DESMOPAZ

Pazopanib versus IV methotrexate/vinblastine in adult patients with progressive desmoid tumors

A randomized phase II study from the French Sarcoma Group.

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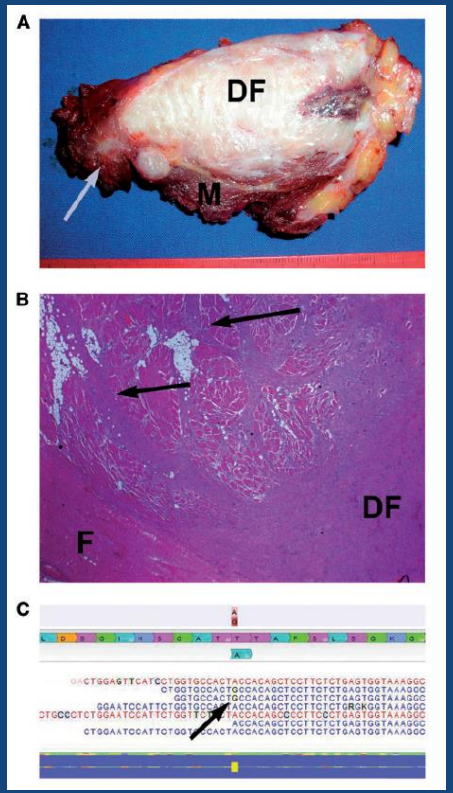
Introduction

- Desmoid tumors (DT) are a group of locally aggressive tumors of fibroblastic origin that can lead to significant morbidity due to local invasion.
- No randomized trial assessing systemic treatment activity in this rare disease has been reported.
- IV methotrexate/vinblastine (MV) has the best ratio of response rate (ORR)/level of evidence among conventional systemic agents used in DT
- Pazopanib (PZ) is an oral antiangiogenic agent targeting VEGFR1,2,3,PDGFRα,β and c-KIT tyrosine kinases registered in the treatment of advanced and metastatic soft tissue sarcomas.



Methods

- DESMOPAZ is a multicenter non-comparative randomized phase 2 clinical trial based on a two-stage optimal Simon's design which assessed safety and efficacy of PZ in progressive DT adult patients.

Methods

- Documented progressive disease (PD) according to RECIST 1.1
- Patients (pts) were randomly assigned to receive :
  - PZ 800 mg/day orally continuously,
  - or M (30 mg/m²) + V (5mg/m²) IV, once a week for 6 months and then every 2 weeks for 6 months.
- Treatment (ttmt) was until PD (cross-over then permitted), unacceptable toxicity, and for a maximum of 1 year.
- Archive FFPE samples of tumor tissue were mandatorily collected at baseline, an on-treatment tumor biopsy at Cycle 2 was optional.

