9th SPAEN Annual Conference for Organizations
Representing Patients with Sarcomas, GIST or Desmoid-Tumours
1 – 3 February, 2019

Sarcoma Patients EuroNet

Can wait and see be the standard of care for initial approach to primary sporadic desmoid tumors? Preliminary data from an Italian Sarcoma Group prospective study

Colombo C, Lo Vullo S, Fiore M, Grignani G, Palesandro E, Boccone B, D'Ambrosio L, Bianco A, Collini P, Palassini E, Stacchiotti S, Paolo Dei Tos A, Casali P, Perrone F, Mariani, L, Gronchi A

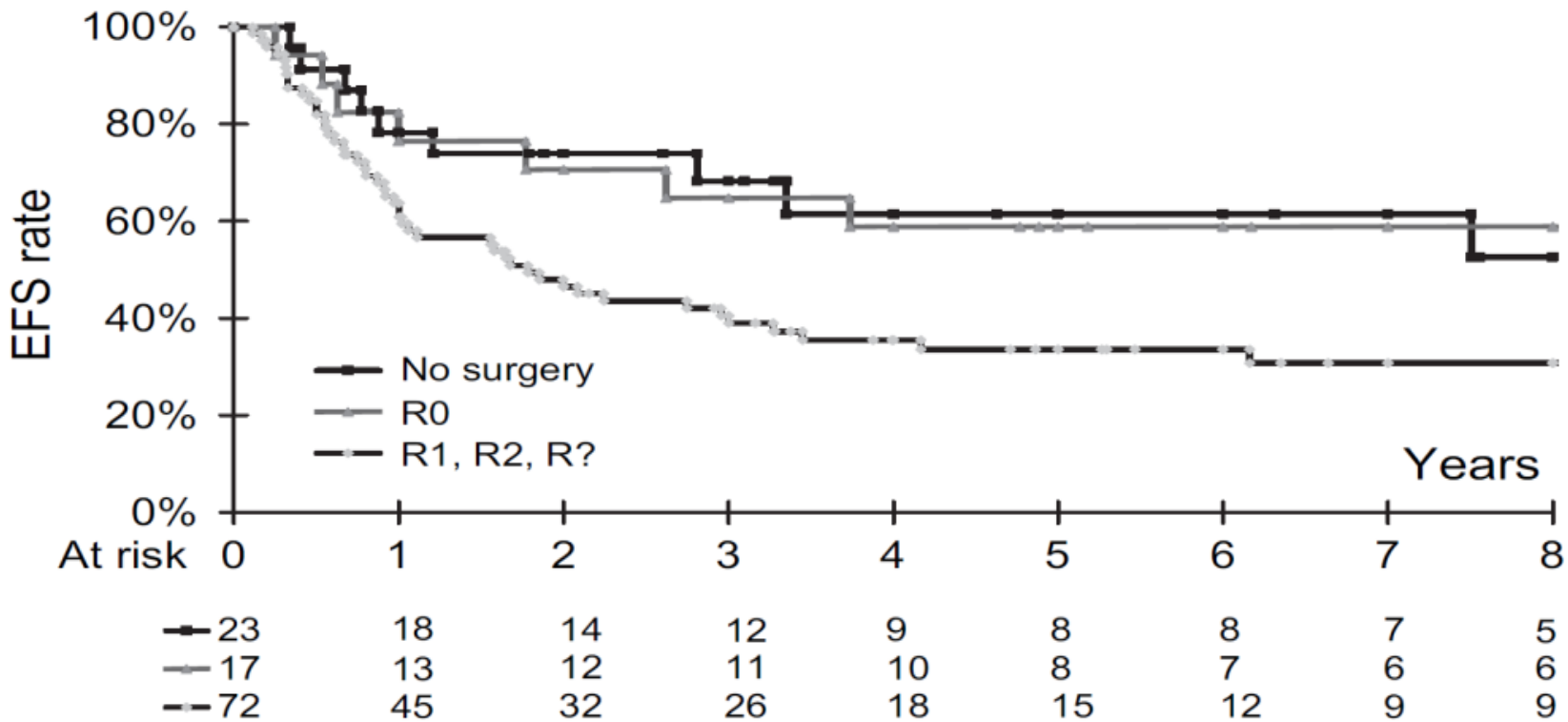
No disclosure

Background

Available online at www.sciencedirect.com
ScienceDirect
EJSO 34 (2008) 462–468
EJSO
the Journal of Cancer Surgery
www.ejso.com

Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients☆

S. Bonvalot [a,*], H. Eldweny [a], V. Haddad [b], F. Rimareix [a], G. Missenard [a], O. Oberlin [c], D. Vanel [d], P. Terrier [e], J.Y. Blay [f], A. Le Cesne [g], C. Le Péchoux [h]



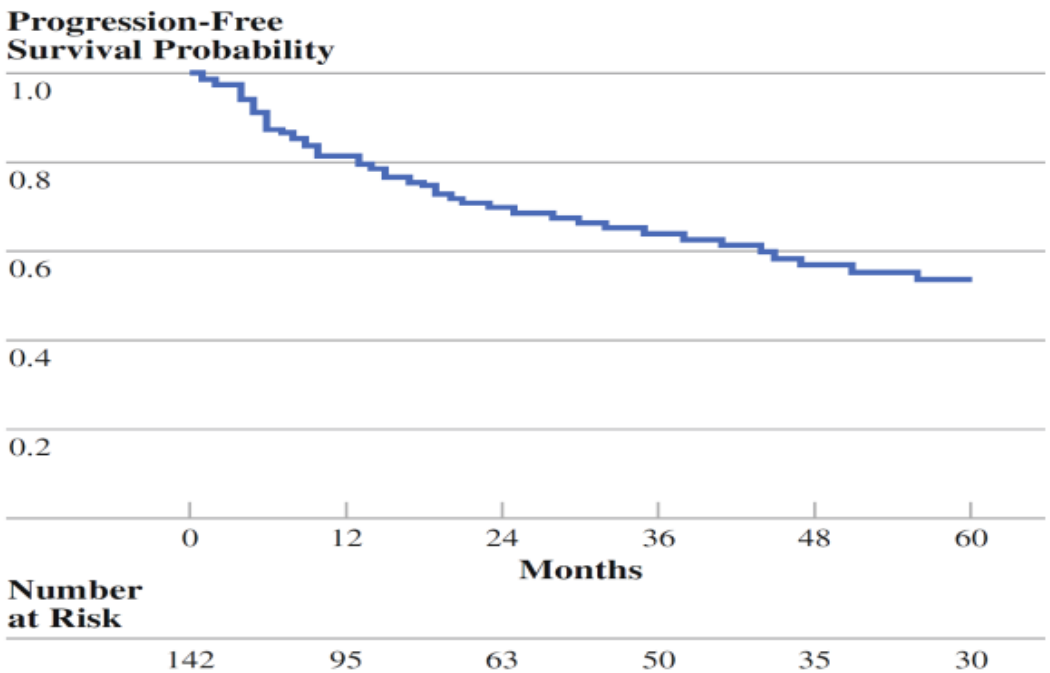
Ann Surg Oncol (2009) 16:2587–2593
DOI 10.1245/s10434-009-0586-2

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

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Desmoid-Type Fibromatosis: A Front-Line Conservative Approach to Select Patients for Surgical Treatment

Marco Fiore, MD[1], Françoise Rimareix, MD[2], Luigi Mariani, MD[3], Julien Domont, MD[4], Paola Collini, MD[5], Cecile Le Péchoux, MD[6], Paolo G. Casali, MD[7], Axel Le Cesne, MD[4], Alessandro Gronchi, MD[1], and Sylvie Bonvalot, MD, PhD[2]



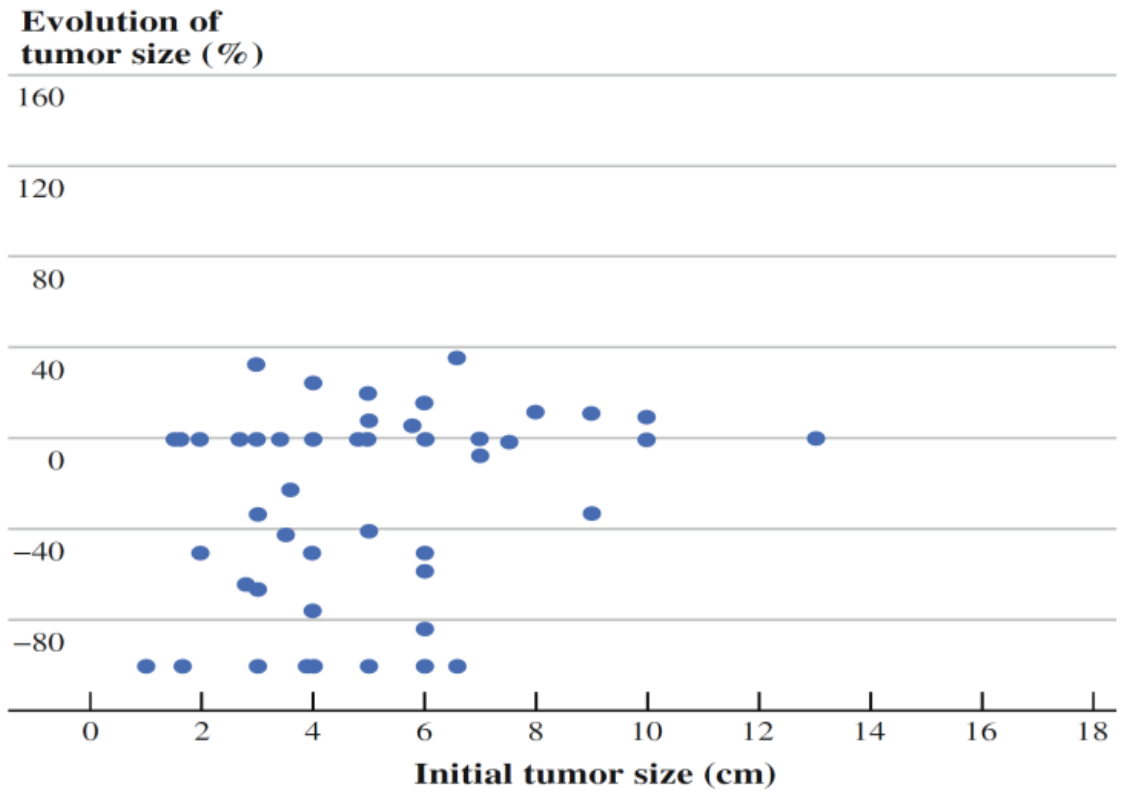
Ann Surg Oncol (2013) 20:4096–4102
DOI 10.1245/s10434-013-3197-x

