

Dermatofibrosarcoma protuberans

Piotr Rutkowski

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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.

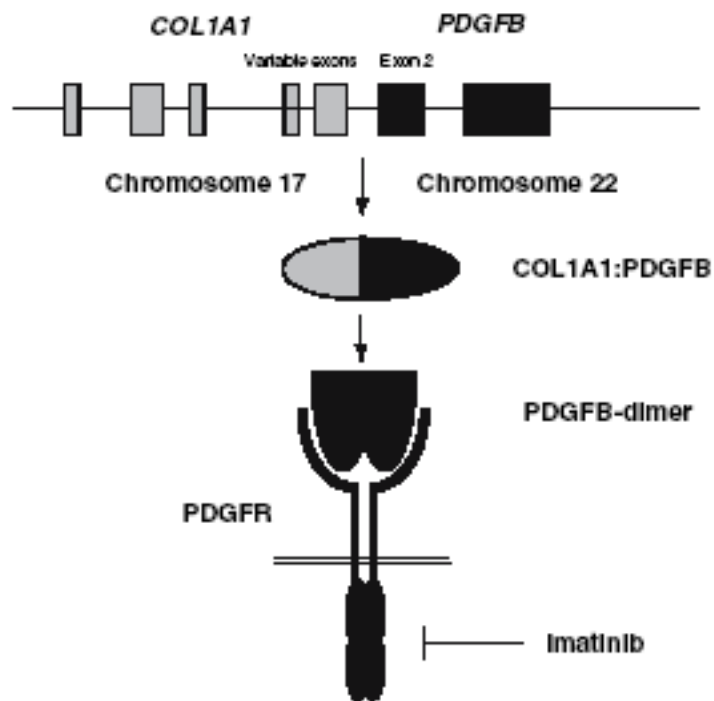
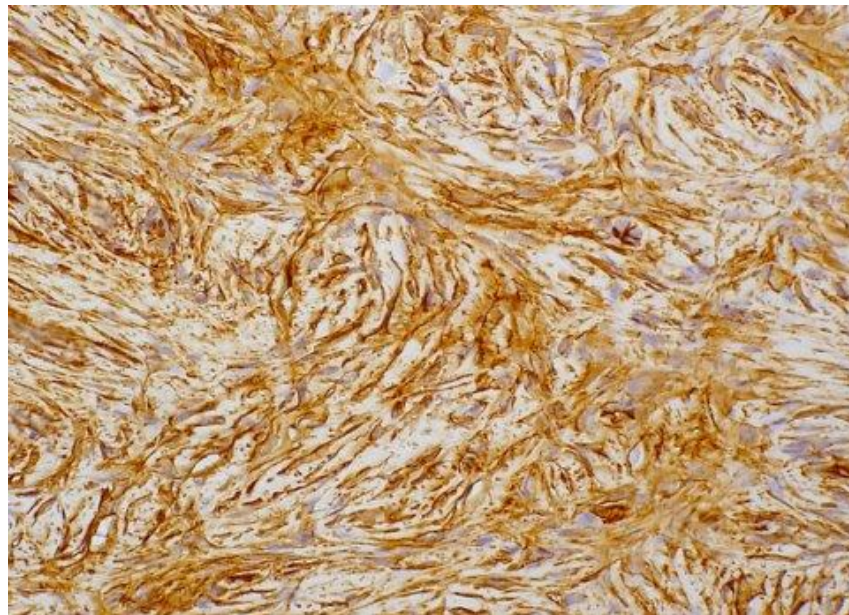


FIG. 1. The molecular biology of dermatofibrosarcoma protuberans (DFSP) is characterized by fusion of the *COL1A1* and *PDGFB* (platelet-derived growth factor B chain) genes as a result of the chromosomal translocation t(17;22). Constitutively expressed

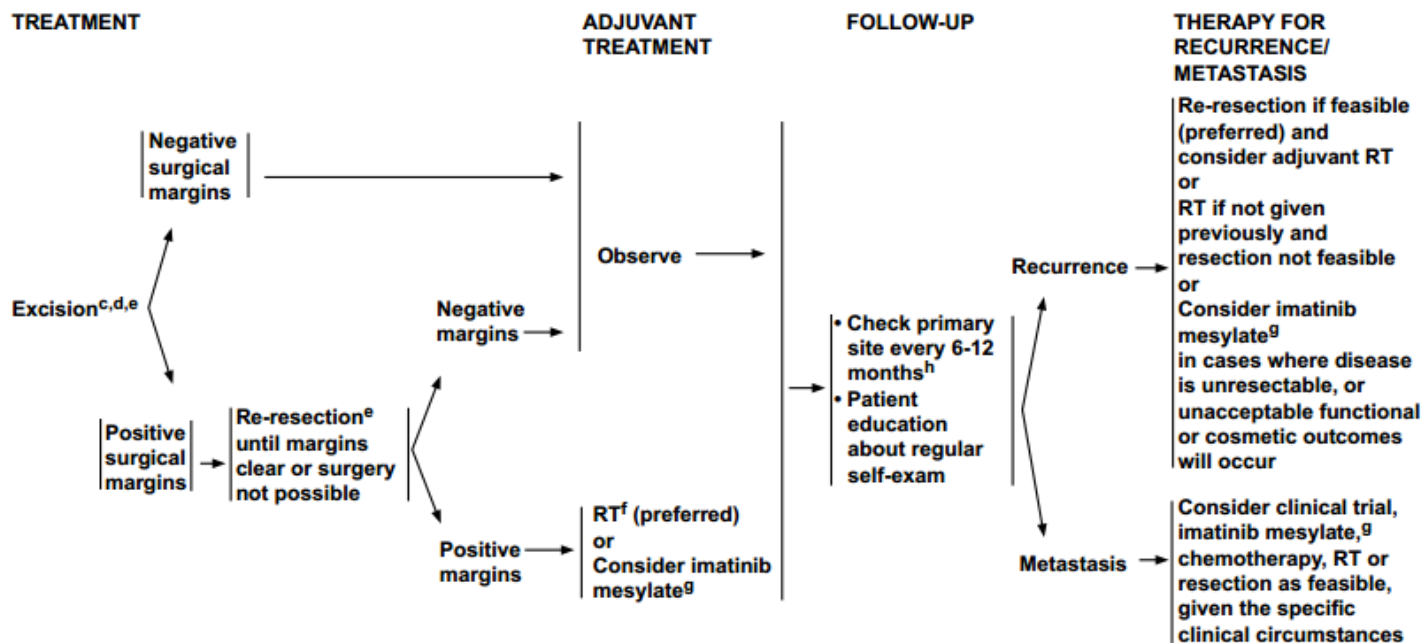


Grant McArthur,

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)





^cIf fibrosarcomatous changes/malignant transformations are noted see the [NCCN Guidelines for Soft Tissue Sarcoma](#). Multidisciplinary consultation is recommended for other high-risk features.

