Sorafenib for renal cell carcinoma

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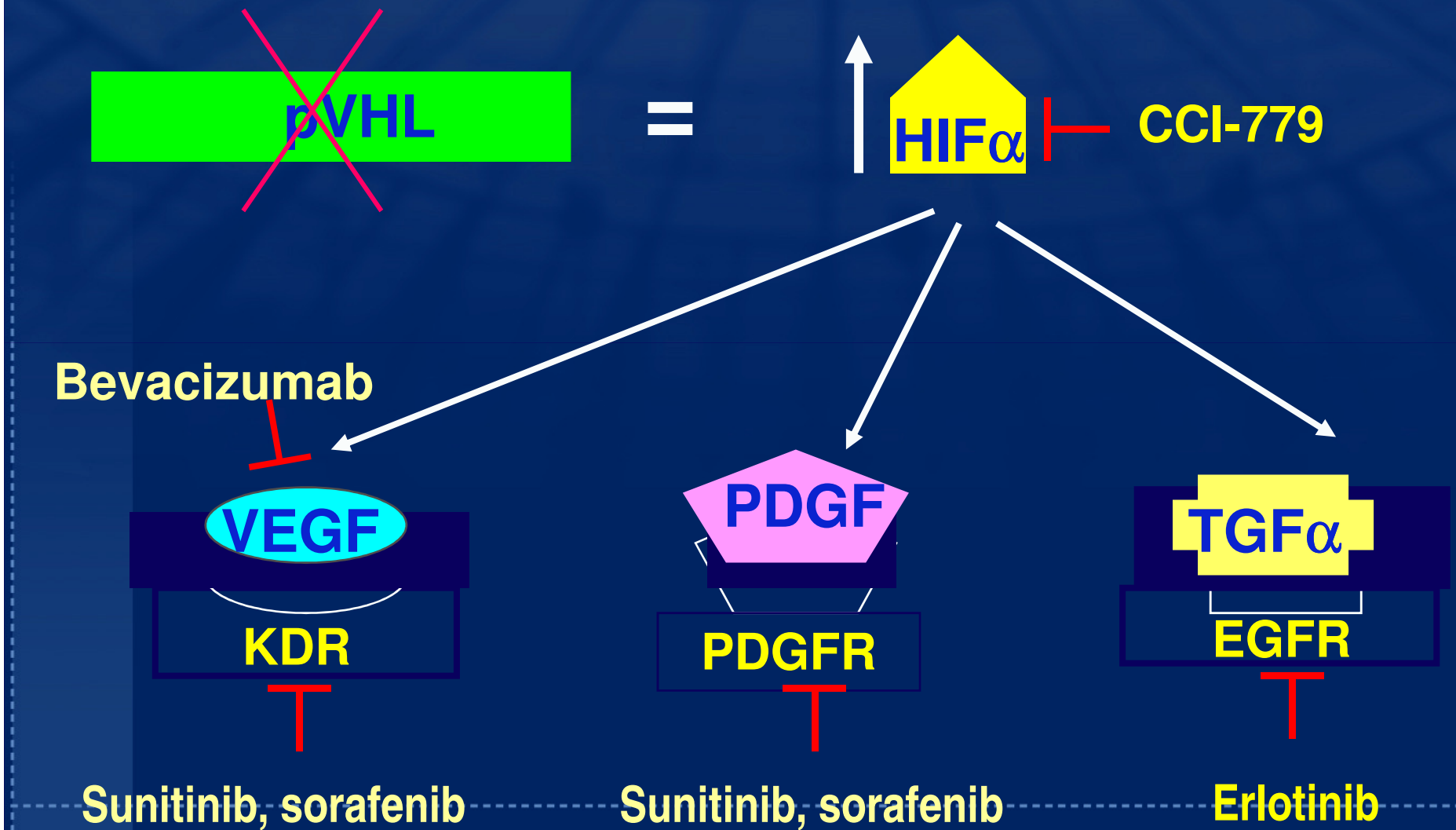
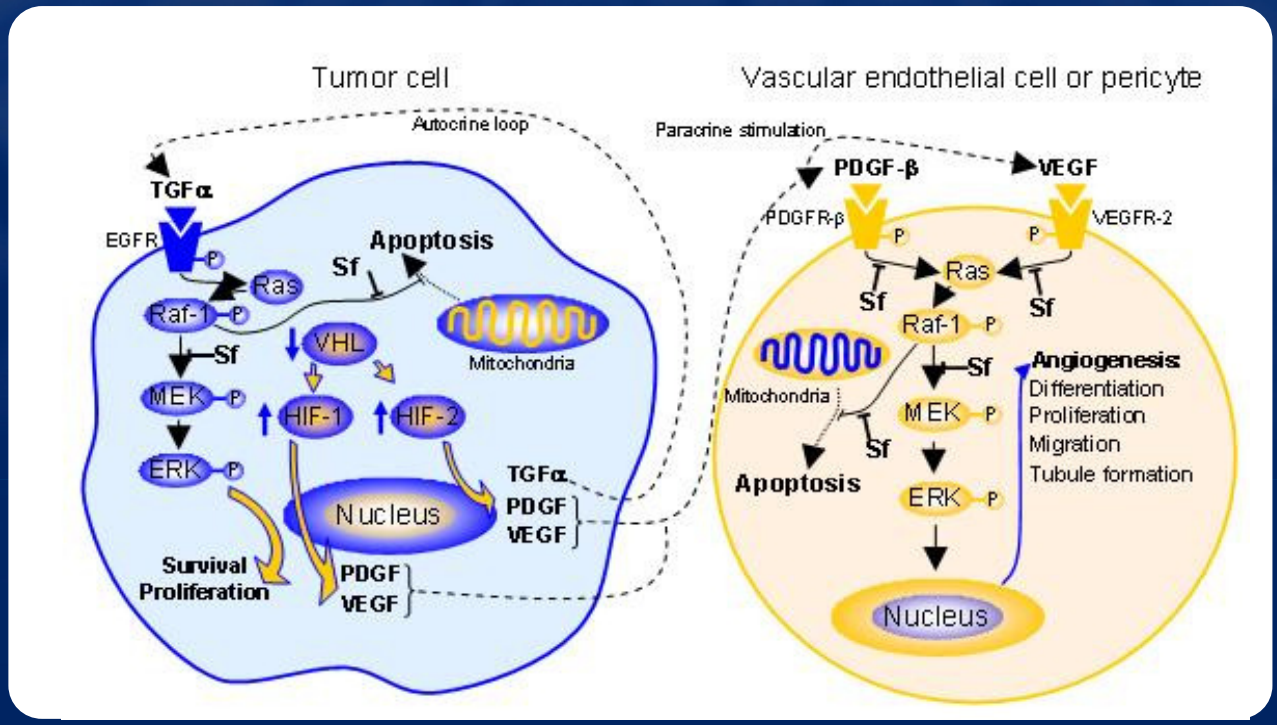
Renal Cell Carcinoma: Drugs and Targets



Sorafenib (Nexavar®)
A Novel, Orally-Active Multi-Kinase Inhibitor



- **Approved in the US in Dec 2005 for advanced RCC**
- ***In vitro* inhibitor of C-Raf, wild-type B-Raf, *b-raf* V600E, VEGFR -1/-2/-3, PDGFR-β, c-Kit, and Flt-3[1]**
- **Broad-spectrum anti-tumour activity and inhibition of angiogenesis in several tumour xenografts[1]**
- **Sorafenib prevented tumour growth in RCC $VHL^{-/-}$ xenografts, via inhibition of angiogenesis[2]**

