ELDERLY (SOFT TISSUE) SARCOMA PATIENTS

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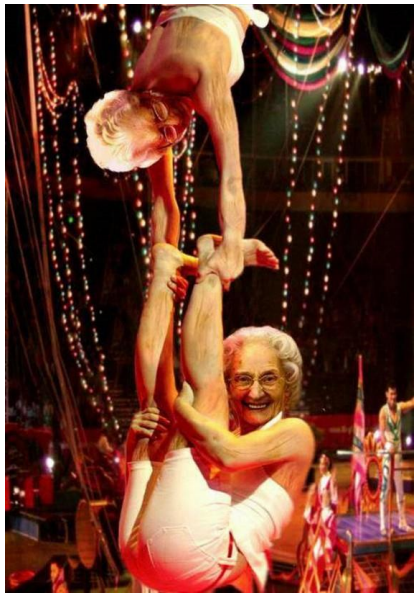
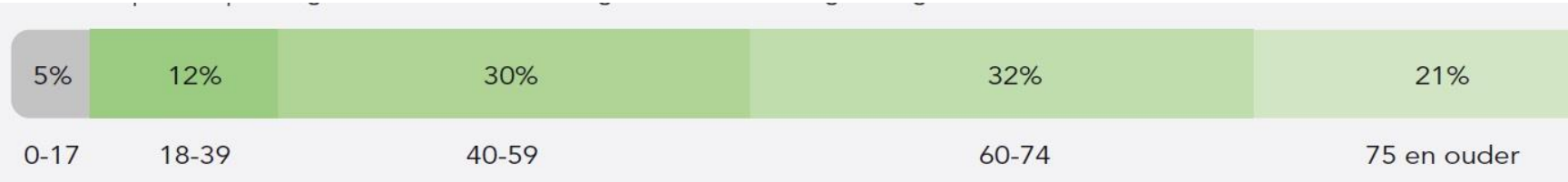
Elderly population is heterogeneous in many aspects: frail and fit and all-in between



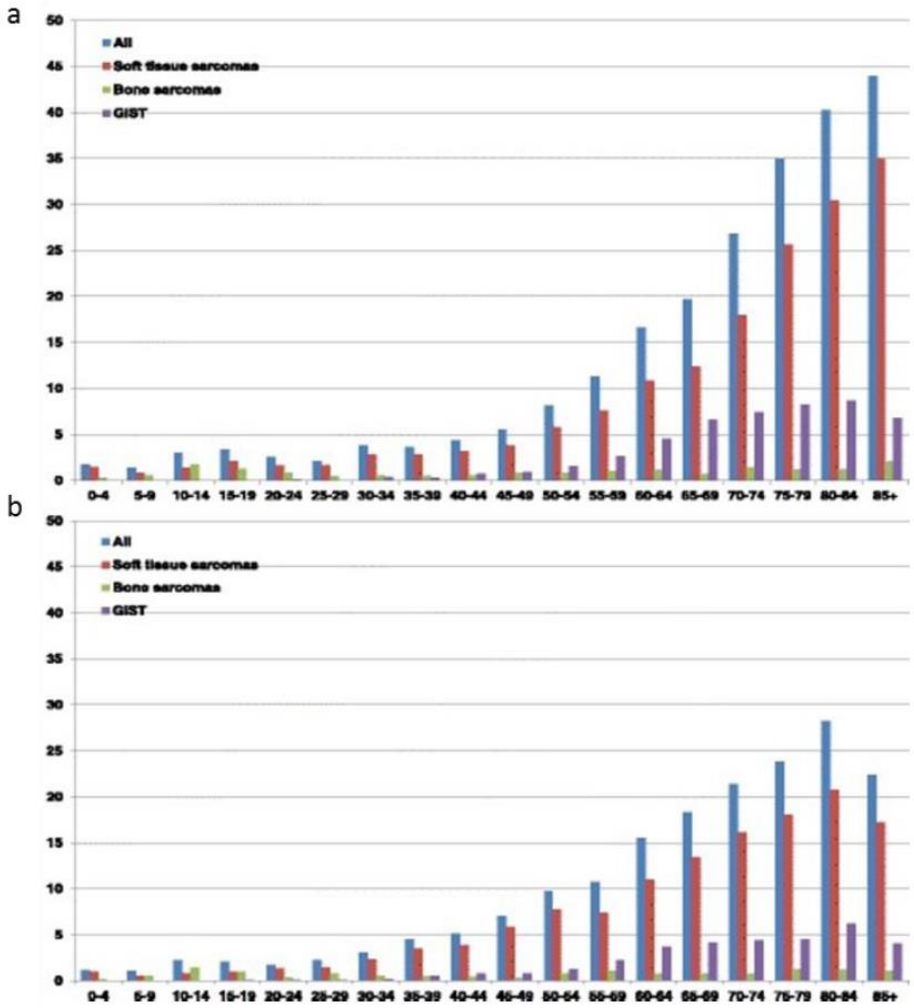
Over 50% of sarcoma patients are older than 60 years



