



**Appendix Fig. 1: PFS for chemotherapy plus anlotinib maintenance treatment.** Kaplan-Meier curves of PFS for chemotherapy plus anlotinib maintenance treatment, the median was 14.0 months (95% CI 10.1-17.8). Note that progression cannot occur during the initial period of chemotherapy, because of the conditions for inclusion in this study. PFS = progression-free survival.

**Appendix Table 1: Subgroup analysis for PFS based on patient characteristics**

| Patient characteristics                          | PFS   |             |                 |
|--|-------|-------------|-----------------|
|  | HR    | 95% CI      | <i>p</i> -value |
| Sex  |       |             |                 |
| Female vs. male                                  | 0.482 | 0.213-1.092 | 0.080           |
| Age, years                                       |       |             |                 |
| ≤ 40 vs. > 40                                    | 2.632 | 1.165-5.945 | <b>0.020</b>    |
| ECOG performance status score                    |       |             |                 |
| 0 vs. 1, 2                                       | 0.634 | 0.268-1.501 | 0.30            |
| Histologic subtype                               |       |             |                 |
| Liposarcoma vs. others                           | 0.886 | 0.407-1.926 | 0.76            |
| Leiomyosarcoma vs. others                        | 1.822 | 0.808-4.110 | 0.15            |
| Synovial sarcoma vs. others                      | 0.488 | 0.108-2.209 | 0.35            |
| Primary site                                     |       |             |                 |
| Head and neck vs. others                         | 0.449 | 0.060-3.332 | 0.43            |
| Extremities vs. others                           | 1.315 | 0.451-3.833 | 0.62            |
| Trunk & retroperitoneum/intra-abdomen vs. others | 2.411 | 0.973-5.973 | 0.057           |
| Viscera vs. others                               | 0.138 | 0.019-1.022 | 0.053           |
| Metastatic site                                  |       |             |                 |

|                            |       |             |       |
|----------------------------|-------|-------------|-------|
| Yes vs. no                 | 1.745 | 0.516-5.904 | 0.37  |
| Lung vs. others            | 1.242 | 0.582-2.653 | 0.58  |
| Liver vs. others           | 1.143 | 0.477-2.741 | 0.76  |
| Bone vs. others            | 1.802 | 0.615-5.279 | 0.28  |
| Number of metastatic sites |       |             |       |
| ≤ 1 vs. > 1                | 0.612 | 0.289-1.296 | 0.20  |
| First-line chemotherapy    |       |             |       |
| Cycles: ≤ 4 vs. > 4        | 1.187 | 0.564-2.499 | 0.65  |
| Cycles: ≤ 6 vs. > 6        | 0.335 | 0.112-0.999 | 0.050 |
| Best response: PR vs. SD   | 1.092 | 0.413-2.891 | 0.86  |

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PFS = progression-free survival. CI = confidence interval. ECOG = Eastern Cooperative Oncology Group. PR = partial response. SD = stable disease.

