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# Advances in systemic treatment of advanced soft tissue sarcomas

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### ABSTRACT

Systemic treatment in soft tissue sarcoma (STS) is an important element of therapy in a disease eligible for combined treatment with a radical intention and is the basis for the treatment of an unresectable or metastatic disease. The possibilities of treating STS are limited and for many years progress in this area was minor and the main drugs used in this indication were and still remain anthracyclines and alkylating agents. Clinical trials with new drugs are difficult for STS due to the heterogeneity of these tumours and due to their rare occurrence. Over the past two decades, there have been tested many substances in this indication, including molecularly targeted drugs. Great success was imatinib in the treatment of gastrointestinal stromal tumours (GIST). Other drugs in STS have been tested and approved for use, e.g. sunitinib and regorafenib in the treatment of GIST, pazopanib in the treatment of non-GIST STS, trabectedin and olaratumab in the treatment of STS. First reports on the effectiveness of immunotherapy in the treatment of rare subtypes of STS are also available.

**Key words:** soft tissue sarcoma, advanced sarcoma, metastatic sarcoma, chemotherapy, tyrosine kinase inhibitors, VEGF inhibitors, immunotherapy, PDGFR $\alpha$  inhibitor

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## Introduction

Soft tissue sarcomas (STSs) are a heterogeneous group of very rarely occurring malignancies derived from connective tissue. They constitute less than 1% of all malignant tumours. There are many (over 50) STS subtypes arising from cartilage, muscles, blood vessels, nerves, and adipose tissue. Diagnosis of these cancers in relationship with their heterogeneity and rare occurrence is often delayed. The basis of STS treatment is surgery; in many subtypes of sarcomas combined treatment with systemic therapy, radiotherapy, and surgery is necessary [1]. Thanks to progress in the field of radiotherapy as well surgical and systemic treatment, mortality due to these cancers has significantly decreased, and the goal of limb-sparing treatment in patients with sarcomas located in the limbs is increasingly achieved. In the advanced stage the basis for STS treatment is systemic therapy. The options for systemic STS treatment are still limited, and despite many studies on new molecules the basic medicines used in this indication are still anthracyclines and alkylating agents. Clinical trials

with new drugs are, in the case of STS, difficult due to the heterogeneity of these tumours and due to their rare occurrence. Current knowledge about molecular mechanisms and genetic disorders leading to the formation individual STS subtypes is the basis for research aimed at introducing new drugs for use in these rare diseases. Over the last two decades, many clinical trials have been carried out to evaluate the efficacy of various cytotoxic and molecular-targeted drugs in individual STS subtypes. Subsequently, they have been tested and approved for use as new drugs to treat STS, e.g. trabectedin and olaratumab, sunitinib in alveolar soft part sarcoma (ASPS), and pazopanib in non-gastrointestinal stromal tumours (non-GIST). The new tested substances are targeted at platelet-derived growth factor alpha receptor (PDGFR $\alpha$ ), colony-stimulating factor 1 receptor (CSF-1R), proteins involved in nuclear transport, cyclin-dependent kinase 4/6, mdm2, and epigenetic regulators. Checkpoint inhibitors are being tested as well, also in combination with other molecules that potentially modulate the tumour microenvironment. These include drugs targeting the receptor of

programmed cell death (PD-1) and its ligand (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), also in combination with antiangiogenic molecules, as well as antigen NY-ESO-1 associated with cancer, the presence of which is found in synovial sarcoma, myxoid round cell liposarcoma, viral vaccines, and adoptive T-cells. The first reports on the effectiveness of immunotherapy in the treatment of these rare diseases are already available. The aim of this publication is to summarise the latest reports on systemic treatment in STS (with the exception of GISTs, which are described in another chapter), including drugs approved for use in recent years and drugs that are still in clinical trials.

## Drugs approved in EU countries for the treatment of STS

### Molecularly targeted drugs

#### Olaratumab

Olaratumab is a human monoclonal antibody, IgG1 class, binding platelet-derived growth factor receptor alpha (PDGFR $\alpha$ ). This binding prevents connection this receptor with its ligand (PDGF), which in turn does not allow transfer of activation signal to consecutive pathway proteins [2]. This medicine has been registered for use in combination with doxorubicin in patients with advanced STS, not amenable to curative treatment with surgery or radiotherapy, and who have not been previously treated with doxorubicin, based on the results of the study consisting of two parts — phase Ib and phase II. Phase Ib was designed to assess the safety of the combination of olaratumab and doxorubicin. The primary endpoint of the phase II study was the median progression-free survival (PFS), and secondary goals were OS (overall survival), objective response rate, safety, and pharmacokinetics. For both phases of the study, the inclusion criteria were diagnosis of metastatic or locally advanced, unresectable soft tissue sarcoma, untreated previously with anthracyclines or drugs directed against PDGF or PDGFR, and performance status 0–2 according to the

Eastern Cooperative Oncology Group (ECOG). In phase II of the study, patients were randomly assigned in a 1:1 ratio to the treatment (n = 66) or control groups (n = 67) (Table 1).

Median PFS in the olaratumab and doxorubicin group was 6.6 months (95% CI 4.1–8.3), whereas in the doxorubicin group it was 4.1 months (95% CI 2.8–5.4). The difference in favour of the combination reached the assumed level of statistical significance (HR 0.672, 95% CI 0.442–1.021; p = 0.0615). The percentage of objective responses was 18.2% (95% CI 9.8–29.6%) for olaratumab and doxorubicin and 11.9% (95% CI 5.3–22.2) for doxorubicin (p = 0.3421).

The median overall survival was 26.5 months (95% CI 20.9–31.7) in the treatment arm and 14.7 months (95% CI 9.2–17.1) in the control arm. The difference in favour of olaratumab and doxorubicin was 11.8 months (HR 0.46, 95% CI 0.3–0.71, p = 0.0003).

More than 65% of patients in each of the two groups received another line of treatment after disease progression (Table 2). The frequency of using regimens in further lines of treatment did not differ significantly; later treatment did not affect the benefit of treatment with olaratumab.

The most common adverse event leading to doxorubicin discontinuation was reduction of ejection fraction in three (5%) of 64 patients treated with the combination and in four (6%) of 64 patients treated with monotherapy. For olaratumab, infusion-related reactions were such an adverse event; therefore, the drug was stopped in two (3%) of 64 patients. Adverse reactions associated with doxorubicin (neutropenia, mucositis, nausea, vomiting) were more frequent in the olaratumab and doxorubicin group. However, this did not translate into an increased incidence of neutropenic fever, hospitalisation, decision about treatment discontinuation, or death. Eight (13%) of 64 patients from the arm treated with olaratumab plus doxorubicin discontinued treatment due to adverse events; in the doxorubicin group it was 12 (18%) of 65 patients. PDGFR $\alpha$  expression was not important for OS (p = 0.3209) and PFS (p = 0.5924) [3].

