Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

IMATINIB INDUCES PROGRESSION ARREST IN RECIST PROGRESSIVE DESMOID TUMOR PATIENTS - A PHASE II STUDY OF THE GERMAN INTERDISCIPLINARY SARCOMA GROUP (GISG)

B. Kasper[1], V. Gruenwald[2], P. Reichardt[3], S. Bauer[4], G. Rauch[5], M. Sommer[1], P. Hohenberger[1]

[1] University of Heidelberg, Mannheim University Medical Center, Interdisciplinary Tumor Center Mannheim, Sarcoma Unit, Mannheim, Germany; [2] Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [3] HELIOS Klinikum Bad Saarow, Sarcoma Center Berlin-Brandenburg, Bad Saarow, Germany; [4] Sarcoma Center, West German Cancer Center, Essen, Germany; [5] University of Heidelberg, Institute of Medical Biometry and Informatics, Heidelberg, Germany.

Connective Tissue Oncology Society

Introduction: Desmoid tumors describe a rare monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course. Surgery is one therapeutic option for progressing patients, except if mutilating and associated with considerable function loss. Different treatment approaches have been investigated for advanced disease and promising results could be demonstrated using imatinib.

Patients and Methods: Therefore, we initiated a phase II trial within the GISG evaluating imatinib to induce progression arrest in RECIST progressive desmoid tumor patients not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss (NCT01137916). Major eligibility criteria were a histological confirmed desmoid tumor showing progressive disease according to RECIST 1.0 within six months. Patients were treated with a planned dose of 800 mg imatinib daily over two years. Primary endpoint was the non-progression rate after six months of treatment. Eleven out of 37 evaluable patients would be necessary to conclude a positive study result. Accrual started in July 2010 in five GISG centers and finalized in September 2013 (*Table 1*).

Results: The final analysis for the primary endpoint showed that 24 out of 37 evaluable patients were progression-free at six months of imatinib treatment and reached the primary endpoint. Response assessment after six months revealed one partial response (3 %; *Figure 1*) and 23 stable diseases (62 %). Out of the 13 patients counted as non-successors, ten patients had documented disease progression (27 %). One patient terminated due to toxicity and there were two study withdrawals.

Conclusion: With a 65 % progression arrest rate at six months after start of treating RECIST progressive patients, imatinib clearly exceeded the primary endpoint in this GISG trial (*Table 2*). Follow-up will continue until the end of the two years treatment period.

Table 1: Patients' characteristics (n = 37)

Median age	40 years (range: 19 - 80)	
Gender (**female**/male)	26/11	**70 %**
ECOG (**0**/1)	33/4	**89 %**
Prior surgery (**yes**/no)	32/5	**87 %**
R0 resection (**yes**/no)	4/27	**13 %**
Prior radiotherapy (**yes**/no)	9/28	**24 %**
Prior medical therapy (**yes**/no)	11/26	**30 %**
Site of primary tumor:		
Extremity	20	54 %
Chest	5	13 %
Head & neck	1	3 %
Abdomen	6	17 %
Other	5	13 %

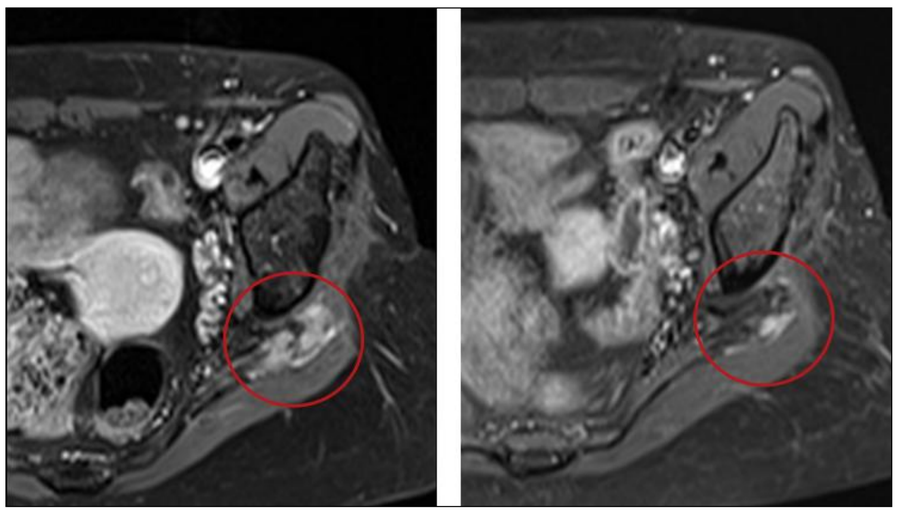

Figure 1:
Example of a patient with a desmoid tumor located in the left gluteal area showing a partial response after six months of imatinib therapy with a treatment duration of ≥ 36 months now.

Table 2:
Comparison of our data with the other prospective trials using imatinib in desmoid tumor patients.

	n	Inclusion criteria	Treatment dose [mg]	Treatment duration	Response rate [%]	6-month-PFS [%]	12-month-PFS [%]
Heinrich et al. ***JCO 2006***	19	No PD required "heavily pretreated patients"	800	325 days	16	53	36.8
Penel et al. ***Ann Oncol 2010***	35	No RECIST PD "radiological evidence for PD"	400	1 year	11	80	67
Chugh et al. ***Clin Cancer Res 2010***	49	No PD required "locally advanced disease"	200-600 BSA adjusted	until PD 9 pts. > 3 years	6	84	66
Kasper et al. ***ESMO 2014***	37	**RECIST PD required**	800	**2 years**	3	65	not yet reached

Take-home-messages

- Prospective studies in this rare entity are feasible (4 studies with 140 patients).
- GISG-01 study is positive and met its primary endpoint.
- Imatinib is active with a progression arrest of 65 % at 6 months in the small subgroup of RECIST progressive patients.
- "Selling points" of the GISG study compared to previous trials:
  - Inclusion of patients with RECIST 1.0 progressive disease only
  - Long treatment duration of 2 years