



# Langdurige behandeling met systemische therapie cq angiogeneseremmers en mTORremmers

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# Patiënt

Man, geboren 7-4-1952

- 2000 niertumor; nefrectomie li; PA: heldercellig niercelca
- Juni 2003 lymfekliermetastasen mediastinaal en retroperitoneaal
  - 06-2003 start IFN- $\alpha$ : SD
    - Bijwerkingen: griepverschijnselen, hoofdpijn, moeheid, koude rillingen
  - 12-2003 stop IFN-  $\alpha$ : met SD

- Jan 2005: PD
  - 02-2005: fase I AZD2171 (cediranib; 25 mg) en ZD1839 (gefitinib; 500 mg)
    - diarree, droge huid, acbe, moeheid, misselijkheid
    - 04-2005: PR
    - 04-2005: dosisreductie cediranib: 20 mg
  - 10-2007: stop AZD2171 en ZD1839 ivm PD

- Okt 2007: PD: ook lok recidief, pleurale meta
  - 12-2007 start sunitinib 50 mg '4 wk op–2 wk af'
    - gewichtsverlies, misselijkheid, anorexie, diarree
    - SD
    - Juli en okt 2009: RT op clavicula meta
    - Dosisreductie uiteindelijk tot 25mg
  - 12-2009 stop sunitinib ivm PD

- Dec 2009: PD
  - 01-2010: start everolimus 1 dd 10 mg
    - Moeheid, heesheid, maagpijn
    - SD
    - 10-2010: dyspnoe
  - 10-2010: stop everolimus ivm K 60 en PD
- Nov 2010: decompensatio cordis en myocardinfarct met goede EF, 3-vatslijden (waarvoor stents)
- Jan 2011: ‘spontane’ PR: expectatief

## Vragen 'langdurig'

- Wat is langdurig?
- Bijwerkingen en kwaliteit van leven?

## Kwaliteit van leven (KvL)

- KvL van sunitinib en sorafenib en pazopanib tov IFN- $\alpha$  of placebo fase III studies
- KvL van temsirolimus en everolimus: niet
- Geen data KvL na langdurig gebruik
  - Sunitinib max 11 cycli, onduidelijke mediane duur
  - Sorafenib max 5 cycli

Cella et al. JCO 2008

Bukowski Am J Clin Oncol 2007

## Langdurig

- Wat is langdurig?
  - Data van sorafenib >1 jaar (TARGET studie)
    - Hutson et al. (Escudier) EJC 2010
  - Data van sunitinib > 6 maanden
    - Porta et al. (Gore) ASCO abstract 2008
  - Data mTOR remmers en bevacizumab met IFN-alpha: niet

# Sorafenib > 1jaar

No. of patients (%)	Long-term treatment subpopulation ( <i>n</i> = 169)	Patients randomized to sorafenib arm ( <i>N</i> = 451)
Sex		
Male	120 (71)	315 (70)
Female	49 (29)	136 (30)
Age, years		
Median (range)	60 (19–80)	58 (19–86)
<65 years	108 (64)	305 (68)
65 years	61 (36)	146 (32)
Median time since diagnosis, years (range)	2.3 (0–19)	1.7 (0–19)
Baseline ECOG PS		
0	96 (57)	219 (49)
1	71 (42)	223 (49)
2	1 (1)	7 (2)
Missing	1 (1)	2 (0)
MSKCC category		
Favourable	113 (67)	233 (52)
Intermediate	56 (33)	218 (48)



