

Review

Genomic Landscape and 3D Functional Assay Combination Bridges Sarcomas Phenotype to Target and Immunotherapy

Filomena de Nigris ¹, Concetta Meo ¹ and Wulf Palinski ²

¹ Department of Precision Medicine, School of Medicine, University of Campania “Luigi Vanvitelli”, 80138 Naples, Italy; concetta.meo@unicampania.it

² Department of Medicine, University of California San Diego, La Jolla, CA 92137, USA; w.palinski@ucsd.edu

* Correspondence: filomena.denigris@unicampania.it

Table S1. Morphologic Appearances, Immunohistochemical Markers and Molecular Alterations observed in selected sarcomas with simple karyotype

Sarcoma Type	Morphology and Immunohistochemical Markers	Chromosomal translocation	Molecular Fusion	Reference
Alveolar rhabdomyosarcoma	Round cell.	t(2;13)(q35;q14)	PAX3-FOXO1	[1]
	Positive for desmin, myogenin, MYOD1	t(1;13)(p36;q14)	PAX7-FOXO1	[1]
	(Myogenic markers)	t(2;2)(q35;p23)	PAX3-NCOA1	[2, 3]
		t(X;2)(q35;q13)	PAX3-AFX	[2]
Alveolar soft part sarcoma	Epithelioid/epithelial-like TFE3 positive	t(X;17)(p11.2;q25)	TFE3-ASPSCR1	[4, 5]
BCOR-rearranged sarcoma	Round cell	Inv(X)(p11p11)	BCOR-CCNB3	[6]
	Positive BCL6 corepressor	Inv(X)(p11p11)?	BCOR-MAML3	[7]
	CD99 variable	Inv(X)(p11p11)?	ZC3H7B-BCOR	[7, 8]
Sarcoma rearranged	CIC- Round cell	t(4;19)(q35;q13) or t(10;19)(q26;q13)	CIC-DUX4	[9]
	Positive ETV4, WT1 (CD99 partially in extent)	t(X;19)(q13;q13.3)	CIC-FOXO4	[10]
Clear cell sarcoma	n.d.	t(12;22)(q13;q12)	EWSR1-ATF1	[11]
	n.d.	t(2;22)(q32.3;q12)	CREB1-EWSR1	

Dermatofibrosarcoma protuberans	n.d.	t(17;22)(q22;q13)	COL1A1-PDGFB	[12]
Desmoplastic round cell tumor	small Round cell. Positive WT1 , CD99 partially	t(11;22)(p13;q12)	EWSR1-WT1	[12]
Endometrial sarcoma, low grade	stromal n.d.	t(7;17)(p15;q21)	JAZF1-SUZ12	
	n.d.	t(6;7)(p21;p15)	PHF1-JAZF1	[13]
	n.d.	t(6;10)(p21;p11)	EPC1-PHF1	
	n.d.	t(1;6)(p34;p21)	MEAF6-PHF1	
	n.d.	t(X;17)(p11;q21)	MBTD1-CXorf67	
Endometrial sarcoma, high grade	stromal n.d.	t(10;17)(q22;p13)	YWHAE-NUTM2	[14]
		t(X;22)(p11;q13)	ZC3H7B-BCOR	
Epithelioid hemangioendothelioma	Epithelioid/epithelial-like Positive ERG, CD31 (Vascular markers), CAMTA1 (90%) or TFE3 (5%)	t(1;3)(p36;q25)	WWTR1-CAMTA1	[15]
		t(X;11)(p11;q22)	YAP1-TFE3	[16]
Epithelioid sarcoma	Epithelioid/epithelial-like Positive EMA/keratins and CD34 (50%)	Deletion 22q	SMARCB1	[17]
	Loss of SMARCB1 (INI1)	t(8;22)(q22;q11)		
Ewing sarcoma	Round cell Positive CD99 (membranous, diffuse) and NKX2-2	t(11;22)(q24;q12)	EWSR1-FLI1	[18]
		t(21;22)(q12;q12)	EWSR1-ERG	
		t(7;22)(p22;q12)	EWS-ETV1	
		t(17;22)(q12;q12)	EWS-ETV4	
		t(2;22)(q33;q12)	EWS-FEV	
Extraskeletal chondrosarcoma	Myxoid in 20% of cases: S100	t(9;22)(q22;q12)	EWSR1-NR4A3	[12]
		t(9;17)(q22;q11)	TAF2N-NR4A3	
		t(9;15)(q22;q21)	TCF12-NR4A3	
		t(3;9)(q11;q22)	TFG-NR4A3	
		t(9;17)(q22;q11)	RBP56-NR4A3	
Inflammatory myofibroblastic tumor	Spindle cell Positive ALK (50%), ROS1 (, 10%), smooth muscle markers positive (subset)	t(1;2)(q22;p23)	TPM3-ALK	[19-21]
		t(2;19)(p23;p13)	TPM4-ALK	
		t(2;17)(p23;q23)	CLTC-ALK	
		t(2;2)(p23;q13)	RANBP2-ALK	
		t(2;2)(p23;q35)	ATIC-ALK	

