Cancer Treatment Reviews 131 (2024) 102846

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Tumour Review

Diagnosis and management of dedifferentiated liposarcoma: A multidisciplinary position statement

Candace L. Haddox [a], Jason L. Hornick [b], Christina L. Roland [c], Elizabeth H. Baldini [a,b], Vicki L. Keedy [d], Richard F. Riedel [e,*]

[a] Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, United States
[b] Brigham & Women's Hospital, Harvard Medical School, Boston, MA, United States
[c] The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[d] Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, United States
[e] Duke Cancer Institute, Duke University, Durham, NC, United States

ARTICLE INFO

Keywords:
Dedifferentiated liposarcoma
Multidisciplinary
Chemotherapy
Radiation
Surgery
Pathology
Novel therapies
MDM2
CDK4

ABSTRACT

Dedifferentiated liposarcoma (DDLPS) is a malignant mesenchymal neoplasm in desperate need of novel therapeutic approaches. Often occurring in conjunction with well-differentiated liposarcoma (WDLPS), DDLPS can behave more aggressively and exhibits a significant risk for developing recurrence or metastatic disease when compared to its well-differentiated counterpart. A multidisciplinary approach is critically important, particularly for patients with localized disease, as disease presentations are often complex, and the management of patients has become increasingly nuanced as treatment approaches have become more refined. Expert pathology review and appropriate application of diagnostic molecular techniques are key components of DDLPS diagnosis and also reflect an improved understanding of the underlying pathogenesis of the disease. Systemic therapies remain limited for DDLPS, but novel therapies targeting important underlying molecular drivers have resulted in ongoing clinical trials aiming to improve outcomes for patients with advanced disease. In recognition of the increased activity and interest within the DDLPS field, a multidisciplinary group of nationally recognized experts in medical oncology, surgical oncology, radiation oncology, and pathology was convened to summarize key insights. This position paper highlights important points from the meeting and provides evidence-based recommendations for practicing clinicians.

Introduction

Liposarcomas (LPS) are among the most common mesenchymal neoplasms encountered in clinical practice. Collectively, liposarcomas represent a family of adipocytic tumors with the most common histologic subtypes including well-differentiated, dedifferentiated, and myxoid; pleomorphic liposarcoma is rare. These tumors most commonly arise in the extremities or trunk (ET) and retroperitoneum (RP), but all areas of the body can be affected. Presenting symptoms can often be vague and non-specific, particularly for patients with retroperitoneal disease, whereas disease in the extremity will often present as a palpable mass.

There are several prognostic factors related to liposarcoma that can impact patient survival [1]. Tumor-specific factors include tumor size, tumor grade, location, and histologic subtype. As an example, WDLPS, when occurring in isolation, is low-grade, relatively indolent in its growth pattern, and not associated with the development of metastatic disease, but can locally recur [2]. In contrast, DDLPS, occurring *de novo* or in conjunction with WDLPS, can behave in an aggressive fashion with significant risk for local recurrence and distant metastatic spread [2].

With an annual incidence of 0.21 cases/100,000 person years, DDLPS accounts for less than 2,500 new cases per year in the United States and is more common in men than women [3]. Retroperitoneal DDLPS can often grow to be quite large, particularly when in association with WDLPS, before symptoms develop or physical exam findings are noted. Symptoms associated with retroperitoneal disease may include increased abdominal girth, early satiety, nausea, changes in bowel habits, and unexplained weight loss. Extremity disease may be painful or painless in nature.

The diagnostic evaluation of DDLPS includes cross-sectional imaging

* Corresponding author at: Box 3198 DUMC, Durham, NC 27710, United States.
E-mail address: richard.riedel@duke.edu (R.F. Riedel).

https://doi.org/10.1016/j.ctrv.2024.102846
Received 30 July 2024; Received in revised form 13 October 2024; Accepted 14 October 2024
Available online 18 October 2024

of the primary tumor site and assessment for potential metastases, as well as pathologic evaluation, ideally from pretreatment biopsy. Since parenchymal lung metastases are the most common site of metastasis, CT scan of the chest is recommended for all patients diagnosed with DDLPS, regardless of the tumor location. For DDLPS of the extremity/trunk, magnetic resonance imaging (MRI) is the preferred modality for evaluating the primary tumor, as it provides optimal assessment of the tumor's proximity to and involvement with adjacent soft tissue and neurovascular structures. Advanced imaging techniques, such as diffusion-weighted (DW) imaging and dynamic contrast-enhanced imaging, can help differentiate inflammation and fibrosis and are particularly useful after neoadjuvant treatments.

For retroperitoneal and intra-abdominal DDLPS, contrasted CT of the abdomen and pelvis is the preferred imaging modality. The relationship of the tumor to major vascular structures, including the superior mesenteric artery (SMA), porta hepatis, aorta, and inferior vena cava (IVC), is critical in determining resectability. Additionally, assessing the extent of involvement of the colon, as well as the ipsilateral and contralateral kidneys and ureters, is essential for planning a safe resection.

Mouse double minute 2 (*MDM2*) and *cyclin-dependent kinase 4* (*CDK4*) gene amplifications are nearly ubiquitous in DDLPS [4]. As a negative regulator of p53, MDM2 overexpression is common in a variety of malignancies and has become an attractive target for several emerging therapies [5]. Similarly, therapies targeting CDK4 are part of ongoing clinical trials in DDLPS.

The sections to follow highlight the multidisciplinary approach required to optimize the management of patients with DDLPS, including the importance of pathologic expertise in making a diagnosis, local control considerations, and management of metastatic disease, as well as novel therapeutic approaches currently under investigation. Recommendations will follow each section to inform the reader of current best practices.

Diagnostic pathways

DDLPS is defined as progression of WDLPS to a (usually) non-lipogenic sarcoma [6]. Pathologically, the transition between WDLPS and DDLPS is usually abrupt, although in some cases the transition may be more gradual; occasionally, no well-differentiated adipocytic component can be identified in the resection specimen (Fig. 1). Now that the molecular pathogenetic basis for these tumor types is understood, the diagnosis of DDLPS can be made without identifying a WDLPS component. It is critical for pathologists to have a high index of suspicion for DDLPS; this diagnosis should always be considered when reviewing a core needle biopsy of a retroperitoneal mass. DDLPS lacks distinctive histologic appearances; morphology is highly variable, ranging from the classic pleomorphic appearance to relatively uniform spindle cell or even epithelioid morphology [7]. Myxoid stroma is commonly identified. The latter may result in diagnostic confusion for the pathologist, leading to consideration for myxoid liposarcoma or myxofibrosarcoma [8]. However, myxoid liposarcoma virtually never arises primarily in central body cavity locations (although such sites are common for metastatic disease), and myxofibrosarcoma only occurs in somatic soft tissue sites (extremities and trunk wall).

