Advanced and metastatic soft tissue sarcoma, a review of aajcc 8th edition staging and the use of olaratumab.

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Abstract

Soft tissue sarcomas represent a rare but histologically variable type of solid malignancy. Doxorubicin based regimens either alone or in combination with other agents had remained unchanged for decades as the standard first line treatment for metastatic disease. The definition of metastatic disease has been changed with the introduction of the American Joint Commission on Cancer (AJCC) 8th edition guidelines. The overall survival for patients with metastatic disease, despite the approval of 2 new agents, had been in the region of 12-19 months.

Olaratumab is a monoclonal antibody directed against PDGFR alpha. The results of a randomized phase 2 study comparing olaratumab plus doxorubicin with doxorubicin alone, showed a statistically significant improvement in progression free survival (PFS) up to 6 months, and a more dramatic improvement in overall survival (OS) to 26.9 months. This was the first randomized trial to show a significant improvement in overall survival compared to doxorubicin alone.

Olaratumab has been granted accelerated approval by the Food and Drug Administration of the United States of America. Ongoing trials are underway to further demonstrate the mechanism of action and also to confirm the benefit in a Phase III study.

Background

Sarcomas

Cancers of mesenchymal tissue or sarcomas, are rare malignancies that are broadly classified as bone or soft tissue tumors [1]. Soft tissue sarcomas (STS) represent about 1% of solid malignancies and account for an estimated 12,310 cases a year in the United States of America [2]. The survival for patients with STS has improved over the past 20 years. About 70-75% of patients with early stage disease now survive for at least 5 years [3]. New treatments including eribulin [4] and trabectedin [5], have shown activity in the second-line post-doxorubicin setting, but prognosis for metastatic disease remains approximately 1 year [4]. This has not changed significantly over the past 25 years [6]. The definition of advanced sarcomas has changed dramatically however in 2017.

Definition of metastatic disease-changes in American Joint Commission on Cancer (AJCC) staging.

The staging of soft tissue sarcomas has changed considerably in the 8th edition of the American Joint Committee on Cancer (AJCC) Handbook. [7] Previously all soft tissue sarcoma sites were staged as one. In the new edition, there are the following subsites; Head and Neck, Extremity and Trunk, Gastrointestinal tract, Genitourinary tract, Viscera and peritoneum, Gynecological sites, Breast, Lung, pleura and mediastinum, other histologies. Desmoid tumors or deep fibromatosis as well as Kaposi's sarcomas are not included in the new staging manual. Gastrointestinal Stromal Tumors continue to have their

own staging system but are collected under sarcomas. A new size category was created to reflect the increased risk of metastasis as the primary site increases. The superficial versus deep distinction is less important and has been eliminated. N1 disease behaves similarly between stages III and IV and is now captured as stage IV.

As there are 50 histologies it was felt impractical to create an individual staging system for each subtype but commonalities allow better ability to stratify risk of recurrence as a group. Some of the anatomical subsites have a considerably greater depth of data eg. retroperitoneal and extremities and trunk, compared with others eg. head and neck and visceral sites. The new staging categories therefore will serve as a starting point for further research on outcomes of soft tissue sarcomas at these sites. Grade remains important and should be assigned to all sarcomas. The French Federation of Cancer Centers Sarcoma Group (FNCLCC) system has become the preferred grading system. The grade is determined based on the sum of 3 parameters: differentiation, mitotic count and tumor necrosis. Each parameter is given a score which are then added together to determine the final grade. Table 1 describes the scoring system in more detail.

Table 1. Tumor Differentiation Score and Grade AJCC 8th edition

Tumor Differentiation Score	Definition
1	Closely resembling mesenchymal tissue eg low grade leiomyosarcoma,

2	Sarcomas in which the histologic typing is certain eg myxoid/round cell liposarcoma
3	Embryonal and undifferentiated sarcomas Sarcomas of doubtful type Synovial sarcomas soft tissue Osteosarcoma Ewing sarcoma/ primitive neuroectodermal sarcoma of soft tissue PNET. Other high grade sarcomas also receive a score of 3.
Mitotic Count Score	Definition
1	0-9 mitoses per 10 high power fields (hpf)
2	10-19 mitoses per 10 hpf
3	>20 mitoses per 10 hpf
Tumor necrosis score	Definition
0	No necrosis
1	<50% necrosis
2	>50% necrosis
Total score	Grade
X	Grade cannot be ascertained
1,2,3	Grade 1
4,5	Grade 2
6,7,8	Grade 3

There are also proposed radiological reporting formats, but these have not been including in the clinical prognostic stage to date. These will assess the following characteristics: Primary tumor MR imaging signal or CT attenuation characteristics, extent and location of necrosis within tumor, location in extremity including relationship to superficial fascia, presence and location of tumor tails, size in 3D.

