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Current Perspective

Olaratumab in soft tissue sarcoma – Current status and future perspectives

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Abstract Recent randomised phase II trial data have indicated that the addition of olaratumab, a novel monoclonal antibody against platelet-derived growth factor receptor alpha (PDGFRα), to doxorubicin confers an unprecedented improvement in overall survival to patients with anthracycline-naïve advanced soft tissue sarcoma. However, this result was disproportionate with progression-free survival and response rate, and consequently there are unanswered questions regarding the precise mechanism of action of olaratumab. While preclinical data show that olaratumab specifically inhibits PDGFRα-mediated oncogenic signalling with attendant anti-tumour effects, a lack of correlation between pharmacodynamics markers of PDGFRα inhibition and clinical benefit from olaratumab suggest other mechanisms beyond modulation of downstream PDGFRα molecular pathways. Proposed mechanisms of olaratumab activity include engagement of anti-tumour immune responses and alterations of the tumour stroma, but these require further evaluation. Meanwhile, the drug-specific contribution of cytotoxic agents to olaratumab-containing combinations has yet to be characterised. Ongoing and future preclinical and translational studies, coupled with the anticipated results of a phase III trial that has completed enrolment, should provide greater insight into the efficacy and mode of action of olaratumab in soft tissue sarcomas.

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1. Introduction

Soft tissue sarcomas (STS) are a group of rare and heterogeneous malignant tumours of mesenchymal origin that represent around 1% of adult malignancy and encompass a broad range of clinical phenotype and underlying biology. Doxorubicin-based chemotherapy has been the standard for first-line treatment of advanced STS for decades, with associated median overall survival (OS) consistently reported at 12–18 months [1]. Meanwhile, over 20 years of clinical studies in advanced STS have rarely provided definitive evidence of survival benefit for investigative agents [2–5]. However, in July 2016, a major breakthrough was achieved by the results of the JGDG study. In this open label phase Ib and randomised phase II trial, olaratumab, a monoclonal antibody (mAb) directed against platelet-derived growth factor receptor-alpha (PDGFRα), was combined with standard doxorubicin chemotherapy in anthracycline-naïve advanced STS [6]. In the phase II component, a near-doubling of median OS was seen in patients who received combined olaratumab–doxorubicin, leading to the accelerated approval of olaratumab in this setting. However, a discrepancy between a large improvement in OS and only modest improvement in disease control end-points in the JGDG trial has given rise to unanswered questions regarding the activity of olaratumab. In this perspective article, we outline the therapeutic rationale and clinical data for olaratumab in advanced STS, before exploring potential explanations for the unresolved enigma of an agent that appears to confer a highly significant survival benefit without a corresponding improvement in disease control.

2. Olaratumab: a novel PDGFRα-targeting antibody

PDGFRα is a receptor tyrosine kinase (RTK) that engages downstream pathways that play important roles in mesenchymal stem cell differentiation and vascular endothelial growth factor–mediated angiogenesis [7]. Overexpression and activating mutations of *PDGFRA* in cancer have been shown to contribute to tumour development, proliferation, metastasis and establishment of a tumour-supporting microenvironment [8–10]. In STS, increased tumour expression of PDGFRα corresponds with higher histological grades and poor prognosis [11]. A range of tyrosine kinase inhibitors with activity against PDGFRα have been evaluated in advanced STS, whereas pazopanib attained approval in the post-1st line setting based on phase III trial evidence of progression-free survival (PFS); but not OS benefit over placebo, a number of other related agents have demonstrated generally disappointing efficacy [12,13].

Olaratumab is a human immunoglobulin G subclass 1 mAb with selective, high affinity binding to the extracellular domain of PDGFRα, disrupting receptor-ligand interactions with resulting downregulation of downstream signal transduction [6,7,14]. Olaratumab has *in vitro* and *in vivo* activity in reducing proliferation and progression of numerous cancer cell lines including sarcomas [14,15]. In addition, combination of olaratumab with doxorubicin resulted in greater inhibition of tumour growth compared with doxorubicin alone in xenograft models of human osteosarcoma [16].

Two open-label dose-escalation Phase I studies evaluated olaratumab as a single agent in patients with advanced solid tumours (Table 1). In both the earlier U.S. and later Japanese studies, the drug was well tolerated and without dose-limiting toxicities [17,18] (Tables 1 and 2). No objective radiological responses were observed in either study—a best response of stable disease was seen in 12 (63%) patients in the US phase I, and in 7 (44%) patients in the Japanese trial.

