Targeted Therapy in Advanced Renal Cell Carcinoma

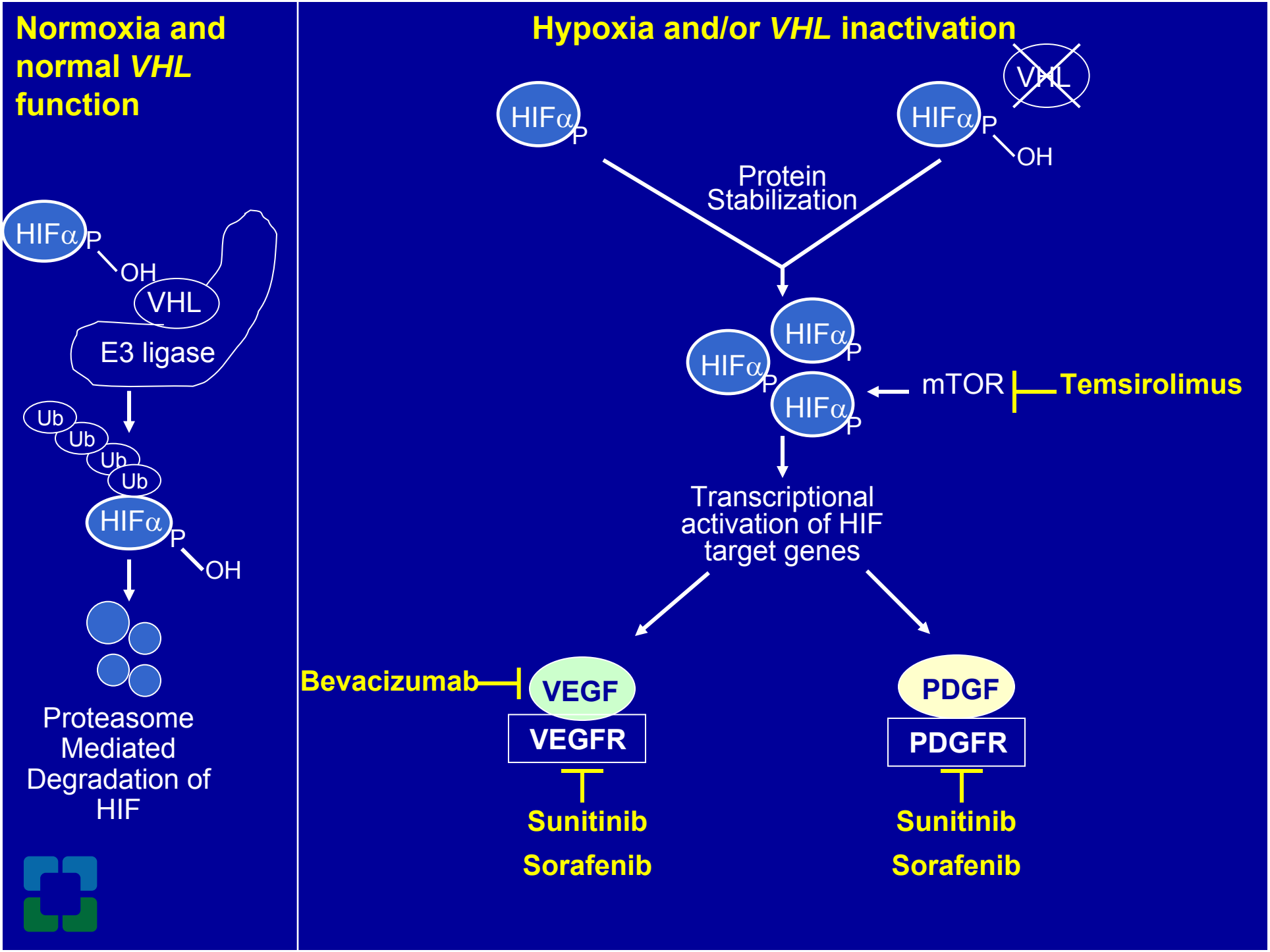
Brian I. Rini, M.D.
Department of Solid Tumor Oncology
Glickman Urologic and Kidney Institute
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio USA

Rini Disclosures

Nature of Relationship	Company
Research funding	Pfizer, Genentech, Wyeth, Bayer/Onyx
Consultant	Pfizer, Genentech, Wyeth, Bayer/Onyx, Gerson-Lehrman group

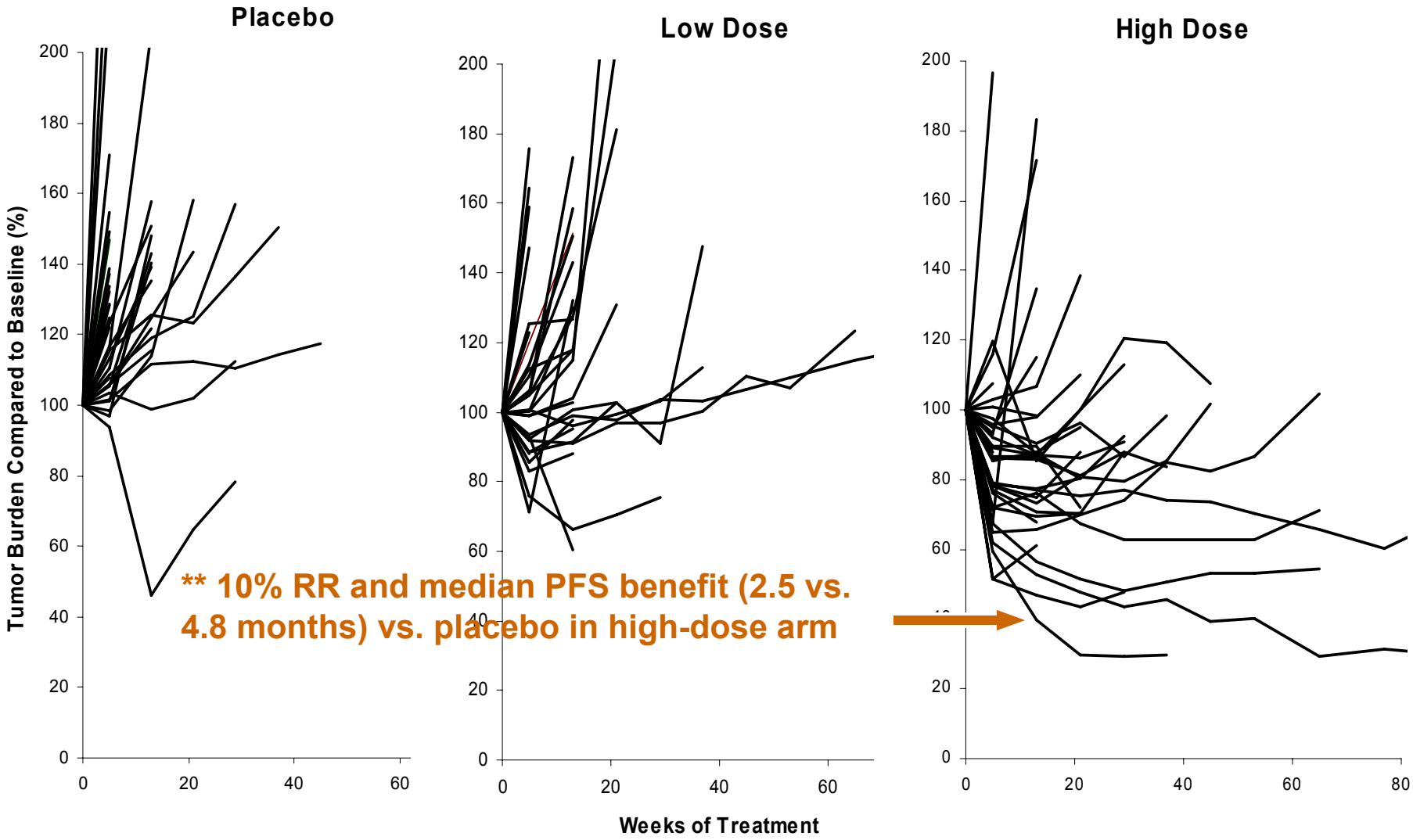
Targeted Therapy in RCC

- Current clinical data with new agents
  - Monotherapy data with VEGF- and mTOR-targeted approaches
- Translational Efforts
  - Immunoregulatory properties of sunitinib
  - *VHL* status and correlation with clinical outcome


Normoxia and normal *VHL* function
HIFα P
OH
VHL
E3 ligase
Ub
Ub
Ub
Ub
HIFα P
OH
Proteasome Mediated Degradation of HIF
Hypoxia and/or *VHL* inactivation
HIFα P
HIFα P
OH
VHL
Protein Stabilization
HIFα P
HIFα P
HIFα P
mTOR
Temsirolimus
Transcriptional activation of HIF target genes
Bevacizumab
VEGF
VEGFR
Sunitinib
Sorafenib
PDGF
PDGFR
Sunitinib
Sorafenib

Bevacizumab (Avastin)

Bevacizumab: change in tumor burden in metastatic RCC patients



** 10% RR and median PFS benefit (2.5 vs. 4.8 months) vs. placebo in high-dose arm

Elaraj et al. *J Immunotx* 27(4), 2004

Bevacizumab ± IFN Phase III: Study Design

Eligibility Criteria

- Confirmed metastatic RCC with >50% clear cell histology
- Prior nephrectomy
- Karnofsky PS of ≥70%
- Measurable or non-measurable disease (by RECIST)
- No prior systemic treatment for metastatic RCC disease