		t(2;11)(p23;p15)	CARS-ALK	
		t(2;4)(p23;q21)	SEC31L1-ALK	
		t(2;12)(p23;p12)	PPFIBP1-ALK	
		?	RRBP1-ALK	
		?	TFG-ROS1	
		?	YWHAE-ROS1	
Low-grade fibromyxoid sarcoma	Myxoid	t(7;16)(q33;p11)	FUS-CREB3L2	[22,23]
	Positive MUC4	t(11;16)(p11;p11)	FUS-CREB3L1	
Mesenchymal chondrosarcoma		t(8;8)(q13;q21)	HEY1-NCOA2	[22]
Myxoid liposarcoma	Myxoid	t(12;16)(q13;p11)	FUS-DDIT3	[22]
		t(12;22)(q13;q12)	EWSR1-DDIT3	
Pseudomyogenic hemangioendothelioma	AP-1 transcription factor subunit (FOSB)	t(7;19)(q22;q13),	SERPINE1-FOSB	[24]
Sclerosing epithelioid fibrosarcoma	Epithelioid/epithelial-like	t(11;22)(p11;q12)	EWSR1-CREB3L1	[22,23]
		t(7;16)(q33;p11)	FUS-CREB3L2	
Solitary fibrous tumor	Spindle cell. Positive STAT6, CD34	Inv(12)(q13q13)	NAB2-STAT6	[25]
Synovial sarcoma	n.d.	t(X;22)(p11.23;q11)	SS18-SSX1	[26,27]
		t(X;18)(p11.21;q11)	SS18-SSX2	[26,27]
		t(X;18)(p11;q11)	SS18-SSX4	[28]

n.d. not determined

Table S2. Genetic alterations cause of complex karyotypes in sarcomas

Sarcoma Type	Genetic alterations	Genes affected	Mutation rate	Reference
Angiosarcoma	Mutations	<i>TP53, PTPRB</i> <i>PIK3K</i>	66 %,26%	[29] [30]
	Overexpression	<i>VEGF</i>	80%	[29]
Chondrosarcoma	Mutations	<i>IDH</i> <i>TP53</i>	50-80% 8%	[31]
Embryonal Rhabdomyosarcoma	Deletions	<i>CDKN2A/B</i> <i>RB</i>	23% 27%	[32] [33]
	Activating Mutation	<i>FGR4</i> <i>Ras family</i>	20% 42%	[32]
Fibrosarcoma	Amplifications	<i>MDM2</i>	Common	[34]
Leiomyosarcoma	Deletions	<i>PTEN</i> <i>RB1</i>	57–69% 27–59%	[35, 36] [35, 36]
	Mutations	<i>TP53</i>	33–49%	[36–38]
		<i>ATRX</i> <i>MED12</i>	17–26% 21%	[36–38] [38]
	Amplification	<i>MYOCD</i>	70%	[39]
Liposarcoma	Amplifications	<i>MDM2</i> <i>CDK4</i> <i>HMGA2</i> <i>c-JUN</i>	86-98% 58–88 75–93% 16-60%	[40,41], [42] [43] [41]
MPNST	Mutations	<i>NF1</i> <i>CDKN2A</i> <i>TP53</i> <i>EED, SUZ12</i>	87.5% 75% 40% Common	[42] [43]
Osteosarcoma	Mutations	<i>TP53</i>	47-82%	[44, 45]
		<i>RB1</i>	29–47%	[44, 45]
		<i>PIK3K</i>		[46]
		<i>DLG2</i>	53%	[44]
		<i>ATRX</i>	29%	[44]