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

ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Spontaneous Regression of Primary Abdominal Wall Desmoid Tumors: More Common than Previously Thought

Sylvie Bonvalot, MD, PhD[1], Nils Ternès, MS[2], Marco Fiore, MD[3], Georgina Bitsakou, MD[1], Chiara Colombo, MD[3], Charles Honoré, MD[1], Andrea Marrari, MD[4], Axel Le Cesne, MD[5], Federica Perrone, MD[6], Ariane Dunant, MS[2], and Alessandro Gronchi, MD[3]



European Journal of Cancer (2015) 51, 186–192

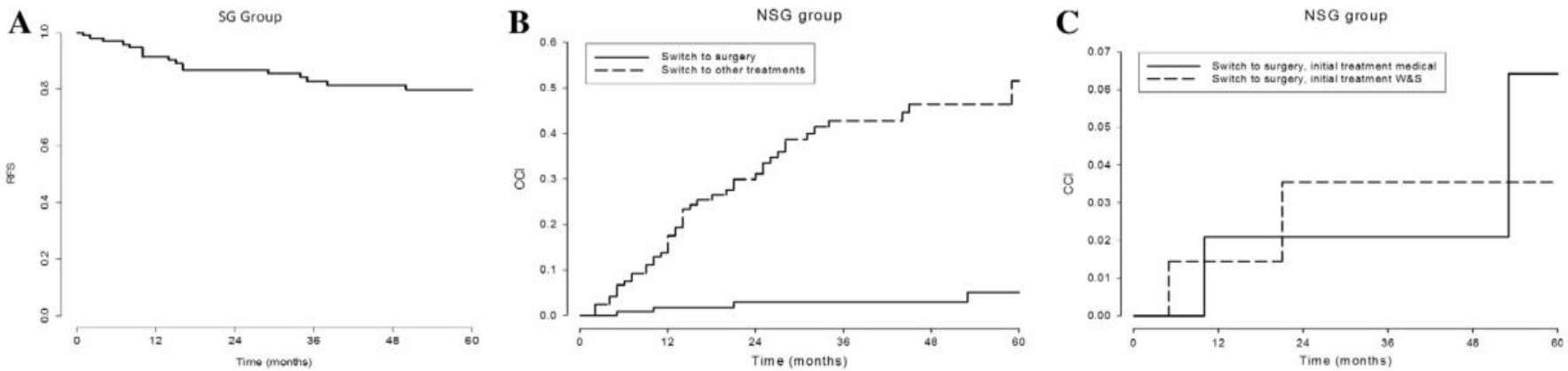
Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Sporadic extra abdominal wall desmoid-type fibromatosis: Surgical resection can be safely limited to a minority of patients

C. Colombo [a], R. Miceli [b], C. Le Péchoux [c], E. Palassini [d], C. Honoré [e], S. Stacchiotti [d], O. Mir [f], P.G. Casali [d], J. Dômont [f], M. Fiore [a], A. Le Cesne [f], A. Gronchi [a,*], S. Bonvalot [e]



European Journal of Cancer 83 (2017) 125–131

Available online at www.sciencedirect.com

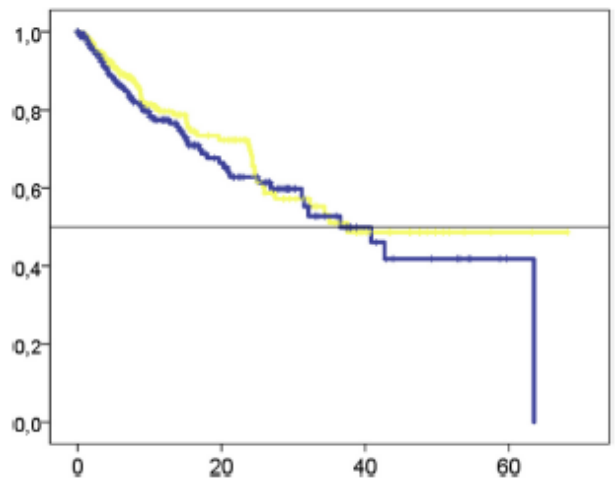
ScienceDirect

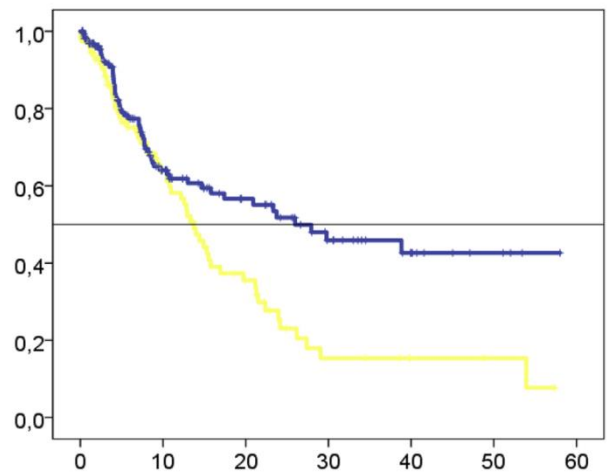
journal homepage: www.ejcancer.com

Original Research

Surgical versus non-surgical approach in primary desmoid-type fibromatosis patients: A nationwide prospective cohort from the French Sarcoma Group

Nicolas Penel [a,*], Axel Le Cesne [b], Sylvie Bonvalot [c], Antoine Giraud [d], Emmanuelle Bompas [e], Maria Rios [f], Sébastien Salas [g], Nicolas Isambert [h], Pascaline Boudou-Rouquette [i], Charles Honore [b], Antoine Italiano [j], Isabelle Ray-Coquard [k], Sophie Piperno-Neumann [l], François Gouin [m,n], François Bertucci [o], Thomas Ryckewaert [a], Jean-Emmanuel Kurtz [p], Françoise Ducimetiere [k], Jean-Michel Coindre [q], Jean-Yves Blay [k]





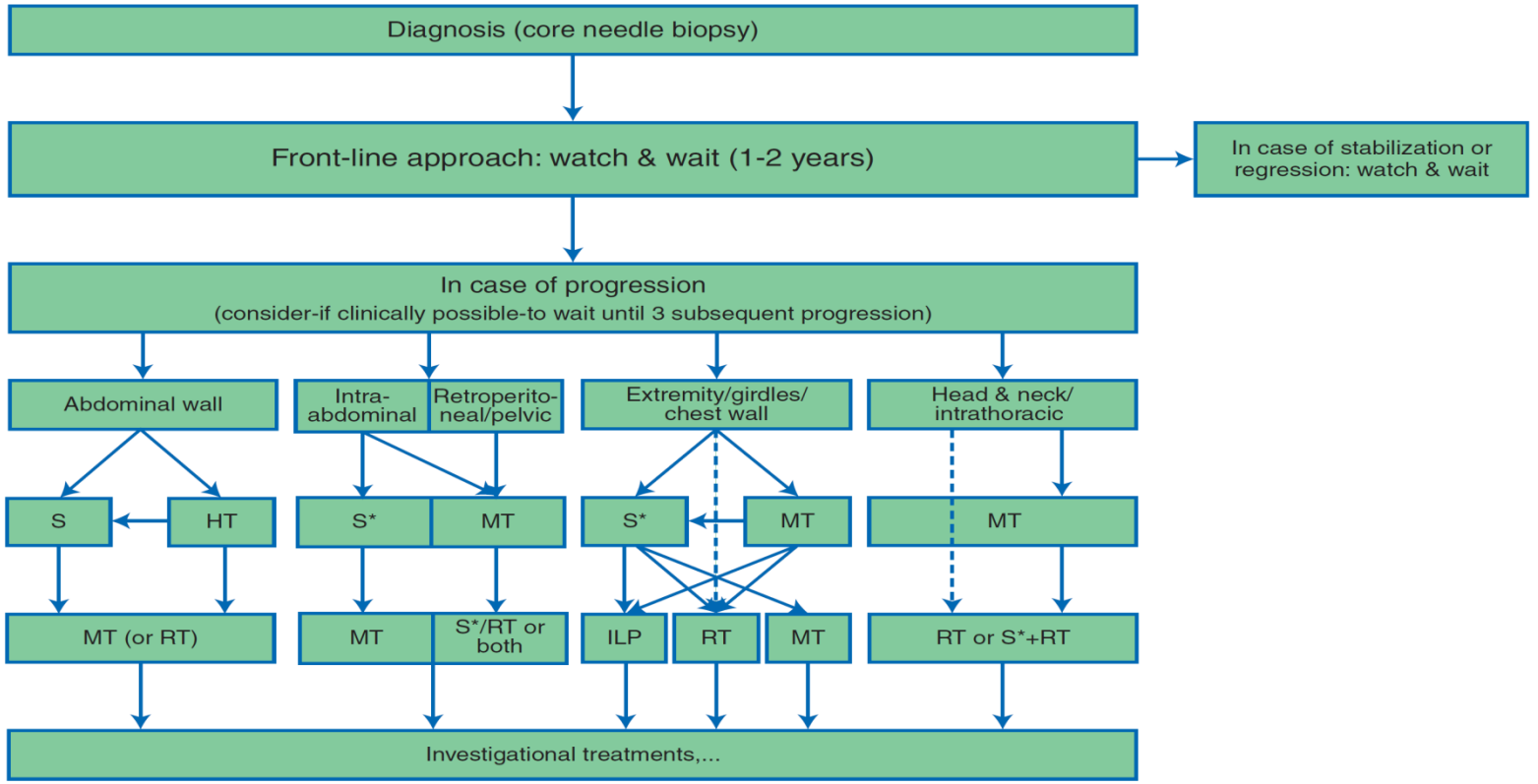
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2399–2408, 2017
doi:10.1093/annonc/mdx323
Published online 23 June 2017

REVIEW

An update on the management of sporadic desmoid-type fibromatosis: a European Consensus Initiative between Sarcoma PAtients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG)

B. Kasper[1*], C. Baumgarten[2], J. Garcia[2], S. Bonvalot[3], R. Haas[4,5], F. Haller[6], P. Hohenberger[1], N. Penel[7], C. Messiou[8], W. T. van der Graaf[9] & A. Gronchi[10*], on behalf of the Desmoid Working Group[†]