→ **Randomization 1:1**

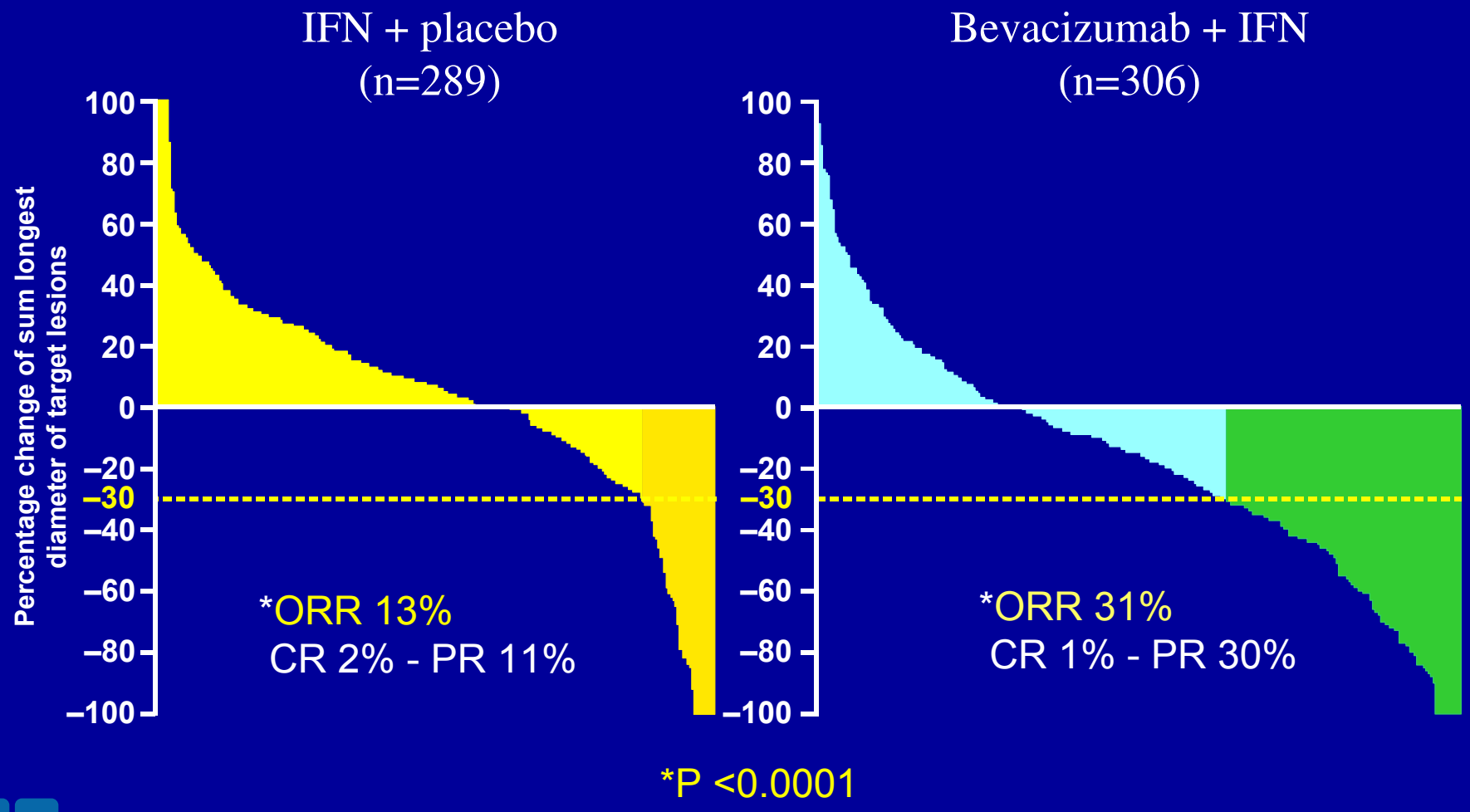
Stratified by:
country
Motzer score
(n=649)

→ **Bevacizumab 10mg/kg IV q2w + IFN-α2a 9MIU sc tiw (n=327)**

→ **IFN-α2a 9MIU sc tiw + placebo (n=322)**

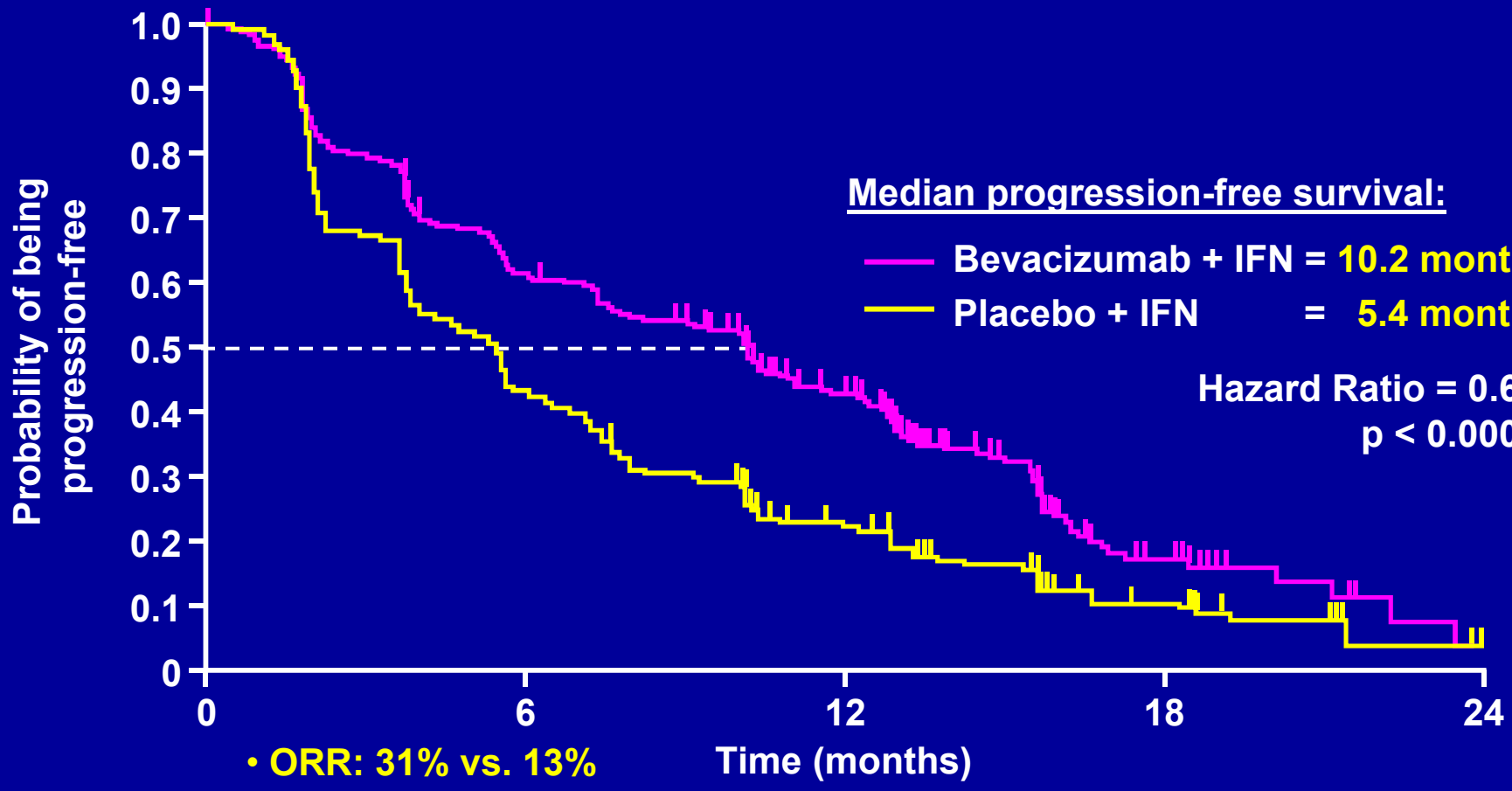
Adapted from Escudier B et al. Presented at ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.

Bevacizumab ± IFN Phase III: Tumor Response



*Patients with measurable disease only; investigator assessed

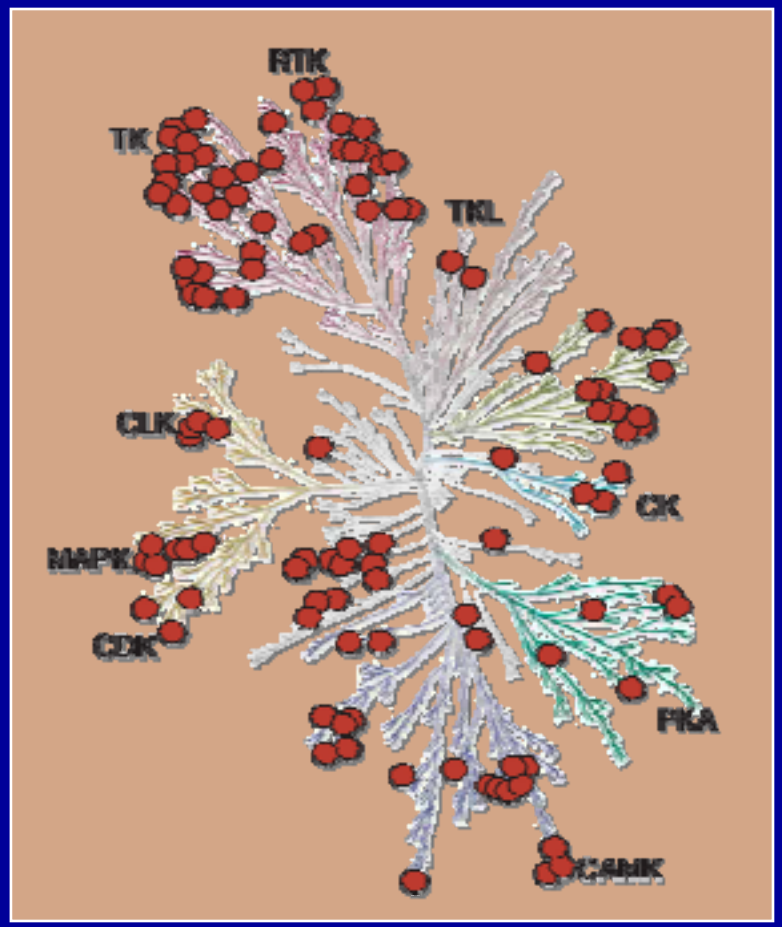
Bevacizumab + Interferon (IFN) vs. IFN in untreated metastatic RCC



Adapted from Escudier B et al. Presented at ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.

