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Systemic treatment in adult uterine sarcomas

I.M.E. Desara, P.B. Ottevanger, C. Benson, W.T.A. van der Graaf

ABSTRACT

Uterine sarcomas (US) are rare mesenchymal tumours of the uterus and are divided mainly into uterine leimyosarcoma (uLMS), low grade endometrial stromal sarcoma (LG-ESS), high grade endometrial stromal sarcoma (HG-ESS), adenosarcomas and high grade undifferentiated sarcoma (HGUS). US are often high-grade tumours with a high local recurrence rate and metastatic risk. We here discuss the current standard of care and knowledge of systemic therapy for adult uterine sarcomas, in particular uLMS, LG-ESS, HG-ESS and HGUS, in both the adjuvant as well as the metastatic setting.

1. Background

Uterine sarcomas are rare. Together, they account for 3–9% of all uterine cancers and the annual incidence is 0.36/100,000 woman-years (Koivisto-Korander et al., 2012; Toro et al., 2006). Uterine sarcomas (US) are classified into mesenchymal tumours or mixed epithelial and mesenchymal tumours. Mesenchymal tumours are further classified as uterine leiomyosarcoma (uLMS, 63%), endometrial stromal sarcoma (ESS, 21%, usually divided into low grade (LG-ESS) and high grade (HG-ESS)), adenosarcomas (AS, 5%), high grade undifferentiated sarcoma (HGUS, 5%) and other rare subtypes (e.g. alveolar or embryonal rhabdomyosarcoma) (Trope et al., 2012; Abeler et al., 2009). Mixed epithelial and mesenchymal tumours include uterine adenosarcomas and carcinosarcomas (Hosh et al., 2016; Benson and Miah, 2017; Nathenson et al., 2016). Adenosarcomas are mixed tumours with a combination of a benign epithelial component and malignant mesenchymal cells. The risk of relapse is markedly increased in case of sarcomatous overgrowth (Nathenson et al., 2016). Carcinosarcomas, also called malignant mixed Müllerian tumours, are generally regarded of epithelial origin, and therefore are not part of this review. The pathology of uterine sarcomas is known to be difficult. In a population-based study of uterine sarcomas from Norway 168 out of 419 (29%) initially classified US were on review excluded or reclassified as for example leiomyomas or leiomyoma variants according to the WHO criteria (Abeler et al., 2009). Furthermore, the nomenclature has been changed several times.

The clinical behaviour of the histological subtypes is different. Uterine leiomyosarcomas usually present as a bulky tumour in women > 40 years with complaints of vaginal bleeding (56%), a palpable pelvic mass (54%) and/or pelvic pain (22%) (Prat and Mbatani, 2015). In a significant part of the patients, the diagnosis is set postoperative, instead of the expected leiomyoma(s). Distinction between leiomyoma and leiomyosarcoma is made with conventional morphological criteria (mitosis, atypia and necrosis). The term STUMP (smooth tumours of undefined malignant potential) is used in a setting when both leiomyoma as well as leiomyosarcoma cannot be diagnosed with certainty. Uterine leiomyosarcoma are usually high grade with typically a mitotic rate > 15/10 HPF. The prognosis of leiomyosarcoma is poor, even when confined to the uterus at the time of diagnosis. Recurrence rates are high; between 53 and 71%, and the overall five-year survival rate is poor (Prat and Mbatani, 2015). In a recent Surveillance Epidemiology and End Results (SEER) database reporting of 13,089 US cases between 2000 and 2012, the five-year relative survival for the group of uLMS patients was 42% (Hosh et al., 2016). An earlier SEER paper reports a 5-year disease specific survival per stage; stage I—76%, stage II—60%, stage III—45%, and stage IV—29% (Kapp et al., 2008). In a Norwegian study, the five-year survival rate for uLMS was 51% for FIGO stage I and 25% for FIGO stage II, whereas all patients with stage III–IV died within 5 years (Abeler et al., 2009).

The term endometrial stromal tumour applies to neoplasms typically composed of cells that resemble endometrial stromal cells of the proliferative endometrium. ESS are predominantly intramural neoplasms exhibiting myometrial invasion and permeation of myometrial lymphovascular spaces. LG-ESS occurs in women between 40 and 55 years old of whom > 50% is premenopausal. Patients can present with vaginal bleeding, dysmenorrhoea or pelvic pain, but as many as 25% is asymptomatic (Prat and Mbatani, 2015). Typically, hormone receptors...
(estrogen, progesterone) are positive on the tumour cells (Prat and Mbatani, 2015). LG-ESS frequently have JAZF1 rearrangements (Huang et al., 2004). Prognosis of LG-ESS is favourable. Recurrences occur in up to one third of the patients and may occur after many years. Five-year survival for stage I–II is 90%, compared to 50% for stage III–IV (Chan et al., 2008). High grade ESS present with abdominal bleeding, an enlarged uterus or pelvic mass at a mean age of 50 years (range 28–67). The tumour may appear as intracavitary polypoid or mural masses. The mitotic rate is >10/10 HPF and estrogen and progesterone receptors are negative (Prat and Mbatani, 2015). Recently, a t(10;17)(q22;p13) translocation has been identified in a large proportion of high-grade ESS. This rearrangement results in an in-frame fusion between YWHAE (exons 1–5) and 1 of the 2 highly homologous genes FAM22A and FAM22B (exons 2–7), formerly designated as YWHAE-FAM22 and nowadays called YWHAE-NUTM2 (Lee et al., 2012a,b,c). The presence YWHAE-NUTM2 helps to discriminate HG-ESS from the more common low-grade ESS with JAZF1 rearrangement and from HGUS with no identifiable molecular aberrations, which is important in guiding clinical management (Lee et al., 2012a; Pautier et al., 2014). Cyclin D1 can be used as an immunohistochemical diagnostic indicator for HG-ESS with YWHAE-NUTM2 rearrangement (Chan et al., 2008). Compared to LG-ESS, patients with HG-ESS more frequently encounter recurrences and they occur earlier after primary diagnosis. In the SEER database, five-year relative survival for all stage low grade and high grade ESS together was 72.7% (Hosh et al., 2016).

