FULL PAPER

BJC

British Journal of Cancer (2013) 109, 1717–1724 | doi: 10.1038/bjc.2013.524

Keywords: trabectedin; STS; sarcoma; elderly; older; age

Trabectedin is a feasible treatment for soft tissue sarcoma patients regardless of patient age: a retrospective pooled analysis of five phase II trials

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Background: This retrospective pooled analysis assessed the effect of age on the efficacy and safety of trabectedin in young and elderly patients with recurrent advanced soft tissue sarcoma (STS).

Methods: Data from 350 adults with STS treated in five phase II trials with trabectedin were divided in the younger (<60 years; $n=267$) and the older cohort (⩾60 years; $n=83$).

Results: The response rate did not differ with age (younger: 10.1% *vs* elderly 9.6%). No significant differences were found in median progression-free survival (PFS) in younger (2.5 months) and older (3.7 months) cohort with a comparable PFS rates at 3 (45.1% *vs* 55.1%) and 6 months (29.5% *vs* 36.4%). Similar median overall survival was observed in both cohorts (13.0 *vs* 14.0 months). Reversible neutropenia and aspartate aminotransferase/alanine aminotransferase elevation were the most common abnormalities. A higher incidence of grade 3/4 neutropenia (43.6% *vs* 60.2%) and fatigue (6.3% *vs* 14.4%) was observed in older patients. In 24 patients aged ⩾70 years, no significant differences in efficacy or safety outcomes were found.

Conclusion: This analysis demonstrated that trabectedin is a feasible treatment in young and elderly patients with STS, with meaningful clinical benefits and an acceptable safety profile, essential in palliative treatment of elderly patients.

Trabectedin (Yondelis), is a synthetic antineoplastic drug originally isolated from the Caribbean sea squirt *Ecteinascidia turbinate* (Carter and Keam, 2010). Trabectedin binds covalently to the minor groove of the DNA double helix, stalling the replication fork and leading to double-strand breaks that triggers a cascade of events that ultimately leads in G2-M cell cycle arrest and apoptosis

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Received 23 April 2013; revised 31 July 2013; accepted 12 August 2013; published online 10 September 2013

(D'Incalci and Galmarini, 2010). In addition to direct growth inhibition, trabectedin at therapeutic concentrations has selective anti-inflammatory and immunomodulatory properties because of the inhibition of production of factors that promote tumour growth, angiogenesis and metastasis (D'Incalci and Galmarini, 2010). Recent data also suggested that trabectedin selectively targets macrophages and downregulates the production of proinflammatory mediators, which induces changes in the tumour microenvironment contributing to its antitumour activity (Allavena *et al*, 2005; D'Incalci and Galmarini, 2010; Germano *et al*, 2010).

The efficacy of trabectedin as salvage chemotherapy in adults with advanced, recurrent soft tissue sarcoma (STS) has been assessed in three non-randomised phase II trials (Garcia-Carbonero *et al*, 2004; Yovine *et al*, 2004; Le Cesne *et al*, 2005) and in chemotherapy-naive patients with unresectable advanced STS (Garcia-Carbonero *et al*, 2005). A phase II randomised trial in advanced lipo- and leiomyosarcomas (L-sarcomas) after failure of prior conventional chemotherapy found a superior disease control of trabectedin 1.5 mg m^{-2} given as a 24-h intravenous (i.v.) infusion every 3 weeks (q3w) compared with a weekly trabectedin regimen (0.58 mg m^{-2}; 3-h i.v. infusion for 3 consecutive weeks in a 4-week cycle; Demetri *et al*, 2009). It is noteworthy that the benefits from trabectedin therapy in patients treated with trabectedin given as a 24-h infusion q3w were highlighted by progression-free survival (PFS) rate at 3 months (51.5%) and 6 months (35.5%), which largely surpassed the thresholds criteria established by the European Organization for Research and Treatment of Cancer to define drug activity in pre-treated STS (i.e., 39% at 3 months and 14% at 6 months; Van Glabbeke *et al*, 2002). Based on these results, in 2007 trabectedin obtained marketing authorisation from the European Commission and in many other countries worldwide for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide, or for those patients who are unsuitable to receive these agents (European Medicines Agency (EMA), 2010).

