

**Supplementary Table 1. Clinicopathological data of 51 osteosarcoma patients**

patientID	Age	Sex	Histological subtype	Tumour Location	Huvos	ToM	ToM (2nd)	ToD	ToF	Origin
L3446	174	M	Giant cell rich	left distal femur	4	0	16	27	27	WWU
L3447	162	M	Osteoblastic	left proximal humerus	2	16		21	21	WWU
L3448	170	M	Osteoblastic	left distal femur	3	0	22		46	WWU
L3449	133	F	Fibroblastic	left distal femur	1	10			28	WWU
L3431	81	F	Osteoblastic	humerus	1	5		11	11	WWU
L3432	144	M	Chondroblastic	tibia	2	30			37	WWU
L3433	204	F	Osteoblastic	left femur	1	9		33	33	WWU
L3434	181	M	Sclerosing	right proximal tibia	1	25			25	WWU
L3435	200	M	Osteoblastic	right proximal femur	1	0	13	30	30	WWU
L3436	205	M	Chondroblastic	left distal femur	3	9		35	35	WWU
L3437	183	M	Osteoblastic	distal femur	2	0	21	27	27	WWU
L3438	220	M	Osteoblastic	right proximal tibia	4	0	18		26	WWU
L3439	385	M	Chondromyxoid fibroma like	right humerus	1	10		18	18	WWU
L3440	264	M	Osteoblastic	femur	1	10			36	IOR
L3441	228	M	Osteoblastic	femur	3	24			123	IOR
L3442	144	F	Osteoblastic	femur	3	44		110	110	IOR
L3443	204	F	Fibroblastic	humerus	2				63	IOR
L3444	264	M	Fibroblastic	humerus	1				60	IOR
L3445	696	F	Telangiectatic	tibia					60	IOR
L1386	101	M	Osteoblastic	diaphysis femur left	1				105	LUMC
L2295	487	F	Anaplastic	proximal femur left	2				97	LUMC
L2611	242	F	Osteoblastic	distal femur right	3				91	LUMC
L2281	212	M	Osteoblastic	proximal fibula left	2	36		64	64	LUMC
L2298	244	F	Anaplastic	distal femur right	3				94	LUMC
L2300	217	M	Osteoblastic	proximal fibula right	3				87	LUMC
L2297	137	F	Osteoblastic	proximal tibia left	2				77	LUMC
L2292	136	M	Osteoblastic	proximal tibia left	3				78	LUMC
L2613	181	M	Osteoblastic	proximal tibia right	3				40	LUMC
L2614	165	M	Osteoblastic	distal femur left	2	0		29	29	LUMC
L2615	261	M	Osteoblastic	proximal tibia left	3				35	LUMC
L2616	218	M	Osteoblastic	proximal fibula left	2	24			32	LUMC
L2617	181	F	Osteoblastic	proximal tibia left	4				32	LUMC
L2618	96	M	Osteoblastic	distal femur left	2	0			31	LUMC
L1368	177	M	Osteoblastic	distal femur left	4	0			95	LUMC
L1369	212	F	Osteoblastic	distal femur right	2	17		83	83	LUMC
L1370	216	M	Osteoblastic	distal femur left	3				246	LUMC
L1016	200	M	Osteoblastic	proximal tibia left	1	6		10	10	LUMC
L2619	128	F	Osteoblastic	distal femur right	1	0		25	25	LUMC
L1372	200	M	Telangiectatic	distal femur right	1	0		25	25	LUMC
L2620	217	M	Osteoblastic	distal femur left	2				219	LUMC
L428	192	F	Osteoblastic	proximal tibia right	2				193	LUMC
L436	37	F	Osteoblastic	proximal tibia left	4				194	LUMC
L1376	164	F	Telangiectatic	proximal tibia right	1	18		40	40	LUMC
L1378	197	F	Fibroblastic, MFH-like	distal femur left	2			14	14	LUMC
L2294	205	F	Osteoblastic	distal femur left	1				147	LUMC
L2289	136	M	Fibroblastic	distal femur left	2				135	LUMC
L2290	440	M	Fibroblastic	distal femur left	2	10		13	13	LUMC
L2301	304	M	Osteoblastic	proximal tibia left	2	27		47	47	LUMC
L1382	175	M	Osteoblastic	distal tibia right	2				143	LUMC
L2302	229	F	Chondroblastic	proximal humerus right	2				120	LUMC
L1385	200	M	Osteoblastic	proximal humerus left		0		11	11	LUMC

Unit of time is months; ToM: time until metastasis detection after diagnosis; ToD: time until death after diagnosis; ToF: total time of follow up after diagnosis; The Origins are WWU: Westfälische Wilhelmsuniversität, Münster, Germany; IOR: Istituto Ortopedico Rizzoli, Bologna, Italy; LUMC: Leiden University Medical Centre, The Netherlands.

