Treatment of metastatic renal cell carcinoma (RCC): Present and future

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Disclosure

- Consultant for Aveo, Bayer Healthcare, BMS, Genentech, GSK, Novartis, Pfizer

Biology of RCC

- **New entities are coming (Vancouver classification)**

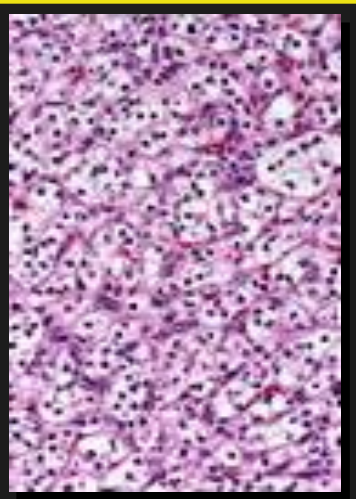
Clear cell renal cell carcinoma
Multilocular clear cell renal cell neoplasm of low malignant potential
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Hybrid oncocytic chromophobe tumour
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
MiT family translocation renal cell carcinoma
Xp11 translocation renal cell carcinoma
t(6;11) renal cell carcinoma
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease–associated renal cell carcinoma
Clear cell papillary (tubulopapillary) renal cell carcinoma
Hereditary leiomyomatosis-associated renal cell carcinoma
Renal cell carcinoma, unclassified

Srigley JR et al. Am J Surg Pathol 2013; 37:1469-1489.

Biology of RCC

- New entities are coming (Vancouver classification)
- **Genomic classification has started….**

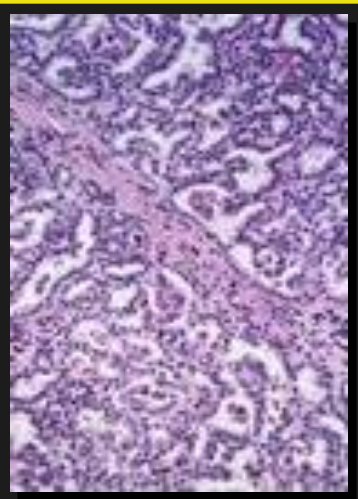
Gene expression



Clear Cell

75%

VHL



Papillary Type 1

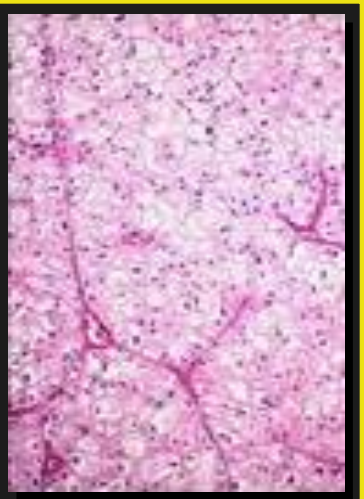
5%

cMET

Papillary Type 2

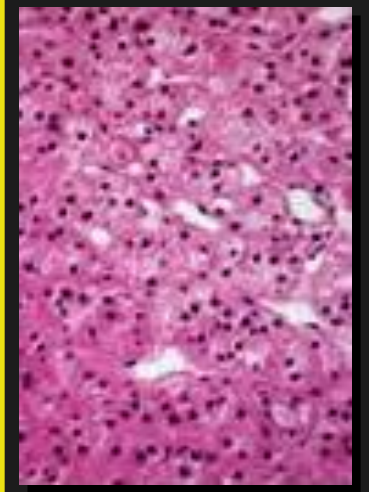
10%

FH
cMYC



Chromophobe

5%



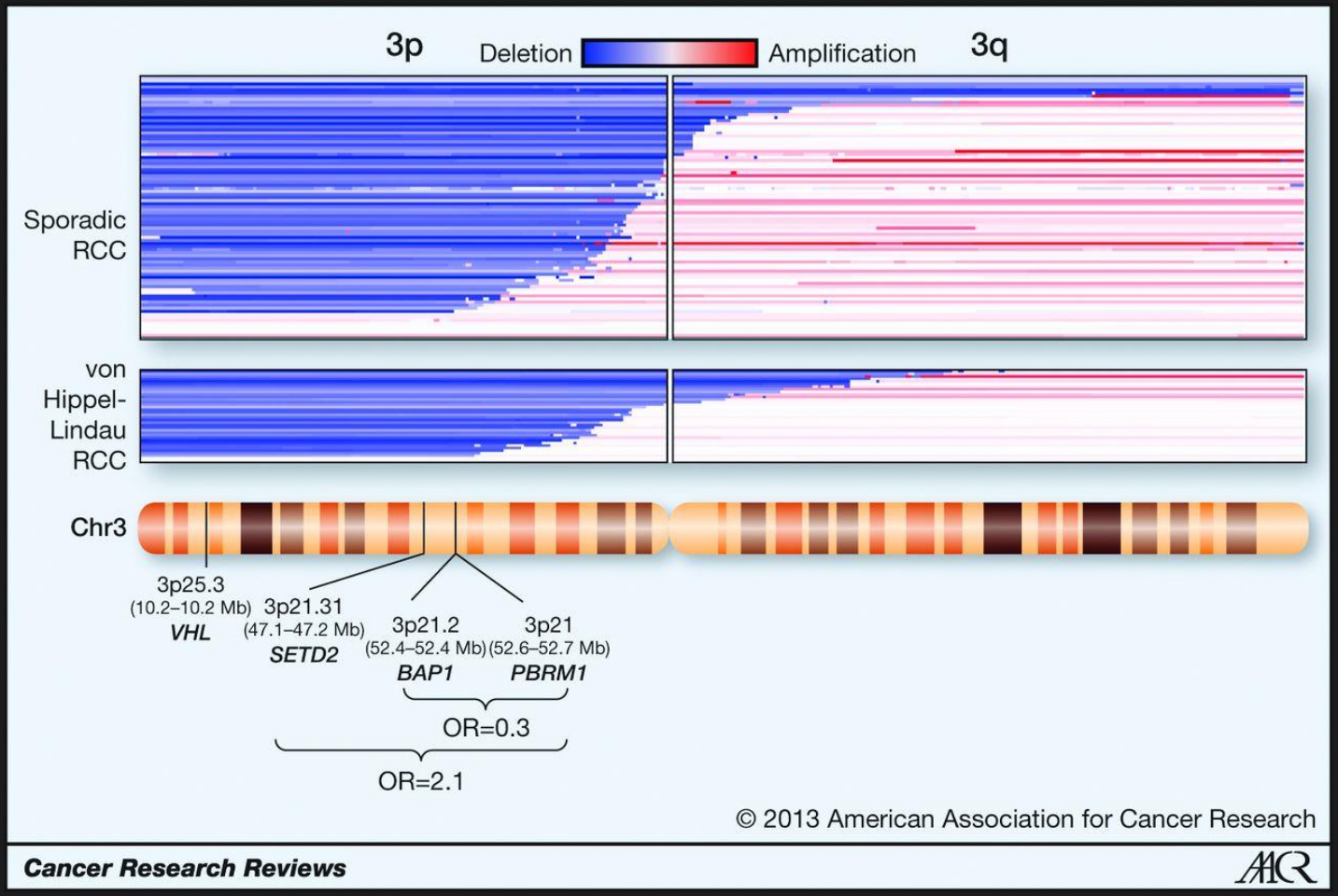
Oncocytoma

5%

BHD

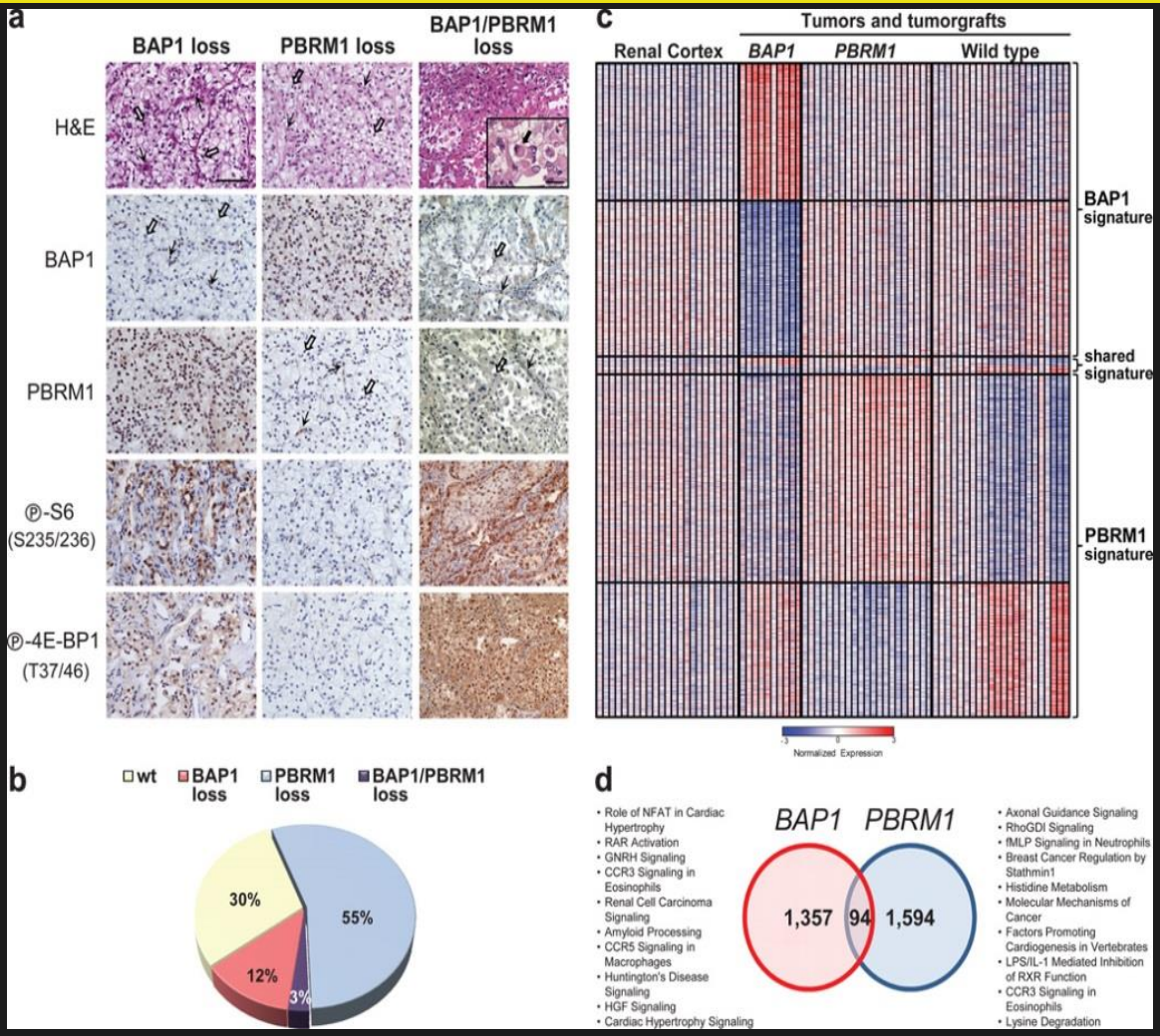
A lot of new genes : SEDT2, PBRM1, BAP 1, KMD61, NF2 …..

Some important genes on chromosome 3



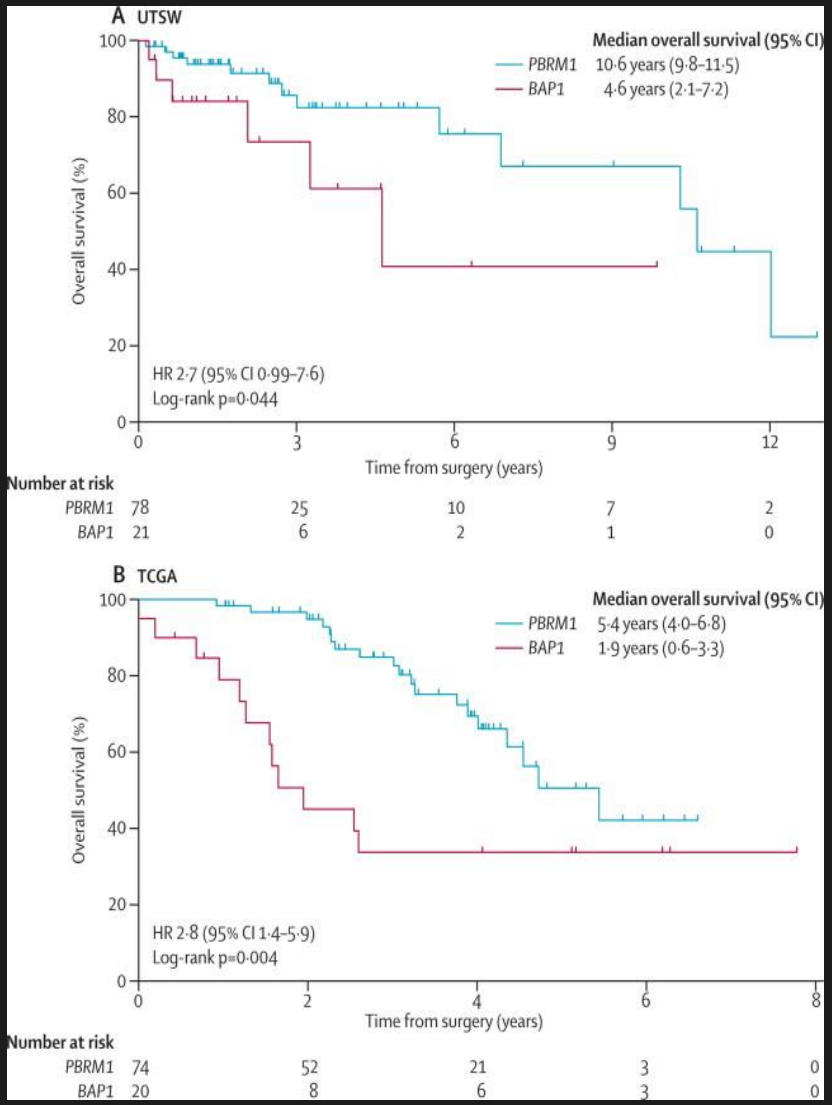
Peña-Llopis S et al. Cancer Res 2013;73:4173-4179

BAP1 and PBRM1 are mutually exclusive



Peña-Llopis S et al. Nat Genetics 2012

BAP1 and PBRM1 are prognostic factors of survival

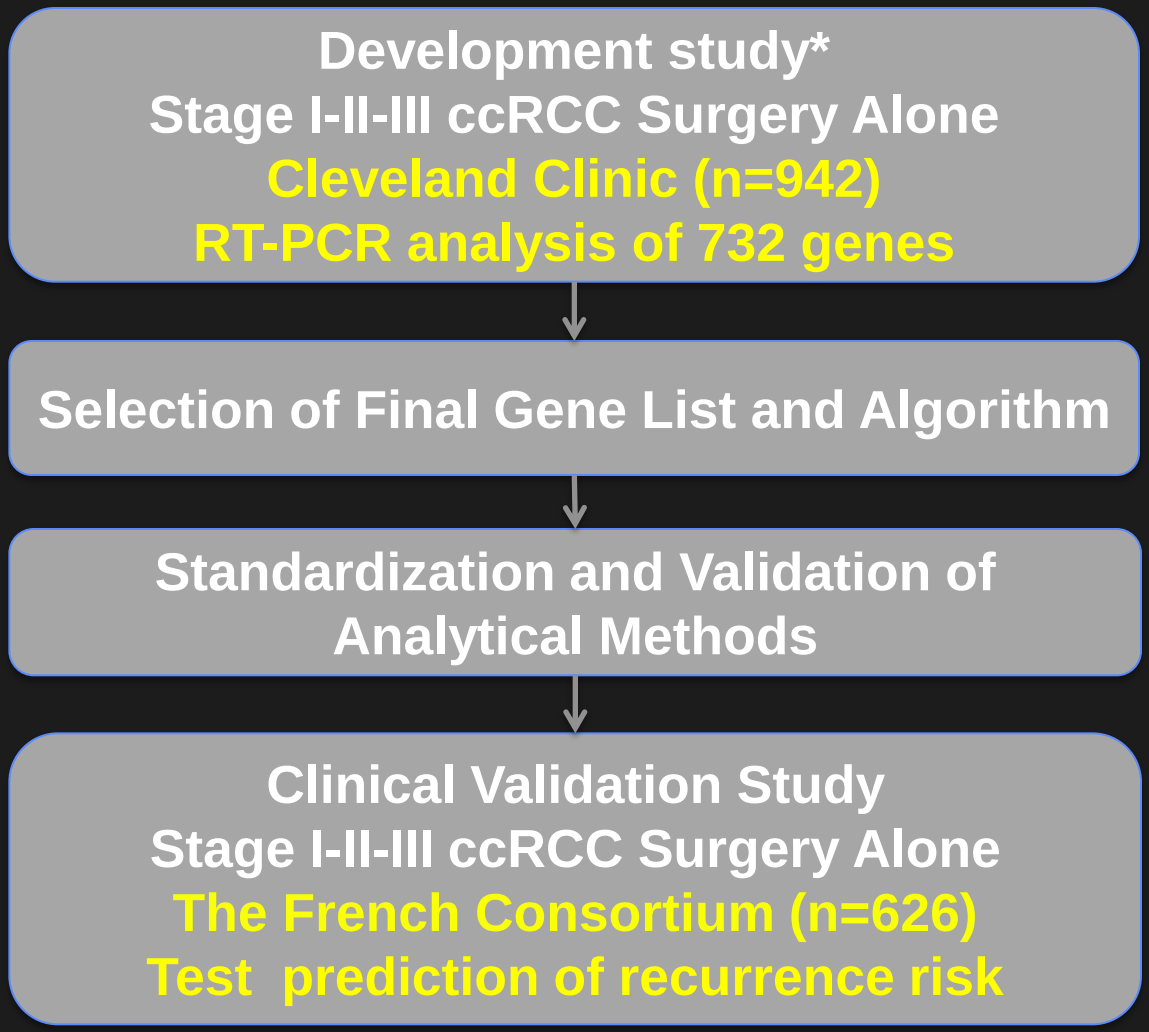


Kapur P et al. Lancet Oncol 2013

Biology of RCC

- New entities are coming (Vancouver classification)
- Genomic classification has started….
- **Genomic signatures are coming**