Data from the Netherlands Cancer registry 2009-2018

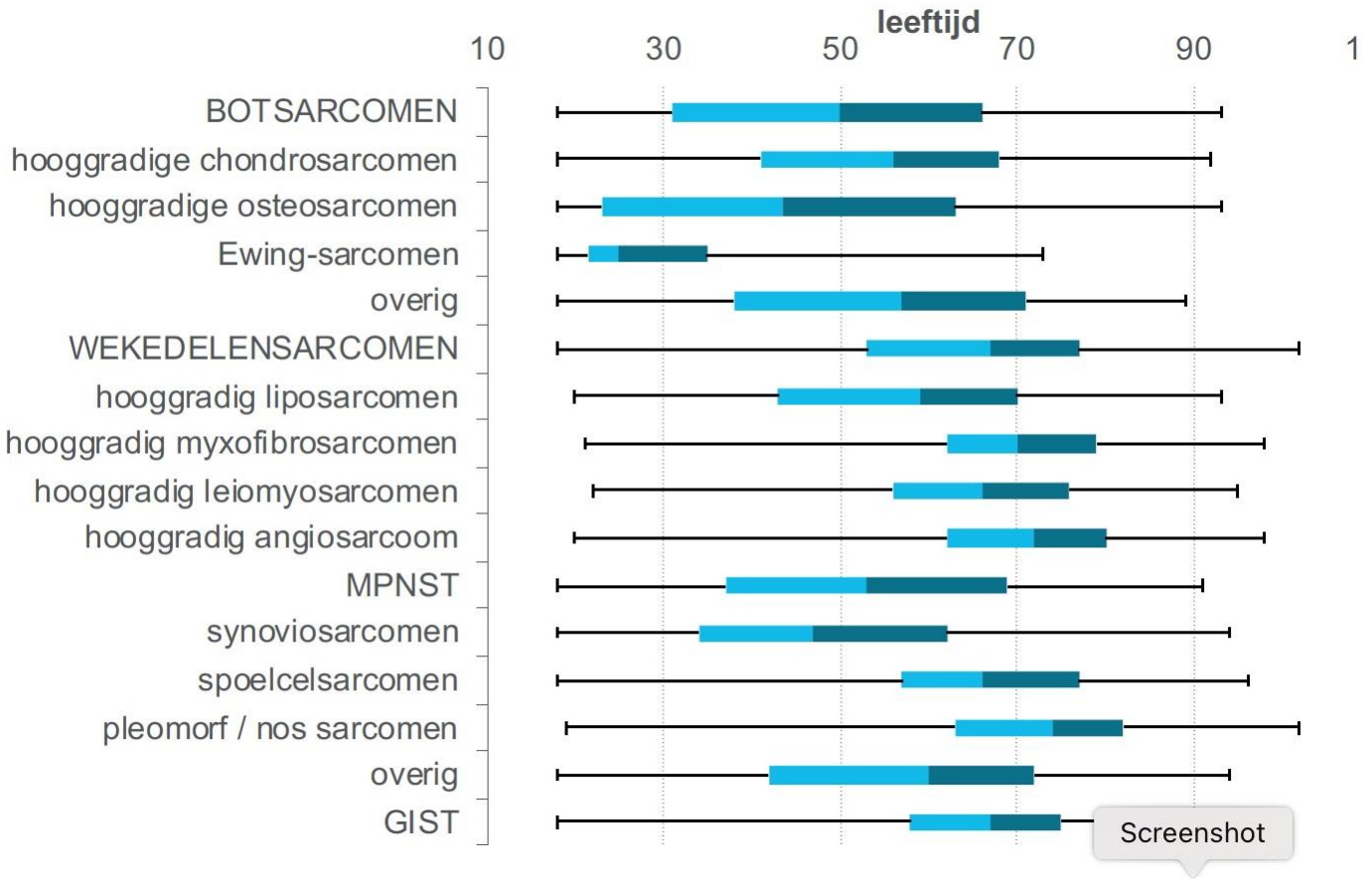
Incidence Sarcoma and GIST Germany 2013

(a:male, b:female)



Kasper, Hohenberger, CROH 2020)

