

Agenda — Renal Cell Carcinoma

- **New Developments in mRCC**
 - Anti-PD-1
 - Tivozanib
 - Axitinib
 - Cabozantinib
 - Pazopanib
- **Algorithm for Selecting Systemic Therapy**
- **Management of Toxicities with Novel Agents**
 - mTOR inhibitors
 - TKIs

Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer

Topalian SL et al.

N Engl J Med 2012;366(26):2443-54.

Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer

Brahmer JR et al.

N Engl J Med 2012;366(26):2455-65.

Phase I Studies of Anti-PD-1/PD-L1 Agents: Advanced RCC Patient Subgroup

Clinical parameter	Anti-PD-1 ^a		Anti-PD-L1 ^b
	1 mg/kg (n = 17)	10 mg/kg (n = 16)	10 mg/kg (n = 17)
Objective response rate	4 (24%)	5 (31%)	2 (12%)
Stable disease at ≥24 weeks	4 (24%)	5 (31%)	7 (41%)
Duration of response (range)	5.6 - >17.5 mo	8.4 - >22.3 mo	4 - 17 mo
PFS rate at 24 weeks	47%	67%	53%

^aTopalian SL et al. *N Engl J Med* 2012;366(26):2443-54. ^bBrahmer JR et al. *N Engl J Med* 2012; 366(26):2455-65.

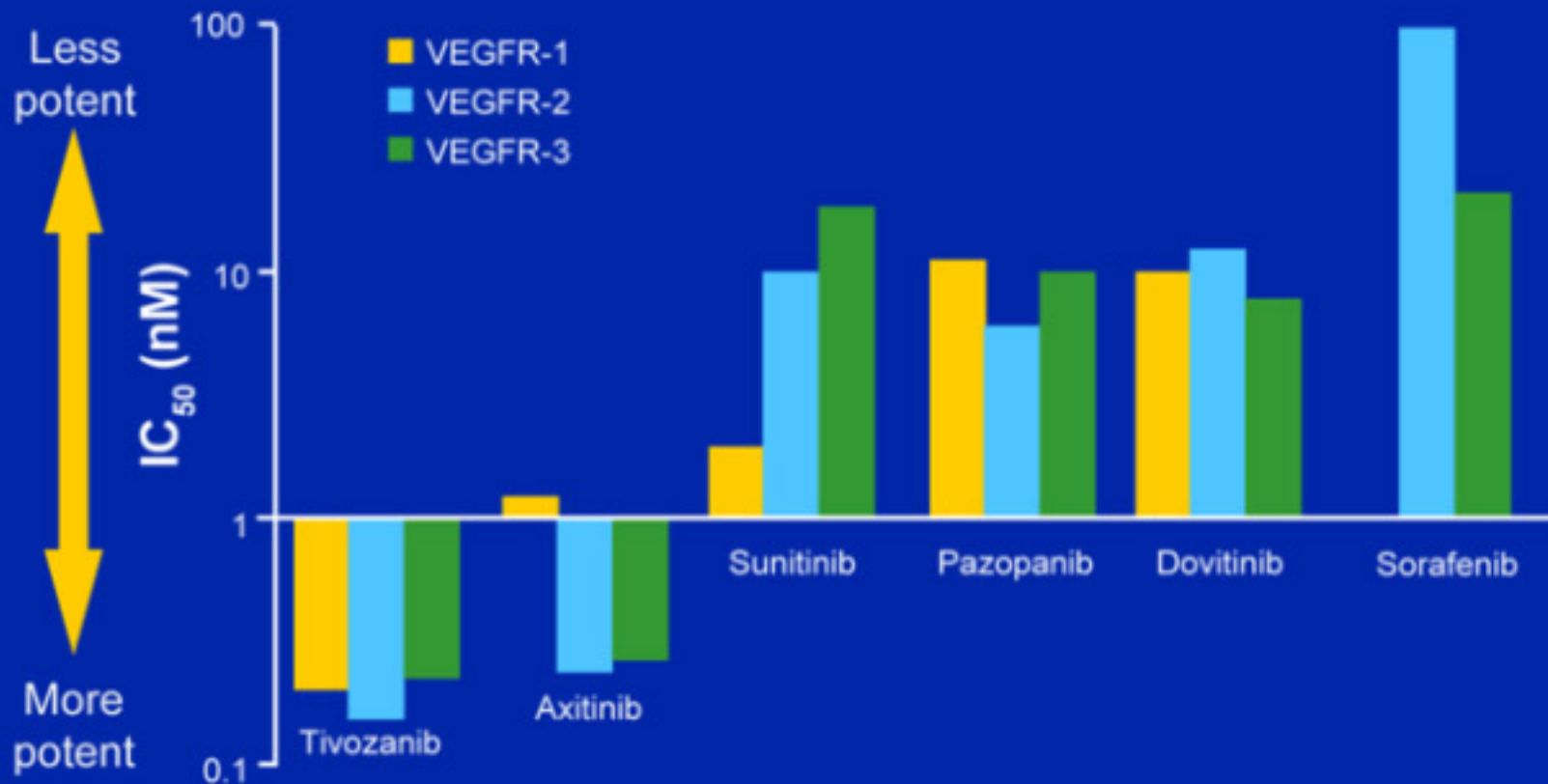
Anti-PD-1 Treatment-Related Adverse Events: Advanced RCC Patient Subgroup (n = 34)