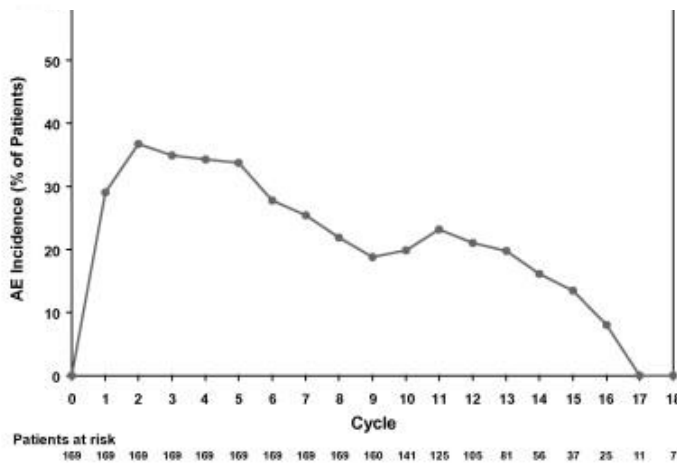
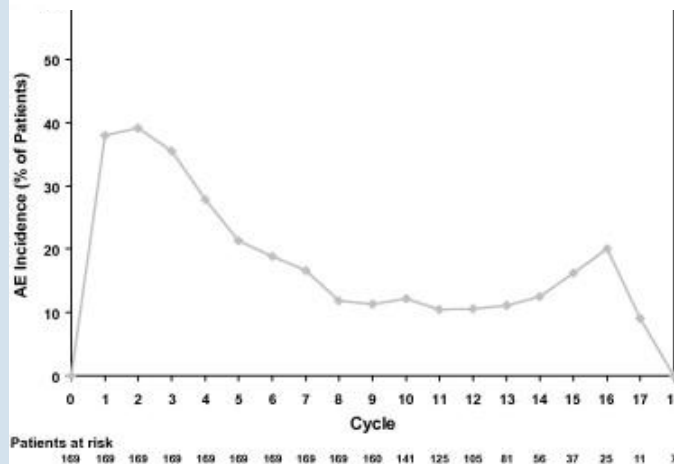
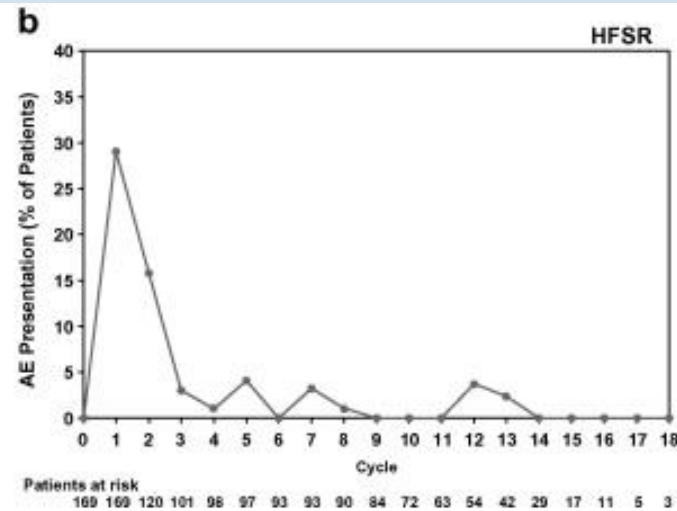
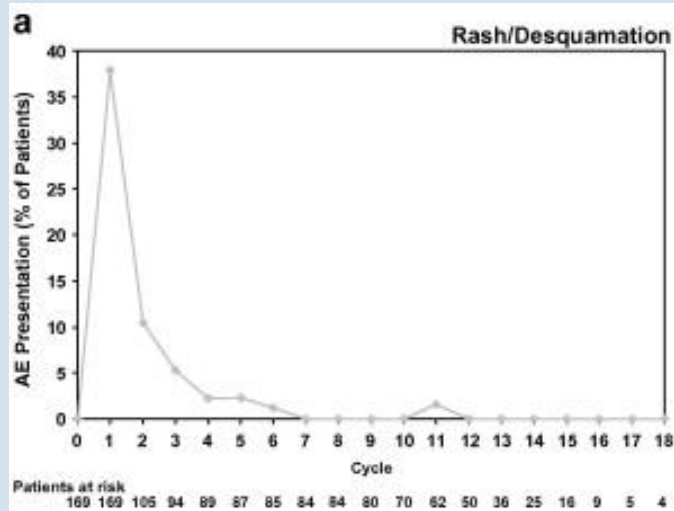
No. of patients (%)	Long-term treatment subpopulation ( <i>n</i> = 169)	Patients randomized to sorafenib arm ( <i>N</i> = 451)
Number of metastatic sites		
1	30 (18)	62 (14)
2	53 (31)	131 (29)
3	46 (27)	114 (25)
4	26 (15)	88 (20)
5 or more	14 (8)	54 (12)
Missing data	0 (0)	2 (0)
Baseline metastatic site		
Lung	125 (74)	348 (77)
Liver	39 (23)	116 (26)
Bone	31 (18)	96 (21)
Prior nephrectomy	162 (96)	422 (94)
Prior cytokine therapy	141 (83)	374 (83)
Prior medical history		
Hypertension	78 (46)	183 (41)
Coronary artery or ischaemic heart disease	22 (13)	53 (12)
High cholesterol	21 (12)	53 (12)
Diabetes	18 (11)	56 (12)
Anaemia	10 (6)	39 (9)