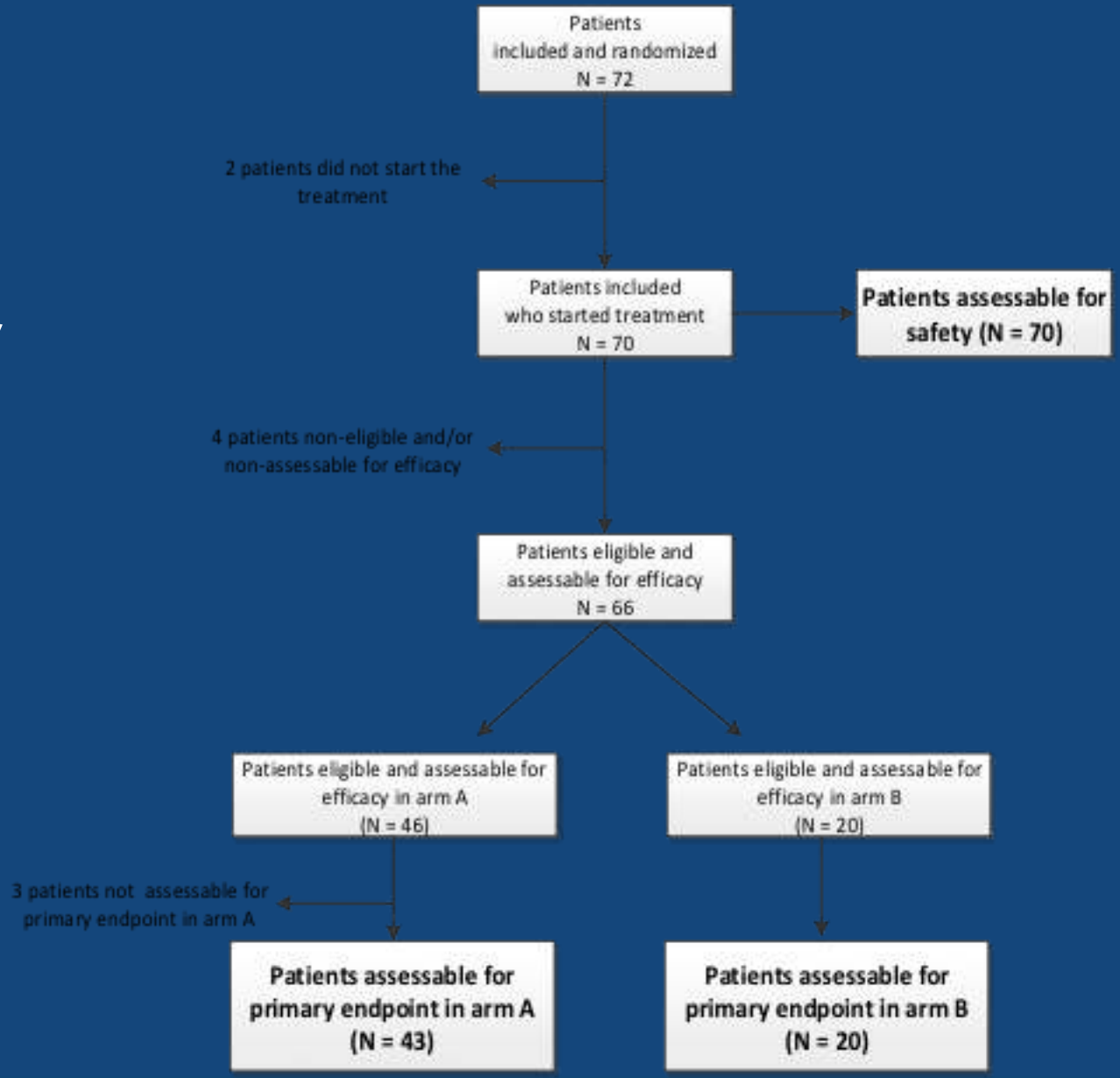
Statistical Hypotheses

- The primary endpoint was 6-month non-PD rate according to RECIST 1.1. on central review.

- The hypotheses were as follow: P0=60%, P1=80%, α=5% and ß=20%, and a 2:1 randomization, a total of 43 assessable pts were needed in PZ-arm and 22 pts in MV-Arm.
- PZ could be regarded as an active drug if there was at least 31 patients non progressive at 6 months in the PZ arm.

Results

- 89 pts were enrolled over 60 months in 12 french centers.
- *REDO FLOW CHART*



Results

- *ADD Table patients characteristics*

Safety

- Median number of cycles received was 12 (1-13) for PZ and 4 (1-13) for MV.
- 36 pts (75%) in PZ arm and 20 pts (91%) in MV arm have had at least one dose modification.
- 6 pts (12.5%) in PZ arm and 6 pts (27%) in MV arm definitively stopped ttmt for toxicity.

Safety

- PZ Arm - 54 pts assessable (48 + 6 cross over)
- 7.5% Grade 3-4 toxicity related to ttmt
- 3 SAE related to ttmt

- MV Arm - 24 pts assessable (22 + 2 cross over)
- 16.7% Grade 3-4 toxicity related to ttmt
- 2 SAE related to ttmt

