

Neoadjuvant Imatinib in Advanced Primary or Locally Recurrent Dermatofibrosarcoma Protuberans: A Multicenter Phase II DeCOG Trial with Long-term Follow-up

Selma Ugurel¹, Thomas Mentzel², Jochen Utikal^{3,5}, Peter Helmbold^{4,6}, Peter Mohr⁷, Claudia Pföhler⁸, Meinhard Schiller⁹, Axel Hauschild¹⁰, Rüdiger Hein¹¹, Eckhardt Kämpgen¹², Ivonne Kellner¹³, Martin Leverkus⁵, Jürgen C. Becker¹⁶, Philip Ströbel¹⁴, and Dirk Schadendorf¹⁵

Abstract

Purpose: Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous tumor. *COL1A1-PDGFB* gene fusion is frequent in DFSP, rendering tumor cell proliferation and survival dependent on PDGFR β (platelet-derived growth factor receptor β) signaling. This trial investigated imatinib as neoadjuvant treatment of DFSP, including long-term follow-up.

Experimental Design: The primary endpoint of this multicenter phase II trial was response; secondary endpoints were safety, tumor relapse, and response biomarkers. Patients with advanced primary or locally recurrent DFSP and measurable disease by RECIST (response evaluation criteria in solid tumors) were eligible and received imatinib 600 mg/d until definitive surgery with histopathologic proof of tumor-free margins.

Results: Sixteen patients received imatinib, and 14 patients were evaluable for all endpoints. Median treatment duration was 3.1 months; median tumor shrinkage was 31.5%. Best overall response was 7.1% complete response (CR), 50.0% partial response (PR), 35.7% stable disease, and 7.1% progressive disease (PD). Toxicity was moderate with 25.0% grade 3 and 4 events. During a median follow-up of 6.4 years, one patient developed secondary resistance to imatinib but responded to second-line sunitinib. This patient also presented local recurrence, distant metastasis, and death from DFSP. Exploratory analysis showed that response to imatinib was associated with decreased tumor cellularity and formation of strong hyaline fibrosis. Weak PDGFR β phosphorylation and pigmented-type DFSP were associated with nonresponse. Additional to PDGFR β , the kinases EGFR and insulin receptor were found activated in a high percentage of DFSPs.

Conclusion: The neoadjuvant use of imatinib 600 mg/d in DFSP is efficacious and well tolerated. Long-term follow-up results do not definitely support smaller surgical margins after successful imatinib pretreatment, and presume that secondary resistance to imatinib might promote accelerated disease progression. *Clin Cancer Res*; 20(2); 499–510. ©2013 AACR.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a malignant tumor of the dermis assumed to be of fibroblastic origin (1–3). DFSP is remarkable for its slow but infiltrative growth, and frequently enforces multiple surgical proce-

dures to ensure complete resection (2, 4). Under the premise of tumor-free surgical margins, the rates of local recurrence and metastasis are low (5, 6), rendering the main therapeutic efforts focused on the primary tumor. This situation is different in fibrosarcomatous DFSP (DFSP-FS),

Authors' Affiliations: ¹Department of Dermatology, University of Würzburg, Würzburg; ²Dermatopathology Bodensee, Friedrichshafen; ³Skin Cancer Unit, German Cancer Research Center, Heidelberg; ⁴Department of Dermatology, University Hospital Heidelberg, Heidelberg; ⁵Department of Dermatology, University Medical Center Mannheim, University of Heidelberg, Mannheim; ⁶Department of Dermatology, Martin Luther University, Halle/Saale; ⁷Department of Dermatology, Elbe Klinikum Buxtehude, Buxtehude; ⁸Department of Dermatology, Saarland University Hospital, Homburg, Saarland; ⁹Department of Dermatology, University Hospital of Münster, Münster; ¹⁰Department of Dermatology, University of Kiel, Kiel; ¹¹Department of Dermatology, Technical University Munich, Munich; ¹²Department of Dermatology, University Hospital Erlangen, Erlangen; ¹³Department of Dermatology, Helios Klinikum Erfurt, Erfurt; ¹⁴Department of Pathology, University of

Göttingen, Göttingen; ¹⁵Department of Dermatology, University of Essen, Essen, Germany; and ¹⁶Department of Dermatology, Medical University Graz, Graz, Austria

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Corresponding Author: Selma Ugurel, Department of Dermatology, Julius-Maximilians University, Josef-Schneider-Strasse 2, 97080 Würzburg, Germany. Phone: 00-49-931-201-26351; Fax: 00-49-931-201-26700; E-mail: ugurel_s@klinik.uni-wuerzburg.de

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Translational Relevance

Dermatofibrosarcoma protuberans (DFSP) frequently presents a constitutive activation of the PDGFR β (platelet-derived growth factor receptor β) signaling pathway. Thus, molecular-driven therapies are promising options in the treatment of inoperable DFSP, but may also be used as neoadjuvant therapy of resectable DFSP. Biomarkers of response to targeted therapies have only marginally been investigated in DFSP. Our present trial allowed a preoperative imatinib treatment of resectable DFSP with individual treatment duration to be determined by the respective investigator. Thus, we observed a significantly higher response rate compared with previously reported data. By molecular workup of fresh and formalin-fixed paraffin-embedded (FFPE) tumor tissue of study patients, we identified weak PDGFRB phosphorylation and pigmented-type DFSP as predictive markers of response, and decreased tumor cellularity and formation of strong hyaline fibrosis as surrogate markers of response. We observed the kinases EGFR and insulin receptor to be activated in DFSP, thus providing new molecular candidates for the future targeted therapy of DFSP.

which presents several characteristics of high-grade sarcoma and accordingly shows an increased risk of relapse as well as a worse prognosis (7).

