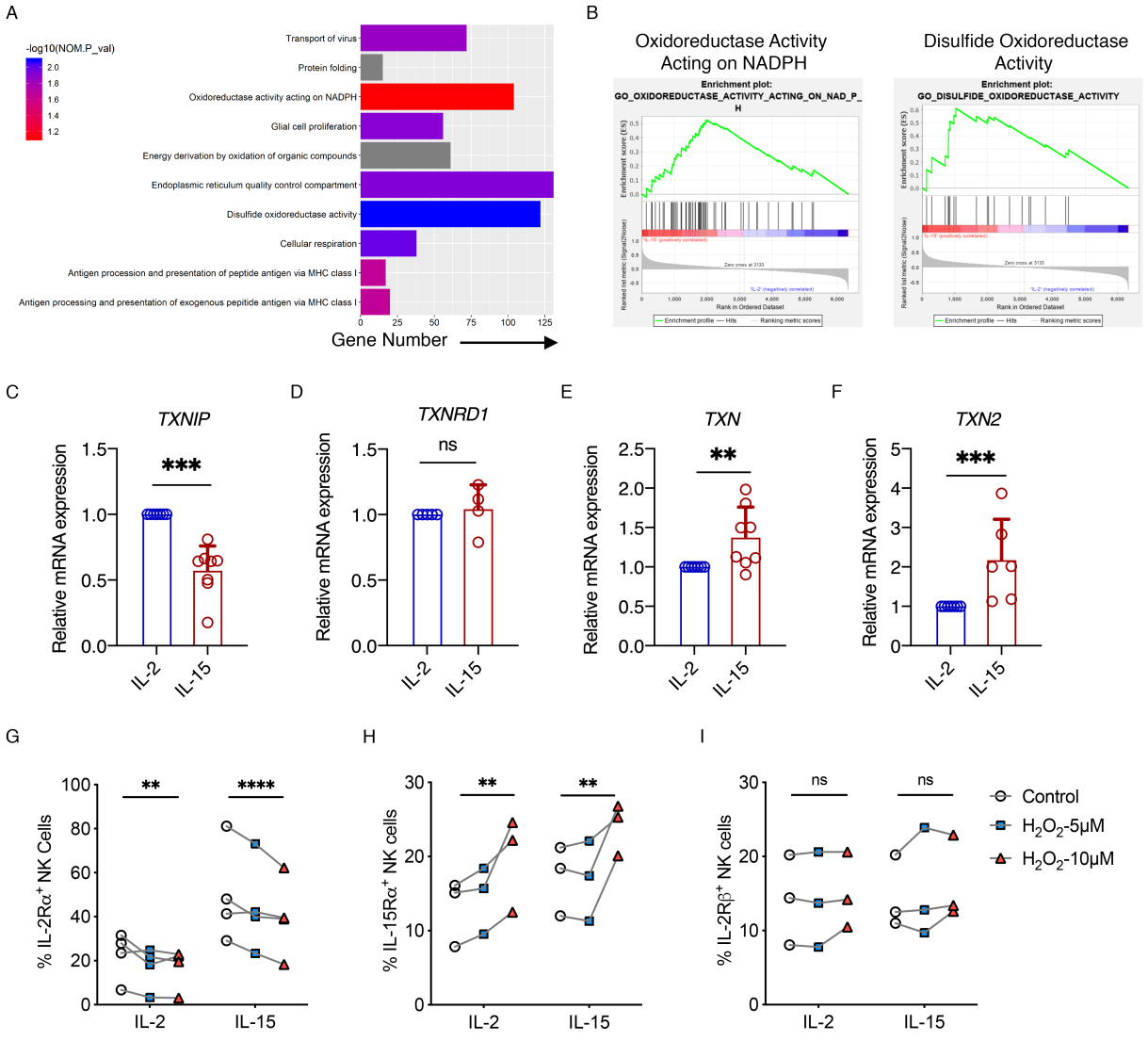
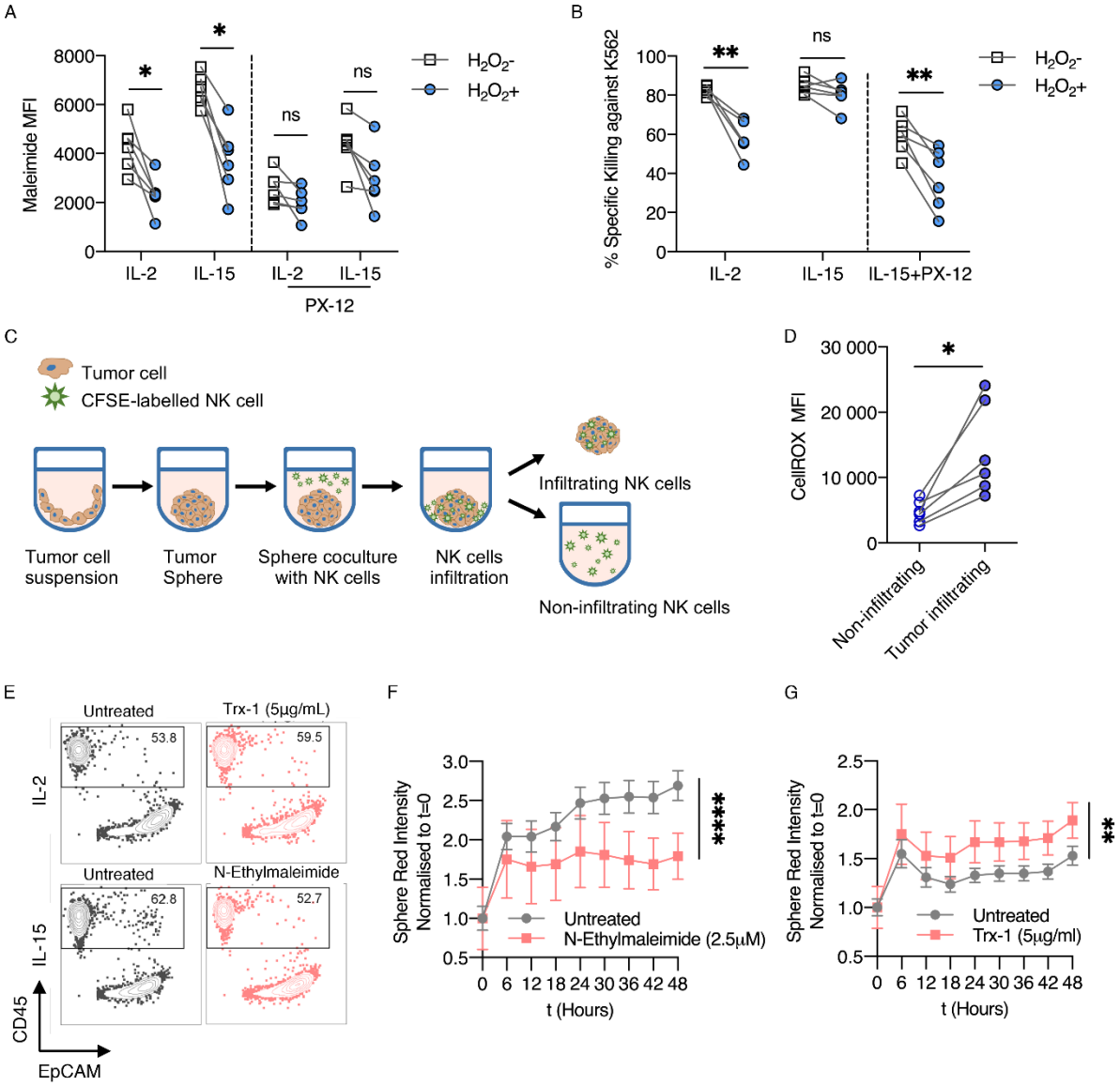
Supplementary Figure 1.