Sunitinib (Sutent)

Inhibitory Profile of Kinases for Sunitinib



Fabian MA, et al. *Nature Biotechnology* 2005;23:329–336

Sunitinib: Phase II trials in RCC Best Response by RECIST

	Trial 1	Trial 2
Patients	63	106
Overall objective response	44%*	43%*
	36%**	35%**
Median progression-free survival	8.2 months	

*investigator review; **independent review

J Clin Oncol 2006;24:16–24; JAMA 2006;295:2516–24.

Phase III Sunitinib vs. Interferon

N=750

Stratification Factors

- **LDH ≤1.5 vs >1.5xULN**
- **ECOG PS 0 vs 1**
- **Presence vs Absence of Nephrectomy**

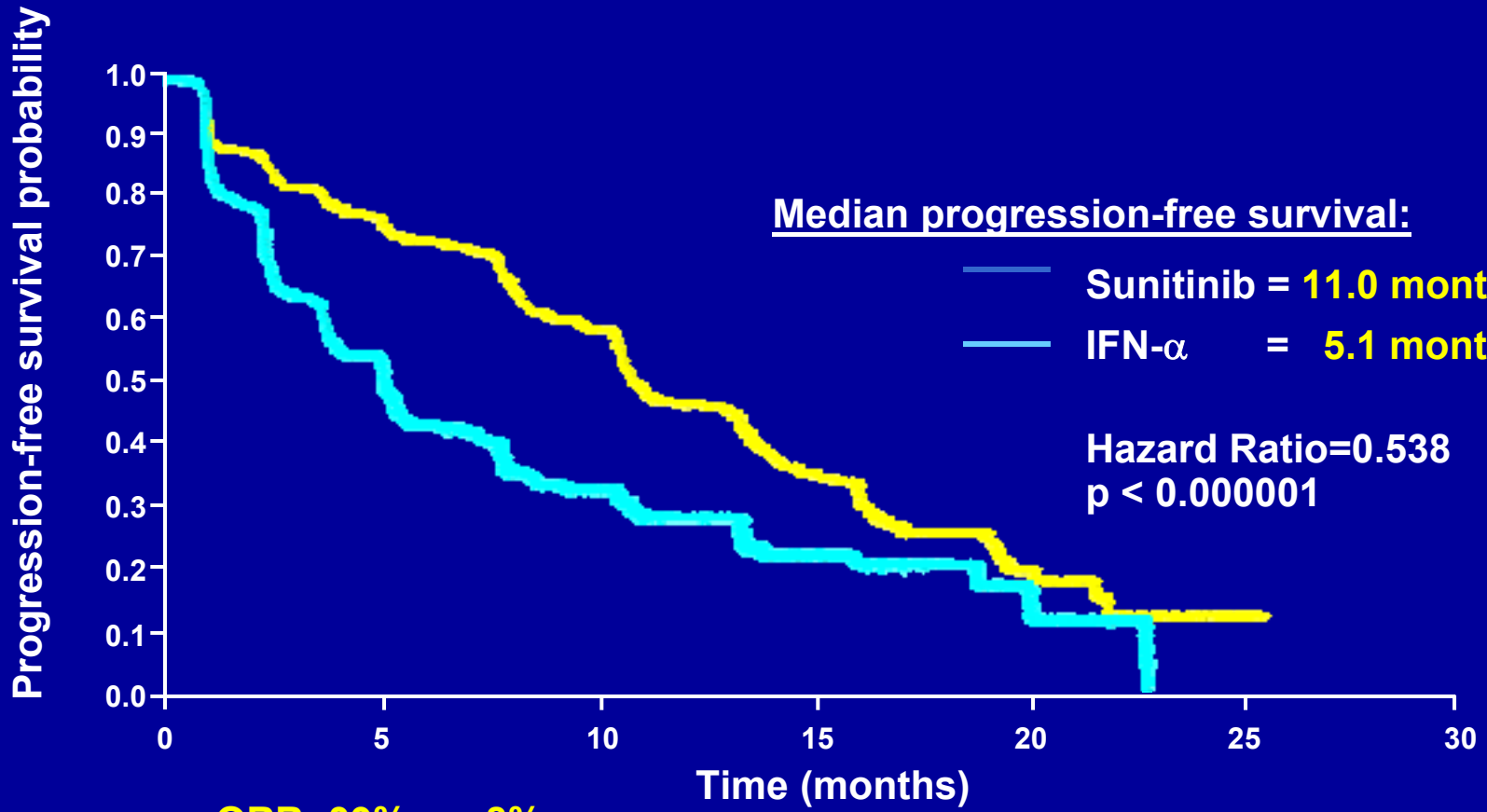
RANDOMIZATION

Sunitinib (N=375)

IFN-α (N=375)

