Trials that will change my practice

(or provide some evidence to justify current aspects of it)

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Questions in my practice

Do we need to start targeted therapy immediately?

Can we ever pause therapy once it has started?

(Do we need to do a nephrectomy?)

What is the best first line therapy?

Can we combine current systemic therapies?

How should we sequence them?

How can we utilise toxicity as a guide to efficacy?

Is immunotherapy the next big thing (again)?

How should we treat non clear cell mRCC?

Will we need to start using adjuvant therapy?

Delayed systemic therapy?

- Low-volume, slow-growing, asymptomatic disease is often observed initially
- Little evidence to support this but widely accepted
- How to select when to start treatment?
  - Increased pace of disease?
  - New metastatic sites?
  - Symptoms from disease?
  - Clinician/patient anxiety?

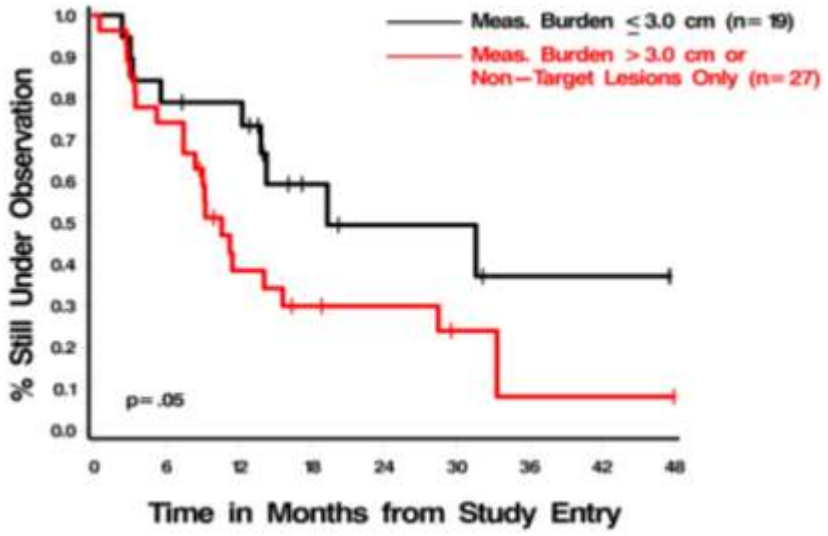
- Prospective single arm trial
  - n=49, median age 67
  - 94% ECOG 0, 96% clear cell histology
  - 92% prior nephrectomy
  - 74% lung, 28% nodes, 17% renal, 17% adrenal, 11% bone, 7% liver

Rini et al, abstr 4520, ASCO meeting 2014

Results (n=49)

- Median baseline tumour burden 3.2 cm
  (0.8 - 19.6)
- Median change 0.09 cm/month (-0.51 - 3.6)
- Observation time
  - Median 14.1 months (95% C.I. 9.2-28.5)
  - 3 patients > 4 years
- Location/number metastatic sites did not impact length of observation (numbers small)
- Anxiety/depression were not prevalent at baseline and did not worsen
  (trial possibly selecting for this?)

Median observation 19.3 v 10.6 months (p=0.05)

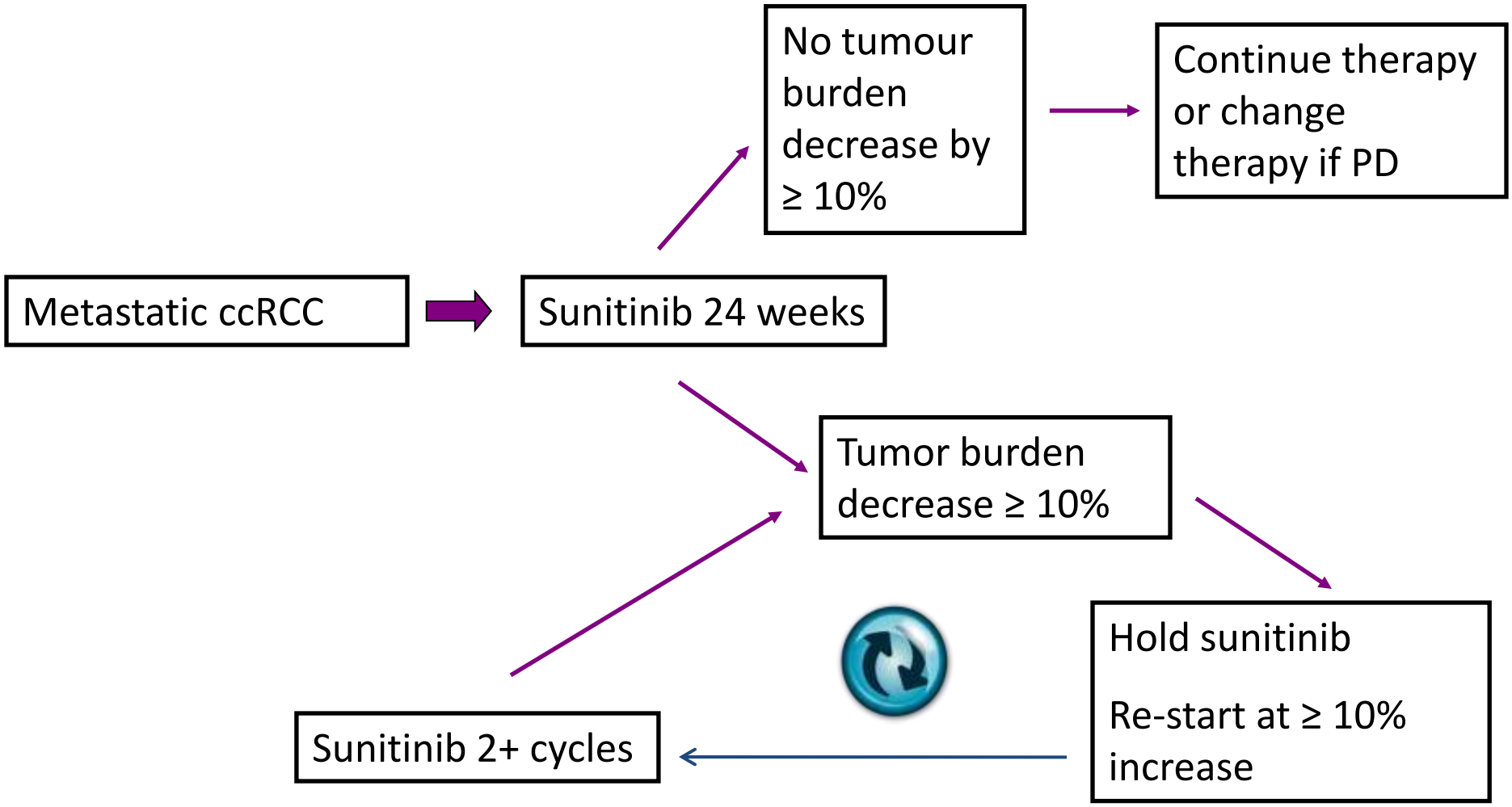


Rini et al, abstr 4520, ASCO meeting 2014

Intermittent Therapy?