**Appendix Table 2: Anlotinib treatment in advanced STS.**

| <b>Author and year</b>                | <b>Study</b>  | <b>Therapy</b>            | <b>Line of treatment</b>  | <b>Patient</b>                 | <b>ORR (95% CI, %)</b>          | <b>Median PFS (95% CI, months)</b>                       | <b>Median OS (95% CI, months)</b>          |
|---------------------------------------|---------------|---------------------------|---|--------------------------------|---------------------------------|--|--|
| Sun Y, et al. 2016 <sup>1</sup>       | Phase 1       | Anlotinib                 | ≥ 1 <sup>st</sup> line  | 9 advanced STS                 | 11.1                            | Not reported   | Not reported                               |
| Chi Y, et al. 2018 <sup>2</sup>       | Phase 2       | Anlotinib                 | ≥ 2 <sup>nd</sup> line  | 166 refractory metastatic STS  | 13 (7.6-18)                     | 5.6 (4.4-7.7)  | 12 (11-16)                                 |
| Chi Y, et al. 2018 <sup>3</sup>       | Phase 2b      | Anlotinib vs. placebo     | 2 <sup>nd</sup> line  | 233 advanced STS (158 vs. 75)  | 10.13                           | 6.27 vs. 1.47; <i>p</i> < 0.0001                         | Not reported                               |
| van Tine BA, et al. 2021 <sup>4</sup> | Phase 3       | Anlotinib vs. dacarbazine | ≥ 2 <sup>nd</sup> line  | 79 advanced SS (52 vs. 27)     | Not reported                    | 2.89 (2.73-6.87) vs. 1.64 (1.45-2.70); <i>p</i> = 0.0015 | Not reported                               |
| Liu J, et al. 2020 <sup>5</sup>       | Retrospective | Anlotinib vs. pazopanib   | ≥ 1 <sup>st</sup> line  | 47 metastatic ASPS (16 vs. 31) | 31.2 vs. 35.5; <i>p</i> = 0.772 | 23.6 (16.2-31.0) vs. 13.7 (10.8-16.7); <i>p</i> = 0.023  | Not reached                                |
| Liu J, et al. 2021 <sup>6</sup>       | Retrospective | Anlotinib                 | Initial: ≥ 1 <sup>st</sup> line, rechallenge: ≥ 1.5 months of initial TKI | 16 advanced STS                | Initial: 12.5<br>Rechallenge: 0 | Initial: 4.7<br>Rechallenge: 4.7                         | Initial: 26.5<br>Rechallenge: not reported |
| Zou H, et al. 2022 <sup>7</sup>       | Retrospective | Anlotinib                 | ≥ 1 <sup>st</sup> line  | 19 advanced LMS                | 15.8                            | 4.1 (3.0-5.2)  | 23.5 (14.2)                                |

|                                     |               |                            |                        |   |      |                |                  |
|-------------------------------------|---------------|----------------------------|------------------------|---|------|----------------|------------------|
|                                     |               | Total                      |                        | 31 refractory STS                           | 19.4 | 5.4 (4.1-6.8)  | 17.9 (11.2-24.6) |
| Cai M, et al. 2022 <sup>8</sup>     | Retrospective | Anlotinib alone            | ≥ 1 <sup>st</sup> line | 16 patients                                 | 6.3  | 5.4 (4.9-6.0)  | 22.8 (12.4-33.2) |
|                                     |               | Anlotinib + chemotherapy   |                        | 13 patients                                 | 38.5 | 5.7 (3.3-8.1)  | 17.9 (13.3-22.5) |
|                                     |               | Anlotinib + radiotherapy   |                        | 2 patients                                  | 0    | 1.4 (-)        | 6.3 (-)          |
| Zhang XY, et al. 2022 <sup>9</sup>  | Retrospective | Total                      |                        | 35 unresectable or metastatic STS (≥ 60 yr) | 8.6  | 5.5 (1.4-9.6)  | 14.3 (9.6-19.0)  |
|                                     |               | Anlotinib alone            | ≥ 1 <sup>st</sup> line | 30 patients                                 | 6.7  | Not reported   | Not reported     |
|                                     |               | Combination therapy        |                        | 5 patients                                  | 20.0 |                |                  |
| Zhang RS, et al. 2022 <sup>10</sup> | Retrospective | Total                      |                        | 209 advanced STS                            | 13.4 | 6.1 (4.9-7.2)  | 16.4 (13.6-19.1) |
|                                     |               | Anlotinib alone            | ≥ 1 <sup>st</sup> line | 112 patients                                | 8.0  | 4.0 (2.8-5.1)  | 12.8 (9.3-16.2)  |
|                                     |               | Combination therapy        |                        | 62 patients                                 | 24.2 | 7.9 (5.5-10.2) | 18.1 (7.3-28.8)  |
|                                     |               | Switch maintenance therapy |                        | 35 patients                                 | 11.4 | 7.8 (4.6-10.9) | Not reached      |

