Dermatofibrosarcoma protuberans

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IM. MARII SKŁODOWSKIEJ-CURIE

Disclosure

- Advisory board: Novartis, MSD, BMS, Bayer
- Honoraria: Novartis, Pfizer, MSD, Roche, GSK, Amgen
- Travel grants: Novartis

Background

- Dermatofibrosarcoma protuberans (DFSP) - rare soft tissue tumor (comprising approximately 1% of sarcomas) with typically indolent growth over years and probability of regional/distant metastases less than 5% (especially in DFSP with fibrosarcoma transformation DFSP-FS)
- Typically DFSP is characterized by a specific rearrangement of chromosomes 17 and 22 in the form of translocation t(17;22)(q22;q13) and often supernumerary ring chromosome that leads to the fusion of collagen type I A1-chain gene (COL1A1) to the platelet-derived growth factor B-chain gene (PDGFB).

- The result of this rearrangement is upregulation of the COL1A1/PDGFB fusion protein, processing to a mature homodimer PDGF-BB, and consequently continuous autocrine activation of the PDGFB receptor (PDGFRB), a protein tyrosine kinase acting as a potent growth factor.
- These mechanisms contribute directly to development and growth of DFSP, but also of giant cell fibroblastoma (GCF), which from a pathogenetic point of view can be called the juvenile form of DFSP.

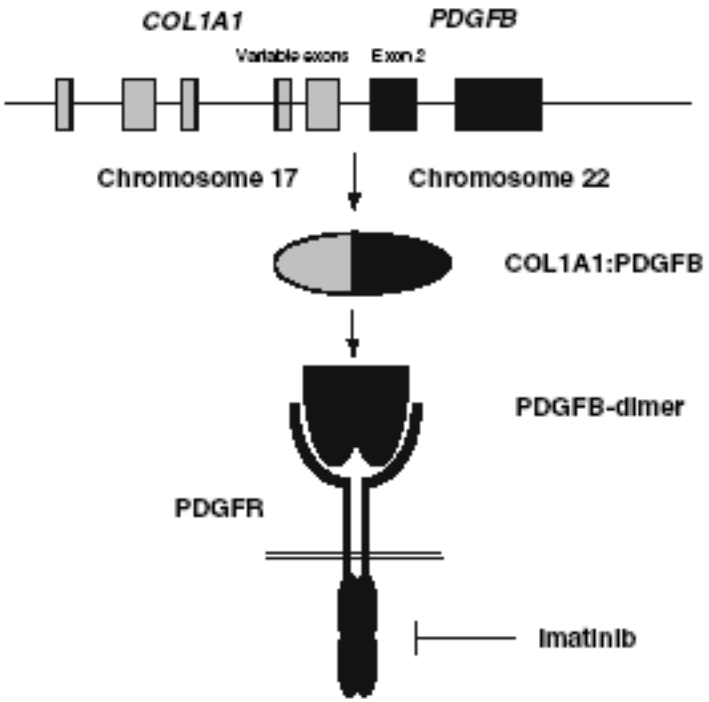
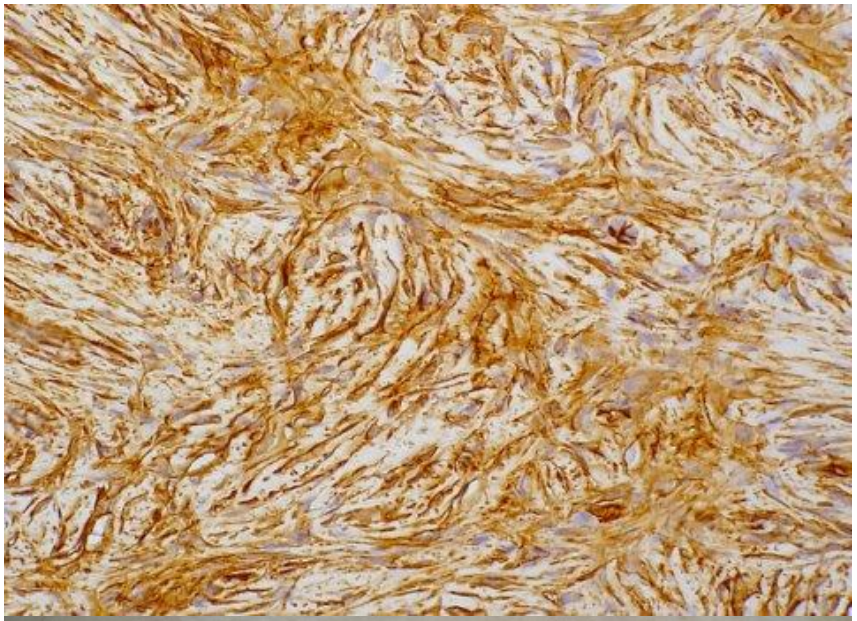
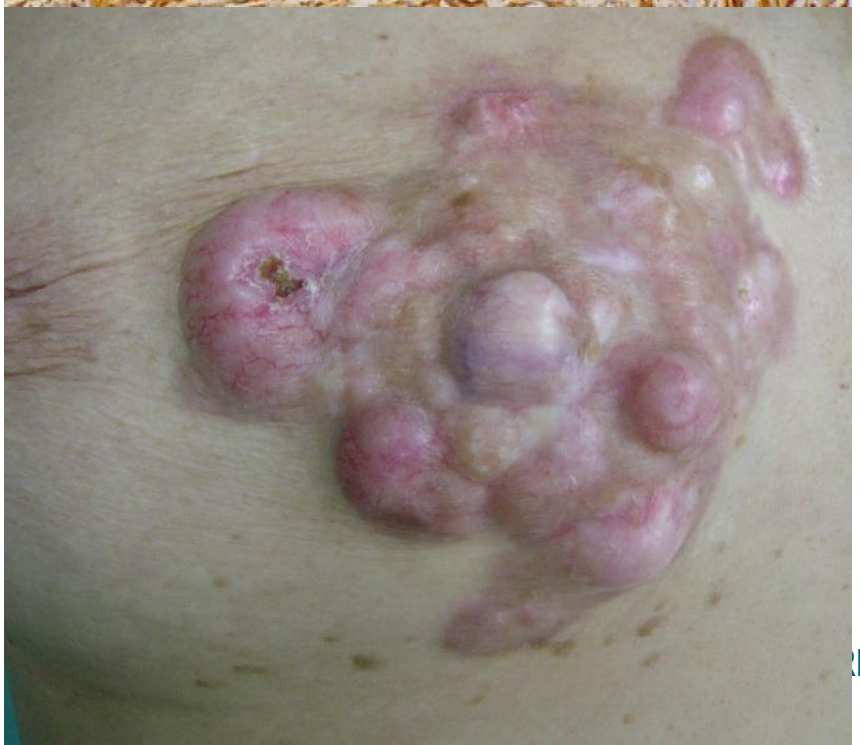


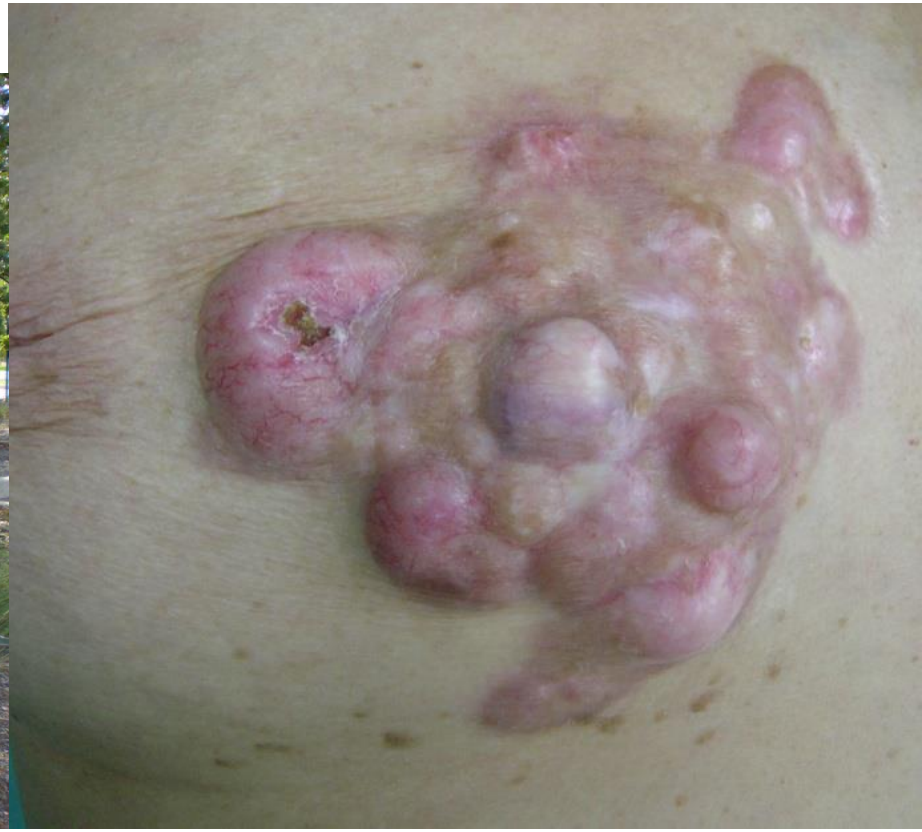
FIG. 1. The molecular biology of dermatofibrosarcoma protuberans (DFSP) is characterized by fusion of the *COL1A1* and *PDGFB* (platelet-derived growth factor B chain) genes as a result of the chromosomal translocation t(17:22). Constitutively expressed

Grant McArthur, *Annals of Surgical Oncology* 14(10):2876–2886
DOI: 10.1245/s10434-007-9480-y



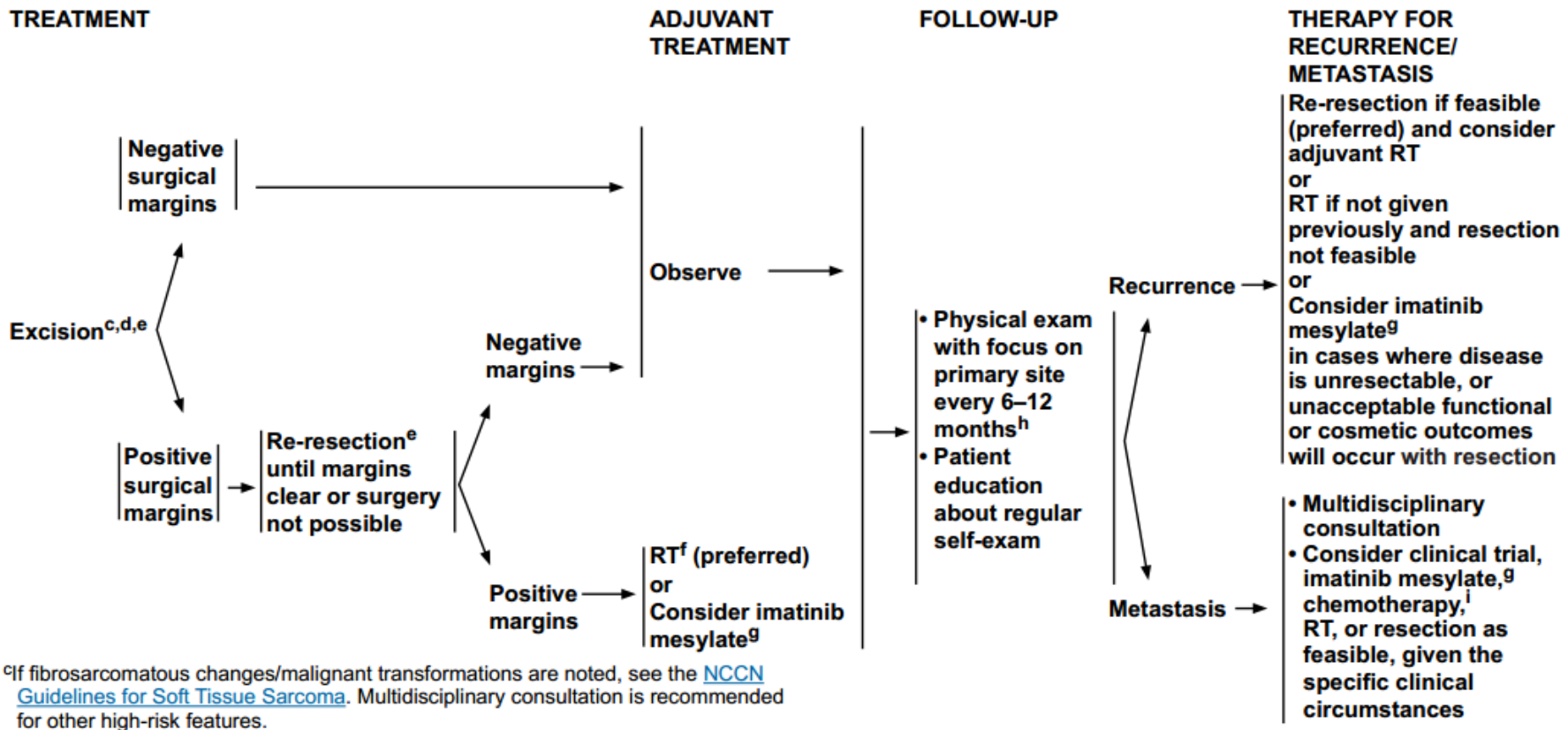


Localized DFSP – Surgery (no clear margins and pseudocapsule; wider margins of surgery required or Mohs' technique)



NCCN Guidelines Version 1.2016
Dermatofibrosarcoma Protuberans

NCCN Guidelines Index
DFSP Table of Contents
Discussion



[c]If fibrosarcomatous changes/malignant transformations are noted, see the NCCN Guidelines for Soft Tissue Sarcoma. Multidisciplinary consultation is recommended for other high-risk features.

[d]The surgical approach to DFSP must be meticulously planned. Size and location of the tumor and cosmetic issues will dictate the most appropriate surgical procedure. See Principles of Excision (DFSP-B).

[e]Wide undermining is discouraged due to the difficulty of interpreting subsequent re-excisions pathologically and of preventing possible tumor seeding if margins are not histologically clear.

[f]5,000-6,000 cGy for close-to-positive or positive margins (200 cGy fractions per day). Fields to extend widely beyond surgical margin (eg, 3-5 cm) when clinically feasible.

[g]Tumors lacking the t(17;22) translocation may not respond to imatinib. Molecular analysis of a tumor using cytogenetics may be useful prior to the institution of imatinib therapy.

[h]Radiologic imaging may be helpful to detect early recurrence in patients with high-risk lesions or who have had more extensive surgery.

