Supplemental Figure Legend

Supplemental Figure 1

(**A**) Principal component analysis of gene expression of Panc-1 and BxPC3 cells. All controls: [Ctrl: untreated cells, Ctrl Exo: control exosomes (no siRNA payload), Scr (siScrbl Exo), sirnaExo (exosomes with $Kras^{G12D}$ siRNA payload)]. (**B-E**) Heat map depicting expression of top 1,000 genes (**B-D**) and differentially expressed genes (statistically significant) (**C-E**) in Panc-1 (**B, C**) and BxPC3 (**D, E**) cells. Red: sirnaExo: exosomes with $Kras^{G12D}$ siRNA payload, black: Scr: siScrl Exo, dark grey: CtrlExo: control exosomes (no siRNA payload), light grey: Ctrl (untreated cells). (**F**) Gene set enrichment plot for significantly down and up-regulated genes in $siKras^{G12D\text{-}1}$ Exo treated Panc-1 cells compared to all controls.

Supplemental Figure 2

(**A**) Sanger sequencing of PDX tumors (n=2 mice), to confirm the G to A base substitution associated with the glycine to aspartic acid mutation at codon 12 (G12D). (**B**) Comparison of quantification of tumor burden pre-treatment (baseline) by ultrasound (US, day 58 post tumor induction), and MRI (day 60 post tumor induction), $siKras^{G12D\text{-}1}$ iExo (n=7) and siScrbl iExo (n=7). Each set of bars for US and MRI represents measures for individual mice. (**C**) Detailed findings from individual PDX mouse treated with $siKras^{G12D\text{-}1}$ iExo (n=7) and siScrbl iExo (n=7), showing survival post treatment start (PTS) and post birth (PB), baseline pre-treatment tumor volumes as measure by both ultrasound (US) and MRI, post-treatment MRI measurements of tumor volume, tumor weight (TW) and body weight

(BW) at end point, and observations at necropsy/euthanasia. No measurements for MRI was recorded if the mice were euthanized or the imaging was of poor quality (CNBM: could not be measured). N/A: not applicable. (**D**) Pictures of H&E stained tissue sections showing lesions of inflammation observed in organs of a siKras^{G12D-1} iExo treated mouse (A1-B). See accompanying source data.

Supplemental Figure 3

(**A**) Number of exosomes per cell per hour determine by NanoSight^{TM} for each MSC donors listed. Donor 3 was used for all subsequent MSCs-derived exosomes studies. Three independent measurements from distinct conditioned media collection are shown. (**B-C**) Flow cytometry analyses histogram plots of the listed cell surface markers for BJ fibroblast cells (B) and mesenchymal stem cells, MSCs (C). The inset numbers depict the percent positive cells. In grey: isotype control. See accompanying source data.

Supplemental Figure 4

(**A**) Schematic detailing the procedure for MSCs bioreactor culture for collection of exosomes (**B**) Schematic of the isolation and electroporation procedures of exosomes from MSCs conditioned media. (**C**) Schematic depicting the generation of MSCs-derived iExosomes.

Supplemental Figure 5

(**A**) Tabulated data depicting the quantitation of total exosomal protein and number of exosomes in each of the 6 consecutive 48 hours harvests of 250 ml MSCs conditioned

media from the bioreactor. The data are also depicted in Figure 3A-C. (**B**) Quantitation of the number of exosomes produced from three distinct bioreactors. (**C**) Quantitation of the levels of glucose and lactose in the bioreactor, for the total duration of bioreactor experiment (21 days). (**D**) Representative histogram of flow cytometry analysis of exosomal markers (CD9, CD63, CD81) and CD47 on exosomes from all bioreactor harvests (Bioreactor harvests 1 and 6 data are also shown in Figure 3E). Inset numbers represent the percent positive beads. In grey: isotype control. See accompanying source data.

Supplemental Figure 6

(**A**) Quantification of apoptosis assayed by flow cytometry analyses in 689KPC cells (n=2 distinct experiments). One-way ANOVA comparing experimental groups to untreated. (**B**) Images of H&E stained tissue sections showing representative lesions observed in the pancreas, liver, spleen and kidney of KPC689 mice at experimental endpoint. Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and MSCs siKras^{G12D-1} iExo (n=6). Scale bar: 100 μm. (**C**) Percent mice with macroscopic metastases in the indicated organs at time of necropsy. Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and MSCs siKras^{G12D-1} iExo (n=6). (**D**) Detailed findings from individual mice with KPC689 tumors treated with Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and BJ siKras^{G12D-1} iExo (n=6), showing survival post treatment start (PTS) and post birth (PB), tumor weight (TW) and body weight (BW), number of lung macrometastases, and observations at necropsy/euthanasia. (**E**) Tumor burden (%) of KPC689 mice at experimental endpoint. Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and MSCs siKras^{G12D-1} iExo (n=6). (**F**) Tumor weights (g: grams) of KPC689

mice at experimental endpoint. Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and MSCs siKras^{G12D-1} iExo (n=6). (**G**) KPC689 orthotopic tumor growth (bioluminescence), and average total flux at day 51, post tumor induction. Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and MSCs siKras^{G12D-1} iExo (n=6). The mean +/- SEM is depicted and statistical tests are listed for relevant panels. ** $p<0.01$. See accompanying source data.

Supplemental Figure 7

(**A**) Detailed findings from individual mice with Panc-1 tumors treated with Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and BJ siKras^{G12D-1} iExo (n=6), showing survival post treatment start (PTS) and post birth (PB), tumor weight (TW) and body weight (BW), and observations at necropsy/euthanasia. ** this tumor weight was not included; the pancreas of this mouse was found grossly and histopathologically normal. (**B**) Pictures of H&E stained sections of tumors from Panc-1 tumor bearing mice. Control Exo (n=5), MSCs siKras^{G12D-1} iExo, CB (n=5), MSCs siKras^{G12D-1} iExo, RB (n=4), BJ siKras^{G12D-1} iExo, RB (n=5). Scale bars: 100 μm (top) and 50 μm (bottom). These data are also depicted in Figure 4O. (**C**) Representative pictures of luciferase activity of Panc-1 orthotopic tumors at day 35 and day 84, post tumor induction. Control Exo (n=5), MSCs siKras^{G12D-1} iExo, CB (n=5), MSCs siKras^{G12D-1} iExo, RB (n=4), BJ siKras^{G12D-1} iExo, RB (n=5). (**D**) Panc-1 orthotopic tumor growth (bioluminescence) over time. Control Exo (n=5), MSCs siKras^{G12D-1} iExo, CB (n=5), MSCs siKras^{G12D-1} iExo, RB (n=4), BJ siKras^{G12D-1} iExo, RB (n=5). (**E**) Tumor burden (%) of Panc-1 tumor bearing mice at experimental endpoint. Control Exo (n=5), MSCs siKras^{G12D-1} iExo, CB (n=5), MSCs siKras^{G12D-1} iExo, RB (n=4), BJ siKras^{G12D-1} iExo, RB (n=5). (**F**) Tumor weights (g: grams) of Panc-1 tumor bearing

mice at experimental endpoint. Control Exo (n=5), MSCs siKras^{G12D-1} iExo, CB (n=5), MSCs siKras^{G12D-1} iExo, RB (n=4), BJ siKras^{G12D-1} iExo, RB (n=5). (**G**) Flow cytometry analyses and quantification of apoptosis in Panc-1 cells comparing the efficacy of 48 distinct electroporation conditions (A1-A16; B1-B16; C1-C16) of MSCs and BJ Fibroblast siKras^{G12D} iExosomes, using a large volume electroporation system and CB (n=2 distinct experiments). The electroporation condition subsequently chosen was A-14. The mean +/- SEM is depicted. See accompanying source data.

Supplemental Figure 8

(**A**) Schematic representation of the experiment using KPC689 orthotopic tumor bearing mice (related to experiment in Figure 5E). (**B**) Comparison of baseline tumor bioluminescence (total Flux) pre-treatment, of KPC689 orthotopic experiments 1 and 2, to show baseline tumor measurements pre-treatment of Experiment-2 was higher than that of Experiment-1. Experiment-1: Control Exo (n=4), BJ siKras^{G12D-1} iExo (n=6) and MSCs siKras^{G12D-1} iExo (n=6). Experiment-2: CB/PBS (n=7), Control Exo (n=7), Gemcitabine (n=8), MSCs siKras^{G12D-2} iExo (n=8), Gemcitabine + MSCs siKras^{G12D-2} iExo (n=8). Two-tailed unpaired t test between experiment 1 and 2. (**C**) Detailed findings from individual mice with KPC689 tumors (Experiment-2) treated with CB/PBS (n=7), Control Exo (n=7), Gemcitabine (n=8), MSCs siKras^{G12D-2} iExo (n=8), Gemcitabine + MSCs siKras^{G12D-2} iExo (n=8), showing survival post treatment start (PTS) and post birth (PB), tumor weight (TW) and body weight (BW), number of lung macrometastases, and observations at necropsy/euthanasia. (**D**) Representative images of H&E stained sections of pancreatic tumors from KPC689 tumor bearing mice. Scale bars 100 μm (top)

and 50 µm (bottom). CB/PBS (n=7), Control Exo (n=7), Gemcitabine (n=8), MSCs siKras^{G12D-2} iExo (n=8), Gemcitabine + MSCs siKras^{G12D-2} iExo (n=8). The mean +/- SEM is depicted. See accompanying source data.

Supplemental Figure 9

(**A**) Schematic representation of the experiment using KPC689 orthotopic tumor bearing mice (related to experiment in Figure 5F). (**B**) Detailed findings from individual mice with KPC689 tumors treated with CB/PBS (n=7), Control Exo (n=7), Gemcitabine (n=7), MSCs siKras^{G12D-2} iExo (n=7), Gemcitabine + MSCs siKras^{G12D-2} iExo (n=7), showing survival post treatment start (PTS) and post birth (PB), tumor weight (TW) and body weight (BW), number of lung macrometastases, and observations at necropsy/euthanasia.

Supplemental Figure 10

(**A**) Cytotoxicity tests performed on the blood collected from adult C57Bl/6J mice injected i.p. every other day for 120 days. PBS (n=3), BJ fibroblasts exosomes (n=4). ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen. The grey highlight defines the normal range. (**B**) Representative pictures of H&E stained tissue sections showing lesions of inflammation observed in the mesenteric lymph node, kidney, liver and gall-bladder.

Supplemental Figure 11

(**A**) Immunotyping analyses of spleen, bone marrow and thymus of immunocomptent non-tumor bearing mice administered with the indicated treatments. ‡: these values are not

erroneous despite their similarities. #: this group shows statistical significant differences with exosomes treated mice but not with CB. (**B**) ELISA for IL-6 in the indicated groups. 0 denotes that the levels were below the limits of the assay (not detected).

Supplemental Figure 12

(**A**) Biodistribution in the indicated organs of DiR labeled MSCs exosomes 6 hours post i.v. injection in nude mice (left) or 3 hours post i.v. injection in tumor bearing (KPC689) C57BL/6 mice. DiR only (n=1), DiR labeled MSCs exosomes (n=2). (**B**) Biodistribution in the indicated organs of DiR labeled MSCs exosomes 3 hours post i.p. or i.v. injection of C57BL/6 non-tumor bearing mice. (**C**) Biodistribution in the indicated organs of DiR labeled MSCs exosomes 24 and 48 hours post i.p. injection tumor bearing (KPC689) C57BL/6 mice. These tumors are depicted in Figure 7B.