Patients with sarcomas are heterogenous in more aspects: subtypes are related to age

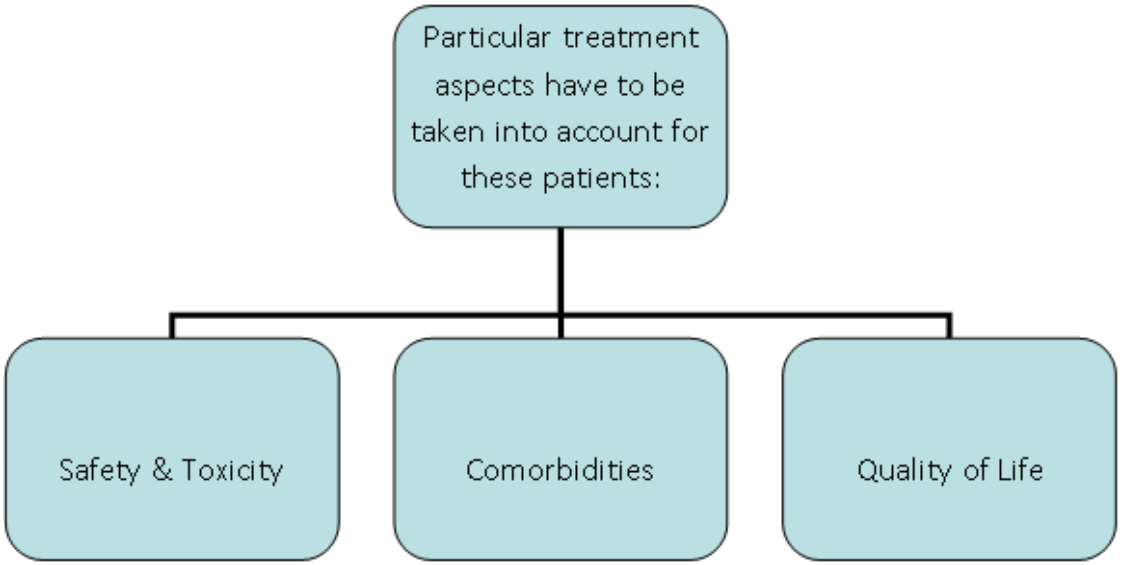


Data from the Netherlands Cancer registry 2009-2018

- There is only **limited data** and clinical studies available evaluating **elderly sarcoma** patients.
- Inclusion into **clinical trials** takes place only in a very small percentage of patients and should be encouraged.
- Old **age** should **not per se** be considered as a **contraindication** for the administration of chemotherapy or for carrying out a necessary tumor operation; in contrast, one should take specific aspects such as safety, comorbidities, toxicities, and quality of life into account.
- **Pre-treatment assessments** should focus on functional status, physical performance, social activity, nutritional status, depression and cognition. *And patient's preferences*
- **Specific geriatric screening instruments may be useful** to optimize treatment strategies for the elderly sarcoma patient population.

Kasper B, CROH 2020

Toxicity of treatment maybe considerably more in elderly



Kasper B, CROH 2020

Clinical trials in elderly are challenging

- Do they measure what is most meaningful?
- Is the study population representative for all elderly?
- Are the studies done with the optimal and available, not too toxic drugs?

- What do we know from standard doxorubicine in elderly patients with metastatic STS?

HOLISTIC STUDY in mSTS Age-specific priorities UK and Dutch population

	Preference for Quality of Life (QoL) vs. Length of Life (LOL)			
Variable	QoL N (%)	LoL N (%)	Equal N (&)	p-value
Age				
18-39 years	0 (0)	11 (100)	0 (0)	0.001
40-65 years	29 (42)	36 (52)	4 (6)	
>65 years	27 **(50)**	19 (**35**)	8 (**15**)	

Spring 2019 a call from the EORTC QoLG

for funding of proposals for a randomised trial with HRQoL as primary endpoint

The TOLERANCE trial was developed

- Elderly
- Metastatic soft tissue sarcoma treated with systemic treatment (med OS only 10 -12 months)
- Very few clinical trials/ trial data in patients with mSTS > 65 years of age. UNMET clinical NEED
- Input from elderly: Quality of Life equally or more important than length of life

EORTC 1976-STBSG-QLG-ETF
TOLERANCE

A 3 arm randomized study on healTh-related quality Of Life of EldeRly pAtients with advaNced STS undergoing doxorubicin three weekly or doxorubicin weekly or cyclophosphamide plus prednisolone treatment

Study coordinator: Winette van der Graaf, NKI, Amsterdam

Study co-coordinator: Olga Husson, NKI, Amsterdam

Young coordinator: Gloria Marquina, Hospital Universitario San Carlos, Madrid

ETF representative: Antonella Brunello, Istituto Oncologico Veneto, Padova

Strong Support and input from Roger Wilson

Why these drugs?

