ELSEVIER

European Journal of Cancer 40 (2004) 1327–1331

European Journal of Cancer

www.ejconline.com

A phase II study of ET-743/trabectedin ('Yondelis') for patients with advanced gastrointestinal stromal tumours

J.-Y. Blay [a,*], A. Le Cesne [b], J. Verweij [c], M. Scurr [d], C. Seynaeve [c], S. Bonvalot [b], P. Hogendoorn [e], J. Jimeno [f], V. Evrard [g], M. van Glabbeke [g], I. Judson [d]

[a] *Hop Edouard Herriot and INSERM U590 Centre Leon Berard, Lyon, France*
[b] *Institut Gustave Roussy, Villejuif, France*
[c] *Rotterdam Cancer Institute, Rotterdam, The Netherlands*
[d] *Royal Marsden Hospital, London, UK*
[e] *LUMC, Leiden, The Netherlands*
[f] *Pharma-Mar, Tres Cantos, Spain*
[g] *EORTC Data Center, Brussels, Belgium*

Received 29 January 2004; accepted 2 February 2004
Available online 10 May 2004

Abstract

Primary or secondary resistance to imatinib may occur in patients with gastrointestinal stromal tumours (GISTs) while these tumours have repeatedly been shown to be highly resistant to conventional doxorubicin- and ifosfamide-containing regimens. The investigation of new drugs is therefore warranted in GIST. A phase II study was conducted between May 1999 and November 2000 in eight centres of the EORTC STBSG group to establish the efficacy and safety of ET743 ('Yondelis') in GIST previously untreated with cytotoxic chemotherapy before the imatinib era. ET-743 was given was given at 1.5 mg/m^2 per course as a 24-h continuous intravenous infusion every 3 weeks. Twenty-eight patients were included, 16 males and 12 females. Median age was 54 years (range 25–73 years). Median performance status was 0 (range 0–1). 17 (63%), 4 (12%) and 7 (25%) patients, received 0–2, 3–5, and $\geqslant 6$ courses of ET-743, respectively. The best response was stable disease in 9 (33%) patients, and disease progression in 18 patients (67%), with a median time to disease progression and overall survival of 51 days and 589 days, respectively. The treatment was well tolerated: there were grades 3–4 neutropenia, thrombocytopenia, and transaminase increases in 13 (48%), 1 (4%) and 16 (59%) patients, respectively. There were no toxic deaths. ET-743 at this dose and schedule is not an effective treatment for advanced GIST.

1. Introduction

Gastrointestinal stromal tumour (GIST) is a recently described entity among the visceral sarcomas [1–7]. It mimics histologically a cellular progenitor of smooth muscle of the digestive tract and the interstitial cells of Cajal, and expresses almost consistently CD117, and frequently CD34 [6,7]. The oncogenic process of GIST transformation involves a specific activating mutation of the *Kit* gene, most often in the juxtamembrane domain of the molecule, resulting in a constitutional activation of kit protein in the absence of stem-cell factor, its natural ligand [8–12]. Imatinib, an inhibitor of activated c-*kit*, has been shown to yield high response rates, and prolonged progression-free survival and overall survival in these patients, although 10% of patients are primarily refractory to the molecule and 25–30% subsequently relapse [13–20]. There are few alternative therapeutic options to imatinib in GIST. Although doxorubicin and ifosfamide remain the most effective treatments in patients with advanced soft tissue sarcomas [21–24], they are poorly effective for the treatment of GIST [24–27]. Alternative treatment options are therefore required. Trabectedin is a marine-derived tetrahydroisoquinoline alkaloid with cytotoxic activity against a variety of tumours of mesenchymal origin in preclinical and phase I studies. It has shown activity in soft tissue sarcoma, with a response rate in the range of 10–20% and with some long-term

* Corresponding author. Present address: Equipe Cytokine et Cancer, Unité INSERM U 590, Centre Léon Bérard, 28, rue Laennec, 69008 Lyon, France.

0959-8049/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.02.005

stabilisation in previously treated and untreated patients, in particular those with leiomyosarcoma [28–32].

Here, we report a phase II study initiated before the imatinib era of the administration of trabectedin to patients with advanced GIST previously untreated with cytotoxic chemotherapy.

