REVIEW

Pharmacokinetics and systems pharmacology of monoclonal antibody olaratumab for inoperable soft tissue sarcoma

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Abstract: Olaratumab, a human IgG1 monoclonal antibody, has received accelerated approval from the US Food and Drug Administration (FDA), and conditional marketing authorization by the European Medicines Agency’s (EMA) accelerated assessment program, for metastatic soft tissue sarcoma. This is a heterogeneous group of diseases with several subtypes, and the current standard of care since the past few decades has been primarily doxorubicin. Olaratumab is an antagonist of platelet-derived growth factor receptor alpha (PDGFRα) that prevents the binding of PDGF ligands to this receptor, consequently inhibiting subsequent dimerization of the receptor and downstream signal transduction, thereby inhibiting carcinogenesis. In Phase 1 and Phase 2 clinical trials, olaratumab demonstrated acceptable safety profile including lack of cardiac toxicity or immunogenicity, with most common adverse effects being nausea, fatigue, infusion-related reactions, and neutropenia. Encouragingly, patients who were administered olaratumab in combination with doxorubicin received an overall survival benefit of 11.8 months as compared to doxorubicin alone. The Phase 3 trial of olaratumab is ongoing and a pediatric Phase 1 trial is also underway. Future studies may help to stratify the target population and leverage the power of precision medicine to benefit patients through tailor-made olaratumab or olaratumab/doxorubicin regimens and the use of potential companion diagnostics to optimize and personalize therapy. The “financial toxicity” of olaratumab is also discussed in light of the rising costs of cancer care and the associated burden to patients, families, and caregivers.

Keywords: olaratumab; orphan drug; cancer; sarcoma; PDGFR; monoclonal antibody; pharmacokinetics; pharmacology; precision medicine; financial toxicity


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Introduction

In February 2015, the European Medicines Agency (EMA) designated Lartruvo® (olaratumab), a human IgG1 monoclonal antibody (mAb) from Eli Lilly and Company (who acquired the original inventor ImClone Systems), as an orphan medicinal product, and in September 2016, EMA’s Committee for Medicinal Products for Human Use (CHMP) recommended a conditional marketing authorization for olaratumab for advanced soft tissue sarcoma under EMA’s accelerated assessment program[1,2]. Across the Atlantic, in October 2016, the United States Food and Drug Administration (FDA) granted accelerated approval to olaratumab for patients with soft tissue sarcoma who are not eligible for radiotherapy or surgery and with a histologic subtype for which therapy with drugs of the anthracycline class (such as doxorubicin) is clinically appropriate[3]. The FDA also granted orphan drug status, fast track and breakthrough therapy designation, and priority review status apart from accelerated approval to olaratumab.

Olaratumab is an anti-platelet-derived growth factor
receptor alpha (PDGFRα) mAb with efficacy in metastatic soft tissue sarcoma, for which doxorubicin is the current standard of care[4]. Given its discovery at ImClone, olaratumab has also been alternatively known in the literature as IMC-3G3[5]. Sarcomas, which are rare tumors arising or differentiated from mesodermal tissues, are categorized mainly into two groups—soft tissue sarcomas and bone tissue sarcomas—both of which have different staging and therapeutic approaches[6]. Soft tissue sarcomas are a heterogeneous group of tumors comprising more than fifty different subtypes[7]. The reader is referred to an excellent review of WHO classification of tumors of soft tissue and bone by Doyle that presents in a tabular format the key changes and updates based on the 2013 WHO recommendations[8]. The reader is also recommended an excellent review on refinements in sarcoma types based on 2013 WHO classification as well as an overview of soft tissue sarcomas[9,10].

