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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 vs the combination with ifosfamide (in the randomized 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, less toxic, fosfamides namely evofosfamide and palifosfamide have recently been tested in randomized phase III clinical trials in STS in an attempt to minimize toxicity. The TH CR-406/SARC021 (June 2017) and the PICASSO III (Sept 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% CI 10.5-14.1) 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 randomized 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.

To the Editor-in-Chief of the European Journal of Cancer

June 14th 2017

Dear Professor Eggermont,

We respectfully submit our manuscript entitled "The fate of new fosfamides in phase III studies in advanced soft tissue sarcoma" for editorial consideration and publication in the European Journal of Cancer.

Recently the TH CR-406/SARC021 study results were published on line in Lancet Oncology comparing evofosfamide plus doxorubicin to doxorubicin single agent (Tap et al, Lancet Oncology, June 23 2017 epub ahead of print) in advanced soft tissue sarcoma. This study was highlighted in the ASCO Post last week. The study did not meet its primary endpoint and it is the third phase III study in advanced/metastatic soft tissue sarcoma over the last 4 years a "fosfamide" compound combination arm versus monotherapy doxorubicin showing lack of survival benefit of the combination arm.

Conduct of clinical research in soft tissue sarcoma remains challenging, owing not only to the rarity and the heterogeneity of the disease but also to limitations in the clinical trial design. Important information derived from randomized controlled trials such as the TH CR-406/SARC021 and the PICASSO III (palifosfamide plus doxorubicin versus doxorubicin plus placebo, Ryan et al, Journal of Clinical Oncology, 2016) should be used to guide efforts in the design of future clinical studies in soft tissue sarcoma. We discuss critical points raised by these 2 studies and in relation to the benchmark EORTC 62012 study (Ifosfamide plus doxorubicin versus doxorubicin, Judson et al, Lancet Oncology 2014).

With this Current Perspective we aim to contribute to the ongoing debate about trial design in rare and heterogeneous cancers, such as sarcomas, to prevent further costly negative phase III studies with new compounds in this disease.

With kind regards

Professor Winette T.A. van der Graaf

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THE FATE OF NEW FOSFAMIDES in PHASE III
STUDIES IN ADVANCED SOFT TISSUE SARCOMA

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"I confirm that all the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *European Journal of Cancer*".

Signed (corresponding author): Professor Winette Van der Graaf

Date: 14/07/2017

Title:

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

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Highlights

- Newer, less toxic, fosfamides namely evofosfamide and palifosfamide have recently been tested in randomized phase III clinical trials in soft tissue sarcoma in an attempt to minimize toxicity.
- In the TH CR-406/SARC021 (June 2017) and the PICASSO III (Sept 2016) the combination arm (doxorubicin in combination with evofosfamide and palifosfamide respectively) produced increased response rates compared to doxorubicin alone but at the expense of higher toxicity.
- 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 to 22.9) (PICASSO III) and 19.0 months (95% CI 16.2–22.4) (TH CR-406/SARC021).
- Balancing different subtypes between two treatment arms is extremely challenging in phase III studies in a biologically and clinically heterogeneous disease such as soft tissue sarcoma therefore to the extent that this is feasible, efforts should be made to focus on specific tumour subtypes. To illustrate, the subgroup of synovial sarcomas in the TH CR-406/SARC021, had a significant overall survival benefit from the combination therapy, but a prospective trial needs to prove that.
- More emphasis should be placed on the appropriate design and conduct of clinical trials in soft tissue sarcoma.

Title:

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 vs the combination with ifosfamide (in the randomized 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, less toxic, fosfamides namely evofosfamide and palifosfamide have recently been tested in randomized phase III clinical trials in STS in an attempt to minimize toxicity. The TH CR-406/SARC021 (June 2017) and the PICASSO III (Sept 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% CI 10.5–14.1) 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 randomized 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.

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 (STS), 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 randomized 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 isophosphoramidate mustard, the active metabolite of ifosfamide. Another analogue is evofosfamide, a hypoxia-activated prodrug of bromo-isophosphoramidate 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, randomized, 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 over, 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 6 cycles of doxorubicin 75mg/m² intravenously on day 1 of every 21-day cycle, or doxorubicin plus evofosfamide 300 mg/m² intravenously on days 1 and 8 of every 21-day cycle, plus continuation of single agent evofosfamide in non-progressive patients. The OS endpoint was not reached (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 0.31 [95% CI 0.14–0.73]; 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 vs 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% vs 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 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 randomized 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, randomized, 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 to 22.9) (PICASSO III) and 19.0 months (95% CI 16.2–22.4) (TH CR-406/SARC021) (**table 1**).