1. Wilhelm S, Chien DS. *Curr Pharm Des* 2002;8:2255–2257
2. Chang YS, et al. *Clin Cancer Res* 2005;11:9011S

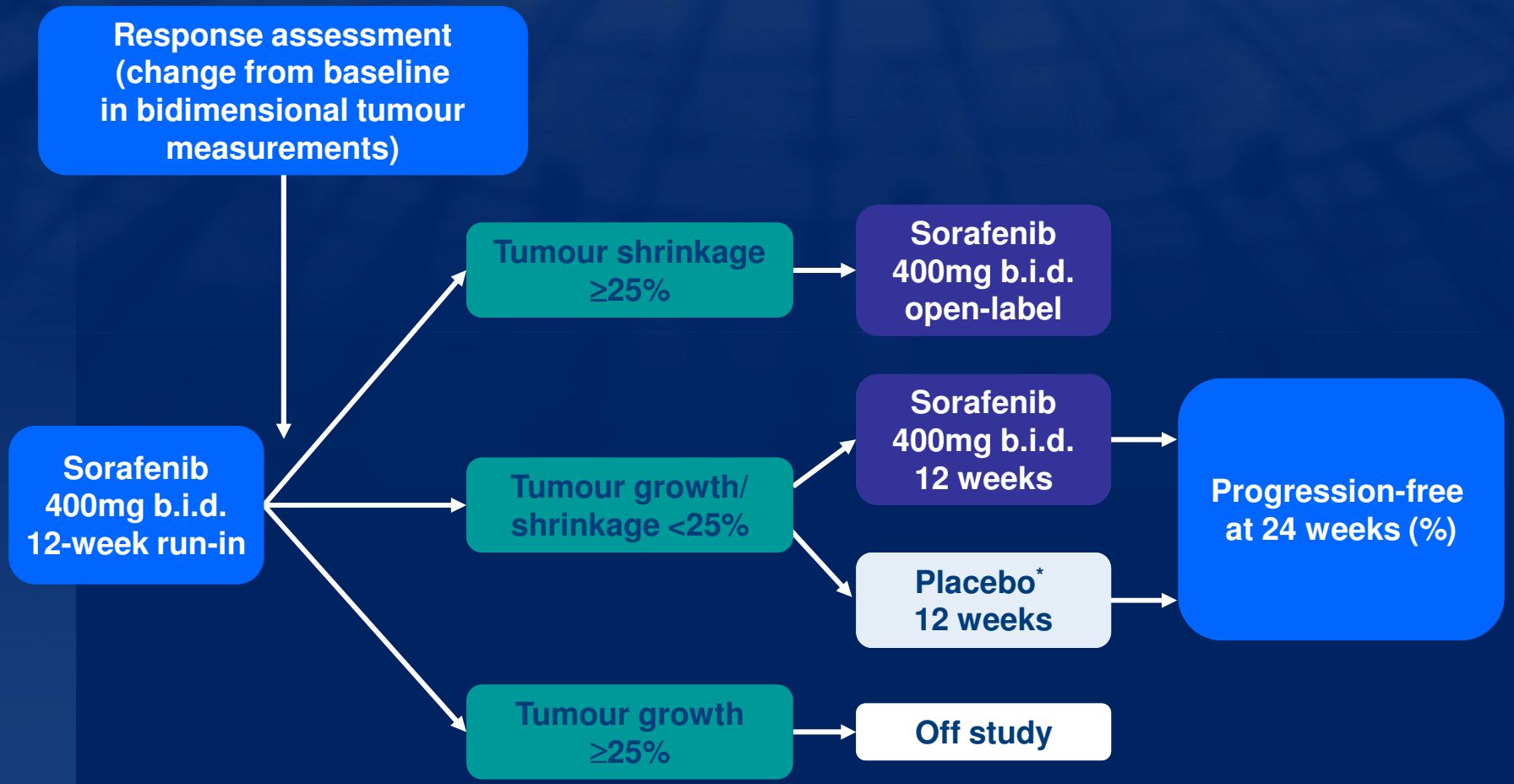
Sorafenib: phase II and III studies

Based on phase I data, continuous oral dosing of sorafenib 400mg twice daily (b.i.d.) was selected for further evaluation in patients with advanced RCC

Sorafenib phase II and III clinical trials:

- phase II Randomised Discontinuation Trial (RDT)
- phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs)
- randomised phase II trial of sorafenib versus IFN (first-line)
- phase II trial in Japanese patients

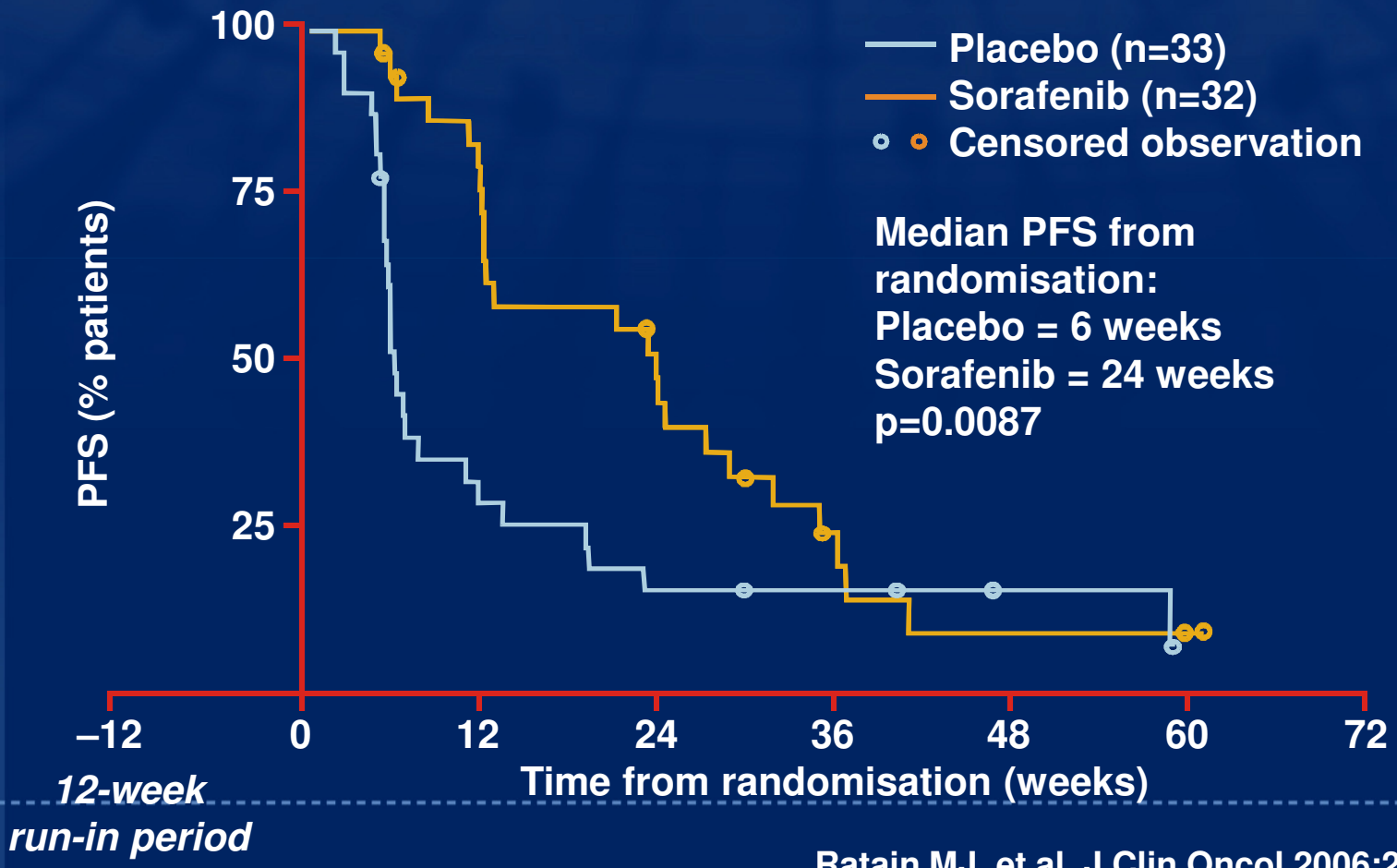
Phase II RDT: study design



*Patients who progressed on placebo could cross over to sorafenib

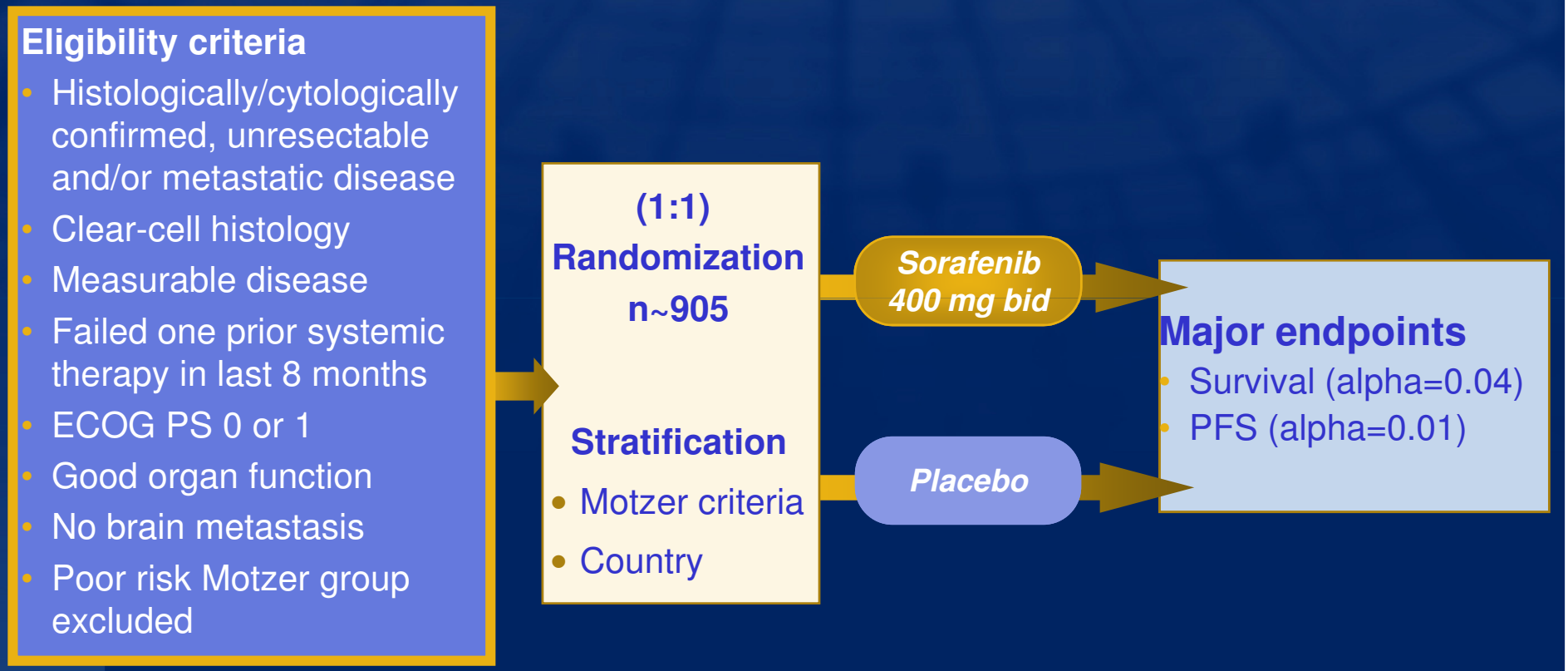
Phase II RDT: sorafenib significantly delayed progression compared with placebo

