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DRUG EVALUATION

Pazopanib in patients with advanced intermediate-grade or high-grade liposarcoma

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ABSTRACT

Introduction: Liposarcomas (LPS) are a heterogeneous group of adipocytic soft tissue sarcomas with limited treatment options in the advanced/metastatic setting. Pazopanib is a multi-target tyrosine kinase inhibitor (TKI) with anti-angiogenic and antitumorigenic properties. Whilst targeted agents including TKIs have been extensively studied in other solid tumors and the sarcoma subtype gastrointestinal stromal tumor (GIST), we currently lack effective treatments for the liposarcoma subtype. Several phase II and III studies of oral TKIs in soft tissue sarcomas have excluded liposarcoma because of a reported lack of activity following the EORTC 62043 study.

Areas: We review the use of pazopanib in advanced intermediate and high-grade liposarcomas where complete surgical resection is not possible.

Expert opinion: The current clinical and pharmacological data demonstrate the efficacy of pazopanib in soft tissue sarcomas, but new data suggest that anti-angiogenic agents may have limited activity in liposarcoma. Anti-angiogenic TKIs are generally well tolerated and liposarcomas vary in their response to systemic chemotherapy; hence, there is a role for further exploration of the efficacy of this treatment amongst the histological subtypes of liposarcoma. This affords further understanding of biomarkers which may be associated with response to pazopanib and other anti-angiogenic TKI treatments.

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Liposarcomas; Pazopanib; tyrosine kinase inhibitor; soft tissue sarcomas; angiogenesis; targeted therapy

1. Introduction

Liposarcomas (also known as adipocytic soft tissue sarcomas) are a histological subtype of soft tissue sarcomas. The incidence of liposarcoma in the United States is 0.59 per 100,000 age-adjusted person-years based on data from 1978 to 2001 in the United States [1], and 0.62 per 100,000 population age-standardised in the United Kingdom from 2008 to 2010 [2]. However, incidence in the United Kingdom is reported to have increased by approximately 30% since 1996 and it is therefore likely that incidence in 2019 is higher [2]. There is male predominance and 5-year survival is approximately 50–90% (50% for pleomorphic liposarcomas and 90% for WDLPS) [3].

Liposarcomas arise from adipocyte tissue in any part of the body; however, these tumors usually originate in the retroperitoneum and proximal regions of the limbs. They are classified into several histopathological subtypes. These subtypes include well-differentiated (WDLPS)/de-differentiated liposarcoma (DDLPS), myxoid/round cell and pleomorphic liposarcoma. WDLPS and DDLPS have distinct histological features but can be considered part of a spectrum, frequently displaying features of both subtypes within the same mass. WDLPS/DDLPS are the most common subtype of liposarcoma, representing 50–60% [4]. Myxoid/round cell liposarcoma is seen in approximately 30–40% of all liposarcomas which are also considered as part of a spectrum of tumors with distinct histological features. The remaining 5–10% of liposarcomas is pleomorphic. As well as histopathological subtype, these tumors are also classified according to grade (high, intermediate and low grade) which corresponds to the anticipated clinical behavior of the tumor [5].

The current standard of care for patients with intermediate and high-grade liposarcoma includes complete resection for localized disease where clear margins are possible, with or without radiation. In locally advanced, recurrent or metastatic disease, management is tailored to the individual taking into consideration the tumor size and anatomical location as well as patient factors [6]. Outcomes in surgical re-excision of relapsed disease are poor with approximately 30% overall survival (OS) at 5 years [7].

Systemic chemotherapy may also be offered to patients with advanced or metastatic intermediate or high-grade liposarcoma. Single-agent doxorubicin remains the first line treatment after neither combination anthracycline and ifosfamide [8] nor high dose single-agent ifosfamide [9] were able to demonstrate superiority in OS. However, there was a longer progression-free survival (PFS) and higher response rate with combination anthracycline and ifosfamide but with a significant increase in grade 3–4 toxicity [9]. Two multicentre randomized phase III trials have shown both trabectedin [10] and eribulin [11] to have activity in intermediate and high-grade liposarcoma compared to dacarbazine. In the analysis of the liposarcoma subgroup in the eribulin phase III trial, there was a significant improvement in median OS among all liposarcoma subtypes (15.6 months vs 8.4 months, respectively, p = <0.001) as well as PFS (2.9 vs 1.7 months, p = 0.0015) without an increase in toxicity [12].

