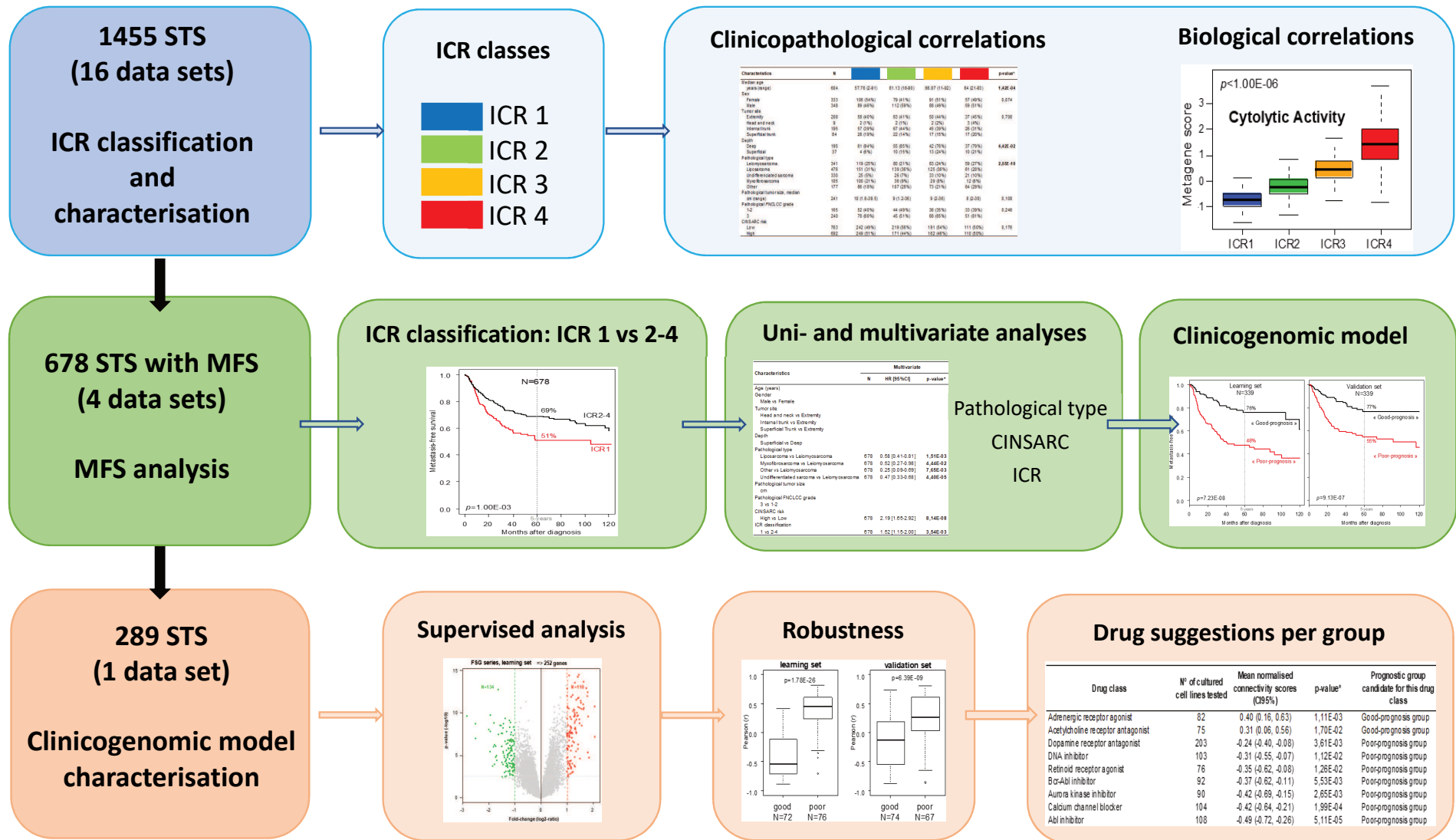


Supplementary Table 1: List of soft tissue sarcoma (STS) data sets included.