[i]AIM (doxorubicin/ifosfamide/mesna) regimen or single-agent therapy with doxorubicin, ifosfamide, epirubicin, gemcitabine, dacarbazine, liposomal doxorubicin, temozolomide, vinorelbine, or pazopanib may be considered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Diagnosis and treatment of dermatofibrosarcoma protuberans. European consensus-based interdisciplinary guideline ☆

European Journal of Cancer (2015)

Philippe Saiag [a,*], Jean-Jacques Grob [b], Celeste Lebbe [c], Josep Malvehy [d], Veronique del Marmol [e], Hubert Pehamberger [f], Ketty Peris [g], Alexander Stratigos [h], Mark Middelton [i], Lars Basholt [j], Alessandro Testori [k], Claus Garbe [l]

Treatment recommendations:

- Treatment is mainly surgical, with the aim to achieve complete resection of the tumour. Complete assessment of all surgical margins before definitive reconstruction is necessary. Surgery of DFSP must be meticulously planned, with size, type of margin control, location of the tumour and cosmetic issues influencing the most appropriate surgical procedure.
- Whatever variations of surgical techniques used, the excision of the deep fascia to remove any infiltrating tumour cells seems important.
- In order to reduce the recurrence rate, the treatment of choice of DFSP seems to be Mohs' micrographic surgery (MMS) and related variants, with 1 to 1.3 cm lateral safety margins.
- In hospitals where only standard histopathological procedures are available, standard excision with lateral safety margin of 3 cm is advisable.
- Imatinib (Glivec®) is approved in Europe for the treatment of inoperable primary tumours, locally inoperable recurrent disease, and metastatic DFSP. Imatinib has also been given to patients with extensive, difficult-to-operate tumours for preoperative reduction of tumour size, but the usefulness of this attitude should be confirmed by clinical trials.
- Therapeutic decisions for patients with fibrosarcomatous DFSP should be primarily made by an interdisciplinary oncology team ('tumour board').

Dermatofibrosarcoma protuberans: Recurrence is related to the adequacy of surgical margins☆

S. Ten Heuvel [a], A. Suurmeijer [b], E. Pras [c], R.J. Van Ginkel [a], H.J. Hoekstra [a,*]

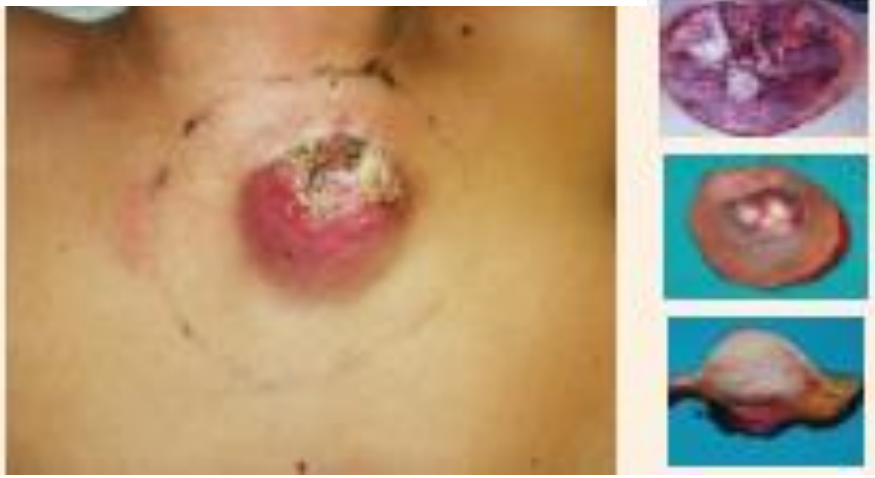
After a median follow-up of 89 (12–271) months, the 10-year disease-free survival was 85% and the 10-year disease specific survival was 100%.

Conclusion: After wide surgical resection of a DFSP or DFSP-FS, or an R1 resection combined with adjuvant radiotherapy the risk of local recurrence

CONTROVERSY

Dermatofibrosarcoma protuberans: Wide local excision vs. Mohs micrographic surgery

Conclusions. Using a standardized surgical approach including meticulous pathologic evaluation of margins, a very low recurrence rate (1%) was achieved with relatively narrow margins (median 2 cm), allowing primary closure in 69% of patients. This approach spares the additional morbidity associated with wider resection margins and in our experience represents the treatment of choice for DFSP occurring on the trunk and extremities.



Dermatofibrosarcoma Protuberans: How Wide Should We Resect?

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Jeffrey M. Farma, MD[1], John B. Ammori, MD[2], Jonathan S. Zager, MD[3], Suroosh S. Marzban, BS[3], Marilyn M. Bui, MD, PhD[4,5], Christopher K. Bichakjian, MD[6], Timothy M. Johnson, MD[6], Lori Lowe, MD[7], Michael S. Sabel, MD[8], Sandra L. Wong, MD[8], G. Douglas Letson, MD[5], Jane L. Messina, MD[3,4,9], Vincent M. Cimmino, MD[2], and Vernon K. Sondak, MD[3]

Authors/year	Patient (*N*)	Margin size	Negative margins (%)	Positive margins (%)	Recurrence (%)
Farma et al.	206	2 cm (median)	97	3	1
Heuvel et al.[17] (2009)	38	2–3 cm	95	5	7
Meguerditchian et al.[24] (2009)	28	2 cm	88	22	3.6
	20	Mohs	100	0	0
Yu et al.[7] (2008)	25	3 cm	n/a	n/a	0
Kimmel et al.[14] (2007)	98	n/a	n/a	n/a	41
		2.0 cm			24
		2.5 cm			11–20
		3.0 cm			
Monnier et al.[4] (2006)	4	<0.9 cm	n/a	n/a	50
	31	1–2.9 cm			46
	31	≥3.0 cm			7
Fiore et al.[18] (2005)	136 primary	n/a	88	12	4
	82 recurrence		85	15	5
Dubay et al.[5] (2003)	11	Mohs	85	15	0
	43	1–2 cm	95	5	0
Chang et al.[16] (2003)	60	≥3.0 cm	n/a	n/a	16
Bowne et al.[6] (2000)	159	n/a	58	32	21

+RTH?

Dermatofibrosarcoma Protuberans: How Wide Should We Resect?

Jeffrey M. Farma Ann Surg Oncol (2010) 17:2112–2118

CONFERENCE 2016

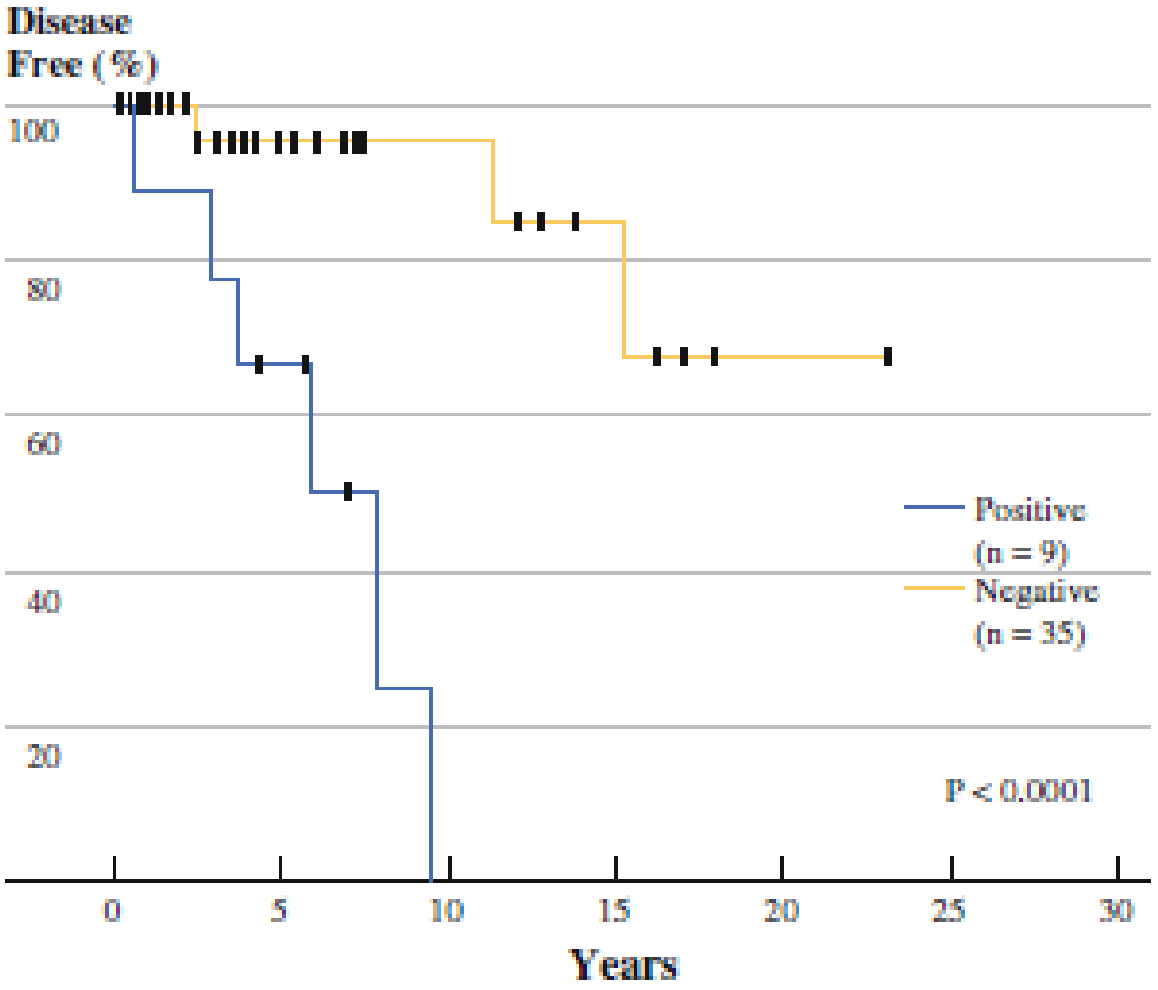


FIG. 3 Kaplan–Meier curve of disease-free survival in patients presenting with locally recurrent DFSP stratified by margin status

Dermatofibrosarcoma protuberans (DFSP): Predictors of Recurrence and the Use of Systemic Therapy

Ann Surg Oncol (2011) 18:328–336

Ryan C. Fields, MD[1], Meera Hameed, MD[2], Li-Xuan Qin, PhD[3], Nicole Moraco, MA[1], Xiaoyu Jia, MS[3], Robert G. Maki, MD, PhD[4], Samuel Singer, MD[1], and Murray F. Brennan, MD[1]

EXPERT REVIEWS

Current treatment options for dermatofibrosarcoma protuberans

Expert Rev. Anticancer Ther. Early online, 1–9 (2015)

Piotr Rutkowski*[1] and Maria Debiec-Rychter[2]