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Article highlights

- Pazopanib is an oral multi-target tyrosine kinase inhibitor (TKI) with anti-angiogenic and anti-tumourigenic properties used in a range of soft tissue sarcomas.
- Pazopanib was deemed inactive in liposarcomas based on preliminary results of a phase II study where it did not meet the predefined criteria for accrual into the second stage of the study.
- Pazopanib was therefore excluded from the subsequent phase III study of pazopanib in soft tissue sarcomas. However, in the final analysis of the antecedent phase II study, pazopanib did meet the predefined criteria in liposarcoma, therefore the opportunity to investigate its activity in this subtype was missed.
- Pazopanib is well tolerated and demonstrates improved haematological toxicity profile compared to existing systemic anticancer treatments.
- Phase II data supporting the use of pazopanib in intermediate and high grade liposarcoma are mounting and phase III studies in selected histological subtypes are warranted.

Box 1. Drug summary

Drug name (generic)	Pazopanib
Phase (for indication under discussion)	Phase II
Indication (specific to discussion)	Intermediate and high-grade liposarcomas
Pharmacology description/ mechanism of action	Pazopanib is a multi tyrosine kinase inhibitor that inhibits tumor angiogenesis. This is mediated via several growth factor receptors such as VEGFR, PDGFR and FGFR.
Route of administration	Oral
Chemical structure	$C_{21}H_{23}N_7O_2S$
Pivotal trial(s)	[19,20,33]

CDK inhibitors, which target the CDK amplification seen in approximately 90% of WDLPS/DDLPS, have also shown promising results in the phase II trial of palbociclib in liposarcoma [13]. Studies of other CDK inhibitors in liposarcoma include ribociclib [14] and abemaciclib [14,15].

2. Body of review

2.1. Overview of the market

2.1.1. Unmet needs of currently available therapies

However, response to systemic chemotherapy varies among the histological subtypes as well as among grades [16]. Due to the heterogenicity of DDLPS/WDLPS tumors, response to chemotherapy may vary according to the tumor components; those with a predominance of DDLPS component typically respond better than those with predominant WDLPS component. Response to chemotherapy is reported between 11% and 24% [4,16,17]. There are limited data supporting the use of chemotherapy in pleomorphic liposarcoma; and objective response rates are reported as 33–37% based on retrospective studies [16,18], whilst myxoid/round cell liposarcomas are typically more responsive to systemic chemotherapy [16]. There is therefore an unmet need for effective, well-tolerated treatments in this sarcoma subtype and the aim of this manuscript is to review the existing evidence for the use of pazopanib in this rare tumor.

The multicentre phase III placebo-controlled randomized PALETTE trial demonstrated an increase in median PFS in soft tissue sarcoma patients treated with pazopanib (4.6 months) compared to placebo (1.6 months) ($p < 0.0001$) [19]. However, the PALETTE trial excluded liposarcomas due to the antecedent EORTC 62043 phase II study where pazopanib was deemed inactive in liposarcomas based on pre-defined progression-free rate (PFR) at 12 weeks of >20% in the first stage of the study [19,20]. PFR at 12 weeks in the first stage of the liposarcoma arm of the EORTC 62043 was only 3/17 patients (17.6%), which was insufficient to enable accrual into the second stage of the study. However, following a centralized histopathological review, several patients were re-assigned to the liposarcoma cohort and PFR at 12 weeks would have been met in 5/19 patients (26.%) and liposarcoma would have been included in the second stage of the study [20]. Had liposarcomas not been deemed inactive based on the results of the first stage of the EORTC 62043 study [20], liposarcomas may have been included in the subsequent PALETTE trial [19]. The SPIRE study performed a retrospective review of 211 patients treated with pazopanib via an expanded access scheme. All patients were heavily pretreated, however, since the study mirrored the PALETTE trial inclusion and exclusion criteria, liposarcomas were also excluded in this study [19,21].

