

# The Management of Desmoid Tumors: A joint global evidence-based consensus guideline approach for adult and pediatric patients



## The Desmoid Tumor Working Group

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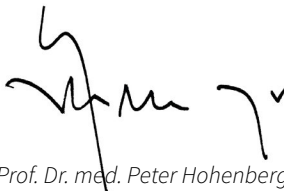
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## FOREWORD

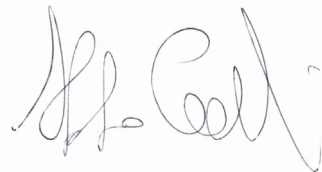
Desmoid tumor (DT; other synonymously used terms: Desmoid-type fibromatosis, aggressive fibromatosis) is a rare and locally aggressive monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course. Previously surgery was the standard primary treatment modality; however, in recent years a paradigm shift towards a more conservative management has been introduced and an effort to harmonize the strategy amongst clinicians has been made. We present herein an evidence-based, joint global consensus guideline approach to the management of this disease focusing on: molecular genetics, indications for an active treatment, and available systemic therapeutic options. This paper follows a one-day consensus meeting held in Milan, Italy, in June 2018 under the auspices of the European Reference Network for rare solid adult cancers, EURACAN, the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG), as well as Sarcoma Patients EuroNet (SPAEN) and The Desmoid Tumor Research Foundation (DTRF). The meeting brought together over 50 adult and pediatric sarcoma experts from different disciplines, patients and patient advocates from Europe, North America and Japan.



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## INTRODUCTION

### General issues and epidemiology

Desmoid tumor (DT) is a rare monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course. In the International Classification of Diseases (ICD) it is classified as D48.1. According to the World Health Organization (WHO), DT is a “clonal fibroblastic proliferation that arises in the deep soft tissues and is characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize,” even though it may be multifocal in the same limb or body part <sup>[1]</sup>. DT is a distinctly rare entity (incidence 5-6 cases per 1 million of the population per annum <sup>[2]</sup>) with a peak age of 30-40 years <sup>[3]</sup>. DT may occur at abdominal, intra-abdominal, and extra-abdominal locations and approximately 5-10 % arise in the context of familial adenomatous polyposis (FAP). Efforts to standardize the management of this disease have been undertaken in recent years <sup>[4,5]</sup>.

A global consensus meeting involving experts from Europe, North America and Japan was organized to further define the appropriate clinical management of DT, reducing inconsistent care around the world and suboptimal outcomes for many patients. The focus of the meeting was to discuss the molecular genetics of this disease, the indications for an active treatment as well as available systemic treatment options. The consensus was reached by: an initial evidence-based systematic literature search that was performed by an independent institute involving methodological experts and an analysis of the identified literature according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) followed by the consensus meeting. The meeting involved sarcoma experts with expertise in both adult and pediatric DT patients from Europe, North America and Japan, as well as patients and patient advocates from Sarcoma Patients EuroNet (SPAEN) and the USA-based Desmoid Tumor Research Foundation (DTRF). The meeting was held on June 18, 2018 in Milan, Italy, under the auspices of the European Reference Network for rare solid adult cancers, EURACAN, and with the support of the patient advocacy groups DTRF, “sos desmoid” Germany and SPAEN.

### Methodology

#### Literature search

In advance of the consensus meeting a literature search was performed to elicit data upon which consensus recommendations were based. All literature searches (MEDLINE and EMBASE) were performed in January 2018. We only searched for English and German articles; no other limitations were applied in the search strategy. In addition, we requested that the guideline panel members cross-check the references of all included articles and systematic reviews on similar topics to identify articles that might have been missed by the search strategy. For the five different topics the following pre-defined inclusion criteria to select studies were applied:

Pathology and molecular genetics	
Patients	Patients with sporadic desmoids
Exposure	β-catenin mutated desmoids (CTNNB1 T41A, S45F, S45P, S45N)
Comparison/Control	Wild-type desmoids
Outcomes/Endpoints	RFS, PFS
Study types	Comparative studies with at least two arms (at least 20 patients)
Indications for an active treatment	
Patients	Patients with sporadic (β-catenin mutated vs wild-type) and FAP-associated desmoids
Intervention	Active treatment (surgery, radiotherapy, medical therapy)
Comparison/Control	No intervention/watch and wait
Outcomes/Endpoints	RFS, PFS, side effects, health-related quality of life (HRQoL)
Study types	Comparative studies with at least two arms (at least 20 patients)

<b>Hierarchy of medical therapies</b>	
<b>Patients</b>	Patients with sporadic and FAP-associated desmoids
<b>Intervention</b>	Medical therapies (antihormonal therapies, NSAIDs, interferon, imatinib, nilotinib, sorafenib, pazopanib, PF-03084014, chemotherapy: methotrexate, vinblastine, vinorelbine, doxorubicin, dacarbazine, cyclophosphamide, pegylated liposomal doxorubicin)
<b>Comparison/Control</b>	No intervention
<b>Outcomes/Endpoints</b>	RFS, PFS, side effects, HRQoL
<b>Study types</b>	Comparative studies with at least two arms (at least 20 patients)
<b>Pain control and physical therapy</b>	
<b>Patients</b>	Patients with sporadic and FAP-associated desmoids
<b>Intervention</b>	Pain medication, physical therapy
<b>Comparison/Control</b>	No intervention
<b>Outcomes/Endpoints</b>	RFS, PFS, side effects, HRQoL
<b>Study types</b>	Comparative studies with at least two arms (at least 20 patients)
<b>Radiotherapy</b>	
<b>Patients</b>	Patients with sporadic and FAP-associated desmoids
<b>Intervention</b>	Radiotherapy
<b>Comparison/Control</b>	No intervention/surgery only
<b>Outcomes/Endpoints</b>	RFS, PFS, side effects, HRQoL
<b>Study types</b>	Comparative studies with at least two arms (at least 20 patients)

Abbreviations: RFS, recurrence-free survival; PFS, progression-free survival; QoL, quality of life.

Titles / abstracts of all articles were screened by two reviewers independently. Subsequently, the full text of all potentially relevant articles was obtained and screened by two reviewers independently. Randomized controlled trials (RCTs) were assessed for risk of bias with the Cochrane risk of bias tool, while non-randomized studies were assessed with the Newcastle-Ottawa scale for cohort studies ([www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)). All assessments were performed by two reviewers independently. All descriptive data (patient characteristics, intervention / exposure, comparison, setting, study design) were extracted in previously piloted standardized tables. Data on outcomes (measurement, follow-up, results) were extracted directly into RevMan or GRADEpro / GTD software. Data extraction was performed by one reviewer and verified by a second. Meta-analyses were performed in case of the absence of clinical heterogeneity. For meta-analysis a standard inverse variance random effects model was used and pooled relative risks with 95 % CI for all outcomes were calculated. Statistical heterogeneity was quantified with I-square. The quality of evidence was graded and “Summary of findings” tables were prepared using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach <sup>[6]</sup>. One author graded the quality of evidence and prepared the “Summary of findings” tables and a second author verified all ratings and entries.

After removing duplicates the search in the electronic databases resulted in 2489 hits. 2390 articles were excluded based on titles / abstracts. The titles / abstracts of 99 articles seemed potentially relevant and were assessed against the inclusion criteria in detail. Finally, 40 articles (39 studies) were included. The study selection process is illustrated in the flow chart in Figure 1.

This position paper adheres to the European Organization for Research and Treatment of Cancer (EORTC) Policy 19 on “Guidelines, Expert Opinions, and the use of EORTC Results in Promotional Material on Cancer Care” (<http://www.eortc.org/app/uploads/2017/03/POL019.pdf>). It received formal EORTC Board approval on September 28, 2018.

**Figure 1**  
Flow-diagram  
of the  
study selection process.



### *Consensus meeting*

To develop recommendations a consensus group meeting was organized in Milan, Italy, in June 2018. Representatives from all disciplines involved in treatment and care of patients with DT participated in the meeting including specialists in pathology, molecular biology, radiology, orthopedic surgery, general surgery, radiotherapy, medical oncology, pediatric oncology and supportive oncology, joining from European, North American and Japanese sarcoma centers. Additional participants were European and North American patient representatives. Based on the literature review and the discussion, the Desmoid Tumor Working Group reached consensus about key aspects of the management of DT patients requiring a systematic approach summarized in this position paper.

## PATHOLOGY AND MOLECULAR GENETICS

### Morphology

Accurate morphologic recognition remains crucial in order to plan treatment. The French registry reported that one third of cases were misdiagnosed [2]. Diagnosis depends on a combination of morphologic as well as immunohistochemical findings. On a surgical specimen, DT is most often poorly circumscribed, featuring a scar-like, whitish cut surface, and ranging in size. Microscopically, a DT is composed of a cytologically bland, at most moderately cellular, infiltrative spindle cell proliferation, set in a variably collagenous stroma. Peripheral infiltration of skeletal muscle is often seen. Spindle cells are organized in fascicles wherein they often appear regularly spaced. Mitotic figures are infrequent and always typical. Keloid-like areas as well as myxoid stromal change can be observed.

### Immunohistochemistry

Most DTs stain variably positive for smooth muscle actin. However, the key immunophenotypic feature is the presence of nuclear immunopositivity for  $\beta$ -catenin, observed in approximately 80-98 % of sporadic DT [7,8]. Familial adenomatous polyposis (FAP)-associated DTs have been reported to express nuclear  $\beta$ -catenin in a lower percentage of cases ranging between 60 and 70-100 % [7-8].

### Differential diagnosis

The differential diagnosis is broad and includes both benign and malignant myofibroblastic proliferations including hypertrophic or other procedure related scars, keloids and nodular fasciitis and low grade fibromyxoid sarcoma and low grade myofibroblastic sarcoma, respectively. Nerve sheath tumors such as schwannoma and smooth muscle tumors such as leiomyomas can also enter the differential diagnosis. Limited sampling such as with the commonly-used core needle biopsy, broadens the potential diagnostic possibilities. Low grade fibromyxoid sarcoma represents the most challenging differential diagnosis as it may exhibit significant morphologic overlap with DT [9]. However, the combination of MUC4 expression and lack of nuclear  $\beta$ -catenin expression allows proper classification in most cases [10]. Demonstration of the *FUS-CREB3L1* or *CREB3L2* gene fusion characteristic of low grade fibromyxoid sarcoma is another distinguishing feature. Another important differential diagnosis is gastrointestinal stromal tumor (GIST) as some cases of DT may express CD117 (KIT receptor). The additional use of DOG1 immunohistochemistry helps to identify true GIST and demonstration of characteristic *KIT* or *PDGFRA* mutations may also be helpful.