Supplementary Figure 1. IL-15 primed NK cells differentially expressed thioredoxin system to mount superior immune responses.
(A) Gene Enrichment Analysis using C5 GO set for biological processes with cut-off at nominal P-value < 0.01 and the maximum and minimum size for selection were 500 and 15 genes, respectively. X-axis represents the number of genes while the y-axis represents the top 10 GO gene sets based on enrichment sore. **(B)** GSEA analysis in oxidoreductase activity based on differential gene expression of IL-15 versus IL-2primed NK cells. **(C-F)** Relative mRNA expression of **(C)** *TXNIP* (n=8), **(D)** *TXNRD1* (n=5), **(E)** *TXN* (n=8) and **(F)** *TXN2* (n=6) based on qRT-PCR; data points are presented as mean ± SD; Mann-Whitney test was used to test for significance. **P<0.01, ***P<0.001 and ns for non-significant.**(G-I)** Percentage of NK cells expressing **(G)** IL-2Rα(n=4), **(H)** IL-15Rα(n=3), **(I)** IL-2Rβ(n=3) after primed with either IL-2 or IL-15, in the present or absence of H_2O_2 treatment, data points are connected for matching replicates; two-way ANOVA with Sidak's multiple comparisons were used to test for significance, **P<0.01, ***P<0.001 and ns for non-significant.