2.1.2. Competitor compounds/classes of compounds are in the clinic/late development

TKIs have also been under investigation for use in a range of soft tissue sarcomas in phase II trials including liposarcoma such as axitinib in the Axi-STS trial [22] sunitinib [23], anlotinib [24] and regorafenib in the REGOSARC trial [25]. None are currently licenced for use in liposarcoma.

2.2. Introduction to the compound

Pazopanib (VOTRIENT®) is an oral TKI with anti-angiogenic effect which is used in the treatment of several solid tumors including renal cell carcinoma [26]. Pazopanib possesses both antitumorigenic and anti-angiogenic properties. Its anti-angiogenic effect is mediated via semi-selective inhibition of growth factor receptors including VEGFR, PDGFR, FGFR, c-kit. These proteins are also known as tyrosine kinase receptors and may be mutated or upregulated in certain tumor cells, which along with other mechanisms, enables the tumor to undergo rapid and uncontrolled growth and cell proliferation [27]. Pazopanib is a synthetic agent from the indazolyl pyrimidines class. It is only slightly soluble at pH values <4 but is otherwise an insoluble hydrochloride salt and highly plasma protein bound (>99%) to circulating albumin [28].

In vitro studies of pazopanib have demonstrated an affinity for inhibition of the tyrosine kinase receptors. These tyrosine kinase receptors include VEGFR types 1, 2 and 3, PDGFR α and β, c-Kit and FGFR1 types 3 and 4, and the greatest receptor affinity is displayed with VEGFR types 1, 2 and 3. *In vivo* studies of pazopanib in animal models in a range of tumor xenografts have demonstrated dose-dependent relationship between pazopanib and its antitumor activity. In mouse studies, maximal inhibition of VEGFR was achieved at a concentration of

approximately 40 µmol/L. In pharmacokinetic studies of 10 participants at 800 mg terminal elimination half-life of pazopanib at this dose was 31.1 h, thus there was accumulation at repeated daily dosing leading to steady state at day 22. Excretion of pazopanib is found to be predominantly via the gastrointestinal tract (82.2%) in pharmacokinetic studies and <5% is thought to be renally excreted [28,29].

In a 2014 animal study, patient-derived DDLPS orthotopic xenografts were implanted into nude mice. Mice were either treated with sterile water, single agent doxorubicin, single agent pazopanib or combination doxorubicin and pazopanib. There was a reduction in tumor growth in mice treated with either single agent pazopanib and combination doxorubicin and pazopanib, however, combination treatment did not improve efficacy above that of single agent pazopanib [30]. In a 2018 animal study, a patient-derived orthotopic xenograft was formed by implantation of doxorubicin-resistant pleomorphic liposarcoma onto the biceps femoris of nude mice. The xenografts were then either treated with pazopanib, temozolomide, doxorubicin or no treatment. There was a statistically significant reduction in the size of the implanted tumor as well as extensive tumor necrosis in the mice treated with pazopanib compared to the untreated mice ($p = 0.0008$) [31].

2.3. Clinical efficacy

2.3.1. Phase I studies

The first dose escalation study of pazopanib enrolled 43 patients with a range of solid tumors (including renal cell carcinoma, melanoma, lung, and soft tissue sarcomas). The patients were treated with pazopanib doses increasing from 50 mg three times weekly to 2000 mg daily in cohorts. The primary endpoint was safety whilst secondary endpoints included biomarkers and clinical efficacy. Frequently reported toxicities of grade 3–4 were nausea (n = 1), fatigue (n = 1), hypertension (n = 6) and vomiting (n = 1). Hypertension was dose dependent but responded to treatment discontinuation and standard anti-hypertensive treatment in all cases [32]. The study subsequently recruited to a dose expansion phase of pazopanib at doses of 300 mg twice daily and 800 mg once daily in a further 20 patients, all with solid tumors. Toxicities were reported in similar frequencies as in the dose escalation study – the majority of which was grade 1–2. Dose-limiting toxicity was seen in four participants in daily dosing of 50 mg, 800 mg, and 2000 mg. The drug reached steady state in doses ≥800 mg daily and clinical benefit was seen in doses ≥800 mg once daily or 300 mg twice daily. Three patients had partial response, and 14 patients had stable disease lasting >6 months. Among the cohort of patients with soft tissue sarcomas, 3/8 (37.5%) maintained stable disease for >6 months (chondrosarcoma (n = 1), leiomyosarcoma (n = 1) and GIST (n = 1)). Although maximum tolerated dose was not reached within this study, steady-state exposure of pazopanib plateaued at doses >800 mg; therefore, this was the dose selected for ongoing clinical studies [32].

