European Journal of Cancer 76 (2017) 60–67

Available online at www.sciencedirect.com

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Clinical Trial

Imatinib induces sustained progression arrest in RECIST progressive desmoid tumours: Final results of a phase II study of the German Interdisciplinary Sarcoma Group (GISG)

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Received 5 December 2016; received in revised form 30 January 2017; accepted 1 February 2017

KEYWORDS
Desmoid tumour;
Imatinib;

Abstract ***Background:*** Desmoid tumours describe a rare monoclonal, fibroblastic proliferation characterised by an often unpredictable clinical course. Surgery is one therapeutic option for progressing patients, except if mutilating and associated with considerable function loss.

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http://dx.doi.org/10.1016/j.ejca.2017.02.001
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Nilotinib;
Positron emission tomography;
Progression arrest

Different systemic treatment approaches have been investigated and promising results could be demonstrated using imatinib.

Patients and methods: We initiated a phase II trial within the German Interdisciplinary Sarcoma Group (GISG) evaluating imatinib to induce progression arrest in desmoid tumour patients being Response Evaluation Criteria in Solid Tumours (RECIST) progressive, not amenable to surgical resection with R0 intent or accompanied by unacceptable function loss (NCT01137916). Thirty-eight patients (median age 44 years [range: 19–80]; 68% female; 90% Eastern Cooperative Oncology Group (ECOG) performance status 0) were treated with a daily dose of 800 mg imatinib planned over 2 years. The progression arrest rate after 6 months of imatinib treatment (PAR_{6mo}) was the primary end-point. Patients showing disease progression under imatinib could be treated with nilotinib 800 mg daily. Accrual started in July 2010 in four GISG centres and finalised in September 2013.

Results: The final analysis for the primary end-point in the evaluable patients of the full analysis set revealed a PAR_{6mo} of 65%. Subsequent progression arrest rates at 9, 12, 15, 18, 21 and 24 months were 65%, 59%, 53%, 53%, 50% and 45%, respectively. None of the patients died within the study observational period. Best reported response was seven partial responses at 21 months revealing an overall response rate of 19%. Eight patients treated with nilotinib demonstrated a PAR at 3 months of 88% (7/8); no more disease progressions occurred until end of study. In general imatinib adverse events were mild to moderate.

Conclusions: Imatinib induces sustained progression arrest in RECIST progressive desmoid tumour patients. In addition, nilotinib had the potential to stabilise desmoid tumour growth after treatment failure with imatinib.

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1. Introduction

Desmoid tumours are rare monoclonal, fibroblastic proliferations characterised by an often unpredictable clinical course. Although histologically benign, desmoid tumours are locally invasive and associated with a high local recurrence rate, but lack any metastatic potential. According to the World Health Organization, they are defined as 'clonal fibroblastic proliferation that arises in the deep soft tissues and is characterised by infiltrative growth and a tendency toward local recurrence but an inability to metastasise' [1]. Considering the variable clinical presentations, anatomic locations and biological behaviours, an individualised treatment approach is required and different treatment recommendations and therapeutic algorithms have been developed recently [2,3]. The incidence is less than 3% of soft tissue tumours with a peak age of about 30 years [4]. Although most desmoid tumours occur sporadically, approximately 5–10% arises in the context of familial adenomatous polyposis (FAP). Sporadic ones predominantly affect young adults, especially females and sometimes related to pregnancy. Desmoid tumours often involve the extremities (including pelvic and shoulder girdles), the trunk (mostly abdominal wall), and the abdominal cavity (mostly within the mesentery or the pelvis) and the head and neck.

No evidence-based approach for the treatment of this disease is available as of today [3]. A careful counselling at a reference centre is mandatory and should be offered to all patients affected by sporadic desmoids from the time of their diagnosis. It is reasonable to consider watchful waiting as an initial step before undertaking subsequent treatments [5]. Surgery with or without radiotherapy is one therapeutic option for progressing patients, except if mutilating and associated with considerable function loss [6]. The Soft Tissue and Bone Sarcoma Group of the European Organisation for Research and Treatment of Cancer identified moderate dose radiotherapy as an effective treatment option for desmoid tumour patients with slow responses after radiation and continuing regressions documented even after 3 years [7]. Different systemic treatment approaches have been investigated for advanced disease [8] and promising prospective but uncontrolled data could be demonstrated using the tyrosine kinase inhibitor imatinib.