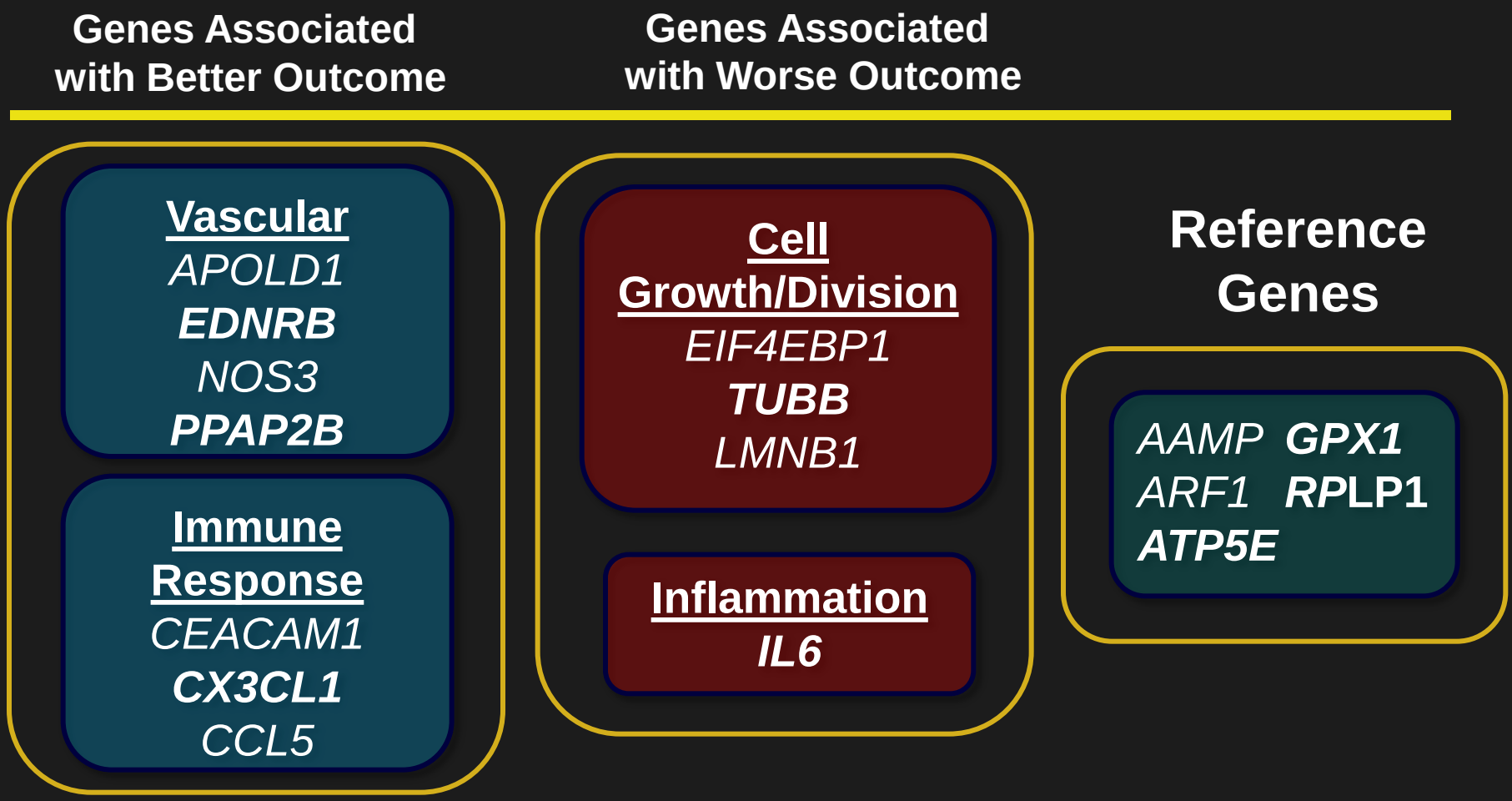
Development and Validation of a 16-gene signature in localized RCC



* Rini *et al*., ASCO 2010

Escudier et al, ASCO 2014

Final genes and algorithm

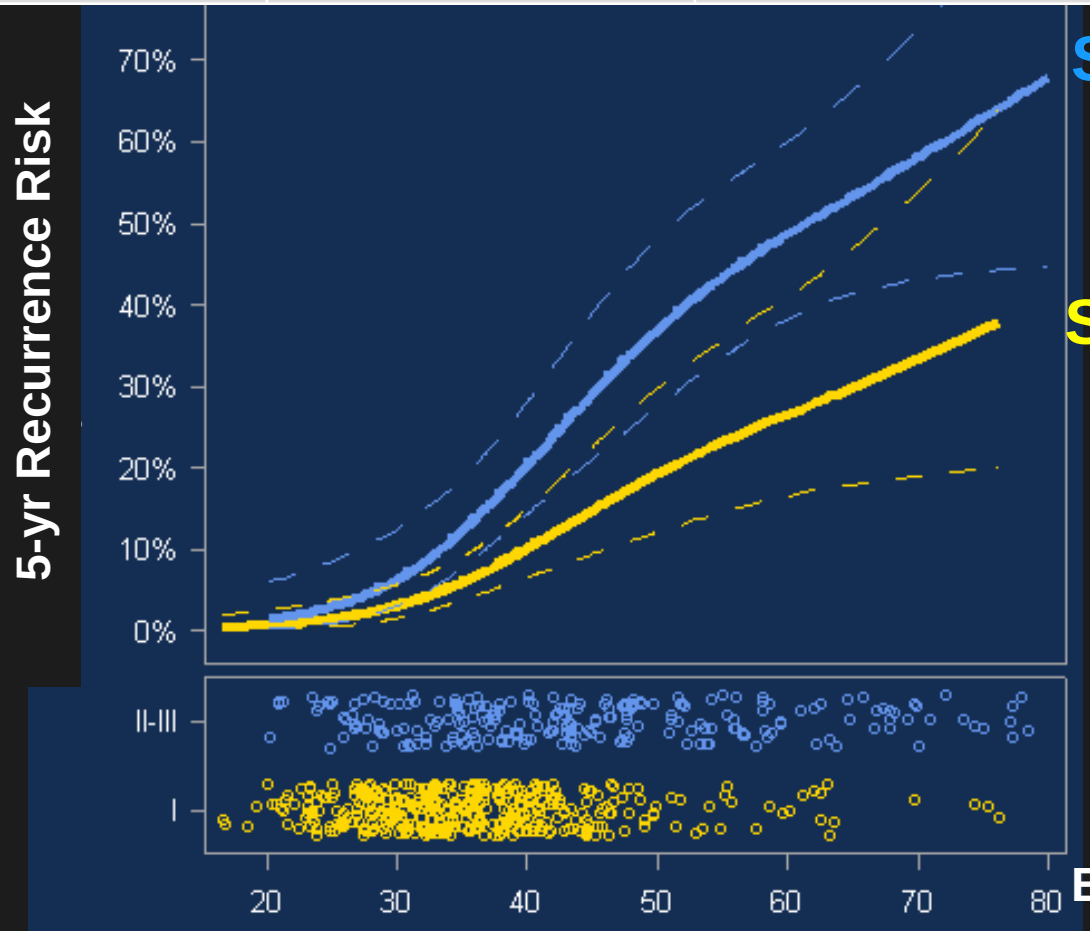


Recurrence Score = - 0.45 x Vascular Group Score – 0.31 x Immune Response Score + 0.27 x Cell Growth/ Division Score + 0.04 x Inflammation
Scaled to 0-100

Escudier et al, ASCO 2014

Recurrence Score quantified wide ranges of recurrence risks for each stage

Variable	Value	HR (95% CI)	*p*-value
RS	per 25 units	3.9 (2.6, 5.8)	<.001



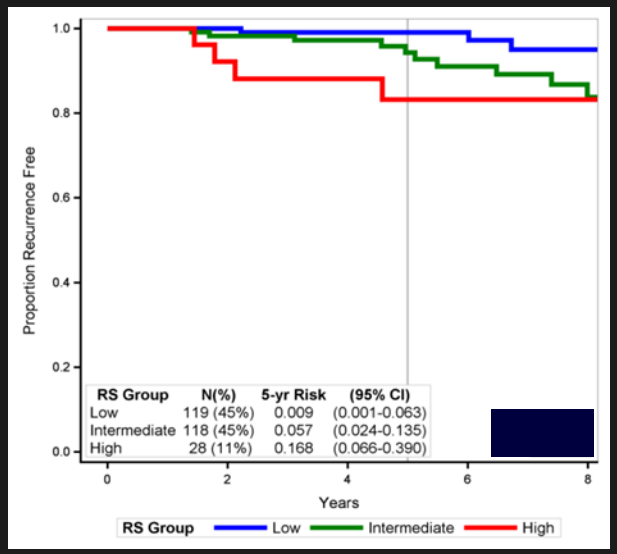
Stages II-III

Stage I

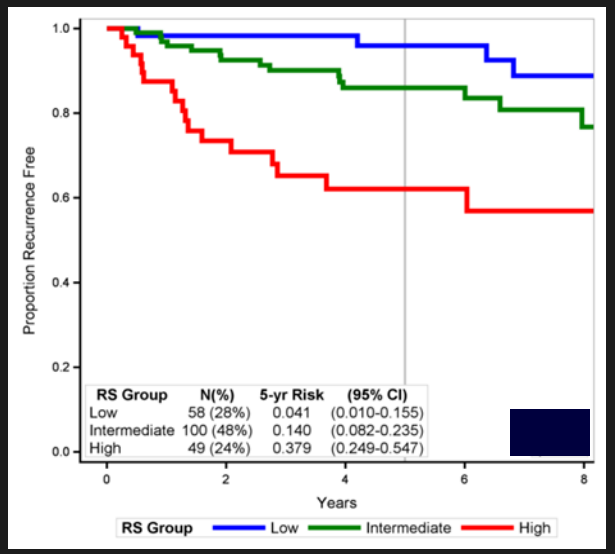
Escudier et al, ASCO 2014

This score is better than current prognostic models

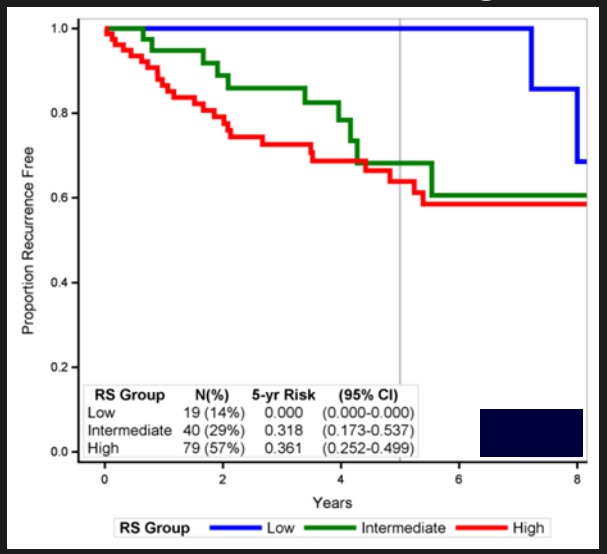
Leibovich Low



Leibovich Intermediate



Leibovich High



Variable	HR	HR 95% CI	DF	LR ChiSq	P value
Leibovich Score			2	5.75	0.057
Leibovich High vs Low	1.96	(0.72,5.34)			
Leibovich Int vs Low	2.59	(1.13,5.95)			
RS (per 25 units)	4.20	(2.76,6.40)	1	41.01	<0.001

What is the current treatment in mRCC?

- VEGF inhibition is key
  - In first line
  - In second line
  - In third line
- mTOR inhibition is active
  - In second and third line
  - In first line in poor risk patients
- Third line recommendations do exist

Risk assessment is important in mRCC: IMDC classification

- Six risk factors:
  - Karnofsky performance status < 80%
  - Haemoglobin < lower limit of normal
  - Time from diagnosis to treatment < 1 year
  - Corrected calcium > upper limit of normal
  - Platelets > upper limit of normal
  - Neutrophils > upper limit of normal

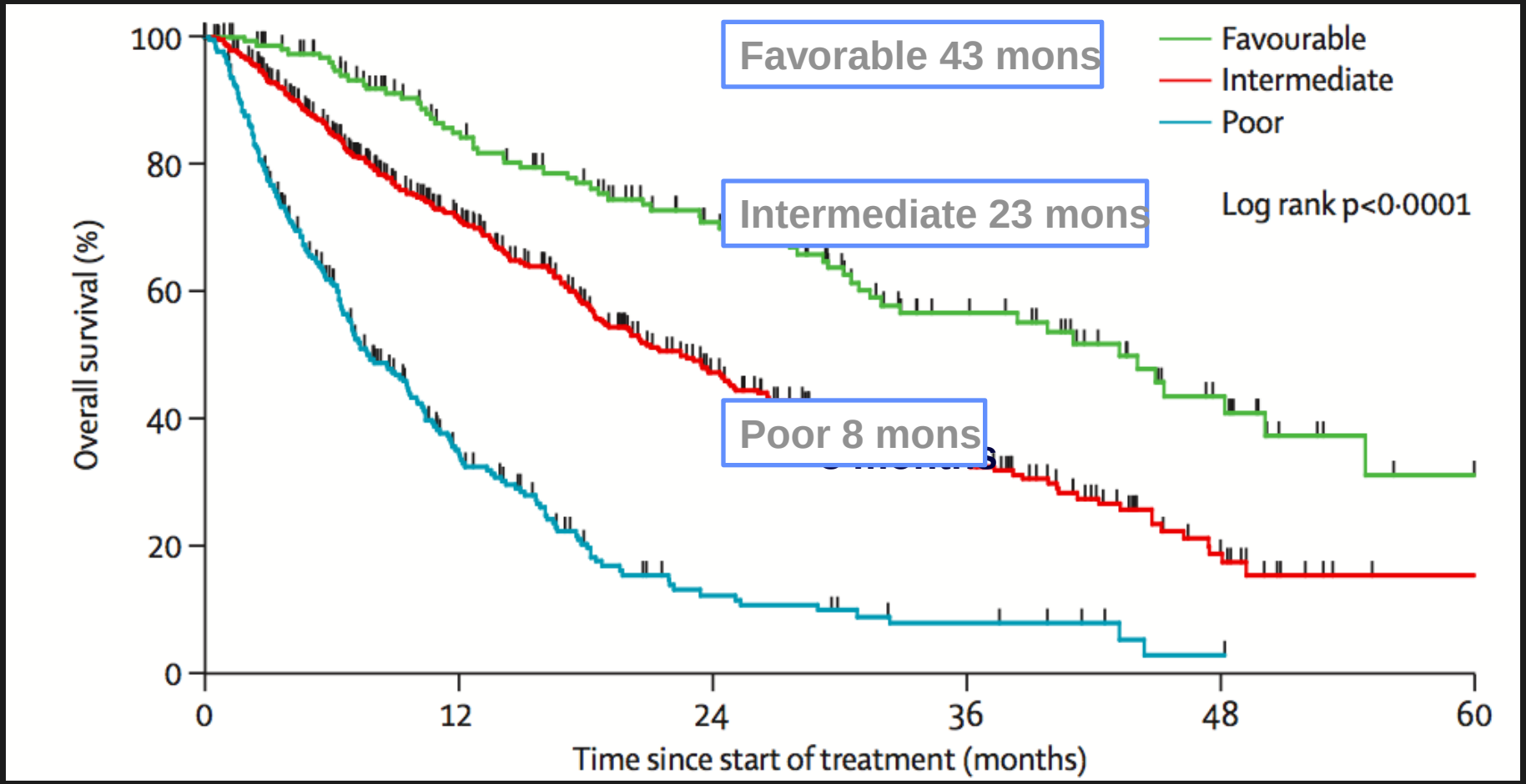
Risk groups are useful

If patient has 0 factors:
Favorable Prognosis

If patient has 1-2 factors:
Intermediate Prognosis

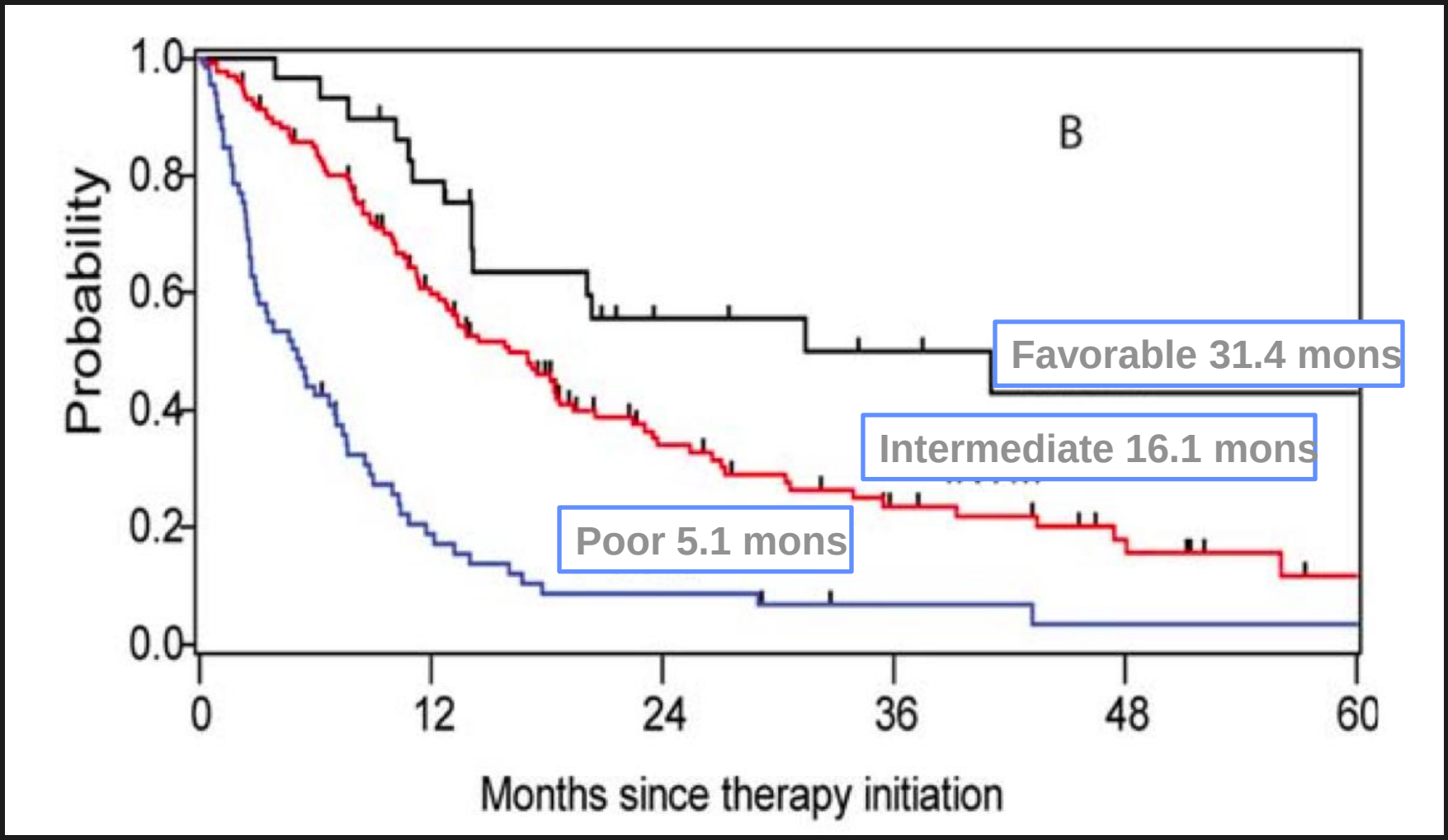
If patient has 3-6 factors:
Poor Prognosis