Considering that nearly 50% of the patients with a newly diagnosed STS are over the age of 60 years at diagnosis, we performed a pooled analysis of data from five completed phase II trials (Garcia-Carbonero *et al*, 2004; Yovine *et al*, 2004; Garcia-Carbonero *et al*, 2005; Le Cesne *et al*, 2005; Demetri *et al*, 2009) to assess the age-related effects on the efficacy and safety of trabectedin.

PATIENTS AND METHODS

For this retrospective analysis, we have pooled all available data obtained in adult patients with STS treated in clinical trials with single-agent trabectedin at the approved dose and regimen: 1.5 mg m^{-2} given as a 24-h infusion q3w. We retrospectively analysed pooled data from 350 adult patients with STS treated in five phase II completed clinical trials. The efficacy and safety analysis of trabectedin in patients aged <60 and >60 years was performed by pooling individual data from 184 STS patients treated in three early non-randomised, single-arm, multicentre trials (Garcia-Carbonero *et al*, 2004; Yovine *et al*, 2004; Le Cesne *et al*, 2005), 36 chemotherapy-naive STS patients (Garcia-Carbonero *et al*, 2005) and 130 patients with L-sarcomas assigned to the 24-h q3w arm from the a pivotal, open-label, two-arm randomised trial (Demetri *et al*, 2009; Figure 1). In addition, a subset of 24 patients aged $\geqslant 70$ years was also analysed. All studies were conducted in European countries, the USA, Canada and Australia in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice and local regulations on clinical trials, and were approved by the institutional review boards of each participating centre. Signed informed consents were obtained from all study participants before registration.

All patients were required to have unresectable advanced or metastatic, histologically proven STS. Patients with refractory STS were allowed to receive combined or sequential prior chemotherapies and must have documented progressive disease (PD) less than or within 6 months of last treatment. Other eligibility criteria included patients $\geqslant 18$ years old, a minimum life expectancy of $\geqslant 3$ months, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leqslant 1$, advanced disease with at least one unidimensionally or bidimensionally measurable lesion, adequate renal, hepatic, and bone marrow function according to