Based on preclinical evidence of potential synergy with doxorubicin, the combination of olaratumab with chemotherapy was investigated in advanced STS in the JGDG study. Fifteen patients were enrolled in the phase Ib component, and all were treated with olaratumab (15 mg/kg on D1+D8 q3w) and doxorubicin (75 mg/m^2 on D1 q3w) for up to eight cycles, with the addition of dexrazoxane during cycles 5–8, at the discretion of the treating investigator. Patients then continued with olaratumab monotherapy until disease progression. Having satisfactorily met the primary safety end-points of the initial phase 1 b stage, the study rolled out to an open-label phase II stage, with patients randomised 1:1 to receive doxorubicin alone or in combination with olaratumab as per phase Ib schedule. The phase II study was designed to detect a 50% improvement in median PFS (hazard ratio [HR] 0.67) with 80% power and two-sided significance level of 0.20.

In the intention-to-treat (ITT) analysis of 133 randomised patients, a significant improvement in the primary end-point of investigator-assessed PFS was seen in the olaratumab–doxorubicin arm, albeit at the prestated significance level (HR 0.672, 95% confidence interval [CI] 0.442–1.021, p = 0.0615), while there was a non-significant increase in objective response rate from 11.9% to 18.2% between control and investigational arms respectively (p = 0.34). However, the 2-month improvement in median PFS (4.1 months in the control arm vs. 6.6 months in olaratumab arm) was dwarfed by a 12-month improvement in median OS (14.7 vs 26.5 months; OS HR 0.46; 95% CI 0.30–0.71; p = 0.0003). OS benefit from olaratumab-containing therapy was seen across all analysed pre-planned and post-hoc subgroups, including prospectively stratified leiomyosarcoma vs. other histological subtype subgroups. Prospective IHC assessment of tumour PDGFRα expression was performed using an assay later recognised as being insufficiently specific. A post-hoc repeat analysis of tumour PDGFRα using a more specific IHC assay found that most enrolled patients' tumours (67%) were PDGFRα negative, whereas PDGFRα expression was not found to be associated with OS or PFS.

Table 1
Summary of selected toxicities from reported clinical trials of olaratumab.

Trial	Phase I single agent olaratumab		Phase I single agent olaratumab		Randomised open-label phase II in anthracycline-naive advanced STS				Randomised open-label phase II in untreated advanced NSCLC			
Arm	Olaratumab (N = 19)		Olaratumab (N = 16)		Olaratumab + doxorubicin (N = 64)		Doxorubicin (N = 65)		Olaratumab + paclitaxel–carboplatin (N = 67)		Paclitaxel–carboplatin (N = 64)	
	Any grade	G3-4	Any grade	G3-4	Any grade	G3-4	Any grade	G3-4	Any grade	G3-4	Any grade	G3-4
Any AEs	18 (95)	1 (5)	16 (100)	1 (6)	63 (98)	51 (80)	64 (98)	45 (69)	67 (100)	54 (81)	64 (100)	40 (63)
TRAEs	8 (42)	1 (5)	8 (50)	1 (6)	33 (98)	43 (67)	63 (97)	36 (55)	NR	NR	NR	NR
SAEs	9 (47)	0	2 (13)	2 (13)	27 (42)	27 (42)	25 (38)	22 (34)	30 (45)	27 (40)	19 (30)	17 (27)
Anaemia	0	0	1 (6)	0	26 (41)	8 (13)	24 (37)	6 (9)	23 (34)	4 (6)	27 (42)	6 (9)
Thrombocytopaenia	1 (5)	0	0	0	NR	NR	NR	NR	29 (43)	9 (13)	15 (23)	3 (5)
Neutropaenia	0	0	1 (6)	0	37 (58)	24 (38)	23 (35)	21 (32)	35 (52)	25 (37)	21 (33)	14 (22)
Febrile Neutropaenia	0	0	0	0	8 (13)	8 (13)	9 (14)	9 (14)	4 (6)	4 (6)	1 (2)	1 (2)
Infusion reaction	2 (11)	0	0	0	8 (13)	2 (3)	0	0	17 (25)	1 (2)	5 (8)	1 (2)
Pyrexia	1 (5)	0	1 (6)	0	15 (23)	0	12 (18)	0	NR	NR	NR	NR
Vomiting	1 (5)	0	0	0	29 (45)	0	12 (18)	0	28 (42)	0	22 (34)	0
Diarrhoea	1 (5)	0	1 (6)	0	22 (34)	2 (3)	15 (23)	0	29 (43)	2 (3)	19 (30)	0
Mucositis	0	0	0	0	34 (53)	2 (3)	23 (35)	3 (5)	19 (28)	1 (2)	10 (16)	0
Fatigue	2 (11)	0	1 (6)	0	44 (69)	6 (9)	45 (69)	2 (3)	43 (64)	7 (10)	33 (52)	2 (3)
Evidence of cardiac dysfunction	NR	NR	NR	NR	15 (23)	1 (2)	11 (17)	0	NR	NR	NR	NR
Other:	**G3:** Raised serum ALP 1 (5) **G1-2:** Constipation 1(5) Chills 1(5) Headache 1(5) Tumour haemorrhage 1(5)		**G3:** Tumour haemorrhage 1 (6) Raised serum AST 1(6) **G1-2:** Proteinuria 4 (25) Raised serum AST 2 (13) Anorexia 1 (6) Constipation 1 (6) Cough 1 (6) Dermatitis 1(6) Hyperglycaemia 1 (6) Rash 1 (6)									