^dThe 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 \(DFSP-B\)](#).

^eWide undermining is discouraged due to the difficulty interpreting subsequent re-excisions pathologically and to prevent possible tumor seeding if margins are not histologically clear.

^f5,000-6,000 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.

^gTumors 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.

^hRadiologic imaging may be helpful to detect early recurrence in patients with high-risk lesions or who have had more extensive surgery.

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?

Jeffrey M. Farma, MD¹, John B. Ammori, MD², Jonathan S. Zager, MD³, Suroosh S. Marzban, BS³, Marilyn M. Bui, MD, PhD^{4,5}, Christopher K. Bichakjian, MD⁶, Timothy M. Johnson, MD⁶, Lori Lowe, MD⁷, Michael S. Sabel, MD⁸, Sandra L. Wong, MD⁸, G. Douglas Letson, MD⁵, Jane L. Messina, MD^{3,4,9}, Vincent M. Cimmino, MD², and Vernon K. Sondak, MD³

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



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

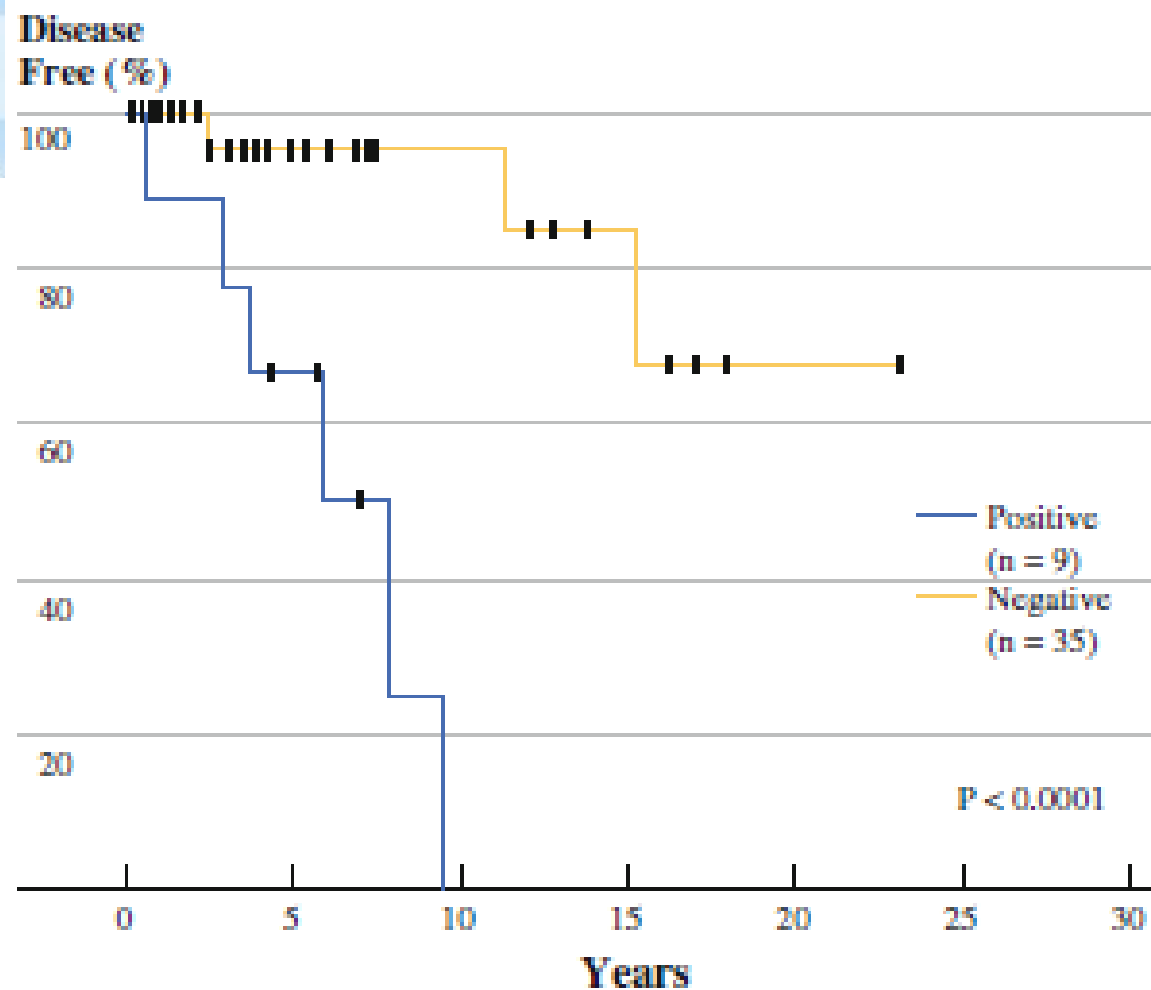
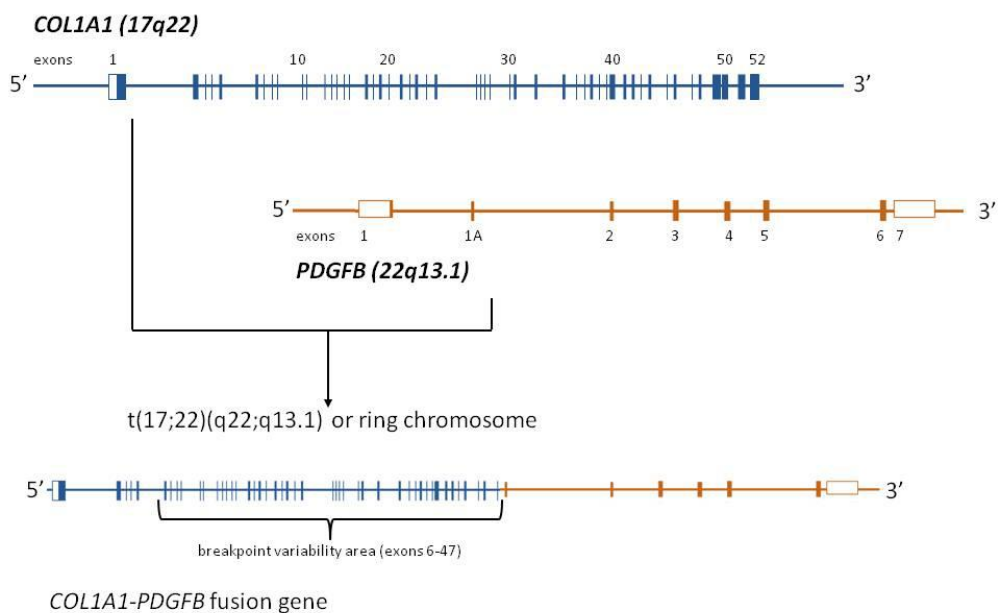