The results of confirmatory phase III trial did not confirm the benefits in terms of OS and PFS for com-

**Table 1. Histologic subtypes of STS in patients enrolled in phase II study comparing the efficacy of olaratumab in combination with doxorubicin vs. doxorubicin alone**

Histologic subtype	Olaratumab + doxorubicin	Doxorubicin
LMS	24 (36%)	27 (40%)
Pleomorphic sarcoma	10 (15%)	14 (21%)
LPS	8 (12%)	15 (22%)
Angiosarcoma	4 (6%)	3 (5%)
Others	20 (32%)	8 (12%)

LMS — leiomyosarcoma; LPS — liposarcoma

**Table 2. The next treatment lines (number) that were received by the patients participating in the study after the end of treatment in this study**

	Olaratumab + doxorubicin (n = 66)	Doxorubicin* (n = 67)
Any further treatment line	44 (67%)	33 (49%)
1	18 (27%)	16 (24%)
2	12 (18%)	10 (15%)
3	9 (14%)	2 (3%)
4	1 (2%)	1 (2%)
> 4	4 (6%)	4 (6%)

\*Olaratumab monotherapy after progression of the disease during doxorubicin treatment was not treated as another treatment line

**Table 3. Results of the phase II clinical trial dedicated to the assessment of pazopanib efficacy in the treatment of advanced STS**

	LMS	LPS	SS	Other STS
Number of patients	41	19	37	41
PR	1	0	5	3
PFR at 12 weeks (%)	43,9%	26,3%	48,6%	39%
Median PFS (95% confidence interval)	91 days (84–168)	80 days (62–113)	161 (80–193)	91 days (84–172)
Median OS (95% confidence interval)	354 days (318–544)	197 days (128–610)	310 days (230–405)	299 days (245–671)

LMS — leiomyosarcoma; LPS — liposarcoma; SS — synovial sarcoma; PFR — progression-free rate; PFS — progression-free survival; OS — overall survival; PR — partial response

combination of doxorubicin and olaratumab, so the use of this drug in advanced STS is not further recommended.

### Pazopanib

Pazopanib is an oral inhibitor of VEGFR, PDGFR, FGFR, c-kit, and many other tyrosine kinases (available in Poland as part of the drug program), and the first molecularly targeted drug that has been used to treat STS other than GIST. Based on a phase I study that included 63 patients with solid tumours, including six patients with STS, the tolerance was assessed, and the dose was determined for further studies [4]. The efficacy and safety of pazopanib were then evaluated in a multicentre, open, non-randomised, phase II study [5] in patients with recurrent or treatment-resistant intermediate or high-grade STS, who received no more than two previous lines of systemic therapy. Four cohorts of patients with STS were included in the phase II study: leiomyosarcoma (LMS), liposarcoma (LPS), synovial sarcoma (SS), and STS of other histological type. The primary endpoint was progression-free rate (PFR) after 12 weeks from the start of treatment; secondary endpoints included: PFS, OS, RR (response rate), duration of response, and safety. In total, 142 patients with STS were enrolled into this study. The median age was 51 years (range: 18–79 years), the male to female ratio

was balanced, 50.7% of patients were in performance status (PS) 0 according to ECOG and 49.3% in PS 1, and 98.6% of patients were previously treated with chemotherapy (24.6% in an adjuvant setting, 58.4% due to advanced disease, and 15.5% in an adjuvant and in an advanced setting). Efficacy results from this study in individual STS subtypes are summarised in Table 3.

Due to encouraging phase II study results, the study phase III was carried out in selected STS subtypes. It was a randomised, multicentre, double-blind trial (PALLETTE), which evaluated the efficacy and safety of pazopanib compared with placebo in patients with STS excluding liposarcomas, with disease progression during or after prior chemotherapy [6]. Patients were randomly assigned in a 2:1 ratio to the pazopanib group (administered orally at a dose of 800 mg once a day) or to the placebo group. Treatment was continued until disease progression (in the central view), unacceptable toxicity, withdrawal of consent, or death. The primary endpoint was PFS, the secondary endpoints included: OS, ORR, quality of life, and safety. The STS subgroups included: LMS, SS, and other relevant STS subtypes (i.e. among others, fibroblastic and fibrohistiocytic sarcomas). In this study some subtypes of sarcoma have been excluded, such as LPS, Ewing sarcoma, osteosarcoma, and GIST. In total 369 patients were enrolled into this study (246 in

the pazopanib group and 123 in the placebo group). The median age of patients participating in this study was 56 years, and  $\geq 65\%$  had high-grade STS at the time of diagnosis. Most patients had received at least two previous chemotherapy regimens; in addition to anthracyclines these were mostly ifosfamide, gemcitabine, and docetaxel. The median follow-up time was 15 months. A three-fold increase in median PFS in patients receiving pazopanib compared to the placebo group (20 vs. 7 weeks, HR = 0.31, 95% CI 0.24–0.40;  $p < 0.0001$ ) was achieved, which translated into a 69% reduction in the risk of progression or death compared to placebo. OS evaluated in the interim analysis was 11.9 months for pazopanib versus 10.4 months for placebo (median; HR = 0.83, 95% CI 0.62–1.09); the difference was not statistically significant. The clinical benefit of pazopanib was observed in 73% of patients (6% partial response, 67% disease stabilisation). In this phase III study the activity reported based on the phase II study was confirmed. Pazopanib was shown to be an active drug in patients with STS diagnosis after failure of anthracycline treatment. Based on the results of the PALETTE study, pazopanib has been approved for STS treatment in Europe and in the United States.

In 2017, the results of pazopanib treatment in patients with vascular STS (AS, angiosarcoma; IS, intimal sarcoma; HE, epithelioid haemangioendothelioma) were presented [7]. Fifty-two patients were identified, 40 (76.9%), 10 (19.2%), and two (3.8%) with AS, HE, and IS, respectively. The response rate was eight (20%), two (20%), and two (100%) in the AS, HE, and IS subtypes, respectively. There was no significant difference in response rate between cutaneous and non-cutaneous AS and similarly between radiation-associated and non-radiation-associated AS. Median PFS and median OS from commencing pazopanib were three months (95% CI 2.1–4.4) and 9.9 months (95% CI 6.5–11.3) in AS, respectively.

### Sunitinib

Sunitinib is a multikinase inhibitor that is used in the treatment of ASPS (in Poland it is available within the drug program in patients with locally advanced ASPS not amenable to curative treatment with surgery or radiotherapy and metastatic ASPS). In 2011 results of treatment of nine patients with metastatic ASPS with sunitinib (in a dose of 37.5 mg daily) were published. There were patients with disease progression included (median age of all patients 24 years, location of primary tumour: in eight patients on the limbs, in one case in the retroperitoneal area; location of metastases: in nine patients in the lungs, in two in the skeleton, in four in the liver, in two in the brain, in three in other locations). The response assessment was done after the first two months, then every three months, according to the RECIST

criteria. Median duration of treatment was 10 months (range 3–33). After three months five patients (55%) had partial response by RECIST criteria, with subjective improvement in three, three patients had disease stabilisation, and one patient progressed. Response to treatment persisted in the assessment carried out after six months. The median OS was 19 months, and median PFS was 17 months (range 2–33); in 88% of patients no disease progression after the sixth month of treatment was reported. When necessary to stop treatment due to toxicity, after improvement the patients were returned to the same dose of the drug. The main adverse reactions observed during treatment were fatigue G2 (in one patient), hypothyroidism G2 (2), G2 hypertension (2), hepatic toxicity G2 (1), nausea and vomiting G2 (1), neutropaenia < G3 (4), anaemia < G3 (1), and thrombocytopenia < G3 (2). In two cases, after treatment discontinuation, disease progression was observed. In both cases sunitinib retreatment lead to response to therapy [8]. These results were confirmed in a Polish single-centre group of patients treated in the Maria Skłodowska-Curie Institute — Oncology Center in Warsaw [9].