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; AST, aspartate aminotransferase; NR, not reported; SAE, serious adverse event; TRAE, treatment-related adverse event.
Frequency of AEs expressed as number (%).

Table 2
Early-phase clinical trials of olaratumab.

Study	Phase/cohort	Feature	N	Treatment	Dosage (mg/kg)	Schedule
JGDC	Phase I/1	Solid tumour	5	Olaratumab	4	Weekly (4/2)
	Phase I/2		3		8	Weekly (4/2)
	Phase I/3		5		16	Weekly (4/2)
	Phase I/4		3		15	Biweekly
	Phase I/5		3		20	Biweekly
JGDF	Phase I/1 Japanese	Solid tumour	3	Olaratumab	10	D1–D8, q3w
	Phase I/2 Japanese		7		20	Biweekly
	Phase I/3 Japanese		3		15	D1–D8, q3w
JGDG	Phase II/experimental	Soft Tissue Sarcomas	79	Olaratumab + doxorubicine	15 mg/kg + 75 mg/m2	D1–D8, q3w D1, q3w
	Phase II/control		65	Doxorubicine	75 mg/m2	D1–D8, q3w

Abbreviations: STS, soft tissue sarcomas; D, day; q3w, every 3 weeks.

Safety data from the JGDG trial indicated an increased rate of severe toxicity associated with the addition of olaratumab to doxorubicin, with 67% of patients treated in the investigational arm experiencing a grade 3–4 treatment-related adverse event, compared with 55% in the monotherapy arm (Table 1), a difference largely accounted for by an excess of fatigue and haematological toxicity that did not translate into a significant difference in febrile neutropaenia. Of note, there was a small excess of non-severe cardiac dysfunction in the olaratumab arm (23% vs 17%)—the increase in this consolidated cardiac measure was primarily due to a higher incidence of grade 1–2 peripheral oedema. Treatment discontinuations due to toxicity and deaths were infrequent and evenly balanced across both arms. Quality-of-life data were not collected during the JGDG study.

3. Unanswered questions

The efficacy data from the JGDG trial undoubtedly indicate that olaratumab is a promising agent for the treatment of advanced STS. Furthermore, the inclusion of patients with a variety of different STS histotypes and performance status of 2 or less is representative of real-life clinical practice and, with doxorubicin as a comparator, allow for direct conclusions. However, these randomised phase II results must be carefully interpreted, particularly given the lack of intuitive association of an improved life expectancy with increased delay in disease progression. Early-phase studies are subject to selection, surveillance and publication bias, contributing to the frequent failure to replicate early-phase outcomes in subsequent larger randomised studies [19]. Meanwhile, although data are awaited from the ANNOUNCE III study, a subsequent double-blinded phase III trial that mirrors the design of JGDG, a number of key questions regarding olaratumab remain:

1. What is the explanation for the mismatched degree of OS and PFS gains in the JGDG study?

Although PFS is a widely used end-point and accepted by regulatory bodies as a legitimate efficacy measure, it is a subjective measure that is vulnerable to bias in open label trials, a fact that likely contributes to instances of poor correlation between PFS and OS [20]. PFS may underestimate the benefit of treatments associated with unusual patterns of response, such as in the case of immune-mediated pseudo-progression resulting in PFS data significantly underestimating the survival benefit of ipilimumab in advanced melanoma. Data regarding patterns of radiological response to olaratumab-containing treatment are currently not available, but given previously noted inadequacies of RECIST in the assessment of STS and the possibility of an antibody-dependent cell-mediated cytotoxicity (ADCC) component of olaratumab effect, unanticipated phenomena such as immune-related responses cannot yet be ruled out [21].

