Helios Klinikum Berlin-Buch
Department of Oncology and Palliative Care
Sarcoma Center Berlin-Buch

DKG KREBSGESELLSCHAFT | Zertifiziertes Sarkomzentrum

SARKOME.DE UTSCHE SARKOM STIFTUNG

Improving the outcome of GIST-treatment – 2 case stories

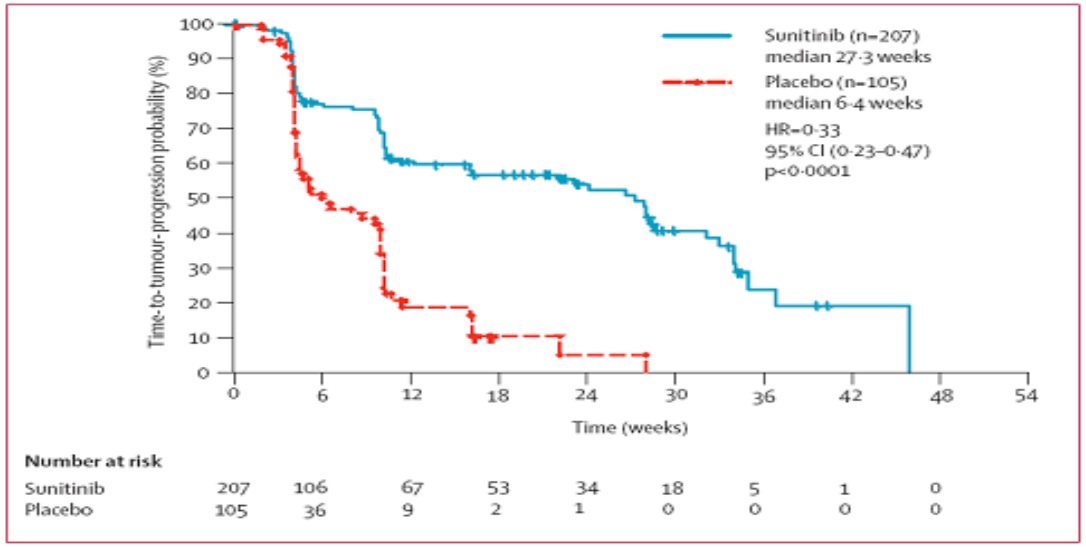
Peter Reichardt

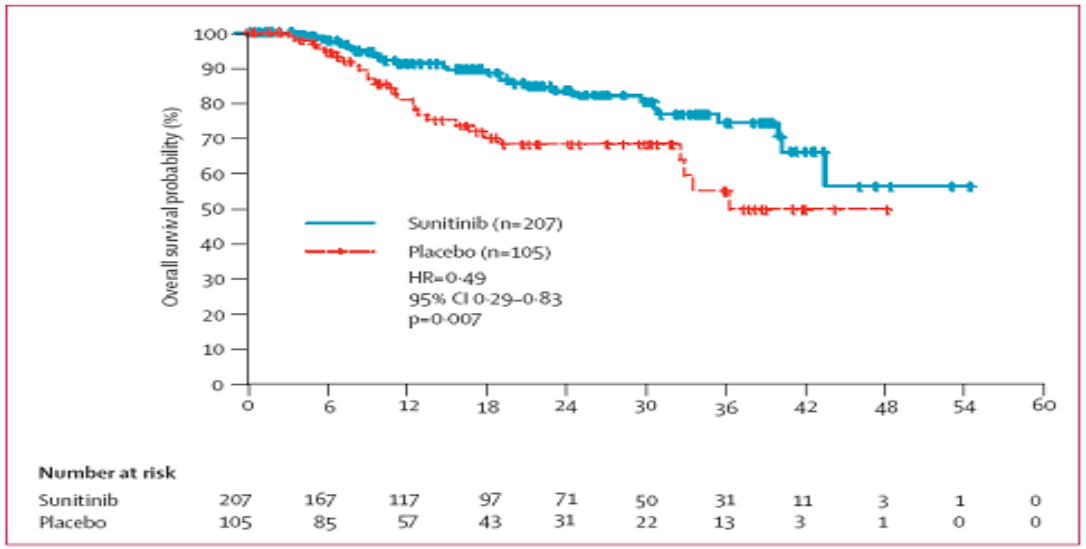
Helic

Phase III Trial: Sunitinib in advanced GIST after imatinib failure

Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali





Demetri GD et al., Lancet. 2006;3681329-1338.

