European Journal of Cancer 76 (2017) 84–92

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Patient-derived solitary fibrous tumour xenografts predict high sensitivity to doxorubicin/dacarbazine combination confirmed in the clinic and highlight the potential effectiveness of trabectedin or eribulin against this tumour☆

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Received 9 November 2016; received in revised form 27 January 2017; accepted 1 February 2017
Available online 8 March 2017

☆ Presented at the 20th Connective Tissue Oncology Society (CTOS) annual meeting, Salt Lake City, November 2015, abs # 039 and at the 52nd American Society of Clinical Oncology (ASCO) annual meeting, Chicago, June 2016, abs # 11042.

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http://dx.doi.org/10.1016/j.ejca.2017.02.002

KEYWORDS
Sarcoma;
Solitary fibrous tumour;
Treatment;
Metastasis;
Chemotherapy;
Anthracycline;
Doxorubicin;
Ifosfamide;
Dacarbazine;
Trabectedin;
Eribulin;
Xenograft;
Mice model

Abstract ***Background:*** Preclinical models that mimic pathological and molecular features of solitary fibrous tumour (SFT) represent an important tool to select effective regimes and novel compounds to be tested in the clinic. This study was aimed at developing two preclinical models of SFT, assessing their predictive value in the clinic and selecting potential novel effective treatments.

Material and methods: Two dedifferentiated-SFT (D-SFT) models obtained from patients' biopsies were grown in immunodeficient mice. The antitumour activity on these models of doxorubicin, dacarbazine (DTIC), ifosfamide (monotherapy or combination), trabectedin and eribulin was tested. Twelve SFT patients were treated with doxorubicin and DTIC. Response by RECIST, progression-free survival and overall survival were retrospectively evaluated, distinguishing malignant-SFT (M-SFT) and D-SFT.

Results: Two D-SFT patient-derived xenografts (PDXs) that represent the first available preclinical *in vivo* models of SFT were developed and characterised. Doxorubicin/DTIC, DTIC/ifosfamide, doxorubicin/ifosfamide combinations consistently induced better antitumour activity than the single-agents. Particularly, doxorubicin/DTIC combination caused a max tumour volume inhibition >80% in both models. Doxorubicin/DTIC combo showed activity also in the case-series. Best RECIST responses were: 6 responses (M-SFT = 2 of 7, D-SFT = 4 of 5), 1 stable disease, 5 progressions, with a 6-month median progression-free survival (M-SFT = 6, D-SFT = 10 months). The PDXs were very sensitive to trabectedin and eribulin.

Conclusion: Doxorubicin plus DTIC combination was effective in our two D-SFT mice models and appeared to be active also in the clinic, especially in high-grade D-SFT patients. Among additional drugs tested in the PDXs, trabectedin and eribulin were highly effective, providing a rational to test these drugs in D-SFT patients.

1. Introduction

Solitary fibrous tumour (SFT) is a rare sarcoma [1,2], marked by a recurrent *NAB2-STAT6* gene fusion that is responsible for the nuclear expression of the transcription factor STAT6 [3]. Three clinical-pathologic variants of SFT are identified: typical (T-SFT), malignant (M-SFT) and dedifferentiated (D-SFT) SFT [1,4]. M-SFT is marked by a greater mitotic index (≥4/10 HPF) compared with T-SFT. D-SFT shows the transition to a high-grade morphology. Notably, STAT6 nuclear immunopositivity can be lost in D-SFT [5]. SFT has a low metastatic potential (≤15%), but a greater metastatic rate (40%) is observed in D-SFT [6,7].

Preliminary evidence is available that both anthracyclines and temozolomide are effective in SFT [8,9]. We had already tested the activity of temozolomide and dacarbazine (DTIC) in a patient-derived xenograft (PDX) model of high-grade SFT, confirming that they looked equally active [10]. In the same paper we reported 8 patients undergoing DTIC, with 3 responses.

The good consistency observed between preclinical and clinical observations encouraged us to develop further this approach. In this study, we report the development and characterisation of two preclinical models of SFT and the results of the experiments aimed at comparing the activity of cytotoxic agents currently used for treatment of soft tissue sarcoma, including the doxorubicin-DTIC combination, trabectedin and eribulin. We also assessed retrospectively the clinical activity of doxorubicin in combination with DTIC in a small population of advanced SFT patients.

