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ORIGINAL ARTICLE

The combination of olaratumab with gemcitabine and docetaxel arrests a chemotherapy-resistant undifferentiated soft-tissue sarcoma in a patient-derived orthotopic xenograft mouse model

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Abstract

Purpose Olaratumab (OLA) is a monoclonal antibody against platelet-derived growth factor receptor alpha. OLA has recently been used against soft-tissue sarcoma (STS) combined with doxorubicin (DOX), but with limited efficacy. The goal of present study was to determine the efficacy of OLA combined with gemcitabine (GEM) and docetaxel (DOC) on a chemotherapy-resistant STS patient-derived orthotopic xenograft (PDOX).

Methods Undifferentiated soft-tissue sarcoma (USTS) from a striated muscle of a patient was grown orthotopically in the right biceps femoris muscle of nude mice to establish the PDOX model. The USTS PDOX was treated with GEM alone, GEM combined with DOC, OLA combined with DOX or GEM, and OLA combined with GEM and DOC. Tumor size and body weight were measured during the 14 days of treatment.

Results Tumor growth was arrested only by OLA combined with GEM and DOC. Tumors treated with OLA combined with GEM and DOC also had the most necrosis.

Conclusions The present study demonstrates the power of the PDOX model to identify the novel effective treatment strategy of the combination of OLA, GEM and DOC for drug-resistant soft-tissue sarcoma.

Keywords Undifferentiated soft-tissue sarcoma · Olaratumab · Doxorubicin · Gemcitabine · Docetaxel · Patient-derived orthotopic xenograft · PDOX

Introduction

High-grade soft-tissue sarcomas (STS) including undifferentiated soft-tissue sarcoma (USTS) are recalcitrant neoplasms in need of new treatment strategies [1]. The American Cancer Society has estimated that about 12,750 new cases will be diagnosed and approximately 5270 American are expected to die from STS in the United States in 2019 [2]. More than 50 subtypes of STS have been recognized by the World Health Organization (WHO) [3]. Currently, surgical resection is the best treatment option for USTS because of their resistance to radiation and chemotherapy.

Overexpression of platelet-derived growth factor receptor alpha (PDGFRα) has been shown to enhances tumor growth and progression with poor prognosis in STS [4–8]. Olaratumab (OLA) is a monoclonal antibody that is directed against PDGFRα and is being used in STS treatment recently, but with limited efficacy when administrated

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alone [8]. It has been reported that combining OLA with chemotherapy drugs increases its effectiveness [8]. OLA in combination with DOX demonstrated a significant improvement in survival compared to DOX alone in patients with STS [8], but still this combination may have limited efficacy especially in DOX-resistant-STS patients [4].

Gemcitabine (GEM) and docetaxel (DOC) combination therapy has been shown to be effective against STS and is occasionally used for second-line therapy [9]. A Phase I clinical trial demonstrated the safety and tolerability of adding OLA to the GEM and DOC combination, however the efficacy of this combination is not known [10].

We previously established several types of patient-derived orthotopic xenograft (PDOX) nude mouse models using surgical orthotopic implantation (SOI) [11–15] including a DOX-resistant USTS in the right biceps femoris muscle to determine effective drugs for this recalcitrant disease [14, 15].

The aim of the present study was to identify the efficacy of OLA combined with GEM and DOC on the chemo-resistant USTS PDOX model.

Materials and methods

Mice

Athymic nu/nu nude mice (AntiCancer, Inc., San Diego, CA, USA), 4–6 weeks old, were used. To minimize any suffering of the animals, anesthesia and analgesics were used for all surgical experiments [14]. The mouse investigations presented here were carried out using an AntiCancer, Inc. Institutional Animal Care and Use Committee (IACUC) protocol specifically approved for this study as previously described and as per as the principles and procedures provided in the National Institute of Health Guide for the Care and Use of Animals under Assurance Number A3873-1 [14].

Patient-derived tumor

A 62-year-old female previously diagnosed with undifferentiated sarcoma not-otherwise-specified in her left upper arm, underwent surgical tumor resection. The patient did not receive any chemotherapy or radiotherapy prior to surgery. Written informed consent was obtained from the patient as part of a UCLA Institutional Review Board approved protocol (IRB#10-001857) [14].

Establishment of the USTS PDOX model with surgical orthotopic implantation (SOI)

An approximately 5-mm skin incision was made on the right thigh of nude mice. The biceps femoris was split and a 3–4 mm^3 single tumor fragment was implanted orthotopically into the space to establish the USTS PDOX model [14]. The wound was closed with a 6-0 nylon suture (UNIFY, AD Surgical, Sunnyvale, CA).

Treatment study design in the USTS PDOX model

The USTS PDOX mouse models were randomized into six groups of six mice each and treated with the following drugs with intraperitoneal administration for 2 weeks (Fig. 1): G1, untreated control; G2, GEM (100 mg/kg, once a week) alone [16, 17]; G3, GEM and DOC (20 mg/kg, once a week) [16, 18]; G4, OLA (60 mg/kg, twice a week) [19] combined with DOX (3 mg/kg, once a week) [20]; G5, OLA combined with GEM; G6, OLA combined with GEM and DOC. Treatment started when all tumors reached 100–150 mm^3. Tumor length, width and mouse body weight were measured twice per week. Tumor volume was calculated with the following formula: Tumor volume (mm^3) = length (mm) × width (mm) × width (mm) × 1/2. Data are presented as mean ± standard error of the mean (SEM).