At 24 weeks, 50% of patients with advanced RCC remained progression free in the sorafenib group compared with 18% in the placebo group (p=0.0077)



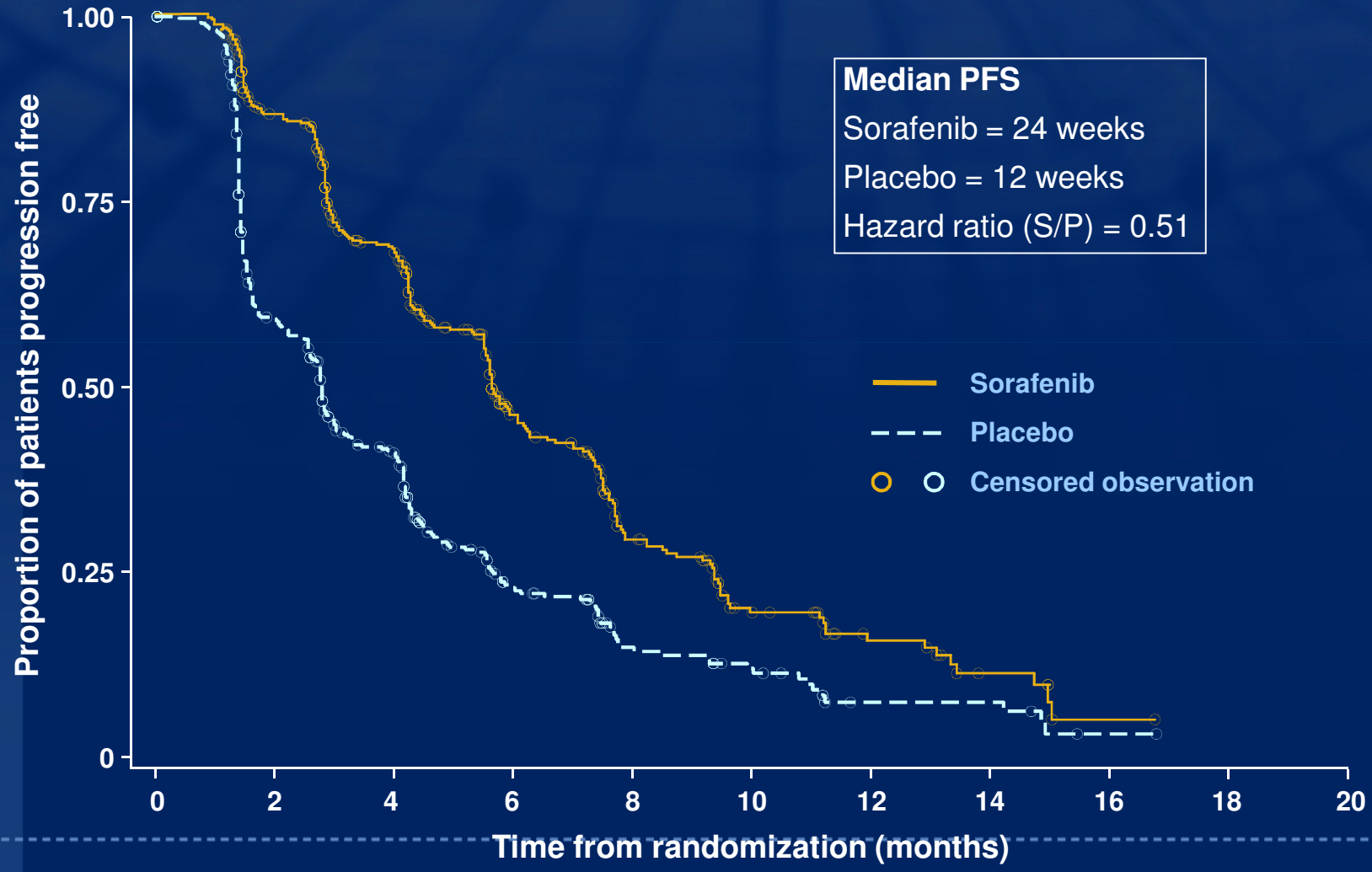
Ratain MJ, et al. J Clin Oncol 2006;24:2505–12

SORAFENIB improves PFS over placebo in 2nd line setting



Escudier et al, NEJM 2007

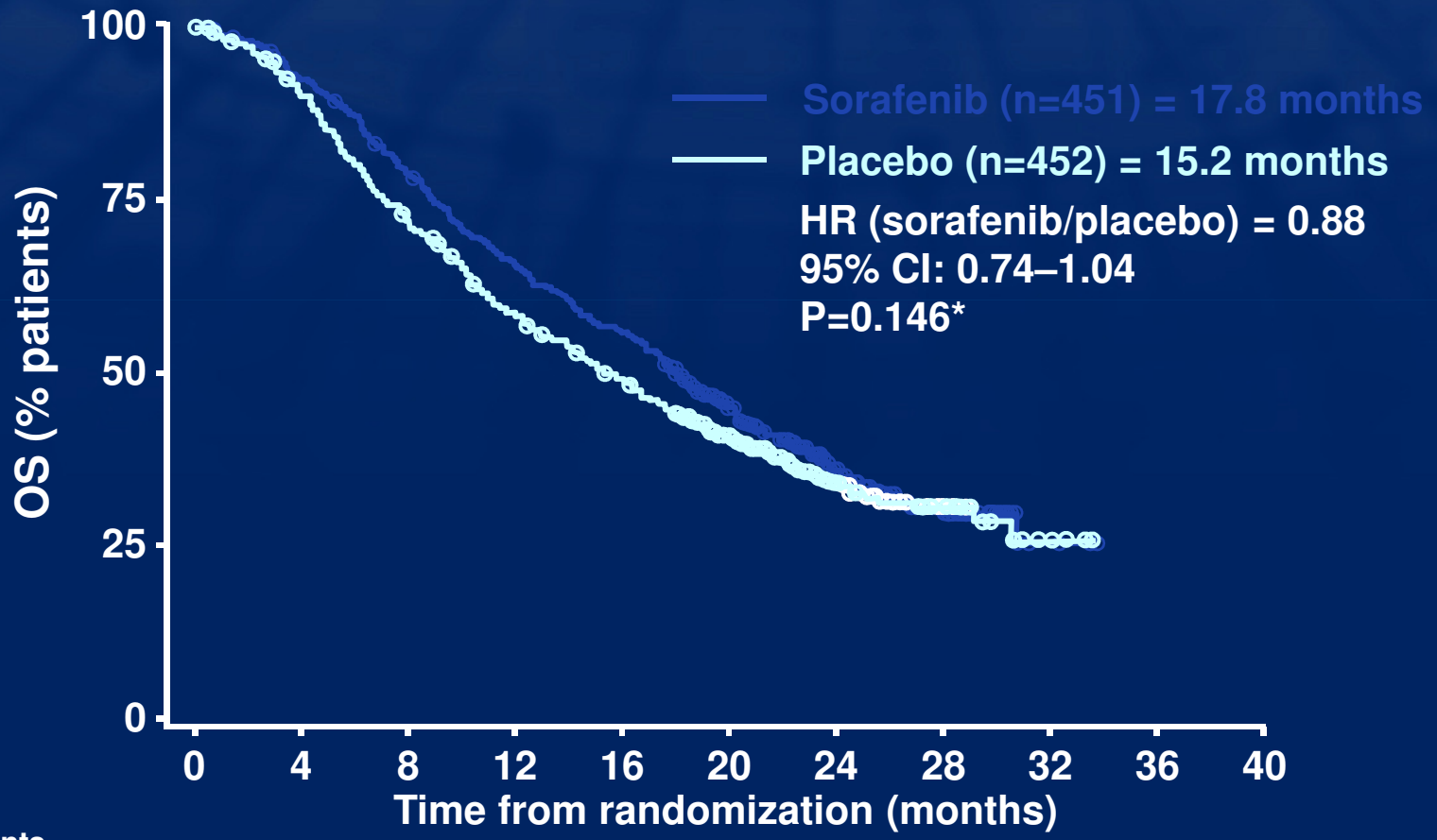
TARGETs
Progression-Free Survival Benefit*