Motzer et al. *NEJM*, 2007

Sunitinib vs. Interferon in untreated metastatic RCC: PFS

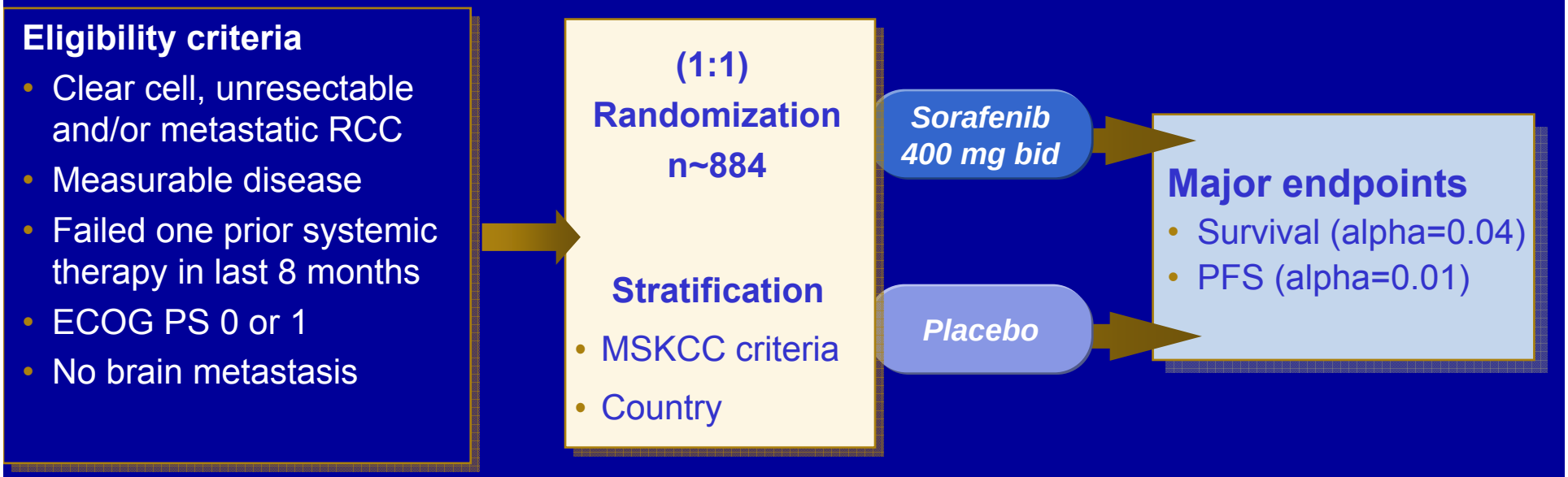


- ORR: 39% vs. 8%
- No CR's observed

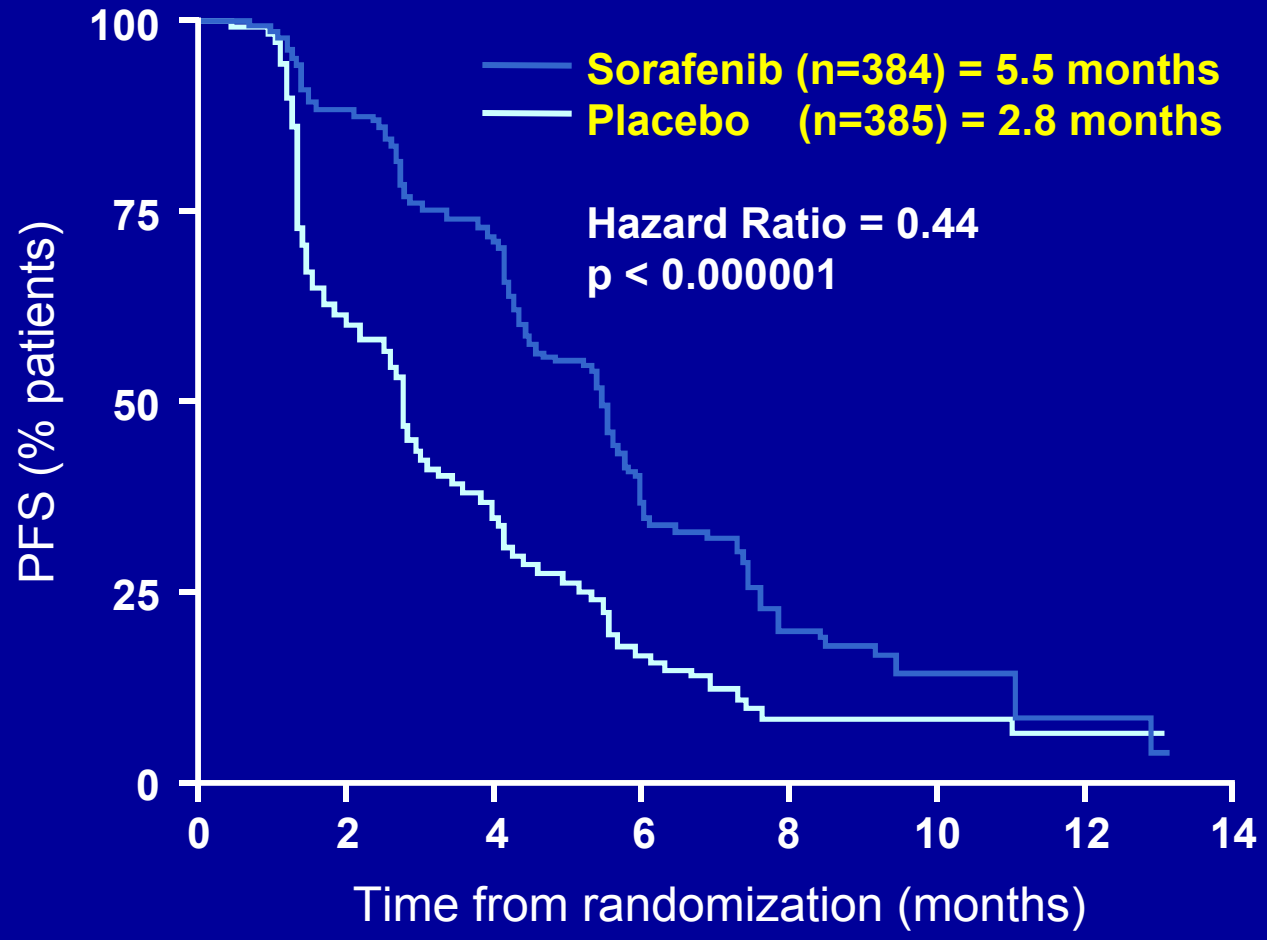
Adapted from Motzer R et al. Presented at ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.

Sorafenib (Nexavar)