Adverse event (AE)*	All grades	Grades 3-4†
Any adverse event	82%	18%
Fatigue	38%	0%
Rash	24%	0%
Pruritis	18%	3%
Diarrhea	15%	0%
Decreased appetite	9%	0%
Nausea	6%	0%

*All doses of anti-PD-1

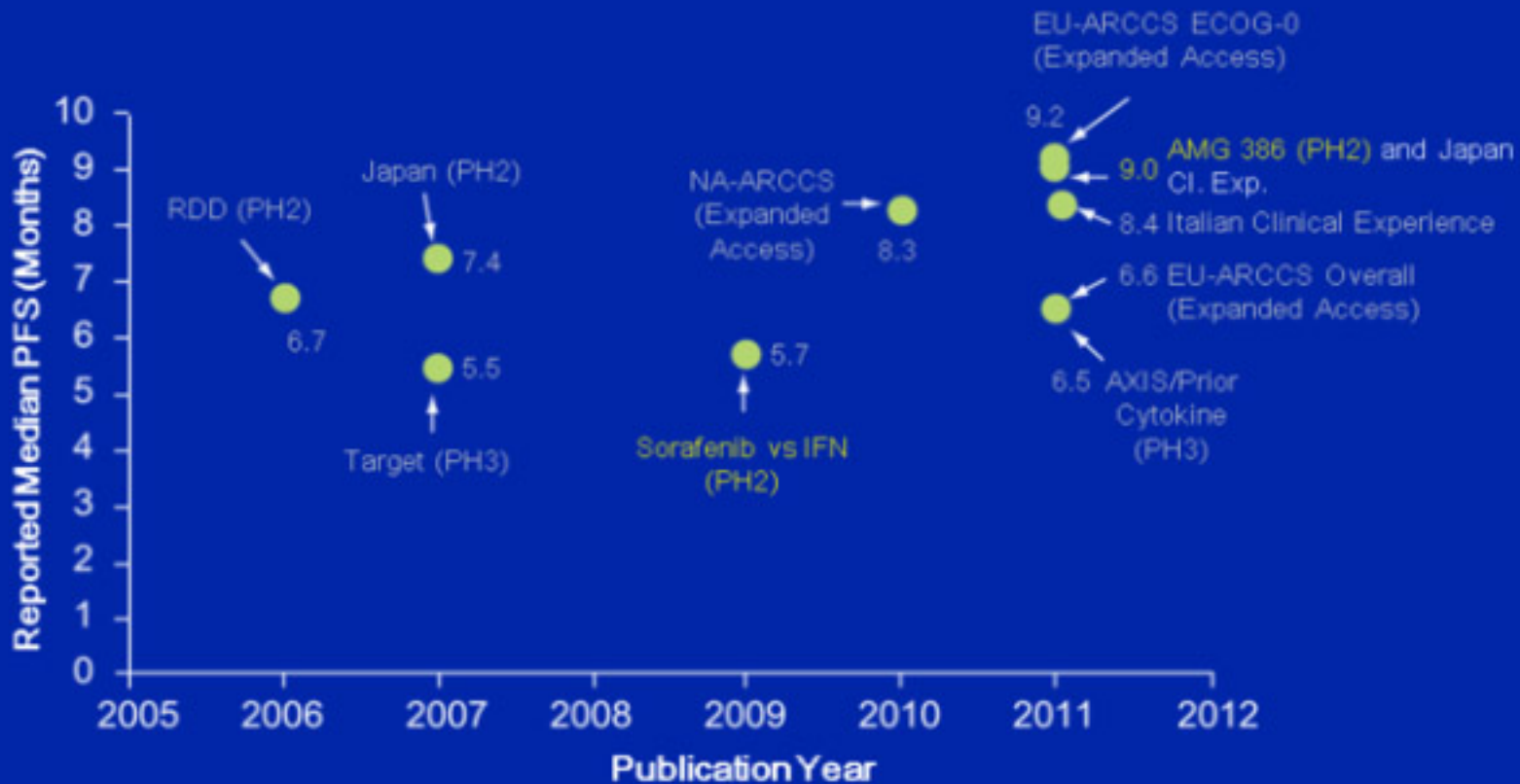
†Most common Grade 3-4 AEs were respiratory system disorders (2 pts) and hypophosphatemia (2 pts).