Safety

PZ arm

	G1		G2		G3		G4	
	n	%	n	%	n	%	n	%
Fatigue	22	41%	16	30%	**3**	**6%**		
Hypertension	4	7%	10	18%	**9**	**17%**	**1**	2%
Headache	17	31%	6	11%	**1**	**2%**		
Anorexia	9	17%	8	15%				
Dysgueusia	12	22%	1	2%				
Gastrointestinal								
Diarrhea	16	30%	20	37%	**7**	**13%**		
Abdominal pain	10	18%	3	6%	**1**	**2%**		
Nausea and vomiting	34	63%	6	11%				
Mucositis	12	22%	4	7%				
Other	4	7%	2	4%	**1**	**2%**		
skin								
Palmar-plantar syndrom	10	18%	8	15%	**1**	**2%**		
Other	34	63%	3	6%				
Investigations								
PNN count decrease	4	7%	3	6%	**1**	**2%**		
ASAT/ALAT increase	10	18%	8	15%	**2**	**4%**		
Bilirubine increase	2	4%	2	4%	**2**	**4%**		
Other - hepatic					**2**	**4%**		
Hypothyroidism	5	9%	5	9%				
Musculoskeletal								
Arthralgia	4	7%	5	9%				
Myalgia	5	9%	3	6%				

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%				

Efficacy – Primary Endpoint - 6-month non-PD

- PZ arm, 43 first pts assessable

6-month non-PD rate = 81.4% (95%CI : 66.6-91.6)

- MV arm, 20 first pts assessable

6-month non-PD rate = 45% (95%CI: 23.1-68.5)

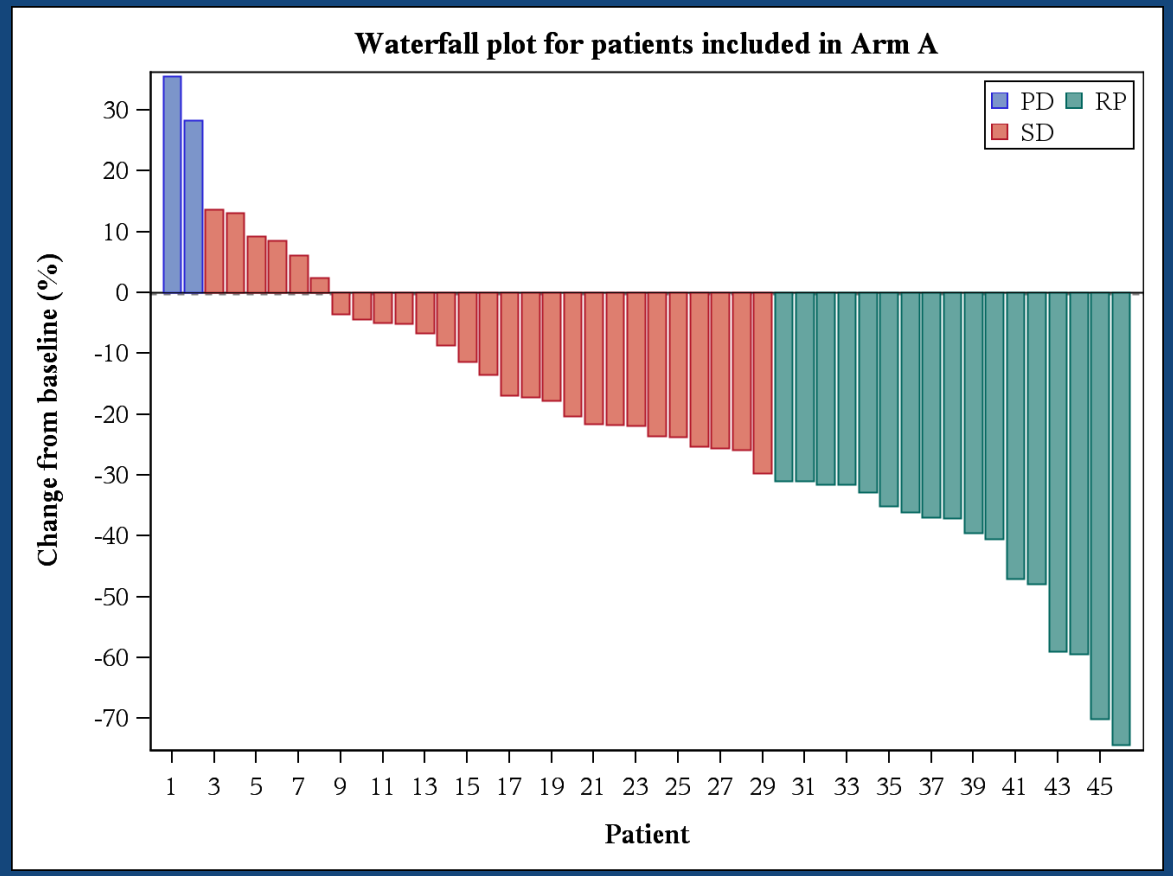
Efficacy - Secondary Endpoints - Best ORR