IMDC Prognostic Factors



Heng et al Lancet Oncology 2013

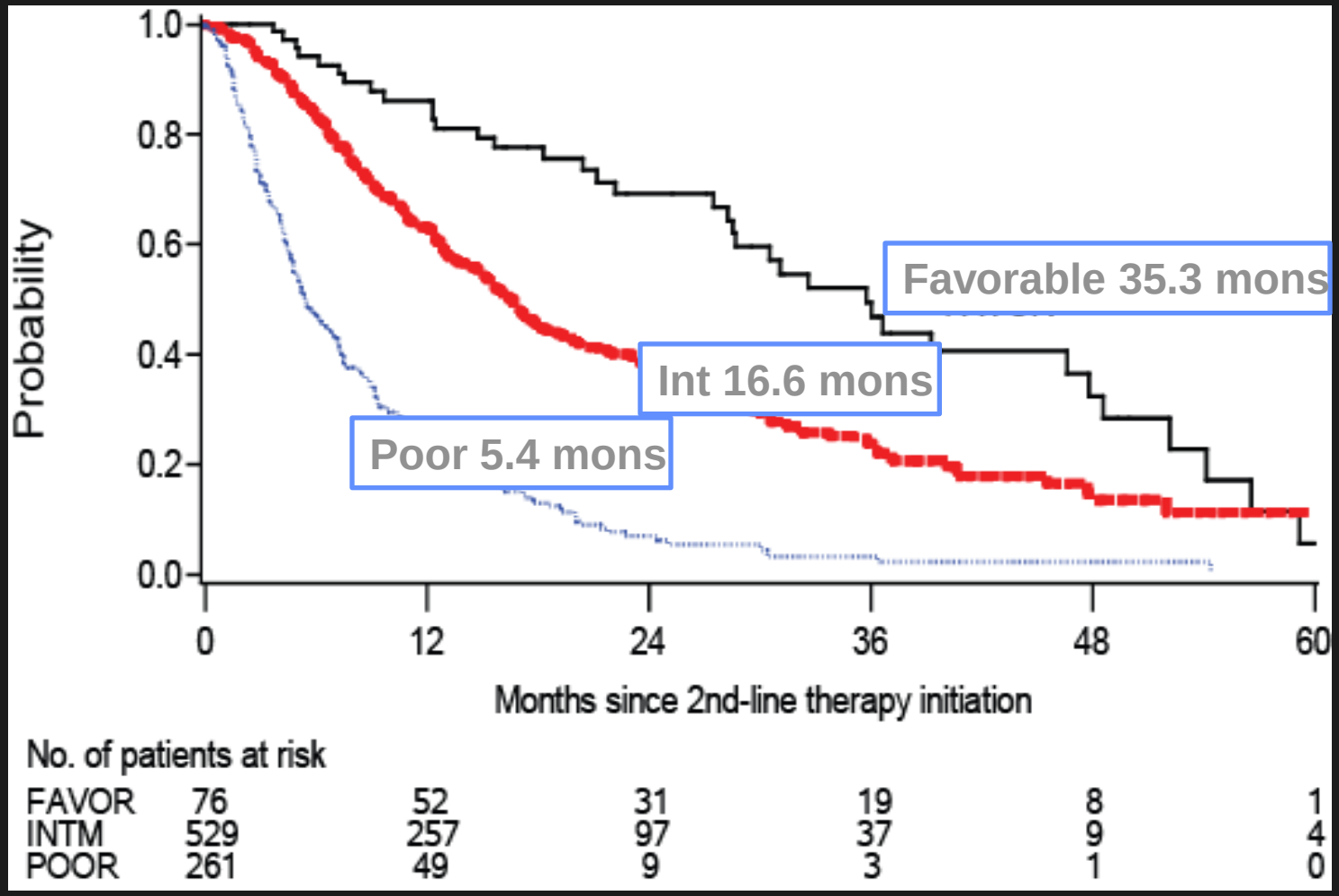
IMDC in non-clear cell RCC



Kroeger et al, Cancer 2013

Kroeger et al Cancer 2013

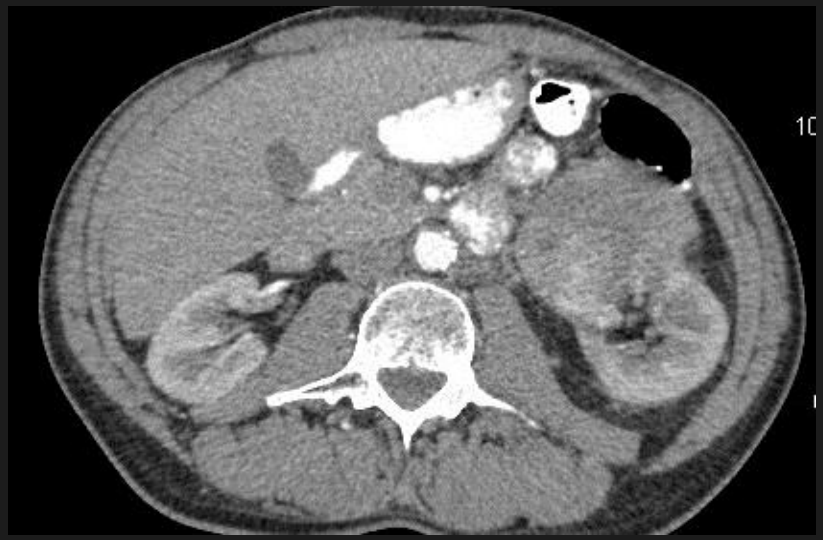
IMDC in 2nd-line targeted therapy

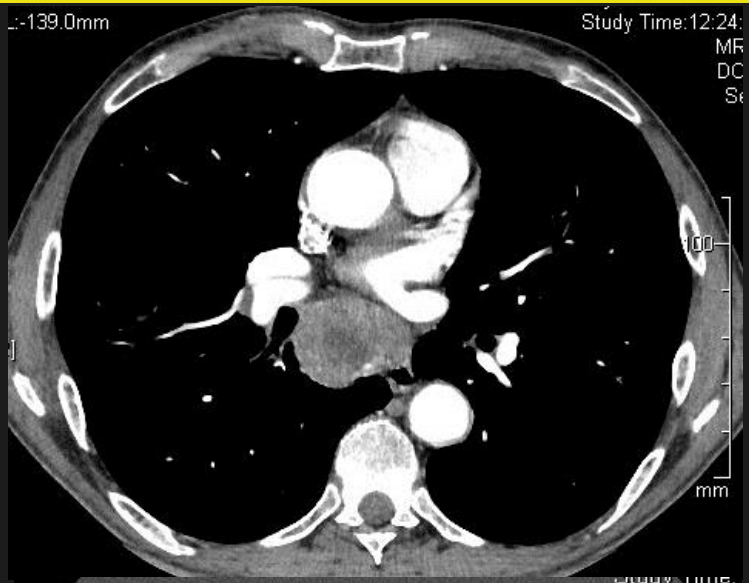


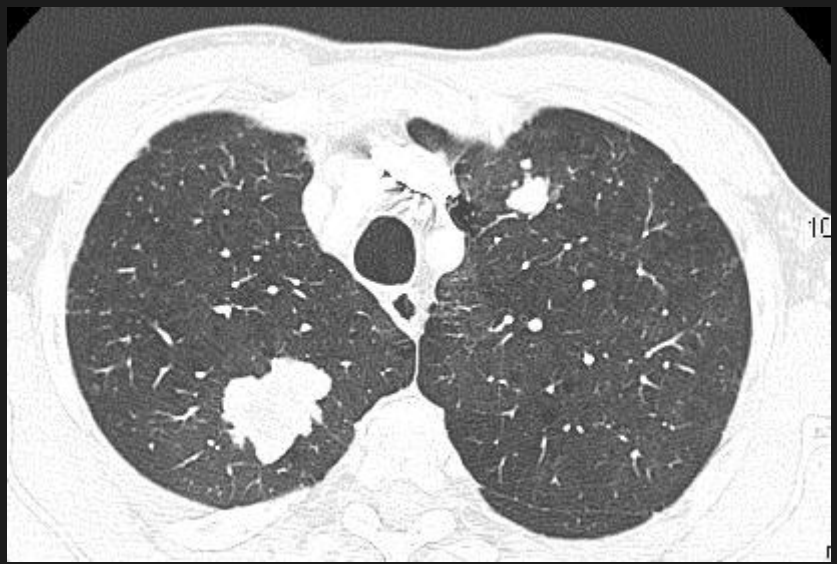
Ko et al GU Cancers Symposium 2014

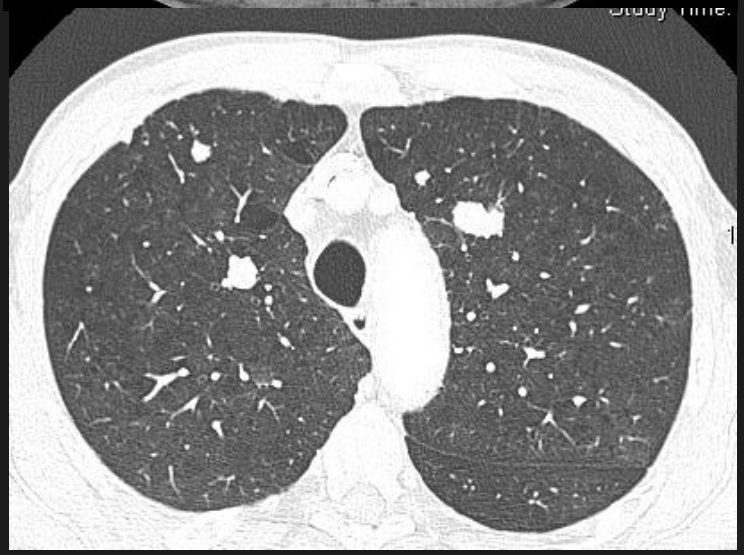
Ko et al GU Cancers Symposium 2014

Role of nephrectomy?

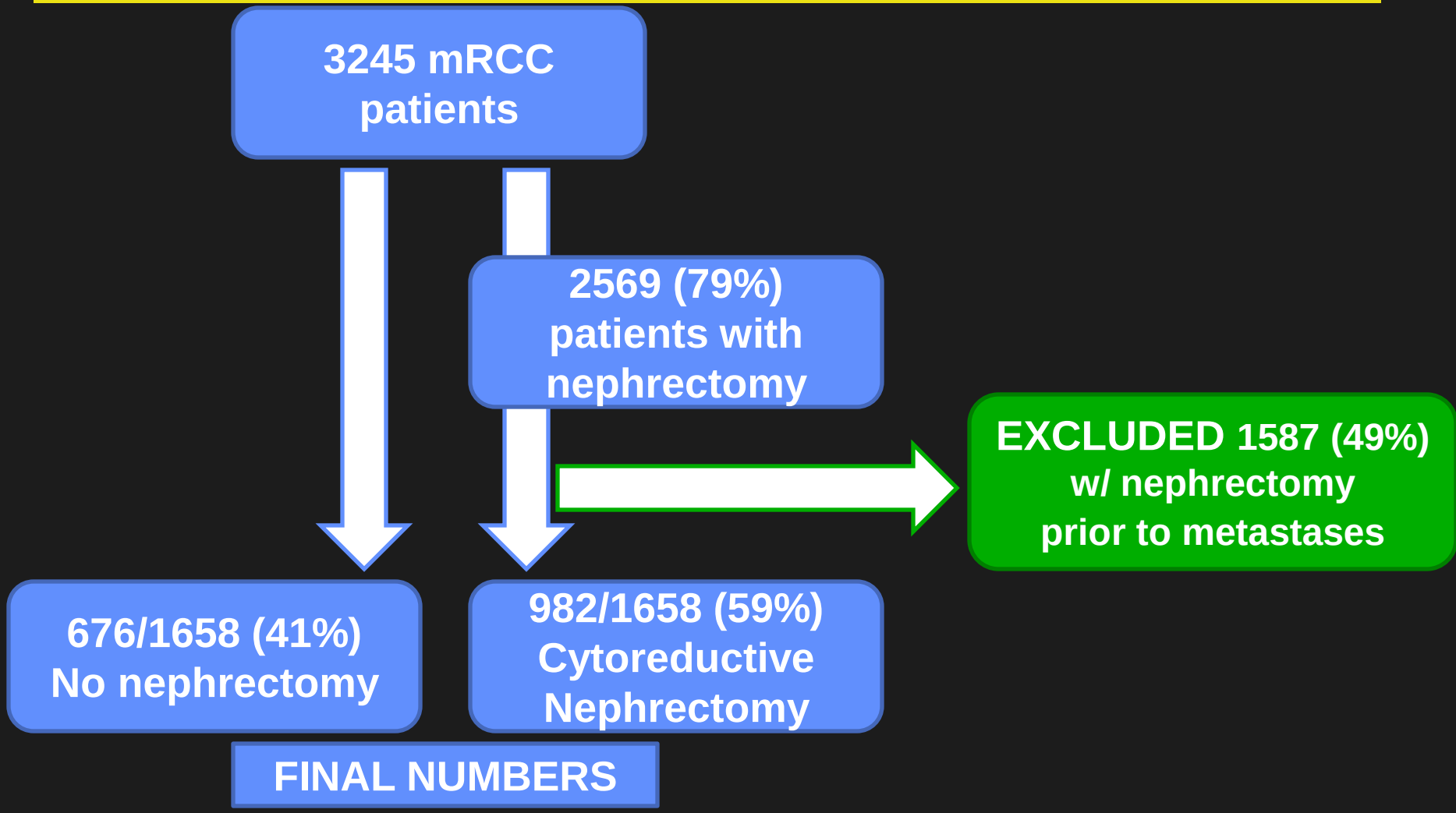






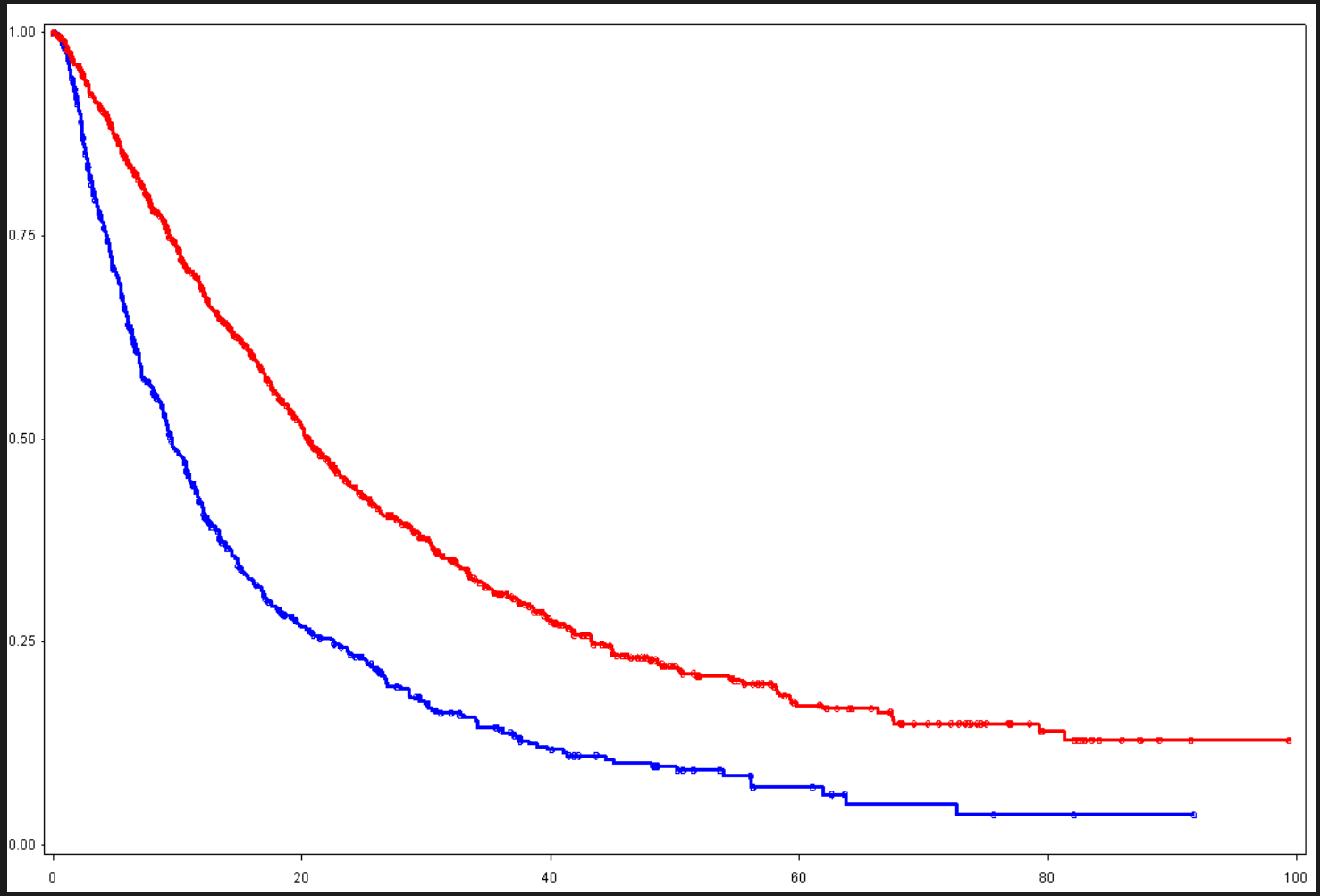


While expecting data from randomized trials…



Heng et al, GU ASCO 2014

Cytoreductive nephrectomy benefit?