2. Patients and methods

2.1. Inclusion and exclusion criteria

Patients were required to be aged >15 years, with a histologically proven locally advanced and/or metastatic GIST with progressive disease, never treated with cytotoxic chemotherapy, an ECOG performance status of 0–1, a life expectancy of at least 3 weeks, measurable disease, and normal organ function as defined by a granulocyte count >1500/μl, a platelet count >100,000/μl, bilirubin <20 μM/l, normal alkaline phosphatase, liver transaminase <2.5 UNL, normal serum creatinine or creatinine clearance >60 ml/mm. All histological slides were externally reviewed, according to the standard procedure of the EORTC STBSG group. No concurrent therapy was allowed and patients were required to give written informed consent before their inclusion.

2.2. Treatment

Patients were given a dose of 1.5 mg/m^2 of trabectedin as a 24-h continuous intravenous infusion every 3 weeks. Dose adaptations were as follows. The dose of trabectedin given in the second and subsequent courses of treatment was based upon the worst grade of selected haematological and non-haematological toxic effects observed following the preceding course, after these had resolved. The dose given was reduced to 1.2 mg/m^2 per course if the patient had experienced grade 4 febrile neutropenia, grades 3–4 non-haematological toxicity of any kind or a grades 1–4 increase in alkaline phosphatase and bilirubin between courses. Further reductions to 1.0 mg/m^2 per course were allowed in case of toxicity. The reduced dose was given in all subsequent courses unless a further dose reduction was necessary and was never reescalated. Patients who developed grades 3 or 4 toxicity in any of the selected effects after receiving a reduced dose were taken off the study. In the event of toxicity, dosing was delayed for a maximum of 21 days until all signs of toxicity had resolved or were resolving. If, after 21 days' delay, these conditions were not met, the patient received no more trabectedin.

2.3. Response criteria

Response to therapy was evaluated every 6 weeks (two courses of therapy) and classified according to World Health Organisation criteria [32]. All objective responses had to be reviewed and confirmed by peer review.

2.4. Follow-up studies and toxicity assessment

Toxicity was scored according to the NCI–CTC scoring system (ref).

2.5. Statistical considerations

The principal objective of the trial was to assess the therapeutic activity of trabectedin in patients with advanced soft tissue sarcoma in terms of complete and partial responses, and duration of response. The trial was conducted in two stages, using the optimal two-stage design described by Simond [33]. The hypothesis was that a response rate of 5% would not warrant further investigation of the drug, and a response rate of 20% would warrant further investigation. The accepted probability for recommending the drug for further trials was α, with a true response rate equal to or lower than 10%: in the present trial, α was taken to be 0.1. The accepted probability for rejecting the drug from further trials was β, with a true response rate = 20%; in the present trial, β was taken to be 0.05. Under this hypothesis, the total sample size for this trial was 44 patients. A first test was to be performed after 27 patients had been included. If $\leqslant 1$ responses were observed, the trial was to be stopped with the conclusion that the drug should not be further investigated. Otherwise, patients would continue to be accrued until 44 were evaluable for response, with a second test performed amongst those 44 patients. If $\leqslant 5$ responses were then observed, the trial was to be stopped with the conclusion that the drug should not be further investigated; if >5 responses were observed, the trial was to be stopped with the conclusion that the drug should be further investigated.

3. Results

3.1. Patients

Twenty-eight patients with histologically proven, locally advanced and/or metastatic GIST with progressive disease were entered into the study; 27 were evaluable for toxicity and response. The clinical and biological characteristics of these patients and their tumours are depicted in Table 1.

3.2. Treatment

One patient received no treatment; 7 (25%) patients received six courses of treatment. A total of 89 courses of trabectedin were given, with a median number of two

Table 1
Description of the patients

	Median (range)	*N* (%)
Age	54 (25–73)	
<40 years		7 (25%)
40–60 years		12 (43.2%)
⩾ 60 years		9 (32.1%)
Sex		
Female		12 (41%)
Male		16 (59%)
Performance status		
0		19 (68%)
1		9 (32%)
Primary tumour sites		
Gastric		4 (14%)
Small bowel		11 (39%)
Colorectal		2 (7%)
Other intra-abdominal		8 (29%)
Retroperitoneal		2 (7%)
Not specified		1 (4%)
Metastatic sites		
Primary		7 (25%)
Liver		19 (68%)
Soft parts (abdominal)		13 (46%)
Lung		2 (7%)
Bone		1 (4%)
Skin		1 (4%)
Node		1 (4%)
Number of involved sites		
1		15 (53%)
2		10 (36%)
3		3 (10%)
Previous surgery		
Yes		24 (86%)
No		4 (14%)
Previous radiotherapy		
Yes		1 (4%)
No		27 (96%)

cycles of trabectedin given to each patient (range 0–8 cycles). The relative dose intensity was 93% (range 66–104%). The dose was reduced at least once in 26% of the patients, and in 9% of the cycles, mostly (4 of 8; 50%) because of non-haematological toxicities. The start of the cycle was delayed at least once in 48% of the patients, and in 30% of the cycles, mostly (13 of 20; 65%) because of haematological toxicities.