Histological analysis

Fresh tumor samples were fixed in 10% formalin and embedded in paraffin before sectioning and staining. Tissue sections were deparaffinized in xylene and rehydrated in an ethanol series. Hematoxylin and eosin staining were performed

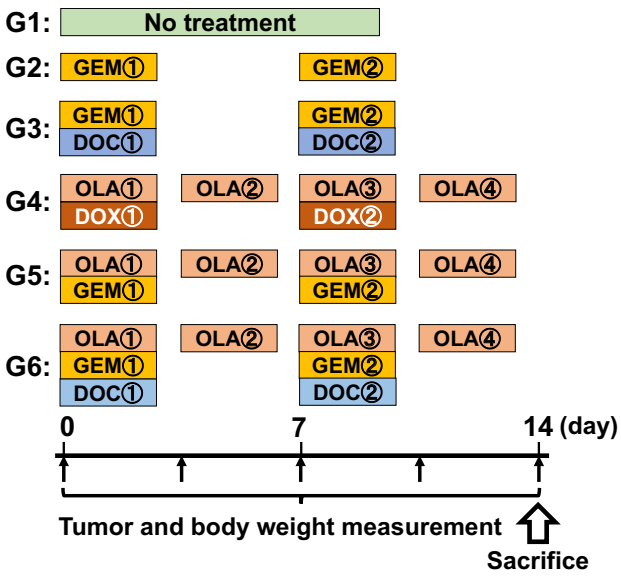

Fig. 1 Treatment regime. G1, untreated control; G2: treated with GEM (100 mg/kg, once a week) alone; G3: treated with GEM and DOC (20 mg/kg, once a week); G4: treated with OLA (60 mg/kg, twice a week) combined with DOX (3 mg/kg, once a week); G5: treated with OLA combined with GEM; G6: treated with OLA combined with GEM and DOC

according to standard protocol. Ki-67 immunohistochemical staining with anti-Ki-67 antibody (Abcam Ltd., Cambridge, MA) in combination with diamino-benzidine (DAB, Dako Japan Inc., Kyoto, Japan), staining and hematoxylin counterstaining was performed according to manufacturer's protocols. The Ki-67 labeling index, the percentage of tumor cell nuclei with positive immunostaining above the background level, was calculated semi-quantitatively [21].

Statistical analysis

All statistical analyses were performed by statistical software EZR (Saitama Medical Center Jichi Medical University, Saitama, Japan). A normal distribution was assessed by Shapiro–Wilk test. Bartlett's test was used to verify the homogeneity of variances across groups. One-way ANOVA with Tukey HSD for post hoc analysis was used for the parametric test to compare intergroup. The Kruskal–Wallis with Steel–Dwass test for post hoc analysis was used for the non-parametric test of intergroup differences. The paired *t* test was used for the parametric test to compare the means between two related groups. All *p* values were two sided and *p* values of 0.05 or less were considered statistically significant.

Results

Efficacy of chemotherapy on the USTS PDOX

OLA combined with GEM ($p < 0.001$) or with DOX ($p < 0.001$), and GEM combined with DOC ($p < 0.001$) treatment significantly, but incompletely, inhibited USTS PDOX growth compared with the untreated control. OLA combined with GEM and DOC ($p < 0.001$) arrested USTS PDOX tumor growth. Only OLA combined with GEM and DOC had a significant increased efficacy compared to GEM alone ($p = 0.001$) (Figs. 2, 3).

Histology of the USTS PDOX

The tumor tissue of the control group mainly comprised viable highly dense spindle-shaped cancer cells with atypical mitosis. Tumors treated with GEM with/without DOC, and OLA combined with DOX or GEM comprised spindle-shaped viable cells, but the cancer-cell density was lower than that of control and degenerative scars in the stroma were detected. The cancer-cell density was lowest and vast degenerative scars along with vacuolar degeneration in the stroma were observed in the tumor treated with OLA combined with GEM and DOC. The strong efficacy of OLA combined with GEM and DOC on the USTS PDOX tumor was thus also shown histologically (Fig. 4).

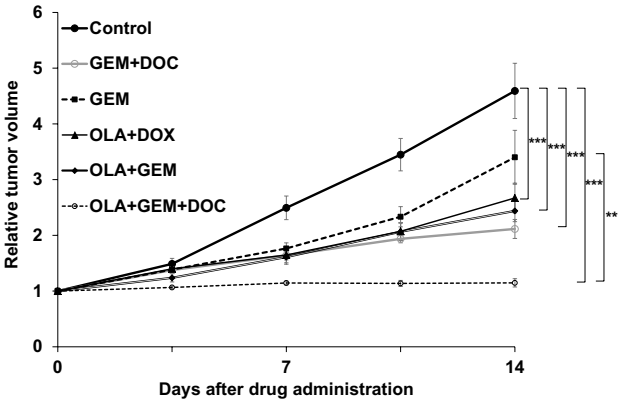

Fig. 2 Quantitative efficacy of chemotherapy on the USTS PDOX model. Line graphs indicate relative tumor volume (tumor volume at each time point/tumor volume at onset of treatment) for each drug and control group. $N = 6$ mice/group. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. Error bars: ± SEM

Ki-67 immunohistochemical staining

Immunohistochemical staining with the Ki-67 proliferation marker, which is present during all active phases of the cell cycle and is absent in resting cells, was performed on tumor sections to evaluate the proliferative capacity of cancer cells after treatment. We found that tumors treated with OLA combined with DOX (mean Ki-67 labeling index, 8.1%, $p = 0.03$), with GEM (14.3%, $p = 0.01$), and with GEM and DOC (6.7%, $p = 0.02$) had significantly lower Ki-67 labeling index compared to the untreated control (37.7%) (Figs. 5, 6).