FIG. 3 Kaplan-Meier curve of disease-free survival in patients presenting with locally recurrent DFSP stratified by margin status

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

Ann Surg Oncol (2011) 18:328–336

Ryan C. Fields, MD¹, Meera Hameed, MD², Li-Xuan Qin, PhD³, Nicole Moraco, MA¹, Xiaoyu Jia, MS³, Robert G. Maki, MD, PhD⁴, Samuel Singer, MD¹, and Murray F. Brennan, MD¹



A

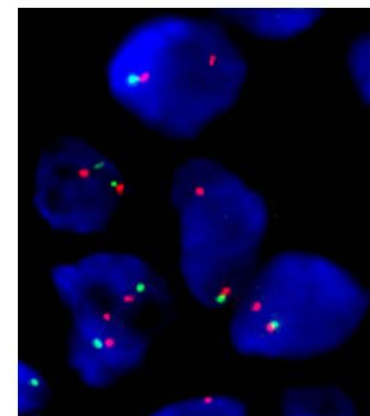
normal chromosome 22



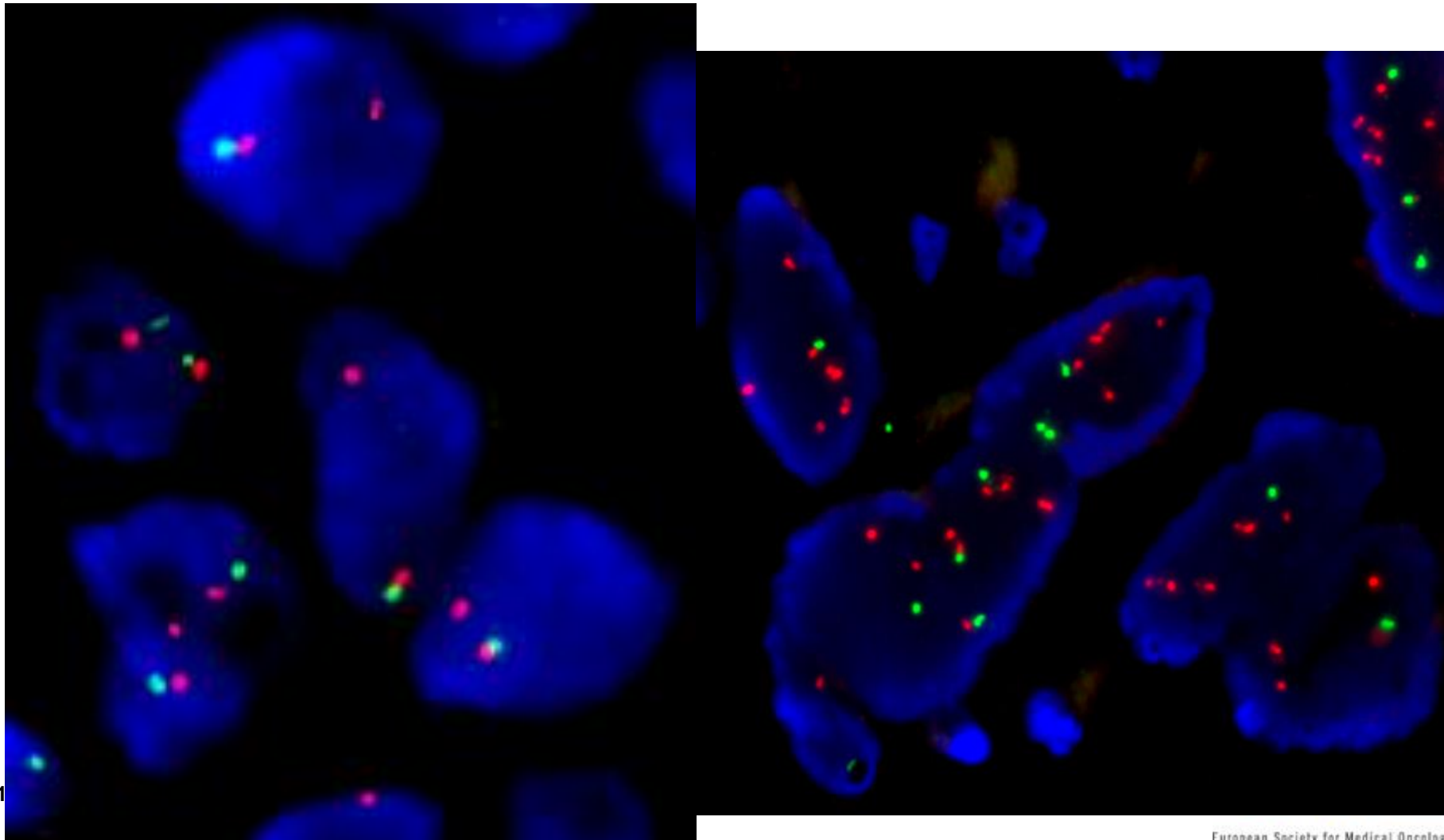
derivative chromosome 17

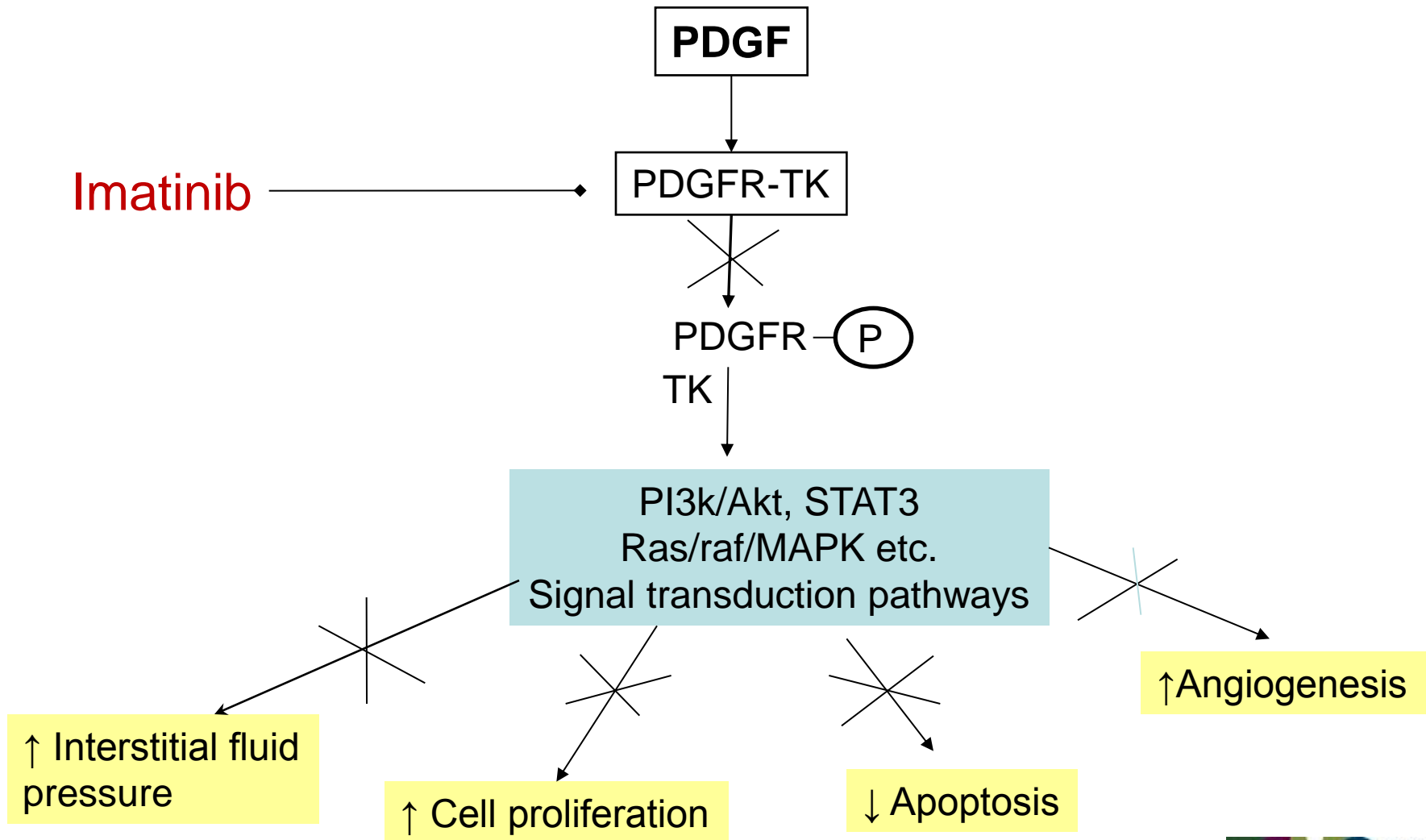


B

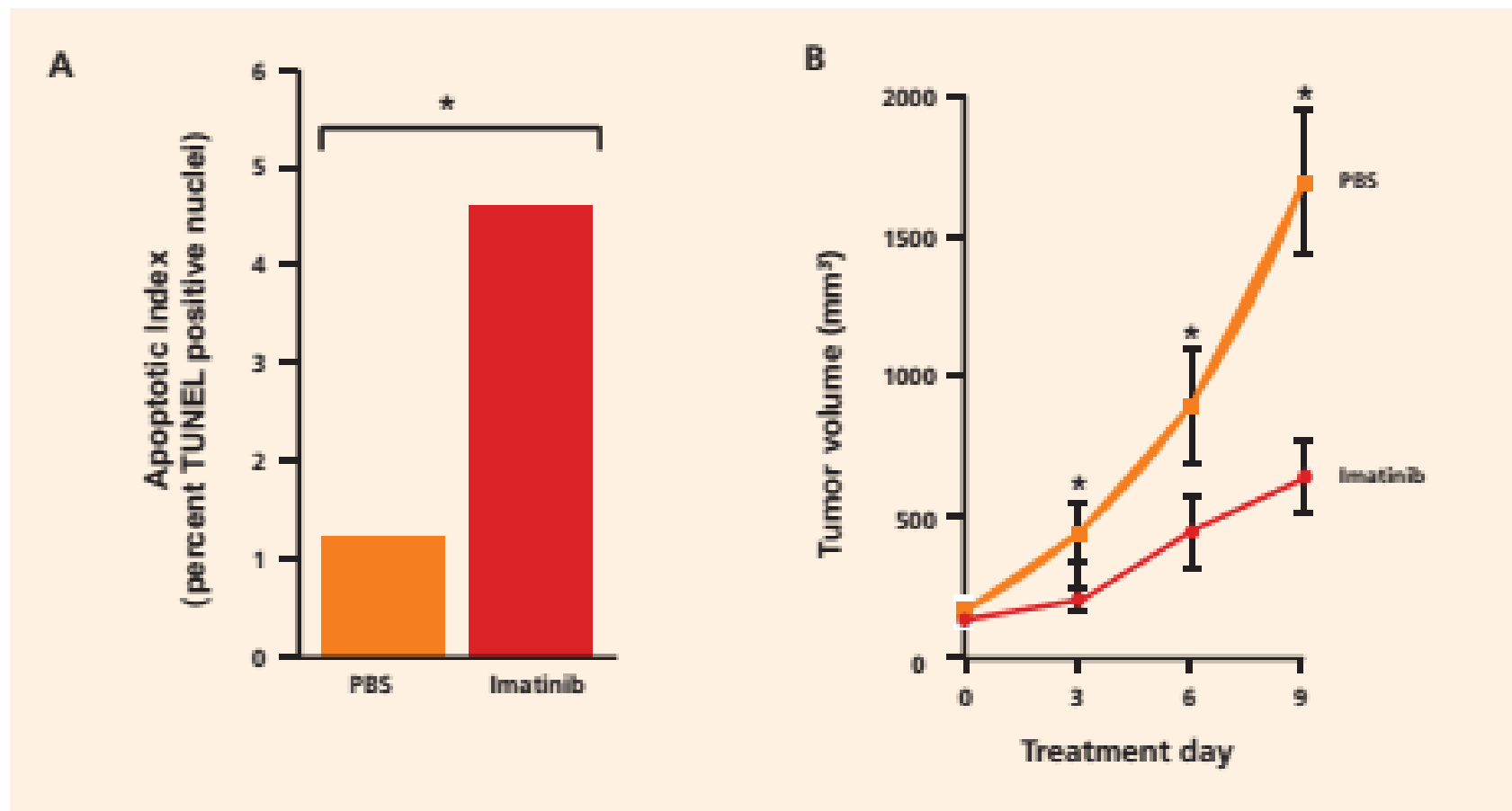


PDGFB split-apart FISH in interphase cells from DFSP, showing *PDGFB* rearrangement, evidenced by one copy (red probe) of the telomeric *PDGFB* signal in tumor cells (by courtesy of Prof. M. Debiec-Rychter)





Imatinib effect in vivo



A. 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 Sjöblom T, et al. *Cancer Res.* 2001;61:5778-5783.²⁴

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, metastatic, 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, Włodzimierz Ruka, Brian P. Rubin, Maria Debiec-Rychter, Alexander Lazar, Hans Gelderblom, Raf Sciort, Dolores Lopez-Terrada, Peter Hohenberger, Allan T. van Oosterom, and Scott M. Schuetz

VOLUME 28 • NUMBER 10 • APRIL 1 2010

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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.