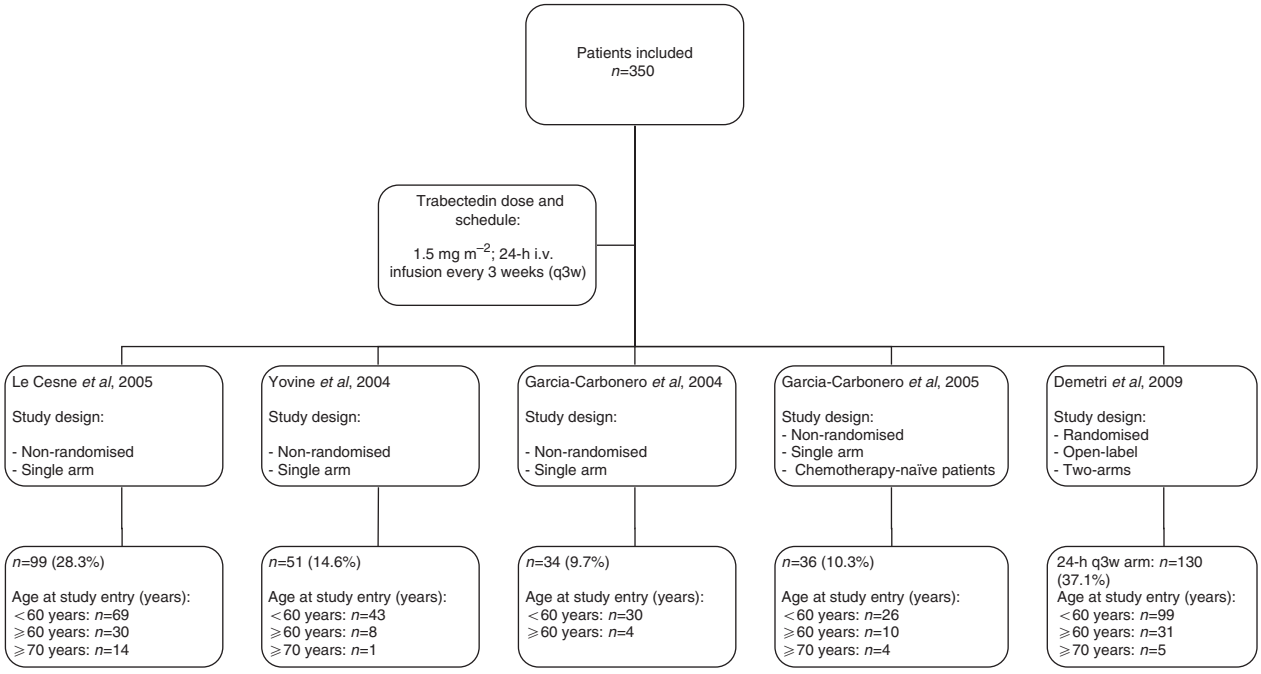

Figure 1. Patients included in pooled analysis.

laboratory standard parameters, and recovery to National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade $\leqslant 1$ derived from any prior treatment-related toxicity. Exclusion criteria included brain or leptomeningeal involvement, prior exposure to chemotherapy or any experimental treatment concomitantly or 30 days before inclusion in the study, patients with a presence of other neoplastic diseases (with the exception of adequately treated non-melanoma skin carcinoma or carcinoma *in situ*), or any other serious or unstable medical or psychiatric condition.

An early phase II clinical trial demonstrated that co-medication with dexamethasone reduced drug-induced hepatotoxicity, without a deleterious effect on its anticancer activity (Paz-Ares *et al*, 2010). Accordingly, dexamethasone pre-treatment is considered mandatory for all patients receiving trabectedin. Additional antiemesis prophylaxis included ondansetron or granisetron, corticosteroids, and/or metoclopramide. Therapeutic use of either granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor or erythropoiesis-stimulating agents were allowed in accordance with American Society of Clinical Oncology guidelines (American Society of Clinical Oncology (ASCO), 1996).

Treatment could continue until PD or discontinuation for other reasons, such as unacceptable toxicity, investigator decision or consent withdrawal. Trabectedin was administered q3w provided the patient had completely recovered to baseline values from haematological and liver adverse events (AEs) and recovered to NCI-CTC grade $\leqslant 1$ from non-haematological AEs other than hepatic. Treatment could be delayed up to 2 weeks to allow recovery. If re-treatment criteria were not met by day 35, the patient was to be withdrawn from the study. A maximum of two dose reductions (from 1.5 to $\sim 1.2\,mg\,m^{-2}$ then to $1.0\,mg\,m^{-2}$) were permitted if any of the following events occurred during the previous cycle of therapy: grade 4 neutropenia longer than 5 days associated with fever; grade 4 thrombocytopenia; grade 2 cardiac or neurological toxicity; alkaline phosphatase or bilirubin increases of any grade; or any other grade 3/4 AEs other than grade 3/4 alanine aminotransferase or aspartate aminotransferase if it was reversed to baseline values by day 21.

The primary end point in all trials was to determine the overall response rate (ORR) as per investigator's assessments or time-to-event end points, while safety was one secondary end point. Tumour response was assessed every two cycles according to the standard WHO criteria (Miller *et al*, 1981) or the Response Evaluation Criteria in Solid Tumors (Therasse *et al*, 2000), and PFS and OS curves were estimated by using the Kaplan–Meier method. The disease control rate (DCR) was defined as the percentage of patients with a complete response (CR) or partial response (PR) and/or stable disease (SD) lasting $\geqslant 6$ months. Eligible patients were considered assessable for response if they had received a minimum of two cycles of treatment and had at least one disease assessment performed at least 4 weeks after entering the study. Safety analyses were based on all-treated population, defined as those patients who received at least one trabectedin dose. Treatment-related AEs were coded using the Medical Dictionary for Regulatory Activities and graded according to the NCI-CTC.