Case 1-1

- Female patient, born 1944
  - **11/2005:** first diagnosis of metastatic GIST (liver); imatinib started at 400 mg/day
  - **10/2009:** PD, dose escalation of imatinib
  - **08/2010:** PD, sunitinib started at 37.5 mg/day, continuous dosing schedule
  - **11/2010:** slight regression; toxicity – HFS, hypertension, diarrhoea, mucositis (manageable in view of regression)

Case 1-2

- Female patient, born 1944
  - **02/2011:** SD, increase in toxicity (weight loss, impaired QoL)

Case 1-3

- Female patient, born 1944
  - **02/2011:** SD, increase in toxicity (weight loss, impaired QoL); change in schedule to 37.5 mg/day 14 days on/3 days off
  - **05/2011:** SD, less toxicity (minimal diarrhoea, no HFS, weight gain)
  - **08/2011:** SD, severe diarrhoea, weight loss; change in schedule to 37.5 mg/day 8 days on/3 days off
  - **12/2011:** SD, diarrhoea, weight loss; change in schedule to 37.5 mg/day 5 days on/3 days off

Case 1-4

- Female patient, born 1944
  - **03/2012:** SD, improved QoL, gained 3 kg of weight, diarrhoea rare; change in schedule to 37.5 mg/day 6 days on/3 days off
  - **06/2012:** SD, good QoL; ongoing 6/3 treatment schedule
  - **06/2013:** SD, good QoL; ongoing 6/3 treatment schedule

Conclusion: SD with sunitinib for 34+ months with individualised dosing/schedule

Sunitinib EAP 2011 and 2012

2011

Optimising management of sunitinib treatment in a worldwide treatment-use trial of patients with advanced GIST

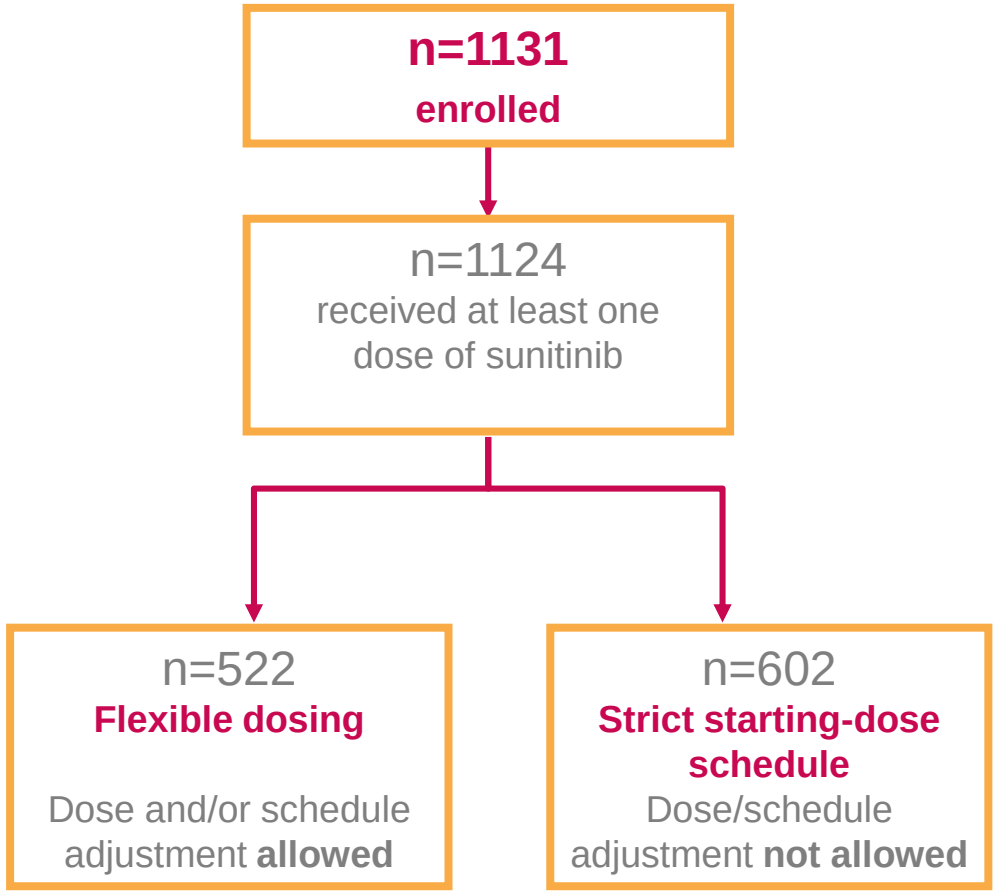
- Ad hoc analysis to evaluate clinical outcomes of patients with advanced GIST in the treatment-use trial after stratification by sunitinib treatment management