According to the U.S. National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Registry with data updated in 2015, primary malignancy of soft tissues (connective, subcutaneous and other nonparenchymatous tissues) comprised 34.8% of all sarcomas including those originating primarily in nonparenchymatous or parenchymatous sites[11]. Pastore et al., in a population-based study of data from the European Automated Childhood Cancer Information System (ACCIS) for 1978–1997, found that soft tissue sarcomas comprise 8% of all childhood malignancies in Europe, with rhabdomyosarcoma comprising 50% of all soft tissue sarcomas[12]. In Asia, Ramaswamy et al. have provided an excellent review on Indian data in bone and soft tissue sarcomas, and stressed the importance of immunohistochemistry (IHC) for the confirmation of soft tissue sarcomas and their specific subtype[7]. For example, transducing like enhancer of split 1 (TLE1) is a useful IHC marker for the diagnosis of synovial sarcoma[7]. In China, the Beijing Cancer Registry reported an annual incidence between 2003 and 2007 of 0.2% and 0.7% in men for mesothelioma and connective/soft tissue sarcomas, respectively, and 0.2% and 0.6% in women for the same sites, respectively[13]. Interestingly, based on the data between 2008 and 2012 in Singapore, the Singapore Cancer Registry reported that soft tissue tumors were the fifth most frequent cancers (7.3%) in childhood for girls between 0 to 14 years of age, but not for boys of the same age group[14].

Given the modest survival benefits of conventional chemotherapeutic options in combating the various histologic subtypes of sarcoma, targeting the tumor milieu with PDGFR inhibitors would be a useful strategy[15]. Amongst FDA-approved drugs, most inhibitors available in the market today are multikinase inhibitors that act on several targets including PDGFR[16,17]. For example, nintedanib, which is approved for idiopathic pulmonary fibrosis, inhibits multiple receptor tyrosine kinases (RTKs) such as PDGFR α and β, fibroblast growth factor receptor (FGFR) 1–3, vascular endothelial growth factor receptor (VEGFR) 1–3 and Fms-like tyrosine kinase 3 (FLT3)[18]. Sunitinib, which is approved for advanced renal cell carcinoma and gastrointestinal stromal tumors (GIST) that are refractory to imatinib treatment, also inhibits multiple RTKs including PDGFR α and β, VEGFR1–3, FLT3, stem cell factor receptor (KIT), colony-stimulating factor receptor Type 1 (CSF-1R), and glial cell line-derived neurotrophic factor receptor (RET)[19]. Ponatinib, which is approved for chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL), is a small-molecule dual Abl/Src protein inhibitor with additional inhibitory activity on kinases such as VEGFR, PDGFR, FGFR, KIT, RET and FLT3[20]. Sorafenib is a popular multikinase inhibitor approved for renal cell carcinoma that inhibits CRAF, BRAF, mutant BRAF, KIT, FLT-3, VEGFR-2, and PDGFRβ[21]. Other experimental molecules still in clinical trials include famitinib and MGCD516[22,23]. In contrast with multikinase inhibitors, olaratumab is an inhibitor of PDGFRα that interferes with downstream PDGFRα pathway signaling[24]. This review purports to describe the current state-of-the-art in therapy of soft tissue sarcoma with anti-PDGFRα mAb olaratumab with emphasis on preclinical data, Phase 1 and Phase 2 clinical trials, safety aspects, and potential for precision medicine with olaratumab therapy.

**Olaratumab structure**

Olaratumab is a glycoprotein with molecular weight of 147.2 kDa without the glycan mass and 154.6 kDa with the glycan mass[25]. Its molecular formula is C6554.H10076.N1736.O2048.S40. Olaratumab includes two heavy chains (gamma-1) and two light chains (kappa), twelve intra-chain disulfide bonds, four inter-chain disulfide bonds, and two glycosylation sites including one at Asn30 in the Fab region of the heavy chain and one at Asn307 in the Fc region of the heavy chain[25]. **Figure 1** is a schematic
representation of the structure of olaratumab.

Furthermore, olaratumab is generated in mouse myeloma NSO cells with a two-tier cell banking system of Master Cell Bank and Working Cell Bank being used for the manufacture[25]. The company prescribing information for olaratumab states that it is produced in genetically engineered mammalian NSO cells[27].

