

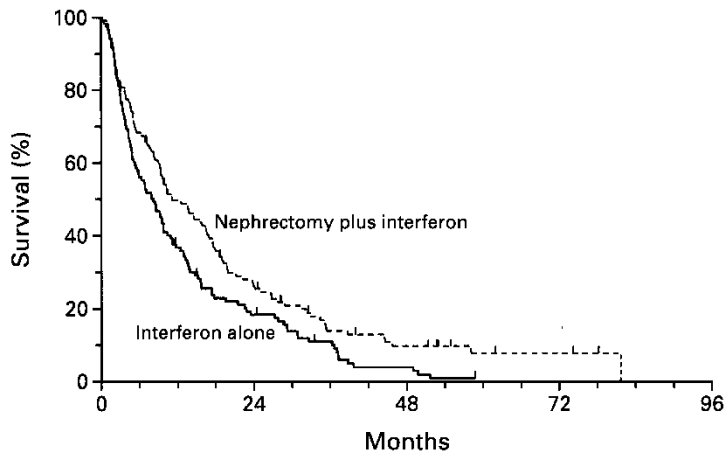
Timing of TKI's pre- or post-nephrectomy

Dr Simon Crabb

Senior Lecturer and Honorary Consultant in Medical Oncology
Cancer Sciences Unit, University of Southampton Faculty of Medicine

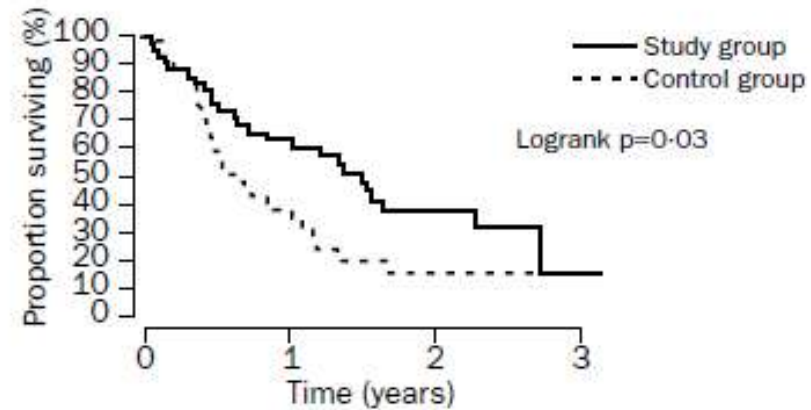


Initial nephrectomy as an addition to (old) systemic therapy



No. AT Risk	0	24	48	72	96
Interferon alone	121	21	4	0	0
Nephrectomy plus interferon	120	29	9	3	0

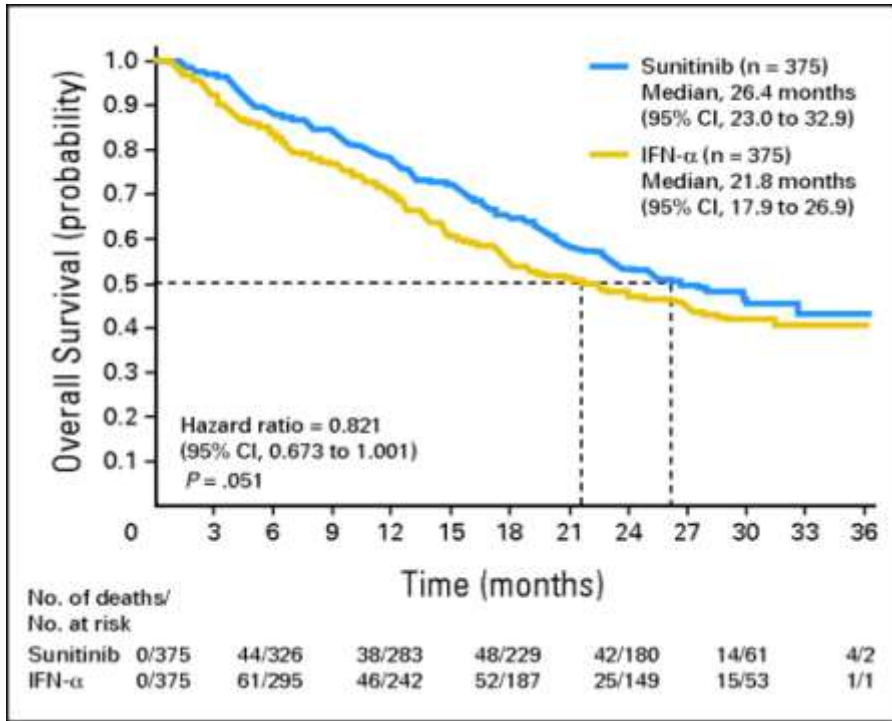
Median survival: 11.1 versus 8.1 months, $p=0.05$



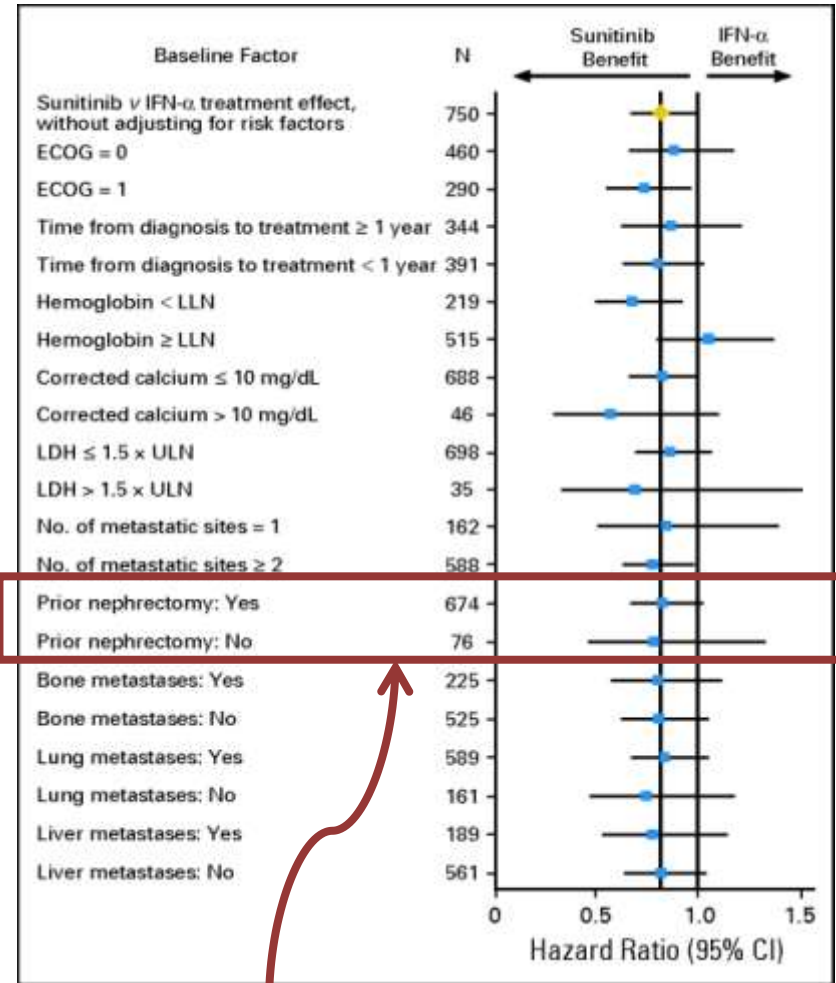
	Observed number of events	Number of patients at risk			
	0	1	2	3	4
Study group	25	42	22	7	1
Controls	30	42	12	2	0

