Retrospective Review of Efficacy and Safety of Anlotinib in Advanced Leiomyosarcoma: A Real-World Study

Hanhui Zou, Liming Xia, Gu Jin, Hao Wu, Wenkang Qian, Dongdong Jia, Haichao Xu, Tao Li

Bone and Soft Tissue Surgery, Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, 310022, People’s Republic of China

Correspondence: Tao Li, Email doctor-litao@foxmail.com

Objective: Retrospective study on the safety and efficacy of anlotinib in the treatment of advanced leiomyosarcoma in real-world.

Methods: Clinical data were collected from patients suffered from advanced leiomyosarcoma who received anlotinib treatment in Cancer Hospital of the University of Chinese Academy of Sciences from January 2018 to December 2020. Objective response rate (ORR) and disease control rate (DCR) were analyzed according to the RECIST 1.1 criteria. The progression free survival (PFS), overall survival (OS) and adverse reactions were recorded and calculated.

Results: A total of 19 patients (14 female, 5 male) were enrolled, 3 (15.8%) achieved partial response (PR), 11 (57.9%) achieved stable disease (SD), with an ORR of 15.8%, a DCR of 73.7%, a median PFS of 4.1 months (95% CI: 3.0~5.2) and a median OS of 23.5 months (95% CI: 14.2~32.7). The majority of adverse events were grade 1/2, the most common grade 3/4 adverse events were hand-foot syndrome (12.5%), hypertension (5.3%) and oral ulcer (5.3%).

Conclusion: Our results forecast that anlotinib is effective, safe and alternative in treatment of advanced leiomyosarcoma in real-world, combined with immunotherapy may become a potential treatment option. Further, more prospective randomized controlled trials are needed to confirm these findings.

Keywords: leiomyosarcoma, anlotinib, efficacy, adverse events

Introduction

Leiomyosarcoma (LMS) is one of the most common subtypes of malignant mesenchymal neoplasms, accounting for 10% to 20% of all newly diagnosed soft tissue sarcomas (STSs). Common locations include the abdomen, larger blood vessels, retroperitoneum and uterus. Surgical resection is the cornerstone treatment for patients with localized LMS, independent of the site of origin. Nevertheless, there is currently no established best first-line treatment for advanced LMS patients. In general, LMS show moderate sensitivity to chemotherapy, alternative first-line chemotherapy including doxorubicin-based therapies such as doxorubicin plus dacarbazine and doxorubicin plus ifosfamide, as well as gemcitabine plus docetaxel; with an objective response rate (ORR) 18.2%~35.8%, and median progression-free survival (mPFS) 4.4 to 7.4 month. Due to the limited benefit of current treatment, there is an urgent need for clinical treatments to improve survival and safety.

Tumor angiogenesis is a critical process of soft tissue sarcoma tumorigenesis and metastasis. Therefore, anti-angiogenic therapy is very important for the treatment of soft tissue sarcoma. Several new drugs for STS have been developed and used in preclinical studies and clinical trials, including regorafenib, pazopanib, anlotinib, etc. Anlotinib was explored by China as a new small molecule oral multitargeted receptor Tyrosine Kinase Inhibitor (TKI). Anlotinib plays a dual role in anti-tumor angiogenesis and tumor growth through high affinity targeting vascular endothelial growth factor receptor (VEGFR) −1/2/3, platelet-derived growth factor receptor (PDGFR) α/β and fibroblast growth factor receptor (FGFR)-1/2/3/4. Anlotinib has shown encouraging antitumor effects and tolerable toxicity in advanced non-small cell lung cancer (NSCLC), soft tissue sarcoma including leiomyosarcoma, medullary thyroid cancer and metastatic renal clear cell cancer. In a Phase II single-arm
multicenter clinical trial, a total of 166 relapsed advanced STS patients had a significant survival benefit after treatment with anlotinib, including 26 LMS patients with a 12-week progression free rate of 75% and an objective response rate of 7.7%. The progression free survival and overall survival were 11 and 15 months, respectively. Subsequently, a randomized, double-blind, placebo-controlled phase Ib study (ALTER0203) recruited 233 advanced STS patients, showed that anlotinib significantly extended progression-free survival by 4.8 months compared with placebo (6.27 months vs 1.47 months, \( P < 0.0001 \)). For 41 LMS patients, the median PFS was 5.83 months versus 1.43 months (HR = 0.19, \( p < 0.0001 \)).