Adenosarcomas are characterized by benign epithelial elements and a malignant mesenchymal component. They most commonly present with vaginal bleeding. Pathologic diagnosis is dependent on the identification of the characteristic morphologic features. The most common immunohistochemical markers for adenosarcoma are CD10 and WT1, but these are not specific. High frequency of TP53 abnormalities has been described in high grade AS (Hodgson et al., 2017). The majority of patients present with stage I disease, with a 5-year overall survival of 60–80%. Survival is influenced by the presence of myometrial invasion, sarcomatous overgrowth, lymphovascular invasion, necrosis, and the presence of heterologous elements including rhabdomyoblastic differentiation. The reported prevalence of sarcomatous overgrowth in patients with uterine adenosarcoma varies greatly, from 8% to 65% (Carroll et al., 2014). Patients with sarcomatous overgrowth have significantly increased risk of recurrence 23 versus 77% and decreased 5-year overall survival 50–60% (Nathenson et al., 2016). Comparable numbers have been reported in a National Cancer Database study, with a ten years overall survival of approximately 60% in a cohort with 1137 uterine AS patients (Seagle et al., 2016).

HGUS are very rare and aggressive. They are poorly differentiated sarcomas composed of cells that do not resemble proliferative-phase endometrial stroma. HGUS are separated into uniform and pleomorphic types. Uniform-type HGUS shows permeative myometrial involvement with lymphovascular embolism and no destructive involvement of the myometrium in contrast to pleomorphic undifferentiated ESSs. Uniform-type HGUS shows fusiform spindle cells or round cells. Pleomorphic-type HGUS exhibits high-grade cytological atypia with marked nuclear pleomorphism accompanied in most instances by a high mitotic rate (almost always exceeding 10 MF/10 HPF and sometimes approaching 50 MF/10 HPF) and the presence of tumour necrosis. HGUS is often heterogeneous and composed of different components, e.g. dedifferentiated ESS, dedifferentiated leiomyosarcomas, the sarcomatous component of adenosarcomas or carcinosarcomas with overgrowth of epithelial elements, etc. (Pau1er et al., 2014). Approximately 60% of the patients present with stage III or IV disease. The prognosis is very poor with a median survival, once metastasised of less than a year (Prat and Mbatani, 2015; Tanner et al., 2012).

We here review the results of systemic treatment in uLMS and ESS in the adjuvant and metastatic settings. The limited available data on AS and HGUS will also be discussed.

2. Adjuvant treatment

As described above, the recurrence rates can be high and disease specific survival may be low in some types of US, especially uLMS. Important risk factors are high mitotic count, tumour spill and morcellation of suspected benign leiomyoma which appear to be leiomyosarcomas by pathology review afterwards. Several attempts have been made to improve disease free survival by adding adjuvant therapy.

2.1. Hormonal therapy

Both uLMS and ESS can express estrogen receptors (ER) and/or progesterone receptors (PR). For uLMS, ER expression has been reported in 18–87% and PR expression in 18–80%. In ESS, ER expression has been shown in 40–100% and PR expression 60–100% (Amant et al., 2009). HGUS do not express hormone receptors. Adenosarcoma may express both estrogen and progesterone receptors in both the epithelial as well as sarcomatous component, although hormone receptor expression has not been seen in the sarcomatous part of tumours with sarcomatous overgrowth (Amant et al., 2004). Conflicting data have been published about the association between hormone receptor expression and prognosis (Davidson et al., 2016; Raspollini et al., 2003; Garcia et al., 2015; Lusby et al., 2013; Koivisto-Korander et al., 2011; Akhan et al., 2005; Leitao et al., 2012; Ioffe et al., 2009).

There are no prospective randomized controlled studies of hormonal therapy in uterine sarcomas, neither in the adjuvant nor in the metastatic setting (Thanopoulou and Judson, 2012). We here summarize the outcome of series of at least ten patients or more.

2.1.1. ESS

In a retrospective series, four out of thirteen ESS patients who received progestins as adjuvant therapy recurred compared with 6 of 9 ESS patients who did not receive adjuvant progestins (31% vs. 67%) (Chu et al., 2003). Another retrospective series reports the results of adjuvant hormonal therapy (mainly megestrol acetate or medroxyprogesterone) in thirty low grade ESS patients. The median overall survival with hormonal therapy was 94 months in the patients with adjuvant hormonal therapy versus 72 months in the observation cohort (p = .07) (Leath et al., 2007). Cheng et al. (2011) reported a series of 25 low grade ESS who had a median time to progression after adjuvant hormonal therapy of 132 months. In 10 FIGO stage I–II ESS patients treated with adjuvant hormonal therapy (megestrol acetate of aromatase inhibitors), no relapse occurred. Patients were treated between 1977 and 2007 and the results were reported in 2010, without mentioning the median follow up time (Malouf et al., 2010). In a Chinese retrospective series, 11 out of 114 low grade ESS received some form of adjuvant hormonal therapy. Disease free survival did not differ from patients without or another type of adjuvant treatment and no other details are available (Zhou et al., 2015). Finally, Amant et al. reported the results of adjuvant hormonal treatment, defined as a minimum of 200 mg medroxyprogesterone acetate, in 2 out of 22 (9%) and 5 out of 9 (56%) of ESS patients with stages I and III–IV, respectively. Among stage I women receiving adjuvant hormonal treatment or not, 0 out of 2 (0%) and 4 out of 20 (20%) relapsed. And among stages III–IV women receiving adjuvant hormonal treatment or not, 1 out of 5 (20%) and 3 out of 4 (75%) relapsed (Amant et al., 2007). All together, there is no evidence to support the use of adjuvant hormonal therapy as standard of care in ESS.

2.1.2. uLMS

Even less data is available for uLMS and the use of adjuvant hormonal treatment. The results of recently finished randomized phase II study of letrozole versus observation in patients with newly diagnosed uLMS limited to the uterus with at least 10% estrogen receptor expression [NCT00414076] are awaited.
### Table 1

<table>
<thead>
<tr>
<th>Adjuvant chemotherapy trials in uterine sarcomas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n phase population</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>doxorubicin 60 mg/m²</strong></td>
</tr>
<tr>
<td><strong>gemcitabine 900 mg/m² d1, d8 + docetaxel 75 mg/m² d8 q 21 d, 4 cycles</strong></td>
</tr>
<tr>
<td><strong>gemcitabine 900 mg/m² d1, d8 + docetaxel 75 mg/m² d8 q 21 d, 4 cycles followed by + doxorubicin 60 mg/m² q21d 4 cycles (SARC-005)</strong></td>
</tr>
<tr>
<td><strong>cytoxan 500 mg/m² d1, d3 and dacarbazine 200 mg/m² d1-4 q28 d 9 cycles</strong></td>
</tr>
</tbody>
</table>

**M; median, DFS; disease free survival, PFS; progression free survival, OS; overall survival, US; uterine sarcomas.**

*a Including carcinosarcomas.*

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2.1.3. HGUS and adenosarcoma

There is no literature about adjuvant hormonal therapy in HGUS and adenosarcomas. This makes sense since the lack of hormone receptor expression in HGUS. In adenosarcomas, hormone receptor expression has been reported, but we did not found any (adjuvant or palliative) trials or series of ten or more patients treated with hormonal therapy (Amant et al., 2004). However, the other way around, adenosarcomas have been associated with tamoxifen use in breast cancer (Clement et al., 1996).

