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Gefitinib in second line treatment of metastatic or locally advanced synovial sarcoma expressing HER1: A phase II trial of EORTC Soft Tissue and Bone Sarcoma Group

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ABSTRACT

Rationale: Synovial sarcomas (SyS) have been reported to over-express HER1 in gene expression profile experiments and immunohistochemistry. On the basis of these observations, gefitinib (IRESSA), an inhibitor of HER1 signalling, was tested in advanced or metastatic SyS failing doxorubicin (Dox) +/- ifosfamide (Ifo).

Patients and methods: This Phase II study was conducted in patients with advanced or metastatic HER1-expressing SyS not amenable to cure with surgery and/or radiation. Patients had measurable progressive lesion(s), pretreatment with up to two lines of single agent therapy with Doxo and Ifo, or one line of a combination in metastatic phase, ECOG performance status 0 to 2, age >=18 years. Gefitinib was given at the dose of 500mg/day until progression or intolerance. Primary endpoint was the rate of progression free survival at 3 months (PFS3). A two step Simon design was used with a p0 of 25% and a p1 of 45%, with α and ß of 0.1. 44 patients were scheduled to be recruited.

Results: Between 10/02 and 10/05, 48 patients were included in 12 EORTC STBSG centers. There were 27 (56%) males and 21 (44%) females, with a median age of 42 years (range 19-66). Primary sites of SyS were lower limb, upper limb and thorax (51%, 16% and 13% respectively). Metastatic sites were lung in 92% and soft tissue or lymph nodes in 42%, of the patients. 42%, 40% and 18 % of the patients had received 1, 2 and >2 lines of CT respectively. As of December 2005, 37 patients were evaluable for toxicity and 39 are evaluable for the primary endpoint. Median treatment duration was 11 weeks (range 2-25).Toxicity (G1-4) reported included fatigue (43%), diarrhea (54%), cough (35%), dyspnea (43%), cutaneous (73%), (or: rash (32%), dry skin (43%), acnea (30%). G3-4 toxicities were dyspnea (9), fatigue (4), cutaneous (2), cough (1), neurological (2), thombosis (2), hypoxia (1), infection (1).There was no drug related death.] No dose reductions have been reported so far, but treatment had to be temporarily interrupted in 23% of the patients. As of December 2005, no objective responses were reported. 7 (18%) patients achieved stable disease as best response. The PFS3 was 13% (5/39 evaluable patients); PFS6 and PFS12 were 10% and 3% respectively.

Conclusion: Disease stabilisation was observed in 18% of patients, but only 13% of SySs expressing HER1 achieved PFS (>=12 weeks) under gefitinib treatment [HER1 gene expression profiling and protein expression were not accurate predictors of gefitinib activity in this study.

STUDY DESIGN

Eligibility criteria

- Histological proven advanced or metastatic synovial sarcoma expressing HER1
- At least one previous line of chemotherapy containing doxorubicin and/or ifosfamide
- Measurable disease (RECIST)
- PS 0-2 (WHO); age >= 18 years
- Normal hematological, liver and renal function

Therapeutic regimen

- Iressa (Gefitinib), 500 mg/day, oral administration
- Duration: until progression, unacceptable toxicity or refusal

Dose and schedule modification

- Treatment interruption (maximum: 14 days for each interruption)
- Dose reduction to 250 mg/day in case of recurrence; no dose re-escalation
- Withdrawal in case of further recurrence

Primary end-point

- Disease evaluation 12 weeks after start of treatment
- Success: CR, PR or SD at 12 weeks
- Failure: PD at 12 weeks or earlier

Statistical design

- Simon optimal design
- P0=25%; P1=45% (EJC 38, 2002, p.543)
- α = β = 0.1
- 1st step: stop if <=3 successes / 14 patients
- 2nd step: further studies if >= 15 successes / 44 patients

DEMOGRAPHIC DATA

Patients	48		
Ineligible	2	Histology, late IC	Excluded from activity analyses
Early death	2	PD, pneumonia	Excluded from safety analyses (no data)

Patients characteristics

		Nbr cases	%
Age (years)	< 40	18	37.5
	40 - 50	18	37.5
	50 - 60	9	18.7
	> 60	3	6.2
Sex	Male	27	56.2
	Female	21	43.7
Performance status (WHO)	0	23	47.9
	1	20	41.7
	2	5	10.4

Prior chemotherapy

		Nbr cases	%
Number and type of regimen	1 regimen single agent	4	8.3
	1 regimen combination	15	31.2
	2 regimen	20	41.7
	3+ regimen	9	18.7

