

Olaratumab in soft-tissue sarcomas

In reply to: Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Tap WD. et al. The Lancet, Volume 388, Issue 10043, 30 July–5 August 2016, Pages 488-497.

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More than 40 years after Benjamin and colleagues¹ reported the benefit of doxorubicin in metastatic soft-tissue sarcomas, doxorubicin either as monotherapy or in combination with ifosfamide is still the standard first-line treatment in most soft-tissue sarcomas.²

In contrast to gastrointestinal stromal tumours in which the introduction of multitargeted tyrosine kinase inhibitors that target KIT or platelet-derived growth factor receptor (PDGFR) mutated tumours have led to an impressive improvement in survival, this success has not been achieved in non-gastrointestinal stromal tumour soft-tissue sarcomas. The development of novel systemic treatments in soft-tissue sarcomas is challenging: there are more than 70 different histological subtypes, with heterogeneous genetic make-up and clinical behaviour including age at diagnosis and disease aggressiveness.^{3,4,5} Data show differences between subtypes of soft-tissue sarcomas in overall survival, measured from the start of the first systemic treatment for advanced disease, from 9.3 months in undifferentiated pleiomorphic sarcoma to 24.4 months in leiomyosarcomas.⁶

William Tap and colleagues⁷ report in *The Lancet* an open-label phase 1b and randomised phase 2 trial of olaratumab and doxorubicin versus doxorubicin alone in unresectable and metastatic soft-tissue sarcomas. Olaratumab is a human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that binds to PDGFR α and blocks the PDGF-AA, PDGF-BB, and PDGF-CC ligands from binding to the receptor. Adult patients with locally advanced or metastatic soft-tissue sarcomas, anthracycline naive with performance status of 0–2, and availability of tumour material were eligible. The primary endpoint of the phase 2 study was progression-free survival (PFS); overall survival, response rate, and safety were secondary endpoints. Patients were either randomly assigned to a maximum of eight courses of 75 mg/m² doxorubicin on day 1 with 15 mg/kg olaratumab on days 1 and 8 with the option to continue with the antibody alone until disease progression, or to doxorubicin, in which patients with disease progression could be treated with olaratumab.

The results of 133 patients in the intention-to-treat analysis, 66 in the combination group and 67 in the doxorubicin group, showed a gain in median PFS of 6.6 months (95% CI 4.1–8.3, IQR 2.7–10.2) versus 4.1 months (2.8–5.4, 1.6–7.4), a significant median overall survival gain in the combination group of 26.5 months (20.9–31.7, 13.8 to not assessable) versus 14.7 months (9.2–17.1, 5.5–26.0), a hazard ratio (HR) of 0.46 (95% CI 0.30–0.71), but no difference in objective response rate, which was 18.2% (9.8–29.6) versus 11.9% (5.3–22.2). The median number of doxorubicin courses in the combination group versus the single agent doxorubicin group was seven and four, the response duration was 8.3 versus 8.2 months, respectively. Of the 129 patients who started their assigned treatment, 38 (59%) of 64 patients in the olaratumab plus doxorubicin group versus 44 (68%) of 65 patients in the doxorubicin group died from disease, and no patients versus six (9%) patients died from adverse events, respectively. The HR for overall survival was 0.38 (95% CI 0.21–0.68) in

those with a disease duration of less than 14.95 months and was 0.68 (0.37–1.25) in those with disease equal to or longer than 14.95 months. In terms of adverse events, neutropenia, mucositis, nausea, vomiting, and diarrhoea were more frequent in the olaratumab and doxorubicin group than in the doxorubicin alone group. Febrile neutropenia of grade 3 or greater was similar in both groups.

It is not the first study targeting PDGFR in non-gastrointestinal stromal tumour soft-tissue sarcomas. Pazopanib, a multitargeted tyrosine kinase inhibitor targeting VEGFR 1, 2, 3 and PDGFR α and PDGFR β was first tested in soft-tissue sarcomas in a multistrata EORTC phase 2 study.⁸ In the subsequent phase 3 PALETTE study,⁹ patients with metastatic non-adipocytic soft-tissue sarcomas were randomly assigned to either pazopanib or placebo after first-line treatment, provided they had progression according to Response Evaluation Criteria In Solid Tumors (version 1.1). This study showed a significant median PFS advantage of 3 months and a non-significant gain in median overall survival of 1.8 months.⁹ Remarkably, pazopanib was introduced as an angiogenesis inhibitor because of its activity in clear cell renal cancer, but it cannot be excluded that its mode of action in soft-tissue sarcomas at least partly encompasses targeting PDGFR.

In Tap and colleagues' study, the difference in overall survival of almost a year, which is far beyond the gain in PFS of 2.5 months, is as much promising as puzzling. Histologies seem to be reasonably balanced between the groups, with leiomyosarcomas as the largest group. The exact effect of various post-study treatments, including local treatments, is not easy to interpret. Differences in the pace of progression before start of treatment might have affected the results because no specific time period in which progression should have occurred before patients entered the study was defined and only the group with shorter history of disease showed a significant increase in overall survival. The double-blind, phase 3 ANNOUNCE study (NCT02451943) with doxorubicin plus olaratumab or placebo, which is currently recruiting, has overall survival as the primary endpoint and because of the higher number of patients, the result will be more powerful than Tap and colleagues' study. Although more toxicity was noted in the combination group, treatment-related deaths were confined to the doxorubicin group. The maximum number of eight courses of doxorubicin, 600 mg doxorubicin/m² cumulative, is unusual and is above the general dosage that is deemed safe of 450–500 mg/m², which raises concern¹⁰ and given the context of the study population long-term follow-up data are absent. The consequential necessity to add the cardioprotective dexrazoxane noticeably increases the total costs of this treatment.

Finally, why does targeting PDGFR α and its combination with doxorubicin lead to this impressive gain in overall survival? In-depth knowledge about PDGFR receptors, the relevance of their presence in tumour and stroma, their ligands, and signalling pathways is still relatively scarce in sarcomas.^{11,12} For successful antibody treatment, the presence of accessible membranous receptors and affinity of the antibody to the receptors are key factors and these will probably be different between soft-tissue

sarcoma subtypes. The evaluation of PDGFR α expression as was done in Tap and colleagues' study showed difficulties in standardisation, which have to be solved, but most probably finding a predictive biomarker will be much more complex and potentially not be universal across all soft-tissue sarcomas.

In view of the desperate need of patients with soft-tissue sarcomas for new active drugs, the findings of Tap and colleagues are promising but need confirmation in a larger study. The results of ANNOUNCE are eagerly awaited, alongside a better understanding of the mode of action of olaratumab and a biomarker related to PDGFR α for optimum patient selection.

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