Review

Heterogeneity of Undifferentiated Pleomorphic Sarcoma Genetic Landscape: Is There a Room for Targeted Therapy?

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Simple Summary

Despite the development of multitargeted anti-cancer drugs and the approaches to personalized cancer treatment, the therapy of soft tissue sarcoma is still challenging. One of the most difficult for diagnostics and targeted treatment is undifferentiated pleomorphic sarcoma with high genetic heterogeneity. The purpose of the presented review is to sum up the latest findings in the genetics and epigenetics of this sarcoma subtype and to discuss possible usage of various targeted pharmaceutics.

Abstract

Undifferentiated pleomorphic sarcoma (UPS) is the most morphologically and genetically heterogeneous subtype of soft tissue sarcoma. UPS could harbor multiple genetic abnormalities including activating and inactivating mutations, amplifications, chromosomal translocation, variations in the copy number of different genes. Along with less widely described epigenetic changes, multiple genetic aberrations result in numerous alterations in signaling; however, no UPS-specific targets are described. It leads to the difficulties in diagnostics, prognosis following by the development of the strategy of targeted therapy. The therapy with immune checkpoint inhibitors (PD-1, PD-L1, CTLA-4) is the only proved targeted option for UPS due to numerous mutational events associated with activation of immune response. As nowadays UPS chemoresistance prognosis based on molecular genetics features seems insufficient, the development of experimental approaches for testing it ex vivo and in vitro may be useful for the exclusion of potentially ineffective targeted therapy courses.

Keywords: undifferentiated pleomorphic sarcoma; genetic heterogeneity; mutation; amplification; chromosomal translocation; signaling alteration; immunotherapy

1. Introduction

Undifferentiated pleomorphic sarcoma (UPS), classified up to 2013 as malignant fibrous histiocytoma), present a heterogeneous group of pleomorphic sarcomas, which show no definable line of differentiation, lack specific molecular features and are still a diagnosis of exclusion [1]. This type of soft tissue sarcoma (STS) is an aggressive malignancy characterized by high rates of

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metastasis, and display limited responsiveness to current therapies, therefore, specific diagnostic and prognostic characteristics as well as the development of novel targeted therapeutic tools based on aberrant signaling in UPS are required.

UPS usually occur in late adult age manifesting between 50 and 70 years with prevalence in white male population [1]. The most favorable areas for UPS development are lower extremities, especially the thigh, followed by the upper extremities and retroperitoneal lesions after the exclusion of dedifferentiated liposarcoma as well as cutaneous UPS subtypes and rare cardiac sarcoma [2–5]. In clinical observation UPS present painless, slowly enlarging tumor. Microscopically, UPS has a highly variable morphologic pattern and shows frequent transitions from storiform with plump spindle cells to pleomorphic areas with the prevalence of the latter. When compared to dermatofibrosarcoma protuberans, they differ by a less distinctive storiform pattern, presence of occasional plump histiocyte-like cells with no specific orientation to vessels, numerous mitoses, xanthoma cells and chronic inflammatory cells[6].

Immunohistochemical findings for UPS are limited as they are mainly use for the exclusion criteria. Analysis of hematoxylin–eosin-stained sections demonstrated the absence of monocyte or macrophage phenotypic features, the presence of focal immunoreactivity for smooth muscle actin and negative staining for desmin and h-caldesmon [7].

Over the past decades, variety of genetic and epigenetic abnormalities associated with diagnosis of UPS was demonstrated in multiple studies but further analysis should be performed to justify the molecular peculiarities found as diagnostic markers for UPS and the criteria for the choice of therapeutic strategy. The difficulties in UPS characterization are presented by complex and nonspecific cytogenetic aberrations as well as by possible similarities between UPS and other STS subtypes.

2. Molecular Genetic Heterogeneity of UPS

Due to the absence of the specific characteristics, UPS is a diagnosis of exclusion in clinical practice. In particular, myxofibrosarcoma (MFS) has been separated from UPS due to its fibroblastic differentiation with myxoid stroma, but in terms of genetic landscape UPS and MFS are still identified as a one sarcoma group [8].

Genetic aberrations in UPS/MFS including chromosomal translocations, mutations, deletions are numerous although not specific. The karyotype of UPS/MFS cells is composite and multiple chromosomes could be affected simultaneously. Translocations were reported for : t (1; 2), t (1; 3), t (1; 7), t (1; 10), t (1; 17), t (2; 3), t (5; 10), t (5; 11), t (5; 17), t (6; 8), t (6; 10), t (7; 10), t (9; 10), t (10; 11), t (10; 12), t (11; 17), and t (15; 21) [9]. Several fusion genes potentially involved into sarcomagenesis were identified: TMTC-NTRK3, DCTN1–NTRK1, *LMNA-NTRK1*, T(12;15)(p13;q25) *ETV6-NTRK3*, inv(X)(p11.4p11.22) *BCOR-CCNB3* [10–14]. One study reported the case of UPS of the pancreas in a pediatric patient whose tumor harbors a novel *NTRK* fusion, *SARM1-NTRK1* with high expression of *NTRK* [15]. In one retrospective study *TRIO::TERT* fusion gene was registered for the patient with UPS [16]. Several studies proved this finding for several STS subtypes including UPS [17]. Moreover, *TRIO* fusions with different partners including separate *TERT* exones were described for UPS/MFS: *TRIO*(ex33)-*TERT*(ex2), *TRIO(ex33)-TERT(ex3)*, *TRIO*(ex34)-*CDH18*(ex2)-*TERT*(ex2), *TRIO(ex34)-CDH18(ex2)-TERT(ex3)*, *TRIO*(ex33)-*LINC01504*(intron2), *TRIO(ex33)-LINC01504(intron3)*, *TRIO(ex33)-LINC01504(exon4)* [18]. *EML4-ALK* gene rearrangement accompanied by brain metastasis was described in one case of primary malignant fibrous histiocytoma of the lung in 59-year-old male patient [19].

Current stage of OMICS techniques allowed to perform large-scale studies of UPS genetics. In the study of 19 UPS tumors including two paired recurrent and re-recurrent samples a total of 66 fusion genes were detected. Among them, 10 novel fusion genes were further confirmed by PCR. Retinoblastoma (RB1) fusions were found in 2 tumors. The gene fusions *RB1-RNASEH2B*, *RB1-FGF14-AS1*, and *E2F6-FKBP4* were correlated with the Rb/E2F pathway. Another targeted fusion genes were detected: pseudogene-related fusions *CIC-DUX4L8* and *EIF2AK4-ANXA2P2* as well as

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PDGFRA-MACROD2 and *NCOR1-MAP2K1* transcripts [20]. In the study of primary UPS multiple but rare fusion genes are described: *CLTC-VMP1* and *FARP1-STK24*, and *PRDM10* with *MED12* and *CITED2* fusion partners [14,21,22]. Importantly, PRDM (positive regulatory domain member) proteins play a critical role in the transmission of signals that control cell proliferation and differentiation, and neoplastic transformation. Gene fusion transcripts containing *PRDM10* were recently identified in low-grade UPS, and associated with pleomorphic morphology. *PRDM10* fusions are present in around 5% of UPS may constitute a clinically important subset of UPS [21–23]. In secondary radiation-induced UPS following primary breast cancer, a novel *COL3A1-GULP1* fusion (*COL3A1*: exon23-*GULP1*: exon5) was detected [24].

"Loss-of-function" or "gain-of-function" mutations as well as gene amplifications are frequent genetic abnormalities in UPS, however, the clear correlations are still under the investigation. Multiple growth factors were demonstrated to be overexpressed in case of UPS and could presents targets for the therapy. For example, high *IGF2* and *FGFR3* expression might indicate a tumor subgroup eligible for a more aggressive treatment. However, within the UPS group, they are no prognostic markers [25]. Amplifications and activating mutations of *PDGFRA*, *PDGFRB*, *EGFR*, were reported for cardiac and rare intracranial UPS and provide the rationale for investigating therapies that target PDGF receptors and EGFR [26,27]. Target of TGF-β, the leucine-rich repeat-containing protein 15 (LRRC15), is frequently overexpressed in UPS cells. It is involved in cell-cell and cell-matrix interactions and came into focus as a promising anticancer target owing to its overexpression in mesenchymal-derived tumors including UPS [28,29]. Increased expression of *WWTR1* and *YAP1* were detected in 50-60% of sarcomas, mostly UPS and dedifferentiated liposarcoma [30].

Several amplifications and activation mutations in the marker genes for other STS subtypes were found in UPS. More specifically, *KIT, KRAS, MDM2, PIK3CA, AKT, AXL, MMP13* and *WNT7B* mutations and amplifications were described in UPS [10,27,31–37]. Amplifications of *VGLL3* encoding mechanosensitive regulator of transcription are also described for UPS [38]. Comprehensive genomic profiling revealed 6 identical genomic alterations in UPS of different localization *TP53* R248W, *ATR* I2435V, *GNAS* P423H, *MKI67* A1493T, *PDCD11* Q838H, and *SF3B1* A263V. In one case of orbital UPS, it was shown additional alterations in *NOTCH1*, *PCLO*, *MYST1*, and *NPM1* [39].

Bioinformatic analysis of the TCGA and an additional gene expression dataset for UPS, immunohistochemical analysis of a tissue microarray (TMA), *in vitro* and *in vivo* experiments reveal that high expression of the adenosine monophosphate deaminase 2 (*AMPD2*) involved in purine metabolism, is associated in all independent cohorts with worse patient outcome, possibly by promoting proliferation of UPS cells [40]. In one study overexpression of serine/threonine-protein kinase 13 Plk1 and DNA replication inhibitor Geminin were identified as biomarkers of poor prognosis and novel component for better understanding of UPS biology [41]. Strong negative correlations of *ABCB1* and *ABCG2* multidrug resistance regulator genes expression and positive correlation of *MVP* expression with the favorable prognosis after Doxorybicine/Gemcytabine therapy were described for 24 UPS samples [42].

In addition, UPS frequently contain inactivating mutations as well as deletions in tumor suppressor genes: *CDKN2A* mutations and deletions, *TP53, CSF2RB*, *RB1*, *PTEN*, *ATM* and *ATRX* mutations but without a unique driver mutation [10,37,43–46]. Interestingly, loss of function of the tumor suppressor genes *RB1* and *TP53* lead to activation of SKP2 and induction of proliferation. Thus, SKP2 inhibition could serve as potential therapeutic target [47].

The availability of OMICS technologies linked with following bioinformatic analysis allowed to perform gene profiling of UPS samples. Though the amount of the data is extensive, the specific gene subsets were highlighted in several studies. In the study of 60 MFH/UPS by cDNA microarray analysis, a 300-gene signature (11% FDR) was identified. Top upregulated functional groups included cathepsins and genes related to protein degradation, inflammatory response, cell motility, proliferation, cell-cycle control, and intracellular signaling [48]. Interestingly, up-regulation of cytoskeleton component COL6A3 as well as biglycan (BGN) was associated with favorable prognosis

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in the study of 46 and 38 UPS patients, respectively, in spite of involvement of potential oncogenic *COL6A3-GULP1* fusion [24,49].