3.3. Response and survival

No objective response was seen. Eighteen (67%) patients were experiencing progressive disease at their first evaluation; 9 (33%) patients experienced no change as a best response. The median time to progression was 51 days and median survival 589 days (Fig. 1). Eighteen patients received further medical treatment after trabectedin.

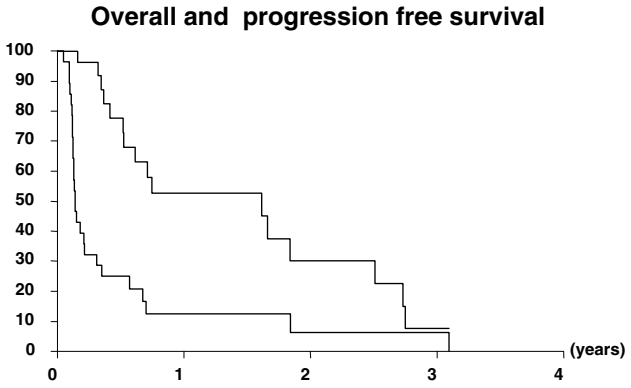

Fig. 1. Percent overall survival (upper curve) and progression-free survival (lower curve) with time (years) in the 28 patients with gastrointestinal stromal tumours.

3.4. Toxicity

The treatment was well tolerated (Table 2). Grades 3–4 neutropenia, thrombocytopenia, and transaminase increases were observed in 13 (48%), 1 (4%) and 16 (59%) patients, respectively. There were no toxic deaths.

4. Discussion

With the demonstration of the antitumour activity of imatinib, GIST has become the model for targeted therapy in solid tumours [13–20]. However, at present 25–35% of patients with advanced GIST will experience immediate or secondary resistance to this compound. Advanced non-resectable GIST are poorly sensitive to cytotoxic chemotherapy. Although there has been no prospective trial of doxorubicin and/or ifosfamide for this recently described entity, retrospective analysis of the EORTC database indicates that these agents are not active in GIST [23,30]. The activity of other drugs has also remained disappointedly low in advanced soft tissue sarcomas at a time when GIST were included in similar clinical trials. Although other tyrosine kinase inhibitors, such as SU11248, may be active in the treatment of imatinib-resistant GIST, most of the patients who fail on imatinib therapy will rapidly progress and die [34]. The identification of new active compounds in this disease therefore remains an important challenge.

This trial was designed and completed before the imatinib era. Its objectives were to investigate the clinical efficacy of trabectedin, a marine-derived tetrahydroisoquinoline alkaloid with cytotoxic activity against mesenchymal tumours in preclinical and phase I studies and demonstrated activity against advanced soft tissue sarcomas in phase II trials, in particular for leiomyosarcomas [28–31].

