Metastatic Renal Cell Cancer - Therapeutic Challanges 2011

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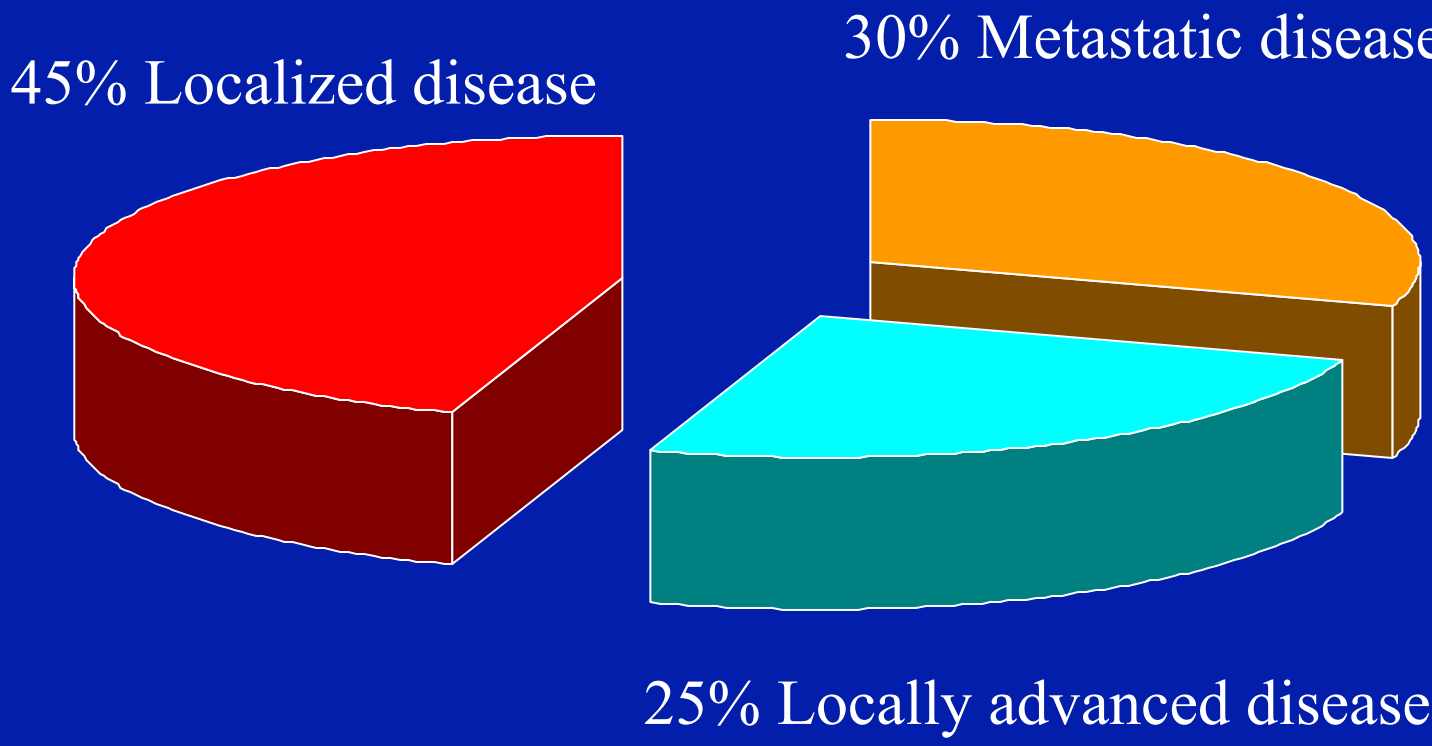
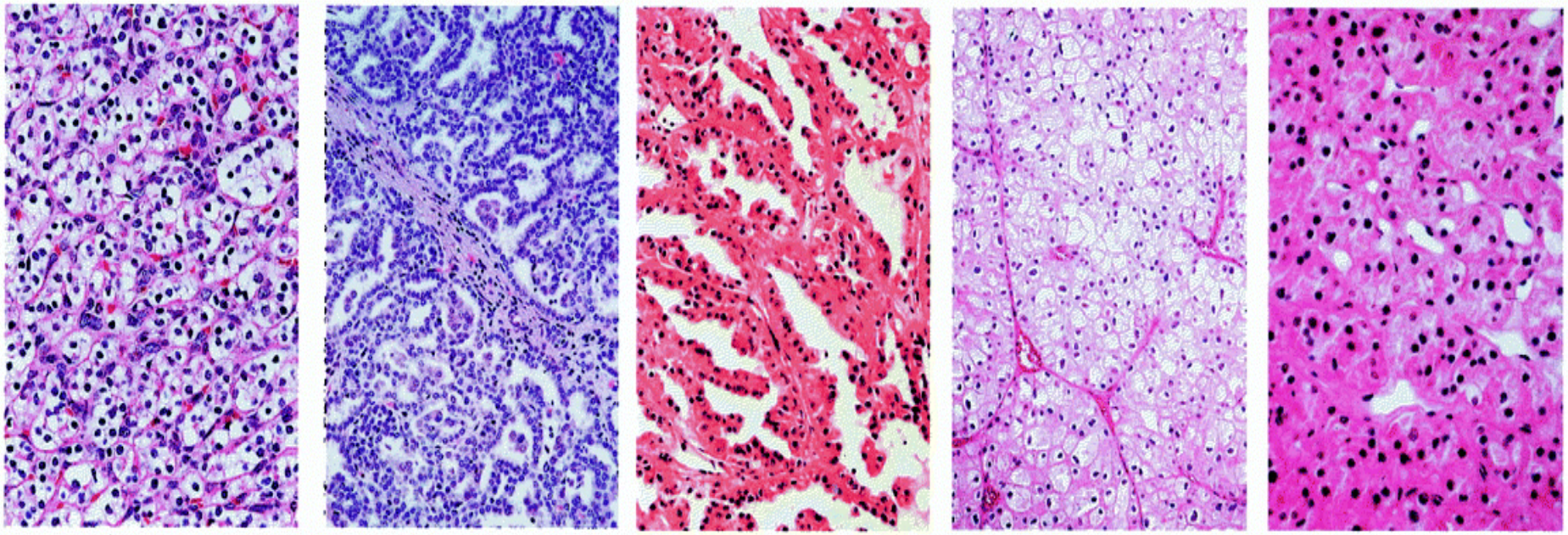
RCC Stage at Diagnosis



Linehan et al. Cancers of the genitourinary system. In: *Cancer: Principles and Practice of Oncology.* 6th ed; 2001.

Human Renal Epithelial Neoplasms



Type	Clear Cell	Papillary Type 1	Papillary Type 2	Chromophobe	Oncocytoma
	75%	5%	10%	5%	5%
Gene	VHL	Met	FH	BHD	

Paradigm shift in mRCC in the last 5 years

- Six new agents approved based on increased efficacy over IFN-α or placebo:

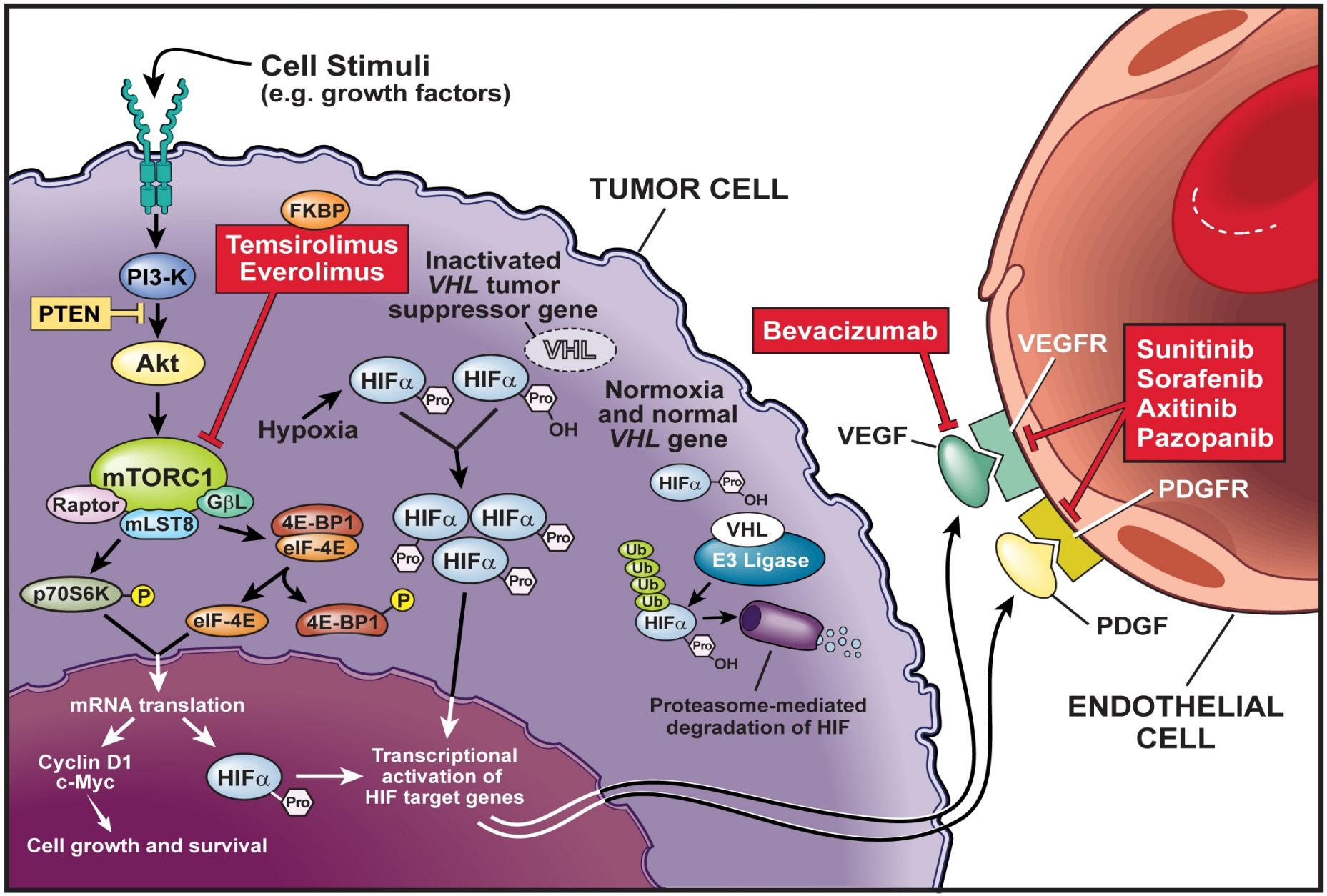
Comparator	
IFN-α	**Placebo**
Sunitinib[1,2]	Sorafenib[3]
Bevacizumab[4,5]	Everolimus[6]
Temsirolimus[7]	Pazopanib[8]

- IFN-α monotherapy is no longer considered the standard of care in mRCC

1. Motzer RJ, et al. *N Engl J Med* 2007; 2. Motzer RJ, et al. *J Clin Oncol* 2009; 3. Escudier B, et al. *N Engl J Med* 2007
4. Escudier B, et al. *J Clin Oncol* 2010; 5. Rini B, et al. *J Clin Oncol* 2010; 6. Motzer RJ, et al. *Lancet* 2008
7. Hudes G, et al. *N Engl J Med* 2007; 8. Sternberg C et al. *J Clin Oncol* 2010

What we know

- RCC is inherently VEGF-driven and responsive to targeting of the VEGF pathway
  - mTOR biology relevance less certain although clinical effects of mTOR-targeted therapy are seen
- Clear OR and PFS advantage (vs. IFN/placebo) to VEGF-targeted therapy and substantial OS (2^+ years)
  - Sunitinib, pazopanib and Bev/IFN are front-line SOC
- Debulking nephrectomy remains a standard of care (although being re-tested with modern drugs)
- Combination therapy has been toxic / ineffective to date


Cell Stimuli
(e.g. growth factors)
TUMOR CELL
FKBP
Temsirolimus
Everolimus
PI3-K
PTEN
Akt
mTORC1
Raptor
GβL
mLST8
4E-BP1
eIF-4E
p70S6K
P
eIF-4E
4E-BP1
P
mRNA translation
Cyclin D1
c-Myc
Cell growth and survival
HIFα
Pro
Transcriptional
activation of
HIF target genes
Inactivated
VHL tumor
suppressor gene
VHL
Hypoxia
HIFα
Pro
OH
Normoxia
and normal
VHL gene
VHL
E3 Ligase
Ub
Proteasome-mediated
degradation of HIF
Bevacizumab
VEGF
VEGFR
Sunitinib
Sorafenib
Axitinib
Pazopanib
PDGFR
PDGF
ENDOTHELIAL
CELL

CCF

Summary of First-Line Phase III Data

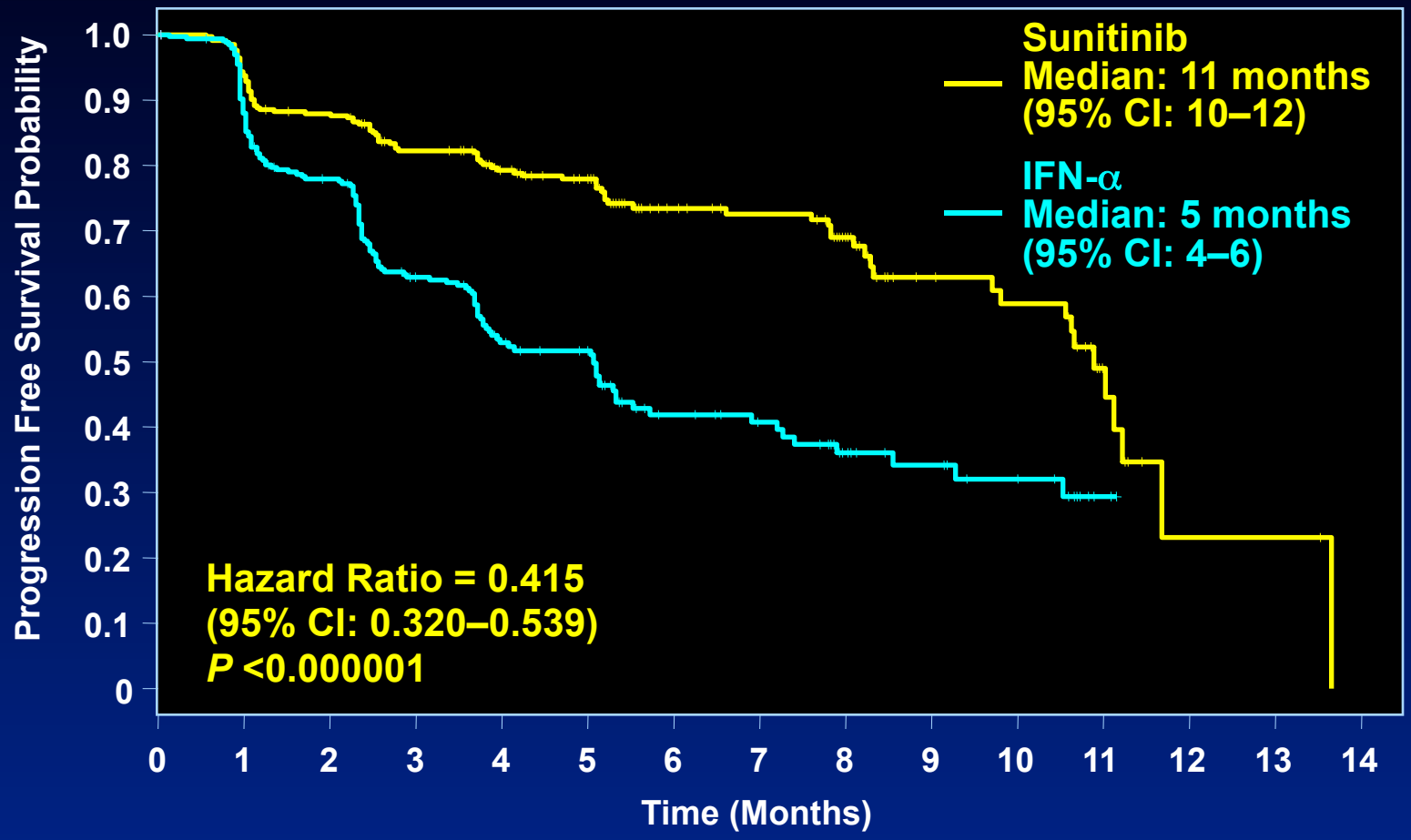
Drug	Control	Study Design	ORR (%)	PFS (months)	OS (months)
Bevacizumab + IFN-α[1]	IFN-α	Randomized 1:1, patients previously untreated (AVOREN/CALGB)	31/26 vs 13	10.2 vs 5.4 (HR=0.63, *P*<0.0001)	23 vs 21 (HR=0.86, *P*=0.1291)
Sunitinib[2,3,6]	IFN-α	Randomized 1:1, patients previously untreated	39 vs 8* 47 vs 12†	11 vs 5 (HR=0.42; *P*<0.001)	26 vs 22‡ (HR=0.82; *P*=0.051)
Pazopanib[6,7]	Placebo	Randomized 2:1, patients previously untreated or 1 prior cytokine	30 vs 3	9.2 vs 4.2 (HR=0.46; P<0.001)	23 vs 20.5 HR=0.91 (p=.224)
Sorafenib[5]	Placebo	Randomized 1:1, patients previously treated with IL-2 or IFN	10 vs 2	5.5 vs 2.8 (HR=0.44; *P*<0.01)	19.3 vs 15.9 (HR=0.77; *P*=0.02)
Temsirolimus[4]	IFN-α	Randomized 1:1:1, patients previously untreated who have poor prognosis	8.6 vs 4.8	5.5 vs 3.1	10.9 vs 7.3 (HR=0.73; *P*=0.008)

*Independent review.
†Investigator.
‡Log-rank.

1. Escudier. *Lancet*. 2007;370:2103-2111. 2. Motzer. *N Engl J Med*. 2007;356:115-124. 3. Figlin. *J Clin Oncol*. 2008;26 (suppl; abstr 5024). Hudes. *N Engl J Med*. 2007;356:2271-2281. 5. Escudier. *N Engl J Med*. 2007;356:125-134.. 6. Prescribing Information Votrient (pazopanib) 2009. 7. Sternberg. ASCO. 2009 (abstr 5021).