Dysregulation of alternative splicing events is involved in UPS pathogenesis and progression. Specifically, exon skipping in *EWSR1* gene correlated with poor prognosis in UPS [50].

Number of copy number variation (CNV) could vary drastically in the case of UPS/MFS; numerous chromosome regions were reported to be affected (gains: 1p36.33–p31.3; 1q21.2–q24.3; 4p16.3; 5p15.33–p13.1; 7p22.3; 7p15.2–7p11.2; 7q32.1–q32.2; 9q34.3; 14q11.2; 14q32.33; 16p13.3; 17q12; 17q21.33; 17q23.3; 19p13.3; 19q13.11–q13.2; 19q13.42; 20q11.21– q13.33; 21q22.3 and X; losses: 1q32.1; 2p25.3; 2q36.1–q37.3; 8p23.3; 9p24.2-9p22.3; 9p21.3–p21.1; 10q21.1–q23.2; 11q22.3; 13q12.11–q31.1; 13q33.3; 16q11.2; and 16q23.1; amplifications: 1p36, 1p32, 1q21→q23, 1q32, 3q26, 6q23, 4q, 5p, 7q, 8q21.2→q22, 8p23.1, 8q24, 9q31→q34, 10q26, 11q, 12q13→q15, 12p, 17q12, 20q) with deletion of 13q chromosomal segment, was the most common deletion observed and recently identified loss of 13q14-21 as the most frequent copy-number alteration in UPS [8,51].

Near-haploidization presents the loss of one copy of most chromosomes, and is a relatively rare in most tumors, but could be specific feature for UPS. Near-haploidization can arise through many mechanisms. In one study it was demonstrated by whole genome and transcriptome sequencing in 2 UPS samples the presence of chromosomal rearrangements in the form of copy number variants of *SMC1A* gene encoding one of the components of the cohesion complex, regulator of S-phase [52].

3. Epigenetic Alterations in UPS

UPS are not characterized by specific epigenetic changes, however, the subsets of epigenetic regulators as well as microRNAs are described in the literature. Thus, genome-wide studies have demonstrated that UPS is characterized by aberrant patterns of DNA methylation. In particular, DNA methyltransferase *DNMT3B* is overexpressed in UPS and is associated with a poor prognosis. In the samples from the UPS patients, histone H3K4me3 and H3K9me3 were found highly overmethylated compared to normal muscle tissue. However, existing DNMT inhibitors 5-aza-2′-deoxycytidine and nanaomycin A, were ineffective in UPS due to unfavorable safety profile [53,54].

MicroRNA profiling was also described in several studies. In one study on 10 high-grade UPS samples microRNA microarray was performed and target genes for differentially expressed microRNA were identified including miR-199b-5p, miR-320a, miR-199a-3p, miR-126, miR-22 and their target genes *IMP3*, *ROR2*, *MDM2*, *CDK4*, and *UPA*. In further series of 27 UPS samples the microarray profiling results were validated by quantitative PCR [55]. Another study reveals the alternative subset of differentially expressed microRNA, mostly with tumor suppressor properties: miR-451, miR-1260, miR-1274a, miR-34a, miR-152 as well as miR-199b-5p and miR-320a described above [56]. Interestingly, in UPS samples with mutated BrafV600E or KrasG12D and increased MAPK signaling, higher levels of mature microRNA was detected. In experiments in vitro and in vivo mutation in Dicer, key enzyme of microRNA production, was demonstrated to cooperate with abovementioned oncogenic mutations in K-RAS/BRAF and promote tumor progression in vivo [57].

In addition, long noncoding RNAs (lncRNAs) could serve as tissue specific regulators of gene expression, and their dysregulation can promote carcinogenesis, in particular, sarcomagenesis. Few data are available for the role of lncRNA in UPS. In the in vivo study it was demonstrated that lncRNA Nuclear Enriched Abundant Transcript 1 (NEAT1) may promote UPS metastasis to lungs [58].

4. Changes in UPS Signaling and Associated Therapeutic Approaches

UPS is clinically and molecularly poorly understood, in great extent due to its intrinsic phenotypic and cytogenetic complexity. As described above, UPS may harbor multiple genetic and epigenetic abnormalities but without the selection of specific prognostic or predictive biomarkers. Complex genetics of UPS restricts the curability of this disease by standard chemotherapy, with the remaining options in surgical resection and complementary radiotherapy. Therefore, the

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identification of a more effective therapy for UPS patients is needed. There are numerous researches on aberrant signaling in UPS cells, and to date a few the most common signaling changes were described.

The aberrations in RB and TP53 genes lead to change of the activation level of corresponding signaling pathways. For example, most tumors without TP53 alterations show deletion or silencing of the *p14ARF* gene, a negative regulator of MDM2 suggesting the role of p14ARF-MDM2-TP53 axis in UPS pathogenesis. Restoring TP53 activity may be the alternative for UPS treatment [59]. In particular, PRB/TP53 alterations were demonstrated to shift the regulation of cancer cell survival to the oncogenic protein SKP2. Thus, tissue microarray analysis identified a correlation between absent RB and TP53 expression and positive expression of SKP2. Inhibition of SKP2 using the neddylation-activating enzyme (NAE) inhibitor pevonedistat decreased growth of patient-derived cells and murine models. Providing the rationale for novel systemic therapies for MFS and UPS [47]. TP53 was demonstrated to negatively interact with aurora kinases, and loss of p53 leads to increase in the level of aurora kinases that in turn could serve as option for targeted therapy. In particular, ENMD-2076, an aurora-A kinase inhibitor with anti-angiogenic properties, has shown activity in phase II study in patients with STS including 3 patients with UPS [60].

The RAS/mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase inhibitor (PI3K)/mammalian target of rapamycin (mTOR) pathways are activated in the most of cases of UPS, are considered to be the major mechanisms for sarcoma progression and associated with worse outcome [61]. Contrariwise, the components of abovementioned signaling could be used as potential therapeutical targets. MEK inhibitor, PD325901, slows tumor growth *in vivo* [62]. Several clinical trials have examined RAS/MAPK inhibitors in large cohorts of patients with STS that include multiple sarcoma histologies but in case of UPS response to sorafenib was not registered [63]. MEK inhibitor selumetinib induced a partial response in 1 of 2 patients with UPS [64]. In phase 2 study with the mTOR inhibitor temsirolimus none of the 8 patients with UPS responded to the therapy [65]. However, mTOR inhibitor ridaforolimus reported on 1 UPS patient with partial response [66]. It has to be mentioned that *in vitro* HrasG12V-driven undifferentiated pleomorphic sarcoma cells rapidly developed the resistance to individual treatment with single MEK inhibitor and ERK inhibitor but combination therapy overcomes the resistance [67].

Phosphorylated AKT (p-AKT), p-mTOR, p-S6RP and p-4EBP as well as HGF, c-Met, MEK/ERK are frequent immunohistochemical observation in UPS samples suggesting the role of PI3K/Akt/mTOR and c-Met signaling in the pathogenesis of the disease. In preclinical studies HSP90 overexpression correlated with p-Akt, p-mTOR and p-S6RP and may be considered as marker of poor prognosis and therapeutical target as well [68]. In particular, selective HSP90 inhibitor SNX-2112 exhibits antitumor activity *in vitro* in UPS cells via induction of apoptosis and autophagy, inhibition of mTOR phosphorylation, and suppression of MAPK signaling [69,70].

Another signaling with oncogenic potential, Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, regulates gene transcription and cell proliferation. In the study of 79 samples from UPS patients phosphorylated STAT3 and its negative regulator SOCS3 were detected in 59.7 and 55.8% of samples and correlated with favorable and unfavorable prognosis, respectively. Thus, STAT3 could be a prognostic factor for UPS as well as a target for the therapeutical approaches [71].

Loss of ATRX expression occurs in 20–30% of UPS and lead to selective sensitivity of ATRX deficient UPS cell to Wnt pathway activation. Inhibitor of Wnt signaling, tegavivint, decrease the viability of UPS cells and may present the therapeutical approach for ATRX-deficient UPS treatment [46].

Aberrant activation of Hedgehog and Notch signaling is another driver of UPS proliferation, involving multiple effectors (NOTCH3, JAG1, *GLI1*, *PTCH1*, *HHIP*, *HES1*, *HEY1*, *HEY2*) and Hedgehog-linked tumor suppressor Hippo pathway deregulation may also contribute in tumor progression [72–74]. Moreover, it was shown that YAP1, the transcriptional regulator and central effector of Hippo pathway, is aberrantly stabilized in UPS, linked to TGFβ signaling, and YAP1-TGFβ

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crosstalk cooperatively enhance proliferation and migration/invasion of UPS in *in vivo* experiments [38,72,74]. YAP1 nuclear localization and subsequent transcriptional activity is enhanced in UPS due to epigenetic silencing of its inhibitor, Angiomotin (AMOT), and Hippo kinase copy number loss [75]. Epigenetic modulators vorinostat and JQ1 restored AMOT expression and wild type Hippo pathway signaling presenting the therapeutic strategy to further study [76]. The expression of another TGF-β-linked target, a membrane protein LRRC15, is detected in several soft tissue sarcoma with urgent need for effective new therapies, in particular, in UPS. The antibody–drug conjugate ABBV-085 was developed to target LRRC15 and showed efficacy in phase I, first-in-human study of ABBV-085 monotherapy in patients with osteosarcoma or undifferentiated pleomorphic sarcoma with good overall response rate of 20% [29,77]. Besides that, YAP1 is involved in activation of NF-kB and VEGF signaling and following inhibition of unfolded protein response (UPR) signaling suggesting the components of abovementioned pathways as therapeutically significant targets [75,78,79]. Furthermore, the overexpression of several proteins from NF-kB, VEGF and UPR could be used as marker to therapeutic sensitivity. In particular, higher levels of CREB3L1 protein are correlated with increased doxorubicin sensitivity in the studies *in vivo* [80].

The distinct approach to UPS therapy is immunotherapy due to highly mutated STS subtype leading to pronounced immune response. In particular, higher levels of PD-L1 and PD1 as well as higher T-cell infiltration evaluated by specific markers (positive CD3, CD8, CD127 or IL7 receptor, CD99, CD68, CD10, negative TIGIT) and the level of tumor-associated macrophages (positive CD163, ionized calcium-binding adaptor molecule 1 (Iba1), MSR1, CD204, SIRPα) together with high tumor mutational burden (TMB-H) in comparison with other STS subtypes was demonstrated for UPS [36,81–90]. Anti-PD1/PD-L1 drugs were introduced into UPS therapy [87,91,92], several clinical trials are ongoing: Pembrolizumab (PD1) + Gemcitabine (chemotheraupetic from pyrimidine antimetabolite group) [85,93,94], Toripalimab (PD1) + Anlotinib (tyrosine kinase inhibitor, TKI) [90,95], Carilizumab (PD1) + Apatinib (TKI) [96], Envafolimab (PD-L1)+ Ipilimumab (CTLA4) [97], Nivolumab (PD1)+ Ipilimumab (CTLA4) [98], Pembrolizumab (PD1) + Cyclophosphamide (alkylating chemotherapeutic) [99], Pembrolizumab (PD1) in monotherapy [100], checkpoint blockage inhibitors + radiation therapy [98,101–103], Nivolumab (PD-L1) + Bempegaldesleukin (CD122-preferential interleukin-2 pathway agonist) [104,105], Nivolumab (PD-L1) + Nab-sirolimus (mTOR inhibitor) [106,107], Pembrolizumab (PD-1) + Eribulin (non-taxane inhibitor of microtubule dynamics) [108,109], Pembrolizumab (PD1) + Doxorubicin (topoisomerase II inhibitor) [110].