- PZ arm

All 46 pts assessable for response

PR = 37% (95%CI: 23.2-52.5)

SD = 58.7% (95%CI: 43.2-73)



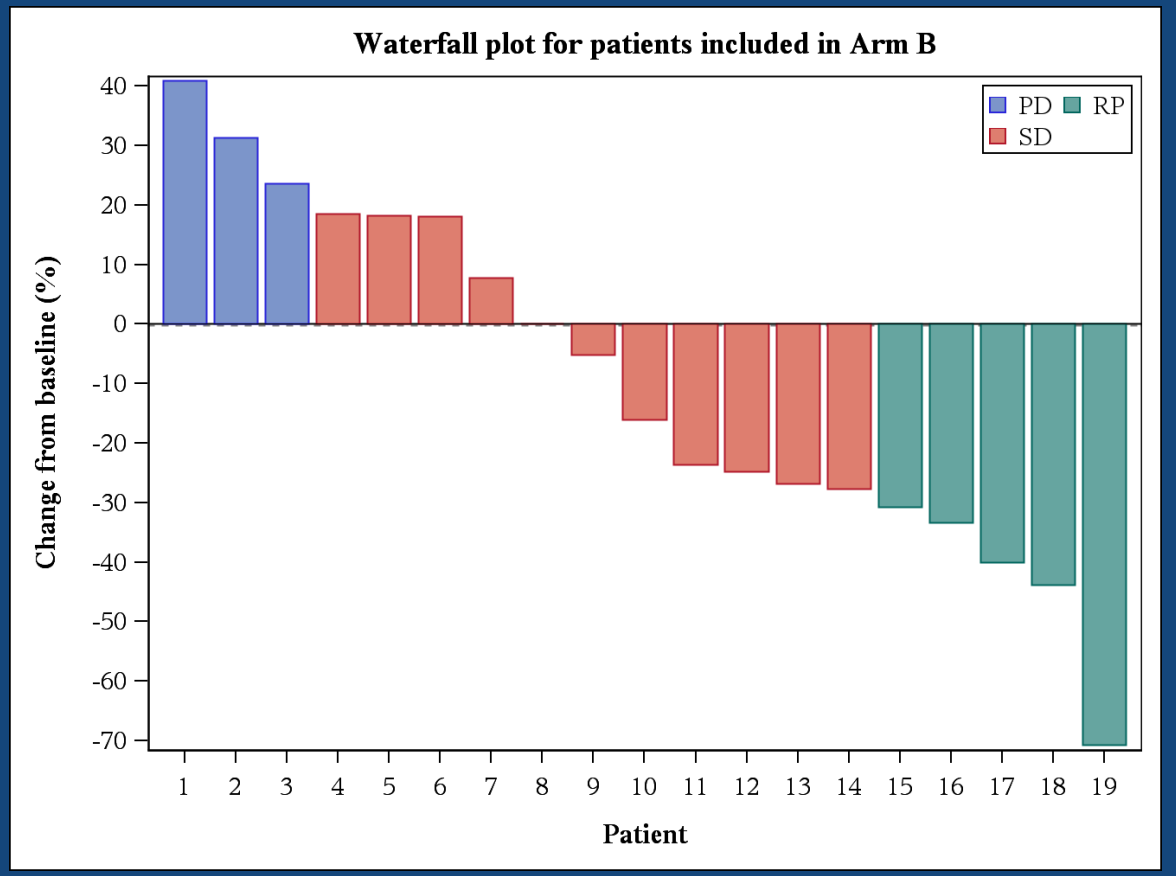
Efficacy - Secondary Endpoints - Best ORR