A recent clinical trial of eribulin, a microtubule inhibitor, in advanced STS reported initial survival data similar to that of the JGDG trial [22]. In this open label phase III RCT, patients with previously treated advanced leiomyosarcoma or liposarcoma were randomised to receive either eribulin or dacarbazine. Results from all 452 randomised patients demonstrated improvement in OS with eribulin (HR 0.77, 95% CI 0.62–0.95, $p = 0.0169$) but no difference in PFS and radiological response rates between the two arms. However, subgroup analysis of this trial has since identified that efficacy of eribulin is largely limited to patients with liposarcoma, in whom HRs for PFS and OS show an almost identical degree of eribulin benefit (HR 0.52 and 0.51 respectively) [23]. Available subtype-specific efficacy data for olaratumab is currently limited, with the JGDG trial reporting no difference in olaratumab benefit between leiomyosarcoma and heterogenous 'other' subgroups. Further analysis of results from the JGDG study and forthcoming phase III data may yet identify a histological subgroup in which olaratumab benefit is enriched. Alternatively, translational studies may identify biologically defined molecular subgroups that transcend histological classifications and exhibit differential sensitivity to olaratumab-based therapy.

Post-trial therapy can introduce imbalances between hitherto controlled trial arms. Systematic biases that see patients from one arm enjoying greater access to effective post-trial treatments could result in divergent OS in the

Table 3
Current trials of olaratumab.

	Title	Phase	Study design	Conditions	Interventions	Recruitment	Study results	URL
1	A study of olaratumab (LY3012207) plus pembrolizumab in participants with advanced or metastatic soft tissue sarcoma	1	Non-randomised Open label	Soft tissue sarcoma	Olaratumab + pembrolizumab	Recruiting	No results available	https://ClinicalTrials.gov/show/NCT03126591
2	A study of olaratumab in soft tissue sarcoma	1/2	Randomised Open label	Soft tissue sarcoma	Olaratumab + doxorubicin	Completed	Has results	https://ClinicalTrials.gov/show/NCT01185964
3	A study of olaratumab (LY3012207) in participants with soft tissue sarcoma	1	Single group Open label	Soft tissue sarcoma	Olaratumab + doxorubicin	Recruiting	No results available	https://ClinicalTrials.gov/show/NCT02783599
4	A study of olaratumab (LY3012207) in participants with advanced soft tissue sarcoma (ANNOUNCE II)	1/2	Double-blind randomised	Soft tissue sarcoma	Olaratumab/placebo + gemcitabine + docetaxel	Recruiting	No results available	https://ClinicalTrials.gov/show/NCT02659020
5	A study of doxorubicin plus olaratumab (LY3012207) in participants with advanced or metastatic soft tissue sarcoma (ANNOUNCE III or JGDJ)	3	Double-blind randomised	Soft tissue sarcoma	Olaratumab/placebo + doxorubic	Active, not recruiting	No results available	https://ClinicalTrials.gov/show/NCT02451943
6	A study of olaratumab and doxorubicin in participants with advanced soft tissue sarcoma	1	Non-randomised Open label	Soft tissue sarcoma	Olaratumab + doxorubicin	Active, not recruiting	No results available	https://ClinicalTrials.gov/show/NCT02326025
7	doxorubicin with upfront dexrazoxane plus olaratumab for the treatment of advanced or metastatic soft tissue sarcoma	2	Non-randomised Open label	Soft tissue sarcoma	Dexrazoxane + doxorubicin + olaratumab	Recruiting	No results available	https://ClinicalTrials.gov/show/NCT02584309
8	A study of olaratumab (LY3012207), doxorubicin, and ifosfamide in participants with advanced or metastatic soft tissue sarcoma	1	Single group Open label	Soft tissue sarcoma	Olaratumab + Doxorubicin + Ifosfamide + Mesna	Not yet recruiting	No results available	https://ClinicalTrials.gov/show/NCT03283696
9	A study of olaratumab in Japanese participants with advanced cancer	1	Non-randomised Open label	Neoplasms	Olaratumab + doxorubicin	Active, not recruiting	No results available	https://ClinicalTrials.gov/show/NCT02377752

Trials taken from U.S. National Library of Medicine, U.S. National Institutes of Health and U.S. Department of Health & Human Services.

absence of differences in PFS, an end-point that is immune to post-trial contamination. In the JGDG trial, data on post-trial treatment was collected for all patients in the ITT cohort. Overall, more patients from the olaratumab-containing arm received any post-trial treatment (67% vs 49%), although not counted in this number were 30 patients in the doxorubicin arm who, per protocol, crossed over to olaratumab monotherapy at disease progression. This crossover to an agent with little demonstrated single-agent efficacy may have limited or delayed the access of patients in the control arm to potentially more effective standard post-trial therapies. More patients from the olaratumab arm went on to receive gemcitabine and docetaxel (10.5% vs 6.0%), trabectedin (8.3% vs 2.3%) and pazopanib (11.3% vs 7.5%), all agents of recognised activity in STS. However, this imbalance might at least be partly explained if patients who received an incrementally active investigational regimen attained greater fitness and life expectancy, and thus were better positioned to be considered for further treatment.