Supplemental Figure 13

(**A**) Representative dot plot of flow cytometry analyses of apoptosis in Panc-1 cells induced by MSCs siKras^{G12D-2} iExosomes freeze/thaw during 3 and 6 months showing similar efficiency that fresh iExosomes. n=2 independent experiments, quantitation is shown in Figure 6I. (**B**) Detailed findings from individual PKS mice treated with MSCs siKras^{G12D-2} iExo (n=4) and Control Exo (n=5), showing treatment groups, start of treatment, survival of mice, body weight (BW) and tumor weight (TW) at experimental endpoint. See accompanying source data.

Supplementary Table 1

Detailed necropsy analyses of C57BL/6 mice injected i.p. with either empty BJ Fibroblast exosomes (n=4) or PBS (n=3), every other day, for 120 days.

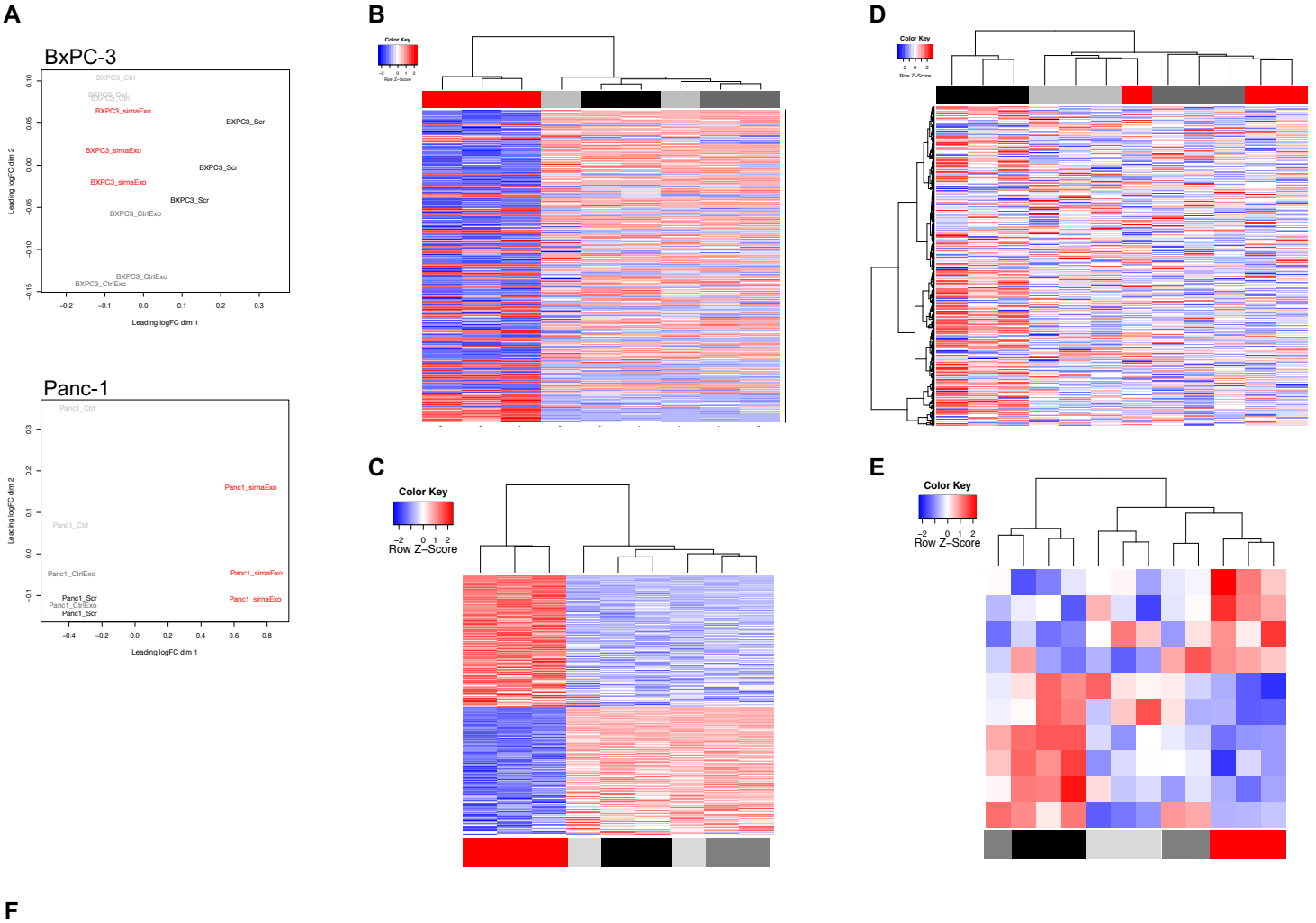
Supplemental Table 2

Summary of treatments for the in vivo experiments.

Supplementary Table 3

Detailed information on the antibodies used in this study.

Supplemental Figure 1



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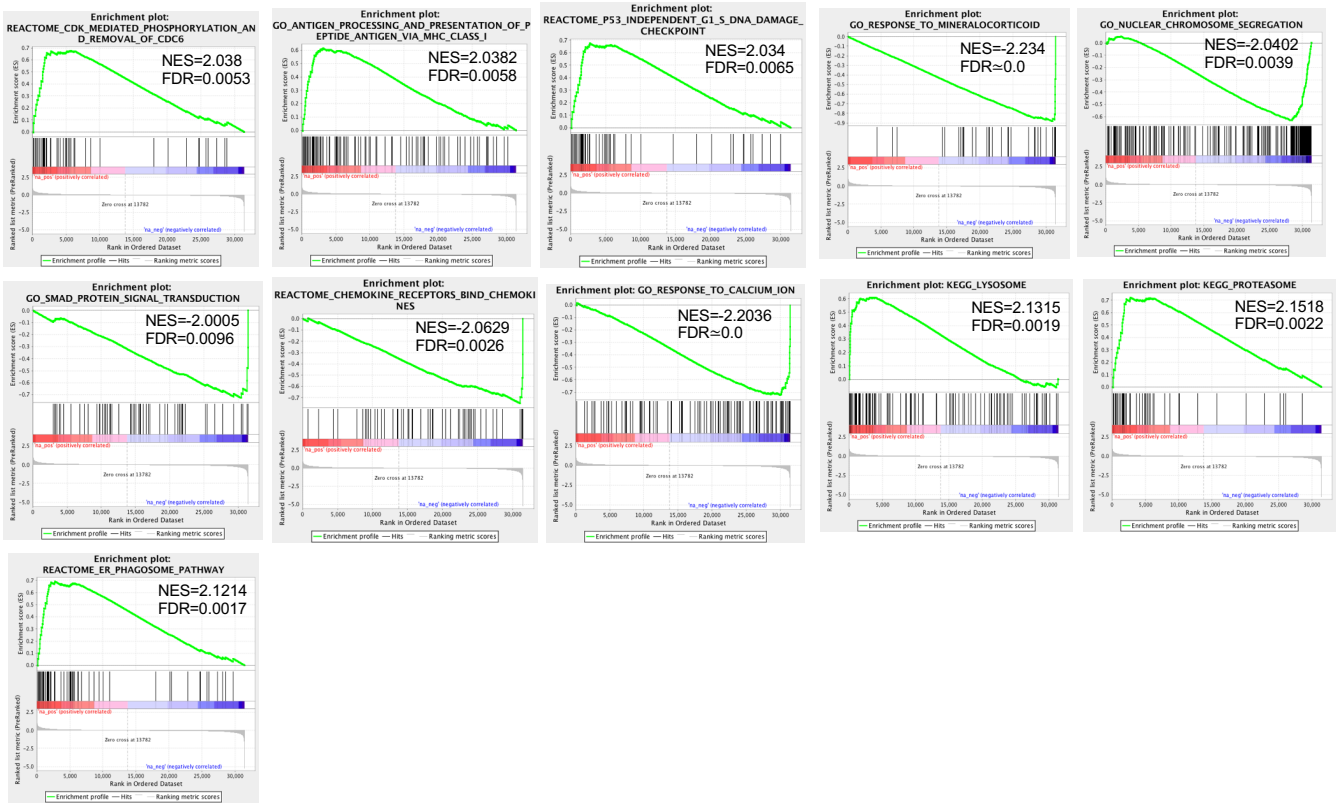
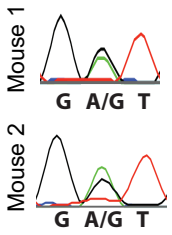