2012

Continued sunitinib treatment after progressive disease in a worldwide treatment-use trial of patients with GIST

- Ad hoc analysis to compare clinical outcomes of patients who continued on sunitinib treatment after progressive disease (PD) vs those who stopped after PD

Study design and patients



Key inclusion criteria

- Adult patients with histologically confirmed, malignant GIST not amenable to standard therapy with curative intent
- Failure of prior treatment with imatinib (progressive disease or significant toxicity)
- Ineligible for participation in ongoing sunitinib clinical studies

Key exclusion criteria

- Receipt of treatment in another clinical study
- Symptomatic central nervous system metastases
- Cardiovascular disease in the previous 6 months

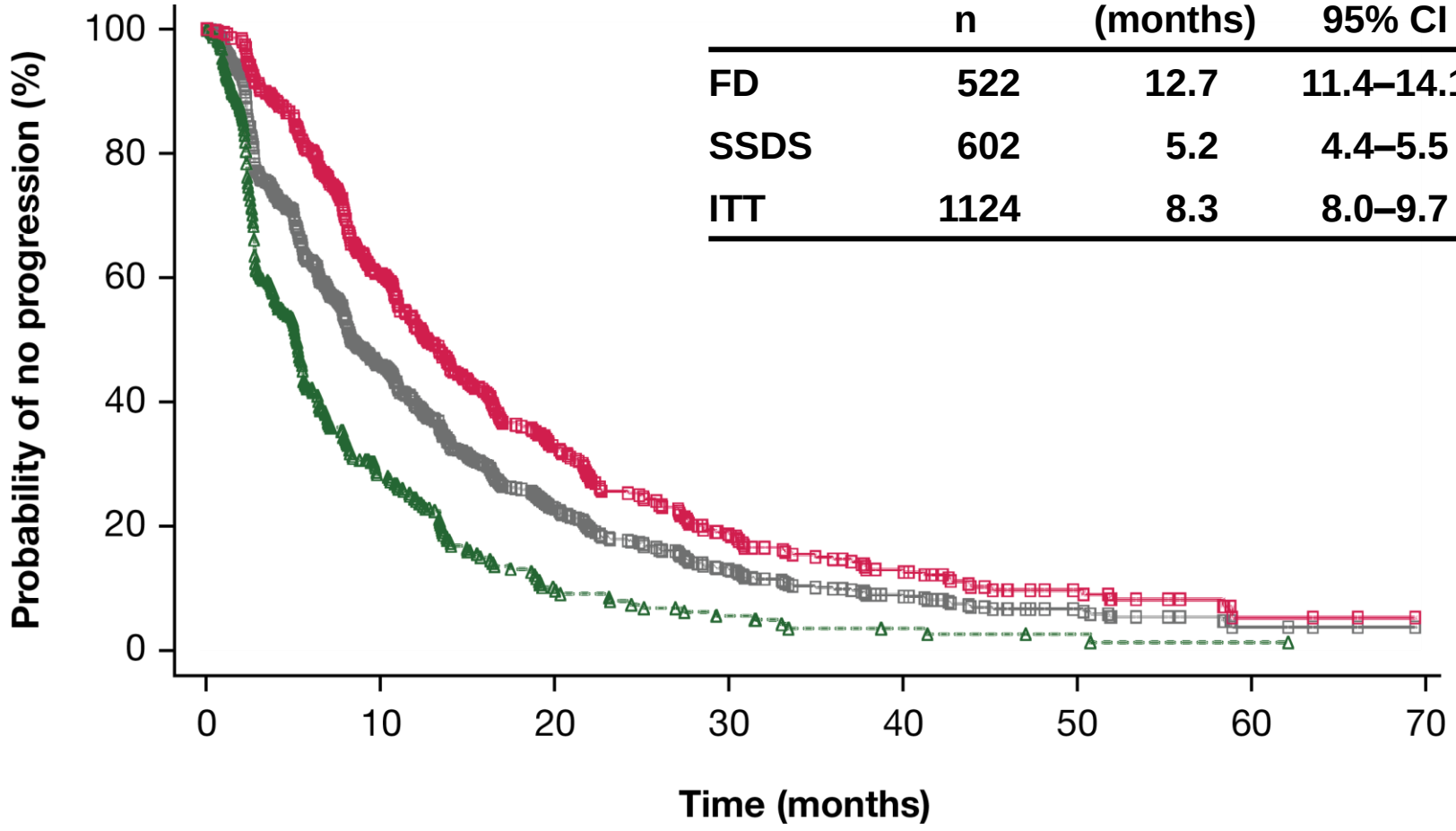
Reichardt P et al., Cancer 2015