Currently, a phase II study is being conducted to compare cediranib and sunitinib in patients with ASPS (NCT01391962) [10].

### Chemotherapeutics

In advanced or metastatic disease chemotherapy is still the basis of systemic treatment in STS. Anthracyclines in monotherapy are a basic treatment option of the first line, allowing a median OS of about 12–14 months. A combination of anthracycline with ifosfamide helps to achieve better PFS and ORR results; however, not significant OS extensions [1]. New chemotherapeutics approved for advanced STS treatment are trabectedin (in LMS and LPS) and eribulin (in LPS).

### Trabectedin

One of the new generation of cytostatics with proven efficacy in STS treatment is trabectedin. In addition to cytotoxic activity, trabectedin modulates the tumour's microenvironment, and it seems to be the most important part of its therapeutic activity. With limited systemic therapy options available to treat STS, trabectedin is an important treatment line in this rare diagnosis. Trabectedin is a synthetic alkylating agent originally isolated from tunicates from the Caribbean Sea [11]. Trabectedin showed in subsequent studies continued activity in patients after doxorubicin treatment failure. In 2004, the results of two trials were published. The studies showed the efficacy of this drug in the treatment of patients with STS after previous systemic therapy, administered at a dose of 1.5 mg/m<sup>2</sup> in an infusion over 24 hours every

three weeks. In the first of these studies ( $n = 54$ ) a low objective response rate was found (4%) and a high disease control rate after six months of treatment (24%) [12]. In the second study, a low response rate at 8% was also reported and an annual OS of 53% [13]. The results of these studies prompted the EORTC (European Organisation for the Research and Treatment of Cancer) to start a phase II study to assess the effectiveness of trabectedin in 104 STS patients in the second and third line of treatment. Again, a low objective response rate was noted amounting to 8%. The six-month PFS was 29%, and the median overall survival was 9.2 months [14]. Subsequently another phase II study was carried out in 36 patients to assess the activity of trabectedin in the first line of treatment. The response rate was 17%, and one-year PFS and OS rates were 21% and 72%, respectively [15].

Another study dedicated to the assessment of this drug's efficacy in STS patients was a phase II randomised study, which included 270 patients with LMS and LPS. The patients were randomly assigned to one of two groups: in the first group the drug was administered at a dose of 1.5 mg/m<sup>2</sup> for 24 hours every three weeks; in the second at a dose of 0.58 mg/m<sup>2</sup> over three hours on day 1, 8, and 15 of the 28-day cycle. The patients with documented disease progression while taking doxorubicin and ifosfamide were enrolled into this study. This study showed that trabectedin administration in a 24-hour infusion allowed a much longer average time to progression (TTP) (3.7 vs. 2.3 months, respectively) and progression-free survival (PFS) (3.3 months vs. 2.3 months, respectively) in comparison to the weekly schedule. Differences in median overall survival were not significant, but the trend to prolong this time in patients receiving 24-hour infusions (13.9 months vs. 11.8 months, respectively) was observed [16].

The next phase II study was a study in which the goal was to determine whether treatment should be continued, as long as it is effective and well tolerated, or if it is possible to interrupt it after obtaining control over the disease. Fifty-three patients participated in the study, who had at least stabilised disease after six cycles of treatment with trabectedin. The patients were randomly assigned to the group receiving the drug until disease progression or to the control group not receiving active treatment after at least stabilisation after the first six cycles of chemotherapy. The PFS rate at six months after randomisation was 51.9% in the study group vs. 23.1% in the control group. No significant increase in toxicity was observed with the continuation of therapy. This study confirmed that trabectedin should not be discontinued after gaining disease control and should be continued after obtaining at least stabilisation of the disease [17]. In the phase III study, the efficacy of trabectedin was compared with the efficacy of dacarbazine in patients with

locally advanced or metastatic LMS and LPS. Patients ( $n = 518$ ) were assigned randomly in a 2:1 ratio to the group receiving trabectedin ( $n = 345$ ) or to the control group treated with dacarbazine ( $n = 173$ ). In the final PFS analysis, the use of trabectedin was associated with a reduction of the risk of disease progression or death compared with dacarbazine by 45% (median PFS in the trabectedin group was 4.2 vs. 1.5 months in the control group, HR = 0.55;  $p < 0.001$ ). Benefits were observed in all predefined subgroups. OS interim analysis (64% censored) showed a 13% reduction of the risk of death in the trabectedin group compared with the control group (median OS for trabectedin was 12.4 vs. 12.9 months for dacarbazine, HR = 0.87,  $p = 0.37$ ). Due to a significant increase of median PFS in the trabectedin group the drug was approved in the United States in October 2015 for the treatment of patients with advanced LPS and LMS [18].

Next was a phase III study, the results of which were published in 2018, which was dedicated to the assessment of efficacy and safety of trabectedin in comparison with the best supportive care (BSC) in patients with STS after failure of at least one systemic treatment line (no more than the previous three lines of chemotherapy). In the case of confirmation of further disease progression, patients from the control group (BSC) could start active treatment with trabectedin (cross-over). The primary endpoint of the study was PFS. There were patients with so-called L-sarcomas (LPS and LMS) as well as other subtypes of STS included in this study. The ORR ratio in the trabectedin group was 11.8%; all responses were observed in the L-sarcoma group (ORR in this group 18.8%). Twenty-three percent of patients from the trabectedin group received more than nine cycles of chemotherapy. The median PFS was 1.5 months in the control group and 3.1 months in the trabectedin group (HR = 0.39,  $p < 0.0001$ ). In the L-sarcoma cohort the median PFS was 1.4 months in the control group and 5.1 months in the trabectedin group (HR = 0.29,  $p < 0.0001$ ), and in patients with other types of STS the median PFS was 1.5 months and 1.8 months ( $p = 0.16$ ), respectively. Active treatment after progression (cross-over) was used in 92% of patients in the control group. At the median follow-up of 25.7 months, the difference in OS between the two groups was not statistically significant, median OS was 13.6 months and 10.8 months, respectively ( $p = 0.86$ ) [19].

In 2015, the results of treatment 50 patients in the Centre Oncology — Institute in Warsaw with LPS and LMS with trabectedin were published. Median number the treatment cycles administered were five (range 2–40); 18 patients (36%) received  $\geq 10$  cycles. Four patients (8%) achieved partial response, 23 (46%) achieved disease stabilisation (for a minimum of three months), and in 23 patients (46%) disease progres-

sion was observed. After half a year of treatment 47% patients were free of disease progression, more in the group of patients diagnosed with LPS — 66% in comparison to 27% in the LMS group ( $p = 0.023$ ). PFS was significantly longer in patients receiving trabectedin in the second or third line of treatment (median seven months) than  $> 3$  treatment lines (median two months),  $p = 0.038$ . Median overall survival (OS) was 13 months [20].

In Poland, trabectedin is available as part of the drug program only for advanced patients LPS and LMS.

### Eribulin

Eribulin mesylate is a microtubule dynamic instability inhibitor and is a structurally simplified synthetic analogue of halichondrin B, a natural substance isolated from sea sponge *Halichondria okadai*. Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. The drug works through an antimetabolic mechanism based on tubulin, leading to arrest of the cell cycle in the G2/M phase, disrupting mitotic spindle and finally leading to the apoptotic cell death as a result of prolonged and irreversible mitotic blockade. In addition, this drug affects mechanisms of angiogenesis [21].