Median survival: 17 versus 7 months, $p=0.03$

But we have better drugs now...



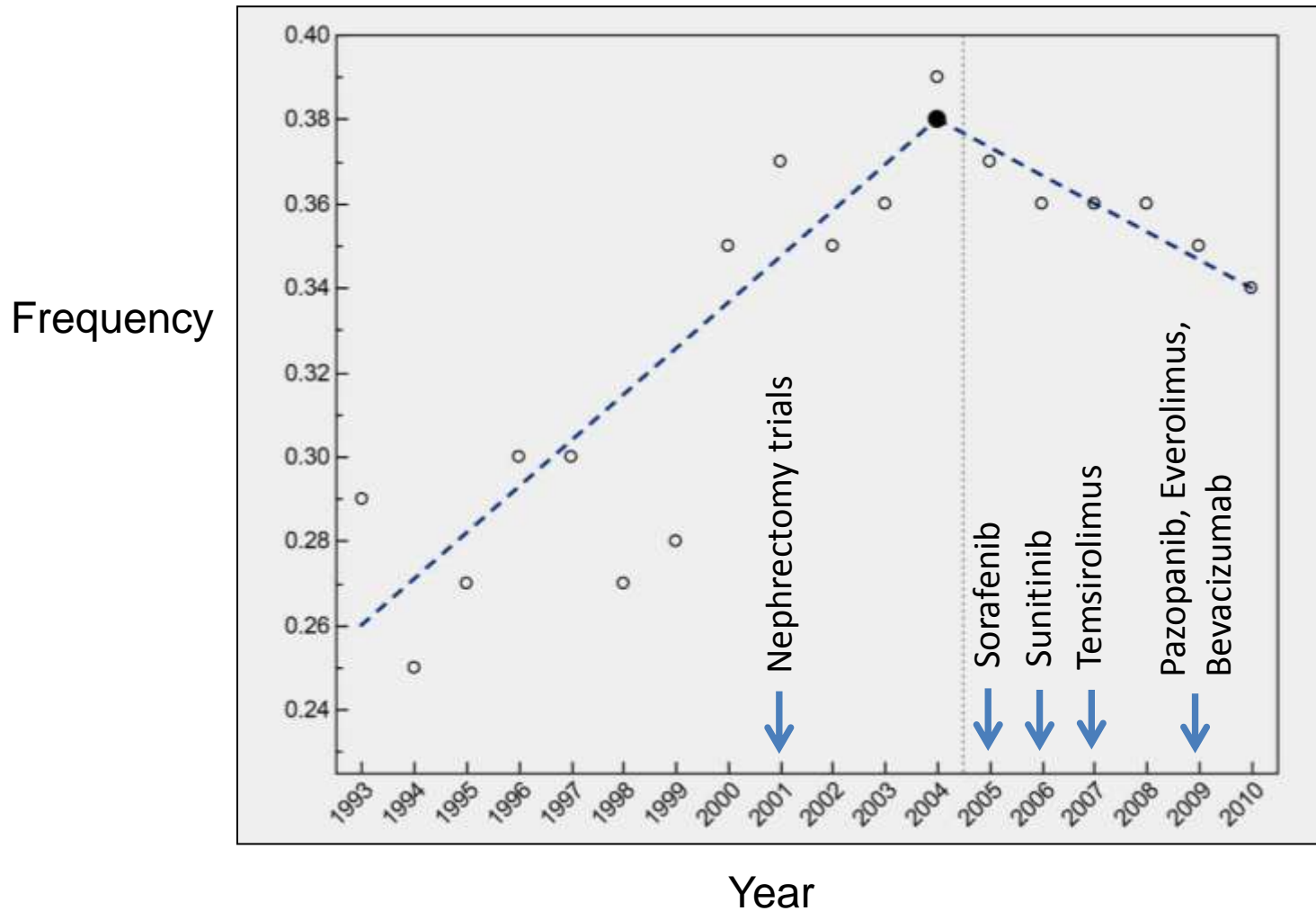
MSKCC risk factors — no. (%) [†]	Sunitinib	IFN- α
0 (favorable)	143 (38)	121 (34)
1–2 (intermediate)	209 (56)	212 (59)
≥3 (poor)	23 (6)	25 (7)