2. Materials and methods

2.1. Experimental models and pharmacological studies

Two D-SFT PDX models were used in the study.

2.1.1. Development and characterisation of the model

The models were established by subcutaneous grafting of tumour fragments obtained at the time of surgery from 2 patients into the right flank of female SCID (SFT-1) or nude (SFT-2) mice (Charles River, Calco, IT). Specifically, SFT-1 was established from a pleomorphic osteochondro-like D-SFT from a patient with recurrent pelvic D-SFT [4]. Both in the patient and in the PDX, the tumour carried the *NAB2-STAT6* fusion transcript (ex6.INT6.ex3int), as detected by RT-PCR [3], but lacked immunohistochemical nuclear STAT6 expression [5]. SFT-2 was derived from a patient with locally relapsed D-SFT, pre-treated with sunitinib. This tumour closely resembled an Ewing sarcoma/peripheral primitive neuroectodermal tumour [4]. It was characterised by *NAB2-STAT6* fusion transcript (ex6.ex18) and negative STAT6 immunohistochemistry [5]. This

PDX showed superimposable morphology and, by contrast, recovered STAT6 nuclear expression (Suppl. Fig. 1). Both PDXs showed MGMT methylation [10]. SFT-1 carried a hemizygous and SFT-2 a homozygous RB1 deletion, as assessed by FISH with BACs mapping on *RB1* locus (RP11-305D15, RP11-174I10) together with a control on 13q 31.3 (RP11-121J7) [5]. TP53 was mutated in SFT-2. 17p deletion, including the TP53 gene, was observed in both clinical tumours by CGH array [5] (Table 1).

Tumour growth was followed by biweekly measurement of tumour diameters with a Vernier calliper, and tumour volume (TV) calculated by the following formula: TV (mm^3) = d^2 *X D/2*, where *d* and *D* are the shortest and the longest diameter, respectively.

The xenograft origin was authenticated through microsatellite analysis [10].

The use of patient material to generate xenografts and all experiments were approved by the institutional Ethics Committees for Animal Experimentation.

2.1.2. Xenograft treatments

Treatments started when xenografts were approximately 300 mm^3. Eight mice for experimental group were used. After dilution in sterile water (doxorubicin, DTIC, ifosfamide) or saline solution (trabectedin, eribulin), drugs were administered at dosage-schedules reported in Table 2. Treatment activity was assessed determining TV inhibition percentage (TVI%) in treated versus control mice, expressed as TVI% = 100 − ([mean TV treated/mean TV control] × 100).

2.1.3. Immunohistochemical assessment of γ-H2AX expression

The immunohistochemical assessment of γ-H2AX was performed on FFPE PDX samples obtained 24 h after the first drug treatment and stained with the anti-phospho-H2AX (Ser139) mouse monoclonal antibody (Millipore).

2.1.4. Western blotting

Lysates from frozen PDX tumours obtained at the end of the last eribulin treatment were prepared [11]. Proteins were separated by SDS-PAGE, transferred onto nitrocellulose membranes and incubated with primary monoclonal antibodies, anti-MPM2, anti-cyclin B1, anti-phospho Cdk1 (Tyr15) and anti-β-actin [12].

Table 1
Molecular features of patient tumours and corresponding PDX models.

Sample	Diagnosis	NAB2-STAT6 fusion transcript	STAT6 nuclear immunopositivity	*MGMT* promoter methylation	*RB1*	TP53 array CGH [4]	TP53 mutation analysis
Human sample 1	Pleomorphic osteochondro-like dedifferentiated-SFT	+	−	+	Hemyzigous deletion	Hemyzigous deletion	WT
SFT-1		+	−	+	Hemyzigous deletion	nd	WT
Human sample 2	Ewing-like dedifferentiated-SFT	+	−	+	Homozygous deletion	Hemyzigous deletion	G245S
SFT-2		+	+	+	Homozygous deletion	nd	G245S

Abbreviations: SFT, solitary fibrous tumour; nd, not done; WT, wild type.