In the case of liposarcoma, efficacy of eribulin was confirmed in the phase III clinical trial. Patients ( $n = 452$ ) with diagnosis of inoperable or metastatic STS belonging to one of the two subtypes — LMS or LPS were included in the study. Patients had previously received at least two chemotherapy regimens, of which at least one contained anthracycline (unless it was contraindicated). Patients had to experience disease progression within six months of the last chemotherapy. Patients were randomised in a 1:1 ratio to the group receiving eribulin at a dose 1.23 mg/m<sup>2</sup> on days 1 and 8 of the 21-day treatment cycle or dacarbazine at a dose of 850 mg/m<sup>2</sup>, 1000 mg/m<sup>2</sup>, or 1200 mg/m<sup>2</sup> (the dose determined by the investigator before randomisation), every 21 days. A statistically significant improvement in OS in patients was observed in the eribulin arm compared to the control arm (13.5 months in patients treated with eribulin *versus* 11.5 months in patients treated with dacarbazine; HR = 0.768; 95% CI 0.6–1.0;  $p = 0.017$ ). In the whole group, no significant difference was found in PFS (median PFS in both groups was 2.6 months) or the overall response between both groups. Patients with LPS achieved greater benefit from treatment with eribulin compared to patients with LMS (HR = 0.511, 95% CI 0.3–0.8 vs. HR = 0.927; 95% CI 0.7–1.2). Median OS in the eribulin group in patients with LPS was 15.6 months in comparison to 8.4 months in the dacarbazine group. There was no difference in efficacy between eribulin and dacarbazine in patients with advanced or metastatic

LMS. Treatment-related adverse events were reported more frequently in the eribulin group and included neutropenia (43% in the eribulin group vs. 24% in the control group), fever (28% vs. 14%), peripheral sensory neuropathy (21% vs. 4%), and alopecia (35% vs. 3%) [22]. Based on the results of this study, in 2016 eribulin was approved for use in patients with advanced LPS after failure to respond to anthracycline treatment.

The drug has been registered for use in Poland, but it is not reimbursed in the treatment of LPS.

### Other drugs tested in treatment of patients with STS

#### Molecularly targeted drugs

Many tyrosine kinases inhibitors and other molecularly targeted drugs have been tested in the treatment of STS. These include, among others, cediranib, tazemetostat, anlotinib, palbociclib, entrectinib, larotrectinib, selinexor, pexidartinib, crizotinib, and sunitinib.

#### Cediranib

Cediranib is an oral small molecule inhibitor of three receptors of vascular endothelial growth factor (VEGFR-1, -2, and -3). In a phase II study, cediranib was used in patients with advanced ASPS. Forty-six patients were included in the study, which in this diagnosis is a large group. They could be treated previously with VEGFR inhibitors. The efficacy analysis was done in 43 patients: 15 patients (35%) achieved partial response; in 26 patients (60%) the best response was stabilisation of the disease [23].

#### Tazemetostat

Another molecularly targeted drug tested in STS is the oral small-molecule histone methyltransferase EZH2 inhibitor, tazemetostat. Inhibition of EZH2 prevents methylation of lysine in 27 histone H3 (H3K27). Reduction in histone methylation changes the system of expression of genes associated with tumorigenesis and inhibits proliferation of cancer cells. This molecule was evaluated in a phase II study in patients with various cancers, including patients with epithelioid sarcoma, whose characteristic molecular feature is the loss of INI1. INI1 is a tumour suppressor gene involved in chromatin modelling. In the epithelioid sarcoma cohort 60 patients with INI1 gene loss were included. In these patients, eight confirmed PR with ORR 13% and DCR 26% were reported. In 35 patients the best reported response was SD. No patient discontinued treatment due to toxicity, and two patients required dose reduction due to adverse events. Side effects (all grades) reported in patients treated with tazemetostat were fatigue (39%),

nausea (32%), and cancer pain (31%) [24]. In another cohort of this study, tazemetostat was used in patients with a diagnosis of recurrent SS (NCT02601950) [25]. This drug has been registered in the United States for the treatment of patients with epithelioid sarcoma.

### Anlotinib

Anlotinib is an inhibitor of tyrosine kinases VEGFR-1, VEGFR-2/KDR, VEGFR-3, KIT, PDGFR $\alpha$  and FGFR-1, and FGFR-2 and FGFR-3. Anlotinib shows anti-angiogenic activity and inhibits cancer cell proliferation. In the phase II clinical trial, the activity of anlotinib in patients with STS after failure of previously used standard methods of treatment was evaluated. A total of 166 patients with advanced pleomorphic sarcomas, LPS, LMS, and SS and other STSs excluding rhabdomyosarcoma, chondrosarcoma, and GIST were included in the study. The progression-free rate at 12 weeks was 57.23%, median PFS was 5.63 months, and ORR was 11.45%. The drug showed a particular activity in patients with ASPS; the progression-free rate at 12 weeks was 76.92% in this group, similarly as in the case of sunitinib [26].

In the next phase IIb study, which enrolled 233 patients with STS (SS, ASPS, LMS, and others), in whom intolerance or ineffectiveness of anthracycline-based chemotherapy was found, anlotinib was evaluated in comparison to placebo (randomisation 2:1). The ORR and DCR were significantly higher in the anlotinib group compared to the control group (ORR 10.13% vs. 1.33%,  $p = 0.0145$ ; DCR 55.7% vs. 22.67%,  $p < 0.0001$ ). Median PFS in the anlotinib group was significantly higher at 6.27 months (95% CI 4.30–8.40) vs. 1.47 months in the control group (95% CI 1.43–1.57) (HR = 0.33,  $p < 0.0001$ ). The most benefit in terms of PFS was gained by the patients with ASPS, whose median PFS was 18.23 months in the anlotinib group versus 3.0 months in the control group (HR = 0.14,  $p < 0.0001$ ) [27].

### Palbociclib

Palbociclib is an oral kinase CDK4/6 inhibitor. CDK4 is amplified in over 90% of well-differentiated and de-differentiated LPS [28]. In the open-label phase II study, moderate efficacy of this drug in the treatment of well-differentiated and dedifferentiated LPS was demonstrated. The primary end-point of this study was PFS at 12 weeks. Of the 48 patients undergoing evaluation procedures for inclusion in this study (44 of 48 had CDK4 amplification; 41 of 44 were RB positive), 30 patients with well-differentiated and dedifferentiated LPS with present CDK4 amplification and/or expression of the RB protein, after failure previous systemic treatment, were included. Grade 3 and 4 events included anaemia (17%), thrombocytopenia (30%), neutropenia (50%), and febrile neutropenia (3%). At 12 weeks, PFS

was 66% (90% CI 51–100%). The median PFS was 18 weeks. There was one partial response [28].