2.2. Adjuvant chemotherapy in US

Only a few prospective studies with adjuvant chemotherapy have been performed and these are summarized in Table 1 (Omura et al., 1985; Hensley et al., 2013, 2009a; Hempling et al., 1995). The populations of these studies were mixed, including also carcinosarcomas, and had small numbers. These prospective results do not support adjuvant treatment so far. However, it is encouraging that in a single arm phase II study of 47 high grade uLMS patients treated with 4 cycles of gemcitabine-docetaxel followed by 4 cycles of doxorubicin, the median PFS was not yet reached after a median of 39.8 months of follow up (Hensley et al., 2013).

To date four retrospective series in US have been reported with at least one chemotherapy containing arm. The largest series is an observational cohort study of the National Cancer Database in FIGO stage I ESSS. Out of 2414 women with LG-ESS, 4.8% (n = 115) received adjuvant chemotherapy. Approximately one-third (33.4%, 444/1383) of women with HG-ESS received primary adjuvant chemotherapy, and of these women 75.9% (337/444) received multi-agent chemotherapy. Use of adjuvant chemotherapy and radiotherapy was associated with increased survival for HG-ESS, but not in LG-ESS (Seagle et al., 2017). A second retrospective study in 108 high grade stage I–II uLMS patients comparing adjuvant chemotherapy to radiotherapy or observation did also report no clinical benefit of any adjuvant treatment (Rici et al., 2013). The same was the case in a very recent retrospective series of 111 stage I uLMS patients of whom 33 patients received a median of 4 cycles of gemcitabine-docetaxel, without survival benefit (Litell et al., 2017). The fourth study by Roque et al. presented a retrospective series of 56 uLMS patients treated with chemotherapy (30 gemcitabine-docetaxel, 26 other) compared to radiotherapy (n = 41) and observation (n = 31). There was no difference in PFS or OS in women with uLMS treated with adjuvant gemcitabine-docetaxel versus those who were observed or received irradiation alone or a chemotherapy regimen other than gemcitabine-docetaxel (Roque et al., 2016).

In July 2016, a systematic review and meta analysis was published. Of 360 early stage uLMS patients included, 40% received adjuvant chemotherapy (with or without radiotherapy). These patients were compared to radiotherapy alone or observation (53 and 155 patients). Chemotherapy did not prove to be of benefit in terms of local or distant recurrence rate (Bogani et al., 2016).

Prospective randomized trials are desperately needed in this disease with high relapse risk. Unfortunately, the Gynaecologic Oncology Group (GOG) 277 phase III trial comparing 4 cycles of gemcitabine-docetaxel followed by 4 cycles of doxorubicin versus observation in high risk uLMS was closed prematurely due to poor accrual [NCT01533207]. One of the important reasons of the difficulty in running this study was the difference between the intensive treatment arm with 8 cycles of chemotherapy and an observation only arm. Also, for patients just recovering from surgical procedures the prospect of 8 cycles of chemotherapy could be felt quite challenging.

The lack of a universally recognised standard chemotherapy comparator arm, continues to hamper the development of future randomised clinical trials in this setting. Currently the general perception is that there is no routine role for adjuvant therapy, although in practice it may be offered in cases where tumour morcellation took place and other indications with obvious tumour spill during surgical removal of...
the tumour.

2.3. Adjuvant radiotherapy alone

Only one prospective trial in early stage (I–II) US is available. Adjuvant radiotherapy was compared to observation and did not result in an improvement of local control, the rate of distant metastases, or OS (Reed et al., 2008). Furthermore, a recent report of the SEER database even concluded that (retrospectively) survival was worse in patient treated with surgery and adjuvant radiotherapy compared to surgery alone (Hosh et al., 2016). Therefore, there is no routine role for radiotherapy in this setting.

2.4. Combined radiotherapy and chemotherapy

In the SARCgyn trial, 81 patients with FIGO stage ≤III US (11% HGUS, including carcinosarcomas) were treated with four cycles of doxorubicin 50 mg/m² d1, ifosfamide 3 g/m², d1-2, cisplatin 75 mg/m² d3, (API) and G-CSF q 21 days followed by radiotherapy compared to radiotherapy alone. This study was closed prematurely because of poor accrual. The 3-year disease free survival rates were 55 vs. 41% (p = .048), respectively, but without improvement of the 3-year OS (81 vs 69%, p = .41), respectively. Toxicity was high with grade 3–4 toxicity (mainly bone marrow suppression) in up to 76% of patients and two toxic deaths due to febrile neutropenia.

2.5. Conclusion—adjuvant setting

Currently, there is neither prospective, nor retrospective, evidence in favour of adjuvant treatment for uterine sarcomas. However, expert opinions mention the possibility to consider adjuvant therapy in selected cases with high risk US. On individual base, for hormone receptor positive HG-ESS hormonal therapy might be considered, carefully balancing the unproven efficacy versus the possible negative effects. Because of its good prognosis, adjuvant hormonal therapy in LG-ESS is not clinically meaningful. For uLMS, adjuvant chemotherapy (e.g. 4–6 cycles of doxorubicin or gemcitabine-docetaxel) might be considered in younger and otherwise healthy patients with a high risk on recurrence (e.g. high grade, tumour spillage or morcellation), after discussion in a multidisciplinary sarcoma tumour board. For HGUS, unfortunately, no conclusion can be made with the unfortunate premature closure of the phase III study.