Although the efficacy and safety data obtained with anlotinib in phase II and Ib clinical trials provided important information that led to its approval in advanced soft tissue sarcoma, these data are obtained from patients with rigorous selection criteria. Moreover, there is no relevant research on anlotinib in treatment of patients with advanced leiomyosarcoma. Therefore, we conducted a single-center retrospective study to investigate the efficacy and safety of anlotinib in the treatment of patients with advanced leiomyosarcoma in real world.

**Patients and Methods**

**Patient Characteristics**

Clinical date of advanced leiomyosarcoma patients who received anlotinib therapy at Cancer Hospital of the University of Chinese Academy of Sciences were analyzed in this retrospective study. The eligibility criteria were as follows: 1. Histologically confirmed leiomyosarcoma with local advanced stage or distant metastasis; 2. Received at least one cycle of anlotinib treatment; 3. At least one measurable metastatic lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; 4. Patients who were lost to contact or follow-up were excluded. From January 2018 to December 2020, a total of 19 advanced/metastatic leiomyosarcoma patients were included.

Clinical characteristics including age, sex, ECOG score, primary sites, previous treatment history, duration of initial treatment with anlotinib, combination therapy, time of disease progression, time of drug withdrawal, cause of drug withdrawal, adverse reactions and survival status were recorded. The study was conducted under the supervision of the Ethics Committee of Cancer Hospital of the University of Chinese Academy of Sciences.

**Treatment and Evaluation**

Advanced LMS patients were treated with anlotinib at an initial oral dose of 12 mg or 10 mg daily for 14 days, and then discontinued for 7 days (3-week cycle), until disease progresses or unacceptable drug toxicity. The anlotinib dose was reduced to 10 mg or 8 mg per day for patients with intolerable or uncontrolled drug-related toxicity. The primary endpoint was progression-free survival (PFS), and the secondary endpoints included overall survival (OS), disease control rate (DCR) and adverse events (AES). PFS was calculated from the date of the first administration of anlotinib until the date of documented disease progression or death from any cause. Tumor responses were assessed according to the RECIST version 1.1 and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The disease control rate (DCR) was defined as the total percentage of SD, PR and CR. Treatment-related adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

**Statistical Analysis**

Statistical data were analyzed by SPSS software (version 24.0). Quantitative variables were expressed as medians (range) or numbers (percentage). PFS and OS was draw with Kaplan–Meier method, with 95% confidence interval (CI).

**Results**

**Patient Characteristics**

The baseline characteristics of the advanced LMS patients, including age, gender, ECOG performance status, Primary site, surgery history, radiotherapy history, chemotherapy history, initial anlotinib dose, combination therapy, are summarized in Table 1. Five patients were male, and fourteen were female, with a median age of 53 years (range: 30–72 years). A total there were 10 patients with ECOG PS score 0–1 (52.6%), 9 patients with ECOG PS score 2, and no patients with
PS score >2. The most common primary site of tumor was retroperitoneal (n=8), followed by extremities (n=5), pelvis (n=4), lung (n=1) and uterus (n=1).

The majority of patients were treated with other regiments prior to anlotinib, including 73.7% (14/19) of the patients had received surgery, 31.6% (6/19) of the patients had received radiotherapy, and 73.7% (14/19) of patients had received first-line or above chemotherapy. Five patients received first-line treatment with anlotinib because of poor general condition or refusal to receive chemotherapy. Fifteen patients (78.9%) received 12 mg of anlotinib as the starting dose, and four patients (21.1%) received 10 mg anlotinib as the initial dose. Additionally, seven patients had received other nonsurgical treatments, including chemotherapy, radiotherapy and immunotherapy.