### Selinexor

Selinexor is the first-in-class oral selective inhibitor of exportin 1 (XPO1), which showed anti-cancer activity in preclinical studies, in vitro as well as in vivo, in different sarcoma cell lines, including GIST, LPS, LMS, ASPS, and undifferentiated sarcomas [29]. Exportin 1 is an important mediator of nuclear transport responsible for carrying over 200 known transport proteins from the nucleus to the cytoplasm, including many suppressor proteins. Selinexor can inhibit XPO1 by covalent and reversible binding to cysteine-528. XPO1 inhibition causes accumulation in the nucleus suppressor proteins such as p53, pRb, p21, and p27, restores cell cycle checkpoints, and induces growth arrest and apoptosis in cancer cells. XPO1 was overexpressed in several types of cancer and it is associated with poor prognosis. Based on the results of preclinical studies, the phase Ib clinical study was done. Unfortunately, none of the 52 subjects in this study assessed for treatment efficacy achieved objective response. Only 17 patients (33%) had disease stabilisation lasting at least four months. In six of 17 patients (40%) with dedifferentiated LPS the reduction of lesions in comparison to the dimensions before the start of treatment was observed, and in seven patients (47%) stabilisation of the disease was maintained for at least four months [30].

There is currently an ongoing clinical study phase II/III with selinexor in patients with advanced unresectable dedifferentiated LPS (NCT02606461) [31].

### Entrectinib and larotrectinib

Entrectinib is an oral inhibitor of tyrosine kinases TRK (TRKA/B/C), ROS1 and ALK. Larotrectinib is targeted at TRK proteins only. TRK glycoproteins (tropomyosin-related kinase) are encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes and play an important role in the development and functioning of nerve cells in the central and peripheral nervous system. Oncogenic *NTRK* gene fusions occur in 1% of neoplasms [32, 33].

Both drugs were tested in patients with advanced cancers with *NTRK* gene rearrangements. During the ESMO Congress in 2018 data on entrectinib activity and safety in this group of patients were presented. Data from the three phase I studies and two phase II studies were analysed: ALKA (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810) and STARTRK-2 (NCT02568267).

In 54 patients with a minimum of six months of follow-up the response to treatment was assessed. Objective response rate was 57.4% (95% CI 43.2–70.8%), with four (7.4%) complete responses. The median duration of response was 10.4 months (95% CI 7.1–not achieved),

median PFS was 11.2 months (95% CI 8.0–14.9), and the median OS was 20.9 months (95% CI 14.9–not achieved).

Twelve patients with metastases in the central nervous system were included. In that subgroup ORR was 50%, including three complete intracranial responses.

The study involved patients with different solid tumours. The most numerous subgroup (13 patients) was patients with soft tissue sarcomas — six of them achieved partial response to treatment.

The safety analysis was done in a group 355 patients treated in clinical trials (in patients with ALK and ROS1 gene rearrangements). Entrectinib was well tolerated; the most frequently observed adverse events were fatigue (46%), taste disorders (42%), paraesthesia (29%), nausea (28%), and muscle pain (23%); fatigue was the most frequently reported adverse event in grade 3 or higher (4%) [34].

Safety and activity of larotrectinib in patients with tumours with *NTRK* gene rearrangements were assessed in an aggregated analysis of the results of the three phase I and II studies. In these studies, 55 patients with oncogenic *NTRK* fusions were treated. The studies were conducted in the paediatric population and adult patients with a total of 17 different tumour types.

The objective response rate was 75%. In 71% of patients in whom the response was found, it continued after one year of treatment. The response was not dependent on age, the type of cancer, or the type of *NTRK* gene fusion.

Larotrectinib was well tolerated. The most frequently reported adverse events grade 3 or above were anaemia (in 11% of patients), increase in ALT or AST activity (7%), weight gain (7%), and decreased neutrophils number (7%) [35].

### Crizotinib

Crizotinib is a small molecule inhibitor of the ALK, ROS1, and c-MET proteins. Oncogenic *ALK* gene fusions are found in over 70% of patients with inflammatory myofibroblastic tumours (IMT). The efficacy of crizotinib was evaluated in the paediatric population in a phase I study in which patients with advanced IMT with confirmed ALK rearrangement were enrolled. The objective response rate was 86%. Five patients (36%) achieved complete response. Median duration of therapy was 1.63 years. The most common adverse event reported in patients treated with crizotinib was neutropenia, observed in 43% of patients [36]. In the multi-cohort EORTC study (CREATE) the efficacy of crizotinib was confirmed among others in ALK-positive IMT [37].

### Sunitinib in solitary fibrous tumour (SFT)

Italian researchers have described a retrospective analysis of 35 cases of patients treated with sunitinib

due to advanced SFT. Patients received sunitinib at 37.5 mg daily in a continuous dosage. In 31 patients the response was assessed according to the RECIST criteria. Two patients had a partial response, 16 the had disease stabilisation, and 13 had disease progression. In 14 out of 29 patients assessed according to the Choi criteria, a partial response was found. The median PFS evaluated according to the RECIST criteria was six months (range 1–22 months) [38].

### Pexidartinib

Pexidartinib is a small-molecule oral inhibitor of the colony stimulating factor-1 receptor (CSF1R, colony stimulating factor-1 receptor). Tenosynovial giant cell tumour (TGCT) is a rare, locally malignant neoplasm of the joints or tendons, characterised by proliferation of synovial cells with inflammatory cell infiltrates such as histiocytes and macrophages [39]. The treatment of the disease is radical tumour resection. However, in some cases surgical treatment can be mutilating — this tumour can occur in a diffuse form. The local recurrence rate reaches 55% [40].

In most of these tumours the translocation causing the *CSF1* and *COL6A3* gene fusion is present [41]. Activation of the CSF1/CSF1R pathway is a mechanism of tumour growth. This mechanism is blocked by pexidartinib.

During the 2018 ASCO Congress in Chicago the results of the ENLIVEN study were presented. It was a phase III study comparing pexidartinib with placebo in patients with locally advanced tenosynovial giant cell tumours. A total of 120 patients were enrolled into this study. It was determined that surgery in these patients would be associated with potentially worsening function or severe morbidity. In the first part of the study patients were randomised in a 1:1 ratio to either the group receiving pexidartinib or placebo. The primary endpoint was response to treatment assessed according to the RECIST 1.1 criteria at the 25<sup>th</sup> week of therapy with magnetic resonance imaging. The secondary endpoints were the assessment of the range of motion, assessment of tumour volume, reduction of stiffness, and pain response. After finishing the first part of the study patients receiving placebo could start the treatment with pexidartinib. The objective response rate was 39% in the pexidartinib group and 0% in the placebo group. The median time of follow-up was six months — at this time, there was disease progression in any of the patients who achieved a response to treatment.

Pexidartinib was associated with hepatotoxicity — 33% of patients treated with this drug experienced AST or ALT increase over 3 × upper limit of normal (ULN); in 5% there was an increase in bilirubin over 2 × ULN. In eight patients, treatment was terminated due to hepatotoxicity. In four patients, serious adverse



events consisting of bilirubin increase were reported, including one adverse event lasting about seven months. In other trials with pexidartinib two serious adverse events related to hepatotoxicity were reported: one requiring liver transplantation, and the second caused the patient's death.

Other side effects reported in the ENLIVEN study included: hair colour changes, pruritus, rash, vomiting, abdominal pain, constipation, fatigue, taste disorders, swelling of the face, decreased appetite, and hypertension. The assessment of treatment by tumour volume reduction showed objective responses in 56% of patients treated with pexidartinib in comparison with 0% in patients receiving placebo [42].