3. Metastatic treatment

3.1. Hormonal therapy

3.1.1. ESS

Again, only case reports and small retrospective series are available. We here discuss series of at least 10 patients. The Royal Marsden Hospital single experience observed objective response in 46.2% and clinical benefit in 92.4% in 13 metastatic ESS patients treated with first line hormonal therapy. Aromatase inhibitors were prescribed as first endocrine line in 11 out 13 patients and progesterins in the remainder, while in second line treatment other aromatase inhibitors were prescribed in 7 out of 10 patients, followed by progesterins and GnRH analogues. Median PFS for first line was 4.0 years, with a 5-year PFS rate of 30.8%. Median PFS for second line hormonal treatment was 3.0 years, with a 2-year PFS rate of 88.9% (95% CI: 68.3-100.0) (Thanopoulou et al., 2015). A Dutch series of 11 LG-ESS patients with residual or recurrent disease treated with megestrol acetate or aromatase inhibitors, observed in 9 (82%) patients an objective response (4 complete responses; 5 partial responses). The response duration ranged from 4 to 252 months (median 48 months) (Dahhan et al., 2009). Ioffe et al. (2009) reported stable disease, complete or partial response in 14 of 18 ESS patients with recurrent or progressive disease who were treated with hormonal therapy (range of follow up: 6–124 months).

In second line, only case reports are available (Shoji et al., 2011; Nakamura et al., 2016).

Importantly, all case series are small and retrospective, and the natural behaviour of ESS can be indolent.

3.1.2. uLMS

Only one prospective phase II trial with letrozole has been performed in 27 ER and/or PR positive uLMS patients with a median of 2 prior lines of systemic therapy. The median PFS was 12 weeks. The best response was stable disease in 14 patients (54%). Three patients, all with tumours expressing ER and PR in > 90% of tumour cells, continued to receive letrozole for > 24 weeks. Median duration of therapy for the study population was 10 weeks. The most common reason for treatment discontinuation was disease progression (85%) (George et al., 2014). In a retrospective series with sixteen patients with measurable advanced uLMS, patients were treated with an aromatase inhibitor (first line mainly letrozole, second line mainly exemestane). Median PFS in first line was 14 months, and prolonged PFS was more likely to be observed in patients with low grade compared to high grade ULMS (20 months vs. 11 months), and in moderate strong ER positive compared to weak ER positive ULMS (20 months vs. 12 months). Best response was a partial response in 2 out of 16 patients (12.5%) and the clinical benefit rate, defined as complete response plus partial response plus stable disease ≥6 months, was observed in 10 out of 16 patients (62.5%). Median duration of second line was 3 months and median PFS was not reached. The 1-year PFS rate for the second line aromatase inhibitor was 80% (Thanopoulou et al., 2014). The Memorial Sloan-Kettering Cancer Centre presented their experience in 34 advanced or recurrent uLMS patients (65% ER+, 29% PR+) treated with aromatase inhibitors. Median PFS was 2.9 months and best objective response was partial response in 3 out of 34 patients (9%) (all of whom were ER positive). In the subgroup with ER or PR positive uLMS, the 1-year progression free survival rate was 28% (O’Cearbhaill et al., 2010).

3.1.3. Conclusion hormonal therapy—metastatic setting

Although prospective evidence is scarce, the series presented do show that in selected cases (e.g. ER and/or PR positive, low grade, low volume disease) hormonal therapy can be attractive in stabilising disease and ultimately postponing chemotherapy. This is more the case in ESS than in uLMS. In the majority of patients, hormonal therapy has the advantage of being well tolerated and less toxic than systemic chemotherapy. However, almost all presented data are retrospective. A selection and publication bias must be considered and there is a lack of systematic analysis of the hormone receptor status. The lack of available data of control patients makes it difficult to interpret the results of the observations as discussed. Objective radiological response is the most convincing indication of efficacy of treatment in these uncontrolled studies and case series.

3.2. Chemotherapy in US

Despite many efforts, the 5-years disease specific survival for all types of locally advanced and metastatic US (including carcinosarcomas) did not improve in the past decade (Hosh et al., 2016; Kapp et al., 2008). Multiple prospective trials with palliative chemotherapy have been done (Table 2). They encompass the whole range, from smaller studies in uLMS only to larger soft tissue sarcoma (STS) trials including also uterine sarcoma or leiomyosarcoma patients of non-uterine origin. Due to its rarity and its more indolent behaviour, only small numbers of ESS and HGUS patients have been included in STS trials. Furthermore, one must consider that part of the prospective trials and all of the retrospective series have been done without central pathology review and that up to 30% of the pathological diagnosis may be wrong (Abelev et al., 2009).

The National Cancer Database of the United States concluded that
Table 2
Chemotherapy trials in advanced or metastatic uterine sarcomas.