IMDC prognostic factors are useful

# of IMDC Criteria Met	No CN OS months (N)	CN OS months (N)	P value
0	92% (65/71) patients had CN, insufficient number to compare		
1	22.5 (n=72)	30.4 (n=178)	0.0024
2	10.2 (n=143)	20.2 (n=253)	<0.0001
3	10.0 (n=113)	15.9 (n=106)	<0.0001
4	**5.4 (n=103)**	**6.0 (n=67)**	**0.1664**
5	**3.6 (n=36)**	**2.8 (n=14)**	**0.5044**
6	**25% (3/12) patients had CN, insufficient number to compare**		

ESMO 2014 guidelines

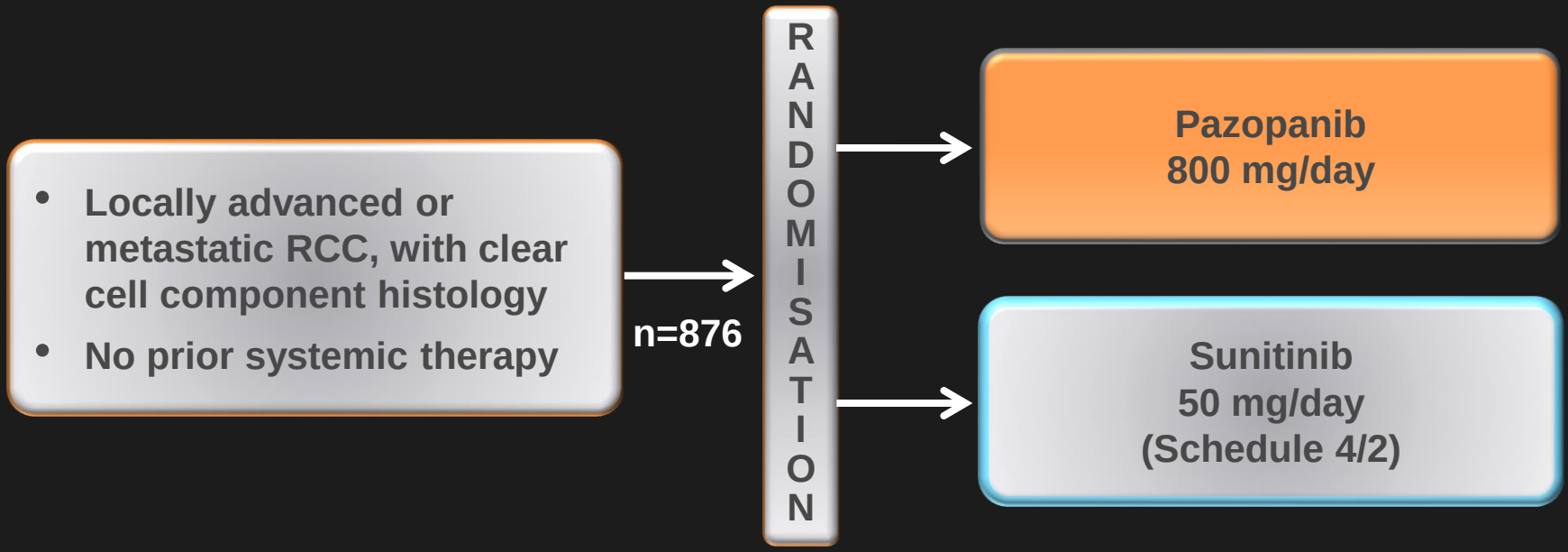
First line

Histology and setting	Risk group	Standard	Option
Clear-cell	Good / intermediate	Sunitinib [I, A] Bevacizumab + IFN [I, A] Pazopanib [I, A]	High dose IL2[III, C] Sorafenib [II, B] Bevacizumab + low dose IFN [III, B]

Escudier , Porta, Schmidinger et al Ann Oncol 2014

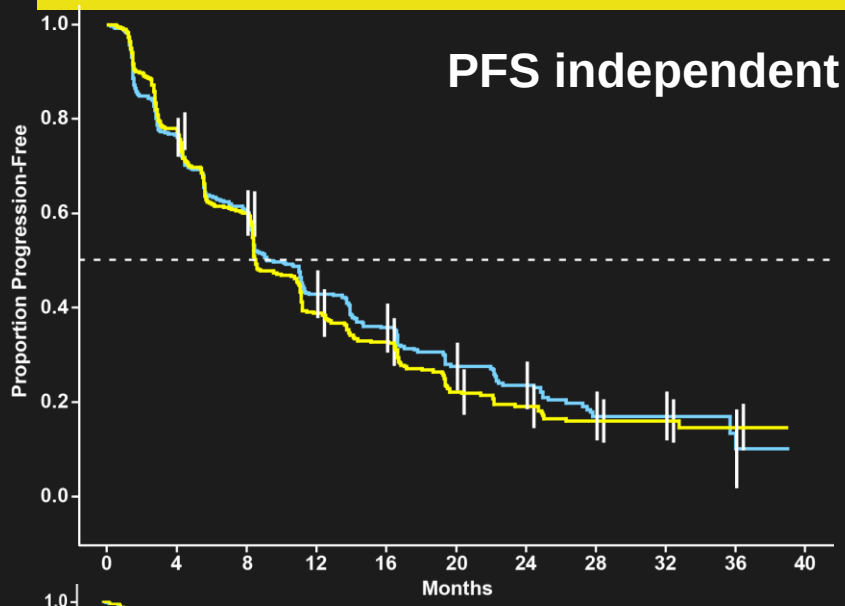
COMPARZ study

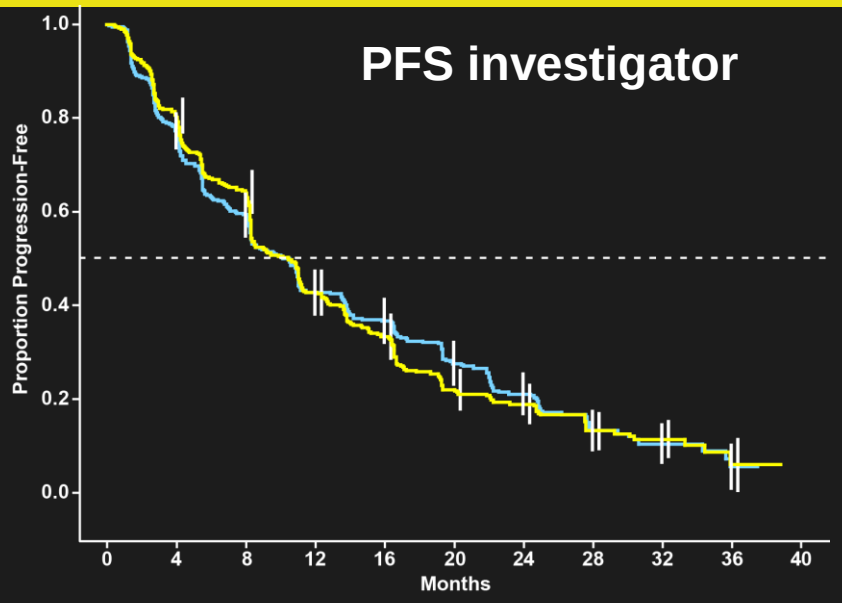
- **Sunitinib versus Pazopanib**

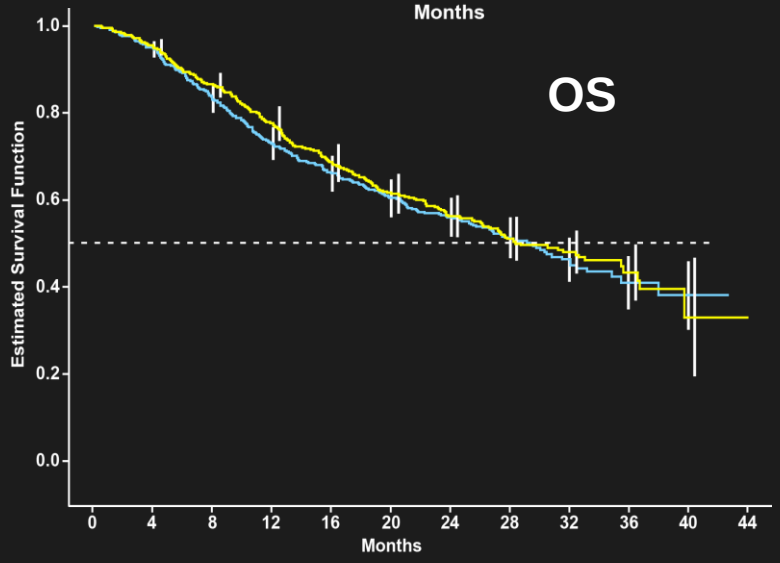


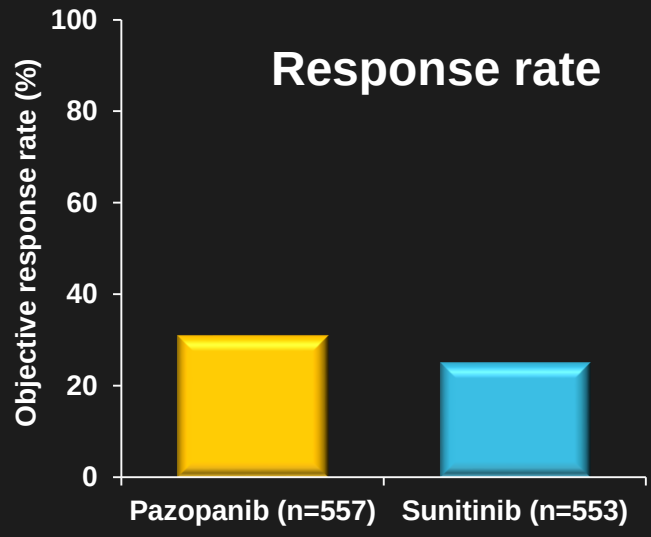
Motzer et al, NEJM 2013

Sunitinib vs Pazopanib: COMPARZ

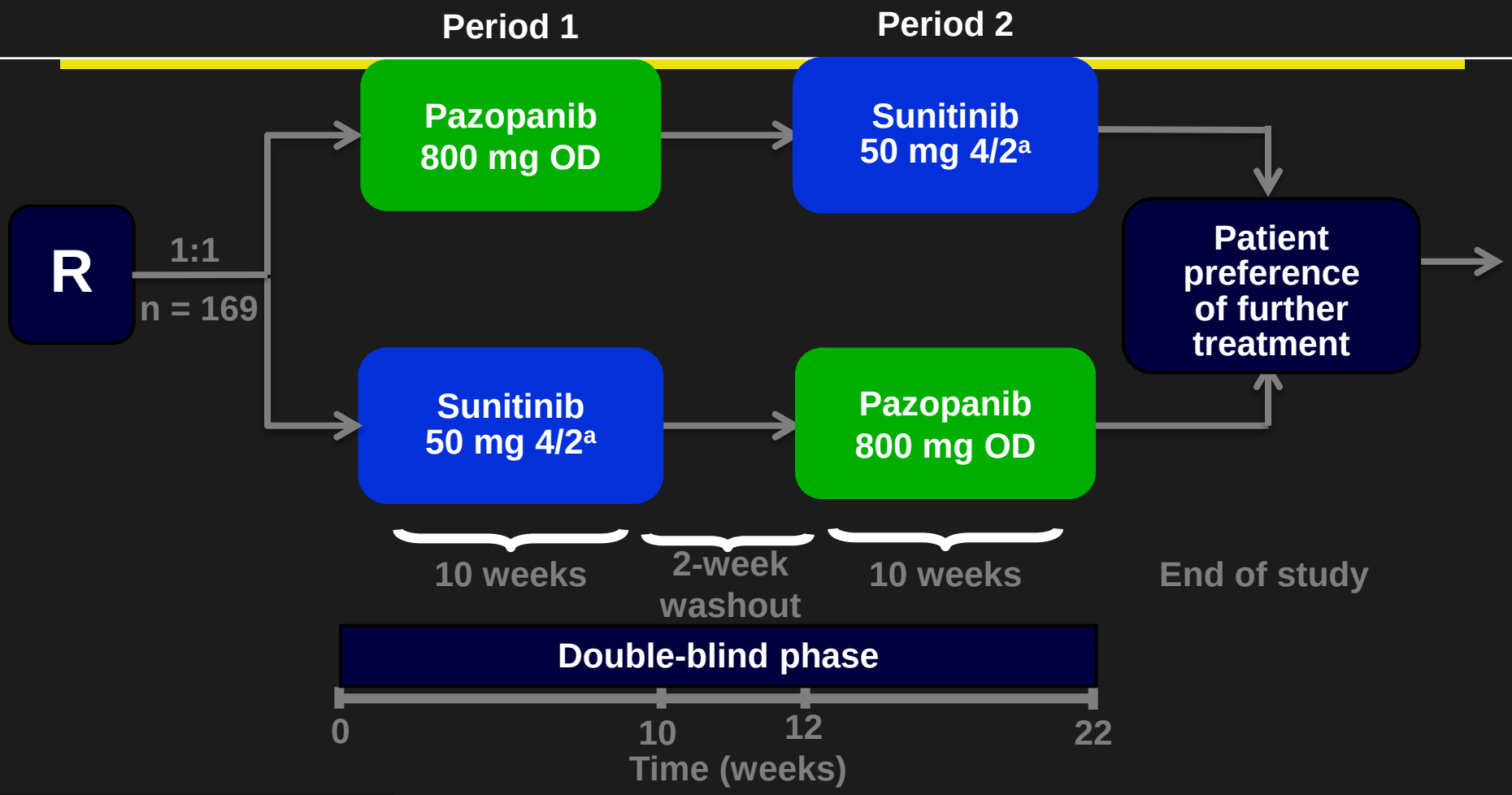








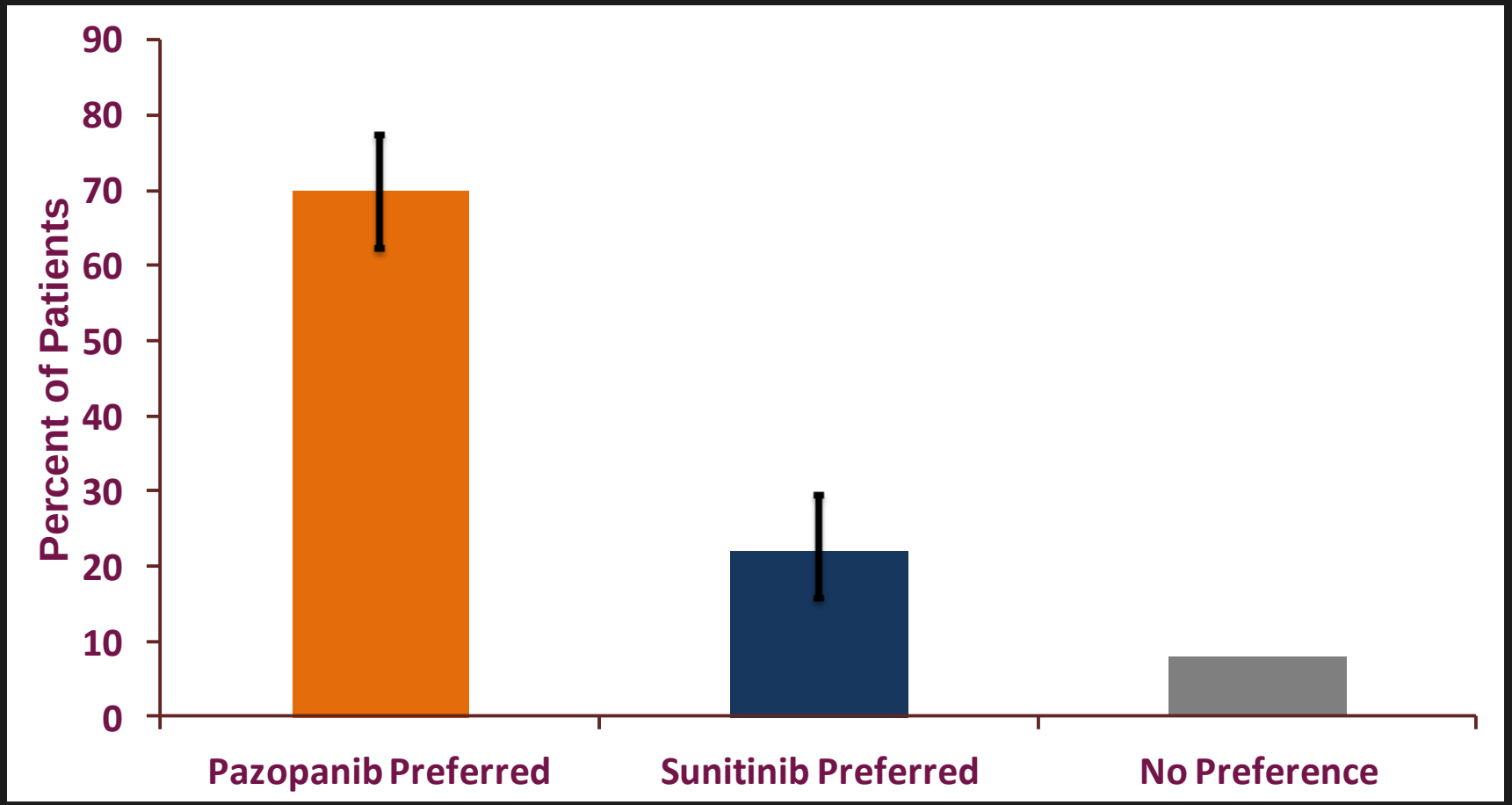
PISCES Design



Stratification factors:
- ECOG PS (0 vs 1)
- Metastatic sites (1 vs ≥ 2)

Escudier et al, JCO 2014

Patient preference in PISCES



Escudier et al, JCO 2014

ESMO 2014 guidelines

First line

Histology and setting	Risk group	Standard	Option
Clear-cell	Poor risk	Temsirolimus [II, A]	Sunitinib [II, B] Sorafenib [III, B]

Escudier , Porta, Schmidinger et al Ann Oncol 2014

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First line

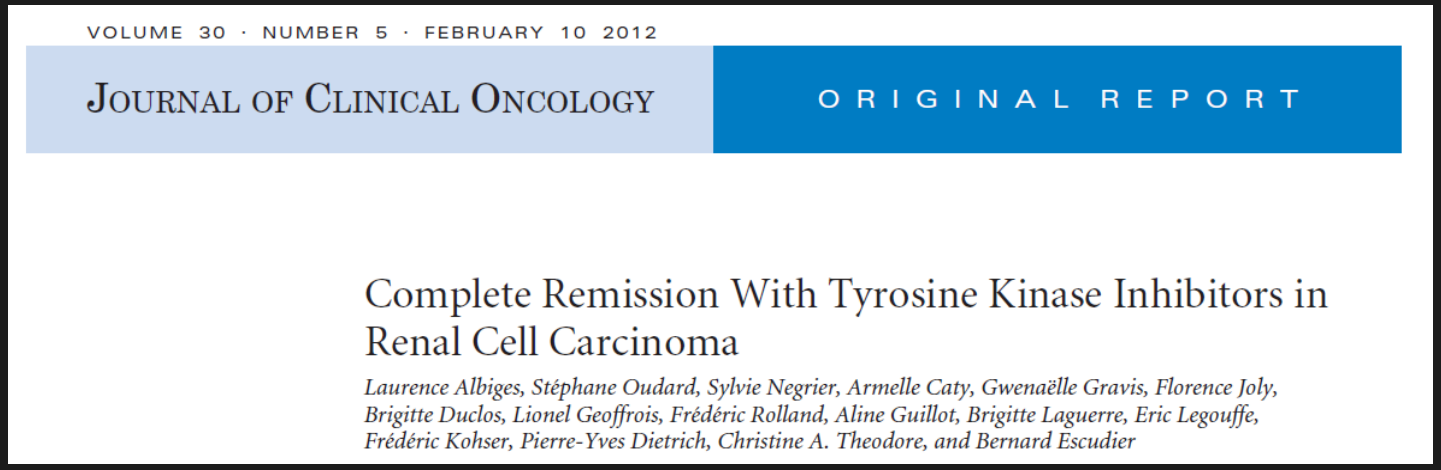
Histology and setting	Risk group	Standard	Option
Non Clear-cell			Temsirolimus [III, B] Sunitinib [III, B] Sorafenib [III, B]

Escudier , Porta, Schmidinger et al Ann Oncol 2014

When to stop therapy?

