# Low dose chemotherapy: experience in sporadic and FAP-related desmoid tumors

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# Systemic therapy

- anti-hormonal therapy (basically SERM) +/- NSAIDs
- low dose chemotherapy: methotrexate plus vinca-alkaloids (vinblastine or vinorelbine)
- conventional chemotherapy: anthracycline-based regimens
- Tyrosine Kinase Inhibitors (TKIs): imatinib, pazopanib, sorafenib
- new agents: gamma secretase inhibitor (Notch signaling inhibition)

# MTX and vinca-alkaloids, first case-series

*Low-Dose Chemotherapy of Desmoid Tumors*

ARTHUR J. WEISS, MD,* AND RICHARD D. LACKMAN, MD,†

***Weiss AJ, Am J Clin Oncol 1989***

**8 adult pts (no FAP pts)**
**Response Rate (RR) = 75%**

**Combination Chemotherapy Using Vinblastine and Methotrexate for the Treatment of Progressive Desmoid Tumor in Children**

***Shapek SX, JCO 1998***

**10 pediatric pts (no FAP pts)**
**RR = 50%**

Low-Dose Chemotherapy With Vinblastine and Methotrexate in Childhood Desmoid Tumors

***Reich S, JCO 1999***

**5 pediatric pts (no FAP pts)**
**RR = 60%**

Therapy of Desmoid Tumors and Fibromatosis Using Vinorelbine

***Weiss AJ, Am J Clin Oncol 1999***

**17 adult and pediatric pts (no FAP pts?)**
**RR = 60%**

# MTX and vinca-alkaloids

**weekly intravenously**

**methotrexate 50 mg or 20-30 mg/m$^2$ plus vinorelbine 20 mg/m$^2$ or vinblastine 5-6 mg/m$^2$**

# MTX and vinca-alkaloids, fase II trial

VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Vinblastine and Methotrexate for Desmoid Fibromatosis in Children: Results of a Pediatric Oncology Group Phase II Trial

*Stephen X. Skapek, William S. Ferguson, Linda Granowetter, Meenakshi Devidas, Antonio R. Perez-Atayde, Louis P. Dehner, Fredric A. Hoffer, Roseanne Speights, Mark C. Gebhardt, Gary V. Dahl, and Holcombe E. Grier*

**27 pediatric pts (2 with FAP)**

**RR = 31%**
**3yr PFS = 32%**

***Skapek S, JCO 2007***

# MTX and vinca-alkaloids, INT experience in sporadic DTs

## Low-Dose Chemotherapy with Methotrexate and Vinblastine for Patients with Advanced Aggressive Fibromatosis


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**BACKGROUND.** This Phase II study was undertaken to assess the activity of methotrexate plus vinblastine in the treatment of patients with inoperable aggressive fibromatosis (AF) and to observe the evolution of the disease after such low-dose chemotherapy.

**METHODS.** Thirty patients with a median age of 27 years who were affected by primary (20%) or recurrent (80%), advanced, inoperable AF were treated with weekly methotrexate at a dose of 30 mg/m² plus vinblastine at a dose of 6 mg/m² for a median interval of 1 year. Patients with recurrent disease had received surgery, radiotherapy, tamoxifen, and antracycline-based chemotherapy. Tumor response was assessed in all patients as well as time to disease progression.

**RESULTS.** Eighteen patients (60%) showed stable disease or minor tumor shrinkage along with symptom relief. A partial response was detected in 12 patients (40%). No complete responses were observed, and no patients had tumor progression during treatment. Four patients received fewer than 15 cycles of chemotherapy, mainly because of severe myelotoxicity. One of these patients died of local disease progression 33 months later, and the other three patients were stable. After a median follow-up of 75 months, the 10-year actuarial progression free interval is 67%.

**CONCLUSIONS.** Methotrexate plus vinblastine given every 7–10 days for several months is associated with prolonged stable disease in a substantial subset of patients with advanced (inoperable) aggressive fibromatosis. ***Cancer* 2001;92: 1259–1264.** *© 2001 American Cancer Society.*



**KEYWORDS: aggressive fibromatosis, chemotherapy, desmoid tumor, vinblastine, methotrexate.**


Aggressive fibromatosis (AF) is a rare, deep-seated, muscoloaponeurotic, borderline tumor with an incidence rate of 0.2–0.5 per 100,000 population per year. Histologically, it is a fibroblastic proliferation with a monoclonal pattern arising from fascial planes and muscoloaponeurotic structures. The tumor is poorly circumscribed and grows along tissue planes with a peculiar, infiltrative-like pattern toward mesenchymal tissues, although it does not spare the connective support of viscera, glands, or teguments. These pathologic features underline the high incidence of local recurrences even after patients undergo pathologically documented, free margin resections.[1–5]

Adequate surgery with or without radiation therapy may achieve a control rate in excess of 60%,[6–16] whereas 40% of patients are not amenable to surgery or radiation therapy at some point during the course of their disease. Some patients may have stable disease for years without undergoing any treatment,[11–16] but most will complain

**from 1989 to 2000**
**30 pts**

***Azzarelli A, Cancer 2001***

# MTX and vinca-alkaloids, INT experience in sporadic DTs

*The Cancer Journal* • Volume 23, Number 2, March/April 2017

## Long-term Efficacy of Methotrexate Plus Vinblastine/Vinorelbine in a Large Series of Patients Affected by Desmoid-Type Fibromatosis

*Elena Palassini, MD,* Anna Maria Frezza, MD,* Luigi Mariani, MD,† Luca Lalli, BSc,† Chiara Colombo, MD,‡ Marco Fiore, MD,‡ Antonella Messina, MD,|| Alessandra Casale, MD,|| Carlo Morosi, MD,|| Paola Collini, MD,¶ Silvia Stacchiotti, MD,* Paolo Giovanni Casali, MD,* and Alessandro Gronchi, MD‡*

**from 1999 to 2014**
**75 pts**
**median FU = 79 months**

***Palassini E, The Cancer Journal 2017***

# MTX and vinca-alkaloids, INT experience in sporadic DTs

**Regimens and treatment duration**

| | |
|---|---|
| MTX + vinblastine | 30 pts (40%) |
| MTX + vinorelbine | 45 pts (60%) |
| median treatment duration | 13.9 (range 3-28) months |
| median n. of cycles - planned 40-50 | 37.5 (range 8-63) |

*Palassini E, The Cancer Journal 2017*

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| median n. of cycles - planned 40-50 | 37.5 (range 8-63) |

**Reason for discontinuation**

| | |
|---|---|
| planned number of cycles reached | 31 pts (41.5%) |
| treatment prolonged at least for 1 yr | 24 pts (32%) |
| progression | 4 pts (5.5%) |
| toxicity | 8 pts (11%) |
| other | 1 pt (1.5%) |

*Palassini E, The Cancer Journal 2017*

# MTX and vinca-alkaloids, INT experience in sporadic DTs

**Toxicity**

| | |
|---|---|
| definitive stop for toxicity | 8 pts (11%) |
| grade 3 or 4 adverse events | 8 pts (11%) |
| mean time between cycles - planned 7 days | 11 (range 7-22) days |

*Palassini E, The Cancer Journal 2017*

# MTX and vinca-alkaloids, INT experience in sporadic DTs

**Activity**

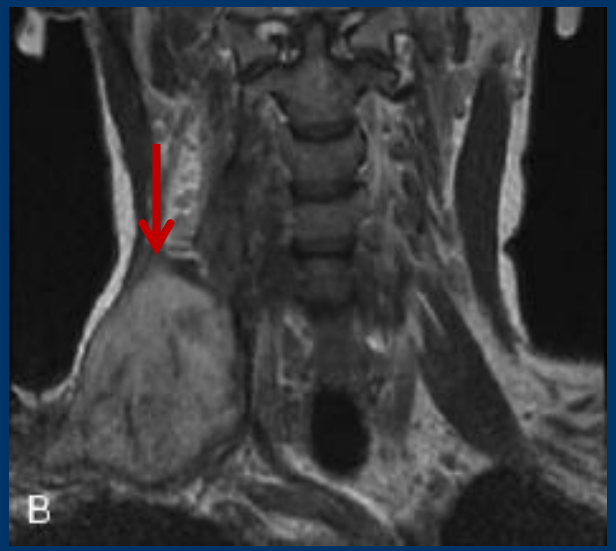
**best response (RECIST criteria)**

| | |
|---|---|
| **Complete Response** | **1 pts (1.5%)** |
| **Partial Response** | **35 pts (46%)** |
| **Stable Disease** | **38 pts (51%)** |
| **Progression Disesae** | **1 pt (1,5%)** |

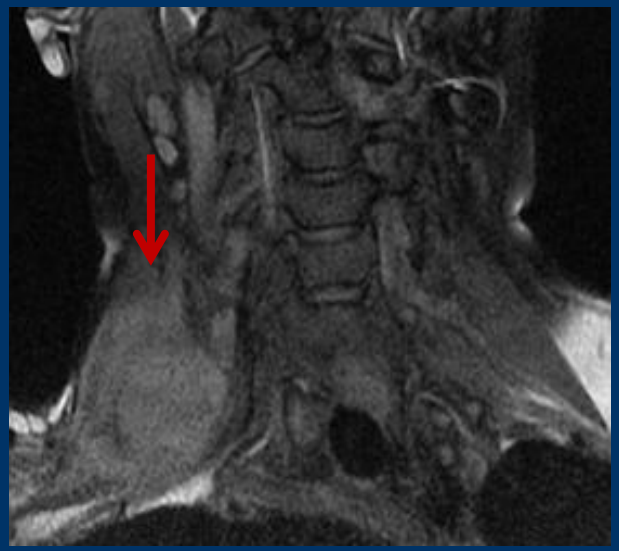
**median time to response** **6 (range 2-24) months**