<table>
<thead>
<tr>
<th>Population</th>
<th>Line of treatment</th>
<th>Phase</th>
<th>n</th>
<th>RR (%)</th>
<th>3mo PFS (%)</th>
<th>6mo PFS (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gemcitabine-docetaxel (Seddon et al., 2015)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>44</td>
<td>25</td>
<td>70.5</td>
<td>59.1</td>
<td>7.1</td>
<td>17.9</td>
</tr>
<tr>
<td>doxorubicin vs. gemcitabine-docetaxel (Seddon et al., 2017)</td>
<td>STS</td>
<td>1</td>
<td>III</td>
<td>257 (71 ulMS, 47 LMS)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>23.3 vs. 23.7 weeks</td>
<td>76.3 vs 67.3 weeks</td>
</tr>
<tr>
<td>gemcitabine-docetaxel vs. gem-doc-bevacizumab (Hensley et al., 2015)</td>
<td>ulMS</td>
<td>1</td>
<td>III</td>
<td>107</td>
<td>31.5</td>
<td>35.8</td>
<td>–</td>
<td>6.2 vs 4.2</td>
<td>26.9 vs. 23.3</td>
</tr>
<tr>
<td>gemcitabine-docetaxel (Hensley et al., 2008a)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>35</td>
<td>30.3</td>
<td>30.3</td>
<td>–</td>
<td>4.6 vs 7.4</td>
<td>12.8 vs. 14.3</td>
</tr>
<tr>
<td>liposomal doxorubicin (Sutton et al., 2005)</td>
<td>uLMS</td>
<td>1</td>
<td>II</td>
<td>35</td>
<td>–</td>
<td>–</td>
<td>Median response duration</td>
<td>4.1 months.</td>
<td>2005</td>
</tr>
<tr>
<td>doxorubicin-ifosfamide (Sutton et al., 1996)</td>
<td>uLMS</td>
<td>1</td>
<td>II</td>
<td>34</td>
<td>30.3</td>
<td>–</td>
<td>Median response duration</td>
<td>4 months.</td>
<td>1996*</td>
</tr>
<tr>
<td>Doxorubicin vs. doxorubicin+ ifosfamide (Judson et al., 2014)</td>
<td>STS</td>
<td>1</td>
<td>III</td>
<td>454 (113 LMS)</td>
<td>14 vs. 19</td>
<td>5.1 vs. 4.9</td>
<td>76.3 vs 67.3 weeks</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin vs. doxorubicin+ cyclophosphamide (Muss et al., 1985)</td>
<td>US</td>
<td>1</td>
<td>III</td>
<td>104 (38 uLMS, 11 ESS)</td>
<td>19 vs. 19</td>
<td>5.1 vs. 4.9</td>
<td>11.6 vs. 10.9</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin-palifosfamide vs. doxorubicin (Ryan et al., 2016)</td>
<td>STS</td>
<td>1</td>
<td>III</td>
<td>447 (138 LMS)</td>
<td>14 vs. 19</td>
<td>5.1 vs. 4.9</td>
<td>76.3 vs 67.3 weeks</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin-evofosfamide (Chawla et al., 2014)</td>
<td>STS</td>
<td>1</td>
<td>III</td>
<td>108 (47 ulMS, 33 uLMS)</td>
<td>18 vs. 12</td>
<td>6.2 vs. 4.2</td>
<td>26.9 vs. 23.3</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin vs. doxorubicin+ cyclophosphamide (Muss et al., 1985)</td>
<td>US</td>
<td>1</td>
<td>III</td>
<td>104 (38 uLMS, 11 ESS)</td>
<td>19 vs. 19</td>
<td>5.1 vs. 4.9</td>
<td>11.6 vs. 10.9</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin+ ifosfamide (Antman et al., 1993)</td>
<td>STS</td>
<td>1</td>
<td>III</td>
<td>340 (59 LMS)</td>
<td>17 vs. 32</td>
<td>6.2 vs. 4.2</td>
<td>26.9 vs. 23.3</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Eribulin vs dacarbazine (Lauria et al., 2015)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>108 (47 ulMS)</td>
<td>18 vs. 19</td>
<td>5.1 vs. 4.9</td>
<td>11.6 vs. 10.9</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea-dacarbazine-etoposide (Carrié et al., 1996)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>18</td>
<td>11</td>
<td>Median duration of response</td>
<td>3.3 months.</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>cisplatin (Thigpen et al., 1991)</td>
<td>US</td>
<td>1</td>
<td>II</td>
<td>33 uLMS</td>
<td>33 uLMS</td>
<td>18 MMT</td>
<td>3 uLMS</td>
<td>14.2</td>
<td>1991</td>
</tr>
<tr>
<td>Topotecan (Miller et al., 2000)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>36</td>
<td>11</td>
<td>Median duration of response</td>
<td>3.3 months.</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine-mitomycin-doxorubicin-cisplatin-sargramostim (Long et al., 2005)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>37</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>6.3</td>
<td>2002</td>
</tr>
<tr>
<td>Mitomycin-doxorubicin-cisplatin (Edmonson et al., 2002)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>28</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>2.1</td>
<td>1996</td>
</tr>
<tr>
<td>Etoposide (Thigpen et al., 1996)</td>
<td>US</td>
<td>1</td>
<td>II</td>
<td>33 uLMS</td>
<td>33 uLMS</td>
<td>18 MMT</td>
<td>3 uLMS</td>
<td>14.2</td>
<td>2000</td>
</tr>
<tr>
<td>Hydrourea-dacarbazine-etoposide (Carrié et al., 1996)</td>
<td>US</td>
<td>1</td>
<td>II</td>
<td>36</td>
<td>11</td>
<td>Median duration of response</td>
<td>3.3 months.</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Topotecan (Miller et al., 2000)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>37</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>6.3</td>
<td>2002</td>
</tr>
<tr>
<td>Topotecan (Miller et al., 2000)</td>
<td>US</td>
<td>1</td>
<td>II</td>
<td>28</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>2.1</td>
<td>1996</td>
</tr>
<tr>
<td>First or second line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gemcitabine-docetaxel (Hensley et al., 2002)</td>
<td>LMS</td>
<td>1</td>
<td>II</td>
<td>34 (85%)</td>
<td>52.9</td>
<td>64.7</td>
<td>47</td>
<td>5.6</td>
<td>17.9</td>
</tr>
<tr>
<td>High dose ifosfamide 12 g/m2 in 3 days every 28 days (Nielsen et al., 2000)</td>
<td>STS</td>
<td>1</td>
<td>II</td>
<td>124 (33)</td>
<td>16% (LMS)</td>
<td>–</td>
<td>–</td>
<td>15 weeks</td>
<td>–</td>
</tr>
<tr>
<td>Paclitaxel-carboplatin (Yoo et al., 2012)</td>
<td>US</td>
<td>1</td>
<td>II</td>
<td>13</td>
<td>15.4</td>
<td>–</td>
<td>–</td>
<td>2.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Trimetrexate (Smith et al., 2002)</td>
<td>ulMS</td>
<td>1</td>
<td>II</td>
<td>23</td>
<td>4.3</td>
<td>–</td>
<td>–</td>
<td>2.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Second line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gemcitabine-docetaxel (Hensley et al., 2008b)</td>
<td>ulMS</td>
<td>2</td>
<td>II</td>
<td>51</td>
<td>27</td>
<td>52</td>
<td>56+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>gemcitabine-docetaxel (Pau et al., 2012)</td>
<td>ulMS</td>
<td>2</td>
<td>II</td>
<td>21</td>
<td>23.8</td>
<td>71.4</td>
<td>47.6</td>
<td>4.7</td>
<td>23</td>
</tr>
<tr>
<td>gemcitabine (Look et al., 2004)</td>
<td>ulMS</td>
<td>2</td>
<td>II</td>
<td>42</td>
<td>20.5</td>
<td>–</td>
<td>–</td>
<td>4.9</td>
<td>–</td>
</tr>
<tr>
<td>Ixabepilone (Duska et al., 2014)</td>
<td>ulMS</td>
<td>2</td>
<td>II</td>
<td>26</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>1.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Etoposide (Rose et al., 1998)</td>
<td>ulMS</td>
<td>2</td>
<td>II</td>
<td>26</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>2.1</td>
<td>7.6+</td>
</tr>
<tr>
<td>Beyond second line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gemcitabine-dacarbazine vs. dacarbazine (Garcia-Del-Muro et al., 2011)</td>
<td>STS</td>
<td>≥ 2</td>
<td>II</td>
<td>109 (32 LMS)</td>
<td>12 vs. 4</td>
<td>56 vs. 37</td>
<td>4.2 vs. 2 (LMS 4.9)</td>
<td>16.8 vs 8.2 (LMS 10.3)</td>
<td>2011</td>
</tr>
<tr>
<td>Eribulin vs dacarbazine (Demetri et al., 2016)</td>
<td>LMS or lipo</td>
<td>≥ 3</td>
<td>III</td>
<td>518 (40% ulMS)</td>
<td>9.9 vs 6.9</td>
<td>4.2 vs. 1.5</td>
<td>12.4 vs. 12.9, HR 0.58 in ulMS subgroup</td>
<td>2016</td>
<td></td>
</tr>
<tr>
<td>Eribulin vs dacarbazine (Schoffski et al., 2016)</td>
<td>LMS or lipo</td>
<td>≥ 3</td>
<td>III</td>
<td>452 (297 LMS of who 131 ulMS)</td>
<td>4.5</td>
<td>33 vs 29</td>
<td>2.6 vs 2.6</td>
<td>13.5 vs. 11.5 (benefit mostly for lipo)</td>
<td>2016</td>
</tr>
</tbody>
</table>