THE MANAGEMENT OF DESMOID TUMORS: A JOINT GLOBAL EVIDENCE-BASED CONSENSUS APPROACH FOR ADULT AND PEDIATRIC PATIENTS

The Desmoid Tumor Working Group

An initial W&S approach does not influence the efficacy of further treatments when needed. Thus being safe and not harmful, this approach is now considered the first step after diagnosis in the majority of patients. Neither surgery nor other forms of active treatments are proposed as primary therapy at diagnosis. Considering the biology and unpredictable course of the disease, active treatments should be considered only in the case of persistent progression. Progression at a single assessment, especially in the absence of specific symptoms and in non-critical anatomic sites, should not per se be considered as an indication to start an active treatment immediately


RETROSPECTIVE

Observational studies in Europe

- Italian study: Tailored β- catenin mutational approach in extra-abdominal sporadic desmoid tumori patients (clinicaltrial.gov identifier *NCT02547831*- Closed*)*

- French study: Peripheral Primitive Fibromatosis. Study Evaluating a Simple Initial Monitoring With Search of Scalability Predictive Factors and Registration of Treatments in Case of Progression (*clinicaltrial.gov identifier NCT01801176*- Closed)

- Netherlands study: GRAFITI Growth of aggressive fibromatosis without therapeutic intervention- Recruiting

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Aims of the study

- To confirm prospectively the retrospective data on *wait and see approach*

- To prospectively correlate the mutational status to the clinical outcome

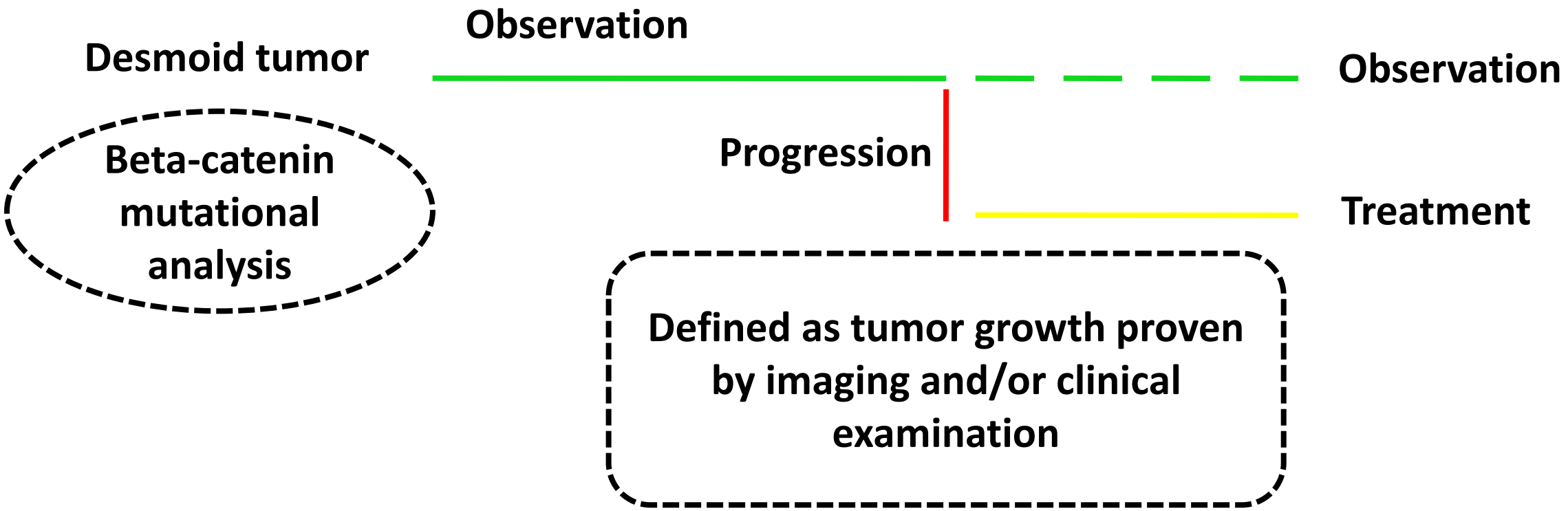
Methods

Inclusion criteria

- Biopsy proven primary tumor or incompletely resected with measurable residual disease (R2 resection)
- No association with FAP
- Any site
- Measurable disease by RECIST

Study design

- This is a prospective multicenter observational study of all consecutive patients affected by histology proven primary sporadic DT observed at the 2 participating centers



Study end-points

- Primary end-point
  - Progression Free Survival (PFS) according to RECIST

  - Secondary end- points
  - Treatment Free Survival (TFS)
  - Correlation of Beta-catenin mutational status with outcome
  - QoL

Statistics

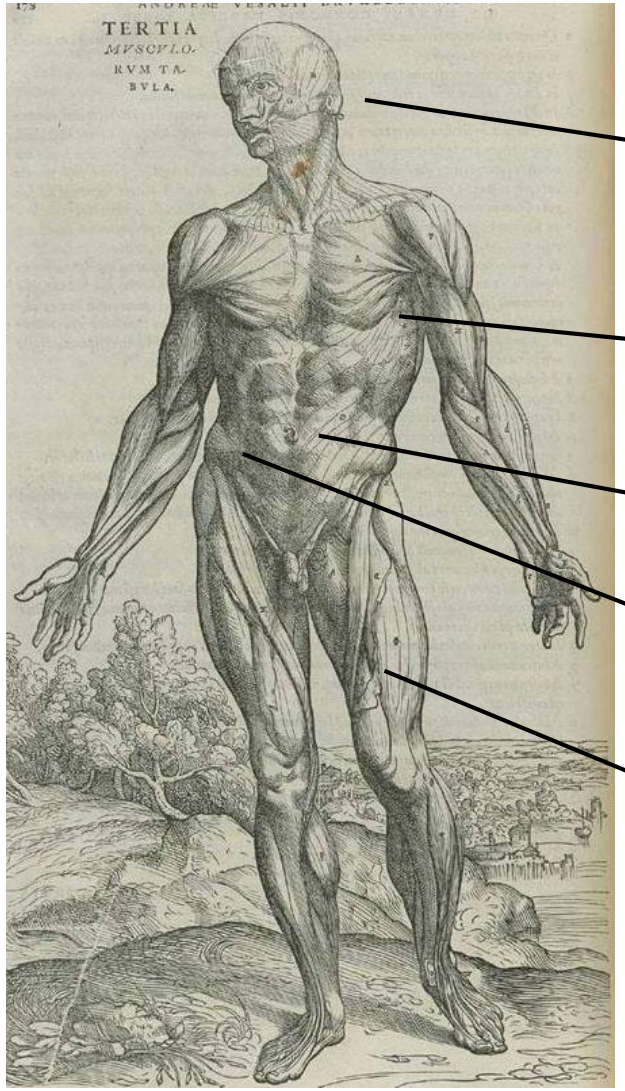
- The analyses were performed using SAS and R software packages
- In the WP, the maximum increase/decrease in patients with unfavorable/favorable outcome were considered
- Regression after PD was calculated based on the size at PD
- PFS and TFS were calculated from the date of biopsy
- The Cox proportional hazard regression model was used for univariable and multivariable analysis (covariates: size, age, anatomical site and Beta- catenin mutational status)

Results

Pts. characteristics

- Between 2013 and 2018 114 pts (82% female, 18% male) were included
- Of them 108 pts had Beta-catenin mutational status available and form the basis of our study
- Median age 39 (IQ range 34-48 years)
- Median size 50 mm (IQ range 40-80 mm)

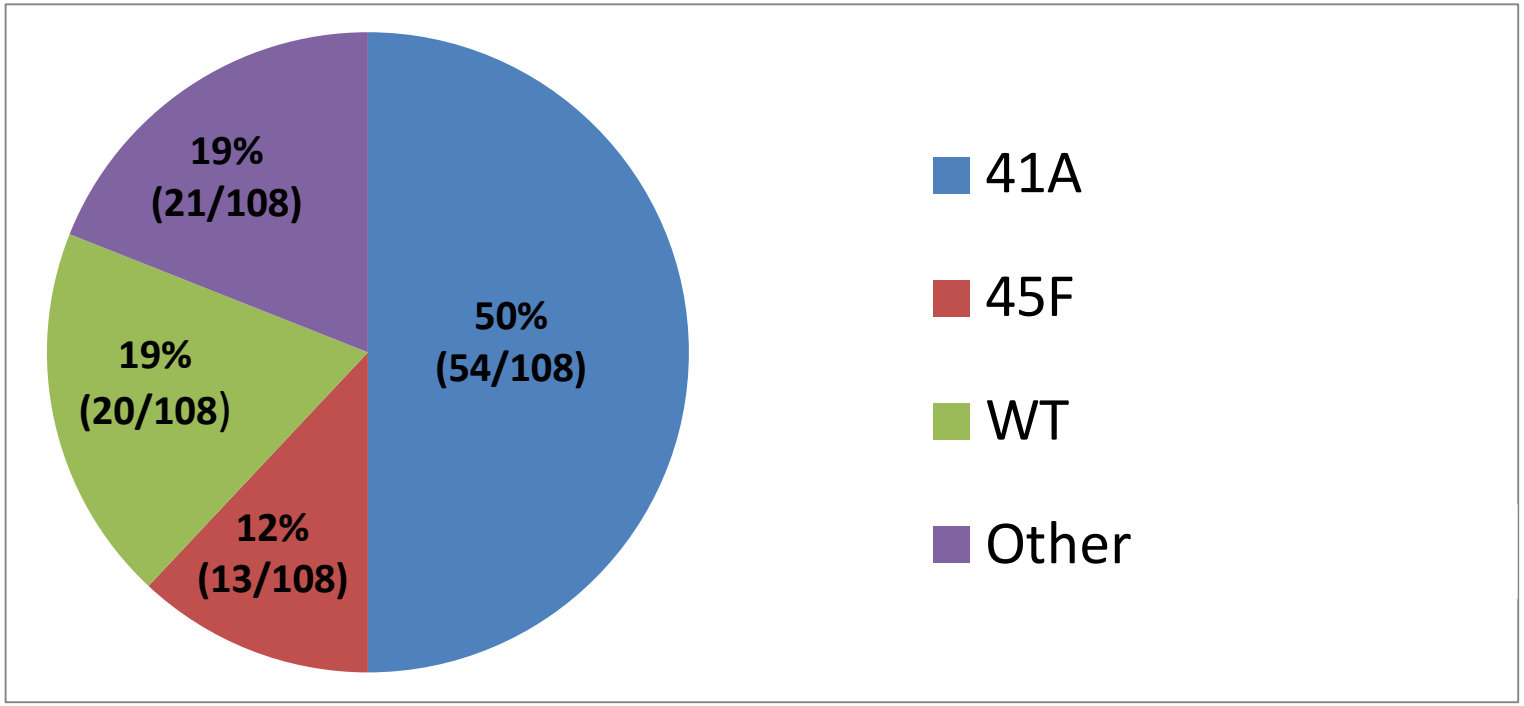
Site distribution



- Head&Neck 4% (4/108)
- Trunk 23% (25/108)
- Abdominal wall 54% (59/108)
- Intra-abdominal 3% (3/108)
- Extremity 16% (17/108)