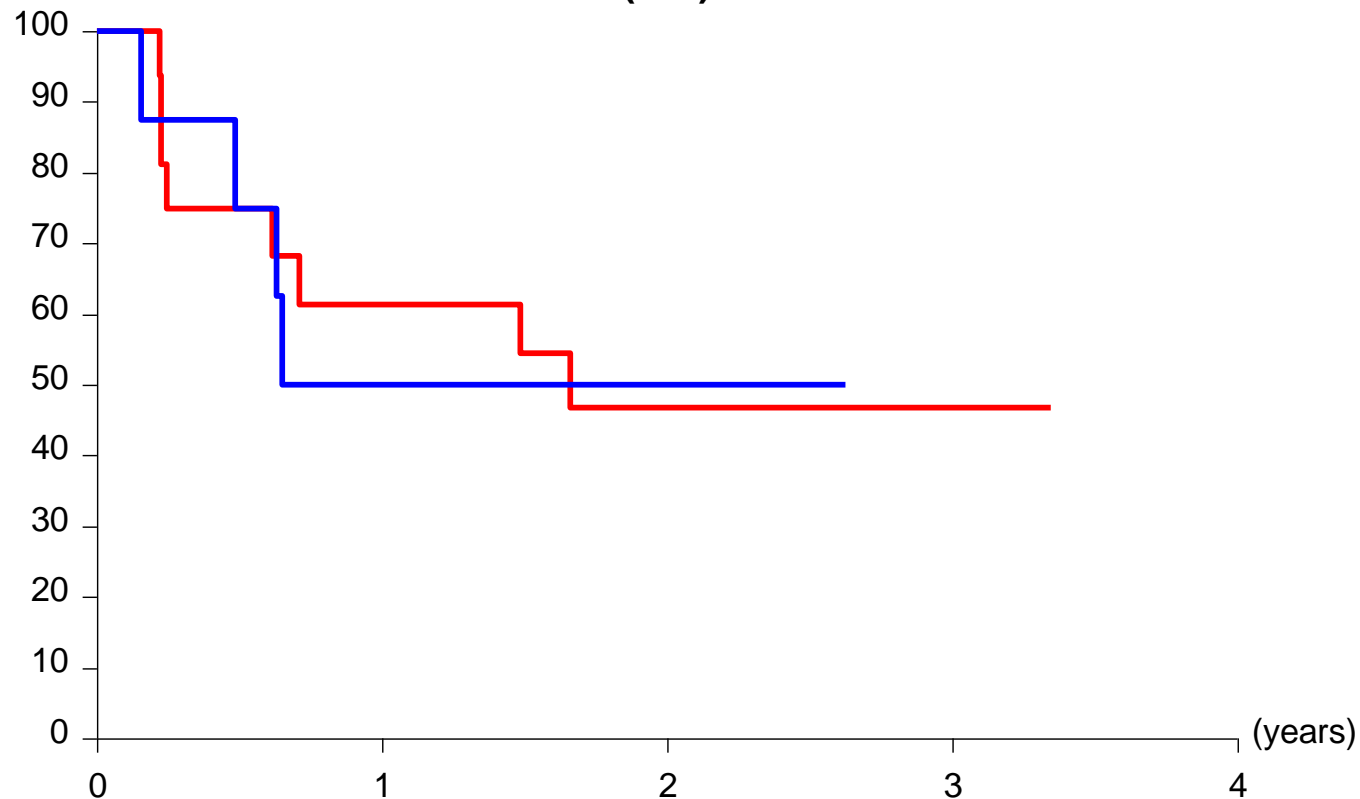
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Time to progression (ITT)



O	N
8	16

Number of patients at risk :

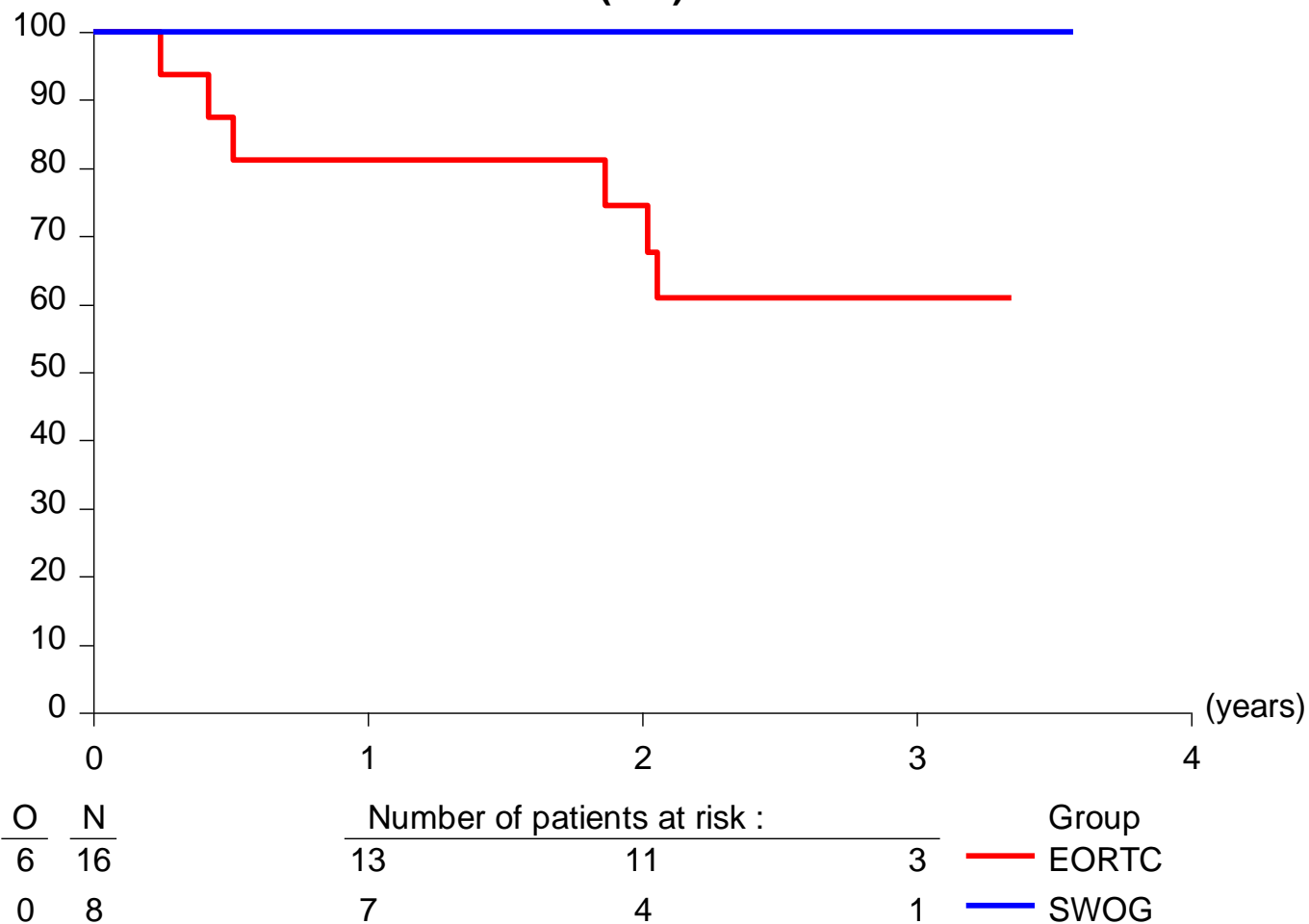
Time (years)	0	1	2	3
9	6	3	0	0
3	2	0	0	0