Relative Potencies of TKIs



Eskens FALM et al. *Proc AACR* 2008;Abstract LB-201; Nakamura K et al. *Cancer Res* 2006;66:9134-42; Chow LQ et al. *J Clin Oncol* 2007;25:884-96; Lee SH et al. *Clin Cancer Res* 2005;11:3633-41.

Sorafenib: Reported Progression-Free Survival Values Over Time



Yellow = includes treatment naïve patients

Gray = prior treatment with cytokine therapy and/or selective therapy targeting the angiogenesis pathway

Eisen T. ASCO 2012 Discussant

Slides

Faculty

Agenda

CME Info

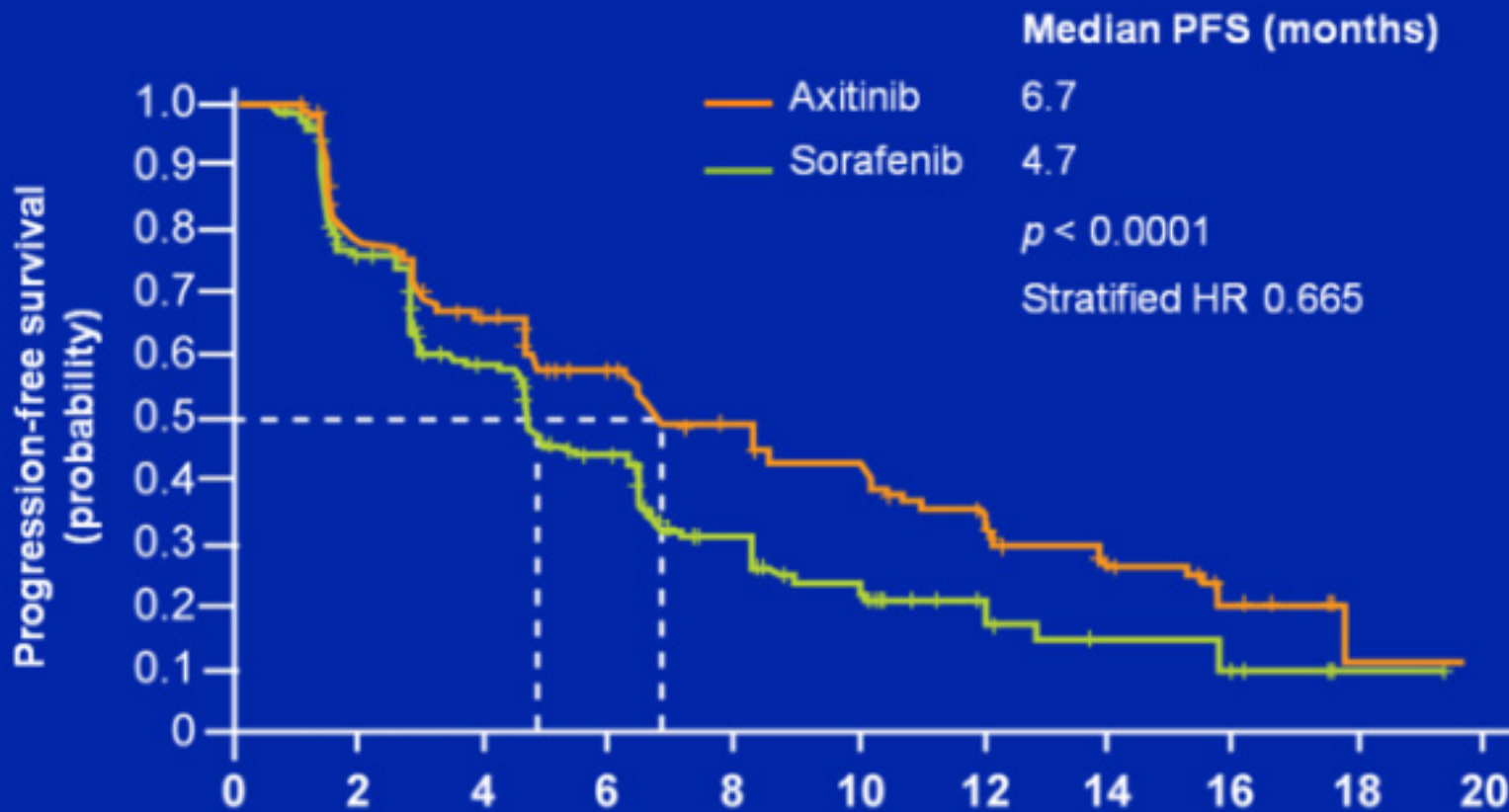
Help

Sorafenib Studies Safety

	TARGET Ph III	AMG 386	TIVO-1
Hypertension (Grade 3-4) %	17 (4)	46 (14)	34 (17)
Fatigue (Grade 3-4) %	37 (5)	22 (0)	16 (4)
HFS (Grade 3-4) %	30 (6)	54 (28)	54 (17)
Diarrhea (Grade 3-4) %	43 (2)	56 (8)	32 (6)
Overall AEs (Grade 3-4) %	95 (38)	100 (86)	NR
Dose reduction/ interruption %	13 DR 21 DI	35 DR 61 DI	43 DR 35 DI