Given these two facts, the burning question about TH CR-406/SARC021 is whether the benefit of the novel agent is indeed absent or whether the control arm is too good to allow the detection of any potential benefit. There are now two similar examples of promising ifosfamide alike agents in sarcoma, palifosfamide and evofosfamide, where phase III trials failed to confirm therapeutic benefits seen in randomized phase II studies (9, 11). Whilst this phenomenon can be attributed to the limitations of study design in randomized trials in heterogeneous diseases like STS, other possible explanations include the incorporation of newer treatments in sarcoma therapeutics particularly in second line treatment and beyond, local procedures in metastatic setting, as well as important advances in palliative and supportive care. One should also consider - as a possible contributing factor - the increased emphasis now placed on accurate histological diagnosis of soft sarcoma subtypes using central pathology review to better specify sarcoma subtypes and to avoid inclusion of non sarcoma malignancies in clinical trials (with worse prognosis and worse response to doxorubicin) which may have partly masked the true median OS of the standard chemotherapy in the past. This is also illustrated in a second analysis of the EORTC 62012 study based on central pathology review showing an OS benefit for the undifferentiated pleiomorphic subgroup (12).

Setting PFS or OS as the primary end point in RCT in STS has been under debate for years. Noticeably, in the EORTC 62012 trial the primary end point was OS benefit but this was subsequently criticized as a complex and easily confounded measure of therapeutic efficacy over PFS and response rate in a diverse group of rare diseases such as STS, where perhaps the bar of treatment success was set too high (13). Interestingly, when PICASSO

III was originally designed the primary end point was OS but in order to obtain accelerated approval by the US Food and Drug Administration– and following completion of recruitment of all patients - the primary end point was changed to PFS without altering the sample size or the statistical considerations made at the start. In the TH CR-406/SARC021 PFS was not set as the primary end point because of concerns that it could have been confounded by inherent weaknesses introduced by the design of the study, such as the absence of placebo or study blind. Data provided by real life observational studies such as the recently published METASARC (14) highlight the limitations associated with the design and outcomes of clinical trials. Time to next treatment (TNT) is suggested as a surrogate endpoint for OS given their strong correlation.

Despite the lack of OS benefit, the proportion of patients who achieved complete or partial response was significantly higher in the doxorubicin plus evofosfamide group than in the doxorubicin alone group. Similarly in the PICASSO III there were more objective responses among patients treated with doxorubicin plus palifosfamide than with doxorubicin plus placebo; and interestingly response rates in both arms were similar to those reported in EORTC 62012. The results of all three studies show that response rate results have limited clinical significance in the absence of survival benefit in STS and, as was shown in the EORTC 62012, absence of progression could be used as a better surrogate for final outcome (15).

Apart from differences in histological subtypes, the biological behaviour and progress of metastases in STS can also differ substantially. Without the requirement of documented progression within a well-defined time period before the start of a study the risk of introducing unwanted bias is realistic. The attraction to put patients on a competitive clinical study with a new drug may introduce a selection of relatively fit patients with lower volume metastatic disease. Prolongation of median PFS to over 6 months in patients treated with single agent doxorubicin could be an indirect reflection of this statement. As shown in **table 2** this information is not provided in the TH CR-406/SARC021 or the PICASSO III although one can appreciate how imbalance in the disease progression status between the groups could have easily affected the survival outcomes in favour of either of the groups. The importance of this observation is lying in the potentially critical role of ensuring homogeneity of clinical/phenotypical data for patients entering clinical trials; in the absence of representative biomarkers and given the biological heterogeneity of the disease, enrolling only patients with the same disease status (i.e. well-defined progressive disease) is important in testing novel agents in STS. The EORTC 62012 study has been the only one requiring documented progression within the last 6 weeks before study entry and as such has probably had patients with more aggressive phenotype on study, leading to the shortest OS of the trials as described.