Supplemental Figure 2

A



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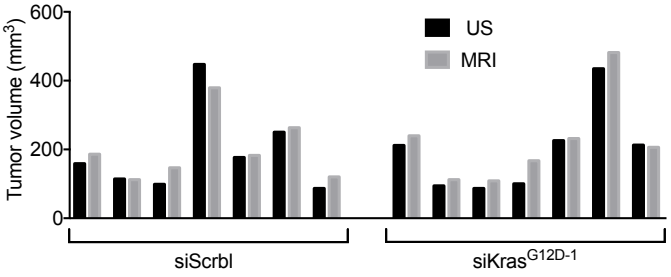
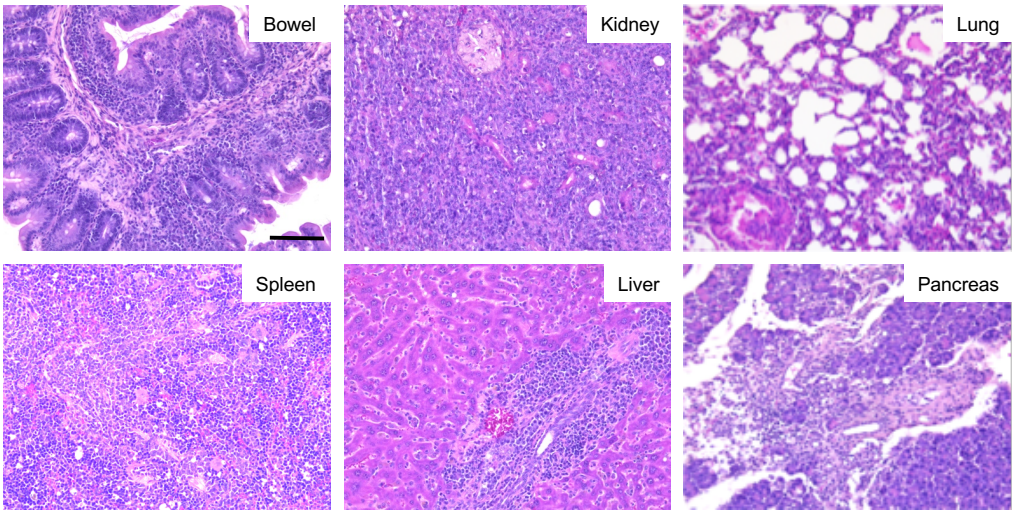
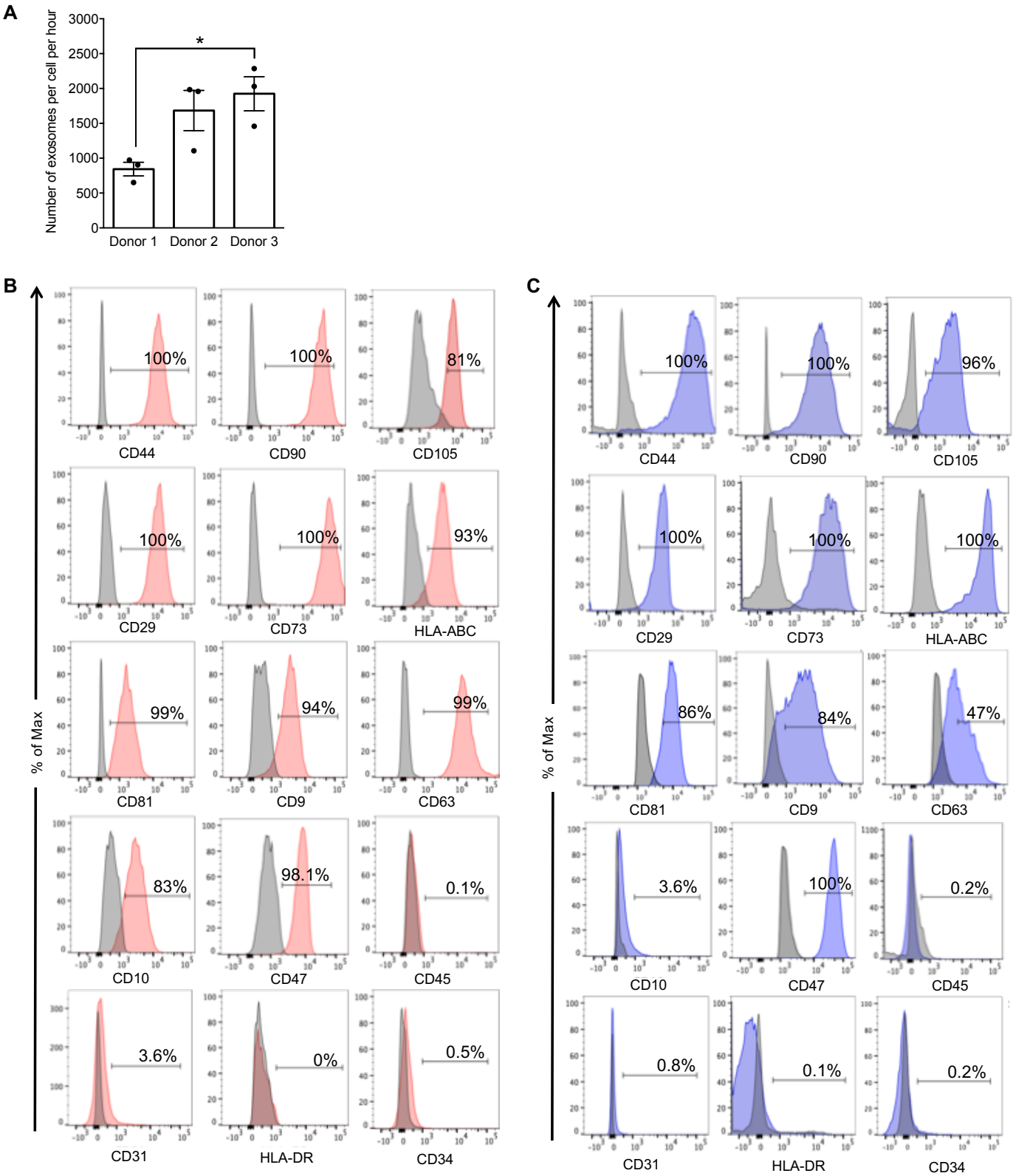


C

		Survival (Days)		Pre-treatment			Post-treatment	Post-treatment	Post-treatment	End-point		Observations	Notes
Mouse ID	Treatment	PTS	PB	Tumor volume (mm3) (US)	Tumor volume (mm3) (MRI)	BW(g)	MRI-2	MRI-3	MRI-4	TW(g)	BW(g)	Necropsy notes	Suspected tumor burden related death
A1-Y	siKrasG12D iExo	133	286	211.87	239.56	23.4	CNBM	CNBM	Euthanized	0.87	28.8	Jaundice, very small tumor burden	No
A1-B	siKrasG12D iExo	316	469	94.49	112.27	24.6	415.44	146.24	26.98	0.38	31.9	Hunched, swollen intestine, kidney atrophy, mesenteric abscess, minimal tumor burden	No
A1-G	siKrasG12D iExo	257	410	86.84	108.52	22.1	515.05	126.97	10.38	0.2	23.8	Hunched, kidney atrophy, minimal tumor buden	No
A1-O	siKrasG12D iExo	360	513	100.08	167.31	25.3	363.45	150.16	63.84	0.24	24.2	Enlarged mesenteric lymph node, minimal tumor burden	No
A1-W	siKrasG12D iExo	254	407	225.92	231.50	23.6	CNBM	212.13	50.44	0.28	28.1	Enlarged eyes, euthanasia due to neurological problems, small tumor	No
A2-Y	siKrasG12D iExo	35	188	434.96	481.62	22.1	642.22	Euthanized	Euthanized	1.4	29.2	Moderate tumor burden, euthanized as an age matched comparison to B1-O	N/A: age-matched
A2-NT	siKrasG12D iExo	178	331	212.71	206.30	25.1	CNBM	965.71	CNBM	1.8	32.2	Small primary tumor, large secondary tumor, euthanized due to tumor burden	Yes
Average:				***195.27***	***221.01***		***484.04***	***320.24***	***37.91***	***0.74***			
B1-Y	siScrbl iExo	206	359	158.60	186.11	25.0	CNBM	654.78	Euthanized	1.21	26.1	Moderate tumor burden, hunched, scaly skin at euthanasia	Yes
B1-B	siScrbl iExo	168	321	114.13	112.30	24.4	773.19	805.08	Euthanized	1.61	26.0	Moderate tumor burden, weak, swollen bowel	Yes
B1-G	siScrbl iExo	144	297	98.81	146.54	23.1	961.41	1977.47	Euthanized	5.84	27.9	Extensive tumor burden, hunched posture, weak	Yes
B1-O	siScrbl iExo	35	188	447.43	379.32	22.9	1254.40	Euthanized	Euthanized	2.3	31.2	Extensive tumor burden, euthanized due to tumor burden, aged matched with A2-Y	Yes
B1-W	siScrbl iExo	102	255	176.84	182.64	24.8	CNBM	2225.12	Euthanized	4.67	34.1	Large primary and secondary tumors, spleen invasion, macroscopic liver nodules	N/A: age-matched
B2-Y	siScrbl iExo	158	311	250.26	263.35	26.1	950.14	CNBM	Euthanized	2.4	28.8	Extensive tumor burden, weak, hunched posture	Yes
B2-NT	siScrbl iExo	69	222	86.75	120.45	25.4	CNBM	969.73	Euthanized	1.69	29.2	Weak, moderate tumor burden, spleen atrophy	Yes
Average:				***190.40***	***198.68***		***984.79***	***1326.43***		***2.82***			

D




A
Number of exosomes per cell per hour
3000
2500
2000
1500
1000
500
0
*
Donor 1
Donor 2
Donor 3
B
% of Max
100%
CD44
100%
CD90
81%
CD105
100%
CD29
100%
CD73
93%
HLA-ABC
99%
CD81
94%
CD9
99%
CD63
83%
CD10
98.1%
CD47
0.1%
CD45
3.6%
CD31
0%
HLA-DR
0.5%
CD34
C
% of Max
100%
CD44
100%
CD90
96%
CD105
100%
CD29
100%
CD73
100%
HLA-ABC
86%
CD81
84%
CD9
47%
CD63
3.6%
CD10
100%
CD47
0.2%
CD45
0.8%
CD31
0.1%
HLA-DR
0.2%
CD34

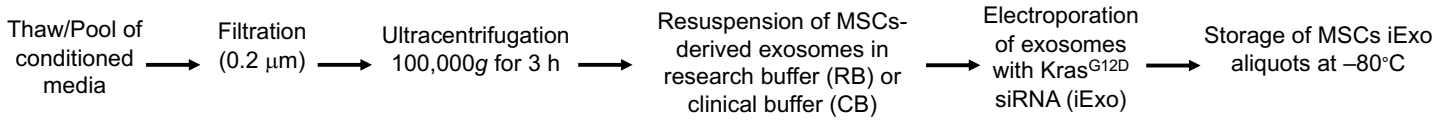
Supplemental Figure 4

A Timeline for MSCs-derived exosomes production using a bioreactor

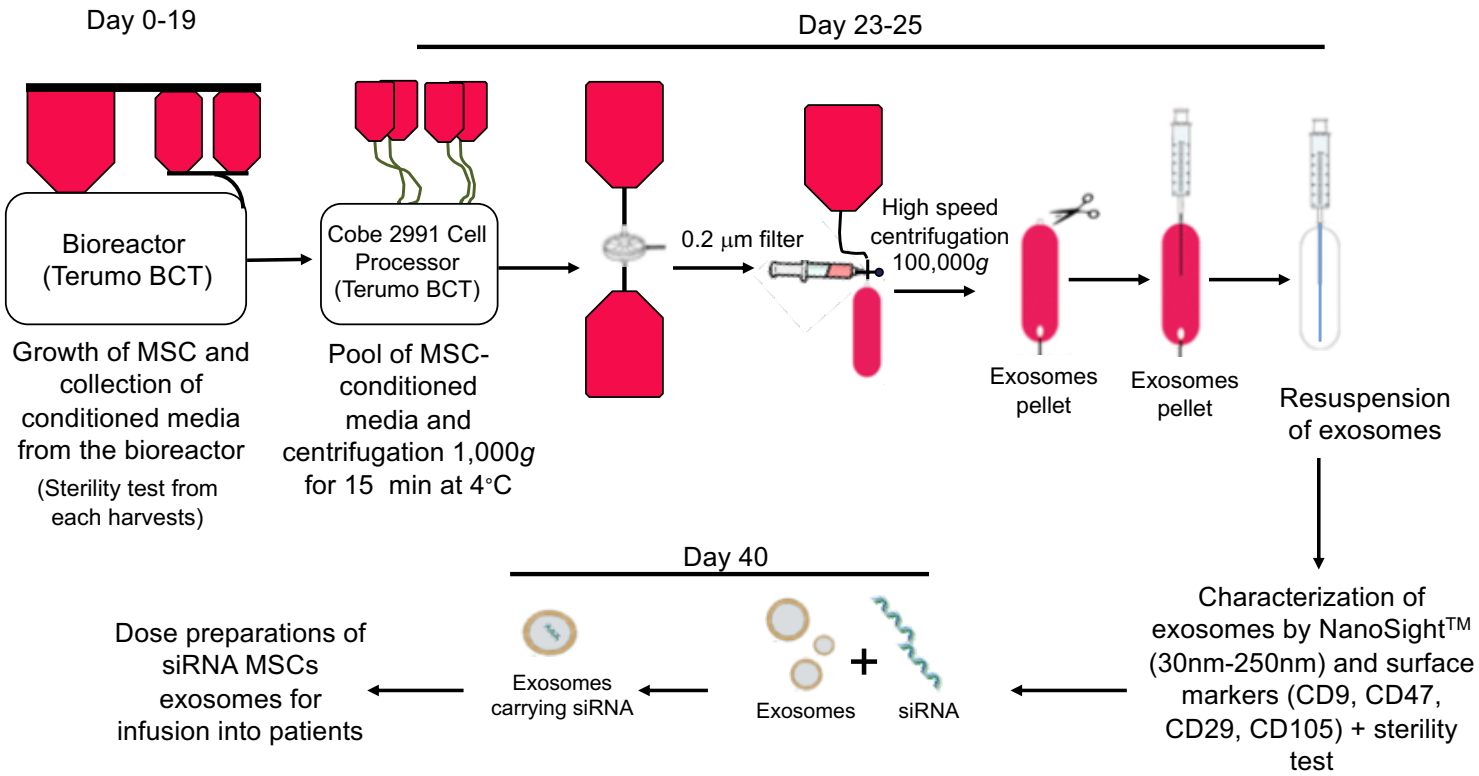
Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Preparation of bioreactor	Seeding of MSCs	Expansion of MSCs in growth media							Wash with PBS and load PLT-free media