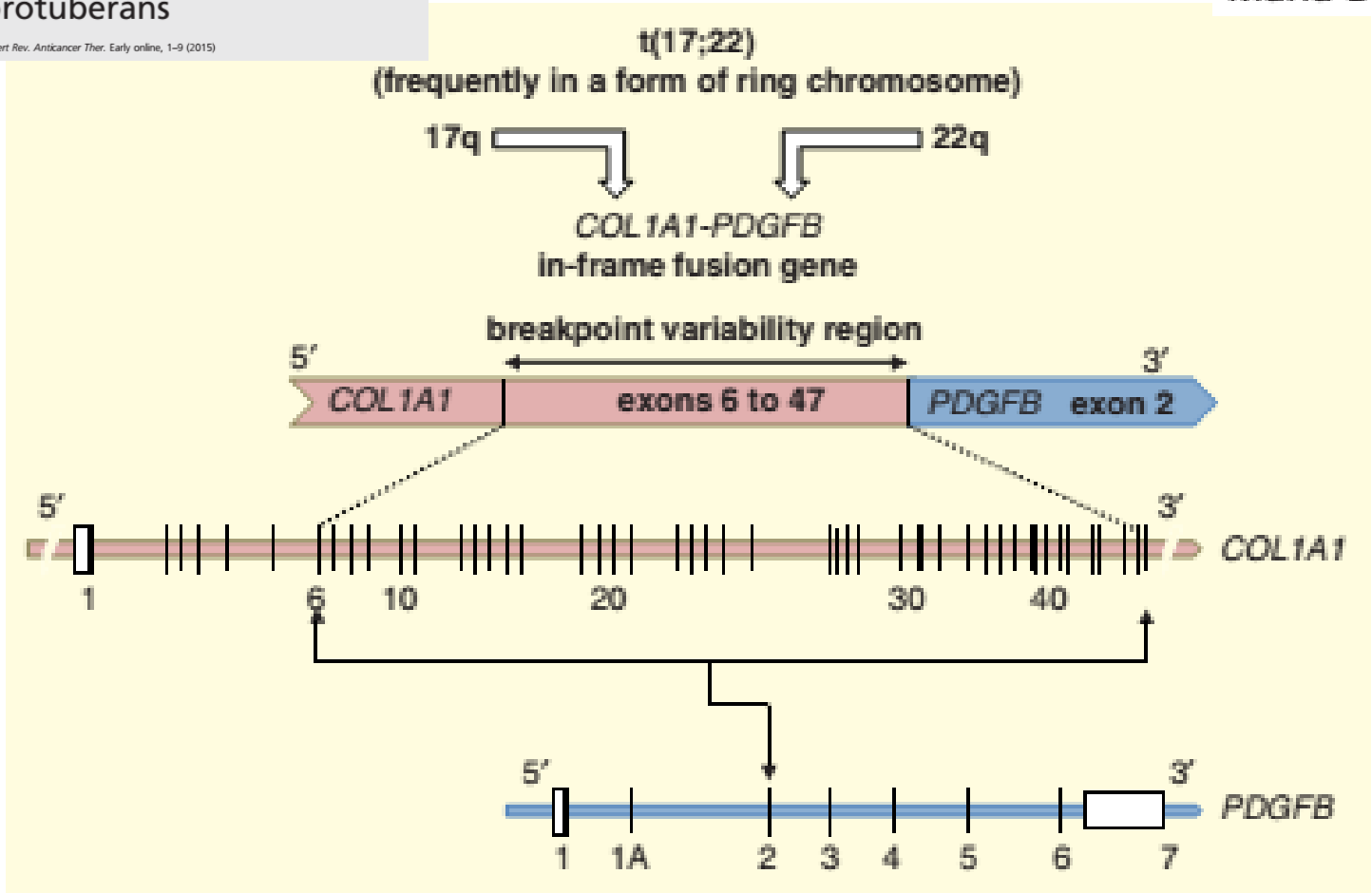
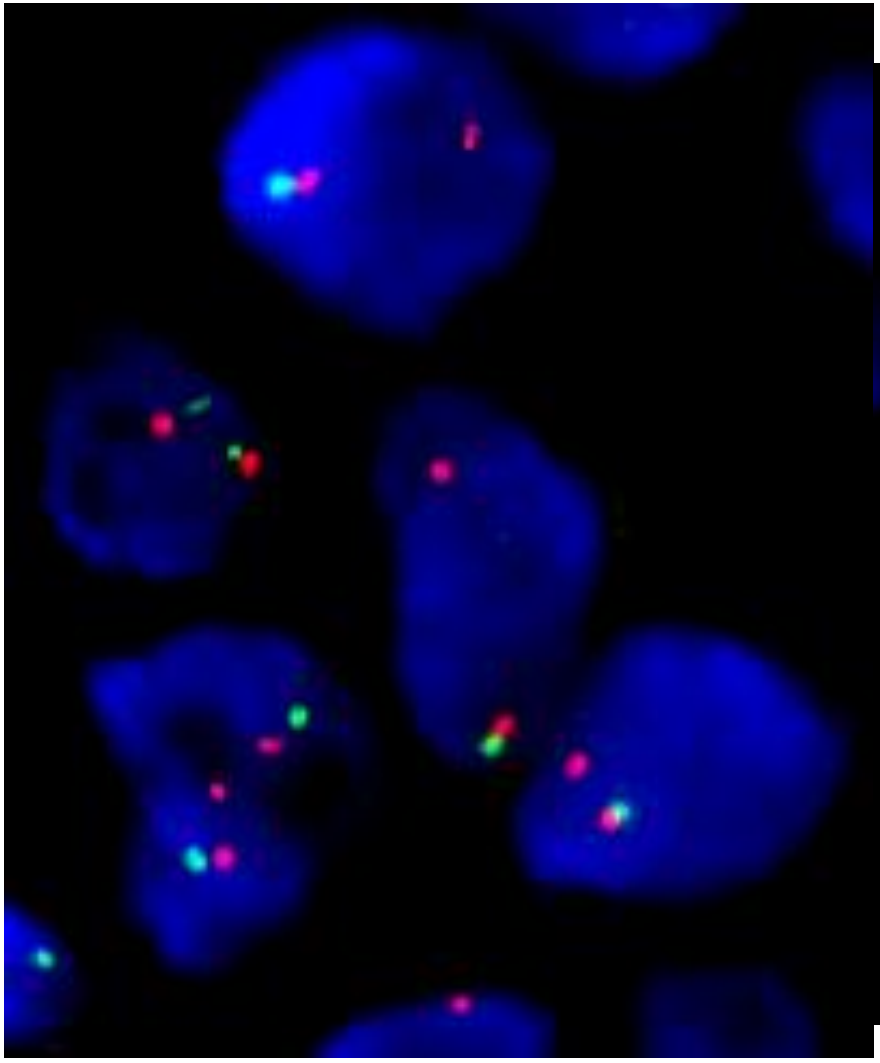
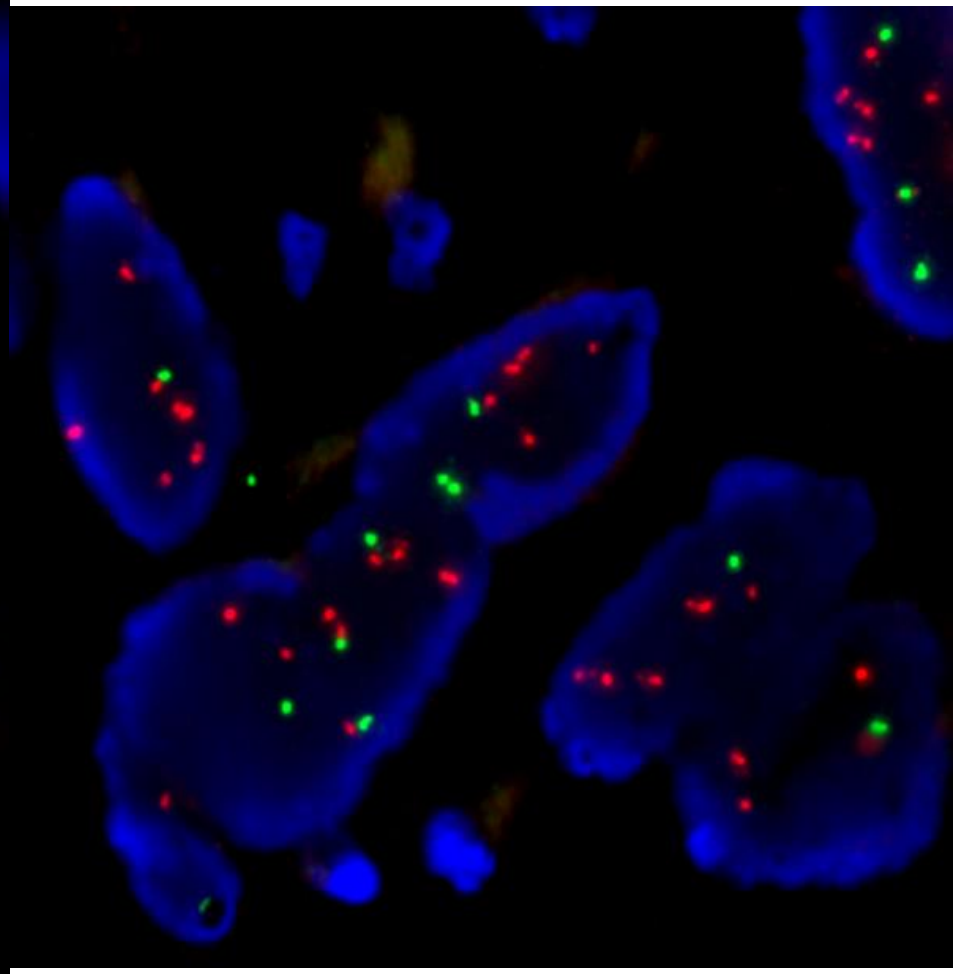
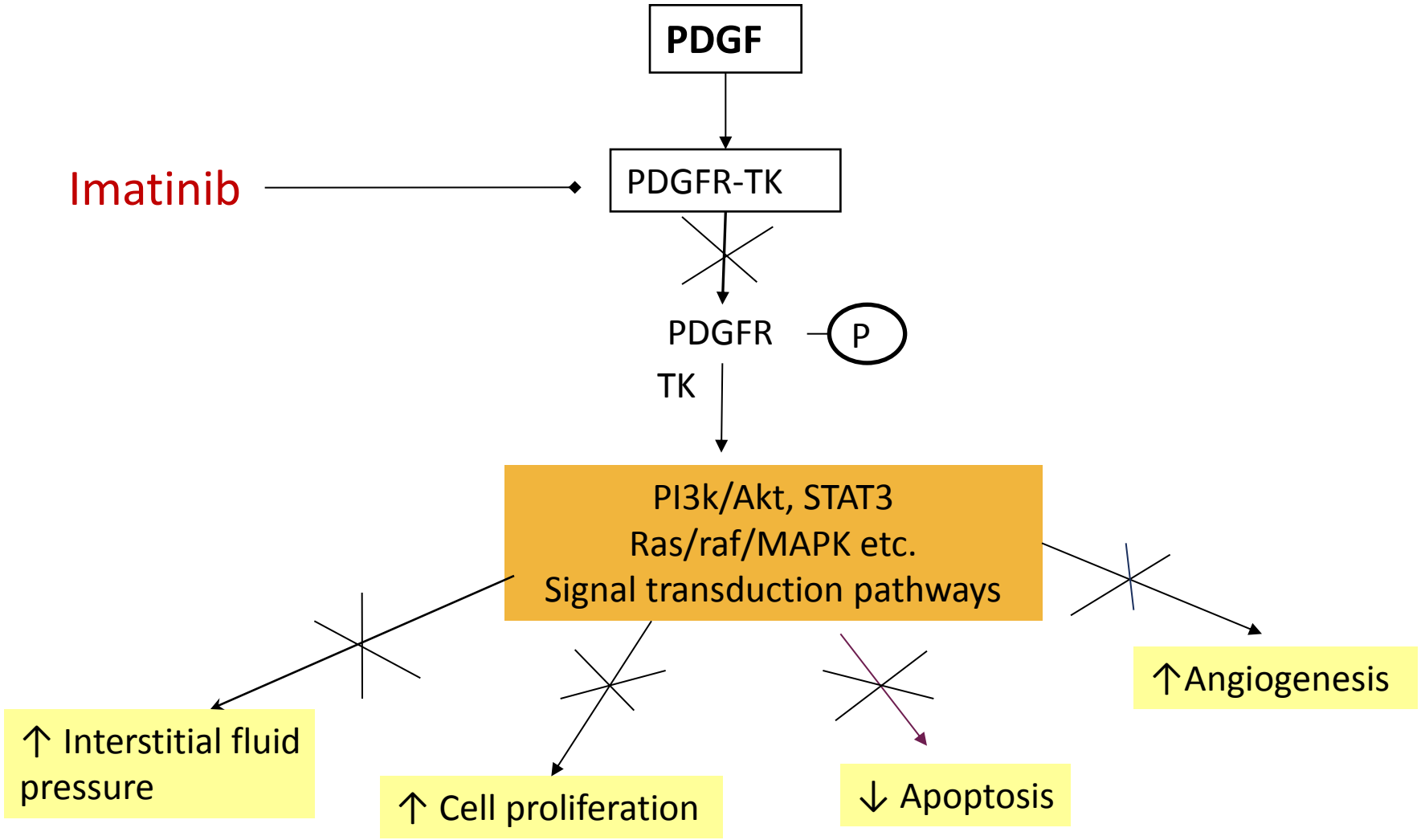


Figure 1. Graphic illustration of *COL1A1–PDGFB* fusion. The break point in *COL1A1* in DFSP and related tumors is highly variable. In contrast, the localization of the breakpoint in *PDGFB* is constantly found in intron 1. The chimeric gene is composed of at least the first 6 exons up to exon 49 of *COL1A1* and a consistent fragment retaining all but exon 1 of the *PDGFB* gene.

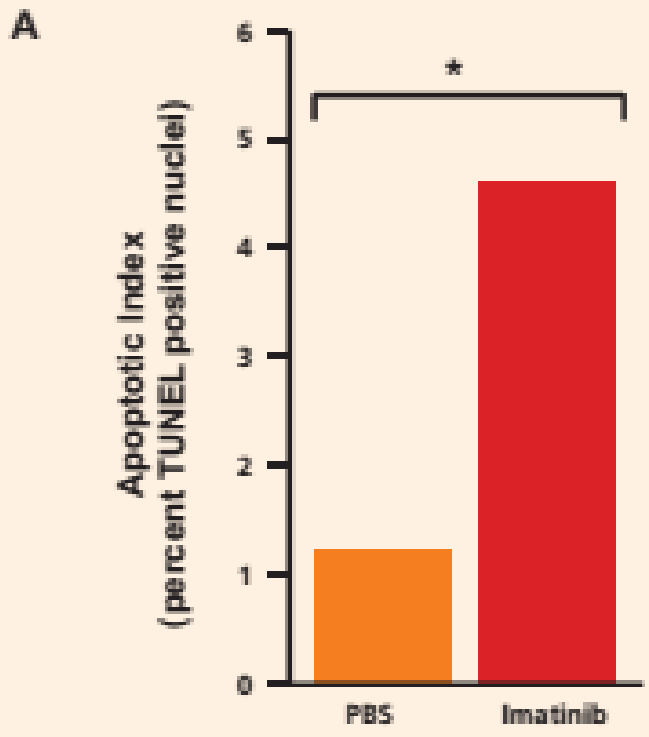
PDGFB split-apart FISH in interphase cells from DFSP, showing *PDGFB* rearrangement, evidenced by one copy (red probe) of the telomeric *PDGFB* signal in tumor cells (by courtesy of Prof. M. Debiec-Rychter)

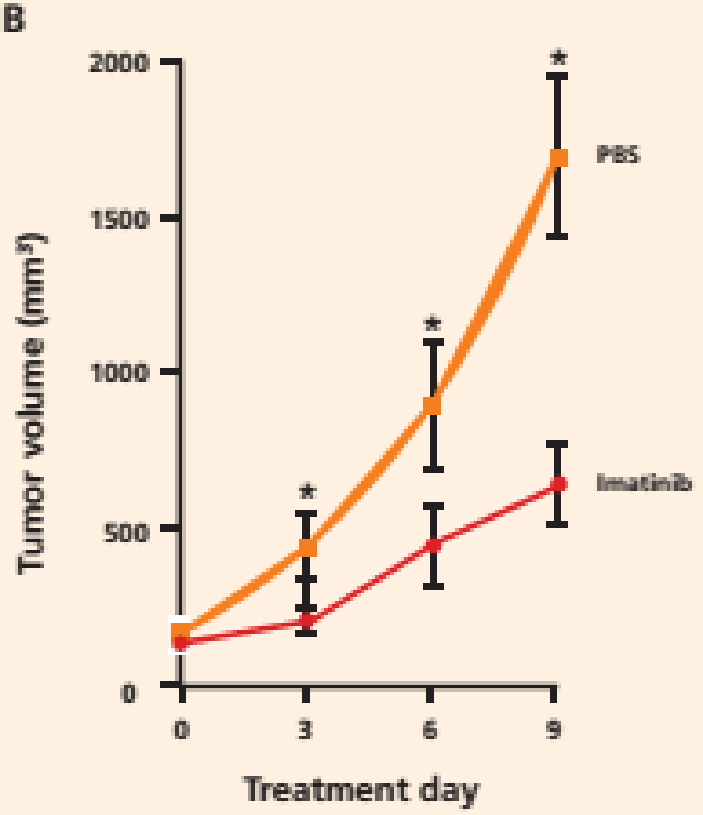





PDGF
Imatinib
PDGFR-TK
PDGFR
P
TK
PI3k/Akt, STAT3
Ras/raf/MAPK etc.
Signal transduction pathways
↑ Interstitial fluid pressure
↑ Cell proliferation
↓ Apoptosis
↑Angiogenesis

Imatinib effect in vivo





. Imatinib-induced apoptosis of DFSP tumor 149333. PBS, phosphate-buffered saline. B. Imatinib-induced inhibition of in vivo growth of DFSP tumor 49333. *P≤0.001. Adapted with permission from Sjoblom T, et al. *Cancer Res.* 2001;61:5778-5783.[28]

PROTOCOL 62027: Phase II study of Glivec (Imatinib) in locally advanced and/or metastatic soft tissue sarcoma expressing the t(17;22)(q22;q13) translocation resulting in a COL1A1/PDGF-beta fusion protein i.e DermatoFibroSarcoma Protuberans (DFSP) and Giant Cell Fibroblastoma (GCF).