The PDGF/PDGFR axis and olaratumab mode of action

PDGFRα is a receptor tyrosine kinase which is expressed on cells of mesenchymal origin but has also been found in tumor and stromal cells where signal transduction cascades are responsible for the proliferation and metastasis of cancer cells and for the maintenance of the tumor milieu[27]. In the largest study till date to investigate protein expression, somatic mutations, and gene amplifications or translocations in 2,539 sarcoma samples comprising 22 sarcoma subtypes, PDGFRα was found to be overexpressed in 22.1% of soft tissue sarcomas[28]. This included 18.3% of non-uterine leiomyosarcoma (LMS), 27.8% of undifferentiated pleomorphic sarcoma (UPS, or formally called malignant fibrous histiocytoma), 27.8% of osteosarcoma, 30.8% of chondrosarcoma, 31.8% of Ewing’s sarcoma, 33.3% of fibrosarcoma, and 38.5% of angiosarcoma[28]. Indeed, PDGFRα has also been implicated in other malignancies with strong expression of PDGFRα in ovarian tumors[29]; also, 70% of hepatocellular carcinoma tissues exhibit elevated PDGFRα levels[30]. In a human tumor array, PDGFRα expression is observed in about 95% of osteosarcomas and chondrosarcomas[5]. Table 1 summarizes PDGFR expression in various tumors and cell lines.

Olaratumab is a human IgG1 receptor antagonist of PDGFRα that inhibits the binding of dimeric ligands PDGF-AA, PDGF-BB, and PDGF-CC to PDGFRα[31]. Olaratumab thus inhibits receptor dimerization and transphosphorylation, thereby inhibiting intracellular

Figure 1. Structure of olaratumab. A schematic representation of the structure of olaratumab is presented. Olaratumab is a glycoprotein with molecular weight of 147.2 kDa without the glycan mass and 154.6 kDa with the glycan mass[25]. Its molecular formula is C6554H10076N1736O2048S40[26]. Olaratumab includes two heavy chains (gamma-1) and two light chains (kappa), twelve intra-chain disulfide bonds, four inter-chain disulfide bonds, and two glycosylation sites including one at Asn30 in the Fab region of the heavy chain and one at Asn307 in the Fc region of the heavy chain[25].
Olaratumab may also act by promoting receptor internalization of PDGFRα with a consequent decrease in intracellular signaling. Figure 2 is a schematic representation of the mechanism of action of olaratumab.

**Olaratumab in vitro and pre-clinical studies**

Given the high affinity \( K_D = 0.04 \) n mol/L or 40 pmol/L of olaratumab binding to PDGFRα, it blocks both PDGF-AA and PDGF-BB ligands from binding to PDGFRα and does not exhibit cross-reactivity with isoform PDGFRβ or with murine PDGFRα. The affinity constant \( K_D = K_{off}/K_{on} \) is determined by BIAcore analysis.

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Table 1. PDGFR expression in various tumors and cell lines

<table>
<thead>
<tr>
<th>Source</th>
<th>Tumor Location</th>
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<tbody>
<tr>
<td>Hermanson et al.[59]</td>
<td>Brain (Glioma)</td>
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<tr>
<td>Maderna et al.[60]</td>
<td>Brain (Glioma)</td>
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<tr>
<td>Peng et al.[61]</td>
<td>Gastric</td>
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<tr>
<td>Heinrich et al.[62]</td>
<td>Gastrointestinal stromal tumors (GIST)</td>
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<tr>
<td>Henriksen et al.[63]</td>
<td>Ovaries</td>
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<tr>
<td>McDermott et al.[64,65]</td>
<td>Human cancer cell lines of epidermoid carcinoma (A431), melanoma (A375), colon (C0lo205), NSCLC (H460), glioma (SF763T and SF767T), breast (MDA-BM-453)</td>
</tr>
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Figure 2. Mechanism of action of olaratumab. The overexpression of platelet-derived growth factor receptor alpha (PDGFR alpha) is implicated in the carcinogenesis of soft tissue sarcoma by facilitating cell proliferation, survival, migration and metastasis, and recruitment of angiogenic stromal fibroblasts, which are responsible for cellular proliferation, migration, and survival. Olaratumab is expected to target both tumor and stromal PDGFRα in humans, thus exhibiting potential inhibition of vasculature, tumor, and stroma. Olaratumab may also act by promoting receptor internalization of PDGFRα with a consequent decrease in intracellular signaling. Figure 2 is a schematic representation of the mechanism of action of olaratumab.