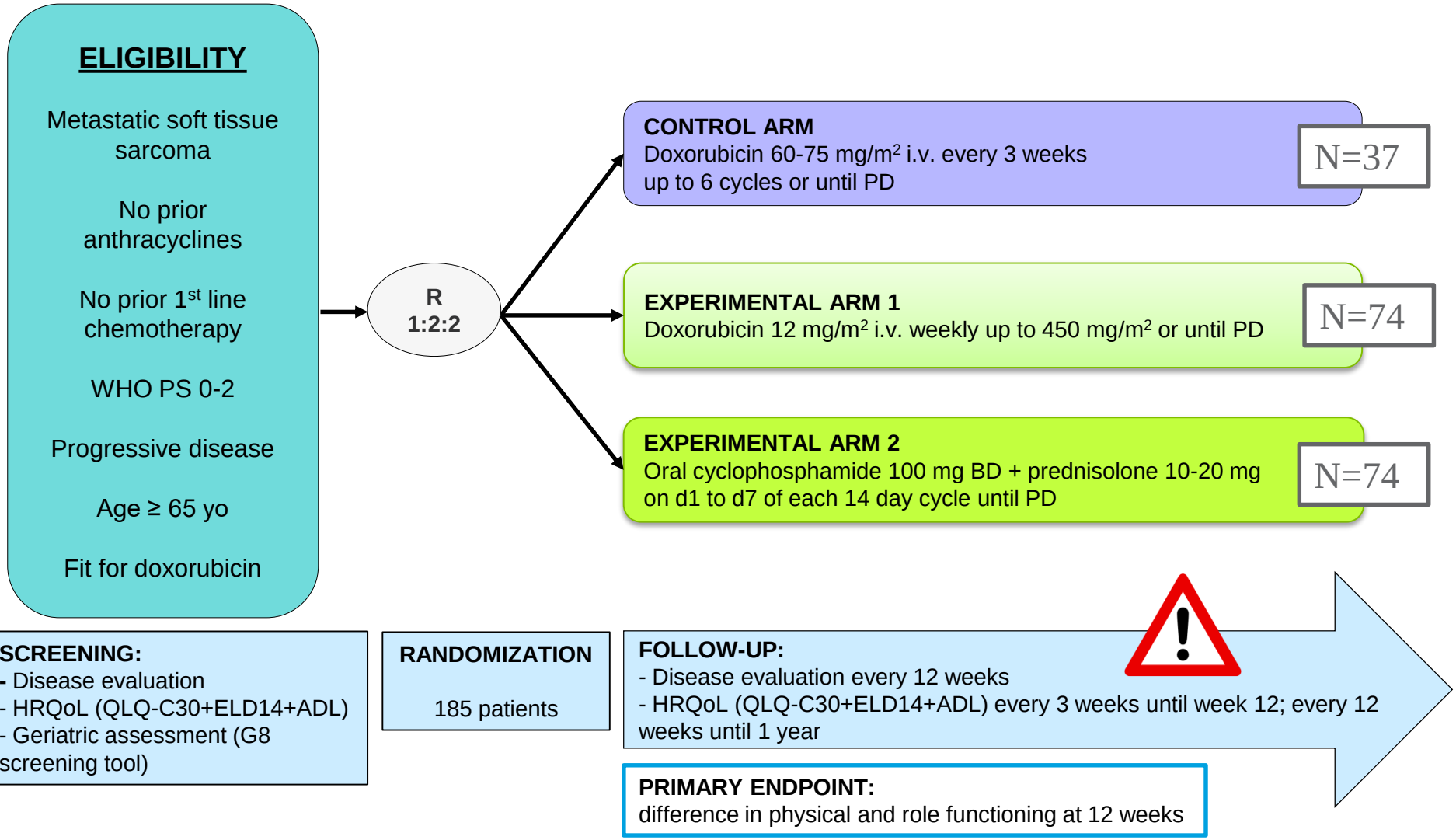
- Doxorubicin 60-75 mg/m2 **3 weekly** is the standard

- "**Weekly low dose doxorubicin** monotherapy in metastatic breast cancer resistant to previous hormonal and cytostatic treatment" Scheithauer, Christoph Zielinksi, et al 1985 Breast Cancer Res Treatm
- "The tolerance for this regimen was remarkable, with neither serious acute toxicity nor any signs of congestive cardiomyopathy"

Feasibility of metronomic oral cyclophosphamide plus prednisolone in elderly patients with inoperable or metastatic soft tissue sarcoma Olivier Mir, *Eur J Cancer 2011*

Conclusion: Metronomic CPM showed good safety results for this frail population, with promising activity in patients with radiation-induced sarcoma. Toxicity profile was favourable, allowing prolonged home staying and rare treatment discontinuations. A larger prospective study is warranted to confirm these encouraging results in elderly with STS.

