

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)

Letter to the Editor

## Olaratumab failure in sarcomas: what are the lessons learned?

Antoine Italiano<sup>a,b</sup><sup>a</sup> *Institut Bergonié, Early Phase Trials and Sarcoma Units, Bordeaux, France*<sup>b</sup> *University of Bordeaux, France*

Received 3 April 2019; accepted 8 April 2019

Available online 27 June 2019

Antoniou *et al.* [1] published an excellent review describing the potential of development of Platelet-derived growth factor receptor (PDGFR $\alpha$ ) targeting with olaratumab in sarcomas in a recent issue of the *European Journal of Cancer*.

Indeed, in 2016, Tap *et al.* published the results of a randomised phase II study showing that treatment with olaratumab in combination with doxorubicin reduced the risk of death by 53.7% (hazard ratio = 0.463;  $p = 0.0003$ ) in comparison with doxorubicin alone, representing an 80% longer median overall survival (OS) for patients in the investigational arm (26.5 months, compared with 14.7 months) [2].

Few months after the publication of these data, the US Food and Drug Administration and European Medicines Agency (EMA) granted accelerated and conditional approval, respectively, for olaratumab for the treatment of patients with soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate. Thousands of sarcoma patients were treated with olaratumab across the globe between 2016 and early 2019. However, the efficacy results observed in this phase II study were associated with several uncertainties; we pointed out in a review published in 2017 that render, in our opinion,

this market authorisation by the regulatory agencies premature [3]. Indeed, the survival gain was too substantial for it not to be related to a systemic bias inherent to the study [3]. In June 2019, Tap *et al.* reported that the phase III study investigating olaratumab, in combination with doxorubicin versus doxorubicin alone in patients with advanced or metastatic STS, did not meet the primary end-points of OS in the full study population or in the leiomyosarcoma subpopulation; there was no difference in survival between the study arms for either population [4].

What should be the lessons learned by such a failure?

First, physicians and regulators should remember that a randomised phase II trial is not a phase III trial and is, therefore, not intended to demonstrate the superiority of an experimental drug in comparison to standard therapy. The now-defunct investigational drug iniparib featured prominently at the 2009 meeting of the American Society of Clinical Oncology. Preliminary data from a study of 123 women with triple-negative breast cancer suggested that treatment with a combination of iniparib, gemcitabine and carboplatin extended progression-free survival (PFS) from a median of 3.6 months to 5.9 months and prolonged OS from 7.7 to 12.3 months. This drug attracted substantial interest. Indeed, at that point, iniparib was the only targeted therapy that had been tested against triple-negative breast cancer for which randomised data existed. The results proved to be optimistic. However, in 2011, less

DOI of original article: <https://doi.org/10.1016/j.ejca.2017.12.026>.  
E-mail address: [a.italiano@bordeaux.unicancer.fr](mailto:a.italiano@bordeaux.unicancer.fr).

than 1 month after the complete phase II study was published [5], the iniparib sponsor Sanofi announced that the drug failed in an expanded phase III study. Although iniparib did extend the median PFS by 1 month and median OS by approximately 2.5 months, the results were not statistically significant.

Second, convincing preclinical data are needed to support the clinical development of a specific targeted therapy in sarcomas. Indeed, no clear relationship was established between PDGFR $\alpha$  expression in preclinical sarcoma models and olaratumab activity echoing the findings of the phase II study [1,6].

Finally, given their heterogeneity, histology- and/or biomarker-directed therapy should be regarded now as the gold standard for clinical research in sarcomas, and early or late-phase clinical studies mixing all histologies should be definitely abandoned and considered as unethical because none of them met its primary end-point [7].

#### Conflict of interest statement

The authors have no conflict of interest.

#### References

- [1] Antoniou G, Lee ATJ, Huang PH, Jones RL. Olaratumab in soft tissue sarcoma - current status and future perspectives. *Eur J Cancer* 2018 Mar;92:33–9.
- [2] 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;388:488–97.
- [3] O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med* 2011;364:205–14.
- [4] Tap W, Wagner A, Papai Z, Ganjoo K, Yen CC, Schoffski P, et al. ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). *J Clin Oncol* 2019;37(Sppl; abstr LBA3).
- [5] Teyssonneau D, Italiano A. Olaratumab for soft tissue sarcoma. *Expert Opin Biol Ther* 2017;17:1019–25.
- [6] 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; 24:847–57.
- [7] Toulmonde M, Bellera C, Mathoulin-Pelissier S, Debled M, Bui B, Italiano A. Quality of randomized controlled trials reporting in the treatment of sarcomas. *J Clin Oncol* 2011;29:1204–9.