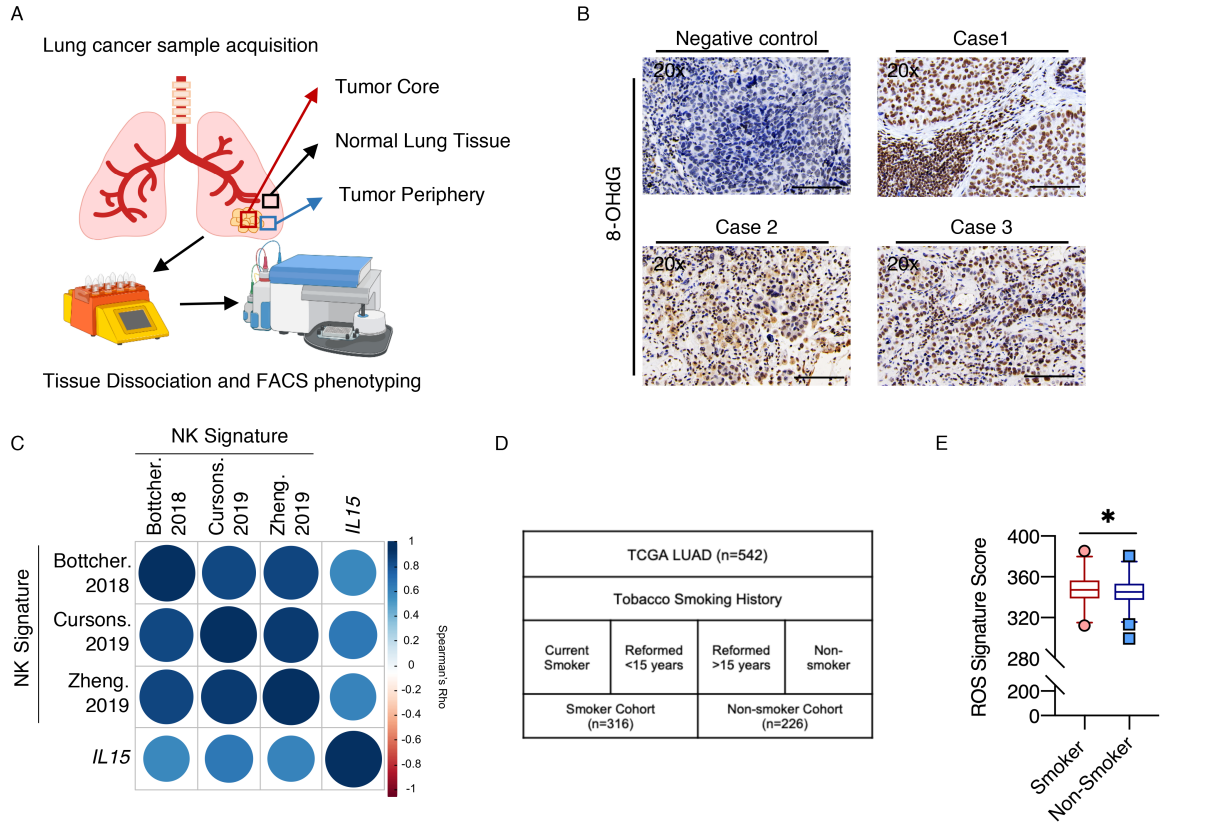
Supplementary Figure 2.