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**Figure 2. Mechanism of action of olaratumab.** The overexpression of platelet-derived growth factor receptor alpha (PDGFR alpha) is implicated in the carcinogenesis of soft tissue sarcoma by facilitating cell proliferation, survival, migration and metastasis, and recruitment of angiogenic stromal fibroblasts. In the cell, dimeric ligand PDGF-AA (or PDGF-BB or PDGF-CC) binds to PDGFR alpha resulting in dimerization of the receptor, trans-phosphorylation and activation of subsequent signal transduction pathways in carcinogenesis. For example, the activation of JAK leads to cell proliferation via the JAK/STAT1 or JAK/VEGF/STAT3 pathway. The activation of COX2 may also contribute to proliferation. The involvement of the classical RAS/RAF/MAPK pathway is also seen with PDGFR alpha receptor dimerization. Other putative signaling mediators such as the PI3K/AKT pathway, GAP, SOS, GRB2, SHC, PTKs, SYP, and PLC gamma may also contribute to cell proliferation. PLC gamma may also facilitate migration and invasion. The activation of SPHK1 may result in the migration and metastasis via TRAF2. When olaratumab is administered by intravenous infusion, it binds with high affinity to PDGFR alpha receptor and inhibits the binding of dimeric ligand PDGF-AA (or others) to the receptor. This prevents the initiation of downstream signal transduction cascades and results in anti-tumor efficacy in soft tissue sarcoma. The figure was generated using Protein Lounge® Pathway Builder and Protein Interaction Database and was also adapted from Eli Lilly and Company.
Olaratumab is about 100-fold more potent than imatinib for the inhibition of PDGF-induced cell proliferation, with IC50 of the former being 1 n mol/L and that of the latter being 100 n mol/L [5]. Similarly, olaratumab is about 100-fold more potent than imatinib for the inhibition of PDGF-mediated PDGFRα signaling, with IC50 of the former being 10 n mol/L and that of the latter being 1 μ mol/L [5]. In addition, olaratumab inhibits ligand binding with an IC50 of 0.24 n mol/L to 0.58 n mol/L [5,33].

In C57BL/6 mice (n = 3) which were administered a single intravenous (IV) bolus of olaratumab, clearance was found to be 29.3 mL/day/kg [33]. Further, in athymic nude mice, olaratumab inhibits U118 glioblastoma and SKLMS-1 leiomyosarcoma human xenografts (both of which express PDGFRα) by 65% and 69%, respectively [5,32,34]. In glioblastoma xenografts, olaratumab suppresses the activation of MAPK proliferation and Akt survival signal transduction pathways, whereas a combination of olaratumab and doxorubicin exhibits greater degree of tumor inhibition than monotherapy with either agent in KHOS/NP human osteosarcoma xenografts [5]. When administered to cynomolgus monkeys at doses up to 75 mg/kg, olaratumab does not show any adverse events [5,34].

Table 2 summarizes in vitro and in vivo pre-clinical studies on olaratumab.

**Olaratumab Phase 1 and Phase 2 clinical trials**

A few Phase 1 studies on olaratumab have been completed and several studies are currently in Phase 2 for olaratumab alone or in combination. The half-life (t1/2) of olaratumab ranges from 4.06 to 9.38 days after single- and multiple-dose administration [25]. Nineteen patients with advanced solid tumors were enlisted in a Phase 1 dose-escalation study consisting of four weeks per cycle and comprising five cohorts with 3–6 patients each, of which cohorts 1, 2, and 3 were administered intravenous olaratumab weekly at doses of 4, 8, or 16 mg/kg [34]. The remaining two, cohorts 4 and 5, received IV olaratumab at 15 or 20 mg/kg once every other week [34]. Indeed, in this study, there were no dose-limiting toxicities and the maximum tolerated dose (MTD) was not defined, whereas 63.2% (12 out of 19 patients) had a best response of stable disease with 3.9 months as median duration [34]. Further, the trough concentrations (Cmin) for the 16 mg/kg weekly cohort and the 20 mg/kg biweekly cohort were higher than 155 μg/mL, and the recommended Phase 2 doses for olaratumab were 16 mg/kg weekly and 20 mg/kg biweekly [34]. Furthermore, in a single-center Japanese Phase 1 study which was a dose-escalation trial of intravenous olaratumab in 16 patients with advanced or refractory solid malignancies, three dose levels were administered to three cohorts, each comprising 3–6 patients [35]. In this study, the first cohort received 10 mg/kg on Days 1 and 8 every three weeks, cohort 2 received 20 mg/kg every two weeks and cohort 3 was administered 15 mg/kg on Days 1 and 8 every three weeks [35]. In this particular study, the MTD again could not be defined as there were no dose-limiting toxicities encountered and 43.8% (7 out of 16) patients had a best response of stable disease [33]. The trough concentrations (Cmin) were above the target of 155 μg/mL for cohorts 2 and 3, and thus these two dose schedules were recommended as Phase 2 doses in the Japanese population [35].