Local extent invasion of muscles bones joints, contact with or encasement of blood vessels and nerves extension into lumen of blood vessels presence of nearby satellite nodules and Regional nodes.

Risk categories have also been defined but not yet fully incorporated into staging groups-low risk <=10% risk of recurrence or recurrence or metastases, intermediate risk >10% to <=30% and high risk >30%.

New soft tissue sarcoma subsites

Historically all soft sarcomas were staged the using the same criteria–superficial or deep tumors that were either less than or greater than 5 cm. However, sarcomas of some sites eg. Head and Neck because of anatomical and challenging surgery, have a worse prognosis at smaller sizes than those of the extremities. These subsites are classified in Table 2. How the new staging system will affect treatment of sarcomas and design of future trials remains to be seen. The inclusion criteria will have to specify individual subsites separately as the staging can be different in different sites as shown in the table 2. The published studies on the treatment of metastatic sarcomas have used prior staging systems which usually required the presence of unresectable, metastatic or regional nodal spread of disease. One target for systemic treatments has been the platelet derived growth factor receptor.

Table 2. New AJCC 8th edition soft tissue sarcoma subsites Staging Groups

Subsite	T stage	Definition	Stage Group
Head and Neck	T1	≤ 2 cm	Not yet defined
	T2	2 cm ≤ 4 cm	
	T3	>4 cm	
	T4	Invasion of adjacent structure	
	T4a	Orbital, skull base, central compartment viscera facial skeleton or pterygoid muscles	
	T4b	Brain parenchyma carotid artery encasement prevertebral muscle or cns via perineural	
Trunk and extremities	T1	5 cm or less	Stage IA: T1 N0 M0 G1
	T2	>5 to ≤ 10 cm	Stage IB: T2,3, 4 N0 M0 G1
	T3	>10 to ≤ 15 cm	Stage II: T1 N0 M0 G2, 3
	T4	>15 cm	Stage IIIA: T2 G 2,3
			Stage IIIB: T3,4 G2,3
			Stage IV: Any T,G N1 or M1
Retroperitoneum		As above but staging groups differ slightly	Stage IIIB Any T,G,N1, M0 Stage IV Any T,G,N M1

Thoracic viscera	T1	Organ Confined	Not yet defined
	T2	Extension beyond organ. T2a invades serosa or visceral peritoneum, T2b beyond serosa (mesentery)	
	T3	Invades another organ	
	T4	Multifocal: T4a: 2 sites; T4b; 3-5 sites T4c >5 sites	
GIST gastric and omental	T	T1: 2 cm or less T2: 2-5 cm T3: >5 cm <10 cm T4 >10 cm	Stage IA: T1,2 low Stage IB: T3 low Stage II: T1,2 high or T4 low Stage IIIA: T3 high Stage IIIB: T4 high Stage IV: Any T N1, M1
	Mitoses	Low: 5 or fewer per 50 HPF High: >5 per 50 HPF	
GIST small intestinal, esophageal, colorectal, mesenteric, peritoneal		Same as above but staging groups differ slightly	Stage I: T1,2 low Stage II: T3 low Stage IIIA: T1 high or T4 low Stage IIIB: T2,3,4 high Stage IV: Any T N1, M1
Unusual Histologies		Stage according to Subsite	

Long term effects of revised staging system

The long term effect of this new staging system can only be estimated at this time. Certain changes such as the addition of new T stage categories, are a long overdue step in the right direction. Further changes however will need to be made to make the staging system acceptable to all users.

Platelet-derived growth factor receptors (PDGFR)

PDGFR alpha and beta, are cell surface receptor tyrosine kinases activated by the platelet-derived growth factor (PDGF A-D) family of ligands. Normally, PDGF/PDGFR signaling has a role in cell differentiation, cell growth, angiogenesis and wound healing [8-10]. PGDFR alpha is genetically mutated or overexpressed in multiple tumor types including sarcomas, which increase their metastatic potential. Mutations in PDGFR alpha have been noted in gastrointestinal stromal tumors and downstream mutations in PIK3CA are seen in myxoid/round-cell liposarcomas [11-13,8,14-16]. PDGFRα and PDGFRβ stimulation both affect signal transduction pathways but there are some differences between the two receptors. [17,18]. PDGFR alpha signaling on tumor stromal cells can enhance tumor growth and contribute to angiogenesis [19,20].