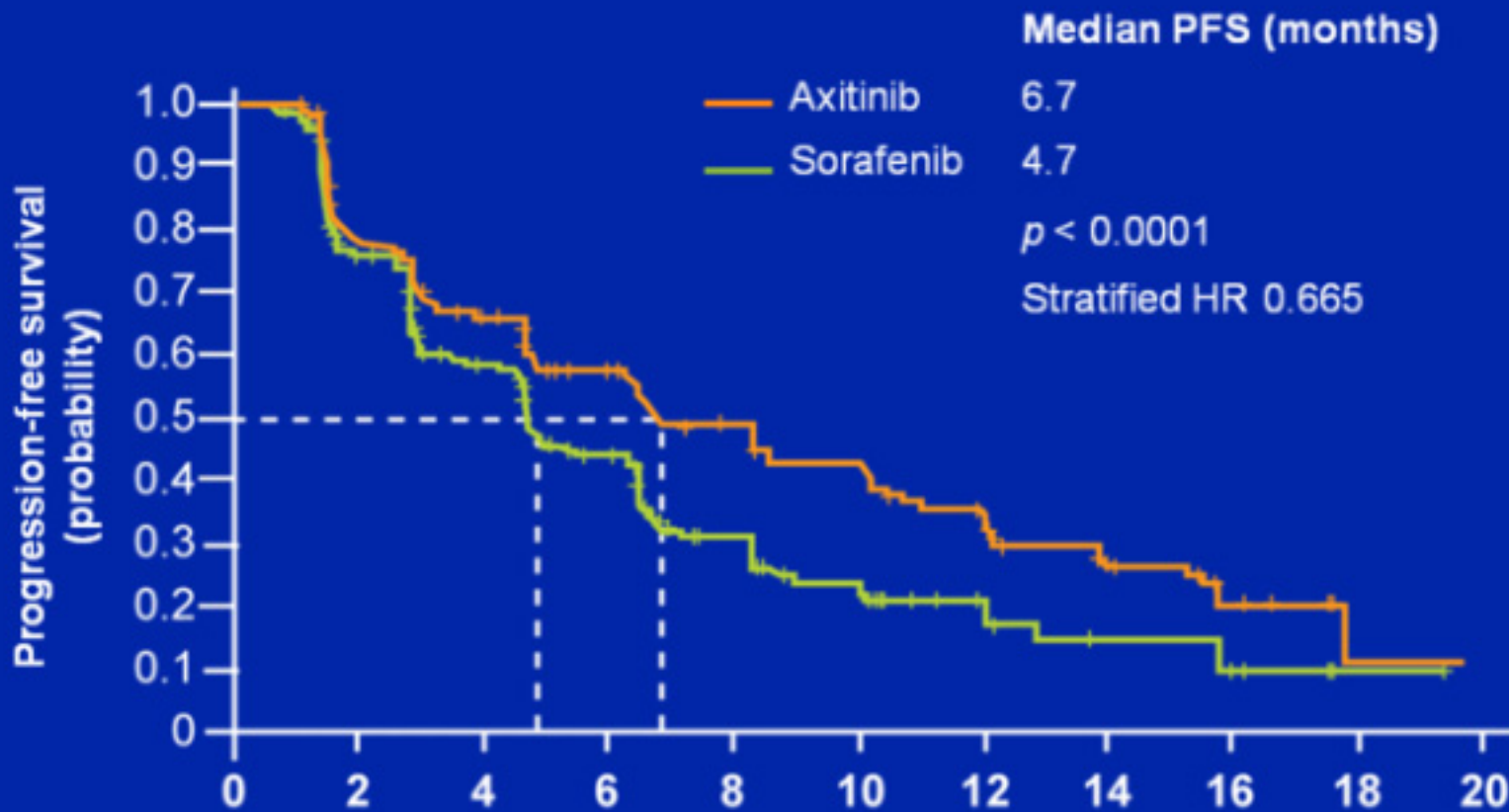
Eisen T. ASCO 2012 Discussant

AXIS: Progression-Free Survival in Patients with RCC Receiving Second-Line Axitinib or Sorafenib



Rini B et al. *Lancet* 2011;378(9807):1931-9.