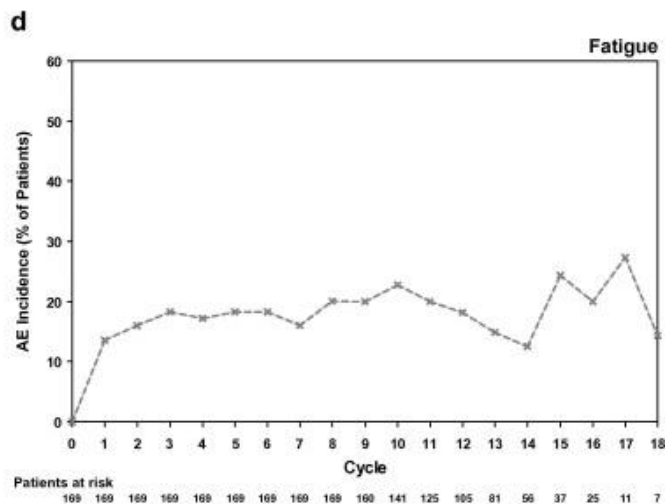
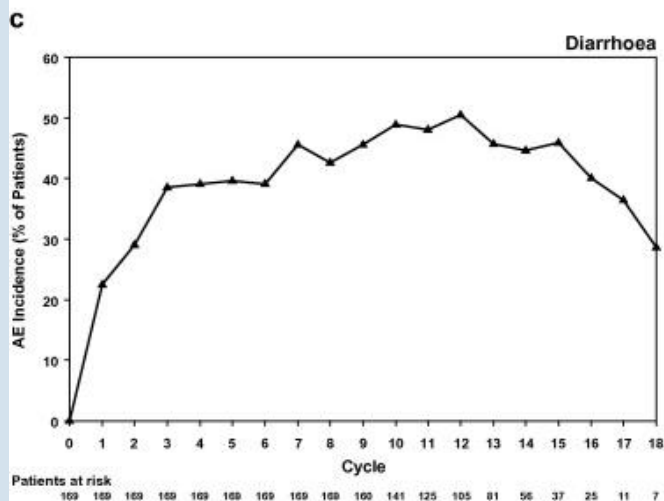
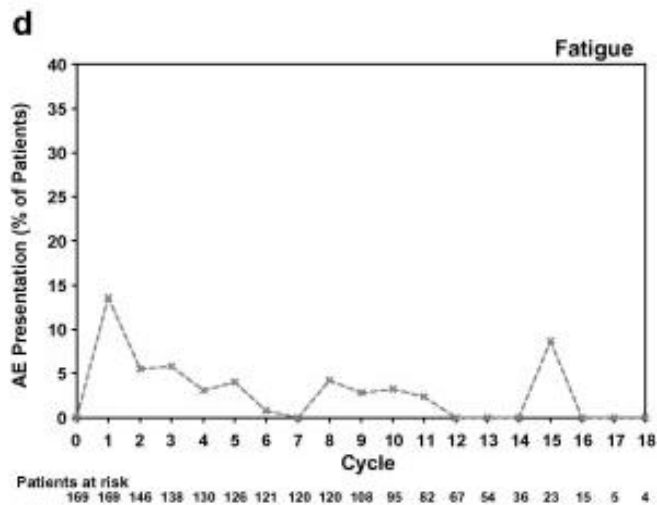
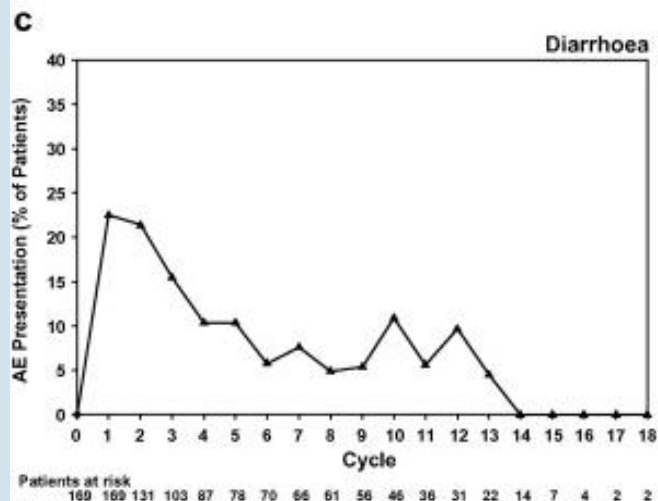
- Mediane duur sorafenib 18.9 mnd (12.1-30.2)
- 55% dosis reductie of interruptie:
  - Diarree : 14.7%
  - Hand-foot skin reaction (HFSCR): 11.7%
  - Hypertensie: 7%
- Langdurig behandelen is ‘acceptabel’