(continued on next page)
chemotherapy adds 8.5 months benefit compared to untreated patients with metastatic uLMS (19.4 vs. 10.9 months) in an observational cohort study of patients diagnosed between 1998 and 2013 (Seagle et al., 2017). Recently, a pooled analysis of 269 metastasised US patients treated within 13 trials (total 3270 STS patients) of the EORTC Soft Tissue and bone Sarcoma has been published (Ray-Coquard et al., 2016). Median OS was 10.4 months, median PFS 4.1 months. Four categories of chemotherapy were evaluated; anthracyclines alone, ifosfamide alone, combined doxorubicin-ifosfamide and the combination of cyclophosphamide, doxorubicin, vincristine and dacarbazine (CYVADIC). Clinical outcome was not influenced by category of chemotherapy. Histological subtypes were grouped as LMS versus others. Lower response rates were observed in LMS (19 versus other 33%) and the response for ifosfamide as single agent was only 5% for al US. Gemcitabine-docetaxel was not part of this analysis.

In Table 2 we summarize the prospective trials with palliative chemotherapy in US or STS trials important for the nowadays insights in the standard of care for STS in general including US. Where available, numbers of (u)LMS within general STS trials have been provided. The majority of the studies had negative results and did not improve the survival of patients with advanced or metastatic uterine sarcomas. We here discuss the prospective trials summarized in Table 2.

### 3.2.1. Efficacy of chemotherapy in first line

As in other soft tissue sarcomas, doxorubicin is still the first line treatment in uterine sarcomas. Mainly all first line trials in US or (u)LMS were doxorubicin based or used gemcitabine-docetaxel (Seddon et al., 2015; Hensley et al., 2015, 2002, 2008b; Long et al., 2005; Edmonson et al., 2002; Pautier et al., 2012). For a long time, it was debated whether single agent doxorubicin or the combination of gemcitabine-docetaxel was best in (u)LMS. Recently, the results of the UK GeDDIS Phase III trial have been published. This trial included 257 patients with STS who were randomized between doxorubicin 75 mg/m² q 21 days or the combination of gemcitabine 650 mg/m² Day 1 and 8, q21 days and docetaxel 75 mg/m² every 21 days. No significant difference in median PFS (23.3 and 23.7 weeks) or median OS (76.3 vs. 76.3 weeks) for doxorubicin versus gemcitabine-docetaxel was reported and response rates of 20 and 19% for both treatment arms. Further subgroup analyses were done comparing leiomyosarcoma versus other sarcomas (p = .14), and uterine leiomyosarcoma versus other sarcomas (p = .38), but again no differential effect was evident between the two treatment groups (Seddon et al., 2017). The authors concluded that single agent doxorubicin is still the preferred first line treatment in STS and the results in the (u)LMS cohort do not support other preferences. The addition of olaratumab to doxorubicin showed an impressive improvement of OS compared to doxorubicin alone in the Phase Ib-II trial (26.5 vs. 14.7 months) in unslected STS but needs confirmation in a Phase III trial, which has recently completed accrual and results are expected around 2019–2020 (Tap et al., 2016) [NCT02451943]. In those STS patients in need for a volume response (e.g. induction therapy or because of palliative reasons) the combination of doxorubicin and ifosfamide is recommended (Judson et al., 2014). However, the European Society of Medical Oncology (ESMO) guidelines suggests the combination of doxorubicin-dacarbazine (Antman et al., 1993; Omura et al., 1983). Instead of doxorubicin combined with ifosfamide in case combination therapy is warranted, since the activity of ifosfamide is limited in uterine leiomyosarcomas (Ray-Coquard et al., 2016; Antman et al., 1993; Casali et al., 2014). Anthracycline based combination therapy in first line palliative treatment is considered to be more toxic and should be reserved for patients in need for a volume response, e.g. in case of severe symptoms.

Based on an encouraging objective response rate of 60% in the uLMS subgroup treated with the combination of doxorubicin and trabectedin in a non-randomised phase II trial (Pautier et al., 2015), a phase III trial; combining doxorubicin plus trabectedin versus doxorubicin followed by trabectedin in uterine or soft tissue leiomyosarcoma...
patients is currently in preparation [NCT02997358]. Recently, a randomised phase II study of Martin-Broto et al. (2016) with the same combination in STS patients versus doxorubicin was closed because of futility after interim analysis.