- MV arm

All 19 pts assessable for response

PR = 25% (95%CI: 8.6-44)

SD = 45% (95%CI: 23.1-68.5)



Efficacy – Secondary Endpoints – PFS

- PZ arm, all 46 pts

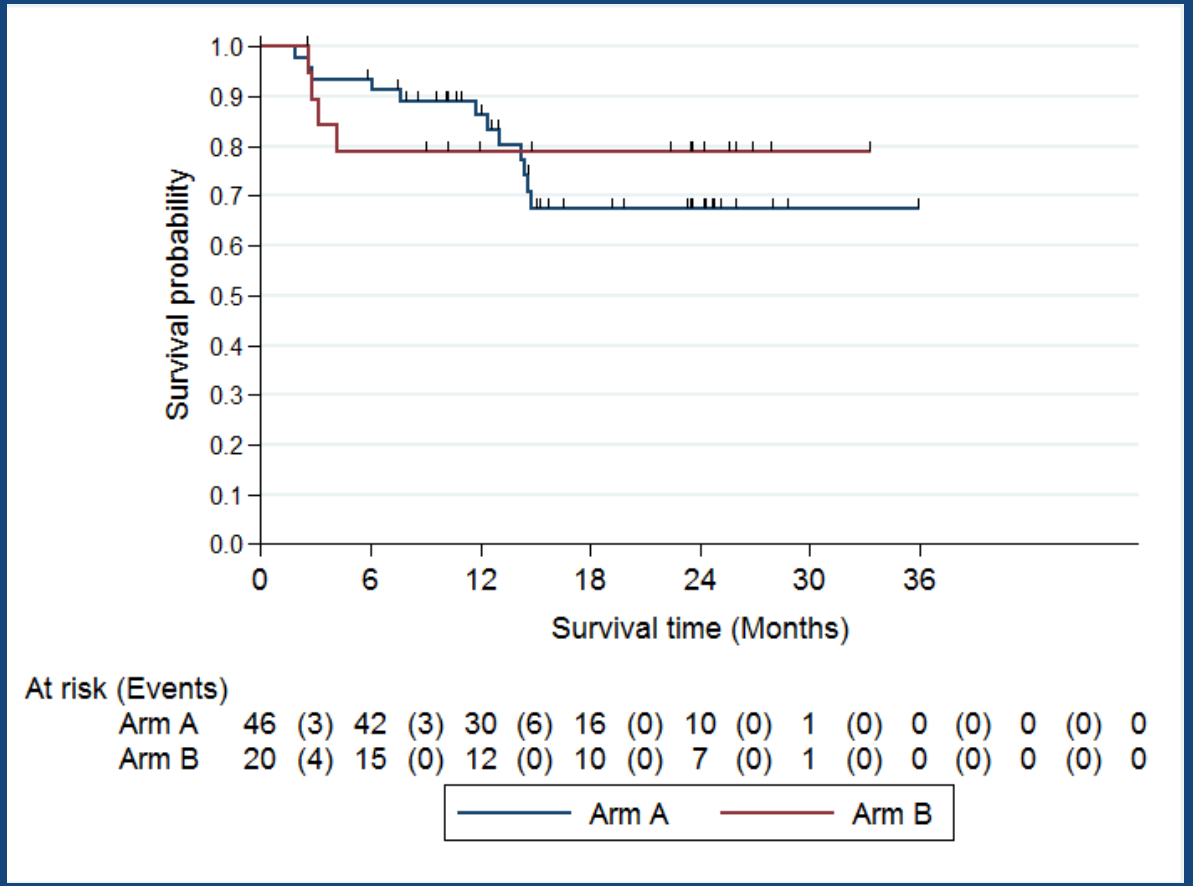
1y-PFS = 86.2% (95%CI: 71.7-93.6)