It is not known in humans whether the overexpression or mutation of PDGFR alpha is the driver event for the growth of sarcomas but pre-clinical studies suggest that regression occurs when the receptor is inhibited [21].

Targeted therapy in STS

Gastrointestinal stromal tumors (GIST) are a group of STS that have successfully been treated with tyrosine kinase inhibitors of PDGFR and KIT, including imatinib [22], sunitinib [23] and regorafenib [5].

PDGFR and vascular endothelial growth factor receptor (VEGFR) pathways are also thought to be involved in the growth of other subtypes of STS [9,24]. Pazopanib is a multi-targeted tyrosine kinase inhibitor of cell signaling enzymes including VEGFR and PDGFR [25]. In a phase 2 study pazopanib showed a sufficient PFS at 12 weeks in all STS except adipocytic STS, to justify further study [26]. A Phase 3 trial known as PALETTE randomized 369 patients with previously treated non-adipocytic metastatic STS, to receive pazopanib or placebo. Median progression-free survival was 4.6 months for pazopanib and 1.6 months for placebo with a hazard ratio (HR) of 0.31, p<0.0001. OS was 12.5 months for the pazopanib arm and 10.7 months for placebo [27]. The United States Food and Drug Administration (FDA) approved pazopanib based on these results (https://www.cancer.gov/about-cancer/treatment/drugs/fda-pazopanibhydrochloride).

More specific angiogenesis inhibitors had little activity in STS treatment [25] and therefore further targeting of PDGFR was pursued in developing new agents for STS.

Olaratumab

Olaratumab was developed as a fully human monoclonal antibody of immunoglobulin G class 1 (IgG1) that selectively binds PDGFR alpha. It was known initially as IMC-3G3 [28]. Antibodies were generated using hybridomas in transgenic mice, and IMC-3G3 had the best characteristics to merit further development [29]. Olaratumab, as IMC-3G3 was later known, binds to PDGFR alpha with high affinity (Kd 0.04 nM) inhibits ligand binding with a 50% inhibitory concentration (IC 50) of 0.24 nM to 0.58 nM [29]. The antibody does not cross react with PDGFR beta [29]. Olaratumab is significantly more potent than imatinib with respect to the inhibition of the PDGF

pathway (IC 50 10 nM for olaratumab and 1 µMfor imatinib [28].

Olaratumab has demonstrated antitumor activity alone or in combination with cytotoxic chemotherapy in pre-clinical studies [28]. Treatment with single agent olaratumab In the leiomyosarcoma cell line SKLMS-1, resulted in a 69% tumor growth inhibition in human xenografts, [29] and a combination study of olaratumab and doxorubicin had more activity than either agent alone in KHOS/NP human osteosarcoma cancer xenografts [28].

Pharmacokinetics and metabolism

Initial xenograft studies suggested that the plasma olaratumab concentration should be in the 155–258 mg/ml range level to obtain antitumor activity [29]. A phase 1 trial was designed to find the dose that would achieve these concentrations [30]. In this study, the individual patient terminal elimination half life (t ½) of olaratumab ranged from 3.08 to 7.79 for the first dose and 3.69 to 11.3 days for subsequent doses respectively. Serum concentrations were noted to be higher after multiple doses compared to the first dose of olaratumab, and doses of 20 mg/kg every 2 weeks and 16 mg/kg weekly were noted to achieve the required concentrations [30].

Interactions

No interactions with olaratumab have been described to date. Care should be taken when giving CYP3A4 inducers or inhibitors as they may affect the metabolism of doxorubicin which is given in combination with olaratumab for the first 8 cycles.

Clinical studies: safety and tolerability

Olaratumab was tested in a phase I trial in 19 patients with advanced solid tumors. Olaratumab was given intravenously weekly at 4, 8, or 16 mg/kg (cohorts 1-3) or once every other week at 15 or 20 mg/kg (cohorts 4-5), with 4 weeks/cycle. There were no dose-limiting toxicities and the MTD (maximum tolerated dose) was not reached. Fatigue and infusion reactions were the most common side effects noted in 2 patients. Twelve patients (63.2%) had a best response of stable disease [median duration of 3.9 months (95% CI 2.3-8.7)]. The recommended phase II doses were 16 mg/kg weekly and 20 mg/kg biweekly [30].