Table 2
Toxicity of the treatment

	N	Number of patients (%)				
		CTC grade				
		0	1	2	3	4
Haematological toxicity						
Leucocytes	27	4 (15)	9 (33)	8 (30)	4 (15)	2 (7)
Neutrophils	27	4 (15)	4 (15)	6 (22)	6 (22)	7 (26)
Platelets	27	23 (85)	2 (7)	1 (4)	0	1 (4)
Haemoglobin	27	1 (4)	16 (59)	7 (26)	1 (4)	2 (7)
Non-haematological toxicity						
Creatinine	27	21 (78)	6 (18)	0	0	0
Bilirubin	27	20 (74)	5 (18)	0	0	2 (7)
Alkaline phosphatase	27	9 (33)	18 (67)	0	0	0
ASAT	27	1 (4)	4 (15)	9 (33)	11 (41)	2 (7)
ALAT	27	1 (4)	3 (11)	7 (26)	12 (44)	4 (1)
Allergy	27	25 (93)	2 (7)	0	0	0
Fever	27	24 (89)	2 (7)	1 (4)	0	0
Febrile neutropenia	27	25 (93)	0	0	2 (7)	0
Infection	27	22 (81)	0	3 (11)	2 (7.4)	
Lethargy	27	7 (26)	7 (26)	11 (41)	2 (7)	0
Myalgia	27	24 (89)	3 (11)	0	0	0
Anorexia	27	18 (67)	6 (22)	2 (7)	1 (4)	0
Diarrhoea	27	20 (74)	5 (18)	1 (4)	1 (4)	0
Nausea	27	4 (15)	7 (26)	14 (52)	2 (7)	0
Vomiting	27	12 (44)	6 (22)	6 (22)	3 (11)	0
Abdominal pain	27	24 (89)	0	2 (7)	1 (4)	0
Stomatitis	27	22 (81)	1 (4)	4 (15)	0	0
Headache	27	23 (85)	1 (4)	1 (4)	2 (7)	0
Alopecia	27	27 (100)	0	0	0	0

Unfortunately, the results obtained in this trial indicate that trabectedin is an inactive drug for GIST at this dose and schedule, with only 33% of the patients achieving stable disease as a best response, and no objective responses, in agreement with a recently reported study [35]. The progression-free survival (PFS) rate at 6 months has been proposed as a more relevant clinical endpoint in soft tissue sarcoma than the objective response, with an expected PFS rate of 40–60% at present for active agents [32]. The PFS rate at 6 months is, however, only 25% with trabectedin in GIST, probably putting this compound in the list of inactive agents for GIST, in agreement with a recently reported trial [36]. The regimen was, however, well tolerated in this cohort of patients, with no toxic deaths.

Trabectedin therefore adds to the long list of ineffective agents in GIST. New therapeutic compounds with novel mechanisms of action, such as inhibitors of downstream proteins in the kit pathways or more active inhibitors of activated kit, are probably better candidates as second-line treatments for imatinib-resistant GIST in the future.

References

1. Berman J, O'Leary TJ. Gastrointestinal stromal tumor workshop. *Hum Pathol* 2001, **32**, 578–582.
2. Pidhorecky I, Cheney RT, Kraybill WG. Gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. *Ann Surg Oncol* 2000, **7**, 705–712.
3. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999, **30**, 1213–1220.
4. Nishida T, Hirota S. Biological and clinical review of stromal tumors in the gastrointestinal tract. *Histol Histopathol* 2000, **15**, 1293–1301.
5. Rubin BP, Fletcher JA. Molecular insights into the histogenesis and pathogenesis of gastrointestinal tumors. *Int J Surg Pathol* 2000, **8**, 5–10.
6. Fletcher CDM, Berman JJ, Corless CL, *et al*. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002, **33**, 459–465.
7. Miettinen M, Lasota J. Gastrointestinal stromal tumors – definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001, **438**, 1–12.
8. Hirota S, Osizaki K, Moriyama Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998, **279**, 577–580.
9. Nishida T, Hirota S, Taniguchi M. Familial gastrointestinal stromal tumours with germline mutations of the KIT gene. *Nat Genet* 1998, **19**, 323–324.
10. Hirota S, Okazaki T, Kitamura Y. Cause of familial and multiple gastrointestinal autonomic nerve tumors with hyperplasia of interstitial cells of Cajal is germline mutation of the c-kit gene. *Am J Surg Pathol* 2000, **24**, 326–327.
11. Lux ML, Rubin BP, Biase TL. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol* 2000, **156**, 791–795.