Group
— EORTC
— SWOG



European Society for Medical Oncology

Overall survival (ITT)

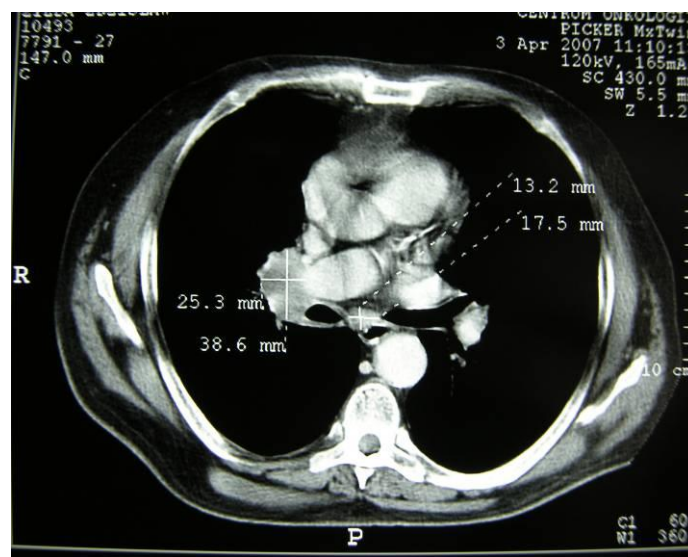






18-19 February 2014, Milan, Italy

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



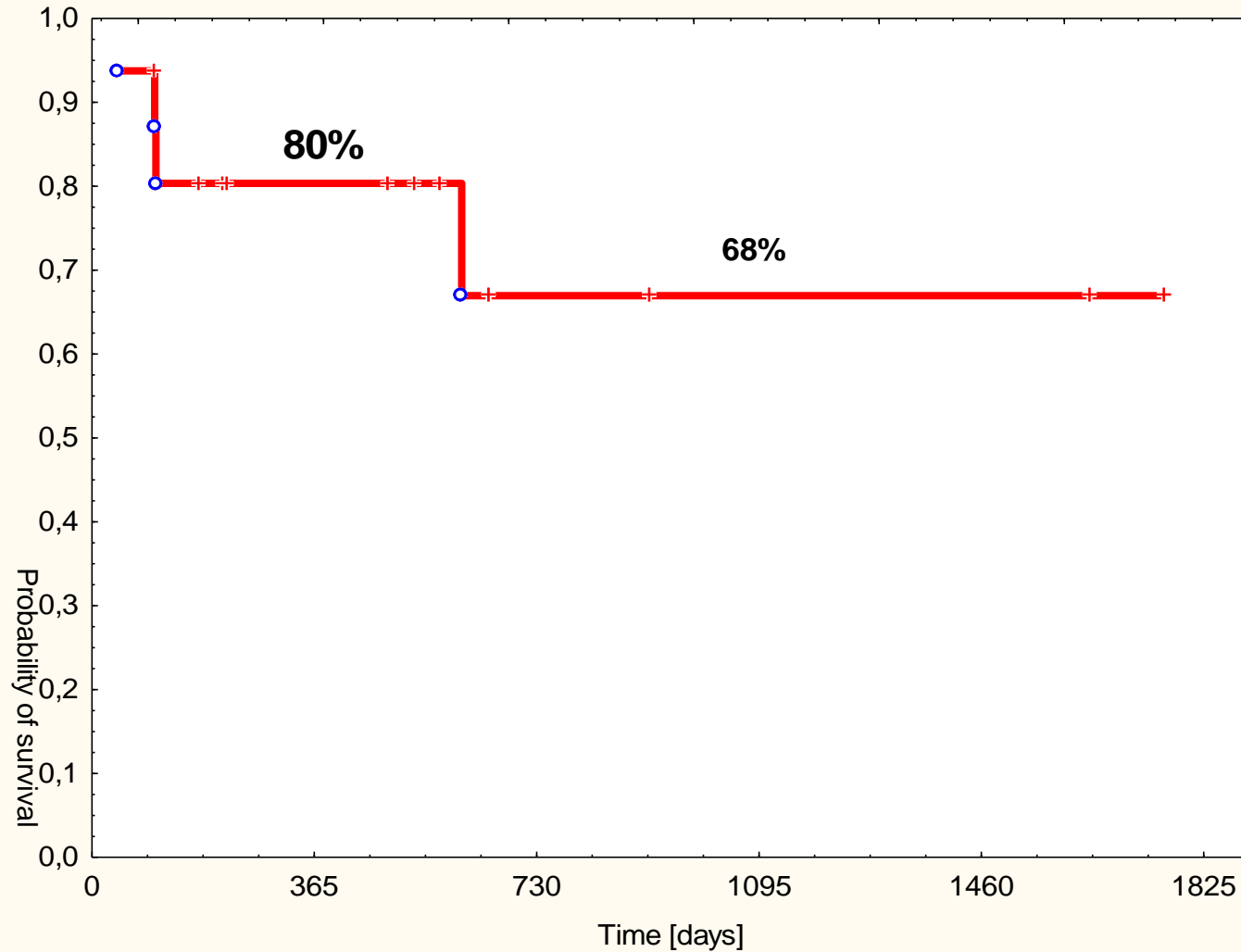
Multifocal recurrent tumor on the scalp, clinically CR after 5 years of imatinib therapy