Approximately 10 % of DDLPS cases show heterologous differentiation, including rhabdomyoblastic (skeletal muscle), chondro-osseous, or, less often, other elements [9]. DDLPS with rhabdomyoblastic elements pursues a particularly aggressive clinical course [10]. Encountering such components may lead to consideration for a rhabdomyosarcoma or extraskeletal osteosarcoma, for example; again, the presentation as a large retroperitoneal or abdomino-pelvic mass should lead to the correct diagnosis. Finally, rare cases of DDLPS show "homologous" lipoblastic differentiation, resembling pleomorphic liposarcoma [11]. Any of these less common histologic features should not dissuade the pathologist from pursuing confirmatory ancillary techniques.

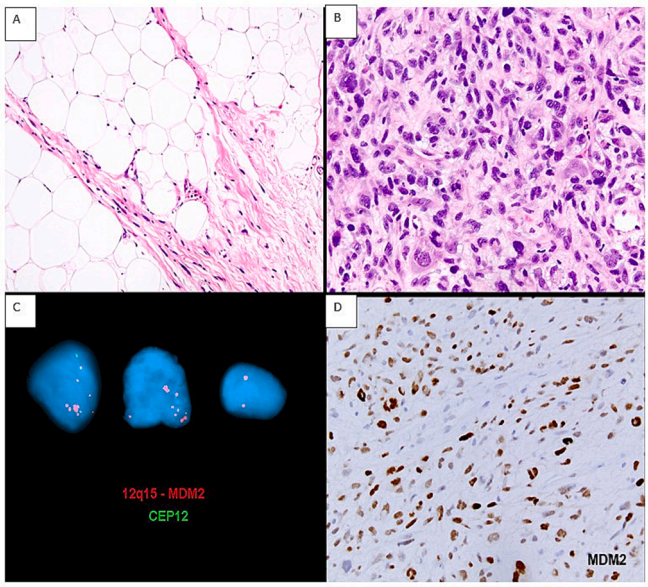


Fig. 1. Pathology of dedifferentiated liposarcoma. A. Well-differentiated liposarcoma component showing variation in adipocyte size and thickened fibrous septa containing atypical cells with hyperchromatic nuclei. B. Dedifferentiated liposarcoma composed of sheets of pleomorphic cells showing widely variable nuclear morphology including very large, bizarre forms and a high mitotic rate. C. Fluorescence in situ hybridization (FISH) analysis showing high-level *MDM2* gene amplification in tumor cells (left and middle cells; red signal). The normal cell on the right contains 2 copies of *MDM2*. CEP12, signal directed against the centromere of chromosome 12 (green signal). D. Immunohistochemistry for MDM2 showing strong nuclear staining in tumor cells.

DDLPS shows amplification of the chromosome 12q13-15 region, in the form of ring and giant marker (rod) chromosomes, including the critical driver gene *MDM2* and often *CDK4* [12]. Fluorescence in situ hybridization (FISH) for *MDM2* is routinely applied to confirm the diagnosis; overexpression of the MDM2 protein can also be assessed by immunohistochemistry (IHC) (Fig. 1) [13]. IHC is less specific than FISH, although in the context of a large retroperitoneal sarcoma, IHC is often sufficient. Histologic grading of resected DDLPS (using the FNCLCC system) appears to predict metastatic risk: high-grade DDLPS has higher metastatic potential than intermediate-grade tumors [14].

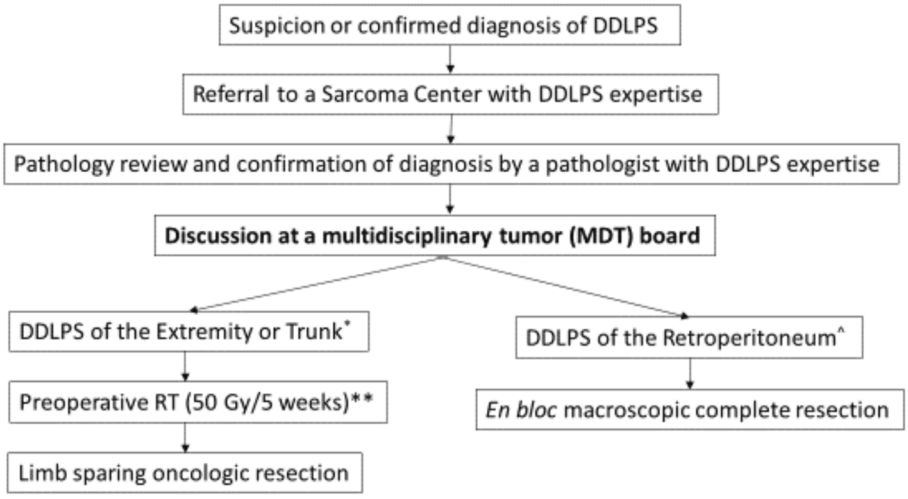
Recommendations:

1. Given the increasing role of histology-specific therapeutic approaches, individuals with a suspected DDLPS should have pathology reviewed at a center with sarcoma expertise.
2. DDLPS should always be considered in the differential when reviewing a core needle biopsy of a retroperitoneal mass.
3. The use of molecular diagnostics, including the assessment of *MDM2* amplification by FISH, or, in the appropriate clinical context, overexpression by IHC, can help confirm a diagnosis of DDLPS.

Management of localized disease

Surgical considerations

For localized DDLPS, whether it arises in the RP or the ET, surgery remains the only potentially curative option. The optimal surgical strategy includes an oncologically complete resection at the time of the initial operation, which ideally involves 1–2 cm of normal tissue as the margin. The feasibility of this differs based on anatomic location and individual management plans, and all patients with DDLPS should be discussed in a specialized sarcoma multidisciplinary tumor board (Fig. 2).



*The roles of neoadjuvant or adjuvant chemotherapy are unclear and may be used on occasion after a MDT discussion and shared decision making with the patient.
**Preoperative RT is preferred, but postoperative RT is also an option
^ The roles of neoadjuvant RT or chemotherapy are unclear and may be used on occasion after a MDT discussion and shared decision making with the patient.

Fig. 2. Proposed treatment algorithm for DDLPS.

A complete *en bloc* resection is the cornerstone of management for RP DDLPS [15]. In the RP, DDLPS typically arises from the perinephric fat and is large, abutting, or involving multiple intra-abdominal organs, most commonly the kidney and colon. To achieve complete removal, a multi-visceral resection is often necessary, aiming for a macroscopically complete resection [16,17]. Anatomic constraints in the abdomen prevent wide resection margins, which contribute to high rates of local recurrence. An extended resection approach for RP DDLPS has been proposed, which involves resection of the adjacent viscera, typically the colon, even in the absence of macroscopic infiltration. However, this approach should be weighed against the short-and long-term morbidity and mortality associated with such extensive surgery [18]. Regardless of the surgical approach taken, DDLPS often consists of a combination of a solid DDLPS component and an associated, fattier WDLPS component. Therefore, a careful review of preoperative imaging with sarcoma radiologists is crucial to ensure removal of all the abnormal ipsilateral fat.

In the extremity, limb-sparing surgery is considered the standard of care. Amputation should be performed in < 5 % of patients with primary ET sarcoma, including DDLPS. Radical resection of the DDLPS with 1–2 cm of normal muscle is required, with sparing of critical structures such as major nerves or blood vessels, unless directly invaded [19]. For deep tumors, the periosteum can be resected as a margin using a periosteal elevator to spare the need for bone resection.