Supplementary Figure 2. Inhibition of thioredoxin-1 abrogates IL-15-mediated protection against oxidative stress.

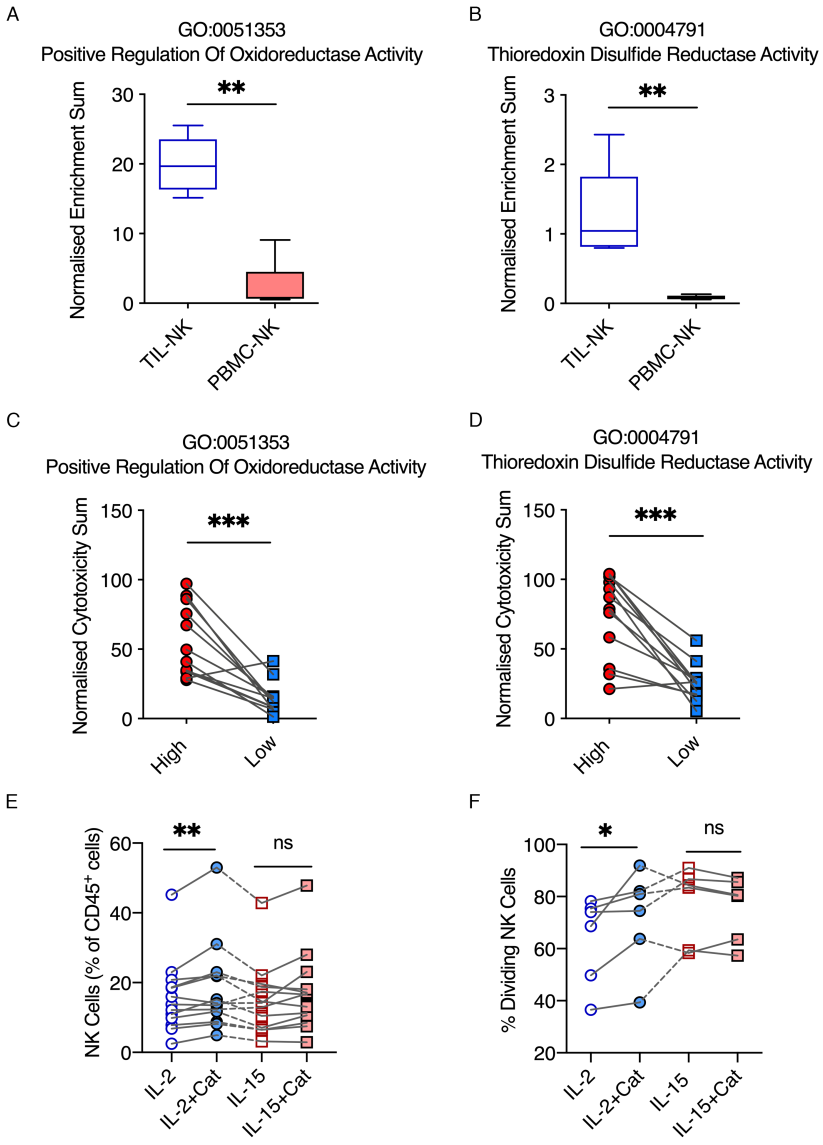
(A) MFI of maleimide staining on cytokine-primed NK cells treated with PX-12 and 10µM H_2O_2 (n=6). **(B)** Percentage killing of K562 targets by cytokine-primed NK cells treated with PX-12 and H_2O_2, NK: K562 at the ratio of 5:1 (n=6). **(A and B)** RM two-way ANOVA with Sidak's multiple comparisons test was used to test for significance. **(C)** Diagram depicting tumor sphere model with CFSE-labelled NK cells to investigate NK cell infiltration. **(D)** MFI of CellROX staining comparing tumor-infiltrating and non-infiltrating NK cells outside and within tumor spheroids (n=6). Wilcoxon rank sum test was used to test for significance. **(E)** Representative FACS plot showing percentage of CD45-positive infiltrating NK cells into H1299 tumor sphere (n=3). **(F and G)** Mean red intensity of spheres infiltrated with fluorescence-labelled NK cells over time with treatment of **(F)** N-ethylmaleimide (2.5mM) and **(G)** recombinant thioredoxin-1 (5mg/ml) (n=3). **(A, B and D)** Data points are connected for matching replicates. **(F and G)** Data are presented as mean±SD; two-way ANOVA was used to test for significance between treatment conditions. *P<0.05, **P<0.01, ****P<0.0001 and ns for non-significant.