A single-center Japanese phase I study of olaratumab treated patients with advanced malignancies at doses of 10 mg/kg on Days 1 and 8 every 3 weeks, 20 mg/kg every 2 weeks or 15 mg/kg Days 1 and 8 every 3 weeks. Out of sixteen patients treated across these cohorts, there were again, no dose-limiting toxicities and the maximum tolerated dose was not reached. In this study, the most common olaratumab-related treatment-emergent adverse events (TEAEs) were proteinuria in 4 patients (25.0%) and elevated aspartate transaminase (12.5%). Seven patients (43.8%) had a best response of stable disease. The concentrations following single and multiple doses at 15 mg/kg on Days 1 and 8 every 3 weeks (cohort 3) and multiple doses at 20 mg/kg every 2 weeks for cohort 2 were

above the 155 µg/mL target. It was felt that these two doses could represent an acceptable schedule for future trials in Japanese patients [5]. The best response in both studies was stable disease.

Phase Ib and randomized Phase II trial in the treatment of STS. Safety and Tolerability

The results of a subsequent multicenter trial were first reported at the American Society of Clinical Oncology (ASCO) meeting in 2015 (J Clin Oncol 33, 2015 (suppl; abstr 10501) and later published in 2016 [31]. This was an open label phase 1b and randomized phase 2 trial, which enrolled patients at multiple sites in the USA. For both the phase 1 b and phase 2, patients aged 18 or older who had a histologically confirmed diagnosis of locally advanced or metastatic soft-tissue sarcoma that was not previously treated with an anthracycline, an ECOG performance status of 0-2, and available tumour tissue to determine PDGFR alpha expression by immunohistochemistry were included. In the phase 2 part of the study, patients were randomized in a 1:1 ratio to receive olaratumab plus doxorubicin or doxorubicin alone. Patient groups were balanced with respect to ECOG performance status (0-1 or 2), histological tumour type (leiomyosarcoma versus synovial sarcoma versus other), immunohistochemical PDGFR expression (positive versus negative) and previous lines of treatment.

In the phase 1b part, the primary endpoint was safety. Fifteen patients were treated with olaratumab 15 mg/kg Days 1 and 8 and doxorubicin 75 mg/m^2 Day 1 every 21 days for up to 8 cycles. Patients could continue single agent olaratumab after 8 cycles if there was no progression or unacceptable toxicities. During cycles 5-8, dexrazoxane was allowed on Day 1 of each cycle to reduce the potential for doxorubicin-related cardiotoxicity.

In the phase 2 portion, patients were randomly assigned to receive either the 1B dose for olaratumab plus doxorubicin or doxorubicin 75 mg/m^2 as a single agent for 8 cycles. After 8 cycles of doxorubicin, patients in the combination group could receive olaratumab monotherapy until disease progression, and patients in the doxorubicin group were observed and could receive olaratumab monotherapy after documented disease progression.

The assay used to determine PDGFR expression was later found to recognize both PDGFR alpha and beta, so an additional PDGFR alpha specific assay was developed and used for all post-hoc efficacy analyses.

The aim of the phase 1 was to provide an initial look at safety outcomesand therefore the enrollment of 10-15 patients was made without formal statistical considerations.

The primary endpoint in the phase 2 trial was progression free survival (PFS). Secondary endpoints included OS, objective response rate (ORR) and PFS at 3 months. The phase 2 planned sample size was 130 patients and statistical methods used in the protocol resulted in a final nominal adjusted two sided alpha level of 0.19999.

In total, 133 patients were enrolled; 66 received olaratumab and doxorubicin and 67 doxorubicin alone. The groups were well balanced. In both arms leiomyosarcoma was the most common histological subtype, around one third of patients in each arm. The median number of infusions of doxorubicin in the olaratumab combination arm was 7 and in the doxorubicin alone arm was 4. The median cumulative doxorubicin dose in the combination arm was 525 mg/m^2 and 300 mg/m^2 in the doxorubicin arm. The median number of infusions of olaratumab in the combination arm was 16.5 (range 1-83) and a median of 5 (range 1-68) infusions was administered post combination. In the doxorubicin arm a median of 4 (range 1-60) olaratumab infusions were given post progression. 14 patients (22%) in the combination arm and 16 patient (25%) in the doxorubicin arm had at least grade 3 serious adverse events. Neutropenia ≥ Grade 3 was more common in the combination arm (34 patients (53%)) compared with 19 (33%) in the monotherapy group, but the rates of neutropenic fever were similar (13 and 14% respectively). Fatigue ≥ Grade 3 was 9% in the olaratumab arm compared with 3% for patients receiving doxorubicin alone. The overall incidence of any cardiac adverse event was 23% in the olaratumab arm compared to 17% in the doxorubicin single-agent arm. This difference was thought to be a result of the higher cumulative dose of doxorubicin administered in the olaratumab arm (Table 3).