Given that DDLPS is a rare tumor requiring complex surgical management, it is best treated by an experienced multidisciplinary team at a specialized referral center. In common cancers, surgical treatment of cancer at high-volume centers is associated with improved outcomes [20]. Recent studies from the US and Europe have demonstrated a positive relationship between hospital volume and outcomes for patients with sarcoma [21–23]. Patients treated at high-volume hospitals (performing more than 10–13 primary sarcoma operations per year) had lower 30-day readmission rates, reduced 30- and 90-day mortality rates, and longer overall survival (OS). These findings underscore the importance of patients receiving treatment by sarcoma specialists.

Radiation therapy considerations

Indications for radiation therapy (RT) for DDLPS vary by the anatomic location of disease. DDLPS of the ET is treated with a similar approach to most soft tissue sarcomas of ET. For ET soft tissue sarcoma, several randomized trials have demonstrated a local control benefit with the addition of RT to limb-sparing surgery [24–26]. In these studies, with the addition of RT, risk of local recurrence is <15 %. Furthermore, in experienced hands at high-volume sarcoma centers, risk of local recurrence following limb-sparing surgery and RT is <10 % [27–29]. Accordingly, North American and European guidelines recommend the addition of RT to limb-sparing surgery for soft tissue sarcomas of ET felt to be at risk of local recurrence (e.g. large tumors, high-grade, or those expected to have close or positive resection margins) [30,31]. On the other hand, because sarcomas of RP are less common, we do not have a similar series of high-quality randomized trials to guide management. The available data are conflicting with respect to the potential benefit of RT in the management of RP DDLPS. The recent EORTC-STRASS trial randomized 266 patients with primary resectable RP sarcoma to either 50.4 Gy preoperative RT followed by surgery vs surgery alone [32]. The primary endpoint was abdominal recurrence-free survival and there was no demonstrated improvement with the addition of RT. Interestingly, post-hoc analyses showed a potential benefit for low-grade or well-differentiated LPS, but not for high-grade DDLPS. Thus, macroscopic complete resection is the standard of care for RP sarcoma and routine treatment with RT is not recommended for DDLPS of RP (or any RP sarcoma) [30].

If RT is delivered in combination with surgery, the sequencing can be preoperative or postoperative. For ET sarcoma, a sentinel randomized trial comparing preoperative vs postoperative RT showed no difference in local control or survival outcomes, but the side effect profiles differed [27,33]. There was a higher risk of temporary major wound complications with preoperative RT compared to a higher risk of permanent long-term side effects including edema, subcutaneous fibrosis, and joint stiffness with postoperative RT [33]. Due to its association with fewer permanent long-term side effects, preoperative RT is typically preferred [30]. For RP DDLPS, there are no clear data demonstrating the benefit of RT, but if it is delivered, preoperative RT is preferred [28]. The reasons for this are that, in the preoperative setting, standard sarcoma doses are lower (50 Gy) and achievable with respect to the tolerance of adjacent normal organs, whereas in the postoperative setting, standard sarcoma doses are higher (60–66 Gy), and such doses exceed the tolerance of adjacent normal organs, most notably bowel.

Lastly, conventional RT dose fractionation (2 Gy) is recommended for DDLPS of both ET and RP. For ET, the standard-of-care RT regimen is 50 Gy delivered in 2 Gy fractions over 5 weeks preoperatively or 60–66 Gy postoperatively [28]. The potential role of hypofractionated

preoperative RT regimens for soft tissue sarcoma of ET whereby treatment is delivered over 1 or 3 weeks rather than 5 weeks is being studied, but data are not yet sufficiently mature to change standard of care [34–39]. For RP sarcoma, if RT is recommended after multidisciplinary discussion and shared decision making with the patient, the same preoperative dose of 50 Gy delivered over 5 weeks is recommended.

Perioperative chemotherapy considerations

Determining the impact of perioperative chemotherapy in adult soft tissue sarcomas has proven to be a difficult task. Clinical trials are confounded by the heterogeneity of both histology and primary location of the sarcoma, as well as the variable treatment regimens used. To answer this question, LPS of the ET must be considered separately from LPS of the RP, as these each have a different clinical course and recurrence rate.

Multiple randomized trials have been performed looking at the role of anthracycline-based regimens in the ET. While doses studied in each trial varied significantly, more modern trials have included epirubicin or doxorubicin 60–75 mg/m^2 with higher doses of ifosfamide, 9000–10,000 mg/m^2 for 3–5 cycles [40,41]. Despite discordant results, a meta-analysis suggested an improvement in OS for anthracycline plus ifosfamide trials with an odds ratio (OR) of 0.56 (95 % CI, 0.36–0.85; $P = 0.01$) and an absolute risk reduction of 12 % (95 % CI, 3 %–21 %; $P = 0.01$) [42]. Attempts to further define which patients may benefit the most from chemotherapy focused on defining high-risk patient populations using the prognostic nomogram Sarculator [43]. These studies suggest patients with a predicted 10-year OS of less than 60 % benefit from chemotherapy, while patients with intermediate or lower risk do not [44,45]. Based on these data, the use of perioperative chemotherapy may be considered for patients who are at high risk for recurrence. It is important, however, to balance this discussion with both the short- and long-term risks of these regimens.

For RP DDLPS, the discussion is much more difficult. Most modern trials trying to answer this question have focused on sarcomas of the ET. For RP sarcomas, data are limited, and, in at least 1 study, have suggested a worse OS for patients who received neoadjuvant chemotherapy (HR, 1.17; 95 % CI, 1.04–1.31; $P = 0.009$) despite controlling for high-risk features [46]. Extrapolating from randomized trials in extremity sarcomas is also difficult, as no trial has specifically investigated DDLPS, and the impact of local and metastatic recurrences differs between locations. In a prospective, neoadjuvant, single-arm trial using high-dose ifosfamide (14 g/m^2) administered as a long infusion in patients with localized RP sarcomas, distant metastasis rates at 7 years were 6 % and 19 % for WDLPS and DDLPS respectively, yet 7-year OS was 82 % and 53 %, respectively [47]. This suggests that death from disease may be impacted more from local recurrence than distant metastasis. The currently enrolling STRASS 2 trial (NCT04031677), investigating preoperative doxorubicin/epirubicin in combination with either ifosfamide, in patients with grade 2 and 3 retroperitoneal DDLPS, or dacarbazine, in patients with leiomyosarcoma, will hopefully answer the question regarding the role of neoadjuvant chemotherapy in RP sarcoma.

Despite the lack of robust data for the use of chemotherapy in this setting, there are patients for whom preoperative chemotherapy may be considered: particularly large, grade 3 DDLPS where complete resection may have high morbidity; or when there is concern for a particularly aggressive disease course. This decision requires a multidisciplinary discussion amongst liposarcoma specialists, along with a risk–benefit discussion with the patient. The focus of perioperative chemotherapy has shifted to neoadjuvant treatment in recent years. For retroperitoneal DDLPS, this approach is even more important, given the frequent use of ifosfamide-based regimens which require adequate kidney function. As surgery for a RP DDLPS frequently requires a nephrectomy, chemotherapy, if being considered, is best given in the neoadjuvant setting.