- A minority of patients are treated for many years with targeted drugs
- Standard of care is treatment to progression
- Potential benefits to an intermittent treatment strategy
  - Toxicity is generally modest but common
  - Hypothetically emergence of resistant clones might be reduced by intermittent therapy
  - Intermittent therapy is cheaper in terms of the drugs and might alter cost effectiveness

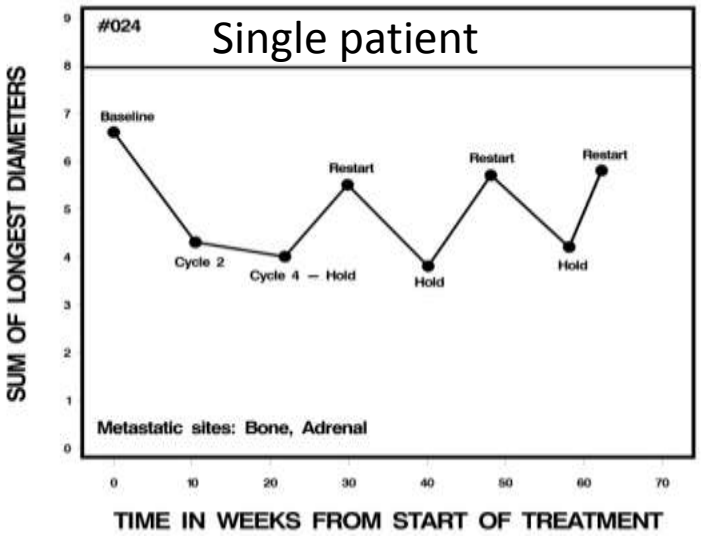
Study Schema

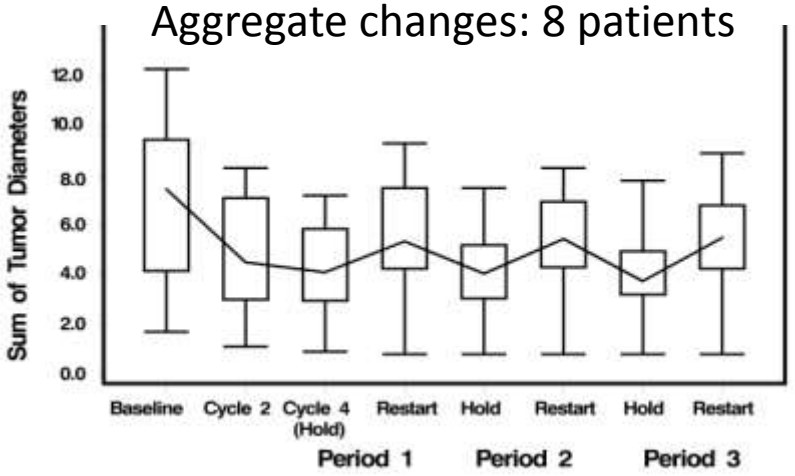


Rini et al, abstr 4515, ASCO meeting 2013

Results

- n=37
- 17 not eligible for intermittent therapy
  - PD (n=13)
  - Toxicity (n=1)
  - Patient choice (n=3)
- 20 proceeded to intermittent therapy
  - 16 (80%) had ≥ 10% increase off sunitinib
  - 4 (20%) did not have ≥ 10% increase off sunitinib

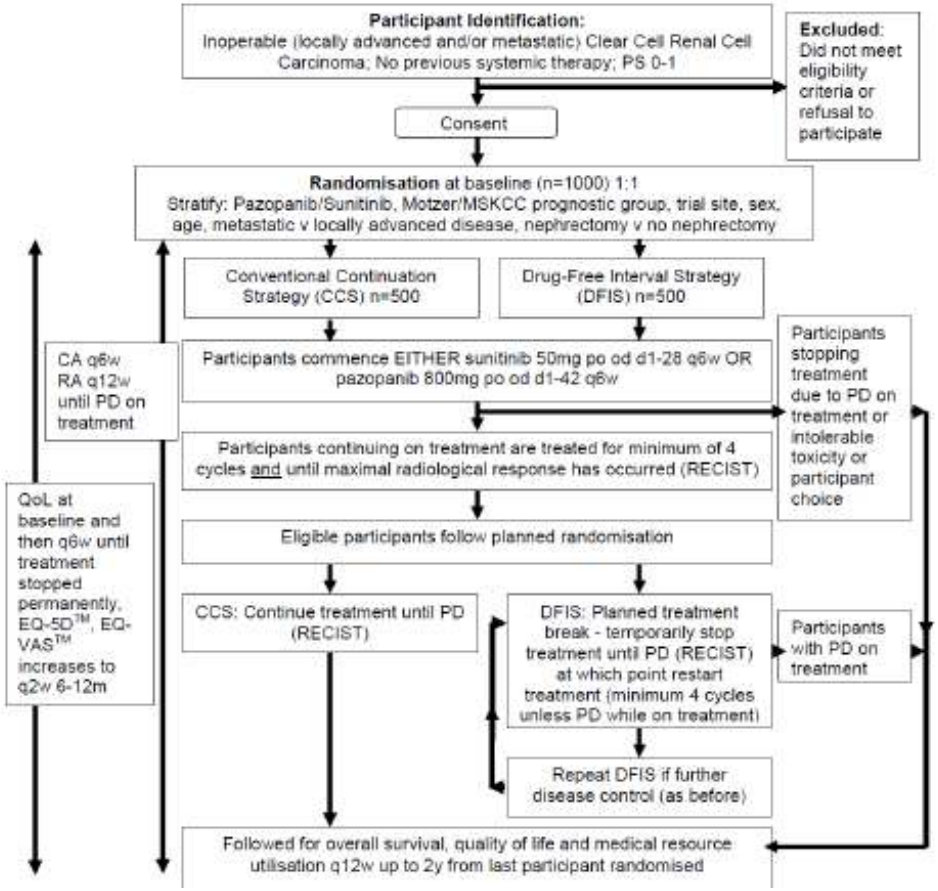




Rini et al, abstr 4515, ASCO meeting 2013

STAR Trial

- Intermittent versus continuous therapy.
- Phase II feasibility complete
- Multiple sites
- Easy to recruit
- CI: Janet Brown, Leeds

