascularization,
11 representing the % of the area covered by CD31-positive vessels by IHC for each group. **(B)**
12 Representative images of the co-staining of CD8 (pink) and CD31 (red) by IHC on head and
13 neck tumors. **(C)** Histogram shows the density of CAIX+ cells by IHC to quantify hypoxia in the
14 tumors of the different groups. **(D)** Representative images of the CAIX staining. For A-B, D,
15 n=8-9 mice from 2 independent experiments, **: p<0.01; ***: p<0.001 (Kruskal-Wallis with
16 Dunn's multiple comparison test).

17 **Supplementary Figure 3: Immunodeficient mice do not respond to the RT+MT1**
18 **combination. (A)** Quantification of the bioluminescent signal from individual tumors was
19 performed at different time points post treatment in immunodeficient nude mice. **(B)** Kaplan-
20 Meier mouse survival curves. For all panels: n = 7-8 mice/group from one experiment, ***:
21 p<0.001; ****: p<0.0001.

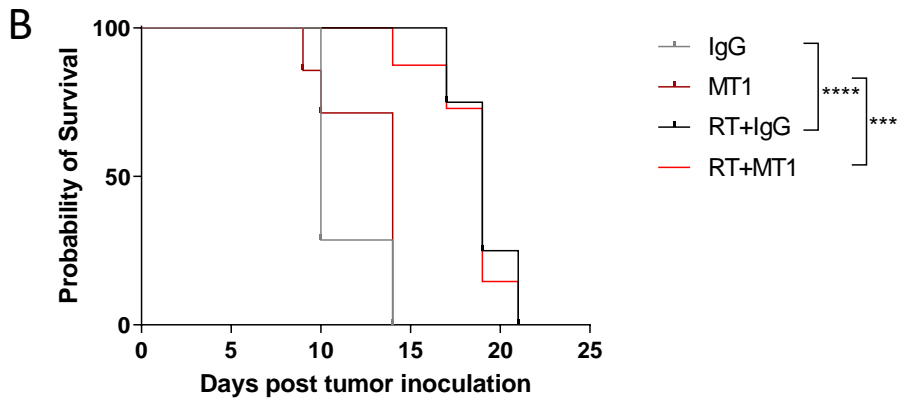
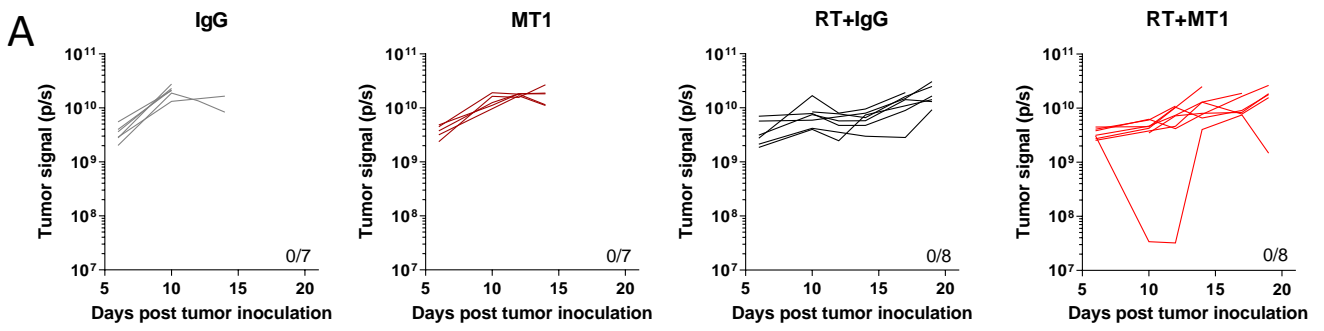
1 **Supplementary Figure 4: TGF β R2 blockade induce IFN β production by macrophages**
2 **following radiotherapy in head and neck and lung tumor models. (A)** Mice were injected with
3 SCC VII cells at a submucoal site in the inner lip to establish a head and neck model. They were
4 then irradiated and treated with or without MT1 before sacrifice and tumor macrophages
5 sorting (left panel). The right panel represents the quantification of IFN β mRNA in the sorted
6 tumor macrophages analyzed by qPCR. **(B)** Orthotopic lung tumor model was established by
7 transpleural injection of LL2/Luc in the lung. Mice were then irradiated and treated or not with
8 MT1 before sacrifice and macrophage sorting (left panel). The right panel shows the
9 quantification of IFN β mRNA in the sorted tumor macrophages analyzed by qPCR. For all
10 panels: **: p<0.01; (Welch's t test).