Recommendations:

1. Surgical resection for a localized DDLPS should be performed in a high-volume center, as outcomes are improved compared to low-volume centers
2. Radiation therapy should be considered, either preoperatively or postoperatively, for a high-grade DDLPS of the extremity, given improvement in local control when combined with limb-sparing surgery.
3. The use of radiation therapy for retroperitoneal DDLPS is not routinely recommended
4. Despite limited data, perioperative chemotherapy with an anthracycline in combination with ifosfamide, for example, may be considered for patients with DDLPS at high risk for recurrence. If perioperative chemotherapy is being considered for RP DDLPS, neoadjuvant chemotherapy is preferred.

Management of advanced disease

While significant progress has been made in the systemic treatment of liposarcoma, standard first-line chemotherapy for DDLPS remains an anthracycline-based regimen, most commonly doxorubicin at a dose of 75 mg/m^2/cycle. As trials have not consistently demonstrated an OS benefit for anthracycline combination treatments in the metastatic setting, monotherapy is commonly used [48]. However, response rates are higher with combination treatment, thus the addition of ifosfamide is considered in patients with oligometastatic disease who could go on to potentially curative treatments or for those patients with rapidly progressive and/or symptomatic disease.

Available second-line treatments include gemcitabine plus docetaxel, trabectedin, and eribulin. Of note, multi-tyrosine kinase inhibitors have failed to show benefit for DDLPS in multiple clinical trials [49–51]. Gemcitabine plus docetaxel improved both progression-free survival (PFS) and OS compared to gemcitabine alone in a trial of all soft tissue sarcomas; however, the degree of benefit for DDLPS specifically is unknown [52]. Both trabectedin and eribulin were compared to dacarbazine in similarly designed randomized phase III trials for both liposarcomas and leiomyosarcoma, showing superiority to dacarbazine in patients with DDLPS (Table 1) [53,54]. In the pre-planned LPS (all subtypes) analysis, trabectedin improved PFS by 1.5 months compared to dacarbazine, but showed no OS benefit [55]. In the DDLPS subset analysis, eribulin improved OS by 10 months, with no improvement in PFS [56]. As this is consistent with results seen in breast cancer, there is speculation that eribulin impacts sensitivities to later-line therapies.

Immunotherapy approaches have been tested in DDLPS with intriguing responses or durable disease control in a small subset of patients, yet broad activity appears to be lacking. For example, the phase II study evaluating pembrolizumab in soft tissue and bone sarcomas (SARC028) included a cohort of 10 patients with DDLPS. Two patients (20 %) achieved partial response (PR), leading to an expansion cohort with 30 additional DDLPS participants [57,58]. Across the 39 patients evaluated, the overall response rate (ORR) was 10 % and median progression free survival (mPFS) was 2 months, suggesting limited activity for pembrolizumab monotherapy (Table 1). Pembrolizumab or nivolumab (with or without ipilimumab) are listed in NCCN guidelines for subsequent lines of therapy for advanced or metastatic disease. Given limited systemic therapy options, we typically incorporate immune checkpoint inhibitors after approved chemotherapies.

As these regimens have not been compared to each other in randomized trials, decisions regarding the order in which they are given involve shared decision making with the patient and consideration of patient comorbidities and unique toxicities. In particular, the logistics of treatment schedules, such as 24-hour infusions for trabectedin and Day 1 and 8 treatments for gemcitabine plus docetaxel and eribulin, may impact patient decision making. In the end, sequential use of each of these regimens is important, and patients appropriate for cytotoxic chemotherapies will often receive each of them at some point in their treatment course. As the current treatment paradigm for DDLPS involves

Table 1
Clinical trials impacting standard of care in DDLPS.

Common Name	Phase	Drugs	Mechanism	Design	Outcome	Ref
–	III	Trabectedin	Chemotherapy; alkaloid agent	Subgroup of advanced or metastatic LPS after anthracycline; randomized 2:1 to trabectedin vs dacarbazine (T vs D)	Overall survival 13.1 mo vs 12.6 mo (T vs D). HR 1.05 (95 % CI 0.69–1.60) Median PFS 3.0 mo vs 1.5 mo (T vs D). HR 0.55 (95 % CI 0.34–0.87)	[53,55]
–	III	Eribulin	Chemotherapy; Non-taxane microtubule inhibitor	Subgroup of advanced or metastatic DDLPS after 2 prior lines (including anthracycline); randomized 1:1 to eribulin vs dacarbazine (E vs D)	Overall survival 18 mo vs 8.1 mo (E vs D). HR 0.429 (95 % CI 0.232–0.792) Median PFS 2 mo vs 2.1 mo (E vs D). HR 0.691 (95 % CI 0.359–1.328)	[54,56]
SARC028	II	Pembrolizumab	PD-1 inhibitor	Subgroup of advanced or metastatic DDLPS who received up to 3 prior lines; single arm. Included 10 initial and 30 additional patients in expansion.	ORR 10 % (4 of 39 evaluable) Median PFS 3 mo (95 % CI 2–4 mo)	[57,58]
–	II	Palbociclib	CDK4/6 inbitor	Nonrandomized, open label; single arm. Enrolled 30 in initial cohort and 30 in expansion cohort	12 week PFS 57.2 % (95 % CI 42.4 %-68.8 %). Median PFS 17.9 weeks (95 % CI 11.9–24 weeks). 1 PR	[63]

multiple cytotoxic agents, toxicities will accumulate, and it is important to provide systemic treatment breaks when appropriate. Given the limited number of treatment options available for metastatic DDLPS, clinical trial participation is strongly recommended (Table 2).

Recommendations:

1. Anthracycline-based therapy, either as a single agent (doxorubicin or epirubicin) or as part of a combination (doxorubicin or epirubicin in combination with ifosfamide), is considered the front-line standard for metastatic DDLPS
2. Treatment options in the second and later lines of therapy for DDLPS remain limited and include gemcitabine-based regimens as well as trabectedin and eribulin. Clinical trial participation is strongly encouraged

Novel therapies

The unique molecular features of DDLPS provide potential actionable targets for novel drug development. The disease-defining 12q13-15 amplification leads to near-ubiquitous amplification of *CDK4* and *MDM2* in DDLPS, which are attractive targets for clinical evaluation.

Cyclin-dependent kinases (CDKs) perform diverse functions in cells, including cell cycle control and transcriptional regulation. Several studies have investigated CDK inhibitors in DDLPS, particularly CDK4/6 inhibitors [59–64]. Palbociclib was explored in 2 phase II trials using different dosing strategies for patients with WD/DDLPS. Although 2 patients across the 2 studies achieved a RECIST-defined response (1 complete response (CR), 1 PR), most patients experienced tumor growth with a mPFS of 18 weeks in both studies [62,63]. Of note, palbociclib is listed in NCCN guidelines for WD/DDLPS (Table 1), but given poor activity in trials to date, we generally prioritize the approved chemotherapy options mentioned above unless the patient is not a suitable candidate for chemotherapy.