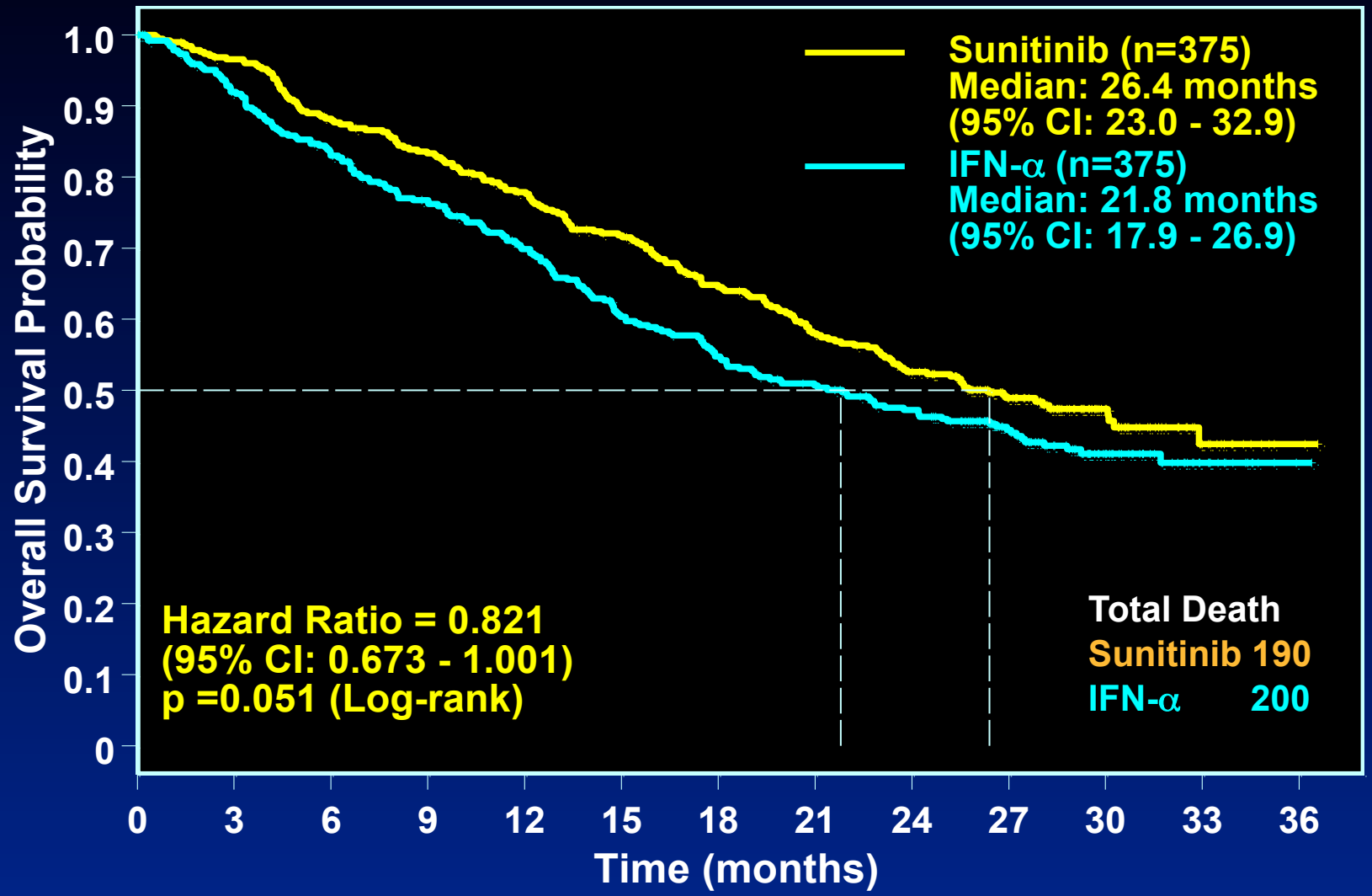
Progression-Free Survival

(Independent Central Review)



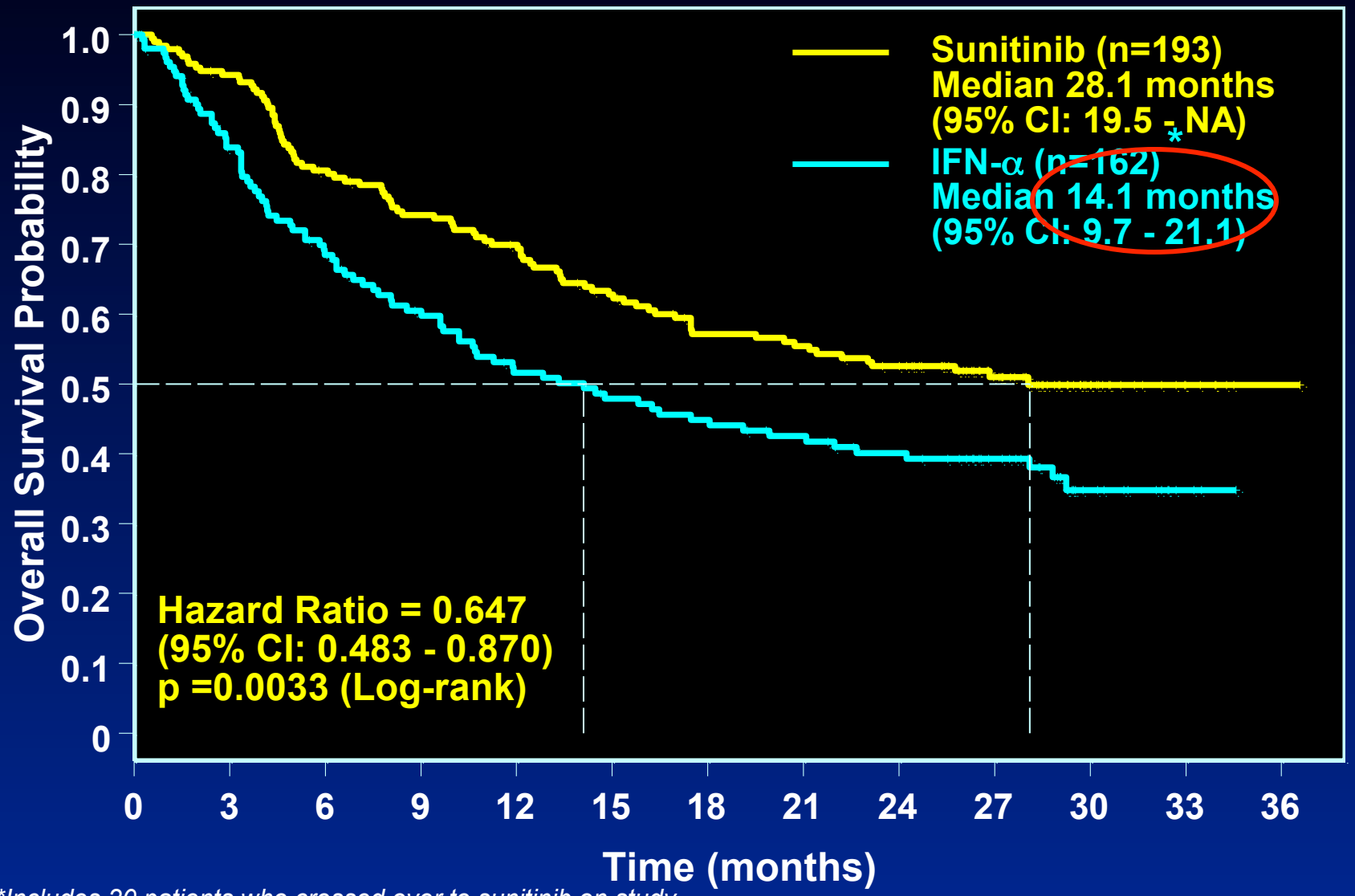
No. at Risk Sunitinib:	235	90	32	2
No. at Risk IFN-α:	152	42	18	0

Final Overall Survival



nDeath/nRisk Sunit	375	44 / 326	38 / 283	48 / 229	42 / 180	14 / 61	4 / 2
nDeath/nRisk IFN-α	375	61 / 295	46 / 242	52 / 187	25 / 149	15 / 53	1 / 1

OS in patients who did not receive any post-study treatment



*Includes 20 patients who crossed over to sunitinib on study

PFS in Untreated RCC by Risk Group

Agent(s)	PFS (mos)	Good	Int	Poor	HR vs. IFN
Sunitinib	11	14.5	10.6	3.7	0.54
Pazopanib	11.1				0.40 (vs. placebo)
Bev + IFN (AVOREN)	10.2	12.9	10.2	2.2	0.63
Bev + IFN (CALGB)	8.5	11.1	8.4	3.3	0.71
Sorafenib	5.7	?	?	?	0.88
Temsirolimus	3.7	NA	NA	3.7*	NR

• Included 31% of pts classified as intermediate risk per MSKCC

1. Motzer RJ, et al. JCO 2009
2. Escudier, et al. JCO, 2009
3. Hudes G, et al. N Engl J Med. 2007
4. Escudier B, et al. Lancet. 2007
5. Rini BI, et al. JCO, 2008

Overall Survival in Untreated RCC by Risk Group

Agent(s)	OS (mos)	Good	Int	Poor	HR vs. IFN
Sunitinib	26.4	Not reached**	20.7	5.3	0.82
Pazopanib	21.1				0.73 (vs. placebo)
Bev + IFN (AVOREN)	23.3	35.1	22.6	6.0	0.86
Bev + IFN (CALGB)	18.3	32.5	17.7	6.6	0.86
Temsirolimus	10.9	NA	NA	10.9*	0.73

** Median overall survival had not been reached with either treatment in the favorable risk group. At 12 months, 91% of patients in the sunitinib group were alive compared with 92% of patients in the IFN group; and at 2 years, 72% *v* 76%, respectively, were alive.

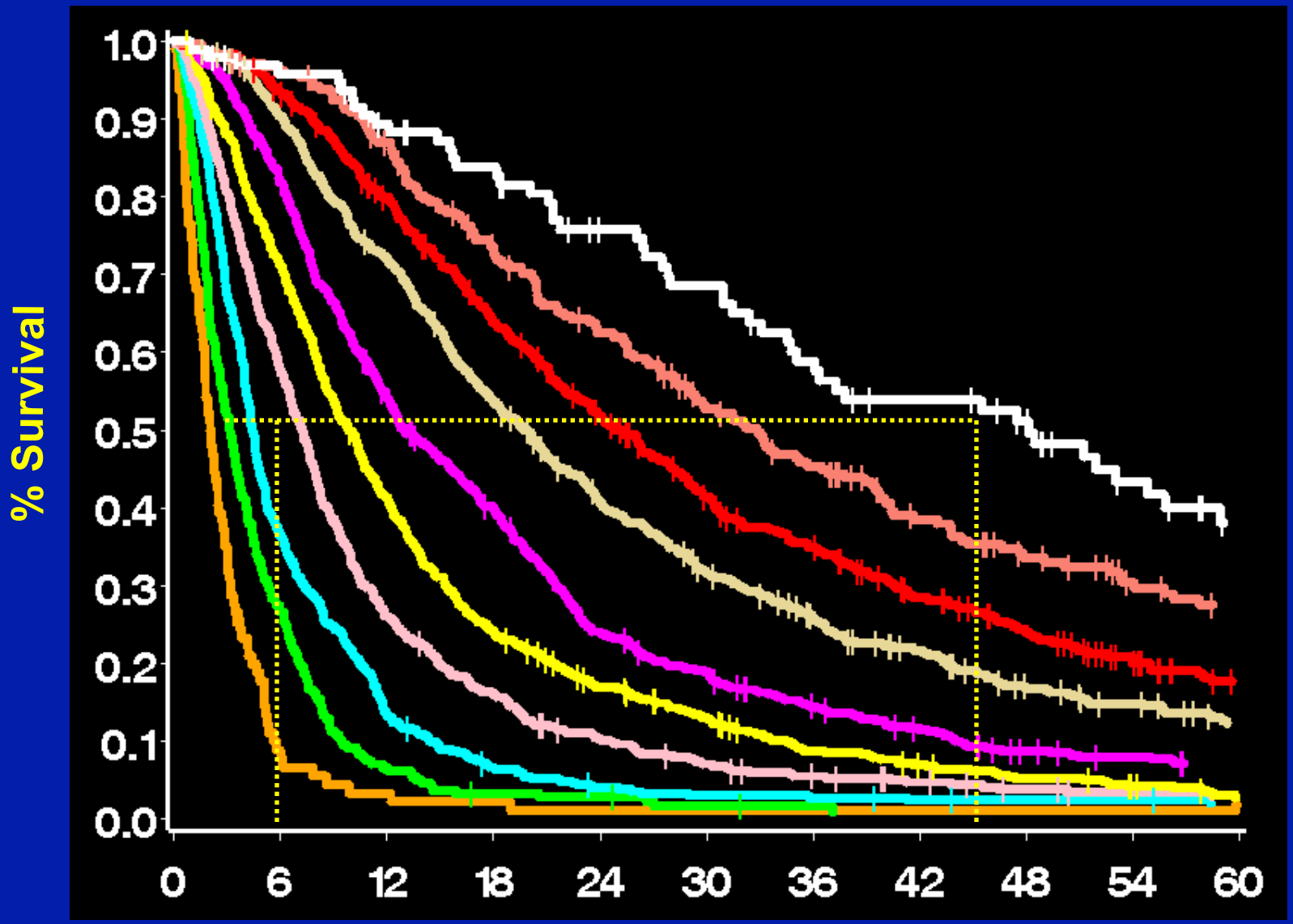
What we don't know

- When do we start therapy for indolent patients?
- Which is the 'best' drug for initial therapy?
- Will next-generation, more potent VEGFR TKIs (axitinib/tivozanib) be substantial advances?

What we don't know

- What is the best way to administer these drugs chronically?
- Mechanisms/biomarkers of response/resistance to targeted therapy?
  - No clear biologic rationale for tx sequences
- Activity of VEGF-targeted therapy in the (neo)/ adjuvant setting?

RCC is an Inherently Diverse Disease



When to Start Therapy?

- Our job as RCC doctors is to optimize the **timing** and type of therapy in order to delay as long as possible a patient from reaching a lethal tumor burden while maintaining maximal quality of life.

- This means that select patients may have inherent ‘control’ of tumor burden and thus immediate systemic treatment is not indicated. Such patients may be served best in the long run with initial surveillance.

Active Surveillance of the Small Renal Mass: A meta-analysis

Study	Institution	N	Mean Lesion Size (cm)	Mean Growth Rate (cm/yr)	Mean F/U Duration (months)
Fujimoto et al	Sendai Shakaihoken Hospital Sendia, Japan	6	2.47	0.47	29
Bosniak et al	NYU Medical Center New York, USA	40	1.73	0.36	39
Kassouf et al	McGill University Health Center Montreal, Canada	26	3.27	0.09	32
Volpe et al	Princess Margaret Hospital Toronto, Canada	32	2.48	0.1	35
Wehle et al	Mayo Clinic Jacksonville, USA	29	1.83	0.12	32
Kato et al	Tohoku School of Medicine Sendia, Japan	18	1.98	0.42	27
Sowery et al	Kingston General Hospital Kingston, Canada	22	4.08	0.86	26
Current Series	Fox Chase Cancer Center Philadelphia, USA	61	2.97	0.20	36
TOTAL		234	2.60	0.28	34

Uzzo et al. J Urol 175 (2): 425, 2006

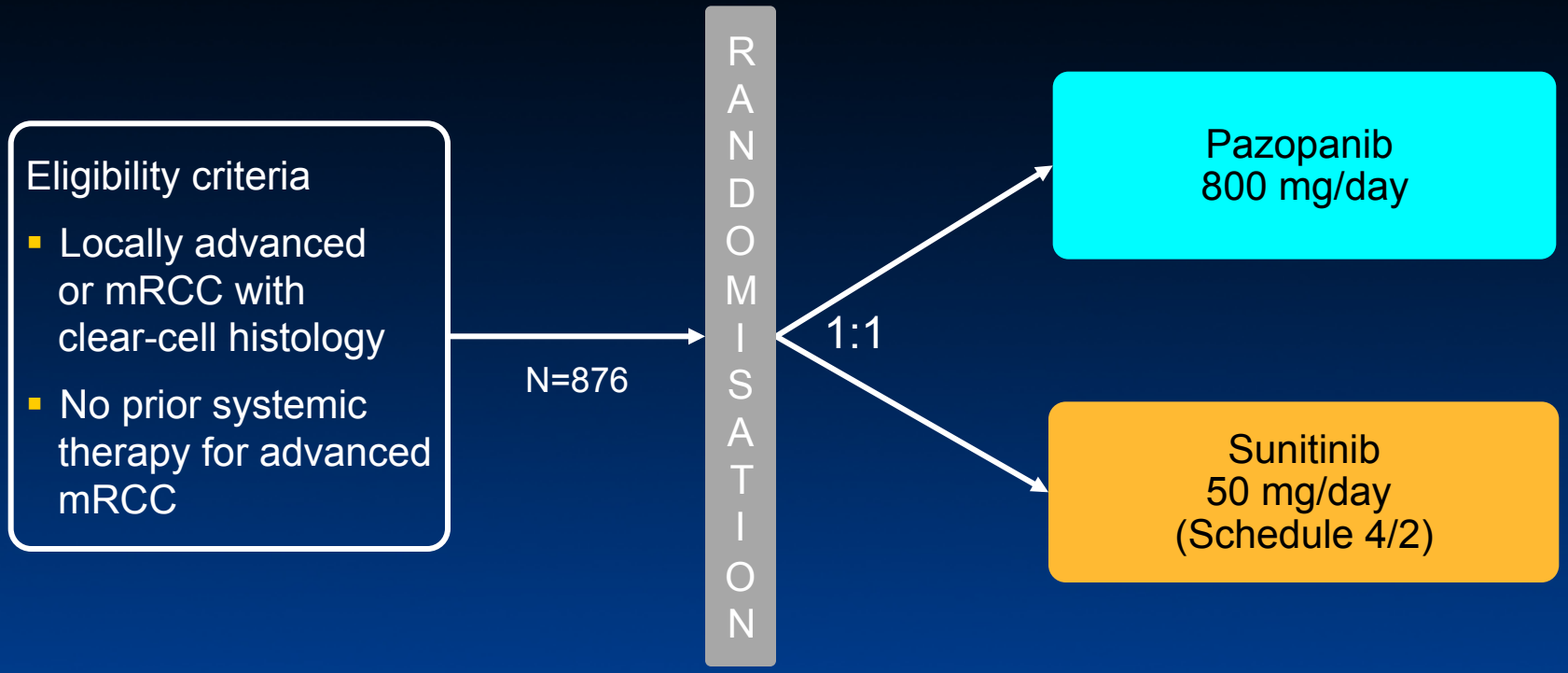
Whom to observe?

- Limited modern data exists.
- Good performance status patients with ‘low-volume’, ‘slow-growing’ and asymptomatic disease are candidates after risk/benefit discussion with the patient.
- A prospective study is underway at The Cleveland Clinic and other centers
  - What is the natural growth rate?
  - What is the clinical outcome when treatment is started?
  - Anxiety/depression associated with observation?
  - Translational studies in untreated population . .