The initial data on the use of imatinib in desmoid tumours were generated by Mace *et al.* who observed a response in 2 patients with extra-abdominal aggressive fibromatosis [9]. In contrast to other imatinib responsive tumours, no genomic changes of *KIT* have been observed in desmoids showing that the response to imatinib is not attributable to *KIT* alteration [10]. Despite a rather low response rate ranging from 5 to 15%, high rates of stabilisation of around 60–80% with a favourable toxicity profile were documented in three prospective, non-randomised trials [11–13].

The objective of the present study of the German Interdisciplinary Sarcoma Group (GISG) was to evaluate the activity and safety of imatinib over a planned treatment period of 2 years in patients with Response Evaluation Criteria in Solid Tumours (RECIST)

progressive desmoid tumours not amenable to surgery or to prevent patients from function loss.

2. Patients and methods

2.1. Study design

Enrolled patients were at least 18 years old with histological proven and RECIST 1.0 [14] progressive desmoid tumour within the last 6 months. Tumours were measurable according to RECIST 1.0 by computed tomography (CT) or magnetic resonance imaging (MRI) and not amenable to radiotherapy or non-mutilating surgery; prior systemic therapy was allowed. Additional inclusion criteria were as follows: contraception during imatinib treatment, adequate haematological function (absolute neutrophil count $\geq 1.5 \times 10^3/mm^3$ and platelets count $\geq 100.000/mm^3$), adequate liver function (total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase $\leq 2.5 \times$ ULN), adequate renal function (creatinine $< 2.5 \times$ ULN). Exclusion criteria included the following: surgical intervention <4 weeks, pregnant or breast-feeding patients, a previous history of cancer, prior therapy with imatinib, known allergic reaction to imatinib or one of its components. Patients received 800 mg of imatinib daily until disease progression according to RECIST 1.0, unacceptable toxicity or withdrawal. Dose reductions were planned according to the occurrence and recurrence of grade II/III toxic effects. The maximum duration of study treatment was planned to be 24 months. Patients with progressive disease or intolerance under imatinib could be treated with nilotinib 800 mg daily in an extended study. Study investigations were carried out after approval by the local ethics committee. Written informed consent was obtained from each patient.

2.2. Response assessment

During the study, patients underwent clinical, haematological and biological evaluations every 4 weeks within the first 6 months. After 6 months, visits were performed every 3 months. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Response was assessed by comparing unidimensional tumour measurements (CT or MRI) on pre- and per-treatment imaging studies every 3 months according to RECIST 1.0.

2.3. Therapy monitoring

A total of 19 patients treated at the Mannheim University Medical Center and at HELIOS Klinikum Bad-Saarow were examined using ^{18}F-FDG positron emission tomography (PET) prior to onset of therapy with imatinib and during treatment. The treatment/imaging algorithm was as follows: (a) an initial PET examination was performed at baseline before start of imatinib treatment, (b) a second PET examination was done for therapy monitoring after 4–8 weeks, (c) another follow-up PET was performed after 6 months for further treatment monitoring in selected patients. Dynamic PET studies were performed after intravenous injection of 300–370 MBq 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) for 60 min. A dedicated PET system (ECAT EXACT HR plus, Siemens, Erlangen, Germany) or a PET-CT system (Biograph mCT, S128) was used for patient studies as described before [15]. PET-CT studies were performed using a low dose CT (30 mA) with current modulation without any contrast material. The CT data were used for attenuation correction and for the image fusion. The last images (55–60 min post-injection) were used for semi-quantitative analysis. PET cross-sections were reconstructed with an image matrix of 256×256 (for ECAT EXACT HR plus) or 400×400 (for Biograph mCT) using an iterative reconstruction programme. Images were scatter- and attenuation-corrected. Volumes of interest (VOI) were placed over the lesion. The standardized uptake value (SUV) in the tumour was calculated according to the following equation: SUV = tissue concentration (MBq/g)/[injected dose (MBq)/body weight (g)]. The SUV reflected the average SUV value provided by the quantification software in a VOI. The analysis of the PET images was performed by two nuclear medicine physicians using a dedicated software package.