3.2.2. Efficacy of chemotherapy after failure of the first line

Multiple trials have been performed in second line and further. The results are summarized in Table 2. Proportions of (u)LMS patients in US or STS trials have been mentioned but should be interpreted with caution since these trials were not powered for subgroup analyses. The results do not warrant a different approach for uterine sarcomas as for STS in general, although details may be slightly different. Again, ifosfamide is less frequently used in (u)LMS both in first as well as in second line (Ray-Coquard et al., 2016). Trabectedin (Pautier et al., 2011; Schoffski et al., 2016) is the most frequently used drugs. A direct comparison has been made in a phase III trial with trabectedin vs. dacarbazine in patients with leiomyosarcomas and liposarcomas in third line and further (Demetri et al., 2016). A total of 518 patients were enrolled and randomly assigned to either trabectedin (n = 345) or dacarbazine (n = 173). Median PFS for trabectedin vs. dacarbazine was 4.2 vs. 1.5 months; hazard ratio, 0.55; P < .001). In the pre-defined sub-analyses all subgroups benefited from trabectedin, although the benefit was not statistically significant in all these subgroups. The interim analysis of OS (64% censored) demonstrated a non-significant 13% reduction in risk of death in the trabectedin arm compared with dacarbazine (median OS for trabectedin v dacarbazine, 12.4 v 12.9 months; hazard ratio, 0.87; P = .37). In a post hoc subset analysis of the uLMS cohort of this trial, trabectedin treatment resulted in significantly longer PFS versus dacarbazine (4.0 vs. 1.5 months), without difference in OS (14.4 v 12.9 months). Objective response rate was 11% with trabectedin vs. 9% with dacarbazine (P = .82) and clinical benefit rate for trabectedin was 31% vs. 18% with dacarbazine (P = .05) (Hensley et al., 2017).

Despite the negative results for leiomyosarcoma in the recently published phase III eribulin trial, the results of the comparator dacarbazine arm are interesting (Schoffski et al., 2016). A total of 452 patients with intermediate-grade or high-grade advanced liposarcoma or leiomyosarcoma (28–30% uLMS) who had received at least two previous systemic regimens for advanced disease (including an anthracycline) were 1:1 randomized to eribulin mesilate or dacarbazine (850–1200 mg/m² intravenously on Day 1) every 21 days until disease progression. OS was significantly improved in patients assigned to eribulin compared with those assigned to dacarbazine (median OS 13.5 v 11.5 months; hazard ratio 0.77). This OS benefit was only seen in liposarcoma patients (median OS 15.6 months v 8.4 months, respectively) and not in those with leiomyosarcoma (12.7 v 13.0 months). Median PFS was similar in both treatment groups: 2.6 months. Remarkably, this trial confirms the activity of dacarbazine in leiomyosarcoma by its relatively long survival of LMS patients who were included in a third line or higher trial. Temozolomide, the prodrug of dacarbazine, has been reported to induce some (partly prolonged)

responses in a retrospective series of in total 19 patients (Anderson and Aghajanian, 2005).

Due to its rarity, the data on chemotherapy in metastatic ESS are sparse. For both ESS and HGUS, no specific conclusions can be withdrawn due to the lack of evidence.

3.2.3. Conclusion chemotherapy—metastatic setting

Most trials focused on STS or (u)LMS, and rarely include patients with ESS or HGUS. By evidence and efficacy, first line treatment of choice still remains doxorubicin (+/− olaratumab if available) or perhaps doxorubicin-dacarbazine in case of the need of combination therapy. Within the next few years, the results of the ongoing phase III trials may (or may not) change this into doxorubicin-olaratumab or maybe doxorubicin-trabectedin. After first line therapy, many drugs have some activity but in general the prognosis remains poor. Choice of treatment in this setting includes consideration of toxicity profile and patient preference. Trabectedin, dacarbazine and gemcitabine based chemotherapy are active options. Clinical trial options should always be considered.

3.3. Other, non cytotoxic, systemic therapy in second line and further

Many cancer patients benefit from the big breakthroughs of the past few years, such as immunotherapy and targeted therapy. Unfortunately, this is not the case for uterine sarcomas.

3.3.1. Immunotherapy

Only a limited number of studies have been performed to assess efficacy in uterine sarcomas (Table 3). Uterine LMS exhibit moderate immunohistochemical expression of PDL1 (46.9%) and PDL1 (36%) (Herzog et al., 2015). Only one phase II trial and only one case report on immunotherapy in uterine sarcomas have been published so far (George et al., 2017; Ben-Ami et al., 2017). In twelve uLMS patients treated with PD-1 inhibitor nivolumab 3 mg/kg every two weeks, no objective responses were found and median PFS was only 1.8 months. Due to a lack of clinical benefit the second part of the study wasn’t opened. Archival samples were available for 83% of patients. PD-1 (> 3% of cells), PD-L1, and PD-L2 (> 5% and > 10% of tumour cells, respectively) expression were observed in 20%, 20%, and 90% of samples, respectively (Ben-Ami et al., 2017). Very recently, a phase II trial testing nivolumab in all types of uterine cancer, including uLMS, HG-ESS and HGUS, started recruitment (NCT03241745).

Other ongoing immunotherapy studies are not specifically focused on uterine sarcomas. An active phase II study is investigating the role of the anti-PD-1 antibody, pembrolizumab, in patients with advanced soft tissue and bone sarcomas (NCT02301039). Furthermore, a phase I–II trial combining pembrolizumab with doxorubicin in advanced or metastatic STS is open (NCT02888665), as is a phase II study of Tali mogene Laherparepvec (T-VEC) combined with pembrolizumab (NCT03069378). In the neoadjuvant setting, anti-PD-L1 (Durvalumab/MEDI4736) plus anti-CTLA-4 (Tremelimumab) and radiation is tested for high risk STS (NCT03116529). The combination of tyrosine kinase

Table 3

Systemic non-cytotoxic treatment trials in advanced or metastatic uterine sarcomas.