How I decide on initial therapy

- I tell the patient:
  - "I don't know which drug is the best one for YOU"
  - "It's not so much which one, but which one FIRST. Other drugs don't go away, they are just put to the side."
  - I list drug names and general categories
- I make decisions one treatment at a time
- I always consider clinical trial options first
- I consider a patient's histology, tumor burden/pace, route of administration/co-pay issues, fitness to 'tolerate' a given therapy, and of course the clinical data

Phase III non-inferiority trial of pazopanib vs sunitinib in first-line mRCC (COMPARZ)



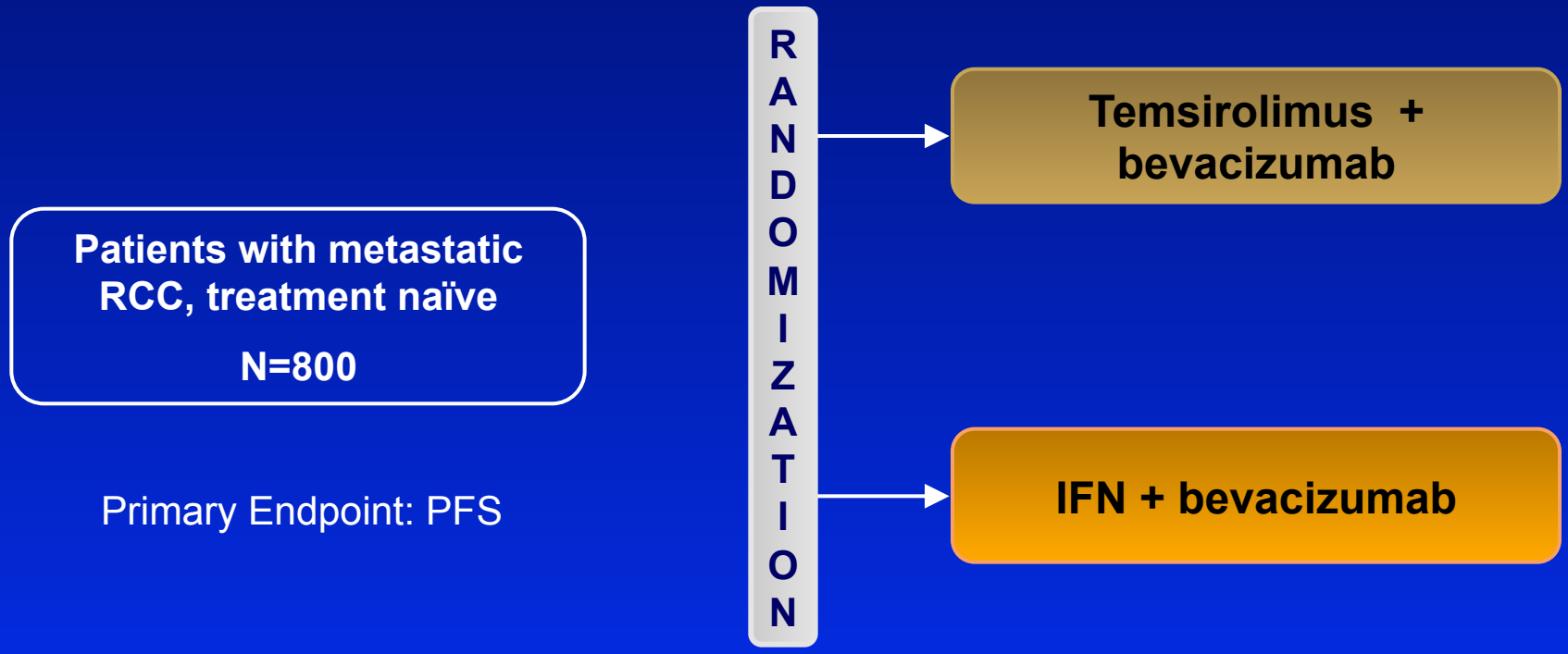
Primary endpoint: PFS

Secondary endpoints: OS, ORR, time to response, duration of response, safety, QoL

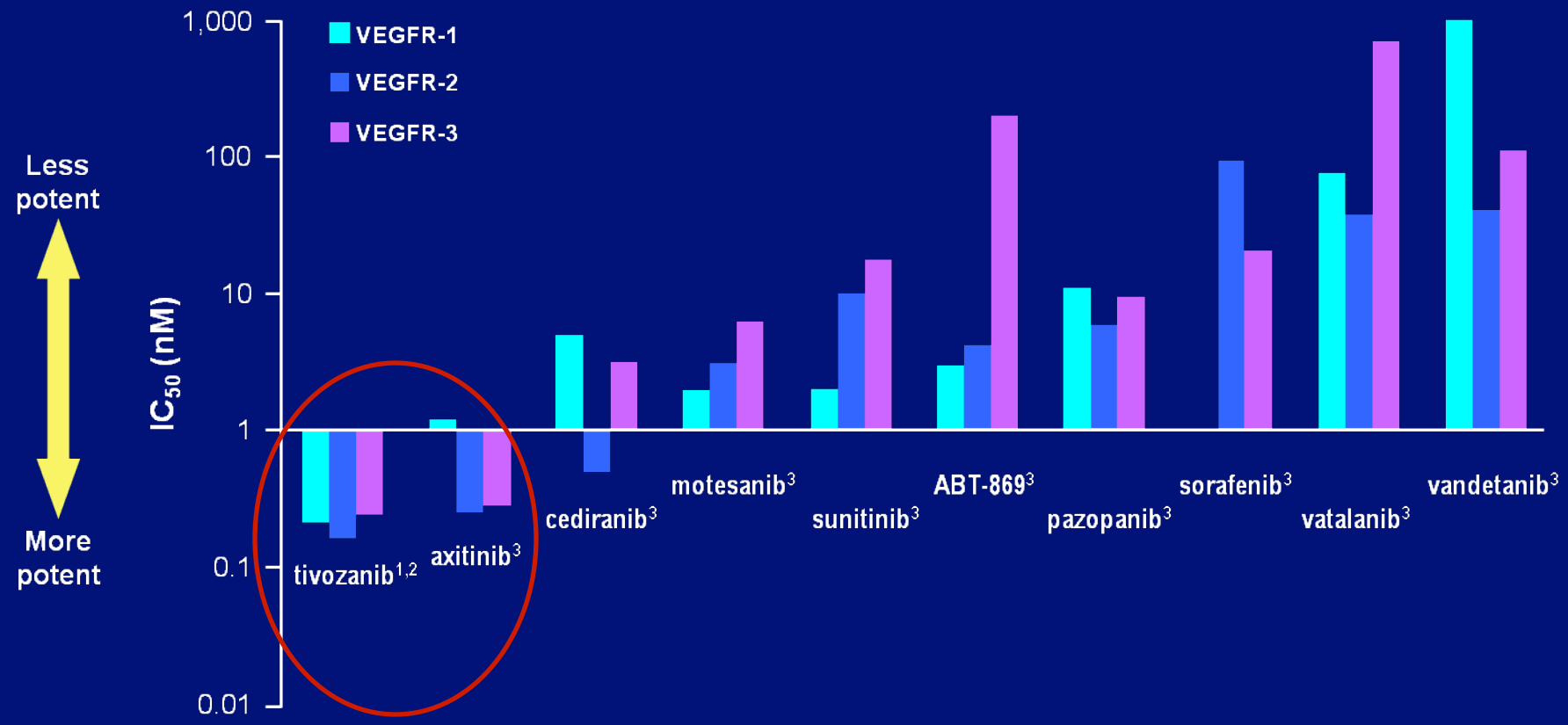
PI: Robert J Motzer

www.clinicaltrials.gov (NCT00720941)

Randomized Phase III Trial of Temsirolimus + Bevacizumab vs IFN + Bevacizumab in Metastatic Renal Cell Carcinoma



More potent VEGF-R TKIs in RCC

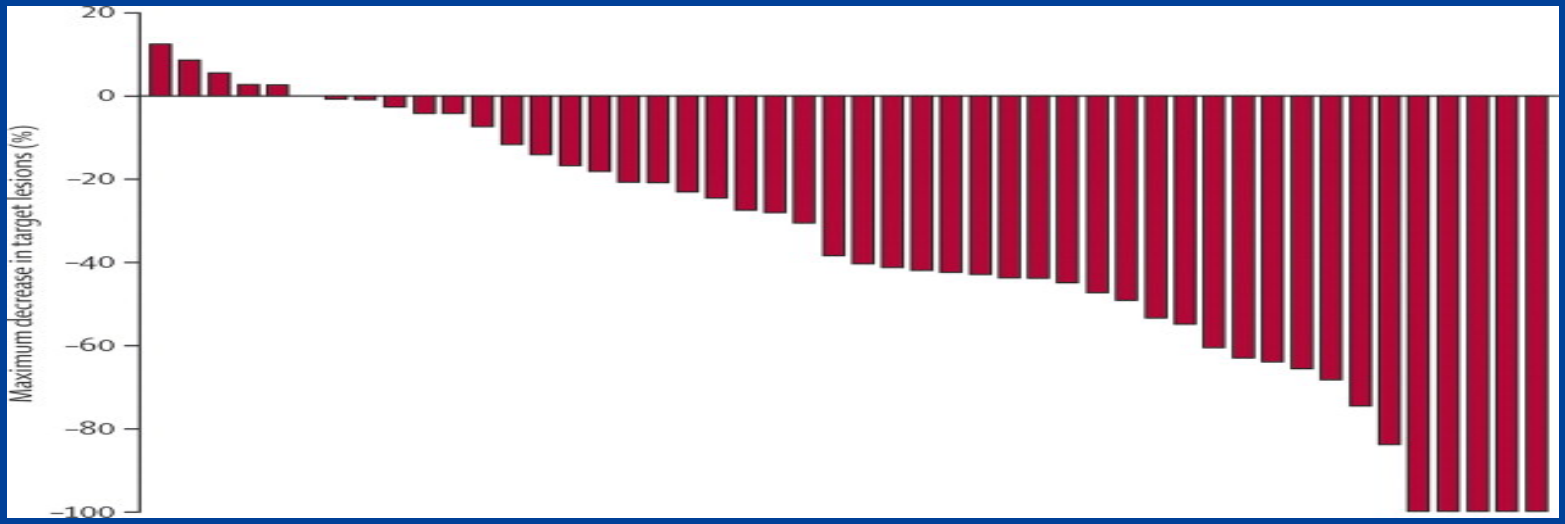


1. Eskens FALM, et al. In: *Proceedings of the 99th Annual Meeting of the AACR*. San Diego, CA: AACR; 2008. Abstract LB-201.

2. Nakamura K, et al. *Cancer Res*. 2006;66(18):9134-9142.

3. Chow LQM, Eckhardt SG. *J Clin Oncol*. 2007;25(7):884-896.

Axitinib in cytokine-refractory RCC



- **Objective response rate of 44.2%**
- **Median response duration was 23.0 months**
- **Progression-free survival was 13.7 months**

Rixe et al. *Lancet Oncology* 8 (11), 2007

Phase III study of axitinib vs sorafenib as second-line therapy for mRCC (AGILE 1032)

Eligibility criteria:

- Histologically confirmed mRCC with clear-cell component
- Failure of <u>one</u> prior first-line regimen containing ≥1 of:
  - Sunitinib
  - Bevacizumab + IFN-α
  - Temsirolimus
  - Cytokine(s)

Stratification
- Prior regimen
- ECOG PS 0 vs 1

N=723

RANDOMISATION

Axitinib
5 mg BID

Sorafenib
400 mg BID

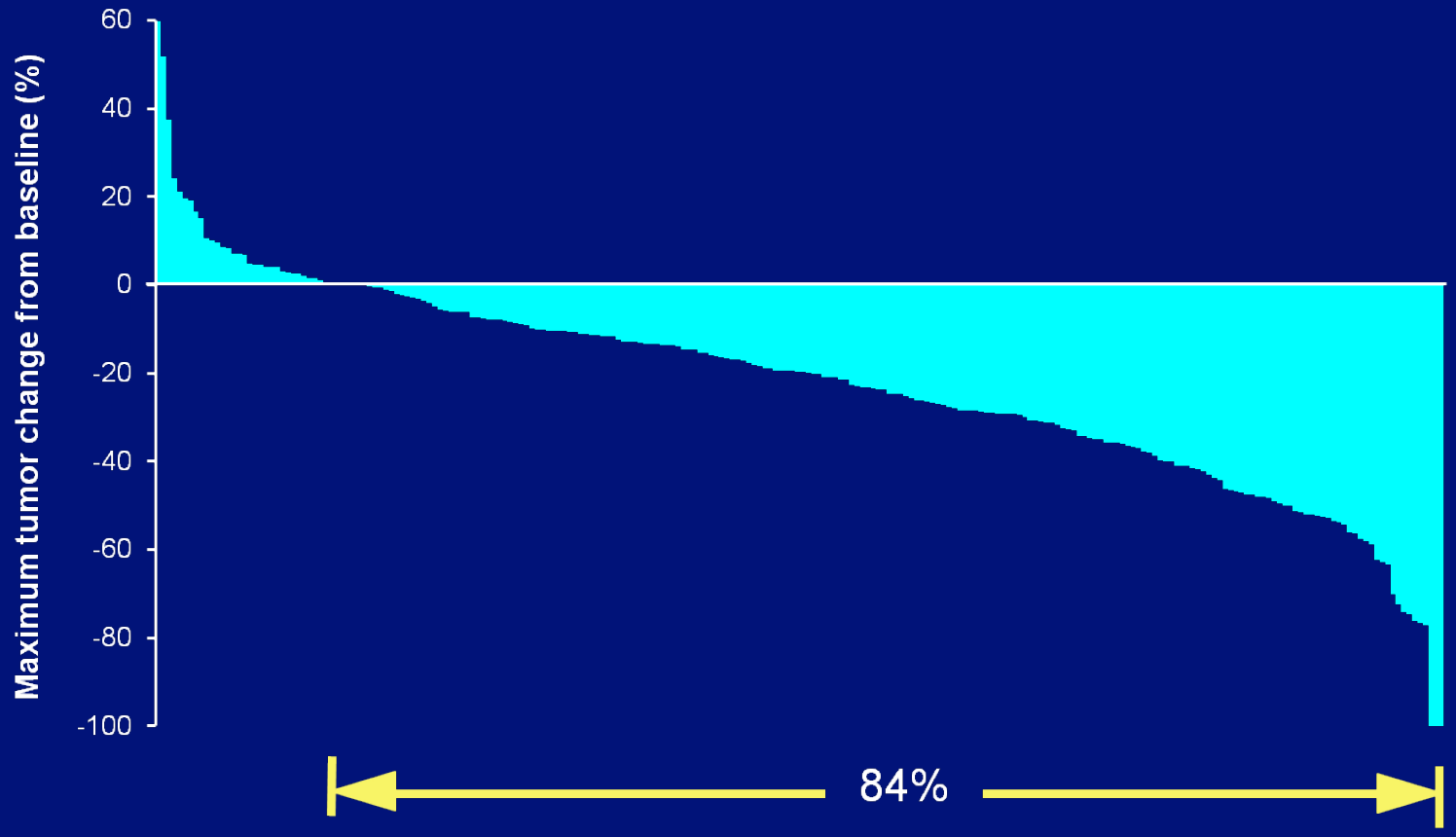
Primary endpoint: PFS

Secondary endpoints: OS, ORR, duration of response, safety, QoL

PI: Brian Rini

www.clinicaltrials.gov (NCT00920816)

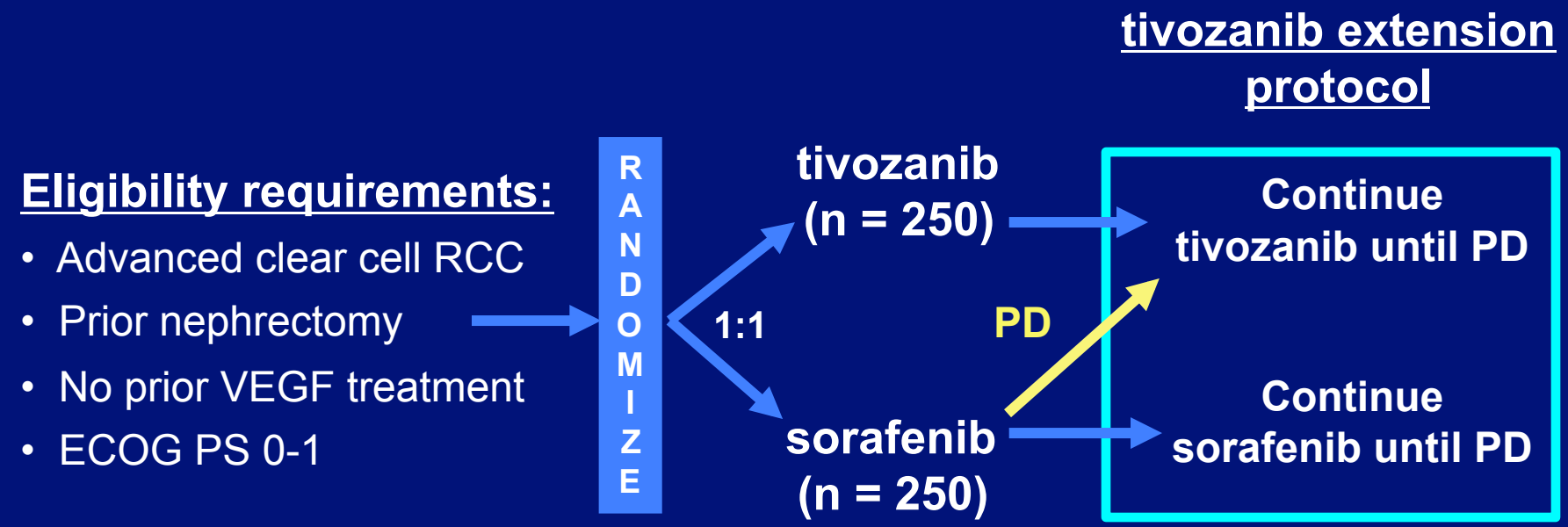
Tivozanib Clinical Responses by Independent Radiology Assessment



* Median PFS 11.8 months

Bhargava P, et al. Presented at the 2009 ASCO Annual Meeting; May 29-June 2, 2009; Orlando, FL. Abstract 5032.

TIVO-1 Trial: Phase 3 Head-to-Head Trial of Tivozanib vs Sorafenib



- Primary endpoint: PFS
- Secondary endpoints: overall survival, ORR, quality of life

ClinicalTrials.gov Identifier: NCT01030783, NCT01076010.