The recommendations for surgical margins in the primary care of DFSP range between 0.5 and 3.0 cm (2, 4, 6, 8). This is a wide range, particularly with regard to the surgical efforts necessary for a wide margin often requiring reconstructive procedures. Especially in younger patients and also taking into account that DFSP frequently occur at the upper trunk, strategies are needed to either reduce the tumor size before surgery and/or reduce the risk of recurrence, thus allowing smaller surgical margins. Because DFSP is known to frequently harbor the fusion gene *COL1A1-PDGFB*, resulting from a chromosomal translocation t(17;22) and activating the PDGFR β (platelet-derived growth factor receptor β) signaling pathway via an autocrine loop (9, 10), inhibitors of this pathway are promising candidates in the nonsurgical treatment of DFSP. The first receptor tyrosine kinase (RTK) inhibitor used in DFSP was imatinib, which was originally developed for the treatment of chronic myelogenous leukemia by inhibition of the RTK BCR-ABL. Imatinib was demonstrated to successfully inhibit growth and survival of DFSP cells *in vitro* (11, 12), and clinical case reports of its use in metastatic DFSP showed impressive responses (13, 14). The rationale for the use of PDGFRB pathway inhibitors in metastatic DFSP was obvious, particularly due to the lack of other effective systemic therapeutics at this date. However, the role of these inhibitors in surgically manageable DFSP in terms of a neoadjuvant therapeutic approach was unclear.

The present trial was designed to investigate imatinib as neoadjuvant treatment in advanced but surgically manageable primary or locally recurrent DFSP before definitive tumor surgery. Tumor response was assessed as an indicator of tumor shrinkage by imatinib to facilitate the later surgical procedures. Assuming that the pretreatment with a PDGFRB inhibitor would allow smaller surgical margins, in this trial a wide excision was not necessarily required for definitive surgery. A long-term patient follow-up of at least 5 years was set to determine the rate of relapse after completed imatinib therapy and subsequent surgery. In addition, to identify biomarkers of imatinib response, histopathologic and molecular tumor characteristics were correlated with treatment outcome. Taking account of the extreme rarity of the entity DFSP leading to low numbers of patients eligible for this study, the analysis of the study data was done on an exploratory, hypothesis-building basis without the application of statistical methods.

Patients and Methods

Study design

The primary endpoint of this open single-arm multicenter prospective phase II trial (ADO-DFSP-001; ClinicalTrials.gov: NCT00122473) initiated by the Dermatologic Cooperative Oncology Group (DeCOG/ADO) was tumor response in terms of best overall response and response at 12 weeks, respectively. Secondary endpoints were safety, tumor relapse, and biomarkers correlating with response. Safety was evaluated in the intention to treat (ITT) population; all other endpoints were evaluated in the per protocol population. The study was planned to be open for patient accrual until approval of imatinib for the treatment of DFSP by German health authorities.

Patients

Patients were enrolled in accordance with the following main eligibility criteria: Histologically proved diagnosis of advanced but surgically manageable primary or locally recurrent DFSP; any histologic subtype of DFSP, including fibrosarcomatously transformed tumors; no metastasis; measurable disease according to response evaluation criteria in solid tumors (RECIST 1.0; ref. 15); ECOG (Eastern Cooperative Oncology Group) performance status ≤ 2 ; adequate organ function; and written voluntary informed consent. The study protocol was approved by the Ethics Committees/Institutional Review Boards of all participating centers.

Study procedures

After enrollment, all patients received imatinib (Glivec; Novartis) 600 mg orally once daily for at least 6 weeks. Thereafter, treatment was continued if tumor response was stable disease or better. At week 12, either tumor surgery or continuation of imatinib was performed at the discretion of the investigator. Definitive surgery had to be performed with histopathologic proof of tumor-free margins; however,

neither wide excision nor Mohs surgery was mandatory. Treatment was stopped at any time point due to disease progression or intolerable side effects. Toxicity was evaluated in all patients who received study treatment using common toxicity criteria (CTC) 2.0 (<http://ctep.cancer.gov/reporting/ctc.html>), and assessed at weekly intervals within the first 4 weeks of therapy, followed by 2-week intervals thereafter. Imatinib doses were adjusted due to toxicity as described previously (16). After completion of study treatment, the patients were followed in 3-month intervals. Patients who completed at least 6 weeks of imatinib were considered evaluable for all study endpoints (per protocol). Tumor response was assessed at week 6 and 12, and in case of ongoing treatment every 3 months thereafter, by either color/ruler photography combined with ultrasound or by computer tomography (CT)/MRI scan. The longest tumor diameter was evaluated over time according to RECIST 1.0 (15). Best overall response was defined as the best response achieved during the study period (15).

Histopathology and immunohistochemistry

Formalin-fixed paraffin-embedded (FFPE) tumor tissue samples obtained from study patients before and after imatinib treatment were analyzed by central pathologic review. Four-micron thick sections were stained with hematoxylin and eosin. Elastic fibers were detected by means of the elastica-orcein method. Morphologic parameters studied were histopathologic subtype, tumor localization in relation to the skin layers, cell density, cellular and nuclear pleomorphism, mitotic count, vascularization, and hemorrhages. After antigen retrieval with proteinase K, immunohistochemical stainings were performed using the streptavidin-biotin method on a TechMate 500 (DAKO). Parameters analyzed were CD34 (HPCA-1, clone MY10, dilution 1:100; BD Biosciences), S100 (polyclonal anti-S100 antibody, dilution 1:2,000; DAKO), and Ki67 (SP-6, dilution 1:300; Roche Diagnostics). Appropriate positive and negative controls were used in all cases. Fibrosarcomatous transformation was defined as a gradual or abrupt transition from low-grade storiform areas to areas composed of spindle cell fascicles with a herringbone appearance in at least 5% of the neoplasm. Neoplastic cells of fibrosarcomatous areas were characterized by increased cytologic atypia and proliferative activity.