AXIS: Progression-Free Survival in Patients with RCC Receiving Second-Line Axitinib or Sorafenib



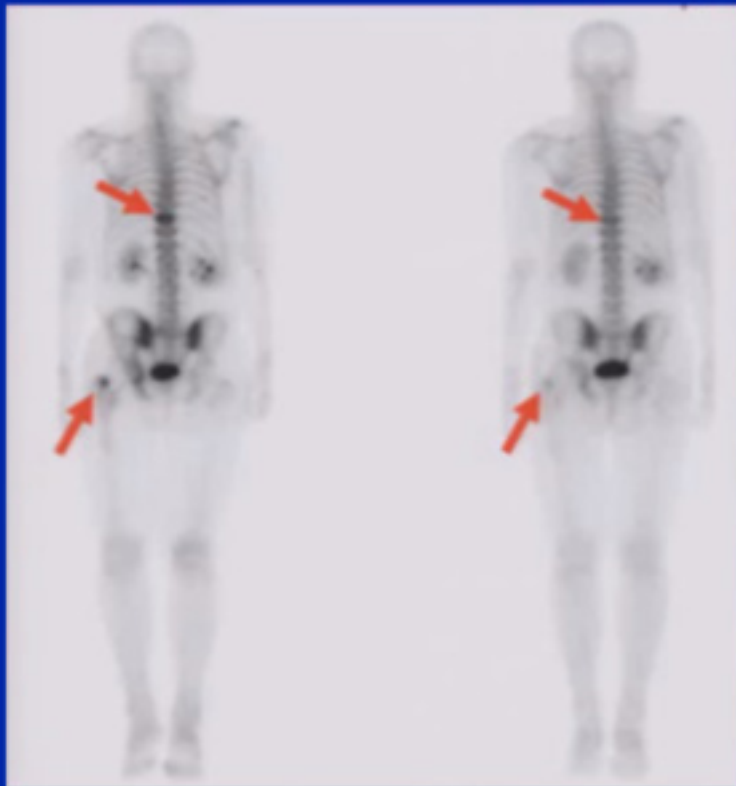
Rini B et al. *Lancet* 2011;378(9807):1931-9.

