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Clinical Trial

# Retrospective inter- and intra-patient evaluation of trabectedin after best supportive care for patients with advanced translocation-related sarcoma after failure of standard chemotherapy

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**KEY WORDS**
Trabectedin;
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**Abstract** ***Aim:*** Our randomised phase II study showed the clinical benefit of trabectedin compared with best supportive care (BSC) in patients with advanced translocation-related sarcomas after the failure of standard chemotherapy. The aim of the present study was to evaluate efficacy and safety of trabectedin in the identical patients crossed over to trabectedin after

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sarcoma;
Soft tissue sarcoma;
Crossover;
Intra-patient;
Retrospective analysis

disease progression in the BSC arm of the randomised study.

***Patients and methods:*** This was a single-arm study of the BSC patients of the randomised study in whom disease progressed. Trabectedin (1.2 mg/m$^2$) was administered over 24 h on day 1 of a 21-d treatment cycle. The efficacy and safety of trabectedin after BSC were evaluated and retrospectively compared with the results of the randomised study.

***Results:*** Thirty patients crossed over to trabectedin. Median progression-free survival (PFS) was 7.3 months (95% confidence interval [CI]: 2.9–9.1) after crossover compared with 0.9 months (95% CI: 0.9–1.0) at BSC in the randomised study. PFS in the present study was comparable to that of the trabectedin arm in the randomised study. The number of patients with growth modulation index ≥1.33 was 25 (86%). Individual tumour volume was decreased in 11 patients after crossover. Adverse drug reactions (ADRs) were observed in 27 patients (96.4%). ADRs of grade III–IV were mainly bone marrow suppression and abnormal liver functions.

***Conclusion:*** Trabectedin was revealed to be effective and well tolerated in the identical patients crossed over to trabectedin after disease progression in BSC.

The present study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-121853.



## 1. Introduction

Soft tissue sarcomas (STS) are remarkably rare solid tumours, accounting for <1% of all adult malignancies, and classified into more than 50 histological subtypes. Molecular biology has recently played a strong role in STS diagnosis. One-third of STS subtypes are classified as translocation-related sarcomas (TRS) [1], which can be particularly interesting as a therapeutic target because TRS provide specific biological insights and mechanisms of action that may have an impact on prognosis or therapy [2]. Chemotherapy is used for the treatment of advanced STS. Over the past decades, doxorubicin, either alone or in combination with ifosfamide, has been used as first-line chemotherapy in most of STS subgroups; however, the response rates are as low as 20–30% [3,4]. Furthermore, therapeutic options after failure of doxorubicin and/or ifosfamide are limited [5].

Trabectedin is a marine-derived tetrahydroisoquinoline alkaloid [6]. Trabectedin is approved by the European Medicines Authority for the treatment of advanced STS in adults after failure of anthracyclines and ifosfamide or when unsuited to receive these agents based on the results of a pivotal phase II study, which indicated superior disease control by trabectedin given 1.5 mg/m$^2$ as a single infusion lasting 24 h every 3 weeks (q3week, 24 h) [7]. Trabectedin binds to the DNA minor groove, and has indirect anti-inflammatory and anti-angiogenic activity via tumour-associated macrophages [8]. It is noted that trabectedin also modulates the transcription of oncogenic fusion protein of TRS. Interestingly, the cytotoxic sensitivity of trabectedin correlates to the expression of different variants of the fusion protein [9,10].

We conducted a multicentre, open-label, randomised phase II study comparing trabectedin with the best supportive care (BSC) in patients with advanced TRS after failure of standard chemotherapy [11]. As previously reported, this randomised study showed the clinical benefit of trabectedin when administered at 1.2 mg/m$^2$ q3week, 24 h. The trabectedin dose of 1.2 mg/m$^2$ was based on the result of a phase I study in STS patients in Japan [12]. Seventy-six patients were randomised to receive either trabectedin or BSC in the randomised study, and 73 patients (37 in the trabectedin arm and 36 in the BSC arm) were included in the efficacy analysis [11].

The aim of the present study was to evaluate the efficacy and safety of trabectedin in patients crossed over to trabectedin after disease progression while undergoing BSC. We report a retrospective comparison of these two studies.

## 2. Patients and methods

### 2.1. Patients

Patients who were assigned to BSC in the randomised study and whose disease progressed afterwards according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 were allowed to crossover to trabectedin (Fig. 1). During BSC, patients did not receive anti-tumour therapy but did receive treatment to relieve symptoms induced by primary disease and improve quality of life. Most eligibility criteria of the present study were the same as in the randomised study [11]. In brief, eligible patients were pathologically diagnosed as a subtype of TRS: myxoid/round cell liposarcoma (MRCL), synovial sarcoma (SS), alveolar