The more potent CDK4/6 inhibitor, abemaciclib, was evaluated in a phase II trial, which revealed a numerically higher response rate of 10 % (3 out of 30) and 6 patients had durable disease control for $\geq$ 2 years [64]. A phase III randomized trial comparing abemaciclib with placebo in DDLPS (SARC041; NCT04967521) is underway (Table 2). Correlative studies show that CDK4/6 inhibitors can cause DDLPS cell growth arrest by inducing prolonged quiescence or senescence, and the latter may augment tumor immune cell infiltration [65]. In general, hematologic toxicity due to CDK6 inhibition narrows the therapeutic index for these agents, and this limitation may be subverted by CDK4 selective inhibitors.

MDM2 is an E3 ubiquitin ligase that targets p53 for degradation, in addition to other p53-independent functions. At the supraphysiologic levels observed in DDLPS, MDM2 impacts a broad array of oncogenic transcriptional circuits. Accordingly, MDM2 inhibitors are a rational treatment strategy in DDLPS. The MANTRA phase III registration trial compared milademetan, which inhibits the MDM2-p53 interaction, against trabectedin in 175 patients with DDLPS, but failed to meet its primary PFS endpoint [66]. Although the mechanism of resistance has not been determined, preclinical studies show that MDM2 is amplified on neochromosomes, which are segregated between daughter cells in a non-Mendelian fashion, leading to heterogeneity in *MDM2* copy number within a tumor. Cells with very high copy numbers were primarily resistant to MDM2 inhibition [67]. Further, MDM2 inhibition caused an initial surge in p53 levels, which further drives expression of MDM2 [67]. These findings provide insights into mechanisms of resistance, and it will be critical to develop predictive biomarkers further to aid in patient selection. Although the MANTRA trial results were disappointing, another MDM2 inhibitor in development, brigimadlin (BI 907828), showed promising activity in DDLPS. Preliminary analysis of 85

Table 2
Ongoing key clinical trials in DDLPS.

Common Name	NCT	Phase	Investigational Drugs	Mechanism	Design
STRASS 2	NCT04031677	III	Doxorubicin + Ifosfamide/Mesna (AIM)	Cytotoxic chemotherapy	Neoadjuvant AIM vs placebo for localized, resectable RP DDLPS
SARC041	NCT04967521	III	Abemaciclib	CDK4/6 inhibitor	Abemaciclib vs placebo for advanced DDLPS
Brightline-1	NCT05218499	III	Brigimadlin	MDM2 inhibitor	Brigimadlin vs doxorubicin for advanced DDLPS
–	NCT05694871	II	Palbociclib + Cemiplimab	CDK4/6 inhibitor + PD-1 inhibitor	Palbociclib + cemiplimab vs palbociclib alone for advanced DDLPS

evaluable patients in the phase Ib study showed a mPFS of 8.1 months (95 % CI 5.7–9.9), 1 CR and 15 PR [68]. Additionally, 31 evaluable patients with WDLPS had a mPFS of 25.1 months and 3 patients achieved PR [69]. Of note, the phase II/III trial (Brightline-1) comparing front-line brigimadlin to doxorubicin in patients with advanced DDLPS has recently completed accrual (NCT05218499) (Table 2).

Although PD-1 inhibitor monotherapy has a relatively low response rate in DDLPS, combinations or predictive biomarkers that enrich for patients most likely to benefit may improve outcomes [70–72]. For instance, CDK4/6 inhibition appears to impact the immune microenvironment of DDLPS, which prompted studies investigating combinations with PD-1 inhibitors. The PD-1 inhibitor retifanlimab was combined with palbociclib in a phase II study (NCT04438824) of 30 patients. A preliminary analysis of 28 enrolled patients revealed the study met its primary endpoint with an ORR of 14.3 % [73] and correlative studies are forthcoming. Additionally, the PD-1/CDK4/6 inhibitor combination strategy is under evaluation in the ongoing randomized phase II trial testing palbociclib alone or palbociclib combined with the PD-1 inhibitor cemiplimab in patients with DDLPS (NCT05694871) (Table 2).

In summary, several novel therapies are under active investigation and may change the management paradigm for patients with inoperable or metastatic DDLPS. Further discovery work on DDLPS biology is needed to promote drug development in this rare disease. Where appropriate and accessible, patients should be referred for consideration of trial participation at sarcoma centers familiar with the dynamic landscape of trials for DDLPS.

Recommendations:

1. Despite limited activity observed in trials, CDK4/6 inhibitors remain an option for patients with advanced disease where chemotherapy is inappropriate or ineffective. Clinical trials investigating CDK4/6 inhibitors, where available, are favored over off-label administration. Activity to date has been modest and these approaches remain investigational.
2. Clinical trial enrollment should be an important consideration for patients with DDLPS at all stages of the disease course

Conclusion

A multidisciplinary approach is critically important in providing the best care for patients with DDLPS. An improved understanding of the molecular underpinnings of the disease has resulted in the use of molecular techniques to aid in the confirmation of the diagnosis, as well as the introduction of novel therapies targeting key signaling pathways involved in its development. Multidisciplinary teams with disease-specific expertise are required to ensure that outcomes for patients are optimized.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This Position Statement was supported by a scientific advancement grant from Boehringer Ingelheim Pharmaceuticals, Inc. Administrative support was provided by i3 Health. The authors were involved in all aspects of the manuscript development and were soley responsible for the content, writing and review of the manuscript, independent of any funding sponsor.

References

[1] Knebel C, Lenze U, Pohlig F, et al. Prognostic factors and outcome of Liposarcoma patients: a retrospective evaluation over 15 years. BMC Cancer 2017 Jun 12;17(1):410. https://doi.org/10.1186/s12885-017-3398-y. PMID: 28606068; PMCID: PMC5469180.

[2] Anju MS, Chandramohan K, Bhargavan RV, et al. An overview on liposarcoma subtypes: Genetic alterations and recent advances in therapeutic strategies. J Mol Histol 2024 Jun;55(3):227–40. https://doi.org/10.1007/s10735-024-10195-4. Epub 2024 May 2 PMID: 38696048.

[3] Bock S, Hoffmann DG, Jiang Y, et al. Increasing incidence of liposarcoma: a population-based study of national surveillance databases, 2001–2016. Int J Environ Res Public Health 2020 Apr 15;17(8):2710. https://doi.org/10.3390/ijerph17082710. PMID: 32326423.

[4] Cassinelli G, Pasquali S, Lanzi C. Beyond targeting amplified MDM2 and CDK4 in well differentiated and dedifferentiated liposarcomas: From promise and clinical applications towards identification of progression drivers. Front Oncol 2022 Sep;2(12):965261. https://doi.org/10.3389/fonc.2022.965261. PMID: 36119484.

[5] Traweek RS, Cope BM, Roland CL, et al. Targeting the MDM2-p53 pathway in dedifferentiated liposarcoma. Front Oncol 2022 Nov;10(12):1006959. https://doi.org/10.3389/fonc.2022.1006959. PMID: 36439412.