Partial Bone Scan Resolution and Pain Relief in a Symptomatic Patient with Bone Metastases

Prior therapies include sorafenib, everolimus, and sunitinib

Baseline

7-week follow-up



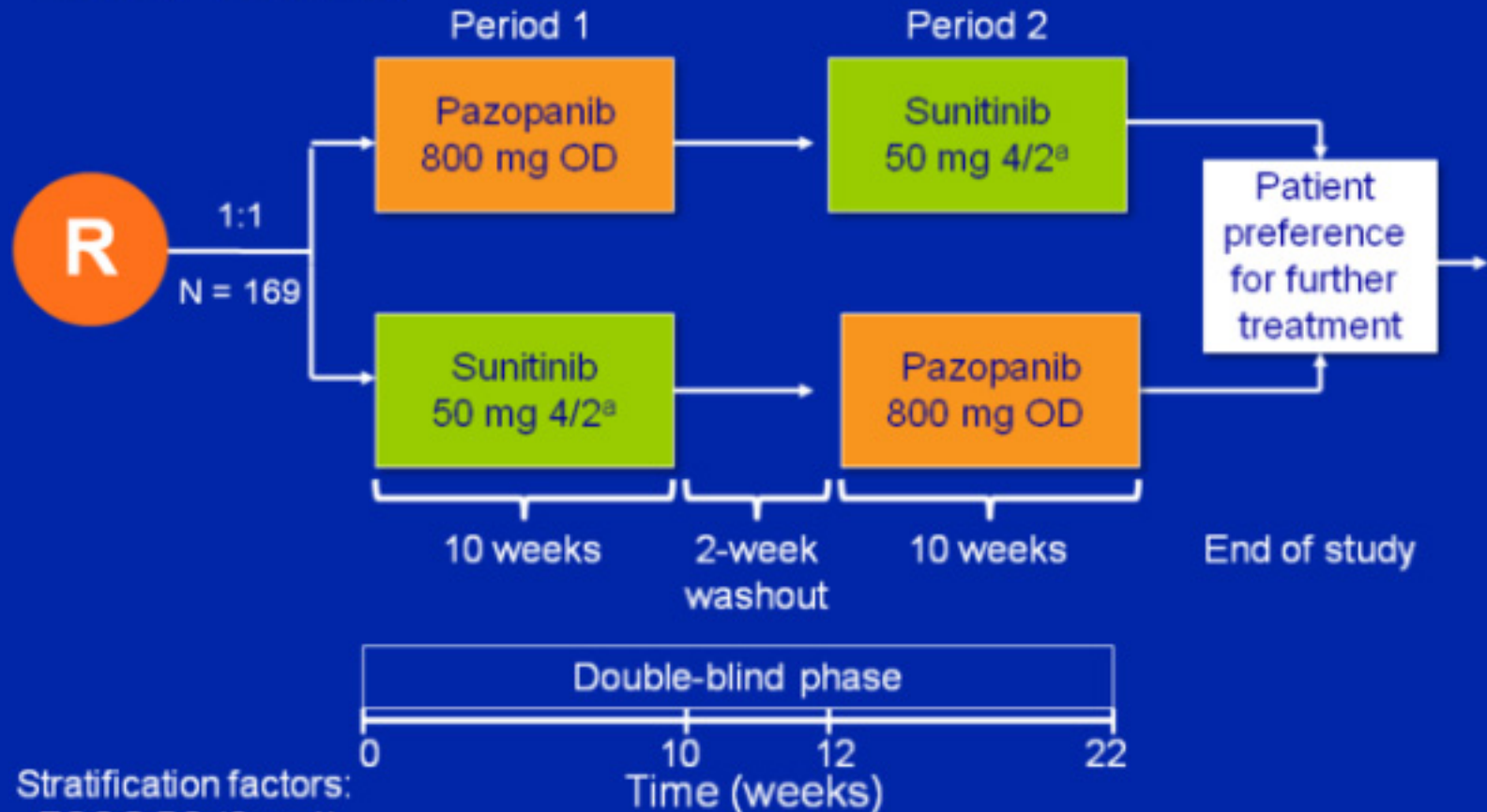
- Patient substantially reduced narcotic use by 7 weeks; continued on reduced narcotics until week 25
- Another patient with bone metastases and pain at baseline reported complete resolution of pain by 4 weeks
 - Pain free 90+ weeks on study

Cabozantinib Efficacy Summary

Clinical parameter	Cabozantinib (N = 25)
Objective response rate, n (%)	
Confirmed partial response	7 (28%)
Stable disease	13 (52%)
DCR at 16 weeks	18 (72%)
Median duration of response	Not yet estimable
Median PFS	14.7 mo
Median OS	Not reached

DCR = disease control rate defined as partial response + stable disease at 16 weeks

Study Design



Stratification factors:

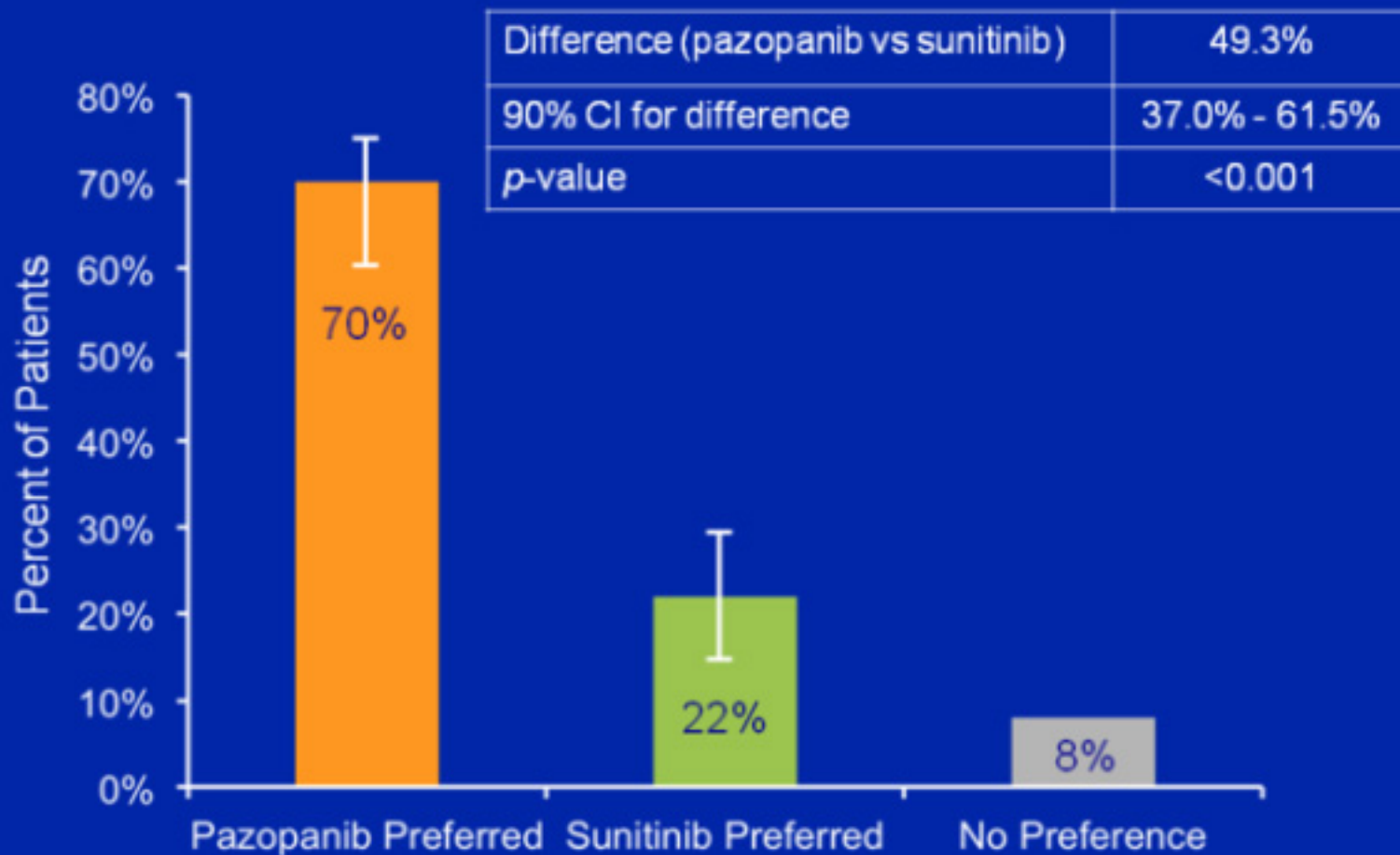
- ECOG PS (0 vs 1)
- Metastatic sites (1 vs ≥ 2)

^a 4 weeks on treatment → 2 weeks matching placebo → 4 weeks on treatment.

ECOG PS, Eastern Cooperative Oncology Group performance status

Escudier BJ et al. *Proc ASCO* 2012;Abstract CRA4502.

Primary Endpoint: Patient Preference Primary Analysis Population



Escudier BJ et al. *Proc ASCO 2012*;Abstract CRA4502.