Reference	Source of data	Technological platform	N° of probe sets/genes	All samples	STS primary tumor samples included in the present analysis	STS primary tumor samples included in the present MFS analysis
Baird K et al., Cancer Res 2005	GEO database, GSE2553	Homemade, spotted DNA/cDNA	12K	181	146	0
Barretina J et al., Nat Genet 2010	GEO database, GSE21124	Affymetrix, array U133 A	22K	158	126	0
Beck A et al., Oncogene 2010	GEO database, GSE17555	Stanford, spotted DNA/cDNA	24K	51	26	0
Chibon F et al., Nat. Med. 2010	GEO database, GSE21050	Affymetrix, array U133 Plus 2.0	54K	310	310	289
Detwiller K et al., Cancer Res 2005	GEO database, GSE2719	Affymetrix, array U133 A	22K	54	37	0
Gibault L et al., J Pathol 2011	GEO database, GSE23980	Affymetrix, array U133 Plus 2.0	54K	171	140	0
Gobble R et al., Cancer Res 2011	GEO database, GSE30929	Affymetrix, array U133 A	22K	140	34	140
Hadju M et al., J Pathol 2010	http://cbio.mskcc.org/public/SFT/	Affymetrix, array U133 Plus 2.0	54K	56	30	0
Henderson S et al., Genome Biology 2007	Array Express database, E-MEXP-353	Affymetrix, array U133 A	22K	96	42	0
Nakayama R et al., Modern Pathol 2007	GEO database, GSE6481	Affymetrix, array U133 A	22K	105	99	0
Nielsen TO et al., Lancet 2002	GEO database, GSE3443	Stanford, spotted DNA/cDNA	24K	46	31	0
Renner M et al., Genome Biol 2013	GEO database, GSE52392	Illumina, array Human HT-12 V3.0	48K	94	79	0
Skubitz et al., Cancer 2012	Masonic Cancer Center	Homemade, spotted DNA/cDNA	16K	73	71	68
TCGA, Cell 2017	TCGA portal, https://tcga-data.nci.nih.gov	Illumina, RNA sequencing V2	25K	265	224	181
West R et al., PLoS Biology 2005	http://microarray-pubs.stanford.edu/tma-portal/DTF_SFTbreast	Stanford, spotted DNA/cDNA	24K	57	29	0
Ylipää A et al., Cancer 2011	http://www3.mdanderson.org/~genomics/sarcoma_data_matrix_for_supplemental.zip	Agilent, array 44K G4112A (012391)	44K	68	31	0
Total					1,455	678

Supplementary Figure 1: Diagram of analytic workflow



Supplementary Table 2: ICR classification and correlations with clinicopathological characteristics

Characteristics	N	ICR1 N=491 (34%)	ICR2 N=390 (27%)	ICR3 N=353 (24%)	ICR4 N=221 (15%)	p-value*
Median age						
years (range)	604	57.76 (2-91)	61.13 (16-90)	66.07 (11-92)	64 (21-93)	1.42E-04
Sex						
Female	333	106 (54%)	79 (41%)	91 (51%)	57 (49%)	0.074
Male	348	89 (46%)	112 (59%)	88 (49%)	59 (51%)	
Tumor site						
Extremity	208	58 (40%)	63 (41%)	50 (44%)	37 (45%)	0.708
Head and neck	9	2 (1%)	2 (1%)	2 (2%)	3 (4%)	
Internal trunk	195	57 (39%)	67 (44%)	45 (39%)	26 (31%)	
Superficial trunk	84	28 (19%)	22 (14%)	17 (15%)	17 (20%)	
Depth						
Deep	195	61 (94%)	55 (85%)	42 (76%)	37 (79%)	4.42E-02
Superficial	37	4 (6%)	10 (15%)	13 (24%)	10 (21%)	
Pathological type						
Leiomyosarcoma	341	119 (25%)	80 (21%)	83 (24%)	59 (27%)	2.55E-10
Liposarcoma	476	151 (31%)	139 (36%)	125 (36%)	61 (28%)	
Undifferentiated sarcoma	330	86 (18%)	107 (28%)	73 (21%)	64 (29%)	
Myxofibrosarcoma	105	25 (5%)	26 (7%)	33 (10%)	21 (10%)	
Other	177	100 (21%)	36 (9%)	29 (8%)	12 (6%)	
Pathological tumor size, median						
cm (range)	241	10 (1.6-39.5)	9 (1.2-36)	9 (2-36)	8 (2-30)	0.108
Pathological <i>FNCLCC</i> grade						
1-2	165	52 (40%)	44 (49%)	36 (35%)	33 (39%)	0.246
3	240	78 (60%)	45 (51%)	66 (65%)	51 (61%)	
CINSARC risk						
Low	763	242 (49%)	219 (56%)	191 (54%)	111 (50%)	0.176
High	692	249 (51%)	171 (44%)	162 (46%)	110 (50%)	