[6] Dei Tos AP, Pedeutour F, Marino-Enriquez A. Dedifferentiated liposarcoma. In: WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. Lyon (France): International Agency for Research on Cancer; 2020.

[7] McCormick D, Mentzel T, Beham A, et al. Dedifferentiated liposarcoma. Clinicopathologic analysis of 32 cases suggesting a better prognostic subgroup among pleomorphic sarcomas. Am J Surg Pathol 1994 Dec;18(12):1213–23. https://doi.org/10.1097/00000478-199412000-00004. PMID: 7977944.

[8] Sioletic S, Dal Cin P, Fletcher CD, et al. Well-differentiated and dedifferentiated liposarcomas with prominent myxoid stroma: analysis of 56 cases. Histopathology 2013 Jan;62(2):287–93. https://doi.org/10.1111/j.1365-2559.2012.04348.x. Epub 2012 Sep 28 PMID: 23020289.

[9] Evans HL, Khurana KK, Kemp BL, et al. Heterologous elements in the dedifferentiated component of dedifferentiated liposarcoma. Am J Surg Pathol 1994 Nov;18(11):1150–7. https://doi.org/10.1097/00000478-199411000-00009. PMID: 7943536.

[10] Gronchi A, Collini P, Miceli R, et al. Myogenic differentiation and histologic grading are major prognostic determinants in retroperitoneal liposarcoma. Am J Surg Pathol 2015 Mar;39(3):383–93. https://doi.org/10.1097/PAS.0000000000000366. PMID: 25581729.

[11] Mariño-Enríquez A, Fletcher CD, Dal Cin P, et al. Dedifferentiated liposarcoma with "homologous" lipoblastic (pleomorphic liposarcoma-like) differentiation: clinicopathologic and molecular analysis of a series suggesting revised diagnostic criteria. Am J Surg Pathol 2010 Aug;34(8):1122–31. https://doi.org/10.1097/PAS.0b013e3181e5dc49. PMID: 20588177.

[12] Dei Tos AP, Doglioni C, Piccinin S, et al. Coordinated expression and amplification of the MDM2, CDK4, and HMGI-C genes in atypical lipomatous tumours. J Pathol 2000 Apr;190(5):531–6. https://doi.org/10.1002/(SICI)1096-9896(200004)190:5<531::AID-PATH579>3.0.CO;2-W. PMID: 10727978.

[13] Binh MB, Sastre-Garau X, Guillou L, et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. Am J Surg Pathol 2005 Oct;29(10):1340–7. https://doi.org/10.1097/01.pas.0000170343.09562.39. PMID: 16160477.

[14] Keung EZ, Hornick JL, Bertagnolli MM, et al. Predictors of outcomes in patients with primary retroperitoneal dedifferentiated liposarcoma undergoing surgery. J Am Coll Surg 2014 Feb;218(2):206–17. https://doi.org/10.1016/j.jamcollsurg.2013.10.009. Epub 2013 Oct 25 PMID: 24315890.

[15] Bonvalot S, Raut CP, Pollock RE, et al. Technical considerations in surgery for retroperitoneal sarcomas: position paper from E-Surge, a master class in sarcoma surgery, and EORTC-STBSG. Ann Surg Oncol 2012 Sep;19(9):2981–91. https://doi.org/10.1245/s10434-012-2342-2. Epub 2012 Apr 3 PMID: 22476756.

[16] Swallow CJ, Strauss DC, Bonvalot S, *et al*; Transatlantic Australasian RPS Working Group (TARPSWG). Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: An Updated Consensus Approach from the Transatlantic Australasian RPS Working Group. Ann Surg Oncol. 2021 Nov;28(12):7873-7888. 10.1245/s10434-021-09654-z. Epub 2021 Apr 14. PMID: 33852100; PMCID: PMC9257997.

[17] Ikoma N, Roland CL, Torres KE, *et al.* Concomitant organ resection does not improve outcomes in primary retroperitoneal well-differentiated liposarcoma: A retrospective cohort study at a major sarcoma center. *J Surg Oncol.* 2018 May;117(6):1188-1194. 10.1002/jso.24951. Epub 2017 Dec 11. PMID: 29228466; PMCID: PMC7703862.

[18] Bonvalot S, Miceli R, Berselli M, et al. Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control. Ann Surg Oncol 2010 Jun;17(6):1507–14. https://doi.org/10.1245/s10434-010-1057-5. PMID: 20393803.

[19] American College of Surgeons Clinical Research Program. Operative Standards for Cancer Surgery: Volume III: Hepatobiliary, Peritoneal Malignancies, Neuroendocrine, Sarcoma, Adrenal, Bladder. Lippincott Williams & Wilkins (LWW); 2022.

[20] Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002 Apr 11;346(15):1128–37. https://doi.org/10.1056/NEJMsa012337. PMID: 11948273.

[21] Bonvalot S, Gaignard E, Stoeckle E, et al. Survival benefit of the surgical management of retroperitoneal sarcoma in a reference center: a nationwide study