In the clinical trial SARC028, revealed the efficacy of anti-PD-1 drugs against UPS [87,92], the association between PD-L1 and CKLF-like MARVEL transmembrane domain containing 6 (CMTM6) was demonstrated, and CMTM6 was identified as a novel regulator of PD-L1 expression and a prognostic marker for poor prognosis. Therapeutic strategy could be developed based on CMTM6 expression as well [111]. In addition, it was demonstrated that collagen-modifying enzyme, procollagen-lysine,2-oxoglutarate 5-dioxygenase 2 (Plod2), which is over-expressed in many tumors relative to normal tissues, promotes immune evasion in UPS following by tumor metastasis and enhancement of CD8+ T cell dysfunction. *In vivo* study demonstrates that inhibition of Plod2 reduces tumor growth and enhances the efficacy of anti-Pd1 therapy suggesting PLOD2 to be a novel therapeutic target in UPS immunotherapy [112]. Several additional potential targets for UPS are undergoing preclinical trials. CB-839, a bioavailable glutaminase inhibitor, exhibited therapeutic efficacy in murine UPS model [113]. Therapeutic potential of inhibition of BET/EP300, epigenetic modifier NEO2734, was demonstrated *in vitro* and *in vivo* in murine models of UPS characterized by expression of MYC-targets pathway [114]. Co-treatment of UPS xenograft in immunodeficient mice with a dual PI3K/mTOR inhibitor and an anti-IGF1R kinase inhibitor reduced *in vivo* tumor growth. *In vitro* decrease in UPS cell migration and invasion was [115]. By comparative oncology approach, DNMT3B was identified as potential therapeutic target, however, anti-methylation drugs currently in clinical use have not yet been able to provide effective treatment [54,116]. Another epigenetic modifier, HDAC inhibitor LBH589, reveals anti-cancer effect *in vitro* and *in vivo* by down-regulation of the FOS-like antigen 1 (*FOSL1*) gene [117]. Neurotensin receptor 1 (NTSR1) and anti-human tumor

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endothelin 1 (TEM1) were described as potential targets; antitumor activity of SR48692, an inhibitor of NTSR1, was proved *in vitro* [118–120]. ATM inhibitor AZD0156 works synergistically with ATR inhibitor AZD6738 abolishes UPS growth *in vitro* and *in vivo* [121]. *In vitro* and *in vivo* anti-tumor activity of FGFR inhibitor JNJ-42756493 was selectively shown in cell lines and patient-derived xenograft models of UPS, with distinct immune phenotypes, prognosis, molecular features and MRI textures [122].

UPS are not frequently characterized by expression cancer-testis antigens (CTAs) that could potentially be targeted by T-cell receptor (TCR) gene therapy. Thus, it was reported about the case of one patient with UPS. The patient received NY-ESO- 1 TCR transgenic T cells combined with DC vaccination and anti-PD- 1 therapy resulted in durable antitumor response [123]. Anti-MAGE-A3 T-cell receptor (TCR)-engineered T cells recognizing epitopes in MAGE-A3 could be another option [124].

Some other clinical trials on the therapy of UPS are listed in the Table 1.

Table 1. Clinical trials on UPS treatment.

Type of sarcoma	Therapy	Trial registration number
Unresectable or metastatic UPS	Anlotinib Hydrochloride+Toripalimab	NCT03946943
UPS, MFS	Envafolimab/Envafolimab+Ipilimumab	NCT04480502
UPS, MFS	Mecbotamab vedotin/Mecbotamab vedotin+Nivolumab	NCT03425279
Liposarcoma, leiomyosarcoma, UPS	Eribulin+Pembrolizumab	NCT03899805
Leiomyosarcoma, UPS	Pembrolizumab+Gemcitabine	NCT03123276
Recurrent or resectable UPS, dedifferentiated liposarcoma	Nivolumab/Nivolumab+Ipilimumab and radiation therapy	NCT03307616
Advanced angiosarcoma, UPS	Propranolol+Pembrolizumab	NCT05961761
MFS, UPS, alveolar soft part sarcoma	Pembrolizumab+Melphalan+Dactinomycin	NCT04332874
Advanced UPS	Recombinant anti-PD-1 humanized monoclonal antibody (609A)	NCT05193214
Unresectable UPS and alveolar soft part sarcoma	Carilizumab+Apatinib	NCT04447274
Leiomyosarcoma, UPS, MFS, dedifferentiated liposarcoma	CSF1R Inhibitor (DCC-3014)+Avelumab	
Ewing sarcoma, osteosarcoma, UPS	Pembrolizumab+Cabozantinib	NCT05182164
Metastatic or unresectable UPS	doxorubicin and pembrolizumab	NCT06422806
Advanced STS	MAGE-12 Peptide Vaccine	NCT00020267
Advanced or metastatic STS	Brostallicin (PNU-166196A)/Doxorubicin	NCT00410462
Leiomyosarcoma, synovial sarcoma,	Doxorubicin hydrochloride+Trabectedin	NCT01189253

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osteosarcoma, malignant peripheral nerve sheath tumor, neurofibrosarcoma, desmoplastic small round cell tumor fibrosarcoma, alveolar soft part sarcoma, UPS, hemangiopericytoma, chondrosarcoma, epithelioid sarcoma, malignant mesenchymoma		
Leiomyosarcoma, liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, neurofibrosarcoma, alveolar soft part sarcoma, UPS, hemangiopericytoma, epithelioid sarcoma malignant mesenchymoma	Caelyx (pegylated liposomal doxorubin hydrochloride)+Ifosfamide	NCT00030784
Leiomyosarcoma, liposarcoma, synovial sarcoma, fibrosarcoma, UPS, hemangiopericytoma	Soblidotin	NCT00064220
Leiomyosarcoma, liposarcoma, synovial sarcoma, osteosarcoma, Ewing sarcoma, malignant peripheral nerve sheath tumor, neurofibrosarcoma, UPS, chondrosarcoma	Torisel+liposomal Doxorubicin	NCT00949325
UPS	XmAb®23104	NCT03752398
Multiple STS subtypes including adult UPS	Gemcitabine+Pazopanib	NCT01532687
Non small cell lung cancer, head and neck squamous cell carcinoma, pancreatic adenocarcinoma, colorectal cancer, MFS, UPS, solitary fibrous tumors,	OKN4395/OKN4395+Pembrolizumab	NCT06789172

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dedifferentiated liposarcoma		
High grade sarcoma, metastatic leiomyosarcoma, metastatic malignant peripheral nerve sheath tumor, metastatic synovial sarcoma, metastatic UPS, unresectable sarcoma, MFS,, recurrent leiomyosarcoma, recurrent malignant peripheral nerve sheath tumor, recurrent synovial sarcoma, recurrent UPS	Sapanisertib (MLN0128 [TAK-228])	NCT02601209
Metastatic UPS and other multiple STS subtypes	Nivolumab/Nivolumab+Ipilimumab	NCT02500797
MFS, recurrent adult STS, recurrent leiomyosarcoma, recurrent liposarcoma, recurrent malignant peripheral nerve sheath tumor, recurrent UPS	MLN8237 (alisertib)	NCT01653028
Osteosarcoma, Ewing sarcoma, MFH, synovial fibrosarcoma, leiomyosarcoma	Reolysis (oncolytic virus)	NCT00503295
Advanced solid tumors, UPS, squamous cell carcinoma of the head and neck, carcinoma of the breast	ABBV-085	NCT02565758
Multiple STS subtypes including adult UPS	Epirubicin+Ifosfamide+Nivolumab	NCT03277924
Multiple STS subtypes including adult UPS	BO-112/BO-112+Nivolumab	NCT04420975
Multiple STS subtypes including adult UPS	Talimogene laherparepvec (T-VEC)+Radiotherapy	NCT02923778

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Fibrosarcoma, leiomyosarcoma, liposarcoma, myosarcoma, histiocytic sarcoma, synovial sarcoma, lymphangiosarcoma, malignant peripheral nerve sheath tumors, MFS, UPS, dedifferentiated liposarcoma, pleomorphic rhabdomyosarcoma, malignant triton tumor	Radiotherapy+Sequential Doxorubicin and Ifosfamide	NCT03651375
UPS, synovial sarcoma, myxoid liposarcoma and de-differentiated liposarcoma	Sintilimab+Doxorubicin+Ifosfamide	NCT04356872
Extraskeletal myxoid chondrosarcoma, leiomyosarcoma, liposarcoma, UPS	Ipilimumab+Nivolumab/Cabozantinib+Nivolumab+Ipilimumab	NCT05836571
Metastatic dedifferentiated liposarcoma, metastatic leiomyosarcoma, metastatic MFS, metastatic synovial sarcoma, metastatic UPS, unresectable dedifferentiated liposarcoma, unresectable leiomyosarcoma, unresectable MFS, unresectable synovial sarcoma, unresectable UPS	Peposertib+liposomal Doxorubicin	NCT05711615
Leiomyosarcoma, malignant peripheral nerve sheath tumor, UPS	Gemcitabine+Docetaxel+Pazopanib	NCT01418001
Leiomyosarcoma, liposarcoma, synovial sarcoma, angiosarcoma, UPS, epithelioid sarcoma, malignant peripheral nerve sheath tumors,	Doxorubicin+Ifosfamide	NCT06277154

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fibrosarcoma, pleomorphic rhabdomyosarcoma, endometrial stromal sarcoma, desmoplastic small round cell tumor		
Metastatic leiomyosarcoma, metastatic synovial sarcoma, metastatic UPS, advanced myxoid liposarcoma, advanced STS, metastatic myxoid liposarcoma, metastatic round cell liposarcoma, metastatic STS, refractory leiomyosarcoma refractory myxoid liposarcoma, refractory round cell liposarcoma, refractory STS, refractory synovial sarcoma, refractory UPS advanced leiomyosarcoma, advanced synovial sarcoma, advanced UPS, metastatic chondrosarcoma	Itacitinib	NCT03670069
Liposarcoma, leiomyosarcoma, UPS	Sunitinib	NCT00400569
UPS, leiomyosarcoma, liposarcoma, synovial sarcoma, MFS, angiosarcoma	Olaratumab (Lartruvo)+Doxorubicin	NCT02451943 NCT02584309
Multiple STS subtypes including adult UPS	Ribociclib+Doxorubicin	NCT03009201

5. Conclusions

UPS present STS subtype with the most heterogeneous genetics causing multiple obstacles in the development of treatment strategy for the specific patient. Numerous genetic and several epigenetic aberrations in UPS have been explored, but only a few of them could contribute to the development of targeted UPS therapy. But multiple genetic abnormalities may lead to the hyperactivation of immune system, which, in turn could the subject of immunotherapy with checkpoint inhibitors (anti-PD1, anti-PD-L1, anti-CTLA4). But still UPS is the diagnosis of exclusion

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and potentially the exclusion of ineffective therapeutics in advance could be a better option for the choice of optimal treatment of UPS patients. The development of experimental approaches for testing it ex vivo and in vitro may be useful for the exclusion of potentially ineffective targeted therapy courses.