Tap et al. reported a multi-center trial at 16 sites within the US that included an open-label Phase 1b study and a randomized Phase 2 study of either doxorubicin alone, or olaratumab plus doxorubicin combination, in patients with unresectable or metastatic soft tissue sarcoma [4]. In the combination arm, patients were administered IV olaratumab at 15 mg/kg on Days 1 and 8 along with

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<thead>
<tr>
<th><strong>In vitro studies</strong></th>
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<tr>
<td>Affinity of binding to PDGFRα [32]</td>
<td>Determined by BIAcore analysis where the Affinity constant Kd = kon/koff = 0.04 n mol/L or 40 pmol/L</td>
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<tr>
<td>Potency for inhibition of PDGF-induced cell proliferation [5]</td>
<td>Olaratumab IC50 = 1 n mol/L; Imatinib IC50 = 100 n mol/L</td>
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<td>Inhibition of ligand binding [5,32]</td>
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<tr>
<th><strong>In vivo studies</strong></th>
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<tr>
<td>C57BL/6 mice [37]</td>
<td>Clearance of 29.3 mL/day/kg after IV bolus</td>
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<tr>
<td>Glioblastoma xenograft [31]</td>
<td>Decreased MAPK and Akt</td>
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<tr>
<td>U118 glioblastoma [32,34]</td>
<td>Tumor reduction by 65%</td>
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<td>SKLMS-1 leiomyosarcoma [32,34]</td>
<td>Tumor reduction by 69%</td>
</tr>
<tr>
<td>KHOS/NP human osteosarcoma xenografts [5]</td>
<td>Tumor inhibition greater with combination of olaratumab with doxorubicin than monotherapy alone</td>
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<tr>
<td>Cynomolgus monkeys [35,34]</td>
<td>No adverse effects at doses up to 75 mg/kg</td>
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doi:10.18282/amor.v3.i3.194
doxorubicin at 75 mg/m² on Day 1 of each 21-day cycle up to eight cycles, whereas in the doxorubicin-only arm, patients were administered only doxorubicin at 75 mg/m² on Day 1 of each 21-day cycle up to eight cycles[4]. In the Phase 1b study, whose primary endpoint was safety, 15 patients were administered the combination whereas in the Phase 2 study, whose primary endpoint was progression free survival (PFS), 66 patients were administered the combination and 67 doxorubicin alone[41]. In Phase 2, the median PFS was 6.6 months for the combination versus 4.1 months for doxorubicin alone, median overall survival was 26.5 months with combination versus 14.7 months with doxorubicin alone, and the objective response rate was 18.2% for the combination versus 11.9% with doxorubicin alone[4]. A Phase 3 trial is currently enrolling patients and a Phase 1 pediatric trial is also underway[38,39].