Table 2
Pharmacological treatments and tumour responses of PDXs treated with doxorubicin, dacarbazine (DTIC), ifosfamide (IFO) and trabectedin, singly administered and in combination.

Treatment	Dose (mg/kg)	Schedule	Route	SFT-1	SFT-2
				Max TVI%[a]	Max TVI%[a]
Doxorubicin	*2.5*	*q7d × 4*	*i.v.*	27 (83)	29 (98)
IFO	*90*	*qd × 3 q 2w*	*i.p.*	45 (90)	44 (98)
DTIC	*105*	*q7d × 4*	*i.p.*	54 (97)	55 (94)
Doxorubicin/DTIC	2.5	*q7d × 4*	*i.v.*	83 (90)	96 (98)
	105	*q7d × 4*	*i.p.*		
IFO/DTIC	90	qd × 3 q 2w	*i.p.*	74 (97)	96 (98)
	105	q7d × 4	*i.p.*		
IFO/doxorubicin	90	qd × 3 q 2w	*i.p.*	68 (97)	93 (98)
	2.5	q7d × 4	*i.v.*		
IFO/doxorubicin/DTIC	90	qd × 3 q 2w	*i.p.*	97 (97)	–
	2.5	q7d × 4	*i.v.*		
	105	q7d × 4	*i.p*		
Trabectedin	0.15	q7d × 3	*i.v.*	70 (90)	98 (103)
Eribulin	1	q4d × 3 q3w	*i.p.*	92 (77)	–

Abbreviations: SFT, solitary fibrous tumour; TVI, tumour volume inhibition; i.v., intravenous; i.p., intraperitoneal.
[a] Maximum tumour volume inhibition% in treated versus control mice. In parentheses, the day on which it was assessed.

2.2. Patients

We retrospectively identified 12 patients affected by advanced SFT treated with doxorubicin plus DTIC within 3 centres of the Italian Rare Cancer Network from February 2012 to July 2016. All patients provided a written informed consent to the treatment.

Diagnosis was confirmed by expert sarcoma pathologists, according to the WHO classification [1] and updated criteria [6], reviewing the available tumour sample closest to the start of chemotherapy. STAT6 immunohistochemistry was performed [5]. Seven cases were consistent with M-SFT and 5 with D-SFT.

Table 3 summarises patient characteristics.

Patients received doxorubicin (75 mg/mq, i.v., bolus) and DTIC (800 mg/mq, intravenously over 60 min, in 2 days), every 3 weeks, until a maximum of 6 cycles, unacceptable toxicity or progression. Adverse events were recorded. Disease status was assessed at baseline by a whole body computed tomography scan (CT), a CT or magnetic resonance (MR) of the site(s) of disease, and a whole body bone scan. CT/magnetic resonance scans were repeated every 2 cycles. Response was assessed by RECIST 1.1.

Progression-free survival (PFS) and overall survival (OS) were estimated with Kaplan–Meyer method. Failure for PFS was progressive disease by RECIST, or death. Failure for OS was death due to any cause. Patients alive were censored at the time of the last contact.

3. Results

3.1. Experimental model and pharmacological studies

The antitumour activity of doxorubicin, DTIC and ifosfamide, administered as monotherapy or in combination, was tested against late-stage SFT-1 and SFT-2 xenografts. As monotherapy, DTIC and ifosfamide induced a significant and superimposable tumour growth inhibition in SFT-1 and SFT-2, whereas an almost negligible antitumour activity was observed following doxorubicin treatment in both models (Fig. 1, Table 2). Notably, drugs were delivered at suboptimal doses to highlight the effects of the combined treatments. Doxorubicin/DTIC, DTIC/ifosfamide and doxorubicin/ifosfamide combinations consistently induced an enhanced antitumour activity compared with single-agents, which was mainly appreciable in SFT-2, as indicated by max TVI (mTVI) always >90% and long-lasting tumour regressions observed in all mice (Fig. 1, Table 2). Although to a lesser extent, an enhanced therapeutic effect of the two-drug combinations was also observed in the SFT-1, in particular with the doxorubicin/DTIC combination (mTVI = 83%). In SFT-1, the three-drug combination (doxorubicin/DTIC/

Table 3
Clinical and molecular characteristics of patients at the time of treatment with doxorubicin plus DTIC.