?Intermittent TKI treatment

- Retrospective series from Germany/Netherlands of pts on TKI (n=12;11 sunitinib) with CR / surgical CR in whom TKI was stopped, and pts were observed.
  - Median time off therapy was 7.5 months (range, 3-25)
  - 5 with recurrent disease at a median of 6 months (range, 3-8); 1 pt with spinal cord compression at recurrence
  - TKI re-administered with tumor burden reduction in all 5

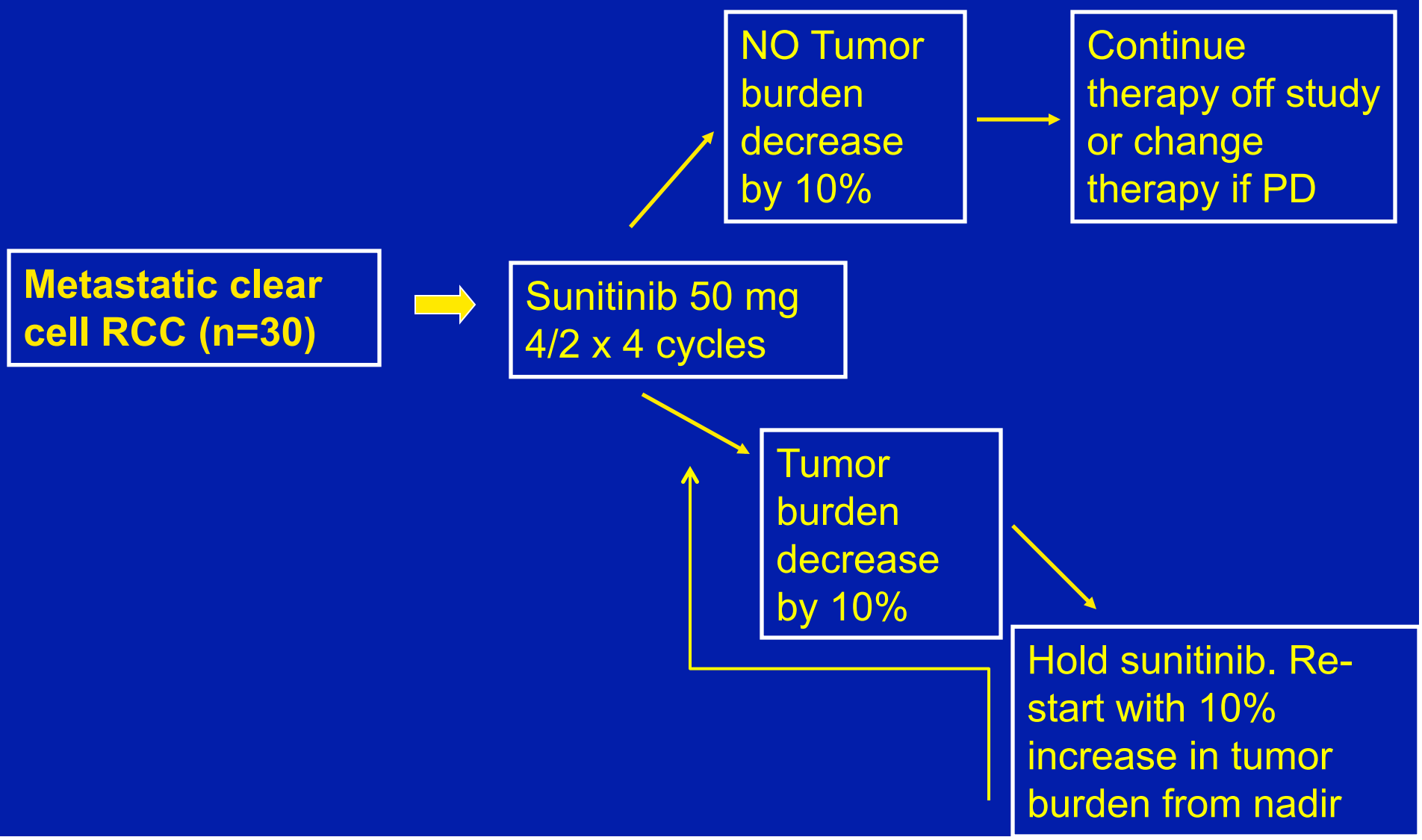
Johannsen et al. Eur Urol, 2008

Holding VEGF Therapy

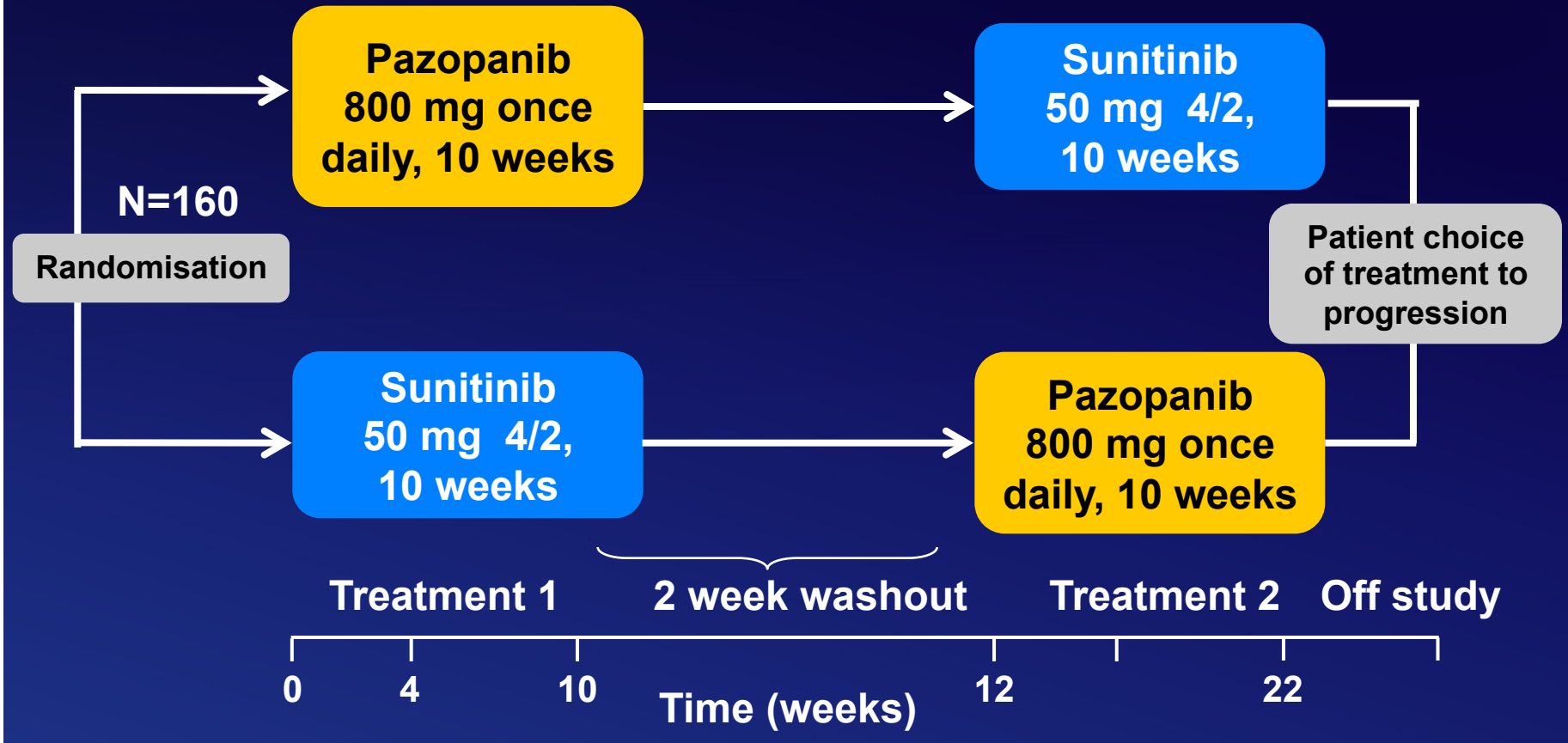
- 40 mRCC patients with disease control (RECIST SD or better) on VEGF-targeted therapy (median 15 months) observed off therapy
- Twenty five patients (63%) had progression of disease.
  - Median PFS in these patients was 10 (1.4 to 27.2) months.
- Fifteen patients (37%) had stable disease as of ESD documented by staging studies.
  - Median PFS for patients who remained progression-free as of ESD was 8.9 (4.6 to 28.2) months.

Sadeghi et al. KCA 2010 and ASCO GU 2011

CCF Intermittent Sunitinib Study



PISCES Patient Preference Study Design[1]

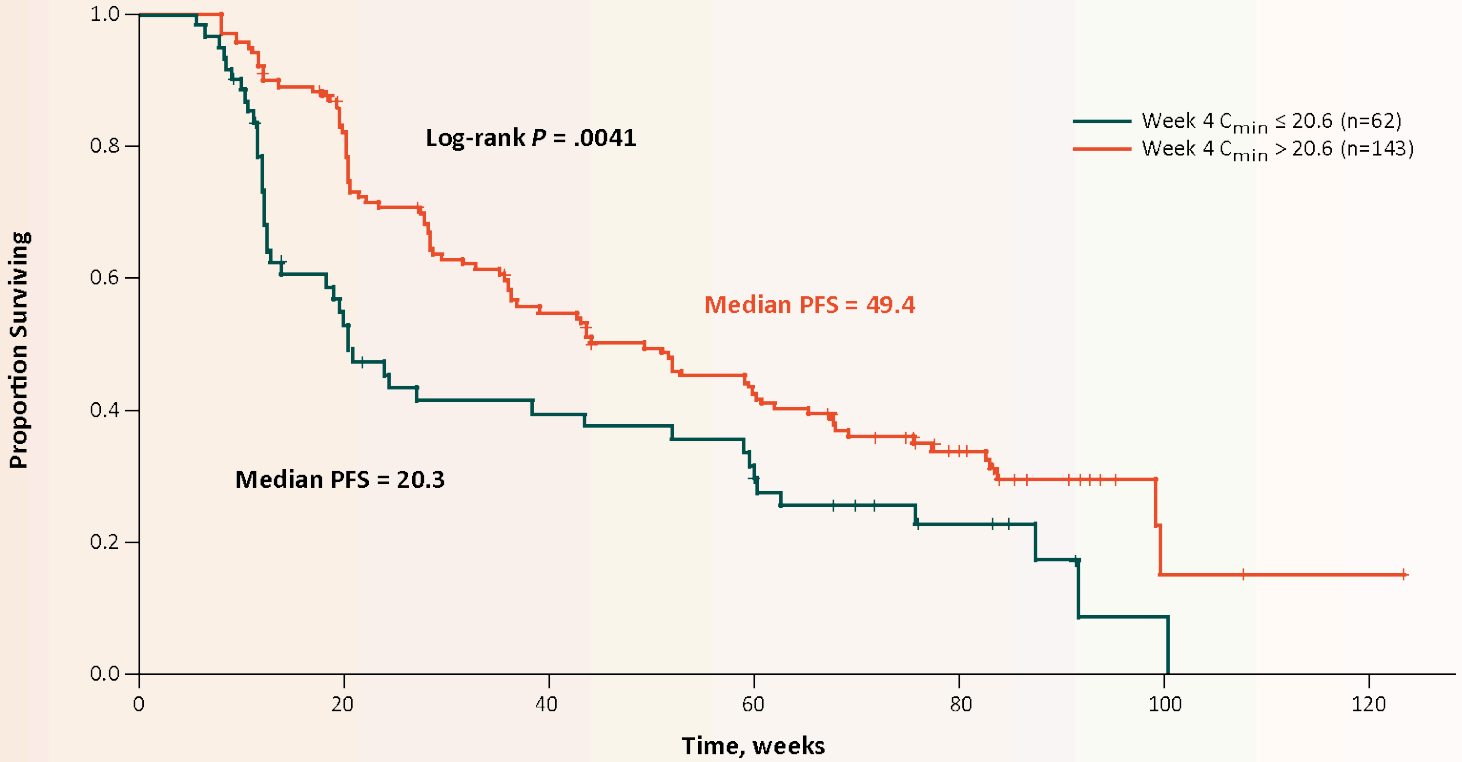


- **Primary endpoint**
  - Patient preference
- **Secondary endpoints**
  - Quality of life (EQ-5D)
  - Safety (FACIT-Fatigue)
  - Pharmacokinetics
  - Biomarkers

1. http://clinicaltrials.gov/ct2/show/NCT01064310

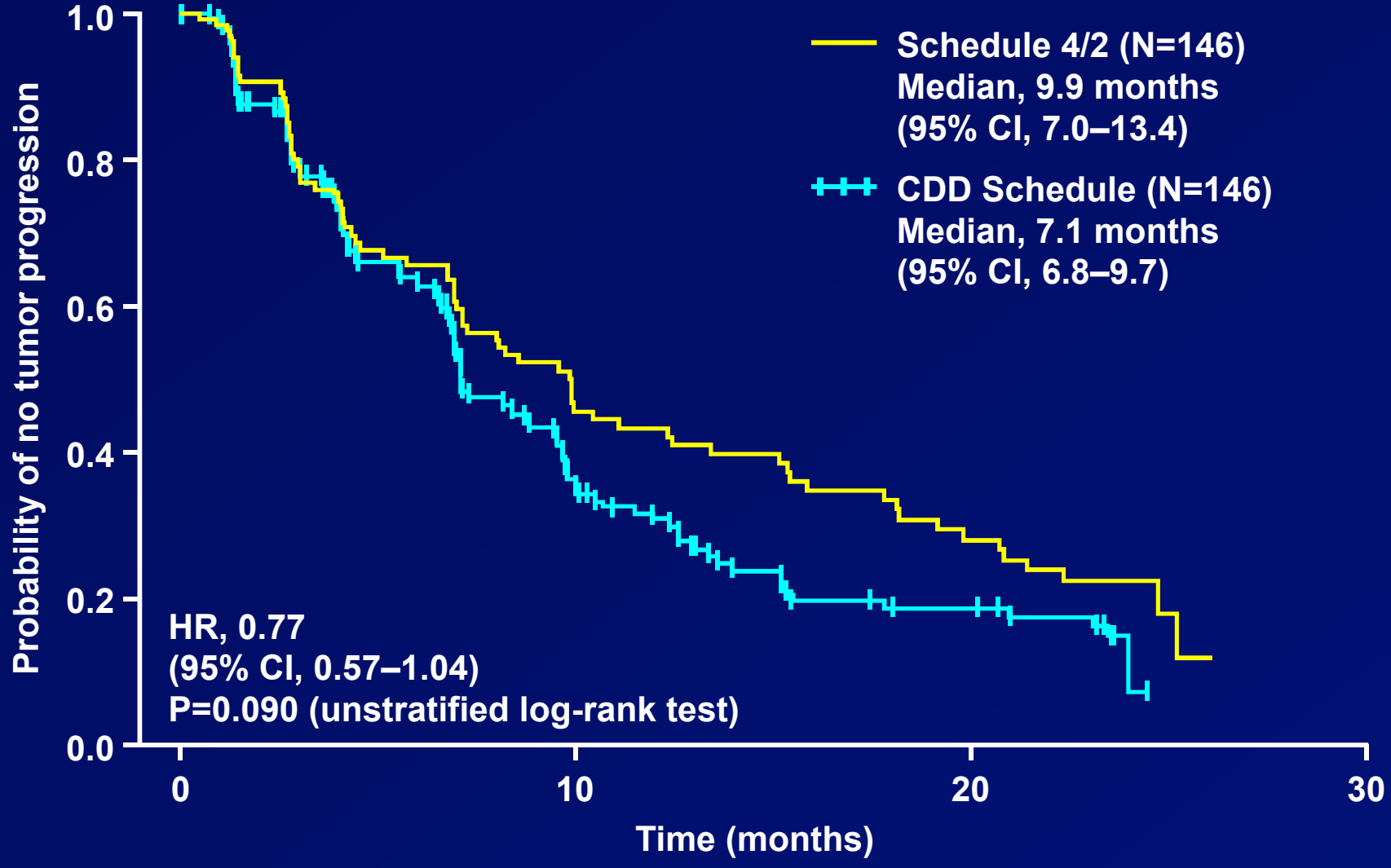
Progression-free Survival Grouped by Threshold Week 4 Pazopanib C_{min}

Kaplan-Meier progression-free survival (PFS) curves for patients with Week 4 pazopanib Cmin > 20.6 and ≤20.6 μg/mL



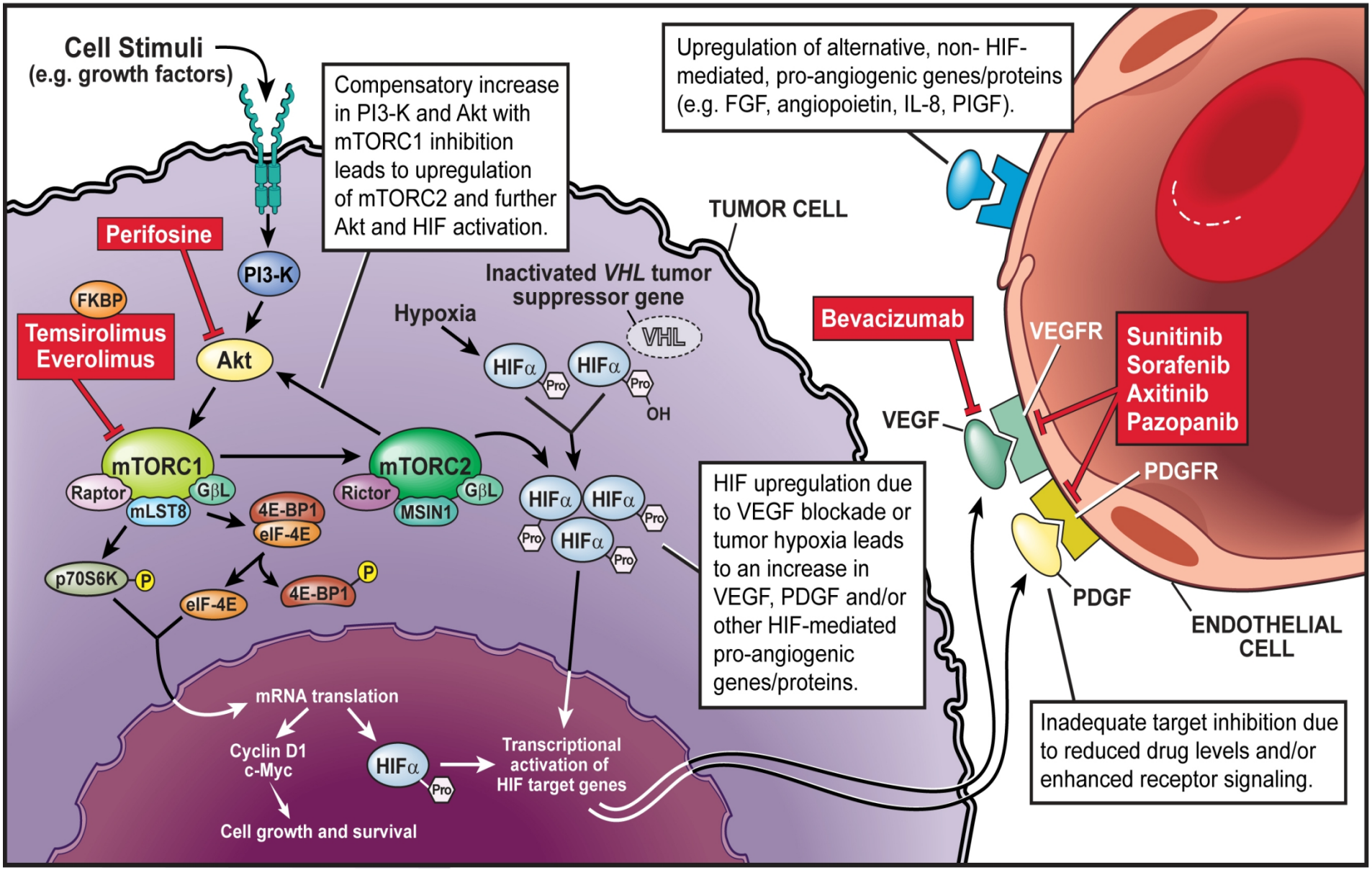
– Median PFS was 49.4 weeks for patients with Week 4 Cmin >20.6 μg/mL, whereas median PFS was 20.3 weeks for patients with Cmin ≤20.6 μg/mL (P = 0.0041)

Time to Tumor Progression on Sunitinib 50mg 4/2 vs. 37.5mg continuous (EFFECT trial) –Dose matters!