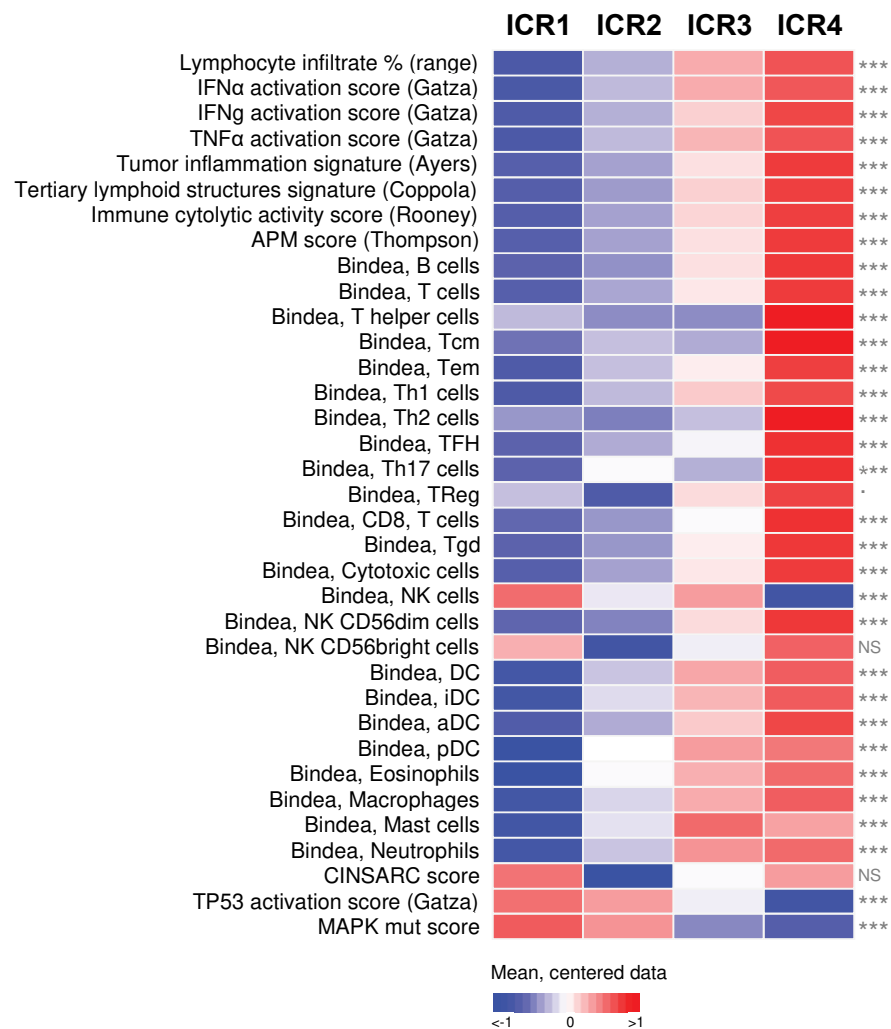
FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; *, One-way ANOVA test for continuous variables and Fisher's exact test for discrete variables

Supplementary Table 3: ICR classification and correlations with biological parameters.