Pts	ID	Gender (M/F)	Age (years)	ECOG	Diagnosis	Site of primary tumour	Disease extent	STAT6 IHC (N/C)	Previous medical treatment	# of cycles	G3-G4 toxicity	Best response by RECIST	PFS	Status	OS
1		M	37	0	D-SFT	Meninges	Lung	+	N	5	No	PR	32	AWD	44+
2		F	40	1	M-SFT	Cerebellum	Primary, lung, bone	+	Su, DTIC, Trabe	3	Neutropenia	PD	3	DOD	9
3		M	66	0	D-SFT	Glutaeus	Lung	+	N	6	No	PR	10	DOD	19
4		M	67	0	M-SFT	Pleura	Primary, lung	+	N	3	No	PD	2	AWD	25+
5		M	69	1	D-SFT	Pleura	Primary, lung	+	N	3	GGT increased	PD	2	LFU	3+
6		M	31	1	D-SFT	Kidney	Lung, bone, head	+	N	6	Neutropenia, thrombocytopaenia	PR	5	DOD	10
7		M	40	0	M-SFT	Ethmoid	Lung, kidney, bone, meninges	+	Epi+Ifx	6	No	PR	5	AWD	7+
8		F	58	0	M-SFT	Leg	Lung	+	N	6	No	PR	23+	NED (radical surgery)	23+
9		F	63	1	M-SFT	Retroperitoneum	Primary, lung	+	N	6	Neutropenia, mucositis	PD	6	DOD	12
10		M	43	0	M-SFT	UNK	Lung, bone	+	N	6	No	SD	9	DOD	30
11		F	52	0	M-SFT	Retroperitoneum	Abdomen	+	N	6	Neutropenia	PD	6	DOD	16
12		M	42	2	D-SFT	Pleura	Lung, Bone	+	N	4	No	PR	9	AWD	9+
												mPFS	6	**mOS**	19

Abbreviations: Pt, patient; M, male; F, female; CT, chemotherapy; UN, unknown; D-SFT, dedifferentiated SFT; M-SFT, malignant SFT; IHC, immunohistochemistry; N, nuclear; C, cytoplasmic; Su, sunitinib; DTIC, dacarbazine; Trabe, Trabectedin; Epi, epirubicin; Ifx, ifosfamide, GGT, gamma-glutamyltransferase; PFS, progression-free survival; AWD, alive with disease; DOD, dead of disease; LFU, lost at follow-up; NED, no evidence of disease; OS, overall survival; mPFS, median PFS; mOS, median OS; SFT, solitary fibrous tumour; PR, partial response.