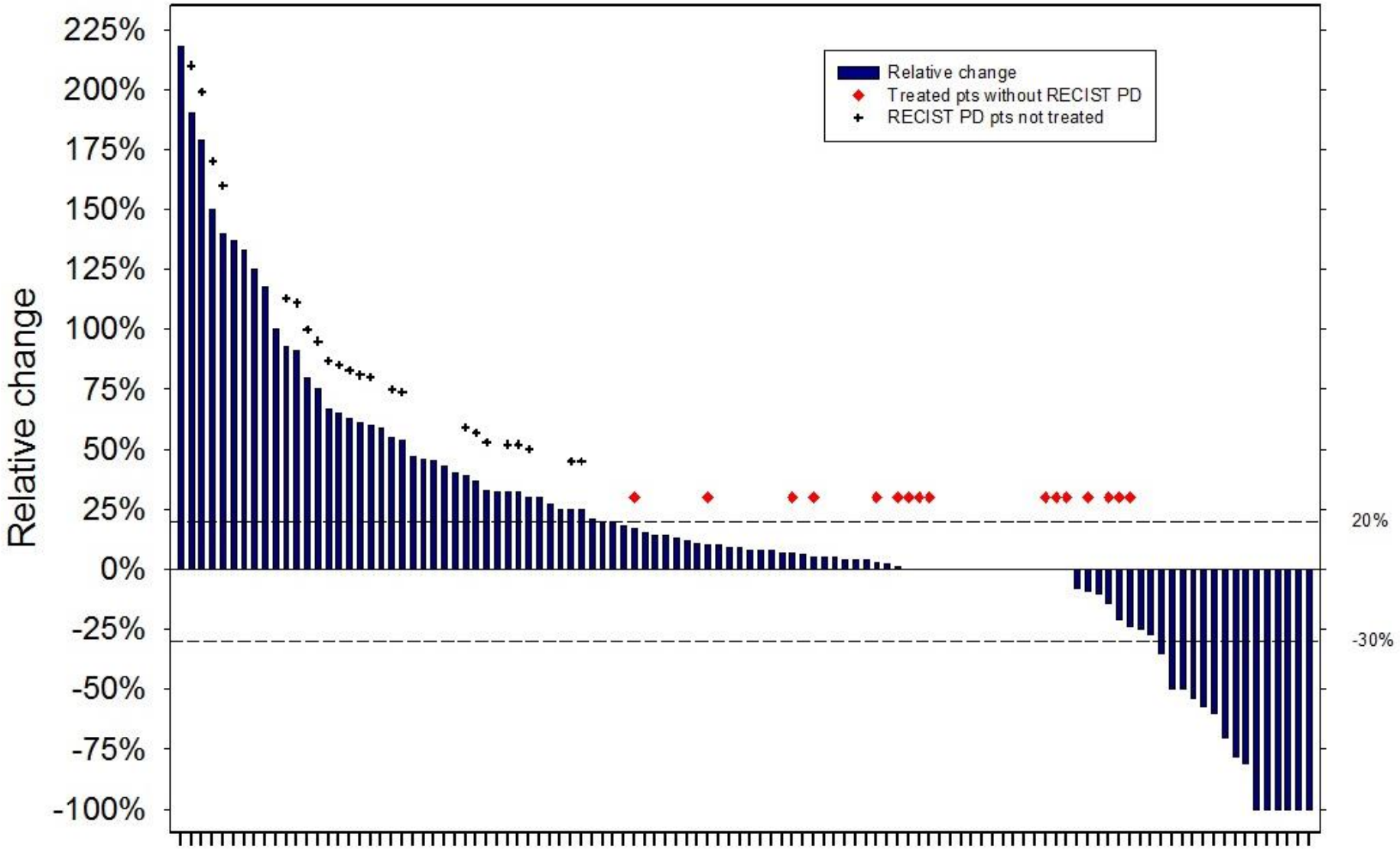
Beta-catenin mutational analysis

- Beta-catenin mutational status was performed using Sanger sequencing

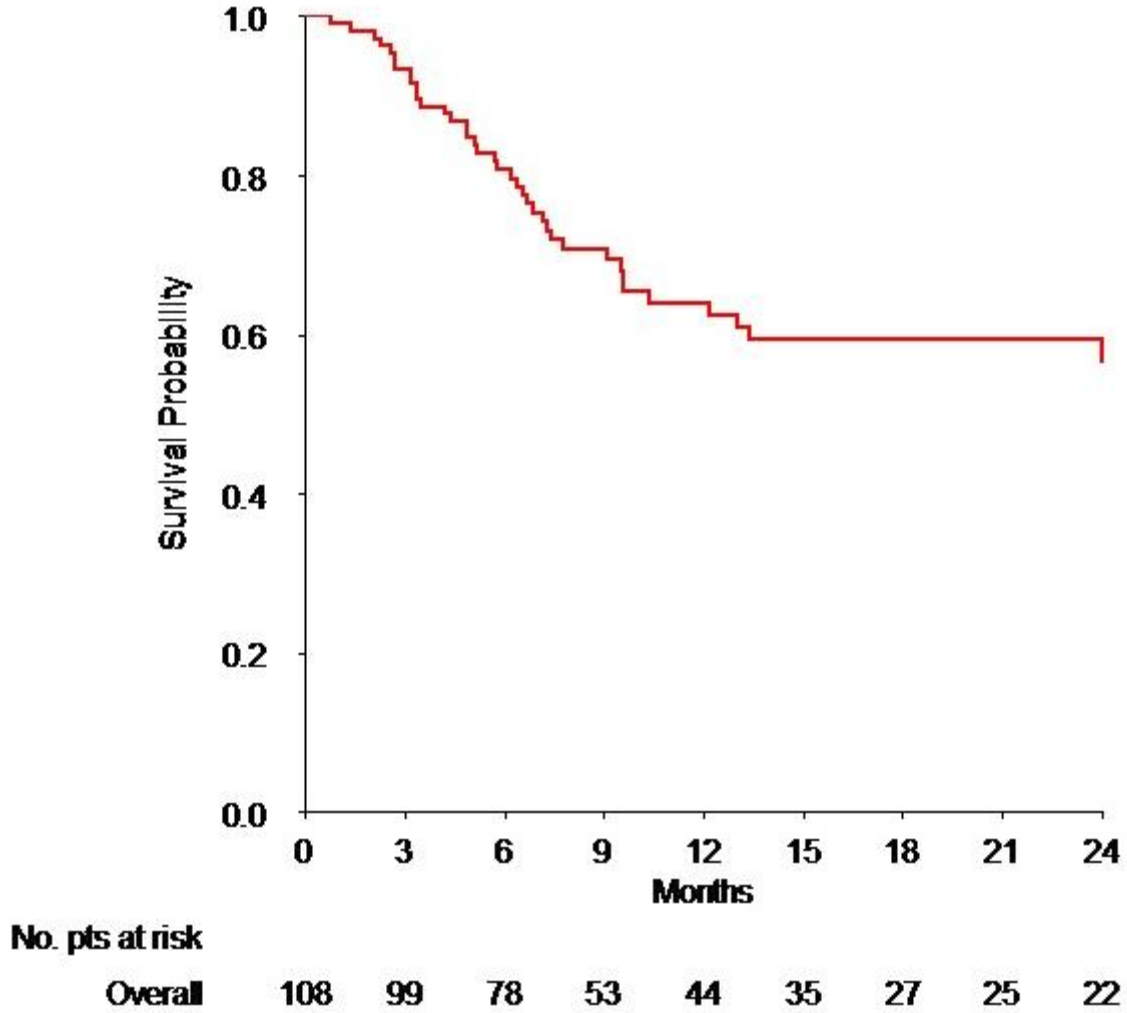


For WT DT, NGS was conducted according to the material availability on 6. A specific mutation was identified in 4 (1 45F, 2 45P, 1 deletion). In 2 pts, WT was confirmed. For 8 pts material was not available. In 10 pts, NGS is ongoing.

At a median FU of 14.6 months
37% (40/108) of patients experienced a RECIST progression