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Abbreviations

The following abbreviations are used in this manuscript:

ABCB1	ATP Binding Cassette Subfamily B Member 1
ABCG2	ATP Binding Cassette Subfamily G Member 2 (JR Blood Group)
AKT	AKT Serine/Threonine Kinase
ALK	Anaplastic Lymphoma Kinase
AMOT	Angiomotin
AMPD2	Adenosine Monophosphate Deaminase 2
ANXA2P2	Annexin A2 Pseudogene 2
ATM	Ataxia Telangiectasia Mutated
ATR	ATR Serine/Threonine Kinase
ATRX	ATRX Chromatin Remodeler
AXL	AXL Receptor Tyrosine Kinase
BCOR	BCL6 Corepressor
BET/EP300	BET and CBP/EP300 bromodomain
BGN	Biglycan
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
CCNB	Cyclin B
CD	Cluster Of Differentiation
CDH	Cadherin
CDK4	Cyclin Dependent Kinase 4
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A
CIC	Capicua Transcriptional Repressor
CITED2	Cbp/P300 Interacting Transactivator With Glu/Asp Rich Carboxy-Terminal Domain 2
CKLF	Chemokine Like Factor
CLTC	Clathrin Heavy Chain
CMTM6	CKLF Like MARVEL Transmembrane Domain Containing 6
COL3A1	Collagen Type III Alpha 1 Chain
CSF2RB	Colony Stimulating Factor 2 Receptor Subunit Beta
CTLA4	Cytotoxic T-Lymphocyte Antigen-4
DC	Dendritic Cells
DCTN1	Dynactin-1

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DNMT3B	DNA Methyltransferase 3 Beta
DUX4L8	Double Homeobox 4 Like 8
E2F6	E2F Transcription Factor 6
4EBP	Eukaryotic Translation Initiation Factor 4E Binding Protein 1
EGFR	Epidermal Growth Factor Receptor
EIF2AK4	Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4
EML4	Echinoderm Microtubule-Associated Protein-Like 4
ETV6	ETS Variant Transcription Factor 6
EWSR1	Ewing Sarcoma RNA Binding Protein 1
FARP1	FERM, ARH/Rhogef And Pleckstrin Domain Protein 1
FDR	False Discovery Rate
FGF	Fibroblast Growth Factor
FGFR	Fibroblast Growth Factor Receptor
FKBP4	FK506-Binding Protein 4
FOSL1	FOS Like 1, AP-1 Transcription Factor Subunit
GLI1	GLI Family Zinc Finger 1
GNAS	Guanine Nucleotide Binding Protein (G Protein), Alpha Stimulating Activity Polypeptide
GULP1	GULP PTB Domain Containing Engulfment Adaptor 1
HES1	Hes Family BHLH Transcription Factor 1
HEY	Hes Related Family BHLH Transcription Factor With YRPW Motif
HGF	Hepatocyte Growth Factor
HHIP	Hedgehog Interacting Protein
HSP90	Heat Shock Protein 90
Iba1	Ionized Calcium-Binding Adapter Molecule 1
IGF1R	Insulin Like Growth Factor 1 Receptor
IL-7	Interleukin-7
IMP3	IMP U3 Small Nucleolar Ribonucleoprotein 3
JAG1	Jagged Canonical Notch Ligand 1
JAK	Janus Kinase
KIT	KIT Proto-Oncogene, Receptor Tyrosine Kinase
KRAS	KRAS Proto-Oncogene, Gtpase
LINC	Linkers Of Nucleoskeleton And Cytoskeleton
LMNA	Lamin A/C
lncRNA	Long Non-Coding RNA
LRRC15	Leucine Rich Repeat Containing 15
MACROD2	Mono-ADP Ribosylhydrolase 2
MAGE-A3	Melanoma-Associated Antigen 3, Family Member A3
MAPK	Mitogen-Activated Protein Kinase
MDM2	Mouse Double Minute 2
MED12	Mediator Complex Subunit
MEK (MAP2K1)	Mitogen-Activated Protein Kinase Kinase 1
MFH	Malignant Fibrous Histiocytoma
MFS	Myxofibrosarcoma
MKI67	Marker Of Proliferation Ki-67
MMP	Matrix Metallopeptidase
MRI	Magnetic Resonance Imaging
MSR1	Macrophage Scavenger Receptor 1
mTOR	Mechanistic Target Of Rapamycin Kinase
MVP	Major Vault Protein
MYST1	MYST Histone Acetyltransferase 1
NAE	NEDD8 Activating Enzyme

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NCOR1	Nuclear Receptor Corepressor 1
NEAT1	Nuclear Enriched Abundant Transcript 1
NF-kB	Nuclear Factor Kappa B
NOTCH	Notch Receptor
NPM1	Nucleophosmin 1
NTRK	Neurotrophic Tropomyosin Receptor Kinase
NTSR1	Neurotensin Receptor 1
NY-ESO- 1	New York esophageal squamous cell carcinoma 1
PCLO	Piccolo Presynaptic Cytomatrix Protein
PCR	Polymerase Chain Reaction
PD1	Programmed Cell Death Protein 1
PDCD11	Programmed Cell Death 11
PDGFR	Platelet Derived Growth Factor Receptor
PD-L1	Programmed Cell Death Protein Ligand 1
PI3K	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PLK1	Polo Like Kinase 1
PLOD2	Procollagen-Lysine,2-Oxoglutarate 5-Dioxygenase 2
PRDM	PR/SET Domain
PTCH1	Patched 1
PTEN	Phosphatase And Tensin Homolog
RB1	Retinoblastoma
RNASEH2B	Ribonuclease H2, Subunit B
ROR2	Receptor Tyrosine Kinase Like Orphan Receptor 2
S6RP	Ribosomal Protein S6
SARM	Sterile Alpha And TIR Motif Containing
SF3B1	Splicing Factor 3b Subunit 1
SIRPα	Signal Regulatory Protein Alpha
SKP2	S-Phase Kinase Associated Protein 2
SMC1A	Structural Maintenance Of Chromosomes 1A
SOCS3	Suppressor Of Cytokine Signaling 3
STAT	Signal Transducer And Activator Of Transcription
STK24	Serine/Threonine Kinase 24
STS	Soft Tissue Sarcoma
TCGA	The Cancer Genome Atlas
TEM-1	Tumor endothelin 1
TGFβ	Transforming Growth Factor Beta
TIGIT	T Cell Immunoreceptor With Ig And ITIM Domains
TKI	Tyrosine Kinase Inhibitor
TMA	Tissue Microarray
TMB	Tumor Mutational Burden
TMTC	Transmembrane And Tetratricopeptide Repeat Containing
TP53	Tumor Protein P53
TRIO	Trio Rho Guanine Nucleotide Exchange Factor
VEGF	Vascular Endothelial Growth Factor
VGLL3	Vestigial Like Family Member 3
VMP1	Vacuole Membrane Protein 1
WNT7B	Wingless-Type MMTV Integration Site Family, Member 7B
WWTR1 (TAZ)	WW Domain Containing Transcription Regulator 1
UPA	Plasminogen Activator, Urokinase
UPS	Undifferentiated Pleomorphic Sarcoma
UPR	Unfolded Protein Response
YAP1	Yes1 Associated Transcriptional Regulator

 doi:10.20944/preprints202509.1095.v1

References

1. Sbaraglia, M.; Bellan, E.; Dei Tos, A.P. The 2020 WHO Classification of Soft Tissue Tumours: News and Perspectives. *Pathologica* **2020**, *113*, 70–84, doi:10.32074/1591-951X-213.
2. Goldblum, J.R. An Approach to Pleomorphic Sarcomas: Can We Subclassify, and Does It Matter? *Modern Pathology* **2014**, *27*, S39–S46, doi:10.1038/modpathol.2013.174.
3. Carter, C.S.; Patel, R.M. Cutaneous Soft Tissue Tumors: Diagnostically Disorienting Epithelioid Tumors That Are Not Epithelial, and Other Perplexing Mesenchymal Lesions. *Mod Pathol* **2020**, *33*, 66–82, doi:10.1038/s41379-019-0387-5.
4. Vaitiekiene, A.; Vaitiekus, D.; Urbonaite, L.; Jankauskas, A.; Portacenko, J.; Lapinskas, T.; Benetis, R.; Siudikas, A.; Veikutiene, A.; Poskiene, L.; et al. Multidisciplinary Approach to Rare Primary Cardiac Sarcoma: A Case Report and Review. *BMC Cancer* **2019**, *19*, 529, doi:10.1186/s12885-019-5705-2.
5. Chen, S.X.; Eichenfield, D.Z.; Orme, C.; Hinds, B. Pleomorphic Dermal Sarcoma in a Man with HIV: Report with next-Generation Sequencing Analysis and Review of the Atypical Fibroxanthoma/Pleomorphic Dermal Sarcoma Spectrum. *Dermatol Online J* **2019**, *25*.
6. Jibbe, A.; Worley, B.; Miller, C.H.; Alam, M. Surgical Excision Margins for Fibrohistiocytic Tumors, Including Atypical Fibroxanthoma and Undifferentiated Pleomorphic Sarcoma: A Probability Model Based on a Systematic Review. *J Am Acad Dermatol* **2022**, *87*, 833–840, doi:10.1016/j.jaad.2021.09.036.
7. Tchernev, G.; Tronnier, M.; Ananiev, J.; Taneva, T.; Patterson, J.W.; Gulubova, M.; Trafeli, J.P.; Gegova, A.; Harrell, M.; Guarneri, C.; et al. Atypical Fibroxanthoma—a Diagnosis of Exclusion! *Wiener Medizinische Wochenschrift* **2013**, *163*, 380–386, doi:10.1007/s10354-012-0173-1.
8. Sun, H.; Liu, J.; Hu, F.; Xu, M.; Leng, A.; Jiang, F.; Chen, K. Current Research and Management of Undifferentiated Pleomorphic Sarcoma/Myofibrosarcoma. *Front Genet* **2023**, *14*, doi:10.3389/fgene.2023.1109491.
9. Mairal, A.; Chibon, F.; Rousselet, A.; Couturier, J.; Terrier, P.; Aurias, A. Establishment of a Human Malignant Fibrous Histiocytoma Cell Line, COMA. *Cancer Genet Cytogenet* **2000**, *121*, 117–123, doi:10.1016/S0165-4608(00)00261-2.
10. Stefano, S.; Giovanni, S. The PTEN Tumor Suppressor Gene in Soft Tissue Sarcoma. *Cancers (Basel)* **2019**, *11*, 1169, doi:10.3390/cancers11081169.
11. Bai, C.; Zhang, L.; Wang, Y.; You, X.; Ju, Y.; Sun, T.; Fan, Z. A Novel TMTC2-NTRK3 Fusion in Undifferentiated High-Grade Pleomorphic Sarcoma. *J Cancer Res Clin Oncol* **2022**, *148*, 2933–2937, doi:10.1007/s00432-022-04249-x.
12. Goh, X.N.; Seng, M.S.-F.; Loh, A.H.P.; Gupta, A.; Chang, K.T.E.; Iyer, P. Larotrectinib Followed by Selitrectinib in a Novel *DCTN1–NTRK1* Fusion Undifferentiated Pleomorphic Sarcoma. *Journal of Oncology Pharmacy Practice* **2021**, *27*, 485–489, doi:10.1177/1078155220938849.
13. Zhou, N.; Schäfer, R.; Li, T.; Fang, M.; Liu, L. A Primary Undifferentiated Pleomorphic Sarcoma of the Lumbosacral Region Harboring a LMNA-NTRK1 Gene Fusion with Durable Clinical Response to Crizotinib: A Case Report. *BMC Cancer* **2018**, *18*, 842, doi:10.1186/s12885-018-4749-z.
14. Ali, N.M.; Niada, S.; Brini, A.T.; Morris, M.R.; Kurusamy, S.; Alholle, A.; Huen, D.; Antonescu, C.R.; Tirode, F.; Sumathi, V.; et al. Genomic and Transcriptomic Characterisation of Undifferentiated Pleomorphic Sarcoma of Bone. *J Pathol* **2019**, *247*, 166–176, doi:10.1002/path.5176.
15. Bou-Maroun, L.M.; Hoff, L.; Joshi, A.; Bloom, D.A.; Heider, A.; Geiger, J.D.; Wu, Y.; Robinson, D.; Mody, R.; Rao, R.J. Undifferentiated Pleomorphic Sarcoma of the Pancreas with Novel *SARM1-NTRK 1* Gene Fusion and Associated Pancreatitis, Panniculitis, and Polyarthritis Syndrome. *Pediatr Blood Cancer* **2024**, *71*, doi:10.1002/pbc.30819.
16. Goffinet, S.; Di Mauro, I.; Doyen, J.; Boyer, J.; Birtwisle-Peyrottes, I.; Keslair, F.; Pedeutour, F.; Dadone-Montaudie, B. Vanished *MDM2* Amplification in Multiple Recurrences of an Irradiated Poorly Differentiated Sarcoma with Amplified *TRIO::TERT* Fusion Gene. *Genes Chromosomes Cancer* **2023**, *62*, 342–352, doi:10.1002/gcc.23137.
17. Suster, D.I.; Deshpande, V.; Chebib, I.; Taylor, M.S.; Mullen, J.; Bredella, M.A.; Nielsen, G.P. Spindle Cell Liposarcoma with a TRIO-TERT Fusion Transcript. *Virchows Archiv* **2019**, *475*, 391–394, doi:10.1007/s00428-019-02545-5.