Characteristics	N	ICR1 (N=491, 34%)	ICR2 (N=390, 27%)	ICR3 (N=353, 24%)	ICR4 (N=221, 15%)	p-value*	ICR2-4 (N=964, 66%)	p-value**
Lymphocyte infiltrate % (range)	224	0.54 (0-3)	0.82 (0-3)	1.11 (0-5)	1.31 (0-8)	4,63E-04	1.02 (0-8)	7,68E-04
IFN α activation score (Gatza)	1455	0.24 (0.01-0.95)	0.48 (0.04-1)	0.7 (0.01-0.98)	0.85 (0.13-1)	1,25E-246	0.64 (0.01-1)	1,50E-168
IFN γ activation score (Gatza)	1455	0.35 (0.04-0.99)	0.46 (0.05-0.99)	0.56 (0.03-1)	0.7 (0.07-1)	2,80E-58	0.55 (0.03-1)	6,22E-39
TNF α activation score (Gatza)	1455	0.31 (0.01-0.96)	0.48 (0.02-0.98)	0.63 (0-0.99)	0.76 (0.06-1)	3,23E-117	0.6 (0-1)	1,13E-76
T-cell-inflamed signature (Ayers)	1455	7.61 (4.24-10.41)	8.17 (6.32-10.24)	8.83 (5.99-10.78)	9.94 (7.43-12.42)	8,21E-193	8.82 (5.99-12.42)	8,69E-85
Tertiary lymphoid structures signature (Coppola)	1455	7.08 (1.14-11.14)	7.77 (3.23-10.53)	8.73 (5.67-11.58)	9.94 (6.5-13.23)	1,88E-126	8.62 (3.23-13.23)	6,36E-62
Immune cytolytic activity score (Rooney)	1384	-0.72 (-2.67-1.63)	-0.19 (-2.32-2.24)	0.45 (-1.08-1.62)	1.34 (-1.55-3.82)	1,97E-279	0.38 (-2.32-3.82)	3,72E-161
APM score (Thompson)	1455	-4.58 (-26.37-11.15)	-1.3 (-16.91-21.37)	2.6 (-37.99-20.36)	9.27 (-4.79-26.32)	6,30E-153	2.55 (-37.99-26.32)	7,26E-82
Bindea, B cells	1455	-0.18 (-1.3-0.94)	-0.08 (-1.08-3.43)	0.1 (-1.39-3.21)	0.37 (-0.97-2.68)	2,85E-66	0.09 (-1.39-3.43)	6,05E-41
Bindea, T cells	1455	-0.49 (-1.81-0.46)	-0.13 (-1.18-2.65)	0.25 (-0.81-1.66)	0.97 (-0.79-2.74)	3,17E-261	0.26 (-1.18-2.74)	6,82E-155
Bindea, T helper cells	1455	-0.01 (-1.38-0.98)	-0.04 (-1.06-0.99)	-0.04 (-1.71-1.72)	0.21 (-0.99-1.23)	1,13E-09	0.02 (-1.71-1.72)	1,31E-01
Bindea, Tcm	1455	-0.05 (-1.57-0.96)	-0.01 (-1.29-1.13)	-0.02 (-0.85-1.92)	0.14 (-0.9-1.01)	1,10E-09	0.02 (-1.29-1.92)	6,87E-05
Bindea, Tem	1455	-0.06 (-1.28-1.57)	0 (-0.81-0.89)	0.03 (-1.25-1.49)	0.11 (-1.03-1.25)	2,49E-12	0.04 (-1.25-1.49)	2,59E-08
Bindea, Th1 cells	1455	-0.15 (-1.01-0.6)	-0.01 (-0.72-0.83)	0.1 (-0.54-1.21)	0.25 (-0.59-1.27)	1,52E-95	0.09 (-0.72-1.27)	1,68E-62
Bindea, Th2 cells	1455	-0.01 (-1-0.83)	-0.02 (-0.9-1.01)	0.01 (-1.15-1.01)	0.15 (-0.72-1.33)	3,93E-08	0.03 (-1.15-1.33)	0,0295
Bindea, TFH	1455	-0.08 (-1.28-0.74)	-0.02 (-0.88-1.3)	0.02 (-1.1-1.69)	0.17 (-0.45-1.39)	2,52E-29	0.04 (-1.1-1.69)	2,16E-15
Bindea, Th17 cells	1448	-0.12 (-4.11-4.64)	0.01 (-1.8-3.1)	-0.04 (-3.25-3.37)	0.2 (-1.33-3.28)	1,18E-06	0.04 (-3.25-3.37)	1,10E-04
Bindea, TReg	1152	0.03 (-2.35-3.94)	-0.07 (-2.22-2.67)	0.09 (-2.33-9.37)	0.21 (-2.89-3.4)	5,92E-02	0.05 (-2.89-3.37)	7,90E-01
Bindea, CD8, T cells	1455	-0.09 (-0.9-0.71)	-0.04 (-1.02-0.78)	0.03 (-0.8-1.8)	0.22 (-0.78-1.35)	1,10E-50	0.05 (-1.02-1.8)	1,09E-24
Bindea, Tgd	1384	-0.24 (-1.8-2.42)	-0.1 (-1.63-1.52)	0.12 (-1.36-2.11)	0.51 (-1.05-2.92)	1,84E-59	0.11 (-1.63-2.92)	4,28E-29
Bindea, Cytotoxic cells	1455	-0.4 (-1.51-1.04)	-0.12 (-1.43-1.46)	0.21 (-0.75-1.29)	0.79 (-0.47-2.53)	5,76E-229	0.21 (-1.43-2.53)	9,37E-126
Bindea, NK cells	1455	0.03 (-0.99-0.82)	0 (-0.75-0.63)	0.02 (-1.03-1.33)	-0.04 (-0.79-1.01)	6,53E-03	0 (-1.03-1.33)	1,95E-02
Bindea, NK CD56dim cells	1455	-0.07 (-1.97-4.43)	-0.04 (-1.29-1.68)	0.06 (-1.48-2.22)	0.19 (-1.86-1.55)	3,23E-14	0.05 (-1.86-2.22)	2,53E-06
Bindea, NK CD56bright cells	1455	0.01 (-1.91-2.28)	-0.06 (-1.18-2.23)	-0.01 (-2.25-1.69)	0.03 (-1.31-1.33)	6,69E-01	-0.02 (-2.25-2.23)	0,191
Bindea, DC	1455	-0.27 (-1.54-1.4)	0.01 (-1.38-1.82)	0.23 (-1.09-2.15)	0.37 (-0.96-1.75)	1,32E-68	0.17 (-1.38-2.15)	2,65E-56
Bindea, iDC	1455	-0.17 (-1.17-1)	0.02 (-0.75-0.79)	0.11 (-0.69-1.42)	0.21 (-0.61-1.02)	2,58E-70	0.1 (-0.75-1.42)	2,28E-54
Bindea, aDC	1455	-0.41 (-1.66-1.58)	-0.07 (-2.06-1.27)	0.28 (-1.01-1.94)	0.72 (-0.69-2.79)	5,48E-164	0.24 (-2.06-2.79)	1,29E-99
Bindea, pDC	1152	-0.31 (-3.06-3.33)	0.09 (-2.18-3.07)	0.24 (-2.36-2.97)	0.31 (-1.86-3.32)	5,16E-17	0.2 (-2.36-3.32)	3,52E-18
Bindea, Eosinophils	1455	-0.05 (-0.75-0.81)	0.01 (-0.92-0.81)	0.03 (-0.6-1.94)	0.05 (-0.64-0.87)	2,94E-08	0.03 (-0.92-1.94)	2,78E-08
Bindea, Macrophages	1455	-0.23 (-1.13-0.89)	0.02 (-0.78-1.15)	0.17 (-0.77-1.25)	0.28 (-0.74-1.82)	3,46E-87	0.13 (-0.78-1.82)	8,89E-68
Bindea, Mast cells	1455	-0.15 (-1.11-2.65)	0.01 (-1.01-1.48)	0.15 (-0.88-3.17)	0.1 (-0.66-1.43)	4,37E-23	0.08 (-1.01-3.17)	5,09E-24
Bindea, Neutrophils	1455	-0.21 (-1.31-0.95)	0 (-0.79-2.28)	0.18 (-0.82-3.24)	0.24 (-0.61-1.17)	2,70E-74	0.12 (-0.82-3.24)	7,23E-60
CINSARC classification								
Low	763	242 (49%)	219 (56%)	191 (54%)	111 (50%)	0,176	521 (54%)	0.0963
High	692	249 (51%)	171 (44%)	162 (46%)	110 (50%)		443 (46%)	
TP53 activation score (Gatza)	1455	0.55 (0-1)	0.52 (0-1)	0.45 (0-1)	0.31 (0-1)	1,18E-26	0.44 (0-1)	2,62E-11
MAPK mut score	1455	0.04 (-0.5-0.8)	0.02 (-0.53-0.58)	-0.04 (-0.49-0.41)	-0.06 (-0.61-0.57)	2,67E-14	-0.02 (-0.61-0.58)	2,72E-07