Median PFS not reached

- MV arm, 20 pts

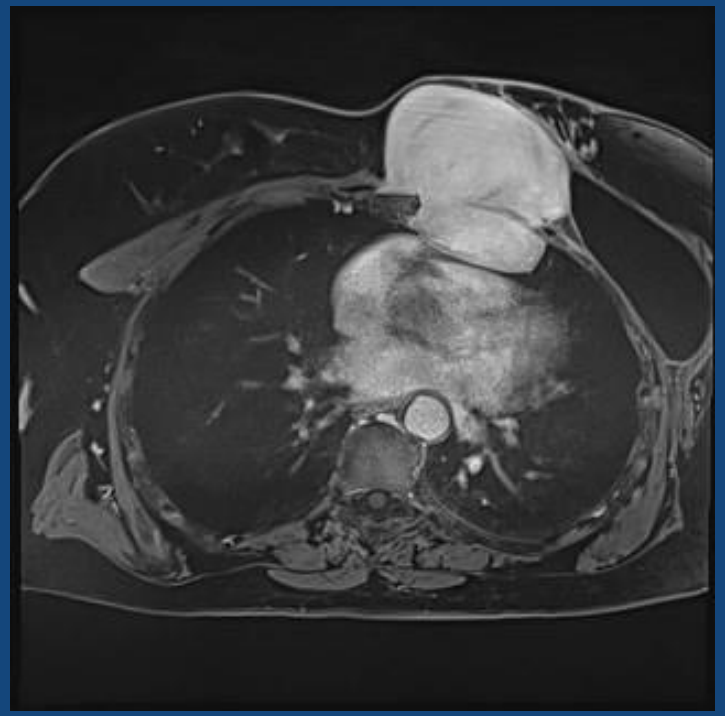
1y-PFS = 79% (95%CI: 53.2-91.5)

Median PFS not reached

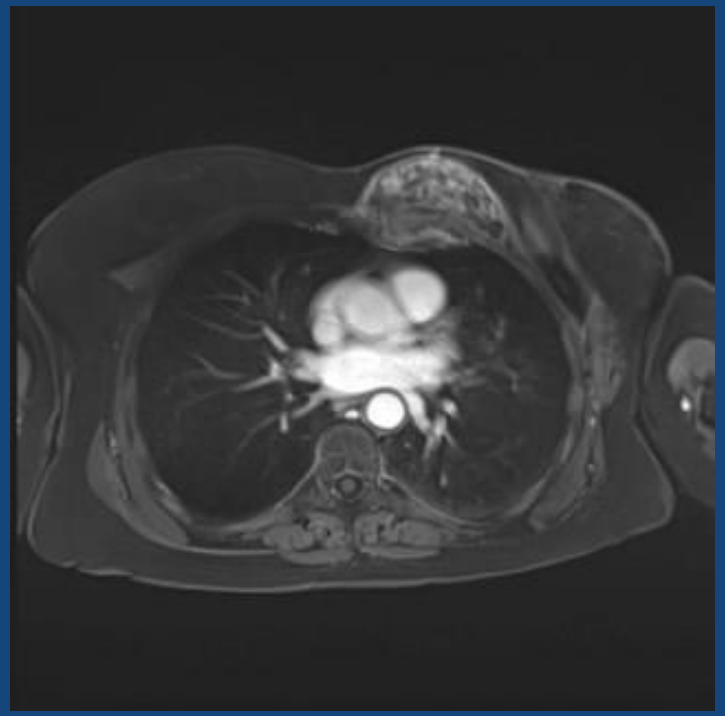


Early and Long lasting responses

April 2016



June 2016



→ Ttmt stopped in April 2017

→ No progression in April 2018

Results - Quality of life - QLQ-C30 EORTC

	Pazopanib 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)

Discussion

- 1rst randomized trial in progressive DT
- Documented progressive disease according to RECIST 1.1
- 36% internal tumors, worse prognosis
- 6-month non PD = 81%
- Partial Response = 37%
- Ancillary study with transcriptomics and proteomics ongoing

Conclusion

- The primary endpoint of the DESMOPAZ study was reached.

- PZ has meaningful clinical activity in pts with progressive DT.
- Pharmacodynamics translational study ongoing for sensitivity/resistance mechanisms and better patients selection.

Aknowledgements

- All patients
- All investigators
- Study team