***Palassini E, The Cancer Journal 2017***

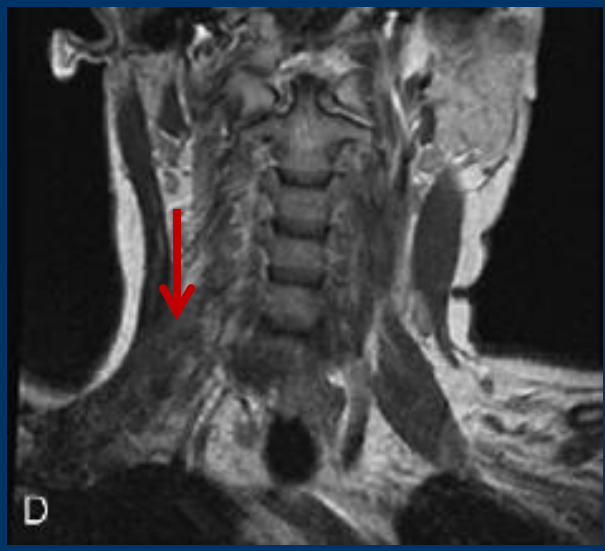
# Patient #1, late dimensional response




baseline, 06/2014

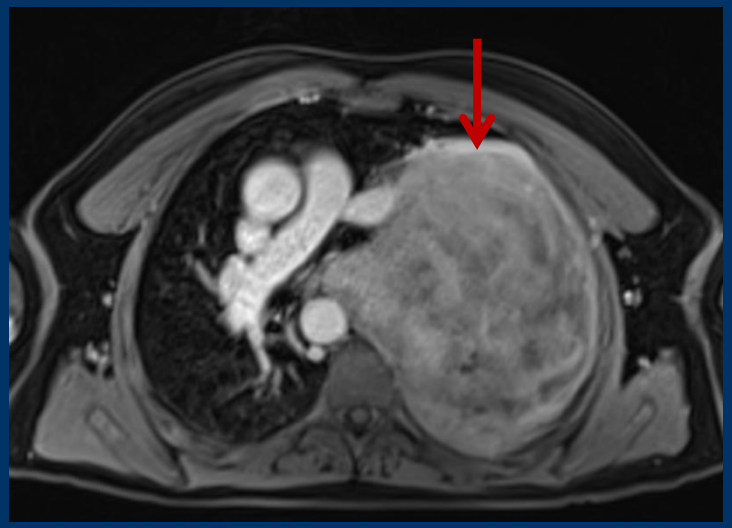


after 10 cycles, 09/2014

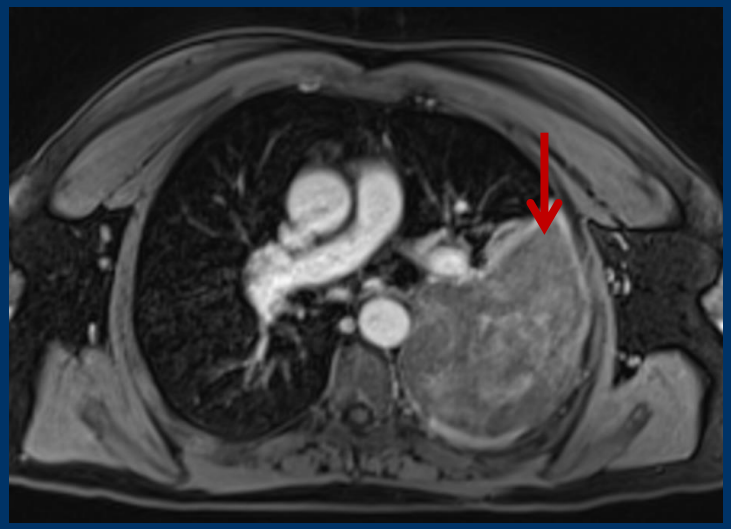



after 33 cycles, 05/2015

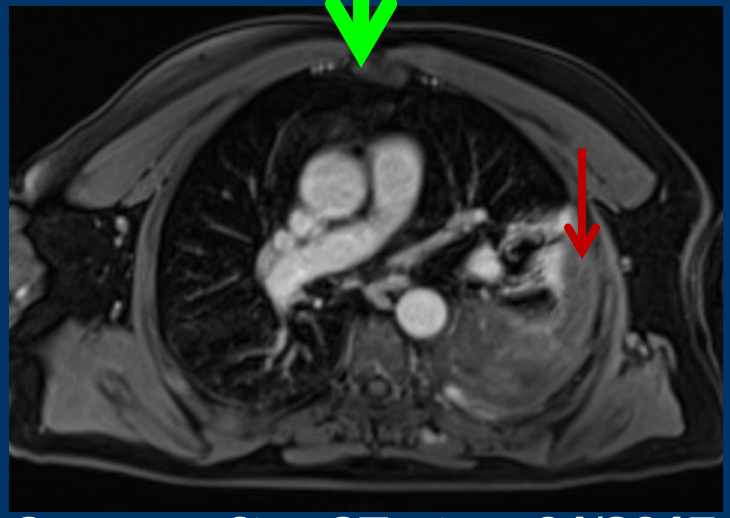
# Patient #2, regression after CT stop



baseline, 01/2013

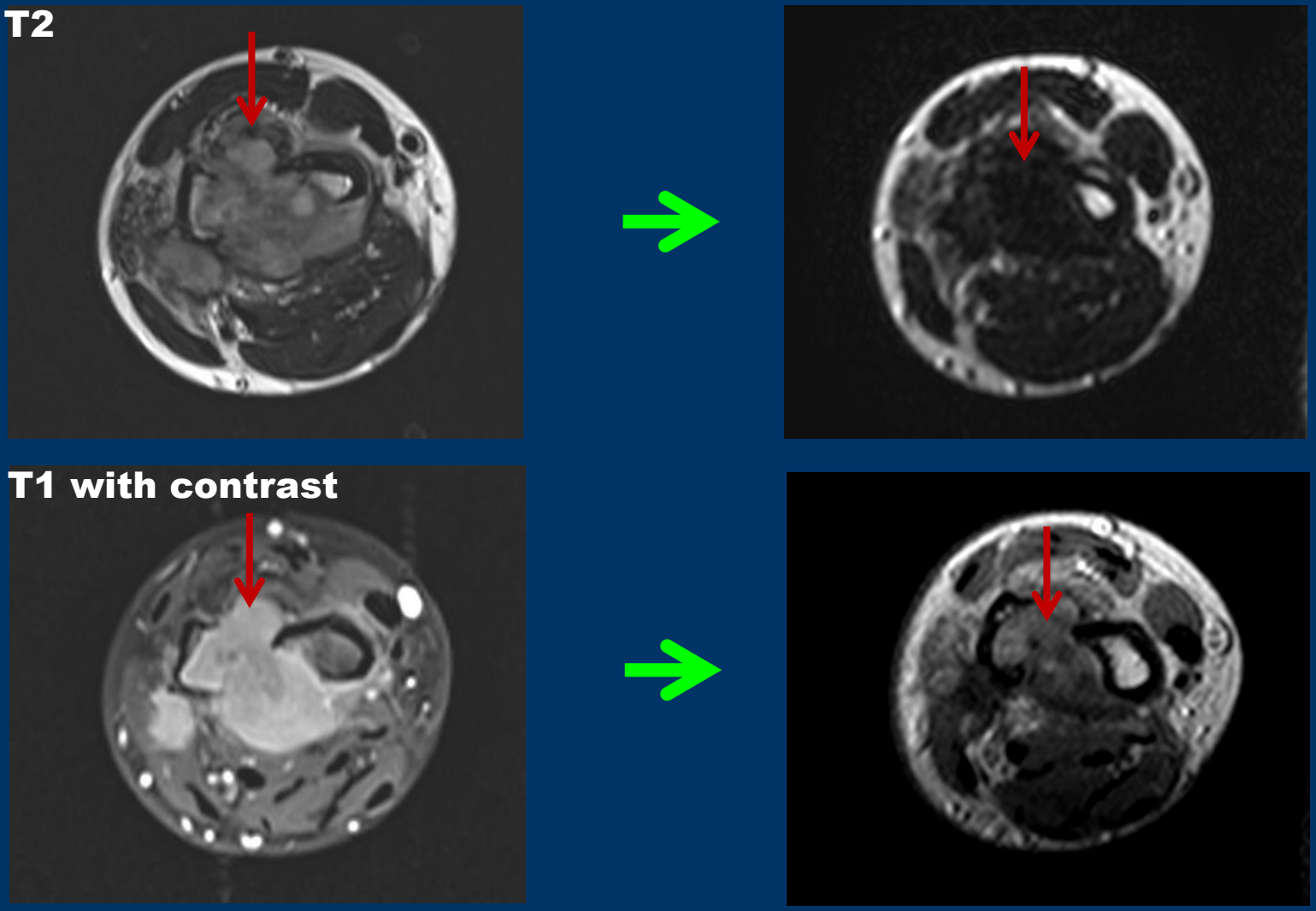


after 49 cycles, 01/2014



3 years after CT stop, 01/2017

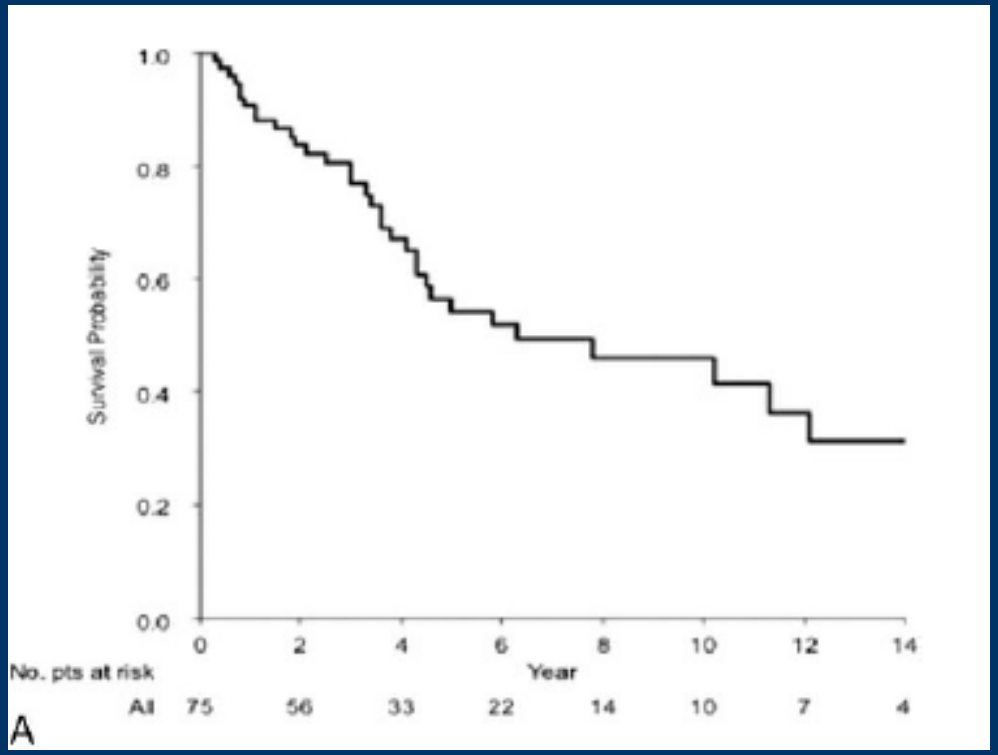
# Patient #3, non-dimensional response



# MTX and vinca-alkaloids, INT experience in sporadic DTs

## Efficacy

**median PFS = 75 months**

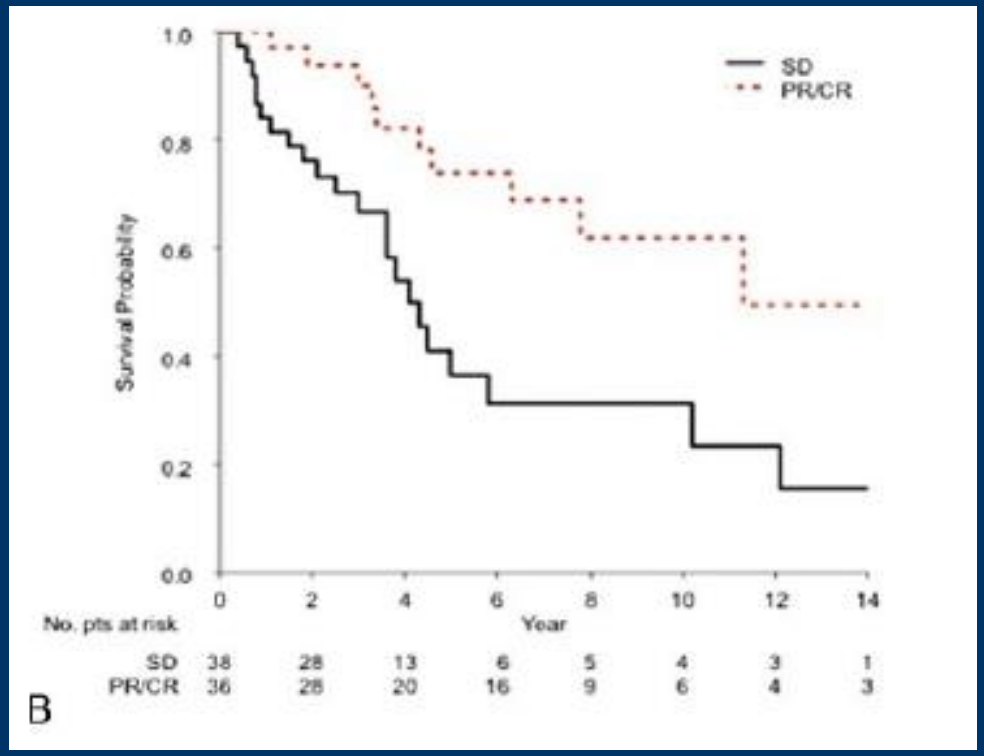



*Palassini E, The Cancer Journal 2017*

# MTX and vinca-alkaloids, INT experience in sporadic DTs

## Efficacy

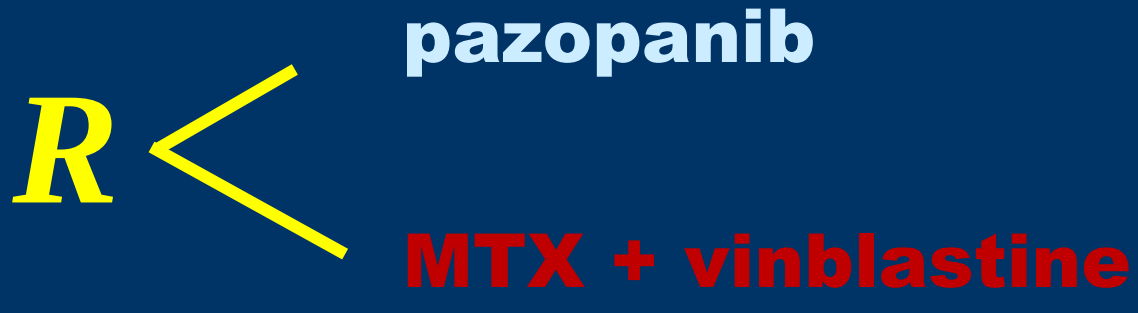
**median PFS in responding pts = 135 months (11 years)**
**median PFS in SD pts = 49 months (4 years)**