FD allowed patients to stay on sunitinib for longer

Parameter	All patients (n=1124)	SSDS (n=602)	FD (n=522)
Cycles started, n	5 (1–59)	3 (1–45)	9 (1–59)
Days drug administered, n	140 (1–1647)	72 (1–1259)	248 (12–1647)
Days on treatment, n	214 (1–2124)	117 (1–1890)	388 (13–2124)
Patients with dosing interruptions, n (%) Due to AE* Other reason*	605 (54) 483 (43) 249 (22)	225 (37) 163 (27) 84 (14)	380 (73) 320 (61) 165 (32)
Days with interruption, %	5 (0–96)	7 (0–96)	5 (0–60)
Patients with dose reductions, n (%)	485 (43)	0	485 (93)
Total dose, mg	6075 (50–62,950)	3575 (50–62,950)	9925 (450–62,812)
Daily dose, mg	50 (15–53)	50 (50–50)	41 (15–53)
Relative dose intensity†, %	95 (19–175)	100 (19–175)	81 (30–141)

Reichardt P et al., Cancer 2015

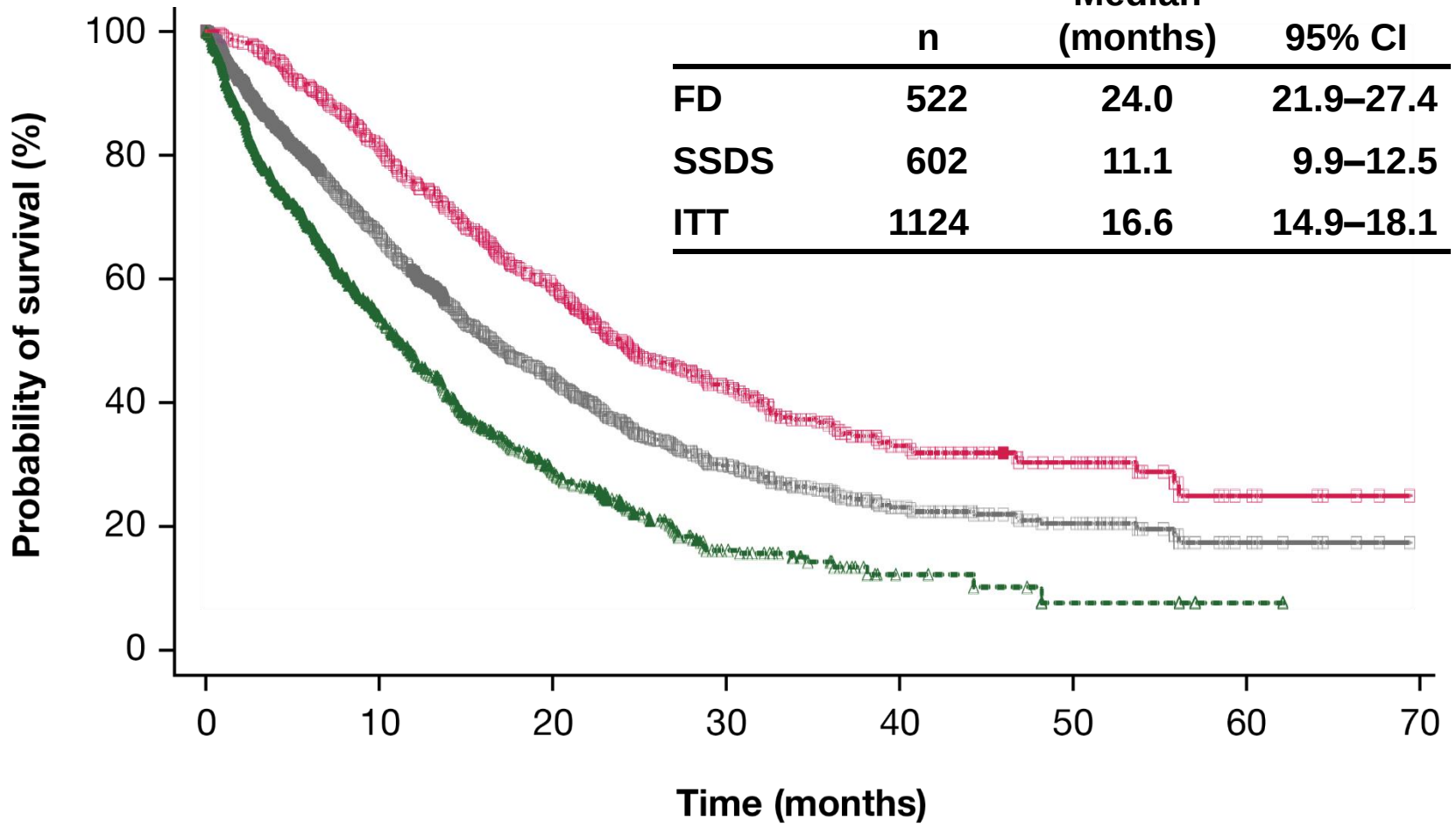
FD increased time to progression vs SSDS