11 **Supplementary Figure 5: Anti-IFNAR administration impairs the RT and MT1 combination**
12 **efficacy. (A)** Quantification of the bioluminescent signal from individual TC1/Luc tumors was
13 performed at different time points post treatment in the different groups treated with anti-
14 IFNAR (IFNAR) antibody or isotype control (IgG) (n = 6-12 mice from 2 independent
15 experiments). **(B)** Quantification of the tumor vascularization (% of the area covered by CD31-
16 positive vessels) by IHC for each group. **(C)** Histogram shows the density of CAIX positive cells
17 by IHC to quantify hypoxia in the tumors of the different groups. **(D)** Kaplan-Meier survival
18 curves of SCC VII head and neck model in the different groups (n=5-12 mice per groups from
19 2 independent experiments). **(E)** Kaplan-Meier survival curves of LL2/Luc orthotopic lung
20 tumor model in the different groups (n=4-6 mice per groups from 2 independent
21 experiments). For all panels, *: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001 (C one-way
22 ANOVA with Tukey's multiple comparison test, D-E log-rank test).

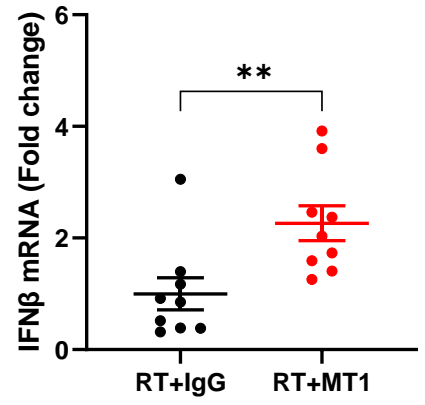
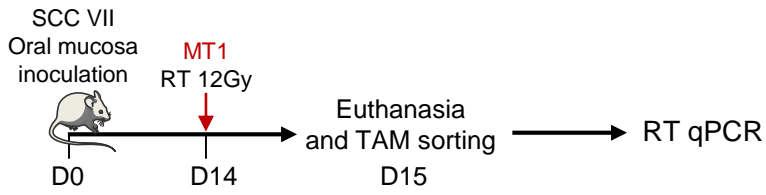




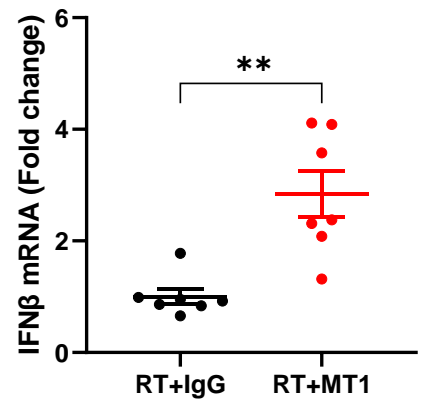
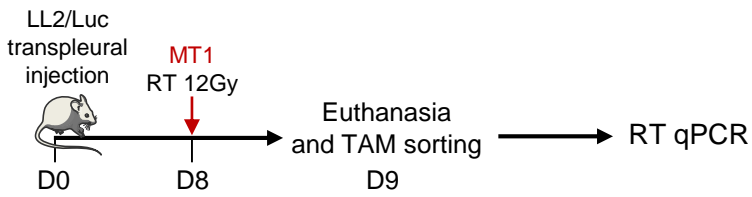
Supplementary Figure 2