Effect of treatment on body weight

Mouse body weight was measured pre-treatment and post-treatment. Final body weight of mice in control ($p < 0.001$) and GEM alone ($p = 0.02$) increased compared with initial body weight. There was no significant difference in body weight among the other groups (Fig. 7). There were no other side effects or animal deaths in any group.

Discussion

Several chemotherapy drugs have been in clinical trials for the treatment of STS [9, 22–27]. In addition, some of these drugs have been tested in combination on STS in clinical trials [28–30]. However, no effective clinical treatment for USTS has been established as first-line therapy. In the present study, we found OLA combined with GEM and DOC can arrest a recalcitrant USTS tumor in a USTS PDOX model. This is the first study which shows that the OLA with GEM and DOC combination is active in USTS, in this case a tumor resistant to GEM or OLA combined with DOX.

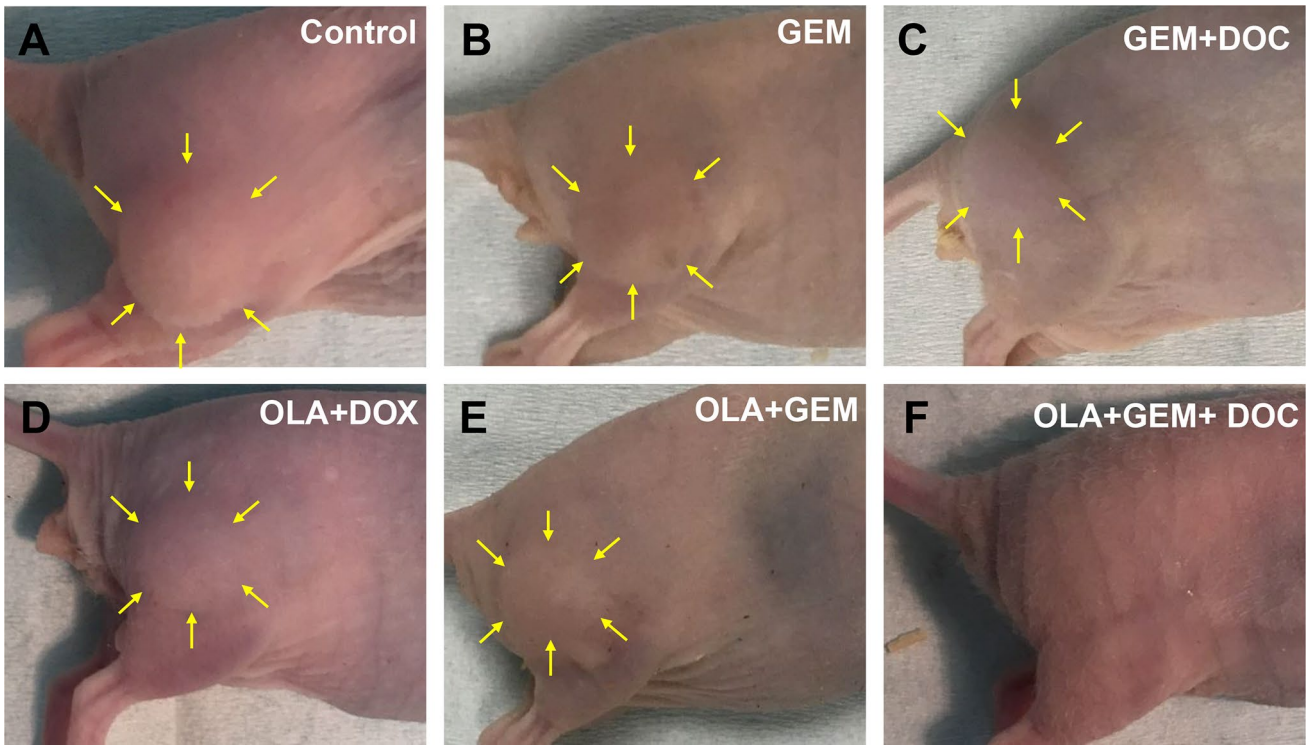

Fig. 3 Photographs of representative PDOX mouse models from each treatment group at day 14. Arrows indicate the margins of the tumors. **a** Untreated control. **b** GEM alone. **c** GEM and DOC. **d** OLA combined with DOX. **e** OLA combined with GEM. **f** OLA combined with GEM and DOC