**Supplementary Table 2. Clinical and histopathological characteristics of the soft tissue sarcoma patients.**

	Number of Patients (%)
<b>Stage</b>	
I	23
II	68
III	51
IV	15
<b>Tumor resection*</b>	
Radical	110
Non-radical	47
<b>Tumor localization**</b>	
Extremities	102
Trunk	13
Head/neck	4
Intraabdominal/retroperitoneum	34
Multiple localizations	2
<b>Tumor type</b>	
Liposarcoma	37
Fibrosarcoma and MFH***	49
Neurogenic sarcoma	22
Rhabdo- and Leiomyosarcoma	34
Others	15

\*Radical resection: primary wide excision, primary resection of compartment; non-radical resection: enucleation, palliative resection

\*\*The tumor localization of 2 patients was not known

\*\*\*Malignant Fibrous Histiocytoma

**Supplementary Table 3. Summary of p53 status, Hdm2 and Hdmx levels in 22 osteosarcoma cell lines.**

#	name	Protein Levels			mRNA Levels				Nutlin-3 response
		p53	Hdm2	Hdmx Rel. Quant.	HDMX splicing	Ratio S/FL	Rel. Quant. HDMX-FL	Rel. Quant. HDMX-S	
0	Osteoblast	wt	n.a	n.a.	FL	0.18	n.a.	n.a.	n.a.
1	U2OS	wt	+	1.89	FL/S	0.71	0.8	0.57	+
2	KPD	wt	+	2.03	FL/S	1.16	0.55	0.64	+
3	MHM	wt(high)	high	0.18	S	1.31	0.54	0.7	+
4	OSA/SJSA1	wt	high	0.22	S	1.4	0.55	0.77	+
5	L2792	wt	high	0.01	S	1.83	0.25	0.46	+
6	L2962	wt (low)	very low	0.29	FL	0.61	0.58	0.36	+
7	OST	mt	low	0.24	S	2.31	0.48	1.1	-
8	HOS	mt(high)	low	0.84	S	1.27	0.75	0.95	-
9	HOS-143b	mt(high)	low	0.11	S	2.34	0.34	0.8	-
10	HOS-MNNG	mt(high)	low	0.51	S	1.77	0.33	0.59	-
11	IOR/OS15	mt(high)	low	0.3	S	2.63	0.4	1.04	-
12	HAL	mt	low	3.44	FL	0.39	1.45	0.56	-
13	IOR/OS18	neg	+	0.93	S	1.56	0.7	1.09	-
14	MG-63	neg	low	3.58	S	1.46	0.85	1.24	-
15	ZK58	neg	low	1.6	S	1.51	0.41	0.62	-
16	HOS58	neg	+	0.45	S	1.56	0.84	1.31	-
17	IOR/OS9	neg	low	0.38	S	2.05	0.76	1.56	-
18	SaOS2	neg	low	0.24	S	2.78	0.39	1.09	-
19	L2531	neg	low	0.54	S	2.07	0.56	1.16	-
20	L2857	neg	low	0.74	S	1.31	0.48	0.62	-
21	L2826	neg	low	0	S	3.18	0.39	1.23	-
22	L2635	neg	low	0.65	S	1.32	1.5	1.97	-

**Supplementary Table 4. Ratio of HDMX-S and HDMX-FL mRNA in 51 osteosarcomas.**

#	Sample ID	Ratio S:FL	#	Sample ID	Ratio S:FL
1	L1368	0.9	31	L2616	1.74
2	L1376	2.17	32	L2618	3.42
3	L2290	1.13	33	L3446	3.72
4	L1385	0.38	34	L3447	2.24
5	L2295	0.72	35	L3448	2.92
6	L2611	1.77	36	L3449	n.d.*
7	L2300	1.17	37	L3431	4.07
8	L2614	4.86	38	L3432	1.29
9	L2617	1.19	39	L3433	1.56
10	L1369	1.25	40	L3434	3.29
11	L1370	0.85	41	L3435	1.89
12	L1016	3.18	42	L3436	2.06
13	L2619	0.84	43	L3437	1.44
14	L1372	1.19	44	L3438	2.89
15	L2620	2.77	45	L3439	1.2
16	L436	1.39	46	L3440	2.3
17	L428	0.83	47	L3441	2.02
18	L1378	1.12	48	L3442	2.63
19	L2294	1.15	49	L3443	n.d.*
20	L2289	0.44	50	L3444	1.8
21	L2301	1	51	L3445	2.8
22	L1382	0.91		OB	0.18
23	L2302	1.88		MCF7	0.15
24	L1386	0.82			
25	L2281	0.68			
26	L2298	0.85			
27	L2297	1.3			
28	L2292	1			
29	L2613	0.8			
30	L2615	0.69			