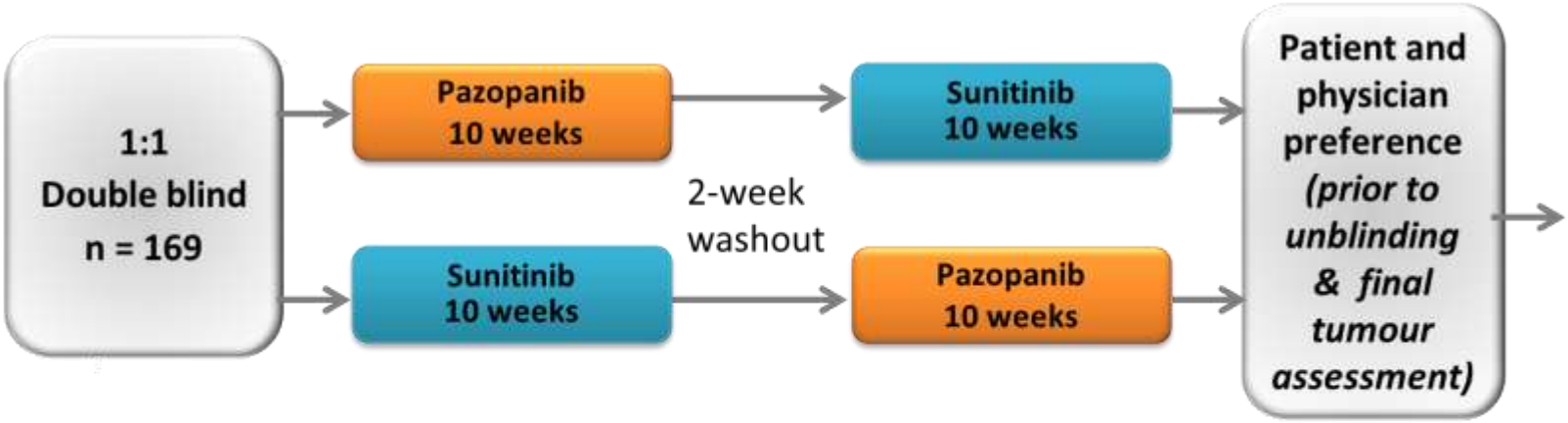


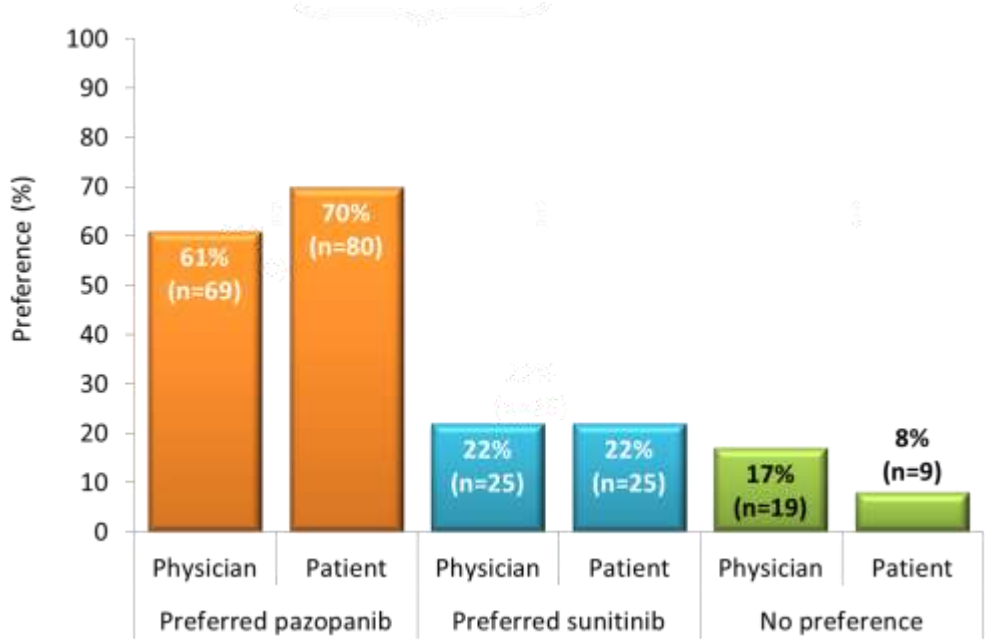
What is the best first line therapy?

Drug	Comparators	PFS	OS
Sunitinib	IFNα	11 v 5 months HR 0.42 p < 0.001	26.4 v 21.8 months HR 0.82 p = 0.051
Pazopanib	Placebo	9.2 v 4.2 months HR 0.46 p < 0.0001	22.9 v 20.5 months HR 0.91 p = 0.224
Bevacizumab/IFNα	IFNα	8.5 v 5.2 months HR 0.71 p < 0.0001	18.3 v 17.4 months HR 0.86 p = 0.097
Temsirolimus	IFNα Both	3.8 v 1.9 v 3.7 months P<0.001 (T v I)	10.9 v 7.3 v 8.4 months HR 0.73 (T v I) p = 0.008

Sternberg et al, J Clin Oncol, 2010; Sternberg et al, Eur J Cancer, 2013; Motzer et al, J Clin Oncol, 2009; Motzer et al , N Engl J Med, 2007; Rini et al, J Clin Oncol, 2008; Hudes et al , N Engl J Med, 2007; Rini et al, J Clin Oncol, 2010

PISCES study

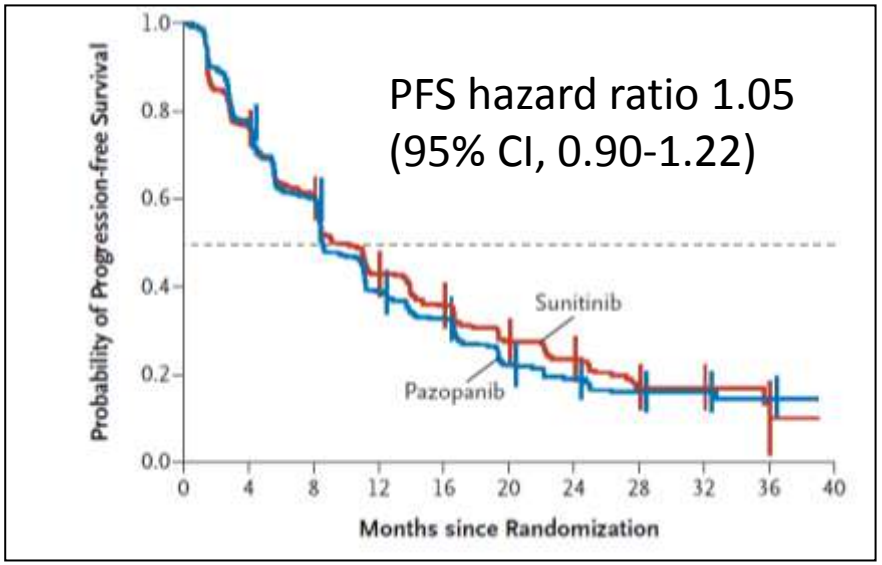


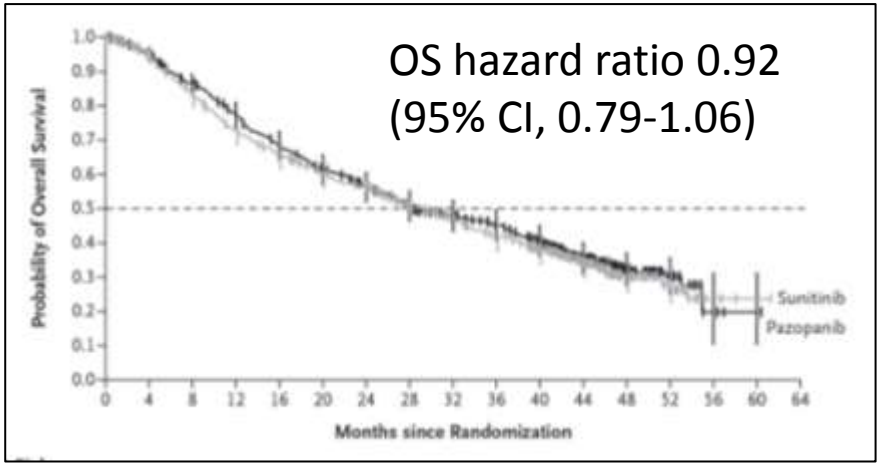


Escudier et al, J Clin Oncol, 2014

COMPARZ trial

- n = 1100
- Non-inferior
- Higher incidence with sunitinib of:
  - Fatigue (63% v 55%)
  - Hand–foot syndrome (50% v 29%)
  - Thrombocytopenia (78% v 41%)
- Higher incidence with pazopanib of
  - ALT rise (60% v 43%)
- QOL changes favoured pazopanib