*Palassini E, The Cancer Journal 2017*

# DESMOPAZ

**A multicenter, non-comparative, randomized, phase 2 clinical trial assessing safetyand efficacy of pazopanib in progressive DT adult patients**




Pazopanib is an oral antiangiogenic agent targeting VEGFR 1,2,3, PDGFRα, β and c-KIT tyrosine kinases registered in the treatment of advanced and metastatic STS

***Toulmonde M, 2018 ASCO Annual Meeting***

# DESMOPAZ

**RECIST responses**

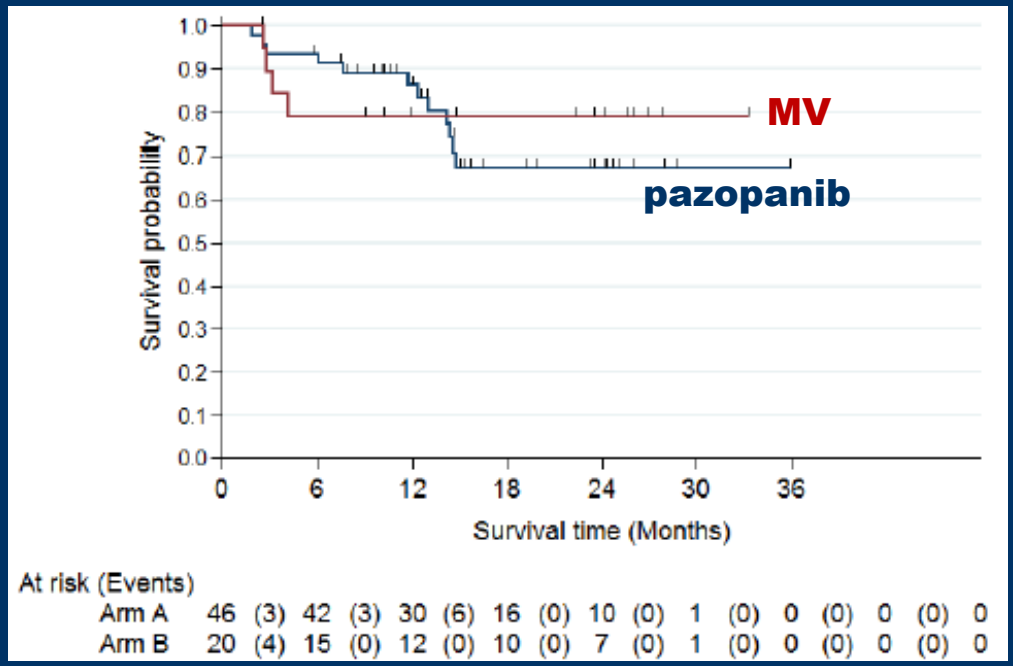
**pazopanib arm**

**PR = 37%**
**SD = 59%**
**PD = 14%**

**MV arm**

**PR = 25%**
**SD = 45%**
**PD = 30%**

**PFS (median PFS not reached in both arms)**




*Toulmonde M, 2018 ASCO Annual Meeting*

# DESMOPAZ

## Safety

| | Pazo arm | MV arm |
|---|---|---|
| median number of cycles | 12 (1-13) | 4 (1-13) |
| at least one dose modification | 36 pts (75%) | 20 pts (91%) |
| definitive stop for toxicity | 6 pts (12.5%) | 6 pts (27%) |
| SAE | 3 | 2 |

*Toulmonde M, 2018 ASCO Annual Meeting*

# DESMOPAZ

## Safety

## MV arm

| | G1 | | G2 | | G3 | | G4 | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| **Fatigue** | 8 | 33% | 7 | 29% | **1** | **4%** | | |
| Anorexia | 4 | 17% | | | | | | |
| *Nervous system* | | | | | | | | |
| **Paresthesia** | 3 | 12% | 2 | 8% | **1** | **4%** | | |
| **Peripheral Neuropathy** | 1 | 4% | | | **2** | **8%** | | |
| *Gastrointestinal* | | | | | | | | |
| Constipation | 9 | 38% | | | | | | |
| Diarrhea | 6 | 25% | 2 | 8% | | | | |
| Nausea and vomiting | 16 | 66% | 8 | 33% | | | | |
| Mucositis | 7 | 29% | 1 | 4% | | | | |
| *Investigations* | | | | | | | | |
| **PNN count decrease** | 2 | 8% | 2 | 8% | **10** | **42%** | **3** | 12% |
| **ASAT/ALAT increase** | 2 | 8% | 1 | 4% | **3** | **12%** | **1** | 4% |
| **Other hepatic disorder** | 1 | 4% | 1 | 4% | **3** | **12%** | | |
| **Other investigations** | | | 1 | 4% | **2** | **8%** | | |
| *Musculoskeletal* | | | | | | | | |
| Myalgia | 5 | 21% | 2 | 8% | | | | |

***Toulmonde M, 2018 ASCO Annual Meeting***

# DESMOPAZ

## QoL – EORTC QLQ-C30

### Pazo arm

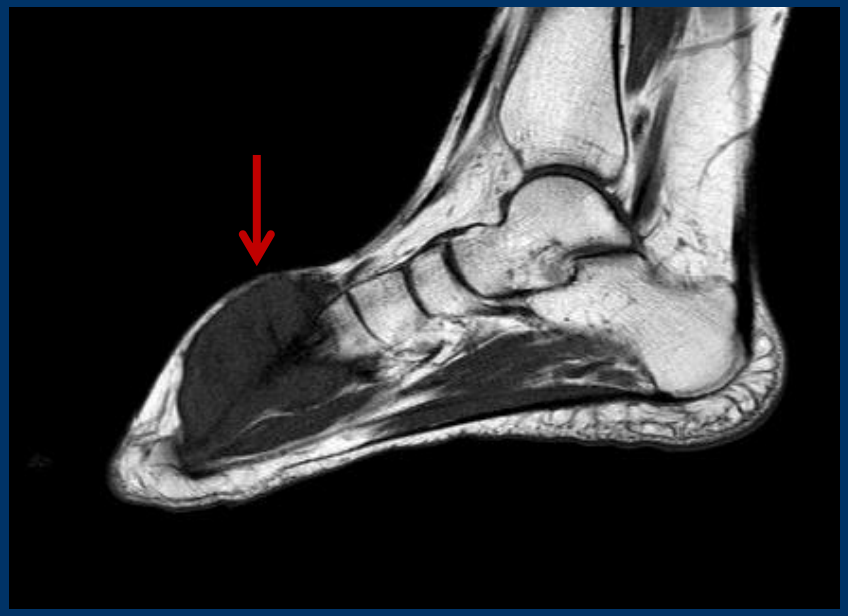
| | Cycle 1 (N= 44) | | Cycle 6 (N = 41) | |
|---|---|---|---|---|
| | Median | (Q1-Q3) | Median | (Q1-Q3) |
| **Global Health status** | **67** | (50-83) | **67** | (50-70) |
| Physical functioning | 93 | (77-100) | 87 | (73-93) |
| Emotional Functioning | 75 | (54-88) | 83 | (67-100) |
| **Pain** | **33** | (17-67) | **17** | (0-33) |
| Fatigue | 28 | (6-56) | 44 | (33-56) |
| Appetite loss | 0 | (0-33) | 33 | (0-33) |
| Diarrhoea | 0 | (0-17) | 33 | (0-67) |

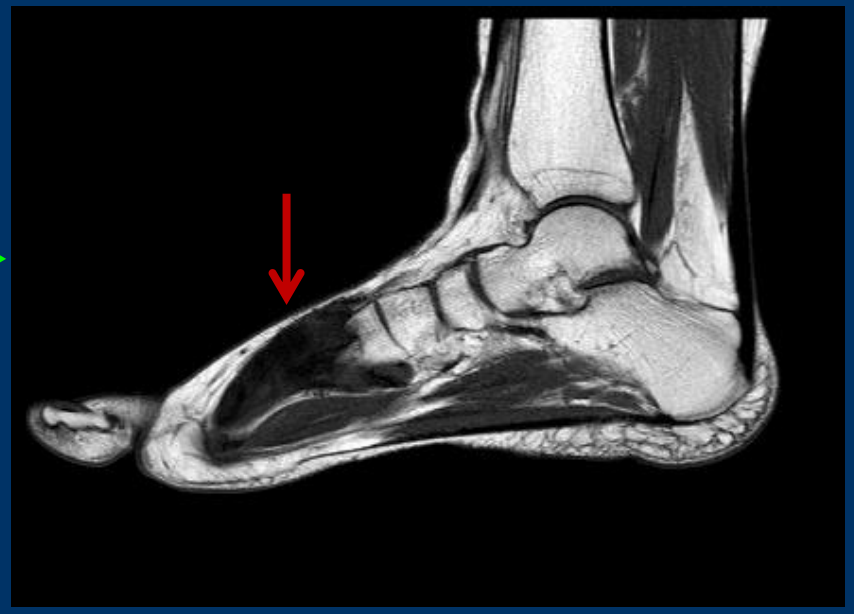
### MV arm

| | Cycle 1 (N= 19) | | Cycle 6 (N = 6) | |
|---|---|---|---|---|
| | Median | (Q1-Q3) | Median | (Q1-Q3) |
| **Global Health status** | **67** | (42-83) | **50** | (33-50) |
| Physical functioning | 87 | (73-100) | 80 | (73-80) |
| Cognitive Functioning | 100 | (83-100) | 67 | (67-100) |
| **Pain** | **33** | (0-50) | **33** | (17-50) |
| Fatigue | 22 | (11-44) | 44 | (44-67) |
| Nausea vomiting | 0 | (0-0) | 17 | (0-17) |
| Dyspnea | 0 | (0-0) | 33 | (0-33) |

*Toulmonde M, 2018 ASCO Annual Meeting*

# Patient #4, clinical benefit





baseline, 06/2016

after 41 cycles, 12/2017

# Oral vinorelbine as single agent

**Regimens and treatment duration**

| | |
|---|---|
| vinorelbine alone | 25 pts (50%) |
| vinorelbine plus hormonal therapy | 25 pts (50%) |
| total | 50 pts |
| median treatment duration | 11 months |

**Toxicity**

| | |
|---|---|
| grade 3 or 4 adverse events | 0 |

**Activity**

| | |
|---|---|
| Partial Response | 32% |
| Stable Disease | 58% |
| Progression Disease | 10% |

*Mir O, 2016 ASCO annual meeting*

# In brief

- low-dose chemotherapy is active, with long-lasting response in DT patients
- radiological responses occur generally late; non-dimensional response can be observed
- good toxicity profile but…
- available QoL tests are not specific for this disease
- oral vinorelbine alone is an option
- limited data on role of this regimen in FAP-related DTs

# Low dose chemotherapy in FAP-related desmoid tumors: results from a multicentre retrospective analysis

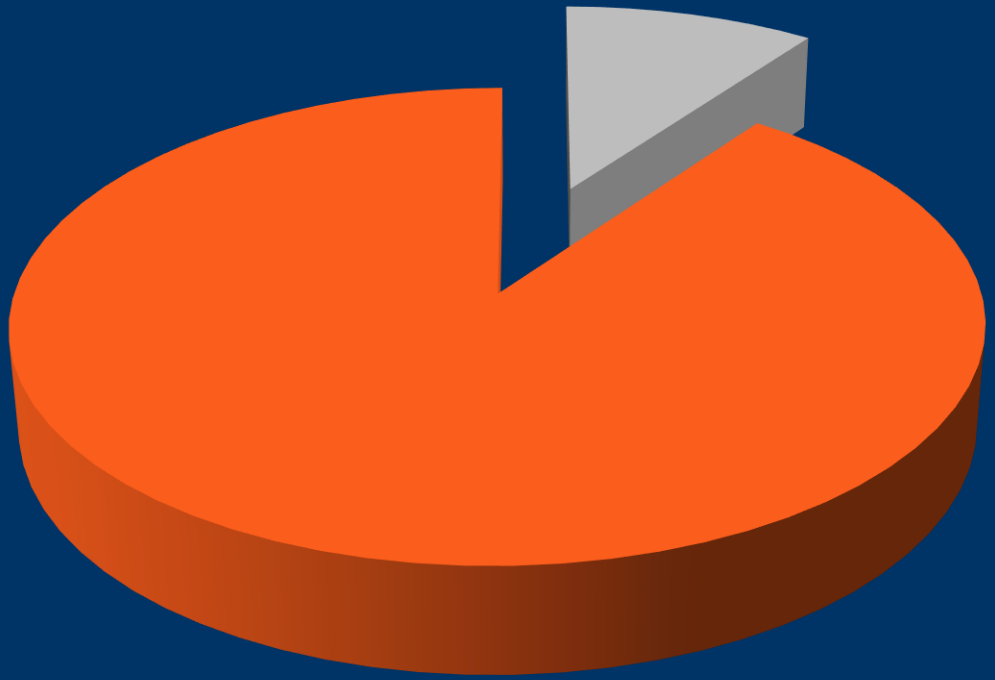
**Bruno Vincenzi, Salvatore Provenzano, Antonella Brunello, Giuseppe Badalamenti, Margherita Nannini, Toni Ibrahim, Peter Hohenberger, Silvia Gasperoni, Andrea Napolitano, Marianna Silletta, Marco Vitellaro, Angelo Paolo Dei Tos, Daniele Santini, Giuseppe Tonini, Elena Palassini**