Detection of *COL1A1-PDGFB* gene fusion

Detection of *COL1A1-PDGFB* was done on FFPE tumor tissue samples by either real-time (RT) PCR plus sequencing or FISH, or both.

RT-PCR and sequencing. RNA isolation was performed by extraction with acid phenol and isopropanol precipitation. Primer sequences and PCR conditions were used as previously described (17). Briefly, cDNA was amplified after RT by three multiplex PCRs with 51 different *COL1A1* primers and one *PDGFB* primer. After extraction from agarose gels with the Gfx Kit (GE Healthcare), sequencing of the PCR products was performed with the Cy5.5 cycle

sequencing Kit (GE Healthcare) following the manufacturer's instructions. After sequencing, the fragments were precipitated with ethanol and dissolved in formamide buffer before loading on an Alf Express II (GE Healthcare). Sequences were evaluated with the Alf Express sequence analyzer software and aligned by BLAST (www.ncbi.nlm.nih.gov/blast).

FISH. Bacterial artificial chromosomes (BAC) DNA clones NM00088 and NM002608 of *COL1A1* (17q21.33) and *PDGFB* (22q13.1) loci, respectively, were kindly provided by Pancras Hogendoorn and Karoly Szuhai, University of Leiden (Leiden, the Netherlands). BAC labeling was performed by nick translation (DIG nick translation mix and Rhodamine nick translation mix; Roche Diagnostics). FISH was performed as published previously (17).

RTK phosphorylation array analysis

Cryopreserved tumor tissue samples obtained before and after imatinib treatment were analyzed for RTK activation. The Human Phospho RTK Array Kit (R&D Systems) was used according to the manufacturer's instructions to simultaneously detect and semiquantitatively grade the relative phosphorylation levels of 42 different RTKs, as previously described (18).

Results

Patient characteristics

Between March 2004 and October 2006, 16 patients (ITT) from 10 clinical centers were enrolled and started imatinib treatment (Table 1). In 11/2006 imatinib obtained early approval for the treatment of DFSP by European and German health authorities, leading to a premature stop of patient accrual into this trial. Of note, 14 of 16 patients (87.5%) were evaluable for all study endpoints (per protocol); 2 of 16 patients (12.5%) had to be excluded from all endpoint analyses besides safety, because pathologic review revealed they had no DFSP but other cutaneous tumors. The per protocol population consisted of 3 men (21.4%) and 11 women (78.6%); the median age was 51.3 years. Of note, 3 of 14 patients (21.4%) had locally recurrent disease, and 11 of 14 patients (78.6%) were enrolled with primaries. The tumors were mainly located on the trunk (85.7%); 2 patients (14.3%) presented with primaries on the extremities. The median longest tumor diameter at enrollment was 4.3 cm.

Study treatment and response

The trial database cutoff was December 2012 with a median follow-up time of 6.4 years. The median duration of imatinib therapy was 3.1 months (Table 2). Of note, 4 of 16 ITT patients were treated less than 12 weeks. Hereof, treatment was discontinued because pathologic diagnosis revealed no DFSP but other cutaneous tumors ($n = 2$), due to probably therapy-related side effects (angina pectoris; $n = 1$), and due to early disease progression ($n = 1$). The longest treatment duration was 16.7 months leading to a complete response (CR). Median maximum tumor shrinkage was 31.5%. In the per protocol population, tumor response at

Table 1. Patient characteristics at enrollment (per protocol)

Patient ID	Age y	Gender	History of histologically confirmed DFSP (mo)	Disease stage	Location	Longest tumor diameter (method of assessment)	ECOG performance state	Previous therapy of DFSP
ADO-01	52	F	177	Local recurrence	Trunk (presteral)	3.4 cm (ultrasound)	0	Surgery
ADO-02	50	M	1	Primary	Trunk (presteral)	9.5 cm (ultrasound)	0	None
ADO-03	66	M	2	Primary	Extremities (upper arm)	3.6 cm (MRI)	0	None
ADO-04	74	F	1	Primary	Trunk (inframammary)	5.0 cm (MRI)	0	None
ADO-05	37	F	1	Primary	Extremities (upper leg)	5.9 cm (MRI)	0	None
ADO-06	69	F	10	Primary	Trunk (upper back)	18.3 cm (MRI)	1	None
ADO-07	51	F	1	Primary	Trunk	9.2 cm (ultrasound)	0	None
ADO-09	27	F	27	Local recurrence	Trunk (shoulder/upper back)	1.7 cm (ultrasound)	0	Surgery
ADO-10	56	F	1	Primary	Trunk (lower abdomen)	2.7 cm (ultrasound)	0	None
ADO-11	43	F	1	Primary	Trunk (presteral)	4.0 cm (MRI)	0	None
ADO-12	57	M	294	Local recurrence	Trunk (shoulder/upper back)	6.0 cm (CT)	2	Surgery, radiation
ADO-13	39	F	1	Primary	Trunk (presteral)	4.5 cm (MRI)	0	None
ADO-15	72	F	17	Primary	Trunk (upper abdomen)	6.8 cm (MRI)	2	None
ADO-16	37	F	3	Primary	Trunk (lower abdomen)	4.0 cm (MRI)	0	None

NOTE: Characteristics of the per protocol patient population at study enrollment.

week 12 showed seven partial responses (PR; 50.0%), five stable disease (35.7%), and two progressive disease (PD; 14.3%). Best overall response revealed one unconfirmed CR (7.1%), seven PR (50.0%), five stable disease (35.7%), and one PD (7.1%); objective response (CR + PR) was 57.1%. Tumor response was measured by CT/MRI in 8 patients (57.1%), and by ultrasound/photography in 6 patients (42.9%), respectively.