	Amplifications	<i>c-Myc</i>	39–42%	[47,48]
		<i>CCNE1</i>	33%	[48]
		<i>RAD21</i>	38%	[48]
		<i>VEGFA</i>	23%	[48]
		<i>RUNX2</i>	Common	[49,50]
Undifferentiated pleomorphic sarcoma	Deletions	<i>RB1</i>	30–35%	[51,52]

Reference Table S1

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Table S3. Clinical trials with target therapy in sarcoma (source: www.clinicaltrials.gov, accessed on July, 2023).

Clinical trials with CDKi therapy in sarcoma					
NCT Number	Study Title	Sarcoma Type	Target	Drug Name	Study Status/ Phase
NCT05905341	Study of PF-07224826, as a Single Agent or in Combination With Endocrine Therapy in Participants With Breast Cancer and Other Advanced Solid Tumors.	Liposarcoma	CDK2/4/6	PF-07224826	Not yet Recruiting/ Phase 1
NCT05655598	TAS-116 Plus Palbociclib in Breast and Rb-null Cancer	Soft Tissue Sarcoma	CDK4/6	TAS-116 Plus Palbociclib	Not yet Recruiting/ Phase 1
NCT05496569	TQB3616 Capsules in the Treatment of Dedifferentiated Liposarcoma	Dedifferentiated Liposarcoma	CDK4/6	TQB3616	Not yet Recruiting/ Phase 2

NCT05159518	A Study of PRT2527 in Participants With Advanced Solid Tumors	Sarcoma	CDK9	PRT2527	Recruiting/ Phase 1
NCT03242382	Trial of Palbociclib in Second Line of Advanced Sarcomas with CDK4 Overexpression	Advanced Sarcomas with CDK4 Overexpression	CDK4/6	Palbociclib	Recruiting/ Phase 2
NCT04040205	Abemaciclib for Bone and Soft Tissue Sarcoma with Cyclin-Dependent Kinase (CDK) Pathway Alteration	Advanced sarcoma (CS, OS, soft tissue sarcoma except LPS) with CDK pathway alteration	CDK4/6	Abemaciclib	Recruiting/ Phase 2
NCT03604783	Phase 1, First-in-human Study of Oral TP-1287 in Patients with Advanced Solid Tumors	Sarcoma	CDK9	TP-1287	Recruiting/ Phase 1
NCT04941274	Abemaciclib in Patients With HIV-associated and HIV-negative Kaposi Sarcoma	Kaposi Sarcoma	CDK4/6	Abemaciclib	Recruiting/ Phase 1-2
NCT02644460	Abemaciclib in Children with DIPG or Recurrent/Refractory Solid Tumors	Ewing Sarcoma, Rhabdomyosarcoma, Osteosarcoma Recurrent/Refractory,	CDK4/6	Abemaciclib	Recruiting/ Phase 1
NCT04557449	Study to Test the Safety and Tolerability of PF-07220060 in Participants with Advance Solid Tumors	Liposarcoma	CDK4/6	PF-07220060 administered as a single agent and then in combination with endocrine therapy	Recruiting/ Phase 1-2
NCT04438824	Palbociclib and INCMGA00012 in People with Advanced Liposarcoma	Well-differentiated/Dedifferentiated Liposarcoma	CDK4/6	Palbociclib and INCMGA00012	Recruiting/ Phase 2
NCT03784014	Molecular Profiling of Advanced Soft-tissue Sarcomas	Advanced Soft-tissue Sarcomas	CDK	Nilotinib, Ceritinib, Capmatinib, Lapatinib, Trametinib, Trametinib and Dabrafenib, Olaparib and Durvalumab,	Recruiting/ Phase 3