Table 3. *Selected Adverse events (>grade 2) related to olaratumab alone or with doxorubicin*

Combination [33] Doxorubicin alone [33] Olaratumab alone [30]						
AE	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	6%	0	2%	0	0	0
Infusion reactions	0	2%	0	0	0	0
Nausea	2%	0	2%	0	0	0
Neutropenia	19%	34%	8%	25%	0	0
Febrile Neutropenia	11%	2%	14%	0	0	0
Anemia	8%	0	6%	0	0	0
Diarrhea	2%	0	0	0	0	0
Decreased ejection fraction	1%	0	0	0	0	0

Efficacy

The ORR was higher in the olartumab arm-18% (95% Confidence Interval (CI) 9.8–29.6) compared to 11.9% with doxorubicin alone (CI 5.3-22.2) with a p-value of 0.34. The median PFS was 6.6 months (CI 4.1-8.3) in the combination arm and 4.1 months (CI 2.8-5.4) HR 0.672 with a stratified p-value 0.0615. This was statistically significant based on the predefined statistics mentioned earlier. The study therefore met its primary endpoint. The median OS was 26.5 months (CI 20.9-31.7) in the combination arm and 14.7 months (9.2-17.5)

in the doxorubicin alone arm. The stratified p-value was 0.0003 and HR 0.46 (CI 0.3-0.71). A post hoc adjusted analysis gave a HR of 0.444 and p-value 0.0016. The OS based on stratification factors favored the olaratumab group for all factors evaluated. More patients in the combination group received gemcitabine based and pazopanib treatments, but overall, the number of subsequent treatments was similar in both arms.

Ongoing trials

NCT02451943 is a phase 3 randomized double blind, placebo controlled trial of doxorubicin plus olaratumab versus doxorubicin plus placebo in patients with advanced or metastatic soft tissue sarcoma has completed accrual and the results are being analyzed. Two other trials are evaluating olaratumab in combination with other agents, or looking further at the biological markers during treatment with olaratumab:

NCT02659020 A Phase 1 b (open label)/phase 2 (randomized double-blinded) trial evaluating gemcitabine/docetaxel with or without olaratumab in the treatment of advanced soft tissue sarcomas.

NCT02783599 A phase 1b trial to assess the modulation of biological markers in patients with potentially resectable soft tissue sarcoma treated with olaratumab monotherapy followed by olaratumab plus doxorubicin combination therapy.

Indication

On 19th October 2016, the US FDA granted accelerated approval to olaratumab (Lartruvo) for the treatment of patients with soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery and with a histological subtype for which an anthracycline containing regimen is appropriate.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761038lbl.pdf

Ongoing studies hope to answer some questions raised by the phase 2 trial. The significant improvement in overall survival seen represented the first time that any treatment had a superior survival compared to doxorubicin alone, [31] This benefit however will have to be confirmed in the ongoing phase 3 trial. In contrast, concerns have been raised that the PFS was only raised by 2.5 months [31,32]. The differences in PFS and OS outcomes may suggest an inhibitory effect of olaratumab on tumor and stromal PDGFR alpha signaling that might persist beyond the immediate treatment period [31]. The difference could also be related to diversity in histological types with more indolent types in the combination arm, a higher percentage of women in the combination arm, and differences in post trial therapies [32].

Summary

The staging of soft tissue sarcomas has changed significantly with the publication of the 8th edition of the AJCC handbook. The definition of stage IV disease has changed to include patients with nodal disease. This may affect results of future

clinical trials. Historically metastatic soft tissue sarcomas have been treated with doxorubicin based therapies. No combinations or single agents have previously shown a benefit in survival compared with doxorubicin alone. The results of a randomized phase 2 trial of olaratumab and doxorubicin represent the first time a significant improval in survival has been seen compared to single agent doxorubicin; a difference of around 12 months. Ongoing studies will help explain and confirm this benefit.

References

1. Doyle, LA. Sarcoma classification: an update based on the 2013 World Health Organization Classification of Tumors of Soft Tissue and Bone. Cancer. 2014;120(12):1763-74.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2016;66(1):7-30.

3. Jacobs AJ, Michels R, Stein J, et al. Improvement in Overall Survival from Extremity Soft Tissue Sarcoma over Twenty Years. Sarcoma. 2015;2015:279601.