Sorafenib phase III vs. placebo in cytokine-refractory

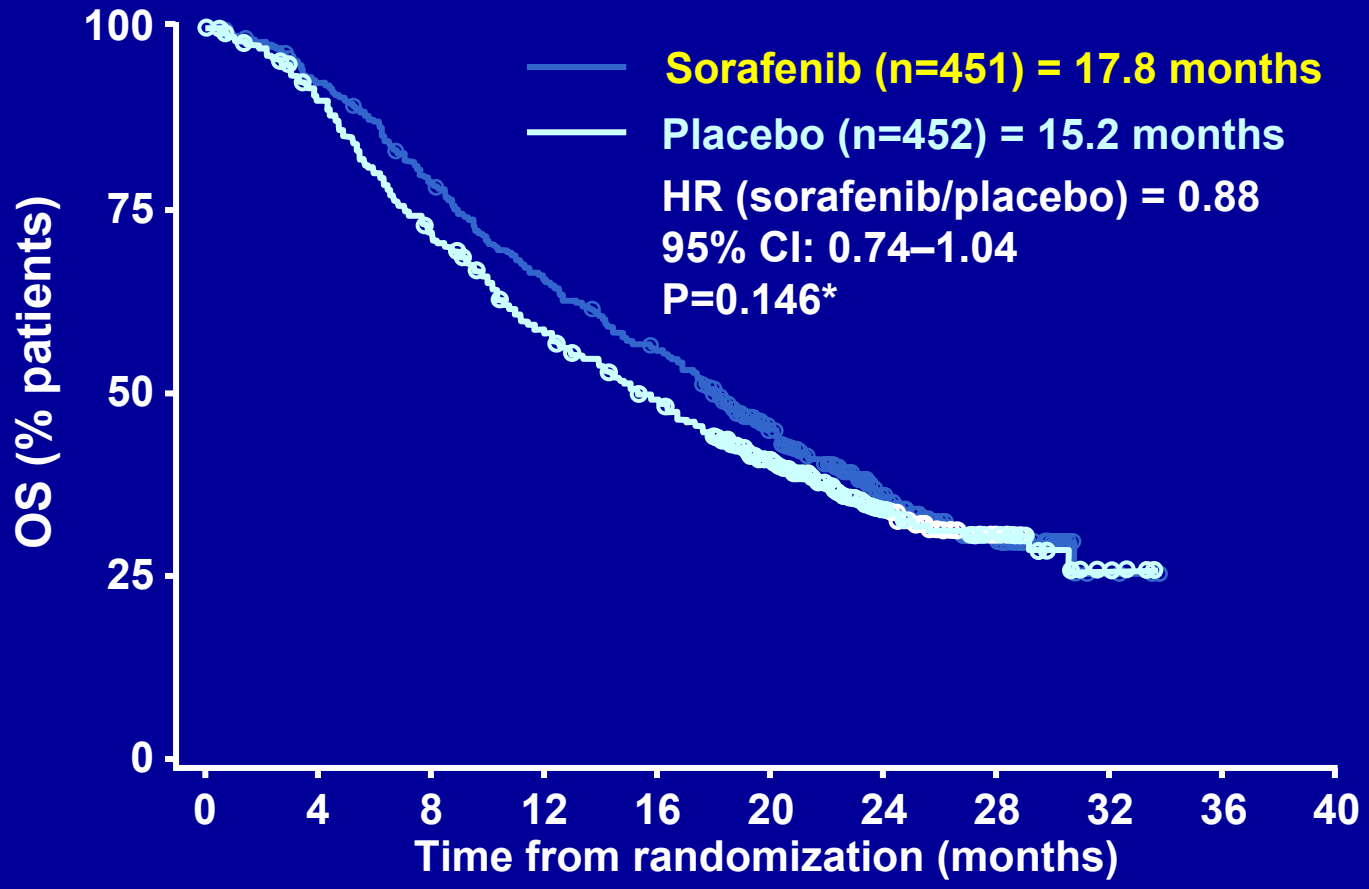


Sorafenib vs. placebo in cytokine-refractory metastatic RCC: PFS

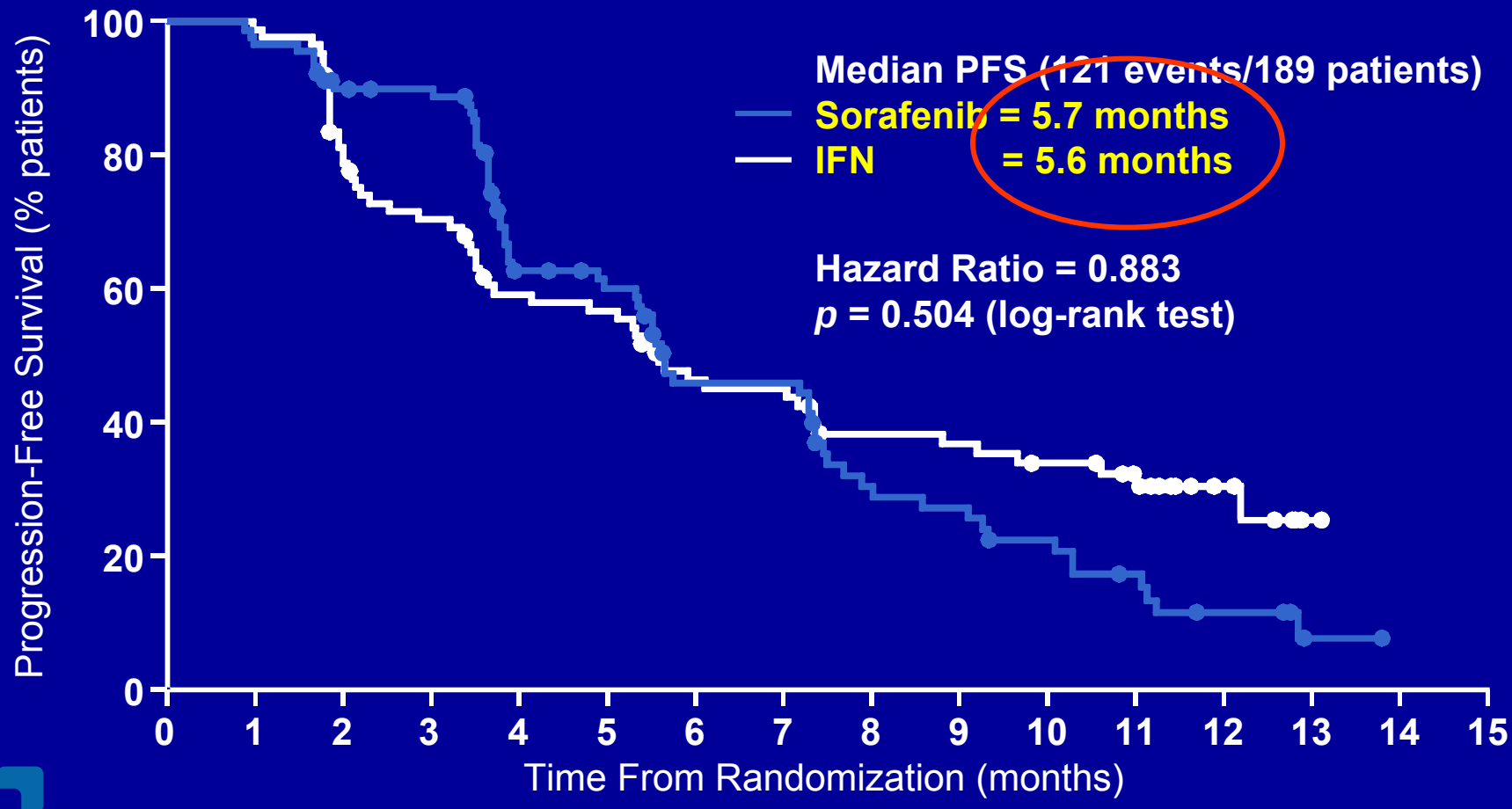


Escudier B, et al. N Engl J Med 2007;356:125–34

Final OS Analysis
16 Months Post-Crossover: Intent-to-Treat



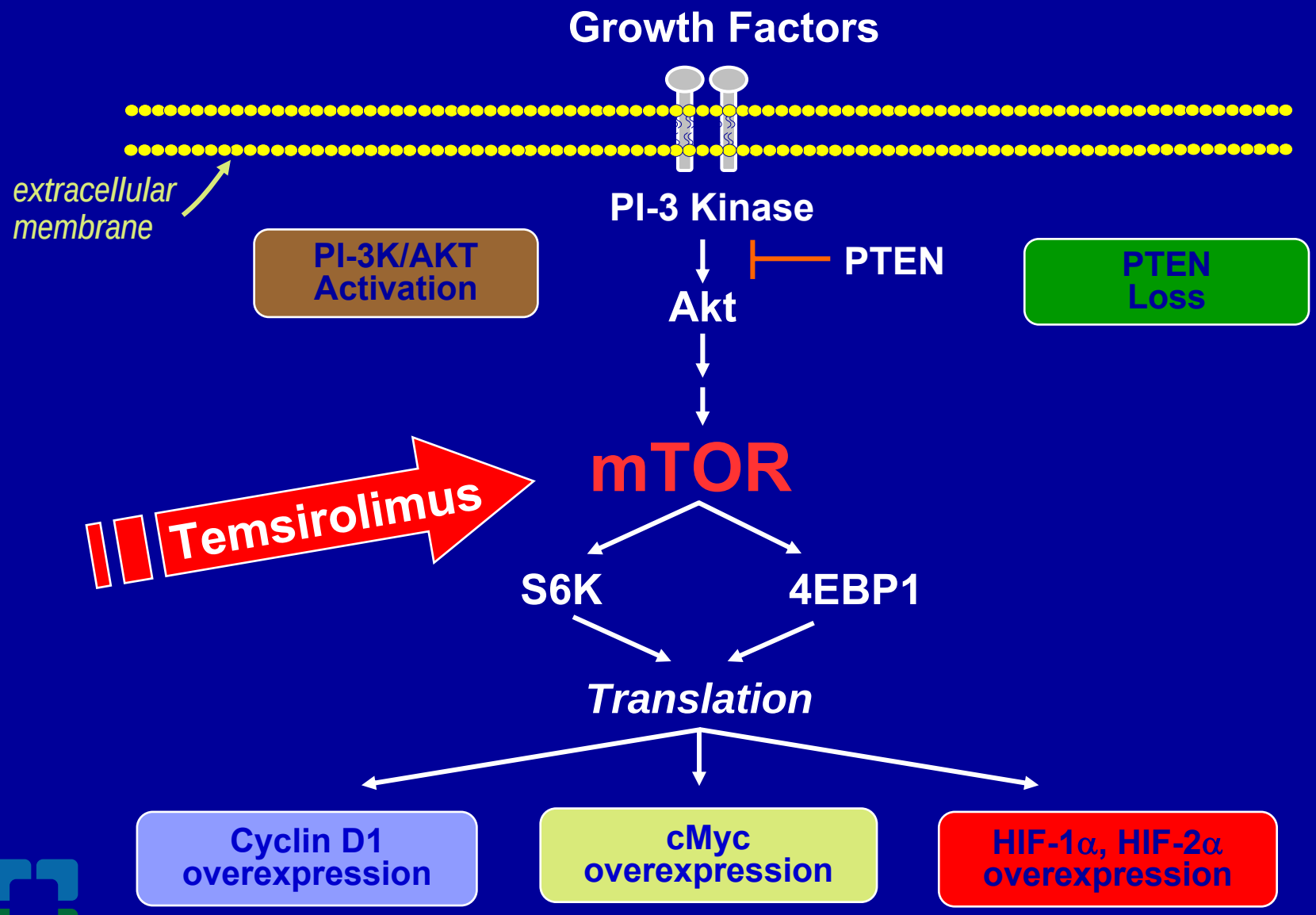
Sorafenib vs IFN in untreated metastatic RCC: PFS



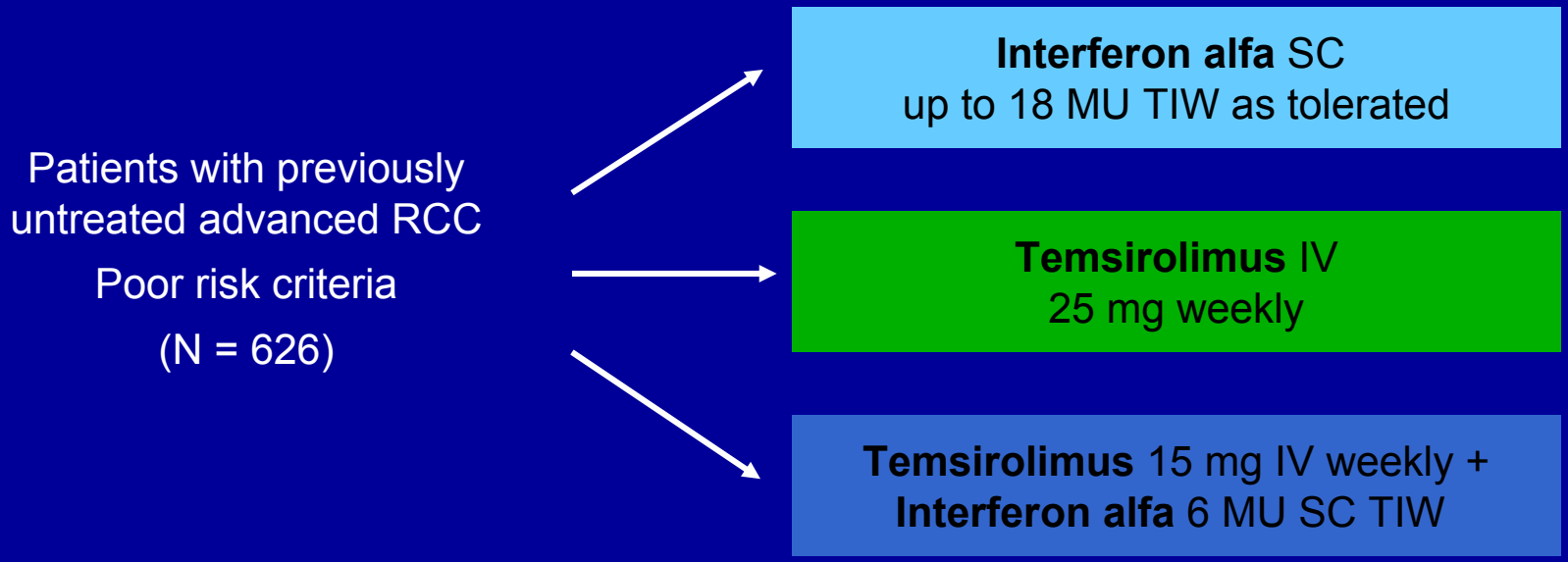
Adapted from Szczylik C et al. Presented at ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.

Temsirolimus (Toricel)