2.3.2. Phase II studies

The phase II EORTC 62043 study assessed pazopanib in several soft tissue sarcoma subtypes including liposarcoma. In this study, pazopanib was deemed inactive in liposarcomas, based on the predefined study requirement that pazopanib should achieve a PFR at 12 weeks of >20% in any subtype of sarcoma for that subtype to continue to full accrual in the trial [20]. The phase III PALETTE trial excluded liposarcomas on this basis [19]. However, in the final analysis of the EORTC 62043 study, two patients were reclassified into the liposarcoma cohort from another cohort after central pathological review, therefore, 5/19 liposarcoma patients (26.3%) met the primary endpoint at the end of the trial [20].

Despite the preliminary findings of pazopanib inactivity for liposarcoma in the EORTC 62043 study, a phase II multicentre study evaluated the use of pazopanib in 41 patients with advanced and metastatic intermediate-grade or high-grade liposarcoma. Participants were treated with once-daily pazopanib at a dose of 800 mg in 28-day cycles until disease progression which was evaluated every three cycles. The primary endpoint was PFR at 12 weeks, and secondary endpoints were safety and tolerability. Overall median PFR at 12 weeks was 4.4 months with OS of 12.6 months. The 41-patient cohort was comprised of 27 patients with DDLPS, 12 patients with myxoid liposarcoma, 2 patients with pleomorphic liposarcoma, whilst WDLPS was excluded from study recruitment. PFR at 12 weeks for DDLPS was 20/27 patients (74.1%) and for myxoid LPS 8/12 patients (66.7%). Subgroup analysis of the pleomorphic liposarcoma group was not considered due to the small group size [33].

A further phase II trial also explored the use of pazopanib in patients with advanced intermediate or high-grade liposarcoma and results were presented ahead of publication in 2016. Fifty-two patients were recruited, divided into two cohorts (WDLPS/DDLPS and myxoid/round cell) with pleomorphic LPS excluded. Primary endpoint was PFS at 12 weeks. The myxoid/round cell cohort was closed to recruitment early after 15 patients due to failure to meet the primary endpoint, whilst in the WDLPS/DDLPS subgroup, 43.2% of patients met the primary endpoint. In the WDLPS/DDLPS subgroup, median PFS and OS was 3.5 and 16.4 months, respectively; whilst in the myxoid/round cell cohort it was 1.99 and 22.3 months, respectively. However, no objective response as per RECIST 1.1 was demonstrated on local review and final results are awaited [34].

The provisional results of the phase II randomized EPAZ trial were recently presented ahead of publication. The study compared the efficacy of pazopanib to single-agent doxorubicin in elderly patients with locally advanced and metastatic soft tissue sarcomas, including liposarcomas. The primary endpoint of the study was non-inferiority of pazopanib to doxorubicin and secondary endpoints included OS, toxicity, and quality of life assessments. One hundred and twenty patients were randomized in a 2:1 ratio to pazopanib and doxorubicin, respectively. For both PFS and OS, pazopanib showed non-inferiority compared to doxorubicin in this cohort with similar quality of life measure outcome, however, with the benefit of an absence of hematological toxicity in the pazopanib cohort [35].

2.3.3. Phase III studies

There are currently no published phase III studies which investigate the use of pazopanib in the treatment of liposarcomas.