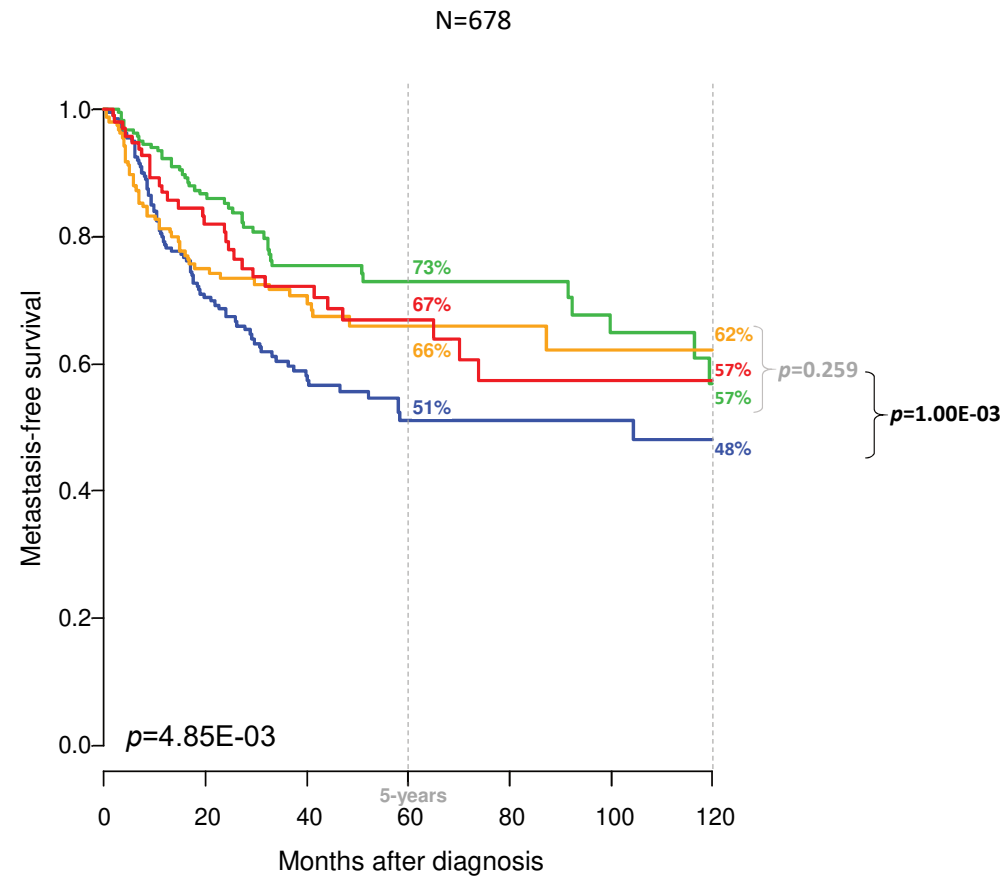
*, One-way ANOVA test to compare the four ICR groups; **, Student t-test to compare ICR2-4 versus ICR1 groups

Supplementary Table 4: ICR classification and correlations with biological parameters