***Presented as poster at 2018 ASCO annual meeting***

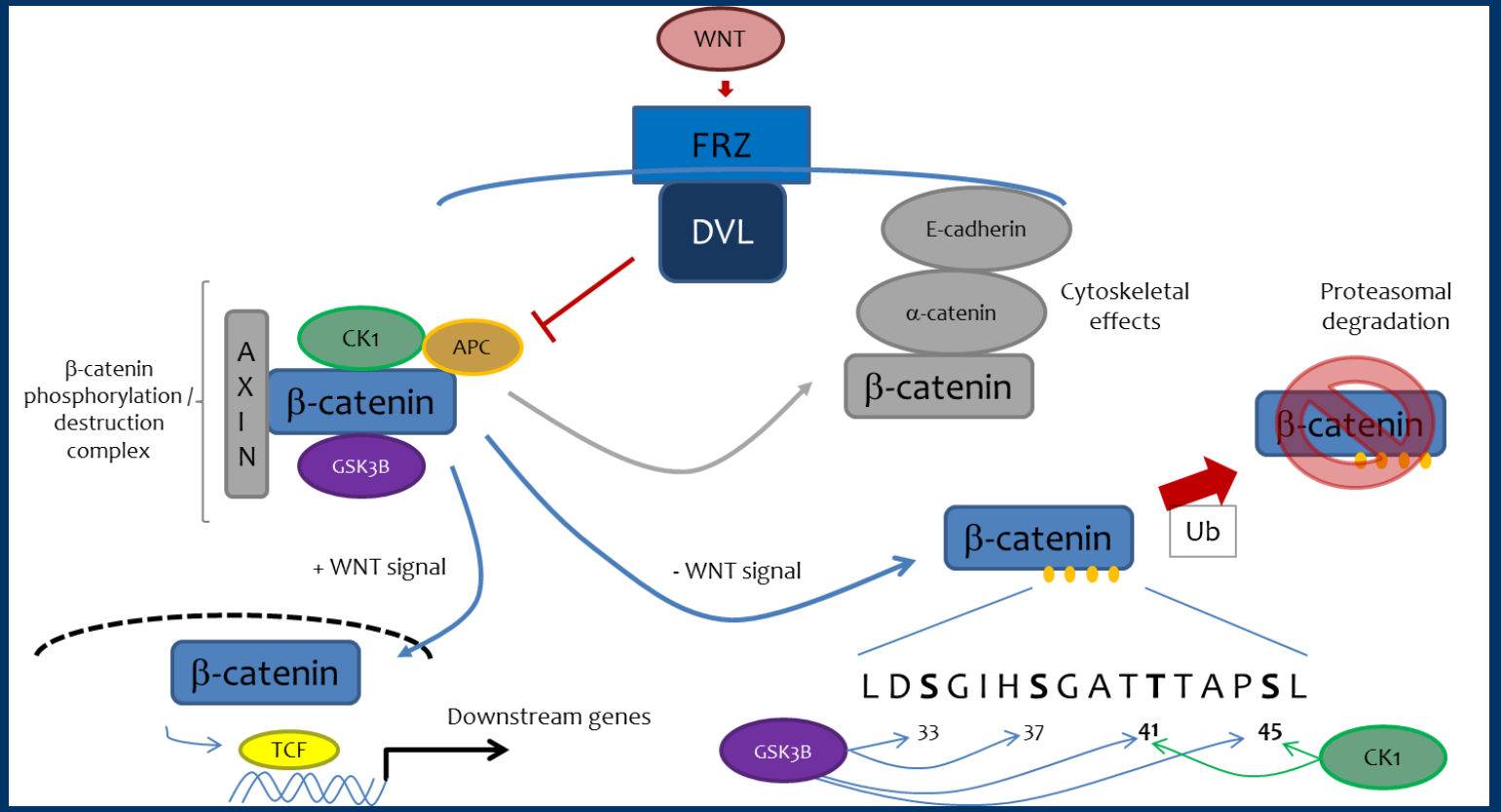
# FAP-related desmoid tumors

sporadic desmoid tumors
(90-95%)

FAP–related desmoid tumors
(5-10%)



# WNT pathway dysregulation



# Incidence

**sporadic desmoid tumors (90-95%)**

***0.2-0.4*/100,000/year**

# Incidence

**sporadic desmoid tumors (90-95%)**

***0.2-0.4*/100,000/year**

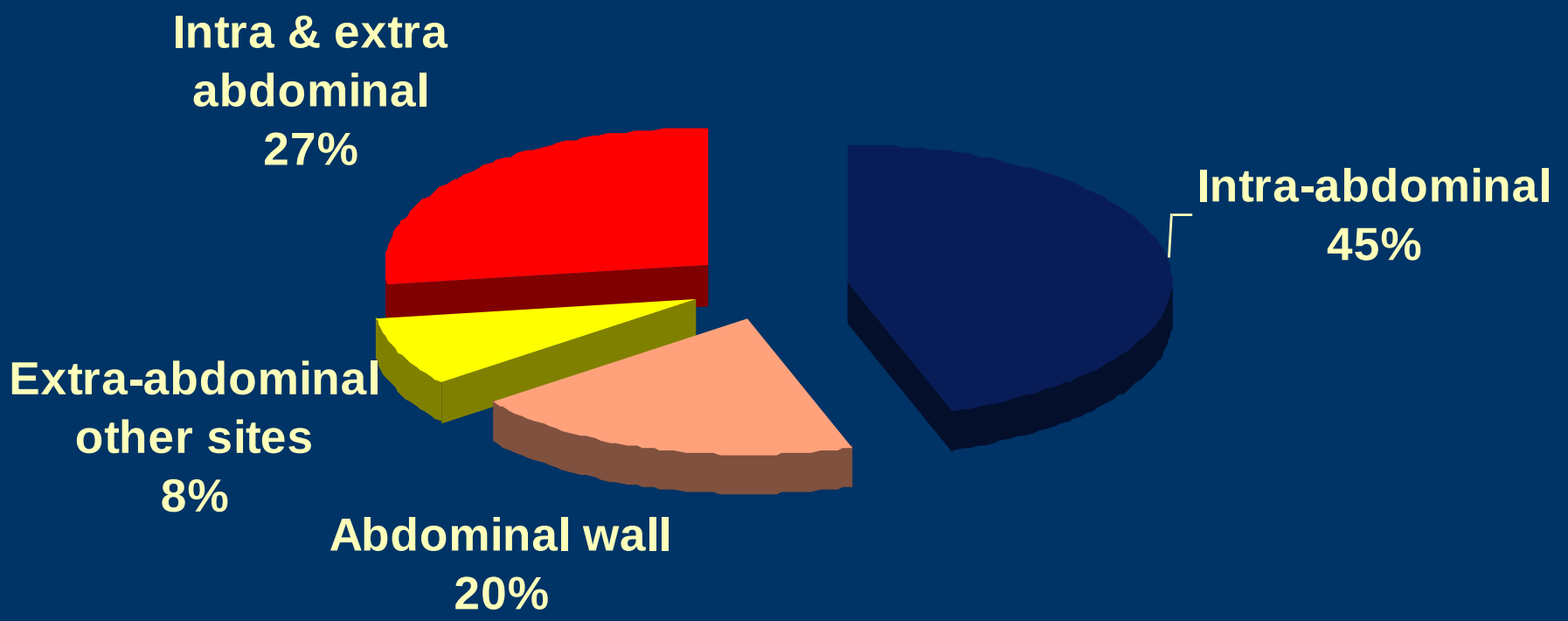
**FAP–related desmoid tumors (5-10%)**

***200*/100,000 FAP/year**

| Institution | N. FAP pts | N. of FAP pts with DT |
|---|---|---|
| Cleveland Clinic | 325 | 29 (9%) |
| MSKC | 496 | 40 (8%) |
| University of Helsinky | 168 | 19 (11%) |
| Univeristy of tokio | 1050 | 71 (7%) |
| The Johns Hopkins Hospital | 825 | 83 (10%) |
| INT- Milano | 894 | 107 (12%) |

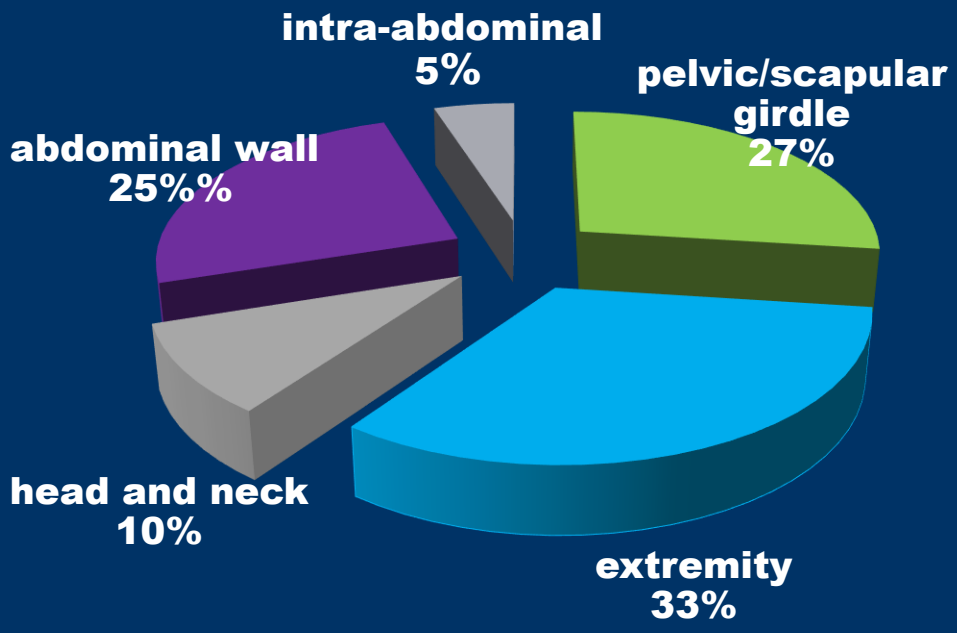
| Institution | N. FAP pts | N. of FAP pts with DT | mean age at DT diagnosis yrs | F/M ratio |
|---|---|---|---|---|
| Cleveland Clinic | 325 | 29 (9%) | 30 | 3.0 |
| MSKC | 496 | 40 (8%) | 29 | 1.8 |
| University of Helsinky | 168 | 19 (11%) | 29 | 1.3 |
| University of Tokio | 1050 | 71 (7%) | 30 | 1.8 |
| The Johns Hopkins Hospital | 825 | 83 (10%) | 32 | 1.4 |
| INT- Milano | 894 | 107 (12%) | 32 | 1.5 |

# Site

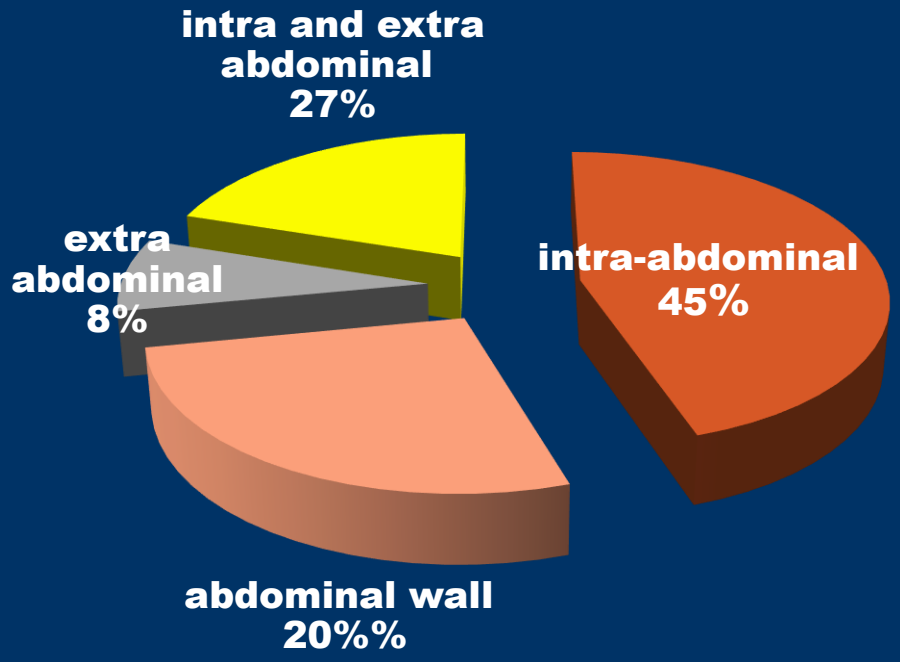

Intra & extra abdominal 27%
Intra-abdominal 45%
Extra-abdominal other sites 8%
Abdominal wall 20%