### Molecular genetics

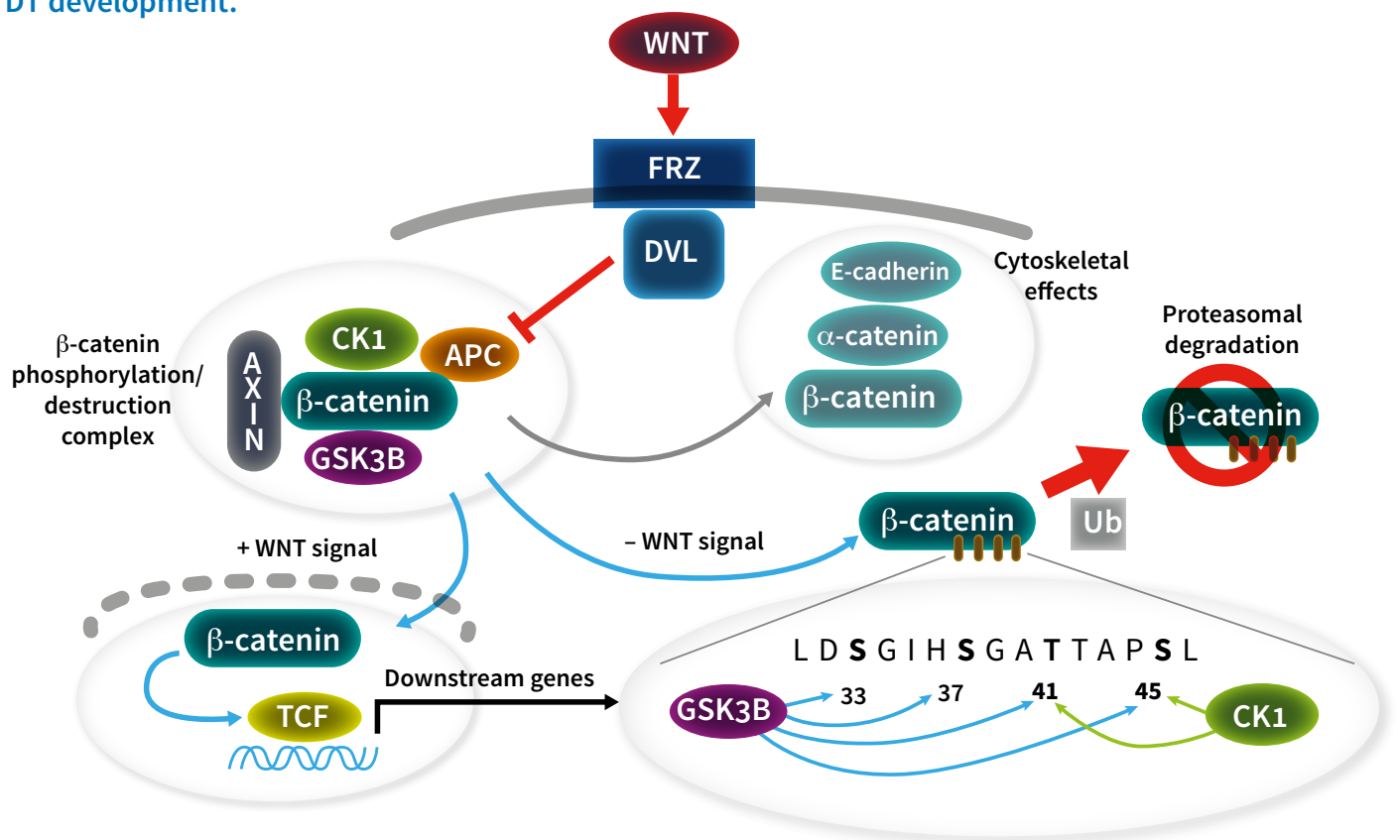
DT may occur in patients either in the context of Gardner syndrome (a variant of FAP variably associated with osteomas, epidermoid cysts and intra-abdominal fibromatosis) or as sporadic forms [11,12]. The molecular events underlying these two etiological distinct categories involve two different proteins that are both members of the Wnt signaling pathway (Figure 2). In fact, familial DT displays germline inactivating mutations in the adenomatous polyposis coli (*APC*) gene [12], whereas most sporadic DTs harbor activating mutations in exon 3 of the *CTNNB1* gene which encodes  $\beta$ -catenin [13, 14].

In addition, a small subset of sporadic DTs is characterized by biallelic *APC* inactivation [15]. Consecutively ordered phosphorylation of  $\beta$ -catenin at amino acids Ser33, Ser37, Thr41 and Ser41 by the *APC* protein complex ultimately leads to the destruction of  $\beta$ -catenin in the proteasome. Mutations in exon 3 of *CTNNB1* encoding the phosphorylation domain of  $\beta$ -catenin prevent phosphorylation and allow the nuclear accumulation of  $\beta$ -catenin, which can then be detected by immunohistochemistry. In the nucleus,  $\beta$ -catenin interacts with other proteins including LEF/TCF family proteins to ultimately drive transcription of genes with promoters susceptible to such regulation.

Most sporadic DTs harbor exon 3 mutations occurring most commonly in codons S45 and T41 [16]. A significant correlation between *CTNNB1* S45F mutation and an increased risk of recurrence after resection was observed in four independent studies [17,18,19,20]. Moreover, S45F mutations appeared to predominate in a recent clinical trial on RECIST progressive DTs treated with imatinib [21]. One additional study failed to prove a prognostic role for *CTNNB1* gene variant mutations but has suggested that “wild-type” DT represents a subgroup associated with better outcome [22]. The different mutational subtypes of *CTNNB1* vary between different primary locations as one possible explanation for the diverse biological behavior of DT in different sites.



**Figure 2**  
Either *APC* loss or  
*CTNNB1* mutation  
can lead to  
DT development.



Understanding the true prevalence of *CTNNB1* gene mutations in DT is evolving. Previous data would indicate that approximately 15 % of lesions are “wild-type;” however, recent data indicate that when using more sensitive molecular detection tools, such as next generation sequencing, the number of “wild-types” drops dramatically from 15 % to less than 5 %<sup>[23]</sup>. Thus, any “wild-type” DT appears to harbor much lower variant allele frequencies than expected and thus requires more sensitive techniques for detection of mutations. Interestingly, not only a higher rate of both characteristic *CTNNB1* and *APC* gene mutations and uncommon novel mutational subtypes such as intergenic deletions in *CTNNB1* are observed, but very rarely mutation of other genes involved with Wnt pathway activation. These data challenge the prognostic value of “wild-type” status claimed in studies in which a Sanger-based sequencing approach has been used. Aside from prognosis, mutated and “wild-type” DTs appear to represent distinct molecular subgroups, both in terms of β-catenin stability and affinity as well as from the standpoint of gene profiling<sup>[24]</sup>.

Diagnosis of DT should be confirmed by an expert soft tissue pathologist. *CTNNB1* mutations and *APC* mutations are mutually exclusive in DT, thus, detection of a somatic *CTNNB1* mutation can help to exclude a syndromic condition. Vice versa, *CTNNB1* wild-type status in DT, especially in an intra-abdominal tumor, should raise suspicion for FAP, with more extensive diagnostic clinical work-up (e.g. colonoscopy or germline testing). Therefore, our group gives a strong recommendation to perform a mutational analysis in DT biopsy specimens to confirm diagnosis and guide the work-up when appropriate.

## INDICATIONS FOR ACTIVE TREATMENT

Several papers have addressed the role of active treatments in the management of DT. The definition of these active treatments has been the following: surgery, radiotherapy and systemic treatment. Comparisons have been conducted to understand if any initial strategy is superior to others for long-term disease control. It has to be taken into account that a potential post-biopsy increase in size or pain may be due to bleeding from the biopsy rather than true tumor growth.

### Surgery compared to observation

One of the most recent and largest prospective randomized series comparing initial surgery to initial observation was reported by Penel et al.<sup>[25]</sup> The results did not show any difference in event-free survival (EFS, 53 % versus 58 %;  $p = 0.415$ ) and long-term disease control between patients undergoing surgery and those managed with a conservative approach. In addition, anatomic location seemed to influence the course of the disease. Among patients with favorable locations, defined as abdominal wall (AW), intra-abdominal (IA), breast, digestive viscera and lower limb, the 2-year EFS was similar in patients treated by surgery (70 %) and non-surgically (63 %;  $p = 0.41$ ). Among patients with unfavorable locations, defined as chest wall, head & neck and upper limb, the 2-year EFS was significantly better in those patients managed non-surgically (52 %) compared to those who underwent initial surgery (25 %;  $p = 0.001$ ). Likewise, Salas et al. showed a benefit of a surveillance approach although they did not perform a true comparison between groups<sup>[26]</sup>. Other reports focused on specific anatomical sites: mesenteric (FAP and sporadic patients<sup>[27]</sup>), AW<sup>[28]</sup>, extra-abdominal (EA including extremity / girdles, head & neck, and trunk<sup>[29]</sup>) and abdominal (including both IA and AW<sup>[30]</sup>). In both AW and EA sites, an initial non-surgical approach was shown to be safe, although surgery was offered as an option in a few selected cases. In fact, for AW the switch to surgery or to medical therapy at 3 years was 16 % and 25 %, respectively. After a median follow up of 97 months, only 1 out of 41 patients recurred after R1 resection<sup>[28]</sup>. Similarly for EA, the RFS at 5 years was 80 % with switch to surgery in 5 %, to medical therapy in 51 % and spontaneous regression in 20 %<sup>[29]</sup>.