Disease characteristics

		Nbr cases	%
Original localisation	Lower extremities	25	52.1
	Upper extremities	8	16.7
	Thorax	6	12.5
	Head and Neck	3	6.2
	Other	2	4.2
	Trunk	1	2.1
	GU visceral	1	2.1
	GI visceral	1	2.1
	UNKNOWN	1	2.1
Time since initial diagnosis	< 6 months	3	6.2
	6 - 12 months	3	6.2
	12 - 24 months	10	20.8
	24 - 36 months	7	14.6
	36 - 60 months	12	25.0
	> 60 months	13	27.1
Involved sites at entry (patients may be counted more than once)	Lung	44	91.7
	Primary tumor / recurrence	12	25.0
	Lymph node	11	22.9
	Other soft tissue	10	20.8
	Other	4	8.3
	Liver	2	4.2

TREATMENT ADMINISTRATION

Treatment duration (days)

Median	78
Minimum	13
Maximum	408

Dose and schedule modifications

	Nbr patients	%	
Treatment interrupted	4	8.3	18 days (skin toxicity) 6 days (diarrhea) 15 days (liver dysfunction) 1 day (surgery)
Dose reduced to 250 mg/day	1	2.1	250 mg from day 33 (diarrhea, skin toxicity)

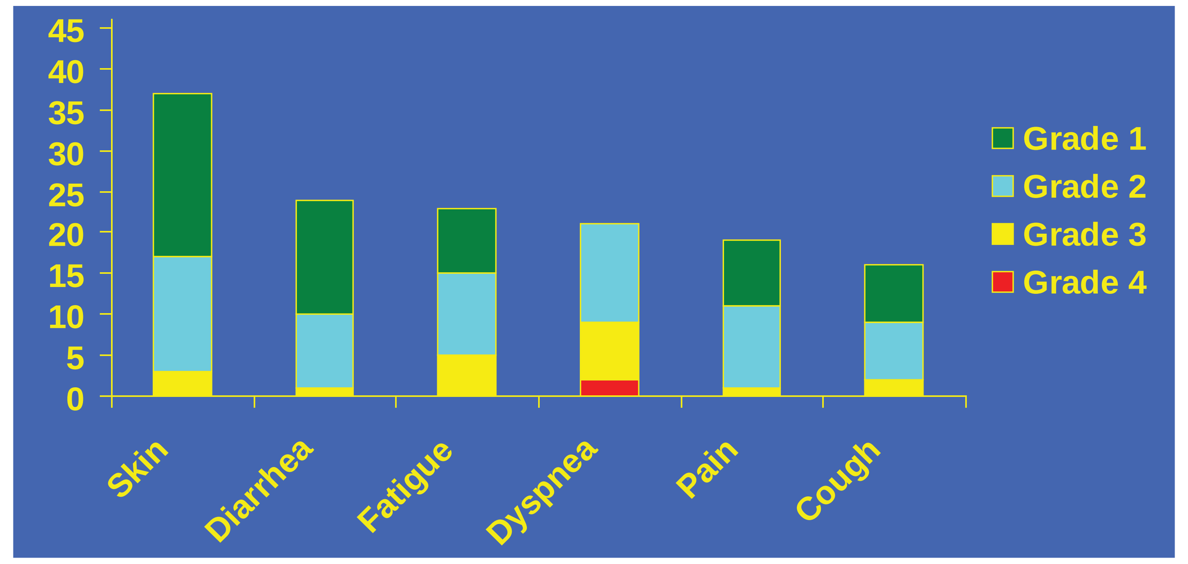
Reason for treatment discontinuation

	Nbr cases	%	
Progression	44	91.7	
Toxicity	2	4.17	Day 14: interstitial pneumopathy Day 39: stomatitis, diarrhea and rash
No improvement	1	2.08	
Death	1	2.08	Day 17: Pneumonia
Total	48	1	

SAFETY PROFILE

This table describes adverse events that have been observed at least once with a grade 3.

	Grade 1	Grade 2	Grade 3	Grade 4
Skin	20 (43.5%)	14 (30.4%)	3 (6.5%)	
Diarrhea	14 (3.04%)	9 (19.6%)	1 (2.2%)	
Fatigue	8 (17.4%)	10 (21.7%)	5 (10.9%)	
Dyspnea		12 (26.1%)	7 (15.2%)	2 (4.3%)
Pain	8 (17.4%)	10 (21.7%)	1 (2.2%)	
Cough	7 (15.2%)	7 (15.2%)	2 (4.3%)	
Neurological	6 (13%)		2 (4.3%)	
Weight loss	7 (15.2%)		1 (2.2%)	
Infection	1 (2.2%)	5 (10.9%)	1 (2.2%)	
Hemorrhage	3 (6.5%)		1 (2.2%)	
Thrombosis			1 (2.2%)	
Hypoxia			1 (2.2%)	
Pneumothorax			1 (2.2%)	