				Palbociclib, Glasdegib, TAS-120	
NCT05252416	(VELA) Study of BLU-222 in Advanced Solid Tumors	Carcinosarcoma	CDK 2	BLU-222, Carboplatin, Ribociclib, Fulvestrant	Recruiting/ Phase 1-2
NCT01209598	PD0332991 (Palbociclib) in Patients With Advanced or Metastatic Liposarcoma	Advanced/Metastatic Liposarcoma	CDK4/6	Palbociclib	Completed/ Phase 2
NCT04129151	Palbociclib + Ganitumab In Ewing Sarcoma	Ewing Sarcoma	CDK4/6 + IGF1R	Palbociclib + Ganitumab	Completed/ Phase 2
NCT03709680	Study Of Palbociclib Combined with Chemotherapy In Pediatric Patients With Recurrent/Refractory Solid Tumors	Recurrent/Refractory Ewing Sarcoma, Rhabdomyosarcoma in children	CDK4/6 + chemotherapy	Palbociclib + Temozolomide + Irinotecan	Recruiting/ Phase 2
NCT02897375	Palbociclib With Cisplatin or Carboplatin in Advanced Solid Tumors	Sarcoma	CDK4/6 + chemotherapy	Palbociclib + Cisplatin or Carboplatin	Active, not recruiting
NCT02846987	Study of Abemaciclib in Dedifferentiated Liposarcoma	Sarcoma/ Dedifferentiated Liposarcoma	CDK4/6	Abemaciclib	Active, not recruiting
NCT02784795	A Study of LY3039478 in Participants With Advanced or Metastatic Solid Tumors	Soft Tissue Sarcoma	Notch + CDK4/6	LY3039478 + Abemaciclib	Completed/ Phase 1
NCT03009201	Ribociclib and Doxorubicin in Treating Patients With Metastatic or Advanced Soft Tissue Sarcomas That Cannot Be Removed by Surgery	Metastatic or Advanced, Unresectable Soft Tissue Sarcomas	CDK4/6	Ribociclib + Doxorubicin	Active, not recruiting
NCT03114527	Phase II Trial of Ribociclib and Everolimus in Advanced Dedifferentiated Liposarcoma (DDL) and Leiomyosarcoma (LMS)	Soft Tissue Sarcoma	CDK4/6 + mTOR	Ribociclib + Everolimus	Active, not recruiting
NCT02343172	Study of Safety and Efficacy of HDM201 in Combination With	Liposarcoma	HDM2 + CDK4/6	HDM201 + Ribociclib	Completed/ Phase 1

	LEE011 in Patients With Liposarcoma				
NCT03310879	Study of the CDK4/6 Inhibitor Abemaciclib in Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6	Cancer with Genetic Alterations in D-type Cyclins or CDK4/6 Amplification	CDK4/6	Abemaciclib	Recruiting/ Phase 2
NCT01907607	Efficacy and Safety of PD-0332991 in Advanced Gastrointestinal Stromal Tumors Refractory to Imatinib and Sunitinib	Advanced Gastrointestinal Stromal Tumors	CDK4/6	Palbociclib	Completed/ Phase 2
NCT02571829	A Phase II Study Assessing Efficacy & Safety of Ribociclib in Patients With Advanced Well/Dedifferentiated Liposarcoma	Liposarcoma/ Soft Tissue Sarcoma	CDK4/6	Ribociclib	Phase 2