Supplementary Figure 3.



Supplementary Figure 3. Relationship between tobacco smoking, *IL15* gene expression and NK cell gene signature in NSCLC patients.
(A) Graphic description of lung cancer sample acquisition (n=28). **(B)** IHC staining of 8-OHdG in NSCLC tumor tissues from 3 patients. Negative control was done without primary antibody. Scale bar denotes 50µm. **(C)** Correlation matrix between 3 versions of NK cell signature and *IL15* gene expression in TCGA LUAD cohort. All correlation shown has a p value<0.0001. **(D)** Classification of TCGA-LUAD cohort based on smoking history. **(E)** ROS-related gene signature score comparing smoker (n=316) and non-smoker (n=226) cohort. Data are presented as Tukey boxplots; Mann Whitney test was used to test for significance. *P<0.05. **(F)** Overall survival of TCGA-LUAD cohort non-smoker group based on median of NK gene signature score. **(G)** Progression Free interval of TCGA-LUAD cohort non-smoker group based on median of NK gene signature score. **(H)** Progression Free interval of TCGA-LUAD cohort non-smoker group based on median of *IL15* gene expression. **(F-H)** Logrank test was used to test for significance in differences in survival distribution (n=226).

Supplementary Figure 4.



Supplementary Figure 4. Oxidoreductase activity is associated with NK cytotoxicity and recruitment of immune cells.
(A) Geometric mean of normalized enrichment score for GO:0051353 comparing tumor-infiltrating NK cells versus peripheral blood NK cells. **(B)** Geometric mean of normalized enrichment score for GO:0004791 comparing tumor-infiltrating NK cells versus peripheral blood NK cells. **(A and B)** Data was analyzed from pooled NSCLC tumors(n=7) and patients' peripheral blood(n=6), and presented as Tukey boxplots; Mann-Whitney test was used to test for significance. Geometric mean of normalized cytotoxicity score comparing NK cell populations defined by **(C)** GO:0051353 enrichment and **(D)** GO:0004791 enrichment. **(C and D)** Wilcoxon signed rank test was used to test for significance. **(E)** Percentage of NK cells in NSCLC TILs cultures primed with either IL-2 or IL-15 with catalase treatment. **(F)** Percentage of dividing NK cells in sarcoma TILs cultures primed with either IL-2 or IL-15 with catalase treatment. **(E and F)** RM two-way ANOVA with Sidak's test was used to test for significance. *P<0.05, **P<0.01 and ns for non-significant. All individual data points are connected for matching replicates.

Supplementary Table 1. Clinical characteristics of non-small lung cancer patient cohort