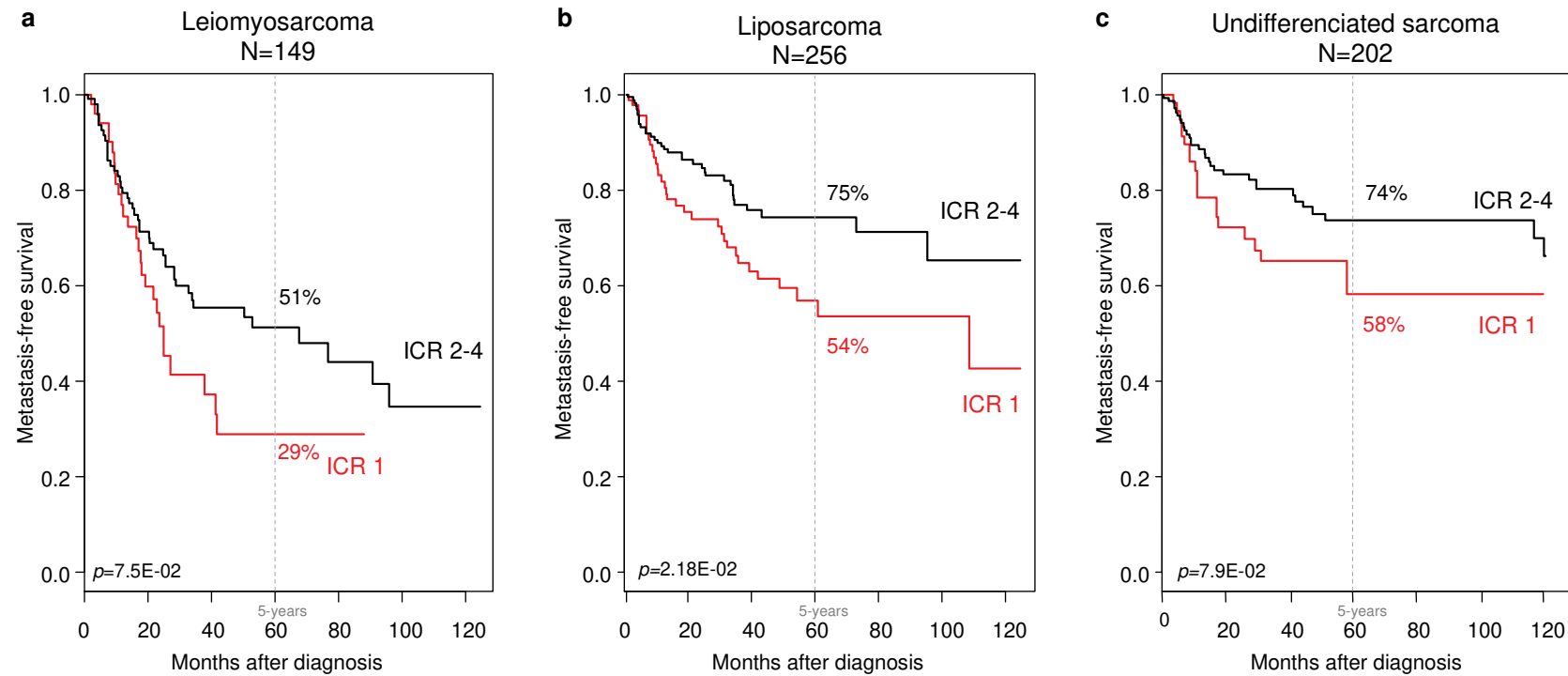
Heatmap representation of expression scores of several immune-related factors and non-immune related variables in the four ICR classes. The mean scores are shown as median-centered according to the colored scale shown at the bottom. The p-values of comparison between the four classes (one-way ANOVA test) are shown on the right (NS, not significant; ***, <0,001).

Supplementary Figure 2: Metastasis-free survival in patients with STS according to the four ICR classes.
Kaplan-Meier MFS curves according to the 4 ICR classes in all patients. The p-values are for the log-rank test.



Supplementary Figure 3: Metastasis-free survival in patients with STS according to ICR classification in each major pathological type.

Kaplan-Meier MFS curves according to the ICR classification in patients with leiomyosarcoma (a), with liposarcoma (b), and with undifferentiated pleomorphic sarcoma (c).



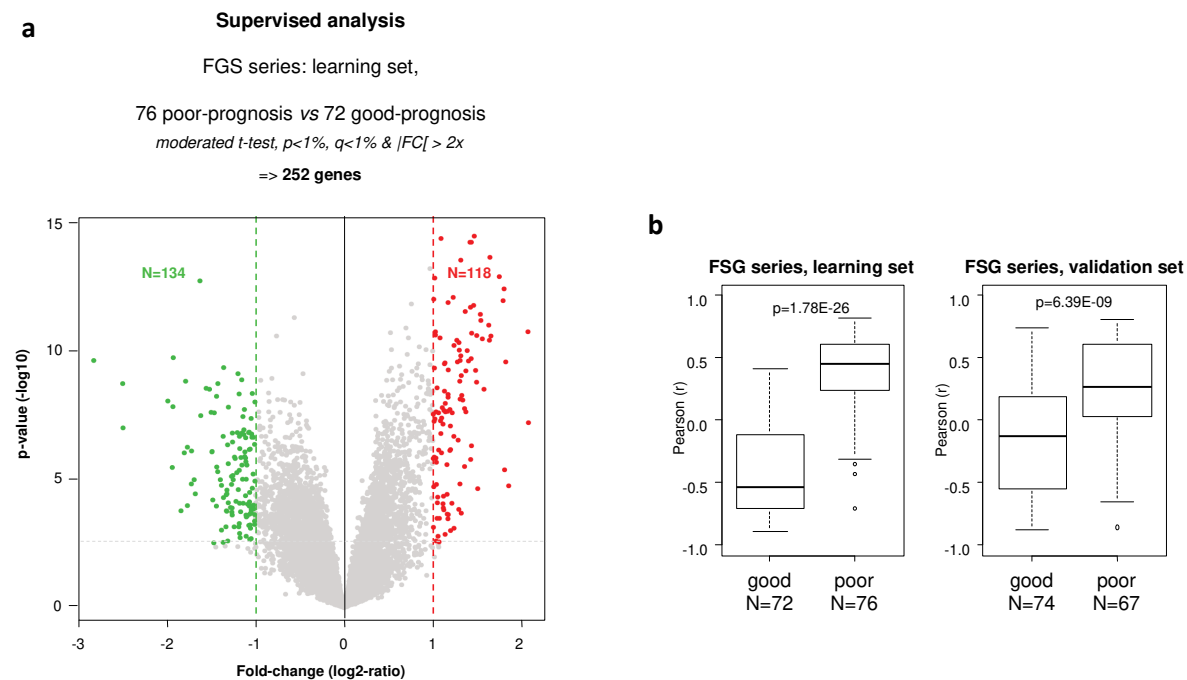
Supplementary Table 5: Comparison of prognostic information of several models based on unique and combined variables in the validation set (N=339)