of the French Sarcoma Group from the NetSarc Database. Ann Surg Oncol 2019 Jul; 26(7):2286–93. https://doi.org/10.1245/s10434-019-07421-9. Epub 2019 May 7 PMID: 31065964.
[22] Keung EZ, Chiang YJ, Cormier JN, *et al.* Treatment at low-volume hospitals is associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma. *Cancer.* 2018 Dec 1;124(23):4495-4503. 10.1002/cncr.31699. Epub 2018 Oct 14. PMID: 30317543; PMCID: PMC6289614.
[23] Villano AM, Zeymo A, Chan KS, et al. Identifying the Minimum Volume Threshold for Retroperitoneal Soft Tissue Sarcoma Resection: Merging National Data with Consensus Expert Opinion. J Am Coll Surg 2020 Jan;230(1):151–160.e2. https://doi.org/10.1016/j.jamcollsurg.2019.09.013. Epub 2019 Oct 28 PMID: 31672672.
[24] Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982 Sep;196(3):305–15. https://doi.org/10.1097/00000658-198209000-00009. PMID: 7114936; PMCID: PMC1352604.
[25] Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998 Jan;16(1):197–203. https://doi.org/10.1200/JCO.1998.16.1.197. PMID: 9440743.
[26] Pisters PW, Harrison LB, Leung DH, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996 Mar;14(3):859–68. https://doi.org/10.1200/JCO.1996.14.3.859. PMID: 8622034.
[27] O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002 Jun 29;359(9325):2235–41. https://doi.org/10.1016/S0140-6736(02)09292-9. PMID: 12103287.
[28] Baldini EH, Lapidus MR, Wang Q, et al. Predictors for major wound complications following preoperative radiotherapy and surgery for soft-tissue sarcoma of the extremities and trunk: importance of tumor proximity to skin surface. Ann Surg Oncol 2013 May;20(5):1494–9. https://doi.org/10.1245/s10434-012-2797-1. Epub 2012 Dec 15 PMID: 23242820.
[29] Folkert MR, Singer S, Brennan MF, *et al.* Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. J Clin Oncol. 2014 Oct 10;32(29):3236-41. 10.1200/JCO.2013.53.9452. Epub 2014 Sep 2. PMID: 25185087; PMCID: PMC4178522.
[30] Salerno KE, Alektiar KM, Baldini EH, et al. Radiation Therapy for Treatment of Soft Tissue Sarcoma in Adults: Executive Summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2021 Sep-Oct;11(5):339-351. 10.1016/j.prro.2021.04.005. Epub 2021 Jul 26. PMID: 34326023.
[31] Gronchi A, Miah AB, Dei Tos AP, *et al.*; ESMO Guidelines Committee, EURACAN and GENTURIS. Electronic address: clinicalguidelines@esmo.org. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2021 Nov;32(11):1348-1365. 10.1016/j.annonc.2021.07.006. Epub 2021 Jul 22. PMID: 34303806.
[32] Bonvalot S, Gronchi A, Le Péchoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020 Oct;21(10):1366–77. https://doi.org/10.1016/S1470-2045(20)30446-0. Epub 2020 Sep 14 PMID: 32941794.
[33] Davis AM, O'Sullivan B, Turcotte R, et al. Canadian Sarcoma Group; NCI Canada Clinical Trial Group Randomized Trial. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005 Apr;75(1):48–53. https://doi.org/10.1016/j.radonc.2004.12.020. PMID: 15948265.
[34] Guadagnolo BA, Bassett RL, Mitra D, *et al.* Hypofractionated, 3-week, preoperative radiotherapy for patients with soft tissue sarcomas (HYPORT-STS): a single-centre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2022 Dec;23(12):1547-1557. 10.1016/S1470-2045(22)00638-6. Epub 2022 Nov 4. PMID: 36343656; PMCID: PMC9817485.
[35] Kalbasi A, Kamrava M, Chu FI, *et al.* A Phase II Trial of 5-Day Neoadjuvant Radiotherapy for Patients with High-Risk Primary Soft Tissue Sarcoma. *Clin Cancer Res.* 2020 Apr 15;26(8):1829-1836. 10.1158/1078-0432.CCR-19-3524. Epub 2020 Feb 13. PMID: 32054730; PMCID: PMC7189949.
[36] Kosela-Paterczyk H, Szacht M, Morysiński T, et al. Preoperative hypofractionated radiotherapy in the treatment of localized soft tissue sarcomas. Eur J Surg Oncol 2014 Dec;40(12):1641–7. https://doi.org/10.1016/j.ejso.2014.05.016. Epub 2014 Sep 20 PMID: 25282099.
[37] Bedi M, Singh R, Charlson JA, et al. Is 5 the New 25? Long-term oncologic outcomes from a phase ii, prospective, 5-fraction preoperative radiation therapy trial in patients with localized soft tissue sarcoma. Adv Radiat Oncol 2022 Jan 25;7(3):100850. https://doi.org/10.1016/j.adro.2021.100850. PMID: 35647402; PMCID: PMC9133395.
[38] Guadagnolo BA, Baldini EH. Are we ready for life in the fast lane? A critical review of preoperative hypofractionated radiotherapy for localized soft tissue sarcoma. Semin Radiat Oncol 2024 Apr;34(2):180–94. https://doi.org/10.1016/j.semradonc.2023.12.003. PMID: 38508783.
[39] Baldini EH, Guadagnolo BA, Salerno KE, *et al.* Hypofractionated Preoperative Radiation Should Not Yet Be Used as Standard of Care for Extremity and Truncal Soft Tissue Sarcoma. J Clin Oncol. 2024 Sep 4:JCO2400238. 10.1200/JCO.24.00238. Epub ahead of print. PMID: 39231372.
[40] Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol 2001 Mar 1;19(5):1238–47. https://doi.org/10.1200/JCO.2001.19.5.1238. PMID: 11230464.
[41] Gronchi A, Ferrari S, Quagliuolo V, *et al.* Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol. 2017 Jun;18(6):812-822. 10.1016/S1470-2045(17)30334-0. Epub 2017 May 9. Erratum in: Lancet Oncol. 2017 Jun;18(6):e301. 10.1016/S1470-2045(17)30371-6. PMID: 28499583.
[42] Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008 Aug 1;113(3):573–81. https://doi.org/10.1002/cncr.23592. PMID: 18521899.
[43] Pasquali S, Colombo C, Pizzamiglio S, et al. High-risk soft tissue sarcomas treated with perioperative chemotherapy: Improving prognostic classification in a randomised clinical trial. Eur J Cancer 2018 Apr;93:28–36. https://doi.org/10.1016/j.ejca.2018.01.071. Epub 2018 Feb 21 PMID: 29475197.
[44] Pasquali S, Pizzamiglio S, Touati N, et al. EORTC – Soft Tissue and Bone Sarcoma Group. The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial. Eur J Cancer 2019 Mar;109:51–60. https://doi.org/10.1016/j.ejca.2018.12.009. Epub 2019 Jan 25. PMID: 30690293.
[45] Pasquali S, Palmerini E, Quagliuolo V, *et al.* Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: A Sarculator-based risk stratification analysis of the ISG-STS 1001 randomized trial. Cancer. 2022 Jan 1;128(1):85-93. 10.1002/cncr.33895. Epub 2021 Oct 13. Erratum in: Cancer. 2022 Sep 1;128(17):3265. 10.1002/cncr.34361. PMID: 34643947.
[46] Miura JT, Charlson J, Gamblin TC, et al. Impact of chemotherapy on survival in surgically resected retroperitoneal sarcoma. Eur J Surg Oncol 2015 Oct;41(10):1386–92. https://doi.org/10.1016/j.ejso.2015.07.014. Epub 2015 Jul 29 PMID: 26251340.
[47] De Sanctis R, Giordano L, Colombo C, et al. Long-term Follow-up and Post-relapse Outcome of Patients with Localized Retroperitoneal Sarcoma Treated in the Italian Sarcoma Group-Soft Tissue Sarcoma (ISG-STS) Protocol 0303. Ann Surg Oncol 2017 Dec;24(13):3872–9. https://doi.org/10.1245/s10434-017-6105-y. Epub 2017 Oct 17 PMID: 29043525.
[48] Bramwell VH, Anderson D, Charette ML. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft-tissue sarcoma: a meta-analysis and clinical practice guideline. Sarcoma 2000;4(3):103–12. https://doi.org/10.1080/13577140020008066. PMID: 18521288; PMCID: PMC2395439.
[49] Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016 Dec;17(12):1732–42. https://doi.org/10.1016/S1470-2045(16)30507-1. Epub 2016 Oct 14 PMID: 27751846.
[50] Riedel RF, Ballman KV, Lu Y, *et al.* A Randomized, Double-Blind, Placebo-Controlled, Phase II Study of Regorafenib Versus Placebo in Advanced/Metastatic, Treatment-Refractory Liposarcoma: Results from the SARC024 Study. *Oncologist.* 2020 Nov;25(11):e1655-e1662. 10.1634/theoncologist.2020-0679. Epub 2020 Aug 20. PMID: 32701199; PMCID: PMC7648334.
[51] Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 2009 Jul 1;27(19):3126–32. https://doi.org/10.1200/JCO.2008.21.3223. Epub 2009 May 18 PMID: 19451427.
[52] Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol 2007 Jul 1;25(19):2755–63. https://doi.org/10.1200/JCO.2006.10.4117. Erratum. In: J Clin Oncol. 2007 Aug 20;25(24):3790. PMID: 17602081.
[53] Demetri GD, von Mehren M, Jones RL, *et al.* Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. *J Clin Oncol.* 2016 Mar 10;34(8):786-93. 10.1200/JCO.2015.62.4734. Epub 2015 Sep 14. PMID: 26371143; PMCID: PMC5070559.
[54] Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016 Apr 16;387(10028):1629–37. https://doi.org/10.1016/S0140-6736(15)01283-0. Epub 2016 Feb 10 PMID: 26874885.
[55] Patel S, von Mehren M, Reed DR, et al. Overall survival and histology-specific subgroup analyses from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Cancer 2019 Aug 1;125(15):2610–20. https://doi.org/10.1002/cncr.32117. Epub 2019 Jun 7 PMID: 31173362.
[56] Demetri GD, Schöffski P, Grignani G, *et al.* Activity of Eribulin in Patients With Advanced Liposarcoma Demonstrated in a Subgroup Analysis From a Randomized Phase III Study of Eribulin Versus Dacarbazine. *J Clin Oncol.* 2017 Oct 20;35(30):3433-3439. 10.1200/JCO.2016.71.6605. Epub 2017 Aug 30. Erratum in: *J Clin Oncol.* 2018 Feb 1;36(4):432. 10.1200/JCO.2017.77.4950. PMID: 28854066.
[57] Tawbi HA, Burgess M, Bolejack V, *et al.* Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol.* 2017 Nov;18(11):1493-1501. 10.1016/S1470-2045(17)30624-1. Epub 2017 Oct 4. Erratum in: *Lancet Oncol.* 2017 Dec;18(12):e711. PMID: 28988646.