Day 11	Day 13	Day 15	Day 17	Day 19	Day 21
Bioreactor Harvest 1 ↓ Freeze (-80°C)	Bioreactor Harvest 2 ↓ Freeze (-80°C)	Bioreactor Harvest 3 ↓ Freeze (-80°C)	Bioreactor Harvest 4 ↓ Freeze (-80°C)	Bioreactor Harvest 5 ↓ Freeze (-80°C)	Bioreactor Harvest 6 ↓ Freeze (-80°C)

B Isolation of and generation of MSCs-derived iExosomes



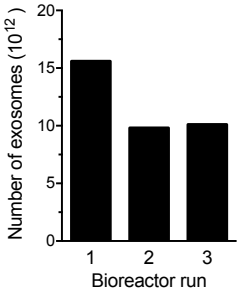
C Generation of GMP grade MSCs-derived iExosomes



A

Bioreactor harvests:	Harvest time (days)	Volume (ml)	Protein (mg)	Exosomes (x10^9)
Harvest 1	10	250	2.641	2010
Harvest 2	12	250	6.222	4493
Harvest 3	14	250	3.606	3402
Harvest 4	16	250	3.534	3472
Harvest 5	18	250	0.992	983
Harvest 6	20	250	1.040	1210

B



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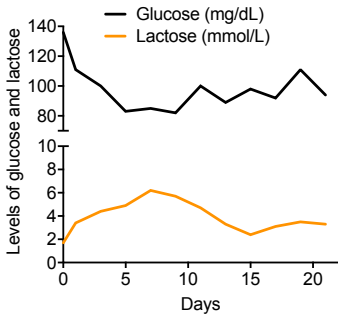

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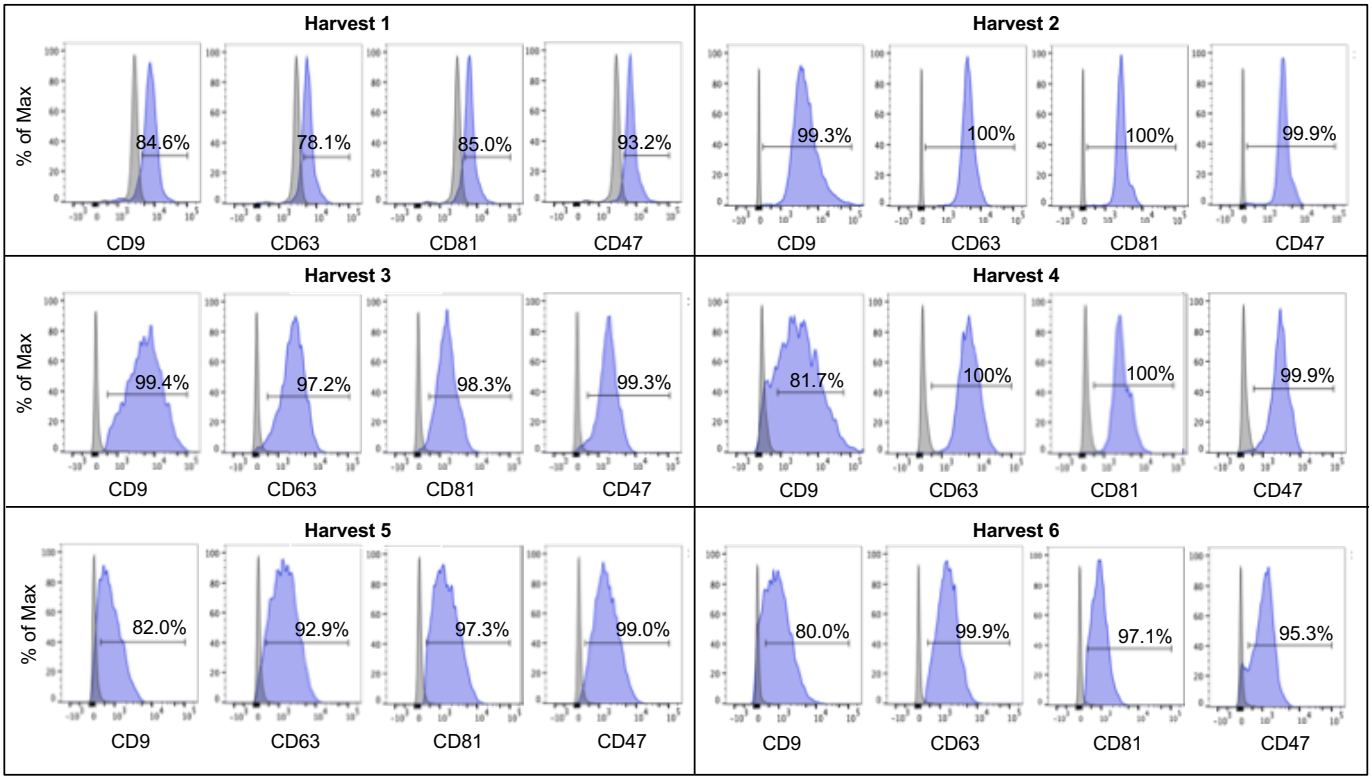
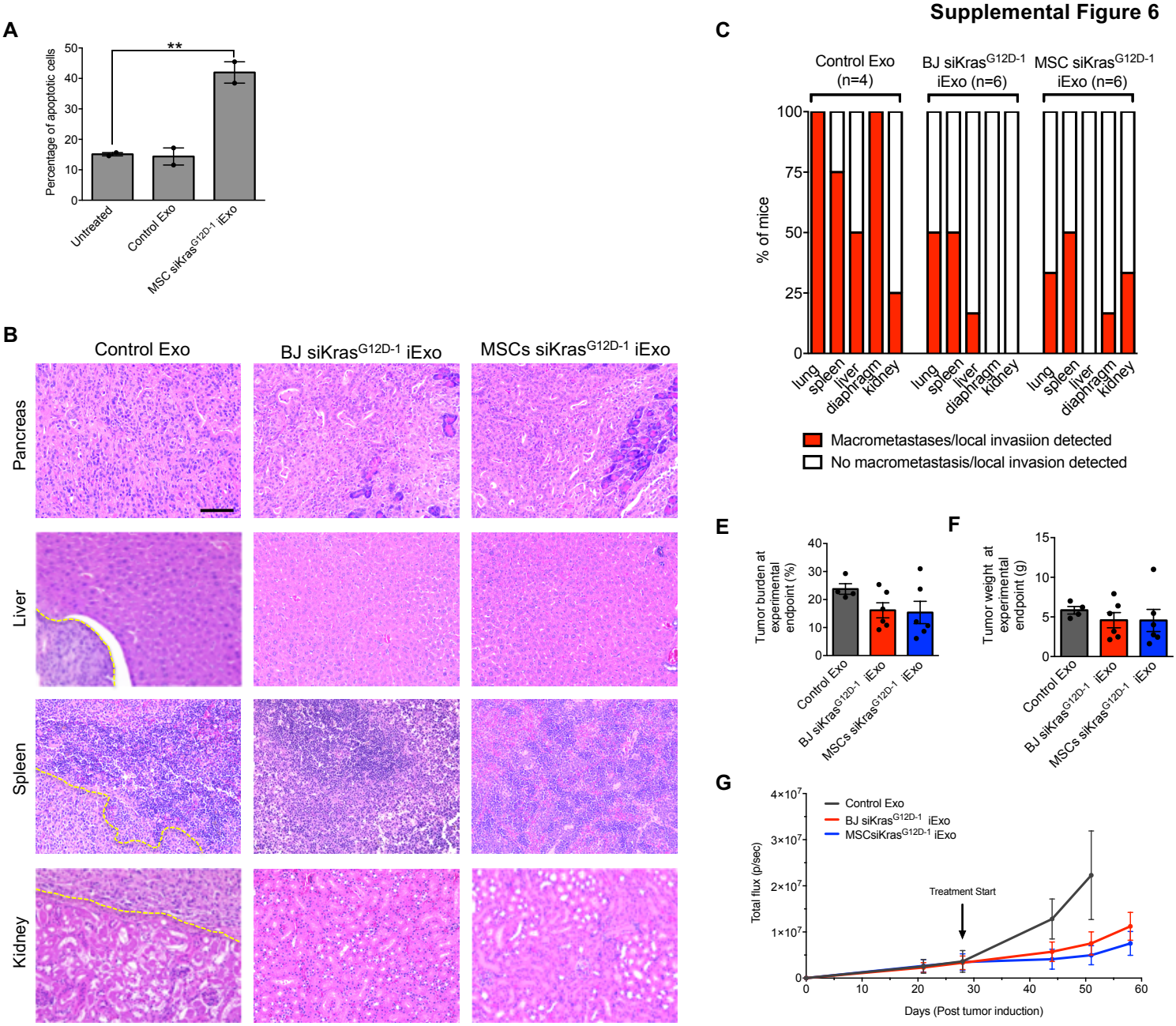