2.4. Statistical analysis

The primary end-point of the study was the progression arrest rate (including stable diseases, complete and partial responses according to RECIST 1.0) at 6 months imatinib treatment (PAR_{6mo}). The number of patients was calculated according to a Simon optimal two-stage design [16]. The study requires 37 eligible patients to decide with a power of 90% at a one-sided significance level of 10% whether the non-progressive disease proportion p was less than or equal to $p_0 = 20\%$ or greater than or equal to $p_1 = 40\%$. At the interim stage including 17 patients at least four successes are required to continue the trial. At the final analysis, imatinib is considered as effective if at least 11 non-progressive patients are observed at the end of the second stage (11/37). Planned accrual was 39 patients in order to allow for 5% of ineligible or untreated patients. Secondary end-points included progression arrest rates after 9, 12, 15, 18, 21 and 24 months, overall response rate, progression-free survival and overall survival. Progression-free survival was defined as the time from inclusion to the date of progression or death or censored at the last follow-up. Overall survival was defined as the time from inclusion to the date of death due to any cause. Survival functions were calculated by the Kaplan–Meier method [17].

For PET analysis, descriptive statistics were calculated with StatXact-9 (Cytel Studio, Version 9.0.0); all other calculations were performed with SAS software 9.4 (SAS Institute Inc, Cary, NC, USA). The comparison of response stratified variables was done by unpaired t-tests; since some of the distributions of measurements were biased Wilcoxon rank sum test was also used. Box-plots were drawn for each of the variables and Kaplan–Meier statics was used for exploiting the progression-free survival time. Level of significance was set to $\alpha = 0.05$.

3. Results

3.1. Patient characteristics

Thirty-nine patients were enrolled from July 2010 to September 2013 in four GISG centres and 38 patients were included in the full analysis set (Table 1). The mean age (±standard deviation) was 44.4 ± 17.6 years (range: 19–80). There were 26 women (68%) and 12 men (32%). Eastern Cooperative Oncology Group (ECOG) performance status was documented: ECOG = 0 in 34 cases (89%) and ECOG = 1 in 4 cases (11%). The tumour was multifocal in 13 cases (34%), while in 66% of patients there was only one desmoid tumour lesion. Primary tumour locations were as follows: abdominal wall 5.3%, intra-abdominal/retroperitoneal/pelvic 13.2%, extremity/girdles/chest wall 68.4% and head and neck/intrathoracic 13.2%. The mean tumour size was 7.5 ± 4.2 cm (min. 1 cm, max. 16.4 cm). FAP was documented only in 1 patient. The patients had previously undergone the following treatments: surgery (32 cases, 84%), radiotherapy (9 cases, 24%) and medical therapy (11 cases, 29%).

Table 1
Patients' characteristics (n = 38).

Gender	
Female	26 (32%)
Male	12 (68%)
Age	
Mean (years)	44.4 ± 17.6 [19–80]
Histology	
Desmoid tumour	38
ECOG performance status	
ECOG 0	34 (89%)
ECOG 1	4 (11%)
Tumour site at initial diagnosis	
Abdominal wall	2 (5%)
Intraabdominal/retroperitoneal/pelvic	5 (13%)
Extremity/girdles/chest wall	26 (69%)
Head & neck/intrathoracic	5 (13%)
Number of lesions per patient	
One lesion	25 (66%)
Two lesions	7 (18%)
Three lesions	4 (11%)
Four lesions	2 (5%)
Tumour extension	
Mean (cm)	7.5 ± 4.1 [10–16.4]
Previous treatment	
Surgery	32 (84%)
Radiotherapy	9 (24%)
Medical therapy	11 (29%)

ECOG, Eastern Cooperative Oncology Group.

3.2. Treatment

Imatinib treatment was administered at a planned dose of 800 mg/day. The median treatment duration with imatinib was 434 days (range: 14–749). The median dose per day was 771 mg (range: 371–800). Dose reductions to 600 mg imatinib daily were necessary in 8 patients with a median duration of 72 days (range: 8–509); dose reductions to 400 mg imatinib/day were performed in 18 patients for a median duration of 16 days (range: 1–701). The mean final dose of imatinib patients completed on study was 642 mg per day.