Study Coordinator: A.T. Van Oosterom, Leuven; Piotr Rutkowski, Warsaw

IMATINIB 400 mg bid for at least 14 weeks

1*/17: ineligible/evaluated

*** seqid 17: no DFSP**

Eligibility:

- Histologically proven locally advanced or metastatic DFSP or GCF
- Progressive disease documented in the last 3 months
- Disease not amenable to surgery, radiation or combined modality treatment with curative intent
- Frozen tumor or paraffin embedded tissue available for immunohistochemical, molecular analysis and central path. review
- No prior chemotherapy or no more than 1 line combination chemo with Ifosfamide and Doxorubicin or 2 lines of single agent therapy or relapsing within 6 months after end of adjuvant chemo.
- WHO PS 0-2, age 18 years or more

EORTC 62027	SWOG S0345
Selection criteria	
DFSP or GCF Advanced or metastatic, not amenable to surgery and/or XRT with a curative intent	DFSP or transformed fibrosarcomatous DFSP Recurrent, metatastic, or R0 resection not feasible with acceptable cosmetic/functional results
External confirmation of COL1A1/PDGF-beta expression	
Prospective, by FISH	Retrospective, by RT-PCR, DNA seq. and FISH
Protocol treatment	
Initial dose: 800 mg (400 mg bid) Duration: 14 weeks Surgery allowed after 14 weeks, if all lesions can be radically resected	Initial dose: 400 mg; escalation to 800 mg after PD Duration: 48 weeks Surgery/radiotherapy allowed after 48 weeks, according to local standards
End-point	
Primary: Progression free (RECIST) at 14 weeks **Secondary:** Objective response rate Overall PFS and OS Safety profile (CTCAE 3.0)	**Primary:** Confirmed CR or PR (RECIST) within 48 weeks **Secondary:** PFS at 1 year Frequency and severity of toxicities (CTCAE 3.0)
Statistical design	
Fleming one step design P0=20%, P1=40%, alpha=0.1, beta=0.05 44 patients	Two steps design P0=5%, P1=20%, alpha=0.05, beta=0.08 20 + 20 patients
Recruitment	
16 patients recruited from 2/12/2004 to 15/3/2007	8 patients recruited from 9/2/2005 to 9/10/2006

Imatinib Mesylate in Advanced Dermatofibrosarcoma Protuberans: Pooled Analysis of Two Phase II Clinical Trials

Piotr Rutkowski, Martine Van Glabbeke, Cathryn J. Rankin, Wlodzimierz Ruka, Brian P. Rubin, Maria Debiec-Rychter, Alexander Lazar, Hans Gelderblom, Raf Sciot, Dolores Lopez-Terrada, Peter Hohenberger, Allan T. van Oosterom, and Scott M. Schuetze

VOLUME 28 · NUMBER 10 · APRIL 1 2010

JOURNAL OF CLINICAL ONCOLOGY

Table 3. DFSP Best Response by Subtype

DFSP Subtype	No. of Patients					
	PR		SD		PD	
	Imatinib 400 mg/d	Imatinib 800 mg/d	Imatinib 400 mg/d	Imatinib 800 mg/d	Imatinib 400 mg/d	Imatinib 800 mg/d
DFSP classic	2	4	3	2		
DFSP fibrosarcomatous	2	3		1		2
DFSP pigmented						1
Not DFSP					1	

Abbreviations: DFSP, dermatofibrosarcoma protuberans; PR, partial response; SD, stable disease; PD, progressive disease.

Imatinib Mesylate in Advanced Dermatofibrosarcoma Protuberans: Pooled Analysis of Two Phase II Clinical Trials

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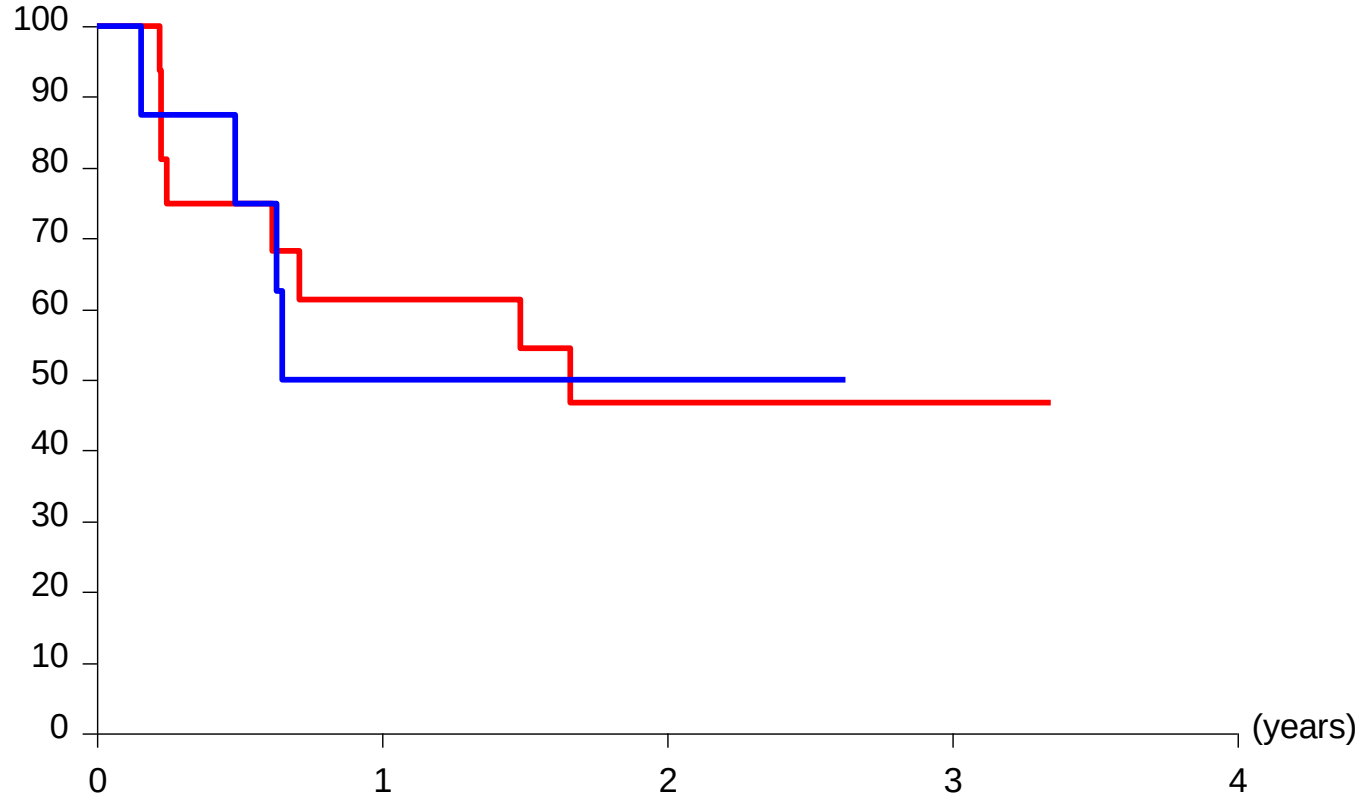
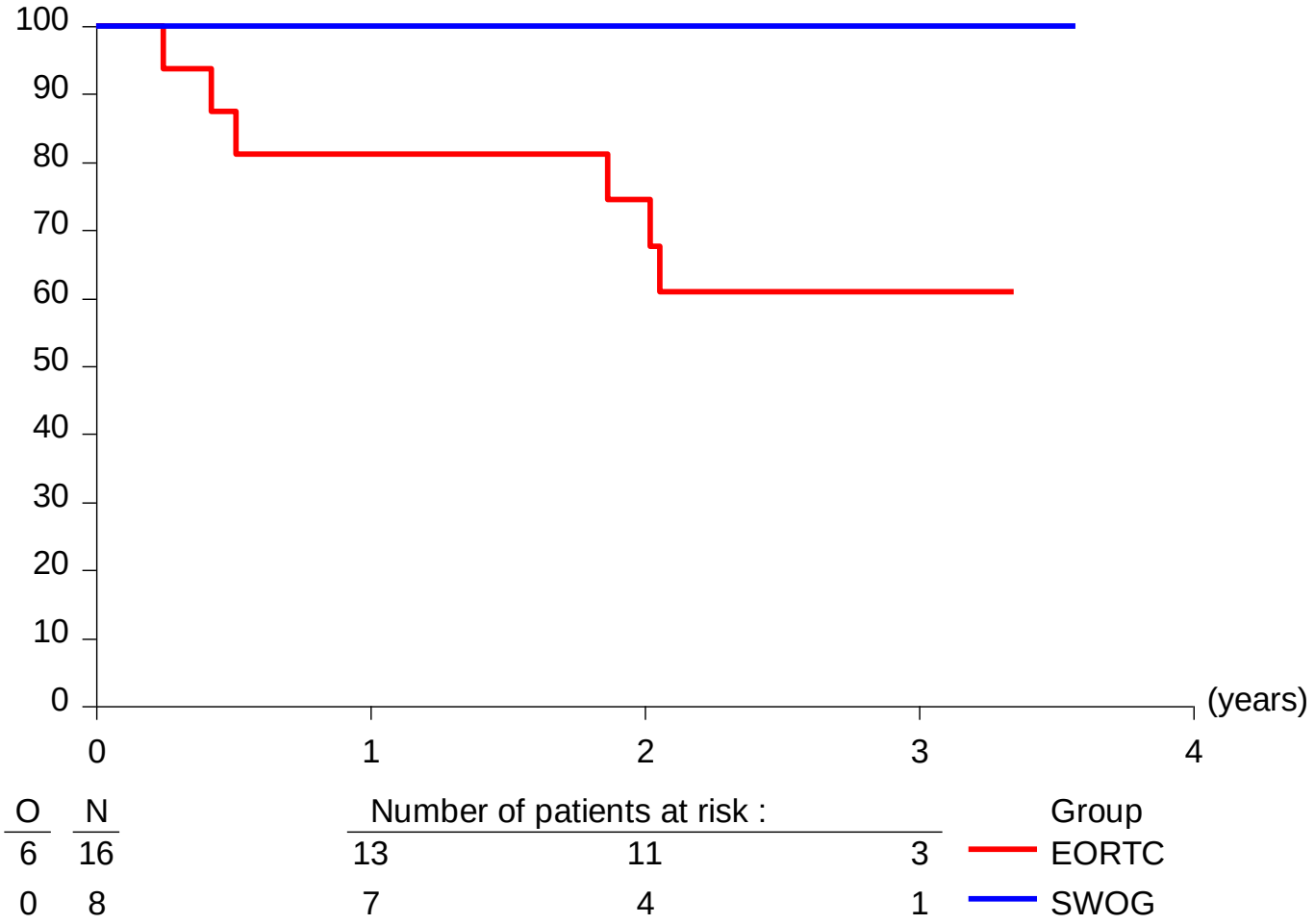
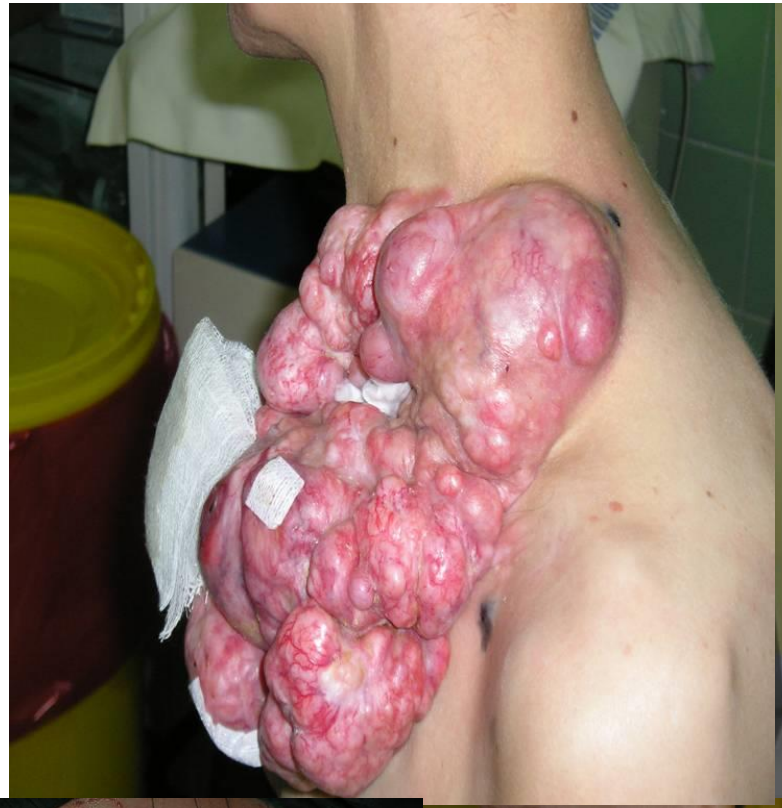
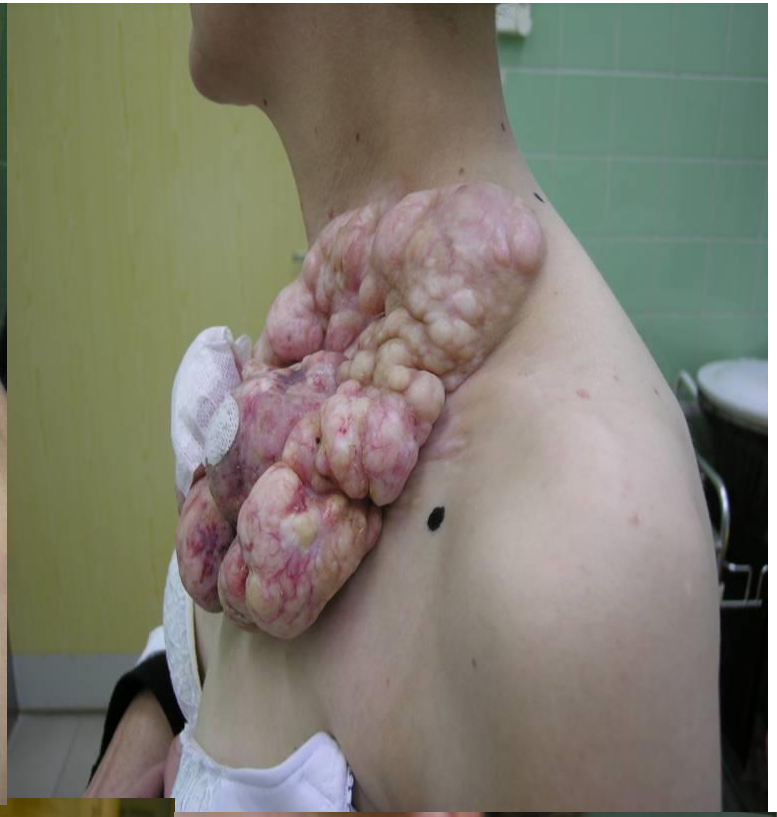
Time to progression
(ITT)