# Bijwerkingen

	<b>Any grade</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
Any	160 (95)	21 (12)	81 (48)	49 (29)	9 (5)
Diarrhoea	125 (74)	52 (31)	69 (41)	4 (2)	0
Rash/desquamation	86 (51)	54 (32)	31 (18)	1 (1)	0
HFSR	83 (50)	33 (20)	38 (23)	12 (7)	0
Alopecia	66 (39)	62 (37)	4 (2)	0	0
Fatigue	64 (38)	36 (21)	24 (14)	4 (2)	0
Hypertension	43 (25)	9 (5)	25 (15)	8 (5)	1 (1)
Pruritus	37 (22)	30 (18)	6 (4)	1 (1)	0
Nausea	35 (21)	27 (16)	8 (5)	0	0
Flushing	20 (12)	18 (11)	2 (1)	0	0
Dry skin	29 (17)	23 (14)	6 (4)	0	0
Anorexia	29 (17)	16 (10)	12 (7)	1 (1)	0
Sensory neuropathy	28 (17)	20 (12)	8 (5)	0	0
Weight loss	26 (15)	8 (5)	14 (8)	4 (2)	0
Vomiting	23 (14)	16 (10)	7 (4)	0	0
Oral mucositis	17 (10)	13 (8)	4 (2)	0	0

# Initiele presentatie en totale incidentie





## Bijwerkingen

- Vroeg ontstaan-daarna afname:
  - rash, HFSR, HT
- Tijdens gehele traject:
  - Diarree, moeheid
- Laat ontstaan:
  - Anaemie, cardiale tox, LV systolische dysfunctie (5-2-1%)

# Sunitinib

## > 6 maanden

Table 1. Baseline characteristics for patients with <6 months or ≥6 months of sunitinib treatment by trial disposition.

Characteristic	<6 months of sunitinib treatment		≥6 months of sunitinib treatment	
	Ongoing (n=142)	Discontinued <sup>a</sup> (n=1,696)	Ongoing (n=1,083)	Discontinued <sup>a</sup> (n=1,264)
Median age, years (range)	59 (21–81)	60 (19–88)	59 (19–89)	59 (21–85)
Male, n (%)	110 (77)	1,227 (72)	795 (73)	954 (75)
ECOG PS, n (%) <sup>b</sup>				
0	69 (49)	503 (30)	595 (55)	582 (46)
1	56 (39)	780 (46)	420 (39)	546 (43)
2	12 (8)	315 (19)	46 (4)	104 (8)
3	3 (2)	52 (3)	6 (1)	7 (1)
4	0	5 (<1)	0	0
Histology, n (%) <sup>b</sup>				
Clear cell	125 (88)	1,389 (82)	973 (90)	1,117 (88)
Other	17 (12)	299 (18)	105 (10)	144 (11)
Prior nephrectomy, n (%)	122 (86)	1,443 (85)	992 (92)	1,160 (92)
Disease site, n (%)				
Brain	6 (4)	180 (11)	33 (3)	94 (7)
Lungs	119 (84)	1,339 (79)	766 (71)	992 (78)
Lymph nodes	67 (47)	957 (56)	478 (44)	654 (52)
Bone	39 (27)	677 (40)	312 (29)	442 (35)
Liver	26 (18)	537 (32)	243 (22)	327 (26)
Prior therapy, n (%)				
Antiangiogenic	3 (2)	112 (7)	33 (3)	86 (7)
Cytokines <sup>c</sup>	63 (44)	1,167 (69)	691 (64)	1,002 (79)
Risk factors, n (%) <sup>d</sup>				
0 (favorable)	21 (15)	191 (11)	268 (25)	315 (25)
1 (intermediate)	28 (20)	424 (25)	199 (18)	315 (25)
2 (poor)	4 (3)	181 (11)	24 (2)	55 (4)
Missing	10 (7)	371 (22)	200 (18)	317 (25)

ECOG PS = Eastern Cooperative Oncology Group performance status.