2.3.4. Post-marketing studies

A multicentre retrospective review of post-marketing surveillance data of patients treated with pazopanib for soft

tissue sarcoma identified 156 patients across 37 Japanese institutions. Pazopanib has been licenced for use in pre-treated liposarcoma in Japan despite exclusion from the PALETTE trial. The primary endpoint of this study was to evaluate the efficacy of pazopanib in soft tissue sarcomas outside the setting of a clinical trial. Secondary endpoints included safety, PFS and radiological response to pazopanib. Mean follow up after the commencement of pazopanib was 11.4 months. Of the 32 included patients with liposarcoma, 17 had DDLPS, 11 myxoid liposarcoma and 4 had pleomorphic liposarcoma. Average dose was 609 mg, with grade 3–4 events reported in 48/156 (30.8%) of participants, of which hypertension was the most frequently seen (10/156 participants). Pneumothorax (8/156 participants), liver dysfunction (8/156 participants), thrombocytopaenia (8/156 participants) grade 3–4 were also frequently observed. Adverse events of any grade occurred in 127/156 participants (81.4%) resulting in nearly half of the study cohort (70/156) requiring a dose reduction whilst on treatment. Thirty-one patients were not eligible for evaluation of tumor response (as per RECIST criteria) due to early discontinuation of pazopanib (n = 14), clinical progression (n = 9) and hospital admission (n = 8). 87/125 patients (69.6%) had a partial response or stable disease. However, only 3/22 (14%) of patients with liposarcoma achieved at least stable disease with a median PFS of 8 weeks compared to 17.7 weeks in all sarcoma tumor types [36].

2.3.5. Other studies of interest

In the multicentre phase, II REGOSARC trial 182 patients with anthracycline pre-treated soft tissue sarcomas were randomized in a 1:1 ratio to receive the oral TKI regorafenib or a placebo. The primary endpoint was PFS according to RECIST. Although there was a statistically significant improvement in PFS in the synovial sarcoma cohort compared to placebo, this was not seen in liposarcomas, where PFS was 1.1 months with regorafenib and 1.7 months with placebo (p = 0.07). Results for a further arm which compares the above cohorts of patients who have received prior treatment with pazopanib are awaited [25].

Two other anti-angiogenic TKIs have also recently demonstrated efficacy in a range of soft tissue sarcomas including liposarcomas. A phase II single center study in the United States treated 48 patients with advanced soft tissue sarcomas with sunitinib. PFS in the liposarcoma cohort was 3.9 months with OS 10.1 months warranting further investigation in a phase III trial [23]. Results of the safety and efficacy phase II trial of anlotinib in soft tissue sarcomas were recently published. The primary endpoint was PFS at 12 weeks, with anlotinib deemed an active second-line agent in soft tissue sarcomas if $PFS_{12\ weeks}$ was greater than 40%. In the study, PFS at 12 weeks was observed in 68% of all sarcoma subgroups (n = 166) and in 63% of patients with liposarcoma (n = 13), whilst overall median PFS across all sarcoma subgroups was 5.6 months with a median PFS in the liposarcoma subgroup of also 5.6 months. Median OS was 12 months across all subgroups and 13 months in the liposarcoma cohort [24].

2.4. Safety and tolerability

The toxicity profile of pazopanib is comparable to other oral TKIs. The most frequently reported toxicity is hypertension which is dose dependent and may be present in up to 80% of patients treated with pazopanib. It is mediated via a reduction in nitric oxide and an increase in endothelin production within the vascular endothelium leading to vasoconstriction [37]. Other toxicities commonly reported in pazopanib use include reductions of ≥15% in left ventricular ejection fraction (10% of patients), dysrhythmias (<5% of patients) hair depigmentation (40% of patients) and hypothyroidism (<10% of patients) [26,38,39].

Hepatotoxicity from pazopanib is frequently reported, and it is thought that grade 1–2 hepatotoxicity occurs in 30–50% of patients, whereas grade 3–4 hepatitis occurs in <10% of patients. A meta-analysis of fatal hepatotoxicity in patients treated with pazopanib treated in 10 clinical trials found an incidence of <1% and relative risk 2.51 (p = 0.55). Onset of hepatotoxicity is typically within 4 months of commencing pazopanib and requires careful monitoring, dose reduction and treatment discontinuation in certain cases [40].

2.5. Regulatory affairs

Currently, there are no randomized data to support the regulatory approval of pazopanib for any liposarcoma subtype. Pazopanib and other anti-angiogenic agents are currently only used within the context of clinical trials for the treatment of liposarcomas.