Clinical trials with target P53 and MDM2/X interactions in sarcoma

NCT Number	Study Title	Sarcoma Type	Target	Drug Name	Study Status/ Phase
NCT02432963	Vaccine Therapy and Pembrolizumab in Treating Patients With Solid Tumors That Have Failed Prior Therapy	Solid Tumors/ Soft Tissue Sarcoma	P53	Modified Vaccinia Virus Ankara Vaccine Expressing p53 and Pembrolizumab	Active, not recruiting/ Phase 1
NCT01386502	CT-011 and p53 Genetic Vaccine for Advanced Solid Tumors	Sarcoma	P53	p53: 264-272 peptide and CT-011	Withdrawn
NCT03727789	CBL0137 in Treating Patients With Advanced Extremity Melanoma or Sarcoma	Advanced Sarcoma of the Extremity/ Recurrent Sarcoma of the Extremity	Active p53, inhibits the histone chaperone and inhibits NF-κB	Complex-targeting Curaxin CBL0137	Recruiting/ Phase 1
NCT00676910	A Research Study of JNJ-26854165 to Determine the Safety and Dose in Patients With Advanced Stage or Refractory Solid Tumors	Neoplasm/Sarcoma	P53 Activator	JNJ-26854165	Completed/ Phase 1
NCT03217266	Navtemadlin and Radiation Therapy in Treating Patients With Soft Tissue Sarcoma	Resectable Soft Tissue Sarcoma	MDM2	Navtemadlin and Radiation Therapy	Active, not recruiting/ Phase 1

NCT02343172	Study of Safety and Efficacy of HDM201 in Combination With LEE011 in Patients With Liposarcoma	Liposarcoma	Selective inhibitor of the p53-Mdm2 interaction	HDM201 and LEE011	Completed/Phase 1
NCT05180695	HDM201 and Pazopanib in Patients With P53 Wild-type Advanced/Metastatic Soft Tissue Sarcomas	Advanced Soft-tissue Sarcoma Metastatic Soft-tissue Sarcoma	Selective inhibitor of the p53-Mdm2 interaction	HDM201 and Pazopanib	Recruiting/Phase 1-2
NCT03611868	A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors	Unresectable or Metastatic Melanoma or Advanced Solid Tumors P53 Mutation MDM2 Gene Mutation	MDM2/p53 inhibitor	APG-115+ Pembrolizumab	Recruiting/Phase 1-2
NCT01143740	A Study of RO5045337 in Patients With Liposarcomas Prior to Debulking Surgery	Sarcoma	Selective inhibitor of the p53-Mdm2 interaction	RO5045337	Completed/Phase 1
NCT00559533	A Study of RO5045337 [RG7112] in Patients With Advanced Solid Tumors	Neoplasm/Sarcoma	Selective inhibitor of the p53-Mdm2 interaction	RO5045337	Completed/Phase 1
NCT00223184	Genetic Characterisation of High-grade Paediatric Osteosarcomas	Paediatric Osteosarcomas			
NCT00898755	Collecting and Storing Tissue From Young Patients With Cancer	Rhabdomyosarcoma Soft Tissue Sarcoma			
Clinical trials with target PI3K or PI3K/Akt/mTOR pathway in sarcoma					
NCT Number	Study Title	Sarcoma Type	Target	Drug Name	Study Status/Phase
NCT01833169	BKM120 for Patients With PI3K-activated Tumors	PI3K Pathway Activated Tumors	PI3K Pathway	BKM120	Completed/Phase 1
NCT01357330	Oral SAR245408 (XL147) and Oral MSC1936369B in Patients With Locally Advanced or Metastatic Solid Tumors	Solid Tumors/Sarcoma	PI3K Pathway	SAR245408 (XL147) and MSC1936369B	Completed/Phase 2