CASE NO.	AGE (YEARS)	GENDER	SMOKING HISTORY	TUMOR SIZE (CM)	PATHOLOGY TYPE	TNM CLASSIFICATION	STAGE (AJCC)	TUMOR LOCATION
1*	56	F	N	5.0x5.0	LUAD	T2bN0M0	IB	LLL
2*	55	M	N	3.0x2.7	LUSC	T1cN0M0	IA3	RUL
3*	64	M	N	4.2x3.0	LUSC	T2bN1M0	IIB	LLL
4*	75	M	N	2.0x2.0	LUAD	T1bN0M0	IA2	LUL
5*	76	F	N	1.5x1.2	LUAD	T1bN0M0	IA2	LLL
6*	61	F	N	5.5x2.5	LUAD	T3N1M0	IIIA	RLL
7*	46	F	N	1.4x1.0	LUAD	T3N0M0	IIB	LLL
8*	63	M	Y	2.5x2.0	LUAD	T1cN0M0	IA3	RML
9*	71	M	Y	2.6x1.6	LUAD	T1cN0M0	IA3	RLL
10*	60	M	Y	1.2x1.1	LUAD	T1bN0M0	IA2	LUL
11*	67	M	Y	2.5x2.0	LUAD	T2sN1M0	IIB	RUL
12*	73	M	Y	1.0x0.7	LUAD	T1aN0M0	IA	RLL
13*	51	M	Y	2.0x2.0	LUSC	T1bN2M0	IIIA	RML
14*	67	F	N	1.2x0.6	LUAD	T1bN0M0	IA2	LLL
15*	65	M	N	2.5x1.5	LUAD	T1cN0M0	IA3	LUL
16*	70	F	N	2.8x2.0	LUAD	T1cN0M0	IA3	RLL
17*	56	M	Y	1.7x1.3	LUSC	T1bN2M0	IIIA	RML
18*	61	M	Y	1.5x1.1	LUAD	T1aN0M0	IA2	RML
19*	71	M	N	4.0x3.0	LUSC	T2aN0M0	IB	RML
20*	55	M	N	2.5x1.0	LUAD	T1cN0M0	IA3	RUL
21*	44	M	N	2.5x0.7	LUAD	T1cN0M0	IA3	RLL
22*	52	F	N	2.0x1.2	LUAD	T1bN0M0	IA2	LUL
23*	59	M	N	1.1x1.0	LUAD	T1bN0M0	IA2	LUL
24	63	M	Y	1.5x1.0	LUSC	T1bN0M0	IA2	LUL
25	71	F	N	1.4x1.0	LUAD	T1bN0M0	IA2	RLL
26	55	F	Y	2.2x1.0	LUAD	T1cN0M0	IA3	RML
27	66	M	N	3.0x3.0	LUSC	T1cN1M0	IIB	LLL
28	49	F	N	2.0x1.3	LUAD	T1bN0M0	IA2	LLL
29	55	M	Y	2.5x2.3	LUAD	T1cN0M0	IA3	RUL

AJCC: American Joint Committee on Cancer: 8thedition. **LLL**: Left lower lobe. **LUL**: Left upper lobe. **RUL**: Right upper lobe. **RML**: Right middle lobe. **RLL**: Right lower lobe. ***** Cases were separated into Smoker and Non-smoker cohorts for CellROX staining, the rest were only used for TILs culture.

Supplementary Table 2. Clinical characteristics of sarcoma patient cohort

Case No.	*Age (years)*	*Gender*	*Tumor size (cm)*	*Type*	*Site*	*Pathology type*	*Necrosis*	*Mitotic rate*	*Grade*	*Grading system*
1	81	M	6.5 x 5.3 x 3.0	Primary	Subcutaneous	Myxofibrosarcoma	<50%	>20 / 10 HPF	3	FNCLCC
2	86	M	5.0 x 3.2 x 2.5	Primary	Subcutaneous	Undifferentiated pleomorfic sarcoma (OPS), spindle cell	<50%	>20 / 10 HPF	3	FNCLCC
3	42	F	12.0 x 9.0 x 6.0	Recurrence	Subcutaneous	Malignant peripheral nerve sheet tumor (MPNST)	<50%	>20 / 10 HPF	n.a.	
4	76	M	6.0 x 6.0 x 5.0	Recurrence	Retroperitoneal	Inflammatory myofibroblastic tumor (IMT)	0%	<10 / 10 HPF	1	FNCLCC
5	62	F	28.0 x16.0x 8.0	Primary	Retroperitoneal	Well-differentiated liposarcoma	0%	<10 / 10 HPF	1	FNCLCC
6	33	F	6.0 x 4.0 x 3.0	Recurrence	Intramuscular	Pleomorfic liposarcoma	0%	>10 / 10 HPF	2	FNCLCC
7	77	F	6.5 x 5.5 x 4.5	Recurrence	Intramuscular	Myxofibrosarcoma	0%	>10 / 10 HPF	2	FNCLCC
8	80	F	16.0x13.0x10.0	Primary	Intraabdominal	Abdominal desmoid	0%	0 / 10 HPF	n.a.	
9	76	K	10.0 x 7.0 x 7.0	Primary	Subcutaneous	Undifferentiated pleomorfic sarcoma (OPS), epitheloid	>50%	>20 / 10 HPF	2	FNCLCC
10	67	F	9.5 x 8.0 x 6.0	Primary	Subcutaneous	Well-differentiated liposarcoma	0%	0 / 10 HPF	1	FNCLCC
11	28	F	8.0 x 6.0 x 5.0	Primary	Thorax	Aggressive fibromatosis	0%	<10 / 10 HPF	n.a.	
12	39	F	5.0 x 5.0 x 5.0	Primary	Retroperitoneal	Pleomorfic leiomyosarcoma	<50%	>20 / 10 HPF	3	FNCLCC
13	81	K	11.0 x 8.0 x 8.0	Primary	Intramuscular	Undifferentiated pleomorfic sarcoma (OPS), spindle cell	<50%	>20 / 10 HPF	3	FNCLCC
14	73	K	7.5 x 5.5 x 4.5	Primary	Subcutaneous	Spindle-cell lipoma	0%	0 / 10 HPF	n.a.	
15	77	K	8.0 x 4.0 x 3.5	Primary	Subcutaneous	Angiosarcoma	0%	<10 / 10 HPF	2	WHO