Efficacy

All patients were followed up to March 2021, with a median follow-up time of 17.8 months (range 4.3–23.5). In all 19 patients, none achieved CR, 3 patients achieved PR and 11 patients experienced SD, yielding an overall ORR of 15.8% (3/19) and DCR of 73.7% (14/19). By the end of the follow-up, all patients showed disease progression and 12 patients died, with a median PFS of 4.1 months (Figure 1A; 95% CI: 2.96–5.24), and the median OS of 23.5 months (Figure 1B; 95% CI: 12.3–34.7) (Table 2).

The clinical characteristics of anlotinib therapy in this study are detailed in Table 3. The average change in target lesion size compared with baseline is shown in Figure 2. Tumor retraction was observed in 8 patients (42.1%), with an average tumor reduction rate of 31.7%. Tumor retraction rate was more than 70% in 2 patients treated with anlotinib combined with immunotherapy.

Safety and Toxicity

Treatment-related adverse events are summarized in Table 4. The most common 1–2 grade adverse reactions included fatigue (6, 31.6%), hand and foot syndrome (5, 26.3%), and hypertension (5, 26.3%). Grade 3/4 adverse events occurred
in 4 patients, including Hand foot skin syndrome (2, 10.5%), hypertension (1, 5.3%), and Oral ulcers (1, 5.3%). All adverse events can be relieved by symptomatic treatment, reduction of anlotinib dose, or discontinuation of treatment. Five patients (26.3%) reduced the dosage of anlotinib, and two patients (10.5%) discontinued medication due to severe adverse reactions. No treatment-related deaths have occurred.

Discussion
Treatmet of leiomyosarcoma, especially advanced leiomyosarcoma, has always been a challenge in clinical work. Over the past few decades, doxorubin-based regimens and gemcitabine-based regimens are still the backbone of early-line therapy for metastatic disease.\textsuperscript{18} When patients fail in first-line chemotherapy, there is no standard second-line treatment option in China, and few therapeutic drugs are available for treatment. As a newly novel tyrosine kinase inhibitor independently developed in China, anlotinib has shown promising antitumor activity in many advanced STS. Based on

![Figure 1](https://doi.org/10.2147/CMAR.S357334)  

**Figure 1** Progression-free survival (A) and Overall survival (B) of all patients.
the results of phase II study\textsuperscript{11} and phase IIb study (ALTER0203),\textsuperscript{17} anlotinib has been approved by China Food and Drug Administration (CFDA) for the treatment of advanced alveolar soft-part sarcoma and clear cell sarcoma as first-line systemic therapy, and other advanced STS after the failure of anthracycline-based chemotherapy.

As far as we know, our study is the first real-world study to evaluate the efficacy and safety of anlotinib in advanced leiomyosarcoma. In this study, the ORR and DCR of all patients were 15.8% and 73.7%, similar with the phase II study\textsuperscript{11} (ORR: 13%, DCR: 74%), a slightly higher than phase IIb (ALTER0203) clinical study\textsuperscript{17} (ORR: 10.1%, DCR: 55.7%), and also the ORR (13.79%) and DCR (55.17%) in a retrospective study reported by Tian et al.\textsuperscript{19} Admittedly, the results of these clinical studies included a variety of STSs, and secondly, our study included 5 patients (26.3%) who had not received first-line chemotherapy, and 7 patients (36.8%) received combination therapy during the treatment of anlotinib. Although in the subgroup analysis, there was no significance benefit in ORR or DCR in the combination group compared with the anlotinib monotherapy group, a higher rate of PR was achieved in the combination group (2/7, 28.6%) than in the anlotinib monotherapy group (1/12, 8.3%). The median PFS of this study from the beginning of anlotinib treatment was 4.1 months, which were numerically lower than the median PFS of LMS group in phase II\textsuperscript{11} (11 months) and phase IIb\textsuperscript{17} (5.83 months) clinical studies. As a real-world study, the general condition of the patients with leiomyosarcoma we included was relatively poor, with 47.4% (9/19) of patients with PS score ≥ 2 and 87.5% (16/19) of patients with distant metastasis.