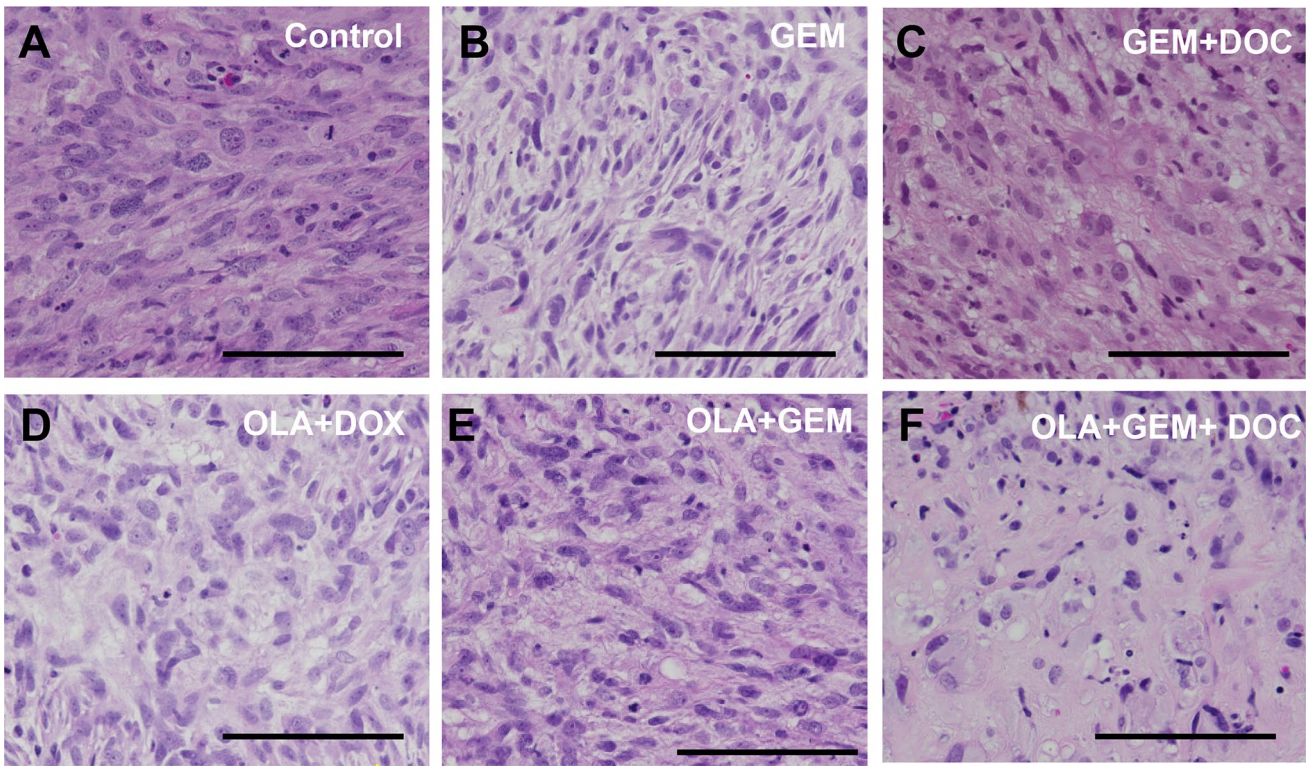

Fig. 4 Tumor histology. **a** Untreated control. **b** GEM alone. **c** GEM and DOC. **d** OLA combined with DOX. **e** OLA combined with GEM. **f** OLA combined with GEM and DOC. Scale bars 100 µm