Patient follow-up

Definitive tumor surgery was done in 13 of 14 patients of the per protocol population after a median imatinib treatment duration of 3.1 months (Table 2). In 3 patients imatinib was given for more than 6 months followed by surgery; 1 patient was treated 16.7 months until clinical CR with the refusal of the patient of definitive surgery. The safety margins of definitive surgery were narrow to intermediate in the majority of cases and ranged from 0.5 to 2.0 cm (Table 2). In 6 to 13 patients (46.2%) surgical margins were 1.0 cm or below. A wide excision (≥ 2.0 cm) was performed in 3 patients. One patient (ADO-06) who achieved a pronounced PR of a giant DFSP at week 12 developed a secondary resistance with outgrowth of new tumor lesions in the primary location at 5.7 months of ongoing imatinib treatment (Fig. 1 and 2A). The same patient developed a local recurrence after definitive surgery with tumor-free margins, and later distant metastasis to the lung, vertebral bodies and spinal cord, which led to the death of the patient. No other patient with DFSP of this trial showed secondary resistance, local recurrence, or metastasis during long-term follow-up.

Toxicity

As presented in Supplementary Table S1, the majority of side effects were mild to moderate (CTC grade 1–2). The most common toxicities were nausea and vomiting in 31.3%, fatigue in 31.3%, peripheral edema in 25.0%, and depression in 18.8% (ITT). About 25.0% severe side effects (CTC grade 3–4) were observed (4 events/16 patients). In 2 patients imatinib had to be discontinued due to newly developed angina pectoris and uncontrollable vomiting, respectively, both resolved after withdrawal of imatinib. Dose reductions of imatinib due to side effects were necessary in 4 of 16 patients (25.0%).

Histopathology and molecular analysis

Central histopathologic review revealed 14 DFSP and two non-DFSP tumors (Table 3). The DFSP subdivided into 10 classical DFSP (71.4%), one myxoid-type DFSP (7.1%), one pigmented-type DFSP (Bednar tumor; 7.1%), two DFSP-FS (14.3%), and one of which arose from a pigmented-type DFSP. All DFSP stained positive for CD34, all but one (92.9%) stained negative for S100; the S100⁺ case was a pigmented-type DFSP. The *COL1A1-PDGFB* fusion gene was analyzed in 11 of 14 DFSP; the remaining three cases did not provide enough tissue material. Five of 11 (55.6%) analyzed DFSP were *COL1A1-PDGFB*⁺, 3 of 11 (33.3%) were *COL1A1-PDGFB*⁻, and additional 3 of 11 (33.3%) were noninformative. Cryopreserved tumor tissue obtained before imatinib onset was available from 7 (50.0%), and paired materials obtained before and after imatinib were available from 4 (28.6%) patients. RTK phosphorylation analysis of these materials showed a moderate to strong

Table 2. Treatment characteristics, response, and follow-up (per protocol)

Patient ID	Longest tumor diameter at enrollment (method)	Longest tumor diameter at 6 weeks (method) response	Longest tumor diameter at 12 weeks (method) response	Duration of imatinib therapy (months)	Best overall response (diameter change by RECIST)	Progression during ongoing imatinib therapy (subsequent treatment)	Definitive surgery (months from onset of imatinib)	Safety margins at definitive surgery	Relapse after end of imatinib therapy (subsequent treatment)	Follow-up from onset of imatinib (months)
ADO-01	34 mm (Ultrasound)	25 mm (Ultrasound) SD	19 mm (Ultrasound) PR	3.0	PR (-42%)	None	Yes (3.1)	Unknown	None	97.3+
ADO-02	95 mm (Ultrasound)	92 mm (Ultrasound) SD	33 mm (Ultrasound) PR	2.8	PR (-65%)	None	Yes (3.2)	1.5 cm	None	29.9+
ADO-03	36 mm (MRI)	28 mm (Ultrasound) SD	22 mm (Ultrasound) PR	1.5	PR (-40%)	None	Yes (2.8)	0.5 cm	None	89.3+
ADO-04	50 mm (MRI)	35 mm (MRI) PR	29 mm (MRI) PR	2.8	PR (-42%)	None	Yes (2.9)	1.0 cm	None	82.9+
ADO-05	59 mm (MRI)	57 mm (MRI) SD	48 mm (MRI) SD	7.0	PR (-33%)	None	Yes (7.0)	1.0 cm	None	84.2+
ADO-06	183 mm (MRI)	165 mm (MRI) SD	125 mm (MRI) PR	6.3	PR (-45%)	Progression and new lesions in primary location at 5.7 months (surgery; CR)	Yes (6.5)	0.5 cm	Local recurrence at 7 months (imatinib; PD, sunitinib; PR; surgery; CR); distant metastasis at 35 months (radiation; PD)	48.3; Death by DFSP
ADO-07	92 mm (Ultrasound)	115 mm (Ultrasound) PD	NE (tumor excised)	1.5	PD (+25%)	Progression at 1.5 months (surgery; CR)	Yes (1.5)	Unknown	None	23.2+
ADO-09	17 mm (Ultrasound)	17 mm (Ultrasound) SD	15 mm (Ultrasound) SD	2.8	SD (-12%)	None	Yes (2.8)	1.0 cm	None	57.2+
ADO-10	27 mm (Ultrasound)	25 mm (Ultrasound) SD	40 mm (Ultrasound) PD	2.9	SD (-7%)	Progression at 2.9 months (surgery; CR)	Yes (2.9)	2.0 cm	None	79.5+
ADO-11	40 mm (MRI)	36 mm (MRI) SD	32 mm (MRI) SD	2.8	SD (-20%)	None	Yes (3.1)	1.0 cm	None	67.5+
ADO-12	60 mm (CT)	58 mm (CT) SD	62 mm (CT) SD	5.2	SD (±0%)	None	Yes (6.5)	Wide (limb amputation)	None	76.9+
ADO-13	45 mm (MRI)	45 mm (MRI) SD	45 mm (MRI) SD	3.3	SD (±0%)	None	Yes (3.3)	Unknown	None	76.7+
ADO-15	68 mm (MRI)	59 mm (MRI) SD	48 mm (MRI) PR	16.7	CR (clinical evaluation)	None	No (imatinib continued until CR)	NA	None	46.7; Death by other reason
ADO-16	40 mm (MRI)	ND	28 mm (MRI) PR	3.3	PR (-30%)	None	Yes (3.7)	2.0 cm	None	70.2+

NOTE: Course of treatment, outcome and follow-up of the (per protocol) patient population. Abbreviations: NA, not applicable; ND, not done; NE, not evaluable; SD, stable disease.