### **Sirolimus**

Sirolimus belongs to the group of mTOR inhibitors (mammalian target of rapamycin). This drug showed activity in the treatment of PEComa [43]. PEComa is a rare group of cancers of mesenchymal origin, composed of epithelial cells, including, among others, angiomyolipoma (AML) and lymphangioliomyomatosis (LAM) [44].

Sirolimus activity in this group of tumours was found in a clinical trial in a group of 25 patients with LAM and AML. After one year of treatment with sirolimus the reduction of tumour size in the majority of patients with angiomyolipoma (an average of 53% of the baseline volume) and improvement of respiratory function in cases lymphangioliomyomatosis were reported. After a break in the use of the drug, AML growth (up to 85.9% by baseline volume) was observed, which indicates the need for continuous treatment with mTOR inhibitors to maintain the effects of therapy. The most frequently reported adverse events during sirolimus therapy included: leucopenia, thrombocytopaenia, hyperlipidaemia, oral aphthous lesions, gastritis, diarrhoea, upper respiratory tract infections, and peripheral oedema [45].

### **Sorafenib, pazopanib, and imatinib in desmoid tumours**

Desmoid tumours (otherwise known as deep fibromatosis) are locally aggressive tumours of connective tissue occurring in the abdominal wall, the abdominal cavity, or other locations. Invasion of critical structures and internal organs can be the cause of serious morbidity and death, especially for tumours localised in the abdominal cavity in patients with familial adenomatous polyposis (FAP) [1].

Sorafenib is a multi-kinase inhibitor whose activity in the treatment of desmoid tumours has been demonstrated based on the data analysis of 26 patients published in 2011, of whom 11 patients received sorafenib within the first line of treatment, and the remaining 15 within the subsequent treatment lines. In 23 patients radio-

logically confirmed disease progression before starting treatment with sorafenib was observed. As a result of treatment with sorafenib, partial response was achieved in six patients (25%) and disease stabilisation in 17 patients [46]. The efficacy of sorafenib in comparison with placebo in the treatment of unresectable progressive or symptomatic desmoid tumours was then evaluated in the phase III study. During the ASCO Congress 2018 the preliminary data obtained from the analysis of treatment results of 75 patients undergoing efficacy evaluation in this study, after a follow-up of 26 months (median), were presented. Long-lasting responses were found in 14 of 43 patients treated with sorafenib (33%), compared with seven patients out of 32 recipients receiving placebo (21%). The PFS rate at one year was significantly higher in the sorafenib group (87% vs. 43%). The drug was well tolerated, in 16 out of 49 patients, adverse events of at least grade 3 were observed. These were mainly rash, hypertension, fatigue, and pain [47].

In 2017, a retrospective analysis of the results of the treatment with pazopanib of eight patients with desmoid tumours was published. Median treatment duration for these patients was 12 months. Three patients discontinued treatment earlier. No radiological progression was reported during treatment with pazopanib, partial response was observed in three patients, and disease stabilization in five. Median PFS was 13.5 months [48].

In the phase II study, pazopanib was compared with methotrexate and vinblastine in 72 patients with progressive desmoid tumours. Preliminary results published in 2018 during the ASCO Congress indicate greater benefit from pazopanib compared with chemotherapy, assessed using the endpoint defined as no progression after six months (86% vs. 50%) and better disease control (partial response was observed in 37% of patients treated with pazopanib compared with 25% of patients treated with chemotherapy; disease stabilisation in 46% and 30% of patients, respectively) [49].

Imatinib seems to be another treatment option, especially in patients after failure of other available methods of therapy. The efficacy of imatinib in the treatment of desmoid tumours was assessed in three studies. Fifty-one patients were included in the phase II study. In 43 out of 45 patients assessed for efficacy (84%) the primary endpoint defining clinical benefit (partial or complete response within 16 weeks or disease stabilisation lasting for at least 16 weeks) was achieved. In three patients, an objective partial response was observed. The progression-free survival rate after three years was 58% [50].

The benefit of imatinib treatment was demonstrated in the study conducted by the French Sarcoma Group, in which 40 patients after local treatment failure and with documented disease progression were treated with imatinib 400 mg daily. The dose was increased up to

800 mg daily in the case of disease progression. Among 35 patients evaluated after three months, one complete response was found and three partial responses (ORR 11%), 28 patients (80%) had disease stabilisation, and three patients had disease progression. In patients with progression during treatment with imatinib in a dose 400 mg daily, dose escalation up to 800 mg daily allowed for stabilisation of the disease by 12 months (median) [51].

In 2017, the results of a similar phase II study conducted by the German Interdisciplinary Sarcoma Group (GISG) were published. The study involved 38 patients with unresectable desmoid tumours. Patients received imatinib in a dose of 800 mg daily. Non-progression rates after 6, 9, 12, 18, and 24 months were 65, 65, 59, 53, and 45%, respectively. The response rate was 19% [52].

## Chemotherapeutic agents

### Evofosfamide

Evofosfamide (also known as TH-302) is a prodrug, activated by hypoxia. It is built from a bromo-isophosphoramidate mustard and 2-nitroimidazole. In the normo-oxygenic environment, evofosfamide is inactive; in a hypoxic environment, such as in a neoplastic tumour, the bromo-isophosphoramidate mustard, which is an active alkylate, is detached from the imidazole [53].

The efficacy of this drug used in combination with doxorubicin in comparison with doxorubicin alone was evaluated in patients with STS in a phase III clinical trial. In this study, patients were randomly assigned in a 1:1 ratio to treatment with doxorubicin in a dose 75 mg/m<sup>2</sup> (administered every 21 days, maximum up to six cycles) or doxorubicin and evofosfamide 300 mg/m<sup>2</sup> (on days 1 and 8 of every 21-day cycle). Patients could continue therapy with evofosfamide in monotherapy until disease progression. The primary endpoint of this study was overall survival. Between September 2011 and January 2014 640 patients were included in the study: 317 patients were assigned to the doxorubicin plus evofosfamide group, and 323 to the control group. In the doxorubicin plus evofosfamide group haematological toxicity was slightly more frequent. A subgroup that benefited from treatment with evofosfamide were patients with synovial sarcoma; a clear advantage was found in a group of 31 SS patients ( $p = 0.0043$ ) in favour of combination therapy. Median progression-free survival did not differ in both subgroups and was 6.3 months for combination therapy and 6.0 months for doxorubicin in monotherapy. The addition of evofosfamide to doxorubicin resulted in a greater chance of complete or partial response. The ORR in the doxorubicin plus evofosfamide group was 28%, while in the control group it was 18% ( $p = 0.0026$ ). Finally, the addition of evofosfamide did not cause OS improvement; the median OS in the doxorubicin plus

evofosfamide group was 19 months, and in the control group it was 18.4 months (HR 1.06; 95% CI 0.88–1.29;  $p = 0.527$ ). Consequently, adding evofosfamide to doxorubicin is not recommended [54].

### Aldoxorubicin

Aldoxorubicin, which is a prodrug, is built from doxorubicin combined with a hydrazine linker and maleimide group. Following intravenous administration, aldoxorubicin binds to albumin; this happens with the help of a highly selective connection between the thiol group of cysteine at position 34 (Cys34) and a maleimide group. The aldoxorubicin-albumin conjugate moves to the tumour under the influence of acidic tumour environment, and is followed by the disintegration of the hydrazine link, and thus delivery of doxorubicin to tumour cells [55].