# Site

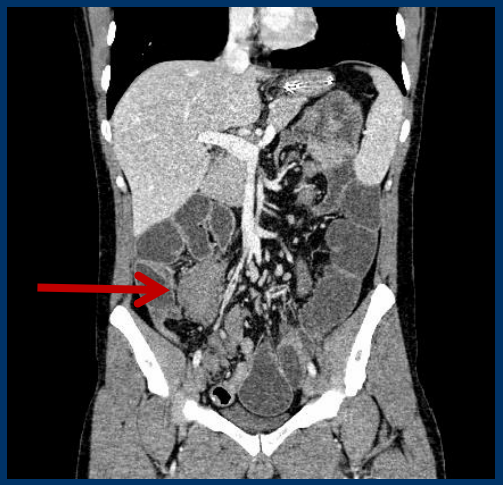
## sporadic desmoid tumors



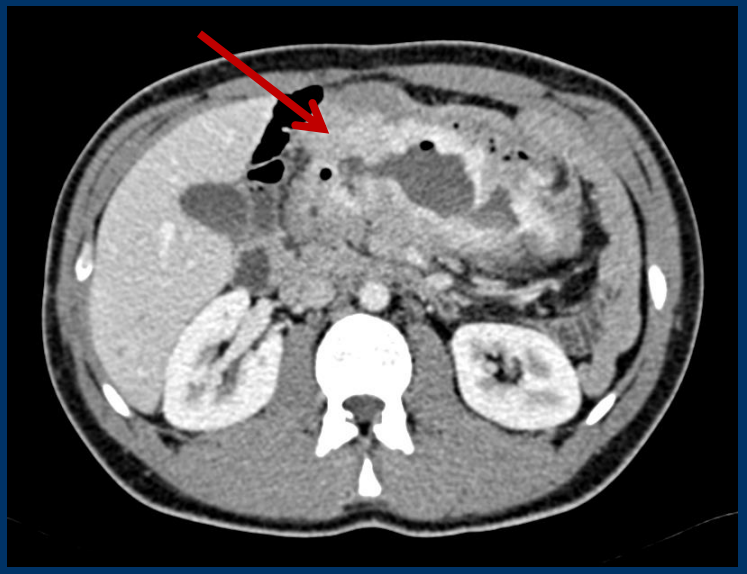

## FAP–related desmoid tumors



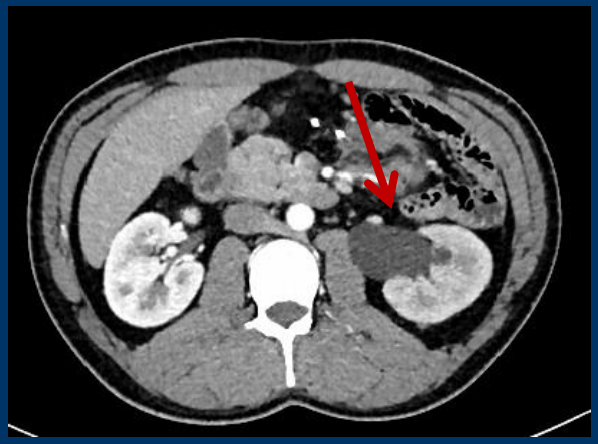
# Complications



intestinal obstruction

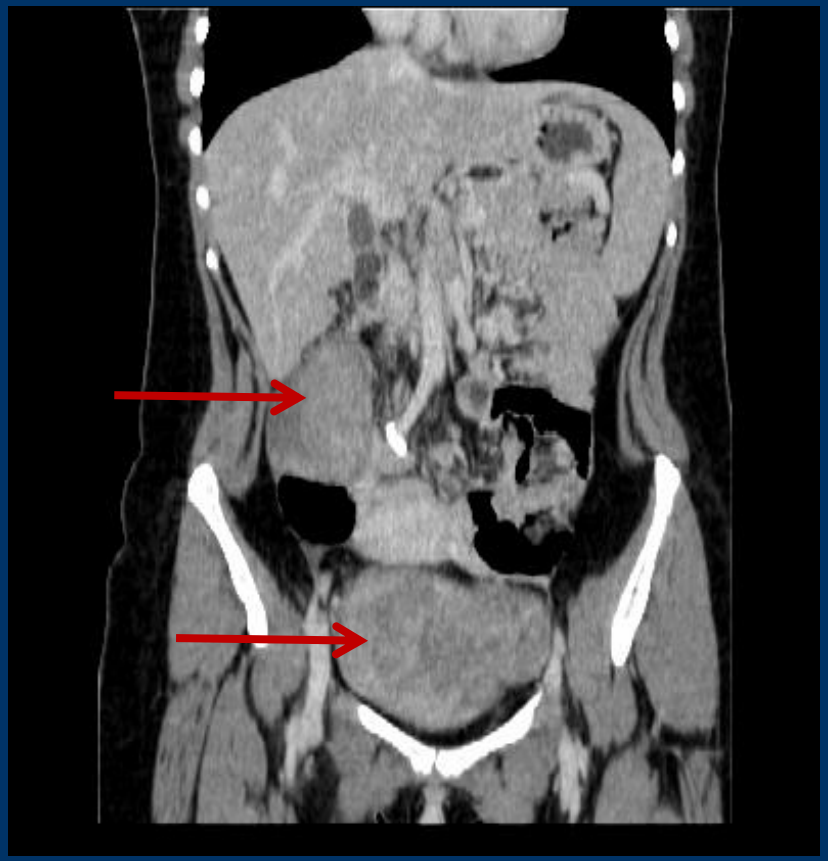


intestinal perforation

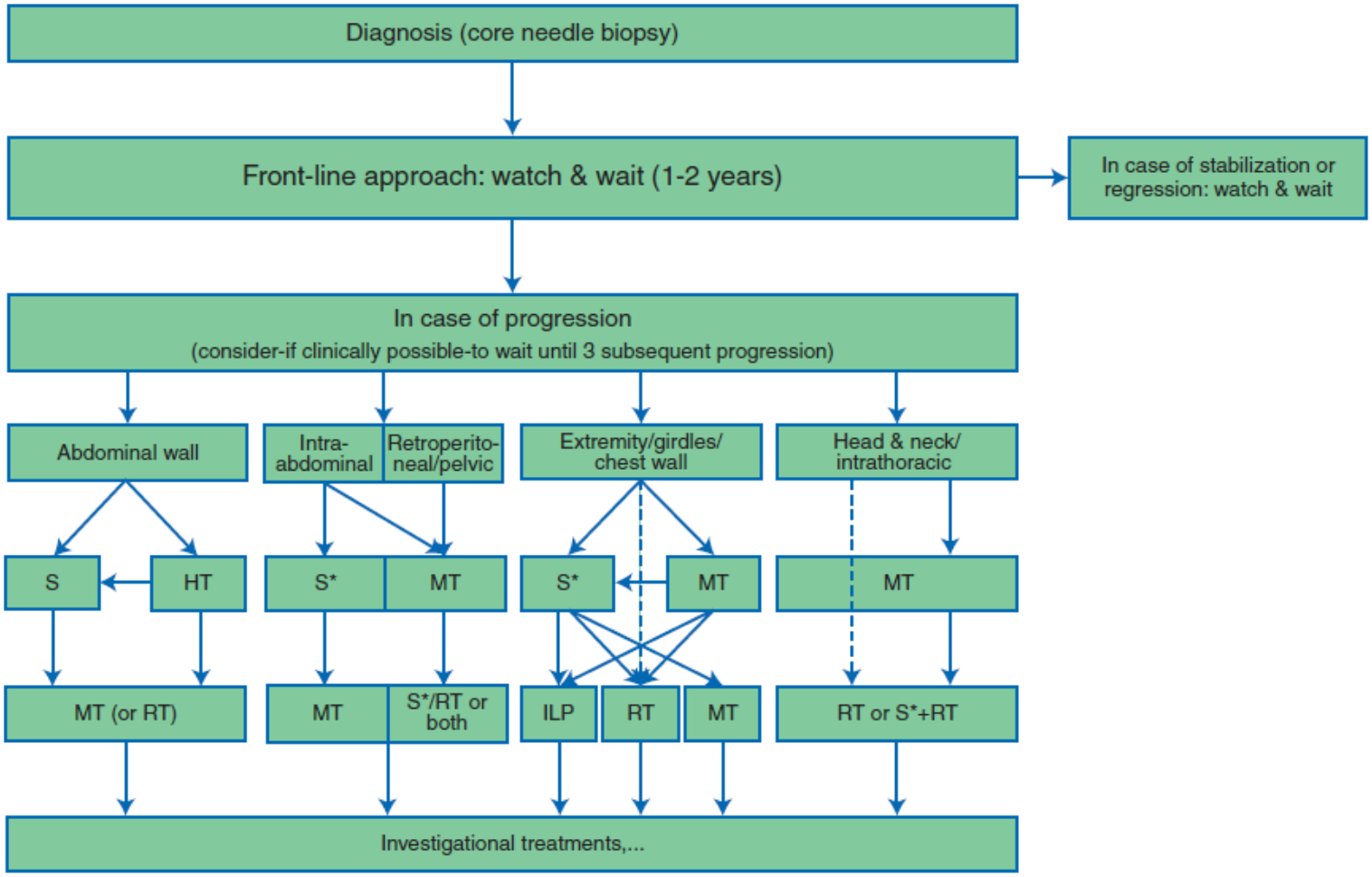


hydroureteronephrosis

# Multifocality



# Sporadic DT: from surgery to a more conservative management. The european therapeutic algorithm




*** Surgery is an option only if morbidity is limited; HT: hormonal therapy; MT: medical therapy; ILP: isolated limb perfusion**

*Kasper B, Ann Oncol 2017*

# International consensus meeting (Europe, US, Japan), including FAP-related DTs

*Milano, June 2018*

# Consensus meeting paper

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

*For intraabdominal / retroperitoneal / pelvic DT, systemic therapy should be considered as the first treatment option. For extremity / girdles / chest wall DT, again surgery should not be the first treatment option unless the expected morbidity is very low (and only following MDT discussion); medical therapy should be administered preferably. Besides surgery, radiotherapy and medical therapy, isolated limb perfusion (ILP) may be part of the further treatment strategy in this location.*

*FAP-associated DT (Gardner syndrome) seems to be more aggressive and multifocal and, therefore, tends to be treated more aggressively in terms of medical management. Act with caution regarding performing a biopsy; however, currently there are insufficient data to totally exclude performing a biopsy. In the setting of a confirmed APC mutation, a mesenteric mass may likely be a DT, particularly if the patient had prior surgery. FAP patients should be jointly managed by sarcoma specialists and experts in gastrointestinal cancer. Surgery should be performed by an experienced surgeon; small bowel transplantation should be discouraged.*

***The desmoid working group, submitted***

# Low dose chemotherapy in FAP-related desmoid tumors: results from a multicentre retrospective analysis

**Bruno Vincenzi, Salvatore Provenzano, Antonella Brunello, Giuseppe Badalamenti, Margherita Nannini, Toni Ibrahim, Peter Hohenberger, Silvia Gasperoni, Andrea Napolitano, Marianna Silletta, Marco Vitellaro, Angelo Paolo Dei Tos, Daniele Santini, Giuseppe Tonini, Elena Palassini**

***Presented as poster at 2018 ASCO annual meeting***

# Centres involved


- University Hospital, Mannheim
- INT, Milano
- IOV, Padova
- Ospedale S. Orsola, Bologna
- Ist. Oncologico Romagnolo, Forlì
- AOU Careggi, Firenze
- Campus Biomedico, Roma
- AOU Policlinico di Palermo, Palermo