Supplemental Figure 6



D

	Survival (Days)		Pre-treatment	End-point			Observations	Notes
Treatment	**PTS**	**PB**	**BW(g)**	**TW(g)**	**BW(g)**	**Lung macro metastases**	**Necropsy notes**	**Suspected tumor burden related death**
MSCs Ctrl Exo	44	107	20.50	4.81	23.11	59	Large primary and secondary tumors, spleen invasion, liver invasion, diapragm invasion, macroscopic lung nodules	Yes
MSCs Ctrl Exo	37	100	20.00	7.00	23.90	49	Large primary and secondary tumors, spleen invasion, diapragm invasion, kidney invasion, macroscopic lung nodules	Yes
MSCs Ctrl Exo	37	100	21.30	5.34	24.12	42	Large primary and secondary tumors, diapragm invasion, macroscopic lung nodules	Yes
MSCs Ctrl Exo	44	107	21.60	6.22	27.26	76	Large primary and secondary tumors, spleen invasion, liver invasion, diapragm invasion, macroscopic lung nodules	Yes
Average:				***5.84***				
BJ siKrasG12D-1 iExo	37	100	20.80	2.14	23.20	35	Moderate tumor, spleen invasion, macroscopic lung nodules	Yes
BJ siKrasG12D-1 iExo	49	112	20.20	3.18	25.89	0	Moderate tumor, hunched, weak	Yes
BJ siKrasG12D-1 iExo	66	129	20.50	7.92	31.24	0	Moderate tumor burden, hunched, spleen invasion, liver invasion	Yes
BJ siKrasG12D-1 iExo	75	138	19.70	2.41	22.87	2	Moderate tumor burden, spleen invasion, necrosis of primary tumor, macroscopic lung nodules	Yes
BJ siKrasG12D-1 iExo	101	164	20.30	6.40	28.31	0	Moderate tumor burden, hole in primary tumor hunched, weak	Yes
BJ siKrasG12D-1 iExo	120	183	19.80	5.43	32.64	5	Moderate tumor burden, macroscopic lung nodules	Yes
Average:				***4.58***				
MSCs siKrasG12D-1 iExo	54	117	21.30	1.62	26.40	0	Small tumor, no invasion	No
MSCs siKrasG12D-1 iExo	54	117	21.60	2.76	31.86	0	Small tumor, no invasion, some internal bleeding	Yes
MSCs siKrasG12D-1 iExo	75	138	19.70	5.64	23.00	0	Moderate tumor burden, no invasion, necrosis of primary tumor	Yes
MSCs siKrasG12D-1 iExo	78	141	19.80	2.46	22.93	0	Moderate tumor, tumour in thoracic cavity, necrosis of primary tumor	Yes
MSCs siKrasG12D-1 iExo	82	145	21.00	4.01	33.46	6	Moderate tumor, necrosis of primary and secondary (subcutaneal) tumors, spleen invasion, kidney invasion, macroscopic lung nodules	Yes
MSCs siKrasG12D-1 iExo	115	178	21.00	11.00	35.48	32	Moderate tumor burden, spleen invasion, kidney invasion, diagraphm invasion, macroscopic lung nodules	Yes
Average:				***4.58***				

Figure 6B

Untreated	LS	HS
13.2	78.0	86.3
12.9	90.0	89.0
11.1	84.0	82.0

Figure 6C

	Delta Ct			fold		
Untreated	11.19	8.69	9.48	1.00	1.00	1.00
LS	13.28	11.10	12.76	0.23	0.19	0.10
HS	13.20	12.95	13.50	0.25	0.05	0.06

Figure 6D

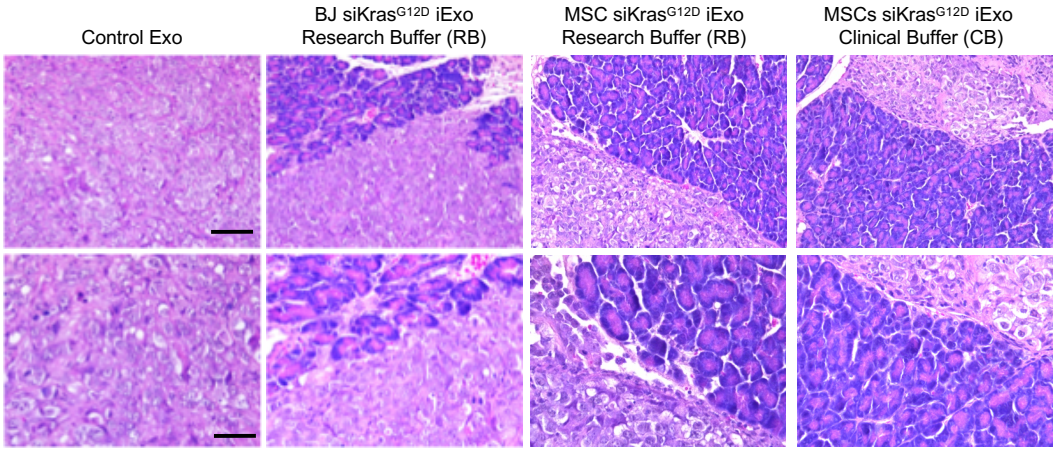
siKras^{G12D-1} input	siKras^{G12D-2} input	MSC siKras^{G12D-1} iExo, HS, CB	MSC siKras^{G12D-1} iExo, HS, CB + RN	MSC siKras^{G12D-1} iExo, HS, CB + T + RN	MSC siKras^{G12D-1} iExo, LS, RB	BJ siKras^{G12D-1} iExo, LS, RB	MSC siKras^{G12D-2} iExo, LS, RB
0.05304851	0.05296884	0.05365822	0.05240104	0.04080845	0.05203353	0.05106859	0.05106397
		0.05272926	0.05380001	0.03918899	0.05270242	0.05184339	0.05157713
		0.05333581	0.05158886	0.04099962	0.05054021	0.05079002	0.05264135

Figure 6E, F: see Supplemental Figures 8C and 9B, respectively.

A

	Survival (Days)		Pre-treatment	End-point		Observations
Treatment	**PTS**	**PB**	**BW(g)**	**TW(g)**	**BW(g)**	**Necropsy notes**
MSCs Ctrl Exo	70	133	29.40	1.89	23.00	Small tumor, hunched, diarrhea, no invasion
MSCs Ctrl Exo	71	134	31.10	2.96	33.26	Moderate tumor burden, spleen and liver invasion, ascistes
MSCs Ctrl Exo	85	148	28.70	2.03	30.57	Moderate tumor burden, diaphragm, spleen and kidney invasion
MSCs Ctrl Exo	99	162	34.90	3.26	36.22	Moderate tumor burden, abdominal inflammation, ascistes, spleen and diaphragm invasion
MSCs Ctrl Exo	113	176	25.50	3.10	28.97	Moderate tumor bourden, diaphragm invasion, ascistis
Average:				***2.65***		
BJ siKrasG12D-1 iExo RB	113	176	29.30	0.30	25.00	No tumor, hunched posture, diarrhea, no invasion
BJ siKrasG12D-1 iExo RB	143	206	28.20	2.83	27.21	Moderate tumor burden, hunched posture weak, no invasion
BJ siKrasG12D-1 iExo RB	145	208	29.00	4.05	38.50	Moderate tumor burden, hepatomegaly and splenomegaly
BJ siKrasG12D-1 iExo RB	165	228	27.80	2.36	28.00	Moderate tumor burden, spleen invasion
BJ siKrasG12D-1 iExo RB	221	284	31.80	2.54	28.20	Moderate tumor burden,diaprahm, liver and spleen invasion
Average:				***2.42***		
MSCs siKrasG12D-1 iExo RB	165	228	31.30	1.47	21.00	Severe abdominal inflammation, diapragm and kidney invasion, mesenteric metastases
MSCs siKrasG12D-1 iExo RB	145	208	33.00	6.27	36.00	Large primary tumor, diaphragm, liver and spleen invasion
MSCs siKrasG12D-1 iExo RB	130	193	32.00	3.39	28.25	Moderate tumor burden, no invasion
MSCs siKrasG12D-1 iExo RB	198	261	27.90	0.5	25.00	Small tumor burden, no invasion
Average:				***2.91***		
BJ siKrasG12D-1 iExo CB	111	174	31.50	1.15	21.30	Moderate tumor burden, diaphragm invasion
BJ siKrasG12D-1 iExo CB	117	180	27.40	1.24	34.40	Moderate tumor, no invasion, ascistes
BJ siKrasG12D-1 iExo CB	221	284	30.40	0.31	18.00	No tumor, hunched posture, weak, diarrhea, severe weight loss, no invasion
BJ siKrasG12D-1 iExo CB	226	289	28.60	2.29	32.71	Moderate tumor burden, diaphragm and, liver invasion
BJ siKrasG12D-1 iExo CB	335	398	27.50	2.27**	30.59	Mouse did not reach moribundancy but showed decreased activity. The pancreas appears normal yet a mesentaric tumor is noted together with invasion in the kidneys.
Average:				***1.25***		

B



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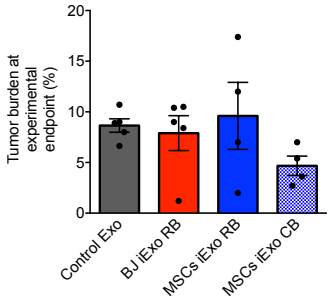

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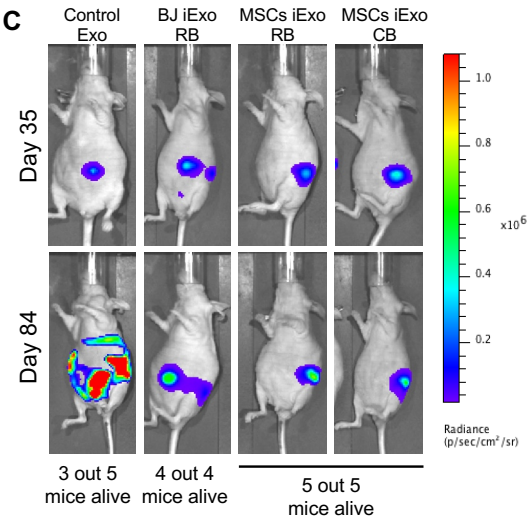

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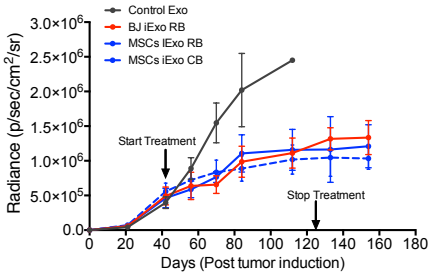

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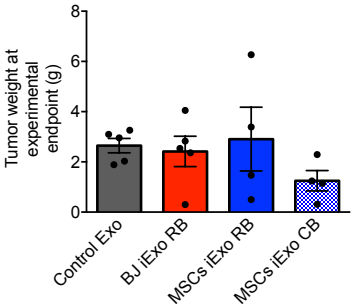

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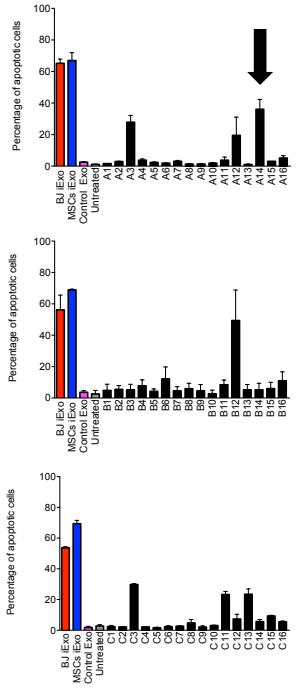
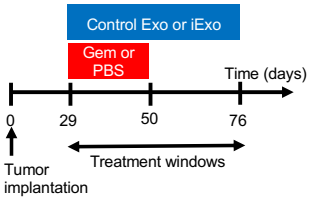