As shown for adults, a 5-year PFS for pediatric patients was 27 % in the observation group and 41 % in the surgery group ( $p = 0.12$ <sup>[31]</sup>). Park et al. observed a statistically superior PFS in the surveillance group ( $p = 0.005$ ) compared to the surgical group<sup>[32]</sup>.

Non-surgical strategies have also been proposed to FAP patients showing comparable PFS at 10 years compared to surgery (33 % and 49 %, respectively;  $p = 0.16$ ). Moreover, none of these DTs could be removed entirely. For EA and AW lesions, the PFS at 10 years after surgery was 63 %<sup>[33,34]</sup>.

In summary, management of asymptomatic patients with initial observation, independently of tumor site and size, can be proposed but only under the supervision of an experienced team in connective tissue tumors from a reference center. To better reflect what we actually do, we hereby introduce the term “active surveillance” and will use this from now on. However, the risk of progression may be higher for larger tumors. Surgery may still be considered as a second line treatment for AW tumors as morbidity and risk of recurrence are limited, while other modalities should be preferred for DT located at other sites. Clearly, patients need to be referred to centers with experience in DT to minimize the risk of active surveillance and avoid unnecessarily debilitating or mutilating surgery when possibly needed. Surgery by surgeons without significant experience in the management of DT is strongly discouraged. Similarly, referral to experienced multi-disciplinary teams is recommended at the time of initial diagnosis, for optimal advice on safety of an initial observation strategy.

### Surgery plus radiotherapy compared to surgery alone

Retrospective studies<sup>[35,36,37,38,39,40,41,42,43,44,45,46]</sup> have been published on the combination of surgery plus radiotherapy compared to surgery alone. While some reduction in the anticipated absolute risk of recurrence after surgery has been observed with the addition of radiotherapy (37 % versus 25 %), this reduction is not statistically significant (RR 0.69, 95 % CI 0.41-1.17). As surgery is less frequently undertaken for DT, the combination of surgery and radiation is currently rarely employed. However, it can still be considered once surgery is offered to patients with recurrent disease, especially if a further recurrence would be difficult to treat.

## Radiotherapy compared to radiotherapy and surgery

Retrospective data comparing radiotherapy alone to the combination of radiotherapy and surgery <sup>[47,48,49,50]</sup> have predominantly been reported in the past. Based on these studies, the anticipated absolute risk of progressive disease after radiotherapy alone is similar to the recurrence rate after surgery plus radiotherapy (23 % versus 22 %). More recently, moderate dose definitive radiotherapy has been employed as an alternative to surgery for symptomatic / growing tumors located at critical sites such as head & neck, scapular girdle, etc. This modality can be a valid alternative to surgery and can be used if medical therapies are not available or not active.

## Radiotherapy compared to surgery

Summarizing the data comparing radiotherapy to surgery <sup>[51]</sup>, the anticipated absolute risk of progressive disease after radiotherapy alone is 19 % versus 29 % after surgery alone, however, not being statistically different (RR 0.65, 95 % CI 0.35-1.22).

In summary, when active management for DT is required, surgery as first-line therapy can be considered, provided expected surgical morbidity is limited. This is particularly true for abdominal wall locations. Wide (R0) microscopic margins resection should be the goal, but positive (R1) microscopic margins can be accepted when function or cosmesis is an issue. However, if positive microscopic margins can be anticipated, other managements than surgery should be preferred. In addition, if R1 resection is obtained in first-line management, there is insufficient evidence to recommend either perioperative radiotherapy or re-operation. Although the risk of a local recurrence seems to be lower after combined modality, the difference between surgery alone and surgery plus perioperative radiotherapy is not statistically significant. When surgery is not an option and active management is required, moderate dose definitive radiotherapy has also been shown to provide adequate local control in a majority of progressive patients and could be considered if medical therapies are not available or not active.

## Initial medical treatment compared to observation

Similar results have been observed comparing initial observation to initial medical therapy <sup>[29]</sup>. Patients undergoing initial observation did not fare any worse than those initially treated by medical therapy, either hormonal or chemotherapy <sup>[52]</sup>. Of note, patients not progressing for two years were very unlikely to need any further active treatment <sup>[52]</sup>.

Similar results were obtained in pediatric patients. The European pediatric Soft tissue sarcoma Study Group (EpSSG) showed a difference in the 5-year PFS between the observation (n = 54) and the chemotherapy group (n = 53) (27 % and 43 %, respectively) but without statistical significance (p = 0.13). An initial observation strategy did not compromise outcomes when compared with a more aggressive approach. Notably, with this conservative strategy more than half of the patients avoided surgery (and its sequelae) and radiotherapy.

An initial “active surveillance” approach does not appear to influence the efficacy of subsequent treatments when needed. Thus being cautious and avoiding potential harm in experienced hands, 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. Active surveillance means that patients need to be continuously monitored with a first MRI (or alternatively CT if MRI is not possible) within 1-2 months, then in 3-6 months intervals. A decision towards an active treatment should be postponed until the occurrence of subsequent progression or increase of symptoms burden, assessed with at least two further assessments and possibly not before one year from diagnosis in the absence of fulfilling RECIST progressive disease. In fact, this policy avoids overtreatment in patients who could spontaneously regress and discourages treatment for stable and pauci-symptomatic patients.

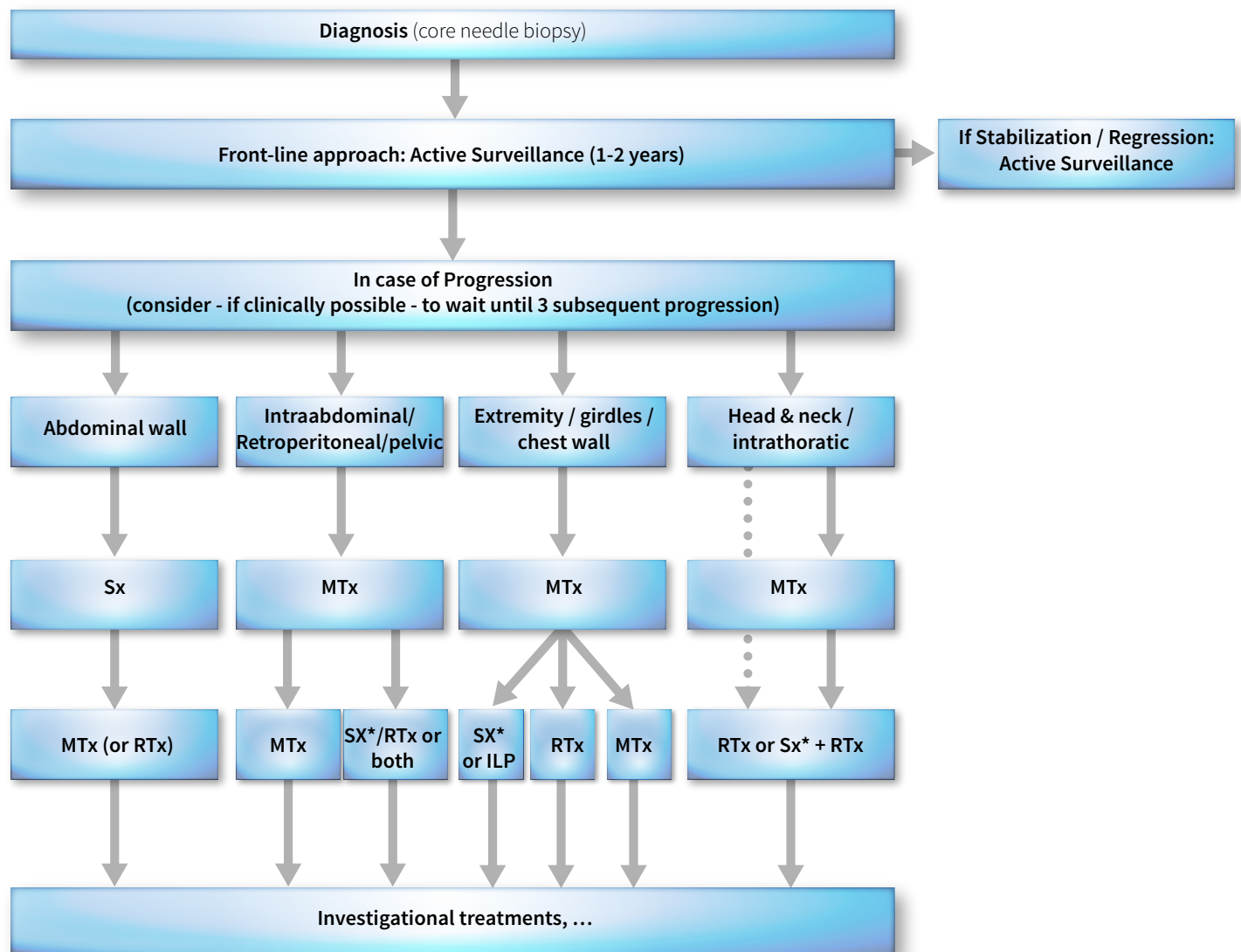
However, when the disease is located close to a critical structure that may pose significant problems to the patient’s life (such as mesenteric or head & neck DT) an earlier decision towards an active therapy may be taken simply because there is a potentially higher risk of morbidity prior to disease stabilization. As depicted in the treatment algorithm in Figure 3, the type of further treatment is generally guided according to the anatomical site and the decision should be made with the patients in a stepwise approach: For abdominal wall DT, surgery is still the first option in case of progression. 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. For head & neck / intra-thoracic DT, medical therapy is generally considered the first line option.

However, in selected conditions (elder age, patient intolerance / preference, comorbidities, lesion growing rapidly and threatening vital organs, etc.) radiotherapy is a reasonable and effective first line alternative.

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.

There is a lack of evidence that pediatric patients need to be treated differently compared to adults. Thus, the management approach is very similar to that of adult patients and should follow the same treatment algorithm.