3.3. Efficacy and survival

The final analysis for the primary end-point in the required set of 37 patients revealed a PAR_{6mo} of 65%. All secondary end-points were analysed in the full analysis set of 38 patients who were included in the trial and received the study medication at least once. Subsequent progression arrest rates given as relative frequencies excluding missing at 9, 12, 15, 18, 21 and 24 months were 65%, 59%, 53%, 53%, 50% and 45%, respectively (Fig. 1). The Kaplan–Meier estimates for the progression-free survival rate are depicted in Fig. 2. None of the patients died within the study observational period; therefore, overall survival was 100%. Best reported response was seven partial responses at the time point 21 months with a median time to response of 11 months (95% confidence interval [CI]: 6–19) revealing an overall response rate of 19%. It could be clearly demonstrated that many responses occurred at a later treatment stage than initially expected and were durable with a median response duration of 413 days (range: 91–572) (Fig. 3). Only few disease progressions occurred after 1 year of treatment although earlier results on the mutational analysis identified a patient cohort characterised by an aggressive clinical course [18]. Responses are depicted in a waterfall-plot showing the percentage of the tumour diameter changes from baseline (Fig. 4).

3.4. Toxicity

In general imatinib adverse events were mild to moderate and comparable to the well-known imatinib safety profile from patients with chronic myeloid leukaemia and gastrointestinal stromal tumours. One hundred seventy-eight adverse events definitely related to study drug were registered in 33 patients; 15 serious adverse events in 10 patients were documented in the core study with imatinib. Grade IV toxicity was seen in 1 patient

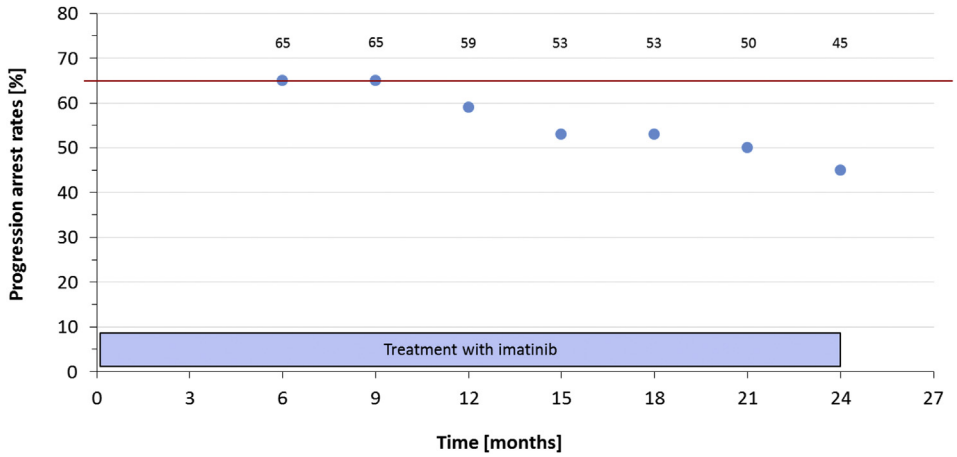

Fig. 1. Progression arrest rates estimated as relative frequencies excluding missing at the different evaluation time points. The progression arrest rate at 6 months, the primary end-point of the study, was 65% (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