\* Upper band below detection limit

**Supplementary Table 5. Summary of the p53 status, the Hdm2 and Hdmx levels in 37 breast cancer cell lines.**

#	name	p53	Protein Levels		mRNA Levels		Ratio S/FL
			Hdmx Rel. Quant.	Hdm2 Rel. Quant.	Rel. Quant. HDMX-FL	Rel. Quant. HDMX-S	
1	BT20		3.36	32.09	1.03	1.14	1.11
2	BT474		12.41	96.58	0.31	0.51	1.63
3	BT549		1.70	47.74	0.78	2.07	2.67
4	CAMA-1		30.34	47.27	2.45	1.22	0.50
5	DU4475	wt	20.42	75.09	0.82	0.41	0.50
6	EVSA-T		8.35	34.60	0.94	2.09	2.22
7	HCC1937		2.02	30.12	0.63	1.43	2.25
8	Hs578T		9.32	76.26	0.51	0.67	1.32
9	MCF-7	wt	38.88	85.31	2.25	0.81	0.36
10	MDA-MB-134VI		9.21	58.12	1.40	1.40	1.00
11	MDA-MB-157		2.30	15.70	0.41	1.69	4.09
12	MDA-MB-175VII	wt	35.74	136.49	2.52	0.92	0.37
13	MDA-MB-231		28.81	81.52	1.37	1.35	0.99
14	MDA-MB-330		4.31	37.12	0.90	1.98	2.20
15	MDA-MB-361		0.21	18.74	0.21	0.70	3.27
16	MDA-MB-415		2.32	21.87	0.21	0.41	1.98
17	MDA-MB-436		2.16	29.48	0.47	1.55	3.33
18	MDA-MB-453		13.44	23.77	2.03	0.83	0.41
19	MDA-MB-468		11.14	49.24	1.41	0.78	0.55
20	MPE600	wt	21.40	62.36	2.06	0.69	0.34
21	OCUB-F		4.07	14.30	1.42	0.62	0.43
22	SK-BR-3		3.32	47.08	0.67	1.07	1.59
23	SK-BR-5		2.06	45.83	0.30	1.03	3.40
24	SK-BR-7	wt	24.31	61.06	1.32	0.54	0.41
25	SUM44PE		6.87	16.85	0.67	0.51	0.76
26	SUM52PE		0.85	147.33	0.30	1.30	4.35
27	SUM149PT		2.02	27.32	0.42	0.70	1.66
28	SUM159PT		10.30	34.75	0.64	0.45	0.69
29	SUM185PE		10.00	24.41	0.62	0.55	0.90
30	SUM190PT		3.06	11.34	0.24	0.18	0.74
31	SUM229PE		2.90	24.70	0.21	0.57	2.64
32	SUM1315M02		0.43	5.41	0.12	0.15	1.26
33	T47D		15.29	31.10	1.08	0.56	0.52
34	UACC-812	wt	45.97	98.83	1.35	1.45	1.07
35	UACC-893		1.01	71.19	0.24	0.63	2.59
36	ZR75-1	wt	13.59	135.77	0.83	1.94	2.33
37	ZR75-30	wt	75.72	63.18	2.00	0.23	0.12