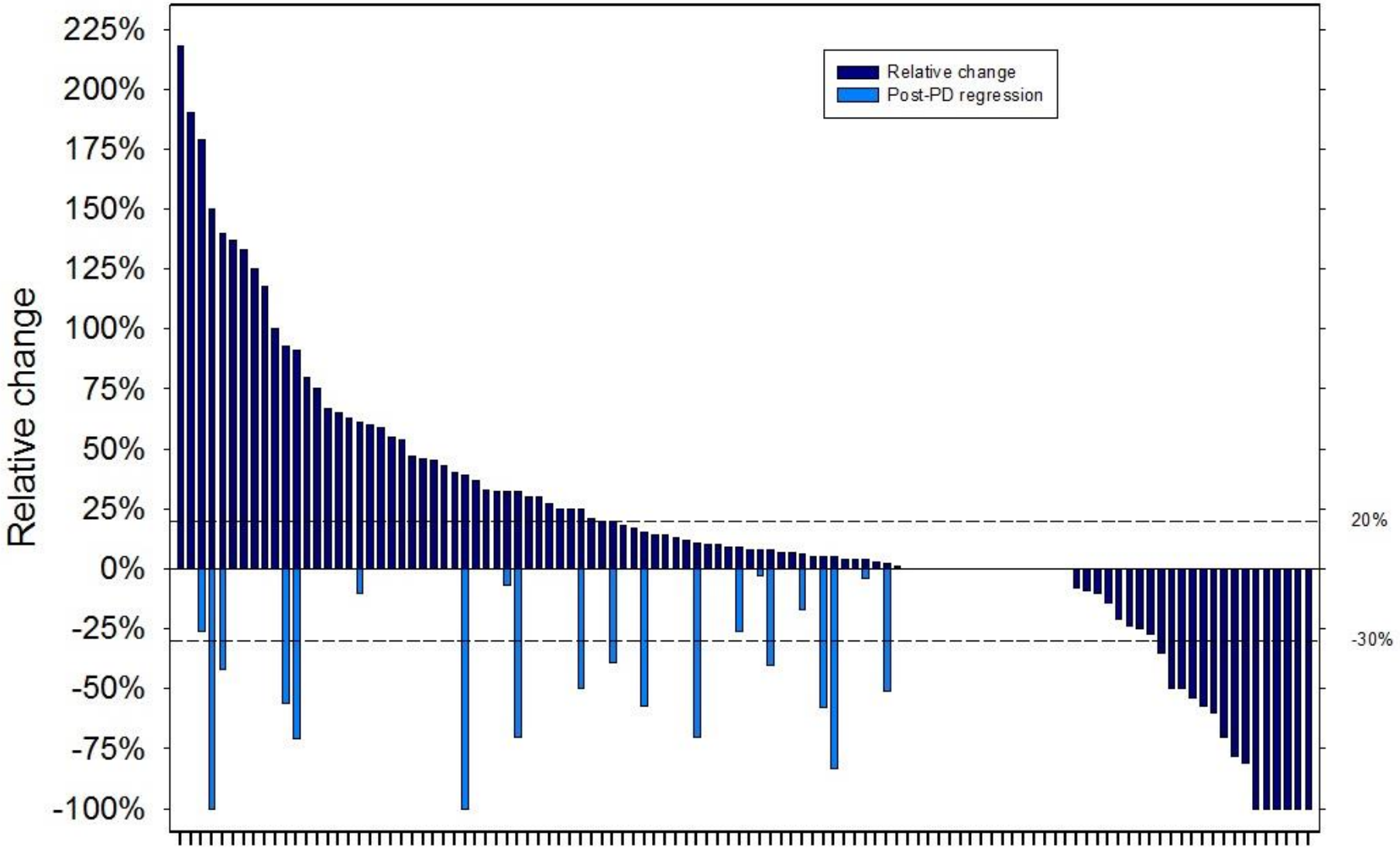


PFS at 2yrs 56.7% (95%, CI 46.5-69.2)



At a median FU of 14.6 months

30% (21/69) of patients had spontaneous regression after initial progression

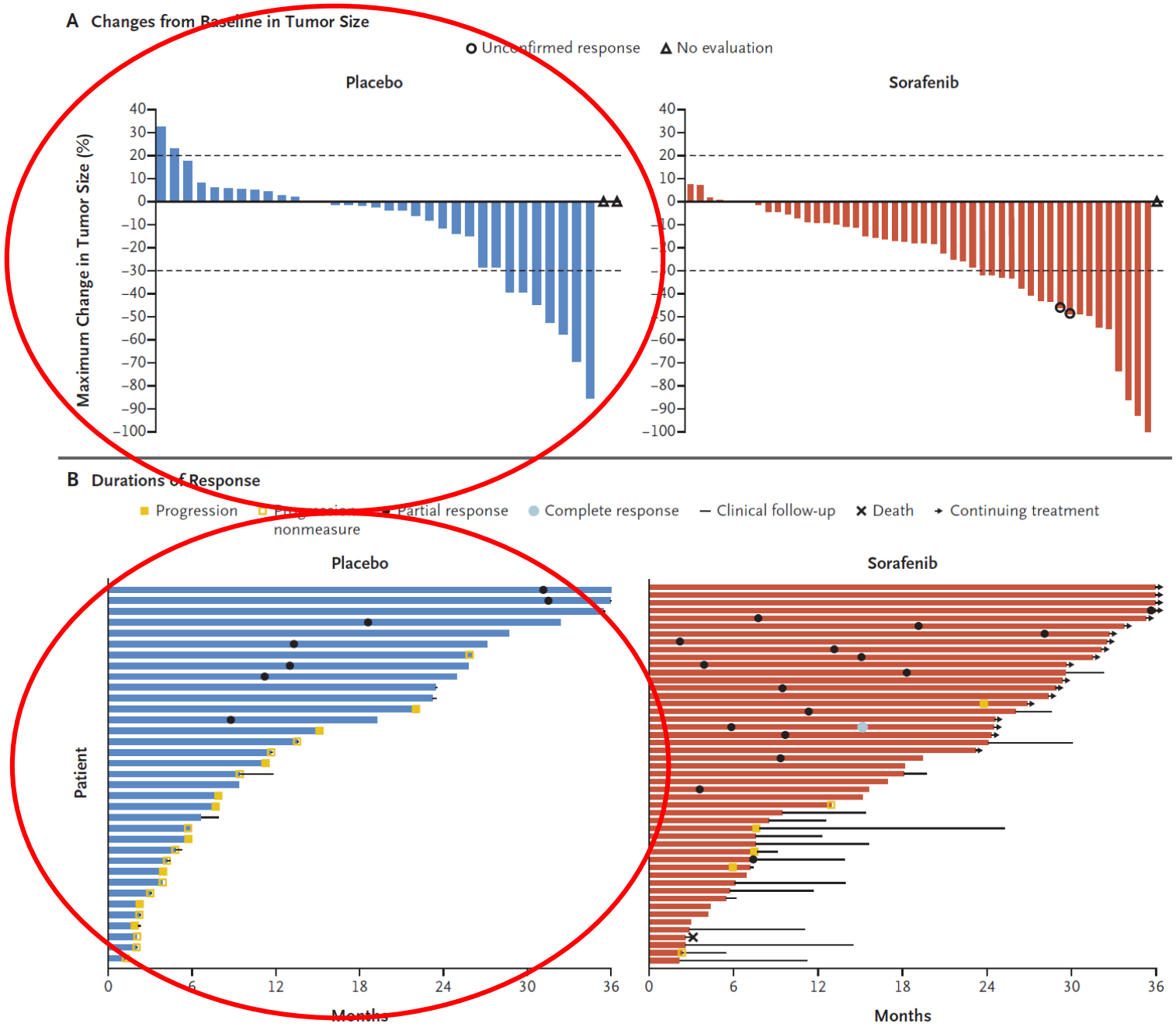


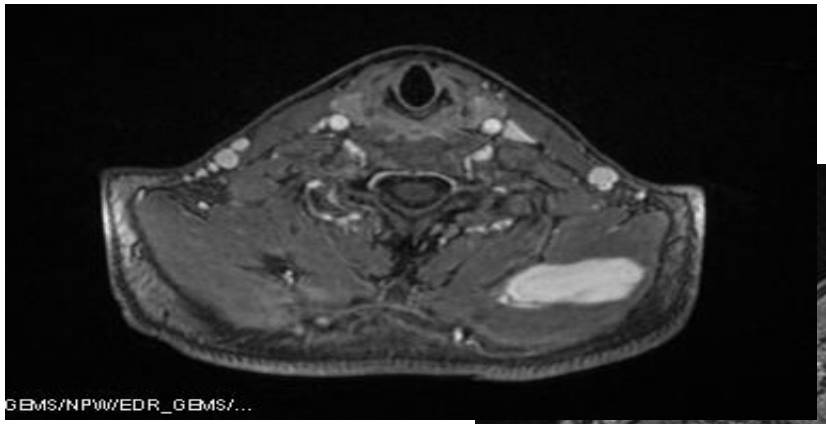
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

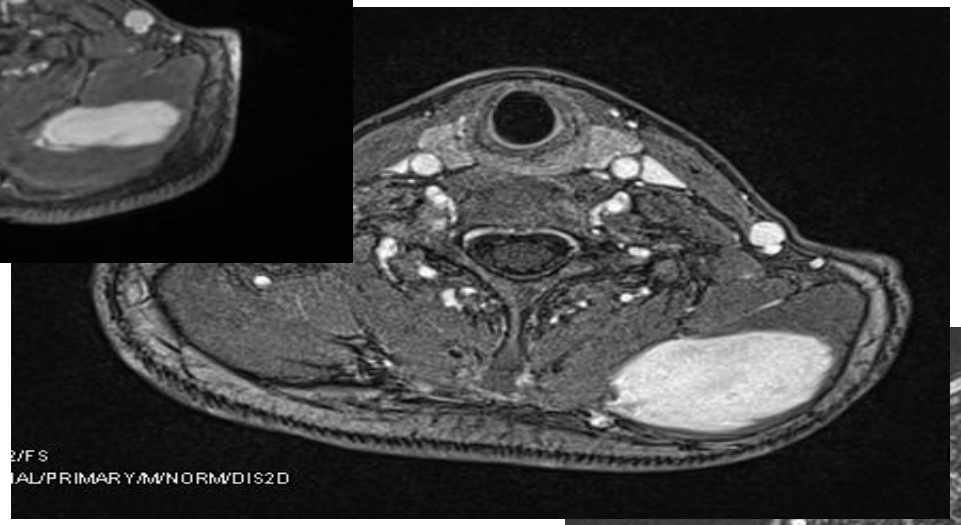
Sorafenib for Advanced and Refractory Desmoid Tumors

Mrinal M. Gounder, M.D., Michelle R. Mahoney, M.S., Brian A. Van Tine, M.D., Ph.D., Vinod Ravi, M.D., Steven Attia, D.O., Hari A. Deshpande, M.D., Abha A. Gupta, M.D., Mohammed M. Milhem, M.D., Robert M. Conry, M.D., Sujana Movva, M.D., Michael J. Pishvaian, M.D., Ph.D., Richard F. Riedel, M.D., Tarek Sabagh, M.D., William D. Tap, M.D., Natally Horvat, M.D., Ethan Basch, M.D., Lawrence H. Schwartz, M.D., Robert G. Maki, M.D., Ph.D., Narasimhan P. Agaram, M.B., B.S., Robert A. Lefkowitz, M.D., Yousef Mazaheri, Ph.D., Rikiya Yamashita, M.D., Ph.D., John J. Wright, M.D., Ph.D., Amylou C. Dueck, Ph.D., and Gary K. Schwartz, M.D.