2.6. Conclusion

Although currently used for a range of pre-treated soft tissue sarcomas, the role of pazopanib in intermediate and high-grade liposarcomas remains unclear and requires further investigation in phase III studies. A summary of published trial data specific to the use of pazopanib in liposarcoma can be found in Table 1. Provisional data from the EORTC 62043 study [20] demonstrated a lack of efficacy in pazopanib to treat liposarcomas which led to exclusion of the liposarcoma subtype from the phase III PALETTE study [19]. However, following reclassification of two patients in the EORTC 62043 study, the liposarcoma cohort would have met the predefined study requirement that pazopanib should achieve a PFR at 12 weeks of >20%, warranting further phase III study [20].

Activity of pazopanib against liposarcoma is supported by animal studies in DDLPS [30] and pleomorphic [31] orthotopic xenografts. A phase II multicentre study of pazopanib in patients with advanced and metastatic intermediate-grade or high-grade liposarcomas was also supportive of pazopanib efficacy in the DDLPS and myxoid LPS subtypes [33]. However, another phase II trial of pazopanib in liposarcomas closed their myxoid/round cell cohort to recruitment early due to failure to meet the primary endpoint, whilst in their WDLPS/DDLPS subgroup, 43.2% of patients met the primary endpoint

Table 1. Summary of published trial data specific to the use of pazopanib in liposarcoma.

	Phase	Number of LPS patients enrolled and histological subtype	Starting dose of pazopanib	Primary endpoint	Study conclusion	Study supports the utility of pazopanib in LPS?
EORTC 62043 trial [20]	II	n = 17	800mg	PFRat 12 weeks	LPS arm closed to recruitment early due to failure to meet primary endpoint*	All subtypes – no
Nakamura et al 2016 [36]	Post marketing	n = 32 DDLPS = 17 Myxoid = 11 Pleomorphic = 4	800 mg (n = 112) 600 mg (n = 12) 400 mg (n = 15) 200 mg (n = 17)	Efficacy of pazopanib	DDLPS – Median PFS 8 weeks Myxoid – median PFS 8.3 weeks Pleomorphic – not evaluable	DDLPS – no Myxoid – no
Valverde et al 2016 [34]	II	n = 52 WDLPS/DDLPS – 37 Myxoid/round cell – 15	800mg	PFR at 12 weeks	WDLPS/DDLPS – median PFS 3.5 months, median OS 16.4 months Myxoid/round cell – closed to recruitment early due to failure to meet primary endpoint median PFS 1.99 months, median OS 22.3 months	WDLPS/DDLPS – yes Myxoid/round cell – no
Samuels et al 2017 [33]	II	n = 41 DDLPS – 27 Myxoid – 12 –	800mg	PFR at 12 weeks	DDLPS – 74.1% (20/27 patients) met primary endpoint Myxoid – 66.7% (8/12 patients) met primary endpoint	DDLPS – yes Myxoid – yes

Progression free rate (PFR), LPS = liposarcoma (LPS), de-differentiated liposarcoma (DDLPS), Progression free survival (PFS), well-differentiated liposarcoma (WDLPS), overall survival (OS).
*In final analysis two patients were reclassified into the liposarcoma cohort. If they had been correctly assigned, and thus included in the stage I analysis, this would have allowed the liposarcoma cohort to have proceeded to full enrolment in stage II.

[34]. The provisional results of the phase II randomized EPAZ trial are also supportive of the activity of pazopanib in liposarcoma by demonstrating non-inferiority to doxorubicin in elderly patients [35].

However, this activity was not demonstrated in the Japanese post-marketing study where only 14% of patients achieved at least stable disease with a median PFS of 8 weeks, half that of the other sarcoma subtypes [36].

Due to the heterogenicity of liposarcoma histopathological subtypes a variable response to systemic anticancer treatments is expected and it may be possible to explore this further with a biomarker led prospective study.. Given the vast heterogeneity between liposarcoma subtypes and grade, any future studies should ensure they stratify patients according to subtype to determine if there are differences in the response to pazopanib or other targeted agents. However, we are yet to identify a biomarker which can help accurately predict response to pazopanib and other oral TKI agents. This should be a focus on further work so that we can select the correct cohort of patients who will derive benefit from pazopanib.