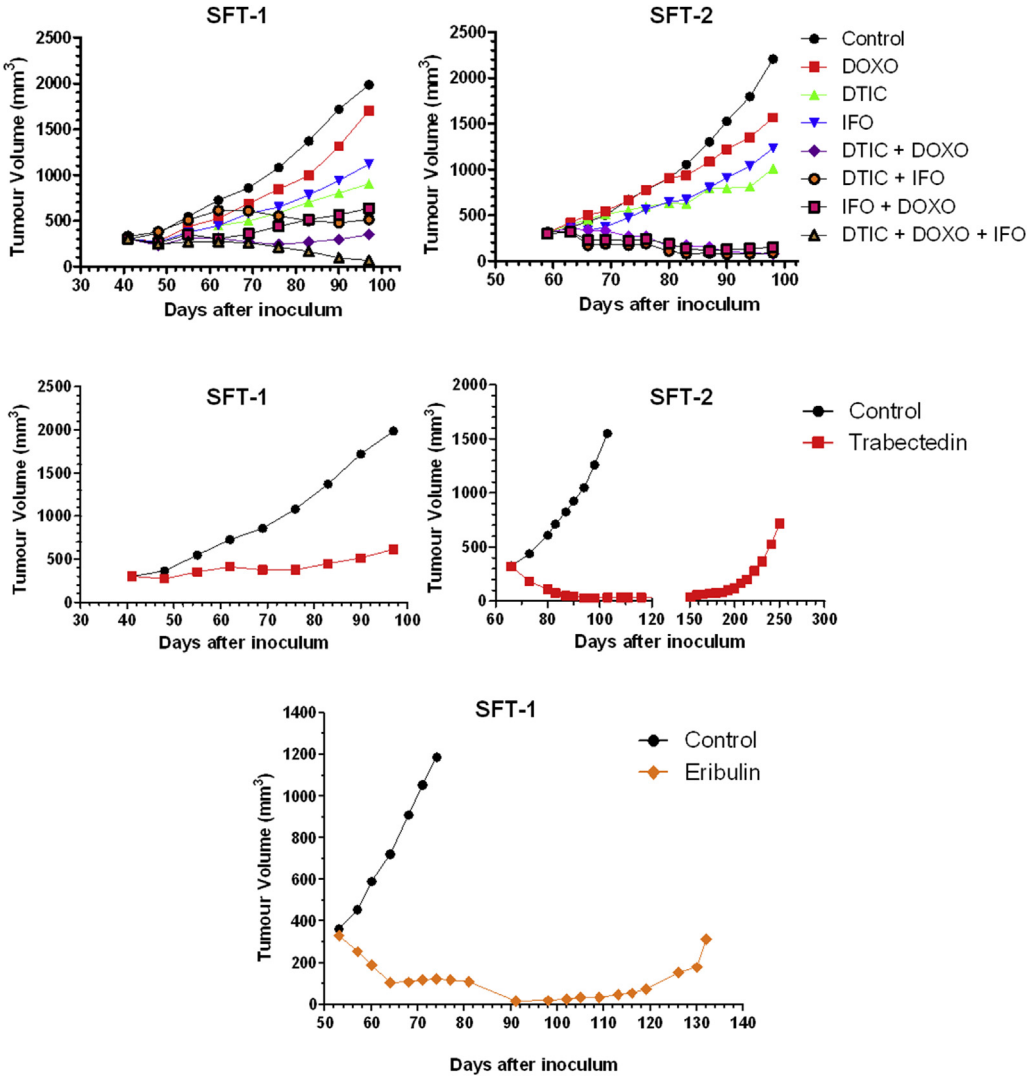

Fig. 1. Antitumour activity of doxorubicin (DOXO), dacarbazine (DTIC), ifosfamide (IFO), trabectedin and eribulin, singly administered and in combination, against solitary fibrous tumours xenotransplanted into SCID (SFT-1) and nude (SFT-2) mice. SFT, solitary fibrous tumour.

ifosfamide) induced the almost complete regression of tumours (mTVI = 97%; Fig. 1, Table 2).

The expression of γ-H2AX, a specific marker for monitoring treatment-induced DNA damage [13], was increased in tumours exposed to the two-drug combinations compared with individual agents in both xenografts (Fig. 2A, Suppl. Fig. 2). A further enhancement was observed in SFT-1 PDXs after treatment with doxorubicin/DTIC/ifosfamide combination (Fig. 2A).

Trabectedin monotherapy induced an mTVI = 70% in SFT-1, whereas an mTVI = 98% was detected in SFT-2, which was appreciable until two months from the end of treatment (Fig. 1, Table 2). γ-H2AX expression levels indicated that trabectedin caused less DNA damage (Fig. 2A, Suppl. Fig. 2) than doxorubicin/DTIC, DTIC/ifosfamide and doxorubicin/ifosfamide combinations, consistent with the notion that trabectedin activity is mainly related to the effect on transcription regulation [14].

Eribulin activity, tested only against SFT-1, induced an mTVI = 92%, with 4 mice experiencing long-lasting complete responses, 2 of which were maintained until the end of the experiment (Fig. 1).

Biochemical analysis on eribulin-treated xenografts showed increased staining of MPM-2 antibody, which recognises mitotic phosphoproteins [15], together with enhanced cyclin B1 levels and dephosphorylation on inhibitory Tyr-15 of Cdk1 [16], consistent with a tumour cell accumulation in the G2/M phase (Fig. 2B).