- What to do if CR occurs?

How to deal with CRs?



VOLUME 30 · NUMBER 5 · FEBRUARY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Complete Remission With Tyrosine Kinase Inhibitors in Renal Cell Carcinoma

Laurence Albiges, Stéphane Oudard, Sylvie Negrier, Armelle Caty, Gwenaëlle Gravis, Florence Joly, Brigitte Duclos, Lionel Geoffrois, Frédéric Rolland, Aline Guillot, Brigitte Laguerre, Eric Legouffe, Frédéric Kohser, Pierre-Yves Dietrich, Christine A. Theodore, and Bernard Escudier

- **Multicenter**
- **Retrospective analysis**

- **Patient developping CR**
  - **With VEGFR-TKI alone**
  - **With VEGFR-TKI plus local treatment**

- **Double radiological review**

Patient characteristics

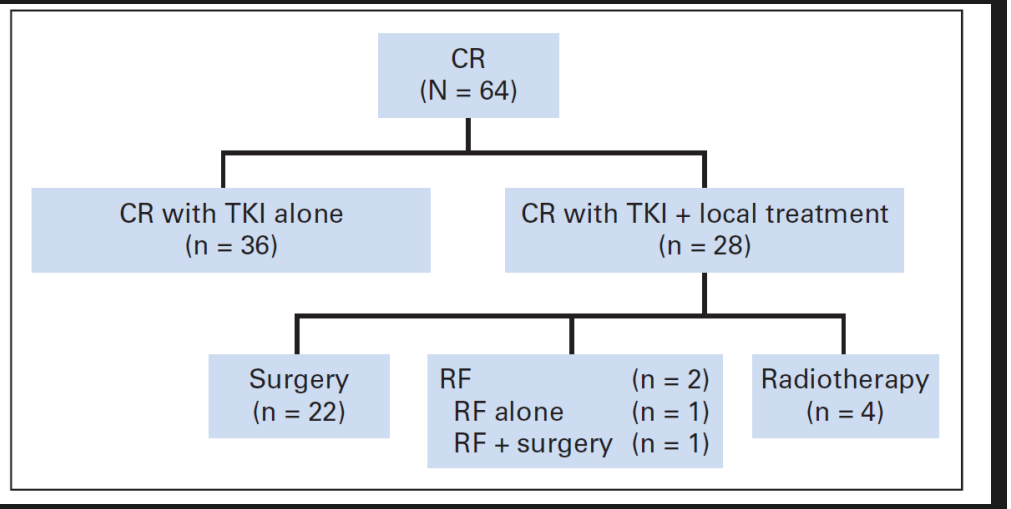
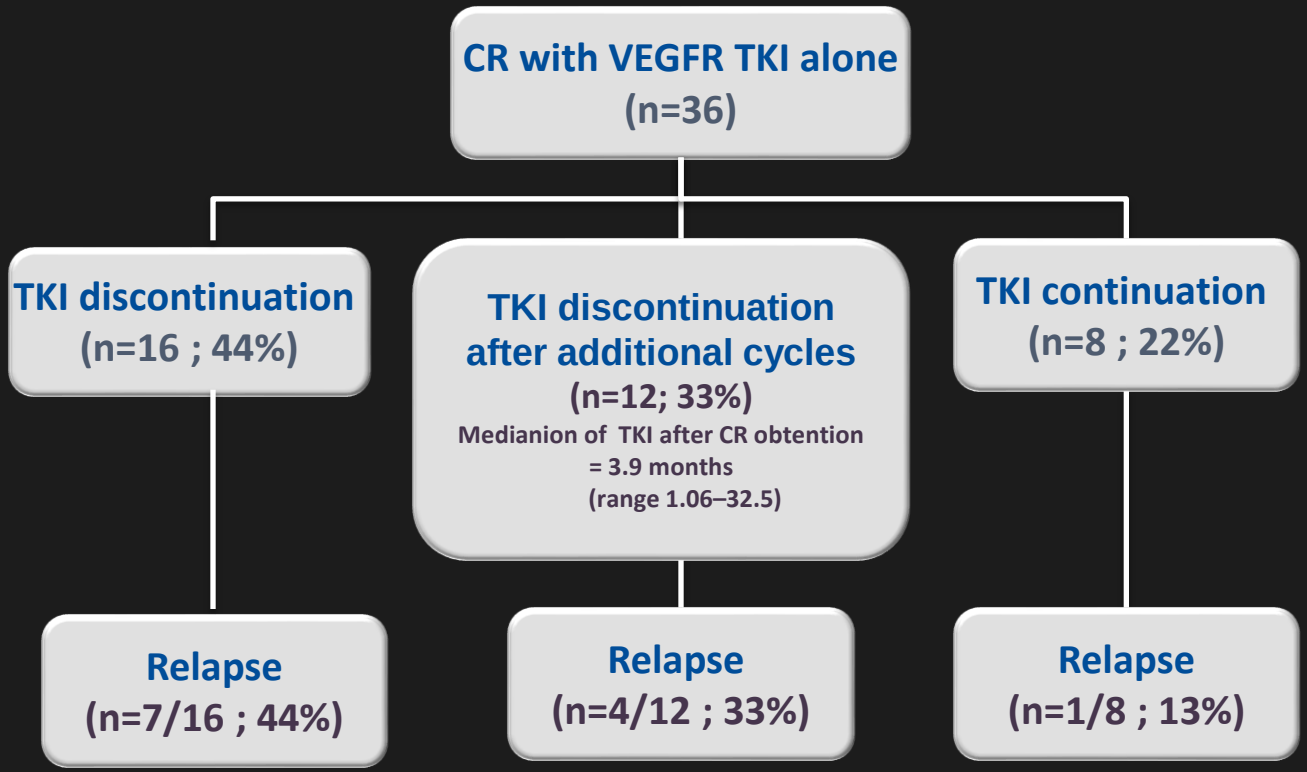


Table 1. Patient Clinical Characteristics

Characteristic	No. of Patients	%
Treatment		
TKI alone	36	56
TKI plus local treatment	28	44
Histology		
Clear cell	60	94
Papillary	4	6
Prior nephrectomy	64	100
Prior treatment		
None	36	56
Cytokine	18	28
Local treatment: surgery/radiotherapy	8	13
Prior TKI	2	3
TKI achieving CR		
Sunitinib	59	92
Sorafenib	5	8
Prognostic group (French classification)		
Favorable	22	34
Intermediate	39	61
Poor	3	5
No. of metastatic sites before TKI		
1	26	41
2	23	36
≥ 3	15	23

Abbreviations: CR, complete remission; TKI, tyrosine kinase inhibitor.

CRs with TKIs alone



Should we continue TKIs if CR ?

- Only half of the patients relapse at 18 months
- Rechallenge is almost always active
- Thus, current attitude in France:
  - If CR with systemic treatment only, continue for 2-3 months to confirm CR and stop
  - If CR with systemic + local treatment, stop after local treatment

When to stop therapy?

- What to do if CR occurs?

- Is it possible to propose drug holiday?

Drug holiday is feasible

- In selected patients
- Preliminary experience reported:
  - Sadeghi et al, Cancer. 2012 Jul 1;118(13):3277-82
  - Update at ASCO 2014 (Mital et al, ASCO 2014)

- 112 patients, with period of drug cessation > 3 months

Mital et al, ASCO 2014

Patient population

- 75% male/ 25% female
- Median age at diagnosis: 56
- 95% clear cell histology
- 19% pts. had received prior systemic therapy
- By Heng criteria, 48% pts. were favorable, 48% intermediate and 4% poor risk.

Mital et al, ASCO 2014

Results

- For the first treatment break: (n=112)
  - Median duration on first line: 13.5 months
  - Median duration of break: 16.8 months

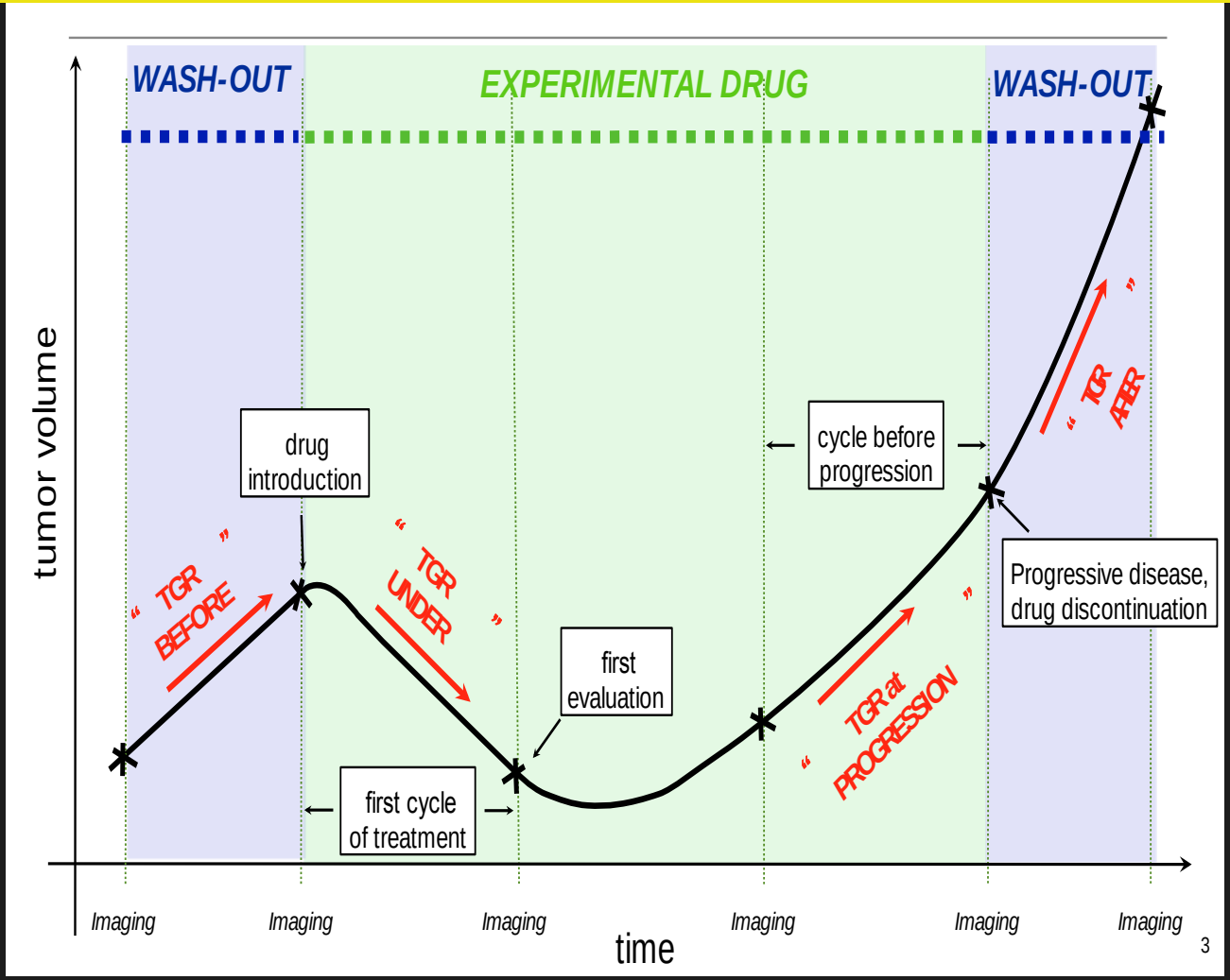
- For second break (n=68)
  - Median duration on first line: 16.1 months
  - Median duration of break: 9.5 months

Mital et al, ASCO 2014

When to switch to second line?

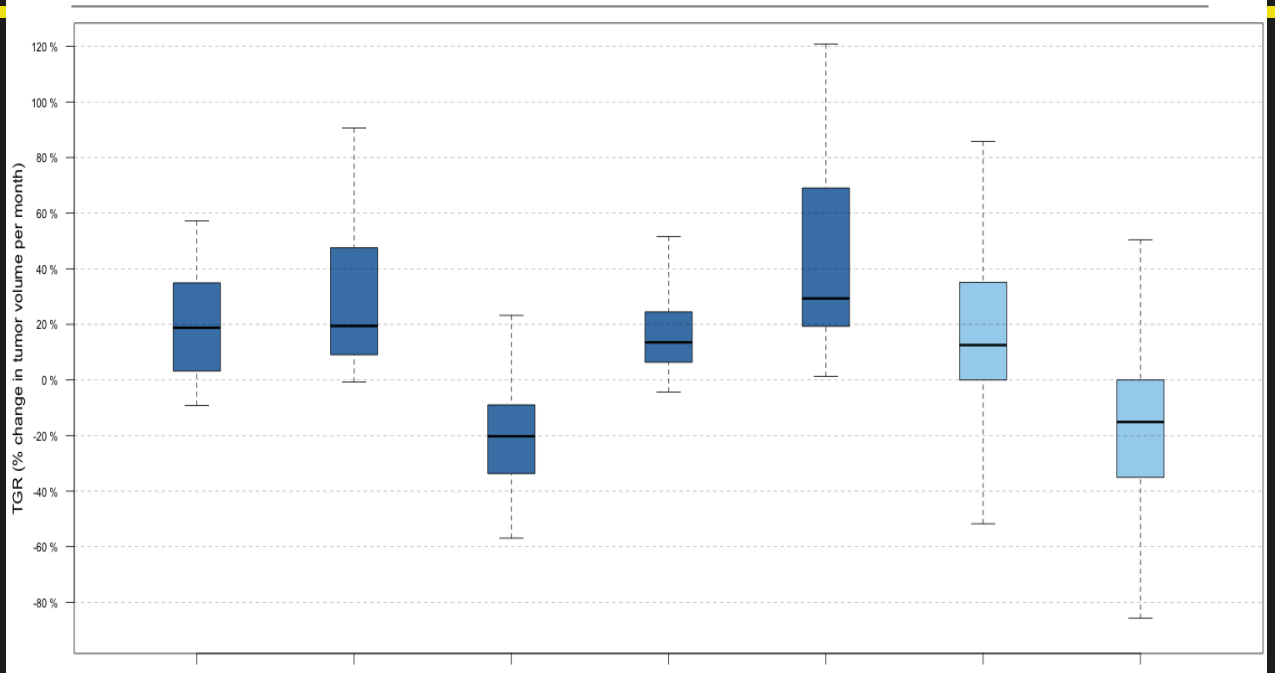
- RECIST progression is not a good choice
- When VEGF inhibition is interrupted, tumor growth increases

Change in tumor growth rate



Ferté et al, Eur Urol 2013

Distribution of TGR in Sorafenib-treated patients according to treatment periods



	PLACEBO (first cycle) n=25	BEFORE receiving Sorafenib (wash-out) n=29	UNDER Sorafenib (first cycle) n=59	at PROGRESSION (still receiving Sorafenib) n=49	AFTER Sorafenib discontinuation (wash-out) n=17
median TGR	18.77	19.42	-20.26	13.51	29.31
CI-95%	13.10 24.43	4.09 34.26	-26.01 -14.51	8.76 18.26	9.80 48.82

(post cross-over data)

	PLACEBO (first cycle) n=451	UNDER Sorafenib (first cycle) n=451
median TGR	12,72	-15.51
CI-95%	6.90 18.54	-19.72 -11.29

(pre cross-over data)

Ferté et al, Eur Urol 2013

When to switch to second line?