**Figure 3**  
**Treatment Algorithm**



**Abbreviations:** Sx = Surgery  
 Sx\* = Surgery is an option if morbidity is limited  
 MTx = Medical treatment  
 RTx = Radiotherapy  
 ILP = Isolated limb perfusion



## AVAILABLE MEDICAL THERAPIES IN DIFFERENT INDICATIONS

The independent literature search regarding systemic treatment options did not reveal any evaluable comparative studies with at least two arms being a prerequisite for an analysis according to GRADE (Grading of Recommendations Assessment, Development and Evaluation). Therefore, IFOM extracted from the initial search results all single-arm studies and provided them in a list. We then defined the following quality criteria / credits for the final analysis and interpretation of the available data: (1)  $n > 20$  patients, (2) confirmation of the histological diagnosis of a DT, (3) study evaluation according to a predefined statistical analysis plan, (4) definition of primary and secondary endpoints as well as (5) response evaluation according to RECIST or WHO. The literature search revealed 22 publications meeting the first criterion of inclusion of at least 20 patients and forming the basis for the following chapter on systemic treatment recommendations.

Systemic treatment options for DT comprise anti-hormonal therapies, non-steroidal anti-inflammatory drugs (NSAIDs), tyrosine kinase inhibitors (TKIs), and “low-dose” or conventional chemotherapeutic regimens including liposomal doxorubicin <sup>[53,54]</sup>.

### Anti-hormonal therapies / NSAIDs

Anti-hormonal agents such as tamoxifen or toremifene have been frequently used alone or in combination with NSAIDs. The retrospective analysis from Fiore et al. (3 credits) included 44 patients (median age 41 years) with radiologically progressive disease (no RECIST progression required) and / or symptomatic deterioration being treated with toremifene 180 mg daily (20 for radiological progression, 16 for pain and 8 for both). In 28 patients, toremifene was offered as first-line therapy while in 11 patients after tamoxifen failure. Progression-free survival (PFS) was 90 % at 12 and 24 months. According to RECIST, partial response (PR), stable disease (SD) and disease progression (PD) were observed in 25 %, 65 % and 10 % of the patients, respectively. Symptomatic relief was achieved in 75 % of all patients. Adverse events (AEs) grade 2 were reported in ten patients (23 %) and included four patients with amenorrhea / dysmenorrhea, three with vaginal discharge and one each with vertigo, palpitations, and fatigue; no grade 3 or above AEs were observed <sup>[55]</sup>. Quast et al. (1 credit) reported outcomes on a cohort of 134 patients (64 with FAP-associated and 70 sporadic DT) treated with combination of sulindac and high-dose selective estrogen modulators, either tamoxifen, raloxifene or toremifene, at a single institution. Patients were scanned every six months during the first two years of therapy, and then every 12 months until sustained stable disease or death. Response was defined as dimensional stabilization or regression of the DT between two CT or MRI scans; no formal response criteria were applied. Even though 114 (85 %) patients showed regressive or stable DT, the definition for initiating treatment remains unclear <sup>[56,57]</sup>. The only prospective data evaluating the combination of high-dose tamoxifen and sulindac is from a phase II study in the pediatric patient population. Over a 5 year period, Skapek et al. (5 credits) enrolled 59 evaluable patients less than 19 years of age who had a measurable DT that was recurrent or not amenable to surgery or radiotherapy. Twenty-two (37 %) of the patients were treatment naïve; 37 (63 %) of the patients had recurrent disease. Six of these 37 patients had received prior systemic chemotherapy and 15 had prior radiotherapy. Tamoxifen and sulindac were both dosed at 3 mg/kg twice daily (maximum daily dose of 300 mg). No life-threatening toxicity was reported; however, 12 of 30 (40 %) females developed ovarian cysts, eleven of which were asymptomatic. Only ten patients (17 %) completed the planned one year of therapy without disease progression or discontinuation of treatment. Tumor responses, defined by WHO criteria, included four patients with PR and one with a complete response (CR) for an overall response rate (ORR) of 8 %. The estimated 2-year progression-free and overall survival rates were 36 % and 96 %, respectively. There were three deaths due to progressive disease in mesenteric locations <sup>[58]</sup>. Beside retrospective case series showing some evidence of activity, some with response rates of 25 % with prolonged disease control in as many as 90 % of patients, the only prospective phase II study evaluating anti-hormonal therapy plus NSAID showed limited activity as measured by WHO response criteria and PFS rates. Moreover, a recently published paper found no clear relationship between size, MRI signal changes and symptom changes with tamoxifen treatment <sup>[59]</sup>. Therefore, a general recommendation for the use of anti-hormonal therapies and NSAIDs cannot be given.

## Tyrosine kinase inhibitors (TKIs): imatinib, nilotinib, sorafenib, pazopanib

The TKI imatinib was evaluated in three prospective, non-randomized studies meeting the criterion of at least 20 treated patients. Chugh et al. (5 credits) enrolled 51 patients (median age 34 years, range 12-67 years) who had unresectable disease or in whom surgical resection would lead to significant functional impairment. Progressive disease was not a required study inclusion criterion. Participants received imatinib twice daily 300 mg, 200 mg or 100 mg based on BSA  $\geq 1.5 \text{ m}^2$ ,  $1-1.49 \text{ m}^2$  or  $< 1.0 \text{ m}^2$ , respectively. The 1-year PFS rate was 66 %; the ORR was 6 % (3 of 51). Best tumor response was achieved after 19, 22 and 26 months of treatment. Over a third of patients required a dose reduction and five patients discontinued therapy due to toxicity <sup>[60]</sup>. The second phase II trial, reported by Penel et al. (5 credits), analyzed 35 evaluable adult patients with unresectable and progressive (no RECIST progression required), symptomatic DTs who received imatinib 400 mg/day for one year. FAP was diagnosed in six cases. The PFS rates at 3, 6 and 12 months were 91 %, 80 % and 67 %, respectively. The ORR was 11 % (4 of 35). Eleven patients (31 %) stopped therapy prior to one year for reasons other than progressive disease <sup>[61]</sup>. The most recent phase II study evaluating imatinib in patients with DT was conducted by the German Interdisciplinary Sarcoma Group (GISG) (5 credits). Thirty-eight patients (median age 44 years, range 19-80) with tumor progression as defined by RECIST within the last 6 months prior to study enrollment received imatinib 800 mg daily (planned for 2 years). The progression arrest rate after 6 months of imatinib treatment was the primary endpoint and was reached in 65 % of patients; the ORR was 19 %. More than 60 % of patients required at least one dose reduction <sup>[62]</sup>. All three prospective, single-arm, phase II trials demonstrated activity of imatinib with high rates of disease stabilization (60-80 %) despite rather low response rates (6-19 %) and with the expected well-known toxicity profile of imatinib. However, the lack of randomization in a disease with the possibility of spontaneous disease regressions makes it difficult to determine the definitive role of imatinib in this condition. Imatinib should clearly not be the treatment of first choice if DT remission is intended.

Of note, eight patients who failed imatinib on the GISG study and subsequently treated with nilotinib demonstrated a progression arrest rate at three months of 88 % (7/8) that was sustained until the end of the study at 24 months <sup>[62]</sup>.

Sorafenib is an active agent and currently the best-studied TKI in DT. After an initial retrospective study (3 credits) reporting a promising ORR of 25 % and disease stabilization and improvement in symptoms in 70 % of patients treated at a dose of 400 mg oral daily <sup>[63]</sup>, a phase III, placebo-controlled, randomized trial (NCT02066181) was conducted. Results were released at the 2018 ASCO Annual Meeting and were included here after formal finalization of the literature search. 87 patients (median age 39 years, range 18-72) were treated with sorafenib 400 mg daily or placebo in a 2:1 randomization (sorafenib: 50 patients, placebo: 37 patients). Median PFS, the primary endpoint of the study, was 11.3 months in the placebo group and was not reached in the sorafenib arm ( $p < 0.0001$ ); the risk of progression could be reduced by the factor 7 in favor of sorafenib ( $\text{HR} = 0.14$ ). The ORR was 33 % for sorafenib; however, the placebo arm ORR was as high as 20 % demonstrating spontaneous regression and giving useful information on the natural history of this disease. The study has been unblinded due to these results. Common toxicities for sorafenib included fatigue, rash, hypertension and gastrointestinal symptoms <sup>[64]</sup>. Of note, responses were also seen in patients receiving a dose as low as 200 mg with a clear benefit in terms of reduced toxicity.

Pazopanib was also studied both retrospectively in a small series (1 credit) <sup>[65]</sup> and prospectively in a phase II randomized study (DESMOPAZ, NCT01876082) evaluating pazopanib 800 mg oral daily versus methotrexate (30 mg/m<sup>2</sup>) plus vinblastine (5 mg/m<sup>2</sup>) including 72 RECIST progressive DT patients (pazopanib: 48 patients, chemotherapy arm: 24 patients; median age 40 years, range 18-79). The 6-month non-progression rate was 82 % for pazopanib, with response rates similar to those of sorafenib <sup>[66]</sup>. However, PFS curves for pazopanib and chemotherapy cross at one year.

Taken together, these findings show clear clinical benefit of TKIs in DT. The effect appears to be more pronounced with sorafenib and pazopanib compared to imatinib and likely achievable with even low dosages, limiting the potential adverse effects.

Chemotherapy options include a “low-dose” regimen with methotrexate plus vinblastine or vinorelbine, or conventional dose chemotherapy using anthracycline-based regimens as similarly instituted for the treatment of soft tissue sarcomas, and pegylated liposomal doxorubicin. Most of the published data have evaluated the “low-dose” chemotherapeutic option, mainly in retrospective series (3 credits each) [67,68,69] and two prospective phase II studies (5 credits each) [70,71]. Response rates are in the range of 35-40 %, but usually occur as late as several months after the start of therapy. Shrinkage can continue even after treatment withdrawal, and long-term disease control is usually achieved in up to 50-70 % of the patients depending on the series. Of note, at recurrence, and especially if the patients responded to the therapy, the treatment can be repeated with substantial benefit. Similar results are observed in children.

Oral vinorelbine alone has also been evaluated retrospectively. The toxicity profile was excellent, with no grade 3-4 toxicity reported. Symptomatic relief at three months was seen in 80 % of patients and best response was 32 % PR, 58 % SD and 10 % PD. PFS rates at 3, 6 and 12 months were 98 %, 92 % and 88 %, respectively [72]. Recent data support the use of hydroxyurea in children [73].