RESULTS

Patient characteristics. This analysis included 350 patients divided in two principal cohorts: the younger cohort included 267 (76%) patients aged <60 years (median age 48 years; range: $19-59$ years) and the older cohort had 83 (24%) patients aged $\geqslant 60$ years (median age 65 years; range: $60-81$ years). The number of patients with age $\geqslant 60$ years in five pooled studies ranged from 4.8% to 37.3%. Among the patients of the older cohort, a subset of 24 (7%) patients aged $\geqslant 70$ years (median age 73 years; range: $70-81$ years) was separately analysed. Patients and tumour characteristics are summarised in Table 1. Patient and disease characteristics at baseline in either age-based group were similar and well balanced. In the younger and older cohort, L-sarcomas were the predominant histological STS subtypes (72% and 75%) and a good ECOG PS score of 0 out of 1 was recorded in 99.6% and 98.8% of patients, respectively. The vast majority of patients had previously undergone surgery (96% and 92%) and were pre-treated with a median of one line of chemotherapy (91% and 90%), respectively. Overall, most patients were exposed to one or two lines of prior chemotherapy (78.7% and 86.7%), respectively.

Treatment delivery. Median number of cycles received was 3, ranging from 1 to 48 and 1 to 59 cycles for younger and older patients, respectively. Patients received a median dose intensity of $0.42\,mg\,m^{-2}$ per week over a median treatment duration of 10 weeks (range: 3.0–181.1) in the younger and $0.40\,mg\,m^{-2}$ per week over a median treatment duration of 12 weeks (range: 3.0–236.7) in the older cohort (Table 2). In the younger and older cohort, 25.1% and 27.7% of patients received 7 or more cycles and 18.4% and 12.0% received 10 or more cycles, respectively, with a maximum of 48 and 59 cycles per cohort. Patients aged $\geqslant 70$ years had shorter median treatment duration (7.5 weeks; range: 3.0–37.3) mainly because of non-treatment-related events and received a median of two trabectedin cycles (range: $1-12$). However, these patients reached a median dose intensity of $0.41\,mg\,m^{-2}$ per week, representing 89% of the planned dose intensity, comparable with that given to patients younger than 70 years (Table 2).

Response rate and survival. Regarding the overall trabectedin activity, the ORR was 10.0% (2 CR and 33 PR; 95% confidence interval (CI): 7.1–13.6%) with no significant differences between patients aged <60 years (10.1%) and $\geqslant 60$ years (9.6%). A numerically lower overall ORR (1 PR, 4.2%; 95% CI: 1.1–21.1%) was observed among the 24 patients aged $\geqslant 70$ years. SD was recorded in 40.4%, 47.0% and 45.8% of patients aged <60, $\geqslant 60$ and $\geqslant 70$ years, respectively, and 17.2%, 21.7% and 20.8% of whom maintained SD for $\geqslant 6$ months for an DCR of 27.3%, 31.3% and 25.0% in each of these age-based groups (Table 3).

No significant differences were found in median PFS: 2.5 months in patients aged <60 *vs* 3.7 months in patients aged >60 (hazard ratio (HR): 0.9, 95% CI: 0.687–1.179; $P=0.4427$; Figure 2). Moreover, in both cohorts a comparable number of patients were progression-free at 3 months (45.1% *vs* 55.1%; $P=0.115$) and 6 months (29.5% *vs* 36.4%; $P=0.2638$). Similar median PFS was observed in $\geqslant 70$ years group (2.4 months; 95% CI: 1.4–6.2), as was the number of patients who were progression-free at 3 and 6 months: 45.8% (95% CI: 25.9–65.8%) and 32.1% (95% CI: 13.0–51.2%), respectively. Similarly, median OS was not statistically different in the two groups (13.0 *vs* 14.0 months in patients aged <60 and $\geqslant 60$ years, respectively; HR: 0.8, 95% CI: 0.61–1.06; $P=0.1216$), and comparable rates of OS were recorded in both cohorts: 55% and 56% at 12 months, and 29% and 38% at 24 months. No statistical differences (HR: 1.2, 95% CI: 0.76–1.86; $P=0.4534$) were observed in median OS in patients aged $\geqslant 70$ years (8.1 months; 95% CI: 4.6–19.4) and those aged <60 years (13.0 months; 95% CI: 11.3–14.9). Similarly, comparable number of patients older than 70 years was still alive at 12 months (41.7%, 95% CI: 21.9–61.4%).