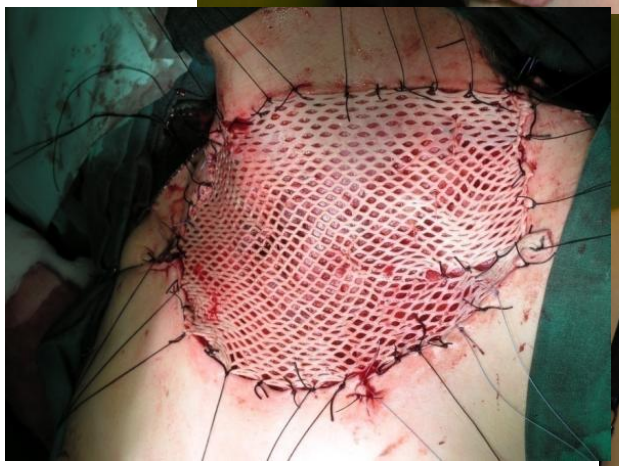


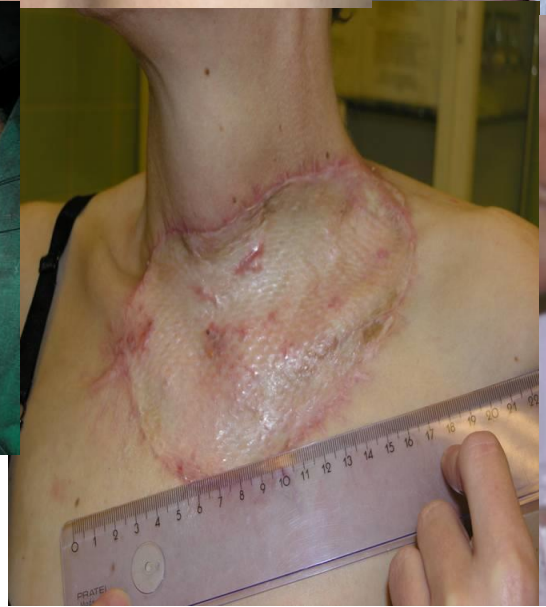
Overall survival
(ITT)

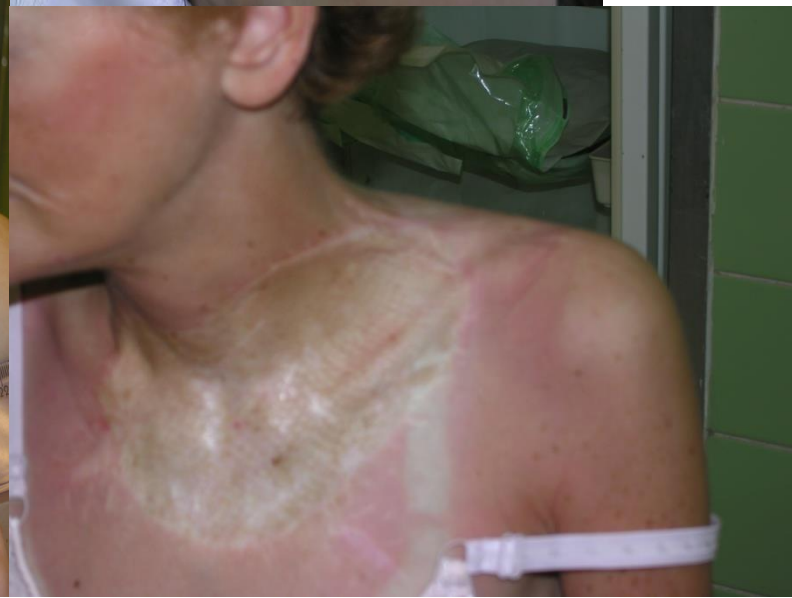




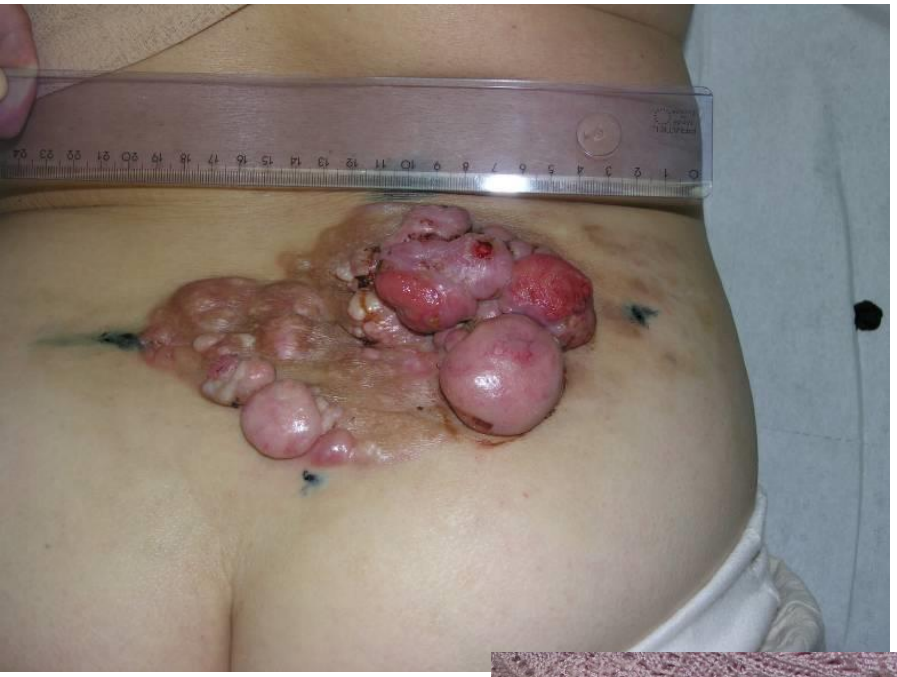


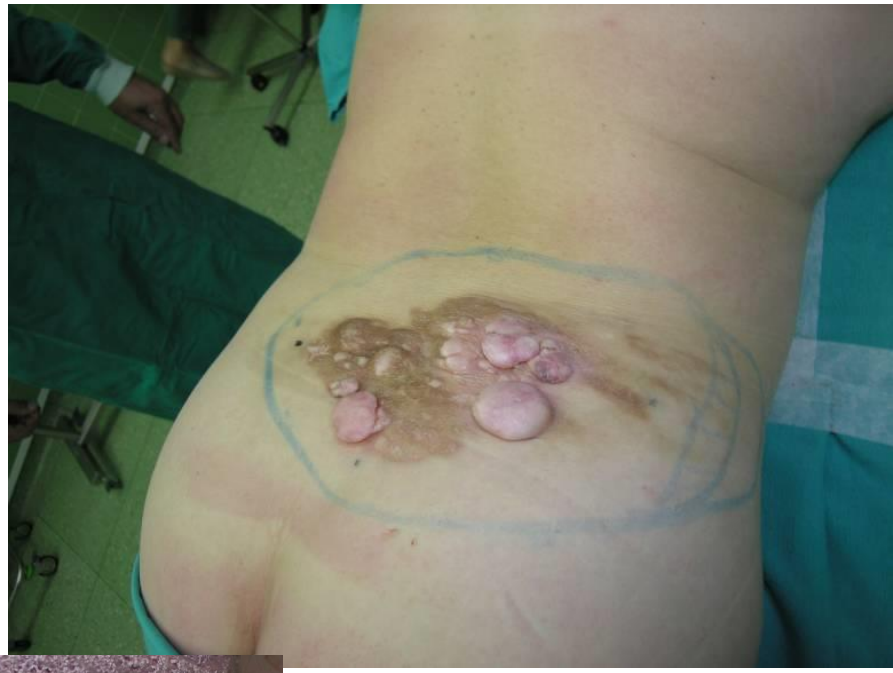


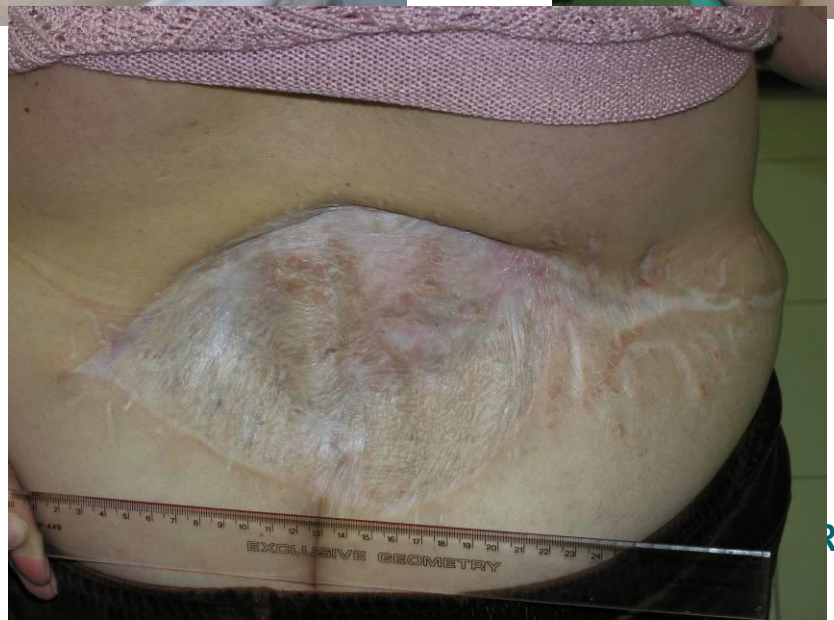




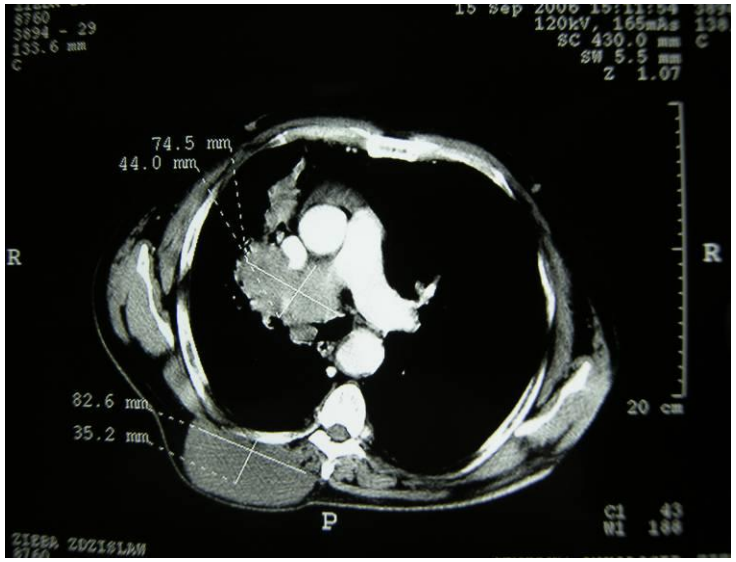
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

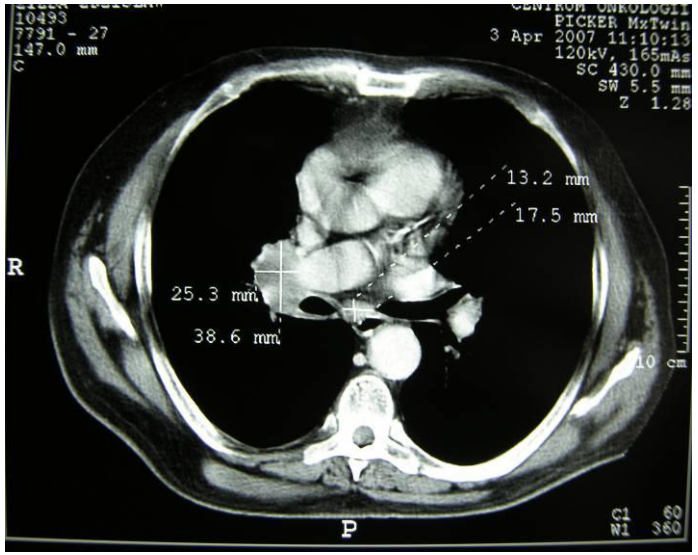


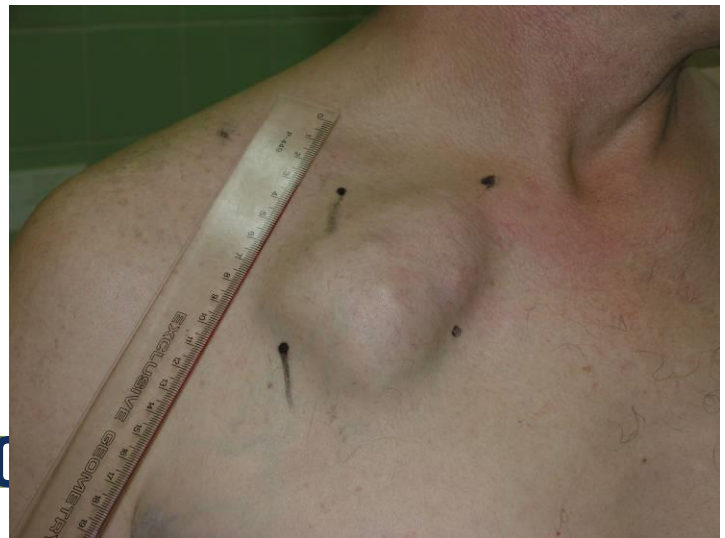


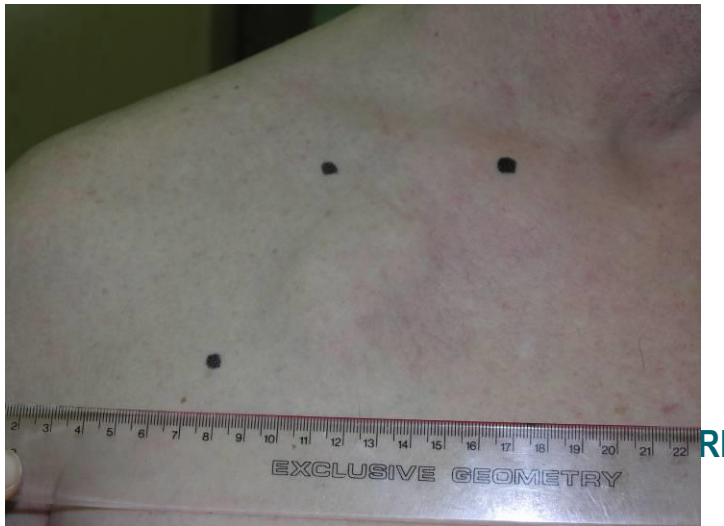

EXCLUSIVE GEOMETRY

FS-DFSP Multiple metastases to subcutaneous tissue and thorax – PR – PR; PD after 1.5 years