Cox models comparison Likelihood ratio (X^2 Chi-squared)			timeROC, 5-year MFS	
Pathological type	LR- X^2	17.61	AUC	0.556
	p-value	1.47E-03	p-value*	1.02E-01
CINSARC	LR- X^2	18.97	AUC	0.606
	p-value	1.33E-05	p-value*	2.29E-03
ICR	LR- X^2	6.65	AUC	0.599
	p-value	9.91E-03	p-value*	2.10E-03
CINSARC+ICR	LR- X^2	23.84	AUC	0.652
	p-value	6.67E-06	p-value*	1.19E-04
CINSARC+Pathological type	LR- X^2	32.29	AUC	0.621
	p-value	5.20E-06	p-value*	2.56E-03
Pathological type+ICR	LR- X^2	24.75	AUC	0.619
	p-value	1.56E-04	p-value*	3.39E-03
CINSARC+Pathological type+ICR	LR- X^2	37.83	AUC	0.659
	p-value	1.21E-06	p-value*	1.49E-04
CINSARC+ICR vs. CINSARC	LR- ΔX^2	4.87	Δ AUC	0.046
	p-value	2.73E-02	p-value**	2.49E-02
Pathological type+ICR vs. Pathological type	LR- ΔX^2	7.13	Δ AUC	0.063
	p-value	7.58E-03	p-value**	7.44E-03
CINSARC+Pathological type+ICR vs. CINSARC+Pathological type	LR- ΔX^2	5.54	Δ AUC	0.037
	p-value	1.86E-02	p-value**	4.66E-03
CINSARC+Pathological type+ICR vs. Pathological type	LR- ΔX^2	20.22	Δ AUC	0.102
	p-value	4.08E-05	p-value**	2.76E-02
CINSARC+Pathological type+ICR vs. CINSARC	LR- ΔX^2	18.86	Δ AUC	0.053
	p-value	2.04E-03	p-value**	1.85E-02
CINSARC+Pathological type+ICR vs. ICR	LR- ΔX^2	31.18	Δ AUC	0.060
	p-value	8.64E-06	p-value**	4.32E-01

*, p-value estimated using bootstrap resampling; **, p-value estimated using timeROC

Supplementary Figure 4: Identification and validation of 252 genes differentially expressed between the two model-based prognostic groups.

(a) Identification of the signature in the learning set (N=148) extracted from the French Sarcoma Group series (FSG). Volcano-plot showing the 254 genes differentially expressed between the two prognostic classes. **(b)** Box plot of the Pearson correlation coefficient of each sample with the mean expression profile of poor-prognosis samples from the learning set in the learning and validation set extracted from the FSG series. The p-value is for the Student t-test.

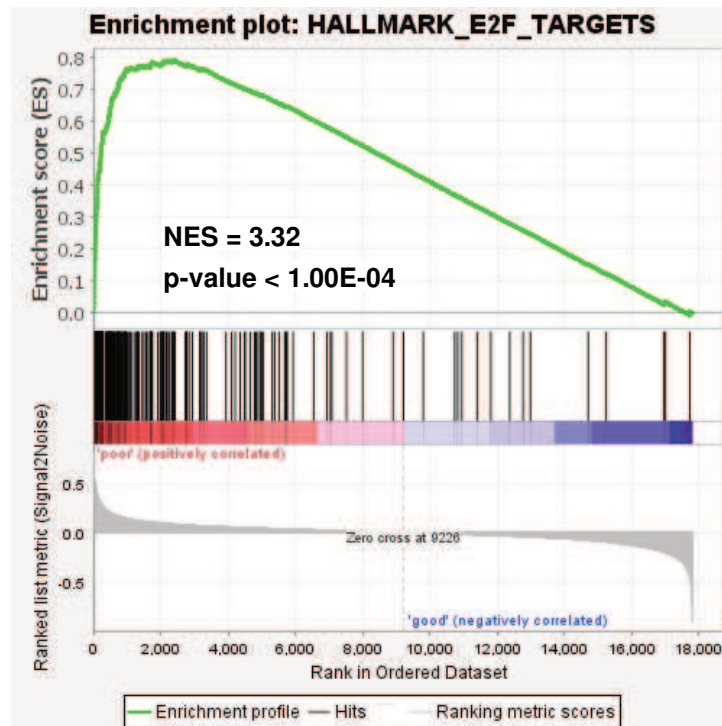


Supplementary Table 6: Hallmark pathways significantly associated with the 252-gene signature according to GSEA.