- RECIST progression is not a good choice
- When VEGF inhibition is interrupted, tumor growth increases
- **Thus, switching should be proposed if second line treatment is active enough (and available)….**
  - **Primary refractory disease**
  - **New site of disease associated with RECIST PD**
  - **Rapidly progressive disease**

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Second line

Histology and setting	Risk group	Standard	Option
Clear-cell	Post cytokines	Axitinib [I, A] Sorafenib [I, A] Pazopanib [II, A]	Sunitinib [III, A]

Escudier , Porta, Schmidinger et al Ann Oncol 2014

ESMO 2014 guidelines

Second line

Histology and setting	Risk group	Standard	Option
Clear-cell	Post cytokines	Axitinib [I, A] Sorafenib [I, A] Pazopanib [II, A]	Sunitinib [III, A]
	Post TKIs	**Axitinib [I, B]** **Everolimus [II, A]**	**Sorafenib [II, A]**

Escudier , Porta, Schmidinger et al Ann Oncol 2014

ESMO 2014 guidelines

Third line

Histology and setting	Risk group	Standard	Option
Clear-cell	Post 2 TKIs	Everolimus [II, A]	

Escudier , Porta, Schmidinger et al Ann Oncol 2014

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Third line

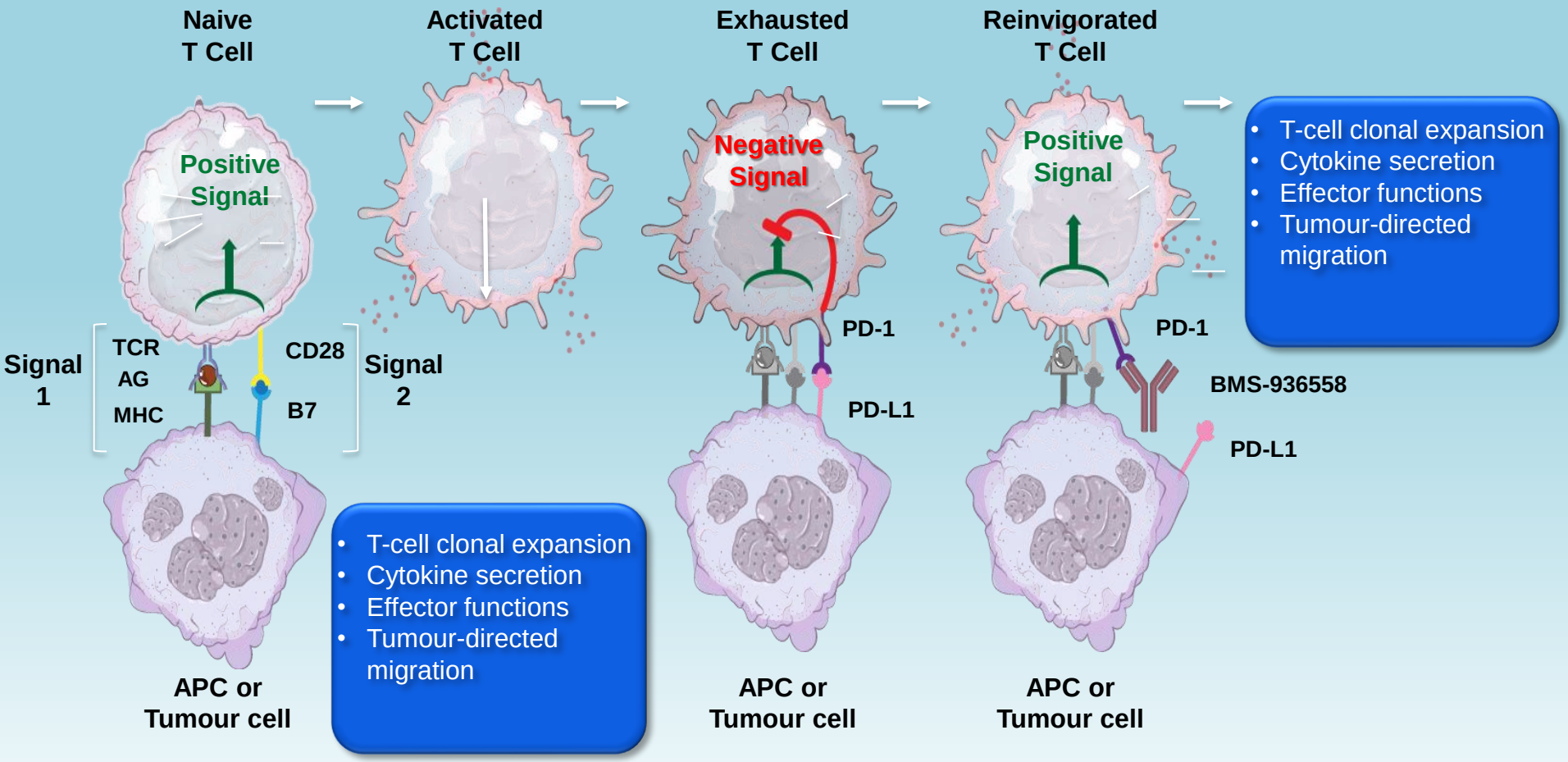
Histology and setting	Risk group	Standard	Option
Clear-cell	Post 2 TKIs	**Everolimus [II, A]**	
	Post TKI and mTOR	**Sorafenib [I, B]**	**Other TKI [IV, B]** **Rechallenge [IV, B]**

Escudier , Porta, Schmidinger et al Ann Oncol 2014

The future of RCC treatment

- Check point inhibitors
- cMET inhibitors

PD-1 Blockade as a Strategy for Cancer Immunotherapy

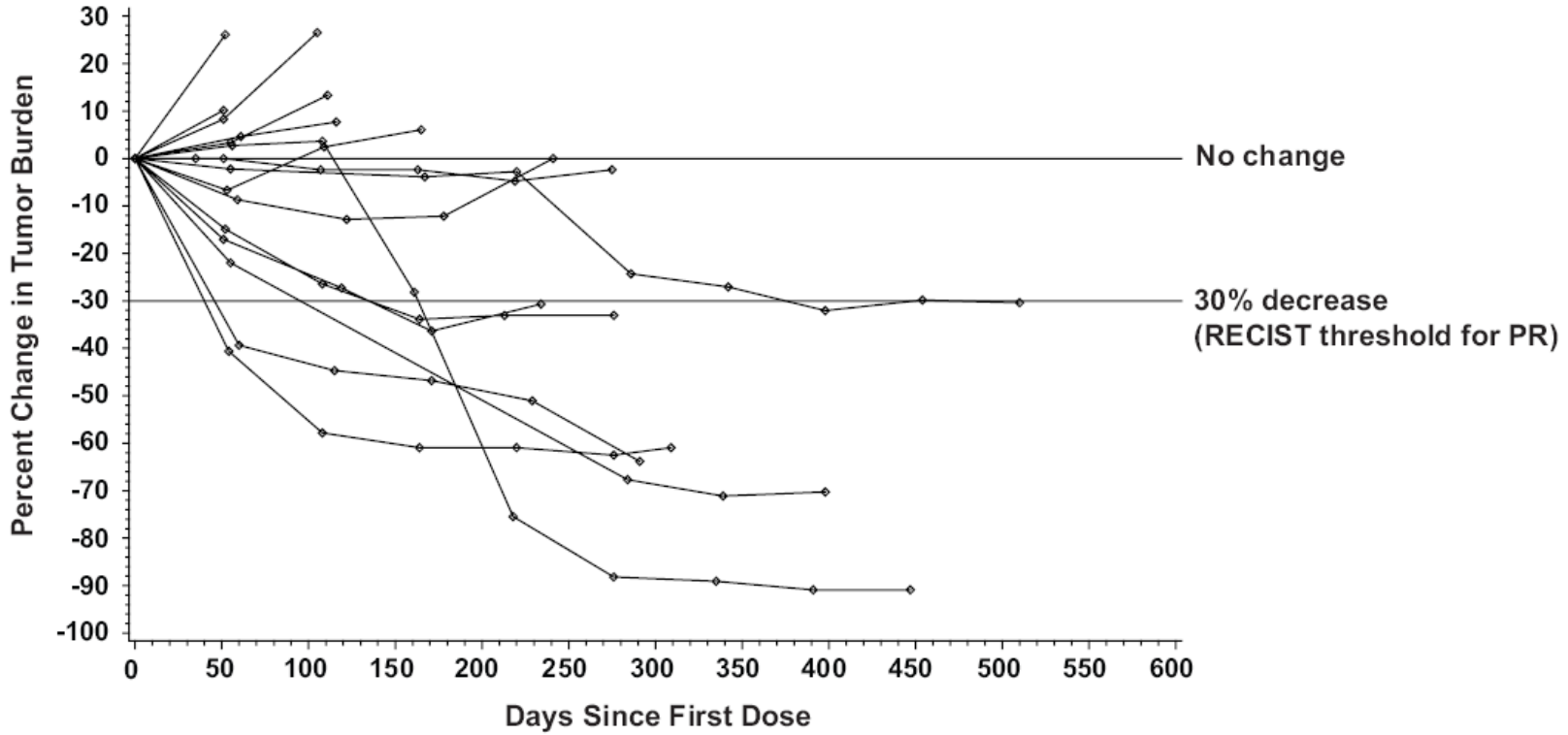


AG, antigen; APC, antigen presenting cell; MHC, major histocompatibility complex; PD-1, programmed death-1; TCR, T-cell receptor.

Adapted from Brahmer JR et al. *J Clin Oncol*. 2010;28:3167-3175 and Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704.

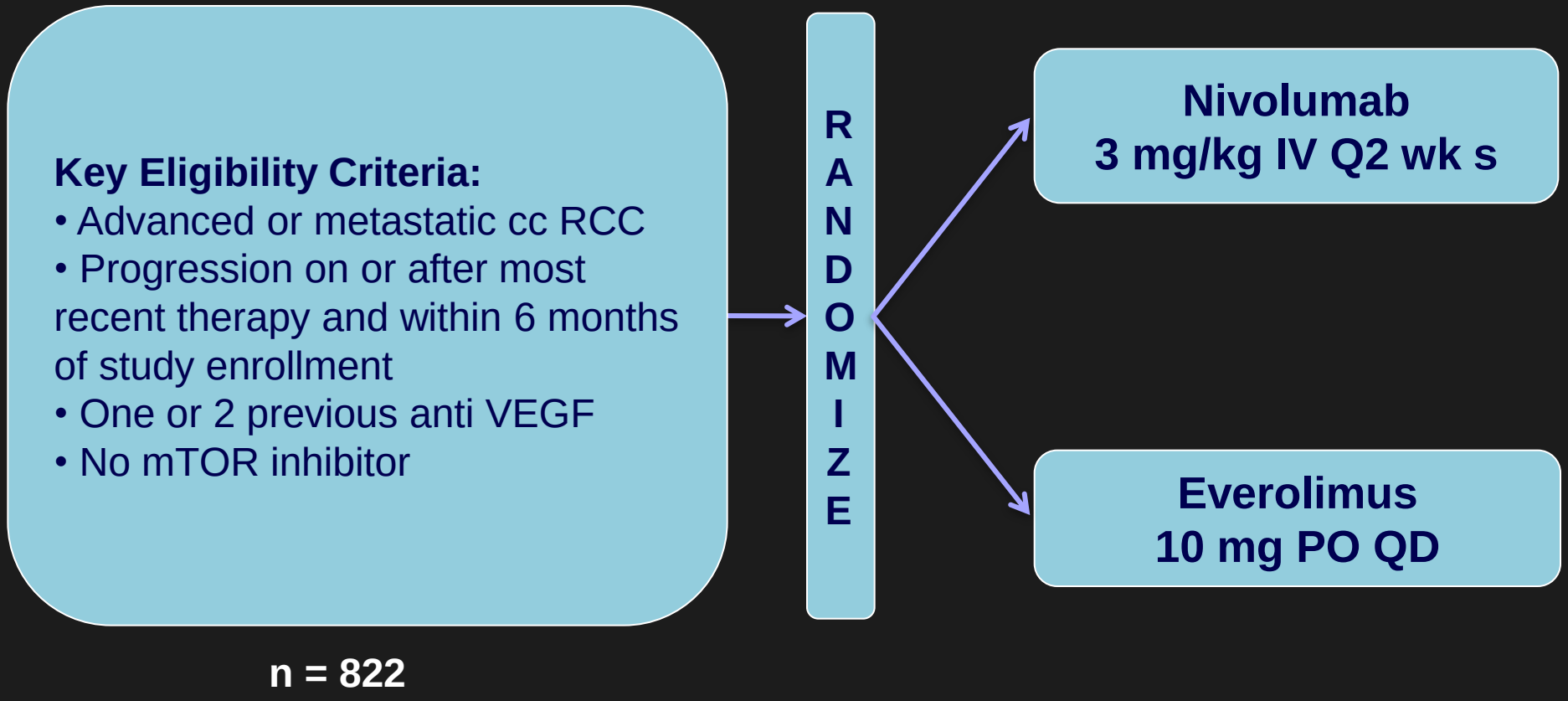
Promising efficacy in RCC

Figure 3. Percent change in tumor burden in RCC patients*



*Patients treated at the 10 mg/kg dose

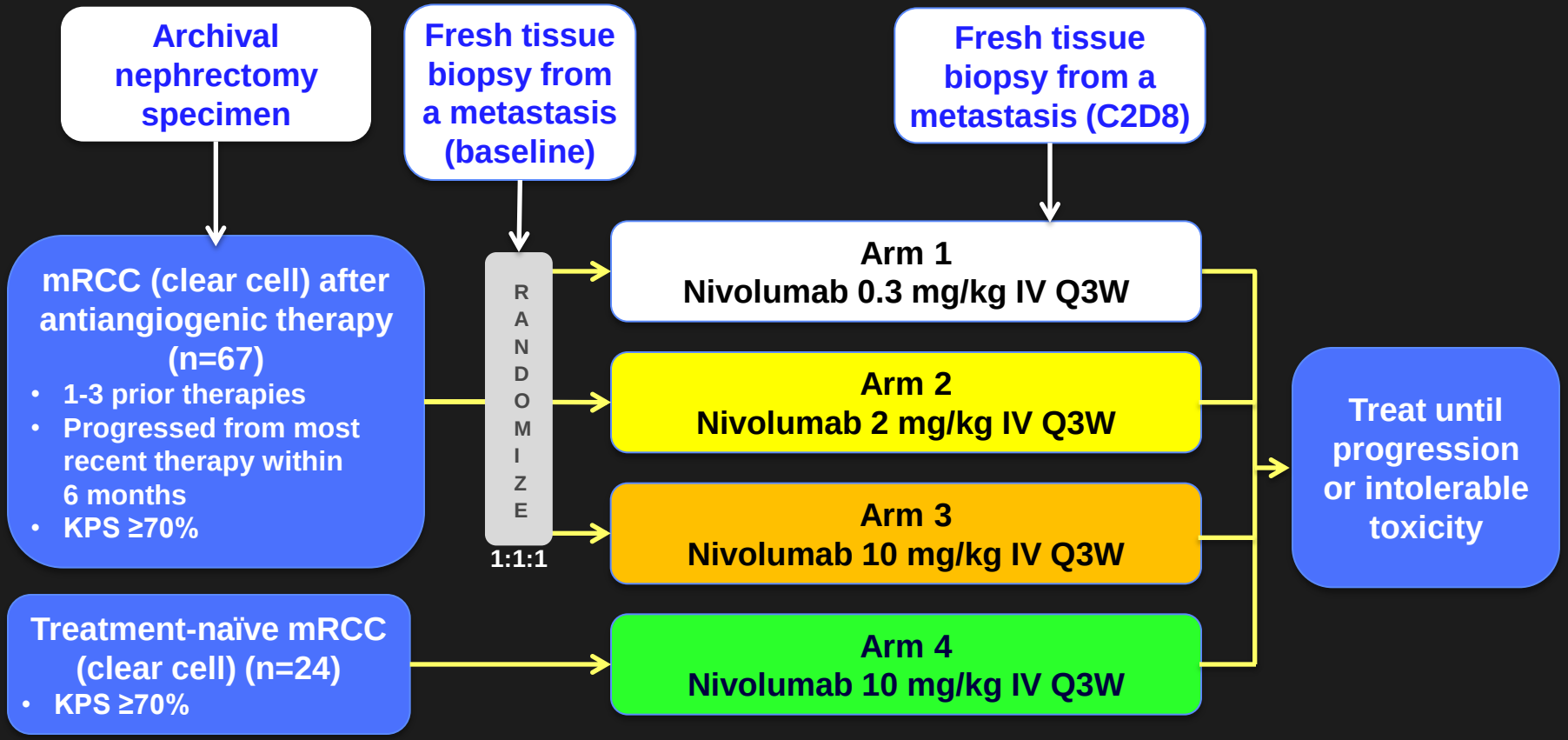
Ongoing phase 3



n = 822

Primary endpoint: Overall Survival

First line data are limited



Choueiri et al, ASCO 2014

Are treatment naive patients better candidates?

	Previously treated (n=67)		
	Nivolumab 0.3 mg/kg (n=22)	**Nivolumab 2.0 mg/kg (n=22)**	**Nivolumab 10 mg/kg (n=23)**
Objective response rate, n (%); (95% CI)[a]	2 (9) (1.1-29.2)	5 (23) (7.8-45.4)	5 (22) (7.5-43.7)
Best response, n (%)			
Partial response (PR)	2 (9)	5 (23)	4 (17)
Unconfirmed PR	0	0	1 (4)
Stable disease (SD)	5 (23)	6 (27)	8 (35)
Progression-free survival rate, % (95% CI)			
24 weeks	18 (6-36)	32 (14-51)	49 (27-68)

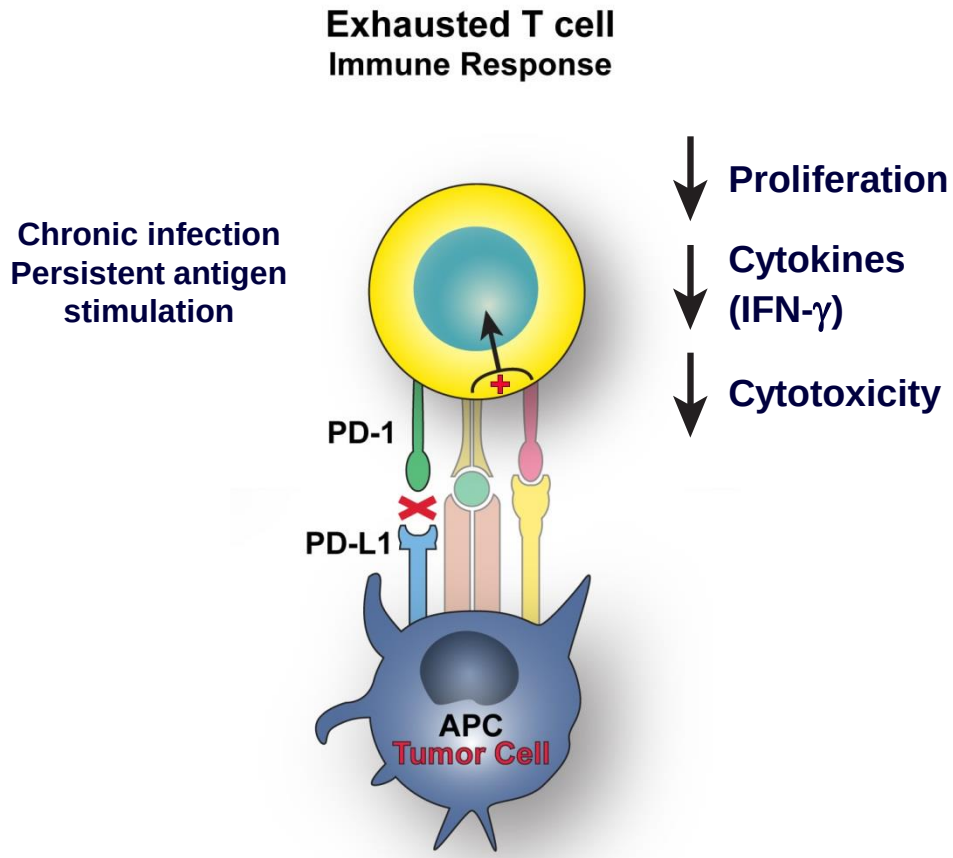
Choueiri et al, ASCO 2014

Are treatment naive patients better candidates?

	Previously treated (n=67)			Treatment-naïve (n=23)	All (N=90)[b]
	Nivolumab 0.3 mg/kg (n=22)	Nivolumab 2.0 mg/kg (n=22)	Nivolumab 10 mg/kg (n=23)	Nivolumab 10 mg/kg (n=23)	
Objective response rate, n (%); (95% CI)[a]	2 (9) (1.1-29.2)	5 (23) (7.8-45.4)	5 (22) (7.5-43.7)	3 (13) (2.8-33.6)	**15 (17) (9.6-26.0)**
Best response, n (%)					
Partial response (PR)	2 (9)	5 (23)	4 (17)	3 (13)	**14 (16)**
Unconfirmed PR	0	0	1 (4)	0	**1 (1)**
Stable disease (SD)	5 (23)	6 (27)	8 (35)	10 (43)	**29 (32)**
Progression-free survival rate, % (95% CI)					
24 weeks	18 (6-36)	32 (14-51)	49 (27-68)	45 (24-64)	**36 (26-46)**

No signal that first line efficacy will be better

Biomarker to select patients?