In recent years there has been criticism about the 'one size fits all' approach in clinical trials design in STS where a specific drug or regimen is given to various histological subtypes lumped together; it has been clear for some time now that certain STS histologies respond better than others to particular agents (16) and lumping different subtypes together may lead to inaccurate and misleading conclusions. Balancing different subtypes between two treatment arms is extremely challenging in a disease that contains over 70 histological subtypes. In the TH CR-406/SARC021 by and large this balance was achieved between the 2 arms (leiomyosarcoma 35% vs 37%, liposarcoma 15% vs 20%) whereas in the PICASSO

III trial some subgroups were less or not balanced (liposarcoma 11.9% vs 18.1% and pleomorphic/undifferentiated/sarcoma, NOS 37.6% vs 28.5%) (**table 3**). Therefore, to the extent that this is feasible, efforts should be made to focus on specific tumour subtypes.

In terms of safety, in both the PICASSO III and the TH CR-406/SARC021, patients in the combination arms experienced more grade 3 and 4 adverse events compared to single agent doxorubicin although the toxicity profile of the newer “fosfamides” (palifosfamide and evofosfamide) appeared better than that of ifosfamide.

Conclusion:

Design and conduct of clinical research in STS is hampered by the rarity and the heterogeneity of the disease. With advances to date, the therapeutic landscape has started to change. Important information derived from RCT trials such as the TH CR-406/SARC021 and the PICASSO III should be used to guide future efforts in clinical and translational research. Collaborative efforts are required to ensure that trial design should lead to as homogeneous groups to compare as possible within the framework of meaningful statistics. Median OS should be reconsidered in control arms of randomised studies taking the biological behaviour of soft tissues sarcomas into account.

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Trial	Primary endpoint	Accrual period	Number of patients	RR (%) doxorubicin versus combination	PFS (months) doxorubicin versus combination	OS (months) doxorubicin (plus placebo) versus combination
SARC 021	OS	2011-14	640	18 vs 28	6.0 vs 6.3 95% CI 4.6-6.2 vs 6.0-7.8	19.0 vs 18.4 95% CI 16.2-22.4 vs 15.6-22.1
PICASSO	PFS	2010-12	447	20 vs 28	5.2 vs 6.0 95% CI 4.2 - 6.0 vs 5.4 - 6.5	16.9 vs 15.9 95% CI 14.8 - 22.9 vs 13.7 - 19.4
EORTC 62012	OS	2003-10	455	14 vs 26	4.6 vs 7.4 95% CI 2.9-5.6 vs 6.6-8.3	12.8 vs 14.3 95% CI 10.5-14.3 vs 12.5-16.5

SARC 021: Doxorubicin versus doxorubicin plus evofosfamide

PICASSO: Doxorubicin plus placebo versus doxorubicin plus palifosfamide

EORTC 62012: Doxorubicin versus doxorubicin plus ifosfamide

Table 1. Accrual and Endpoints of the trials

Trial	Progression before study entry	Percentage female patients Doxorubicin vs combination	Median age (year) Doxorubicin versus combination
SARC 021	Not required	53 vs 55	58 vs 50
PICASSO	Not mentioned	47 vs 46	56 vs 58
EORTC 62012	Yes within 6 weeks before start (RECIST 1.0)	55 vs 50	48 vs 47

Table 2. Phenotypical characteristics

Trial	Pathology review	Leiomyosarcoma (%) D vs C	Liposarcoma (%) D vs C	Synovial sarcoma (%) D vs C	UPS (%) D vs C	Other (%) D vs C
SARC 021	Central	32 vs 36	16 vs 19	3 vs 5	25 vs 21	8 vs 3
PICASSO	Central	31 vs 30	18 vs 12	5 vs 5	29 vs 38	10 vs 7
EORTC 62012	Local	24 vs 26	11 vs 14	17 vs 11	Not mentioned	48 vs 49

Table 3. Histology in the different trials. D= doxorubicin, C= combination of doxorubicin and evofosfamide (SARC 021), palifosfamide (PICASSO III) and ifosfamide (EORTC 62012), UPS= Undifferentiated Pleiomorphic Sarcoma

Title:

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

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Conflict of interest statement

AC has no conflict of interest to declare.

WVG has been in the advisory board of Pharmamar and Bayer, and involved in research projects with Novartis and GSK.