Based on pharmacokinetic studies of aldoxorubicin [56], it was found that after intravenous administration the majority of the doxorubicin remains bound by the albumin. In addition, in the tested urine samples there were very small amounts of doxorubicinol — the doxorubicin metabolite associated with cardiomyopathy. This mechanism is to be responsible for low risk of cardiac muscle damage associated with aldoxorubicin.

A phase II study comparing doxorubicin with aldoxorubicin in the first-line treatment of patients with advanced STS showed statistically significant PFS improvement: PFS was 5.6 months (95% CI 3.0–8.1) for aldoxorubicin vs. 2.7 months (95% CI 1.6–4.3) for doxorubicin,  $p = 0.02$ . However, the objective response rate in the aldoxorubicin group was 25% compared to 0% in the doxorubicin group. The use of aldoxorubicin did not translate in OS improvement; the median OS for aldoxorubicin was 15.8 months *versus* 14.3 months for doxorubicin [57].

In a phase III study conducted in patients with advanced STS aldoxorubicin was compared with the therapy chosen by the investigator (dacarbazine, doxorubicin, pazopanib, ifosfamide, and gemcitabine with docetaxel) [58]. A total of 433 patients were enrolled into this study. The patients received at least one treatment line due to advanced disease. In the study drug group and in the control group about 2/3 of patients had previously received doxorubicin. Progression-free survival was 4.11 months (95% CI 2.92–6.21) in the aldoxorubicin group and 2.96 months (95% CI 2.56–4.16) in the group receiving the therapy chosen by the investigator — this difference was not statistically significant (HR 0.81, 95% CI 0.64–1.03,  $p = 0.087$ ). Interestingly, the difference in PFS turned out to be statistically significant for patients treated in sites in North America and Australia (72% of patients) — 4.21 vs. 2.96 months (HR 0.71, 95% CI 0.53–0.96;  $p = 0.0225$ ). Better results of treatment with aldoxorubicin were achieved in patients with histopatho-

**Table 4. Selected molecularly targeted drugs tested and/or used to treat non-GIST STS**

Drug	Molecular target	Histology subtype	Study phase	Study results
Anlotinib	KIT, FGFR1-4, PDGFR- $\alpha/\beta$ , RET, VEGFR-2/3	Non-GIST STS	II	ORR 11.45%, PFS 5.63 months
Cediranib	VEGFR-1–3	ASPS	II	ORR 35%, disease control rate at 24 weeks of 84%
Crizotinib	ALK	IMT	II	ORR 86% (36% complete remissions); the median duration of therapy 1.63 years
Larotrectinib	TRK fusion	TRK fusion positive STS	I	ORR 75%
Olaratumab	PDGFR $\alpha$	STS, mostly LMS	I, II	ORR 18.2%, PFS 6.6 months, OS 26.5 months
Palbociclib	CDK4/6	LPS	II	PFS 17.9 weeks
Pazopanib	c-kit, FGFR, PDGFR, VEGFR	Other than LPS, non-GIST STS LPS	Approved II	ORR 9%, PFS 4.6 months, OS 12.5 months PFS 4.4 months, OS 12.6 months
Selinexor	XPO1	Non-GIST STS, mostly LPS	I	ORR 0%, SD $\geq$ 4 months 33%
Sunitinib	c-kit, FGFR, PDGFR, VEGFR	Non-GIST STS	II	LPS: PFS 3.9 months, OS 18.6 months LMS: PFS 4.2 months, OS 10.1 months
Tazemetostat	EZH2	Epithelioid sarcoma Synovial sarcoma	II II	ORR 13%, DCR 26% Results not available

IMT — inflammatory myofibroblastic tumour; ASPS — alveolar soft part sarcoma; LMS — leiomyosarcoma; LPS — liposarcoma; SS — synovial sarcoma; ORR — objective response rate; PFS — progression-free survival; OS — overall survival

logical subtypes LPS (15% of patients) and LMS (42.5% of patients). Median PFS in this group was 5.32 months (95% CI 3.45–7.16) for aldorubicin compared to 2.96 months (95% CI 2.10–4.37) in the control group; HR = 0.62 (95% CI 0.44–0.88),  $p = 0.007$ . The objective response rate was higher in the aldorubicin group (8.3%) compared to group treated based on the investigator's choice (4.2%); this difference was not statistically significant at  $p = 0.1106$ . No differences were observed in OS (12.88 months for the aldorubicin group and 12.16 months for the control group) [58].

A phase I/II clinical study is currently being conducted in STS patients, with aldorubicin in combination with ifosfamide (NCT02235701) [59].

#### Amrubicin

Amrubicin is a third-generation anthracycline. It was considered that this drug may be less toxic than doxorubicin. In *ex vivo* studies, it has been shown that the substance is significantly less accumulated in the human myocardium and its use is associated with a lower tendency to oxidative cell damage [60–62]. A phase II clinical trial was conducted with amrubicin monotherapy in

24 STS patients who had not undergone chemotherapy for STS. ORR was 13%, and PFS was 5.8 months. In particular, durable responses were observed in patients with myxoid liposarcomas with TLS-CHOP translocation [61]. However, no randomised clinical trial has been conducted to compare the efficacy and safety of this drug with the standard treatment.

#### Brostallicin

In the treatment of STS the efficacy of brostallicin, an analogue of distamycin with  $\alpha$ -bromoacrylamide moiety functions, was also studied. This compound binds to DNA only in the presence of glutathione (GSH) and S-glutathione transferase (GSH), which are produced to a greater extent in tumour cells than in normal cells [63]. The efficacy of this drug was compared with the efficacy of doxorubicin in the first-line treatment of patients with STS in a phase II clinical trial. Despite good tolerance, the efficacy of this drug was lower compared to doxorubicin. The PFS at one year was 6.5% for brostallicin vs. 15.6% for doxorubicin, ORR was 3.9% vs. 22.2%, and OS at one year was 50.5% vs. 57.9%, respectively [64].

### Palifosfamide

Palifosfamide is a DNA alkylating compound that is an active metabolite of ifosfamide. It is not metabolised to acrolein or to chloroacetaldehyde, i.e. to metabolites associated with cystitis and toxicity to the central nervous system. Because it does not require activation by aldehyde dehydrogenase palifosfamide has the potential to bypass the mechanisms of tumour resistance found for ifosfamide [53].

The phase III study PICASSO III compared doxorubicin with palifosfamide versus doxorubicin alone in patients with advanced STS. A total of 447 patients enrolled in the study were randomly allocated in a 1:1 ratio to either the doxorubicin with palifosfamide group or the doxorubicin group. The median PFS did not differ in both groups — for the combination arm it was 6.0 months, and for monotherapy it was 5.2 months (HR 0.86; 95% CI 0.68–1.08,  $p = 0.19$ ). Median OS in the group treated with doxorubicin in combination with palifosfamide was 15.9 months, in comparison to 16.9 months in the group treated with doxorubicin alone (HR 1.05, 95% CI 0.79–1.39,  $p = 0.74$ ) [65].