4. Ryan CW, Merimsky O, Agulnik M, et al. PICASSO III: A Phase III, Placebo-Controlled Study of Doxorubicin With or Without Palifosfamide in Patients With Metastatic Soft Tissue Sarcoma. J Clin Oncol. 2016.

5. Ben-Ami E, Barysauskas CM, von Mehren M, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ann Oncol. 2016;27(9):1794-9.

6. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol, 1993;11(7):1276-85.

7. Amin MB, EdgeS, Greene F, et al. AJCC Staging Manual 8th edition. 2017.

8. McLendon R, Friedman A, Bigner D, et al. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455(7216):1061-8.

9. Mittal K, Ebos J, Rini B. Angiogenesis and the tumor microenvironment: vascular endothelial growth factor and beyond. Semin Oncol. 2014;41(2):235-51.

10. Andrae, J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008;22(10):1276-312.

11. Carvalho I, Milanezi F, Martins A, et al. Overexpression of platelet-derived growth factor receptor alpha in breast cancer is associated with tumour progression. Breast Cancer Res. 2005;7(5):788-95.

12. Ramos AH, Dutt A, Mermel C, et al. Amplification of chromosomal segment 4q12 in non-small cell lung cancer. Cancer Biol Ther. 2009;8(21):2042-50.

13. Corless CL1, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol. 2005;23(23):5357-64.

14. Dolloff NG, Shulby SS, Nelson AV, et al. Bone-metastatic potential of human prostate cancer cells correlates with Akt/PKB activation by alpha platelet-derived growth factor receptor. Oncogene. 2005;24(45):6848-54.

15. Fitzer-Attas CJ, Do MS, Feigelson S, et al. Modification of PDGFalpha receptor expression or function alters the metastatic phenotype of 3LL cells. Oncogene. 1997;15(13):1545-54.

16. Jordi Barretina, Barry S. Taylor, Shantanu Banerji, et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nat Genet. 2010;42(8): 715-21.

17. Heldin CH, Wasteson A, Westermark B. Platelet-derived growth factor. Mol Cell Endocrinol. 1985;39(3):169-87.

18. Heldin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev. 1999;79(4):1283-316.

19. Dong J, Grunstein J, Tejada M, et al. VEGF-null cells require PDGFR alpha signaling-mediated stromal fibroblast recruitment for tumorigenesis. Embo J. 2004;23(14):2800-10.

20. Skobe M, Fusenig NE. Tumorigenic conversion of immortal human keratinocytes through stromal cell activation. Proc Natl Acad Sci U S A. 1998;95(3):1050-5.

21. McDermott U, Ames RY, Iafrate AJ, et al. Ligand-dependent platelet-derived growth factor receptor (PDGFR)-alpha activation sensitizes rare lung cancer and sarcoma cells to PDGFR kinase inhibitors. Cancer Res. 2009;69(9):3937-46.

22. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. 2008;26(4):626-32.

23. Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer. 2015;121(9): 1405-13.

24. Heldin CH, J. Lennartsson. Structural and functional properties of platelet-derived growth factor and stem cell factor receptors. Cold Spring Harb Perspect Biol. 2013;5(8):a009100.

25. Cranmer LD, Loggers ET, S.M. Pollack. Pazopanib in the management of advanced soft tissue sarcomas. Ther Clin Risk Manag. 2016;12:941-55.

26. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009;27(19): 3126-32.

27. van der Graaf WT, Blay JY, Chawla SP, et al, Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-86.

28. Shah GD, Loizos N, Youssoufian H, et al. Rationale for the development of IMC-3G3, a fully human immunoglobulin G subclass 1 monoclonal antibody targeting the platelet-derived growth factor receptor alpha. Cancer. 2010;116(4 Suppl):1018-26.

29. Loizos N, Xu Y, Huber J, et al. Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: implications as a potential therapeutic target. Mol Cancer Ther. 2005;4(3):369-79.

30. Chiorean EG, Sweeney C, Youssoufian H, et al. A phase I study of olaratumab, an anti-platelet-derived growth factor receptor alpha (PDGFRalpha) monoclonal antibody, in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2014;73(3):595-604.

31. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet. 2016;388(10043):488-97.

32. Judson I, van der Graaf WT. Sarcoma: Olaratumab - really a breakthrough for soft-tissue sarcomas? Nat Rev Clin Oncol. 2016;13(9):534-6.

33. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. The Lancet. 2016;388(10043):488-497.

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