 doi:10.20944/preprints202509.1095.v1

18. Delespaul, L.; Lesluyes, T.; Pérot, G.; Brulard, C.; Lartigue, L.; Baud, J.; Lagarde, P.; Le Guellec, S.; Neuville, A.; Terrier, P.; et al. Recurrent *TRIO* Fusion in Nontranslocation–Related Sarcomas. *Clinical Cancer Research* **2017**, *23*, 857–867, doi:10.1158/1078-0432.CCR-16-0290.
19. Zhang, S.; Liao, X.; Chen, J. EML4-ALK Rearrangement in Primary Malignant Fibrous Histiocytoma of the Lung Treated with Alectinib: A Case Report. *Front Oncol* **2022**, *12*, doi:10.3389/fonc.2022.978327.
20. Zheng, B.; Zhang, S.; Cai, W.; Wang, J.; Wang, T.; Tang, N.; Shi, Y.; Luo, X.; Yan, W. Identification of Novel Fusion Transcripts in Undifferentiated Pleomorphic Sarcomas by Transcriptome Sequencing. *Cancer Genomics - Proteomics* **2019**, *16*, 399–408, doi:10.21873/cgp.20144.
21. Hofvander, J.; Tayebwa, J.; Nilsson, J.; Magnusson, L.; Brosjö, O.; Larsson, O.; Vult von Steyern, F.; Mandahl, N.; Fletcher, C.D.M.; Mertens, F. Recurrent *PRDM10* Gene Fusions in Undifferentiated Pleomorphic Sarcoma. *Clinical Cancer Research* **2015**, *21*, 864–869, doi:10.1158/1078-0432.CCR-14-2399.
22. Hofvander, J.; Puls, F.; Pillay, N.; Steele, C.D.; Flanagan, A.M.; Magnusson, L.; Nilsson, J.; Mertens, F. Undifferentiated Pleomorphic Sarcomas with *PRDM10* Fusions Have a Distinct Gene Expression Profile. *J Pathol* **2019**, *249*, 425–434, doi:10.1002/path.5326.
23. Mistik, O.; Sayar, H. Immunohistochemical Positive Regulatory Domain Member 10 Expression in Soft Tissue Sarcomas. *Polish Journal of Pathology* **2022**, *73*, 223–232, doi:10.5114/pjp.2022.124490.
24. Lei, T.; Shen, Z.; Shen, M.; Du, L.; Shi, Y.; Peng, Y.; Zhou, Z.; Da, W.; Chen, X.; Li, Q. Clinicopathological and Genetic Characterization of Radiotherapy-Induced Undifferentiated Pleomorphic Sarcoma Following Breast Cancer: A Case Series of Three Tumors and Comprehensive Literature Review. *Diagn Pathol* **2024**, *19*, 110, doi:10.1186/s13000-024-01534-w.
25. Rüping, K.; Altendorf-Hofmann, A.; Chen, Y.; Kampmann, E.; Gibis, S.; Lindner, L.; Katenkamp, D.; Petersen, I.; Knösel, T. High IGF2 and FGFR3 Are Associated with Tumour Progression in Undifferentiated Pleomorphic Sarcomas, but EGFR and FGFR3 Mutations Are a Rare Event. *J Cancer Res Clin Oncol* **2014**, *140*, 1315–1322, doi:10.1007/s00432-014-1700-9.
26. Urbini, M.; Astolfi, A.; Indio, V.; Nannini, M.; Pizzi, C.; Paolisso, P.; Tarantino, G.; Pantaleo, M.A.; Saponara, M. Genetic Aberrations and Molecular Biology of Cardiac Sarcoma. *Ther Adv Med Oncol* **2020**, *12*, doi:10.1177/1758835920918492.
27. Hong, C.S.; Partovi, E.; Clune, J.; Huttner, A.; Park, H.S.; Omay, S.B. Genomic Characterization of Radiation-Induced Intracranial Undifferentiated Pleomorphic Sarcoma. *Case Rep Genet* **2021**, *2021*, 1–5, doi:10.1155/2021/5586072.
28. Ray, U.; Pathoulas, C.L.; Thirusangu, P.; Purcell, J.W.; Kannan, N.; Shridhar, V. Exploiting LRRC15 as a Novel Therapeutic Target in Cancer. *Cancer Res* **2022**, *82*, 1675–1681, doi:10.1158/0008-5472.CAN-21-3734.
29. Demetri, G.D.; Luke, J.J.; Hollebecque, A.; Powderly, J.D.; Spira, A.I.; Subbiah, V.; Naumovski, L.; Chen, C.; Fang, H.; Lai, D.W.; et al. First-in-Human Phase I Study of ABBV-085, an Antibody–Drug Conjugate Targeting LRRC15, in Sarcomas and Other Advanced Solid Tumors. *Clinical Cancer Research* **2021**, *27*, 3556–3566, doi:10.1158/1078-0432.CCR-20-4513.
30. Fullenkamp, C.A.; Hall, S.L.; Jaber, O.I.; Pakalniskis, B.L.; Savage, E.C.; Savage, J.M.; Ofori-Amanfo, G.K.; Lambertz, A.M.; Ivins, S.D.; Stipp, C.S.; et al. TAZ and YAP Are Frequently Activated Oncoproteins in Sarcomas. *Oncotarget* **2016**, *7*, 30094–30108, doi:10.18632/oncotarget.8979.
31. Roland, C.L.; May, C.D.; Watson, K.L.; Al Sannaa, G.A.; Dineen, S.P.; Feig, R.; Landers, S.; Ingram, D.R.; Wang, W.-L.; Guadagnolo, B.A.; et al. Analysis of Clinical and Molecular Factors Impacting Oncologic Outcomes in Undifferentiated Pleomorphic Sarcoma. *Ann Surg Oncol* **2016**, *23*, 2220–2228, doi:10.1245/s10434-016-5115-5.
32. Williams, E.A.; Vegas, I.; El-Senduny, F.F.; Zhang, J.; Mata, D.A.; Hiemenz, M.C.; Hughes, S.R.; Sa, B.C.; Kraft, G.P.; Gorbatov, N.; et al. Pan-Cancer Genomic Analysis of AXL Mutations Reveals a Novel, Recurrent, Functionally Activating AXL W451C Alteration Specific to Myxofibrosarcoma. *American Journal of Surgical Pathology* **2024**, *48*, 699–707, doi:10.1097/PAS.0000000000002191.
33. Watson, R.; Frye, J.; Trieu, M.; Yang, M.X. Primary Undifferentiated Pleomorphic Cardiac Sarcoma with *MDM2* Amplification Presenting as Acute Left-Sided Heart Failure. *BMJ Case Rep* **2018**, *2018*, bcr-2018-226073, doi:10.1136/bcr-2018-226073.

