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Commentary

# PDGFRα inhibition in soft-tissue sarcomas: Have we gotten it all wrong?

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Soft-tissue sarcomas (STS) are a wide group of rare cancers of mesenchymal origin. Treatment modalities include surgery, radiotherapy and chemotherapy, mostly depending on the stage of the disease, its anatomical location, and histological subtype [1].

The cornerstone of STS medical therapy for locally unresectable and metastatic cases has been chemotherapy with anthracyclines for more than 40 years [1]; all other therapeutic agents showing little to no benefit compared to an anthracycline monotherapy. Despite seemingly negative results in a large phase III trial, the combination of an anthracycline with ifosfamide is often considered by clinicians in cases where tumor shrinkage or symptoms' control are a priority [2].

In patients with a high-risk disease where surgery alone might severely compromise organ function or anatomy, radiation therapy (RT) is considered a standard treatment modality, especially in the neoadjuvant setting [1], alone or in combination with chemotherapy [3].

In 2016, this scenario was suddenly subverted by an open-label phase Ib and randomized phase II trial showing an impressive 1-year benefit in overall survival with the addition of olaratumab –a monoclonal antibody targeting PDGFRα– to doxorubicin [4]. Surprisingly, in the pivotal phase Ib/II trial, tumor PDGFRα expression did not have any positive predictive value [4], raising questions on the postulated mechanism of action of olaratumab [5]. These data led to the provisional approval of olaratumab in the first-line treatment of STS both in the U.S.A. and in Europe, pending the results of the confirmatory phase III clinical trial ANNOUNCE.

Unfortunately, Eli Lilly and Company in January 2019 reported the results of this trial, which did not meet the primary endpoints of overall survival in the full study population or in the leiomyosarcoma subpopulation, with no difference in survival between the study arms for either population [6]. U.S. and European regulatory agencies decided to halt prescription of olaratumab to newly diagnosed STS patients previously eligible for this treatment. The full publication of these data later this year is awaited for a complete evaluation of the trial.

After these results, it becomes of paramount importance to better understand whether PDGFRα inhibition might still have any role in STS therapy, and if so, the molecular mechanisms involved. To increase the complexity, it must be considered that PDGFRα expression is spatially and temporally dynamic, and it is not restricted to tumor cells, being also present in tumor-associated fibroblasts and vascular endothelial cells. Its inhibition might therefore also have indirect and more subtle effects [5].

The paper by Song et al. published in EBioMedicine [7] investigated the role of PDGFRα inhibition in combination with RT in a genetically engineered and carcinogen-induced mouse model of undifferentiated pleomorphic sarcoma (UPS), a common subtype of STS. The Authors show that 1E10Fc, a specific anti-PDGFRα antibody, does not affect tumor growth alone or in combination with RT. The model here presented is different in many ways from the other preclinical study of PDGFRα inhibition in murine models of sarcoma described by Lowery et al., which instead concluded that olaratumab, alone and in combination with standard of care, blocked the growth of PDGFRα-expressing sarcoma models [8]. Song and colleagues used immune-competent mice and induced spontaneous tumors histologically resembling UPS, whereas Lowery and colleagues used immune-compromised mice transplanted with human xenografts derived from other histologies, i.e. PDGFRα-expressing pediatric osteosarcoma and malignant rhabdoid tumors [8].

After the negative results of the ANNOUNCE trial, it is difficult to imagine a role for PDGFRα inhibition in STS therapy. The paper from Song et al. also showed a negligible effect of PDGFRα inhibition, in monotherapy or in combination with RT. It is however interesting to note that Song et al. reported that fewer mice treated with 1E10Fc developed micrometastases in the lung. This result was not statistically significant, but the in vivo experiment was not powered enough to detect this difference.

If this effect were to be confirmed, it might be important to explore whether olaratumab might be repositioned in the neoadjuvant or adjuvant setting, or PDGFRα inhibition will return a speculative and elusive target in STS therapy.

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## References

[1] Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Supplement_4):iv51–67.

[2] Judson I, Verweij J, Gelderblom H, Hartmann JT, Schoffski P, Blay JY, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of

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https://doi.org/10.1016/j.ebiom.2019.01.062

advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014;15(4):415–23.
[3] Palassini E, Ferrari S, Verderio P, De Paoli A, Martin Broto J, Quagliuolo V, et al. Feasibility of preoperative chemotherapy with or without radiation therapy in localized soft tissue sarcomas of limbs and superficial trunk in the Italian sarcoma Group/Grupo Espanol de Investigacion en Sarcomas Randomized Clinical Trial: three versus five cycles of full-dose epirubicin plus Ifosfamide. J Clin Oncol 2015; 33(31):3628–34.
[4] Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, 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.
[5] Vincenzi B, Badalamenti G, Napolitano A, Spalato Ceruso M, Pantano F, Grignani G, et al. Olaratumab: PDGFR-alpha inhibition as a novel tool in the treatment of advanced soft tissue sarcomas. Crit Rev Oncol Hematol 2017;118:1–6.
[6] Eli Lilly and Company. Available from: https://investor.lilly.com/news-releases/news-release-details/lilly-reports-results-phase-3-soft-tissue-sarcoma-study; 2019.
[7] Song EJ, Ashcraft KA, Lowery CD, Mowery YD, Luo L, Ma Y, et al. Investigating a chimeric anti-mouse PDGFRα antibody as a radiosensitizer in primary mouse sarcomas. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.01.046.
[8] Lowery CD, Blosser W, Dowless M, Knoche S, Stephens J, Li H, et al. Olaratumab Exerts antitumor activity in preclinical models of pediatric bone and soft tissue tumors through inhibition of platelet-derived growth factor receptor alpha. Clin Cancer Res 2018;24(4):847–57.