Temsirolimus: Mechanism of Action



Temsirolimus: Phase III trial in advanced RCC

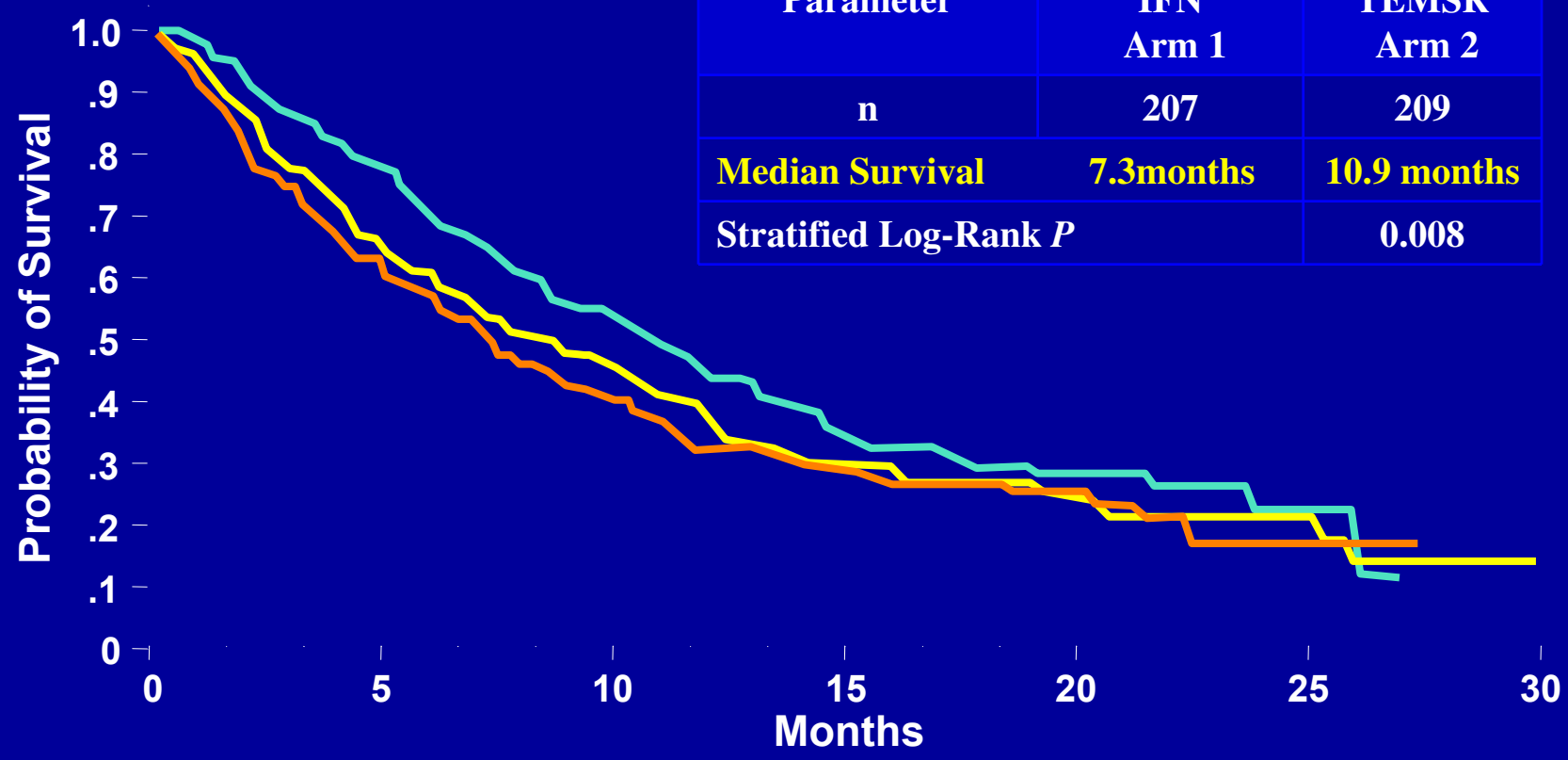


Minimum of 3 poor-risk features required:

1. LDH >1.5 X upper limit of normal
2. Hemoglobin <lower limit of normal
3. Corrected calcium >10 mg/dL
4. Time from diagnosis to first treatment <1 yr
5. Karnofsky performance status 60-70
6. Multiple organ site of metastasis

Overall Survival by Treatment Arm

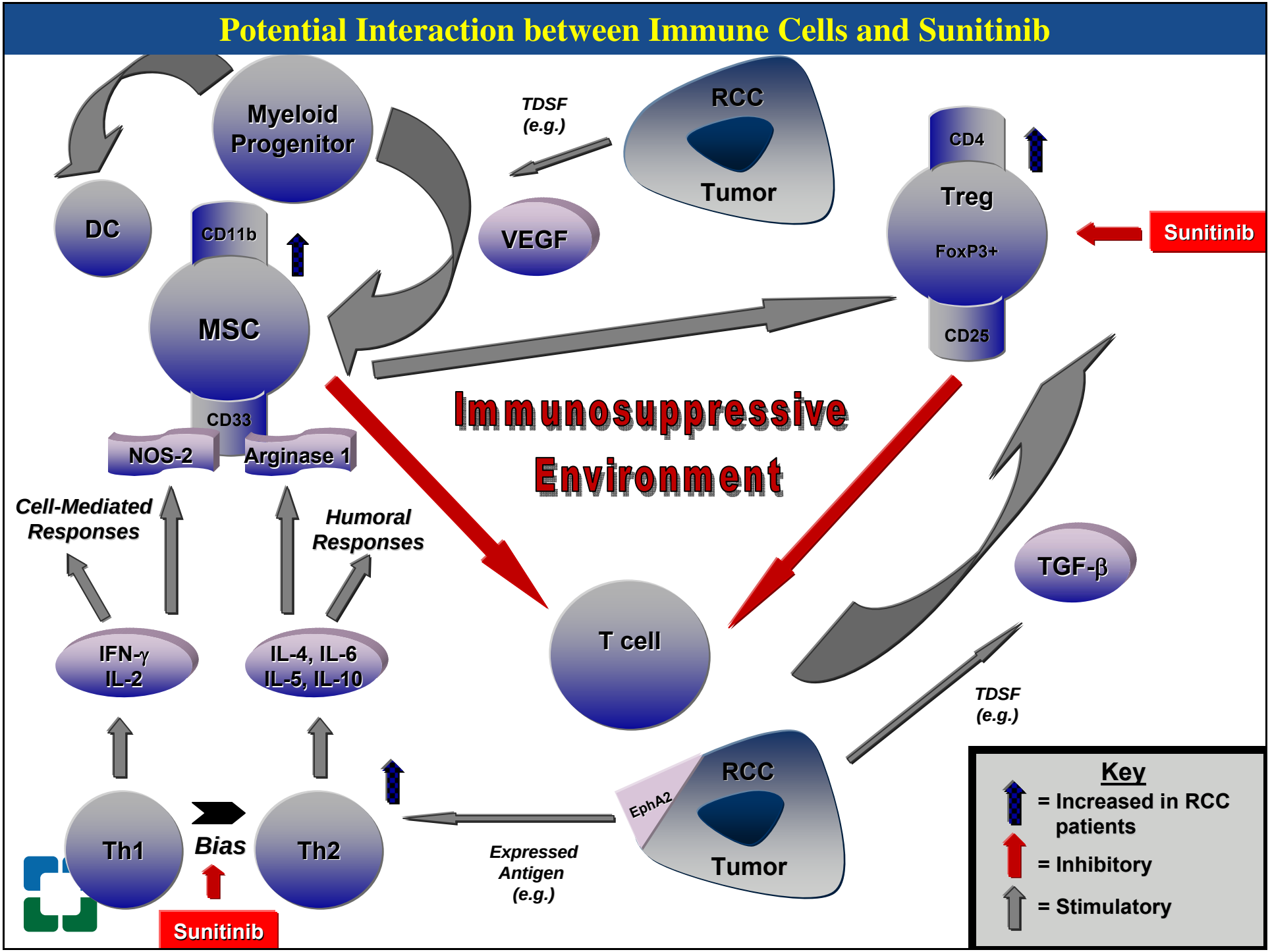
Parameter	IFN Arm 1	TEMSR Arm 2
n	207	209
Median Survival	7.3months	10.9 months
Stratified Log-Rank *P*		0.008



Potential immunoregulatory properties of sunitinib

*Disclaimer: I am not a real Immunologist, nor do I play one on TV.

Potential Interaction between Immune Cells and Sunitinib



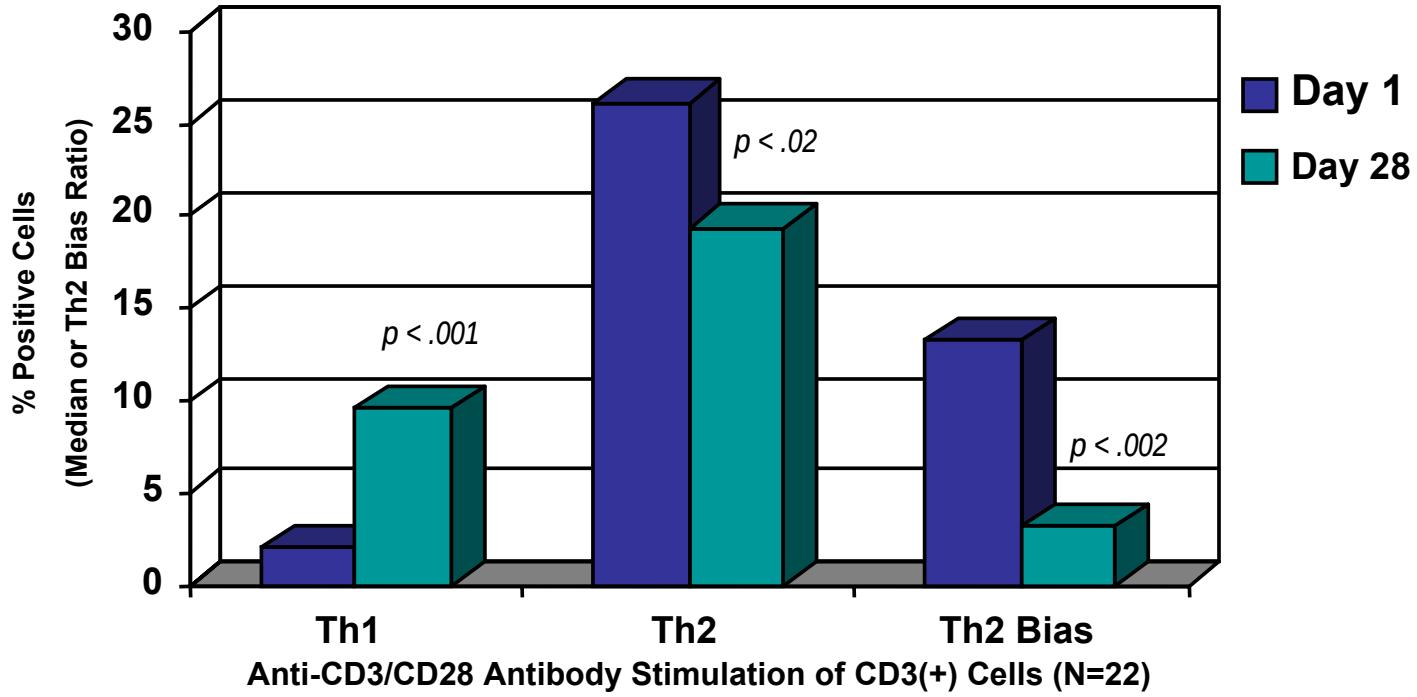
Methods

- Peripheral blood obtained from cytokine-refractory, clear cell mRCC patients on day 1 (pre-treatment) and after 28 days of sunitinib 50 mg daily.