# Patient characteristics

| | |
|---|---|
| - N. pts | 28 |
| - M/F | 13/15 |
| - Median age at time of CT | 34 (range 7-57) years |
| - Site | |
| - intra-abdominal | 23 (82%) |
| - Intra and extra abdominal | 4 (14%) |
| - extra-abdominal | 1 (4%) |
| - Multifocal disease | 12 (43%) |
| - Previous treatment: | |
| - surgical treatment: | 17 (60%) |
| - medical therapy: | 9 (32%) |
| -NSAIDs: | 3 (11%) |
| -anti-hormonal therapy: | 6 (21%) |

# Regimen

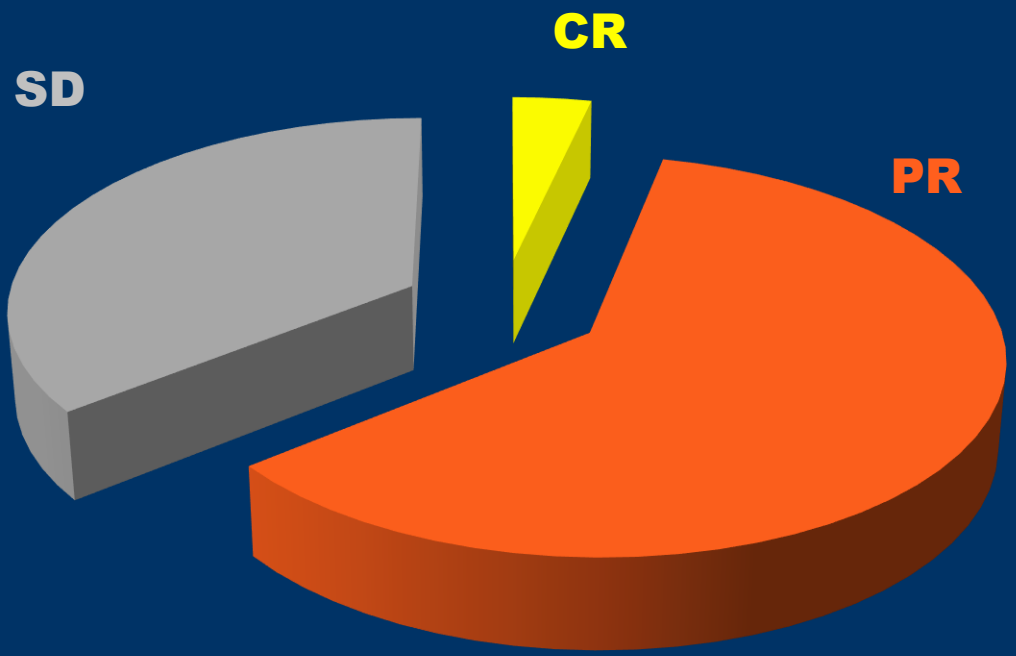
**weekly intravenously**

**methotrexate 50 mg plus**
**vinorelbine 20 mg/m$^2$ or vinblastine 5 mg/m$^2$**

# Treatment duration and toxicity

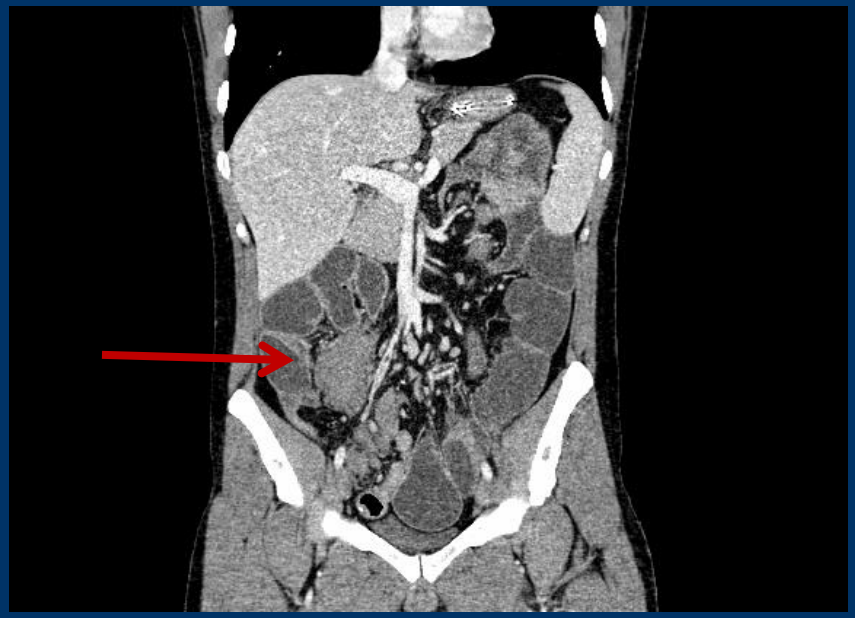
| | |
|---|---|
| median treatment duration | 11 months |
| definitive stop for toxicity | 0 pts |

# Activity



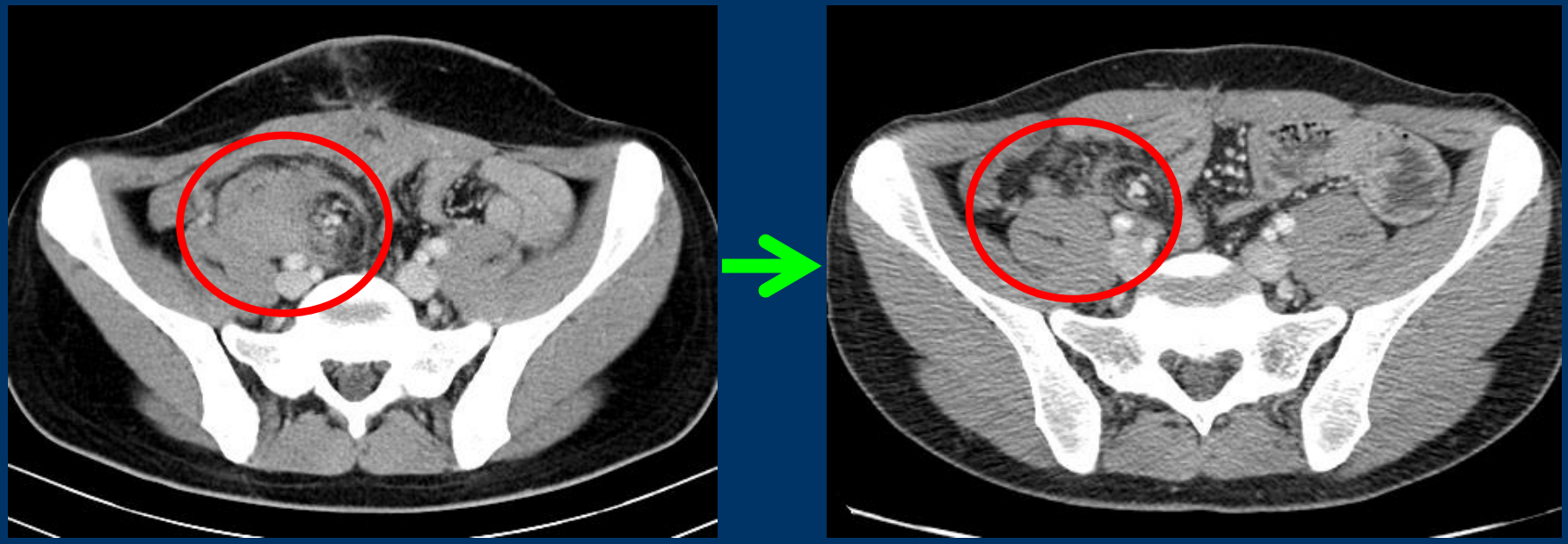

**Complete Response (CR)** = 1/28 (4%)
**Partial Response (PR)** = 17/28 (60%)
**Stable Disease (SD)** = 10/28 (36%)

# Patient #1



M, 26 yrs
10/2014 prophylactic colectomy
03/2016 intestinal obstrucion and evidence of mesenteric lesion treated with ileostomy

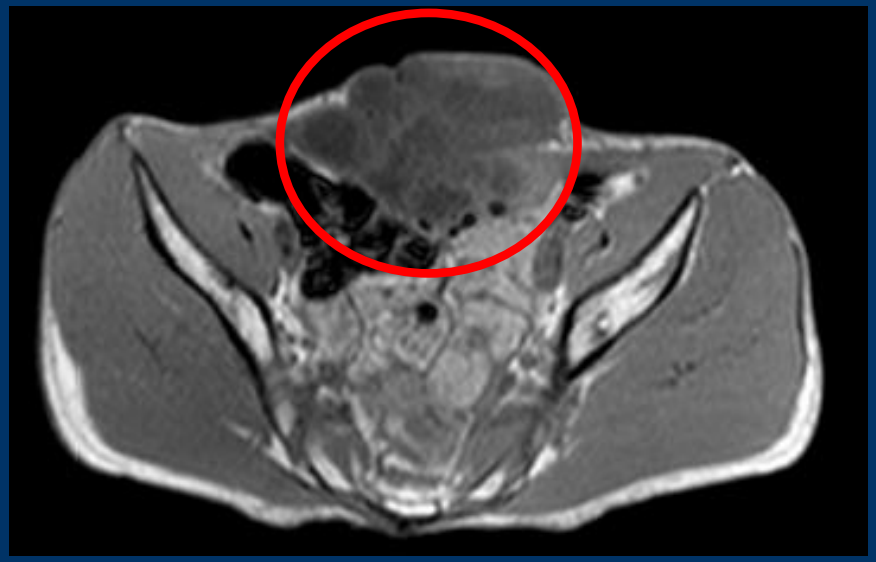
# Patient #1, dimensional response



baseline, 05/2016

after 40 cycles, 11/2017

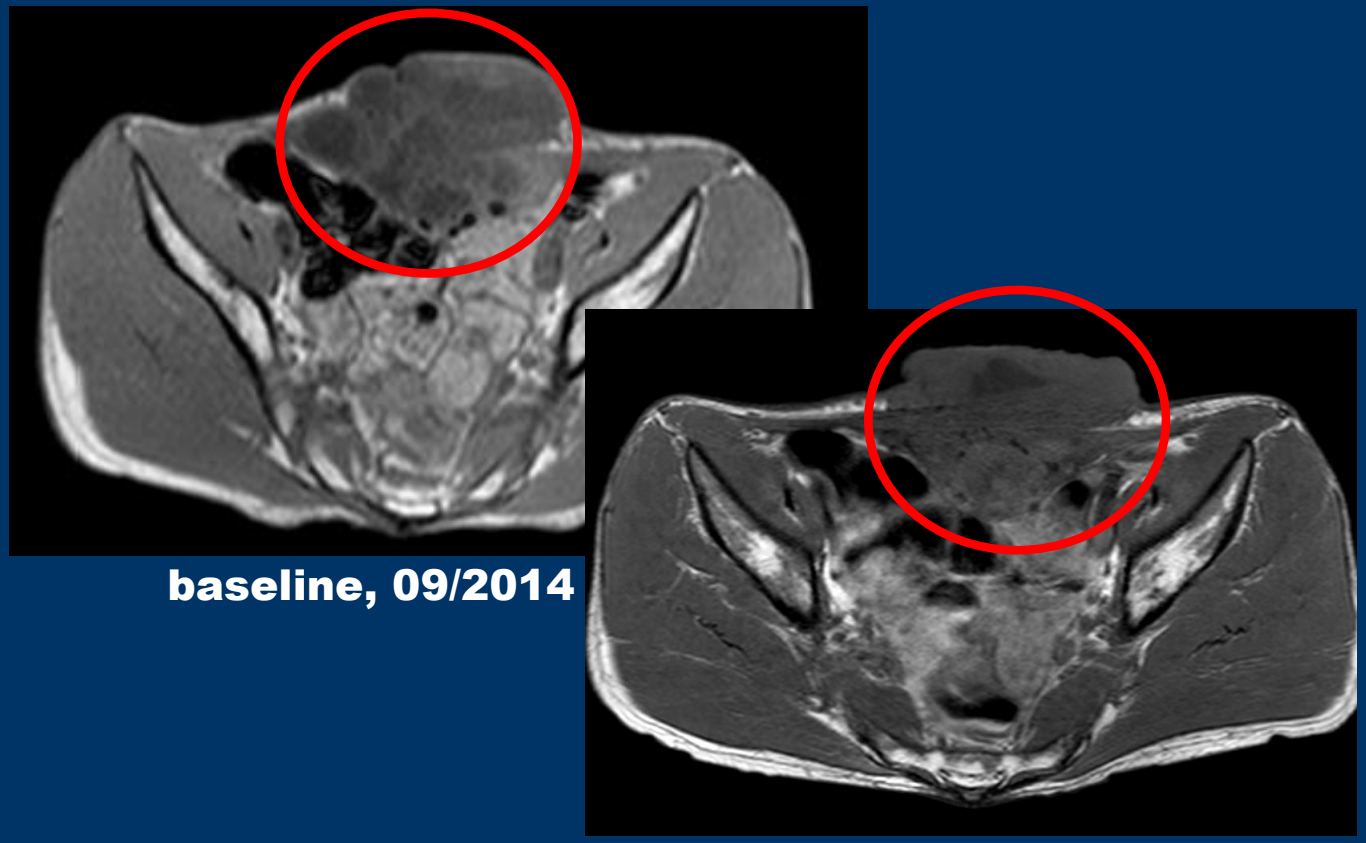
# Patient #2



baseline, 09/2014

M, 29 yrs
11/2009 prophylactic colectmy
2010: evidence of multiple intra-abdominal and adbominal wall lesiones subsequently treated with several surgeries and hormonal therapy