Figure 1. Clinical presentation of patient ADO-06 (A) before treatment; B, at 3 months of imatinib showing marked tumor shrinkage (PR); C, at 6 months of imatinib showing ongoing tumor shrinkage, but also secondary resistance with outgrowth of new tumor lesions (arrows); D, at 13.5 months after onset of imatinib, 7 months after imatinib discontinuation, and definitive surgery with tumor-free margins, showing a good result of skin graft reconstruction but also local tumor recurrence at the left neck (arrow). This recurrent tumor was resistant to imatinib, but sensitive to sunitinib.

PDGFRB phosphorylation in all but one tumor (Supplementary Table S2). In addition, all analyzed tumors revealed a moderate to strong phosphorylation of EGFR and insulin receptor; IGF-IR (insulin-like growth factor-I receptor), PDGFRA, and MCSFR (macrophage colony-stimulating growth factor receptor) were weakly to moderately phosphorylated in 40% to 60% of tumors.

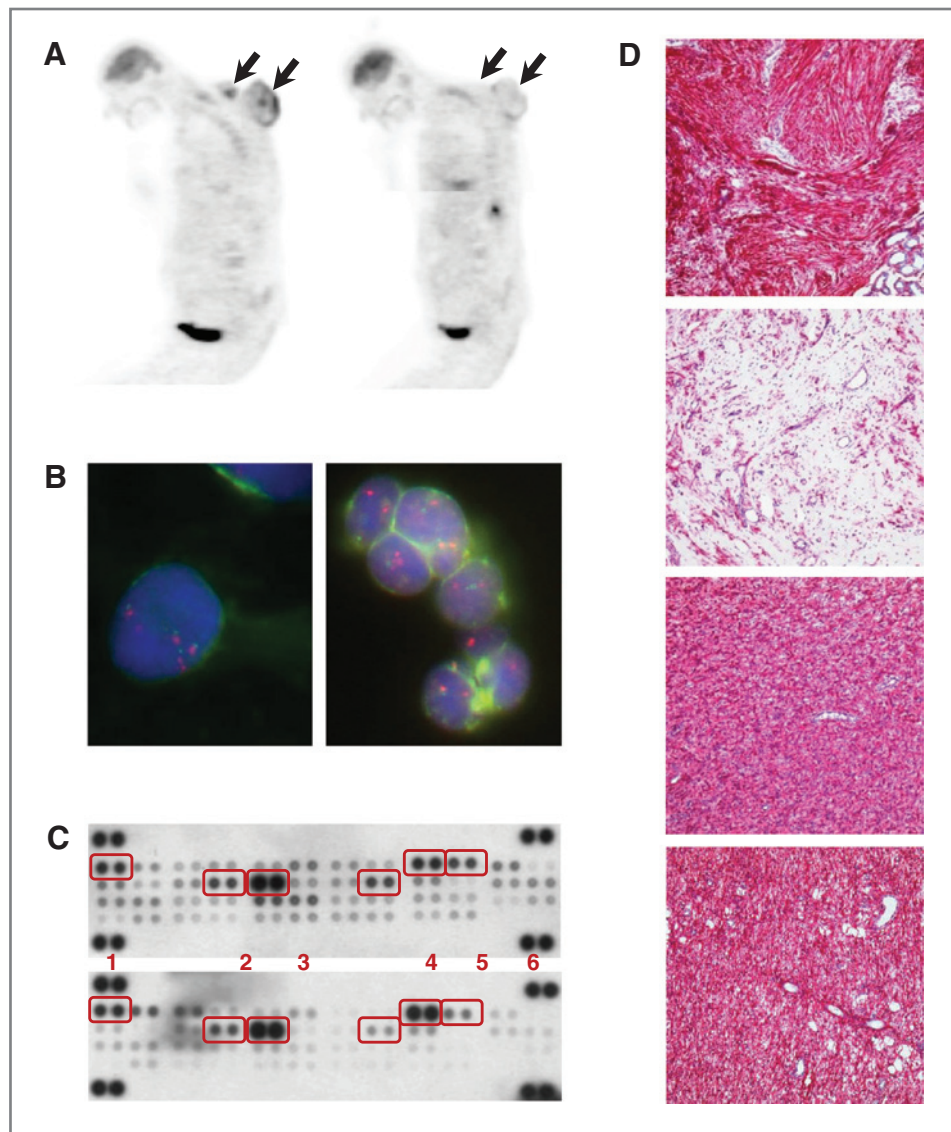
Biomarkers of response

We subdivided the patients into two groups according to best overall response: patients showing CR and PR were summarized as responders ($n = 8$); stable disease and PD were grouped as nonresponders ($n = 6$). Classical DFSP and DFSP-FS were found between both groups; the pigmented-type DFSP were nonresponders. No association could be observed between the presence of the *COL1A1-PDGFB* fusion gene and tumor response. Also, in *COL1A1-PDGFB*⁺ patients the fusion gene was still present after imatinib therapy, in responders as well as in nonresponders (Fig. 2B). Pre-imatinib PDGFRB phosphorylation was moderate to strong in 6 of 7 tumors analyzed, and revealed no significant change during treatment in two *COL1A1-PDGFB*⁺ responders and one *COL1A1-PDGFB*⁻ nonresponder (Supplementary Table S2; Fig. 2C). Remarkably, the only tumor with a weak pre-imatinib PDGFRB phosphorylation originated from the only patient (ADO-10) of this trial presenting a PD as best overall response. Pre-imatinib tumor vascularization, hemorrhages, and cell density was not associated with response. However, after imatinib treatment a decrease in cellularity was observed in 5 of 8 (62.5%) responders, but only in 1 of 6 (16.7%) nonresponders (Supplementary Table S2; Fig. 2D). Pre-imatinib tumor cellular and nuclear pleomorphism, Ki67 positivity, and mitotic count were not related to clinical response. Changes in these parameters during treatment were few and did not correlate with therapy outcome (Supplementary Table S2). Moderate to strong hyaline fibrosis was detected in post-imatinib tumor tissue of 4 of 8 responders (50.0%) but only 1 of 6 nonresponders (16.7%; Supplementary Table S2; Fig. 2D).