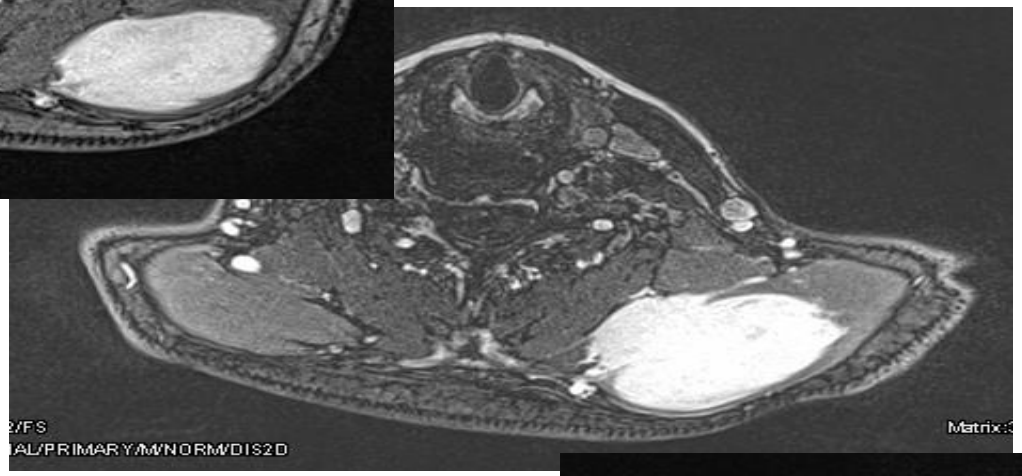




Nov 2015



Feb 2016



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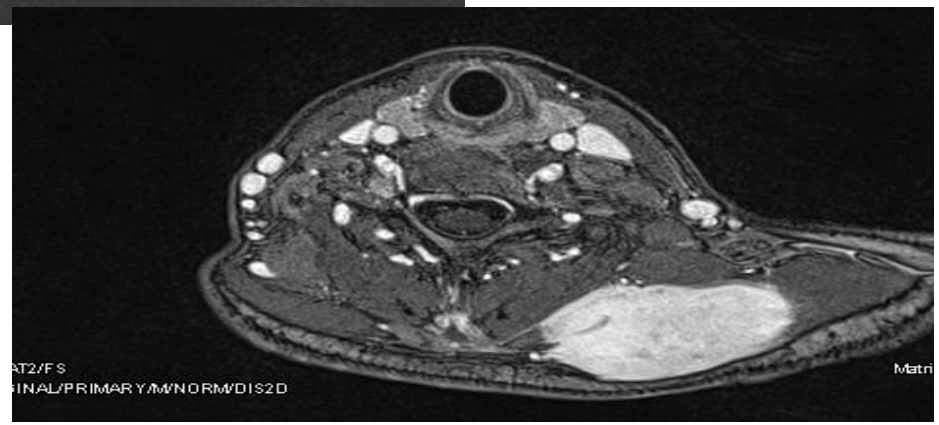
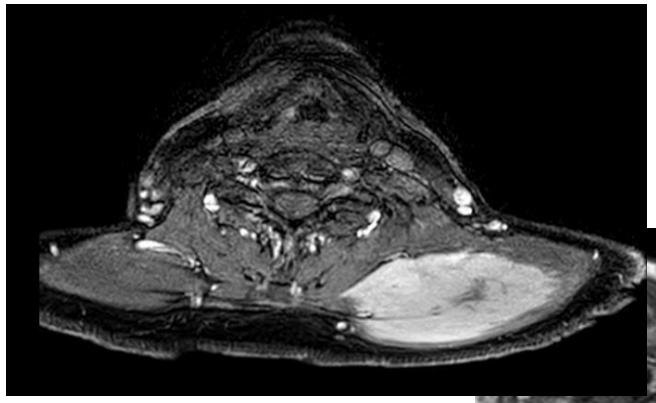


Jul 2016

Female
48 yrs old
Trunk
Initial size: 40 mm



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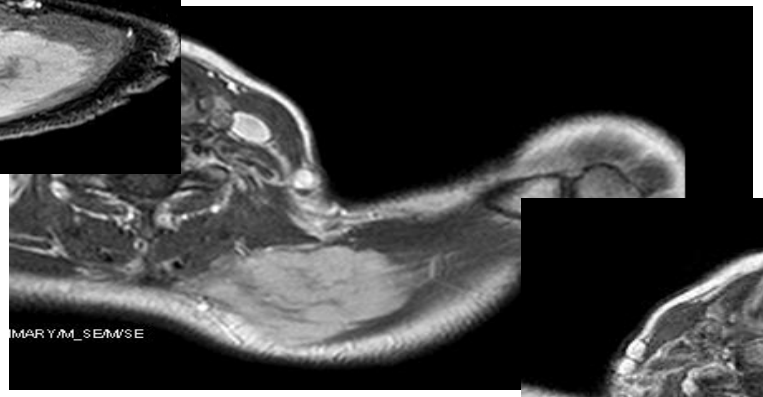
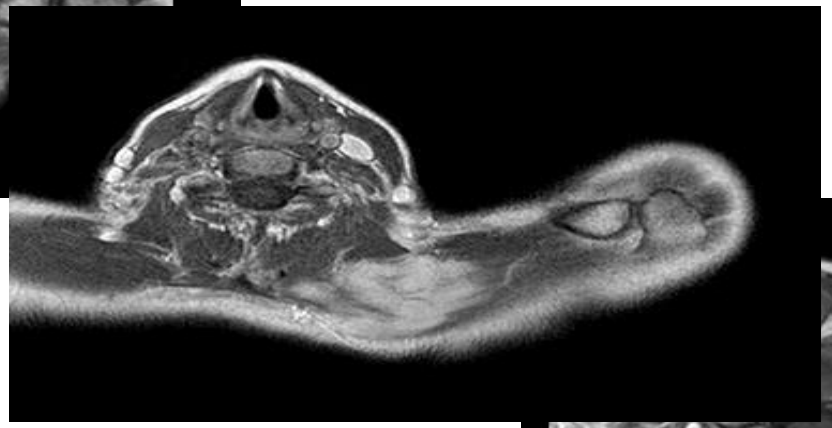


Mar 2017



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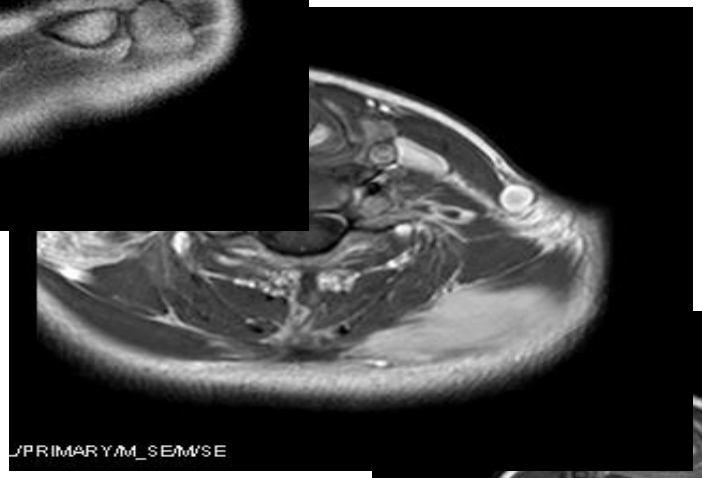

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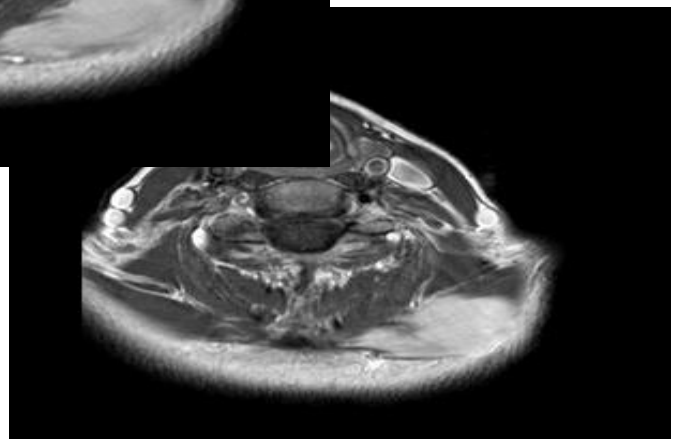

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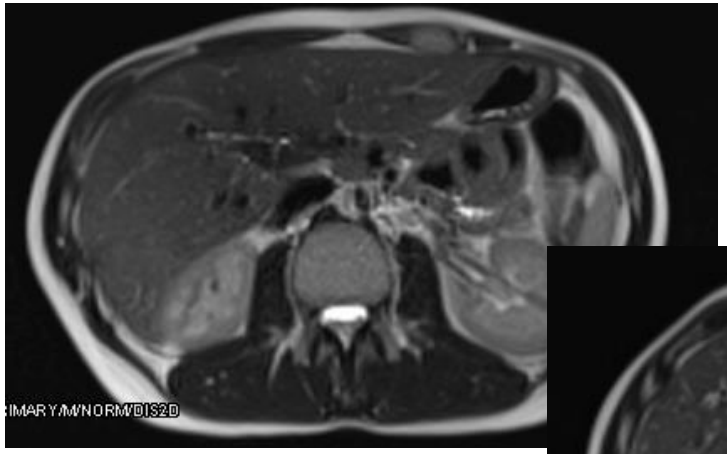

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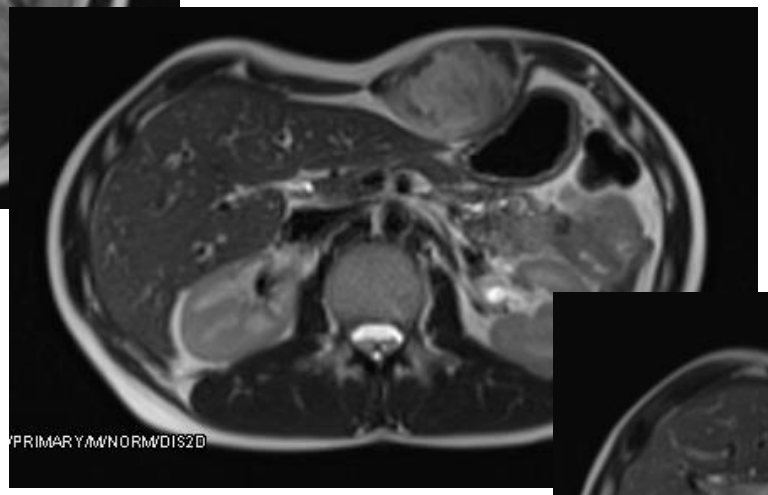