|                                   |               |                             |                           |  |       |                       |                       |
|-----------------------------------|---------------|-----------------------------|---------------------------|--|-------|-----------------------|-----------------------|
|                                   |               | Total                       |                           | 22 advanced STS  | 40.9  |                       |                       |
| Yao W, et al. 2022 <sup>11</sup>  | Retrospective | Anlotinib alone             | $\geq 1^{\text{st}}$ line | 9 patients   | 22.2  | Not reported          | Not reported          |
|                                   |               | Anlotinib + chemotherapy    |                           | 9 patients   | 44.4  |                       |                       |
|                                   |               | Anlotinib + immunotherapy   |                           | 4 patients   | 75.0  |                       |                       |
|                                   |               |                             |                           |  |       |                       |                       |
| Tian Z, et al. 2020 <sup>12</sup> | Retrospective | Anlotinib                   | $\geq 2^{\text{nd}}$ line | 29 advanced STS  | 13.79 | $6.03 \pm 4.50$       | Not reported          |
| Yuan M, et al. 2021 <sup>13</sup> | Prospective   | Anlotinib + anti-PD-1       | $\geq 1^{\text{st}}$ line | 4 advanced STS   | 25.0  | 5.64                  | Not reported          |
|                                   |               | Anlotinib alone or combined |                           | 17 unresectable local recurrence or metastatic WDLS/DDLS |       | 27.9 weeks (3.3-69.7) | 56.6 weeks (3.3-79.4) |
| Li ZK, et al. 2021 <sup>14</sup>  | Retrospective | DDLS                        | $\geq 1^{\text{st}}$ line | 15 patients  | 0     | 27.1 weeks (3.3-59)   | 56.6 weeks (3.3-74.3) |
|                                   |               | 1 <sup>st</sup> line        |                           | 12 patients  |       | 39.1 weeks (3.3-69.7) | 70.4 weeks (3.3-79.4) |

|                                   |               |   |                        |  |                                |   |  |
|-----------------------------------|---------------|---|------------------------|--|--------------------------------|---|--|
|                                   |               | Anlotinib alone                                     |                        | 13 patients                                |                                | 27.1 weeks (3.3-51.7)                             | 56.6 weeks (3.3-70.4)                                  |
| Xu J, et al. 2021 <sup>15</sup>   | Phase 1b/2    | Anlotinib + vincristine + irinotecan                | ≥ 2 <sup>nd</sup> line | 24 adult advanced ES received chemotherapy | 62.5 at 12w                    | 10.2 (6.0-14.2)                                   | Not reached  |
|                                   |               | Gemcitabine + docetaxel vs. gemcitabine + anlotinib |                        | 122 advanced STS (81 vs. 41)               | 18.5 vs. 14.6; <i>p</i> = 0.17 | 5.8 (6.0-8.4) vs. 6.8 (6.2-9.2); <i>p</i> = 0.39  | 14.7 (13.9-18.9) vs. 13.3 (12.8-18.0); <i>p</i> = 0.75 |
| Liu Z, et al. 2022 <sup>16</sup>  | Retrospective | LMS   | ≥ 1 <sup>st</sup> line | 58 advanced STS (38 vs. 20)                | Not reported                   | 6.5 (5.4-7.7) vs. 7.5 (6.2-10.6); <i>p</i> = 0.08 | 17.2 (14.4-20.1) vs. 16.2 (12.1-20.7); <i>p</i> = 0.76 |
|                                   |               | 1st line  |                        | 57 advanced STS (37 vs. 20)                | Not reported                   | 6.2 (5.3-8.2) vs. 7.1 (5.9-9.9); <i>p</i> = 0.51  | 15.7 (12.7-18.5) vs. 13.6 (10.5-17.9); <i>p</i> = 0.62 |
| Sun X, et al. 2022 <sup>17</sup>  | Retrospective | Anlotinib + anti-PD-1                               | ≥ 2 <sup>nd</sup> line | 32 metastatic STS                          | 34.4                           | 7.6 (3.31-11.89)                                  | 14.9 (8.36-21.44)                                      |
| Liu J, et al. 2022 <sup>18</sup>  | Phase 2       | TQB2450 + anlotinib                                 | ≥ 2 <sup>nd</sup> line | 30 locally advanced or metastatic STS      | 36.67                          | 7.85 (2.89-23.06)                                 | Not reached  |
|                                   |               |   |                        | 12 ASPs                                    | 75.0                           | 23.06 (8.97-NE)                                   | Not reached  |
| Tie XJ, et al. 2023 <sup>19</sup> | Retrospective | Anlotinib + S-1                                     | 2 <sup>nd</sup> line   | 21 advanced STS                            | 28.57                          | 8.4   | Not reported   |