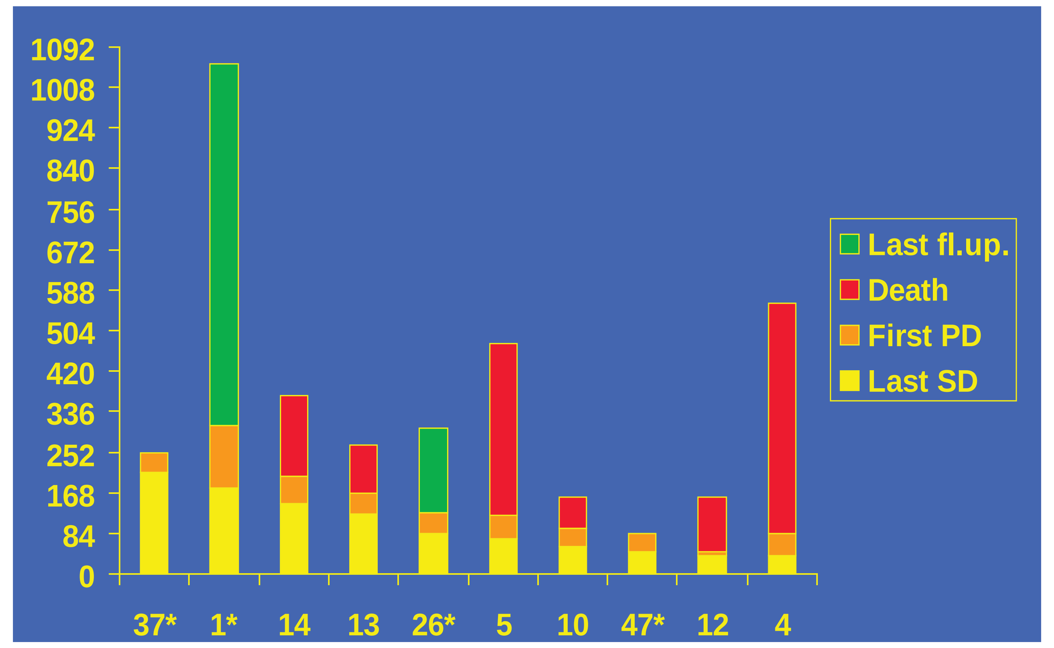


ACTIVITY

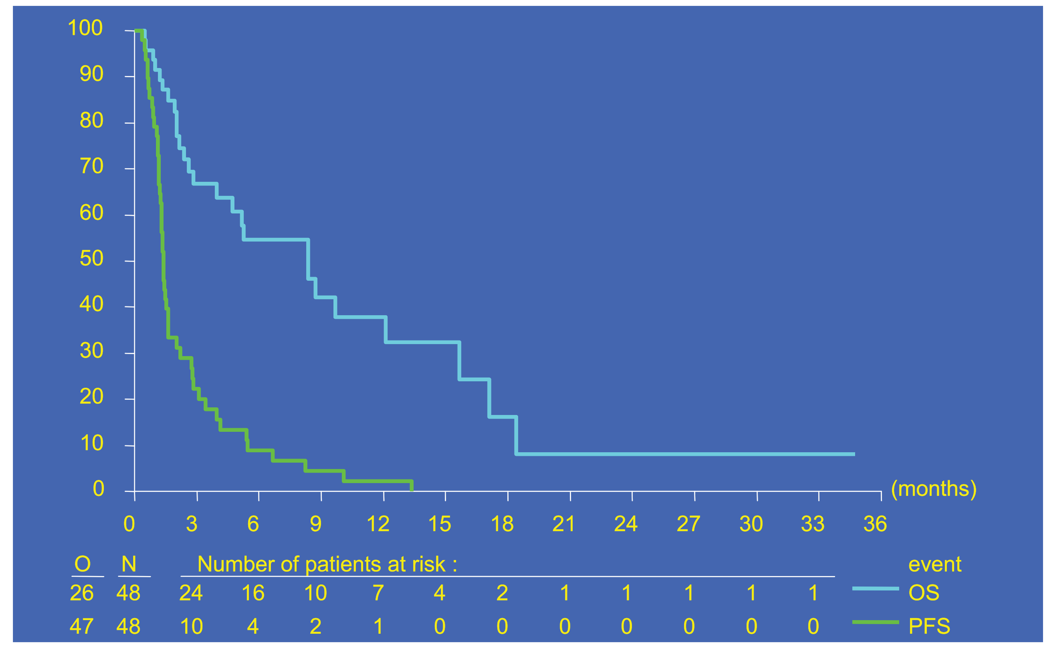
Best overall response

Value	Nbr cases	%
SD > 12 weeks	5	10.9
SD < 12 weeks	5	10.9
PD	35	76.1
Disease not assessed	1	2.2
Total	45	100

Patients with stable disease



Overall and progression free survival



CONCLUSION

Although overexpression of HER1 enables to distinguish synovial sarcomas from other sarcomas in gene expression profile experiments, an inhibitor of HER1 was found inefficient for the treatment of advanced refractory synovial sarcoma expressing HER1.