Redondo et al. reported the commencement in March 2016 of the ANNOUNCE 2 trial, which is a multi-center Phase 1b/2 trial of olaratumab in combination with docetaxel plus gemcitabine in metastatic soft tissue sarcoma with a planned enrolment of 30 patients for Phase 1b and a Phase 2 commencement in December 2016[39]. The Phase 1b trial is an open-label, single-arm, dose-escalation study of olaratumab 15 mg/kg on Days 1 and 8, or 20 mg/kg on Days 1 and 8, along with gemcitabine 900 mg/m² at a fixed dose rate of 10 mg/m²/minute on Days 1 and 8, as well as docetaxel 75 mg/m² on Day 8, all in a 21-day cycle[39]. The primary objective is to determine a safe olaratumab dose in this triple combination, while the secondary objectives are assessment of safety, toxicity, PK, and immunogenicity of olaratumab[39]. The Phase 2 part is a randomized, double-blind, placebo-controlled study design[40]. Table 3 summarizes Phase 1, Phase 2 and Phase 3 clinical trials on olaratumab.

**Olaratumab safety**

Given the accelerated approval of olaratumab, and pending the availability of results from the ongoing Phase 3 trial, it is important to appreciate the available data on the safety of this monoclonal antibody and to make it available to clinicians and patients. Villalobos et al. at the American Association for Cancer Research (AACR) 2016 Meeting presented data from 25 patients enlisted in their Phase 1 open-label trial with a primary objective to assess the effect of olaratumab on the PK of doxorubicin[40]. In this study, the secondary objective was to characterize PK and safety profiles of olaratumab alone and in combination[40]. 21-day cycles were used for drug-drug interaction assessment with patients receiving each drug alone in cycle 1 followed thereafter by the combination in cycle 2[40]. Olaratumab 15 mg/kg was administered IV over 60 min whereas doxorubicin 75 mg/m² was administered IV over ~15 min, and it was reported that olaratumab did not have any effect on the AUC and Cₘₐₓ of doxorubicin[40]. After the olaratumab-only infusion, Cₘₐₓ was 293 μg/mL, median Tₘₐₓ was ~2 h, mean t₁/₂ was ~157 h, and mean clearance was 0.0259 L/h[40]. After the combination infusion, olaratumab Cₘₐₓ was 393 micrograms/mL, median Tₘₐₓ was ~2.8 h, mean t₁/₂ was ~131 h, and mean clearance was 0.0218 L/h, which were all similar to the olaratumab-only PK parameters except for the higher Cₘₐₓ, which was due to residual serum olaratumab from previous olaratumab-only cycle 1[40]. The most frequent adverse events (AE) were nausea (48%) and fatigue (44%) with no deaths occurring and one Grade 4 infusion-related reaction (IRR) being reported, and hence the safety profile of the combination may be considered acceptable[40]. Pyrexia, anorexia, proteinuria, and constipation were noted as main adverse events with olaratumab[41].

The EMA has noted that musculoskeletal pain, nausea, mucositis and neutropenia are the most common adverse effects[1]. The FDA has observed that the most common side effects with frequency equal to or more than 20% are neutropenia, nausea, fatigue, alopecia, vomiting, mucositis, musculoskeletal pain, abdominal pain, diarrhea, neuropathy, decreased appetite, and headache, with infusion-related reactions in 13% of patients[13]. Taken together, the safety profile of olaratumab based on available results, excluding the ongoing Phase 3 study, may be deemed clinically manageable and hence acceptable. Indeed, the enhanced survival benefit and acceptable cardiac safety may ensure a positive risk-benefit scenario for the combination of olaratumab with doxorubicin[41].

**Implications for precision medicine**

Given the tremendous interest in immunotherapy in recent times, it is recently noted that only subsets of patients respond to immune checkpoint inhibitor therapy such as anti-PD-1 nivolumab and ipilimumab, and hence immunopharmacogenomic studies are essential for understanding variability in this population[42,43]. Similarly, given the heterogeneous nature of soft tissue sarcomas, predictive
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Table 3. Phase 1, Phase 2 and Phase 3 clinical trials on olaratumab