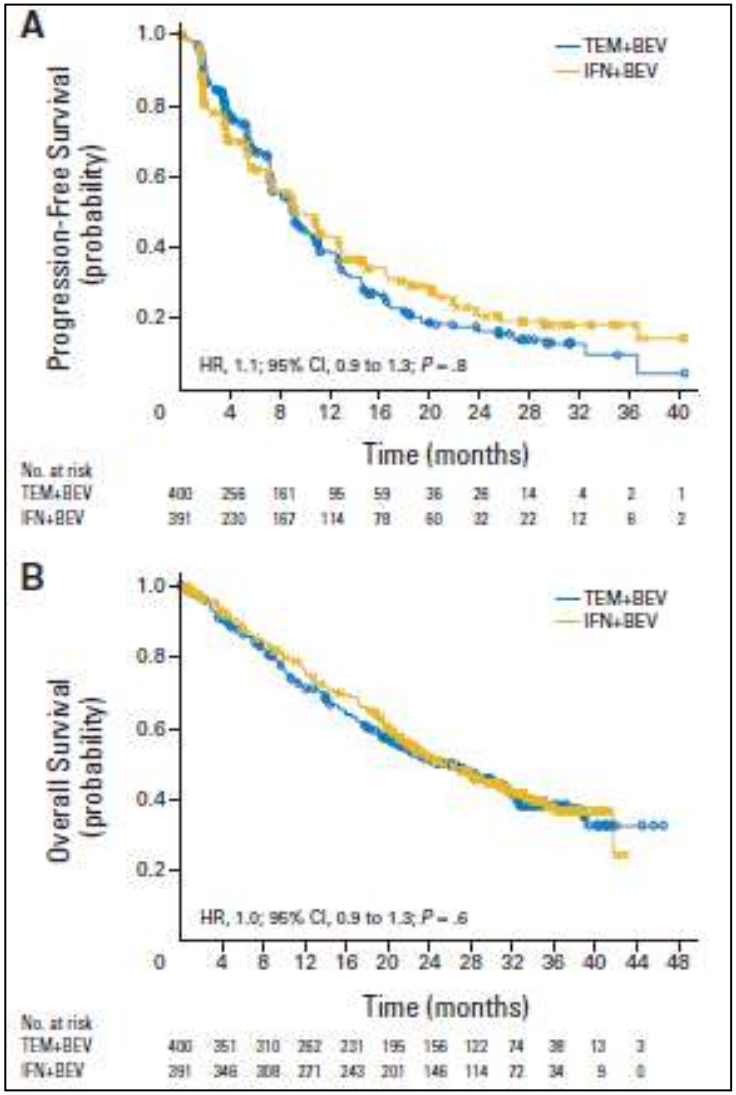


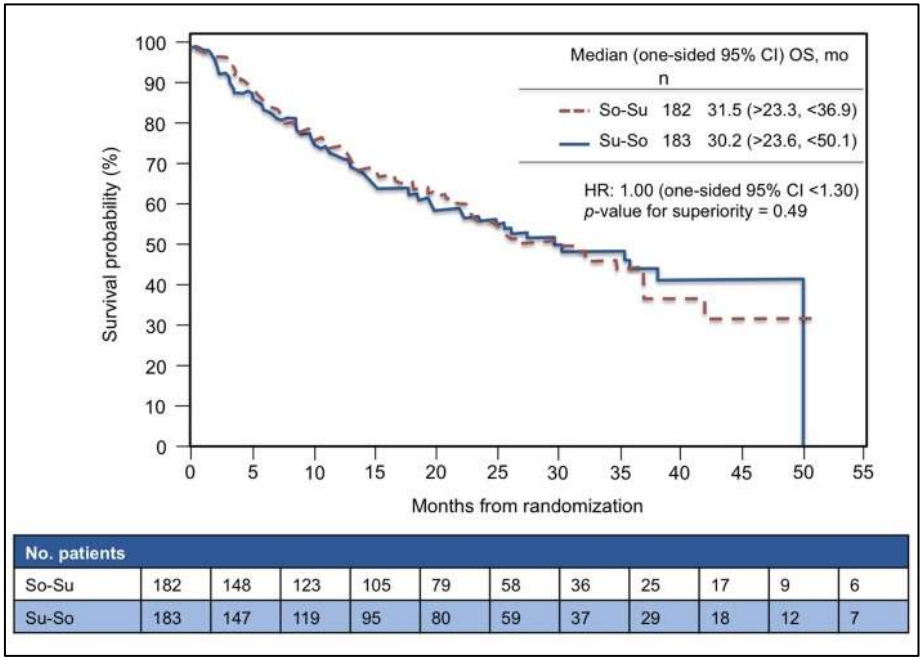


Motzer et al, N Engl J Med, 2013; Motzer et al, N Engl J Med, 2014

Trials that will not change practice…

(amongst various examples of combinations and sequencing)

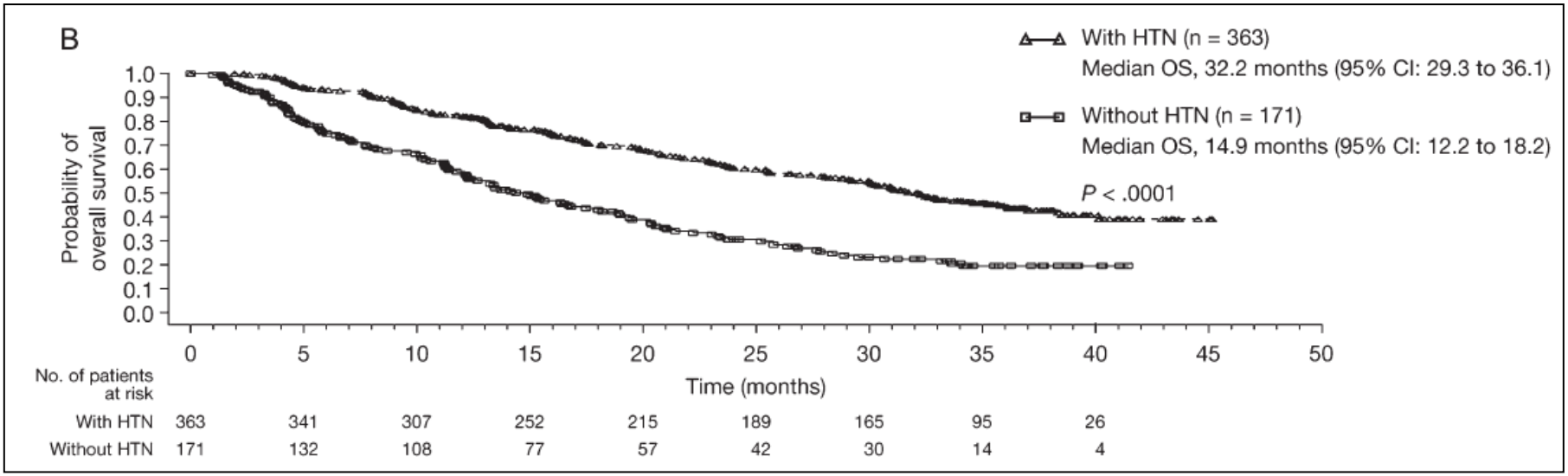




No. patients											
So-Su	182	148	123	105	79	58	36	25	17	9	6
Su-So	183	147	119	95	80	59	37	29	18	12	7