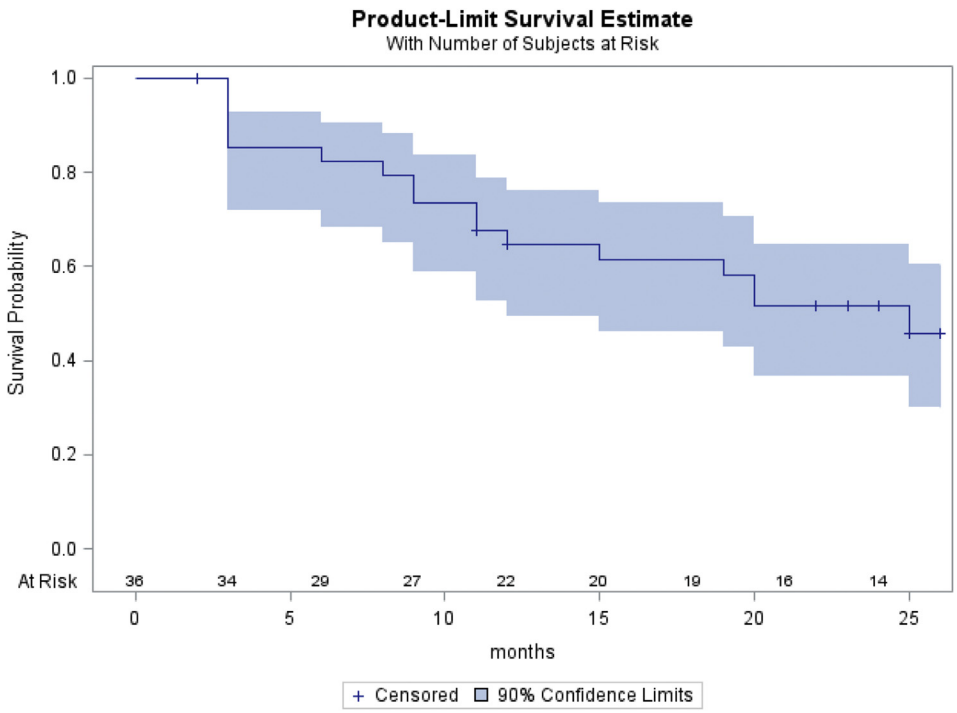

Fig. 2. Kaplan–Meier estimates for the progression-free survival rate and related point–wise 90% confidence intervals.

(neutropenia). Grade III toxicities were seen in 4 patients (11%) including neutropenia, leucopenia, nausea/vomiting, gastritis, rash and contracture. Grade II toxicities were documented in 13 patients (34%) and grade I toxicities were seen in 33 patients including oedema (64%), nausea/vomiting (52%), abdominal pain/diarrhoea (46%), rash (39%) and myalgia (30%).

3.5. Therapy monitoring PET data

Ninteen patients underwent PET analysis as described above. Stratification was made according to therapy response to imatinib with 10 patients (53%) achieving progression arrest and 9 patients (47%) developing progressive disease (PD). None of the comparisons of the two variables—average SUV and SUV_{max}—in the three subsequent measurements stratified by response (progression arrest versus PD) were statistically significant different, respectively. Same was true for the differences and ratios of the average SUV and SUV_{max} if calculated for the three measurement time points and then stratified by response (progression arrest versus PD), respectively. The mean (median) SUV_{max} for the baseline PET was 6.2 (4.8) and for the second PET examination it was 3.7 (3.3), respectively. Median progression-free survival time in this sub-cohort of 19

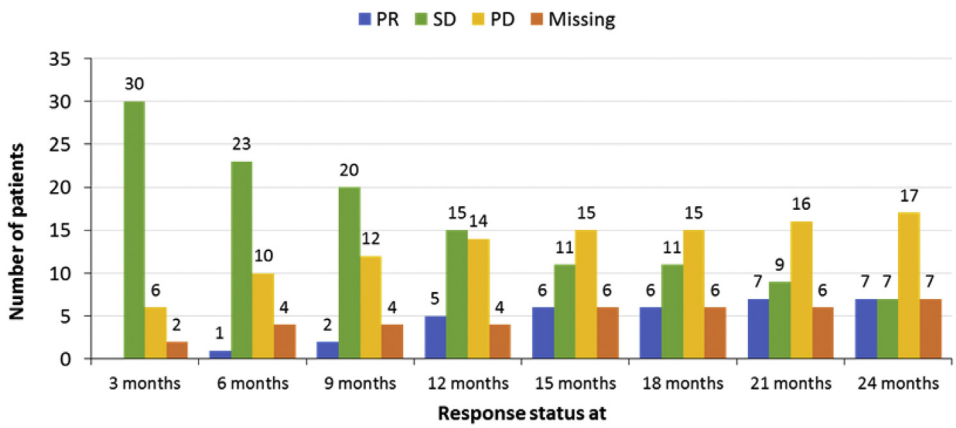

Fig. 3. Response status at the different evaluation time points demonstrating late responses (PR) and durable stable diseases.