*Based on investigator assessment

TARGET: Final OS Analysis

16 Months Post-Crossover: Intent-to-Treat



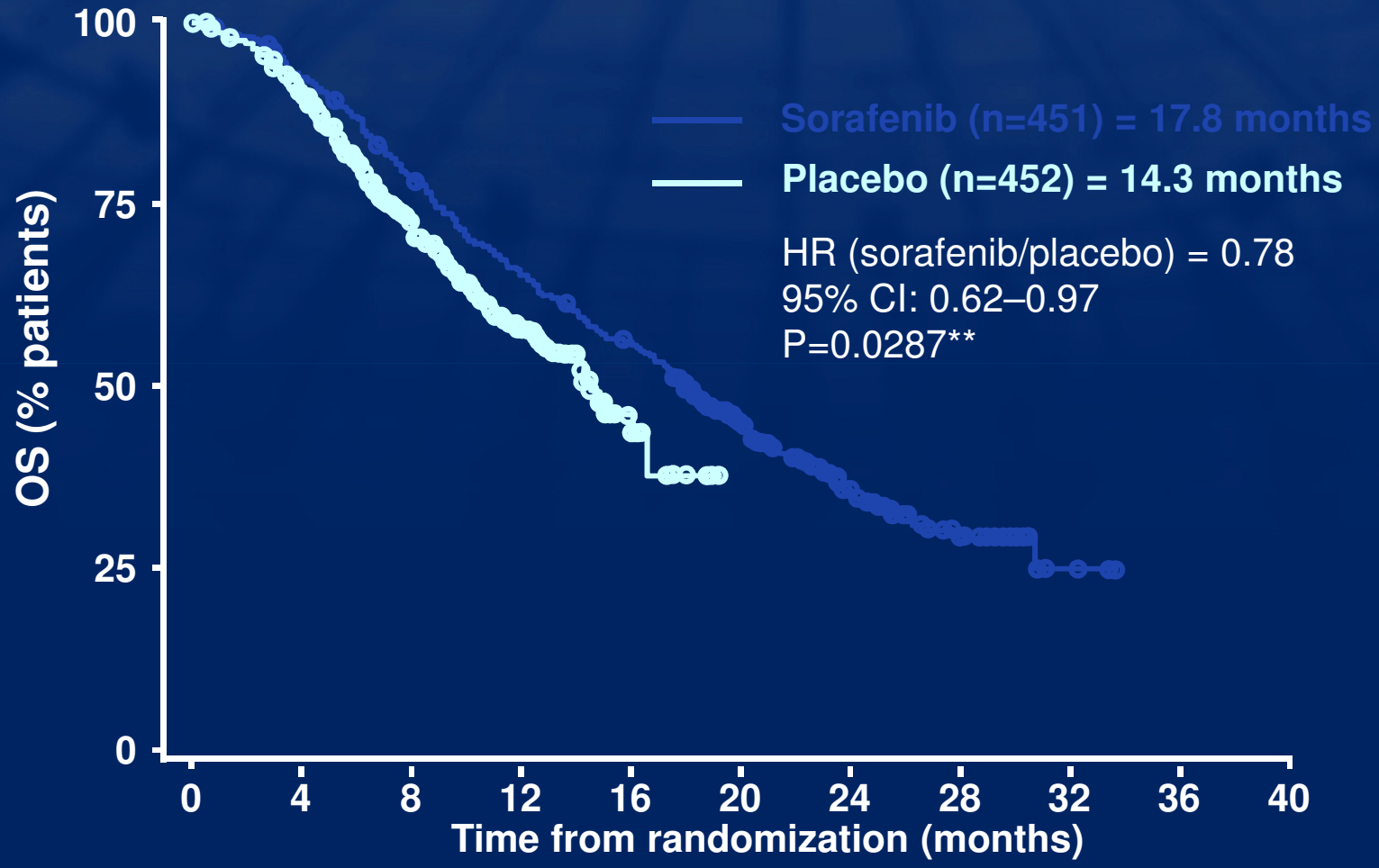
561 events

*Non-significant; O'Brien–Fleming threshold for statistical significance α=0.037

Bukowski et al, ASCO 2007

TARGET: Pre-planned Secondary Analysis

*OS Data for Placebo Patients Censored**



*Censored at 30 June 2005, approx. start of crossover

**Statistically significant: O'Brien–Fleming threshold for statistical significance α=0.037

Bukowski et al, ASCO 2007

TARGETs: sorafenib has a predictable and manageable side-effect profile

	Incidence of adverse events* (%)			
	Sorafenib (n=451)		Placebo (n=451)†	
	Any grade	Grades 3–4	Any grade	Grades 3–4
Diarrhoea	43	2	13	1
Rash/desquamation	40	1	16	<1
Fatigue	37	5	28	4
Hand–foot skin reaction	30	6	7	–
Hypertension	17	4	2	<1
Dyspnoea	14	4	12	2
Decreased haemoglobin	8	3	7	4
Bone pain	8	1	8	3
Tumour pain	6	3	5	2

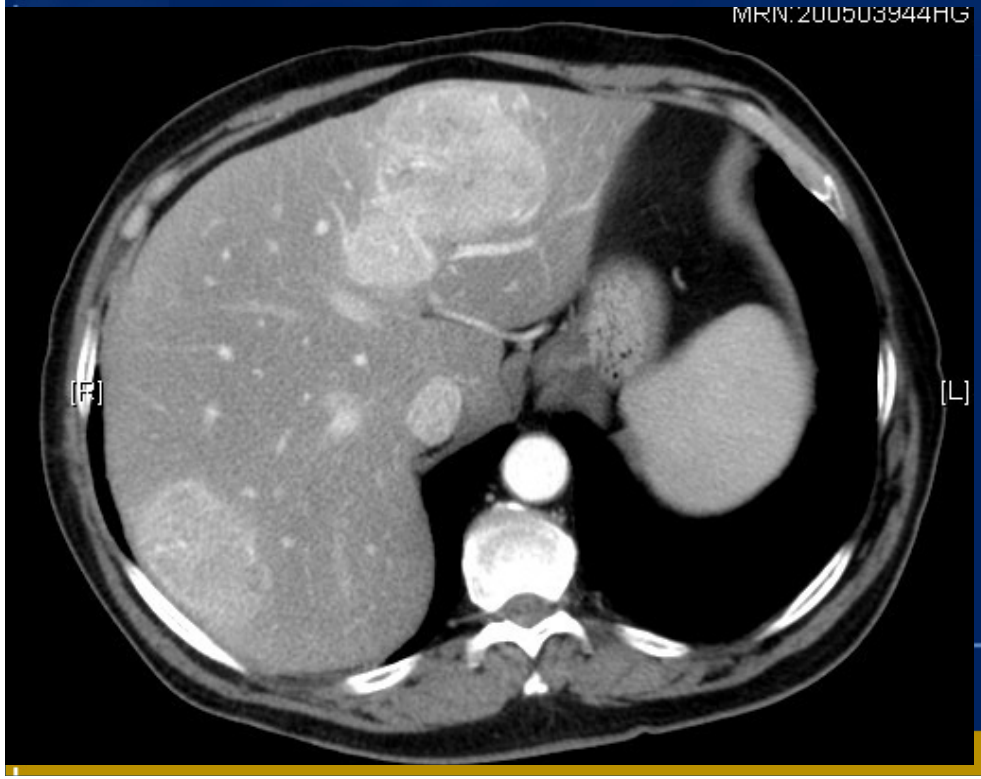
*National Cancer Institute-Common Toxicity Criteria (Version 3); adverse events occurring in ≥2% of patients

†One patient was not evaluable for safety

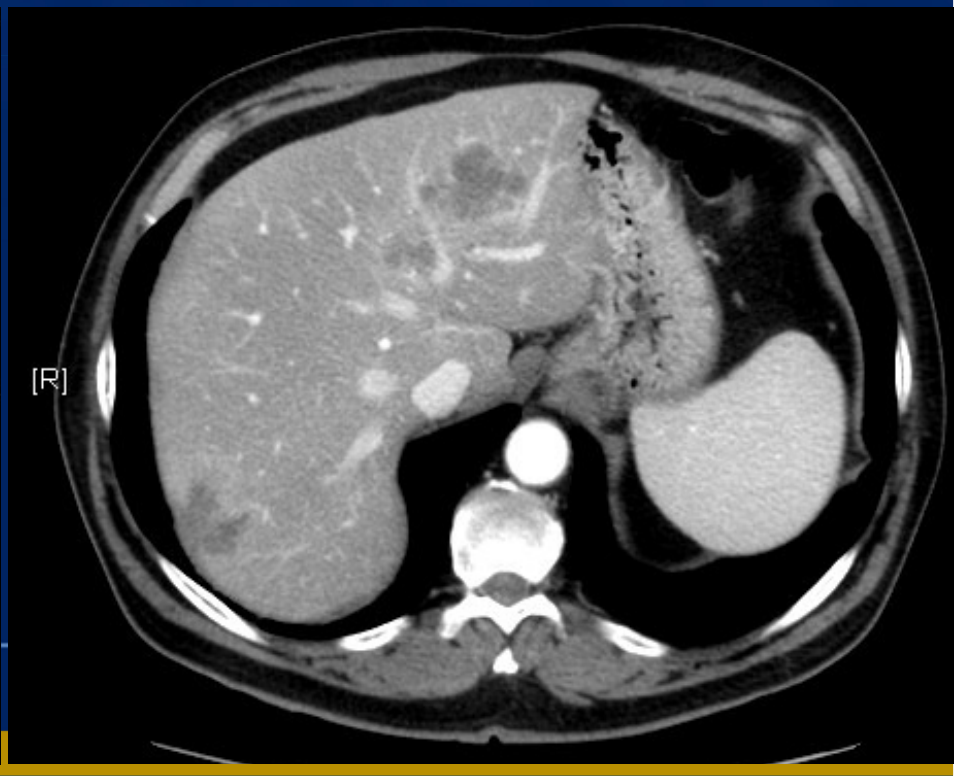
Escudier B, et al. ECCO 2005, Paris, France