Discussion

In nonresectable DFSP, three clinical trials have investigated imatinib until now (Table 4; ref. 19). The first pilot study found 100% response (CR/PR) using a dose of 800 mg/d (20). These promising results were followed by two parallel trials combined in a joint report (21). The authors found 43.7% responders (CR/PR) in the European Organization for Research and Treatment of Cancer (EORTC) trial using imatinib 800 mg/d, and 50.0% responders in the Southwest Oncology Group (SWOG) trial using 400 mg/d. These data indicate that a lower imatinib-dosing regimen is adequate to achieve a sufficient clinical response. In resectable DFSP, two trials have been done up to now, one of a French consortium (22) and the presently reported (Table 4). Both studies were designed immediately after the first positive case reports of imatinib in metastatic DFSP, before any of the above mentioned trials in nonresectable DFSP

Figure 2. Patient ADO-06. A, FDG (2[18F]fluoro-2-deoxy-D-glucose)-positron emission tomography scans showing a decrease of FDG uptake in the tumor area (arrows), (left) before treatment compared with (right) 10 days of imatinib. B, FISH analysis on tumor cells obtained (left) before treatment and (right) at 3 months of imatinib showing colocalization and amplification of *COL1A1* (green) and *PDGFB* (red). C, phosphorylation analysis of 42 RTKs in tumor tissue obtained (top) before treatment and (bottom) at 3 months of imatinib: 1, EGFR; 2, PDGFRA; 3, PDGFRB; 4, MCSFR; 5, insulin receptor; 6, IGF-1R. D, immunohistochemical staining of CD34 in tumor tissue obtained (from top to bottom) before treatment, at 3 months of imatinib showing decreased cellularity and hyaline fibrosis, from local recurrence at 7 months after stop of imatinib, and from tumor mass infiltrating the lung at 35 months after stop of imatinib; magnification 1:100.



had been published. Both used an intermediate dose of 600 mg/d imatinib, and resulted in 36.0% and 57.1% response (CR/PR), respectively. This obvious difference might probably be due to the varying study designs. The French study required the obligatory surgical removal of the tumor as early as 2 months after imatinib onset. The difference in tumor diameters observed in our present study between week 6 and 12 clearly shows that this time point was set too early to reach an objective response in every DFSP sensitive to imatinib. In contrast, in cases of nonprogression our study protocol allowed long-term treatment until definitive surgery. It is likely, that the response rate of the French trial would have been significantly higher if the preoperative treatment duration would have been prolonged. It should be noted that our study involves a number of heterogeneously distributed parameters like safety margins, disease type namely primary or recurrent disease, and different modes of pretreatment. The inclusion criteria were permissive about these points because we aimed at enrolling as

many patients as possible with this rare disease. However, it should be taken into account that these heterogeneities might have influenced the study results, particularly the response rate.

The present study of imatinib in DFSP is the first with a long-term patient follow-up (Table 4). Particularly the rate of tumor relapse during follow-up is an important aspect of this trial because it is unknown if the initial efficacy of the drug later translates into a lower potential of relapse. The French study used wide excision margins, but did not perform a patient follow-up. Therefore, unfortunately, a direct comparison of tumor relapse after wide excision in the French trial and narrow to intermediate excision in the present trial is not possible. However, our assumption that a successful pretreatment with a PDGFRB inhibitor allows smaller surgical margins could not be definitely confirmed, since during long-term follow-up we observed 1 patient with a tumor relapse despite of an initially pronounced response to imatinib and subsequent surgery with tumor-

Table 3. Morphologic and molecular tumor characteristics before imatinib therapy (per protocol)

Patient ID	Tumor type	COL1A1-PDGFB	Localization (tissue layers involved)	CD34	S100	Vascularization	Hemorrhages	Cellular/nuclear pleomorphism	Ki67	Mitoses
ADO-01	DFSP	NE	Dermis + subcutis	Positive (homogeneous)	Negative	Moderate	Several	None/none	5%	None
ADO-02	DFSP	NE	Dermis + subcutis + skeletal muscles	Positive (homogeneous)	Negative	High	None	None/moderate	ND	None
ADO-03	DFSP	ND	Subcutis	Positive (heterogeneous)	Negative	Low	None	None/moderate-high	ND	Several
ADO-04	DFSP-FS	Positive (RT-PCR + sequencing, FISH)	Dermis + subcutis	Positive (homogeneous)	Negative	Moderate	None	Low-moderate/none	6%	Sporadic
ADO-05	DFSP	Positive (RT-PCR + sequencing)	Dermis + subcutis	Positive (homogeneous)	Negative	Moderate	None	None/none	2%	None
ADO-06	DFSP, myxoid type	Positive (RT-PCR + sequencing, FISH)	Dermis + subcutis	Positive (homogeneous)	Negative	Moderate	None	Low/none	3%	None
ADO-07	DFSP-FS, pigmented type	Positive (RT-PCR + sequencing, FISH)	Dermis + subcutis	Positive (heterogeneous)	Positive (heterogeneous)	High	None	Moderate/moderate-high	ND	Sporadic
ADO-09	DFSP, pigmented-type	ND	Dermis + subcutis	Positive (homogeneous)	Negative	Low	None	None/none	ND	None
ADO-10	DFSP	Negative (RT-PCR + sequencing)	Dermis + subcutis	Positive (homogeneous)	ND	Moderate	None	None/none	4%	None
ADO-11	DFSP	Positive (RT-PCR + sequencing)	Dermis + subcutis	Positive (homogeneous)	Negative	Moderate	None	None/none	4%	None
ADO-12	DFSP	ND	Dermis + subcutis + deep soft tissue + bone	Positive-negative (heterogeneous)	Negative	High	Numerous	None/none	5%	None
ADO-13	DFSP	Negative (FISH)	Dermis + subcutis	Positive (homogeneous)	Negative	Moderate	None	Low/none	8%	Sporadic
ADO-15	DFSP	NE	Dermis + subcutis	Positive (homogeneous)	Negative	Low	None	Moderate/none	2%	None
ADO-16	DFSP	Negative (RT-PCR + sequencing)	Dermis + subcutis	Positive (homogeneous)	ND	Moderate	None	Low/none	2%	Several