	n	Median (months)	95% CI
FD	522	12.7	11.4–14.1
SSDS	602	5.2	4.4–5.5
ITT	1124	8.3	8.0–9.7

Reichardt P et al., Cancer 2015

FD improved overall survival vs SSDS



	n	Median (months)	95% CI
FD	522	24.0	21.9–27.4
SSDS	602	11.1	9.9–12.5
ITT	1124	16.6	14.9–18.1

Reichardt P et al., Cancer 2015

Flexible dosing improved safety outcomes

Most common treatment-related AEs (≥20% in either group): incidence overall and adjusted for duration of treatment				
	SSD (n=602; total patient-years=319)		FD (n=522; total patient-years=725)	
	Any Grade*		Any Grade†	
	n (%)	PPY	n (%)	PPY
Any treatment-related AE	519 (86)	163	513 (98)	71
Fatigue	176 (29)	55	303 (58)	42
Diarrhoea	162 (27)	51	292 (56)	40
Hand–foot syndrome	123 (20)	39	239 (46)	33
Nausea	117 (19)	37	209 (40)	29
Decreased appetite	113 (19)	35	189 (36)	26
Mucosal inflammation	99 (16)	31	157 (30)	22
Stomatitis	94 (16)	29	164 (31)	23
Hypertension	91 (15)	29	196 (38)	27
Vomiting	90 (15)	28	157(30)	22
Thromobocytopenia	79 (13)	25	143 (27)	20
Dysgeusia	76 (13)	24	104 (20)	14
Neutropenia	72 (12)	23	139 (27)	19
Anaemia	66 (11)	21	116 (22)	16
Skin discolouration	66 (11)	21	108 (21)	15
Rash	57 (9)	18	119 (23)	16
Hypothyroidism	28 (5)	9	116 (22)	16

Reichardt P et al., Cancer 2015

Which is the best schedule ?

Ask your patient !

Progression ? What to do?

- Progression confirmed ?
- Diagnosis confirmed ?
- Compliance ?
- Symptoms ?
- Emergency ?
- Treatment options ?