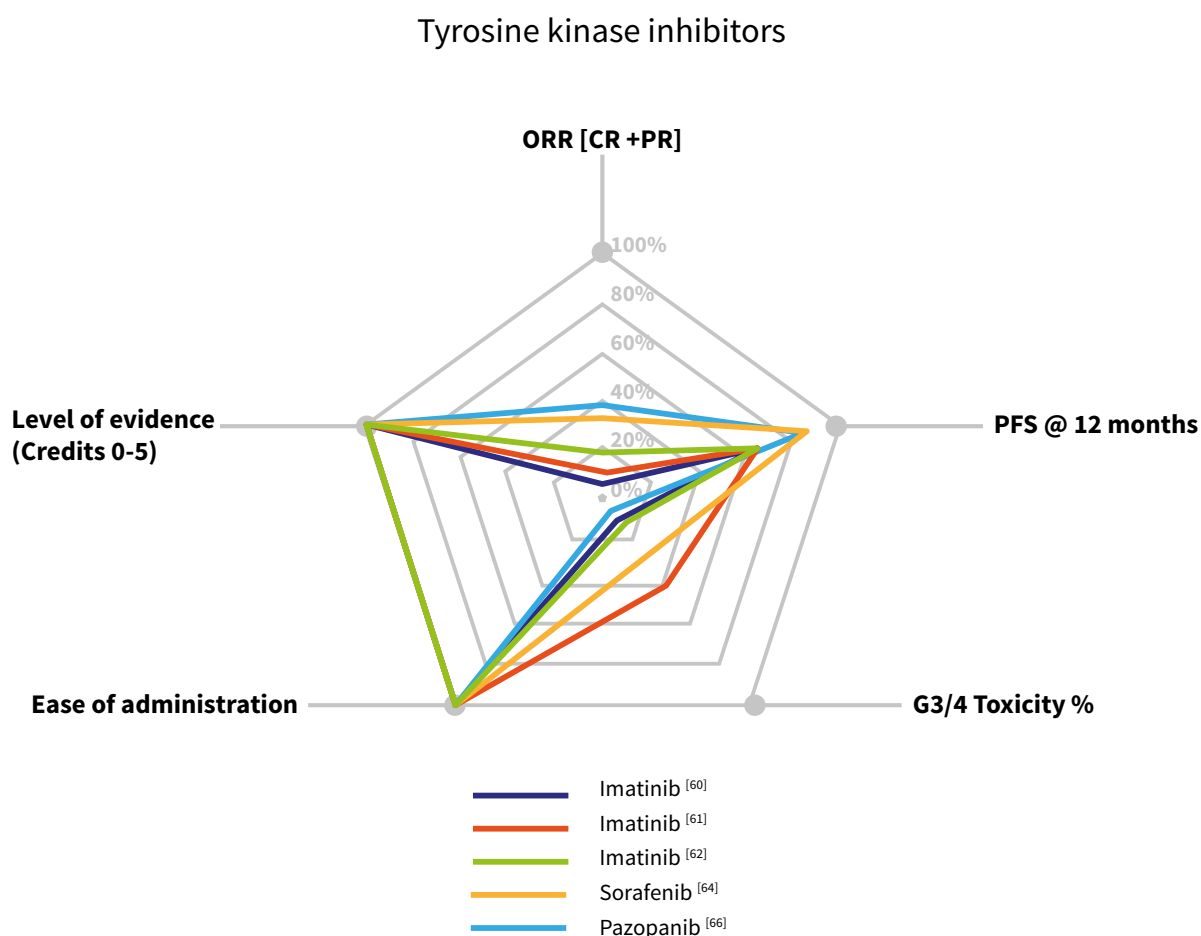
Conventional dose chemotherapy using anthracycline-based regimens is another option and is expected to achieve more rapid tumor responses. It has been evaluated only in two retrospective series (3 credits each) with reported response rates of 37 % (13 of 35 patients) and 54 % (7 of 13 patients) [74,75]. This type of chemotherapy is usually administered for six to eight cycles, i.e. until the maximum tolerated dose of anthracycline is reached. Responses to chemotherapy observed in children is superimposable to those observed in the adult population.

Finally, the administration of pegylated liposomal doxorubicin at 40 mg/m<sup>2</sup> every four weeks has also been reported in two uncontrolled patient series (1 credit each) with a response rate of approximately 35 % and an acceptable toxicity and - importantly in this young patient population - less cardiac toxicity than conventional doxorubicin [76, 69].

The evaluation of the clinical benefit in terms of pain control associated to all these drugs is more complex, as no prospective studies with a rigorous health-related quality of life and pain assessment have been conducted so far.

**In summary, due to the lack of comparative studies we are still not able to propose a definitive sequence of the existing systemic treatment options. Randomized data only exist for sorafenib, pazopanib and methotrexate plus vinblastine. Prospective phase II studies do exist for the administration of low-dose chemotherapy with methotrexate plus vinblastine and for the use of imatinib. In general, it is reasonable to employ less toxic therapy initially followed by more toxic agents in a stepwise fashion. Out of the variety of possible systemic treatment options, one can be chosen taking into account the (1) level of evidence, the (2) overall response rate, the (3) progression free survival rate, the (4) ease of administration, and the (5) expected toxicity of the administered drug following a 5-dimensional model (Figure 4). As an example, in a worst case scenario with a mesenteric, potentially life-threatening DT there is consensus to administer more aggressive therapies.**

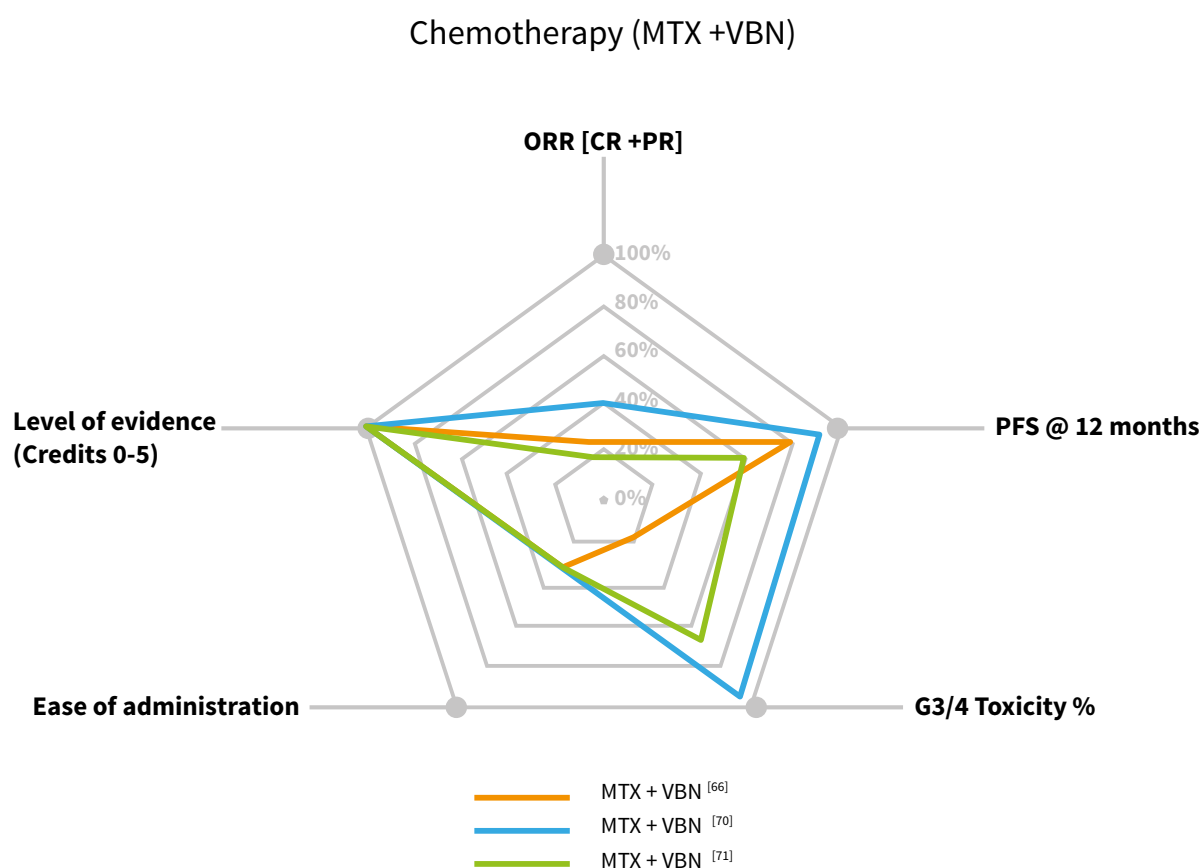
**Figure 4**  
Proposed 5-dimensional model  
for selection from available  
medical therapies in DT



Treatment class	Tyrosine kinase inhibitors				
Drugs	Imatinib	Imatinib	Imatinib	Sorafenib	Pazopanib
ORR (CR + PR) [%]	6	11	19	33	37
PFS @ 12 months [%]	66	67	59	89	86
G3/4 toxicity [%]	10	45	13	31	8
Ease of administration	Oral				
Level of evidence / credits (0-5)	5				
Reference	Chugh <sup>[60]</sup>	Penel <sup>[61]</sup>	Kasper <sup>[62]</sup>	Gounder <sup>[64]</sup>	Toulmonde <sup>[66]</sup>

**Abbreviations:** ORR: overall response rate; CR: complete response; PR: partial response; PFS @ 12 months: progression-free survival rate at 12 months; G3/4 toxicity: grade 3/4 toxicity; level of evidence/credits (0-5): 0 = 0 %, 1 = 20 %, 2 = 40 %, 3 = 60 %, 4 = 80 %, 5 = 100 %; ease of administration: inpatient chemotherapy = 0 %, IV weekly = 30 %, IV monthly = 50 %, oral = 100 %.