|                                    |               |   |  |   |   |   |                                 |
|------------------------------------|---------------|---|--|---|---|---|---------------------------------|
| Wu J, et al. 2023 <sup>20</sup>    | Retrospective | Anlotinib + camrelizumab  | 1 <sup>st</sup> or 2 <sup>nd</sup> line                                      | 57 retroperitoneal STS<br>38 L-sarcoma (liposarcoma and leiomyosarcoma)<br>vs. 19 non-L-sarcoma | 26.3<br><br>13.2 vs. 52.6;<br><i>p</i> = 0.0031 | 9.1 (5.6–16.8)<br><br>6.3 vs. 11.1; <i>p</i> = 0.0256 | Not reported<br><br>Not reached |
| Liu J, et al. 2021 <sup>21</sup>   | Retrospective | Anlotinib switch maintenance  | Achieved PR/SD after 1 <sup>st</sup> or 2 <sup>nd</sup> line of chemotherapy | 21 advanced STS   | 14.3  | PFSa: 7.3<br>PFSc: 13.6                               | Not reported                    |
| Wang HY, et al. 2020 <sup>22</sup> | Retrospective | Chemotherapy + anlotinib followed by anlotinib maintenance          | 1 <sup>st</sup> -3 <sup>rd</sup> line  | 32 advanced or metastatic STS   | 34.4  | 8.2 (5.4-10.6)  | Not reached                     |
| Liu Z, et al. 2021 <sup>23</sup>   | Retrospective | Anlotinib + liposomal doxorubicin followed by anlotinib maintenance | ≥ 1 <sup>st</sup> line   | 27 metastatic STS   | 40.7  | 7.0 (5.3-8.1)   | Not reached                     |
| Wang ZM, et al. 2022 <sup>24</sup> | Phase 2       | Anlotinib + epirubicin followed by anlotinib maintenance            | 1 <sup>st</sup> line   | 30 locally advanced or metastatic STS (13 continued anlotinib maintenance therapy)              | 13.33   | 11.5 (8.6-14.4)                                       | Not reached                     |



ORR = objective response rate. PFS = progression-free survival. CI = confidence interval. OS = overall survival. AE = adverse events. STS = soft tissue sarcoma. SS = synovial sarcoma. WDLS = well-differentiated liposarcoma. DDLS = dedifferentiated liposarcoma. ES = Ewing's sarcoma. ASPS = alveolar soft part sarcoma. PR = partial response. SD = stable disease. NE = not evaluated.

Reference:

1. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. *J Hematol Oncol* 2016; **9**: 105.
2. 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**: 5233-8.
3. 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**: abstr 11503.
4. van Tine B, Chawla S, Trent J, et al. A phase III study (APROMISS) of AL3818 (Catequentinib, Anlotinib) hydrochloride monotherapy in subjects with metastatic or advanced synovial sarcoma. *J Clin Oncol* 2021; **39**: 11505.
5. Liu J, Fan Z, Li S, et al. Target therapy for metastatic alveolar soft part sarcoma: a retrospective study with 47 cases. *Ann Transl Med* 2020; **8**: 1493.