NCT00907205	A Dose Escalation Study of SF1126, a PI3 Kinase (PI3K) Inhibitor, Given By Intravenous (IV) Infusion in Patients With Solid Tumors	Solid Tumors/ Sarcoma	PI3K Pathway	SF1126	Completed/ Phase 1
NCT00996892	Safety, Tolerability and Pharmacokinetics of Cobimetinib in Combination With Pictilisib in Patients With Locally Advanced or Metastatic Solid Tumors	Solid Tumors/ Sarcoma	PI3K Pathway	Cobimetinib + Pictilisib	Terminated/ Phase 1
NCT01343498	Study of PI3 Kinase/mTOR Inhibitor BEZ235 Twice Daily for Advanced Solid Tumors	Advance Solid Tumors/ Sarcoma	PI3K/mTOR	BEZ235	Completed/ Phase 1
NCT00600275	A Phase I/II Study of BGT226 in Adult Patients With Advanced Solid Malignancies Including Patients With Advanced Breast Cancer	Solid Tumors/ Sarcoma	PI3K/mTOR	BGT226	Completed/ Phase 1-2
NCT00485719	Study of the Safety and Pharmacokinetics of XL765 (SAR245409) in Adults With Solid Tumors	Solid Tumors/ Sarcoma	PI3K/mTOR	XL765 (SAR245409)	Completed/ Phase 1
NCT03213678	Samotolisib in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With TSC or PI3K/MTOR Mutations	Soft-tissue Sarcoma/Advance d Solid Tumors	PI3K/mTOR	Samotolisib	Active, not recruiting/ Phase 2
NCT02987959	Study of TAK-228 (MLN0128) in Soft Tissue Sarcomas	Soft-tissue Sarcoma	mTOR	TAK-228	Terminated/ Phase 2
NCT03660930	Nab-Sirolimus and Pazopanib Hydrochloride in Treating Patients With Advanced Nonadipocytic Soft Tissue Sarcomas	Soft-tissue Sarcoma	mTOR	Nab-Sirolimus and Pazopanib	Active, not recruiting/ Phase 2
NCT03190174	Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma and Certain Cancers	Advanced Sarcoma	mTOR	Nab-rapamycin + Nivolumab	Completed/ Phase 1-2
NCT00093080	Study of AP23573/MK-8669 (Ridaforolimus), A Mammalian Target of Rapamycin (mTOR)	Advanced Sarcoma	mTOR	Ridaforolimus	Completed/ Phase 2

	Inhibitor, in Participants With Advanced Sarcoma (MK-8669-018 AM1)(COMPLETED)				
NCT01684449	Gemcitabine Plus Rapamycin Versus Gemcitabine to Treat Advanced Soft Tissue Sarcoma	Advanced Soft Tissue Sarcoma	mTOR	Gemcitabine + Rapamycin	Completed/ Phase 1-2
NCT00949325	Safety and Efficacy Study of Torisel and Liposomal Doxorubicin for Patients With Recurrent Sarcoma	Sarcoma	mTOR	Temsirolimus plus liposomal Doxorubicin	Completed/ Phase 1-2
NCT01614795	Cixutumumab and Temsirolimus in Treating Younger Patients With Recurrent or Refractory Sarcoma	Recurrent or Refractory Sarcoma	mTOR	Cixutumumab and Temsirolimus	Completed/ Phase 2
NCT00996346	Phase I/II Study of Irinotecan and Temsirolimus in Patients With Refractory Sarcomas	Sarcoma	mTOR	Irinotecan and Temsirolimus	Terminated/ Phase 1
NCT03114527	Phase II Trial of Ribociclib and Everolimus in Advanced Dedifferentiated Liposarcoma (DDL) and Leiomyosarcoma (LMS)	Soft-tissue Sarcoma	mTOR	Ribociclib and Everolimus	Active, not recruiting/ Phase 2
NCT02584647	PLX3397 Plus Sirolimus in Unresectable Sarcoma and Malignant Peripheral Nerve Sheath Tumors	Sarcoma	mTOR	PLX3397 + Sirolimus	Recruiting/ Phase 1-2
NCT02821507	Sirolimus and Cyclophosphamide in Metastatic or Unresectable Myxoid Liposarcoma and Chondrosarcoma	Liposarcoma and Chondrosarcoma	mTOR	Sirolimus and Cyclophosphamide	Completed/ Phase 2