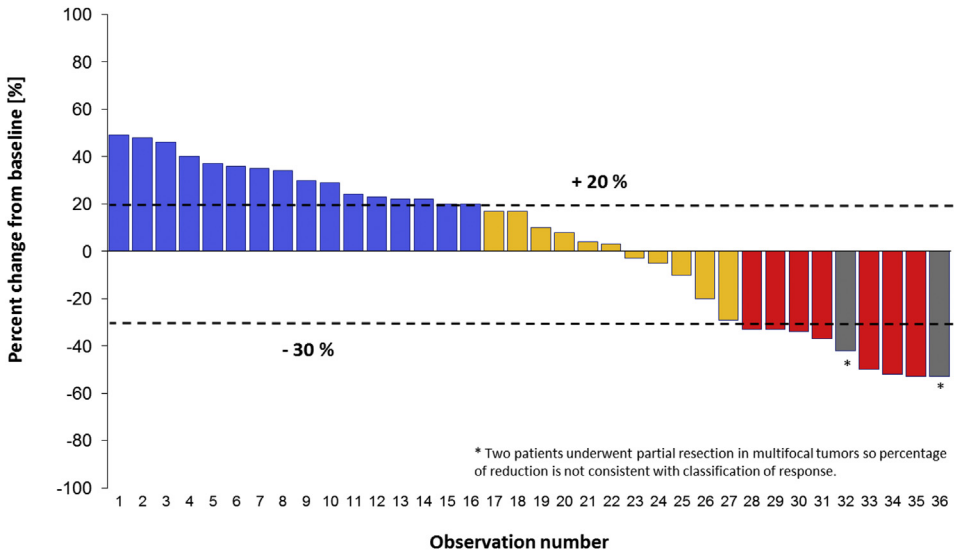

Fig. 4. Waterfall-plot showing the percentage of the tumour diameter changes from baseline.

patients was 40 months with a 95% CI from 19 to 52 months. More than half of the population was censored (10 patients).

3.6. Extended nilotinib study

Interestingly, 8 patients treated with nilotinib due to RECIST-defined disease progression under imatinib (no intolerance) demonstrated a PAR at 3 months of 88% (7/8); no more disease progressions occurred until end of study. Median time to subsequent nilotinib treatment start was 10 months (95% CI: 3–20). Patients were treated with nilotinib for a median duration of 377 days (range: 88–751) without any dose reductions being necessary. In general nilotinib adverse events were mild. Eighteen adverse events definitely related to study drug were registered in 7 patients. Grade III toxicity was documented in 1 patient (13%). There were no grade II and IV toxicities. Grade I toxicities were documented in 6 patients (75%) including rash (43%), oedema (29%), nausea/vomiting (29%), myalgia (29%) and abdominal pain/diarrhoea (14%).

4. Discussion

There is prospective, uncontrolled (non-randomised, phase II) evidence for the activity of the tyrosine kinase inhibitor imatinib in patients with progressive desmoid tumours with high rates of stabilisation of 50–80% despite a rather low response rate ranging from 6 to 16% with a favourable toxicity profile. In the US phase II study 19 patients with desmoid tumours were treated with 800 mg imatinib daily. Three partial remissions and four stable disease courses were observed. Genomic analyses revealed no mutations of *KIT*, *PDGFRA* or *PDGFRB* [11]. A study from the French Sarcoma Group demonstrated 3% complete remissions, 9% partial remissions and 83% stable diseases in 35 patients with relapsing or refractory desmoid tumours [13]. Including our study performed within the GISG, altogether 141 desmoid tumour patients have been

evaluated prospectively with this treatment option and the already published literature in comparison to the presented data is depicted in Table 2.

The final analysis for the primary end-point—the progression arrest rate after 6 months of imatinib treatment—revealed a rate of 65%. Subsequent progression arrest rates reported as relative risks at 9, 12, 15, 18, 21 and 24 months were 65%, 59%, 53%, 53%, 50% and 45%, respectively, suggesting a sustained treatment effect of imatinib. Best reported response was seven partial responses at 21 months revealing an overall response rate of 19% documenting that late responses do occur, even 21 months after start of treatment with a median time to response of 11 months questioning the choice of the primary end-point. Major differences of the current GISG study in contrast to the three previously published trials are the inclusion of patients with RECIST 1.0 progressive disease only, the planned long treatment duration of 2 years and the durable treatment effect. Especially in the subgroup of patients with S45F mutation, the highest progression arrest rate of 85% could be demonstrated as described earlier in our published results on the *CTNNB1* mutational analysis [18]. In line with previous studies, we confirmed the clinical activity of imatinib in desmoid tumours. Possible limitations of the study are the non-randomised character of the trial, the unpredictable clinical course of this histologic subtype including spontaneous regressions having a possible impact on the results and inclusion criteria or different prognosis depending on localisation may have led to an inhomogeneous patient population.

Interestingly, sustained responses were also documented with nilotinib in the extended study even after previous RECIST disease progression under imatinib. None of the patients were switched to nilotinib due to intolerance under imatinib. Eight patients treated with nilotinib demonstrated a PAR at 3 months of 88% (7/8) and no more disease progressions occurred until end of study at 24 months. Hence, this is the first data published in the literature on the effect of nilotinib in desmoid tumour patients.