Sorafenib induces changes in vascularization

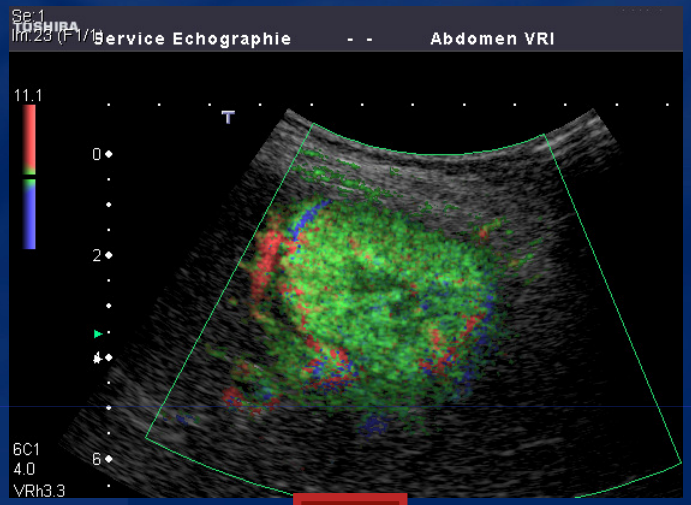
10 Nov 05

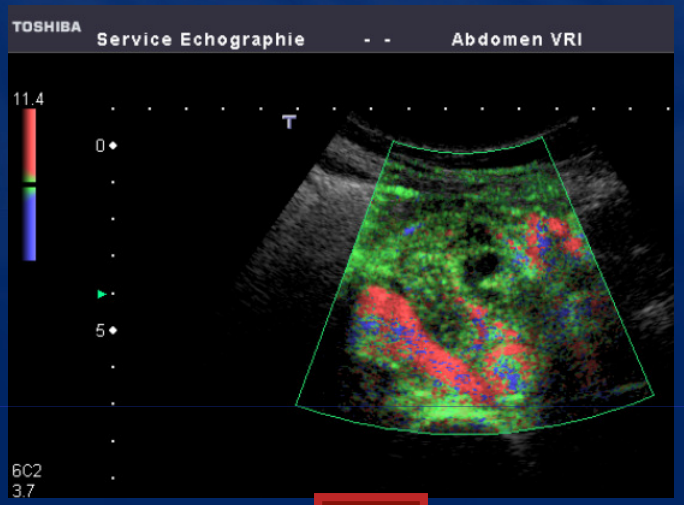


9 Dec 05

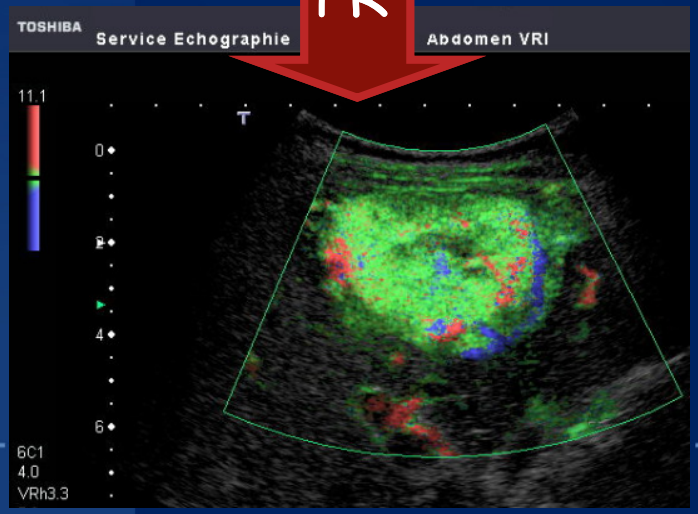


Imaging techniques can show these changes

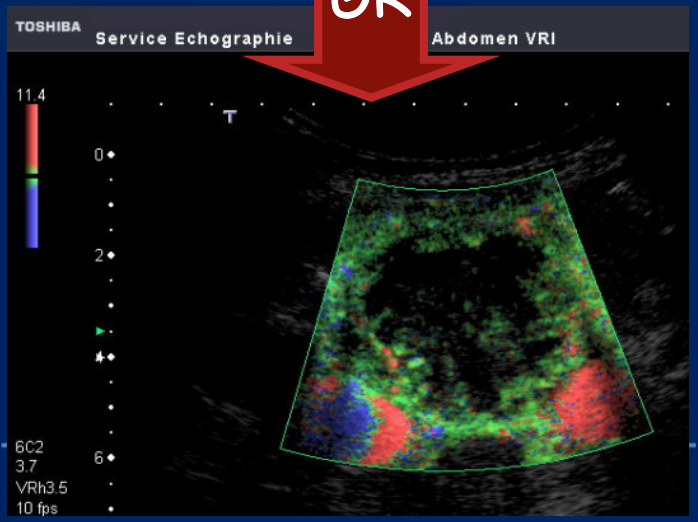




PR



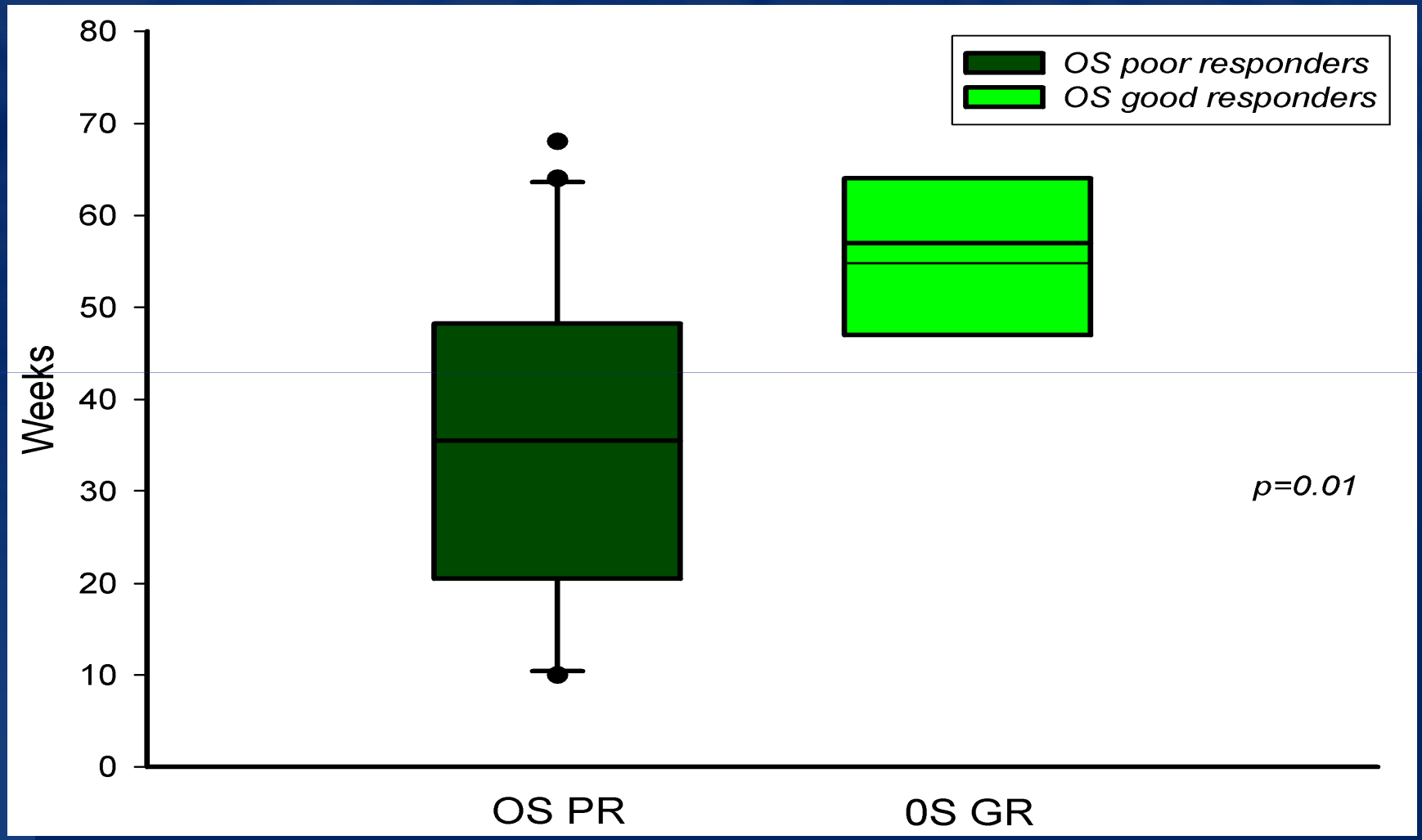
GR



before

after 3W

Changes in tumor vascularization predict OS



Lamuraglia et al, Eur J Cancer, 2006

But sorafenib is not as active as expected in first line

Randomized phase II trial of first-line treatment with sorafenib vs interferon in patients with advanced renal cell carcinoma: final results