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Study Population</th>
<th>Study Attributes</th>
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<tbody>
<tr>
<td>Chiorean et al.[14]</td>
<td>Patients with advanced solid tumors</td>
<td>Phase 1 dose-escalation study</td>
</tr>
<tr>
<td>Doi et al.[35]</td>
<td>Japanese patients with advanced or refractory solid malignancies</td>
<td>Single-center Phase 1 dose-escalation study</td>
</tr>
<tr>
<td>Tap et al.[36]</td>
<td>Patients with unresectable or metastatic soft tissue sarcoma</td>
<td>Multi-center trial including an open-label Phase 1b study and a randomized Phase 2 study of either doxorubicin alone, or olaratumab plus doxorubicin combination</td>
</tr>
<tr>
<td>Eli Lilly and Company[37,39] (currently ongoing)</td>
<td>Pediatric patients with relapsed or refractory solid tumors</td>
<td>Phase 1, open-label, dose-escalation study of olaratumab as a single agent and in combination with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide</td>
</tr>
<tr>
<td>Eli Lilly and Company[38]</td>
<td>Patients with metastatic castration-refractory prostate cancer</td>
<td>Phase 2, randomized study of olaratumab plus mitoxantrone plus prednisone or mitoxantrone plus prednisone</td>
</tr>
<tr>
<td>Eli Lilly and Company[39]</td>
<td>Patients with locally advanced or metastatic non-small cell lung cancer</td>
<td>Phase 2, randomized study of olaratumab with paclitaxel/ carboplatin or paclitaxel/carboplatin alone</td>
</tr>
<tr>
<td>Eli Lilly and Company[40]</td>
<td>Patients with platinum-refractory or platinum-resistant advanced ovarian cancer</td>
<td>Phase 2, randomized trial investigating liposomal doxorubicin with or without olaratumab</td>
</tr>
<tr>
<td>Redondo et al.[39]</td>
<td>Patients with metastatic soft tissue sarcoma</td>
<td>ANNOUNCE-2 study: Multi-center Phase 1b/2 trial of olaratumab in combination with docetaxel plus gemcitabine.</td>
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<tr>
<td></td>
<td></td>
<td>• Phase 1b: an open-label, single-arm, dose-escalation study</td>
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<td>• Phase 2: a randomized, double-blind, placebo-controlled study</td>
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<tr>
<td>Eli Lilly and Company[40] (currently ongoing)</td>
<td>Patients with advanced or metastatic soft tissue sarcoma</td>
<td>ANNOUNCE study: Phase 3, randomized, double-blind, placebo-controlled, trial of doxorubicin plus olaratumab versus doxorubicin plus placebo</td>
</tr>
<tr>
<td>Washington University School of Medicine[40]</td>
<td>Patients with advanced or metastatic soft tissue sarcoma</td>
<td>Non-inferiority study of doxorubicin with upfront dexrazoxane plus olaratumab</td>
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Factors need to be nevertheless identified to better stratify the target population of newer mAb drugs including olaratumab.[35] Important questions that remain unanswered are: (i) whether all soft tissue sarcomas expressing PDGFRα will respond to olaratumab or if there may exist putative subsets of patients that may exhibit non-responsiveness, (ii) whether patients with sarcomas that overexpress PDGFRα to a higher degree may have longer progression free survival or overall survival benefit when compared to sarcomas from patients that overexpress PDGFRα to a relatively lower degree, (iii) whether putative polymorphisms may exist in PDGFRα that may lead to variability in the patient population in response to olaratumab due to differences in target-mediated (PDGFRα-mediated) disposition of mAb olaratumab, (iv) whether any subset of PDGFRα-expressing sarcoma patients exist that may not respond to olaratumab but would benefit from combination therapy with olaratumab plus doxorubicin and the mechanistic basis for the same, (v) whether it may be possible to titrate the dose of olaratumab higher or lower based on a predictive model derived from level of PDGFRα expression assessed by biopsy of tumor in order to enhance therapeutic success, and (vi) whether it may be feasible to develop a low-cost companion diagnostic test that can better inform the clinician on the use of olaratumab in the wide variety of sarcomas and potentially variable populations expressing PDGFRα.