Case 2-1

- Male patient, born 1940
  - **10/2004:** first diagnosis of cystic tumour in left upper abdomen
  - **11/2004:** multivisceral resection with tumour rupture histology – GIST with high proliferative activity (*KIT* exon 11 mutation); no further treatment

Case 2-2

- Male patient, born 1940
  - **06/2005:** multiple peritoneal lesions; histologically-confirmed GIST
  - **07/2005:** start imatinib 400 mg/day
  - **03/2008:** PD, imatinib 800 mg/day
  - **05/2008:** PD

Case 2-3

- Male patient, born 1940
  - **05/2008:** PD; start sunitinib 37.5 mg/day, continuous dosing
  - **08/2008:** slight progression

Case 2-4

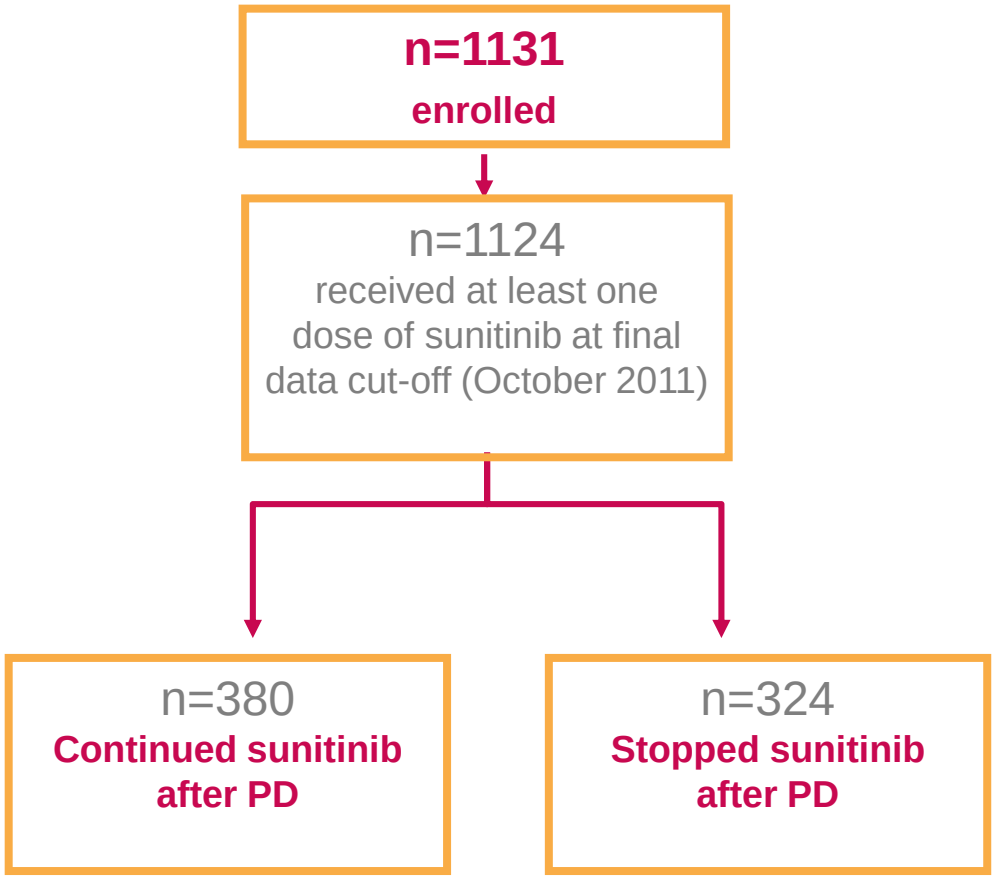
- Male patient, born 1940
  - **05/2008:** PD; start sunitinib 37.5 mg/day, continuous dosing
  - **08/2008:** slight progression; sunitinib 37.5 mg/50 mg every other day
  - **01/2009:** slight further progression; 50 mg/day, continuous dosing
  - **11/2009:** rupture of metastatic lesion; resection of all visible lesions; sunitinib continued at 50 mg/day
  - **02/2010:** residual cystic lesions; reduction of sunitinib to 37.5 mg/day

Case 2-5

- Male patient, born 1940
  - **Until 05/2012:** slight continuous asymptomatic progression
  - **05/2012:** liver metastases; changed to sorafenib 800 mg/day
  - **12/2012:** stable disease

Conclusion: sunitinib for 4 years – symptomatic control of disease

Study design and patients



Key inclusion criteria

- Adult patients with histologically confirmed, malignant GIST not amenable to standard therapy with curative intent
- Failure of prior treatment with imatinib (progressive disease or significant toxicity)
- Ineligibility for participation in ongoing sunitinib clinical studies

Key exclusion criteria

- Receipt of treatment in another clinical study
- Symptomatic central nervous system metastases
- Cardiovascular disease in the previous 6 months