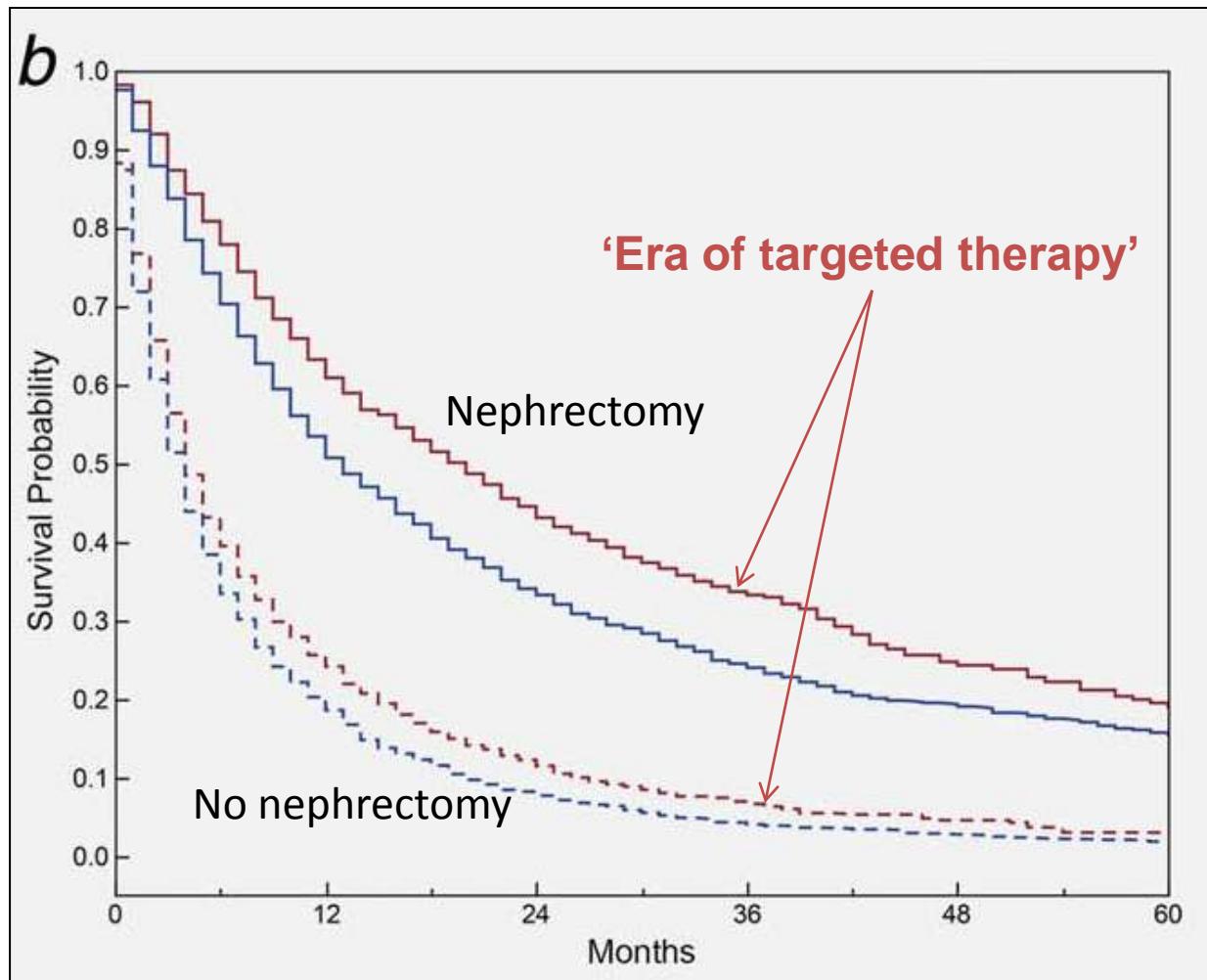
Most had a nephrectomy.

But this was probably not immediately 'prior' for many/most.

The TKI era coincided with reduced use of palliative nephrectomy (SEER data)



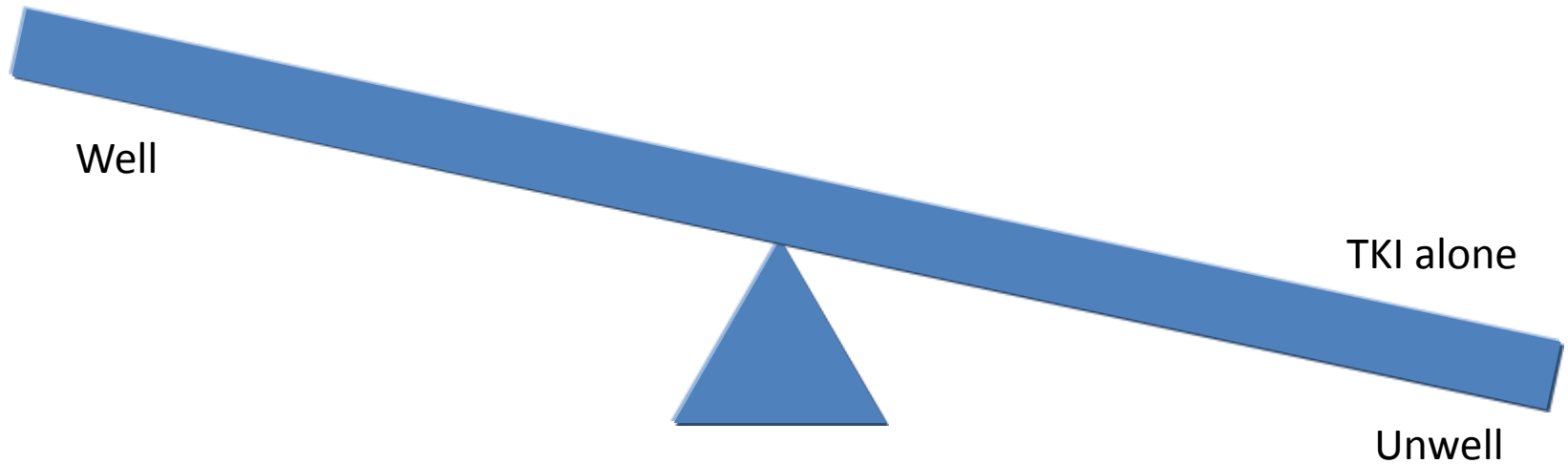
Use of nephrectomy and the 'TKI era' indicate good outcome (SEER data)



Bias in non-randomised data

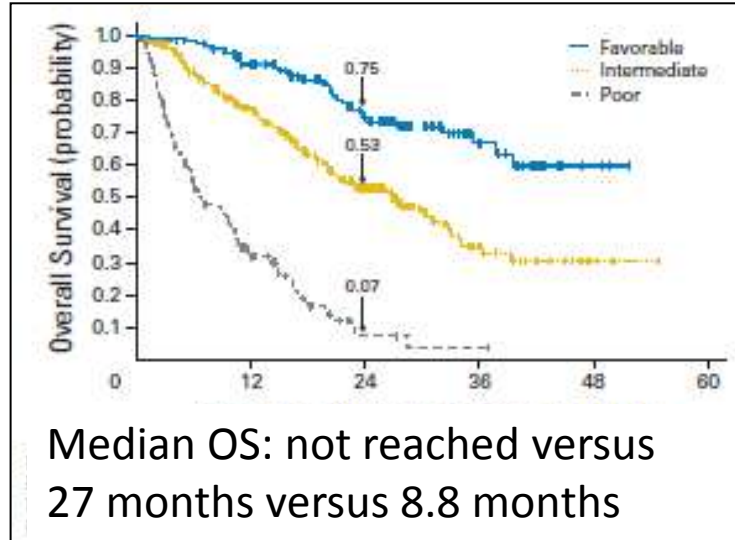
- Less well patients are less likely to be offered nephrectomy
- By the time nephrectomy has been performed and patients have recovered a subset have progressed and become unfit for systemic therapy.