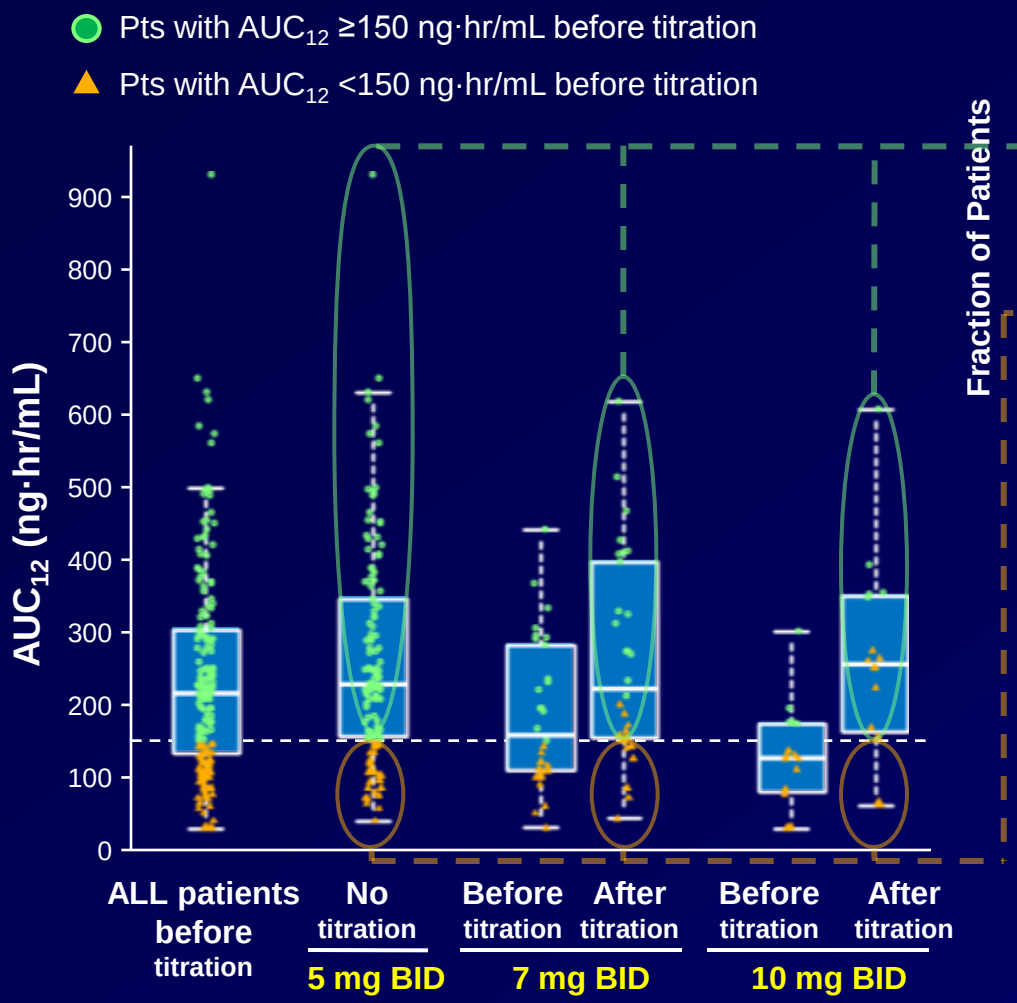
Michel et al, GU ASCO 2014, abstr 393;
Rini et al, J Clin Oncol, 2013

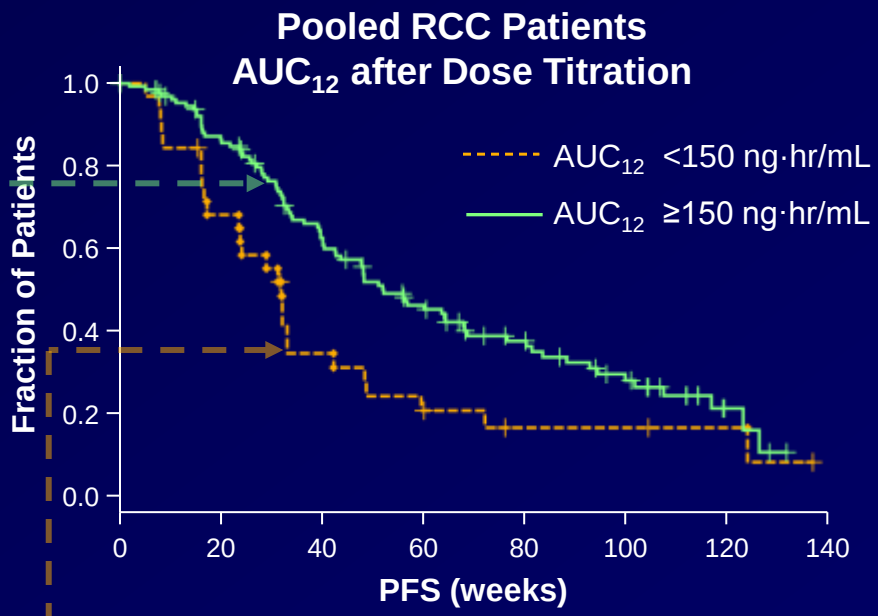
Toxicity, efficacy and dose?



Rini et al, JNCI, 2014

PFS vs AUC in Phase II RCC Patients





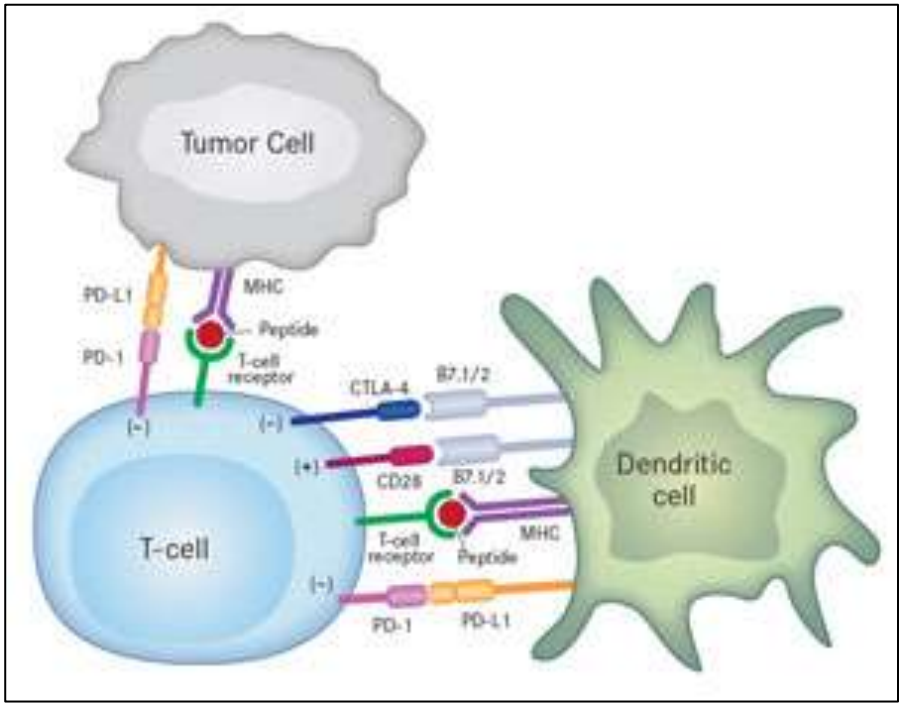
mPFS, wks (95% CI)		HR (95% CI)
AUC_{12} <150 ng·hr/mL	AUC_{12} ≥150 ng·hr/mL	
32 (24, 48) n=36, 26	52 (43, 69) n=139, 83	0.56 (0.359, 0.874)

n=number of patients meeting AUC criterion, number of PFS events assessed by investigator