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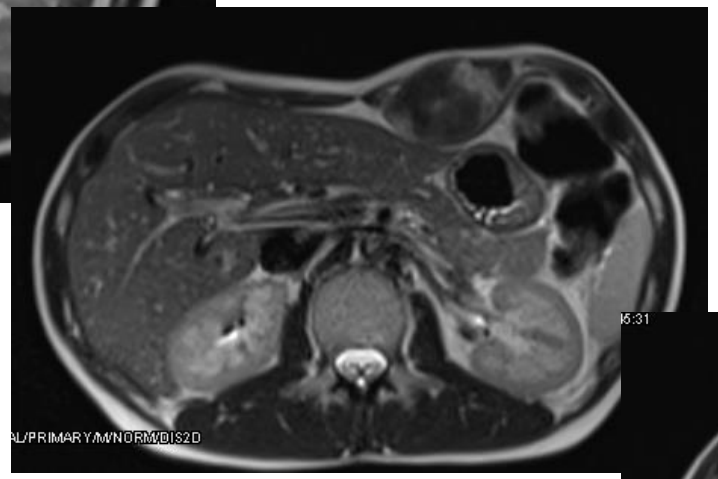

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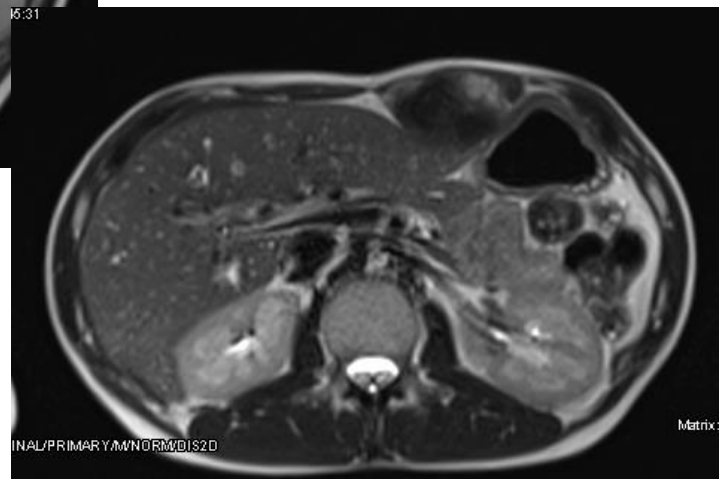
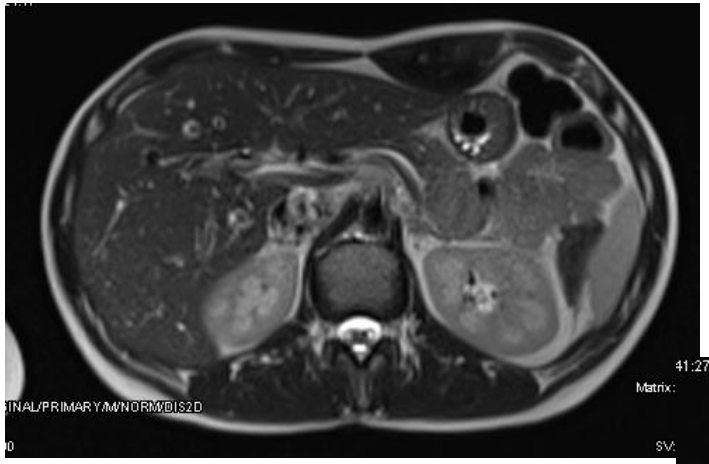


Jan 2017

Female
32 yrs old
Abdominal wall
Initial size: 30 mm



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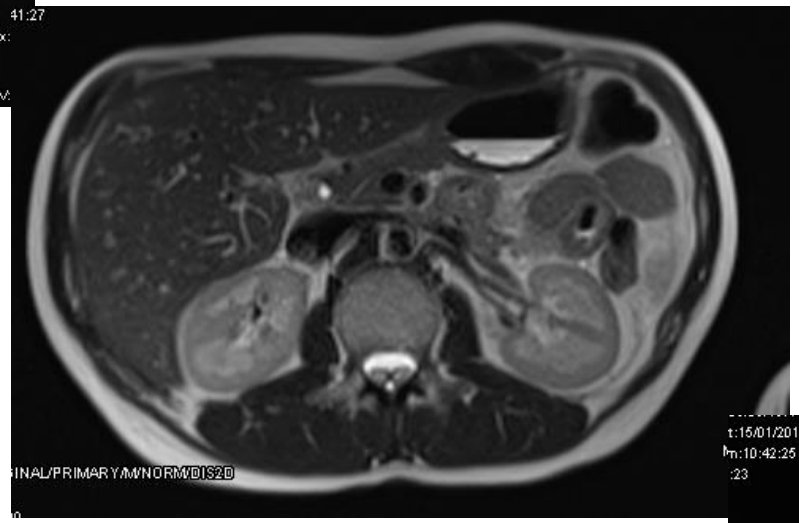
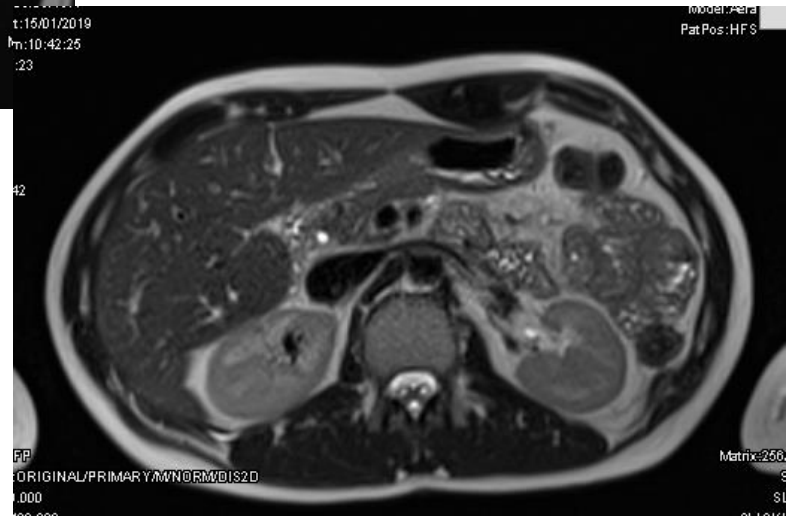


Apr 2018

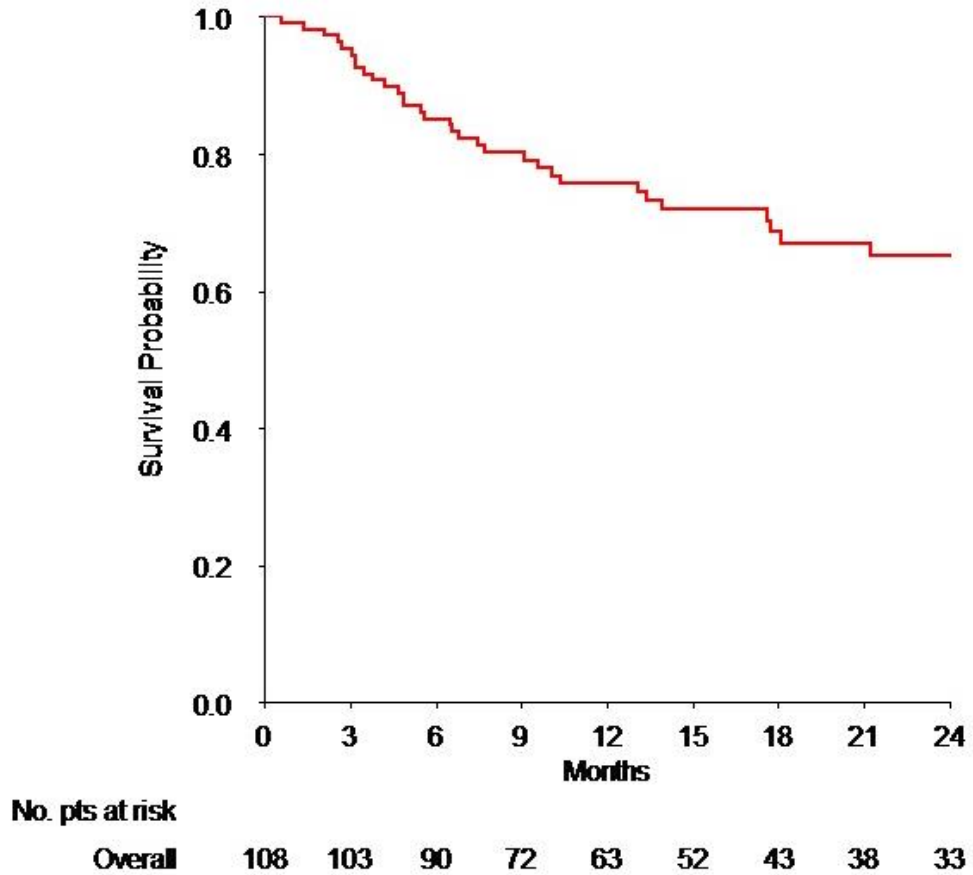


Jan 2019

PD RECIST was not a criterion for starting an active treatment

- In the *PD RECIST group* (40 pts) we observed 10 spontaneous regression (2 complete regression) and 16 pts were treated
- In the *PD non RECIST group (29 pts)* we observed 11 spontaneous regression (no complete regression) and 6 pts were treated
- In the SD RECIST group (16 pts) we did not observe any spontanous regression and 10 patients were treated

TFS at 2 yrs 68.6% (95%CI 59.7-79)