Motzer et al. ASCO GU 2011

Resistance to Targeted Therapy in RCC



Rini, Atkins Lancet Oncology

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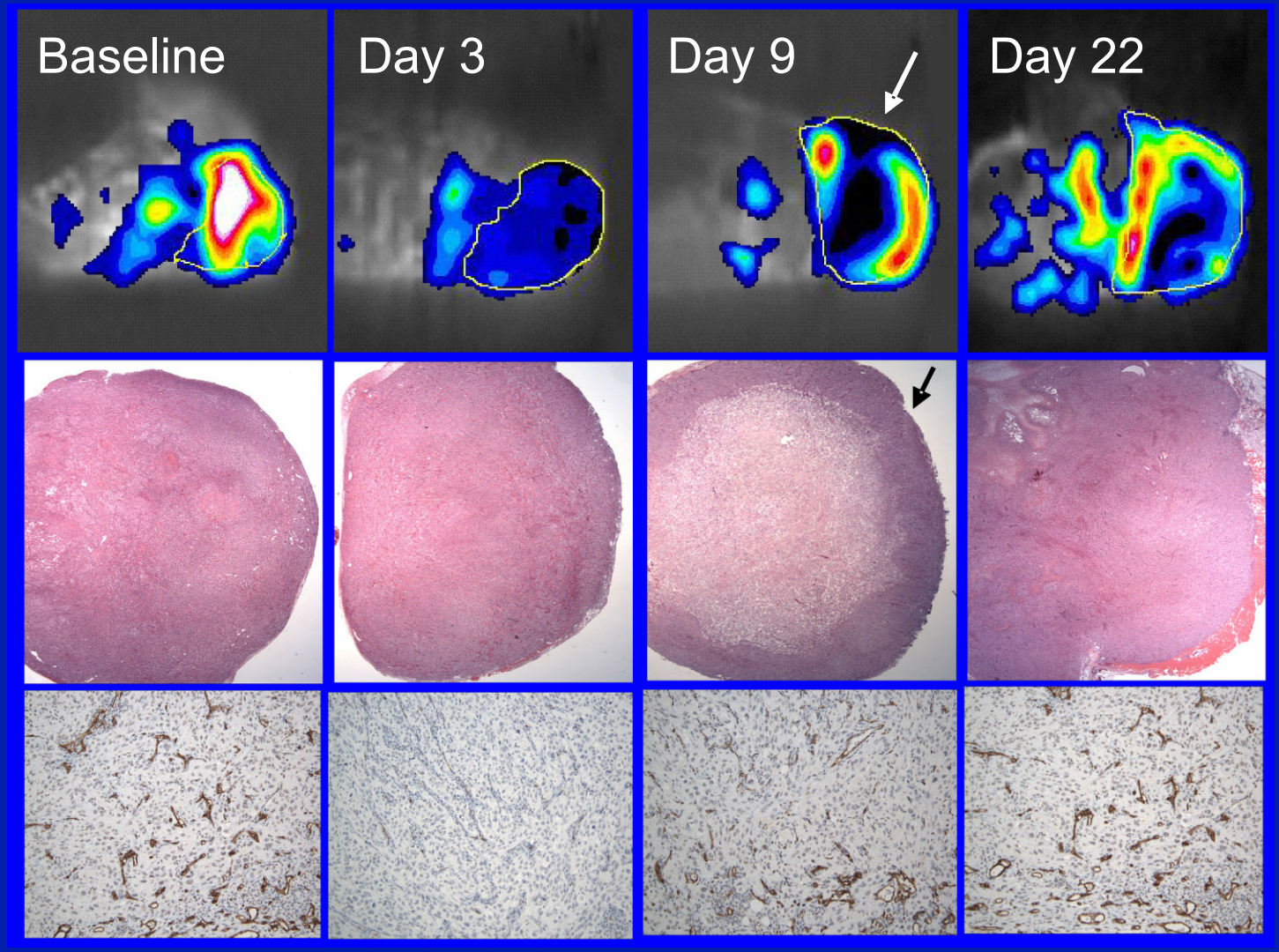
Resistance Appears Mediated by "Angiogenic Escape" - ASL MRI: Rodent model



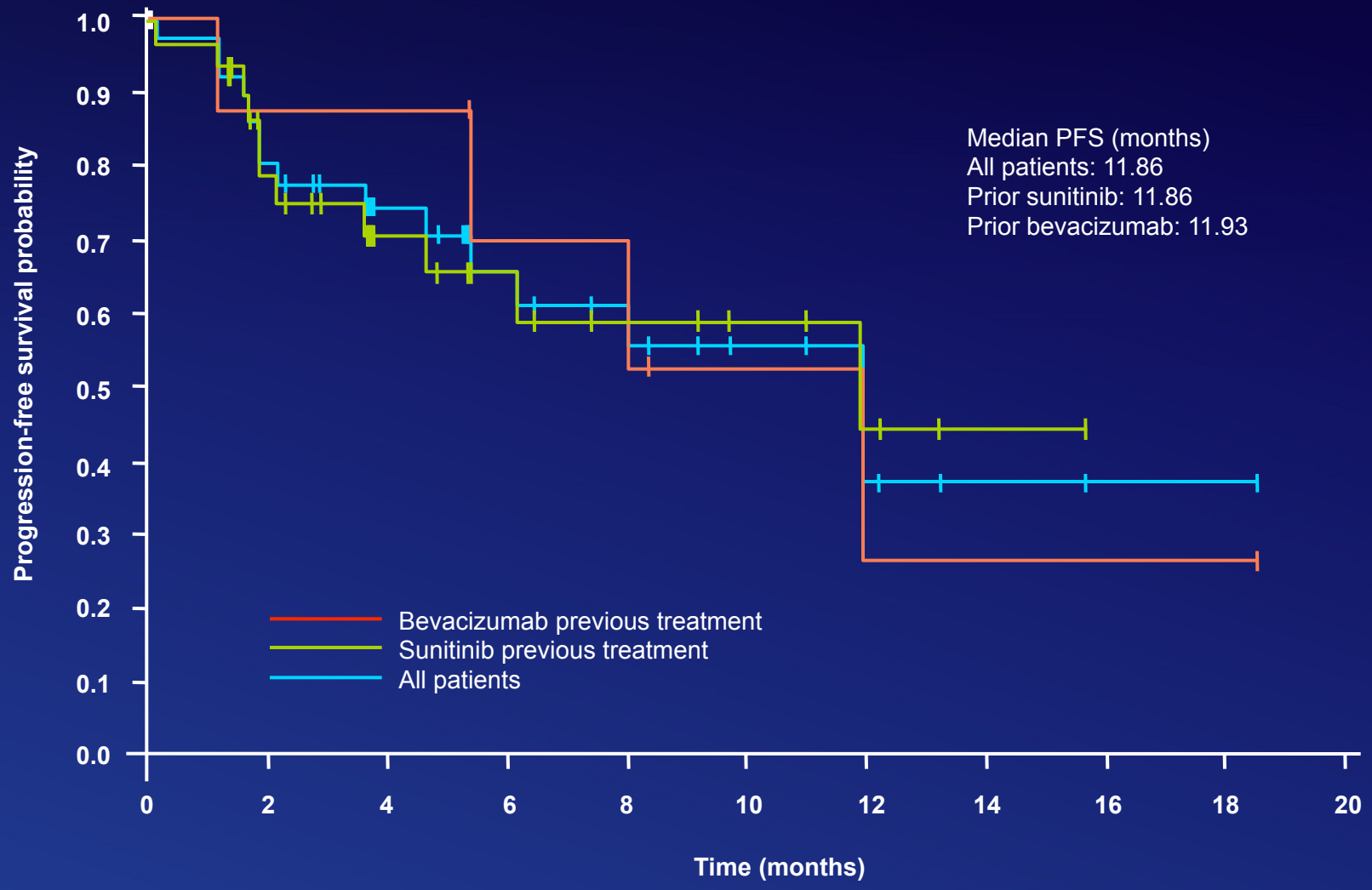
Results in VEGF-targeted Therapy-refractory RCC Patients

Agent	Population	N	OR / TS	PFS
Sunitinib (Rini et al. *JCO*, 2008)	Phase II: Bevacizumab-refractory	62	23% / 75%	7.1 months
Axitinib (Rini et al. *JCO*, 2009)	Phase II: Sorafenib-refractory	62	23% / 55%	7.4 months
Sorafenib (Garcia et al. *Cancer* 2010)	Phase II: Bevacizumab or sunitinib-refractory	49	0% / 30%	4.4 months
Temsirolimus (MacKenzie et al. Ann Oncol. 2010)	Retrospective study	87	5% / n.s.	3.9 months
Everolimus (Motzer et al. *Lancet*, 2008; *Cancer* 2010)	Phase III: TKI-refractory (vs. placebo)	410	2% / 60%	4.9 months (vs. 1.9 months)
Temsirolimus	**Phase III: Sunitinib-refractory (vs. sorafenib)**	**480**		
Axitinib	**Phase III: Front line-refractory (vs. sorafenib)**	**700**		
Everolimus +/- Bevacizumab	**Phase III: TKI-refractory**	**700**		

* Clinical activity is greatest with drugs that more potently inhibit VEGF-R

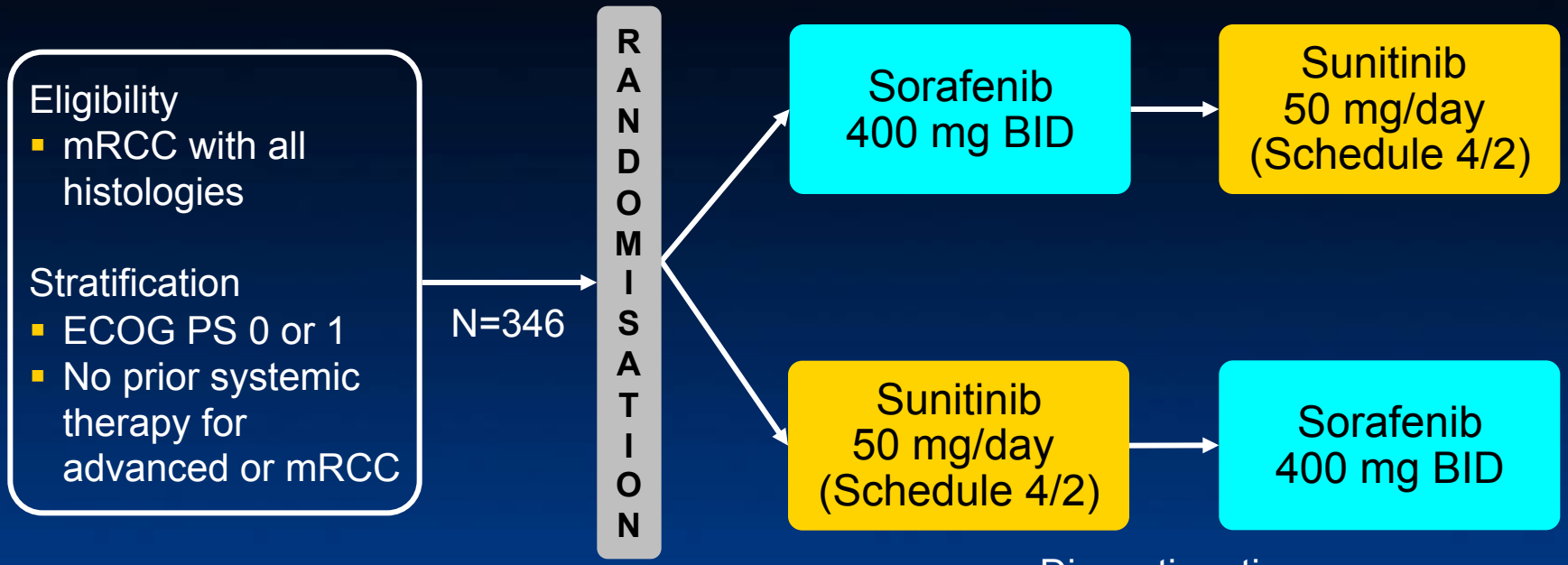
* Mute modest clinical effect is seen with mTOR inhibition in this setting, similar to weak VEGF-R inhibition

Pazopanib in refractory RCC: Progression-free survival (n=41)



Hainsworth *et al*. *Annals Oncol* 2010; 21(Suppl 8): Abstract 910P and poster

SWITCH: Phase III sequential study of sorafenib and sunitinib

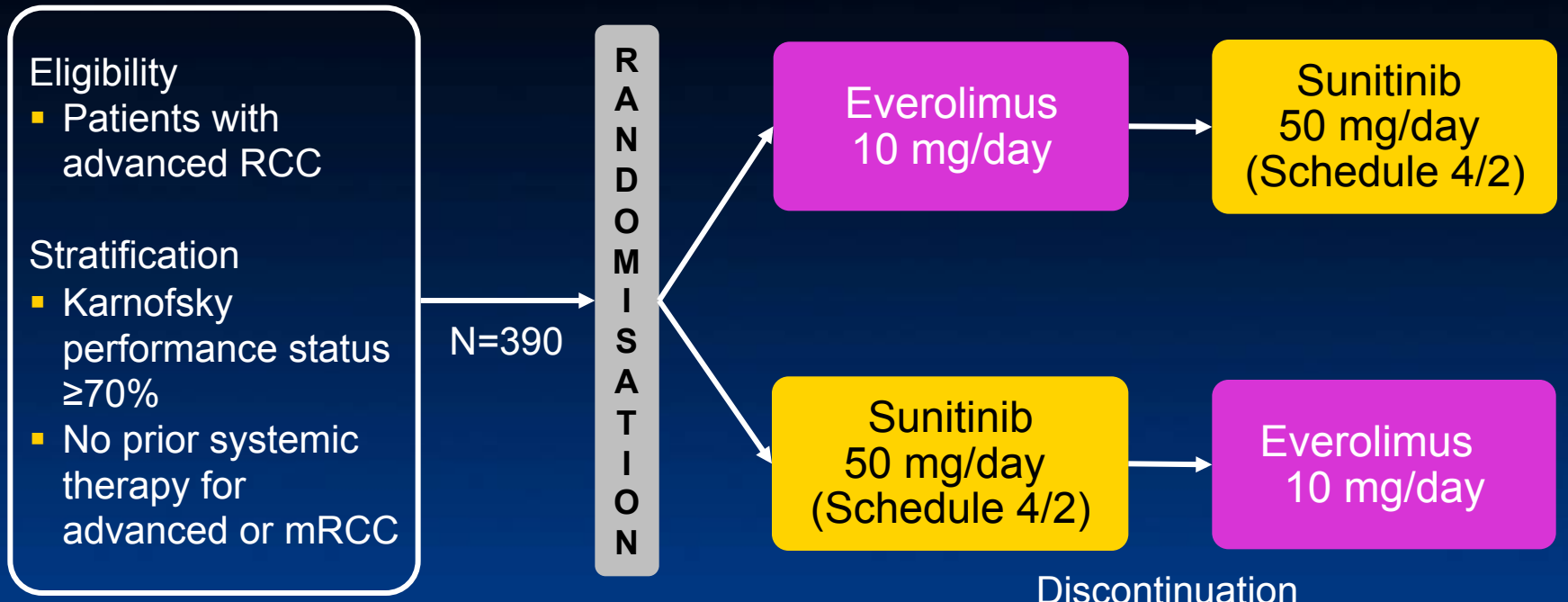


- Primary endpoints: overall PFS
- Secondary endpoints: total time to progression, OS, disease control rate and cardiotoxicity

Study being conducted in Germany

PI: Dr P Goebell
www.clinicaltrials.gov (NCT00732914)