Table 2 Overall Response to Treatment

| Tumor Response | No. | %     |
|----------------|-----|-------|
| Partial response | 3   | 15.8% |
| Stable disease  | 11  | 57.9% |
| Progressive disease | 5  | 26.3% |
| ORR             | 3   | 15.8% |
| DCR             | 14  | 73.7% |
| Median PFS      | 4.1 (2.96–5.24) | Month |
| Median OS       | 23.5 (14.2–32.7) | Month |

Abbreviations: ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.
### Table 3 Clinical Characteristics of Patient with Leiomyosarcoma Treated with Anlotinib

| Patients | Age | Gender | PS | Surgery History | Radiotherapy History | Chemotherapy History | Combination Therapy | Tumor Size Change | RECIST 1.1 Response | PFS (M) | OS (M) |
|----------|-----|--------|----|----------------|----------------------|----------------------|---------------------|-------------------|---------------------|---------|--------|
| 1        | 38  | Female | 0  | Yes            | Yes                  | 2 line               | Immunotherapy       | −76.2%            | PR                 | 10.6    | NA     |
| 2        | 43  | Female | 2  | Yes            | Yes                  | 2 line               | Immunotherapy       | −72.6%            | PR                 | 5.3     | NA     |
| 3        | 44  | Female | 0  | Yes            | No                   | 1 line               | None                | −36.6%            | PR                 | 12.4    | 28.0   |
| 4        | 45  | Female | 1  | Yes            | Yes                  | 1 line               | Radiotherapy        | −26.1%            | SD                  | 5.8     | 10.7   |
| 5        | 50  | Female | 2  | Yes            | Yes                  | No                   | None                | −17.5%            | SD                  | 3.5     | NA     |
| 6        | 72  | Female | 0  | Yes            | No                   | No                   | None                | −14.0%            | SD                  | 4.3     | NA     |
| 7        | 40  | Female | 2  | No             | No                   | 3 line and more      | Immunotherapy+      | −7.0%             | SD                  | 2.1     | 5.2    |
| 8        | 52  | Female | 2  | No             | Yes                  | 2 line               | None                | −4.0%             | SD                  | 6.5     | NA     |
| 9        | 69  | Male   | 2  | No             | No                   | 1 line               | None                | −2.1%             | SD                  | 14.1    | 23.5   |
| 10       | 30  | Female | 1  | Yes            | No                   | 1 line               | Chemotherapy        | 7.8%              | SD                  | 1.5     | NA     |
| 11       | 53  | Male   | 2  | Yes            | No                   | 2 line               | Chemotherapy        | 11.8%             | SD                  | 3.3     | 6.0    |
| 12       | 60  | Male   | 2  | No             | No                   | 3 line and more      | None                | 12.5%             | SD                  | 0.7     | 9.2    |
| 13       | 41  | Male   | 2  | Yes            | No                   | No                   | Radiotherapy        | 17.7%             | SD                  | 3.7     | 6.9    |
| 14       | 70  | Female | 1  | No             | No                   | 1 line               | None                | 19.7%             | SD                  | 1.0     | 4.3    |
| 15       | 65  | Female | 1  | Yes            | No                   | 1 line               | None                | 25.0%             | PD                  | 1.0     | 26.1   |
| 16       | 52  | Male   | 0  | Yes            | No                   | No                   | None                | 36.4%             | PD                  | 1.9     | NA     |
| 17       | 71  | Female | 1  | Yes            | No                   | 1 line               | None                | 47.5%             | PD                  | 4.1     | 6.8    |
| 18       | 60  | Female | 0  | Yes            | No                   | No                   | None                | 60.0%             | PD                  | 8.5     | 17.5   |
| 19       | 50  | Female | 2  | Yes            | Yes                  | 3 line and more      | None                | 89.2%             | PD                  | 6.2     | 25.7   |

