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Letter to the Editor

Negative phase III trials announce the need for biomarkers in sarcoma

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We thank Antoine Italiano for his commentary on our review of the platelet-derived growth factor receptor alpha targeting antibody, olaratumab, in sarcomas [1,2]. On the background of the recently reported negative results of the phase III trial of doxorubicin plus olaratumab versus doxorubicin plus placebo (ANNOUNCE), there are two further crucial points that are important for the general oncology community [3].

The negative results of the ANNOUNCE trial should be considered in the context of two other recent negative phase III trials of novel agents in combination with doxorubicin in advanced soft-tissue sarcomas [4,5]. As was the case in the ANNOUNCE trial, these trials recruited patients across a broad range of sarcoma subtypes, encompassing marked heterogeneity in the clinical phenotype and underlying cancer biology. Such 'all-comer' phase III trials are at risk of cohort heterogeneity diluting any subgroup-specific efficacy signal to a point beyond detection. Indeed, there have been anecdotal reports of benefit to olaratumab in a very rare, chemoresistant subtype called clear-cell sarcoma. It is notable that the successful phase III trials of eribulin, trabectedin and pazopanib in advanced soft tissue sarcoma (STS) all limited their recruitment to patients with sarcoma with subtypes that were preselected on the basis of subtype-specific phase II efficacy data [6–8]. Such considerations suggest effort to identify potentially sensitive histological subtypes in earlier phase studies may help avoid disappointment in future phase III studies in sarcomas.

There have been notable successes with histological subtype–specific trials in sarcomas with relatively simple and homogeneous biology, including gastrointestinal stromal tumours, dermatofibrosarcoma protuberans and inflammatory myofibroblastic tumour. The ANNOUNCE trial was designed to provide some distinction between sarcoma subtypes—randomisation was prospectively stratified on the basis of leiomyosarcoma vs. non-leiomyosarcoma histology, and the primary end-point of the trial was overall survival (OS) by intention-to-treat analysis in the total and leiomyosarcoma-specific cohorts. This followed on from the reported OS benefit of olaratumab in both leiomyosarcoma and heterogeneous 'other' subgroups in the preceding phase II trial [9]. The subsequent absence of the leiomyosarcoma-specific efficacy signal in the ANNOUNCE trial highlights the limitations of current histology-based sarcoma classification in providing predictive biomarkers for treatment response.

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Leiomyosarcoma is not a single disease entity but a group of different cancers that can be distinguished by contrasting tissue of origin, histological grade, molecular pathology and clinical phenotype, including response to systemic therapy. A similar degree of intrasubtype heterogeneity is seen across many sarcoma subtypes, particularly those with complex karyotypes, and indicates that histological classification as a single factor may not be the full answer to treatment selection and trial stratification. This is illustrated by the evaluation of insulin-like growth factor-I receptor inhibitors in Ewing sarcoma [10,11]. Phase I and II clinical trials of these agents demonstrate that approximately 10–15% of patients with advanced Ewing sarcoma can derive durable benefit, but current means of classification have so far failed to identify the population most likely to benefit from these agents.

The development of molecular biomarkers is a currently underdeveloped but promising avenue for the investigation of novel agents and also for the optimised use of currently approved agents in sarcomas. Gene expression–based molecular subgroups have been described in leiomyosarcoma that are associated with contrasting prognosis and that transcend anatomical classification [12]. Meanwhile, a 67-gene signature for chromosomal instability has been successfully validated as a prognostic biomarker across a range of sarcoma subtypes and is under investigation as a predictive biomarker for effect of chemotherapy [13]. Such studies provide a template for the discovery and development of biologically defined biomarkers that could provide an additional stratum of classification both within and across sarcoma subtypes.

The negative results of the ANNOUNCE and other phase III trials have been a huge disappointment to patients and the sarcoma research community. Furthermore, the failure to translate promising early-phase data into the successful registration of effective novel treatments poses a significant threat to future commercial interest in drug development for these rare diseases that are subject to an urgent need for therapeutic advances. We agree with Dr. Italiano that it is imperative that investigators learn from these setbacks when designing future studies.

Conflict of interest statement

R.L.J. has received compensation from Eisai, PharmaMar, Merck, ZIOPHARM and Morphotek for the service as a consultant. A.T.J.L. and P.H.H. declare no competing interests.

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