NOTE: Morphologic and molecular tumor characteristics as analyzed in the per protocol population, for details see Patients and Methods. Abbreviations: ND, not done; NE, not evaluable.

Table 4. Clinical trials of imatinib in DFSP

Clinical trial	Regimen/ imatinib dose	Patients (total)	Patients with DFSP only (tumor type)	Median therapy duration (months)	Grade 3 and 4 toxicity	Best response (DFSP only)	Secondary resistance to imatinib	Relapse after definitive surgery	Biomarkers of response ^a	Median follow-up time (years)
ITECS B2225 (McArthur and colleagues 2005)	Imatinib in nonresectable DFSP, 800 mg/d	10 (8 Locally advanced, 2 metastatic)	10 (8 DFSP Classic, 2 DFSP-FS)	7.0	ND	4 CR 5 PR 1 SD (90% CR/PR)	2/10 (1 PD After 2 years, 1 PD after 7 months)	0/6	Decrease of cellularity (+), formation of hyaline fibrosis (+)	1.1
SWOG S0345 (Rutkowski and colleagues 2010)	Imatinib in nonresectable DFSP, 400 mg/d	8 (7 Locally advanced, 1 metastatic)	7 (5 DFSP Classic, 2 DFSP-FS)	10.8	7 Events/8 patients (87.5%)	4 PR 2 SD 1 PD (57% CR/PR)	ND	ND	ND	2.6
EORTC 62027 (Rutkowski and colleagues 2010)	Imatinib in nonresectable DFSP, 800 mg/d	16 (10 Locally advanced, 6 metastatic)	16 (8 DFSP Classic, 7 DFSP-FS, 1 DFSP pigmented- type)	8.1	13 Events/16 patients (81.3%)	7 PR 4 SD 3 PD 2 NE (44% CR/PR)	ND	ND	ND	2.6
French trial (Kerob and colleagues 2010)	Neoadjuvant imatinib in resectable DFSP, 600 mg/d	25 (All locally advanced)	25 (25 DFSP Classic)	2.0	5 Events/25 patients (20%)	9 CR/PR 15 SD/PD 1 NE (36% CR/PR)	NA (Obligatory tumor excision after 2 months of imatinib)	ND	Decrease of cellularity (+), formation of hyaline fibrosis (+)	No follow- up
ADO DFSP-001 (Ugurel and colleagues)	Neoadjuvant imatinib in resectable DFSP, 600 mg/d	16 (All locally advanced)	14 (10 DFSP Classic, 2 DFSP-FS, 1 DFSP pigmented- type, 1 DFSP myxoid)	3.1	4 Events/ 16 patients (25%)	1 CR 7 PR 5 SD 1 PD (57% CR/PR)	1/14 (PD After 6 months)	1/13 (Local recurrence, metastasis and death)	Low PDGFRB phosphorylation (-), pigmented- type DFSP (-), decrease of cellularity (+), formation of strong hyaline fibrosis (+)	6.4

NOTE: Overview on clinical trials of imatinib in DFSP.

Abbreviations: SD, stable disease; NE, not evaluable; NA, not applicable; ND, not done.

^a(+), favorable prognosis; (-), unfavorable prognosis.

free margins. This recurrent tumor was refractory to newly started imatinib, but could be successfully treated with sunitinib 50 mg/d followed by complete surgery. Later, the patient presented with treatment-refractory metastases to the lung, vertebral bodies, and spinal cord, which led to the death of patient.

To the best of our knowledge, this is the first report of a successful treatment of an imatinib-resistant DFSP with second-line sunitinib. It should be taken into account that the binding capacity of sunitinib to PDGFRB is about 10 times more than that of imatinib (23), presuming a high efficacy of this drug in DFSP although it is lacking approval for this entity.

A recent retrospective multicenter study demonstrated that the recurrence rate of DFSP after tumor-free resection is extremely low (<1%), even without use of Mohs surgery (8). The only two cases of that study showing local recurrences had obtained excisions with tumor-positive margins. These data were confirmed by other groups also reporting very low recurrence rates in DFSP excised with clear margins (24, 25). In the present trial, Mohs surgery was not applied because it is not a common procedure in German clinical routine. Our patient showing a tumor relapse had a myxoid-type DFSP, which is known as a rare DFSP variant revealing the same clinical behavior as classical DFSP, particularly with regard to recurrence and metastasis (26). Notably, this tumor was the largest of our trial. However, it is remarkable that it grew slowly for anamnestically more than 10 years, and started rapid growth acceleration only when secondary resistance developed under imatinib treatment. However, this effect did not translate into morphologic or molecular changes. The tumor recurrence still harbored the *COL1A1-PDGFB* fusion gene, and the histologic and immunohistochemical characteristics were unchanged; particularly, there was no fibrosarcomatous transformation (Fig. 2D). Also, the recurrent tumor responded to sunitinib, indicating that the PDGFRB pathway was still the driving stimulus in this tumor, and imatinib resistance was probably not due to the activation of alternative signaling pathways.