3.2. Patients

Twelve patients with advanced SFT received doxorubicin combined with DTIC. Mean number of cycles was 5. The treatment was well tolerated and toxicity was as expected (Table 3).

All patients were assessable for response. The best RECIST response was partial response (PR) in 6 (50%),

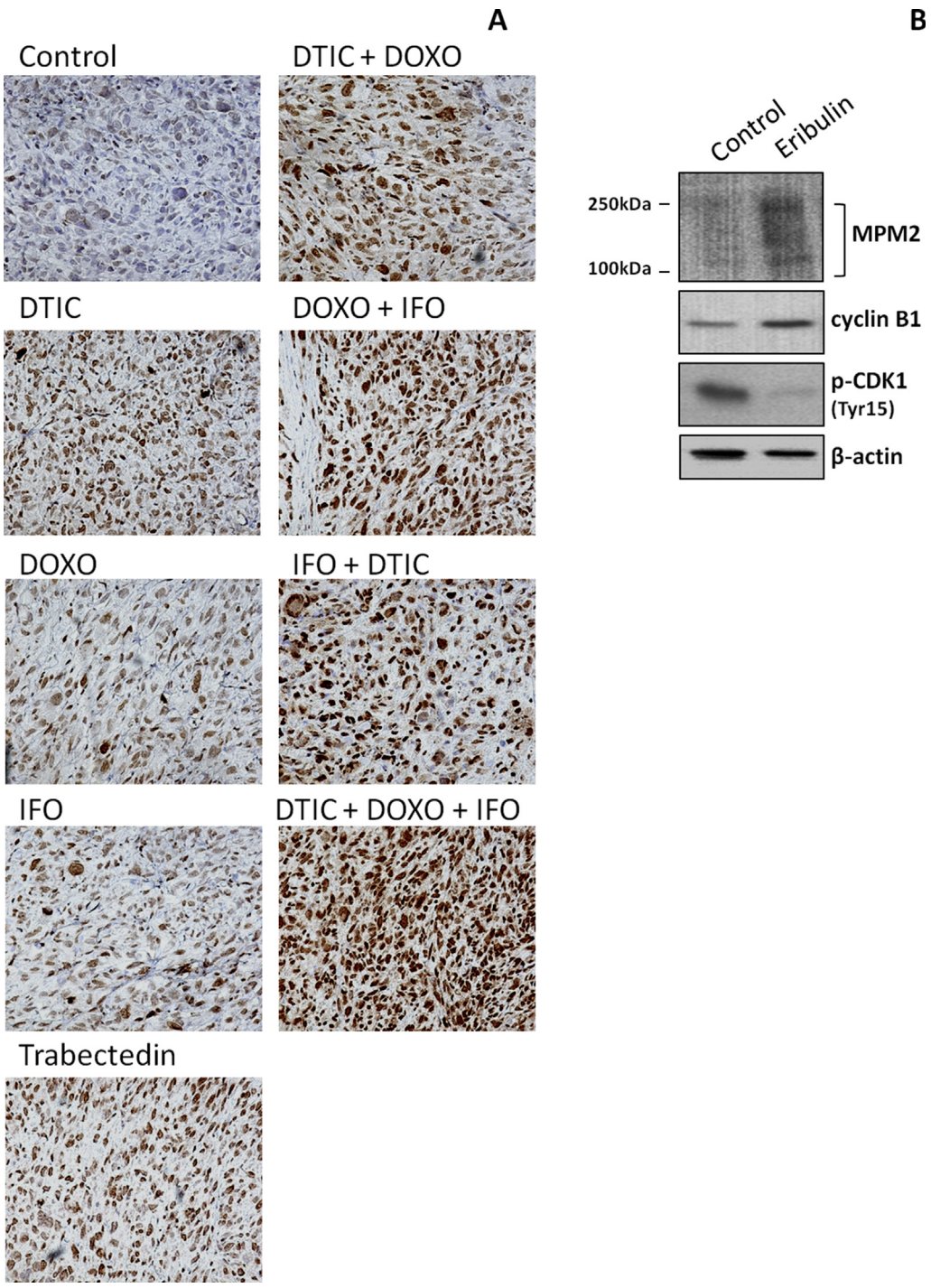

Fig. 2. A) γ-H2AX nuclear immunostaining in SFT-1 tumours following exposure to doxorubicin (DOXO), dacarbazine (DTIC), ifosfamide (IFO) and trabectedin, singly administered and in combination. B) Western blot analysis of mitosis-related factors in SFT-tumour following exposure to eribulin. SFT, solitary fibrous tumour.