### Gemcitabine and docetaxel

Clinical trials dedicated to the assessment of the possibility of using regimens, other than those based on doxorubicin chemotherapy, in the first-line treatment of advanced STS were conducted. An example is the phase III study with the acronym GeDDis, dedicated to the comparison of doxorubicin versus gemcitabine with docetaxel in the first line of treatment of patients with advanced or metastatic STS ( $n = 257$ ). The results of this study indicate comparable efficacy results in PFS (23 weeks in the doxorubicin group compared to 24 weeks in the gemcitabine with docetaxel group; HR = 1.28; 95% CI 1.0–1.7;  $p = 0.07$ ), with much worse tolerability of gemcitabine with docetaxel therapy [66]. Based on previously published research results, anthracycline-based chemotherapy regimens remain the standard for first-line treatment.

### Immunomodulating agents

The immune system plays a very important role in controlling processes related to oncogenesis. The available data confirm that the immune system is involved in sarcoma development, which is a reasonable premise to drive research on the use of immunotherapy in STS treatment [67, 68].

Pembrolizumab (anti-PD1) showed activity in patients with some sarcoma subtypes in the phase II SARCO28 study [69]. This study included 42 adult patients with advanced STS and 42 patients with osteosarcoma at the age of 12 years. The patients had previously received no more than three lines of systemic treatment.

The primary endpoint of the study was the response rate. After a follow-up of 17.8 months, in total a response was found in seven out of 40 STS patients evaluated for their efficacy, including four out of 10 (40%) patients with undifferentiated pleomorphic sarcomas (UPS), two out of 10 patients with LPS (20%), and one of 10 SS patients (1%). There was no response reported in patients with LMS. The most frequently reported adverse events of at least grade 3 in the group of STS patients in this study were anaemia (in 7% of patients), decreased lymphocyte count (7%), and prolonged activated thromboplastin time (aPTT, 7%). Serious adverse events occurred in 10% of patients with STS [69].

A study was also conducted with the use of nivolumab in patients with LMS. It was a phase II study in which none of the 12 included patients with LMS of the uterus had a response to the treatment; therefore, the study was prematurely terminated [70].

As in other cancers, an attempt was made to assess the efficacy of the combination of two drugs, anti-PD1 and anti-CTLA4, in the treatment of STS. The Sarcoma Alliance Study A091401 compared the efficacy of nivolumab versus the efficacy of nivolumab in combination with ipilimumab. The patients receiving single-agent therapy in the case of disease progression could continue to receive combination therapy [71]. Eighty-five patients were enrolled in the study. ORR in the group treated with nivolumab was 5% and in the group receiving nivolumab with ipilimumab it was 16%. The median PFS in the nivolumab group was 1.7 months and in the nivolumab with ipilimumab group it was 4.1 months, and the median OS was 10.7 months and 14.3 months, respectively. The most frequently reported adverse event grade at least 3. in the nivolumab group were: anaemia (10%), decreased number of lymphocytes (7%), increased lipase activity (5%), pain, pleural effusion, respiratory failure, secondary benign tumour, and urinary tract stricture, and in the group treated with nivolumab with ipilimumab: anaemia (19%), hypotension (10%), pain, and urinary tract infections. Serious adverse events were reported in 19% of patients treated with nivolumab and in 26% of patients treated with nivolumab and ipilimumab. Due to achievement of previously assumed efficacy of combination therapy, which was defined before the study, further studies with ipilimumab and nivolumab in this group of patients have been planned [71]. Positive reports of immunotherapy efficacy in advanced STS concern mainly rare subtypes, such as ASPS [72].

NY-ESO-1 is a tumour antigen (TAA, tumour-associated antigen), which physiologically is expressed on germ cells in the foetal testes and ovaries. Its expression can be found in synovial sarcomas and myxoid round cell liposarcomas, respectively, in 50–80% and 70% [73]. In studies on the use of NY-ESO-1 as a therapeutic

target in patients with NY-ESO-1-positive sarcomas two methods are currently used: a viral vector with NY-ESO-1 peptide [74, 75], to stimulate the immunological system, and adoptive therapy with T-cells recognising NY-ESO-1 [76, 77]. Preliminary results of the activity of the above methods assessed in phase I studies are encouraging. The use of adoptive therapy is limited by costs and the necessity of using high-dose chemotherapy before T-cell administration.

### Clinical trials in the treatment of advanced STS

Based on data published in the clinical trials registry ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), there are over 300 clinical trials conducted in patients with different stages of STS. A significant part of these trials (over 100) is dedicated to patients with advanced and/or metastatic STS. They are dedicated to determining dose, and assessing the safety and efficacy of new drugs, including new drugs with new molecular targets, as well as drugs previously tested in early-phase studies, including combinations of drugs targeted at various mechanisms of action and molecular pathways, including radiotherapy. Examples of some of them are presented below:

- phase I study (RADIOSARP) of olaparib with concomitant radiotherapy in locally advanced/unresectable STS (NCT02787642);
- phase I trial using an MDR modulator called CBT-1R in combination with doxorubicin in patients with metastatic, unresectable STS after previous treatment with doxorubicin in a dose of up to 150 mg/m<sup>2</sup> (NCT03002805);
- phase II EORTC study with the acronym ANITA comparing the use of nintedanib with the use of ifosfamide in patients with advanced STS (NCT02808247);
- phase II study with epacadostat (IDO inhibitor) in combination with pembrolizumab in patients with unresectable locally advanced or metastatic STS (NCT03414229);
- phase Ib/II study with vorinostat in combination with gemcitabine and docetaxel in patients with unresectable locally advanced or metastatic STS (NCT01879085);
- phase II study with palbociclib in patients with advanced STS with CDK4 overexpression (NCT03242382);
- phase II study dedicated to the assessment of treatment with apatinib in patients with advanced STS (NCT03104335);
- phase I/II trial with the acronym SAINT dedicated to assessment of the first-line treatment with trabectedin in combination with immunotherapy with nivolumab and ipilimumab in patients with advanced STS (NCT03138161);
- phase III trial with the acronym LEADER assessing eribulin and lenvatinib in patients with advanced STS (NCT03526679);
- phase II study with durvalumab and tremelimumab in patients with various STS subtypes (NCT02815995);
- phase I/II study (ImmunoSarc) with sunitinib and nivolumab in patients with soft tissue and bone sarcomas (NCT03277924);
- phase II study with the use of ribociclib and everolimus in patients with LMS and dedifferentiated LPS (NCT03114527);
- phase I study of olaratumab plus pembrolizumab in patients with advanced or metastatic STS (NCT03126591);
- phase III study dedicated to efficacy assessment of anlotinib in patients with locally advanced or metastatic ASPS, LMS, and SS (APROMISS, NCT03016819).

### Summary

Patients with advanced STS are a group of patients with poor prognosis. Systemic treatment of STS is an essential element of therapy, especially in advanced disease. The number of systemic treatment options in this diagnosis is still limited. For many years, progress in this area was small; the basic medicines used in this indication were, and still are, anthracyclines and alkylating agents. Research carried out in recent years has allowed the approval of new medicines in this indication. One of them is trabectedin — a medicine with proven efficacy, especially among patients diagnosed with so-called L-sarcomas. Other drugs in STS have been tested and approved for use, for example pazopanib in the treatment of non-GIST STSs, sunitinib in the treatment of ASPS, and olaratumab in combination with doxorubicin for STS treatment. The first reports on the effectiveness of immunotherapy in the treatment of these rare diseases have also been published. Currently, many clinical trials are being carried out to assess the efficacy of drugs targeting new molecular targets and immunotherapy, also in combination with radiotherapy or cytotoxic drugs.

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