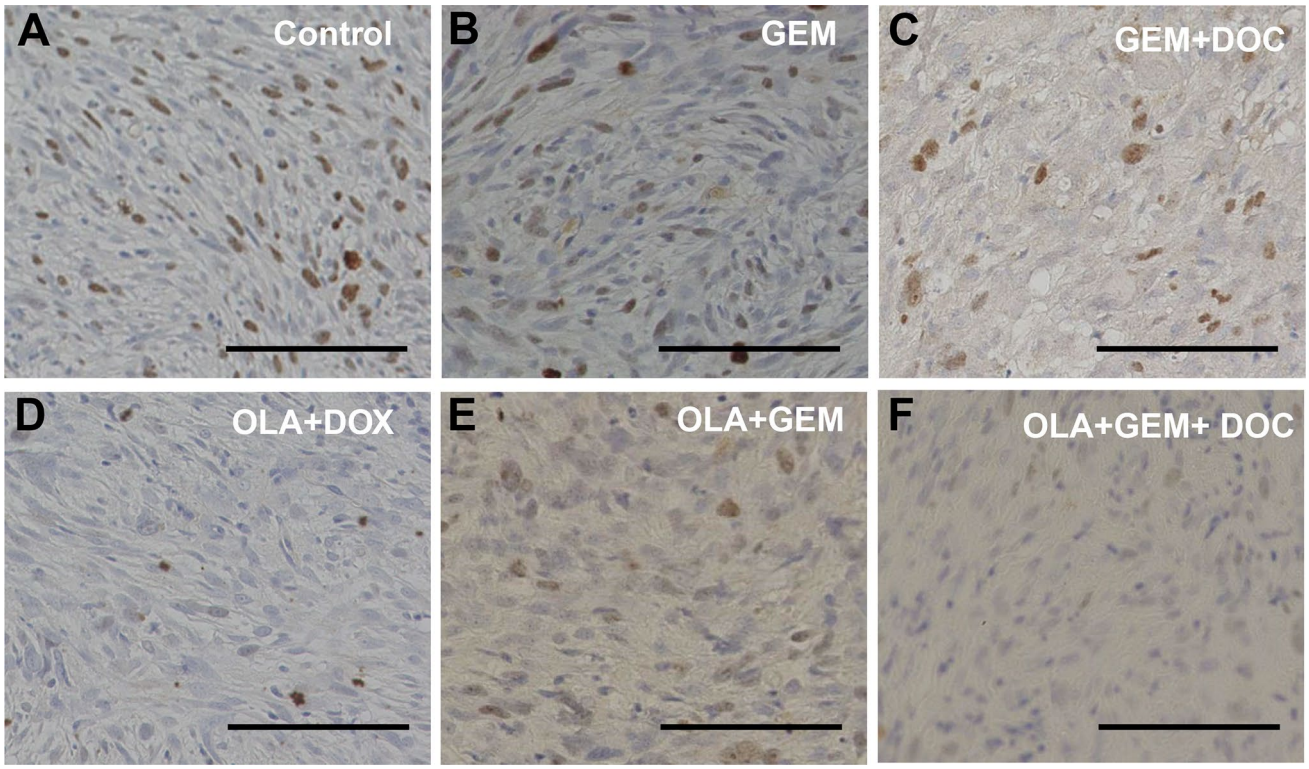

Fig. 5 Ki-67 immunochemical histology. **a** Untreated control. **b** GEM alone. **c** GEM and DOC. **d** OLA combined with DOX. **e** OLA combined with GEM. **f** OLA combined with GEM and DOC. Scale bars 100 µm

The OLA-GEM-DOC combination strongly increased tumor necrosis demonstrating its ability to kill the cancer cells. Detailed studies of the ability of this combination to induce apoptosis will be carried out in the future.

OLA is directed against the PDGFRα [4, 31, 32]. OLA prevents the activation of PDGF-AA, PDGF-BB and PDGF-CC receptors and their downstream signaling [33, 34]. OLA in combination with DOX showed a significant prolongation in survival compared with DOX alone in patients with advanced STS [8]. However, DOX-based treatment might not be suitable for some patients because of its toxicity and/or drug-resistance of the tumors [9]. In the present study, OLA combined with DOX only had moderate efficacy against the USTS-PDOX tumors which was previously shown to be DOX-resistant [14].

A Phase I study of adding OLA to the GEM and DOC combination confirmed its tolerability and this combination now becomes a promising strategy for either DOX- or OLA-resistant STS [10].

OLA in combination with DOX was used to inhibit the growth of osteosarcoma and a malignant rhabdoid tumor [19, 35]. OLA showed efficacy in patients with pretreated GIST [36]. But OLA showed no efficacy when combined with paclitaxel/carboplatinum or paclitaxel/carboplatinum alone in previously-untreated advanced non-small-cell

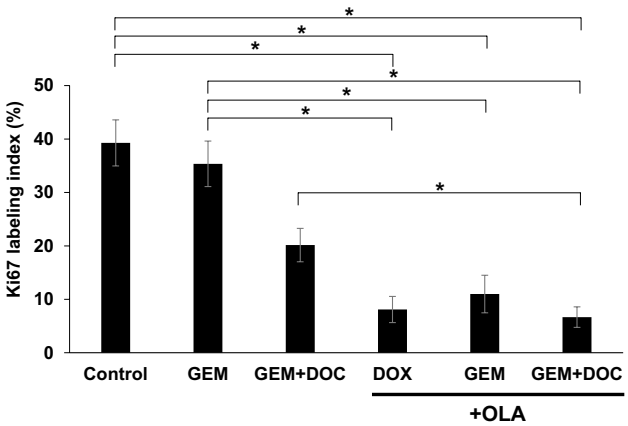

Fig. 6 Ki-67 labeling index. Bar graphs show the percentage of cancer cell nuclei with positive immunostaining. $N=6$ fields/group. $^{*}p<0.05$

lung cancer (NSCLC) [37]. OLA together with liposomal DOX was not effective in platinum-refractory ovarian cancer [38]. The combination of OLA, mitoxantrone and prednisone (M/P) was compared to M/P alone in patients with metastatic castration-resistant prostate cancer, but did not improve the efficacy of M/P [39]. OLA was shown to have a steep dose–response curve, but shallow

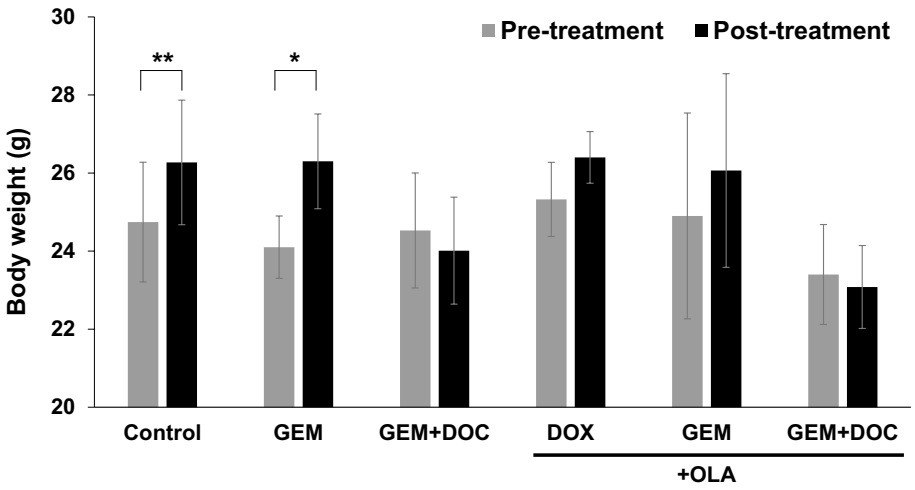

Fig. 7 Mouse body weight. Bar graphs show mouse body weight in each treatment or control group at pre- and post-treatment time. *$p < 0.05$; **$p < 0.01$

dose-toxicity curve [40]. OLA in combination with DOX was also shown to be effective for STS compared with DOX and other standard therapies [41].