Supplemental Figure 8

A



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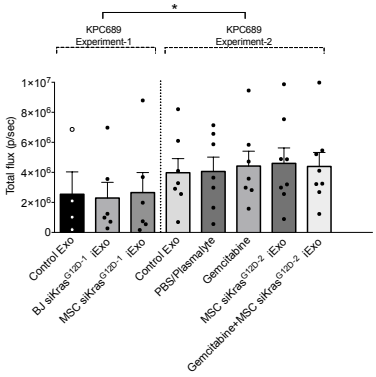
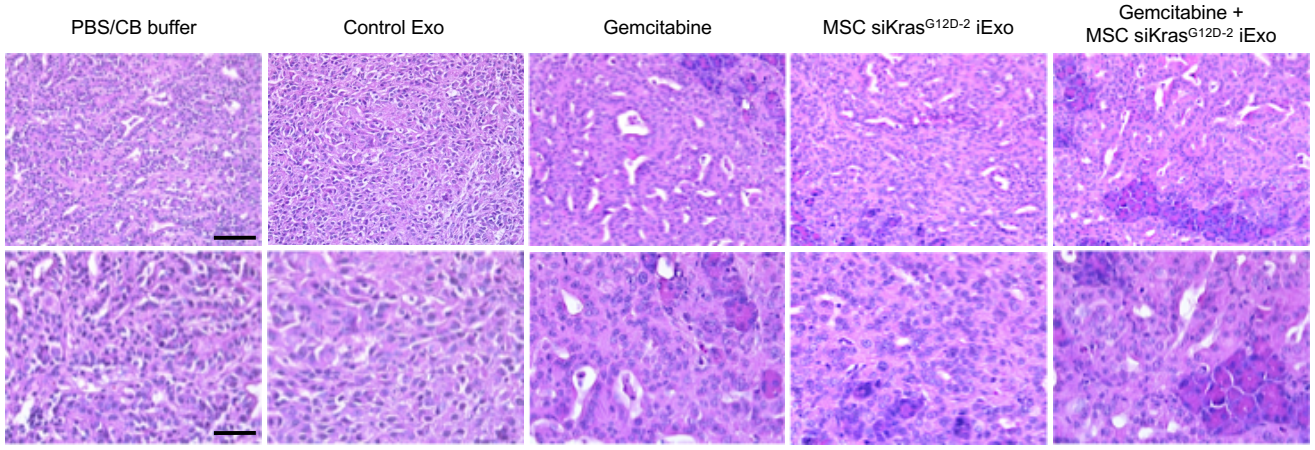


C

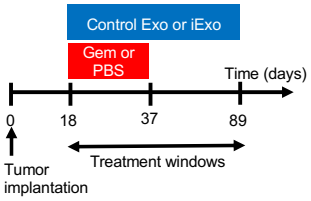
	Survival (Days)		Pre-treatment	End-point			Observations
Treatment	**PTS**	**PB**	**BW(g)**	**TW(g)**	**BW(g)**	**Lung Metastases**	**Necropsy notes**
CB/PBS	32	95	21.20	3.26	24.00	0	Moderate tumor burden, diaphragm invasion
CB/PBS	34	97	20.50	4.90	21.97	4	Moderate tumor burden, spleen and diaphragm invasion, macroscopic lung nodules
CB/PBS	35	98	19.30	2.55	18.22	0	Moderate tumor burden, peritoneal, diaphragm, spleen iand kidney invasion, macroscopic lung nodules
CB/PBS	35	98	20.90	2.86	20.40	0	Moderate tumor burden, diaphragm invasion
CB/PBS	41	104	20.78	2.14	20.78	6	Moderate tumor burden, peritoneal and diaphragm invasion, macroscopic lung nodules
CB/PBS	39	102	19.70	3.75	18.85	0	Moderate tumor burden, spleen, liver and kidney invasion
CB/PBS	41	104	21.50	3.26	24.02	0	Moderate tumor burden, diaphragm invasion
Average:				***3.25***			
MSCs Ctrl Exo	42	105	21.10	3.72	20.20	0	Moderate tumor burden, spleen, diaprahm invasion
MSCs Ctrl Exo	39	102	19.80	5.10	23.60	8	Moderate tumor burden, spleen, kidney, liver and diaprahm invasion, macroscopic lung nodules
MSCs Ctrl Exo	50	113	18.50	6.32	24.98	>200	Moderate tumor burden, spleen, kidney and diaprahm invasion, macroscopic lung nodules
MSCs Ctrl Exo	46	109	19.30	3.67	19.70	2	Moderate tumor burden, spleen and kidney invasion, macroscopic lung nodules
MSCs Ctrl Exo	34	97	20.90	2.86	17.50	0	Moderate tumor burden, spleen, liver and diaphragm invasion
MSCs Ctrl Exo	36	99	21.30	2.83	22.80	0	Moderate tumor burden, spleen and diaphragm invasion
MSCs Ctrl Exo	32	95	18.40	4.52	19.70	2	Moderate tumor burden, diaphragm invasion, macroscopic lung nodules
Average:				***4.15***			
Gemcitabine	39	102	18.70	0.54	23.47	0	Very small tumor, diaphragm invasion
Gemcitabine	41	104	20.20	2.54	24.66	1	Moderate tumor burden, spleen, kidney and diaphragm invasion, macroscopic lung nodules
Gemcitabine	50	113	21.90	2.3	18.00	0	Moderate tumor burden, no invasion
Gemcitabine	44	107	22.20	4.77	28.05	0	Moderate tumor burden, spleen, kidney and diaphragm invasion, ascites
Gemcitabine	60	123	20.20	0.57	13.25	0	Small tumor, diaphragm invasion
Gemcitabine	46	109	19.10	1.5	27.20	0	Moderate tumor burden, no invasion
Gemcitabine	60	123	20.90	2.73	20.07	0	Moderate tumor burden, no invasion
Gemcitabine	57	120	20.40	3.1	22.90	0	Moderate tumor burden, no invasion
Average:				***2.26***			
MSCs siKrasG12D-2 iExo CB	75	138	19.70	5.83	24.26	11	Moderate tumor burden, liver invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	45	108	22.40	1.96	20.00	13	Moderate tumor burden, spleen and diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	45	108	18.80	1.78	16.15	29	Moderate tumor burden, spleen, kidney and diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	44	107	20.60	1.72	18.87	0	Moderate tumor burden, spleen, kidney, peritoneal and diaphragm invasion
MSCs siKrasG12D-2 iExo CB	76	139	21.70	5.3	23.67	48	Moderate tumor burden, spleen, kidney and small intestine invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	44	107	21.30	1.98	24.97	0	Moderate tumor burden, spleen, kidney, liver and diaphragm invasion
MSCs siKrasG12D-2 iExo CB	36	99	21.00	1.34	21.60	0	Moderate tumor burden, diaphragm invasion
MSCs siKrasG12D-2 iExo CB	44	107	18.90	1.86	20.00	15	Small tumor, diaphragm invasion, lymph node metastases, macroscopic lung nodules
Average:				***2.72***			
MSCs siKrasG12D-2 iExo CB+Gem	67	130	20.20	3.32	23.84	>200	Moderate tumor burden, spleen and kidney invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	46	109	20.60	1.14	19.85	0	Small tumor, hunched posture, liver invasion
MSCs siKrasG12D-2 iExo CB+Gem	75	138	19.20	2.27	21.00	8	Moderate tumor burden, spleen, kidney, liver and diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	70	133	19.20	3.87	23.84	11	Moderate tumor burden, spleen, kidney and diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	50	113	21.00	4.56	23.00	71	Moderate tumor burden, ascites, spleen, kidney and diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	50	113	18.40	1.73	19.84	0	No tumor, hunched posture, weak, diarrhea, weight loss, no invasion
MSCs siKrasG12D-2 iExo CB+Gem	95	158	20.20	3.10	25.00	10	Moderate tumor burden, spleen, liver and diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	87	150	20.00	1.46	16.44	0	Moderate tumor burden, spleen, liver and diaphragm invasion
Average:				***2.68***			