Surgery and TKI



Immediate versus no nephrectomy?

- 67 year old female
- Karnofsky PS 90
- PMH - nil of note
- Grade 3 ccRCC
- Lung, liver and bone metastases
- LDH ↑
- Hb ↓
- Ca²⁺ normal

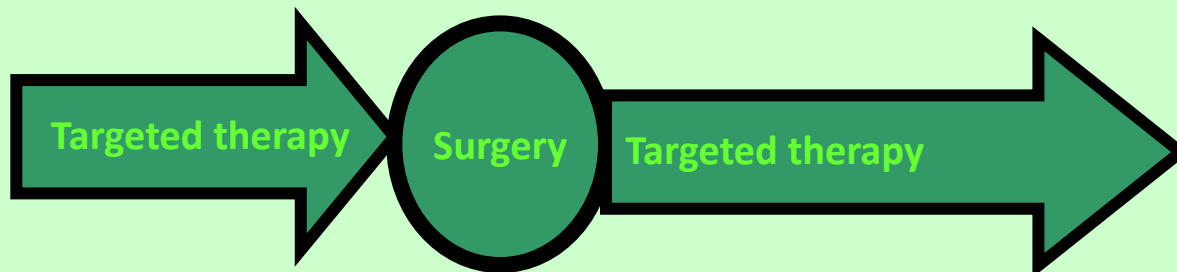


Alternative approach options?

Current standard of care?



Upfront targeted therapy prior to delayed nephrectomy



Potential pros and cons to delayed palliative nephrectomy

For

- Down staging of primary prior to surgery?
- Swift start to systemic therapy to provide immediate global disease control?
- Identify those with primary refractory disease early (pick the winners for surgery)?

Against

- More complex surgery/recovery due to drug induced toxicity or necrosis/fibrosis?
- Delayed wound healing?
- Delayed surgical benefit?
- Diminished response to systemic therapy?
- Rebound disease progression during off period?
- You just never get round to it...

PANTHER: A Phase II study of upfront pazopanib prior to nephrectomy in metastatic clear cell renal cancer

[NCT01512186](https://clinicaltrials.gov/ct2/show/study/NCT01512186)

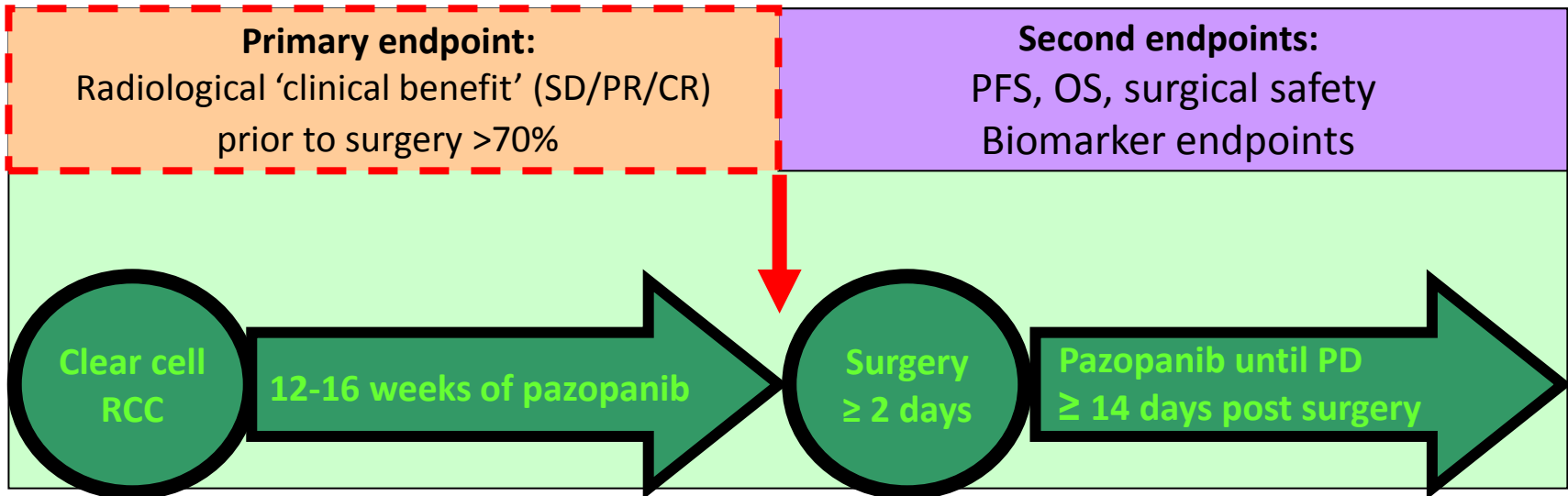
Inclusion criteria

- Metastatic clear cell renal cancer.
- No previous therapy (systemic or surgery)
- Requiring nephrectomy and systemic therapy

[Sponsor: Queen Mary University of London](#)

[Funding: GSK](#)