 doi:10.20944/preprints202509.1095.v1

34. Li, B.; Li, L.; Li, X.; Wang, Y.; Xie, Y.; Liu, C.; Li, F. Undifferentiated Pleomorphic Sarcoma with Co-Existence of KRAS/PIK3CA Mutations. *Int J Clin Exp Pathol* **2015**, *8*, 8563–8567.
35. Vanni, S.; Fausti, V.; Fonzi, E.; Liverani, C.; Miserocchi, G.; Spadazzi, C.; Cocchi, C.; Calabrese, C.; Gurrieri, L.; Riva, N.; et al. Unveiling the Genomic Basis of Chemosensitivity in Sarcomas of the Extremities: An Integrated Approach for an Unmet Clinical Need. *Int J Mol Sci* **2023**, *24*, 6926, doi:10.3390/ijms24086926.
36. Higuchi, M.; Yamada, H.; Machino, K.; Oshibe, I.; Soeta, N.; Saito, T.; Uramoto, H.; Yamada, S.; Hojo, H.; Suzuki, H. Successful Multidisciplinary Treatment for Aggressive Primary Pulmonary Undifferentiated Pleomorphic Sarcoma. *Case Rep Oncol* **2020**, *13*, 385–391, doi:10.1159/000506897.
37. Suzuki, H.; Fukuda, M.; Shirono, T.; Kondo, R.; Tanaka, T.; Niizeki, T.; Akiba, J.; Koga, H.; Kawaguchi, T. A Rare Case of Primary Hepatic Undifferentiated Pleomorphic Sarcoma: Exploring Cancer-Related Gene Mutations. *Internal Medicine* **2025**, *64*, 4368–24, doi:10.2169/internalmedicine.4368-24.
38. Abeshouse, A.; Adebamowo, C.; Adebamowo, S.N.; Akbani, R.; Akeredolu, T.; Ally, A.; Anderson, M.L.; Anur, P.; Appelbaum, E.L.; Armenia, J.; et al. Comprehensive and Integrated Genomic Characterization of Adult Soft Tissue Sarcomas. *Cell* **2017**, *171*, 950-965.e28, doi:10.1016/j.cell.2017.10.014.
39. Ramsey, J.K.; Chen, J.L.; Schoenfield, L.; Cho, R.I. Undifferentiated Pleomorphic Sarcoma Metastatic to the Orbit. *Ophthalmic Plast Reconstr Surg* **2018**, *34*, e193–e195, doi:10.1097/IOP.0000000000001240.
40. Orth, M.F.; Gerke, J.S.; Knösel, T.; Altendorf-Hofmann, A.; Musa, J.; Alba-Rubio, R.; Stein, S.; Hölting, T.L.B.; Cidre-Aranaz, F.; Romero-Pérez, L.; et al. Functional Genomics Identifies AMPD2 as a New Prognostic Marker for Undifferentiated Pleomorphic Sarcoma. *Int J Cancer* **2019**, *144*, 859–867, doi:10.1002/ijc.31903.
41. Cullen, M.M.; Lazarides, A.L.; Pittman, P.D.; Flamant, E.M.; Stoeber, K.L.; Stoeber, K.; Visguass, J.D.; Brigman, B.E.; Riedel, R.F.; Cardona, D.M.; et al. Cell-Cycle Phase Progression Analysis Identifies Three Unique Phenotypes in Soft Tissue Sarcoma. *BMC Cancer* **2024**, *24*, 1288, doi:10.1186/s12885-024-13043-6.
42. Moiseeva, N.I.; Laletina, L.A.; Fetisov, T.I.; Makhmudova, L.F.; Manikaylo, A.E.; Fomina, L.Y.; Burov, D.A.; Lesovaya, E.A.; Bokhyan, B.Y.; Zinovieva, V.Y.; et al. Analysis of Multiple Drug Resistance Mechanism in Different Types of Soft Tissue Sarcomas: Assessment of the Expression of ABC-Transporters, MVP, YB-1, and Analysis of Their Correlation with Chemosensitivity of Cancer Cells. *Int J Mol Sci* **2022**, *23*, 3183, doi:10.3390/ijms23063183.
43. Lewin, J.; Garg, S.; Lau, B.Y.; Dickson, B.C.; Traub, F.; Gokgoz, N.; Griffin, A.M.; Ferguson, P.C.; Andrulis, I.L.; Sim, H.; et al. Identifying Actionable Variants Using next Generation Sequencing in Patients with a Historical Diagnosis of Undifferentiated Pleomorphic Sarcoma. *Int J Cancer* **2018**, *142*, 57–65, doi:10.1002/ijc.31039.
44. Pan, M.; Zhou, M.Y.; Jiang, C.; Zhang, Z.; Bui, N.Q.; Bien, J.; Siy, A.; Achacoso, N.; Solorzano, A. V.; Tse, P.; et al. Sex-Dependent Prognosis of Patients with Advanced Soft Tissue Sarcoma. *Clinical Cancer Research* **2024**, *30*, 413–419, doi:10.1158/1078-0432.CCR-23-1990.
45. Kirilin, E.M.; Fetisov, T.I.; Moiseeva, N.I.; Lesovaya, E.A.; Laletina, L.A.; Makhmudova, L.F.; Manikaylo, A.E.; Fomina, L.Y.; Burov, D.A.; Bokhyan, B.Yu.; et al. Soft Tissue Sarcoma Study: Association of Genetic Alterations in the Apoptosis Pathways with Chemoresistance to Doxorubicin. *Cancers (Basel)* **2022**, *14*, 1796, doi:10.3390/cancers14071796.
46. Fang, Y.; Barrows, D.; Dabas, Y.; Carroll, T.S.; Singer, S.; Tap, W.D.; Nacev, B.A. ATRX Guards against Aberrant Differentiation in Mesenchymal Progenitor Cells. *Nucleic Acids Res* **2024**, *52*, 4950–4968, doi:10.1093/nar/gkae160.
47. Li, G.Z.; Okada, T.; Kim, Y.-M.; Agaram, N.P.; Sanchez-Vega, F.; Shen, Y.; Tsubokawa, N.; Rios, J.; Martin, A.S.; Dickson, M.A.; et al. Rb and P53-Deficient Myxofibrosarcoma and Undifferentiated Pleomorphic Sarcoma Require Skp2 for Survival. *Cancer Res* **2020**, *80*, 2461–2471, doi:10.1158/0008-5472.CAN-19-1269.
48. Francis, P.; Namløs, H.; Müller, C.; Edén, P.; Fernebro, J.; Berner, J.-M.; Bjerkehagen, B.; Åkerman, M.; Bendahl, P.-O.; Isinger, A.; et al. Diagnostic and Prognostic Gene Expression Signatures in 177 Soft Tissue Sarcomas: Hypoxia-Induced Transcription Profile Signifies Metastatic Potential. *BMC Genomics* **2007**, *8*, 73, doi:10.1186/1471-2164-8-73.

 doi:10.20944/preprints202509.1095.v1

49. Klein, J.C.; Wang, L.; Strand, D.; Lastufka, C.; Hosler, G.A.; Hon, G.C. Single-Cell and Spatial Transcriptomics Identify COL6A3 as a Prognostic Biomarker in Undifferentiated Pleomorphic Sarcoma. *Mol Cancer* **2024**, *23*, 257, doi:10.1186/s12943-024-02168-8.
50. Yang, X.; Huang, W.; He, R.; Ma, J.; Lin, P.; Xie, Z.; Ma, F.; Chen, G. Determining the Prognostic Significance of Alternative Splicing Events in Soft Tissue Sarcoma Using Data from The Cancer Genome Atlas. *J Transl Med* **2019**, *17*, 283, doi:10.1186/s12967-019-2029-6.
51. Carneiro, A.; Francis, P.; Bendahl, P.-O.; Fernebro, J.; Åkerman, M.; Fletcher, C.; Rydholm, A.; Borg, Å.; Nilbert, M. Indistinguishable Genomic Profiles and Shared Prognostic Markers in Undifferentiated Pleomorphic Sarcoma and Leiomyosarcoma: Different Sides of a Single Coin? *Laboratory Investigation* **2009**, *89*, 668–675, doi:10.1038/labinvest.2009.18.
52. Ibstedt, S.; Piccinelli, P.; Sydow, S.; Köster, J.; Mertens, F. Structural Variants in the <scp> *SMC1A* </Scp> Gene Associated With Near-Haploidy in Undifferentiated Pleomorphic Sarcomas. *Genes Chromosomes Cancer* **2024**, *63*, doi:10.1002/gcc.23255.
53. Aoki, Y.; Yamamoto, J.; Tome, Y.; Hamada, K.; Masaki, N.; Inubushi, S.; Tashiro, Y.; Bouvet, M.; Endo, I.; Nishida, K.; et al. Over-Methylation of Histone H3 Lysines Is a Common Molecular Change Among the Three Major Types of Soft-Tissue Sarcoma in Patient-Derived Xenograft (PDX) Mouse Models. *Cancer Genomics - Proteomics* **2021**, *18*, 715–721, doi:10.21873/cgp.20292.
54. Fuller, A.M.; DeVine, A.; Murazzi, I.; Mason, N.J.; Weber, K.; Eisinger-Mathason, T.S.K. Comparative Oncology Reveals DNMT3B as a Molecular Vulnerability in Undifferentiated Pleomorphic Sarcoma. *Cellular Oncology* **2022**, *45*, 1277–1295, doi:10.1007/s13402-022-00717-1.
55. Guled, M.; Pazzaglia, L.; Borze, I.; Mosakhani, N.; Novello, C.; Benassi, M.S.; Knuutila, S. Differentiating Soft Tissue Leiomyosarcoma and Undifferentiated Pleomorphic Sarcoma: A MiRNA Analysis. *Genes Chromosomes Cancer* **2014**, *53*, 693–702, doi:10.1002/gcc.22179.
56. Zoroddu, S.; Lucariello, A.; De Luca, A.; Bagella, L. Dysregulation of MiRNAs in Soft Tissue Sarcomas. *Cells* **2024**, *13*, 1853, doi:10.3390/cells13221853.
57. Mito, J.K.; Min, H.D.; Ma, Y.; Carter, J.E.; Brigman, B.E.; Dodd, L.; Dankort, D.; McMahon, M.; Kirsch, D.G. Oncogene-dependent Control of <scp>miRNA</Scp> Biogenesis and Metastatic Progression in a Model of Undifferentiated Pleomorphic Sarcoma. *J Pathol* **2013**, *229*, 132–140, doi:10.1002/path.4099.
58. Huang, J.; Sachdeva, M.; Xu, E.; Robinson, T.J.; Luo, L.; Ma, Y.; Williams, N.T.; Lopez, O.; Cervia, L.D.; Yuan, F.; et al. The Long Noncoding RNA *NEAT1* Promotes Sarcoma Metastasis by Regulating RNA Splicing Pathways. *Molecular Cancer Research* **2020**, *18*, 1534–1544, doi:10.1158/1541-7786.MCR-19-1170.
59. Thoenen, E.; Curl, A.; Iwakuma, T. TP53 in Bone and Soft Tissue Sarcomas. *Pharmacol Ther* **2019**, *202*, 149–164, doi:10.1016/j.pharmthera.2019.06.010.
60. Veitch, Z.; Zer, A.; Loong, H.; Salah, S.; Masood, M.; Gupta, A.; Bradbury, P.A.; Hogg, D.; Wong, A.; Kandel, R.; et al. A Phase II Study of ENMD-2076 in Advanced Soft Tissue Sarcoma (STS). *Sci Rep* **2019**, *9*, 7390, doi:10.1038/s41598-019-43222-6.
61. Serrano, C.; Romagosa, C.; Hernández-Losa, J.; Simonetti, S.; Valverde, C.; Moliné, T.; Somoza, R.; Pérez, M.; Vélez, R.; Vergés, R.; et al. RAS/MAPK Pathway Hyperactivation Determines Poor Prognosis in Undifferentiated Pleomorphic Sarcomas. *Cancer* **2016**, *122*, 99–107, doi:10.1002/cncr.29733.
62. Dodd, R.D.; Mito, J.K.; Eward, W.C.; Chitalia, R.; Sachdeva, M.; Ma, Y.; Barretina, J.; Dodd, L.; Kirsch, D.G. NF1 Deletion Generates Multiple Subtypes of Soft-Tissue Sarcoma That Respond to MEK Inhibition. *Mol Cancer Ther* **2013**, *12*, 1906–1917, doi:10.1158/1535-7163.MCT-13-0189.
63. Maki, R.G.; D'Adamo, D.R.; Keohan, M.L.; Saulle, M.; Schuetze, S.M.; Undevia, S.D.; Livingston, M.B.; Cooney, M.M.; Hensley, M.L.; Mita, M.M.; et al. Phase II Study of Sorafenib in Patients With Metastatic or Recurrent Sarcomas. *Journal of Clinical Oncology* **2009**, *27*, 3133–3140, doi:10.1200/JCO.2008.20.4495.
64. Eroglu, Z.; Tawbi, H.A.; Hu, J.; Guan, M.; Frankel, P.H.; Ruel, N.H.; Wilczynski, S.; Christensen, S.; Gandara, D.R.; Chow, W.A. A Randomised Phase II Trial of Selumetinib vs. Selumetinib plus Temsirolimus for Soft-Tissue Sarcomas. *Br J Cancer* **2015**, *112*, 1644–1651, doi:10.1038/bjc.2015.126.
65. Okuno, S.; Bailey, H.; Mahoney, M.R.; Adkins, D.; Maples, W.; Fitch, T.; Ettinger, D.; Erlichman, C.; Sarkaria, J.N. A Phase 2 Study of Temsirolimus (CCI-779) in Patients with Soft Tissue Sarcomas. *Cancer* **2011**, *117*, 3468–3475, doi:10.1002/cncr.25928.