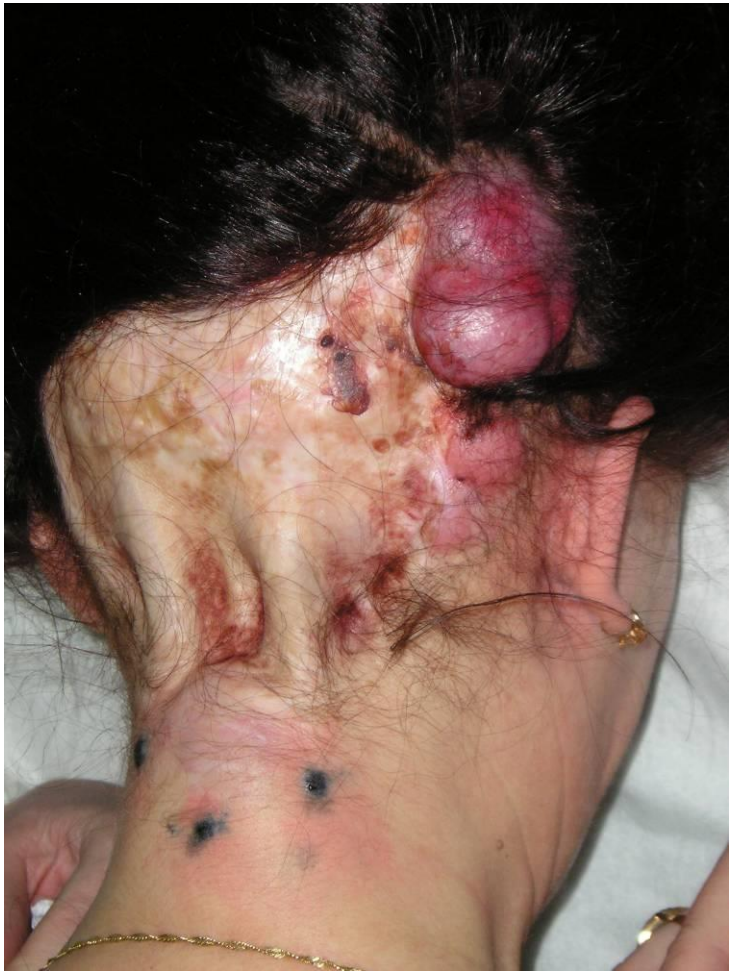


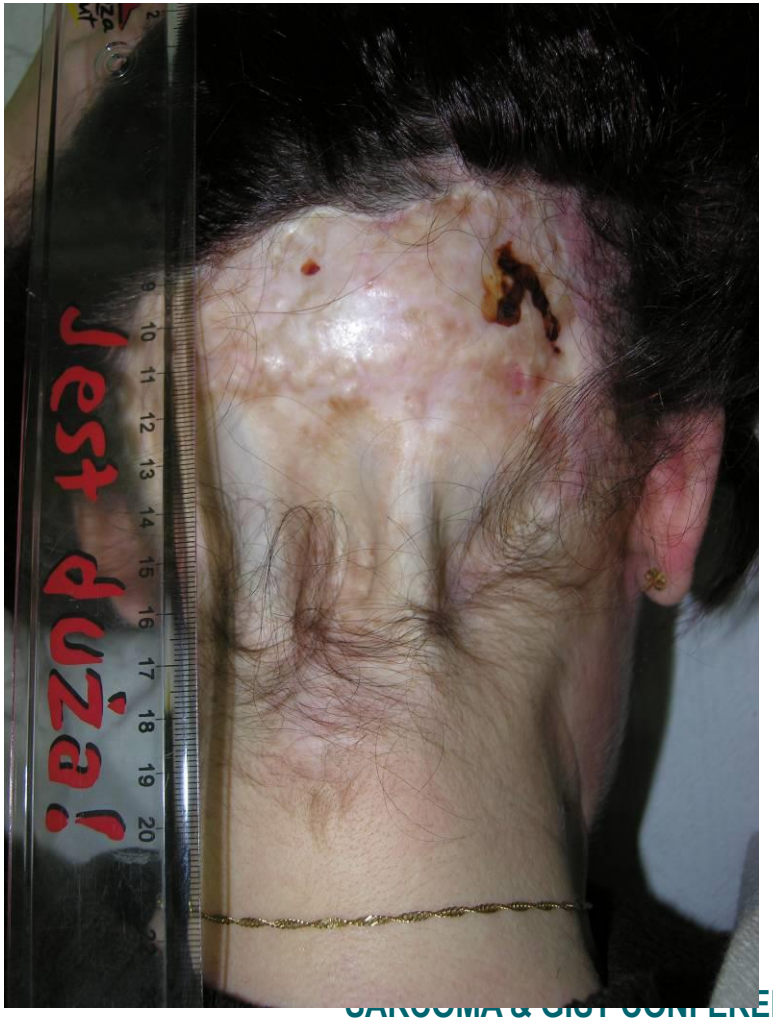






Multifocal recurrent tumor on the scalp, clinically CR after 5 years of imatinib therapy



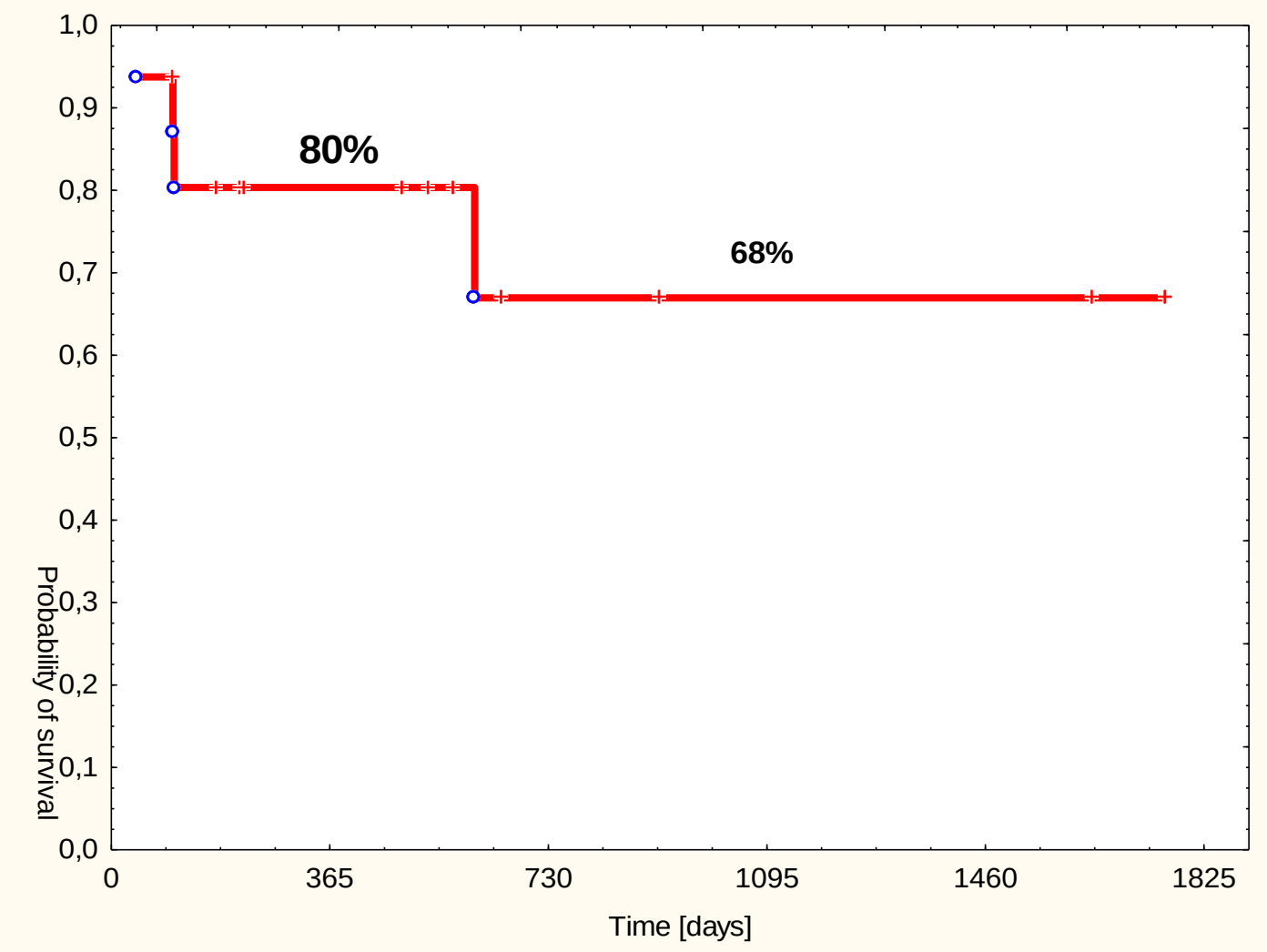


Major series of locally advanced/metastatic DFSP

Advanced (unresectable/metastatic) cases						
Author	No. of patients (FS-DFSP)	Best overall responses n (%)				PFS/TTP
		Partial/complete Responses	*Stable disease*	*Progressive disease*	*Not evaluable*	
McArthur *et al.* (2005)	10 (2)	9 (90%)	1 (10%)	0	0	Not reported
Rutkowski *et al.* (2010)	24 (9)	11 (46)	6 (25)	4 (17)	3 (12)	Median TTP 1.7 years, 1-year PFS rate 60%
Rutkowski *et al.* (2011)	15 (7)	11 (73)	1 (7)	3 (20)	0	Median PFS – not reached; 3-year PFS 68%

Neoadjuvant therapy					
Author	No. of patients (FS-DFSP)	Best overall responses n (%)			The duration of neoadjuvant therapy and imatinib dose PFS/TTP
		Partial/complete responses	*Stable disease*	*Progressive disease*	
Kerob *et al.* (2010)	25 (2)	9 (36%)	na	na	2 months (600 mg daily)
Ugurel *et al.* (2014)	16 (14 evaluable)	8 (57)	5 (36)	1 (7)	Median treatment duration 3.1 months (600 mg daily)