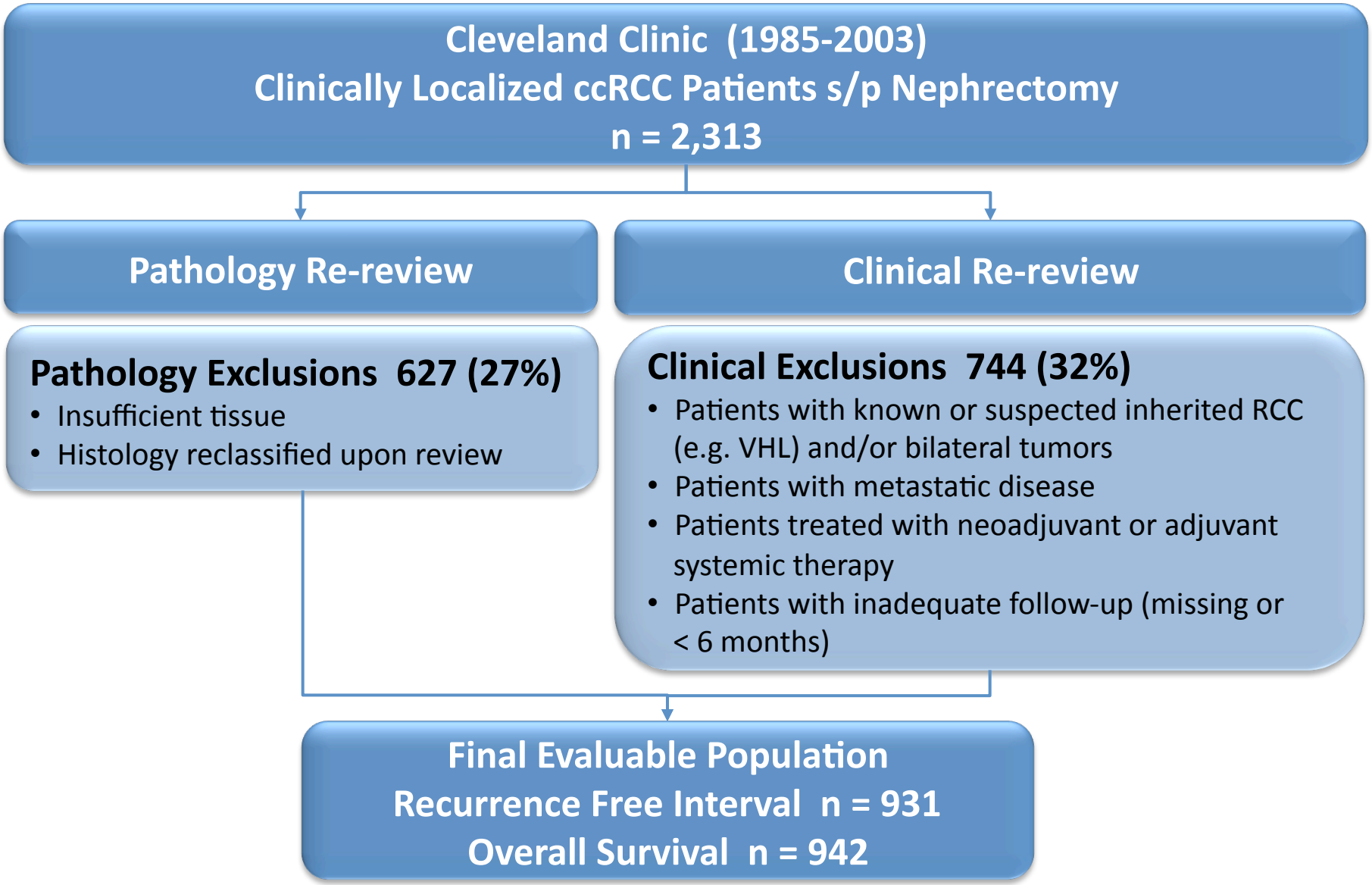
RECORD-3: Phase II sequential study of sunitinib and everolimus



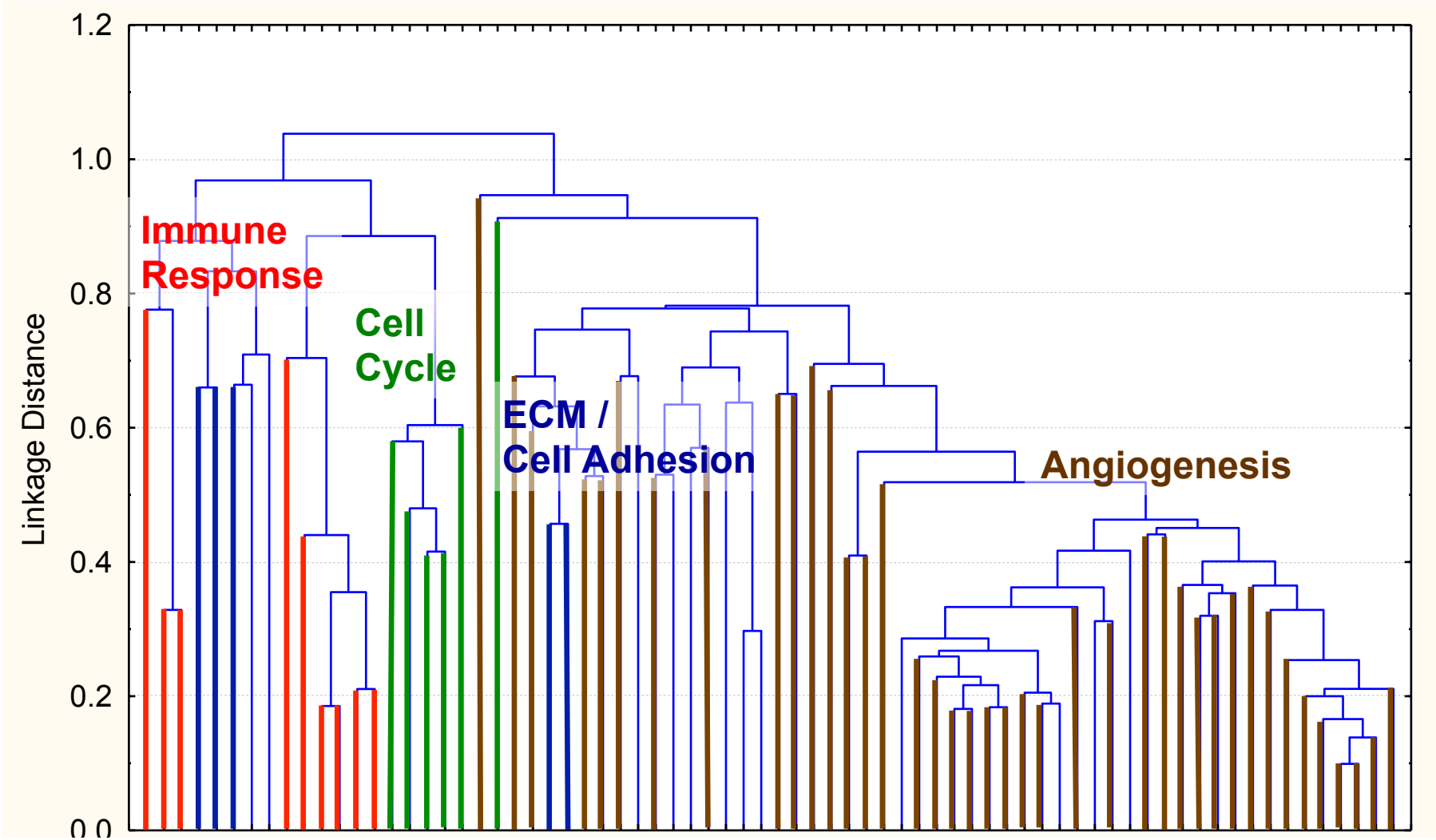
- Primary endpoints: first PFS
- Secondary endpoints: second PFS, ORR, duration of response, patient-reported outcomes, OS

www.clinicaltrials.gov (NCT00903175)

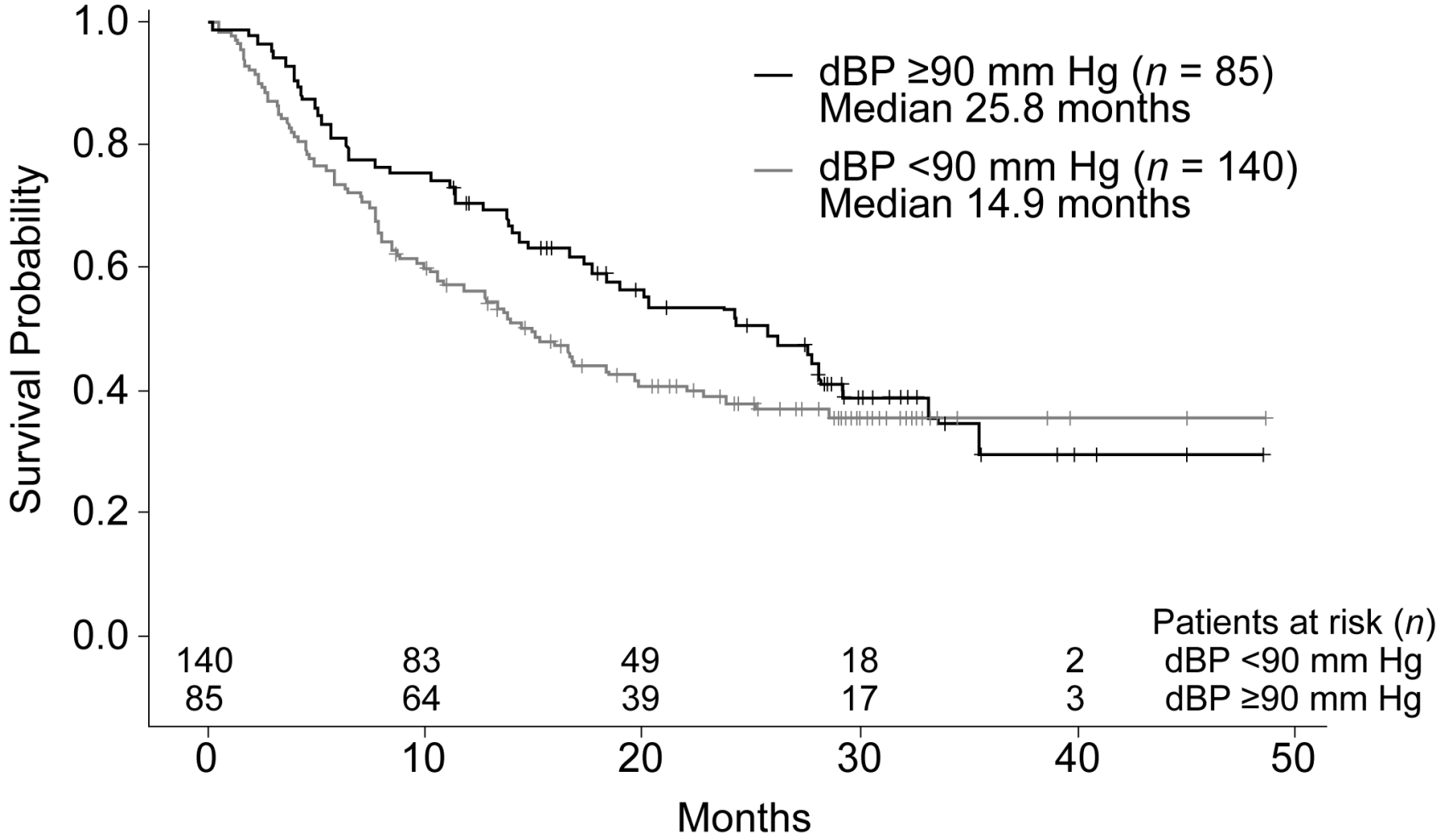
The Search for Predictive Biomarkers



Dendrogram of Key Gene Groups Associated with Recurrence of Localized RCC after Nephrectomy

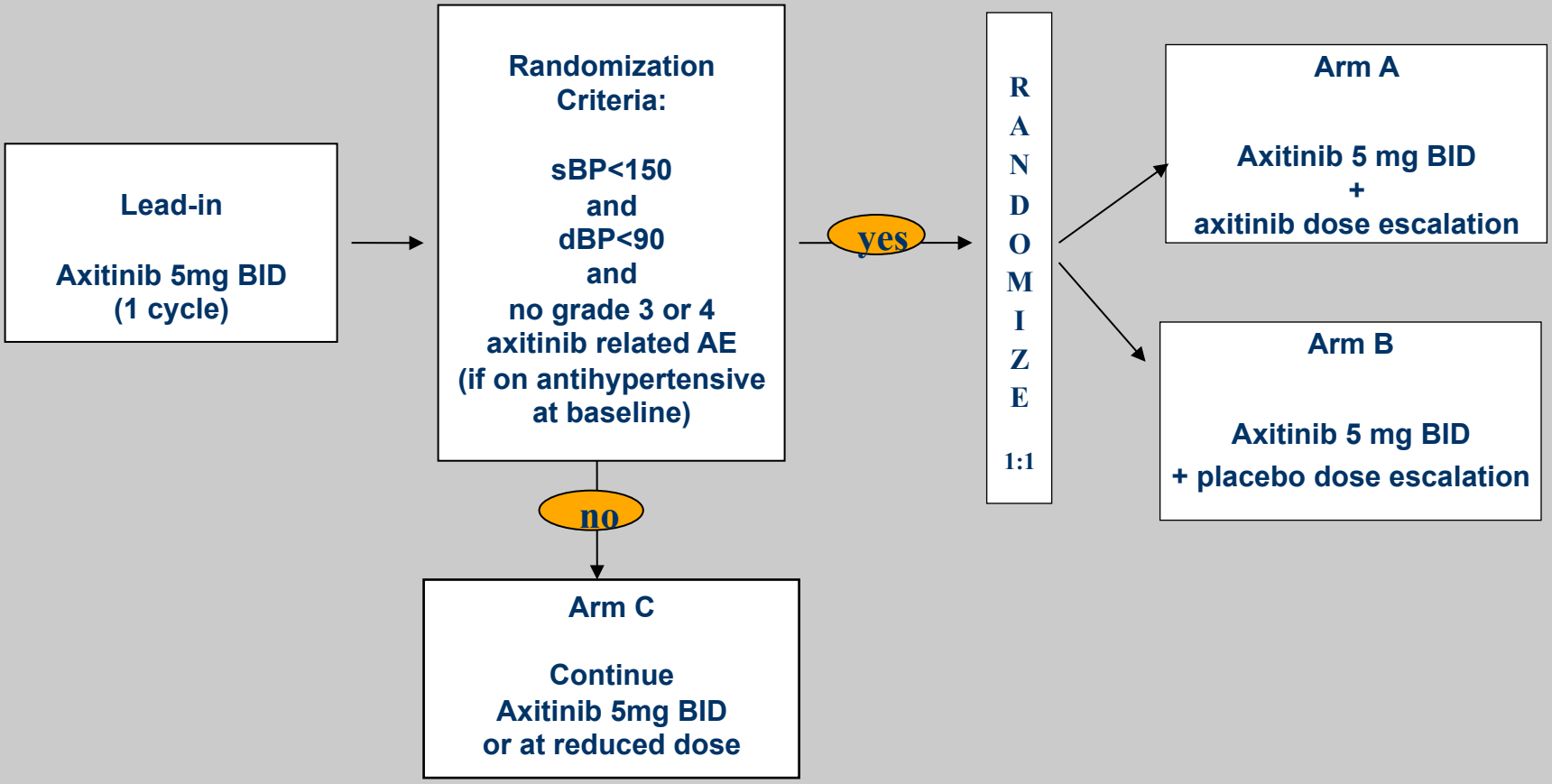


Axitinib: OS in patients with or without dBP ≥ 90 mmHg



Rini BI et al. Clin Ca Res 2011 (in press)

Front-line Axitinib Htn / dose escalation study

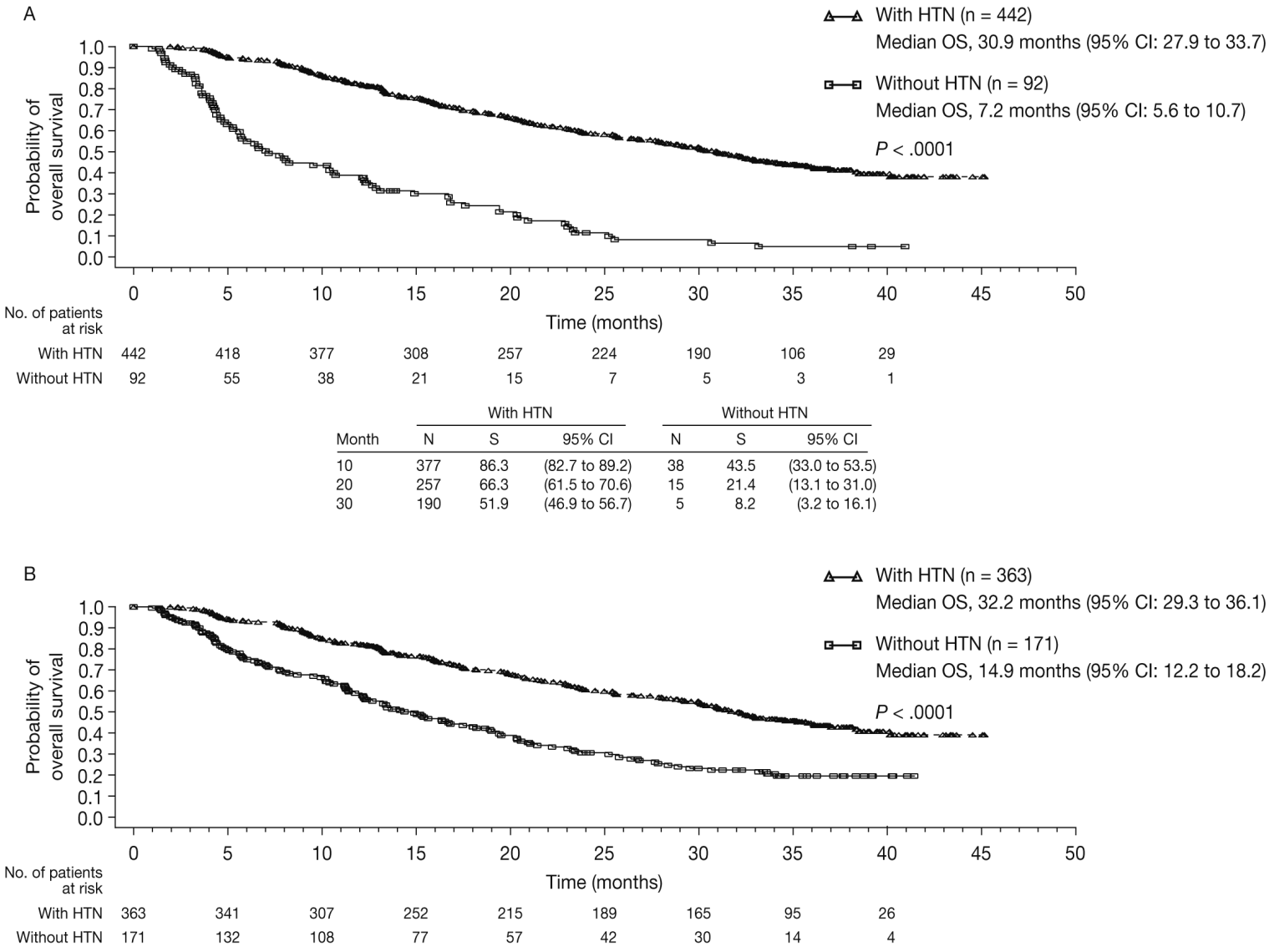


Sunitinib: Clinical Outcome by HTN Status in RCC Patients

	Max. SBP ≥140 mmHg (n=442)	Max. SBP <140 mmHg (n=92)	P-value
Objective response, n (%)	242 (54.8%)	8 (8.7%)	<0.0001
Progression-free survival, months	12.5	2.5	<0.0001
Overall survival, months	30.9	7.2	<0.0001

	Max. DBP ≥90 mmHg (n=363)	Max. DBP <90 mmHg (n=171)	P-value
Objective response, n (%)	208 (57.3%)	42 (25.0%)	<0.0001
Progression-free survival, months	13.4	5.3	<0.0001
Overall survival, months	32.2	14.9	<0.0001