In summary, in the present study, adding OLA to the GEM and DOC combination arrested the tumor growth in the USTS PDOX model. As far as we are aware, this is the first in vivo study demonstrating the efficacy of the combination of OLA and GEM and DOC on STS. The present study demonstrates the power of the PDOX model to identify OLA added to the GEM and DOC combination as effective for recalcitrant USTS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. T.H., K.M., N.S., H.O., Z.Z., S.R., N.Y., K.H., H.K., S.M., K.I., and R.M.H. are or were unsalaried associates of AntiCancer, Inc. AntiCancer, Inc. uses PDOX models for contract research.

Ethical approval All experiments were performed with an AntiCancer Institutional Animal Care and Use Committee (IACUC)-protocol specifically approved for this study and in accordance with the principals and procedures outlined in the National Institutes of Health Guide for the Care and Use of Animals under Assurance Number A3873-1.

Informed consent Written informed consent was obtained from the patient as part of a UCLA Institutional Review Board approved protocol (IRB#10-001857).

References

1. Fletcher CD (2008) Undifferentiated sarcomas: what to do? And does it matter? A surgical pathology perspective. Ultrastruct Pathol 32(2):31–36
2. American Cancer Society (2019) Cancer facts and figs. American Cancer Society, Atlanta
3. Doyle LA (2014) Sarcoma classification: an update based on the 2013 World Health Organization Classification of tumors of soft tissue and bone. Cancer 120:1763–1774
4. Antoniou G, Lee ATJ, Huang PH, Jones RL (2018) Olaratumab in soft tissue sarcoma—current status and future perspectives. Eur J Cancer 92:33–39
5. Demoulin JB, Essaghir A (2014) PDGF receptor signaling networks in normal and cancer cells. Cytokine Growth Factor Rev 25(3):273–283
6. Doi T, Ma Y, Dontabhaktuni A, Nippgen C, Nippgen J, Ohtsu A (2014) Phase I study of olaratumab in Japanese patients with advanced solid tumors. Cancer Sci 105(7):862–869
7. Ehnman M, Missiaglia E, Folestad E, Selfe J, Strell C, Thway K, Brodin B, Pietras K, Shipley J, Östman A, Eriksson U (2013) Distinct effects of ligand-induced PDGFRalpha and PDGFRbeta signaling in the human rhabdomyosarcoma tumor cell and stroma cell compartments. Cancer Res 73(7):2139–2149
8. Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, Agulnik M, Cooney MM, Livingston MB, Pennock G, Hameed MR, Shah GD, Qin A, Shahir A, Cronier DM, Ilaria R Jr, Conti I, Cosaert J, Schwartz GK (2016) Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 388(10043):488–497
9. Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, Rothermundt C, Wood Z, Benson C, Ali N, Marples M, Veal GJ, Jamieson D, Küver K, Tirabosco R, Forsyth S, Nash S, Dehbi HM, Beare S (2017) Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol 18(10):1397–1410
10. Villalobos VM, Redondo A, Tine BAV, Schwartz GK, Dickson MA, Chmielowski B, Peterson P, Cronier D, Wright JA, Attia S (2018) Phase 1b/2 study of olaratumab plus gemcitabine and docetaxel for the treatment of advanced soft tissue sarcoma (STS) (ANNOUNCE 2): phase 1b results. J Clin Oncol 36(15_suppl):11542
11. Igarashi K, Kawaguchi K, Li S, Han Q, Tan Y, Murakami T, Kiyuna T, Miyake K, Miyake M, Singh AS, Eckardt MA, Nelson SD, Russell TA, Dry SM, Li Y, Yamamoto N, Hayashi K, Kimura H, Miwa S, Tsuchiya H, Singh SR, Eilber FC, Hoffman RM (2018) Recombinant methioninase in combination