**Abbreviations:** PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; NA, not achieved.
metastasis of other organs. Of note, although the data of this study showed that the median OS of LMS patients was 23.5 months, significantly longer than the results of most clinical studies, we believed that this was mainly due to insufficient sample size and follow-up time, and the median OS data tended to decline with the extension of follow-up time.

In the analysis of gender, PS score, treatment history, primary site, combination therapy and other subgroups, we did not find significant differences in PFS and OS, which was mainly restricted by the small number of samples. Of our concern, we found that of the 3 patients treated with anlotinib combined with immunotherapy (Pembrolizumab 100mg every 3 weeks), two patients reached PR, another was SD, and two patients with PR achieved a tumor retraction rate of more than 70% and were still alive by the end of follow-up. The efficacy of immunotherapy in leiomyosarcoma has been controversial, a one-arm study of nivolumab in patients with advanced uterus LMS, which closed after the first stage of accrual (12 patients) for lack of efficacy, showing no objective responses and a median PFS of 1.8 months.

Another pooled analysis of clinical trials investigating a PD1 or PD-L1 antagonist in patients with advanced STS also come to conclusion of leiomyosarcoma exhibited the lowest response rates to immunotherapy. Interestingly, in a retrospective analysis of the efficacy of Immunotherapy in metastatic soft-tissue sarcomas of Monga et al forty-five percent (9 of 20) of LMS patients achieved a PR during anti-PD-1 therapy, observed a notable response rate in LMS subtypes. Meanwhile, a few case reports response to checkpoint inhibition in LMS were published. STS exhibit low expression of factors related to immune response, which could explain the modest activity of PD-1 inhibitors. Vascular endothelial growth factor promotes the immunosuppressive tumor microenvironment and contributes to Immune checkpoint inhibitors resistant therapy. Phase I/IIb clinical trial evaluating the combination of sunitinib and nivolumab in advanced sarcomas, although LMS subtype was not included, the 6-month progression-free survival rate was 48%, overall response rate of 21% (12 out of 58). Anlotinib combined with pd-1 antibody also reported in STSs recently. In a single-center retrospective analysis, 61 advanced STS patients were treated with ICIs alone or combined with TKIs, the median PFS was significantly prolonged after ICI treatment in combination with TKIs (11.74 months) compared to ICI treatment alone (6.81 months), with a 12-month PFS rate of 42.9% and overall response rate of 30% in ICI-TKI combination group. We speculate that anlotinib combined with pd-1 inhibitors can play a synergistic role in the treatment of LMS, which still needs to be confirmed by relevant clinical and basic studies.

The safety and tolerability during the treatment of anlotinib were consistent with extensive prior experience and reports. The most frequent adverse events were hand-foot syndrome, fatigue and hypertension, most of which were mild and reversible. The incidence of grade 3/4 adverse reactions was 21.1%, oncologists should be vigilant about the occurrence of dose reduction or drug withdrawal when combined with other antitumor therapies.

Additionally, we acknowledge several limitations of this single-institution retrospective study. First of all, this was a small-sample study. Second, as a retrospective study, not all possible clinical data can be reliably retrieved from records, which may lead to recall bias. Finally, the follow-up period was not long enough to determine the overall survival of all patients.