D



Supplemental Figure 9

A

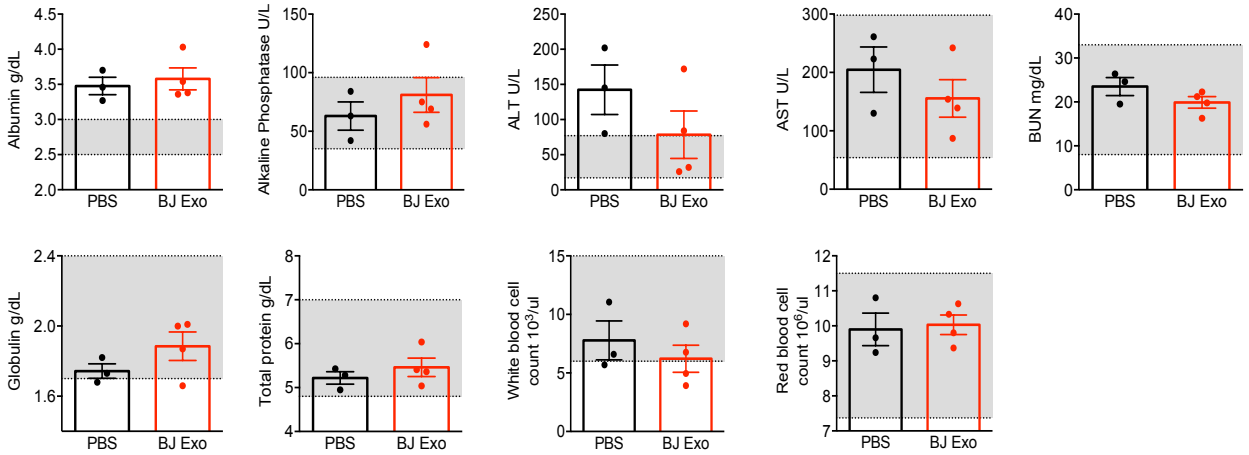


B

	Survival (Days)		Pre-treatment	End-point			Observations
Treatment	**PTS**	**PB**	**BW(g)**	**TW(g)**	**BW(g)**	**Lung Metastases**	**Necropsy notes**
CB	46	116	19.50	4.14	25.50	6	Large primary tumor, secondary tumor, peritoneal, diaphragm, stomach, spleen and liver invasion, mesenteric lymph node metastasis, macroscopic lung nodules
CB	37	107	19.00	5.04	24.95	>100	Moderate tumor, spleen, liver, diaphragm and stomach invasion, macroscopic lung nodules
CB	47	117	20.00	1.36	16.90	0	Small tumor, bleeding, diaphragm invasion, mesenteric lymph node metastasis
CB	37	107	20.00	5.35	22.56	34	Moderate tumor, paraaortic lymph node metastasis, diaphragm and spleen invasion, possible stomach invasion, macroscopic lung nodules.
CB	42	113	19.50	1.80	25.00	14	Moderate tumor, bleeding, mesenteric lymnph node metastases, diaphragm invasion, liver invasion, spleen invasion, macroscopic lung nodules.
CB	37	107	19.00	2.73	18.71	9	Moderate tumor, spleen, lymph node and diaphragm invasion, macroscopic lung nodules
CB	53	124	20.00	3.46	26.04	3	Large primary tumor, secondary tumor, peritoneal, diaphragm, spleen and liver invasion, mesenteric lymph node metastases, macroscopic lung nodules
Average:				***3.41***			
MSCs Ctrl Exo	42	113	19.00	5.43	29.60	9	Large primary tumor, bleeding, ascites, peritoneal, diaphragm, stomach and kidney invasion, lymph node metastases, macroscopic lung nodules
MSCs Ctrl Exo	42	113	20.00	1.63	22.00	2	Moderate tumor, diaphragm, spleen, peritoneal and lymph node invasion, macroscopic lung nodules
MSCs Ctrl Exo	60	131	19.5	7.12	27.8	>100	Large primary tumor, bleeding, ascites, liver, diaphragm, stomach, ovary and spleen invasion, mesenteric lymph noode metastases, macroscopic lung nodules
MSCs Ctrl Exo	39	109	20.00	2.02	22.16	>100	Moderate tumor, diaphragm invasion, liver invasion, spleen invasion, peritoneal invasion, Mesenteric lymph node invasion, macroscopic lung nodules
MSCs Ctrl Exo	41	112	19.50	4.18	23.37	32	Large primary tumor, bleeding, diaphragm invasion, stomach invasion, kidney invasion, spleen invasion, macroscopic lung nodules
MSCs Ctrl Exo	52	123	20.00	3.72	25.18	3	Large primary tumor, ascites, bleeding, diaphragm, stomach, liver, kidney and spleen invasion, lymph node metastases, paraaortic lymph node metastases, hydronephrosis, ovarian metastases, macroscopic lung nodules
MSCs Ctrl Exo	39	109	20.00	2.55	22.50	16	Moderate tumor, bleeding, ascites, diaphragm, stomach, liver, spleen and peritoneal invasion, mesentereic lymph node invasion, macroscopic lung nodules
Average:				***3.81***			
Gemcitabine	54	125	20.00	3.08	25.96	19	Large primary tumor, bleeding, ascites, spleen, liver, stomach, diaphragm, peritoneal, ovarian and left kidney invasion, pleural bleeding, macroscopic lung nodules
Gemcitabine	56	127	20.00	3.49	25.38	>100	Large primary tumor, bleeding, ascites, diaphragm, stomach, ovary, spleen and small instestine invasion, posible liver invasion, macroscopic lung nodules
Gemcitabine	67	138	21.00	2.94	26.80	7	Moderate tumor divided in two masses connected with necrotic core, very discolored liver (potential metastases), ovary and diaphragm invasion, macroscopic lung nodules.
Gemcitabine	89**	160	20.00	1.03	21.90	0	Ascites, small tumor, possible spleen invasion and inflammation, necrotic liver
Gemcitabine	54	125	19.50	2.46	22.47	33	Moderate tumor, bleeding, ascites, spleen, ovary and diaphragm invasion, hepatic lymph node metastases, paraaortic mesenteric lymph node metastases, macroscopic lung nodules
Gemcitabine	67	138	20.00	2.49	27.70	2	Moderate tumor divided in two mass connected, very discolored liver (potential metastases), macroscopic lung nodules
Gemcitabine	89**	160	19.50	1.63	25.60	0	Moderate tumor, bleeding, ascites, primaric tumor attached to the abdominal wall and connected to the pancreas. Possible spleen invasion and inflammation, peripancreatic lymph node metastases, diaphragm invasion
Average:				***2.45***			
MSCs siKrasG12D-2 iExo CB	89**	160	20.00	2.58	23.60	0	Amall primary tumor, some ascites, peritoneal secondary tumor, diaprahgm invasion
MSCs siKrasG12D-2 iExo CB	66	137	20.00	4.18	25.58	5	Large primary tumor with necrotic core, small secondary tumors (2), bleeding, ascites, lymph node metastases, spleen, liver, stomach and kidney invasion, diaphragm metastases, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	43	114	20.00	0.81	16.81	0	Moderate tumor, tumor with necrotic core (hole), bleeding, ascites, diaphragm invasion
MSCs siKrasG12D-2 iExo CB	56	127	20.00	5.06	25.90	34	Large primary tumor, tumor with necrotic core (hole), bleeding, ascites, mesenteric lymph node and colon invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	89**	160	20.00	2.4	16.00	29	Moderate primary tumor, secondary tumor not connected to the primary tumor, tumor with necrotic core (hole), diapragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	67	138	20.00	7.7	30.21	2	Large primary tumor, peritoneal lymph node and diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB	89**	160	20.00	0.2	23.40	0	Remnant of primary tumor, some ascites, no invasion
Average:				***3.28***			
MSCs siKrasG12D-2 iExo CB+Gem	89**	160	20.00	1.80	23.10	0	Small primary tumor, no invasion
MSCs siKrasG12D-2 iExo CB+Gem	89**	160	19.50	0.20	20.10	0	Very small, remnant of tumor, large area of normal pancreas, edema in the capsule, no invasion
MSCs siKrasG12D-2 iExo CB+Gem	89**	160	20.00	2.24	23.30	0	Small primary tumor, area of normal pancreas, edema around the capsule, no invasion
MSCs siKrasG12D-2 iExo CB+Gem	89**	160	20.00	1.70	23.10	7	Some ascites, spleen and diaphragm invasion, possible liver invasion, mesenteric lymph node metastases, lymph node metastases around the stomach, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	59	130	20.00	1.52	22.56	20	Small primary tumor, diaphragm invasion, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	65	136	20.00	3.25	30.88	9	Small primary tumor, bleeding, ascites, spleen, stomach, kidney, ovary and diaphragm invasion, hepatic lymph node metastases, lymph node metastases, macroscopic lung nodules
MSCs siKrasG12D-2 iExo CB+Gem	89**	160	20.00	3.68	25.00	18	Large primary tumor with area of normal pancreas, some ascites, bleeding, subcutaneous edema in the left flank, diaphragm invasion, macroscopic lung nodules
Average:				***2.06***			

Supplemental Figure 10

A



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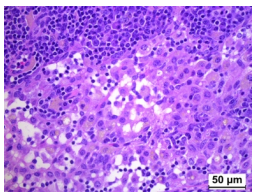
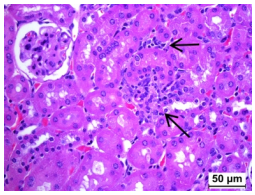
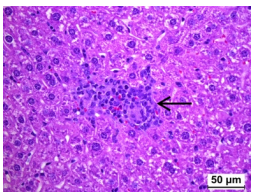


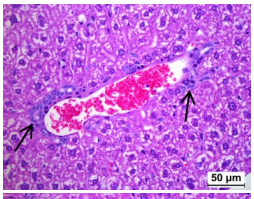
74K-Mesenteric lymph node-macrophages with yellow pigment



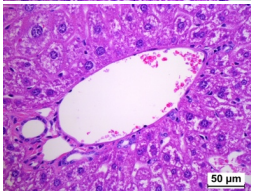
75K-Kidney inflammation, acute multifocal interstitial