stable disease in 1 (8.3%) and progression in 5 (41.7%) cases (Table 3, Fig. 3). A RECIST PR was detected in 2/7 M-SFT and in 4/5 D-SFT.

At a 25-month median follow-up, the median OS was 19 months (range 9–44+), with 7 patients dead at the time of the analysis. The median PFS was 6 months (range 2–32), with 20% of patients progression-free at 12 months. Median PFS was 6 and 10 in M-SFT and D-SFT, respectively ($p = 0.37$).

4. Discussion

No prospective studies focussing on chemotherapy are available in SFT. Of course, their rarity makes

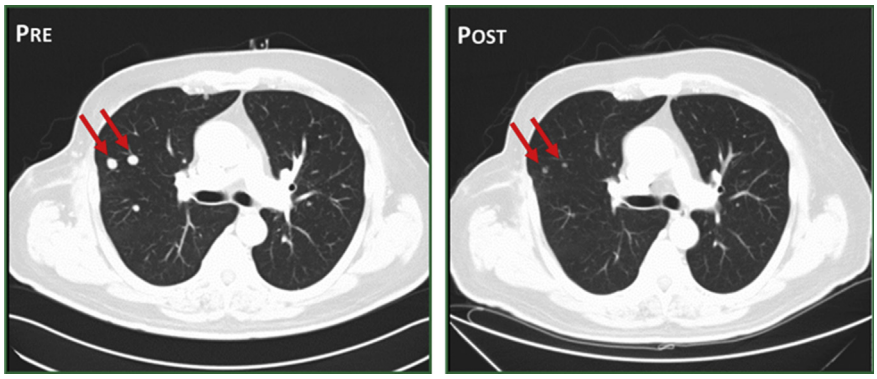

Fig. 3. Axial, contrast enhanced CT scans in a man affected by lung metastases (red arrows) from a dedifferentiated solitary fibrous tumour of the glutaeus, at baseline (left panel) and after 6 cycles of treatment with doxorubicin and DTIC (right panel). The lung lesions in the middle lobe reduced from 12 to 10 mm to 6 and 5 mm, respectively, thus achieving a partial response according to RECIST. SFT, solitary fibrous tumour; DTIC, dacarbazine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

comparative assessments in clinical studies challenging. Thus, retrospective series and predictive preclinical models are important to select treatments to be prospectively tested in clinical trials. PDX models, obtained through the direct implant in immunodeficient mice of surgical tumour specimens, are particularly promising, since they retain the main molecular, genetic and histologic features of donor tumours, closely recapitulating the original heterogeneity [17]. An advantage of PDXs compared with cell-lined–derived xenografts is their ability to better predict the response to therapeutic agents and to provide the insights useful for drug scheduling [18].

We already reported the consistency between preclinical and clinical results concerning the activity of temozolomide and DTIC [10] as well as that of several antiangiogenics [19] in our first D-SFT model (SFT-1). These results prompted us to develop further models and to compare the activity of the cytotoxic drugs available for treatment of sarcomas.

By assessing the activity of doxorubicin, ifosfamide and DTIC (as monotherapy or in combination) in two D-SFT PDXs, we observed that all combinations consistently induced an increased antitumuor activity compared with single-agents. Such an enhancement was mainly appreciable with the doxorubicin/DTIC combination (mTVIs = 83% and 96% observed in SFT-1 and SFT-2, respectively). Interestingly, the three-drug combination doxorubicin/DTIC/ifosfamide induced an almost complete regression of SFT-1 xenograft tumours. The increased antitumour activity was parallelled by an enhanced γH2AX staining in tumours, thus indicating the cumulative induction of lethal DNA lesions as a main mechanism responsible for the therapeutic efficacy of the combinations.