12. Isozaki K, Terris B, Belghiti J. Germline-activating mutation in the kinase domain of KIT gene in familial gastrointestinal stromal tumors. *Am J Pathol* 2000, **157**, 1581–1585.
13. Heinrich MC, Griffith DJ, Druker BJ. Inhibition of c-kit receptor tyrosine kinase activity by STI571, a selective tyrosine kinase inhibitor. *Blood* 2000, **96**, 925–932.
14. Rubin BP, Singer S, Tsao C. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res* 2001, **61**, 8118–8121.
15. Joensuu H, Roberts PJ, Sarlomo-Rikala M. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001, **344**, 1052–1056.
16. van Oosterom AT, Judson I, Verweij J, *et al*. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumors: a phase I study. *N Engl J Med* 2001, **358**, 1421–1423.
17. Demetri GD, von Mehren M, Blanke CD, *et al*. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002, **347**, 472–480.
18. Verweij J, van Oosterom A, Blay JY, *et al*. Imatinib mesylate (STI-571 Glivec(R), Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. *Eur J Cancer* 2003, **39**, 2006–2011.
19. Benjamin RS, Rankin C, Fletcher C, *et al*. Phase III dose randomized study of imatinib mesylate for GIST: intergroup SO033 early results. *Proc Am Soc Clin Oncol* 2003, **22**, 814 (abstract 3271).
20. Verweij J, Casali P, Zalcberg J, *et al*. Early efficacy comparison of two doses of imatinib for the treatment of advanced gastrointextinal stromal tumors: interim results of a randomized phase III trial of the EORTC STBSG, ISG and AGITG. *Proc Am Soc Clin Oncol* 2003, **22**, 814 (abstract 3272).
21. O'Bryan RM, Baker LH, Gottlieb JB, *et al*. Dose response evaluation of adriamycin in neoplasma. *Cancer* 1977, **39**, 1940–1948.
22. Santoro A, Tursz T, Mouridsen H, *et al*. Doxorubicin versus CyVADic versus ifosfamide plus doxorubicin in first line treatment of advanced soft tissue sarcomas. A randomized study of the EORTC Soft tissue and bone sarcoma group. *J Clin Oncol* 1995, **13**, 1537–1545.
23. Van Glabbeke M, van Oosterom AT, Oosterhuis JW. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens. A European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group study. *J Clin Oncol* 1999, **17**, 150–157.
24. Singer S, Rubin BP, Lux ML, *et al*. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. *J Clin Oncol* 2002, **18**, 3898–3905.
25. Nielsen OS, Blay JY, Judson IR, *et al*. Metastatic soft tissue sarcoma in adults. Prognostic and treatment options. *Am J Cancer* 2003, **2**, 1–12.
26. Plaat BE, Hollema H, Molenaar WM. Soft tissue leiomyosarcomas and malignant gastrointestinal tumors: differences in clinical outcome and expression of multidrug resistance proteins. *J Clin Oncol* 2000, **18**, 3211–3220.
27. Delaloge S, Yovine A, Taamma A, *et al*. ET-743: a marine derived compound in advanced pretreated sarcoma patients – preliminary evidence of activity. *J Clin Oncol* 2001, **19**, 1248–1255.
28. Demetri GGD, Seiden M, Garcia-Carbonero A, *et al*. ET-743 shows promising activity in distinct populations of sarcoma patients: summary of 3 phase II trials. *Proc Am Soc Clin Oncol* 2000, **19**, 553a (2177).
29. Lopez-Martin JA, Verweij J, Nieto A, *et al*. Is progression free survival at 6 months in advanced soft tissue sarcoma a measure of clinical benefit? an exploratory analysis of tumor growth rate variation induced by ET743. *Proc Am Soc Clin Oncol* 2003, **22**, 821 (abstract 3293).
30. Van Glabbeke M, Verweij J, Judson IR, *et al*. Progression free survival rate as principal endpoint for phase II trial in soft tissue sarcomas. *Eur J Cancer* 2002, 543–549.
31. Miller AB, Hogestraten B, Staquet M, Winkler A. Reporting results of clinical trials. *Cancer* 1981, **47**, 207–214.
32. Gwyther SJ, Nielsen OS, Judson IR, van Glabbeke M, Verweij J. Radiologist review versus group peer review of claimed responses in a phase II study on high-dose ifosfamide in advanced soft tissue sarcomas of the adult: a study of the EORTC Soft Tissue and Bone Sarcoma Group. *Anticancer Drugs* 2000, **11**, 433–437.
33. Simond R. Optimal two stage designs for phase II clinical trials. *Control Clin Trials* 1989, **10**, 1–10.
34. Demetri GD, Georges S, Heinrich M, *et al*. Clinical activity and tolerability of the multitargeted tyrosine kinase inhibitor SU11248 in patients with metastatic gastrointestinal stromal tumors refractory to imatinib mesylate. *Proc Am Soc Clin Oncol* 2003, **22**, 814 (abstract 3273).
35. Ryan DP, Puchalski T, Supko JG, *et al*. A phase II and pharmacokinetic study of ET743 in patients with gastrointestinal stromal tumors. *The Oncologist* 2002, **7**, 531–538.