- T cell cytokine intracellular expression IL-4 (Th2) and IFN-γ (Th1) determined by stimulating PBMC with plate bound anti-CD3 and anti-CD28 antibodies for 72 hours.

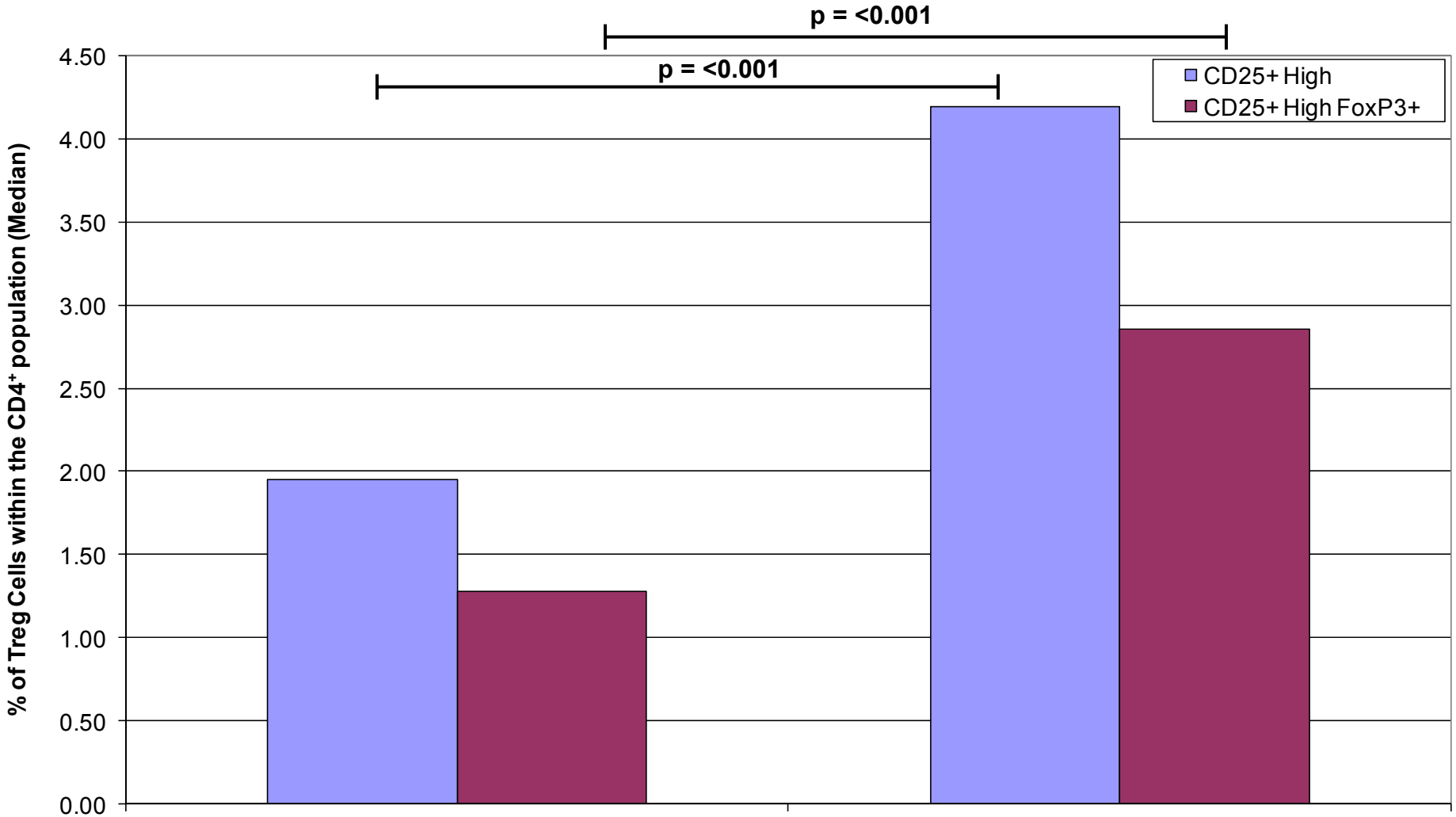
- Percentage of $CD25^{high}$ $FoxP3^{+}$ cells within the $CD3^{+}CD4^{+}$ cell population, and percentage of Treg that were $FoxP3^{+}$ were evaluated using four color flow cytometry.

Sunitinib Reverses RCC Induced Th2 Bias in Peripheral Blood of Metastatic RCC Patients

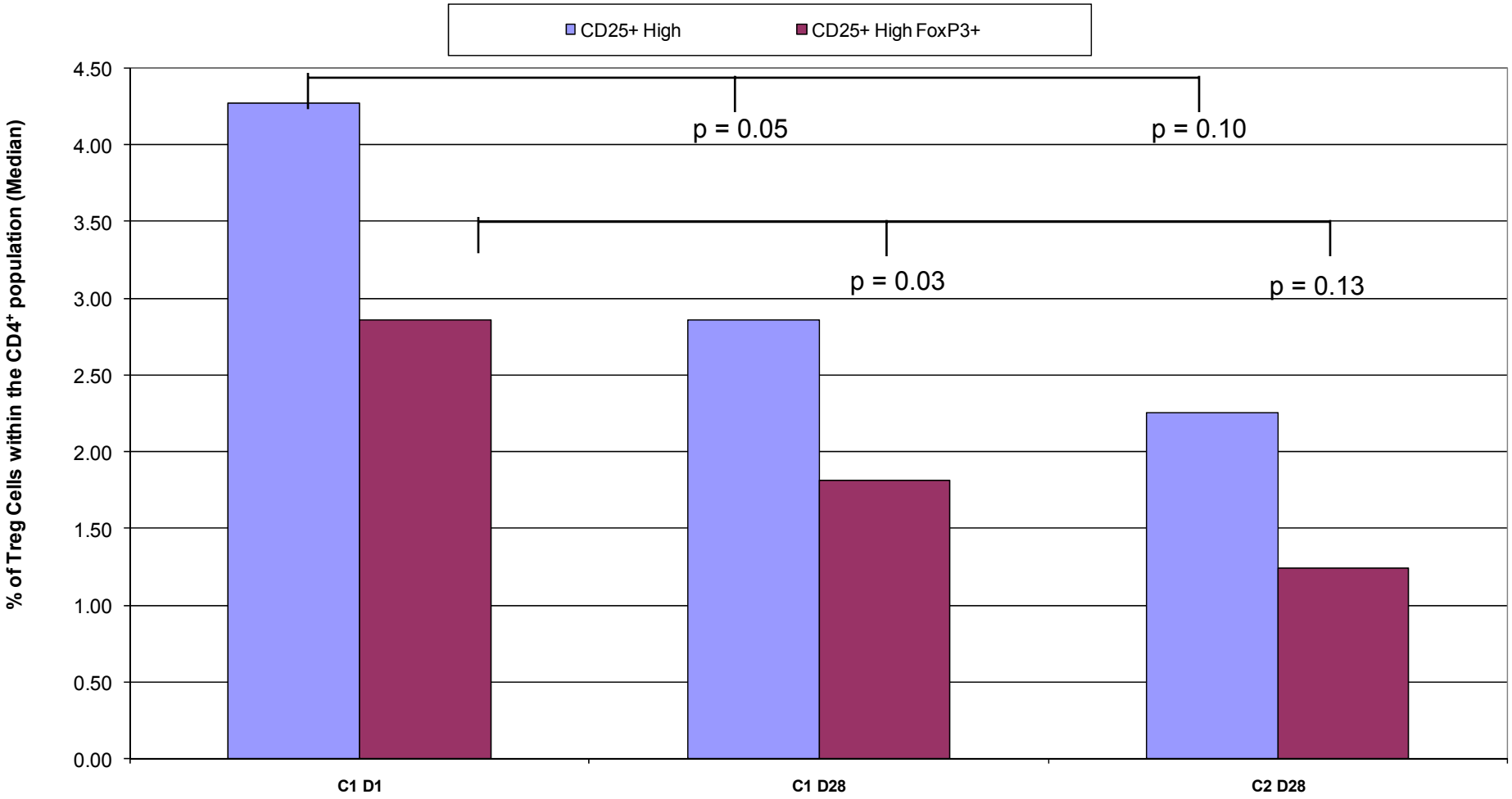


	Day 1 (Median or Th2 Bias Ratio, Range)	Day 28 (Median or Th2 Bias Ratio, Range)	p-value
Th1 Response	2.1% (0.05-20.3)	9.6% (0.2-27.4)	.001
Th2 Response	26.1% (6.0-67.8)	19.3% (0.03-42.6)	.02
Th2 Bias	13.4 (1.2-234.0)	2.2 (0.01-61.3)	.002

mRCC Patients Show Increased Levels of T Regulatory Cells Compared to Age Matched Normal Donors