<sup>a</sup>Percentage of patients with missing data: ECOG PS = 1–2%; histology <1%; prior cytokine therapy <1%.

<sup>b</sup>Modified Metzger risk factors of ECOG PS ≥2, low hemoglobin, and high calcium, available for patients with prior cytokine treatment only.

<sup>c</sup>Patients who completed the study are included.

# Sunitinib > 6 maanden

Table 5. Summary of non-hematologic treatment-related AEs occurring in  $\geq 15\%$  of ongoing patients with <6 months or  $\geq 6$  months of treatment.

Adverse event	Grade 1–2, n (%)		Grade 3–4, n (%)		Total, n (%)	
	<6 months of sunitinib treatment (n=142)	$\geq 6$ months of sunitinib treatment (n=1,078)	<6 months of sunitinib treatment (n=142)	$\geq 6$ months of sunitinib treatment (n=1,078)	<6 months of sunitinib treatment (n=142)	$\geq 6$ months of sunitinib treatment (n=1,078)
Diarhea	26 (18)	500 (46)	1 (1)	62 (6)	27 (19)	562 (52)
Fatigue	20 (14)	310 (29)	2 (1)	70 (6)	22 (15)	380 (35)
Nausea	19 (13)	332 (31)	1 (1)	20 (2)	20 (14)	352 (33)
Mucosal inflammation	16 (11)	291 (27)	1 (1)	28 (3)	17 (12)	319 (30)
Stomatitis	25 (18)	286 (27)	4 (3)	33 (3)	29 (20)	319 (30)
Hand–foot syndrome	17 (12)	213 (20)	4 (3)	66 (6)	21 (15)	279 (26)
Hypertension	11 (8)	198 (18)	2 (1)	58 (5)	13 (9)	256 (24)
Anorexia	22 (15)	219 (20)	1 (1)	15 (1)	23 (16)	234 (22)
Dysgeusia	14 (10)	237 (22)	0	4 (<1)	14 (10)	241 (22)
Vomiting	11 (8)	193 (18)	1 (1)	20 (2)	12 (8)	213 (20)
Asthenia	16 (11)	162 (15)	3 (2)	48 (4)	19 (13)	210 (19)
Rash	10 (7)	191 (18)	0	10 (1)	10 (7)	201 (19)
Dyspepsia	6 (4)	203 (19)	0	5 (<1)	6 (4)	208 (19)

Table 8. Summary of hematologic treatment-related AEs occurring in ≥15% of discontinued patients with <6 months or ≥6 months of treatment.

Adverse event	Grade 1–2, n (%)		Grade 3–4, n (%)		Total, n (%)	
	<6 months of sunitinib treatment (n=1,691)	≥6 months of sunitinib treatment (n=1,263)	<6 months of sunitinib treatment (n=1,691)	≥6 months of sunitinib treatment (n=1,263)	<6 months of sunitinib treatment (n=1,691)	≥6 months of sunitinib treatment (n=1,263)
Thrombocytopenia	148 (9)	231 (18)	120 (7)	111 (9)	268 (16)	343 (27)*
Anemia	129 (8)	218 (17)	52 (3)	62 (5)	181 (11)	280 (22)
Neutropenia	87 (5)	146 (12)	51 (3)	105 (8)	138 (8)	251 (20)

\*One patient with ≥6 months of sunitinib treatment who had discontinued had grade 5 treatment-related thrombocytopenia.

Table 9. Incidence of grade ≥3 treatment-related cardiac disorders in patients with <6 months or ≥6 months of treatment by trial disposition.

Cardiac disorders severity, n (%)	Ongoing patients		Discontinued patients	
	<6 months of sunitinib treatment (n=142)	≥6 months of sunitinib treatment (n=1,078)	<6 months of sunitinib treatment (n=1,691)	≥6 months of sunitinib treatment (n=1,263)
Grade 3 or 4	0	4 (<1)	28 (2)	13 (1)
Grade 5	–	–	3 (<1)*	5 (<1) <sup>†</sup>

\*Two patients with myocardial infarction and one patient with cardiac arrest.

<sup>†</sup>Four patients with cardiac failure and one patient with left ventricular dysfunction.

Geen full paper ?!