6. Liu J, Deng YT, Wu X, Jiang Y. Rechallenge with multi-targeted tyrosine kinase inhibitors in patients with advanced soft tissue sarcoma: a single-center experience. *Cancer Manag Res* 2021; **13**: 2595-601.
7. Zou H, Xia L, Jin G, et al. Retrospective Review of Efficacy and Safety of Anlotinib in Advanced Leiomyosarcoma: A Real-World Study. *Cancer Manag Res* 2022; **14**: 1703-11.
8. Cai M, Zhu J, Zhou G. Efficacy and safety of treating refractory bone and soft tissue sarcoma with anlotinib in different treatment patterns. *Comput Math Methods Med* 2022; **2022**: 3287961.
9. Zhang XY, Liu J, Deng YT, Jiang Y. Anlotinib treatment in elderly patients with unresectable or metastatic soft tissue sarcoma: a retrospective study. *Anticancer Drugs* 2022; **33**: e519-e24.
10. Zhang RS, Liu J, Deng YT, Wu X, Jiang Y. The real-world clinical outcomes and treatment patterns of patients with unresectable locally advanced or metastatic soft tissue sarcoma treated with anlotinib in the post-ALTER0203 trial era. *Cancer Med* 2022; **11**: 2271-83.
11. Yao W, Du X, Wang J, Wang X, Zhang P, Niu X. Long-term efficacy and safety of anlotinib as a monotherapy and combined therapy for advanced sarcoma. *Onco Targets Ther* 2022; **15**: 669-79.
12. 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**: 1559-69.
13. Yuan M, Zhu Z, Mao W, et al. Anlotinib combined with anti-PD-1 antibodies therapy in patients with advanced refractory solid tumors: a single-center, observational, prospective study. *Front Oncol* 2021; **11**: 683502.

14. Li ZK, Liu J, Deng YT, Jiang Y. Efficacy and safety of anlotinib in patients with unresectable or metastatic well-differentiated/dedifferentiated liposarcoma: a single-center retrospective study. *Anticancer Drugs* 2021; **32**: 210-4.
15. Xu J, Xie L, Sun X, et al. Anlotinib, Vincristine, and Irinotecan for advanced ewing sarcoma after failure of standard multimodal therapy: a two-cohort, phase Ib/II trial. *Oncologist* 2021; **26**: e1256-e62.
16. Liu Z, Wang X, Wang J, et al. Gemcitabine plus anlotinib is effective and safe compared to gemcitabine plus docetaxel in advanced soft tissue sarcoma. *Front Oncol* 2022; **12**: 922127.
17. Sun X, Xu J, Xie L, Guo W. Effectiveness and tolerability of anlotinib plus PD-1 inhibitors for patients with previously treated metastatic soft-tissue sarcoma. *Int J Gen Med* 2022; **15**: 7581-91.
18. Liu J, Gao T, Tan Z, et al. Phase II study of TQB2450, a novel PD-L1 antibody, in combination with anlotinib in patients with locally advanced or metastatic soft tissue sarcoma. *Clin Cancer Res* 2022; **28**: 3473-9.
19. Tie XJ, Yang CG, Gao YH, Liu PJ. Efficacy of anlotinib combined with S-1 as the second-line treatment for advanced soft tissue sarcoma. *Asian J Surg* 2023; **46**: 1050-1.
20. Wu J, Li C, Liu B, et al. Efficacy and safety of anlotinib plus camrelizumab in treating retroperitoneal soft tissue sarcomas: a single-center retrospective cohort study. *Ann Transl Med* 2023; **11**: 212.
21. 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* 2021; **39**: 330-6.

22. Wang HY, Chu JF, 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**: 1561-8.
23. Liu Z, Yao W, Zhao Y, Liu O, Zhang P, Ge H. Efficacy and safety of anlotinib combined with liposomal doxorubicin followed by anlotinib maintenance in metastatic soft tissue sarcomas. *Cancer Manag Res* 2021; **13**: 1009-16.
24. Wang Z, Zhuang R, Guo X, et al. Anlotinib plus epirubicin followed by anlotinib maintenance as first-line treatment for advanced soft tissue sarcoma: an open-label, single-arm, phase 2 trial. *Clin Cancer Res* 2022; **28**: 5290-6.