The toxicity profile and frequency of adverse events with pazopanib have been consistent in all studies of pazopanib in liposarcomas [20,33–36]. However, in these studies, dose reductions are occurring in approximately 50% of patients; therefore, patients are not receiving the 800-mg dose which was established as effective in early studies [32]. However, in the non-trial population, patients are often commenced on a lower starting dose (200–600 mg) or significantly dose reduced at clinician discretion to ensure treatment tolerability. Caution must be taken with the management of toxicities (particularly cardio-toxicity [38] and hepatotoxicity [40]) with appropriate surveillance, prompt treatment, specialist referral and treatment adjustment where required.

In the phase II EPAZ trial of elderly patients, whilst there was no statistical difference in the quality of life measures, there was a significant improvement in hematological toxicity but with a similar burden of non- hematological toxicity compared to doxorubicin [35]. Although further investigation is required, pazopanib is potentially a good alternative option for elderly patients that are unfit for or unable to tolerate other systemic therapies.

Additional advantages of pazopanib compared to available treatments for advanced or metastatic liposarcoma includes oral administration whereas most existing systemic therapies for liposarcoma are delivered intravenously. Oral treatment offers the patient more convenience and flexibility of administration and is less invasive compared to intravenous preparations. Additionally, oral preparations reduce the burden of resources required to deliver the treatment compared to intravenous preparations.

The data to support the use of other TKIs in the treatment of intermediate and high-grade liposarcomas also remains unclear. Although regorafenib in the REGOSARC trial did not meet the primary endpoint of improved PFS vs placebo in the liposarcoma cohort [25], both anlotinib [24] and sunitinib [23] performed well against placebo in the liposarcoma arms of their respective phase II trials. Finally, the role of combination pazopanib and other systemic therapies is currently being

explored further with both topotecan [41] and gemcitabine [42].

3. Expert opinion

The use of pazopanib in treating intermediate and high-grade liposarcoma shows promise [33–35] despite exclusion from the phase III PALETTE study [19] for inactivity in phase II trials [20]. Its main advantage includes its oral route of administration [29] compared to licensed existing systemic treatments which are delivered intravenously and similar quality of life measures to the current first-line treatment with doxorubicin [35]. Improvement in hematological toxicity profile but with a similar burden of non-hematological toxicity compared to doxorubicin makes pazopanib a good alternative for patients unfit for systemic chemotherapy [35].

Whilst pazopanib is unlikely to displace doxorubicin as first-line treatment for intermediate and high-grade liposarcoma [8], it is possible that pazopanib could be used as an alternative to trabectedin [10] or eribulin [11] due to its favorable hematological side effect profile [35].

The risks and benefits of pazopanib have been established in other tumor types [39] therefore oncologists are unlikely to be reluctant to prescribe pazopanib, and many will have experience of using it in other soft tissue sarcomas [19]. However, the evidence for the efficacy of pazopanib in advanced intermediate and high-grade liposarcomas is confined to phase II studies and a post-marketing study. Further evaluation of the DDLPS and myxoid LPS subtypes with a prospective randomized phase III study is required before oncologists will start prescribing pazopanib to patients with liposarcoma. It is possible that in five years time pazopanib will be being studied in a randomized prospective phase III study based on the increasing body of early phase studies supporting its activity.

Finally, there also remains an ongoing unmet need for effective treatments for this subtype of sarcoma and for further options for patients who have exhausted conventional lines of therapy.

In addition to pazopanib, the CDK inhibitor palbociclib has shown promising results in the phase II trial [13] and other CDK inhibitors are currently under early phase investigation for liposarcoma including ribociclib [14] and abemaciclib [15]. It is likely that CDK inhibitors will have a role to play in the management of DDLPS in the future. The oral TKI sunitinib [23] and anlotinib [24] have both also demonstrated efficacy in the phase II trial warranting further investigation in a phase III trial. It is possible that these drugs could be approved for the treatment of intermediate-grade and high-grade liposarcomas.

Declaration of interest

RL Jones has received honoraria and consultation fees from Adaptimmune, Blueprint, Clinigen, Eisai, Epizyme, Daichii, Deciphera, Immunedesign, Lilly, Merck and Pharmamar. He is also a co-inventor on patent applications related to biomarkers of pazopanib response in sarcoma. P Huang is a co-inventor on patent applications related to biomarkers of pazopanib response in sarcoma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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