Sub-therapeutic exposure defined as AUC_{12} <150 ng·hr/mL

Immune therapy in metastatic RCC

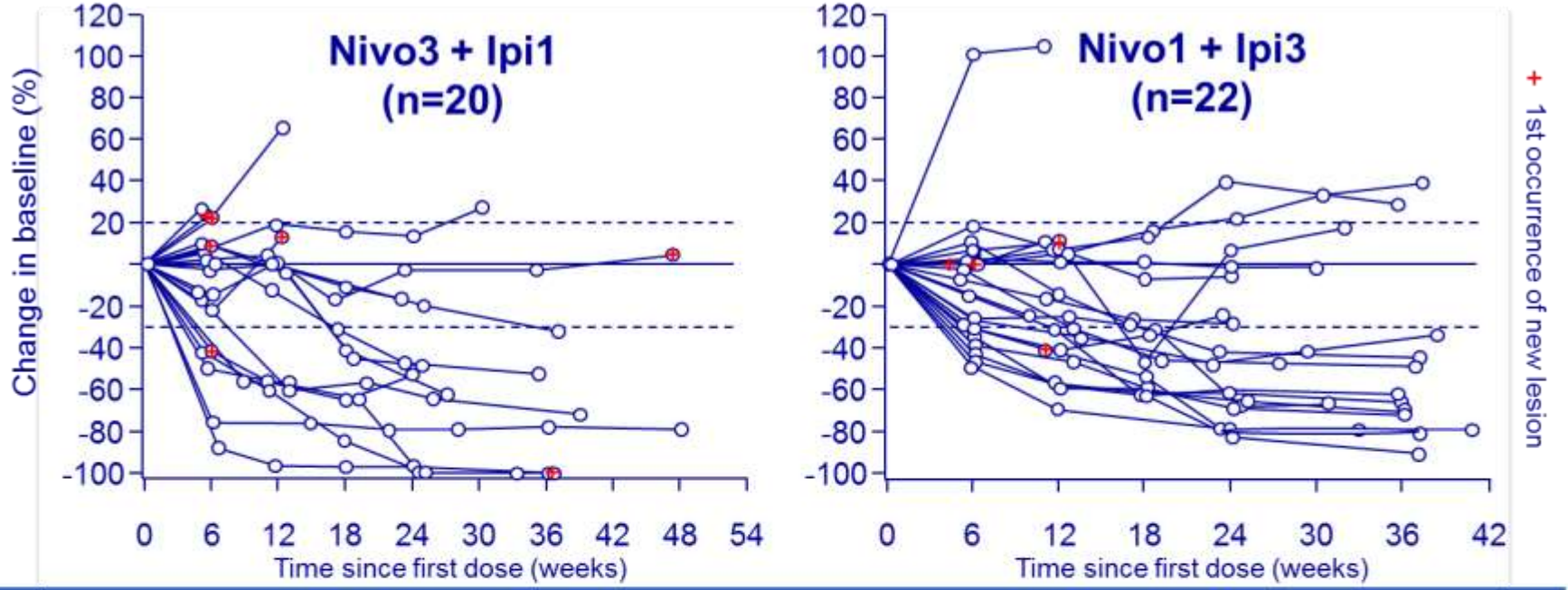
- Established with Il-2 (5-10% durable CR rate in selected patients)
- Development of immune checkpoint inhibitors is a significant area of current drug development in cancer

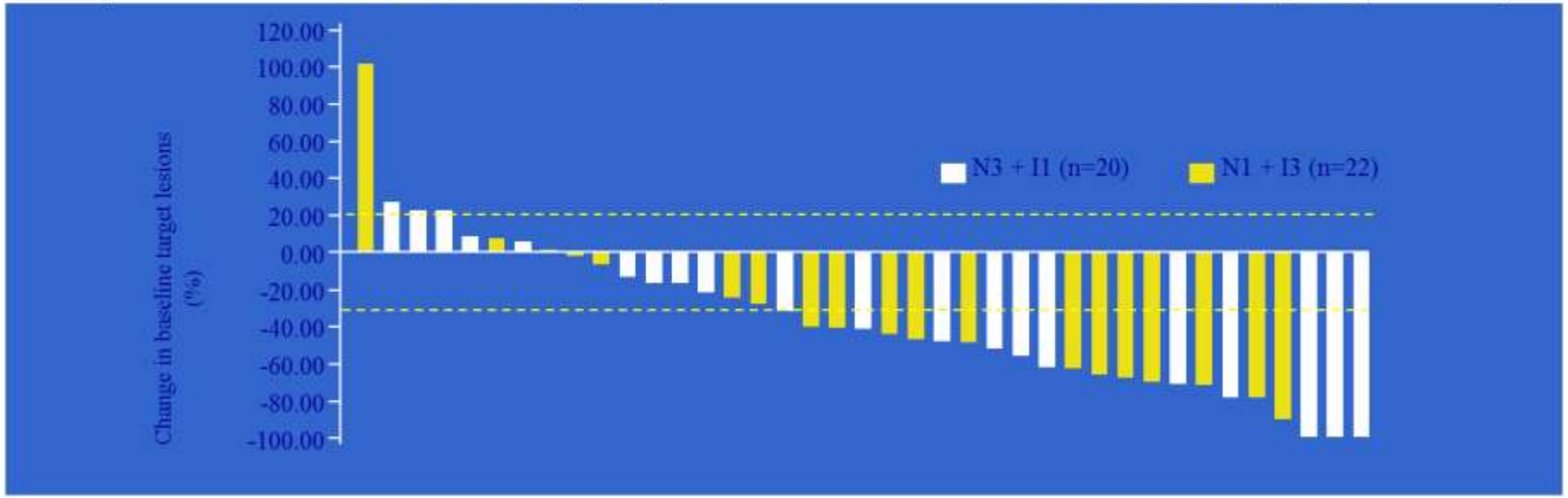


Single agent nivolumab in RCC

	# 5009 MOTZER			#5012 CHOUEIRI			
Design	Randomized, dose-ranging phase II (N=168)			Biomarker-based randomized clinical trial (N=91) *(Baseline and on-therapy fresh tumor biopsies)*			
Dose IV Q3W	0.3mg/kg n =60	2 mg/kg n=54	10 mg/kg n=54	0.3mg/kg n =22	2 mg/kg n=22	10 mg/kg n=23	10 mg/kg n=24 (naïve)
Prior Tx	70% ≥ 2 prior therapies No treatment-naïve pts			74% (1-3) prior therapies 24 (16%) treatment-naïve pts			
ORR (%)	20%	22%	20%	9%	23%	22%	13%
mPFS (m) *1° endpoint*	**2.7**	**4.0**	**4.2**	PFS at 24 weeks: 36%			
mOS (m)	18.2	25.5	24.7	Not Reported			
G3/4 TOX	5%	17%	13%	18%			
Biomarker	None reported			•Increased T-cell tumor infiltrates after nivolumab •Increased serum chemokines post-nivolumab •Numerically higher (22% vs. 8%) ORR in PD-L1 (+) pts			
Perspective	**•Median PFS is not impressive:** **•Axitinib/everolimus: ~5 m (post TKI)** **•mPFS :an appropriate endpoint ?** **•Median OS is impressive:** **•AXIS/RECORD-1: ~20/15 m**			**What is the role of PD/PD-L1 inh in PD-L1 (+) tumors?**			