 doi:10.20944/preprints202509.1095.v1

66. Chawla, S.P.; Blay, J.; Ray-Coquard, I.L.; Le Cesne, A.; Staddon, A.P.; Milhem, M.M.; Penel, N.; Riedel, R.F.; Bui Nguyen, B.; Cranmer, L.D.; et al. Results of the Phase III, Placebo-Controlled Trial (SUCCEED) Evaluating the MTOR Inhibitor Ridaforolimus (R) as Maintenance Therapy in Advanced Sarcoma Patients (Pts) Following Clinical Benefit from Prior Standard Cytotoxic Chemotherapy (CT). *Journal of Clinical Oncology* **2011**, *29*, 10005–10005, doi:10.1200/jco.2011.29.15_suppl.10005.
67. Catalano, A.; Adlesic, M.; Kaltenbacher, T.; Klar, R.F.U.; Albers, J.; Seidel, P.; Brandt, L.P.; Hejhal, T.; Busenhart, P.; Röhner, N.; et al. Sensitivity and Resistance of Oncogenic RAS-Driven Tumors to Dual MEK and ERK Inhibition. *Cancers (Basel)* **2021**, *13*, 1852, doi:10.3390/cancers13081852.
68. Bekki, H.; Kohashi, K.; Maekawa, A.; Yamada, Y.; Yamamoto, H.; Harimaya, K.; Hakozaki, M.; Nabeshima, K.; Iwamoto, Y.; Oda, Y. Elevated Expression of HSP90 and the Antitumor Effect of an HSP90 Inhibitor via Inactivation of the Akt/MTOR Pathway in Undifferentiated Pleomorphic Sarcoma. *BMC Cancer* **2015**, *15*, 804, doi:10.1186/s12885-015-1830-8.
69. Fukuoka, N.; Nakamura, O.; Yamagami, Y.; Nishimura, H.; Ishibashi, Y.; Yamamoto, T. SNX-2112 Induces Apoptosis and Autophagy of Nara-H Cells. *Anticancer Res* **2018**, *38*, 5177–5181, doi:10.21873/anticanres.12840.
70. Lahat, G.; Zhang, P.; Zhu, Q.-S.; Torres, K.; Ghadimi, M.; Smith, K.D.; Wang, W.-L.; Lazar, A.J.; Lev, D. The Expression of C-Met Pathway Components in Unclassified Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma (UPS/MFH): A Tissue Microarray Study. *Histopathology* **2011**, *59*, 556–561, doi:10.1111/j.1365-2559.2011.03946.x.
71. Bekki, H.; Kohashi, K.; Yamada, Y.; Iura, K.; Ishii, T.; Maekawa, A.; Otsuka, H.; Yamamoto, H.; Hakozaki, M.; Nabeshima, K.; et al. Phosphorylation of STAT3 in Undifferentiated Pleomorphic Sarcoma Is Correlated with a Favorable Prognosis. *Pathobiology* **2017**, *84*, 161–169, doi:10.1159/000448524.
72. Wang, C.Y.Y.; Wei, Q.; Han, I.; Sato, S.; Azarnier, R.G.-; Whetstone, H.; Poon, R.; Hu, J.; Zheng, F.; Zhang, P.; et al. Hedgehog and Notch Signaling Regulate Self-Renewal of Undifferentiated Pleomorphic Sarcomas. *Cancer Res* **2012**, *72*, 1013–1022, doi:10.1158/0008-5472.CAN-11-2531.
73. Amm, H.M.; DeVilliers, P.; Srivastava, A.R.; Diniz, M.G.; Siegal, G.P.; MacDougall, M. Mandibular Undifferentiated Pleomorphic Sarcoma: Molecular Analysis of a Primary Cell Population. *Clin Exp Dent Res* **2020**, *6*, 495–505, doi:10.1002/cre2.301.
74. Ye, S.; Liu, Y.; Fuller, A.M.; Katti, R.; Ciotti, G.E.; Chor, S.; Alam, Md.Z.; Devalaraja, S.; Lorent, K.; Weber, K.; et al. TGFβ and Hippo Pathways Cooperate to Enhance Sarcomagenesis and Metastasis through the Hyaluronan-Mediated Motility Receptor (HMMR). *Molecular Cancer Research* **2020**, *18*, 560–573, doi:10.1158/1541-7786.MCR-19-0877.
75. Rivera-Reyes, A.; Ye, S.; E. Marino, G.; Egolf, S.; E. Ciotti, G.; Chor, S.; Liu, Y.; Posimo, J.M.; Park, P.M.C.; Pak, K.; et al. YAP1 Enhances NF-KB-Dependent and Independent Effects on Clock-Mediated Unfolded Protein Responses and Autophagy in Sarcoma. *Cell Death Dis* **2018**, *9*, 1108, doi:10.1038/s41419-018-1142-4.
76. Ye, S.; Lawlor, M.A.; Rivera-Reyes, A.; Egolf, S.; Chor, S.; Pak, K.; Ciotti, G.E.; Lee, A.C.; Marino, G.E.; Shah, J.; et al. YAP1-Mediated Suppression of USP31 Enhances NFκB Activity to Promote Sarcomagenesis. *Cancer Res* **2018**, *78*, 2705–2720, doi:10.1158/0008-5472.CAN-17-4052.
77. Https://Clinicaltrials.Gov/Study/NCT02565758.
78. Washimi, K.; Kasajima, R.; Shimizu, E.; Sato, S.; Okubo, Y.; Yoshioka, E.; Narimatsu, H.; Hiruma, T.; Katayama, K.; Yamaguchi, R.; et al. Histological Markers, Sickle-Shaped Blood Vessels, Myxoid Area, and Infiltrating Growth Pattern Help Stratify the Prognosis of Patients with Myxofibrosarcoma/Undifferentiated Sarcoma. *Sci Rep* **2023**, *13*, 6744, doi:10.1038/s41598-023-34026-w.
79. Lv, X.; Liu, J.; Islam, K.; Ruan, J.; He, C.; Chen, P.; Huang, C.; Wang, H.; Dhar, A.; Moness, M.; et al. Hyperactivated YAP1 Is Essential for Sustainable Progression of Renal Clear Cell Carcinoma. *Oncogene* **2025**, doi:10.1038/s41388-025-03354-8.
80. Denard, B.; Pavia-Jimenez, A.; Chen, W.; Williams, N.S.; Naina, H.; Collins, R.; Brugarolas, J.; Ye, J. Identification of CREB3L1 as a Biomarker Predicting Doxorubicin Treatment Outcome. *PLoS One* **2015**, *10*, e0129233, doi:10.1371/journal.pone.0129233.
81. Pollack, S.M.; He, Q.; Yearley, J.H.; Emerson, R.; Vignali, M.; Zhang, Y.; Redman, M.W.; Baker, K.K.; Cooper, S.; Donahue, B.; et al. T-cell Infiltration and Clonality Correlate with Programmed Cell Death

 doi:10.20944/preprints202509.1095.v1

Protein 1 and Programmed Death-ligand 1 Expression in Patients with Soft Tissue Sarcomas. *Cancer* **2017**, *123*, 3291–3304, doi:10.1002/cncr.30726.

82. Wunder, J.S.; Lee, M.J.; Nam, J.; Lau, B.Y.; Dickson, B.C.; Pinnaduwage, D.; Bull, S.B.; Ferguson, P.C.; Seto, A.; Gokgoz, N.; et al. Osteosarcoma and Soft-Tissue Sarcomas with an Immune Infiltrate Express PD-L1: Relation to Clinical Outcome and Th1 Pathway Activation. *Oncoimmunology* **2020**, *9*, doi:10.1080/2162402X.2020.1737385.
83. Budczies, J.; Mechtersheimer, G.; Denkert, C.; Klauschen, F.; Mughal, S.S.; Chudasama, P.; Bockmayr, M.; Jöhrens, K.; Endris, V.; Lier, A.; et al. PD-L1 (CD274) Copy Number Gain, Expression, and Immune Cell Infiltration as Candidate Predictors for Response to Immune Checkpoint Inhibitors in Soft-Tissue Sarcoma. *Oncoimmunology* **2017**, *6*, e1279777, doi:10.1080/2162402X.2017.1279777.
84. Munuswamy, N.; Sundar, M.; Krishnan, K.; Chandran, M.; R K, K. Undifferentiated Pleomorphic Sarcoma: A Case Report. *Cureus* **2024**, doi:10.7759/cureus.73422.
85. Zając, A.E.; Czarnecka, A.M.; Rutkowski, P. The Role of Macrophages in Sarcoma Tumor Microenvironment and Treatment. *Cancers (Basel)* **2023**, *15*, 5294, doi:10.3390/cancers15215294.
86. Ishihara, S.; Iwasaki, T.; Kohashi, K.; Kawaguchi, K.; Toda, Y.; Fujiwara, T.; Setsu, N.; Endo, M.; Matsumoto, Y.; Nakashima, Y.; et al. Clinical Significance of Signal Regulatory Protein Alpha and T Cell Immunoreceptor with Immunoglobulin and Immunoreceptor Tyrosine-Based Inhibition Motif Domain Expression in Undifferentiated Pleomorphic Sarcoma. *J Cancer Res Clin Oncol* **2023**, *149*, 2425–2436, doi:10.1007/s00432-022-04078-y.
87. Tang, F.; Tie, Y.; Wei, Y.-Q.; Tu, C.-Q.; Wei, X.-W. Targeted and Immuno-Based Therapies in Sarcoma: Mechanisms and Advances in Clinical Trials. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer* **2021**, *1876*, 188606, doi:10.1016/j.bbcan.2021.188606.
88. Yuan, L.-L.; Chen, Z.; Qin, J.; Qin, C.-J.; Bian, J.; Dong, R.-F.; Yuan, T.-B.; Xu, Y.-T.; Kong, L.-Y.; Xia, Y.-Z. Single-Cell Sequencing Reveals the Landscape of the Tumor Microenvironment in a Skeletal Undifferentiated Pleomorphic Sarcoma Patient. *Front Immunol* **2022**, *13*, doi:10.3389/fimmu.2022.1019870.
89. Cheung, L.S.; Chen, L.; Oke, T.F.; Schaffer, T.B.; Boudadi, K.; Ngo, J.T.; Gross, J.M.; Kemberling, H.; Diaz, L.A.; Lipson, E.; et al. Anti-PD-1 Elicits Regression of Undifferentiated Pleomorphic Sarcomas with UV-Mutation Signatures. *J Immunother Cancer* **2021**, *9*, e002345, doi:10.1136/jitc-2021-002345.
90. Li, Y.; Liu, Y.; Qu, Y.; Chen, X.; Qu, X.; Ye, Y.; Du, X.; Cheng, Y.; Xu, M.; Zhang, H. Case Report: Two Cases of Soft-Tissue Sarcomas: High TMB as a Potential Predictive Biomarker for Anlotinib Combined With Toripalimab Therapy. *Front Immunol* **2022**, *13*, doi:10.3389/fimmu.2022.832593.
91. Italiano, A.; Bellera, C.; D'Angelo, S. PD1/PD-L1 Targeting in Advanced Soft-Tissue Sarcomas: A Pooled Analysis of Phase II Trials. *J Hematol Oncol* **2020**, *13*, 55, doi:10.1186/s13045-020-00891-5.
92. Burgess, M.A.; Bolejack, V.; Schuetze, S.; Van Tine, B.A.; Attia, S.; Riedel, R.F.; Hu, J.S.; Davis, L.E.; Okuno, S.H.; Priebat, D.A.; et al. Clinical Activity of Pembrolizumab (P) in Undifferentiated Pleomorphic Sarcoma (UPS) and Dedifferentiated/Pleomorphic Liposarcoma (LPS): Final Results of SARC028 Expansion Cohorts. *Journal of Clinical Oncology* **2019**, *37*, 11015–11015, doi:10.1200/JCO.2019.37.15_suppl.11015.
93. Https://Clinicaltrials.Gov/Study/NCT03123276.
94. Https://Clinicaltrials.Gov/Study/NCT02406781.
95. Https://Clinicaltrials.Gov/Study/NCT03946943.
96. Https://Clinicaltrials.Gov/Study/NCT04447274.
97. Https://Clinicaltrials.Gov/Study/NCT04480502.
98. Https://Clinicaltrials.Gov/Study/NCT03307616.
99. Https://Clinicaltrials.Gov/Study/NCT02406781.
100. Https://Clinicaltrials.Gov/Study/NCT02301039.
101. Https://Clinicaltrials.Gov/Study/NCT03116529.
102. Https://Clinicaltrials.Gov/Study/NCT03092323.
103. Guram, K.; Nunez, M.; Einck, J.; Mell, L.K.; Cohen, E.; Sanders, P.D.; Miyauchi, S.; Weihe, E.; Kurzrock, R.; Boles, S.; et al. Radiation Therapy Combined With Checkpoint Blockade Immunotherapy for Metastatic Undifferentiated Pleomorphic Sarcoma of the Maxillary Sinus With a Complete Response. *Front Oncol* **2018**, *8*, doi:10.3389/fonc.2018.00435.