In total 32/108 patients received an active treatment

Univariable and Multivariable analysis on PFS

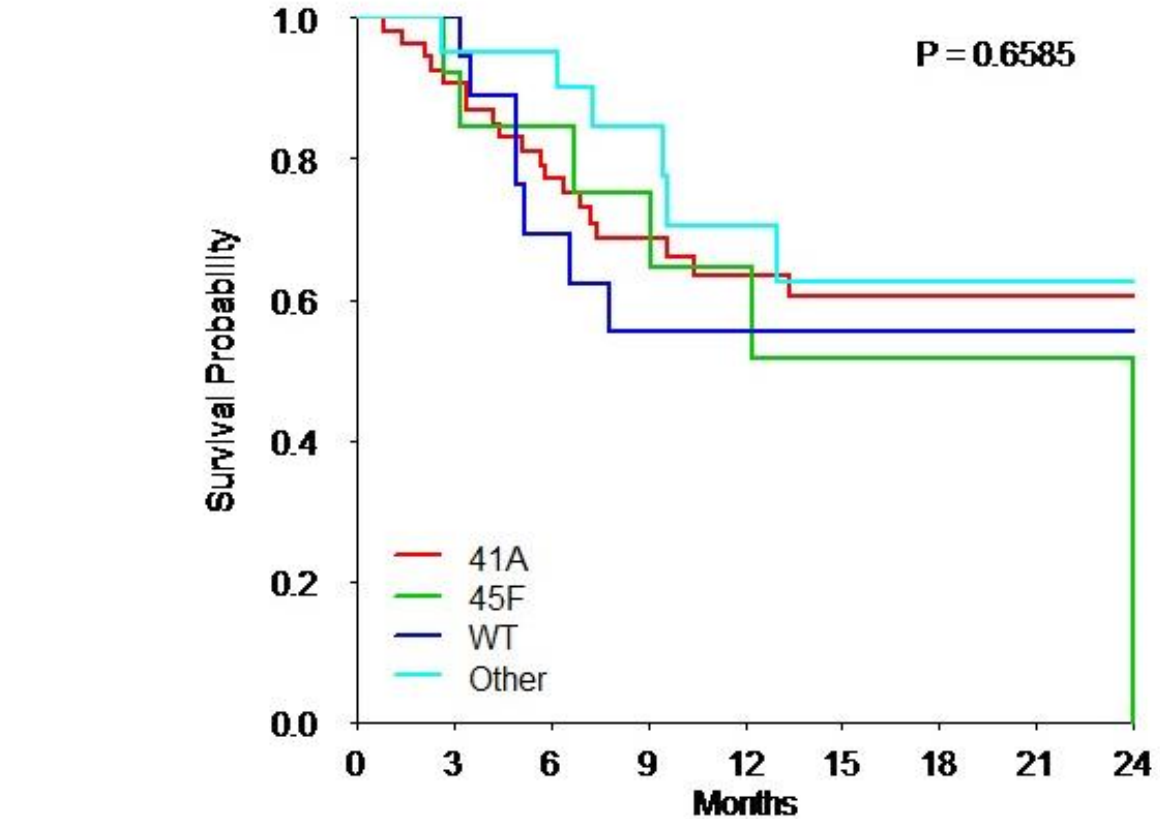
	Univariable models			Multivariable model §		
	HR	95% CI	p*	HR	95% CI	p*
Age at biopsy, *years*			0.326			0.243
48 (Q3) vs 34 (Q1)	0.855	0.624 – 1.169		0.821	0.589 – 1.143	
Lesion size, *mm*			0.254			0.115
80 (Q3) vs 40 (Q1)	0.748	0.454 – 1.232		0.635	0.361 – 1.118	
Tumor site			0.984			0.884
Extremity vs Abdominal wall	1.081	0.438 – 2.667	0.867	1.153	0.438 – 3.035	0.773
Other site vs Abdominal wall	0.996	0.491 – 2.020	0.991	1.212	0.553 – 2.655	0.631
β-catenin mutation *(4 levels)*			0.666			--
45F vs 41A	1.324	0.530 – 3.309	0.548	--	--	
WT vs 41A	1.201	0.527 – 2.740	0.663	--	--	
Other vs 41A	0.686	0.275 – 1.709	0.418	--	--	
β-catenin mutation *(2 levels)*			0.464			0.174
45F vs non-45F	1.385	0.579 – 3.316		2.042	0.730 – 5.710	

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; Q1: 1st quartile; Q3: 3rd quartile.

§ For the sake of parsimony, "β-catenin mutation" was entered into the multivariable model as a binary factor.

* p-value at the Wald's test

PFS according to Beta catenin mutational status



No. pts at risk

41A	54	48	39	26	22	18	16	15	12
45F	13	12	10	7	5	4	1	1	1
WT	20	19	10	8	7	6	5	5	5
Other	21	20	19	12	10	7	5	4	4

Univariable and Multivariable analysis on TFS

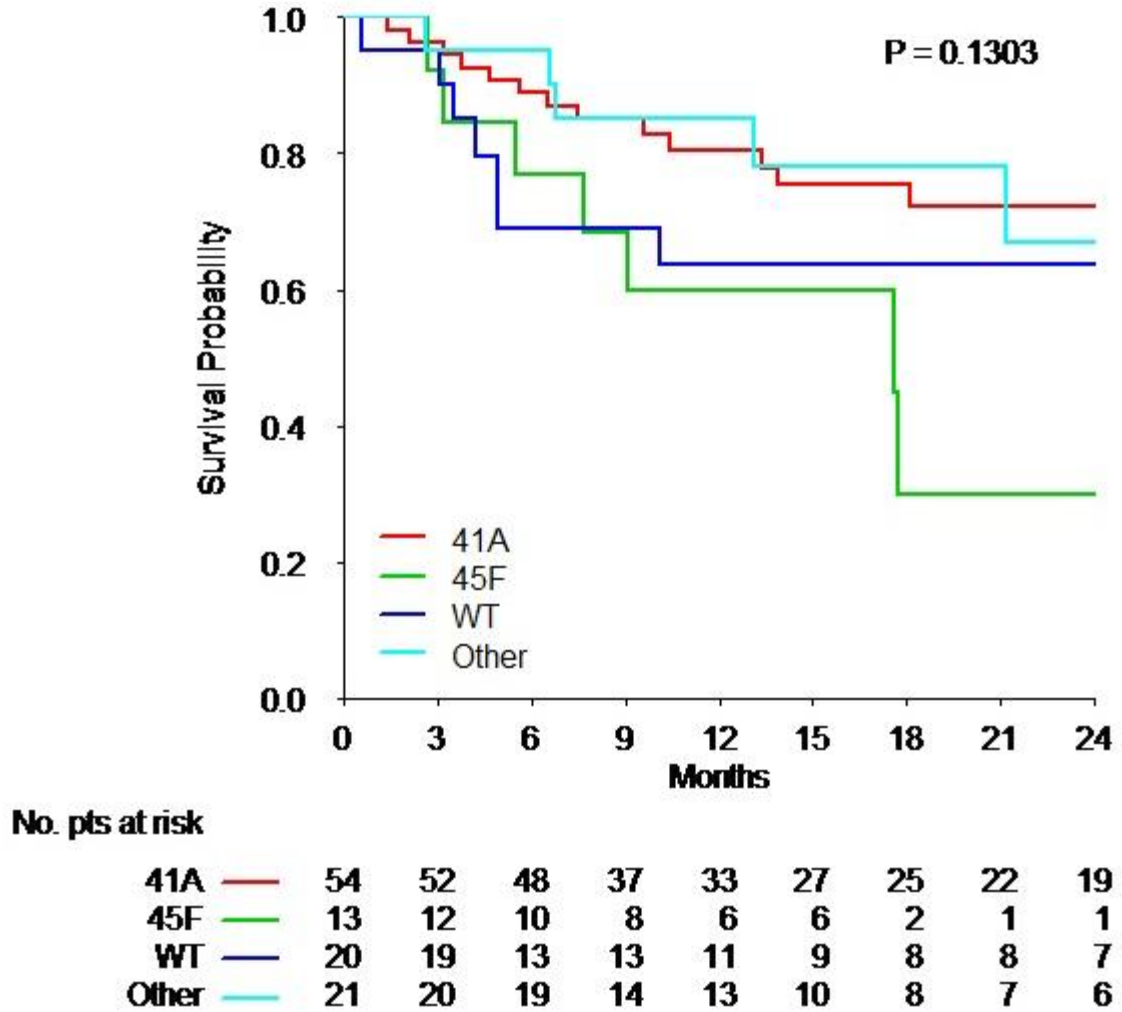
	Univariable models			Multivariable model §		
	HR	95% CI	p*	HR	95% CI	p*
Age at biopsy, *years*			0.615			0.590
48 (Q3) vs 34 (Q1)	1.086	0.787 – 1.500		1.095	0.787 – 1.523	
Lesion size, *mm*			0.001			0.022
80 (Q3) vs 40 (Q1)	2.120	1.346 – 3.339		1.879	1.096 – 3.221	
Tumor site			0.012			0.079
Extremity vs Abdominal wall	3.547	1.526 – 8.243	0.003	2.251	0.881 – 5.750	0.090
Other site vs Abdominal wall	1.448	0.625 – 3.353	0.388	0.834	0.309 – 2.252	0.720
β-catenin mutation *(4 levels)*			0.152			--
45F vs 41A	2.723	1.082 – 6.853	0.033	--	--	
WT vs 41A	1.671	0.666 – 4.191	0.274	--	--	
Other vs 41A	1.007	0.359 – 2.827	0.989	--	--	
β-catenin mutation *(2 levels)*			0.040			0.529
45F vs non-45F	2.414	1.040 – 5.604		1.350	0.530 – 3.435	

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; Q1: 1st quartile; Q3: 3rd quartile.

§ For the sake of parsimony, "β-catenin mutation" was entered into the multivariable model as a binary factor.

* p-value at the Wald's test

TFS according to Beta catenin mutational status



In brief…

- Active surveillance for primary sporadic desmoid tumor was safe and associated to a spontaneous regression in 41% (44/108, 23 initial regression and 21 following initial progression) patients among which a complete remission in 8 pts.
- 30% (21/69) of patients initially experiencing progression had a subsequent spontaneous regression
- Size and location (extremity being the worse) of the initial tumor significantly correlated with the need of an active therapy
- Likewise a trend towards a worse outcome was observed in patients affected by DT harboring 45F point mutation, relative to all others.
- A longer FU is needed to confirm these results

Lessons learnt while conducting the study

- RECIST criteria are not appropriate for
  - defining progression
  - making a decision for an active therapy (also important for future studies, which use progression as an inclusion criterion)

- Alternative methods for assessing the disease course are under evaluation (e.g. changes in T2 weighted MRI sequences, etc)

- Patients' symptoms should be managed separately from desmoid: however if the tumor shrinks, symptoms improve, but a balance between treatment related permanent side effects and the need of tumor shrinkage is critical

- Surgery could be avoided in all cases

Future plans

- Data merge with the other 2 observational studies
- Evaluate the natural history of DT during pregnancy on a larger scale
- Evaluate QoL during W&S
- Characterize the inflammation/immunological profile of DT for patients under W&S focusing on the link with specific Beta catenin mutation

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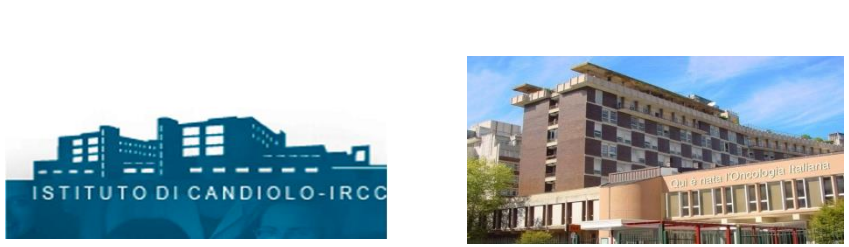

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