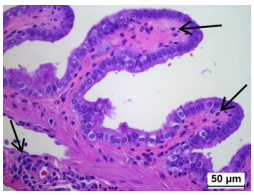
75K-Liver inflammation-acute multifocal



74K-Liver hyperplasia bile ducts



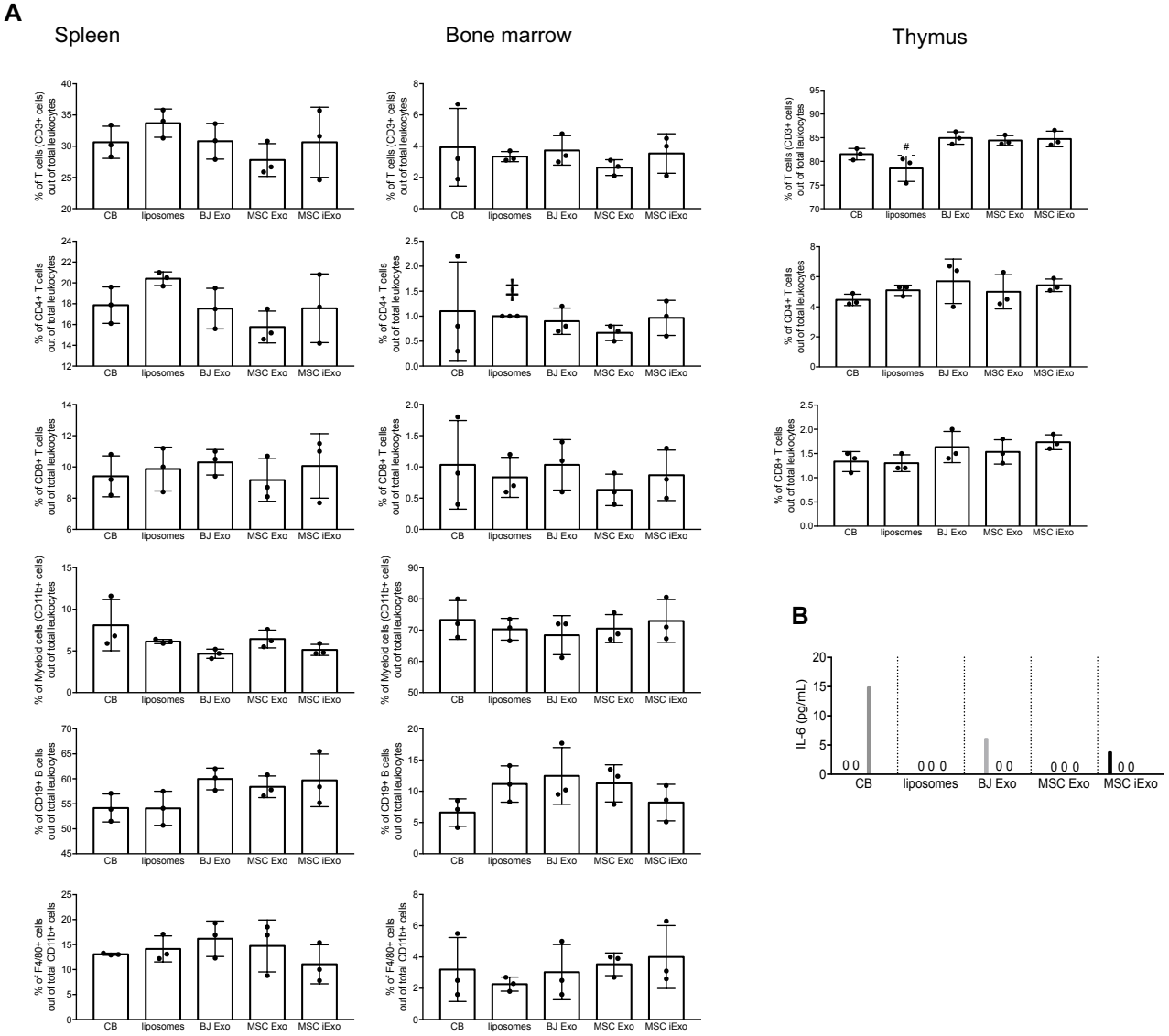
69K-Normal Liver



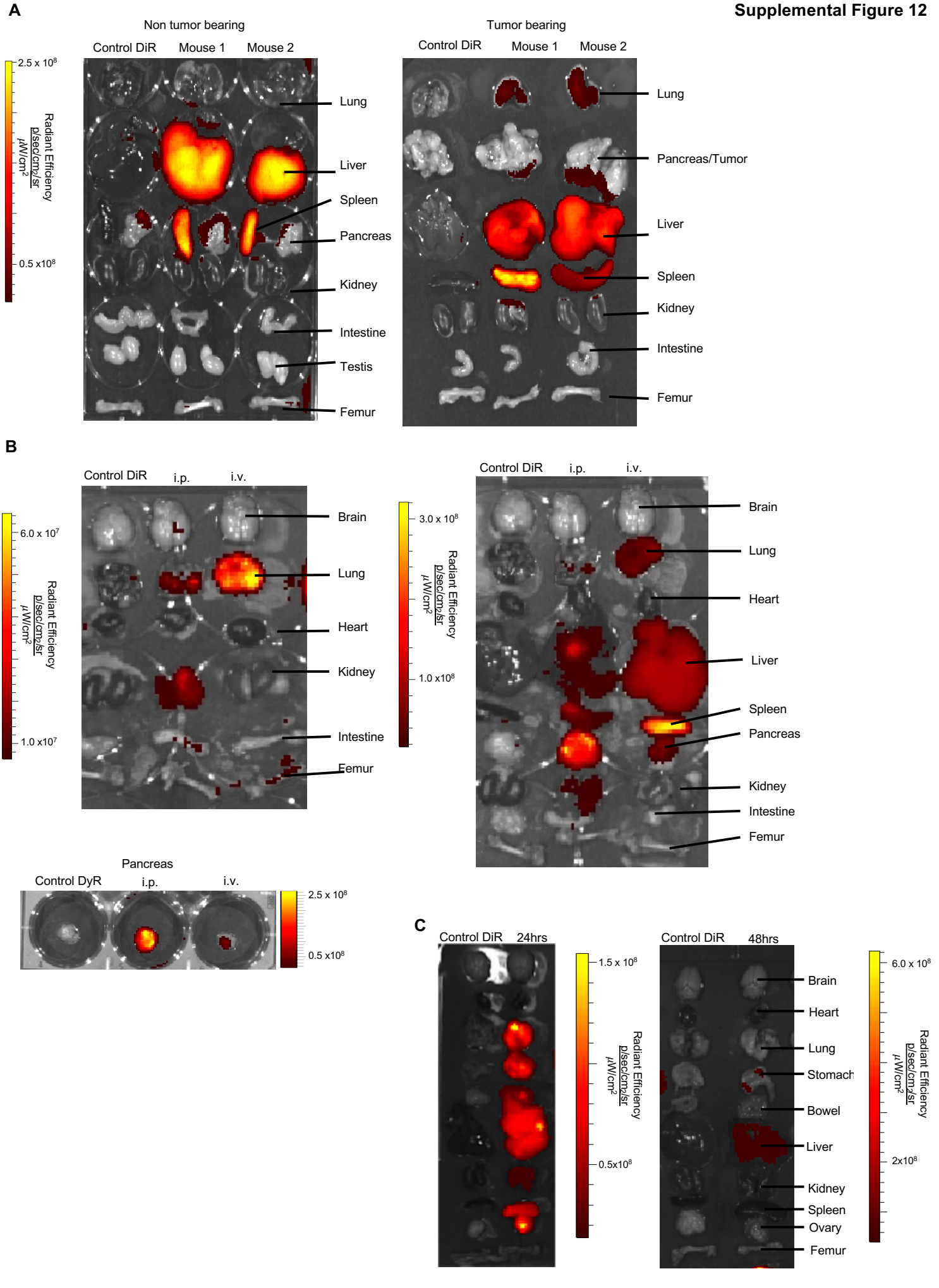
72k-Inflammation gall bladder

69K Normal gall bladder

Supplemental Figure 11

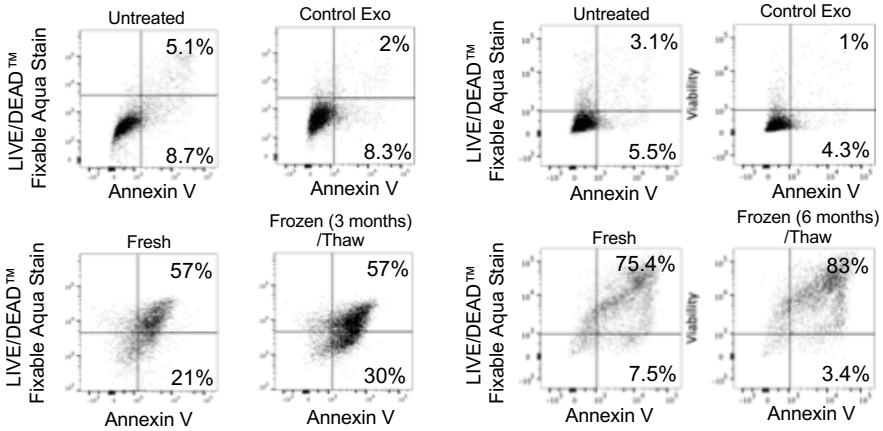


Supplemental Figure 12



Supplemental Figure 13

A



B

				End point	
Mouse ID	**Treatment**	**Age: Treatment start**	**Survival:PB**	**BW (g)**	**TW (g)**
sr31	siKrasG12D iExo	65	117	13.52	0.28
sr96	siKrasG12D iExo	66	112	12.63	1.1
sr23	siKrasG12D iExo	69	122	19.66	0.75
sm782	siKrasG12D iExo	75	140	8.17	0.14
J44	siKrasG12D iExo	60	150	33.1	1.03
J45	siKrasG12D iExo	60	98	16.8	1.44
J43	siKrasG12D iExo	60	158	20.9	<0.1
Average				***17.83***	***0.79***
sr29	Control Exo	64	110	18.73	0.3
sr257	Control Exo	58	92	18.2	1.28
sr270	Control Exo	60	69	N/A	
sr271	Control Exo	60	85	14.45	0.94
sr475	Control Exo	59	101	16.2	1.45
J54	Control Exo	61	113	16.66	1.3
Average				***16.85***	***1.05***

Supplemental Table 1

Treatment Group		PBS	PBS	PBS	Exo	Exo	Exo	Exo
Animal ID		69K	70k	71K	72K	73K	74K	75K
Specie		mouse	mouse	mouse	mouse	mouse	mouse	mouse
Strain/Genotype		C57BL/6J	C57BL/6J	C57BL/6J	C57BL/6J	C57BL/6J	C57BL/6J	C57BL/6J
Terminal body weight (grams)		37.16	35.04	40.28	35.81	32.52	27.84	29.76
Liver weight (grams)		2.02	1.99	1.99	1.97	1.71	1.47	1.52
Kidney weight (grams) - Right/Left		0.49	0.45	0.57	0.51	0.46	0.43	0.45
Heart weight (grams)			0.17		0.21	0.25	0.15	0.16
Spleen weight (grams)		0.08	0.07	0.11	0.08	0.07	0.10	0.10
Block No.	Organ Morphologic Diagnosis	Lesion Grade	Lesion Grade	Lesion Grade	Lesion Grade	Lesion Grade	Lesion Grade	Lesion Grade
A	Liver	A	A	N	N	A	A	A
	Inflammation, acute, mixed, multifocal					1	1	2
	Inflammation, acute, bile ducts					1		2
	Hyperplasia, bile ducts						1	1
	Extramedullary hematopoiesis, (incidental finding)	1	1				2	
A	Gall Bladder	N	N	N	A	A	A	A
	Inflammation, acute, neutrophilic				2	1		1
	Distended/dilated						3	
A	Kidneys	A	A	A	A	A	A	A
	Inflammation, acute, mixed (neutrophils and macrophages), interstitial, multifocal							2
	Chronic Progressive Nephropathy (multifocal hyperplasia of cortical renal tubules; and/or proteinaceous tubular casts in the medullary renal tubules) (incidental age-related change)		1	1	1	1	1	2
	Lymphoplasmacytic infiltration, perivascular, arcuate and mid-size blood vessels (incidental age-related change)	1	1	1	2	1	1	2
B	Lung	A	N	A	N	N	A	N
	Inflammation, acute, mixed, perivascular	1		2			2	
	Increased number of alveolar macrophages, diffuse						1	
C	Heart	N	N	N	N	N	N	N
E	Brain	N	A	N	N	A	N	N
	Mineralization/calcification, multifocal, neuropil, thalamus, (incidental finding)		1			1		
M	Mesenteric Lymph Node and Mesentery	0	A	A	N	A	A	0
	Hyperplasia, paracortex		2	2		2		
	Hyperplasia, lymphoid follicles					2	1	
	Apoptotic lymphocytes with tangible-body macrophages, paracortex		2	3		2	2	
	Macrophages with intracytoplasmic pale-yellow pigment/material in the medullary sinuses			1		2	3	
	Inflammation, acute (infiltration of neutrophils)						2	
	Infiltration of mast cells in the medullary sinuses						2	
	Plasmacytosis (increased number of plasma cells)						2	
M	Spleen	N	N	A	A	A	A	A
	Hyperplasia, lymphocytic, periarteriolar lymphoid sheaths (white pulp)					1	2	1
	Plasmacytosis (increased number of plasma cells)			2	1	2	1	2
T	Bone marrow, femur, knee joint	N	N	N	N	N	N	N
U	Bone marrow, sternum	N	N	N	A	N	N	N
	Plasmacytosis, focal				1			

Comment:

Liver: Minimal to mild acute inflammation around the bile ducts in mice #73K, 74K, 75K, and of gall bladder in mice #72K, 73K, 75K, indicate mild injury to cholangiolar epithelium of bile ducts and gall bladder. Mild multifocal acute inflammation of mononuclear cells and neutrophils in the liver of mouse #75K is consistent with mild injury/toxicity to hepatocytes. Kidney: Mild acute multifocal interstitial inflammation suggests mild toxicity to epithelium of renal tubules. Immune System: Minimal to mild plasmacytosis and lymphoid hyperplasia of spleen and mesenteric lymph nodes in mice 71K, 72K, 73K, 74K, 75K indicate mild immune activation of lymphoid system and increased production of antibodies by plasma cells. Presence of macrophages with intracytoplasmic pale-yellow pigment in the sinusoids of mesenteric lymph nodes indicates increased phagocytosis of either foreign material, red cells, lipofuscin or ceroid material. Additionally, the mesenteric lymph node of mouse 74K had mild acute inflammatory reaction suggesting a regional injury from gastrointestinal tract or peritoneum.

LEGEND

N = Normal tissue or No significant lesion observed
A = Abnormal tissue (Lesion present)
0 = No tissue present on the slide
P = The lesion is present, but not graded
S = Suspected/Presumptive diagnosis (needs more tests to confirm the Dx.)
PMA = Postmortem autolysis
I = Inadequate section
N/A= Not Applicable

GRADING/SCORING OF HISTOLOGICAL LESIONS

Grade 0 = **no histologic lesion** (or normal tissue)
Grade 1 = **minimal**, minor, rare, infrequent, barely noticeable tissue change (lesion affects **1-10%** of the tissue)
Grade 2 = **mild**, slight, sporadic, noticeable but not prominent feature (lesion affects **11-20%** of tissue)
Grade 3 = **moderate**, frequent, typical, common, prominent tissue change (lesion affects **21-40%** of tissue)
Grade 4 = **marked**, extensive, numerous, severe, overwhelming tissue change (lesion affects **41-100%** of tissue)