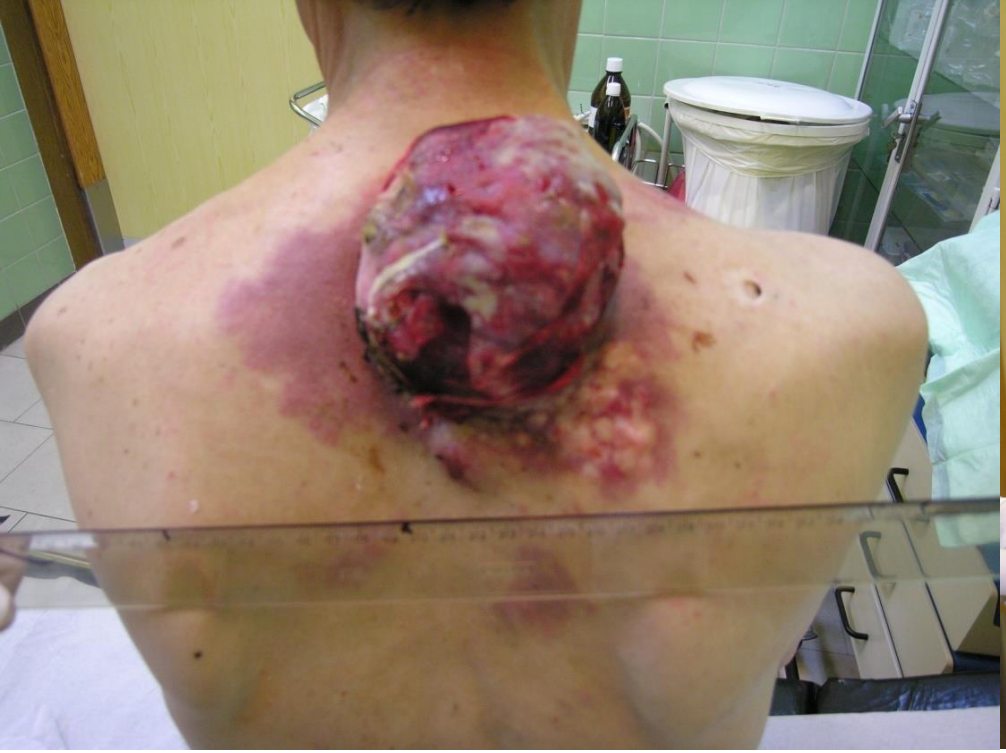
Progression-free survival

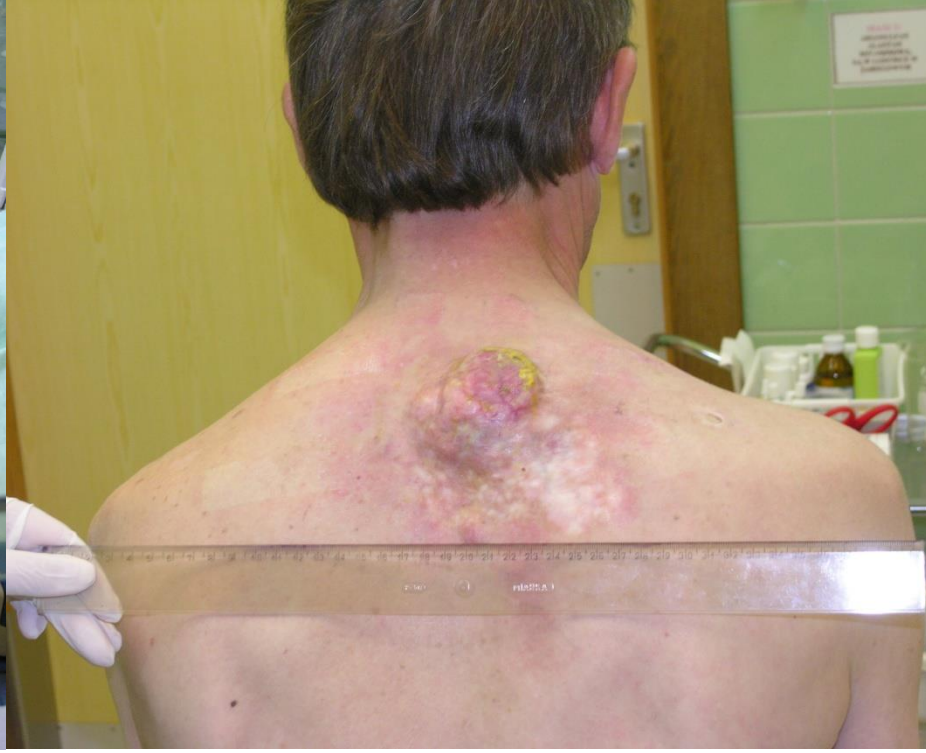


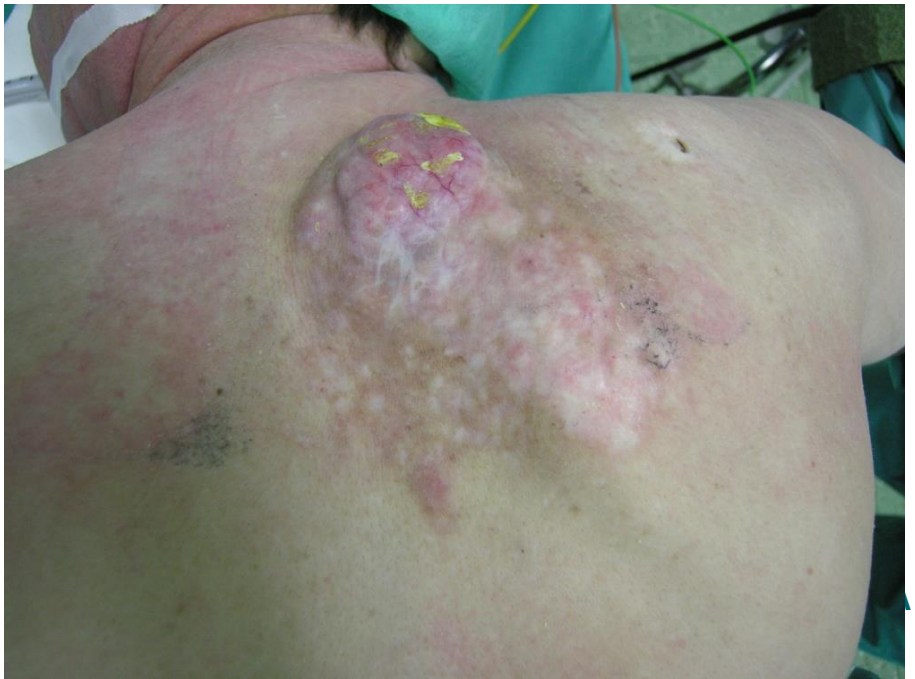
Treatment of advanced dermatofibrosarcoma protuberans with imatinib mesylate with or without surgical resection

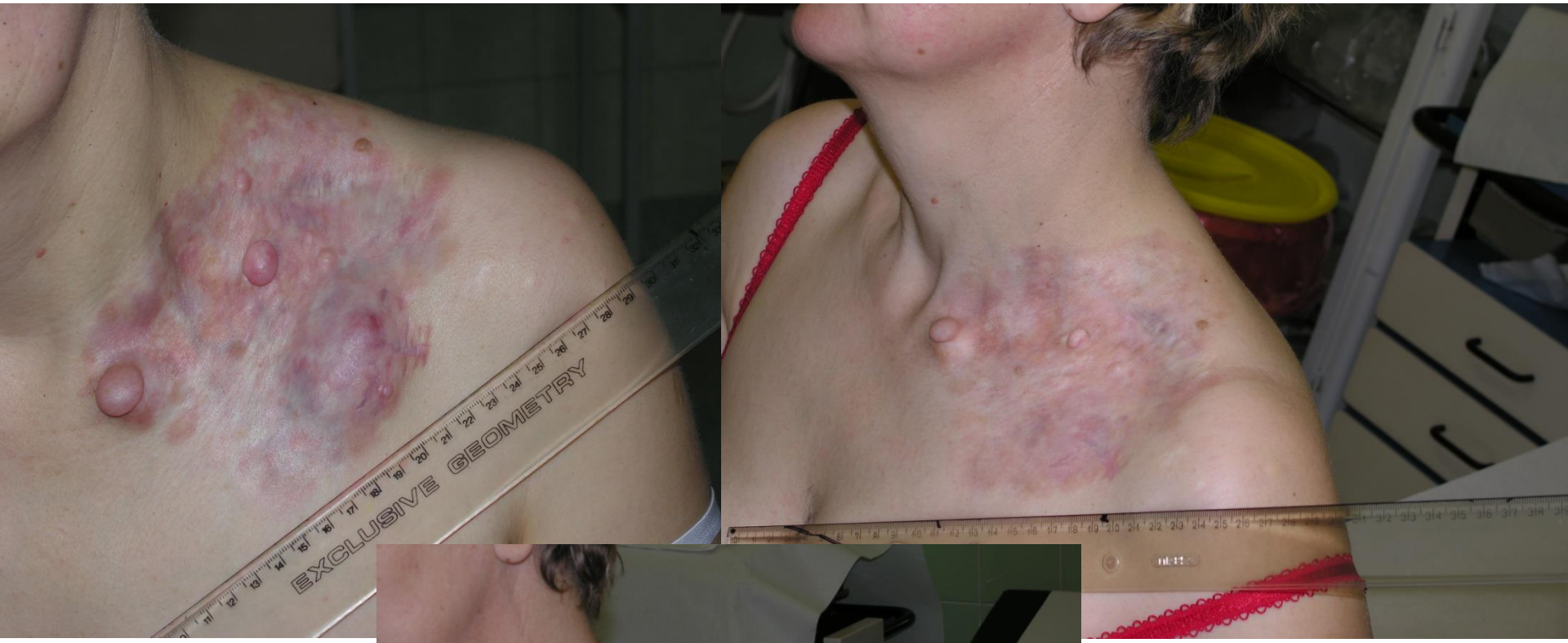
P Rutkowski,[†,*] M Dębiec-Rychter,[‡] ZI Nowecki,[†] W Michej,[§] M Symonides,[¶] K Ptaszynski,[§] W Ruka[†]

JEADV 2010

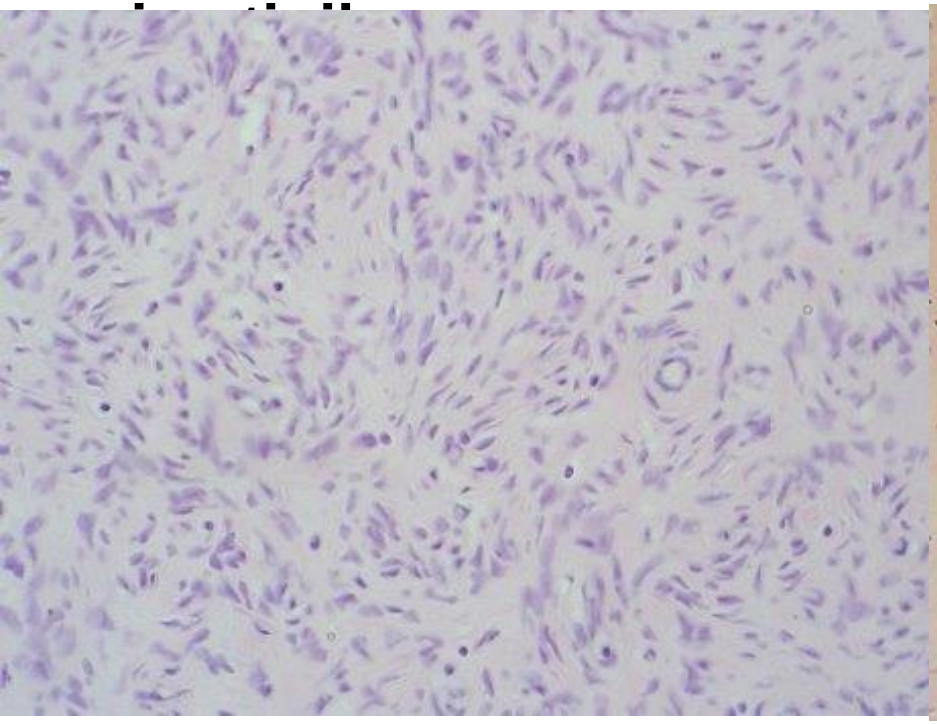


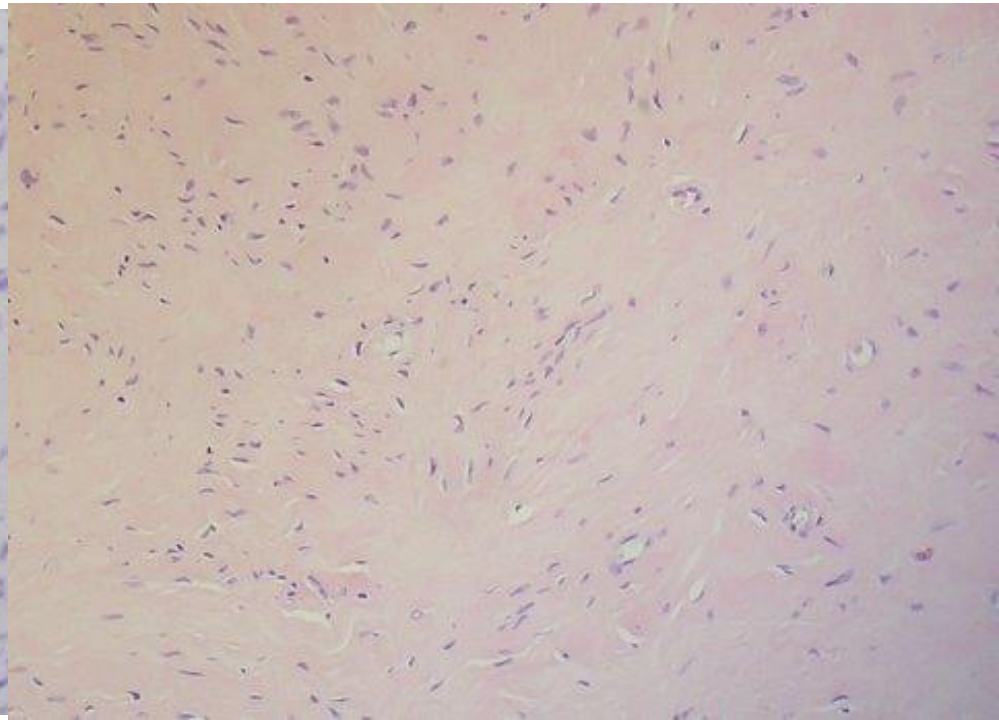


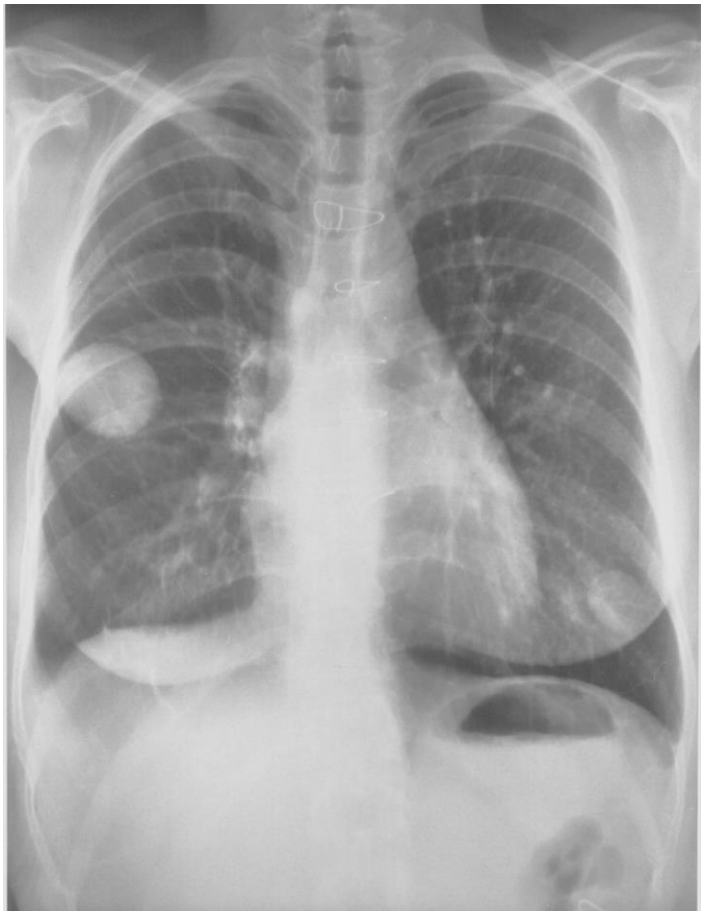



EXCLUSIVE GEOMETRY

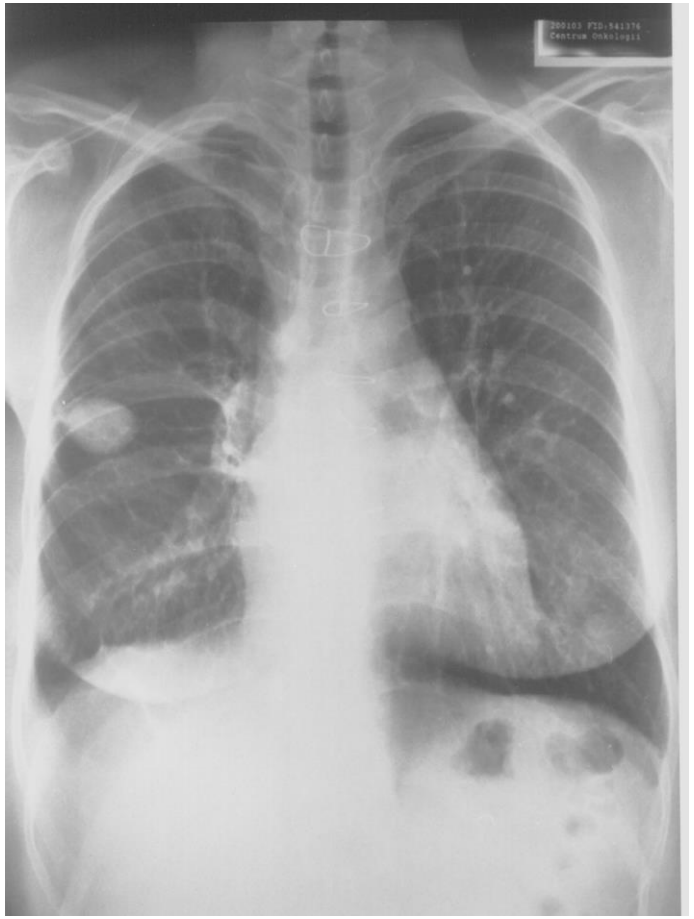
Pathological images before and after removal of residual disease after partial response to therapy with