Safety. Non-cumulative myelosuppression, with reversible neutropenia as the predominant component, and transient transaminase increases were the most common laboratory abnormalities seen with trabectedin associated to very low incidence of relevant clinical consequences. Treatment-related AEs outcomes are summarised in Table 4. Some grade 3/4 AEs were more common in patients aged >60 years, namely anaemia 10.1% *vs* 19.3%,

Table 1. Patient and disease characteristics at baseline

			⩾60 Years					
	<60 Years		⩾60 Years		⩾70 Years		Total	
	n	%	*n*	%	*n*	%	*n*	%
	267	76	83	24	24	7	350	100
Age at study entry (years)								
Median (range)	48	(19–59)	65	(60–81)	73	(70–81)	52	(19–81)
Gender								
Male	105	39	38	46	13	54	207	59
Female	162	61	45	54	11	46	143	41
ECOG PS								
0	136	51	30	36	4	17	166	47
1	131[a]	49	52[b]	63	20	83	182[a,b]	52
Histology								
Leiomyosarcoma	133	50	45	54	10	42	178	51
Liposarcoma	59	22	17	21	4	17	76	22
Synovial sarcoma	23	9	3	4	1	4	26	7
Sarcoma (unclassified)	14	5	3	4	1	4	17	5
MFH	5	2	5	6	4	17	10	3
Fibrosarcoma	7	3	1	1	1	4	8	2
Others[c]	26	10	9	11	3	13	35	10
Grade of differentiation								
G1: well differentiated	24	9	9	11	3	13	33	9
G2: moderately differentiated	54	20	26	31	5	21	80	23
G3: poorly differentiated	115	43	29	35	7	29	144	41
G4: undifferentiated	2	1					2	1
UK/NA	72	27	19	23	9	37	91	26
Prior treatments								
Prior surgery	256	96	76	92	20	83	332	95
Prior radiotherapy	139	52	39	47	9	38	178	51
Prior chemotherapy	242	91	75	90	22	92	317	91
No. of lines of prior chemotherapy								
Median (range)	1	(0–6)	1	(0–5)	1	(0–2)	1	(0–6)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; MFH = malignant fibrous histiocytoma; NA = not available; PS = performance status; STS = soft tissue sarcoma; UK = unknown.
[a]All had ECOG PS 1 save one patient with ECOG PS 2.
[b]All had ECOG PS 1 save one patient with unknown PS at baseline.
[c]In <60 years group: epithelioid and miscellaneous ($n=6$ each); neurogenic sarcoma-schwannoma ($n=5$); alveolar soft part sarcoma, angiosarcoma, endometrial stromal sarcoma and rhabdomyosarcomas ($n=2$ each); and chondrosarcoma ($n=1$). In ⩾60 years group: angiosarcoma/haemangiopericytoma, miscellaneous and rhabdomyosarcomas ($n=2$ each); chondrosarcoma, neurogenic sarcoma-schwannoma and solitary fibrous tumour ($n=1$ each). In ⩾70 years group: angiosarcoma/haemangiopericytoma, rhabdomyosarcomas and miscellaneous ($n=1$ each).

neutropenia 43.6% *vs* 60.2%, thrombocytopenia 11.3% *vs* 20.5% and fatigue 6.4% *vs* 14.5%. Grade 3/4 neutropenia followed a predictable reversible pattern and was rarely associated with fever (one patient in each cohort). Major haematological complications were uncommon given that grade 3/4 febrile neutropenia occurred in 0.4% of patients aged <60 years and in 1.2% of patients aged >60 years, whereas the use of G-CSF was similar in both cohorts (12.7% *vs* 13.3%). Transaminase increases in both cohorts had a conventional self-limited pattern with a peak elevation within the first week of drug administration and returned to baseline values by days 10–15 of each cycle with a clear trend towards reduction with subsequent cycles. With the caveat of the small numbers of patients within the patient subset aged ⩾70 years, no major differences were found in the safety profile in this group with the lower use of G-CSF (4.2%) in this subset. Deaths associated with drug-related AEs were infrequent (1.9% and 2.4% of patients in the younger and older cohort, respectively). Overall, other AEs were infrequent and manageable (Table 4).