Supplementary Table 3. Antibody and reagent information

ANTIGEN	FLUOROCHROME	CLONE	ISOTYPE	COMPANY	CATALOG NO.
CD3	PE	OKT3	Mouse IgG2a, κ	Biolegend	317308
CD3	PE-CF594	SP34-2	Mouse IgG1, κ	BD	562406
CD4	PE	SK3	Mouse IgG1, κ	Biolegend	344606
CD4	Pacific Blue	SK3	Mouse IgG1, κ	Biolegend	344625
CD8	PE-Cy7	RPA-T8	Mouse IgG1, κ	BD	557746
CD8a	PerCP-Cy5.5	RPA-T8	Mouse IgG1, κ	Biolegend	301032
CD16	PerCP-Cy5.5	3G8	Mouse IgG1, κ	Biolegend	302028
CD16	Pacific Blue	3G8	Mouse IgG1, κ	Biolegend	302032
CD56	PE-Cy7	HCD56	Mouse IgG1, κ	Biolegend	318318
CD56	BV785	5.1H11	Mouse IgG1, κ	Biolegend	362550
CD56	BV570	HCD56	Mouse IgG1, κ	Biolegend	318329
CD45	BV650	HI30	Mouse IgG1, κ	Biolegend	304043
CD107a	PerCP-Cy5.5	H4A3	Mouse IgG1, κ	Biolegend	328615
CD107a	FITC	H4A3	Mouse IgG1, κ	Biolegend	328606
IFN-γ	APC	B27	Mouse IgG1, κ	Biolegend	506510
Ki-67	AF700	B56	Mouse IgG1, κ	BD	561277
S6(pS235/pS236)	AF488	N7-548	Mouse IgG1, κ	BD	560434
8-Hydroxy-2'-Deoxyguanosine	/	N45.1	Mouse IgG1	Abcam	Ab48508
NCAM/CD56	/	polyclonal	Rabbit, IgG	Proteintech	14225-1
TXNIP	/	EPR14774	Rabbit, IgG	Abcam	ab188865
Thioredoxin-1	/	EPR6111	Rabbit, IgG	Abcam	ab109385
Cell Trace ™ Violet	/	/	/	Invitrogen	C34557
CFSE	/	/	/	Biolegend	423801
AUQA live/dead	/	/	/	Invitrogen	L34957
Near-IR live/dead	/	/	/	Invitrogen	L10119

Supplementary Table 4. Primers used for qRT-PCR

Gene	**Forward (5'-3')**	**Reverse (5'-3')**
TBP	CCACTCACAGACTCTCACAAC	CTGCGGTACAATCCCAGAACT
TXN	GTGAAGCAGATCGAGAGCAAG	CGTGGCTGAGAAGTCAACTACTA
TXN2	TTCAAGACCGAGTGGTCAACA	CACCTCATACTCAATGGCGAG
TXNIP	GGTCTTTAACGACCCTGAAAAGG	ACACGAGTAACTTCACACACCT
TXNRD1	TAGGACAAGCCCTGCAAGACT	CCCCAATTCAAAGAGCCAATGT