**Figure 4**  
Proposed 5-dimensional model  
for selection from available  
medical therapies in DT



Treatment class	Chemotherapy		
Drugs	MTX + VBN	MTX + VBN	MTX + VBN
ORR (CR + PR) [%]	25	40	19
PFS @ 12 months [%]	79	92	58
G3/4 toxicity [%]	17	93	67
Ease of administration	IV weekly		
Level of evidence / credits (0-5)	5		
Reference	Toulmonde <sup>[66]</sup>	Azzarelli <sup>[70]</sup>	Skapek <sup>[71]</sup>

**Abbreviations:** MTX: methotrexate; VBN: vinblastine; ORR: overall response rate; CR: complete response; PR: partial response; PFS @ 12 months: progression-free survival rate at 12 months; G3/4 toxicity: grade 3/4 toxicity; level of evidence/credits (0-5): 0 = 0 %, 1 = 20 %, 2 = 40 %, 3 = 60 %, 4 = 80 %, 5 = 100 %; ease of administration: inpatient chemotherapy = 0 %, IV weekly = 30 %, IV monthly = 50 %, oral = 100 %.



## ASSESSMENT OF TREATMENT EFFECTS

Whenever a clinical decision is required or a formal study protocol is designed, the following major issues should be taken into account for the assessment of treatment efficacy in DT: (1) spontaneous regression and delayed responses are a well-described phenomenon in DT; (2) response to treatment has been described both in terms of tumor size / volume and in terms of density / signal changes with imaging assessments; (3) clinical benefit for DT patients might be viewed as a combination of tumor response and HRQoL. The majority of historical response data of medical treatment in DT are limited, since the aforementioned issues have been recently appreciated and have not been taken into consideration in previous study designs. In any case, reliability of response assessment in DT is of paramount importance in order to accurately evaluate new active drugs and to objectively distinguish which effects on tumors have to be considered clinically relevant.

### Spontaneous regression

Spontaneous regression is a peculiar well documented phenomenon in DT. It occurred in 20 % of 122 sporadic extra-abdominal DTs prospectively followed with a surveillance approach <sup>[29]</sup>, and in 28 % of 102 DT of the abdominal wall initially observed <sup>[28]</sup>. In pregnancy-related DT, up to 11 % of patients experienced spontaneous regression, and 17 % of patients who had a DT during pregnancy experienced spontaneous regression after delivery including complete regressions <sup>[28]</sup>. Therefore, demonstrated RECIST PD has been included among entry criteria in recent studies investigating active treatments <sup>[55,78,62]</sup>.

### Delayed response

Delayed response after completing prior therapy is peculiar to DT. Response to chemotherapeutic agents such as liposomal doxorubicin has been detected even six months after completion of treatment <sup>[76]</sup>. A partial response to imatinib was achieved after 19 months of treatment <sup>[62]</sup>. Delayed response to toremifene has been described in 16 % of responding patients beyond treatment withdrawal for a median time of 96 months <sup>[55]</sup>. Delayed dimensional response after discontinuation of methotrexate / vinorelbine has been described in 46 % of cases <sup>[79]</sup>. Therefore, previous therapy should be taken into account when assessing the anti-tumor activity of any therapy.

### Tumor changes

#### *Dimensional criteria*

Because of their demonstrated reproducibility, RECIST 1.0 <sup>[80]</sup> and 1.1 <sup>[81]</sup> are the most common research criteria used for response evaluation even in recent prospective trials of medical therapy in DT <sup>[62,82]</sup>. Radiologic assessment of DT is best obtained by MRI for extremity, trunk and other extra-abdominal as well as pelvic / perineal DT, while contrast enhanced CT scan is usually preferred for intraabdominal / mesenteric DT both sporadic and FAP-related <sup>[83]</sup>. However, in a series of 23 DT patients treated with different systemic therapies, those with PR showed a mean reduction in the maximum diameter of the lesion of 11 % <sup>[84]</sup>. Actually, this value is substantially lower than the 30 % reduction required by RECIST to be classified as a PR. Notably, the mean volume decrease was 29 %. This reflects the fact that RECIST is perhaps not ideal to assess anti-tumor activity in DT.

#### *MRI signal evaluation*

Changes in MRI signal have been described both in the case of spontaneous regression and response to treatment. In particular, changes in T2 weighed intensity signal are most useful for assessing changes in DT activity <sup>[82]</sup>. Actually, T2 signal has been correlated to histologic features of mesenchymal tumors including DT: low T2 signal corresponds to relatively lower cellularity and higher collagen content <sup>[85]</sup>. These results have been replicated in a series of pediatric DTs where histologic samples were compared to MRI findings: DT with low cellularity and high collagen had the lowest percentage of volume enhancement in T2 images <sup>[86]</sup>. Therefore, T2 hyperintensity is usually considered as a surrogate of histologic “activity” of DT.

### Enhancement evaluation

At CT scan, DT shows variable attenuation; enhancement is also variable and usually mild to moderate <sup>[87]</sup>. In contrast, in MRI DT commonly demonstrates moderate to marked enhancement after administration of gadolinium-based contrast material. Changes in enhancement during treatment are negligible on CT scan, while relevant on MRI <sup>[87]</sup>.

### Combination of different criteria

Different criteria may be combined to evaluate response to treatment in DT. Bearing in mind the possibility of spontaneous regressions in DT, it is recommended that tumor changes should always be referred to as “regression” rather than “response” unless clearly proven. A proposal of a comprehensive assessment has been put forward recently, although not validated nor commonly used in clinical practice yet <sup>[87]</sup>: Regression/Treatment response (decrease in size), Modified regression/response (no change in size, decreased T2 signal and enhancement at MRI), Heterogeneous regression/response (decrease in size, T2 signal and enhancement changes limited to some areas), Stability (no change), Progression (increase in size), Modified progression (no size change, increased T2 signal and enhancement at MRI), Early progression (decreased size and signal, but new areas of increased T2 signal within the mass). Although this classification appears to be meaningful, no threshold values are given to establish tumor size changes as well as changes in signal intensity and enhancement variations. Other major limitations of this system are that it is strictly limited to radiologic evaluation, and it has not been validated so far.

## Biomarkers

Recent data suggest a possible role of *CTNNB1* detection in circulating cell free DNA to predict DT evolution: the quantity of circulating DNA in the plasma at the time of diagnosis could predict DT evolution for 65 % of patients <sup>[88]</sup>. If these data are confirmed, a possible role for this biomarker may be hypothesized also for the assessment of treatment effects.

## Symptom evaluation

The wide spectrum of clinical symptoms has increasingly guided the (primary) treatment approach of DT and includes the following presentations:

- a (growing) mass with no or minimal complaints
- a (growing) mass that is progressively impeding normal functionality and / or cosmesis
- a (growing) mass that is progressively causing pain and needs pain-relieving medication
- a (growing) mass that is progressively causing functional and / or cosmetic problems, in combination with pain and is not relieved by mere symptomatic treatment
- a (growing) mass that is progressively causing life threatening symptoms.

If an active surveillance policy is adopted or if active treatment is needed, close monitoring of the evolution of the DT mass along with its symptoms is needed. Data on the use of the EORTC QLQ-C30 in two ongoing Italian and Dutch observational studies will be available in the near future <sup>[89]</sup>. Symptom evaluation has also been included in a few recent studies in which worsening of clinical symptoms has been an indication for treatment irrespective of RECIST progression <sup>[55, 65, 82]</sup>. Patient-reported outcome (PRO) measures were also included in a study evaluating gamma-secretase inhibitor treatment by means of the MD Anderson Symptoms Inventory (MDASI) <sup>[90]</sup>. MDASI includes 13 treatment-related symptoms to be rated on a 0 to 10 numerical scale. Symptom interference in general activity, mood, work and walking showed a significant different trajectory between patients experiencing PR and SD during treatment. Interestingly, among the 13-items list of the MDASI the only specific symptoms that demonstrated improvement in this DT population were pain, numbness / tingling, fatigue, sleep disturbance and distress. This suggests that commonly utilized HRQoL tools may not be sufficiently specific in symptom assessment of DT patients. In fact, the pathogenic mechanism of pain in DT is certainly complex and multifold. Pain is not strictly correlated with DT progression and stable DT may also be painful. Pain can even be the consequence of previous loco-regional treatments rather than being caused by the disease itself <sup>[91]</sup>. A specific pathogenic pathway has also been described for pain in DT.

The number of COX-2-positive cells in DT significantly correlates with the prevalence of painful tumors ( $p = 0.036$ ) suggesting a positive correlation between COX-2 expression and tumor-associated pain in individual patients. Interestingly, COX-2 protein is not expressed in tumor cells, but in tryptase-positive mast cells in the DT stroma (documented in 56 % of cases) <sup>[92]</sup>.

Assessment of treatment effects in DT remains an unresolved issue and no standard validated response criteria are available as of today.

RECIST does not robustly identify all clinically relevant responses, though the majority of prospective trials report efficacy using RECIST.

Integration of “tissue response” is probably needed, mainly based on MRI signal changes.

Contrast-enhanced MRI or alternatively CT are the preferred modalities for monitoring DT. A role for FDG-PET in the evaluation of patients with DT has not been demonstrated.

Circulating tumor DNA is presently under evaluation and may become a valid biomarker of response / progression.

HRQoL evaluation should be included in any assessment of clinical benefit; validation of a specific tool for DT patients is currently under way.

A comprehensive consensus definition of clinical benefit from treatment of DT patients needs to be developed. Thus, validation of dedicated response criteria in DT should be included in the design of future clinical studies.

## PAIN, QUALITY OF LIFE, FERTILITY AND PREGNANCY

### Pain

The mechanism of pain is not fully understood (and not appropriately studied either). Causes may include neuropathic pain associated with mood disturbance and reduced general well-being<sup>[93,94]</sup>. There is no consensus on optimal pain management: nature of analgesics, long-term use of NSAIDs, local treatment and physiotherapy. A declarative survey had been conducted by the French patient advocacy group “sos Desmoïde.” The response rate for this survey was 43 % (102/233). Pain was present in 63 % of cases. The median pain intensity was 3 (on a 0-10 visual analogic scale) in the past week. Pain was constant in 38 % of cases. Pain was responsible for work stoppage in 26 % or led to a part-time job in 10 % of cases. Pain was associated with anxiety in 15 % and irritability in 46 % of cases<sup>[95]</sup>.