DISCUSSION

This is the first analysis dealing with safety and efficacy in elderly patients with STS treated with trabectedin. The age of 70 is a chronological landmark commonly used in oncology for the

Table 2. Trabectedin exposure per age group

			⩾60 Years					
	<60 Years		⩾60 Years		⩾70 Years		Total	
	n	%	*n*	%	*n*	%	*n*	%
	267	76	83	24	24	7	350	100
Time on treatment (weeks)								
Median (range)	10	(3.0–181.1)	12	(3.0–236.7)	7.5	(3.0–37.3)	10	(3.0–236.7)
Cycles per patient								
Median (range)	3	(1–48)	3	(1–59)	2	(1–12)	3	(1–59)
Patients with ⩾7 cycles								
	67	25.1	23	27.7	3	12.5	90	25.7
Patients with ⩾10 cycles								
	49	18.4	10	12.0	1	4.2	59	16.9
Dose intensity (mg m^{-2} per week)								
Median (range)	0.42	(0.2–0.6)	0.40	(0.2–0.5)	0.41	(0.3–0.5)	0.41	(0.2–0.6)
Relative dose intensity (%)								
Median (range)	87	(39–120)	87	(39–101)	89	(57–100)	87	(39–120)

Table 3. Responses to trabectedin per age group

			⩾60 Years					
	<60 Years		⩾60 Years		⩾70 Years		Total	
	n	%	*n*	%	*n*	%	*n*	%
	267	76	83	24	24	7	350	100
CR	2	0.7	—	—	—	—	2	0.6
PR	25	9.4	8	9.6	1	4.2	33	9.4
SD	108	40.4	39	47.0	11	45.8	147	42.0
SD ⩾6 months	46	17.2	18	21.7	5	20.8	64	18.3
DCR								
(CR + PR + SD ⩾6 months)	73	27.3	26	31.3	6	25.0	99	28.3
PD	121	45.3	31	37.3	10	41.7	152	43.4
NE patients	11	4.1	5	6.0	2	8.3	16	4.6

Abbreviations: CR = complete response; DCR = disease control rate; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

definition of old patients (Pallis *et al*, 2010). However, this cutoff is arbitrary and the decision to treat or not these patients should be based on patients' biological rather than the chronological age. Older patients may have an increased toxicity risk when treated with chemotherapy, mostly because of not treatment-related factors (Torosian *et al*, 1988). Considering that elderly sarcoma patients are often under-treated, this likely contributed to shorter sarcoma-specific survival rate (Lev and Pollock, 2010). Nijhuis *et al* (1999) reported that at least 50% of patients with metastatic sarcomas aged ⩾70 years were not treated at all and only 20% received chemotherapy, in contrast to the young patients (⩽20 years) who all received chemotherapy. Yet, some elderly patients may be over-treated, given that modest chemotherapy efficacy could be outweighed by its toxicity, thereby negatively affecting survival.

In the present pooled analysis, we considered that 60 years was a reasonable compromise between old age and the age of patients included in phase II trials. Our results show that trabectedin is an active treatment with an overall ORR of 10.0% (younger: 10.1% *vs* older: 9.6% patients). This ORR is comparable to that reported with low-dose ifosfamide (14%) and doxorubicin (13%) in pre-treated STS patients (Le Cesne *et al*, 2009). This benefit in both younger and older patient population was further confirmed by PFS rates at 3 months (45.1% *vs* 55.1%) and 6 months (29.5% *vs* 36.4%). Although in patients with metastatic STS, prolongation of survival may not be correlated with tumour response, high median