It is noteworthy that in these preclinical experiments suboptimal doses of individual agents were used to better appreciate the effect of combos. However, a remarkable therapeutic effect was also appreciable when higher doses of DTIC [10] or doxorubicin (Suppl. Fig. 3) were used as single-agents. This may be relevant for less fit and/or elder patients when a disease stabilisation is acceptable and a monotherapy with an expected better toxicity profile can be the choice.

Available data on the role of chemotherapy in patients with SFT are limited and point to the activity of agents like anthracycline, DTIC, ifosfamide [20,21] and trabectedin [22,23]. Two responses to eribulin were also reported [24,25]. The expected RR is low both with anthracycline-based regimens (0–20%) and with trabectedin (9%) [8,21,23,24,26–28]. In 2013, we published a retrospective series of 31 SFT patients treated with anthracycline-based chemotherapy (anthracycline monotherapy: 8; anthracycline/ifosfamide: 23). We observed 20% RECIST PR and a 4-month median PFS [8]. Notably, PRs were found in 2/18 (11%) M-SFT e 4/12 (30%) D-SFT, with a median PFS of 3.5 and 5 months in M-SFT and D-SFT, respectively. The finding that the doxorubicin/DTIC combination was active in our D-SFT models prompted us to assess the efficacy of this combination in the clinic. The case-series analysis that we could collect and present herein, with all the limitations of a small and retrospective series of patients, confirms that anthracycline-based regimens are effective in SFT, showing that the combination of doxorubicin/DTIC seems to increase both the RR (50% PR by RECIST) and PFS (6-month median PFS) compared with our prior series. As already observed [8], D-SFT appears more sensitive to chemotherapy compared with M-SFT, both in terms of RR and of PFS (10 versus 6 months). This suggests preferring a combination of doxorubicin/DTIC in high-grade cases and when a major tumour response is needed.

In the D-SFT models, we also tested the activity of other drugs of clinical interest for sarcomas, such as trabectedin and eribulin.

Trabectedin showed remarkable antitumour activity in both models. Indeed, a major (SFT-1) or almost

complete (SFT-2) tumour regression was found, in contrast with clinical data that are more consistent with a disease stabilisation without tumour shrinkage [22]. Since clinical reports do not detail which is the SFT subtype of those patients who benefited from trabectedin, the possibility that SFT biologic aggressiveness is responsible for a different sensitivity to the drug cannot be ruled out.

An impressive antitumour activity, with long-lasting complete tumour regressions, was also observed in SFT-1 following treatment with the novel microtubule inhibitor eribulin [29]. Consistently with its antimitotic effect, biochemical analysis on eribulin-treated xenografts was suggestive of tumour cell accumulation in the G2/M phase. Eribulin was recently approved by FDA and EMA for treatment of advanced liposarcoma resistant to anthracycline, based on the results of a phase 3 trial [30]. In two phase 2 studies that were run in soft tissue sarcoma, two anecdotal responses were detected in a SFT patients [24,25]. This preliminary clinical observation, together with the impressive preclinical results, suggests evaluating further eribulin in SFT.

In conclusion, our results provide insights into the activity of cytotoxic agents available in the clinical practice for treatment of STS, confirming that, especially in the more aggressive SFT, they actually belong to the therapeutic medical armamentarium. Based on these results, a prospective phase 2 randomised study on doxorubicin/DTIC versus trabectedin in advanced SFT is starting. In addition, eribulin, the last cytotoxic agent approved for the treatment of sarcoma, deserves further investigations. Finally, additional experiments are ongoing in our PDXs to investigate the efficacy of new molecular targeted agent as single-agents and in combination with cytotoxics in the disease.

Conflict of interest statement

Stacchiotti S, Gronchi A, Casali PG, D'Incalci M: Pharmamar: compensated advisory board, honoraria, research funding; Vincenzi B, Badalamenti G, Casali PG: EISAI: compensated advisory board, honoraria, research funding; and the remaining authors have no conflicts to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.02.002.

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