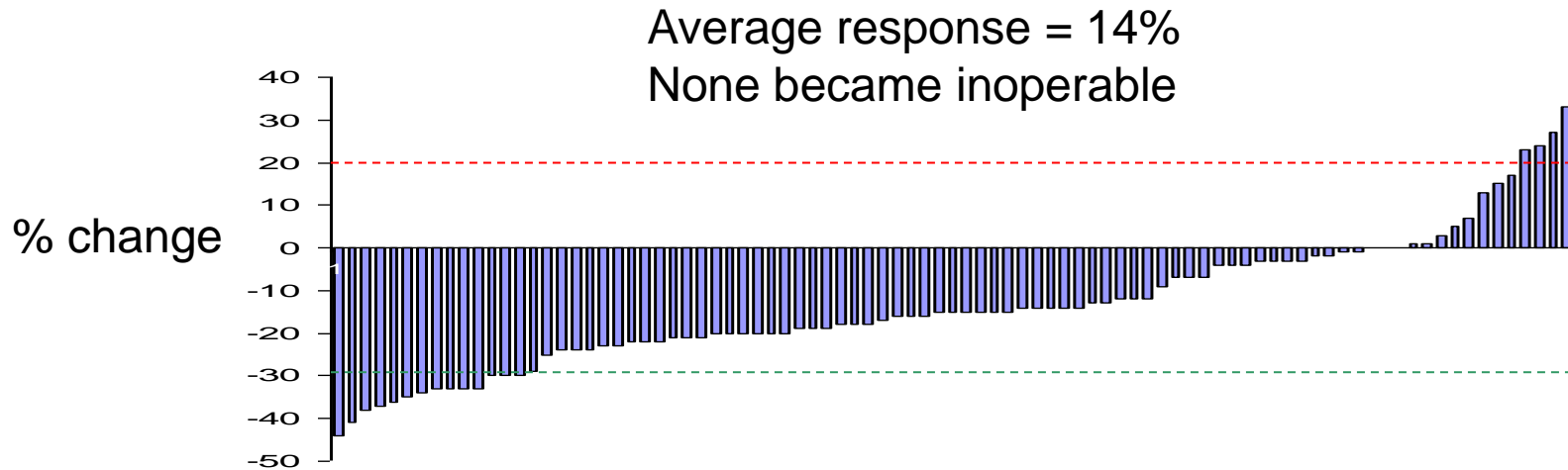
[CI: Tom Powles](#)



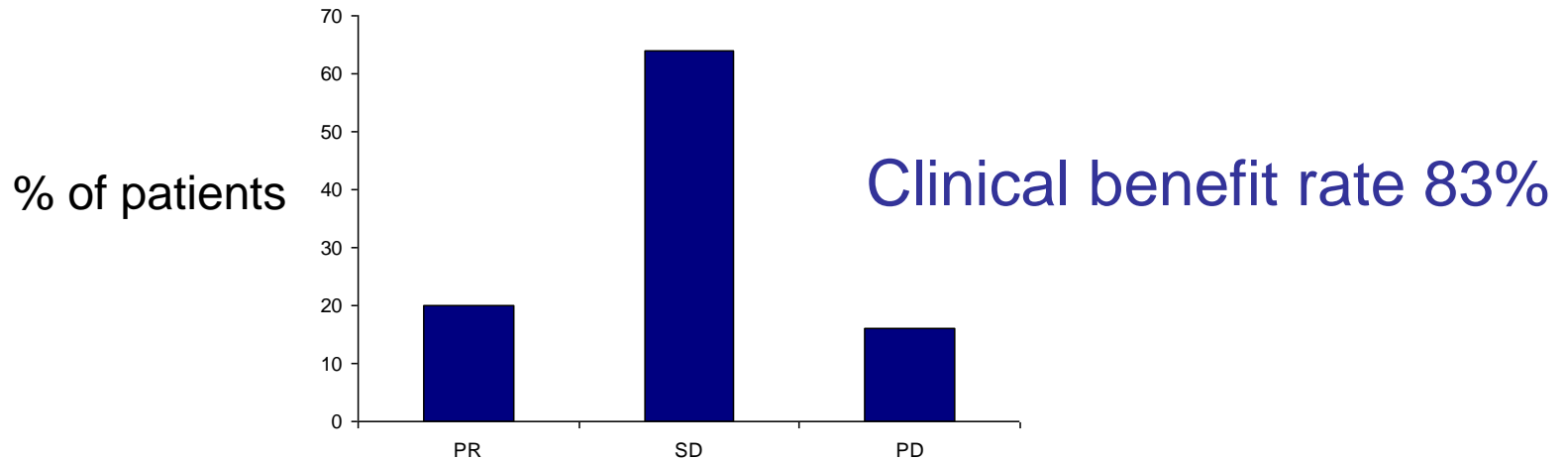
Patient characteristics

Number of patients	102
Male	75%
Age, median (range)	63 years (38-84)
MSKCC risk score	
Intermediate	78%
Poor	22%
Number of metastatic sites	
1	37%
2	34%
>3	29%
Performance status	
0	25%
1	75%

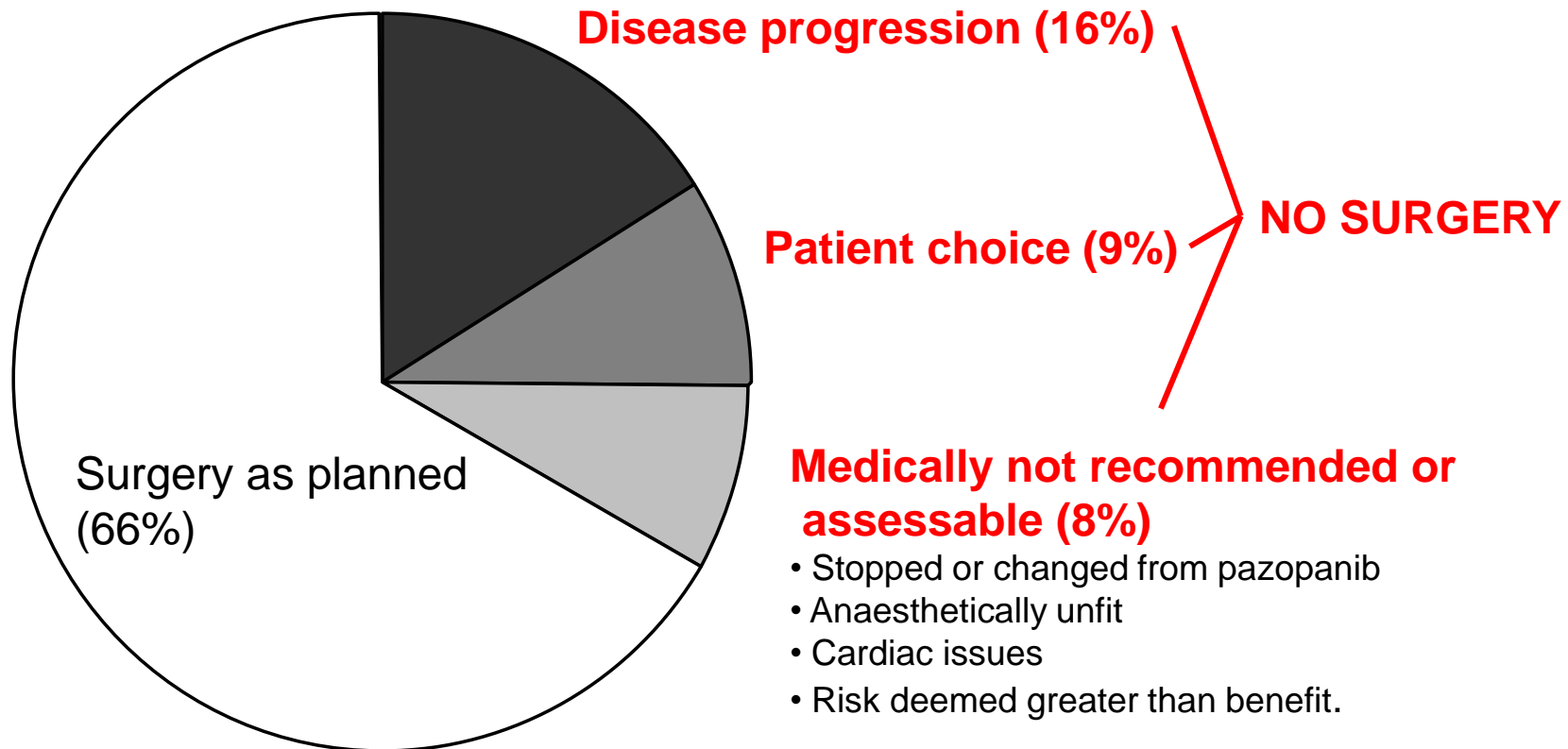
Best response in primary tumour prior to planned surgery