Interestingly, no positive correlation has been reported between tumor PDGFRα positivity and outcome, thus weakening the case for PDGFRα as a reliable biomarker for olaratumab therapy, which is reminiscent of the relationship between PD-1 and nivolumab discussed elsewhere.[45,42,44] No reliable companion assays have been developed yet, although Tap et al. used an immunohistochemistry assay that was reported as non-specific.[4] Future studies may also investigate the regulation, if any, of target PDGFRα by microRNAs and IncRNAs, which are increasingly being implicated in carcinogenesis and may prove to be useful as companion diagnostics or as surrogate biomarkers for target expression.[45,46] It would be interesting to investigate if the liquid biopsy approach, as noted by Deng and Nakamura for monitoring precision medicine in personalized immunotherapy, may also be useful here to monitor disease status either with the target or putative RNA surrogate biomarkers before and after treatment with olaratumab.[47] Indeed, since these are early clinical days
for olaratumab, and the Phase 3 trial is still ongoing, it is difficult to speculate at the current time on how we can truly and surely leverage the power of precision medicine to benefit patients by tailor-made olaratumab or olaratumab/doxorubicin regimens. The jury is still out in the matter but, with the passage of a little time, we should have more data to empower us to assess the olaratumab precision medicine landscape and take appropriate steps in the clinic accordingly.

Financial toxicity

In recent times, there is an increased realization of the tremendously high costs of cancer care for patients and their families or caregivers, suitably termed as “financial toxicity”. It is, indeed, important for the oncologists, health care practitioners, and pharmacists to educate the patients or caregivers on the cost of olaratumab therapy so that they are well-informed ahead of time. An online assessment of the costs of olaratumab reveal that the price ranges approximately between USD 1,800 to USD 2,500 in the United States or in Europe for a 500 mg/mL vial of the drug. Using the upper bound of USD 2,500 for 500 mg, it works out to USD 5 per mg of drug. Assuming an average body weight of 70 kg for an adult male, it would cost USD 5 × 15 × 70 = USD 5,250 for a single 15 mg/kg dose of olaratumab. Since olaratumab is typically given on Day 1 and Day 8 of a 21-day cycle for 8 cycles, it would cost USD5,250 × 2 × 8 = USD84,000 for a therapy regimen of the drug. Alternatively, for the 20 mg/kg dose of olaratumab, it would cost USD 5 × 20 × 70 = USD 7,000 for a single dose, and USD 7,000 × 2 × 8 = USD 112,000 for a complete treatment regimen with the drug. With the drug currently on patent protection, little relief can be expected for patients, families, and caregivers in the near future, especially in countries where the health insurance system does not cover such costs or in the developing world where patients need to pay from their own lifelong savings. Interestingly, as pointed out by Sheffield et al., the use of the 500 mg olaratumab vial that is currently available for sale may cause an estimated waste of 234 mg of olaratumab per patient per administration, which may be mitigated by adding a 190 mg vial size for dispensing this expensive drug without waste.

Conclusion

The FDA’s granting of orphan drug status, breakthrough therapy designation, and accelerated approval of olaratumab is a welcome step in our efforts to treat a rare but complex disease phenotype of soft tissue sarcoma. The encouraging results of Phase 1 and 2 trials and enhanced patient survival in the absence of any serious adverse events enhance enthusiasm for olaratumab as an alternative to, or in combination with, doxorubicin which has long been the standard of care for this disease. We may speculate that exciting possibilities may exist for precision medicine initiatives in cancer care to tailor-make the olaratumab or olaratumab/doxorubicin combination regimen to better suit stratified patient populations amongst those that overexpress PDGFRα. The Phase 3 trial is still ongoing and results will be eagerly awaited to pave the roadmap for the future in the management of soft tissue sarcoma. However, concerns have been raised about the disparity between the PFS (only 2.5 months) and overall survival benefit (11.8 months) as elegantly discussed by Judson and van der Graaf that merit the reader’s attention and may be explained, at least in part, by the heterogeneity between 70 different subtypes of soft tissue sarcomas. In addition, it has been noted that despite the possibility of the observed magnitude of improvement being an overestimate, a clinically important survival benefit appears to be achieved based on the lower limit of about three months, and hence the Biologic License Application (BLA) for olaratumab was granted Priority Review by the US Center for Drug Evaluation and Research (CDER). Since the pediatric Phase 1 trial is also underway, future results will also shed light on the efficacy of this mAb in pediatric population.

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Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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