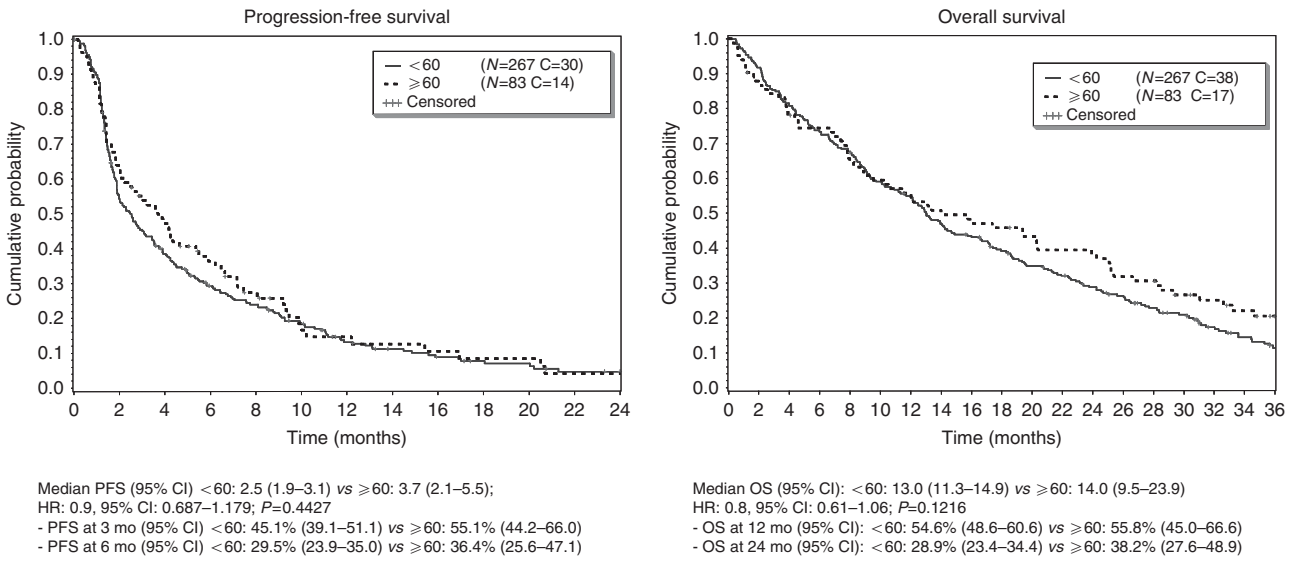

Figure 2. Kaplan–Meier curve for PFS and OS with trabectedin per age group. PFS and OS with trabectedin according to investigator assessment. Abbreviations: CI = confidence interval; HR = hazard ratio; mo = months; OS = overall survival; PFS = progression-free survival.

Table 4. Treatment-related haematological and non-haematological toxicities per patient and age group

					⩾60 Years											
	<60 Years				⩾60 Years				⩾70 Years				Total			
	267		76%		83		24%		24		7%		350		100%	
	Grades 1–4		Grade 3/4		Grades 1–4		Grade 3/4		Grades 1–4		Grade 3/4		Grades 1–4		Grade 3/4	
NCI-CTC grade	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Anaemia	250	93.6	27	10.1	82	98.8	16	19.3	24	100.0	4	16.7	332	94.9	43	12.3
Thrombocytopenia	110	41.4	30	11.3	41	49.4	17	20.5	13	54.2	5	20.8	151	43.3	47	13.5
Neutropenia	194	72.9	116	43.6	66	79.5	50	60.2	20	83.3	14	58.3	260	74.5	166	47.6
Febrile neutropenia	1	0.4	1	0.4	1	1.2	1	1.2	—	—	—	—	2	0.6	2	0.6
Alopecia	7	2.6	1	0.4	2	2.4	1	1.2	—	—	—	—	9	2.6	2	0.6
Fatigue	156	58.4	17	6.4	46	55.4	12	14.5	13	54.2	6	25	202	57.7	29	8.3
Nausea	172	64.4	19	7.1	44	53.0	3	3.6	13	54.2	2	8.3	216	61.7	22	6.3
PSN	6	2.2	—	—	1	1.2	—	—	—	—	—	—	7	2.0	—	—
Vomiting	103	38.6	15	5.6	22	26.5	3	3.6	8	33.3	1	4.2	125	35.7	18	5.1
AP increased	147	55.1	7	2.6	49	59.8	—	—	6	26.1	—	—	196	56.2	7	2.0
ALT increased	254	95.1	121	45.3	76	91.6	35	42.2	23	95.8	9	37.5	330	94.3	156	44.6
AST increased	249	93.6	88	33.1	76	91.6	32	38.6	22	91.7	6	25.0	325	93.1	120	34.4
Bilirubin increased	59	22.1	2	0.7	27	32.5	1	1.2	8	33.3	—	—	86	24.6	3	0.9
CPK increased	39	25.8	5	3.3	13	28.9	3	6.7	1	11.1	—	—	52	26.5	8	4.1
Creatinine increased	77	29.1	4	1.5	42	50.6	2	2.4	12	50.0	—	—	119	34.2	6	1.7