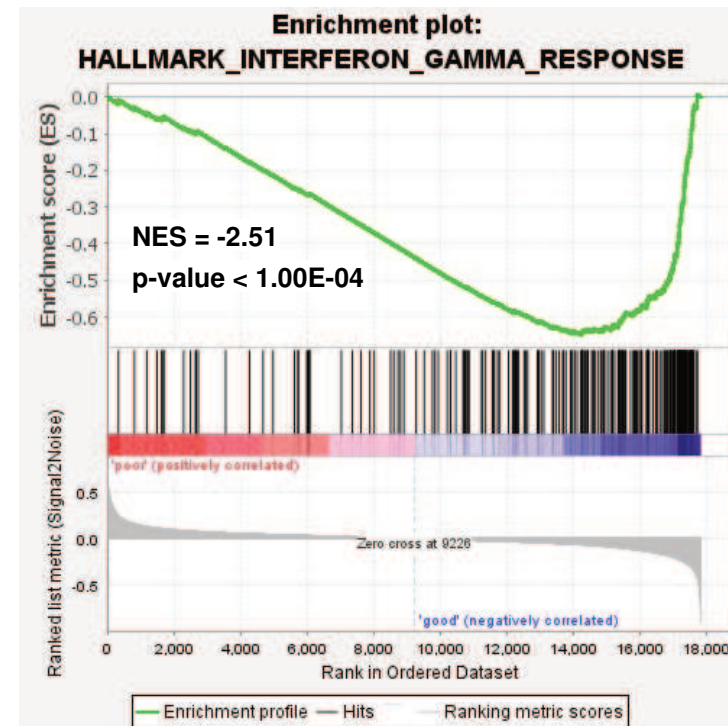
Hallmark (v7.4) terms	SIZE	ES	NES	p-value	q-value	Associated to
E2F_TARGETS	199	0,79	3,32	<1.0E-04	<1.0E-04	Poor-prognosis group
G2M_CHECKPOINT	200	0,77	3,24	<1.0E-04	<1.0E-04	Poor-prognosis group
MYC_TARGETS_V1	200	0,59	2,44	<1.0E-04	<1.0E-04	Poor-prognosis group
MITOTIC_SPINDLE	199	0,58	2,43	<1.0E-04	<1.0E-04	Poor-prognosis group
MTORC1_SIGNALING	200	0,51	2,17	<1.0E-04	<1.0E-04	Poor-prognosis group
SPERMATOGENESIS	127	0,51	1,99	<1.0E-04	1,30E-04	Poor-prognosis group
MYC_TARGETS_V2	58	0,52	1,84	<1.0E-04	1,11E-04	Poor-prognosis group
DNA_REPAIR	150	0,40	1,64	<1.0E-04	2,66E-03	Poor-prognosis group
GLYCOLYSIS	199	0,37	1,57	<1.0E-04	6,48E-03	Poor-prognosis group
ESTROGEN_RESPONSE_EARLY	199	-0,41	-1,59	2,74E-03	6,32E-03	Good-prognosis group
MYOGENESIS	198	-0,41	-1,59	<1.0E-04	6,70E-03	Good-prognosis group
ANGIOGENESIS	36	-0,59	-1,74	3,42E-03	1,33E-03	Good-prognosis group
ADIPOGENESIS	200	-0,46	-1,78	<1.0E-04	7,57E-04	Good-prognosis group
APOPTOSIS	161	-0,47	-1,79	<1.0E-04	7,15E-04	Good-prognosis group
BILE_ACID_METABOLISM	108	-0,50	-1,80	<1.0E-04	5,89E-04	Good-prognosis group
COAGULATION	133	-0,50	-1,82	<1.0E-04	6,38E-04	Good-prognosis group
P53_PATHWAY	200	-0,48	-1,86	<1.0E-04	2,15E-04	Good-prognosis group
IL2_STAT5_SIGNALING	199	-0,48	-1,88	<1.0E-04	2,37E-04	Good-prognosis group
XENOBIOTIC_METABOLISM	195	-0,50	-1,93	<1.0E-04	1,25E-04	Good-prognosis group
IL6_JAK_STAT3_SIGNALING	87	-0,60	-2,09	<1.0E-04	<1.0E-04	Good-prognosis group
COMPLEMENT	200	-0,55	-2,12	<1.0E-04	<1.0E-04	Good-prognosis group
INTERFERON_ALPHA_RESPONSE	97	-0,63	-2,18	<1.0E-04	<1.0E-04	Good-prognosis group
KRAS_SIGNALING_UP	198	-0,59	-2,26	<1.0E-04	<1.0E-04	Good-prognosis group
TNFA_SIGNALING_VIA_NFKB	199	-0,60	-2,30	<1.0E-04	<1.0E-04	Good-prognosis group
INFLAMMATORY_RESPONSE	197	-0,60	-2,31	<1.0E-04	<1.0E-04	Good-prognosis group
ALLOGRAFT_REJECTION	195	-0,61	-2,34	<1.0E-04	<1.0E-04	Good-prognosis group
INTERFERON_GAMMA_RESPONSE	200	-0,65	-2,51	<1.0E-04	<1.0E-04	Good-prognosis group

Supplementary Figure 5: Enrichment plots for the top two significant GSEA signatures associated with the 252-gene signature.

a



b



Supplementary Table 7: ICR classification of baseline mice tumors from Wisdom et al (Nat Commun 2020).

Characteristics	N	Primary tumors	Transplant tumors	p-value*
ICR score	13	-1 (-2.08-0.07)	0.07 (-0.79-0.58)	3.36E-02
ICR class				5.17E-02
ICR1	9	8 (89%)	1 (25%)	
ICR2-4	4	1 (11%)	3 (75%)	

* Wilcoxon or Fisher's Exact test