Best overall systemic response to therapy



68/102 (66%) of patients underwent nephrectomy after commencing pazopanib

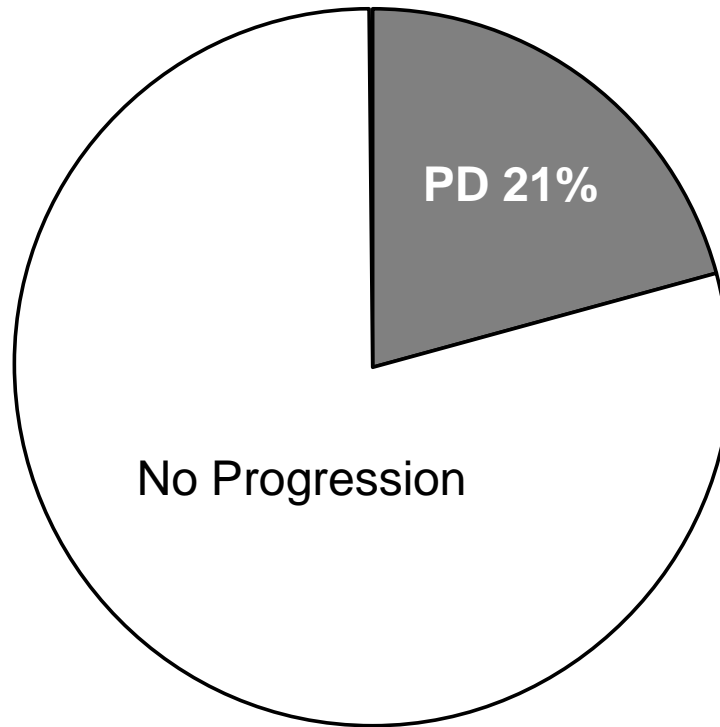


Surgical safety

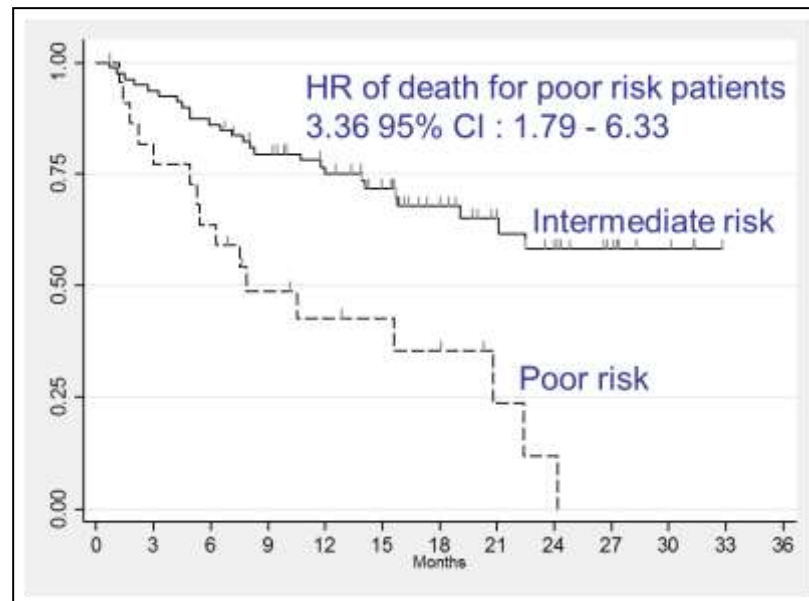
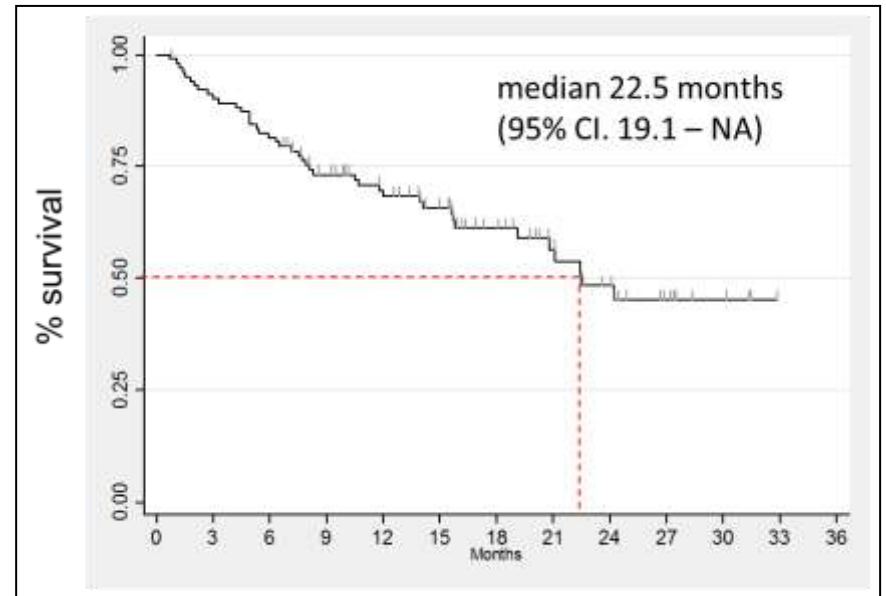
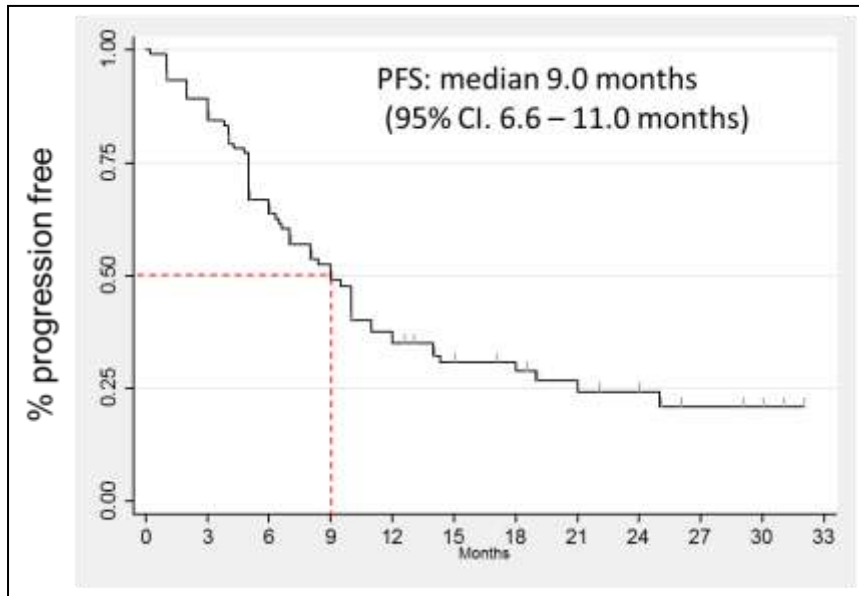
Complication of surgery	Number of patients (%)
Surgery	66
Laparoscopic	31%
Open	69%
Blood loss (median)	420 mls (range: 30-4100 mls)
Post operative cardiac/ resp. complications	2%
Delayed wound healing	2%
Surgical time (median)	180 mins (range: 69-300)
Hospital stay (median)	6 days (range: 2-31)
pT3 or T4 tumors	87%
% Necrosis at surgery >50%	73%
Post operative deaths	3% (1 respiratory, 1 bowel perforation)