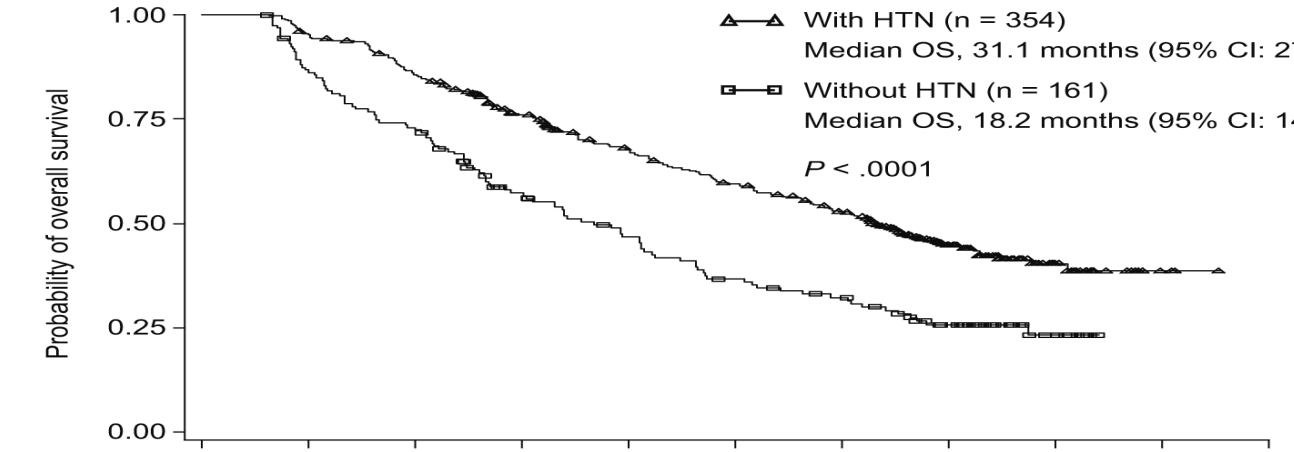
Rini BI et al. *JNCI* 103 (9), 2011



	With HTN			Without HTN		
Month	N	S	95% CI	N	S	95% CI
10	377	86.3	(82.7 to 89.2)	38	43.5	(33.0 to 53.5)
20	257	66.3	(61.5 to 70.6)	15	21.4	(13.1 to 31.0)
30	190	51.9	(46.9 to 56.7)	5	8.2	(3.2 to 16.1)

Rini BI et al. *JNCI* 103 (9), 2011

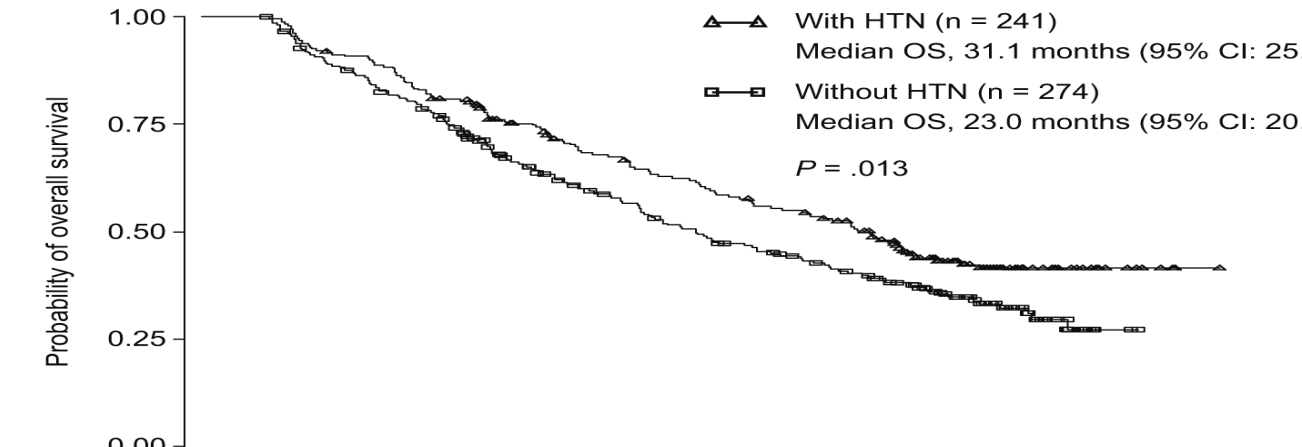
A



No. of patients at risk									
With HTN	354	336	300	247	207	181	154	84	23
Without HTN	161	137	115	82	65	50	41	25	7

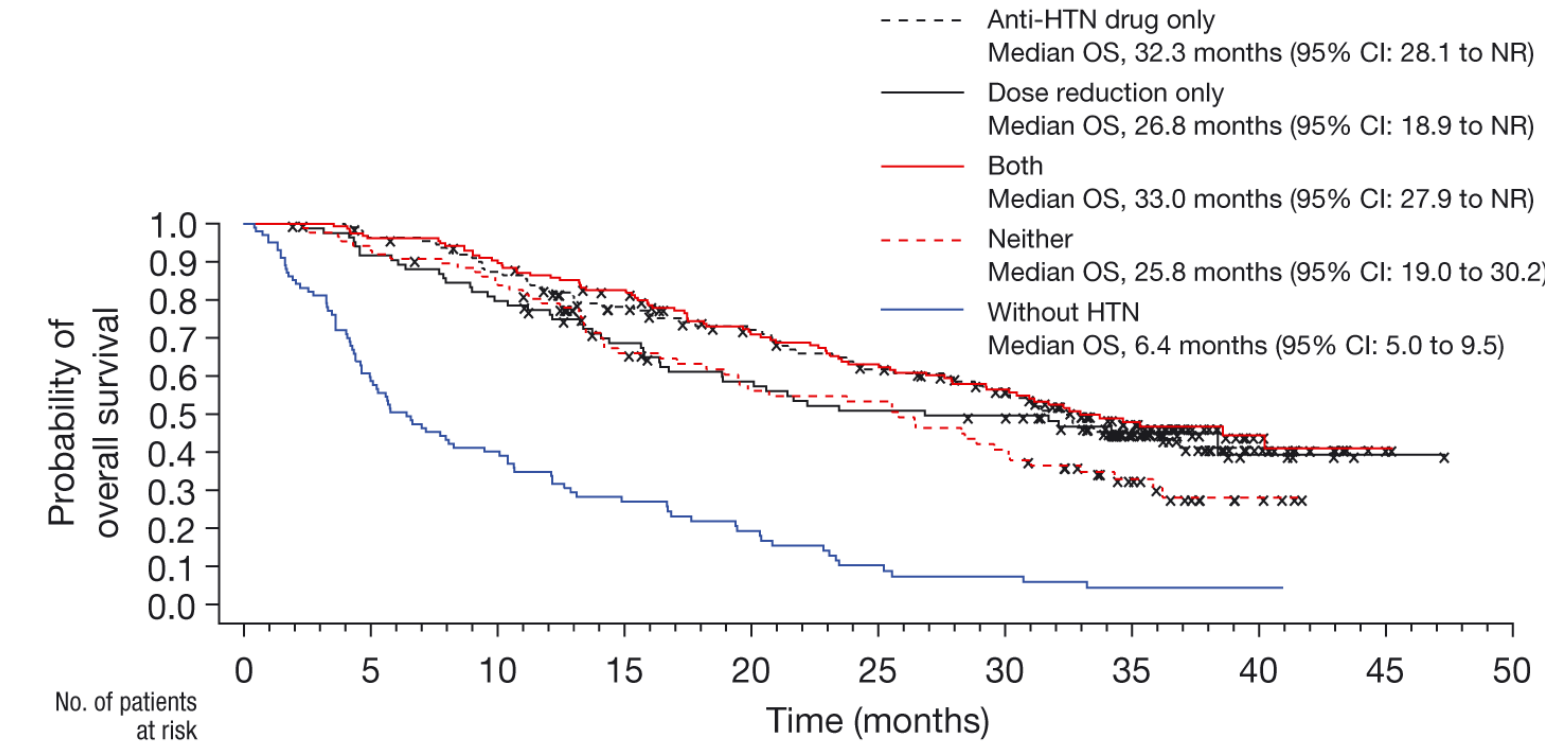
	With HTN			Without HTN		
Month	N	S	95% CI	N	S	95% CI
10	300	85.5	(81.4 to 88.8)	115	72.4	(64.7 to 78.6)
20	207	66.9	(61.5 to 71.6)	65	46.7	(38.6 to 54.5)
30	154	52.8	(47.2 to 58.1)	41	31.4	(24.0 to 39.1)

B



No. of patients at risk									
With HTN	241	225	200	166	140	124	107	58	16
Without HTN	274	248	215	163	132	107	88	51	14

Does Management of Hypertension Matter?



No. of patients at risk									
Anti-HTN drug only	113	108	97	79	70	59	52	29	6
Dose reduction only	85	77	67	55	46	40	37	17	5
Both	157	151	140	125	101	87	72	44	14
Neither	87	82	73	49	40	38	29	16	4
Without HTN	92	55	38	21	15	7	5	3	1

SNPs in *IL8, FGFR2, VEGFR3, VEGFA,* and *NR1I2* Associated with OS in Pazopanib-Treated Patients

GENE	SNP (NCBI)	*P* Value	Allele Frequency Caucasians, %[1]	Allele Frequency Asians, %[1]	Allele Frequency Blacks, %[1]
IL8	rs1126647	0.003	39	32	6
IL8	rs4073	0.01	40	35	83
FGFR2	rs2981582	0.01	42	25	52
VEGFR3	rs307826	0.04	7	0	0
VEGFA	rs1570360	0.05	25	17	3
NR1I2	rs3814055	0.03	41	27	27

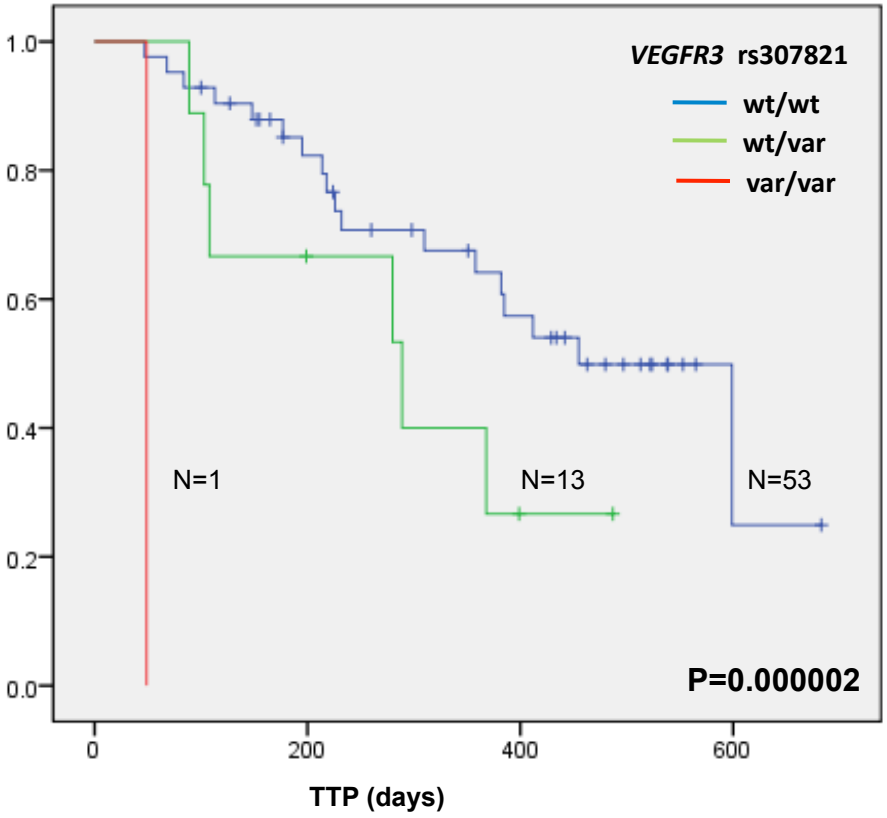
- None of the SNPs associated with OS in patients who did not receive pazopanib
- Limitation: small sample size (N = 37)

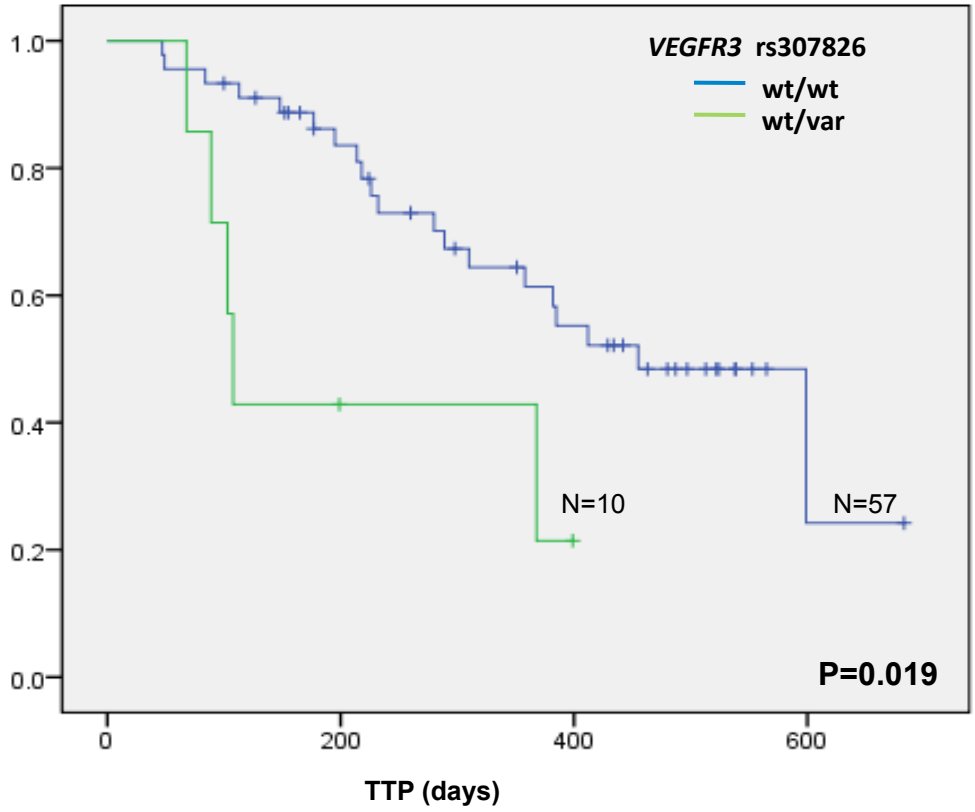
1. Frequency data: HapMap (http://www.ncbi.nlm.nih.gov).

ESMO congress Milan 2010

Time to Progression

VEGFR3





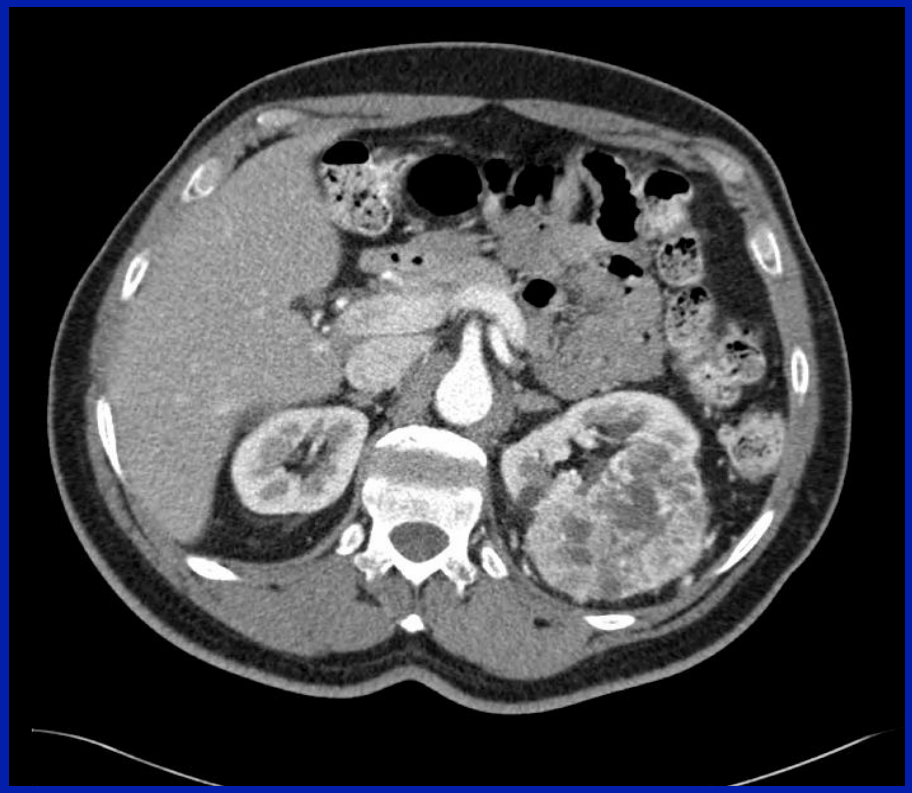
Response
(PD vs CR+PR+SD)

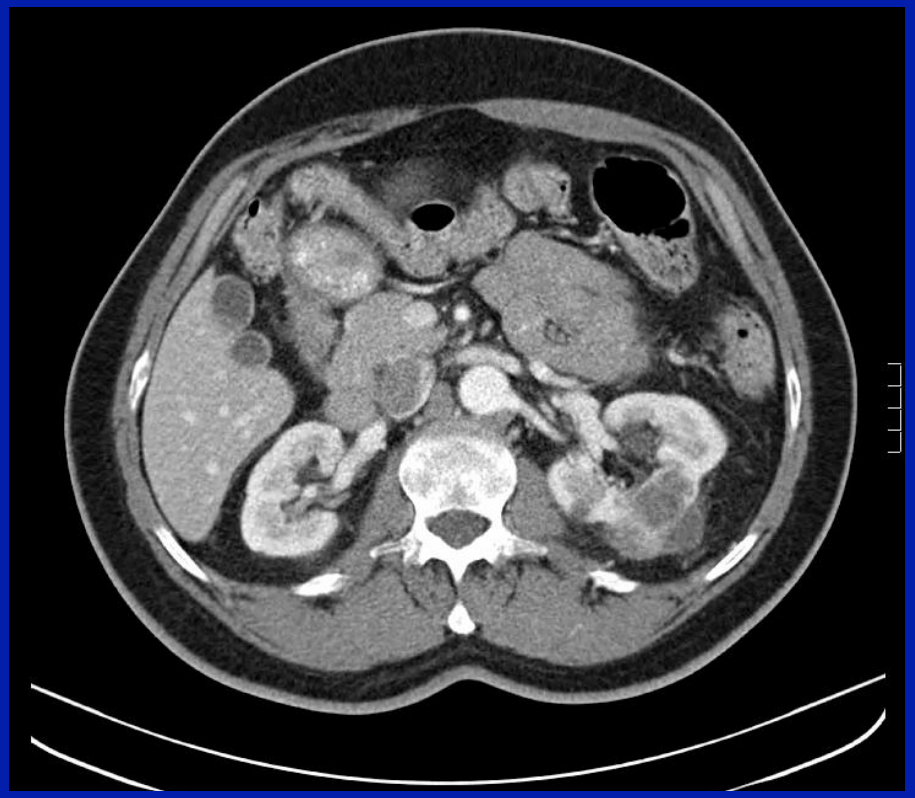
VEGFR3 rs307821 **P=0.045** (Univariate)
VEGFR3 rs307826 **P=0.028** (Univariate)