Study design



The G8 geriatric assessment

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
		1 : moderate decrease in food intake
		2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
		3 : no weight loss
C	Mobility	0 : bed or chair bound
		1 : able to get out of bed/chair but does not go out
		2 : goes out
E	Neuropsychological problems	0 : severe dementia or depression
		1 : mild dementia or depression
		2 : no psychological problems
F	Body Mass Index (BMI (weight in kg) / (height in m^2)	0 : BMI < 19
		1 : BMI = 19 to BMI < 21
		2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
H	Takes more than 3 medications per day	0 : yes
		1 : no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good
		0.5 : does not know
		1 : as good
		2 : better
	Age	0 : >85
		1 : 80-85
		2 : <80
	TOTAL SCORE	**0 – 17**

Screenshot

TOLERANCE Eligible 65-69 years and G8:14 or less; all 70 plus

Objectives

- Primary

To assess whether a **higher HRQoL**, in terms of impact of the disease and its treatment on **physical and role functioning**, is achieved with metronomic schedules of doxorubicin or cyclophosphamide plus prednisolone versus the standard doxorubicin treatment

- Secondary

- To assess whether there is an improvement in QoL, in terms of impact of the disease and its treatment on social, emotional and cognitive functioning as well as self-reported symptoms and overall quality of life/ health perception among the three treatment arms.
- To assess whether there is a difference in the progression free survival, overall survival and tumor response among the three treatment arms.
- Toxicity profile.
- Tolerability of the three treatment arms

Endpoints

Primary endpoints

- Difference in physical and role functioning at 12 weeks.
  - Physical functioning (PF): EORTC QLQ-C30 ability to perform physical activities.
  - Role functioning (RF): EORTC QLQ-C30 ability to perform daily tasks related to household, work or recreation.

Secondary endpoints

- Difference in all other EORTC QLQ-C30 scales at 12 weeks
- Sensitivity: difference in physical and role functioning at 24 weeks
- Efficacy: tumor response, PFS, OS
- PFS at 12 weeks
- Safety: Adverse Events (AEs) according to CTCAE v5.0
- Tolerability: treatment discontinuation, delay and/or reduction
- Exploratory: Difference in QLQ-ELD14 scales; difference in ALD (Activities of Daily Living) scales

Inclusion criteria

- Histologically proven advanced or metastatic STS
- FFPE block or at list 10 slides for central review of histology
- Age: ≥ 65 years of age
  - 65-69 years old if G8 score ≤ 14
  - patients ≥ 70 years old are eligible independently of G8 score
- WHO performance status 0 – 2
- Adequate organ and bone marrow function
- Patients amenable to receive doxorubicin according to investigator
- Life expectancy based on other significant morbidity of ≥ 6 months
- Measurable progressive disease at entry based on RECIST 1.1
- Completion of HRQoL questionnaires at baseline (QLQ-C30 + ELD14) and ability to complete questionnaires throughout the study

Key points TOLERANCE

- Open-label, randomized phase 3 study

- **Duration** ✓ ✓
  - Accrual: 3.5 years
  - Last Treatment Follow Up: 2 years
  - Total duration: 7 years

- **EORTC network**
  - 185 patients
  - 35 sites in 9 countries (Cyprus – Denmark – Germany – Italy – Jordan – The Netherlands – Spain – Switzerland – United Kingdom)

Status

- Protocol version 1.0 ready
  - EORTC PRC approval March 12, 2021.
- Currently:
  - Database and CRFs construction ongoing
  - Site selection is performed

- Regulatory submission and site activation will be done if the study is financially guaranteed.
  - Depends on RTF grant outcome (April 2021)

TOLERANCE challenging aspects

- Totally new concept – primary endpoint HRQoL- believers and non believers
- Number of patients: 185
- No fancy drugs (but study will generate answers to long-standing open questions in this age group)
- **Absolute crucial that patients fill in questionnaires = 1st endpoint!**
- Representative for real life setting: broad inclusion criteria and protocol made a lean as possible
- Competing studies in elderly (France will not participate)
- Budget not 100% secured yet