Progression during the pazopanib gap for surgery

- Median time off treatment 27 days
- 21% progressed during this time
- 79% regained disease control on restarting pazopanib

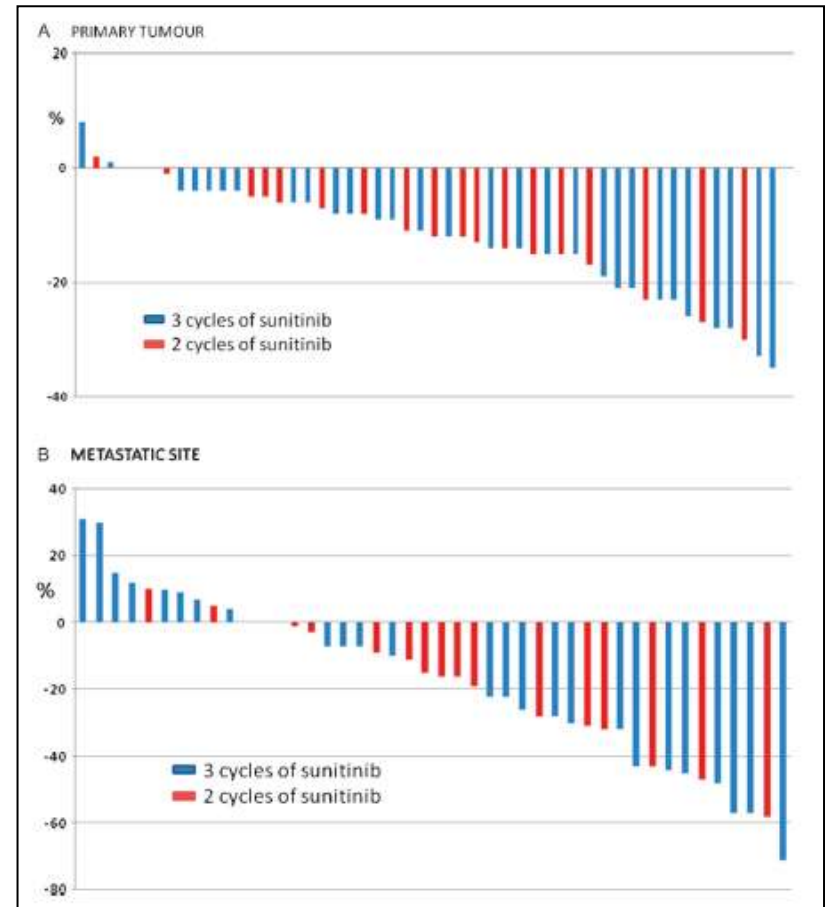


Survival outcomes (n=102)



Other drugs?

- n=52 (2 trials)
- Sunitinib (12 or 18 weeks)
- Surgery at 1 or 14 days
- Drug restarted at 21 or 14 days
- Median time from nephrectomy to sunitinib 21 days (14–82)
- Median time off therapy 28 days (22–96)