Donas JG et al. ESMO 2010

Pre-surgical VEGF-Targeted Therapy in RCC

Approach	Patient population	No. of pts with primary tumor shrinkage	Amount of primary tumor shrinakge
Sunitinib (CCF/ retrospective)	'Unresectable' RCC (n=19)	42%	24% (range, 2-46%)
Sunitinib (Netherlands/ retrospective)	M+ pts with primary in place (n=17)	59%	12% (range, 2-33%)
Sunitinib (CCF/ prospective)	'Unresectable' RCC (n=18)	72%	19% (range, 1-64%)
Sorafenib (UNC/ prospective)	≥T2 RCC; sorafenib 400 mg BID x 4–8 weeks prior to nephrectomy (n=25)	64%	11% (range, 0–40%)
Bevacizumab (+/- erlotinib) (MDACC/prospective)	Metastatic RCC pts prior to nephrectomy; treatment x 8 weeks (n=50)	52%	~ 10% (range, 1-25%)

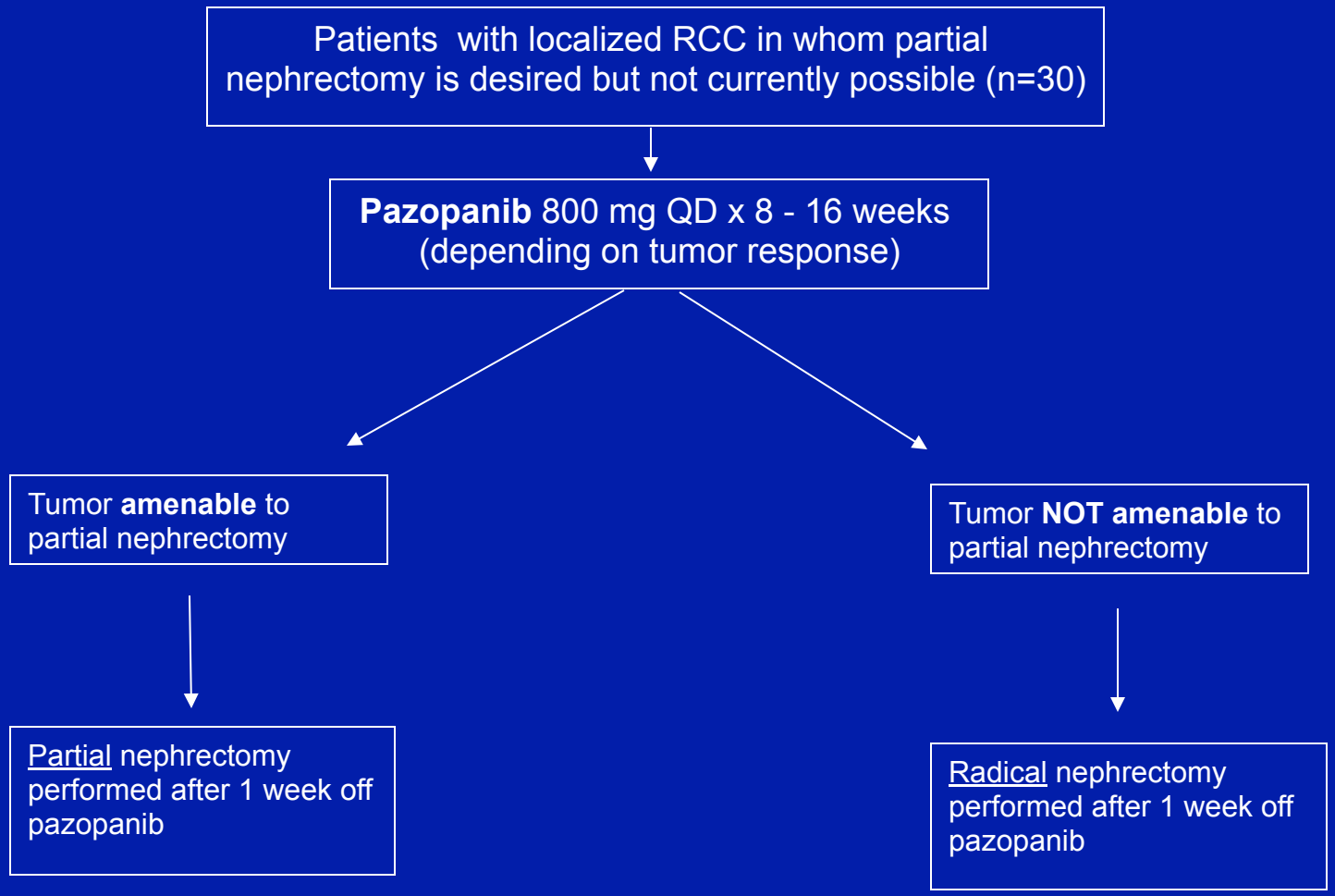




• Primary RCC baseline and after 2 cycles of sunitinib: tumor shrinkage enabled partial nephrectomy as the tumor has pulled away from the renal hilum.

• Viable RCC tumor cells were present in all post-sunitinib surgical specimens. No unexpected surgical morbidity was encountered.

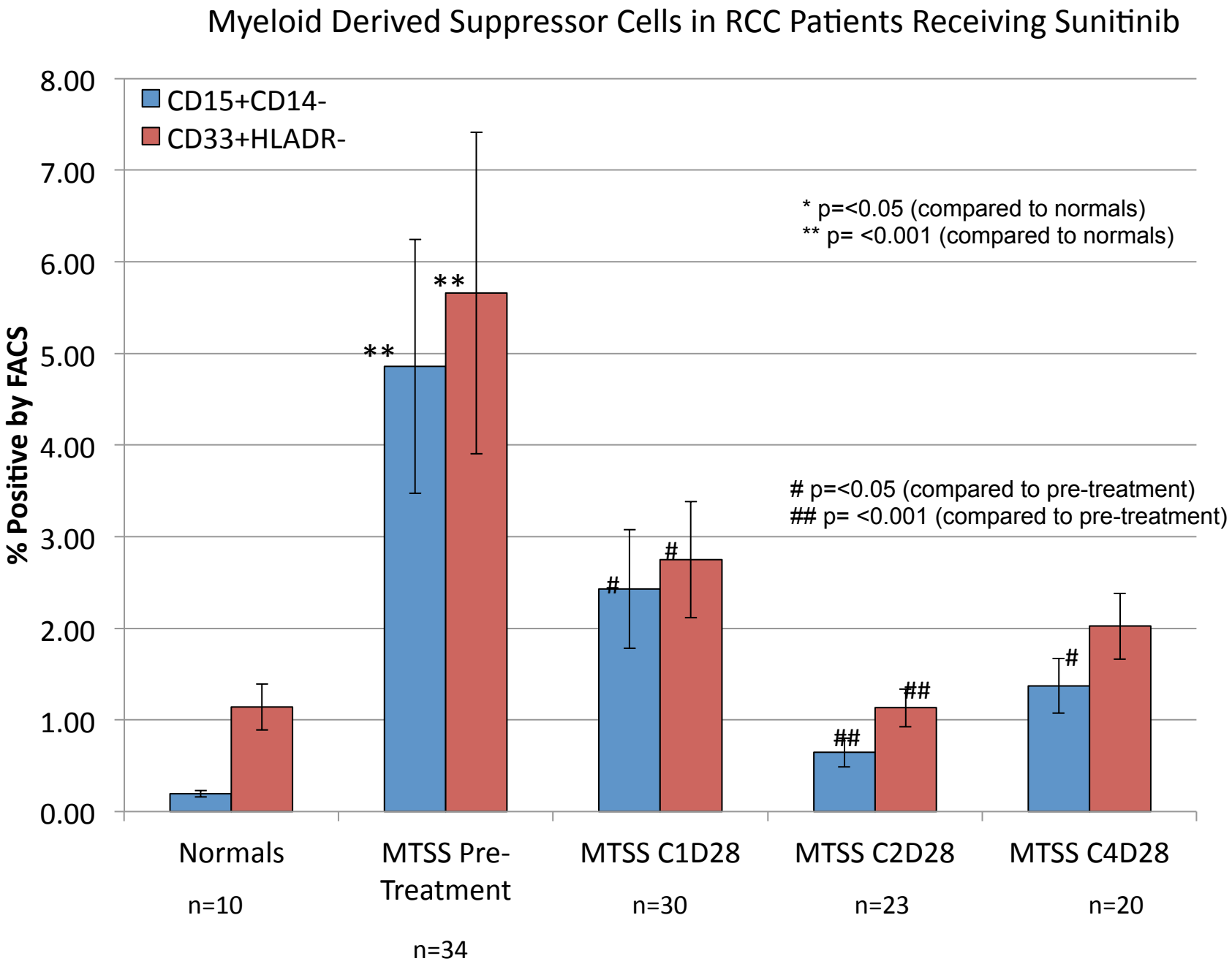
A single arm phase II study of pazopanib in patients with localized RCC to enable partial nephrectomy



On-going/Planned Adjuvant RCC phase III Studies

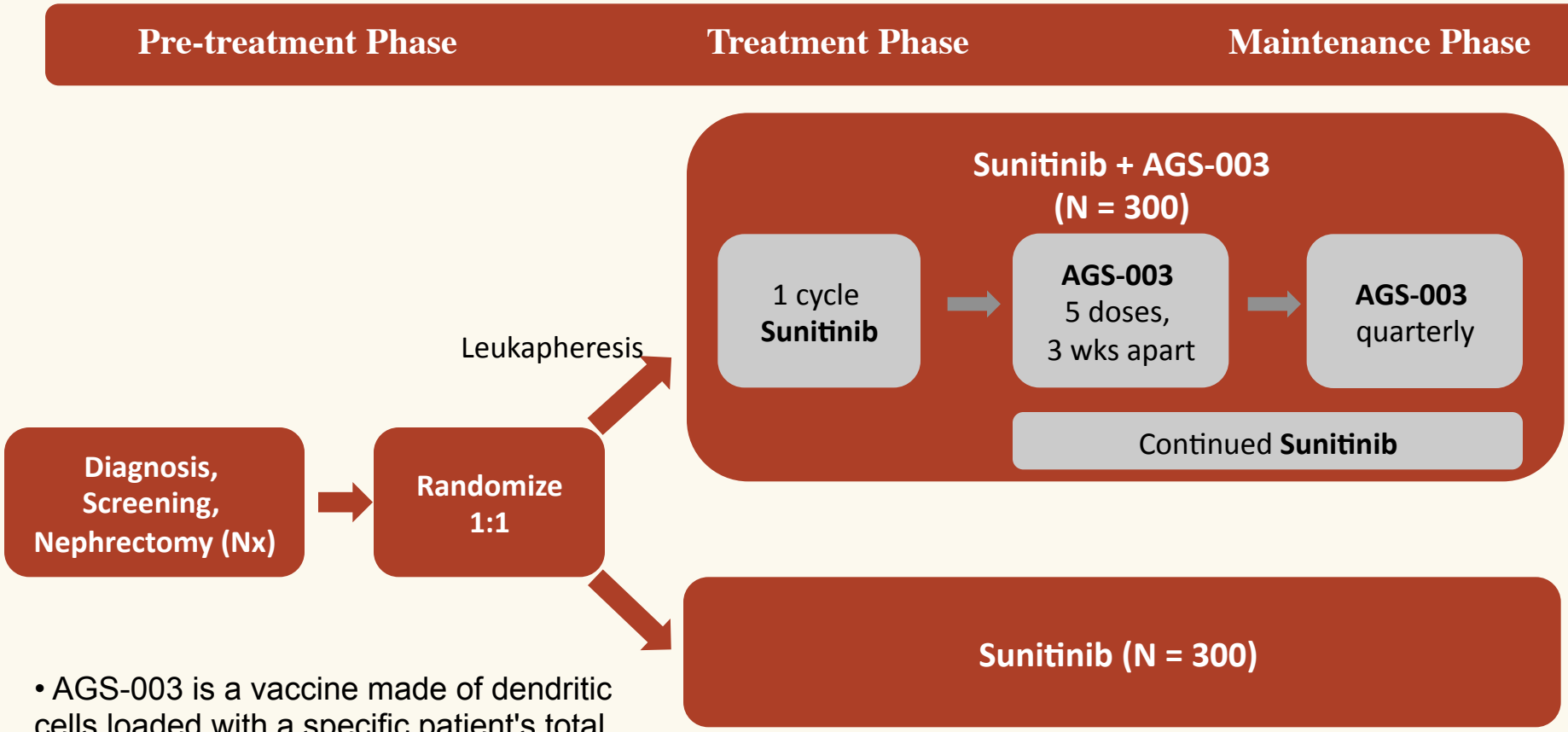
	n	Population/Design	Primary Endpoint	Study Start
ASSURE[1] (ECOG)	1923	Placebo *vs.* sunitinib *vs.* sorafenib, 1 year	DFS	2006
SORCE[2] (MRC)	1656	Placebo *vs.* sorafenib 1 year *vs.* sorafenib 3 years	DFS	2007
S-TRAC[3] (Pfizer)	500	Placebo *vs.* sunitinib 1 year	DFS	2007
Everest[4] (SWOG)	1218	Placebo *vs.* everolimus 1 year	DFS	2010
PROTECT VEG113387 (GSK)	1500	Placebo *vs.* pazopanib 1 year	DFS	Q4 2010

1. ClinicalTrials.gov. NCT00326898.
2. ClinicalTrials.gov. NCT00492258.
3. ClinicalTrials.gov. NCT00375674.
4. ClinicalTrials.gov. NCT01120249.



Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients. Finke J, Rini BI ,*Clin Cancer Res*. 2009

Autologous Vaccine Phase 3 Trial Planned for mid-2011

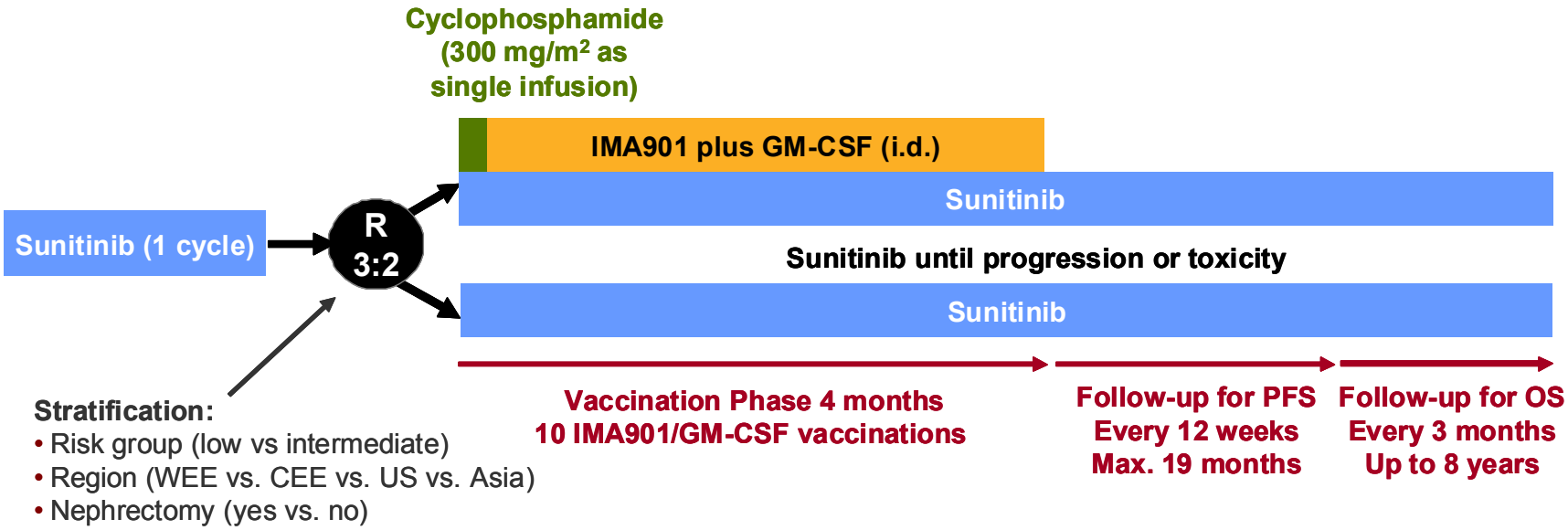


• AGS-003 is a vaccine made of dendritic cells loaded with a specific patient's total tumor RNA

1 Sunitinib cycle = 4 weeks on followed by 2 weeks off

Argos THERAPEUTICS

IMA901 Renal Cell Cancer Phase 3 trial
Study design of planned IMA901-301 study



N=330
- 1st line metastatic and/or locally advanced RCC
- HLA-A*02-positive
- Documented tumor lesions
- Favorable or intermediate risk (Heng et al., 2009)

* IMA091 is a vaccine comprised of multiple, RCC tumor-associated peptides

Primary endpoint

- Overall Survival

Secondary endpoints

- Overall Survival in biomarker-defined subgroup (pre-specified)
- Progression-free survival (PFS)
- Safety and tolerability
- Cellular immunomonitoring

Conclusions

- Therapy targeted at VEGF and mTOR has dramatically changed the therapeutic landscape of metastatic RCC.
- There is no single drug as best choice for initial therapy pending future trials.
- I believe more potent VEGFR TKIs will be substantial clinical advances.
- Intermittent therapy or other novel administration methods warrant investigation.

Conclusions

- Mechanisms/biomarkers that underlie response/ resistance to targeted therapy remain elusive but preliminary data exists and intense efforts are underway.

- The activity/utility of VEGF-targeted therapy in the (neo)/adjuvant setting awaits further investigation.

RCC Treatment Algorithm: 2011

Setting	Patients	Therapy (level 1)	Other Options (≥ level 2)
Untreated	Good or Intermediate risk	Sunitinib Bevacizumab + IFN Pazopanib	HD IL-2 Sorafenib Clinical trial Observation
	Poor risk	Temsirolimus	Sunitinib, Bev/IFN Clinical trial
	Non-clear cell		Anything Clinical Trial
	Sarcomatoid		Sunitinib (+/- Gem) Clinical trial
Refractory	Cytokine	Sorafenib Axitinib	Sunitinib, Bevacizumab
	VEGF	Everolimus	Everything
	mTOR	Clinical trial	Clinical trial