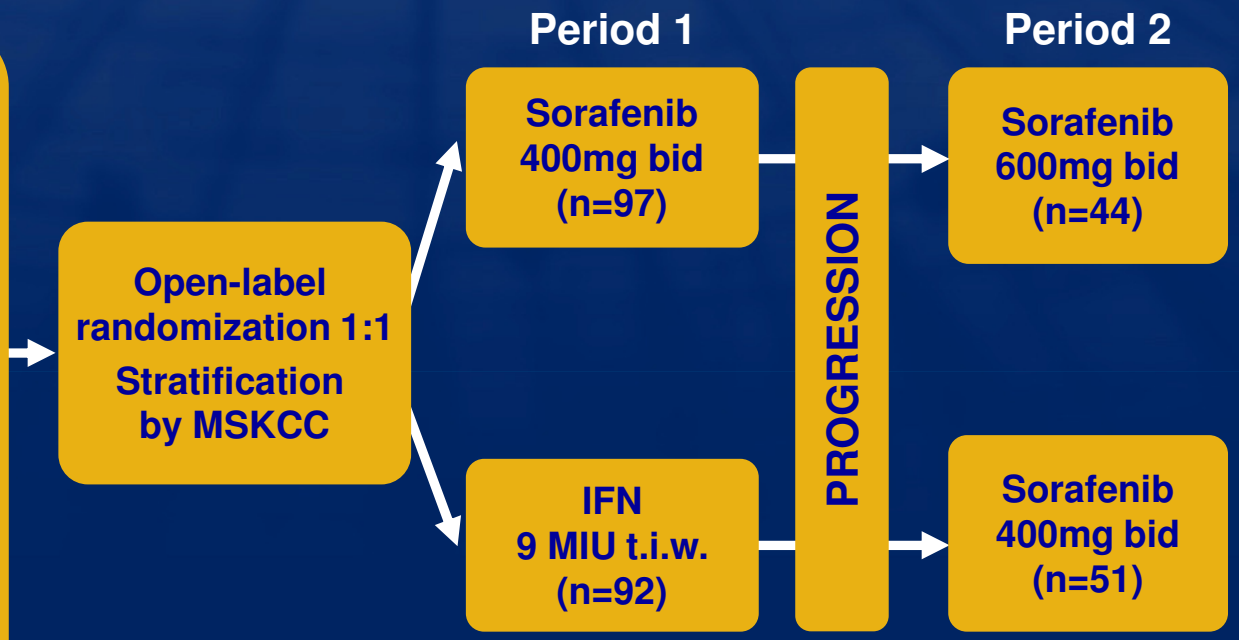
Cezary Szczylik, Tomasz Demkow, Michael Staehler, Frédéric Rolland, Sylvie Negrier, Thomas E Hutson, Ronald M Bukowski, Urban J Scheuring, Konrad Burk, Bernard Escudier

ASCO 2007, abstract 5025

Study 11848: Design
First-line sorafenib versus IFN: randomized phase II trial

ELIGIBILITY CRITERIA

- Unresectable RCC ± metastases
- Clear cell histology
- Measurable disease
- No prior systemic therapy
- ECOG Performance Status 0 or 1
- Good organ function
- No brain metastases
- All MSKCC risk groups

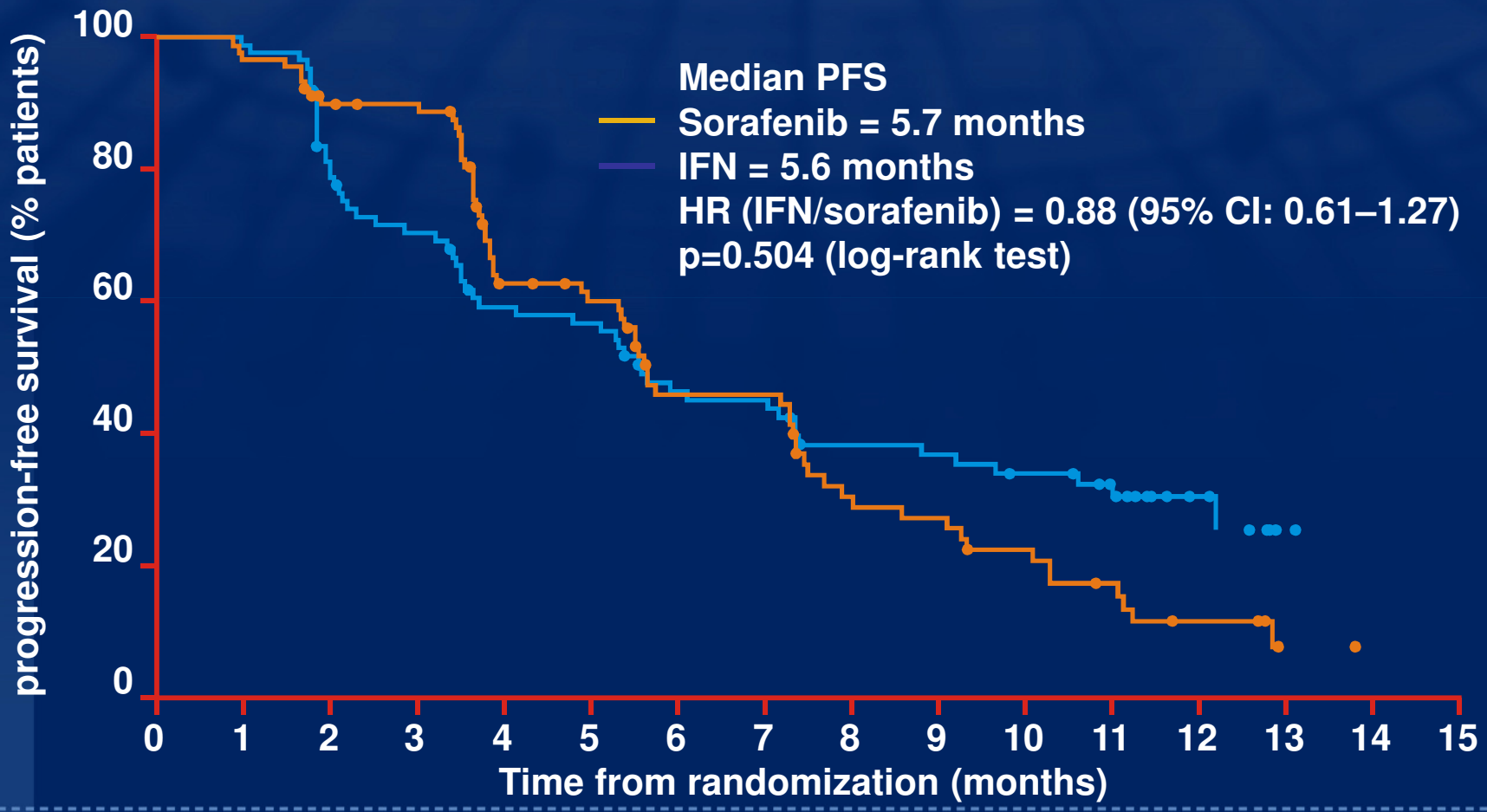


Primary objective Period 1: PFS sorafenib vs IFN *29 Sept 2006: 121 PFS events*

Period 2: PFS and clinical benefit *31 Dec 2006*

Secondary objective Disease Control Rate (DCR); Quality of Life (QoL); best response rate; duration of response; overall survival (OS)

Progression-Free Survival: Period 1



Results: period 2
IFN → sorafenib 400mg bid *versus* sorafenib 400mg bid → 600mg bid