 doi:10.20944/preprints202509.1095.v1

104. D'Angelo, S.P.; Richards, A.L.; Conley, A.P.; Woo, H.J.; Dickson, M.A.; Gounder, M.; Kelly, C.; Keohan, M.L.; Movva, S.; Thornton, K.; et al. Pilot Study of Bempegaldesleukin in Combination with Nivolumab in Patients with Metastatic Sarcoma. *Nat Commun* **2022**, *13*, 3477, doi:10.1038/s41467-022-30874-8.
105. Https://Clinicaltrials.Gov/Study/NCT03282344.
106. Gordon, E.M.; Angel, N.L.; Omelchenko, N.; Chua-Alcala, V.S.; Moradkhani, A.; Quon, D.; Wong, S. A Phase I/II Investigation of Safety and Efficacy of Nivolumab and *Nab* -Sirolimus in Patients With a Variety of Tumors With Genetic Mutations in the MTOR Pathway. *Anticancer Res* **2023**, *43*, 1993–2002, doi:10.21873/anticanres.16360.
107. Https://Clinicaltrials.Gov/Study/NCT05103358.
108. Haddox, C.L.; Nathenson, M.J.; Mazzola, E.; Lin, J.-R.; Baginska, J.; Nau, A.; Weirather, J.L.; Choy, E.; Marino-Enriquez, A.; Morgan, J.A.; et al. Phase II Study of Eribulin plus Pembrolizumab in Metastatic Soft-Tissue Sarcomas: Clinical Outcomes and Biological Correlates. *Clinical Cancer Research* **2024**, *30*, 1281–1292, doi:10.1158/1078-0432.CCR-23-2250.
109. Https://Clinicaltrials.Gov/Study/NCT03899805.
110. Pollack, S.M.; Redman, M.W.; Baker, K.K.; Wagner, M.J.; Schroeder, B.A.; Loggers, E.T.; Trieselmann, K.; Copeland, V.C.; Zhang, S.; Black, G.; et al. Assessment of Doxorubicin and Pembrolizumab in Patients With Advanced Anthracycline-Naive Sarcoma. *JAMA Oncol* **2020**, *6*, 1778, doi:10.1001/jamaoncol.2020.3689.
111. Ishihara, S.; Iwasaki, T.; Kohashi, K.; Yamada, Y.; Toda, Y.; Ito, Y.; Susuki, Y.; Kawaguchi, K.; Takamatsu, D.; Kawatoko, S.; et al. The Association between the Expression of PD-L1 and CMTM6 in Undifferentiated Pleomorphic Sarcoma. *J Cancer Res Clin Oncol* **2021**, *147*, 2003–2011, doi:10.1007/s00432-021-03616-4.
112. Pan, H.; Liu, Y.; Fuller, A.M.; Williams, E.F.; Fraietta, J.A.; Eisinger, T.S.K. Collagen Modification Remodels the Sarcoma Tumor Microenvironment and Promotes Resistance to Immune Checkpoint Inhibition 2024.
113. Lee, P.; Malik, D.; Perkons, N.; Huangyang, P.; Khare, S.; Rhoades, S.; Gong, Y.-Y.; Burrows, M.; Finan, J.M.; Nissim, I.; et al. Targeting Glutamine Metabolism Slows Soft Tissue Sarcoma Growth. *Nat Commun* **2020**, *11*, 498, doi:10.1038/s41467-020-14374-1.
114. Verbeke, S.; Bourdon, A.; Lafon, M.; Chaire, V.; Frederic, B.; Naït Eldjoudi, A.; Derieppe, M.-A.; Giles, F.; Italiano, A. Dual Inhibition of BET and EP300 Has Antitumor Activity in Undifferentiated Pleomorphic Sarcomas and Synergizes with Ferroptosis Induction. *Transl Oncol* **2025**, *52*, 102236, doi:10.1016/j.tranon.2024.102236.
115. May, C.D.; Landers, S.M.; Bolshakov, S.; Ma, X.; Ingram, D.R.; Kivlin, C.M.; Watson, K.L.; Sannaa, G.A. Al; Bhalla, A.D.; Wang, W.-L.; et al. Co-Targeting PI3K, MTOR, and IGF1R with Small Molecule Inhibitors for Treating Undifferentiated Pleomorphic Sarcoma. *Cancer Biol Ther* **2017**, *18*, 816–826, doi:10.1080/15384047.2017.1373230.
116. Lyko, F. The DNA Methyltransferase Family: A Versatile Toolkit for Epigenetic Regulation. *Nat Rev Genet* **2018**, *19*, 81–92, doi:10.1038/nrg.2017.80.
117. Saitoh, Y.; Bureta, C.; Sasaki, H.; Nagano, S.; Maeda, S.; Furukawa, T.; Taniguchi, N.; Setoguchi, T. The Histone Deacetylase Inhibitor LBH589 Inhibits Undifferentiated Pleomorphic Sarcoma Growth via Downregulation of *FOS-like Antigen 1*. *Mol Carcinog* **2019**, *58*, 234–246, doi:10.1002/mc.22922.
118. Diaz, L.A.; Coughlin, C.M.; Weil, S.C.; Fishel, J.; Gounder, M.M.; Lawrence, S.; Azad, N.; O'Shannessy, D.J.; Grasso, L.; Wustner, J.; et al. A First-in-Human Phase I Study of MORAb-004, a Monoclonal Antibody to Endosialin in Patients with Advanced Solid Tumors. *Clinical Cancer Research* **2015**, *21*, 1281–1288, doi:10.1158/1078-0432.CCR-14-1829.
119. Tokumoto, H.; Setoguchi, T.; Saitoh, Y.; Sasaki, H.; Nagano, S.; Maeda, S.; Tanimoto, A.; Taniguchi, N. Neurotensin Receptor 1 Is a New Therapeutic Target for Human Undifferentiated Pleomorphic Sarcoma Growth. *Mol Carcinog* **2019**, *58*, 2230–2240, doi:10.1002/mc.23111.
120. Yu, K.; Wang, L.; Bu, F.; Zhang, J.; Hai, Y.; Hu, R.; Lu, J.; Shi, X. Retroperitoneal Undifferentiated Pleomorphic Sarcoma with Total Nephrectomy: A Case Report and Literature Review. *Front Surg* **2023**, *10*, doi:10.3389/fsurg.2023.1166764.
121. Spalato-Ceruso, M.; Laroche-Clary, A.; Perret, R.; Valverde, Y.; Chaire, V.; Derieppe, M.-A.; Velasco, V.; Bourdon, A.; Italiano, A. Genome-Wide CRISPR/Cas9 Library Screening Identified ATM Signaling

 doi:10.20944/preprints202509.1095.v1

Network Genes as Critical Drivers for Resistance to ATR Inhibition in Soft-Tissue Sarcomas: Synthetic Lethality and Therapeutic Implications. *Exp Hematol Oncol* **2023**, *12*, 51, doi:10.1186/s40164-023-00416-z.

122. Toulmonde, M.; Lucchesi, C.; Verbeke, S.; Crombe, A.; Adam, J.; Geneste, D.; Chaire, V.; Laroche-Clary, A.; Perret, R.; Bertucci, F.; et al. High Throughput Profiling of Undifferentiated Pleomorphic Sarcomas Identifies Two Main Subgroups with Distinct Immune Profile, Clinical Outcome and Sensitivity to Targeted Therapies. *EBioMedicine* **2020**, *62*, 103131, doi:10.1016/j.ebiom.2020.103131.
123. Frankiw, L.; Singh, A.; Peters, C.; Comin-Anduix, B.; Berent-Maoz, B.; Macabali, M.; Shammaie, K.; Quiros, C.; Kaplan-Lefko, P.; Baselga Carretero, I.; et al. Immunotherapy Resistance Driven by Loss of NY-ESO-1 Expression in Response to Transgenic Adoptive Cellular Therapy with PD-1 Blockade. *J Immunother Cancer* **2023**, *11*, e006930, doi:10.1136/jitc-2023-006930.
124. Conley, A.P.; Wang, W.-L.; Livingston, J.A.; Ravi, V.; Tsai, J.-W.; Ali, A.; Ingram, D.R.; Lowery, C.D.; Roland, C.L.; Somaiah, N.; et al. MAGE-A3 Is a Clinically Relevant Target in Undifferentiated Pleomorphic Sarcoma/Myxofibrosarcoma. *Cancers (Basel)* **2019**, *11*, 677, doi:10.3390/cancers11050677.