2. What is the precise mechanism of olaratumab action in STS?

Given the disruption of ligand interaction and downstream signalling of PDGFRα on drug binding, it might be anticipated that the anticancer effect of olaratumab would be via direct inhibition of PDGFRα-driven oncogenicity. Olaratumab has been shown to inhibit ligand-induced phospho-activation of PDGFRα, with attendant reduction in proliferation and invasion across a number of PDGFRα-expressing sarcoma cell lines. Effective inhibition of PDGFRα by olaratumab is indicated by clinical pharmacodynamic data that demonstrate an expected increase in circulating platelet-derived growth factors (PDGFs), cognate ligands of PDGFRα [18,24]. However, the degree of PDGF increase showed no association with anti-tumour efficacy in phase I studies, as was the case with tumour PDGFRα expression in the JGDG study. Absence of differences between PDGFRα positive and negative tumours suggests that PDGFRα inhibition is not the sole mechanism of olaratumab action. Conversely, in other cancer settings where mAbs against oncogenic RTK drivers are established standards of care, expression level of the targeted RTK may either have a strong association or no association with drug efficacy, such as the respective cases of Her2-targeting mAbs in breast cancer and EGFR-targeting mAbs in colorectal or head and neck cancers [25–27]. In addition, it is increasingly recognised that the activity of such drugs is partly through the engagement of an ADCC-mediated anti-tumour response [28]. Should this be the case with olaratumab in STS, the observed discrepancy in degree of effect on PFS and OS may also lie within the very properties of the drug itself.

PDGFRα inhibition reduces the tumour interstitial pressure, resulting in an elevated blood flow within the tumour, thereby potentially improving the delivery and tumour uptake of doxorubicin [9]. The JGDG study only tested the tumour PDGFRα expression, but not the stromal expression, which may be a key point of its mechanism. The authors of the study hypothesised that olaratumab may confer persistent alterations in the host stromal component of the tumour microenvironment that results in a pre-sensitisation of tumour to subsequent cytotoxic therapies, and thus explaining the disparity between PFS and OS benefit—at present, direct evidence of such a mechanism is lacking.

3. What is the therapeutic interaction between cytotoxic chemotherapy and PDGFRα inhibition?

The importance of the cytotoxic component to the efficacy of combination olaratumab–doxorubicin is indicated by the lack of evidence of single-agent activity of the mAb [17,18]. However, data regarding the drug-specific interaction of olaratumab with any given chemotherapeutic are lacking. So far, clinical trials of olaratumab-chemotherapy combinations have been informed by pre-existing standards of care, as seen with the choice of doxorubicin in the JGDG and ANNOUNCE III trials, carboplatin and paclitaxel in a reported randomised phase II trial in advanced non–-small-cell lung cancer, and the use of gemcitabine-docetaxel or doxorubicin-ifosfamide backbones in ongoing studies in STS [29] (Table 3). If the principal mechanism of action of olaratumab is via stromal interactions, then this may result in improved microenvironment pharmacokinetics that is generic to many different cytotoxic drugs. However, given the recognised diversity of different cytotoxic agents in terms of effects on vascular remodelling and immunomodulation, it would seem likely that different drugs would exhibit qualitatively different interactions with olaratumab, thus making choice of combination an important clinical factor. Further *in vitro* and *in vivo* investigation of the additive anti-tumour potential of such chemo-mAb combinations is required across STS and other cancer models to provide greater rationale for future clinical protocols.

4. Conclusions

Despite concerted investigation of many novel agents, treatment options for advanced STS have remained limited. In this context, initial clinical results associated with olaratumab–doxorubicin treatment are the source of considerable excitement. Furthermore, the potential of olaratumab to provide benefit as part of adjuvant treatment of early-stage disease presents a worthwhile avenue of investigation. However, in the context of the high cost (estimated price per quality-adjusted life year £46,000–60,000 [30]) and toxicity associated with this novel regimen, it is crucial that definitive evidence of survival benefit, improvement of quality of life and cost effectiveness is obtained—the highly anticipated results

from the ANNOUNCE III trial, expected in late 2020, should provide valuable data. Meanwhile, key translational research questions regarding the mechanism of action of olaratumab must be tackled to inform how best to employ this promising agent in the treatment of advanced STS and other cancers.

Conflict of interest statement

None declared.

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