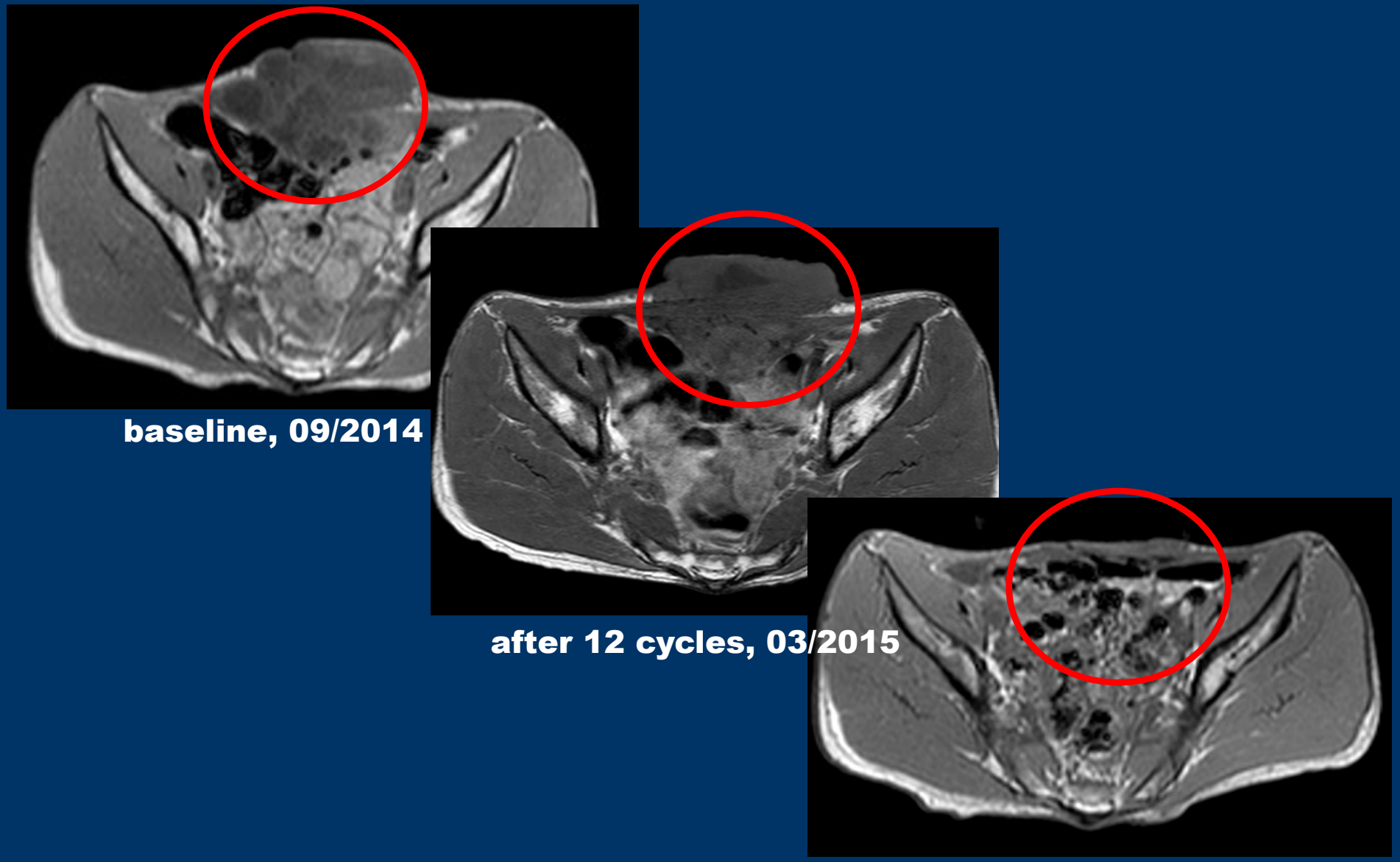
# Patient #2



baseline, 09/2014

after 12 cycles, 03/2015

# Patient #2, late dimensional response

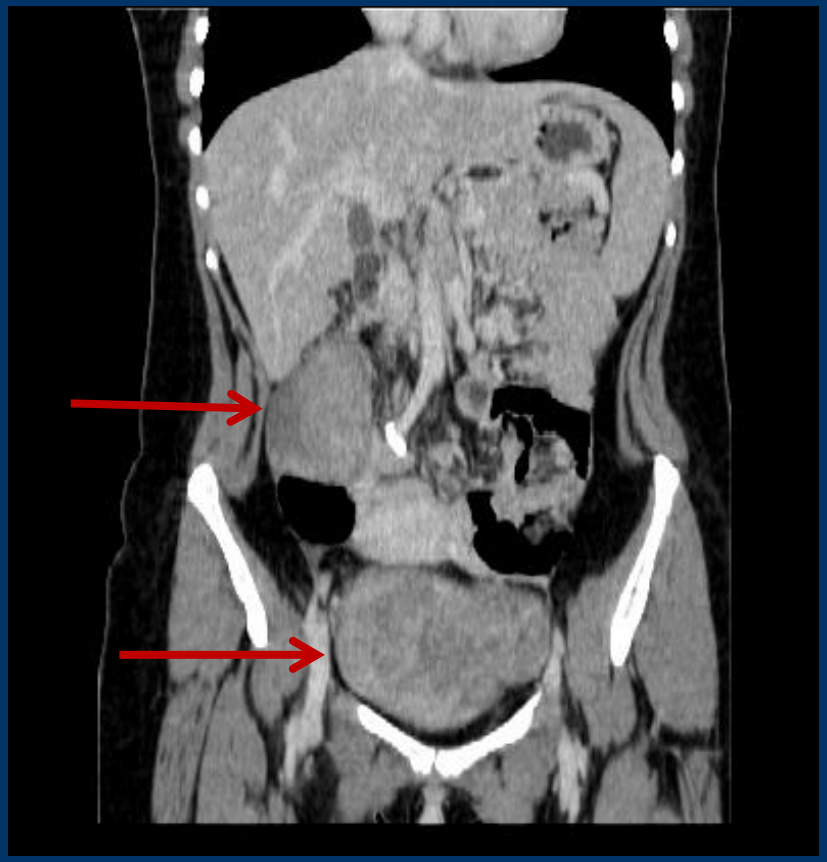


baseline, 09/2014

after 12 cycles, 03/2015

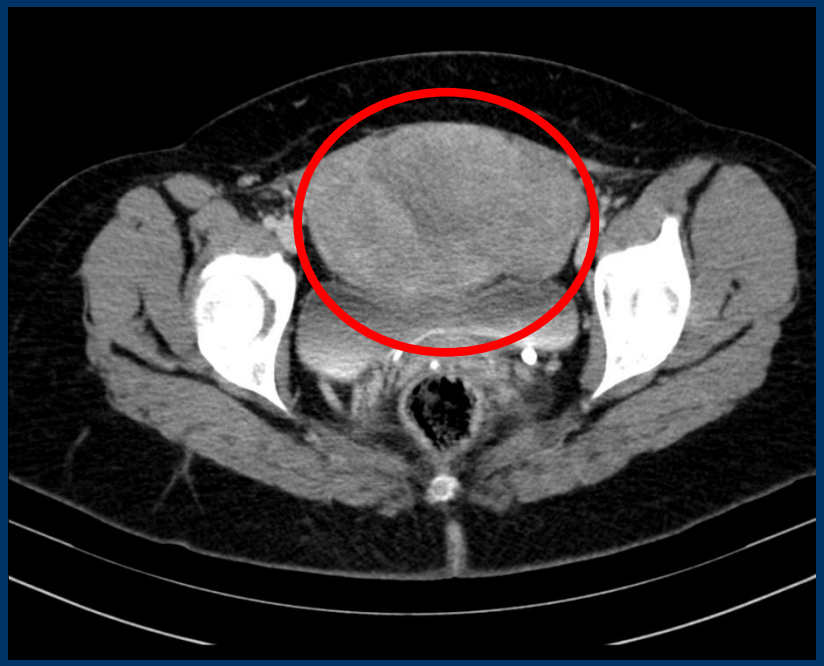
after 32 cycles, 01/2016

# Patient #3

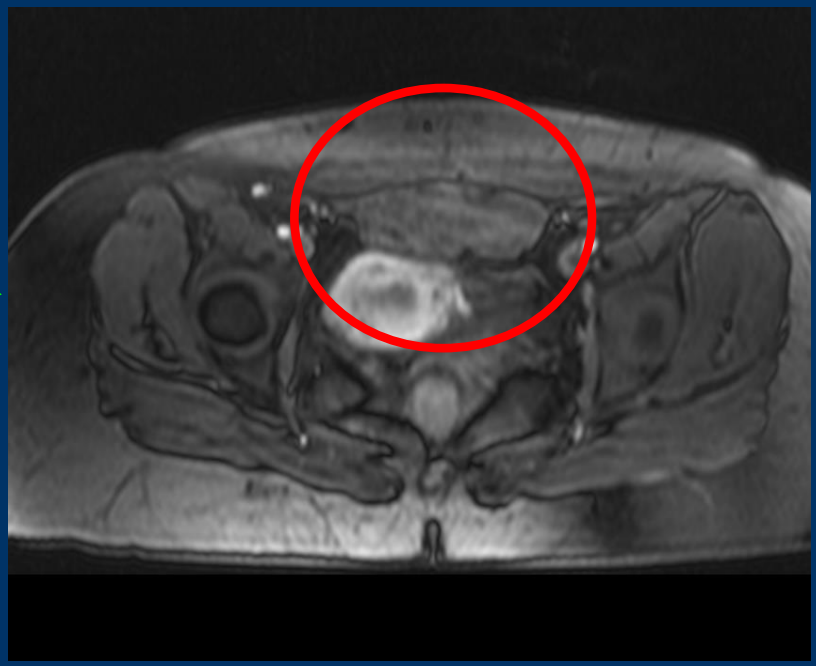


F, 22 yrs
2005: prophylactic colectomy
08/2007: evidence of multiple abdominal lesions