with doxorubicin (DOX) overcomes first-line DOX resistance in a patient-derived orthotopic xenograft nude-mouse model of undifferentiated spindle-cell sarcoma. Cancer Lett 417:168–173
12. Kiyuna T, Tome Y, Murakami T, Kawaguchi K, Igarashi K, Miyake K, Miyake M, Li Y, Nelson SD, Dry SM, Singh AS, Russell TA, Elliott I, Singh SR, Kanaya F, Eilber FC, Hoffman RM (2018) Trabectedin arrests a doxorubicin-resistant PDGFRA-activated liposarcoma patient-derived orthotopic xenograft (PDOX) nude mouse model. BMC Cancer 18(1):840
13. Higuchi T, Kawaguchi K, Miyake K, Oshiro H, Zhang Z, Razmjooei S, Wangsiricharoen S, Igarashi K, Yamamoto N, Hayashi K, Kimura H, Miwa S, Nelson SD, Dry SM, Li Y, Chawla SP, Eilber FC, Singh SR, Tsuchiya H, Hoffman RM (2019) The combination of gemcitabine and nab-paclitaxel as a novel effective treatment strategy for undifferentiated soft-tissue sarcoma in a patient-derived orthotopic xenograft (PDOX) nude-mouse model. Biomed Pharmacother 111:835–840
14. Igarashi K, Kawaguchi K, Kiyuna T, Miyake K, Miyake M, Singh AS, Eckardt MA, Nelson SD, Russell TA, Dry SM, Li Y, Yamamoto N, Hayashi K, Kimura H, Miwa S, Tsuchiya H, Singh SR, Eilber FC, Hoffman RM (2018) Tumor-targeting Salmonella typhimurium A1-R is a highly effective general therapeutic for undifferentiated soft tissue sarcoma patient-derived orthotopic xenograft nude-mouse models. Biochem Biophys Res Commun 497(4):1055–1061
15. Kawaguchi K, Igarashi K, Miyake K, Kiyuna T, Miyake M, Singh AS, Chmielowski B, Nelson SD, Russell TA, Dry SM, Li Y, Unno M, Singh SR, Eilber FC, Hoffman RM (2019) Patterns of sensitivity to a panel of drugs are highly individualised for undifferentiated/unclassified soft tissue sarcoma (USTS) in patient-derived orthotopic xenograft (PDOX) nude-mouse models. J Drug Target 27(2):211–216
16. Morgan M, El Shaikh MA, Abu-Isa E, Davis MA, Lawrence TS (2008) Radiosensitization by gemcitabine fixed-dose-rate infusion versus bolus injection in a pancreatic cancer model. Transl Oncol 1(1):44–49
17. Aston WJ, Hope DE, Nowak AK, Robinson BW, Lake RA, Lesterhuis WJ (2017) A systematic investigation of the maximum tolerated dose of cytotoxic chemotherapy with and without supportive care in mice. BMC Cancer 17(1):684
18. Tampellini M, Filipski E, Liu XH, Lemaigre G, Li XM, Vrignaud P, François E, Bissery MC, Lévi F (1998) Docetaxel chronopharmacology in mice. Cancer Res 58(17):3896–3904
19. Lowery CD, Blosser W, Dowless M, Knoche S, Stephens J, Li H, Surguladze D, Loizos N, Luffer-Atlas D, Oakley GJ III, Guo Q, Iyer S, Rubin BP, Stancato L (2018) Olaratumab exerts antitumor activity in preclinical models of pediatric bone and soft tissue tumors through inhibition of platelet-derived growth factor receptor α. Clin Cancer Res 24(4):847–857
20. Desai VG, Herman EH, Moland CL, Branham WS, Lewis SM, Davis KJ, George NI, Lee T, Kerr S, Fuscoe JC (2013) Development of doxorubicin-induced chronic cardiotoxicity in the B6C3F1 mouse model. Toxicol Appl Pharmacol 266(1):109–121
21. Hida AI, Bando K, Sugita A, Maeda T, Ueda N, Matsukage S, Nakanishi M, Kito K, Miyazaki T, Ohtsuki Y, Oshiro Y, Inoue H, Kawaguchi H, Yamashita N, Aogi K, Moriya T (2015) Visual assessment of Ki67 using a 5-grade scale (Eye-5) is easy and practical to classify breast cancer subtypes with high reproducibility. J Clin Pathol 68(5):356–361
22. Chawla SP, Papai Z, Mukhametshina G, Sankhala K, Vasylyev L, Fedenko A, Khamly K, Ganjoo K, Nagarkar R, Wieland S, Levitt DJ (2015) First-line aldoxorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissuesarcoma: a phase 2b randomized clinical trial. JAMA Oncol 1(9):1272–1280
23. Gupta S, Gouw L, Wright J, Chawla S, Pitt D, Wade M, Boucher K, Sharma S (2016) Phase II study of amrubicin (SM-5887), a synthetic 9-aminoanthracycline, as first line treatment in patients with metastatic or unresectable softtissue sarcoma: durable response in myxoid liposarcoma with TLS-CHOP translocation. Investig New Drugs 34(2):243–252
24. Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, Grignani G, Camargo V, Bauer S, Rha SY, Blay JY, Hohenberger P, D'Adamo D, Guo M, Chmielowski B, Le Cesne A, Demetri GD, Patel SR (2016) Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 387(10028):1629–1637
25. Takahashi M, Takahashi S, Araki N, Sugiura H, Ueda T, Yonemoto T, Morioka H, Hiraga H, Hiruma T, Kunisada T, Matsumine A, Shimura M, Kawai A (2017) Efficacy of trabectedin in patients with advanced translocation-related sarcomas: pooled analysis of two phase II studies. Oncologist 22(8):979–988
26. Agulnik M, Costa RLB, Milhem M, Rademaker AW, Prunder BC, Daniels D, Rhodes BT, Humphreys C, Abbinanti S, Nye L, Cehic R, Polish A, Vintilescu C, McFarland T, Skubitz K, Robinson S, Okuno S, Van Tine BA (2017) A phase II study of tivozanib in patients with metastatic and nonresectable soft-tissue sarcomas. Ann Oncol 28(1):121–127
27. Martin-Liberal J, Pérez E, García Del Muro X (2019) Investigational therapies in phase II clinical trials for the treatment of soft tissue sarcoma. Expert Opin Investig Drugs 28(1):39–50
28. García Del Muro X, Maurel J, Martínez Trufero J, Lavernia J, López Pousa A, de Las Peñas R, Cubedo R, Berros JP, Casado Herráez A, de Juan A, Martín Broto J (2018) Phase II trial of ifosfamide in combination with the VEGFR inhibitor sorafenib in advanced soft tissue sarcoma: a Spanish Group for Research on Sarcomas (GEIS) study. Investig New Drugs 36:468–475
29. Dickson MA, D'Adamo DR, Keohan ML, D'Angelo SP, Carvajal RD, Gounder MM, Maki RG, Qin LX, Lefkowitz RA, McKennon OR, Hirst CM, Schwartz GK, Tap WD (2015) Phase II trial of gemcitabine and docetaxel with bevacizumab in soft tissue sarcoma. Sarcoma 2015:532478
30. Hensley ML, Miller A, O'Malley DM, Mannel RS, Behbakht K, Bakkum-Gamez JN, Michael H (2015) Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. J Clin Oncol 33(10):1180–1185
31. Vincenzi B, Badalamenti G, Napolitano A, Spalato Ceruso M, Pantano F, Grignani G, Russo A, Santini D, Aglietta M, Tonini G (2017) Olaratumab: PDGFR-α inhibition as a novel tool in the treatment of advanced soft tissue sarcomas. Crit Rev Oncol Hematol 118:1–6
32. Chiorean EG, Sweeney C, Youssoufian H, Qin A, Dontabhaktuni A, Loizos N, Nippgen J, Amato R (2014) A phase I study of olaratumab, an anti-platelet-derived growth factor receptor alpha (PDGFRα) monoclonal antibody, in patients with advanced solid tumors. Cancer Chemother Pharmacol 73(3):595–604
33. Loizos N, Xu Y, Huber J, Liu M, Lu D, Finnerty B, Rolser R, Malikzay A, Persaud A, Corcoran E, Deevi DS, Balderes P, Bassi R, Jimenez X, Joynes CJ, Mangalampalli VR, Steiner P, Tonra JR, Wu Y, Pereira DS, Zhu Z, Ludwig DL, Hicklin DJ, Bohlen P, Witte L, Kussie P (2005) Targeting the platelet-derived growth factor receptor-α with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: implications as a potential therapeutic target. Mol Cancer Ther 4(3):369–379
34. Tobias A, O'brien MP, Agulnik M (2017) Olaratumab for advanced soft tissue sarcoma. Expert Rev Clin Pharmacol 10(7):699–705
35. Deevi DS, Lariccia L, Wang S, Joynes C, Steiner P, Bruheim S, Fodstad O, Carrick FE, Tonra JR, Loizos N (2006) Inhibition of human osteosarcoma xenograft growth by anti-platelet derived