| Table 4 Adverse Events |
|------------------------|
| Total n (%) | Grade 1/2 n (%) | Grade 3/4 n (%) |
| Hand foot skin syndrome | 7 (36.8%) | 5 (26.3%) | 2 (10.5%) |
| Fatigue | 6 (31.6%) | 6 (31.6%) | 0 (0.0%) |
| Hypertension | 6 (31.6%) | 5 (26.3%) | 1 (5.3%) |
| Local Pain | 4 (21.1%) | 4 (21.1%) | 0 (0.0%) |
| Nausea/vomiting | 4 (21.1%) | 4 (21.1%) | 0 (0.0%) |
| ALT elevation | 3 (15.8%) | 3 (15.8%) | 0 (0.0%) |
| Insomnia | 3 (15.8%) | 3 (15.8%) | 0 (0.0%) |
| Oral ulcers | 3 (15.8%) | 2 (10.5%) | 1 (5.3%) |
| Diarrhea | 2 (10.5%) | 2 (10.5%) | 0 (0.0%) |
| Anemia | 2 (10.5%) | 2 (10.5%) | 0 (0.0%) |
| Hypoproteinemina | 2 (10.5%) | 2 (10.5%) | 0 (0.0%) |
| Constipation | 1 (5.3%) | 1 (5.3%) | 0 (0.0%) |

Cancer Management and Research 2022:14 https://doi.org/10.2147/CMAR.S357334

Dovepress

Zou et al

Powered by TCPDF (www.tcpdf.org)
Conclusions
In summary, our results indicate that anlotinib is reliable, safe and feasible for advanced leiomyosarcoma. Anlotinib combined with immunotherapy may become a potential treatment option. Ultimately, further long-term randomized controlled trials with larger sample sizes are needed to fully characterized the clinical application of anlotinib in LMS.

Ethics Statement
The studies involving human participants were reviewed and approved by Ethics Committee of Cancer Hospital of the University of Chinese Academy of Sciences. As a non-intervention retrospective study, it has been approved to waive informed consent. Privacy and identity information of all patients were confidentiality and compliance with the Declaration of Helsinki.

Disclosure
The authors report no conflicts of interest in this work.