The use of systemic treatment seems to alleviate pain in some patients. Currently ongoing prospective trials are assessing DT-related pain in more detail and will hopefully provide better evidence on (i) the incidence of pain and (ii) pain relief related to systemic treatment (see Table below). Of note, the impact of local treatments (surgery, radiotherapy, cryotherapy, and / or radiofrequency ablation) on pain has not been documented at all and needs to be captured in future studies.

#### Pain and symptom assessment in ongoing clinical trials.

Trial	NCT number Sponsor	Item assessed
Sirolimus as preoperative treatment in AYA with DT	NCT01265030 Maine Medical Center	Pain improvement as secondary endpoint
Pazopanib versus MTX / Vinblastine	NCT01876082 Institut Bergonié	Pain assessment and HRQoL as secondary endpoints
National Clinical-biological Prospective Cohort of Incident Cases of Aggressive Fibromatosis	NCT02867033 Centre Oscar Lambret	Hospital Anxiety and Depression Scale (HADS) Quality of Life Questionnaire (EORTC QLQ-C30) Pain (VAS)
Trial of Nab-paclitaxel in Patients With DT and Multiply Relapsed / Refractory Desmoplastic Small Round Cell Tumors and Ewing Sarcoma (ABRADES)	NCT03275818 Grupo Espanol de Investigacion en Sarcomas (GEIS)	Brief Pain Inventory (BPI)
Sorafenib Tosylate in Treating Patients With DT or Aggressive Fibromatosis	NCT02066181 National Cancer Institute (NCI)	To assess patient-reported adverse events and HRQoL as measured by the Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) and the single-item overall Linear Analogue Self-Assessment (LASA) (A091105-HO1). (Correlative companion study) To assess pain measured by the Brief Pain Inventory Short Form (A091105-HO1)
Toremifene in DT: Prospective Clinical Trial and Identification of Potential Molecular Targets	NCT02353429 Fondazione IRCCS Istituto Nazionale dei Tumori (INT)	Pain evaluation by a visual analog scale (VAS) every 3 months for the first and second year, twice yearly thereafter. Response will be evaluated either by RECIST and / or symptomatic relief.
Phase I, open-label, non-randomized study to evaluate safety of BC2059 (Tegavivint)	NCT03459469 Beta Cat Pharmaceuticals, Inc.	PRO tool in DT

## Functional impairment

Functional impairment may be caused by DT progressive disease, but tumor shrinkage can also be associated with functional impairment, since regression of DT could be associated with fibrosis. To our knowledge, there is no available data on the role of physiotherapy or any other treatments in this clinical setting.

## Supportive care

It is of major importance to offer interdisciplinary supportive care in such a chronic disease affecting young patients. DT can have a major impact on many aspects of patients' lives, their social interaction, their ability to work, their relationships. Collaborative and personalized management should include, if necessary, pain specialists, physiotherapists, psychologists, and social workers. Nevertheless, these professionals must be trained to the particularity of this disease and notably its unpredictable course.

## Fertility

Although DT tends to impact younger patients and has a higher female predilection, there are no formal reports in the literature about disease management and its impact on fertility. Since exogenous hormonal stimulation (oral contraceptives) may stimulate DT growth, alternate forms of family planning should be discussed with patients who are undergoing active surveillance.

## Pregnancy

The impact of pregnancy on DT course has been assessed by a multicenter retrospective study <sup>[77]</sup>. Different clinical settings have been described, (1) de novo DT diagnosed during pregnancy, (2) pregnancy in patients previously operated for a DT and (3) pregnancy in patients with DT still in situ. DT diagnosed during pregnancy could be managed by an observation policy (16 cases: treated with surgery in four cases, treated with medical therapy in four cases after delivery). Nineteen patients with previous history of resected DT have been followed, four of them experienced local relapse, treated by surgery in two cases, medical treatment in one and observation in another case. This study also describes the outcome of 29 patients with persistent DT at the time of pregnancy. Overall, among the 92 enrolled patients, there was no obstetrical complication, no abortion and in only one case a cesarean delivery was necessary because of the presence of a DT. These data should be confirmed by larger retrospective or prospective series. However, current available evidence suggests that DT is not a contraindication to pregnancy; nevertheless, the following must be considered: precise location of the DT (mesenteric and pelvic locations and head & neck), size of the tumor and potential impact of increase in size. There may be a risk of tumor development during or after pregnancy. However, if the tumor has been stable before pregnancy, it is most likely to regress again afterwards.

**The evidence in this clinical setting is scarce and further clinical trials must integrate HRQoL as an endpoint including levels of functioning and symptoms (most importantly pain). Management of pain or functional impairment urgently needs specific research. Comprehensive programs for DT patients should include physical, psychological and social support. A DT is not a contraindication for future pregnancies in favorable evolution and pregnant DT patients should be followed closely by obstetricians and desmoid clinicians.**



## WHICH ENDPOINTS, STUDY DESIGNS AND REGULATORY REQUIREMENTS DO WE NEED FOR DT?

### Regulatory challenges are plentiful given the rarity of DT

Drugs developed in DT will likely be designated orphan drugs since they affect a rare neoplastic disease (D48.1 in ICD-O), having an incidence lower than 1/100.000/year and prevalence under the threshold of 50/100.000. With this designation, financial incentives, such as market exclusivity guarantees, and tax / fee incentives can occur. However, most of these benefits will apply as long as a drug is approved. Therefore, the DT community should consider the approval risk that will be factored by any company when the risk of failing approval is perceived as high and that may deter it from developing a new drug in DT or even to seek the label extension in the case the drug is already approved for other indications. In the EU, the approval risk comes with an additional risk, the reimbursement risk, the risk that the drug is approved but then not reimbursed by some national health systems across Europe.

In any case, strict regulatory requirements remain in place requiring a drug manufacturer to prove safety and efficacy through clinical studies felt by the regulatory and HTA communities as appropriate to the context. However, regulatory bodies are open to consider the challenges of rare diseases ([www.ema.europa.eu/clinical-trials-small-populations](http://www.ema.europa.eu/clinical-trials-small-populations)).

### Clinical challenges of DT

Behavior patterns of DT can range from the indolent or outright quiescent to aggressive. Survival is often not impacted by the disease except of patients with FAP-associated disease (Gardner syndrome), but QoL may be impacted substantially in a patient group with a median age at disease onset of 35 years.

### Role of medical therapy in DT

Medical therapy, whatever the regimen selected, can be used in DT basically in four clinical scenarios, wherein therapeutic choices may be different: (a) primarily progressive disease, attempting to avoid surgery (felt to be often not rewarding in DT), (b) non progressing symptomatic disease, impacting current QoL, (b) progressing symptomatic disease, impacting current QoL and (d) progressing disease liable to impact future QoL.

Medical options in DT can often be used in a stepwise fashion, going from the least to the most toxic, even if the response rate is lower with the least toxic; although, sometimes those with a higher response rate may be selected (when the disease is highly symptomatic and progressing). Therefore, the clinical problem does not seem one of directly comparing different options in terms of efficacy. The problem is much more one of identifying the differential features of available options and to be able in the clinic to tailor the individual sequence of drugs to the single patient. Thus, in purely clinical terms, and aside from feasibility issues given the rarity of the disease, comparative randomized clinical trials may not necessarily be the ideal study design. Uncontrolled studies or non-comparative randomized studies may better fit the clinical need of knowledge about anti-cancer agents in DT.

### Study endpoints

OS should not be held as a primary endpoint in DT studies since DTs do not impact patients' life expectancy, for the main reason being that DTs do not metastasize. This is less true for intra-abdominal DT (mesenteric fibromatosis) in FAP, since this disease is more likely multicentric and more aggressive, potentially leading to life-threatening complications (i.e. intestinal obstruction, tumor fistula / abscesses, hydronephrosis, etc.). The local consequences of extra-abdominal DT, typically in the girdles, may be substantial on QoL as long as the disease progresses. This is the reason why symptom improvement could be an increasingly valid and meaningful endpoint and thus requires the data to be collected in a thorough and validated manner. However, collection and interpretation of such data are challenging. A frequent issue in relying upon patient reported outcomes (PRO) is missing data and that most studies do not address the issues important for DT patients. Thus, it would be important for the DT community to be able to rely on regulatory acceptable criteria of appropriateness of PRO to be used in DT studies. The first developed PRO tool in DT has identified 11 symptoms and 17 psychosocial parameters as critical to the patient experience [96]. Prospective validation studies are ongoing. It should be taken into account that HRQoL indicators may be affected by possibly spontaneous regressions.

In principle, PFS, progression arrest, and growth-modulation index (GMI) may be clinically sound endpoints in DT. On the other side, a major limitation, especially outside a randomized clinical trial setting, is that the natural history of DT may be one of alternating intervals of progression and stability. In this sense, progression on discontinuation and new response on rechallenge may indicate that response is attributable to therapy. Thus, study designs exploiting discontinuation of treatment and rechallenge may be explored as a means to use progression-free endpoints outside a controlled setting. A limitation is that tumor response and progression may follow treatment by a substantial time interval.

In principle, ORR may be considered a clinically sound endpoint in DT because it can be related to symptomatic improvement. In addition to this, a tumor response objectively implies that a therapy has exerted a degree of anti-tumor activity, such that, a symptomatic improvement or a reversal in an ongoing progression will look much more convincing in the presence of some kind of tumor response. In this sense, tumor response might be exploited within composite endpoints. In other words, any of the other clinically sound endpoints (PFS, HRQoL, etc.) could be investigated in association with tumor response, as a means to decrease uncertainty about the causative effect of the drug. A challenge is that a disease like DT seems to give rise to non-RECIST responses in a good proportion of cases, especially when some agents such as tyrosine kinase inhibitors are used. Thus, any kind of response should be factored including non-RECIST patterns of response such as Choi criteria in GIST (change in contrast enhancement). This might be regulatory acceptable if tumor response is incorporated into a composite endpoint.

## KEY QUESTIONS

- Identify predictive factors for the failure of the active surveillance strategy.
- Provide stronger data about the risk of DT in FAP patients treated by prophylactic surgery.
- Better assess the symptomatic burden and need of supportive care in DT.
- Stimulate specific research on the symptomatic management of DT.
- Better describe the imaging changes observed during active surveillance and during treatment and better define the response or failure to treatment.
- Develop and validate specific HRQoL tools.
- Provide larger data about pregnancy, birth control and fertility in DT patients.
- Provide larger data about the specificity of pediatric patients.