growth factor receptor alpha antibody, IMC-3G3, alone and in combination with chemotherapy. Cancer Res 66:877–877
36. Wagner AJ, Kindler H, Gelderblom H, Schöffski P, Bauer S, Hohenberger P, Kopp HG, Lopez-Martin JA, Peeters M, Reichardt P, Qin A, Nippgen J, Ilaria RL, Rutkowski P (2017) A phase II study of a human anti-PDGFRα monoclonal antibody (olaratumab, IMC-3G3) in previously treated patients with metastatic gastrointestinal stromal tumors. Ann Oncol 28(3):541–546
37. Gerber DE, Swanson P, Lopez-Chavez A, Wong L, Dowlati A, Pennell NA, Cronier DM, Qin A, Ilaria R Jr, Cosaert J, Shahir A, Baggstrom MQ (2017) Phase II study of olaratumab with paclitaxel/carboplatin (P/C) or P/C alone in previously untreated advanced NSCLC. Lung Cancer 111:108–115
38. McGuire WP, Penson RT, Gore M, Herraez AC, Peterson P, Shahir A, Ilaria R Jr (2018) Randomized phase II study of the PDGFRα antibody olaratumab plus liposomal doxorubicin versus liposomal doxorubicin alone in patients with platinum-refractory or platinum-resistant advanced ovarian cancer. BMC Cancer 18(1):1292
39. Hakenberg OW, Perez-Gracia JL, Castellano D, Demkow T, Ali T, Caffo O, Heidenreich A, Schultze-Seemann W, Sautois B, Pavlik I, Qin A, Novosiadly RD, Shahir A, Ilaria R Jr, Nippgen J (2019) Randomised phase II study of second-line olaratumab with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. Eur J Cancer 107:186–195
40. Jones RL, Mo G, Baldwin JR, Peterson PM, Ilaria RL Jr, Conti I, Cronier DM, Tap WD (2019) Exposure-response relationship of olaratumab for survival outcomes and safety when combined with doxorubicin in patients with soft tissue sarcoma. Cancer Chemother Pharmacol 83(1):191–199
41. Zuluaga-Sanchez S, Hess LM, Wolowacz SE, D'yachkova Y, Hawe E, Vickers AD, Kaye JA, Bertwistle D (2018) Cost-effectiveness of olaratumab in combination with doxorubicin for patients with soft tissue sarcoma in the United States. Sarcoma 2018:6703963