[58] Burgess MA, Bolejack V, Van Tine BA, et al. Multicenter phase II study of pembrolizumab (P) in advanced soft tissue sarcoma (STS) and bone sarcomas (BS): Final results of SARC028 and biomarker analyses [abstract]. J Clin Oncol 2017;35 (Suppl). Abstract 11008.
[59] Luke JJ, D'Adamo DR, Dickson MA, et al. The cyclin-dependent kinase inhibitor flavopiridol potentiates doxorubicin efficacy in advanced sarcomas: preclinical investigations and results of a phase I dose-escalation clinical trial. Clin Cancer Res 2012 May 1;18(9):2638–47. https://doi.org/10.1158/1078-0432.CCR-11-3203. Epub 2012 Feb 28 PMID: 22374332.
[60] Abdul Razak AR, Bauer S, Suarez C, et al. Co-Targeting of MDM2 and CDK4/6 with siremadlin and ribociclib for the treatment of patients with well-differentiated or dedifferentiated liposarcoma: results from a proof-of-concept, Phase Ib Study. Clin Cancer Res 2022 Mar 15;28(6):1087–97. https://doi.org/10.1158/1078-0432.CCR-21-1291. PMID: 34921024.
[61] Schwartz GK, LoRusso PM, Dickson MA, et al. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). Br J Cancer 2011 Jun 7;104(12):1862–8. https://doi.org/10.1038/bjc.2011.177. Epub 2011 May 24 PMID: 21610706.
[62] Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol 2013 Jun 1;31(16):2024–8. https://doi.org/10.1200/JCO.2012.46.5476. Epub 2013 Apr 8 PMID: 23569312.
[63] Dickson MA, Schwartz GK, Keohan ML, et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. JAMA Oncol 2016 Jul 1;2(7): 937–40. https://doi.org/10.1001/jamaoncol.2016.0264. PMID: 27124835.
[64] Gleason CE, Dickson MA, Klein Dooley ME, et al. Therapy-Induced Senescence Contributes to the Efficacy of Abemaciclib in Patients with Dedifferentiated Liposarcoma. Clin Cancer Res 2024 Feb 16;30(4):703–18. https://doi.org/10.1158/1078-0432.CCR-23-2378. PMID: 37695642; PMCID: PMC10870201.
[65] https://www.rainoncology.com/news-press-releases/rain-oncology-announces-topline-results-from-phase-3-mantra-trial-of-milademetan-for-the-treatment-of-de differentiated-liposarcoma. Accessed 15-June-2024.
[66] Bevill SM, Casaní-Galdón S, El Farran CA, et al. Impact of supraphysiologic MDM2 expression on chromatin networks and therapeutic responses in sarcoma. Cell Genom 2023 May 11;3(7):100321. https://doi.org/10.1016/j.xgen.2023.100321. PMID: 37492096; PMCID: PMC10363746.
[67] Dickson MA, Koff A, D'Angelo SP, et al. Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma. J Clin Oncol 2019;37:11004. https://doi.org/10.1200/JCO.2019.37.15_suppl.11004.
[68] Schöffski P, Reichardt P, Lorusso P, *et al.* A phase Ia/Ib study of the MDM2–p53 antagonist brigimadlin (BI 907828): safety and efficacy in patients with dedifferentiated liposarcoma. ESMO Sarcoma and Rare Cancers Congress 2024. *Annals of Oncology* (2024) 9 (suppl_2): 1-32. 10.1016/esmoop/esmoop102441 (Abstract 560).
[69] Reichardt P, Schöffski P, Lorusso P, *et al.* Phase Ia/Ib study of the MDM2–p53 antagonist brigimadlin (BI 907828) in advanced solid tumours: overall safety, and efficacy in patients (pts) with well-differentiated liposarcoma (WDLPS). ESMO Sarcoma and Rare Cancers Congress 2024, Annals of Oncology (2024) 9 (suppl_2): 1-32. 10.1016/esmoop/esmoop102441 (Abstract 61MO).
[70] Keung EZ, Burgess M, Salazar R, et al. Correlative Analyses of the SARC028 Trial Reveal an Association Between Sarcoma-Associated Immune Infiltrate and Response to Pembrolizumab. Clin Cancer Res 2020 Mar 15;26(6):1258–66. https://doi.org/10.1158/1078-0432.CCR-19-1824. Epub 2020 Jan 3 PMID: 31900276.
[71] Haddox CL, Nathenson MJ, Mazzola E, et al. Phase II Study of Eribulin plus Pembrolizumab in Metastatic Soft-tissue Sarcomas: Clinical Outcomes and Biological Correlates. Clin Cancer Res 2024 Apr 1;30(7):1281–92. https://doi.org/10.1158/1078-0432.CCR-23-2250. PMID: 38236580.
[72] Italiano A, Bessede A, Pulido M, et al. Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort. Nat Med 2022 Jun;28(6):1199–206. https://doi.org/10.1038/s41591-022-01821-3. Epub 2022 May 26 PMID: 35618839.
[73] Rosenbaum E, Qin L, Dickson M, et al. 1720MO - A phase II study of palbociclib combined with the PD-1 inhibitor retifanlimab in patients with advanced dedifferentiated liposarcoma. Ann Oncol 2024;35(suppl_2):S1031–61. https://doi.org/10.1016/annonc/annonc1610.