<table>
<thead>
<tr>
<th>Population</th>
<th>n (%(u)LMS)</th>
<th>RR (%)</th>
<th>3mo PFR (%)</th>
<th>6mo PFR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nivolumab (Ben-Ami et al., 2017)</td>
<td>uLMS</td>
<td>12</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>1.8</td>
</tr>
<tr>
<td>pazopanib (Benson et al., 2016)</td>
<td>US</td>
<td>44</td>
<td>11</td>
<td>–</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>regorafenib vs. placebo (Mir et al., 2016)</td>
<td>STS, 1 cohort LMS</td>
<td>56 LMS of who 22 uLMS</td>
<td>0</td>
<td>57 vs. 25</td>
<td>21 vs. 7</td>
<td>3.7 vs. 1.8</td>
</tr>
<tr>
<td>sintinib (Hensley et al., 2009b)</td>
<td>uLMS</td>
<td>23</td>
<td>8.7</td>
<td>–</td>
<td>17.4</td>
<td>1.5</td>
</tr>
<tr>
<td>thalidomide (McMeekin et al., 2007)</td>
<td>uLMS</td>
<td>30</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>1.9</td>
</tr>
<tr>
<td>alfilercept (Mackay et al., 2012)</td>
<td>uLMS</td>
<td>41</td>
<td>0</td>
<td>–</td>
<td>17</td>
<td>1.8</td>
</tr>
<tr>
<td>aliserterib (Hyman et al., 2018)</td>
<td>uLMS</td>
<td>21</td>
<td>0</td>
<td>–</td>
<td>0</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Mi, median; mo, months; RR, response rate; PFS, progression free survival; OS, overall survival; US, uterine sarcomas, uLMS, uterine leiomyosarcoma, LMS, leiomyosarcoma, STS; soft tissue sarcoma.
inhibitor axitinib and pembrolizumab is currently tested in specific types of STS, including LMS after failure of anthracyclines (NCT02636725). As a first line therapy, the combination of trabectedin, nivolumab and anti-CTLA-4 ipilimumab is under investigation in a dose finding phase I–II study for advanced STS (NCT03138161).

3.3.2. Targeted therapy

Targeted therapy refers to systemic therapy directed to specific elements or pathways crucial for cancer cells to survive. Only results of a few trials or subgroup analyses in uterine sarcomas are available (Table 3). Some categories of targeted therapy can be distinguished:

3.3.2.1. Tyrosine kinase inhibitors directed against a.o. vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR). A subgroup analysis on 34 patients with uterine sarcomas treated the phase II pazopanib trial or PALETTE trial showed a response rate of 11%, median PFS of 3.0 months and OS of 11.1 months, which was worse compared to the non uterine STS types (mPFS 4.5 months, mOS 17.5 months) (Benson et al., 2016). A randomized phase II study comparing pazopanib combined with gemcitabine to gemcitabine-docetaxel in STS is currently ongoing (NCT01953748). Sunitinib 50 mg OD 4 weeks on–2 weeks of, failed to achieve a sufficient number of objective responses (8.7%) or sustained disease stabilization (mPFS 1.5 months and 6 months PFS rate 17.4%) as second- or third-line treatment for uterine leiomyosarcoma (Hensley et al., 2009b). Cabozantinib, targeting MET as well as VEGFR, is currently under investigation as maintenance therapy after chemotherapy in metastatic HGUS, adenosarcomas, and HG ESS (NCT01979393).

3.3.2.2. VEGF trap/antibody. VEGF trap afibercept 4 mg/kg iv every 2 weeks showed similar disappointing results in patients with uLMS or carcinosarcomas of the uterus: no objective responses were observed, median PFS was 1.8 months and the 6 months PFS was 17% (Mackay et al., 2012). The addition of VEGF antibody bevacizumab to gemcitabine-docetaxel did not improve outcome (Hensley et al., 2015).

3.3.2.3. PDGFR antibody. As described above, in a randomized phase II trial, addition of PDGFR antibody olaratumab improved OS by more than 10 months (Tap et al., 2016). The phase III trial is ongoing (NCT02451943). Currently, the addition of olaratumab to gemcitabine-docetaxel is investigated in a phase Ib-II trial in STS (NCT02659020).

3.3.2.4. Other targets. Although the PI3K/mTOR pathway has been recognised as a potential target for uLMS in preclinical work, no series or (ongoing) trials have been found for US (Cuppens et al., 2017a). The same is the case for VIPR2, a gene affected in 96% of uLMS samples which seems to act as a tumour suppressor gene (Cuppens et al., 2017b).

3.3.2.5. Epigenetic modulators. Histone deacetylase inhibitor panobinostat in a phase II trial for STS with 10 LMS and 3 ESS patients did not result in any objective responses but 2/10 LMS and 2/3 ESS patients had prolonged stable disease for more than six months. Panobinostat was poorly tolerated with the need of dose reduction in up to one third of the patients due to thrombocytopenia, anaemia, lymphocytopenia, fatigue and Qtc prolongation (Cassiller et al., 2013). Aurora A kinase inhibitor alisertib was not effective in 21 uLMS patients as no objective responses or prolonged stable disease were seen. Median PFS and OS were 1.7 and 14.5 months, respectively (Hyman et al., 2017).

In conclusion, currently, with respect to targeted agents, only pazopanib has a place in the treatment of US after failure of at least anthracyclines. Based on promising phase II results and awaiting the outcome of the phase III study, in some countries olaratumab can be added to doxorubicin in first line treatment.

4. Future directions and conclusion

Uterine sarcomas encompass a rare group of diseases with a dismal prognosis of aggressive subtypes. For the choice of systemic treatments, part of the difficulty is the recognition of the specific subtype of uterine sarcoma and an adequate pathology diagnosis, including molecular analyses. Very recently, new genetic and immunological differences between uLMS, ESS and HGUS were shown. Gene expression and immunohistochemical analyses revealed the presence of high numbers of tumour-associated macrophages (TAMs) in HGUS, which makes HGUS patients suitable candidates for therapies targeting TAMs. Furthermore, a high genomic instability of HGUS and downregulation of several TP53-mediated tumour suppressor genes, such as ND, CDH11, and NDRG4 were proven. Moreover, it was demonstrated that HGUS carry somatic mutations in several oncogenes and tumour suppressor genes implicated in RAS/PI3K/akt/mTOR, ERBB3, and Hedgehog signaling for which targeted therapies exist (Przybyl et al., 2017).

After the primary diagnosis and treatment by gynaecologists and their multidisciplinary teams, early involvement of sarcoma specialists is necessary. Many centres are only treating a few patients per year. All together, this makes it difficult to improve the diagnostic and treatment trajectory of US patients. Centralisation of care and the timely collaboration between gynaecological oncologists and sarcoma specialists might help to deliver the best knowledge, experience and trial availability to US patients. By now, despite many attempts to improve the outcome by systemic treatments, the prognosis, both after primary diagnosis and in case of metastatic disease, remains poor. The observation of heterogeneity within uterine sarcoma subtypes warrants a personalised treatment approach. Further studies with realistic analysis of patients numbers are needed to improve patient outcome. Given the experiences so far, this is a challenge at a global level.

Conflicts of interest statement

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