# Patient #3

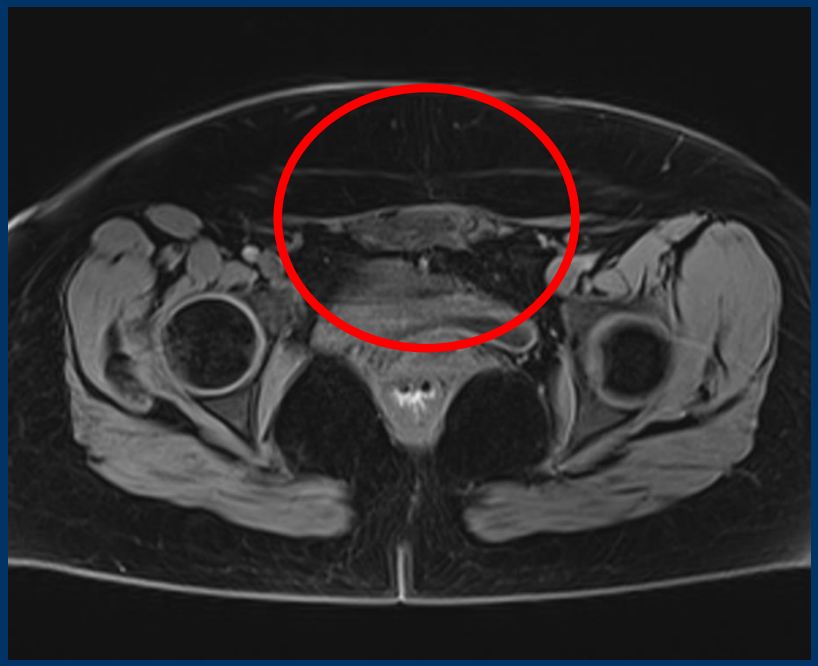


baseline, 10/2007



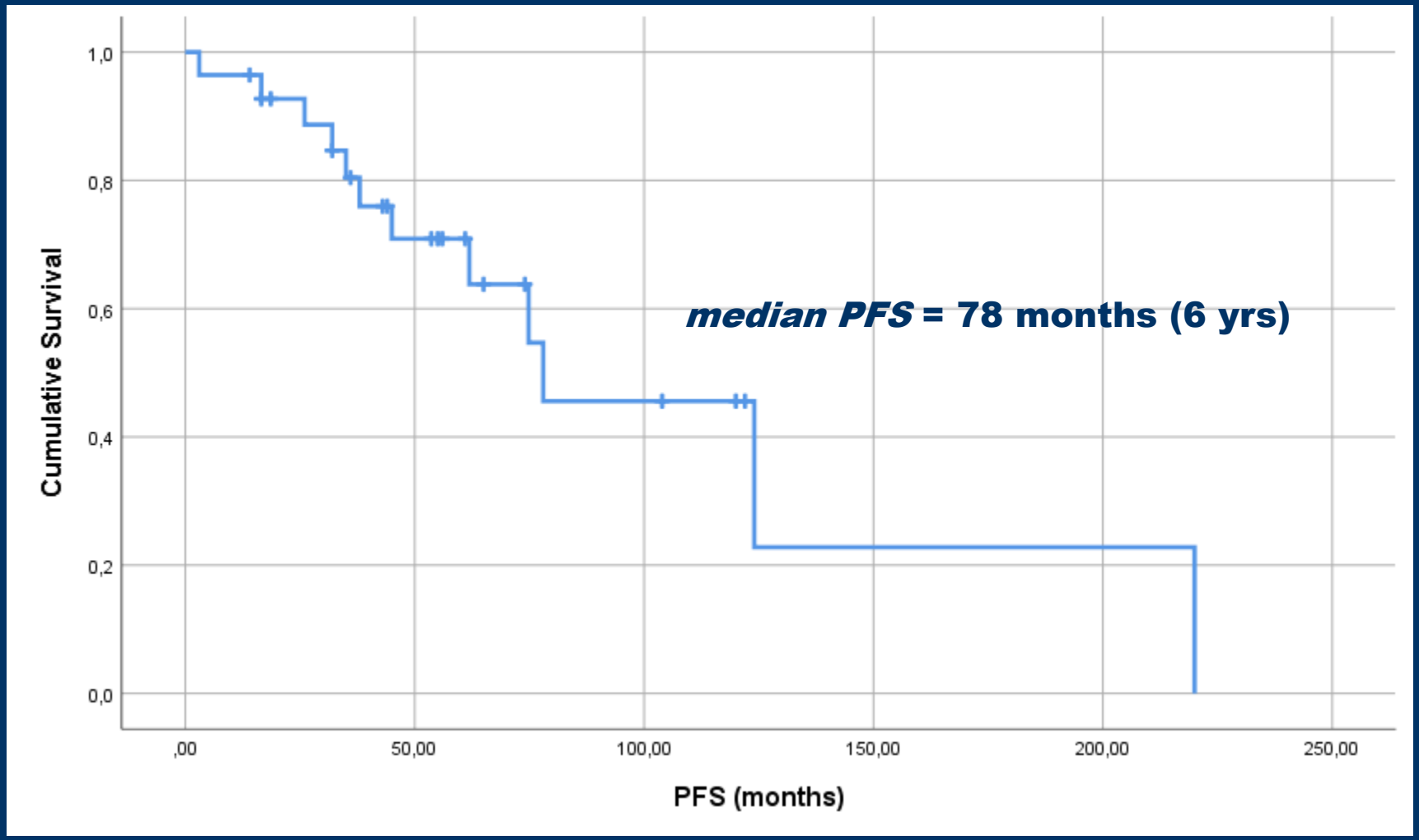
after 30 cycles, 10/2008

# Patient #3, long-lasting response



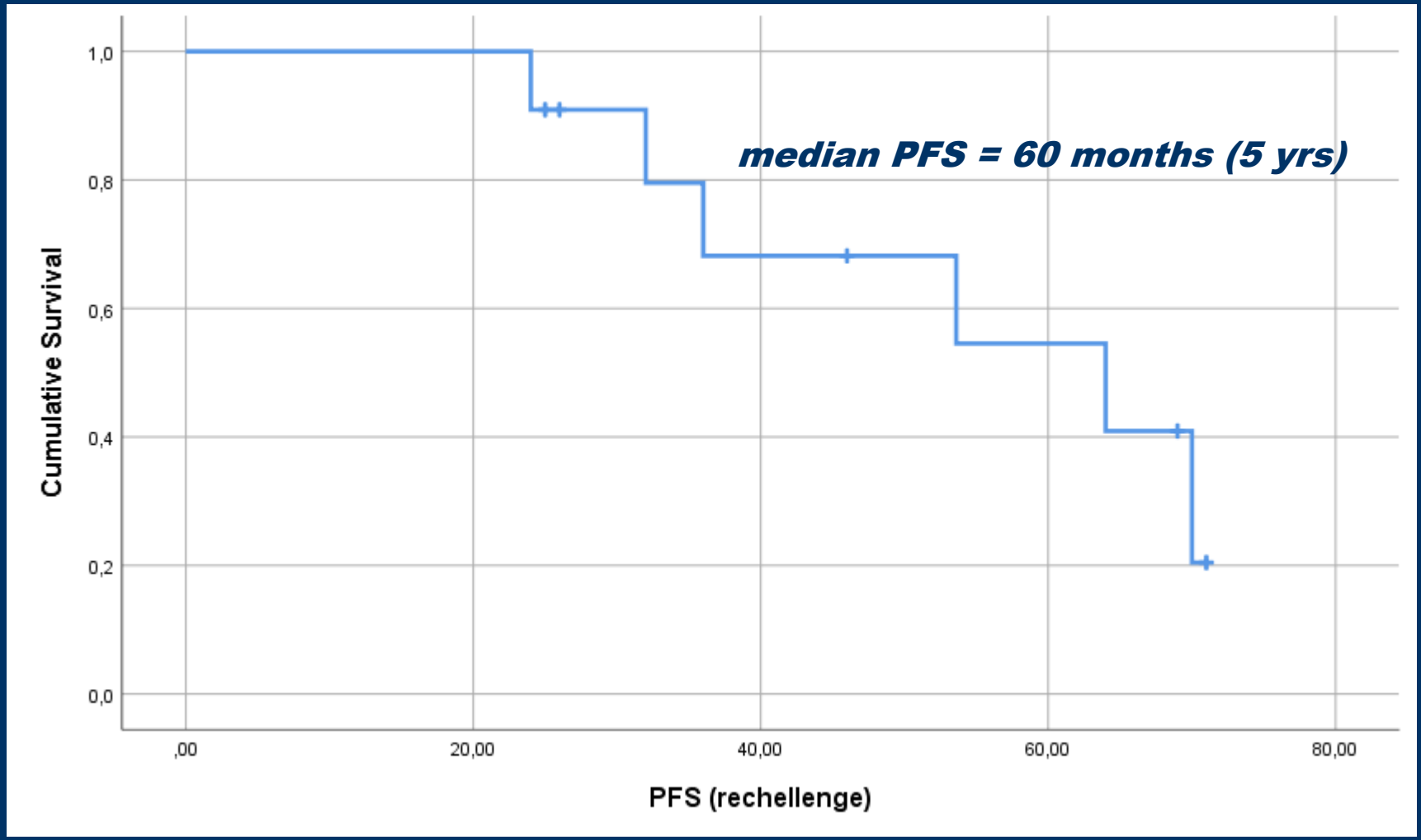
10 years after chemotherapy, 09/2018

# PFS

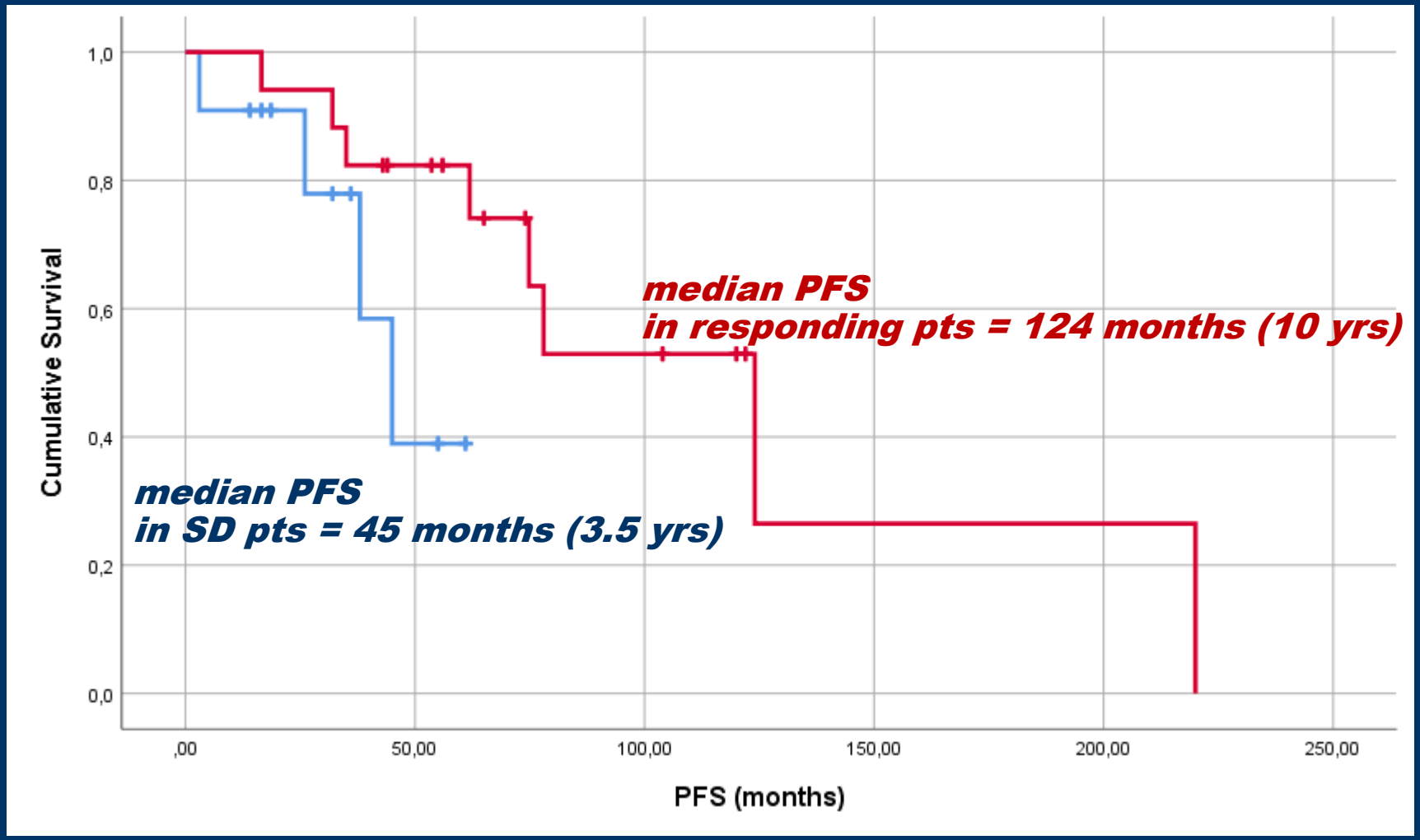

1,0
0,8
0,6
0,4
0,2
0,0
Cumulative Survival
,00
50,00
100,00
150,00
200,00
250,00
PFS (months)
median PFS = 78 months (6 yrs)

# Rechallenge, PFS

**11 patients, upon progression after CT withdrawal**



# PFS


Cumulative Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
50,00
100,00
150,00
200,00
250,00
PFS (months)
median PFS
in responding pts = 124 months (10 yrs)
median PFS
in SD pts = 45 months (3.5 yrs)

# Conclusions

- there is a consensus in favour of a more aggressive management of FAP-related DTs, generally offering an earlier active treatment (because of site, multifocality, higher risk of complications)

- low-dose chemotherapy is active of in FAP-related DTs, with a long median PFS, being higher than 10 years in the group of responding patients

- response may occur late

- in case of progression, after chemotherapy withdrawal, re-challenge with the same regimen was effective

- collaboration between Centres is crucial for improving the knowledge of this disease

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