3 major series of locally advanced/metastatic DFSP

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

Progression-free survival



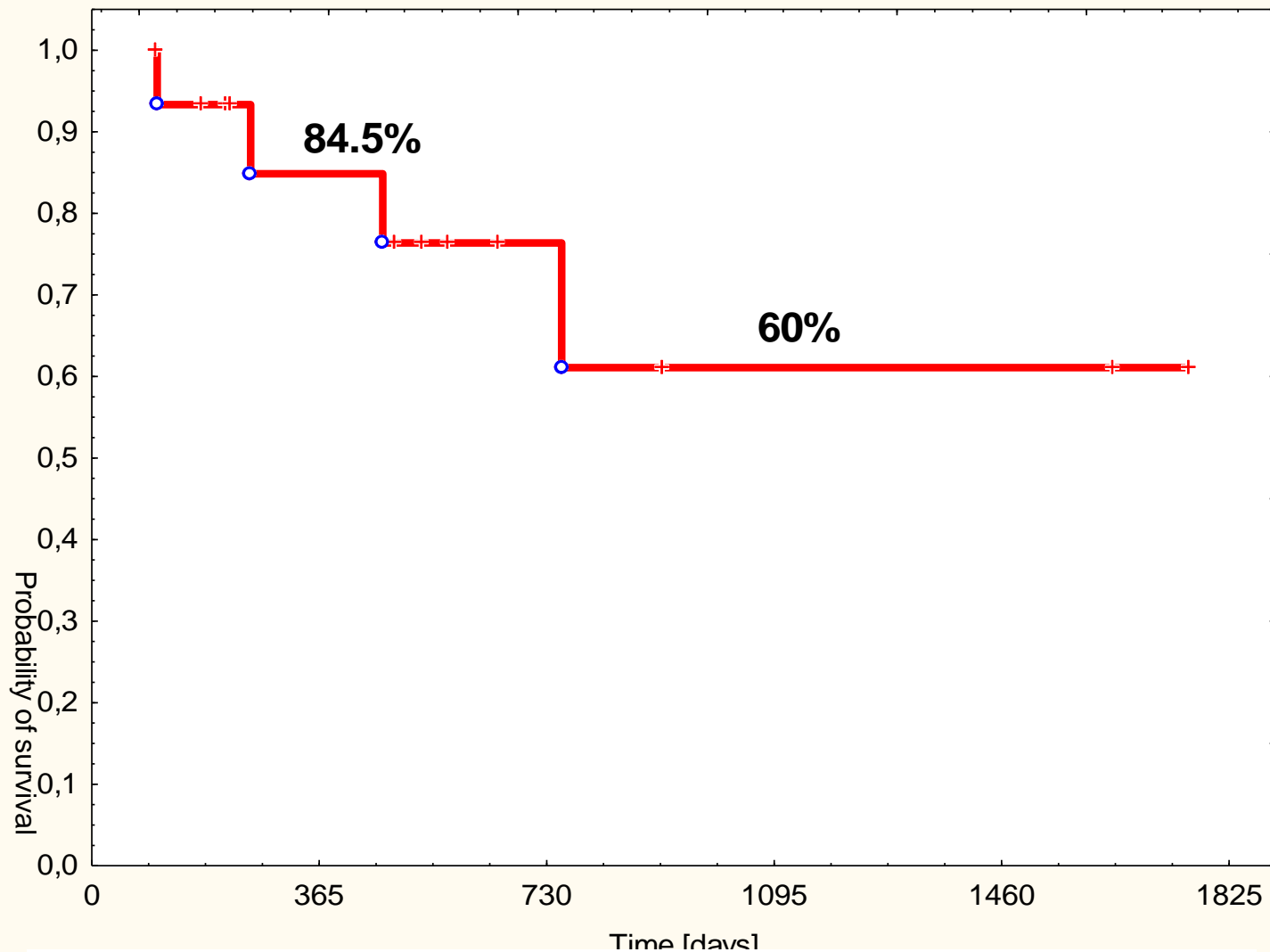
Treatment of advanced dermatofibrosarcoma protuberans with imatinib mesylate with or without surgical resection