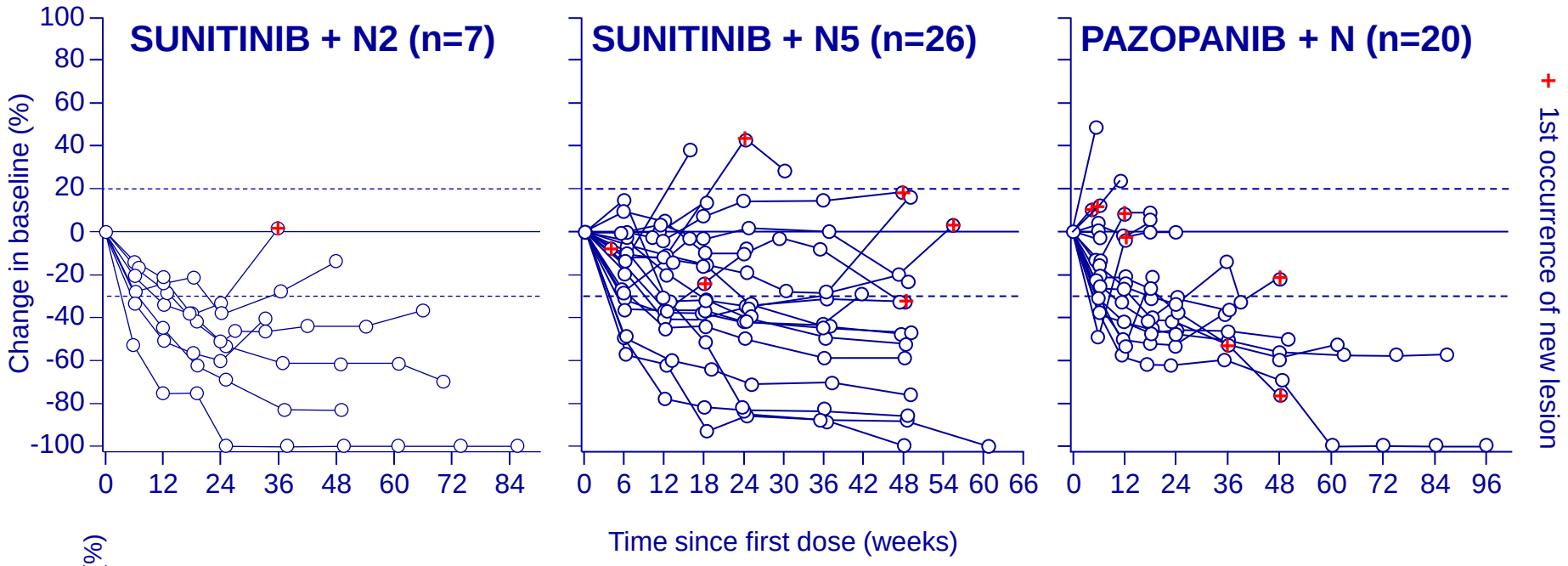
Combination Nivolumab + Ipilimumab

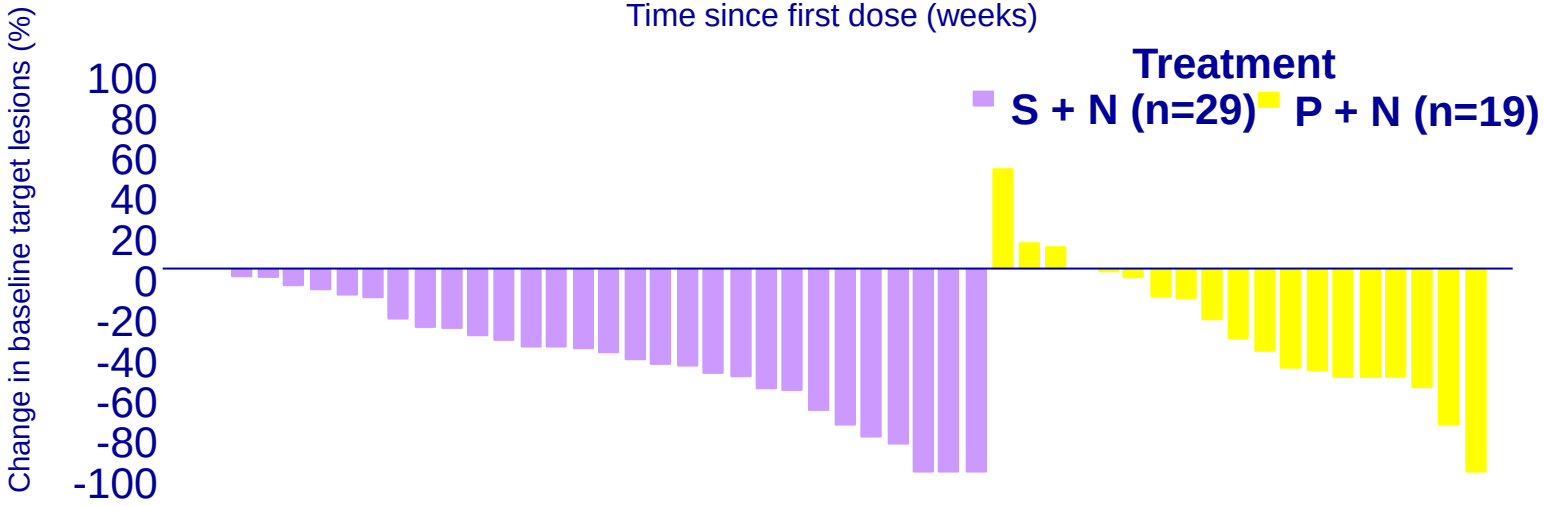




Hammers et al, ASCO Meeting 2014, abstr 4504

Combination Nivolumab + Sunitinib

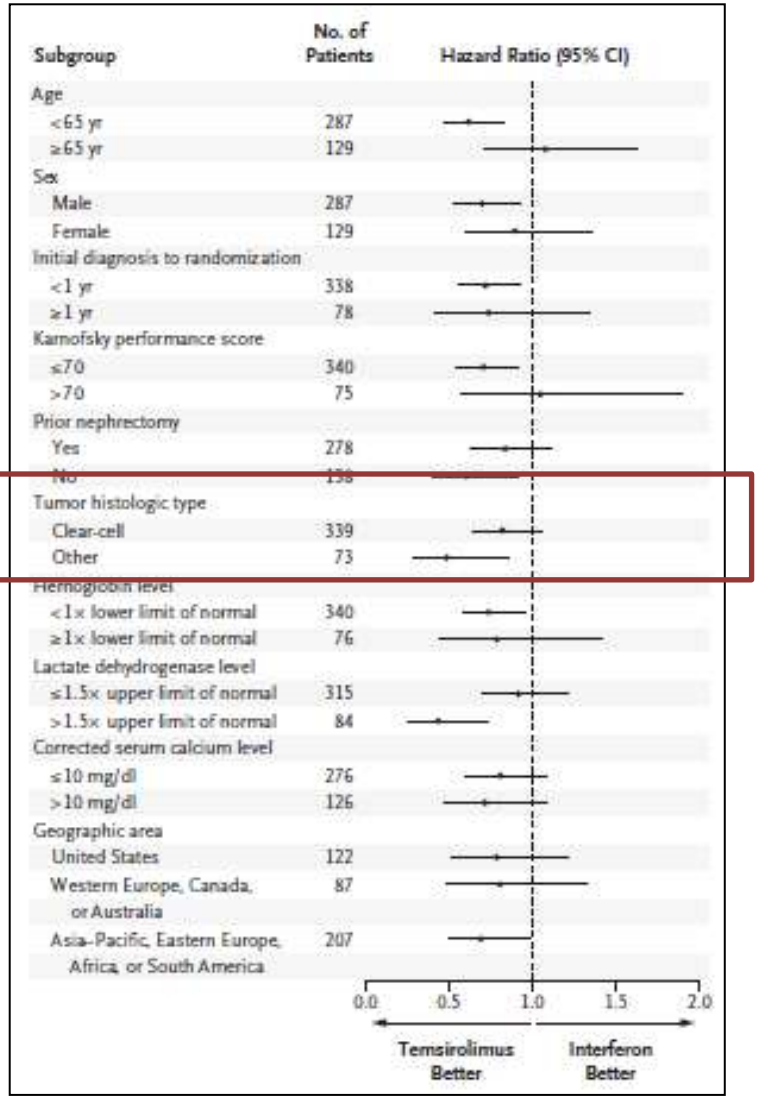




Amin et al, ASCO Meeting 2014, abstr 5010

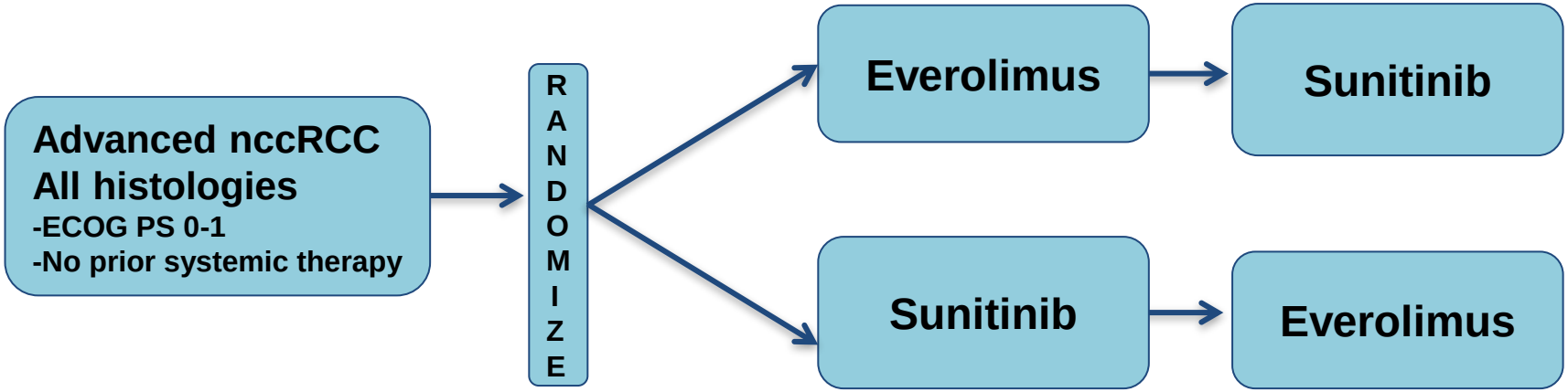
Non clear cell mRCC

- Generally lower response rates than ccRCC
- Some have used mTOR inhibitors on the basis of subset data



Hudes et al , N Engl J Med

Everolimus v sunitinib in metastatic non-ccRCC

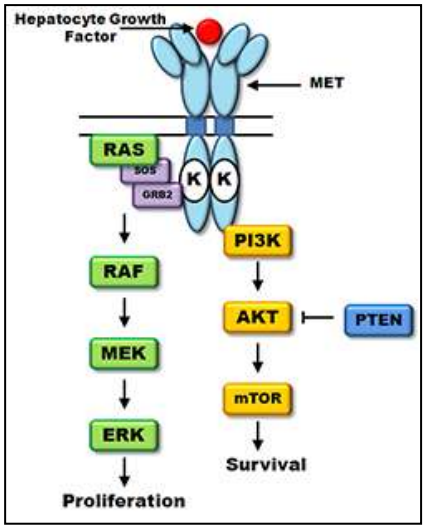


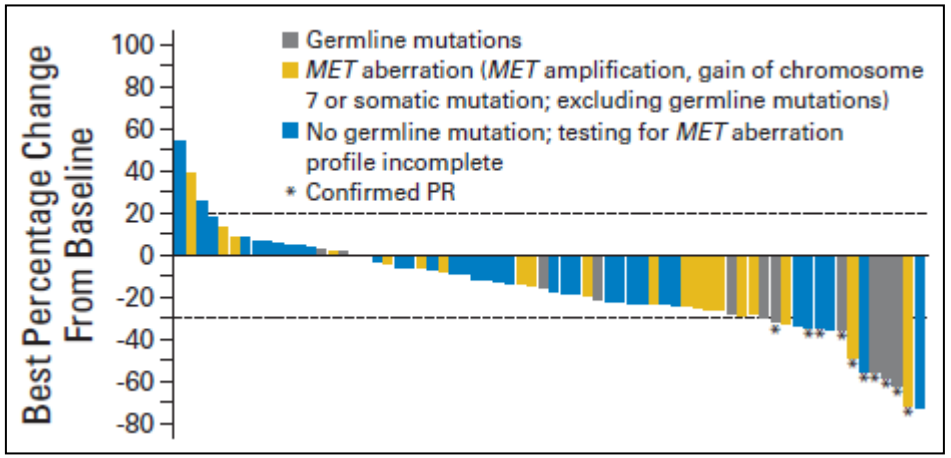
	Everolimus, n=35	Sunitinib, n=33	P-value
ORR 1st line	2.8%	6%	
mPFS 1st line (months)	4.1	6.1	0.6
Nb of pts receiving 2nd line	20	24	
mOS (months) -mOS (non-sarcomatoid), n=49	14.9 10.5	16.2 31.6	0.18 0.07

Tannir, ASCO meeting 2014, abstr 4505

Biological rationale for cMET inhibition in papillary mRCC

- Papillary RCC associated with activating MET gene mutations
- Foretinib: multikinase inhibitor targeting MET, VEGF, RON, AXL, TIE-2
- ORR 13.5%, median PFS 9.3 months
- Germline MET mutation predictive of response
  - 5/10 v 5/57





Choueiri, J Clin Oncol 2012

Adjuvant trials

Trial (sponsor)	Randomization	Duration of therapy (years)	*N*	Start date	End date[a]	Primary endpoint	Clear cell required?	Details
ASSURE (ECOG)	Sunitinib vs. sorafenib vs. placebo	1	1,943	April 2006	September 2010	DFS	No	• Eligibility: pT1bN0M0 (grades 3–4) or pT2-4N1-3M0 RCC • Histology: Any • Cardiac safety substudy reported