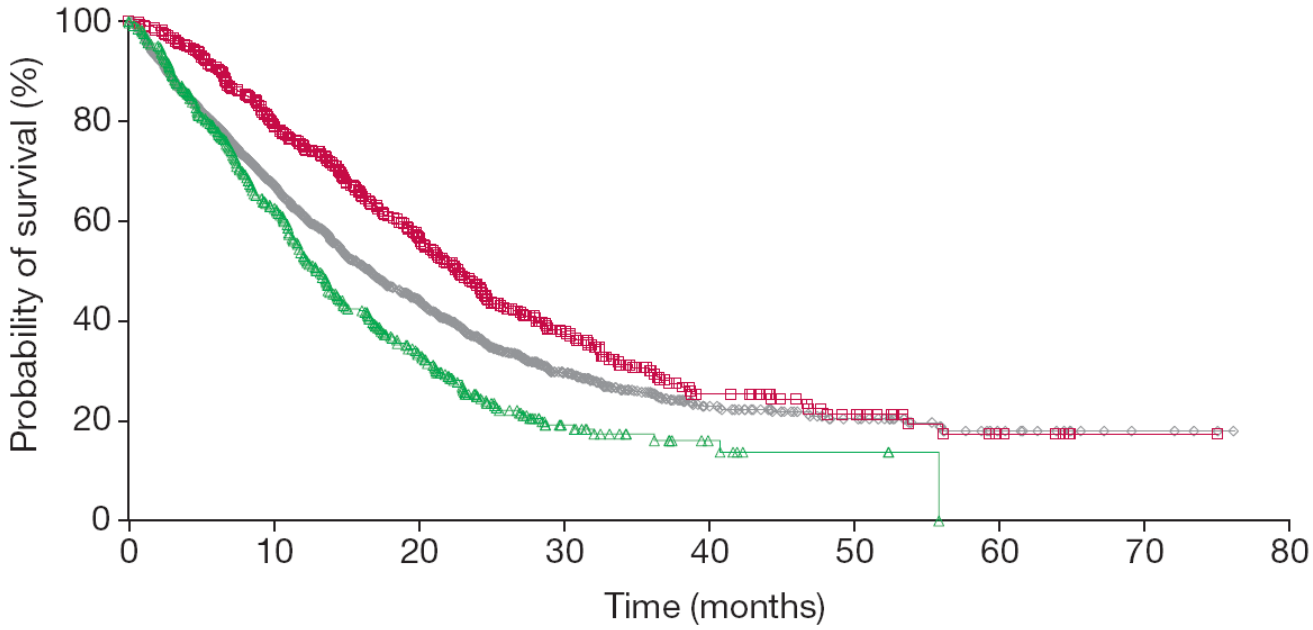
Reichardt P et al., Cancer 2015

Patients continued on sunitinib after PD for a median of 4.7 months

Parameter	All patients (n=1124)	Sunitinib continued after PD (n=380)	Sunitinib stopped after PD (n=324)
Cycles started, n	5 (1–62)	9 (1–62)	4 (1–35)
Months drug administered, n	4.6 (<0.1–56.9)	8.1 (0.4–56.9)	3.7 (<0.1–31.9)
Months on treatment, n*	7.0 (<0.1–75.4)	12.5 (0.7–74.2)	5.5 (<0.1–52.0)
Patients with dosing interruptions, n (%) Due to AE† Other reason†	592 (53) 470 (42) 248 (22)	231 (61) 179 (47) 115 (30)	141 (44) 113 (35) 52 (16)
Days with interruption, %	5 (0–96)	3 (0–49)	6 (0–96)
Patients with dose reductions, n (%)‡	484 (43)	213 (56)	122 (38)
Total dose, mg	6075 (38–69,950)	10,112 (450–65,962)	5238 (50–42,000)
Daily dose, mg	50 (15–53)	46 (15–53)	50 (27–50)

Continuation of sunitinib treatment after PD improved overall survival vs discontinuation of treatment

	n	Median (months)	95% CI
SU continued after PD	380	22.8	20.4–24.7
SU stopped after PD	324	13.2	11.7–14.5
ITT	1,124	16.6	14.9–18.0



Make the best out of each drug !
(the list is growing but not indefinite)