## Cardiale toxiciteit

- Observationele, single-center studie
- 86/74 eligible patiënten met sunitinib of sorafenib
  - Cardiac event 33.8%
  - ECG veranderingen 40.5%
  - 18% symptomatisch
  - 9.4% ernstig

# Cardiale toxiciteit

	Experienced a Cardiac Event		Did Not Experience a Cardiac Event		All
	No.	%	No.	%	
Total No. of patients	25	33.8	49	66.2	74 100
With ECG changes	12	16.2	18	24.3	30 40.5
Without ECG changes	13	17.6	31	41.9	44 59.5
Type of ECG change					
Change in rhythm	5	6.8	3	4.1	8 10.8
Conduction disturbance	1	1.4	2	2.7	1 1.4
Change in axis	1	1.4	1	1.4	2 2.7
Change in QRS amplitude	1	1.4	4	5.4	5 6.8
ST segment change	5	6.8	9	12.2	13 17.6
T wave change	7	9.5	12	16.2	18 24.3
QTc prolongation	4	5.4	3	4.1	7 9.5

# Linker ventrikel ejection fractie (LVEF) en hypertensie (HT)

Hypertension at baseline ( $n = 175$  patients)

Grade 0: 116 (66.3%)

Grade 1: 13 (7.4%)

Grade 2: 46 (26.3%)

Grade 3: 0

Grade 4: 0

LVEF dysfunction at baseline ( $n = 175$ )

Grade 0: 170 (97.1%)

Grade 1: 4 (2.3%)

Grade 2: 1 (0.57%)

Grade 3: 0

Grade 4: 0

Hypertension after sunitinib ( $n = 175$  patients)

Grade 0: 92 (52.6%)

Grade 1: 18 (10.3%)

Grade 2: 48 (27.4%)

Grade 3: 17 (9.7%)

Grade 4: 0

LVEF dysfunction after sunitinib ( $n = 175$ )

Grade 0: 142 (81.1%)

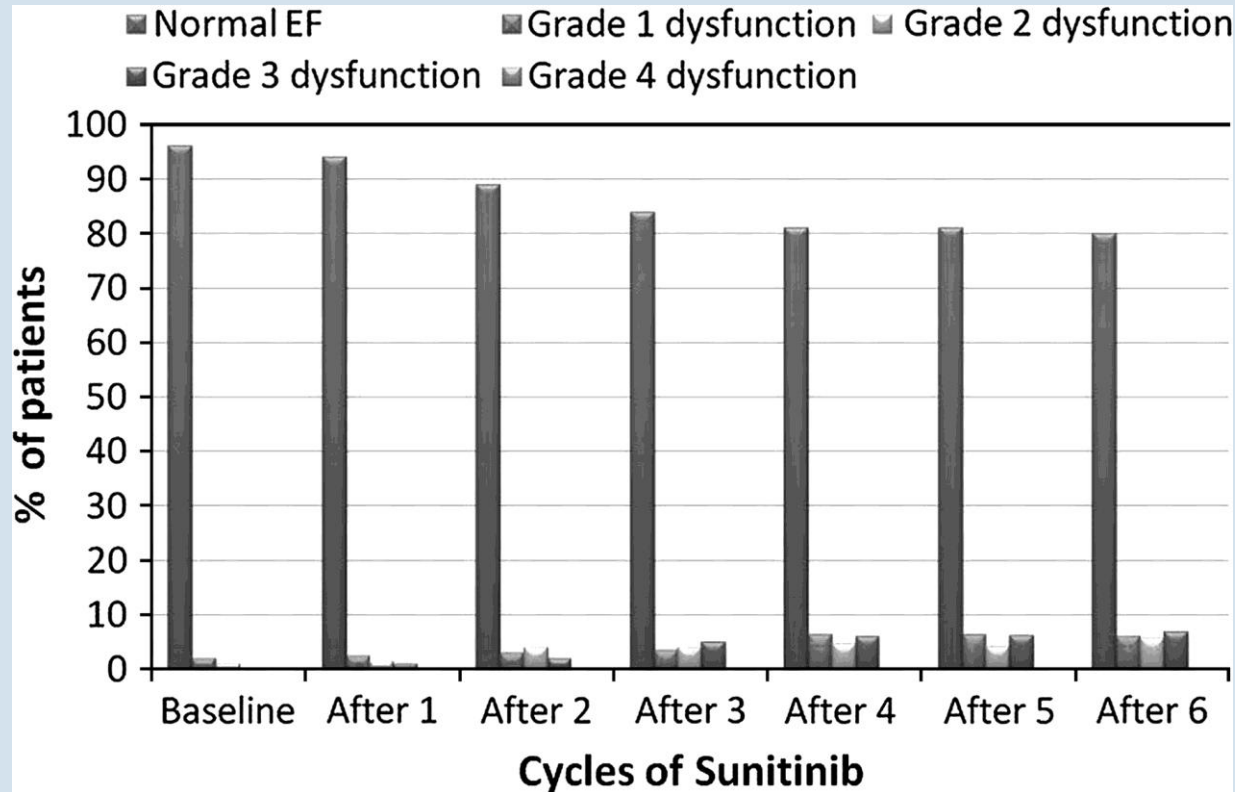
Grade 1: 10 (5.7%)