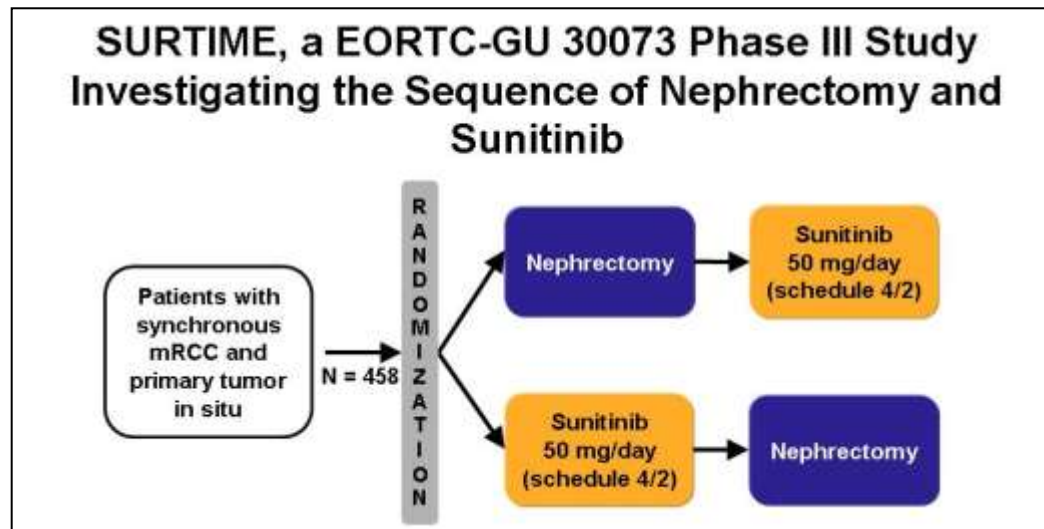
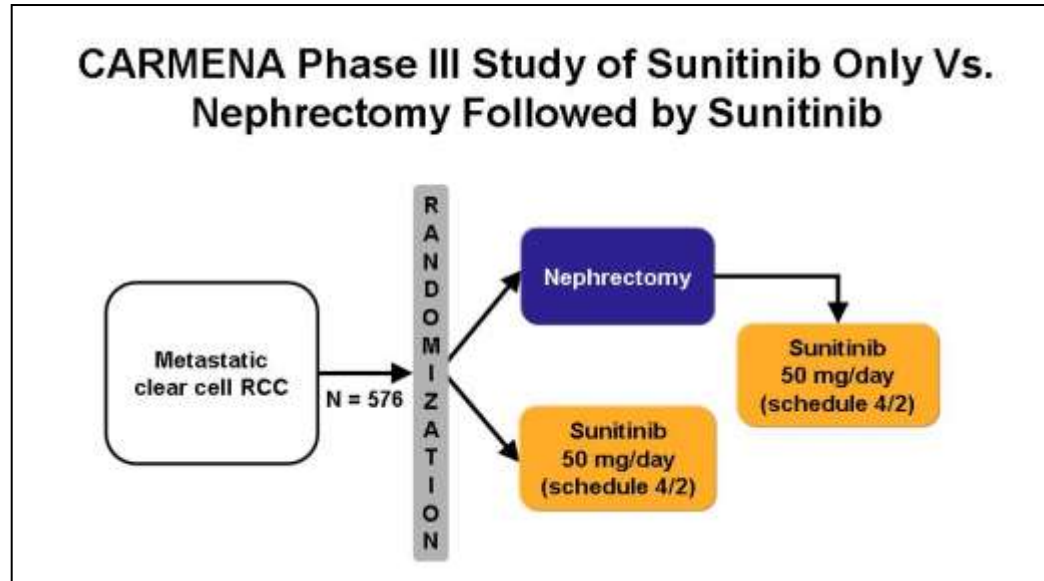
How to select?

Drug alone, initial nephrectomy or delayed nephrectomy?

	Drug alone	Nephrectomy → drug	Drug → nephrectomy → drug
MSKCC risk	Poor risk	Good risk? Intermediate risk?	Intermediate risk? Poor risk?
Symptomatic/large primary	No	Yes?	?
Performance status	Impaired	Good?	?
Metastatic burden	Large	Small	?

But we don't really know...

Phase III nephrectomy trials in mRCC?



Neoadjuvant therapy in locally advanced M0 disease

Axitinib

- n=24, T2-3b N0 M0
- 22 completed 12/52 axitinib
- All got to surgery without progression
- Median tumour diameter reduction 28.3%
- Typical drug toxicity
- Postoperatively: 2 grade 3 and 13 grade 2 complications noted

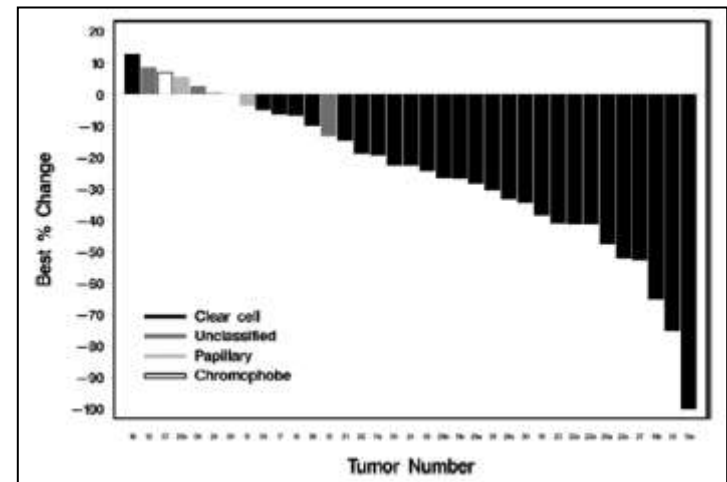
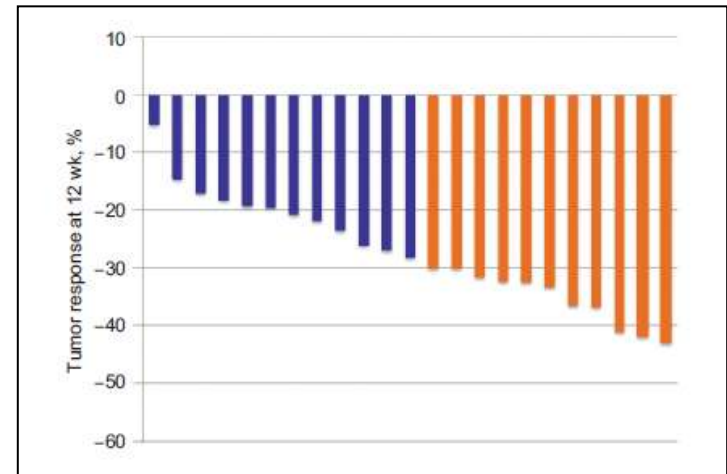
Conclusions: active, feasible and safe

Sunitinib

- N=30
- Unresectable (large tumour, bulky lymphadenopathy, venous thrombosis, proximity to vital structures)
- Median tumour diameter reduction 22%
- 13 (45%) nephrectomy rate

Conclusions: feasible, safe, permits nephrectomy in a subset

Both are investigational approaches and require randomised data



So what can we say?

- Nephrectomy has an ill defined role in the era of TKI therapy (but a role nonetheless)
- Our clinical tools to decide who benefits from nephrectomy are 'blunt' at best
- Specialist MDT consensus and open discussion with patients is critical
- Initial targeted therapy can be started quickly, seems safe, and may 'pick the winners' for subsequent surgery
- Delayed nephrectomy may keep options open for patients where the decision is unclear
- Delayed nephrectomy may risk never doing the operation (particularly off trial?)
- We will not answer these questions without large randomised data