However, the most important question remains for which treatment situation imatinib or alternatively nilotinib might be the best option? Primarily, the treatment goal in the individual patient situation has to be taken into account here. Imatinib reaches a response rate not exceeding 15–20% and responses often occur late. So if prompt response or symptom relief are desired, chemotherapy with an anthracycline-based regimen or liposomal doxorubicin should be preferred because of the higher response rates [19]. In a retrospective cohort, the use of sorafenib revealed a slightly higher response rate compared to imatinib with 25% and a disease stabilisation rate of 70% [20]; however, the update of this retrospective analysis in 62 evaluable patients revealed a response rate of 18% which is in the same range as described for imatinib [21]. However, no prospective data is available yet. Currently, sorafenib is being tested in a phase III, randomised, double-blind, placebo-controlled setting in the United States of America (NCT02066181). The third tyrosine kinase inhibitor which has been evaluated in this setting is pazopanib, a multi-tyrosine kinase inhibitor with antiangiogenic properties. It could demonstrate activity in a small retrospective cohort of 8 patients being treated at the Royal Marsden Hospital in London with partial responses in 3 out of 8 patients and disease stabilisation in 5 of 8 patients; none of the patients showed radiological disease progression. 75% of patients derived clinical benefit in terms of symptom control and improved function and/or pain reduction [22]. A randomised phase II trial (DESMOPAZ) evaluating pazopanib versus chemotherapy with methotrexate plus vinblastine in a cohort of 94 patients is ongoing within the French Sarcoma Group (NCT01876082).

Table 2
Prospective trials with imatinib in desmoid tumour patients (n = 141).

	n	Inclusion Criteria	Treatment dose [mg]	Treatment duration	Overall response rate [%]	6-month-PFS [%]	12-month-PFS [%]	24-month-PFS [%]
Heinrich et al. *J Clin Oncol 2006*	19	"Heavily pretreated patients"	800	325 days	16	53	37	n.e.
Penel et al. *Ann Oncol 2010*	35	"Radiological evidence for PD"	400	1 year	11	80	67	n.e.
Chugh et al. *Clin Cancer Res 2010*	49	"Locally advanced disease"	200–600 BSA adjusted	until PD 9 pts. >3 years	6	84	66	n.e.
GISG-01	38	**RECIST PD required**	800	**2 years**	19	65	59	45
Sorafenib *ASCO 2016*	62	"Progressive or symptomatic"	400	1 year	18	n.e.	n.e.	n.e.
GSI *ASCO 2016*	17	"Progressive/ symptomatic"	300	294 days	29	100	100	n.e.

Abbreviations: BSA, body surface area; GSI, γ-secretase inhibitor; n.e., not evaluable; PD, progressive disease; PFS, progression-free survival; pts., patients; RECIST, Response Evaluation Criteria in Solid Tumors. Bold emphasize the own study data in comparison to the published trials.

Another interesting new systemic treatment strategy in desmoid tumours is Notch signalling. PF-03084014 is an orally available, reversible gamma-secretase inhibitor. Gamma-secretase cleaves intracellular Notch resulting in Notch signalling. A phase II study of PF-03084014 has been conducted in 17 desmoid tumour patients who had progressed following at least one line of therapy. Five partial responses were shown and 12 out of 17 patients (71%) demonstrated stable disease revealing an overall response rate of 29%. With a median follow-up of 17 months, there were no disease progressions in this cohort. Hence, PF-03084014 seems to be an active component with a manageable side-effect profile [23].

However, all of the drugs described above are not licenced for the indication of desmoid tumours and, therefore, are not available or reimbursed in most of the European countries for the treatment of desmoid tumour patients. Efforts are needed to make imatinib, other tyrosine kinase inhibitors or a gamma-secretase inhibitor accessible for advanced desmoid tumour patients in countries where these drugs are not reimbursed. Involving patient advocacy groups such as Sarcoma Patients EuroNet is essential in pushing that forward.

Conflict of interest statement

BK received Honoraria from Novartis; PR was a part of the Advisory board, received honoraria and research funding from Novartis; SB received Honoraria and research funding from Novartis; PH was a part of the Advisory board and received research funding from Novartis.

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