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; NCI-CTC = National Cancer Institute Common Toxicity Criteria; PSN = peripheral sensory neuropathy. Data shown are numbers and percentage of patients with available data.

OS was supportive for clinical activity of trabectedin being comparable in younger (13.0 months) and older (14.0 months) patients (Van Glabbeke *et al*, 1999). The results observed in the small and selected subset of 24 patients older than 70 years with excellent PS are encouraging; however, further exploration in a larger real-life population of elderly patients is warranted.

Beyond a direct and strong growth-inhibitory effect on cancer cells, trabectedin affects the tumour microenvironment by reducing the production of proinflammatory cytokines, such as IL-6, CCL2, CXCL8, VEGF and PTX3 (Germano *et al*, 2010). It is noteworthy that angiogenesis and immunosuppression in tumour biology frequently occur simultaneously in response to diverse

stimuli being cross-regulated by overlapping pathways (Motz and Coukos, 2011). Therefore, the characteristic late and long-lasting responses reported with trabectedin now have gained better theoretical support under the standpoint of trabectedin not only as a cytotoxic but also as an immunomodulating drug with high anti-inflammatory and anti-angiogenic activity (Grosso *et al*, 2006, 2007).

The main AEs reported in all cohorts were reversible neutropenia and transaminase increases with no major differences in the safety profile between age groups. In agreement with the safety profile of trabectedin, the overall incidence and severity of those events decreased in frequency over cycles (Schoffski *et al*, 2007; Carter and Keam, 2010). As no cumulative toxicities were apparent in this analysis, trabectedin could be administered for prolonged periods (e.g., up to 59 cycles). This compares favourably with conventional treatment for STS, as doxorubicin-induced cumulative cardiotoxicity prevents protracted treatment and re-treatments in most cases (Ferreira *et al*, 2008), and renal toxicity and dose-limiting neutropenia have been largely associated with ifosfamide treatment (Le Cesne *et al*, 1995). Recently, in selected patients aged $\leqslant$60 years the combination of doxorubicin and ifosfamide fail to significantly improve OS and was considerably more toxic than doxorubicin alone (van der Graaf *et al*, 2012).

In conclusion, the results of this pooled retrospective analysis have shown that trabectedin has an acceptable and manageable safety profile and antitumour activity in elderly patients with STS, comparable with that observed in overall population. No evidence of cumulative toxicity or end-organ dysfunction was found with trabectedin, and similar antitumour efficacy was recorded in all age-related groups after failure of conventional treatments or in patients who are not candidates to receive these drugs.

ACKNOWLEDGEMENTS

This pooled analysis and all five completed phase II trials were supported by funding from PharmaMar, Madrid, Spain and Janssen Research and Development, LLC, Raritan, NJ 08869, USA.

CONFLICT OF INTEREST

AL Cesne and J-Y Blay received research support, honoraria and travel grants from PharmaMar. A Nieto and A Tanović are employees and stockholders of PharmaMar, SA (Grupo Zeltia). S Schuetze received funding from Janssen to support the cost of conducting the trabectedin clinical trials. The remaining authors declare no conflict of interest.

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