ATLAS (Pfizer)	Axitinib vs. placebo	3	592	April 2012	June 2017	DFS	Yes	• Eligibility: pT2-4N0M0 or pTxN1M0 RCC
EVEREST (SWOG)	Everolimus vs. placebo	1	1,218	April 2011	October 2021	DFS	No	• Eligibility: pT1bN0M0 (grades 3–4) or pT2-4N1-3M0 RCC • Histology: Any • Accrual ~50% complete
PROTECT (GSK)	Pazopanib vs. placebo	1	1,500	November 2010	April 2016	DFS	Yes	• Eligibility: pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 RCC
SORCE (MRC)	Sorafenib vs. placebo	3	1,420	June 2007	December 2012	DFS	No	• Eligibility: Intermediate- or high-risk RCC (Leibovich score, 3–11)
S-TRAC (Pfizer)	Sunitinib vs. placebo	1	720	July 2007	November 2015	DFS	Yes	• Eligibility: High-risk RCC (modified UISS criteria) pT2N0M0 (grades 3–4) or pT3-4N0M0 or pTxN1M0 RCC

Pal and Haas, Oncologist, 2014

Conclusions

- A subset of mRCC can probably be safely observed for a period before systemic therapy – randomised data realistic???
- Treatment breaks seem safe - but we don't know if this is optimal – so support the STAR trial
- Combining established drugs and sequencing trials are largely negative
- We have probably reached a plateau with current VEGF and mTOR targeted drugs and 'me too' agents seem to have brought rather little to the table
- Further significant advance will probably require:
  - New therapeutic targets – Perhaps this is immunotherapy, large trials awaited
  - Predictive biomarkers – Lots of ongoing work, little ready for prime time
- Non clear cell mRCC remains a significant challenge
- Adjuvant trials will start to report soon and may change practice