We observed 25% grade 3 and 4 toxicities using an intermediate imatinib dose of 600 mg/d (Table 4). A similar toxicity was reported in the French trial, indicating that 600 mg/d imatinib is well tolerated, regardless of a short- or long-term regimen. The observed toxicity profile is considerably milder than that of the high-dose regimen used in the EORTC trial (21), which showed 81.3% grade 3 and 4 toxicities. Surprisingly, the toxicity observed in the SWOG trial is of similarly high intensity (21), despite the much lower dose of 400 mg/d. This obvious inconsistency might be explained by the fact that 2 of 8 patients of the SWOG trial were dose escalated to 800 mg/d. With regard to the risks versus benefits of imatinib in patients with DFSP, it is questionable whether the observed decrease in tumor size is worth the high probability of side effects with 25% grade 3 and 4 toxicities, and also the potential risk of transformation to a more aggressive tumor type. These interactions have to be investigated in more detail in future clinical trials.

We performed an extensive analysis of histomorphologic and molecular tumor parameters to identify biomarkers of imatinib response. It should be noted that due to low patient numbers in this study, all biomarker analyses were done on an exploratory, hypothesis-building basis, and need confirmation by future clinical trials. Remarkably, pigmented-type DFSP was associated with nonresponse. This finding is confirmed by the observation of one non-responsive pigmented-type DFSP in a patient treated in the EORTC trial (21), and strikingly, this patient was the only of 25 study patients showing PD as best response. In our present trial, also the only patient with PD as best response was a pigmented-type DFSP. This interesting observation may be explained by the constitutively high treatment resistance of pigmented tumors. With regard to the *COL1A1-PDGFB* fusion gene, we observed no stringent association with response. However, it must be recognized that the sensitivity of our detection method might have been insufficient. Patel and colleagues demonstrated that the *COL1A1-PDGFB* fusion gene could be detected in 96% of DFSP cases so far as the detection method is of high enough sensitivity (27). The authors used multiplex RT-PCR followed by direct sequencing of the amplification product combined with FISH; the same methodology was used in our present study. Patel and colleagues used a set of 18 different *COL1A1* primers, whereas in our study even 51 *COL1A1* primers were used. However, Patel and colleagues used a sample set extracted from the histopathology archive of a single institution. In contrast, we encountered the difficult conditions of the very heterogeneous quality of biomaterials obtained from 10 different study centers. This might explain the much lower *COL1A1-PDGFB* detection rate in our study (62.5%) compared with that of Patel and colleagues (96%). During imatinib treatment a clinical response was associated with a decrease in tumor cell density and with the formation of a moderate to strong hyalinic fibrosis. The replacement of tumor cells by hyalinized collagen was previously reported in imatinib-treated GIST (28). Also, Kerob and colleagues described hyalinic fibrosis of imatinib-treated tumors in 19 of 25 patients of their study (22).

With regard to target phosphorylation, we correlated clinical response with PDGFRB activation. So far, the only clinical trial using this strategy was the pilot study of McArthur and colleagues, who analyzed five DFSP cases responding to imatinib and found a throughout weak phosphorylation of PDGFRB (20). In contrast, we found a moderate to strong phosphorylation in all but one investigated DFSP. Strikingly, a strong PDGFRB activation was not necessarily associated with clinical response. Moreover, no significant changes in PDGFRB phosphorylation intensity could be detected during imatinib therapy; particularly there was no decrease of PDGFRB activation in responders. Remarkably, the only patient showing a weak pre-imatinib PDGFRB phosphorylation revealed an immediate tumor progression during imatinib treatment; this was the only patient of the whole study presenting with PD as best response. These results indicate that moderate to strong

PDGFRB activation is a common event in DFSP and does not necessarily translate into clinical response to imatinib. Nevertheless, a weak PDGFRB phosphorylation seems to be associated with nonresponse. The moderate to strong activation of other RTKs, particularly of EGFR and insulin receptor detected in 100% of the investigated cases, indicates that these RTKs might be interesting candidates for other than PDGFRB directed-targeted therapies of DFSP.

Disclosure of Potential Conflicts of Interest

S. Ugurel has received commercial research grant support and has honoraria from speakers' bureau from Novartis. C. Pfohler has honoraria from speakers' bureau from Psoriasis. A. Hauschild has received commercial research grant support and is a consultant/advisory board member of Novartis. M. Leverkus has honoraria from the speakers' bureau. J.C. Becker has honoraria from speakers' bureau and is a consultant/advisory board member of Novartis. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S. Ugurel, T. Mentzel, P. Mohr, A. Hauschild, J.C. Becker, D. Schadendorf

Development of methodology: S. Ugurel, T. Mentzel, P. Ströbel

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Ugurel, T. Mentzel, J. Utikal, P. Helmbold,

P. Mohr, C. Pfohler, M. Schiller, A. Hauschild, R. Hein, E. Kämpgen, I. Kellner, M. Leverkus, J.C. Becker, P. Ströbel, D. Schadendorf

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Ugurel, T. Mentzel, C. Pfohler, M. Schiller, A. Hauschild, M. Leverkus, J.C. Becker, P. Ströbel, D. Schadendorf

Writing, review, and/or revision of the manuscript: S. Ugurel, T. Mentzel, J. Utikal, P. Mohr, C. Pfohler, M. Schiller, A. Hauschild, R. Hein, E. Kämpgen, M. Leverkus, J.C. Becker, P. Ströbel, D. Schadendorf

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Ugurel, T. Mentzel, C. Pfohler, E. Kämpgen, D. Schadendorf

Study supervision: S. Ugurel, J.C. Becker, D. Schadendorf

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