**Supplemental Table 6. Summary of the p53 status, the Hdm2 and Hdmx levels in the NCI60 cell panel.**

#	Name	origin	p53	relative band intensity		Ratio S/FL	HDM2 RNA
				HDMX-FL	HDMX-S		
1	K-562	Leukemia	mut	302.5	2788.5	9.22	149.51
2	MOLT-4	Leukemia	inc	2176.1	254.6	0.12	73.97
3	CCRF-CEM	Leukemia	mut	1769.3	366.8	0.21	46.01
4	RPMI-8226	Leukemia	mut	714.4	2189.6	3.06	88.77
5	HL-60(TB)	Leukemia	mut	509.4	1526.8	3	35.18
6	SR	Leukemia	wt	1171	354.4	0.3	108.97
7	SF-268	CNS	mut	679.3	1542.4	2.27	36.58
8	SF-295	CNS	mut	611.1	1387.7	2.27	22.44
9	SF-539	CNS	inc	785.5	1924.1	2.45	74.54
10	SNB-19	CNS	mut	405.1	1065.9	2.63	36.73
11	SNB-75	CNS	mut	604.9	1467.3	2.43	50.21
12	U251	CNS	mut	1416.8	495.6	0.35	31.4
13	BT-549	Breast	mut	796.6	1703.8	2.14	47.37
14	HS578T	Breast	mut	563.6	1765.4	3.13	56.01
15	MCF7	Breast	wt	2820.1	707.3	0.25	171.02
16	NCI/ADR-RES	Ovarian	mut	1253.7	425.1	0.34	36.8
17	MDA-MB-231/ATCC	Breast	mut	1517	1017.6	0.67	54.63
18	MDA-MB-435	Melanoma	mut	638.4	1489.3	2.33	25.1
19	T-47D	Breast	mut	2636.3	1367.7	0.52	440.6
20	COLO205	Colon	mut	139.3	1303.7	9.36	36.93
21	HCC-2998	Colon	mut	1294.4	212.8	0.16	29.33
22	HCT-116	Colon	wt	2555.6	4.4	0	94.29
23	HCT-15	Colon	inc	1893.1	0.7	0	75.56
24	HT29	Colon	mut	1257.2	2434.1	1.94	56.22
25	KM12	Colon	mut	1247.3	105.7	0.08	33.69
26	SW-620	Colon	mut	469.3	1325.4	2.82	52.01
27	A549/ATCC	NSCL	wt	1904	352	0.18	64.92
28	EKVX	NSCL	inc	1527.2	427.5	0.28	34.59
29	HOP-62	NSCL	mut	644	864.8	1.34	38.35
30	HOP-92	NSCL	mut	421.8	1493.4	3.54	44.32
31	NCI-H322M	NSCL	mut	852.3	1195.9	1.4	82.82
32	NCI-H226	NSCL	inc	1141.6	598.4	0.52	343.99
33	NCI-H23	NSCL	mut	1994.7	2575.9	1.29	142.03
34	NCI-H460	NSCL	wt	2282.5	438.9	0.19	145.87
35	NCI-H522	NSCL	mut	1549.1	1396.3	0.9	91.74
36	LOXIMVI	Melanoma	wt	1423.3	518.2	0.36	79.69
37	M14	Melanoma	mut	383	2433.5	6.35	49.32
38	MALME-3M	Melanoma	wt	1310.1	1631.5	1.25	280.18
39	SK-MEL-2	Melanoma	mut	2312.4	52.1	0.02	55.74
40	SK-MEL-28	Melanoma	mut	150.8	2812.6	18.65	60.55
41	SK-MEL-5	Melanoma	wt	2293.9	216.1	0.09	82.27
42	UACC-257	Melanoma	wt	179.4	2223.9	12.4	549.69
43	UACC-62	Melanoma	wt	481.3	1383.3	2.87	81.6
44	IGROV1	Ovarian	inc	2769.9	143.4	0.05	139.75
45	OVCAR-3	Ovarian	mut	379.4	2021.8	5.33	64.05
46	OVCAR-4	Ovarian	inc	410.8	1644.2	4	57.66
47	OVCAR-5	Ovarian	inc	2010.4	151.2	0.08	69.08
48	OVCAR-8	Ovarian	mut	1896.1	134.8	0.07	42.99
49	SK-OV-3	Ovarian	mut	649.4	1999.5	3.08	53.9
50	DU-145	Prostate	mut	717.5	1519.2	2.12	41.83
51	PC-3	Prostate	mut	460	1508.5	3.28	72.64
52	786-O	Renal	inc	422.1	1427.9	3.38	27.26
53	A498	Renal	wt	1608.7	271.4	0.17	111.81
54	ACHN	Renal	wt	1274.8	644.4	0.51	179.48
55	CAKI-1	Renal	wt	1832.5	775.4	0.42	506.89
56	RXF-393	Renal	mut	1057.6	894.5	0.85	28.3
57	SN12C	Renal	mut	2178.2	898	0.41	49.42
58	TK-10	Renal	mut	1791.6	93.2	0.05	68.12
59	UO-31	Renal	wt	640.5	1041	1.63	421.72