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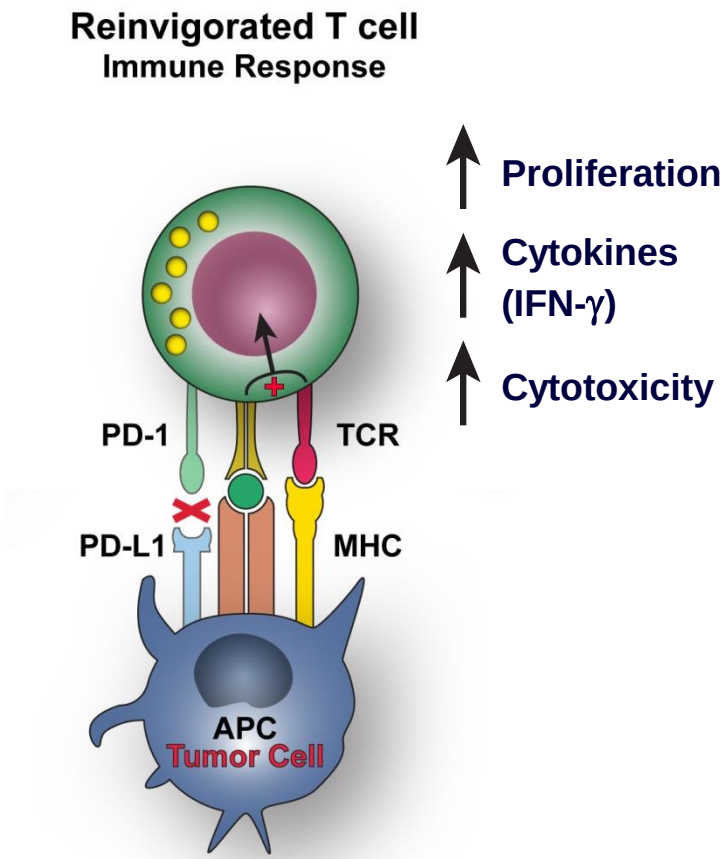
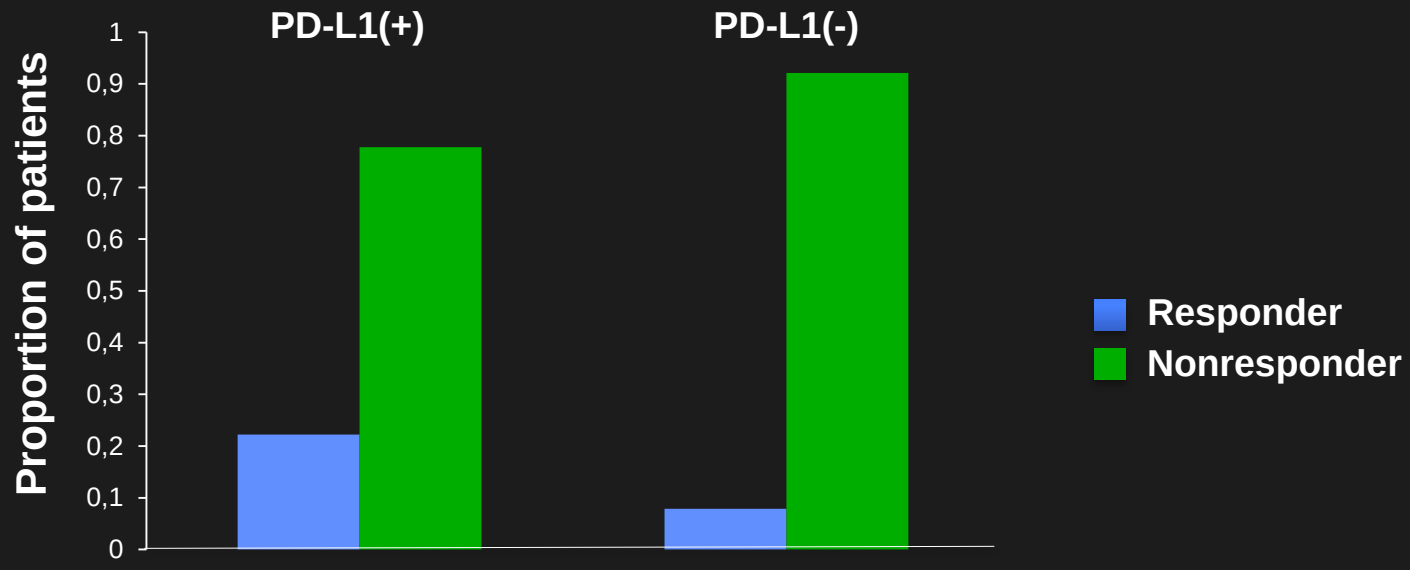


Response according to PD-L1 status by IHC

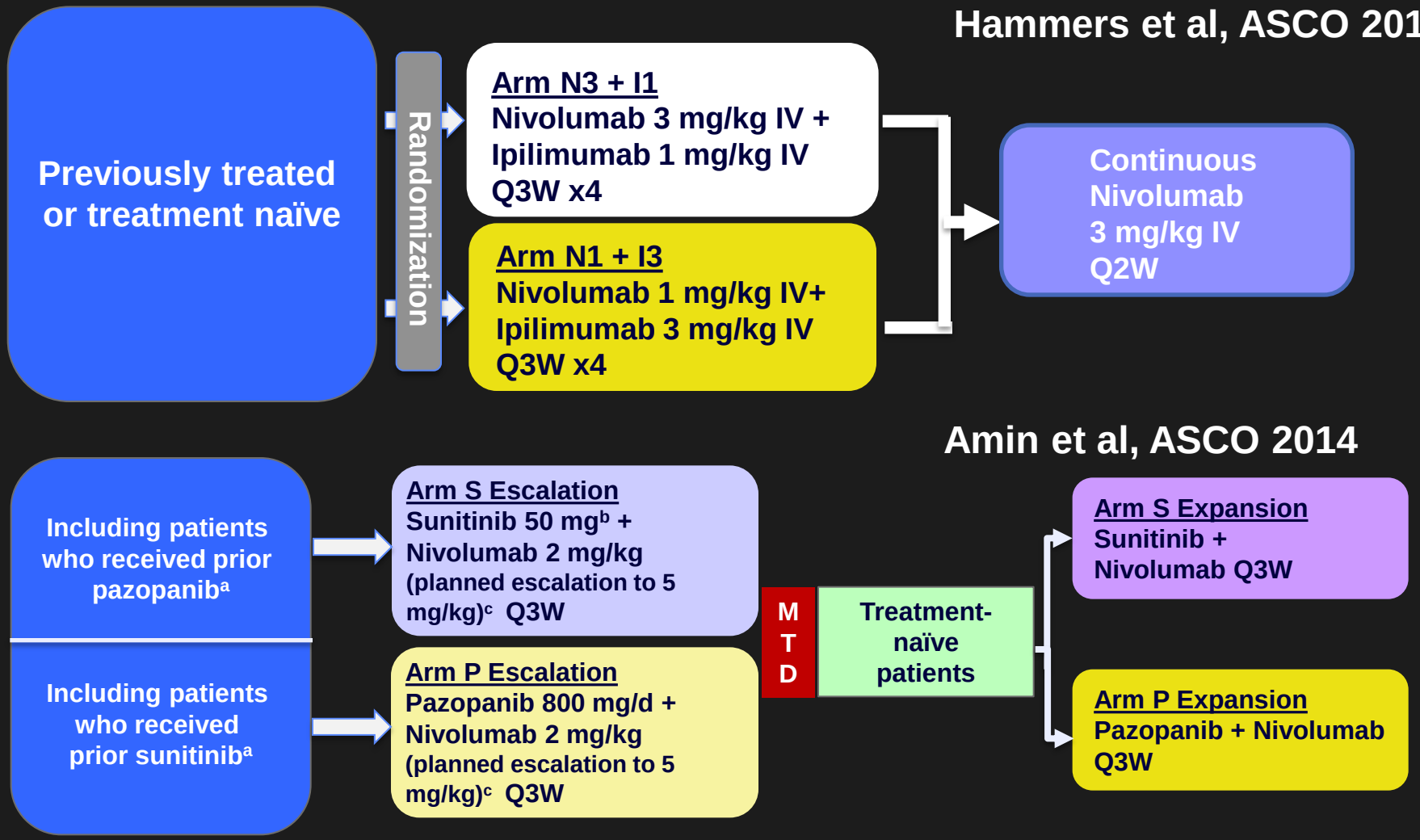
- 56 evaluable fresh pretreatment biopsies:
  - Minimum of 100 tumor cells (DAKO assay; antibody 28-8)
  - PD-L1+ specimens defined by plasma membrane staining on ≥5% of tumor cells
  - 18 of 56 (32%) samples were PD-L1+



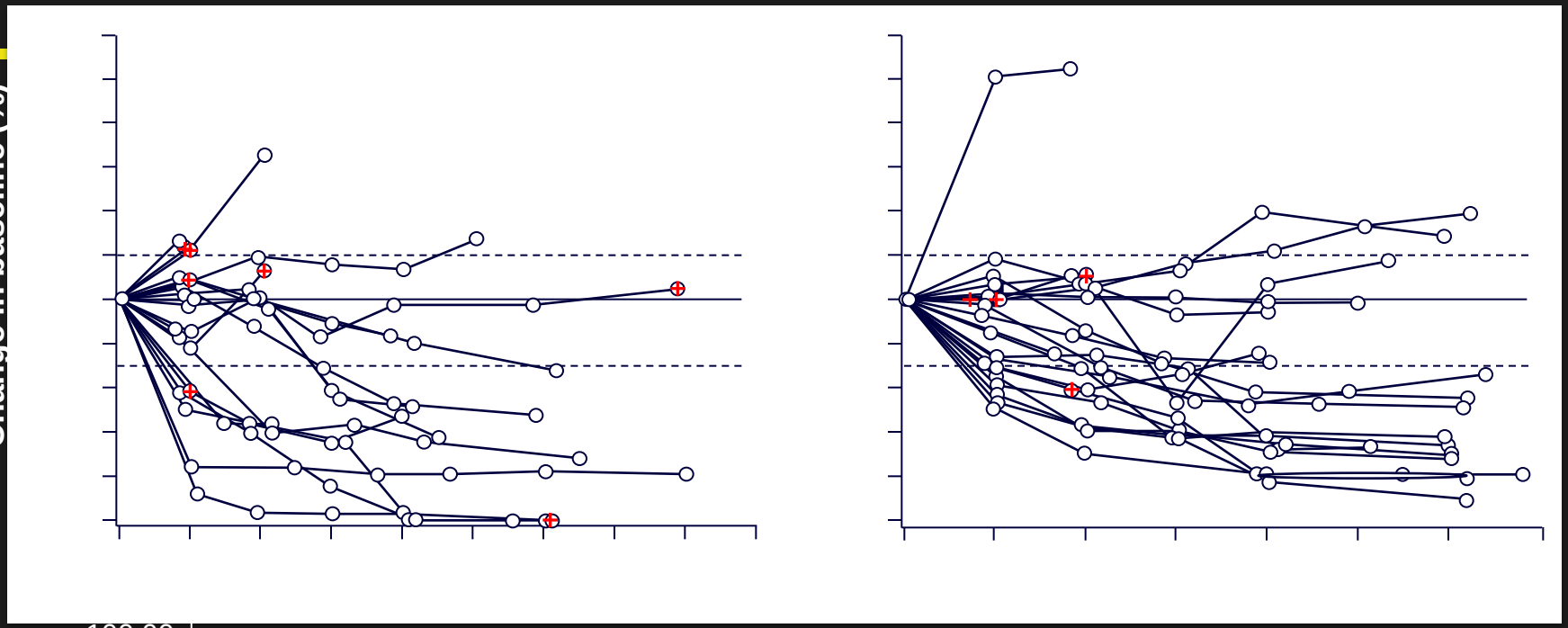
Response rate: 4/18 (22%) 3/38 (8%)

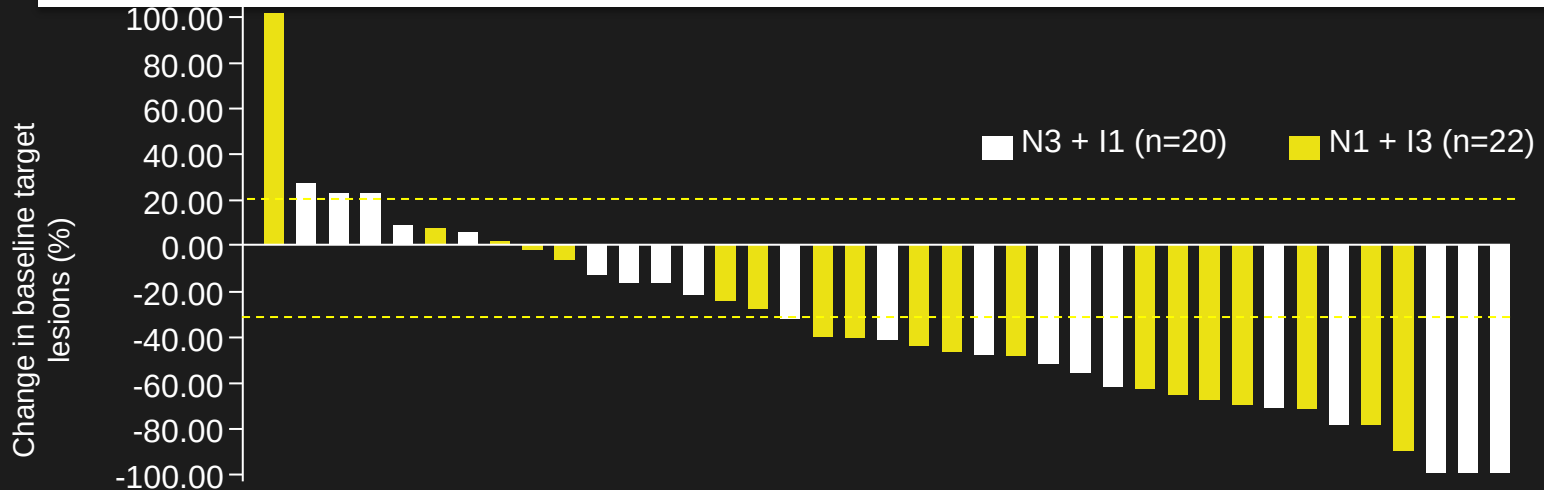
- 81% (22/27) of matched fresh specimens showed a <5% increase in tumor membrane PD-L1 expression from baseline to C2D8

Monotherapy or combination?

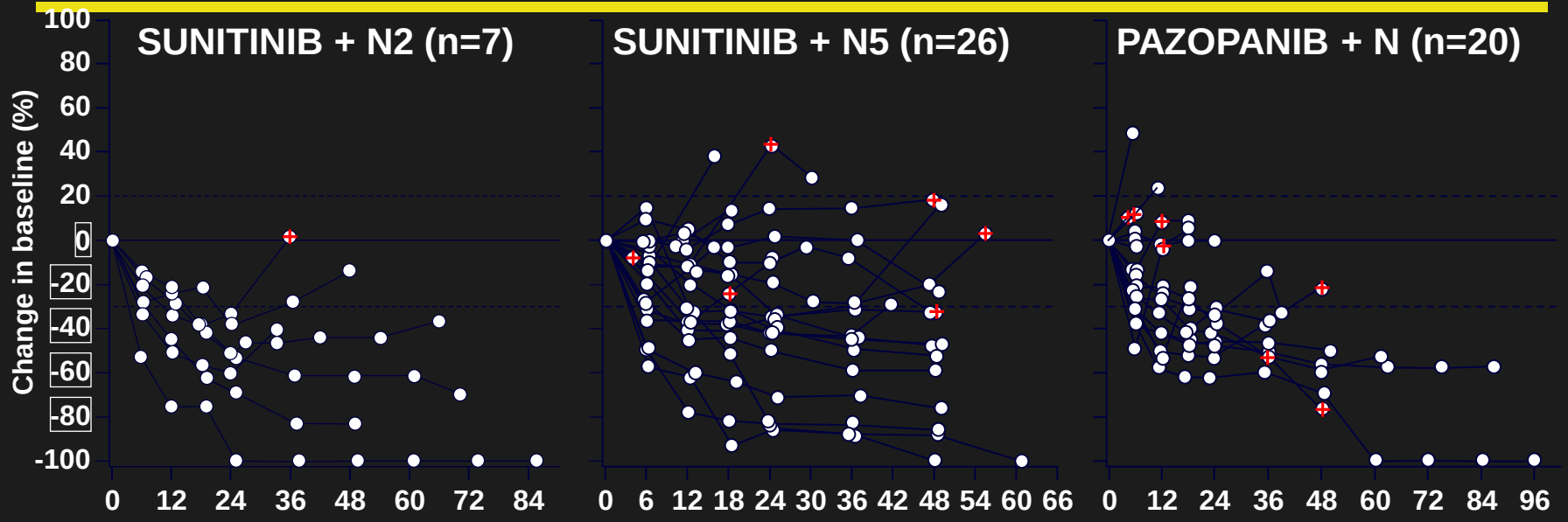


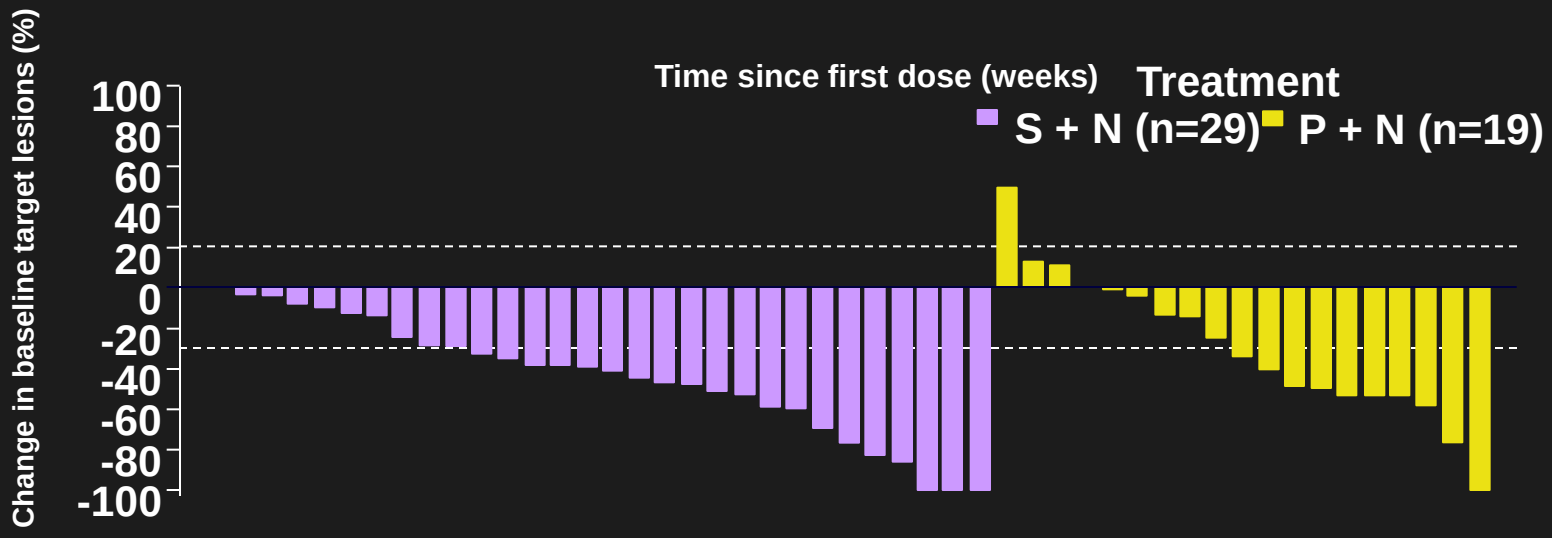
Combination Nivoliumab + Ipilimumab





Combination Nivolumab + TKIs





Is there any ideal combination?