The Percentage of T-Regulatory Cells Decreases in the Peripheral Blood With Sunitinib Treatment in mRCC Patients

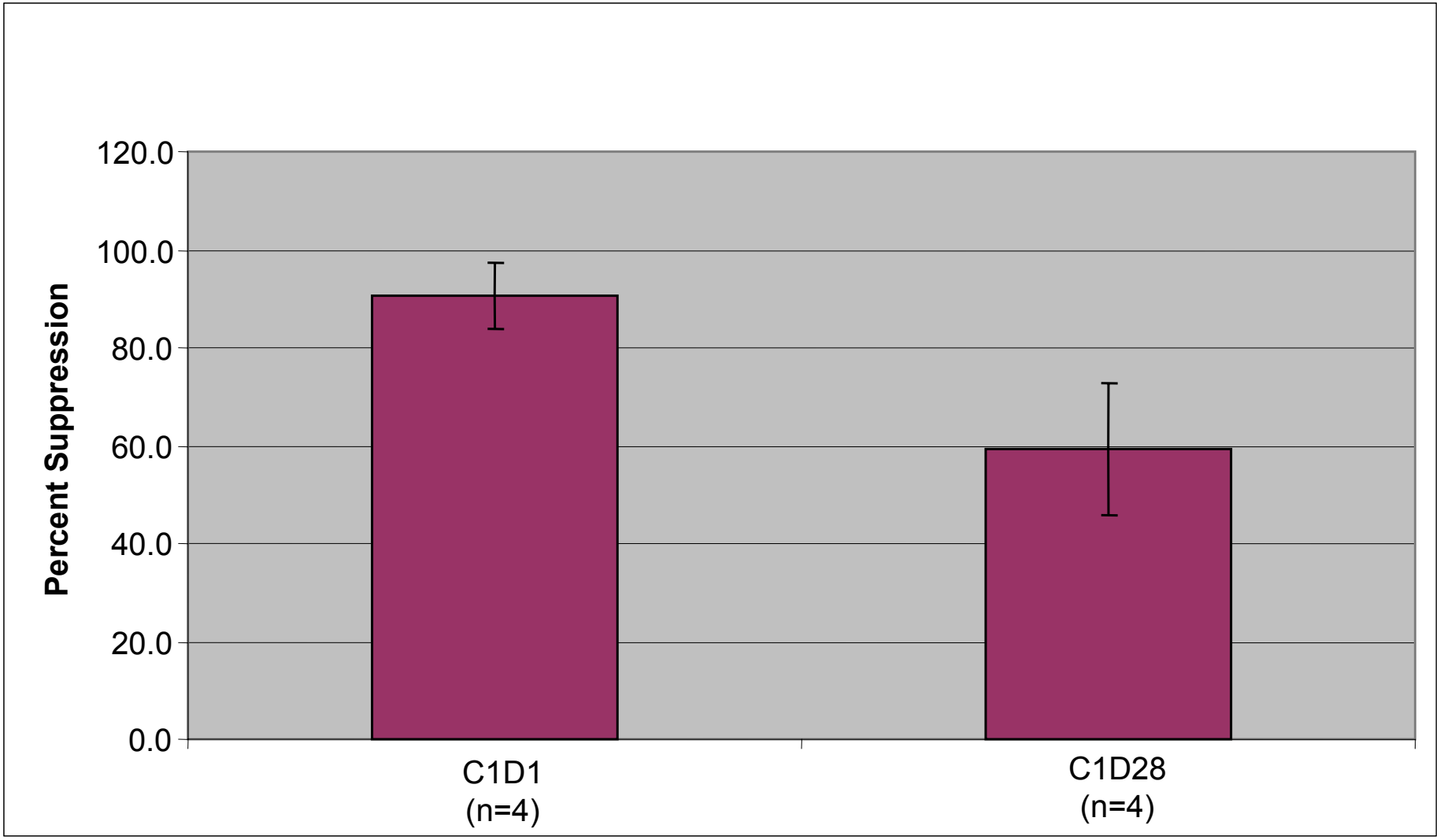


(n=26)
Range ($CD25^{+\ Hi}$): 1.5 – 9.2
Range ($CD25^{+\ Hi}\ FoxP3^{+}$): 0.5 – 8.4

(n=26)
Range ($CD25^{+\ Hi}$): 1.0 – 9.9
Range ($CD25^{+\ Hi}\ FoxP3^{+}$): 0.4 – 9.5

(n=10)
Range ($CD25^{+\ Hi}$): 0.9 – 5.6
Range ($CD25^{+\ Hi}\ FoxP3^{+}$): 0.3 – 4.2

Percent Suppression of $CD4^{+}CD25^{-}$ Cells by Tregs Decreases in Sunitinib Treated Patients



* Does not appear to be a direct effect of sunitinib

VHL status and clinical outcome to VEGF-targeted therapy

HYPOTHESIS

- Tumors with *VHL* gene inactivation will exhibit a better clinical outcome after VEGF-targeted therapy.

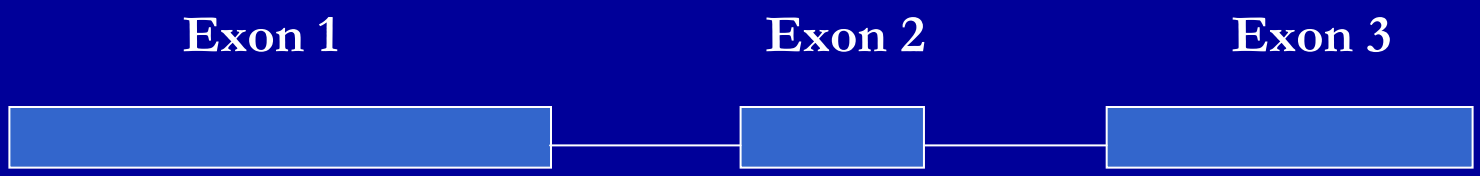
MATERIAL AND METHODS

- 182 patients with metastatic RCC who received sunitinib, sorafenib, bevacizumab or axitinib (AG- 013736) as initial anti-VEGF therapy on a clinical trial at Cleveland Clinic or UCSF between Feb. 2003 and Jan. 2006.

- 59 patients excluded:
  - Missing key data (n=3)
  - Pure non-clear cell histology (n=8)
  - Insufficient tissue for DNA extraction (n=12)
  - Unavailability of tissue at our institutions (n=36)
  -
- 123 patients with available tissue/clinical data were included in the final analysis*.
  - sunitinib: n= 63 (51%), sorafenib: n= 28 (23%), bevacizumab: n=17 (14%), axitinib: n= 15 (12%)

*** A subset of the data (n=45) previously reported: Rini BI, et al. *BJU Int.* 2006;98:756-62**

VHL MUTATION ANALYSIS



- Genomic DNA was extracted from frozen or paraffin-embedded tissue that contained >95% of tumor and manually dissected after pathology review.

- One or more primer sets were used to amplify each of the exons (and exon/intron junctions) of the XJN gene.

- PCR products were sequenced using Big Dye chemistry (Applied Biosystems) at the Core Sequencing Facility of each institution.

- Sequences identified to harbor mutations were confirmed with a second round of PCR and sequencing reactions in the reverse direction.

CHARACTERISTICS of *VHL* MUTATIONS

(49% mutated, 10% methylated)

Location of *VHL* mutation	N (%) of 60 patients
Exon 1	25 (42%)
Exon 2	19 (32%)
Exon 3	16 (27%)
Type of mutation	
Frameshift	29 (48%)
Nonsense (Stop)	6 (10%)
Inframe deletion or insertion	7 (12%)
Splice	5 (8%)
Missense	13 (22%)

RESPONSE AND *VHL* STATUS

Factor	N*	ORR (%)	P Value
Response	**122**	**45/122 (37%)**	
***VHL* Status**			
Mutated	**59**	**27 (46%)**	**41% ORR**
Methylated	**12**	**2 (15%)**	
		vs.	p=0.34
Wild Type	**51**	**16 (31%)**	**31% ORR**

***One patient with inadequate follow-up**

RESPONSE AND *VHL* STATUS

Factor	N*	ORR (%)	P-Value
Overall Response	**122**	**45/122 (37%)**	
***VHL* Status**			
Mutated	59	27 (46%)	
Methylated	12	2 (15%)	
Wild Type	51	16 (31%)	31% ORR
Type of Mutation			vs. p=0.04
Frameshift	28	15 (54%)	52% ORR
Inframe (d/i)	7	4 (57%)	
Nonsense	6	4 (67%)	
Splice	5	1 (20%)	
Missense	13	3 (23%)	

* One patient with inadequate follow-up was excluded

OBJECTIVE RESPONSE IN RELATION TO VHL STATUS BY SPECIFIC DRUG

VHL Status	Sunitinib	Axitinib	Sorafenib	Bevacizumab
Mutated	18/32 (56%)	3/9 (33%)	2/10 (20%)	4/9 (44%)
Methylated	2/6 (33%)	0/1 (0%)	0/2 (0%)	0/3 (0%)
Wild-type	13/25 (52%)	3/5 (60%)	0/16 (0%)	0/5 (0%)

Conclusions

- RCC is heavily reliant of the VEGF pathway
- VEGF pathway inhibition has produced robust clinical results in RCC and is now the standard of care
- Sunitinib may have favorable immunoregulatory properties
  - Immunotherapeutic combinations are being explored, e.g. + anti-CTLA-4 Ab, + vaccine
- The molecular geno/phenotype of response to VEGF-targeted agents in RCC requires further investigation


THE CLEVELAND CLINIC
TAUSSIG CANCER CENTER