18-19 F

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

JEADV 2010

Overall survival



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

18-19 Febr

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

JEADV 2010 n Society for Medical Oncology

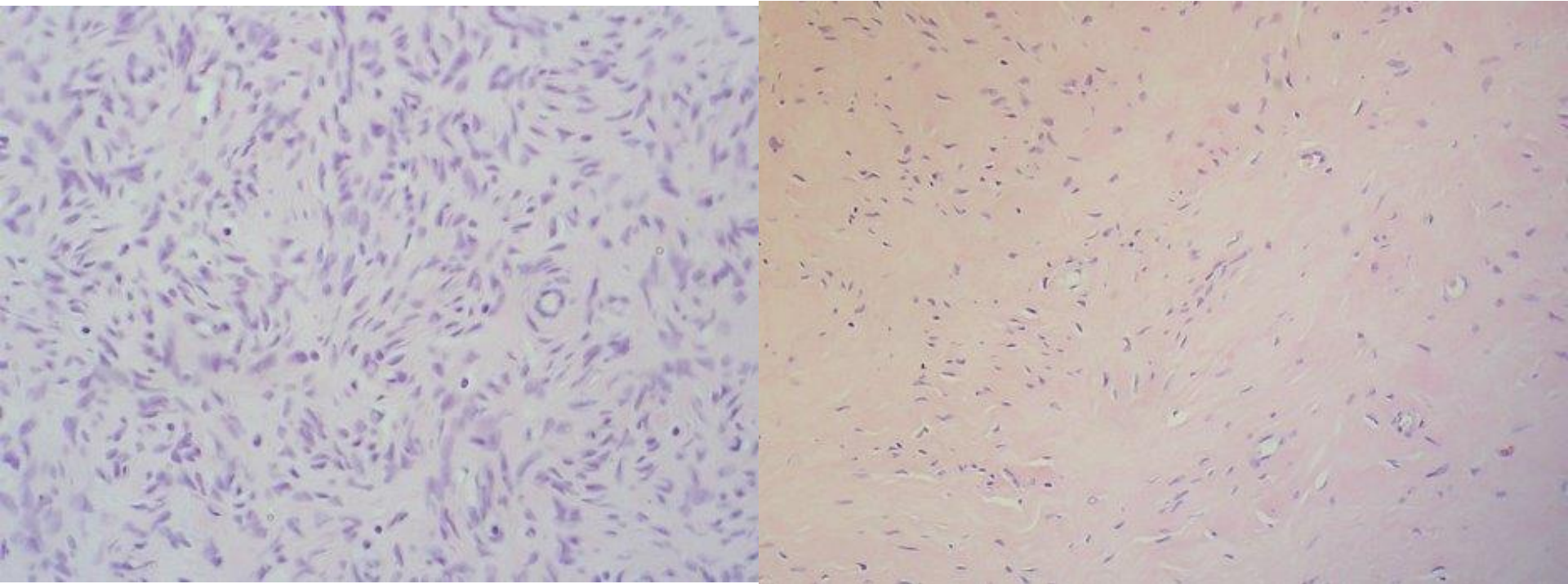


18-19 February 2014, Milan, Italy



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



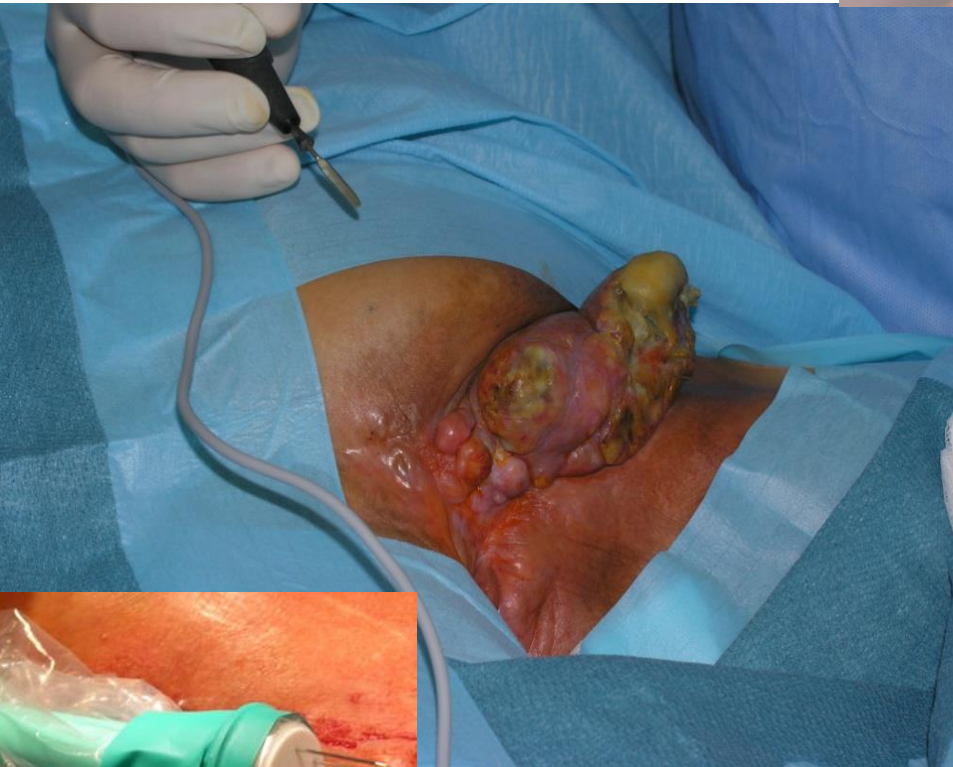


0 weeks



+ 5 weeks

CASE





Progression after imatinib

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

Francois G Kamar^{1*}, Victor F Kairouz² and Alain N Sabri³

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^{1,3}, Xiao Liu^{2,4,3}, Mao Mao³, Miao Li², Dong Il Choi⁵, Shin Woo Kang⁶, Jeeyun Lee^{1*},

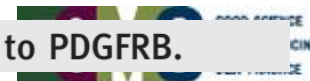
Yoon La Choi⁷ identified during imatinib treatment. Of note, we identified newly emerged 8 non-synonymous somatic mutations of the genes (ACAP2, CARD10, KIAA0556, PAAQR7, PPP1R39, SAFB2, STARD9, and ZFYVE9) in the imatinib-resistant tumor tissue. This

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

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

Silvia Stacchiotti¹, Florence Pedetour², Tiziana Negri³, Elena Conca³, Andrea Marrari¹, Elena Palassini¹, Paola Collini³,

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.



European Society for Medical Oncology

Neoadjuvant imatinib

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

Delphine Kérob¹, Raphael Porcher², Olivier Vérola³, Stephane Dalle⁹, Eve Maubec¹⁰, François Aubin¹¹, Michel D'Incan¹², Isaak Bodokh¹³, Serge Boulinguez¹⁴, Isabelle Madelaine-Chambrin⁴, Anne Mathieu-Boue¹⁵, Jean-Marie Servant⁵, Eric de Kerviler⁶, Anne Janin³, Fabien Calvo^{7,8}, Florence Pedeutour¹⁶, and Celeste Lebbe¹

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.

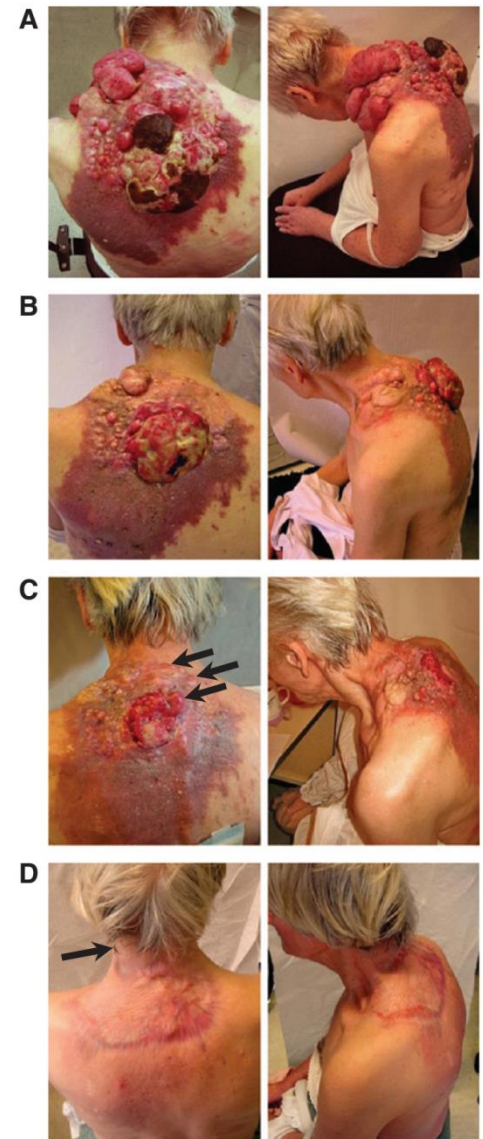


Figure 1. Clinical presentation of patient ADO-06 (A) before treatment; B, at 3 months of imatinib showing marked tumor shrinkage (PR); C, at 6 months of imatinib showing ongoing tumor shrinkage, but also secondary resistance with outgrowth of new tumor lesions (arrows); D, at 13.5 months after onset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

18-19 February 2014, Milan, Italy