ELIGIBILITY CRITERIA

- Unresectable RCC ± metastases
- Clear cell histology
- Measurable disease
- No prior systemic therapy
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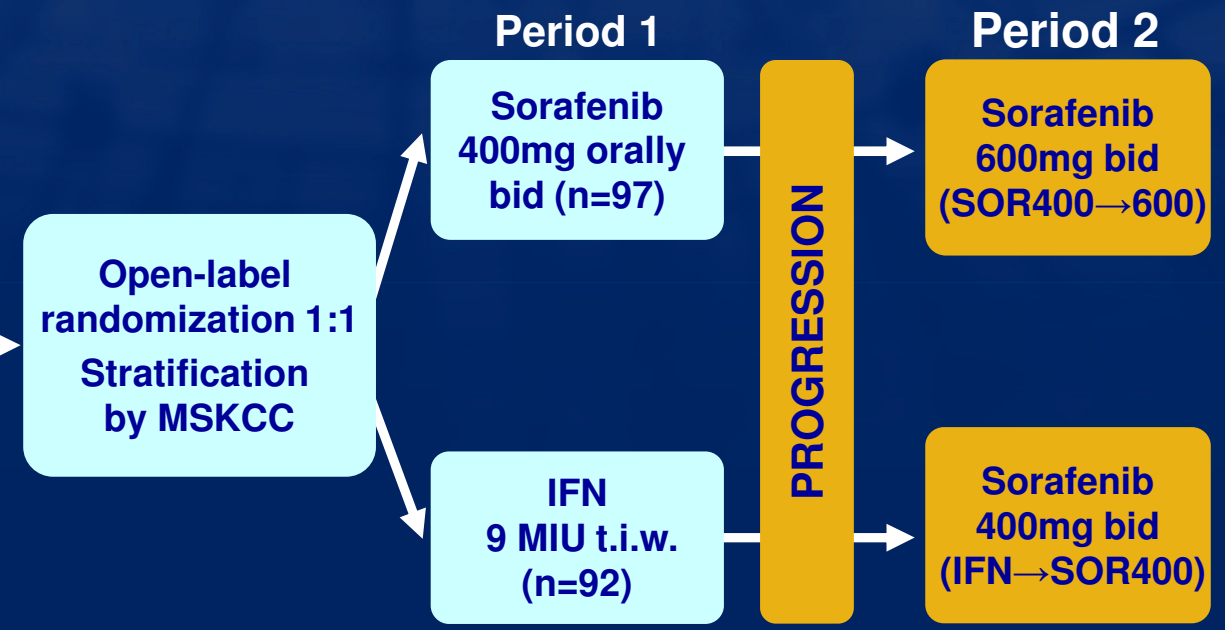
- All MSKCC risk groups



Objectives:

- Is dose escalation useful?
- Does IFN → sorafenib switch mimic TARGET data?

Progression-Free Survival: Period 2

	SOR400→600 N=44	IFN→SOR400 N=51
Total with PFS event,* n	**25**	**28**
Median PFS (K–M) (95% CI)	**4.1 months (1.9–5.3)**	**5.5 months (3.7–7.1)**

***Investigator assessed; 31 December 2006 cut-off**

But dose of sorafenib might be too low?

A Phase II Trial of Intra-Patient Dose-Escalated-Sorafenib in Patients with Metastatic Renal Cell Cancer

R. Amato, P. Harris, M. Dalton, M. Khan, J. Zhai, J. Brady, J. Jac, R. Alter, R. Hauke, S. Srinivas

ASCO 2007, abstract 5026

Dose Escalated Sorafenib for Renal Cell Carcinoma: Phase 2 Study

Treatment regimen:

- 400 mg bid daily oral therapy day 1-28;
- 600 mg bid day 29-56;
- 800 mg bid day 57 throughout

Dose modification for grade 3/4 toxicity

Monitoring of CBC, chemistry, and amylase/lipase

Response assessed by RECIST every 8 weeks

Treatment continued unless progression or intolerability

Dose Escalated Sorafenib for Renal Cell Carcinoma: Intensity of Therapy

At 800 mg dose level

5 patients had dose held between weeks 2 through 4

3 patients were dose reduced

Doses were escalated to 1200 mg in 41 of 44 patients

Doses were escalated to 1600 mg in 32 of 41 patients

SUMMARY

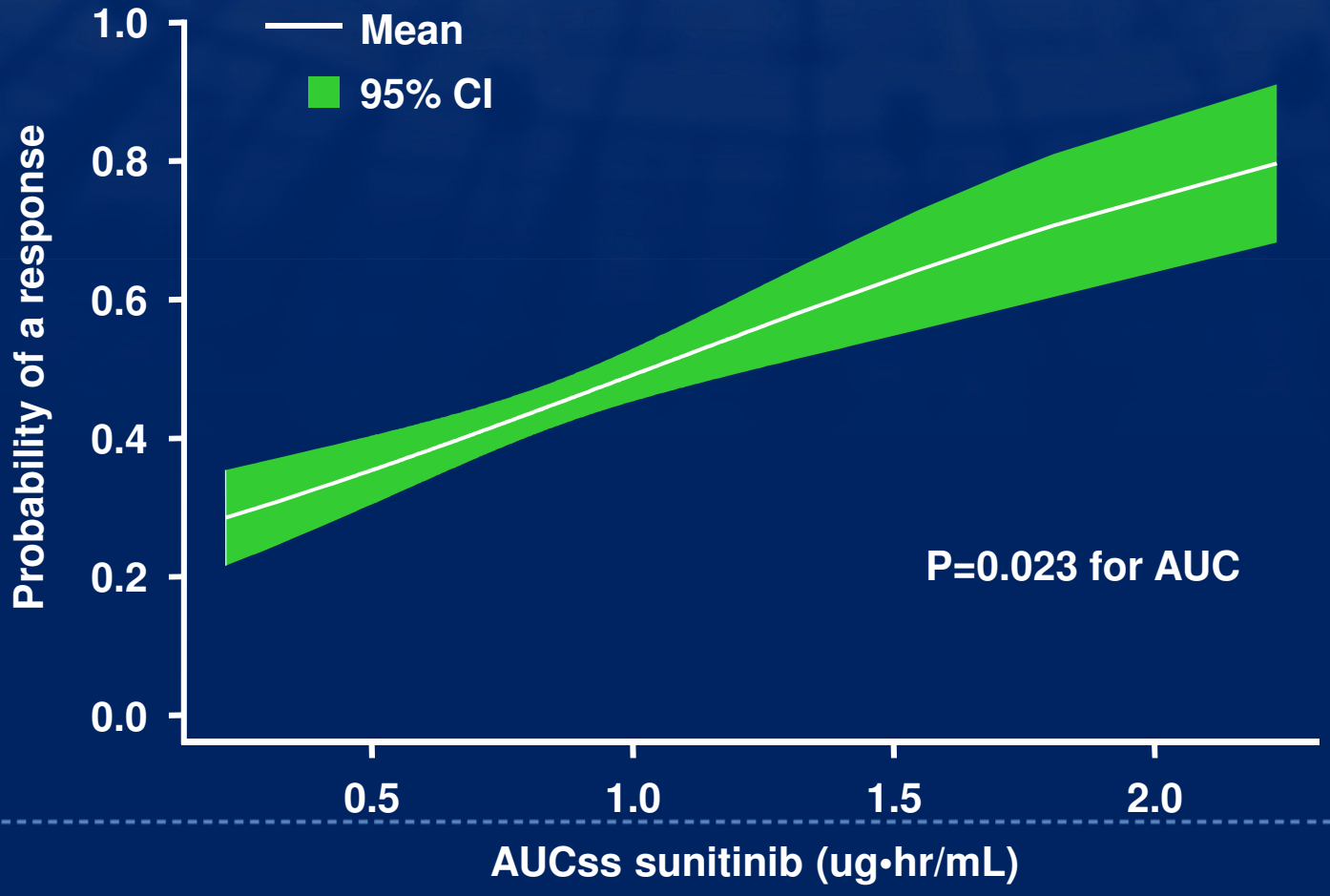
- 41 patients were able to receive 1200 or 1600 mgs per day of Sorafenib
- 3 patients were unable to be dose escalated
- Those with early toxicity have difficulty with dose escalation

Dose Escalated Sorafenib for Renal Cell Carcinoma
Results: Best Response by RECIST

Best Response		No.	(%)
Complete Response		7	16
Partial Response	17		39
Stable Disease ≥ 6 months		9	20
Progression defined as ≤ 4 months		11	25

And dose of TKIs might be an issue:

Probability of PR or CR in mRCC Increased with Mean Daily Sunitinib Exposure
Houk et al, ASCO 2007, abstract 5027