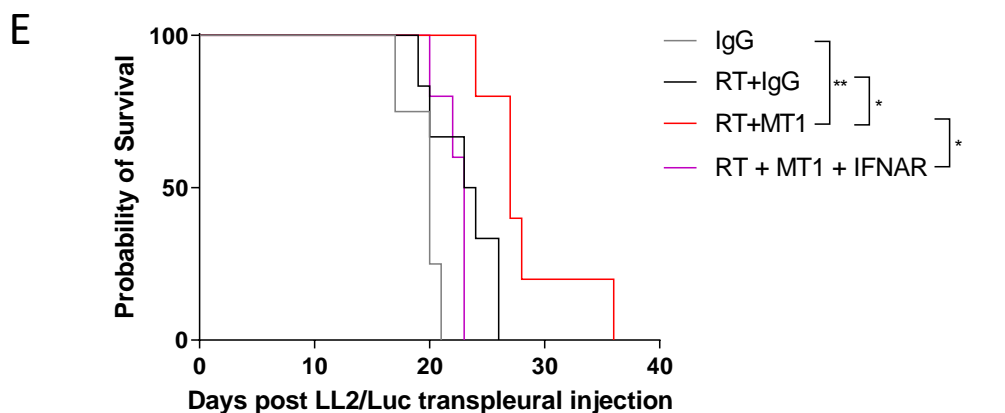
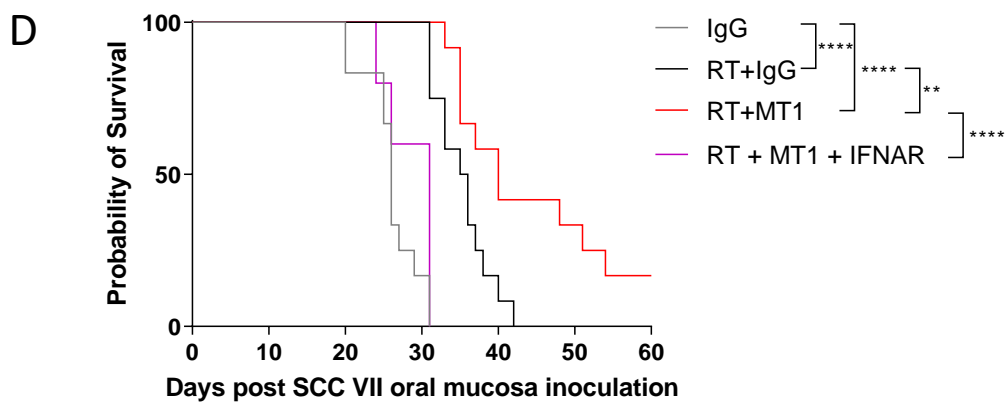
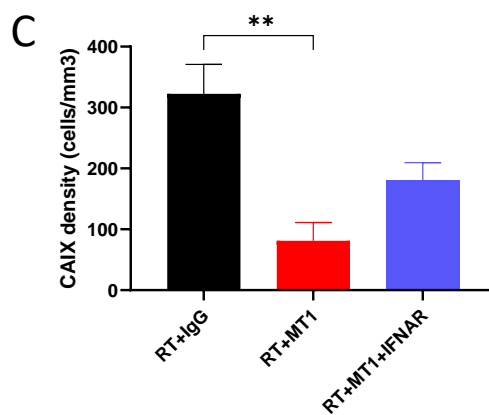
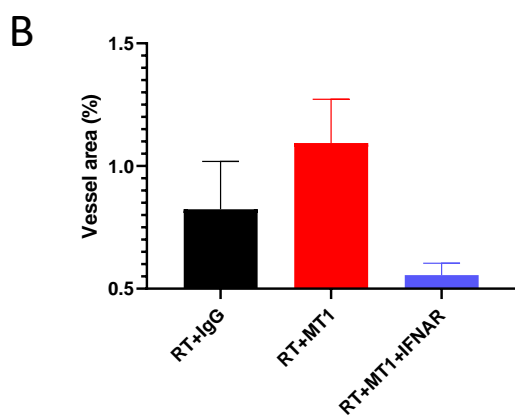
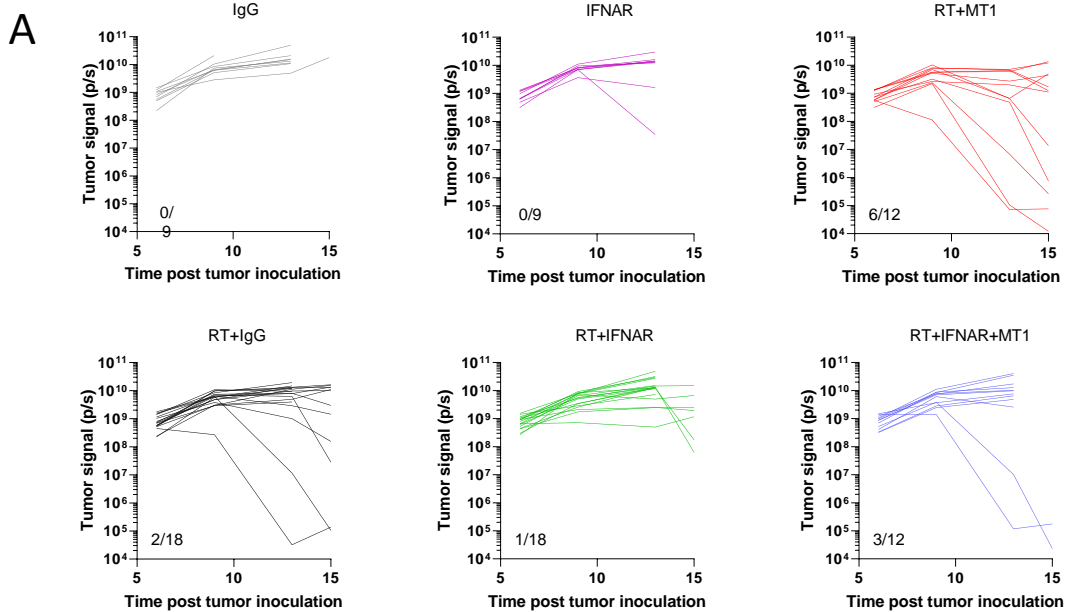


A



B





Supplementary Figure 5