	ARM S Sunitinib + nivolumab	Arm P Pazopanib 800 mg QD +nivolumab 2 mg/kg Q3W (N2)	(N3+I1) Nivolumab 3mg/kg + **Ipilimumab** 1mg/kg	(N1 +I3) Nivolumab 1mg/kg + ipilimumab 3mg/kg
Prior therapy	42% prior therapy	100%	77% prior therapy	
Nb.	n=33	n=20	n=21	n=23
MSKCC risk	Favorable/Intermediate (95%)		Favorable/Intermediate (100%)	
ORR (%)	**52%**	**45%**	**43%**	**48%**
Median DOR range (wks)	54 18.1-80	45 23.1-68.5	31.1 4.1+ – 42.1+	NR 12.1+ – 35.1+
Median PFS (wks)	**48.9**	**31.4**	**36.6**	**38.3**
Gr. 3/4 Toxicity (%)	**24/33 (73%)**	**12/20 (60%)**	**5/21 (24%)**	**14/23 (61%)**
	ALT elevation 18% Hypertension 18% Hyponatremia 15%	**4 DLTs (stopped)** (LFTs=3)	**ALT elevation 0% Diarrhea 4.8% Fatigue 0%**	**ALT elevation 26% Diarrhea 13% Fatigue 8%**

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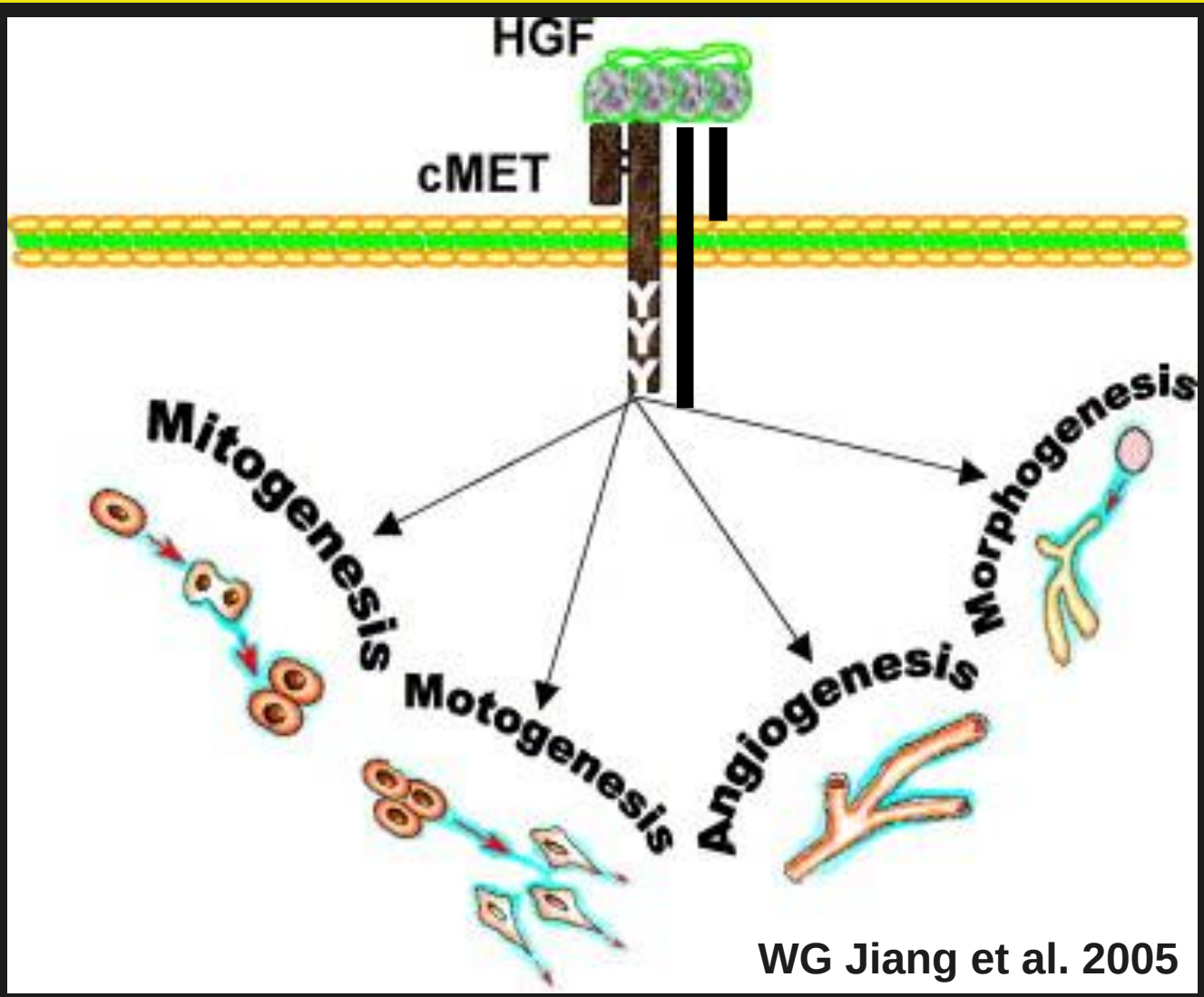
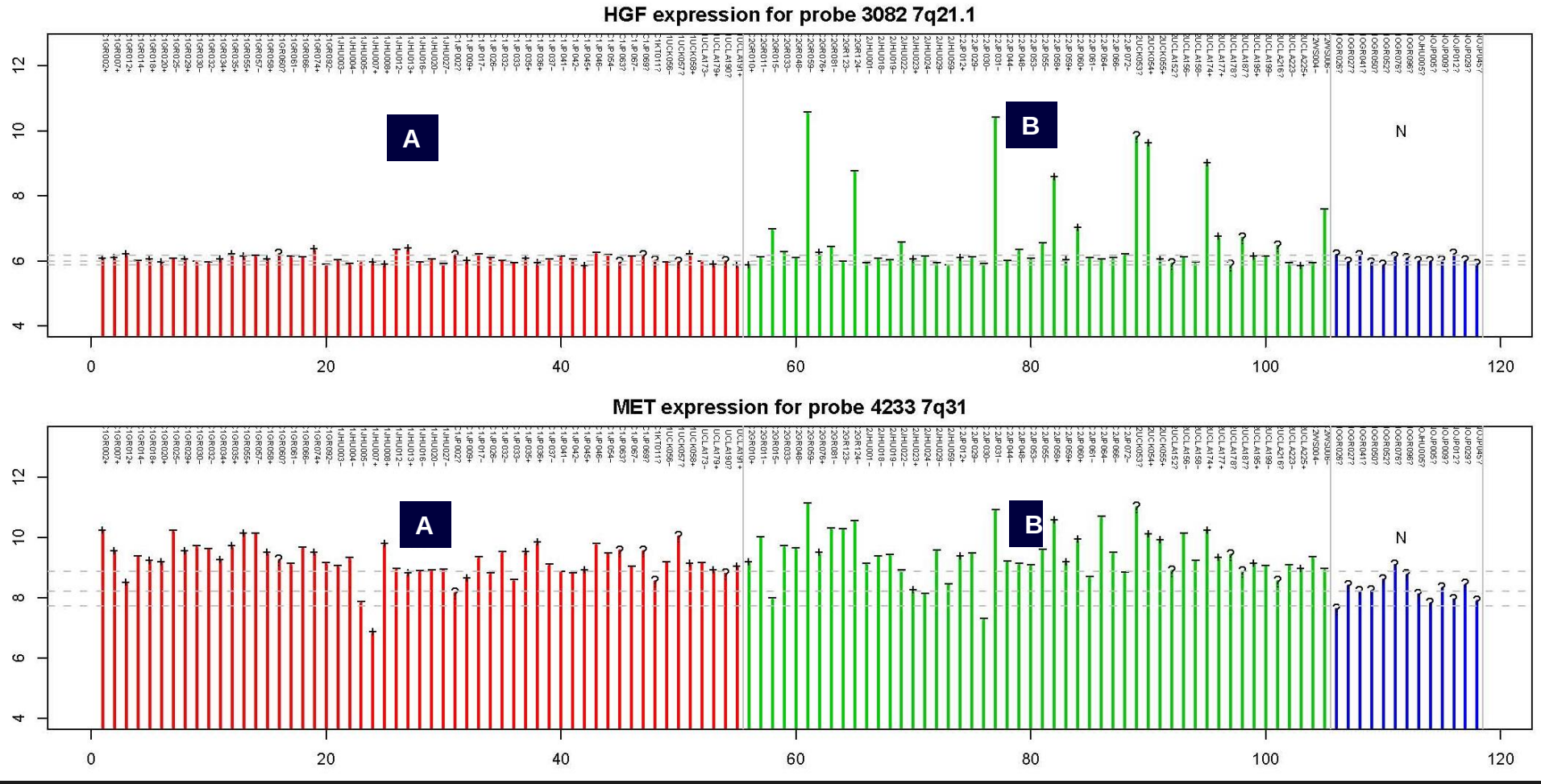
c-Met pathway



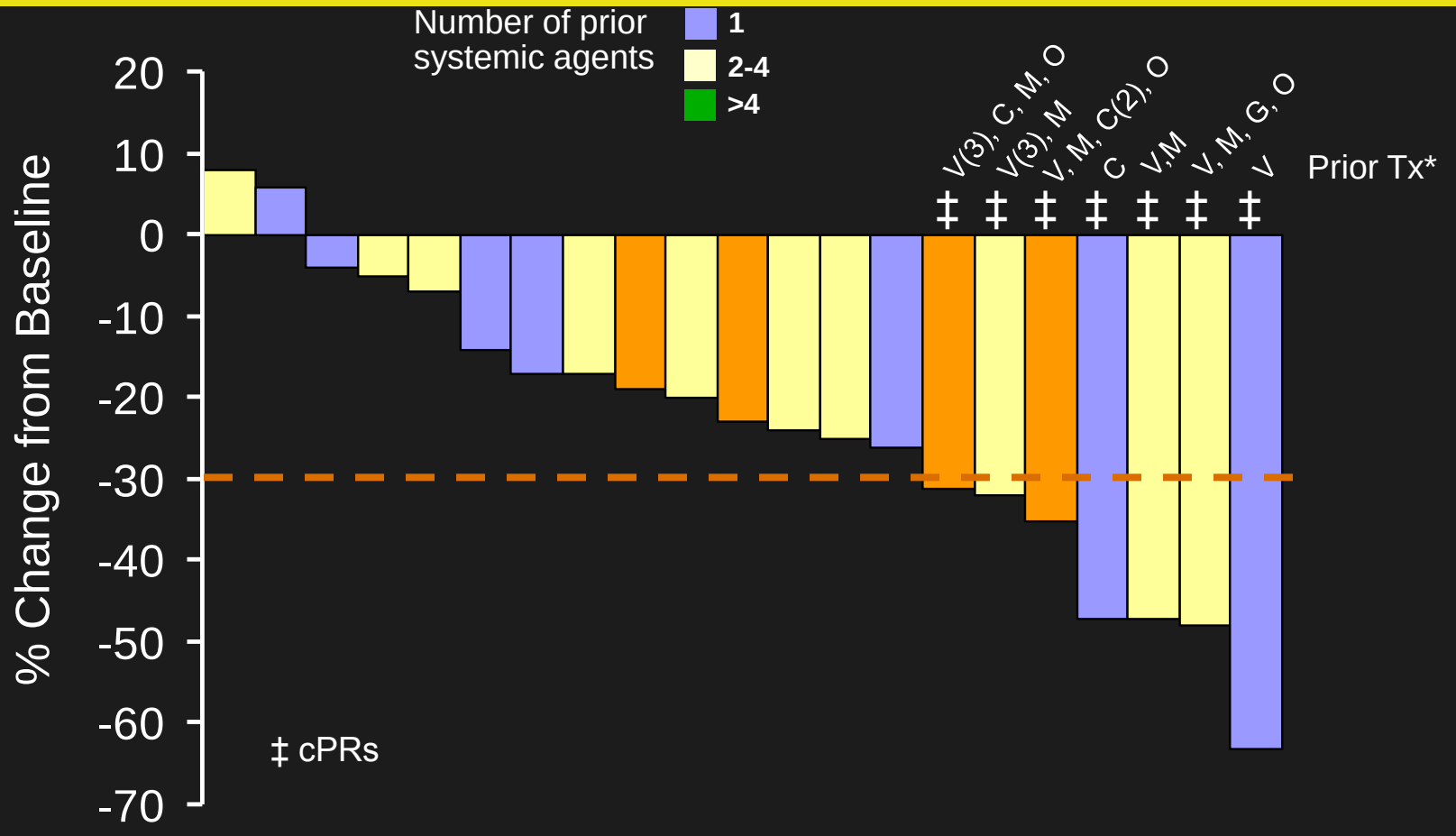
cMET expression in clear cell RCC

Good Prognosis CC **Poor Prognosis CC** **Normal**



Courtesy of Bin Teh

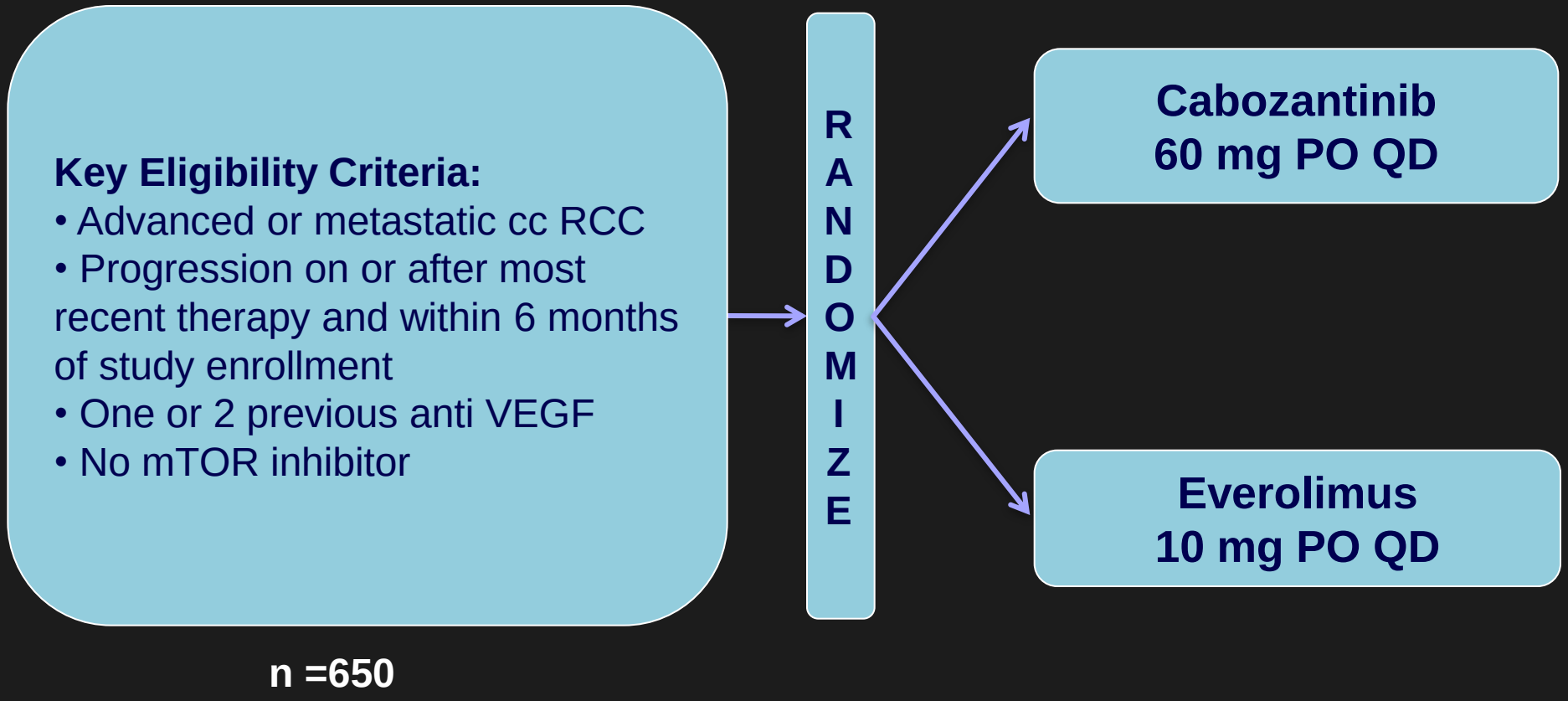
Cabozantinib is active in RCC (n = 21)



*V=VEGF pathway inhibitor; M=mTOR inhibitor; C=cytokine; G=gemcitabine; O=other

Choueiri et al, ASCO 2012

METEOR study



Primary endpoint: PFS

Conclusions

1. Biology of RCC is moving rapidly
2. VEGF inhibition remains key
3. mTOR inhibition is active in poor risk patients, and after VEGF failure
4. New strategies start to be better defined:
   - Drug holiday
   - Management of CR
   - Switching strategies
5. New pathways are under exploration and might change the next ESMO guidelines

THANK YOU……..

My colleagues: Laurence ALBIGES, Yohann LORIOT, Christophe MASSARD, Karim FIZAZI

My research nurse: Stephane LEBORGNE

My assistant: Catherine CORNUAULT