QUESTIONS

1. Benefit of combination?
2. Benefit of sequential treatment?
3. Rôle of sorafenib?

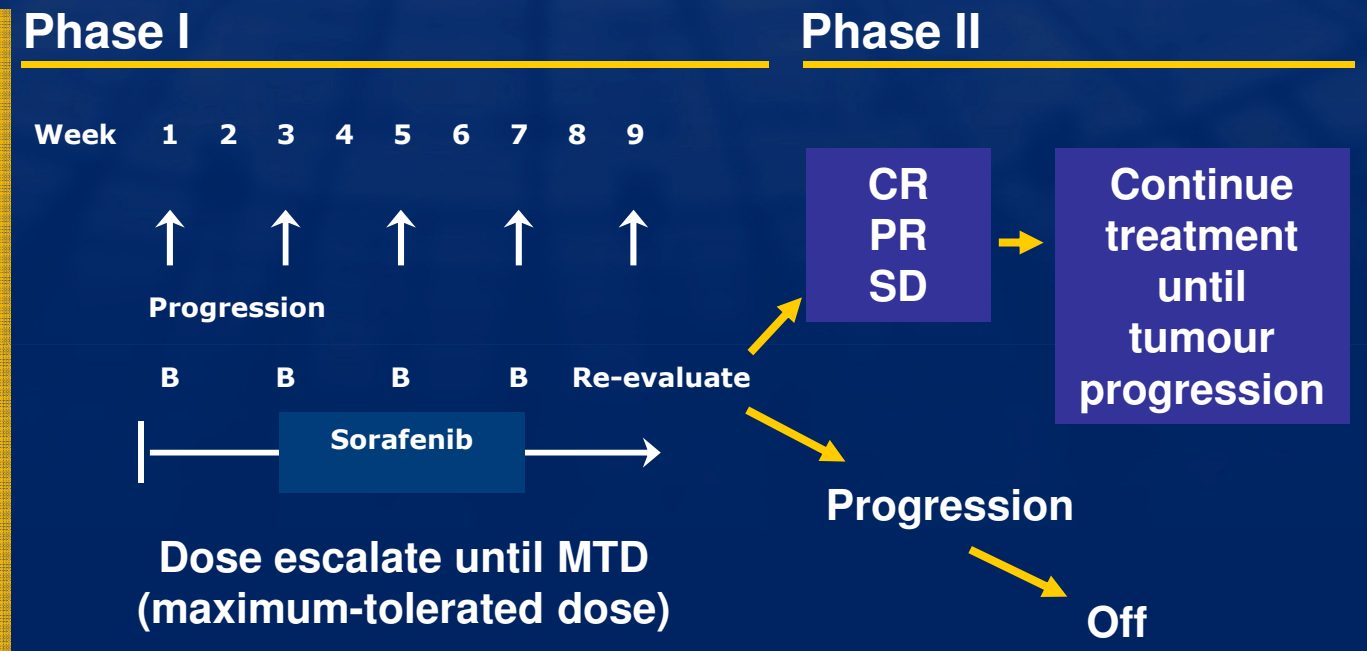
QUESTIONS

1. **Benefit of combination?**
2. **Benefit of sequential treatment?**
3. **Rôle of sorafenib?**

Sorafenib plus bevacizumab: phase I/II study design

ELIGIBILITY CRITERIA

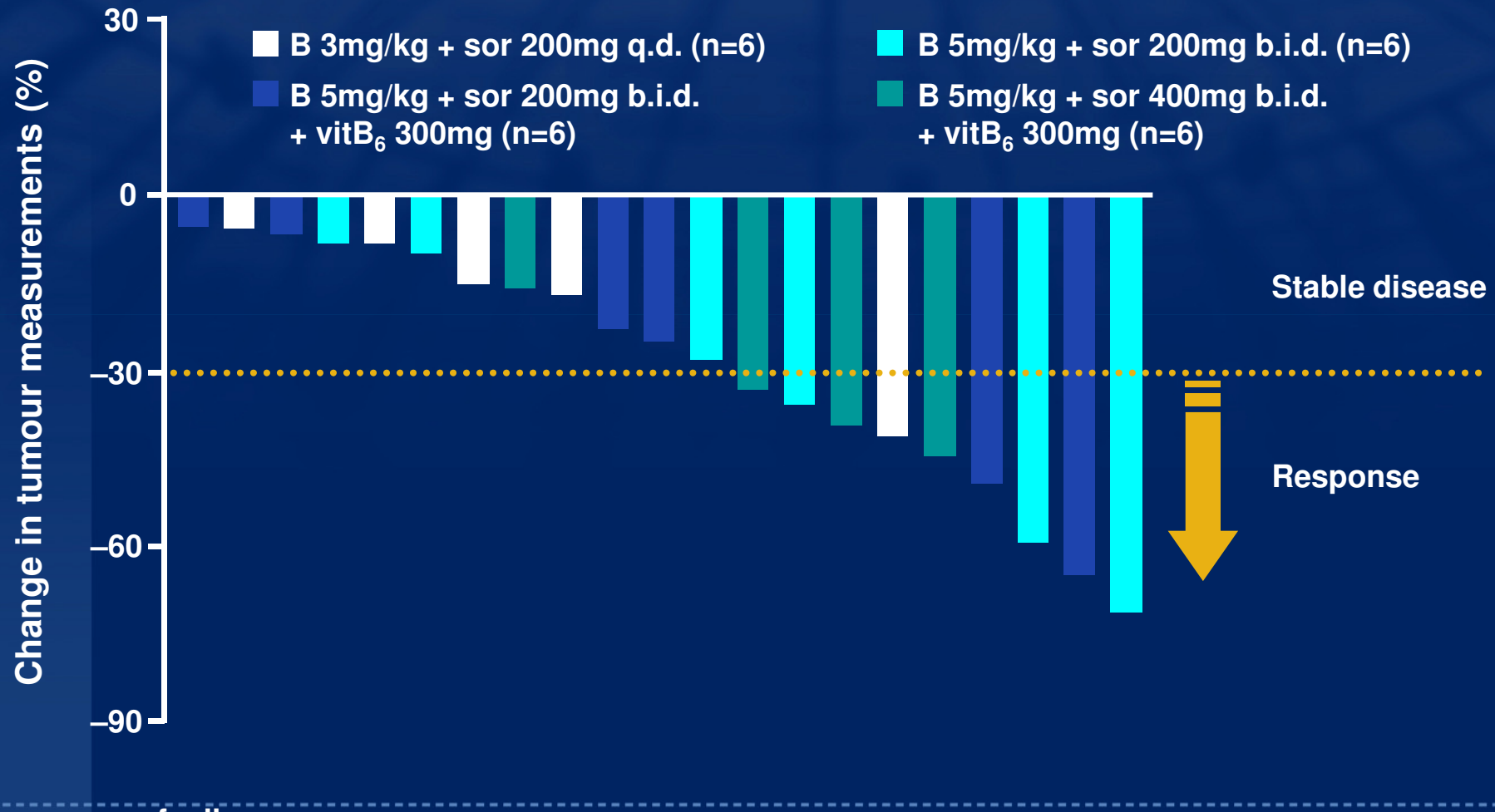
- Advanced RCC
- All histological sub-types
- ECOG PS 0–1
- Prior therapy allowed
  - No VEGF, VEGFR2 or MAP kinase pathways inhibitors
- Prior nephrectomy not required
- No CNS disease
- No active vascular disease (CNS or cardiac) within six months



VEGFR = VEGF receptor; MAP = mitogen-activated protein
CNS = central nervous system; CR = complete response
PR = partial response; SD = stable disease; B = bevacizumab

Adapted from: Sosman JA, et al. ASCO 2006; Atlanta, GA, USA

Sorafenib plus bevacizumab: phase I/II tumour responses



sor = sorafenib

q.d. = once daily; $vitB_6$ = vitamin B_6

Adapted from: Sosman JA, et al. ASCO 2006; Atlanta, GA, USA

QUESTIONS

1. Benefit of combination?
2. Benefit of sequential treatment?
3. Rôle of sorafenib?

Sequential use of sorafenib and sunitinib: retrospective analysis in 90 patients

MP Sablin (1), L Bouaita (1), C Balleyguier (1), J Gautier (2), C Celier (3), S Oudard (4), A Ravaud (3), S Negrier (2) , B Escudier (1)

(1) Institut Gustave Roussy, Villejuif, France
(2) Centre Léon Bérard, Lyon, France
(3) Hôpital Saint-André, Bordeaux, France
(4) Hôpital Européen Georges Pompidou, Paris, France

ASCO 2007

Table 4: Efficacy of Su after So

So		Su			
		PR no. (%)	SD no. (%)	PD no. (%)	NE no. (%)
PR no.	11	2 (18)	7 (64)	2 (18)	-
SD no.	45	6 (13)	24 (53)	11 (25)	4 (9)
PD no.	10	2 (20)	3 (30)	4 (40)	1 (10)
NE no.	2	-	1	-	1

Table 5: Efficacy of So after Su

Su		So		
		PR no.(%)	SD no.(%)	PD no.(%)
PR	5	1 (20)	2 (40)	2 (40)
SD	12	1 (8)	7 (58)	4 (34)
PD	5	0	3 (60)	2 (40)

Conclusions

The sequential administration of sorafenib and sunitinib is beneficial even if this two drugs share the same targets.

The use of sorafenib followed by sunitinib seems to be superior with:

- a better median suvival (not reached *vs 70 weeks*)
- better PFS for each arm.
- the obtention of partial responses after a progression with sorafenib (20%).

QUESTIONS

1. Benefit of combination?
2. Benefit of sequential treatment?
3. Role of sorafenib?

Sorafenib should be used

- as first choice therapy in patients who failed cytokines
- in first line, as a good alternative to interferon
- after sunitinib
- activity of sorafenib should continue to be explored:
  1. in combination with other agents (bevacizumab, temsirolimus, interferon…..)
  2. at higher dose, to confirm Amato's data on dose escalation