Grade 2: 11 (6.3%)

Grade 3: 12 (6.9%)

Grade 4: 0

## Cumulatieve % LVEF



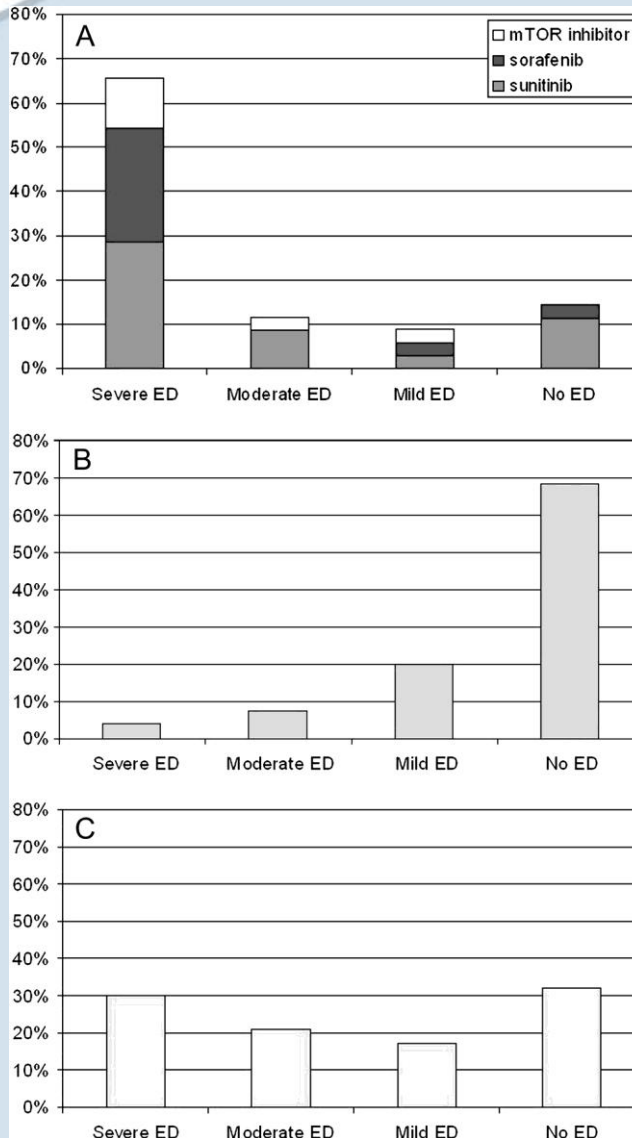
Voorspellers voor LVEF ↓: coronaire hartziekte en HT in voorgeschiedenis

## Sexuele stoornissen

- n=38 mRCC op sunitinib, sorafenib of mTOR remmer
- Interview over hun sex leven, invullen internationale index van erectiele functie (IIEF) vragenlijst
- Cross-sectioneel
- Mediane lft:59 jaar
- Med behandelduur 12 maanden

- Voor 54% kwaliteit van sexleven belangrijk
- Scores in erectiele functie, orgasme tevredenheid, orgasme functie, zin in sex, en overall tevredenheid over sex leven verminderden met 30 tot 60%
- 64% gaf aan dat er verandering was sinds start behandeling

# Erectiele functie



'Normale' Fransen

Fransen die uroloog bezoeken

## Conclusie en toekomst

- Weinig data over langdurig gebruik
- Geen data over kwaliteit van leven
- Diarree meest frequente bijwerking op termijn: oorzaak?
- Cardiale toxiciteit: cave EF verlaging, zeker bij cardiale belasting tevoren
- Sexuele veranderingen: aandacht voor