## PROFILES



### The Desmoid Tumor Research Foundation

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### Organization Profile

#### Mission:

The mission of The Desmoid Tumor Research Foundation is to aggressively fund research to accelerate the development of improved therapies, and ultimately find a cure for desmoid tumors. We collaborate with dedicated researchers and clinicians worldwide to improve the lives of patients through education, awareness and support.

DTRF was co-founded in 2005 by Marlene Portnoy and Jeanne Whiting, with the mission of facilitating and funding research toward a cure and supporting patients with information. Every year DTRF has gained momentum and has seen new clinical trials, emerging therapies and important new discoveries about the disease come to fruition.

#### Successes:

- **Research Funding:** DTRF is the only foundation in the U.S. solely dedicated to funding desmoid tumor research and finding a cure for this rare disease. The funding of cutting-edge collaborative research at the world's top sarcoma cancer research centers is DTRF's priority.
- **Advisory Boards:** DTRF's scientific and medical advisory boards are comprised of the world's top desmoid tumor experts.
- **Collaboration and Education:** DTRF holds an annual fall Patient Meeting which brings patients, physicians and researchers together for education, support and collaboration. In addition, the annual DTRF International Desmoid Tumor Research Workshop brings together a diverse group of scientists from around the world including experts in desmoid tumor research, human genetics, drug development and related fields. The Workshop facilitates an enthusiastic and collegial atmosphere as researchers across disciplines and institutions collaborate around the shared goal of improving treatments for desmoid tumor patients, establishing research priorities and moving the field forward toward a cure.
- **Website:** [www.dtrf.org](http://www.dtrf.org), is a clearinghouse of information on desmoid tumors and published desmoid tumor research papers, reaching physicians and researchers around the globe. The website provides patients with critical information and also directs them to additional resources for support.

- **Tissue donation:** DTRF partners with Pattern.org to enable the patient community, through an online consent form, to contribute excess fresh tissue from surgery to research.
- **PRO tool:** DTRF funded the development of the first Patient Reported Outcome (PRO) tool specific to desmoid tumors, with PI Mrinal Gounder at Memorial Sloan Kettering Cancer Center and IQVIA, a leader in PRO development. The tool is now ready to be validated and plans are under way to use it in upcoming new desmoid tumor trials.
- **Patient registry:** DTRF partnered with the National Organization for Rare Disorders (NORD) and the U.S. Food and Drug Administration (FDA) to launch the first ever U.S. patient registry specifically for desmoid tumor patients. This patient registry collects and aggregates data from patients and makes that de-identified data available to researchers to advance the medical science of desmoid tumors.
- **Virtual Tumor Board:** DTRF founded the international DTRF Virtual Tumor Board where desmoid tumor experts, including clinicians, radiologists, pathologists and others, join from around the world, meeting quarterly via video conference. This resource offers a new source of support and collaboration to physicians who can present their difficult desmoid tumor cases.
- **International Consensus Paper:** As a supporter of this consensus paper DTRF thanks the many professionals who participated to create this important and groundbreaking resource.



## Germany: sos-desmoid e.V.

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## Organization Profile

Sos-desmoid e.V. was founded 2009 as a charitable organization in Mannheim, Germany. The foundation of the group was initiated by Prof. Hohenberger (Mannheim University Medical Center, Germany).

It is the German organization for desmoid tumor patients, their relatives and experts who are interested in the research and treatment of this disease.

Sos-desmoid e.V. created a website ([www.sos-desmoid.de](http://www.sos-desmoid.de)) to provide medical information and offer the possibility to get in contact with other people affected by desmoid tumors.

Besides the national work of the organization, sos-desmoid e.V. puts its focus on international collaboration and exchange with patients, patient organizations and global medical experts.

### Our major aims:

- to be a resource for patients and relatives
- to facilitate the contact between affected persons
- to support interaction and cooperation with medical experts
- to collaborate nationally and internationally with patient organizations/networks
- to raise awareness of desmoid tumors

### Activities:

- to identify the needs of desmoid patients and their relatives
- to organize patient meetings
- presentation of medical information (flyers, etc.)
- to provide information about desmoid tumors to the public
- to develop cooperation with patients and experts
- to develop international contacts with experts and patient organizations





**Sarcoma  
Patients  
EuroNet**

## **Sarcoma Patients EuroNet e.V./Assoc. (SPAEN)**

Sarcoma Patients EuroNet (SPAEN), the International Network of Sarcoma, GIST and Desmoid Patient Advocacy Groups was founded in April 2009. The organization was born from a very strong desire among various national patient groups to network, cooperate and share materials, knowledge and experiences.

Acting in partnership with clinical sarcoma experts, scientific researchers, pharmaceutical industry and other stakeholders, SPAEN is working to support sarcoma research and to improve the diagnosis, treatment and care of sarcoma patients through improving information and support and by increasing the visibility of sarcoma with policymakers and the public.

### **Our Objectives**

- Identify problems, challenges, access issues and unmet medical needs in sarcomas. Find solutions and improve the situation by collaborating with leading sarcoma experts, researchers, industry and other relevant international stakeholders/initiatives in an outcome-oriented way.
- Sarcoma patients need timely and accurate diagnosis and need to be treated according to guidelines; ideally as early as possible in multidisciplinary sarcoma expert centres. SPAEN advocates and supports the implementation of these structures and pan-European collaboration between these centres.
- Clinical research, studies and generating evidence/data are essential parts of the process of developing better and innovative treatment solutions. SPAEN aims to be involved as early as possible in clinical trials, to try to improve patients' access to studies and to support meaningful research – following the specific needs of rare cancer patients.
- Sarcoma patients and their relatives need a strong “United Sarcoma Patient Voice” and strong “National Patient Support Opportunities”. That’s why SPAEN cares for their members – the existing national patient organizations and encourages the creation of new ones.

### **Our Vision**

All sarcoma (incl. GIST) patients have access

- to timely and correct diagnosis,
- to information about their specific sarcoma-subtype
- to treatment and care in specialised centres and
- to innovative treatment options incl. clinical trials.



**Sarcoma  
Patients  
EuroNet**

### **Our Mission**

Improving the situation of sarcoma, GIST and desmoid patients by

- building one strong International Sarcoma Voice
- cooperating with all relevant international stakeholders
- in an outcome-oriented way and
- strengthening this international coalition of national Sarcoma-, GIST- and Desmoid Patient Advocacy- and Support Groups

### **Our Core Values**

- Focused on the needs of the PAGs (patient advocacy groups) and the patients/caregiver
- Willingness to advocate
- High quality of information/education/training: Correct, up to date, understandable, independent
- Cooperative and professional
- Ethical, transparent, behave with integrity
- Innovative spirit

## **DISCLOSURE**

SB: honorarium and travel grants from Nanobiotix and PharmaMar;

MG: Consulting fees from Bayer;

BK: Consulting fees from Bayer;

RM: Consulting fees from Bayer and Janssen;

VV: Advisory boards for Lilly, Janssen, Novartis, Epizyme, AbbVie, Ignyta and Springworks.

All other authors have declared no conflict of interest.

## **Disclaimer**

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations with which the authors are affiliated.

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# EURACAN

## European Reference Network on Rare adult Solid Cancers



> 300  
HOSPITALS



> 900  
HEALTHCARE UNITS

European Reference Networks are virtual networks created under the EU Directive on Patients' Rights. 24 Networks of expertise have thus been labeled at the European level in order to share expertise and improve access to care for patients across the European Union, especially for complex or rare diseases requiring highly specialized health care and a concentration of knowledge and resources.

EURACAN is the ERN on Rare Adult solid Cancers. It gathers together 66 centres from 17 European countries and aims to improve the quality of care and outcome of patients with rare adult solid cancers in the EU: **DIAGNOSIS, TREATMENT MANAGEMENT, KNOWLEDGE, RESEARCH AND COMMUNICATION** for patients, families, physicians and all stakeholders;

PATIENT REPRESENTATIVES associated with EURACAN are called European Patient Advocacy Groups (ePAGs). They work closely with the ten domains and EURACAN to provide information and perspectives on patients' needs and expectations and are coordinated by EURORDIS. The ePAGs are

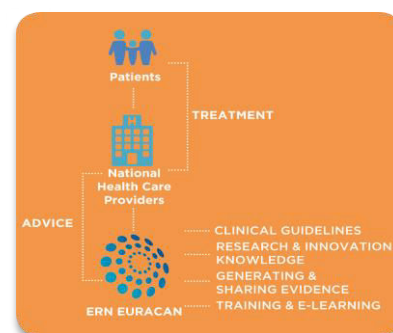


All rare adult solid cancers are grouped into ten "domains" corresponding to the RARECARE list of rare cancers based on the ICD-O:

- sarcoma,
- Gynecological,
- Urological,
- Neuroendocrine,
- Digestive,
- Endocrine,
- Head and Neck,
- Thoracic,
- Skin and Ocular melanoma,
- Brain and central nervous system.



Patients across the EU can have access to the best expertise available on diagnosis and treatments through the Clinical Patient Management System (CPMS), a web-based clinical software application provided by the European Commission. The CPMS allows healthcare providers from all over the EU to organise virtual "advisory committees" composed of medical experts from ERNs to re-read a diagnosis or suggest a patient's treatment.



### First Achievements:

- Homogenisation of Clinical Practice Guidelines to spread and align best practices on GISTs, soft tissues & visceral sarcomas & Bone sarcomas jointly with the ERN Paedcan.
- **Research:** EURACAN is involved in The Rare Disease European Joint Programme and will actively contribute to the creation of a research and innovation pipeline "from bench to bedside". Thirty EURACAN members joined The EORTC SPECTA clinical research infrastructure and 6 applications have been submitted to the Fourth Joint Transnational Call 2017 on Translational Research on Rare Cancers TRANSCAN -2
- **Training and education activities** have been set up on the domains of Sarcoma and Head and Neck cancers in jointly with other EUROPEAN organisations already active and acknowledged in the field.
- **Communication tools:** public website translated into ten Member State languages, Facebook page, Twitter account and leaflets for patients and families.