References
1. George S, Serrano C, Hensley ML, Ray-Coquard I. Soft tissue and uterine leiomyosarcoma. J Clin Oncol. 2018;36(2):144–150. doi:10.1200/jco.2017.75.9845
2. Dangoor A, Seddon B, Gerrand C, et al. UK guidelines for the management of soft tissue sarcomas. Clin Sarcoma Res. 2016;6(1):20. doi:10.1186/s13569-016-0060-4
3. 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):488–497. doi:10.1016/s0140-6736(16)30587-6
4. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, Version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(5):536–563. doi:10.6004/jnccn.2018.0025
5. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a gynecologic oncology group phase II trial. Gynecol Oncol. 2008;109(3):329–334. doi:10.1016/j.ygyno.2008.03.010
6. Seddon B, Scerr M, Jones RL, et al. A phase II trial to assess the activity of gemcitabine and docetaxel as first line chemotherapy treatment in patients with unresectable leiomyosarcoma. Clin Sarcoma Res. 2015;5(1):13. doi:10.1186/s13569-015-0029-8
7. Hensley ML, Miller A, O’Malley DM, et al. 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. 2015;33(10):1180–1185. doi:10.1200/jco.2014.58.3781
8. Li F, Liao Z, Zhao J, et al. Efficacy and safety of Apatinib in stage IV sarcomas: experience of a major sarcoma center in China. Oncotarget. 2017;8(38):64471–64480. doi:10.18632/oncotarget.16293
9. Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2016;17(12):1732–1742. doi:10.1016/s1470-2045(16)30507-1
10. van der Graaf WT, Blay J-Y, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled Phase 3 trial. Lancet. 2012;379(9829):1879–1886. doi:10.1016/s0140-6736(12)60651-5
11. Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res. 2018;24(21):5233–5238. doi:10.1158/1078-0432.Ccr-17-3766
12. Lin B, Song X, Yang D, et al. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRβ and FGFR1. Gene. 2018;654:77–86. doi:10.1016/j.gene.2018.02.026
13. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. Cancer Sci. 2018;109(4):1207–1219. doi:10.1111/cas.13536
14. Chen XZ. Anlotinib for refractory advanced non-small cell lung cancer in China. JAMA Oncol. 2019;5(1):116–117. doi:10.1001/jamaoncol.2018.5526
15. Sun Y, Du F, Gao M, et al. Anlotinib for the treatment of patients with locally advanced or metastatic medullary Thyroid cancer. Thyroid. 2018;28(11):1455–1461. doi:10.1089/thy.2018.0022
16. Zhou AP, Bai Y, Song Y, et al. Anlotinib versus Sunitinib as first-line treatment for metastatic renal cell carcinoma: a randomized phase II clinical trial. Oncologist. 2019;24(8):e702–e708. doi:10.1634/theoncologist.2018-0839
17. Chi Y, Yao Y, Wang S, et al. Anlotinib for metastasis soft tissue sarcoma: a randomized, double-blind, placebo-controlled and multi-centered clinical trial. J Clin Oncol. 2018;36(15_suppl):11503. doi:10.1200/JCO.2018.36.15_suppl.11503
18. Singh EK, Moore DC, Muslimani A. Metastatic soft tissue sarcomas: a review of treatment and new pharmacotherapies. P t. 2018;43(7):410–429.
19. Tian Z, Liu H, Zhang F, et al. Retrospective review of the activity and safety of apatinib and anlotinib in patients with advanced osteosarcoma and soft tissue sarcoma. Invest New Drugs. 2020;38:1559–1569. doi:10.1007/s10637-020-00917-2
20. Ben-Ami E, Barysauskas CM, Solomon S, et al. Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: results of a phase 2 study. Cancer. 2017;123(17):3285–3290. doi:10.1002/cncr.30738
21. Italiano A, Bellera C, D’Angelo S. PD1/PD-L1 targeting in advanced soft-tissue sarcomas: a pooled analysis of phase II trials. J Hematol Oncol. 2020;13(1):55. doi:10.1186/s13045-020-00891-5
22. Monga V, Skubitz KM, Maliske S, et al. A retrospective analysis of the efficacy of immunotherapy in metastatic soft-tissue sarcomas. Cancers. 2020;12(7):1873. doi:10.3390/cancers12071873

23. Xi C, Wencheng Z, Dong Q, et al. Tumor regression after combination of radiation and PD-1 antibody nivolumab treatment in a patient with metastatic mediastinal leiomyosarcoma: a case report. Cancer Biol Ther. 2019;20(4):408–412. doi:10.1080/15384047.2018.1537577

24. Heine A, Kristiansen G, Schild HH, Brossart P. Successful treatment of refractory leiomyosarcoma with the PD-1 inhibitor nivolumab. Ann Oncol. 2016;27(9):1813–1814. doi:10.1093/annonc/mdw243

25. Fukumura D, Kloepper J, Amouzgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol. 2018;15(5):325–340. doi:10.1038/nrclinonc.2018.29

26. Martin-Broto J, Hindi N, Grignani G, et al. Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial. J Immunother Cancer. 2020;8(2):e001561. doi:10.1136/jitc-2020-001561

27. You Y, Guo X, Zhuang R, et al. Activity of PD-1 inhibitor combined with anti-angiogenic therapy in advanced sarcoma: a single-center retrospective analysis. Front Mol Biosci. 2021;8:747650. doi:10.3389/fmolb.2021.747650

28. Liu J, Deng YT, Jiang Y. Switch maintenance therapy with anlotinib after chemotherapy in unresectable or metastatic soft tissue sarcoma: a single-center retrospective study. Invest New Drugs. 2020. doi:10.1007/s10637-020-01015-z

29. Wang HY, Chu J-F, Zhang P, et al. Safety and efficacy of chemotherapy combined with anlotinib plus anlotinib maintenance in Chinese patients with advanced/metastatic soft tissue sarcoma. Onco Targets Ther. 2020;13:1561–1568. doi:10.2147/ott.S235349