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Current Perspective

# The fate of new fosfamides in phase III studies in advanced soft tissue sarcoma

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**Abstract** For decades, doxorubicin alone or in combination with ifosfamide has been used in advanced soft tissue sarcoma (STS). In 2014, a comparison of doxorubicin alone versus the combination with ifosfamide (in the randomised phase III EORTC 62012) showed no difference in overall survival (OS), but a difference in response and progression-free survival (PFS) were observed in favour of the combination but at the expense of increased toxicity. Newer fosfamides, with slightly different modes of action, and potentially less toxicity, namely evofosfamide and palifosfamide have recently been tested in randomised phase III clinical trials in STS. The TH CR-406/SARC021 (June 2017) and the PICASSO III (September 2016) studies compared doxorubicin, as the standard arm, to doxorubicin in combination with evofosfamide and palifosfamide, respectively. In both studies, the combination arm produced increased response rates but at the expense of higher toxicity. However, there was no difference in OS or PFS in favour of the combination. Importantly, the median OS of patients receiving standard of care, doxorubicin, in both studies appeared improved from 12.8 months (95.5% CI 10.5–14·III) in the EORTC 62012 to 16.9 months (95% CI 14.8 to 22.9) in PICASSO III and 19.0 months (95% CI 16.2–22.4) in TH CR-406/SARC021. The results of these three randomised phase III studies highlight several critical issues related to the design and conduct of such trials in STS. We discuss these issues aiming to contribute to the ongoing debate about the optimal approach to perform clinical research in STS.


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Sarcomas are a rare group of heterogeneous mesenchymal tumours comprising over 70 histological subtypes of varying underlying biological and clinical behaviour [1]. Management is challenging because of the rarity and the diversity of the disease. Despite significant advances in the molecular characterisation and classification of sarcomas, effective targeted therapy has only truly influenced the outcomes of patients with gastrointestinal stromal tumours with activating mutations in KIT or PDGFRA after the introduction of multitargeted tyrosine kinase inhibitors [2]. In contrast, for most soft tissue sarcomas (STSs), conventional chemotherapy remains the standard systemic option in the advanced/metastatic setting with two drugs monopolising first-line treatment over the last few decades: doxorubicin [3,4] and ifosfamide [5]. For many years, empirically, doxorubicin was used as monotherapy or in combination with ifosfamide. A head-to-head comparison of the two regimens (EORTC 62012: doxorubicin alone or in combination with ifosfamide) in a randomised controlled phase III trial (RCT) reported in 2014 showed no difference in overall survival (OS), although a difference in progression-free survival (PFS) in favour of the combination was noted at the expense of increased toxicity [6].

Ifosfamide is an alkylating agent undergoing transformation in the liver to become active. The toxicity profile of ifosfamide, primarily the risk of bone marrow suppression, haemorrhagic cystitis and encephalopathy, has provided the rationale for the development of newer analogues with less toxic metabolites. One such agent, palifosfamide, is a tris salt of isophosphoramide mustard, the active metabolite of ifosfamide. Another analogue is evofosfamide, a hypoxia-activated prodrug of bromo-isophosphoramide mustard, which under hypoxic conditions, can function as a DNA cross-linking agent [7]. Tap *et al.* report, in the Lancet Oncology (June 23, 2017 epub ahead of print), the results of TH CR-406/SARC021, a phase III, multicentre, randomised, open-label trial assigning patients with advanced or metastatic STS to receive either doxorubicin alone or in combination with evofosfamide as first-line treatment, with continuation of evofosfamide in non-progressive patients [8]. Evofosfamide had previously demonstrated activity against advanced STS in combination with doxorubicin in a single-arm phase II trial of 91 patients [9], reaching a median OS of 21.5 months (95% CI 16.0–26.2) and a median PFS of 6.5 months (95% CI 5.8–7.7).

One of the main hurdles in clinical research in sarcoma is the difficulty to design and conduct large prospective RCT within reasonable timelines. Given these limitations, the authors of the TH CR-406/SARC021 should be congratulated for performing and completing this phase III study in a timely manner (enrolment of 640 patients between September 2011 and January 2014). Patients were eligible if they were 15 years and older, had advanced or metastatic STS with no standard curative therapy available, measurable disease and performance status of 0–1. The primary objective was OS in the intention-to-treat population. Secondary end-points included PFS and overall response rate. Patients were randomly assigned to a maximum of six cycles of doxorubicin 75 mg/m$^2$ intravenously on day 1 of every 21 d cycle, or doxorubicin plus evofosfamide 300 mg/m$^2$ intravenously on days 1 and 8 of every 21 d cycle, plus continuation of single-agent evofosfamide in non-progressive patients. The OS end-point was not reached (Hazard Ratio (HR) 1.06, 95% CI 0.88–1.29; p = 0.527), but the median OS was 18.4 months (95% CI 15.6–22.1) with doxorubicin plus evofosfamide versus 19.0 months (95% CI 16.2–22.4) with doxorubicin alone. Remarkable benefit was seen in the subgroup of 31 synovial sarcoma patients with a HR 0·III2 (95% CI 0.14–0.73III; p = 0.0043) in favour of the combination treatment.

Median PFS was similar in the two groups (6.3 months (95% CI 6.0–7.8) in the combination group versus 6.0 months (95% CI 4.6–6.2) in the doxorubicin alone group). In contrast, the proportion of patients who achieved complete or partial response was significantly higher in the combination group than in the doxorubicin alone group (28% versus 18% of patients; p = 0·0026). A complete and partial response was documented in 2% and 27% of patients treated with the combination, respectively, and in 1% and 17%, respectively, with doxorubicin alone. The proportion of patients achieving disease control (complete response, partial response or stable disease) was 73% in the combination group and 66% in the doxorubicin alone group (odds ratio [OR] 1.49 [95% CI 0.54–1.36], p = 0.0473).

These results raise two critically important points. The first one is that TH CR-406/SARC021 is yet another randomised controlled phase III study in the recent history of clinical trials in advanced STS to show no difference in PFS or OS between the experimental arm and the control arm; potentially rendering the new agent (in this occasion evofosfamide) 'non-interesting' in sarcoma in the eyes of the pharmaceutical industry. The second point is that TH CR-406/SARC021 and other studies reported recently, including PICASSO III (a phase III, multicentre, randomised, double-blind, placebo-controlled trial assigning patients with STS to receive either doxorubicin plus palifosfamide or doxorubicin plus placebo, as first-line treatment) [10], have shown an impressive increase of the median OS in the control arm compared to what studies in the past had shown (EORTC 62012). It appears that the median OS of patients with advanced disease receiving standard of care treatment (doxorubicin) in first-line phase III studies has improved over the last decade from 12.8 months (95.5% CI 10.5–14.3) (EORTC 62012) to 16.9 months (95% CI 14.8–22.9) (PICASSO III) and 19.0 months (95% CI 16.2–22.4) (TH CR-406/SARC021) (Table 1).