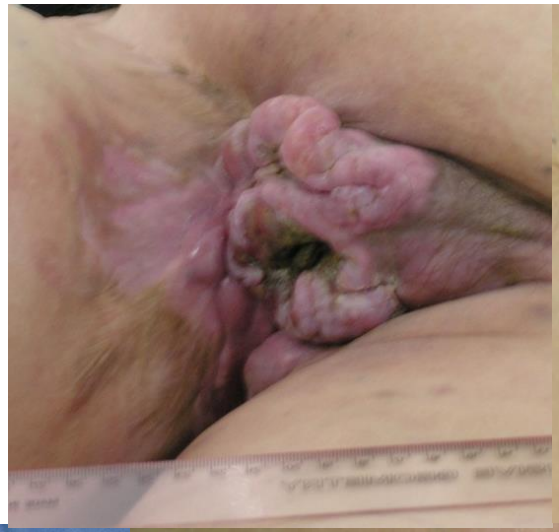


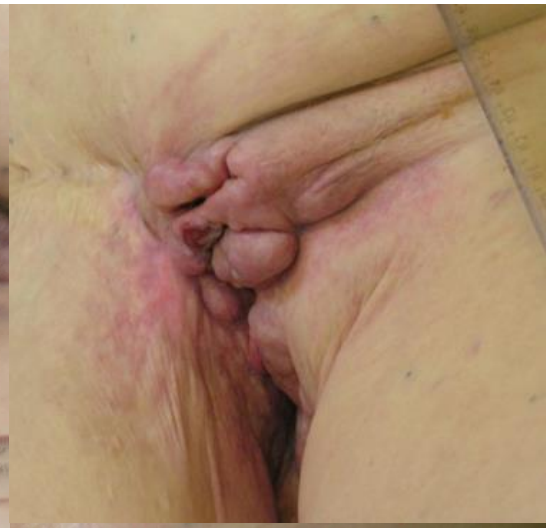
0 weeks

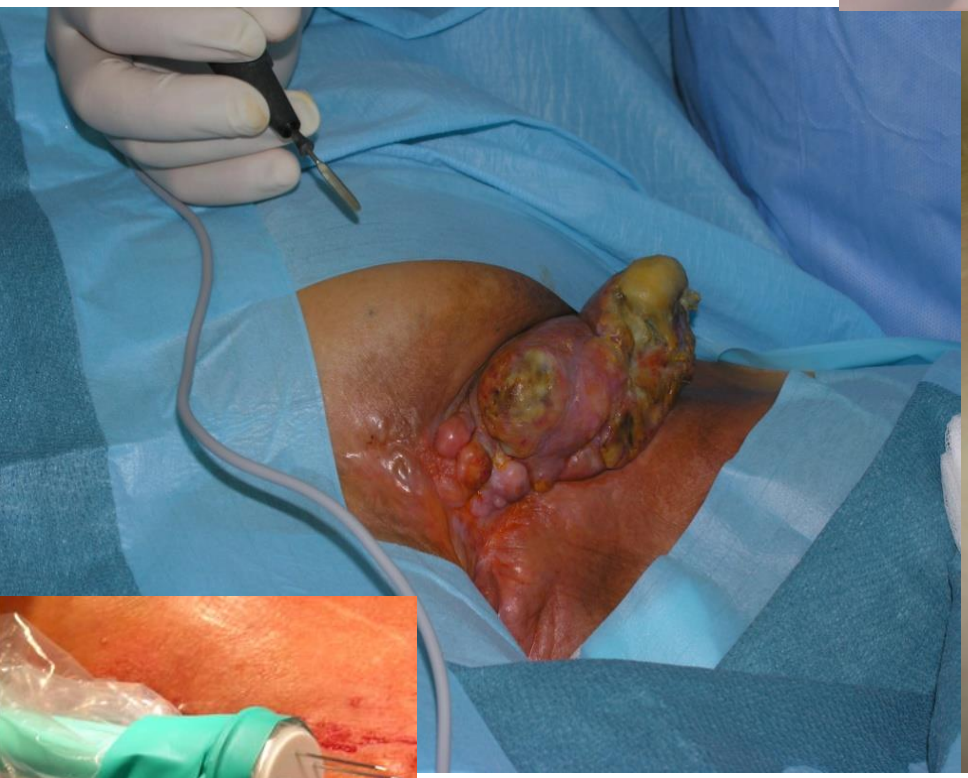


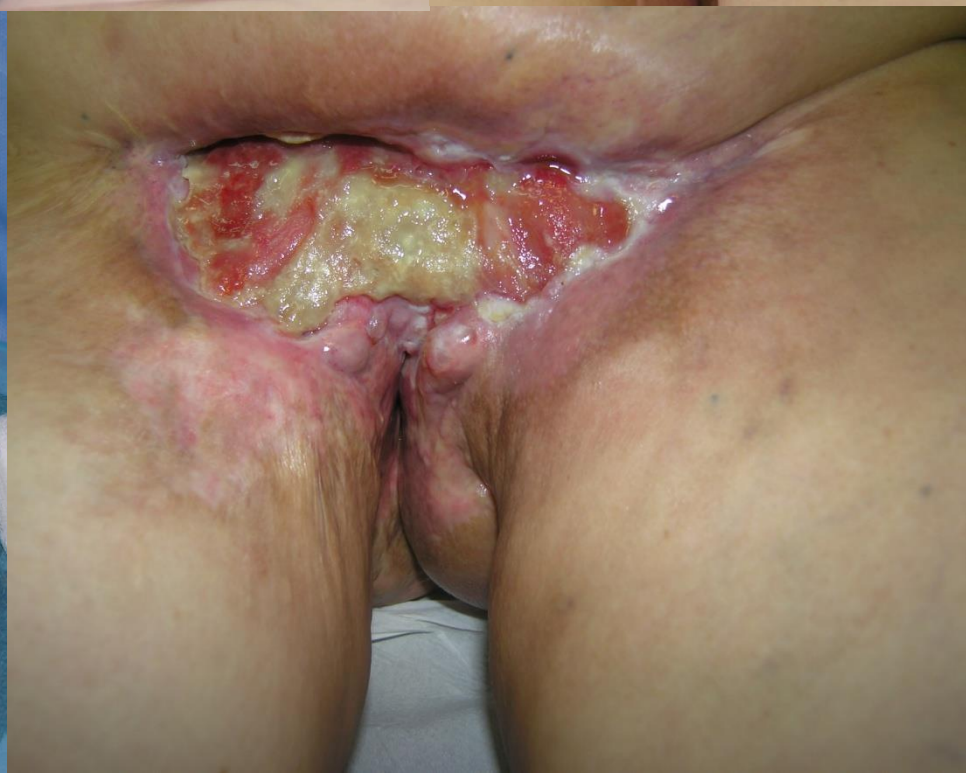
+ 5 weeks

CASE









Progression after imatinib

Dermatofibrosarcoma protuberans (DFSP) successfully treated with sorafenib: case report

Francois G Kamar[1*], Victor F Kairouz[2] and Alain N Sabri[3]

Kamar *et al. Clinical Sarcoma Research* 2013, **3**:5

Abstract

DFSP is a locally invasive, slow-growing tumor of the subcutaneous tissue that rarely metastasizes but recurs frequently after surgical excision. We report herein a case of highly recurrent, locally invasive DFSP that failed both postoperative radiation therapy and complete trial of Imatinib, but was successfully treated with Sorafenib, which showed unprecedented response.

Genetic Aberrations in Imatinib-Resistant Dermatofibrosarcoma Protuberans Revealed by Whole Genome Sequencing

Jung Yong Hong[1,9], Xiao Liu[2,4,9], Mao Mao[3], Miao Li[2], Dong Il Choi[5], Shin Woo Kang[6], Jeeyun Lee[1]*, Yoon La Choi[7]

identified during imatinib treatment. Of note, we identified newly emerged 8 non-synonymous somatic mutations of the genes (*ACAP2*, *CARD10*, *KIAA0556*, *PAAQR7*, *PPP1R39*, *SAFB2*, *STARD9*, and *ZFYVE9*) in the imatinib-resistant tumor tissue. This

Dermatofibrosarcoma protuberans-derived fibrosarcoma: clinical history, biological profile and sensitivity to imatinib

Int. J. Cancer: **129**, 1761–1772 (2011)

Silvia Stacchiotti[1], Florence Pedeutour[2], Tiziana Negri[3], Elena Conca[3], Andrea Marrari[1], Elena Palassini[1], Paola Collini[3], Fred

In conclusion, DFSP-derived FS maintains the fusion-gene, being sensitive to imatinib. However, responses are short-lasting. Secondary resistance to imatinib is not related to PDGFRB.

Sunitinib for patients with locally advanced or distantly metastatic dermatofibrosarcoma protuberans but resistant to imatinib

Yan Fu, Huanrong Kang, Hui Zhao, Jia Hu, Huanhuan Zhang, Xiaosong Li, Nan Du, Yitao Huang

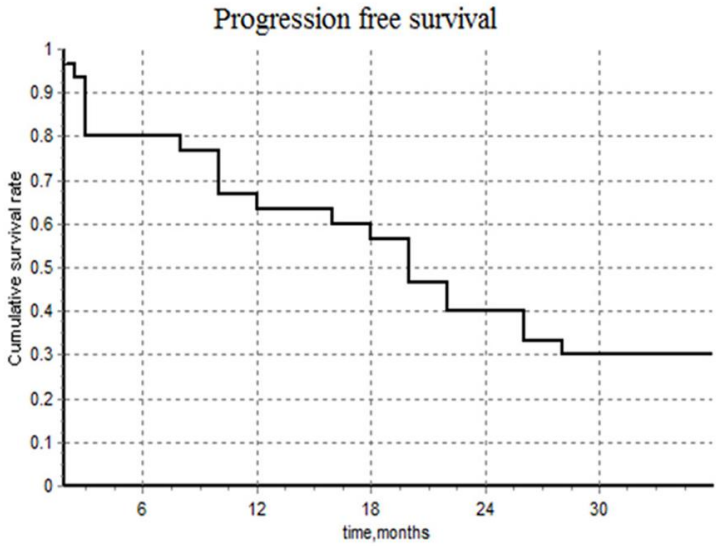


Figure 3. Progression free survival of metastatic DFSP patients treated with Sunitinib after Imatinib resistance.

Table 2. Antitumor response of advanced DFSP patients after Sunitinib treatment

	Patients (n=30)	PFS (median, months)	OS (median, months)
CR (n, %)	2 (6.7)	22	NA
PR (n, %)	10 (33.3)	20	NA
SD (n, %)	12 (40.0)	18	28
PD (n, %)	6 (20.0)	3	11

Neoadjuvant imatinib

Imatinib Mesylate as a Preoperative Therapy in Dermatofibrosarcoma: Results of a Multicenter Phase II Study on 25 Patients

Delphine Kérob[1], Raphael Porcher[2], Olivier Vérola[3], Stephane Dalle[9], Eve Maubec[10], François Aubin[11], Michel D'Incan[12], Isaak Bodokh[13], Serge Boulinguez[14], Isabelle Madelaine-Chambrin[4], Anne Mathieu-Boue[15], Jean-Marie Servant[5], Eric de Kerviler[6], Anne Janin[3], Fabien Calvo[7,8], Florence Pedeutour[16], and Celeste Lebbe[1]

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

Selma Ugurel, Thomas Mentzel, Jochen Utikal, et al.

Clin Cancer Res 2014;20:499-510. Published OnlineFirst October 30, 2013.

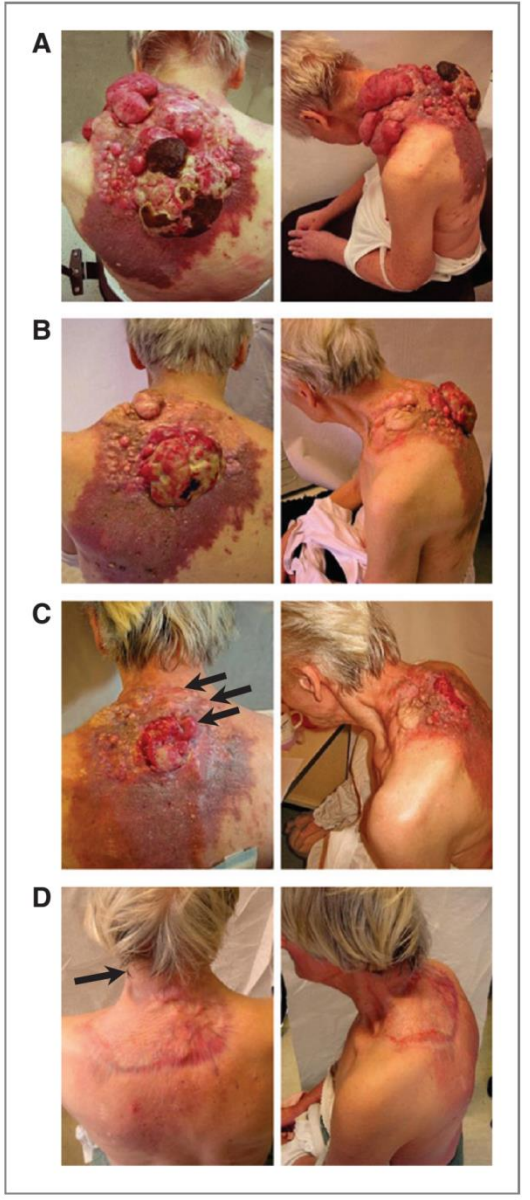


Figure 1. Clinical presentation of patient ADO-06 (A) before treatment; B, at 3 months of imatinib showing marked tumor shrinkage (PR); C, at 6 months of imatinib showing ongoing tumor shrinkage, but also secondary resistance with outgrowth of new tumor lesions (arrows); D, at 13.5 months after onset 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.

CONCLUSIONS

- Targeted therapy with imatinib has profound antitumor effects in advanced DFSP harboring t(17;22), with an objective response rate exceeding 50%, and that imatinib is also active in fibrosarcomatous DFSP. The activity of imatinib is limited in time and no effective options after progression exist. Mechanisms of imatinib resistance are not well understood.
- Although rarely DFSP is present as inoperable or metastatic, imatinib mesylate has become a gold standard treatment in such cases.
- In some cases imatinib therapy leads to resectability of tumors and to diminishing possible disfiguring.
- Responses did not appear to differ between patients taking 400 mg daily *versus* 400 mg bid.

CONCLUSIONS

Current therapy of DFSP with t(17;22) translocation should be definitively conducted by multidisciplinary team, including oncological surgeon, to consider the use of imatinib mesylate as initial therapy to decrease possible extent of surgery and related morbidity.

Cancer Center – Institute, Warsaw, Poland

Thank you for your attention!