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# Phase I clinical and pharmacokinetic study of trabectedin and doxorubicin in advanced soft tissue sarcoma and breast cancer

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ABSTRACT

The combination of trabectedin (T) and doxorubicin (D) was brought into clinical development in soft tissue sarcoma (STS) and advanced breast cancer (ABC) because of its *in vitro* and *in vivo* additive anti-tumour effect, the fact that there are no overlapping toxicities and the anti-tumour activity of T in those tumours. Feasibility and anti-tumour activity of T+D administered every 3 weeks were evaluated in 38 patients (STS=29, ABC=9) untreated for advanced disease. D was given at 60 mg/m$^2$ and T at escalating doses from 600 to 800 μg/m$^2$, which was the maximum tolerated dose due to dose-limiting febrile neutropenia and asthenia. The recommended dose - given to 18 patients in total - was 700 μg/m$^2$ T with 60 mg/m$^2$ D. The pharmacokinetic profile of T and D at cycle 1 was analysed in 20 patients. The most common toxicities included a severe but reversible ASAT/ALAT increase (94%), nausea/vomiting, neutropenia, asthenia/fatigue, stomatitis. Partial response and stable disease were assessed in 18% and 56% of STS patients and in 55% and 33% of ABC patients. No pharmacokinetic interaction between T and D was observed. The lack of cumulative toxicity and related complications and the promising activity in STS support further development of T+D.



## 1. Introduction

Trabectedin (T) (formerly known as ET-743) is a tetrahydroisoquinoline alkaloid isolated from the Caribbean ascidian *Ecteinascidia turbinata* that binds in the minor groove of DNA, forming adducts at the N2 position of guanine.[1] The DNA structural changes that T induces in DNA - with a bending of the minor groove towards the major groove - is different from that induced by any other DNA-interacting agent investigated so far[2] and this possibly explains the unique biological properties of T in relation to DNA repair[3–5] and transcription regulation.[6–8]

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Adult soft tissue sarcomas (STS) are a pathologically heterogeneous group of rare malignant tumours which account for less than 1% of all malignant neoplasms. They arise from a variety of connective tissues, including blood vessels, muscles and Schwann cells, and encompass high-grade and low-grade tumours; histological subtype and grade are the most important prognostic factors.[9]

The results so far achieved with chemotherapy in advanced STS are limited due to an overall intermediate chemosensitivity,[10] heterogeneity of the biological features and of the clinical behaviour of the different subtypes.

The most active single agents are anthracyclines (doxorubicin (D) or epirubicin)[11] and alkylating drugs (mainly ifosfamide)[12]; in combination, a 30% response rate can be achieved with standard doses,[13,14] increasing up to 70% when high doses with colony stimulating factor (CSF) support[15,16] are administered; responses, however, are of short duration and the identification of new active compounds in STS is of high priority.

Long lasting objective responses to T were noted in four out of 20 sarcoma patients resistant to standard chemotherapy, treated across the phase I programme at the recommended doses. The antitumour activity in STS was subsequently confirmed in phase II studies[17–19] and T was approved by the EU regulators as therapy for patients with advanced STS resistant to or relapsed after anthracyclines and ifosfamide or to those cases not suitable for conventional chemotherapy. The observation of very good efficacy of the combination in xenografts that were poorly sensitive to either D or T[20] and the potential efficacy of T in advanced breast cancer, resistant to anthracyclines and taxanes,[21] provided further rationale to investigate this combination. Here we report the clinical and pharmacological results of a Phase Ib study, the primary objectives of which were the definition of the Maximum Tolerated Dose (MTD) of the combination of T and D and the definition of the least toxic sequence of administration of the two drugs. The sequence of administration of the two drugs was investigated because of the potential acute liver impairment caused by T and the consequent pharmacokinetic interaction with anthracyclines.[22,23] In addition, in STS cell lines HT-1080 and HS-18, a sequence dependent enhancement of cytotoxicity by T given 24 h before D had been reported.[24]

A 3-h duration of infusion of T was selected because of good tolerability, the long half-life of T[25] and the ease of administration shown in Phase II[17,18]; a starting dose of T of 600 $\mu g/m^2$, corresponding to about 50% of the recommended dose (RD), was selected because of the expected neutropenia of the combination; D was given at 60 $mg/m^2$ corresponding to the dose more commonly used in combinations.

The study was approved by the Ethics Committee of each participating institution and all enrolled patients gave their informed consent before starting any study-related procedures.

## 2. Patients and methods

### 2.1. *Eligibility*

Eligibility criteria were a diagnosis of STS or advanced breast cancer (ABC). STS patients could have received only prior adjuvant chemotherapy while breast cancer patients could have received a maximum of one prior chemotherapy for advanced disease. ECOG performance status (PS) $\leqslant 1$, measurable disease, $\geqslant$ 55% LVEF by echocardiogram or MUGA scan, adequate haematological, renal and liver function (alkaline phosphatase (AP), total serum bilirubin, ALT, AST within upper normal limit (UNL), $\leqslant 1.5 \times$ UNL in case of liver metastases; if total AP $\geqslant$ UNL, the liver fraction had to be within UNL). In patients with STS no prior chemotherapy for advanced disease was allowed, only chemotherapy with adjuvant intent and completed > 6 months before starting the study. A maximum cumulative dose of D (or D equivalents) $\leqslant 280\ mg/m^2$ was allowed.

Exclusion criteria were serious cardiac disease (e.g. congestive heart failure or angina pectoris, even if medically controlled, documented myocardial infarction within 1 year prior to study entry, uncontrolled hypertension or arrhythmia), chronic active hepatitis or cirrhosis, symptomatic brain metastases or leptomeningeal disease.

### 2.2. *Ethics*

The protocol was approved by the local Ethics Committee of each participating centre and patients had to sign a written informed consent.

### 2.3. *Treatment and study design*

In the first part of the study (dose finding and least toxic sequence definition) patients with STS received increasing doses of T in combination with 60 $mg/m^2$ of D; Three to six patients per dose level were treated according to toxicity.

The starting dose of T of 600 $\mu g/m^2$ was escalated by 100 $\mu g/m^2$ increments up to the MTD, which was defined as the dose at which at least two out of six patients treated with the least toxic sequence experienced a dose limiting toxicity (DLT); the RD was fixed one dose level below.

For the definition of the least toxic sequence, consecutive patients were assigned to receive, at cycle 1, sequence A (T followed by D) or sequence B (D followed by T); in absence of DLT, the same doses with the opposite sequence were given at cycle 2, until the least toxic sequence was determined. After a total of 12 cycles had been administered to the first six patients (six with each sequence) the criteria for DLT were used to define the least toxic sequence; in absence of DLT, the total number of toxic events experienced by each patient was utilised to define the least toxic sequence.

If a patient presented a DLT at cycle 1, the dose of T was reduced by one dose level and the patient continued with the same sequence, while three additional patients had to be treated with the same sequence at cycle 1; if one or more DLTs occurred, the MTD for that sequence was established; in case of no more DLT, three patients were treated with the reverse sequence at the same dose level and in case of no DLT the dose was escalated.

The RD of the least toxic sequence was planned to be tested in the second part of the study (expansion part) in which the endpoint was the assessment of the anti-tumour activity of the combination in patients with STS and ABC. A total of 20 patients was originally planned.