COMPARZ: A Phase III Trial of Pazopanib versus Sunitinib in Locally Advanced or Metastatic RCC

Trial Identifier: NCT00720941 Target Accrual: 927 (Closed)

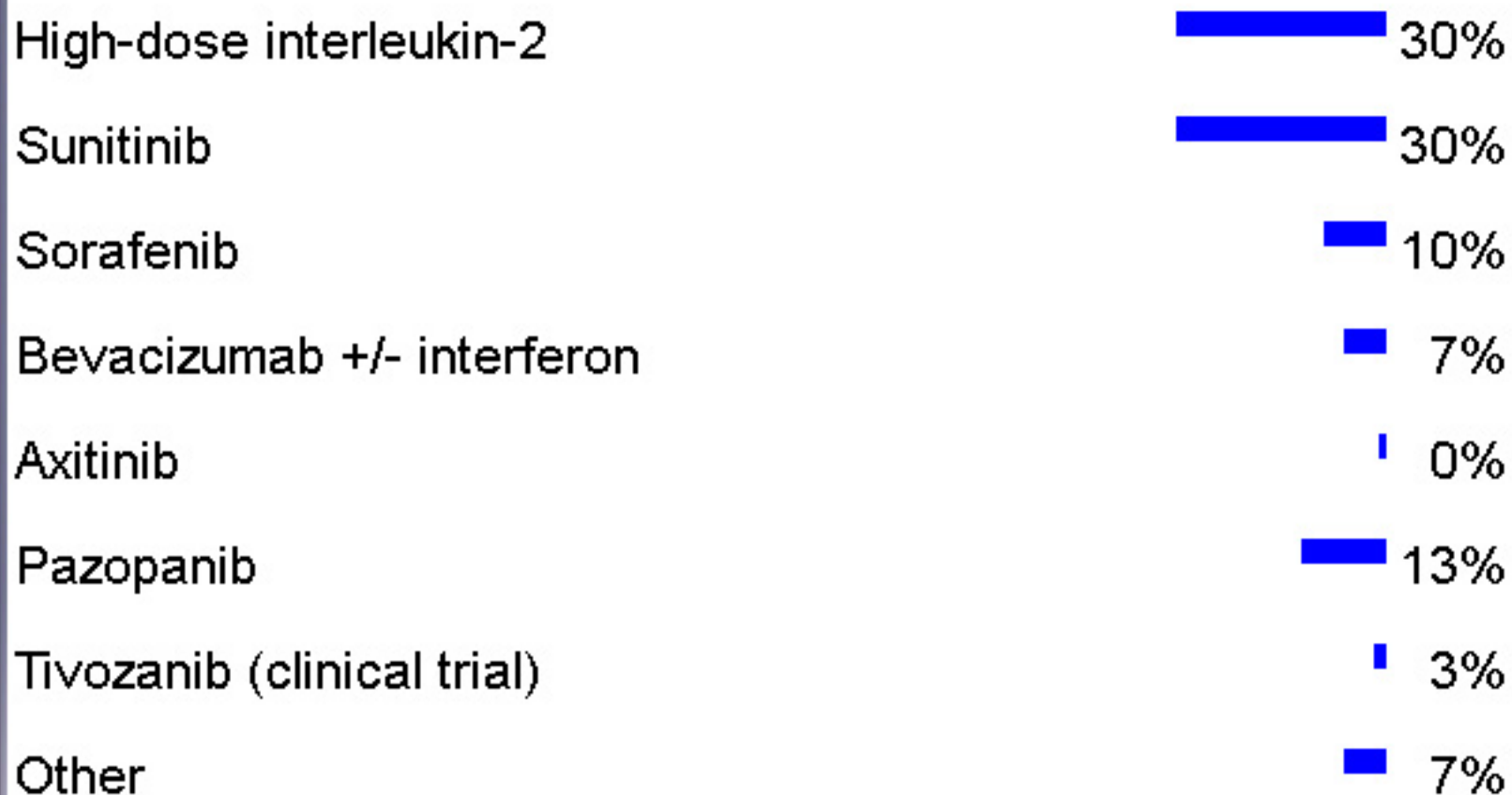


- **Primary endpoint:** Progression-free survival

What is your likely initial systemic treatment for RCC in a younger (age 55), otherwise healthy patient with low-volume asymptomatic mets?

1. High-dose interleukin-2
2. Sunitinib
3. Sorafenib
4. Bevacizumab +/- interferon
5. Axitinib
6. Pazopanib
7. Tivozanib (clinical trial)
8. Other

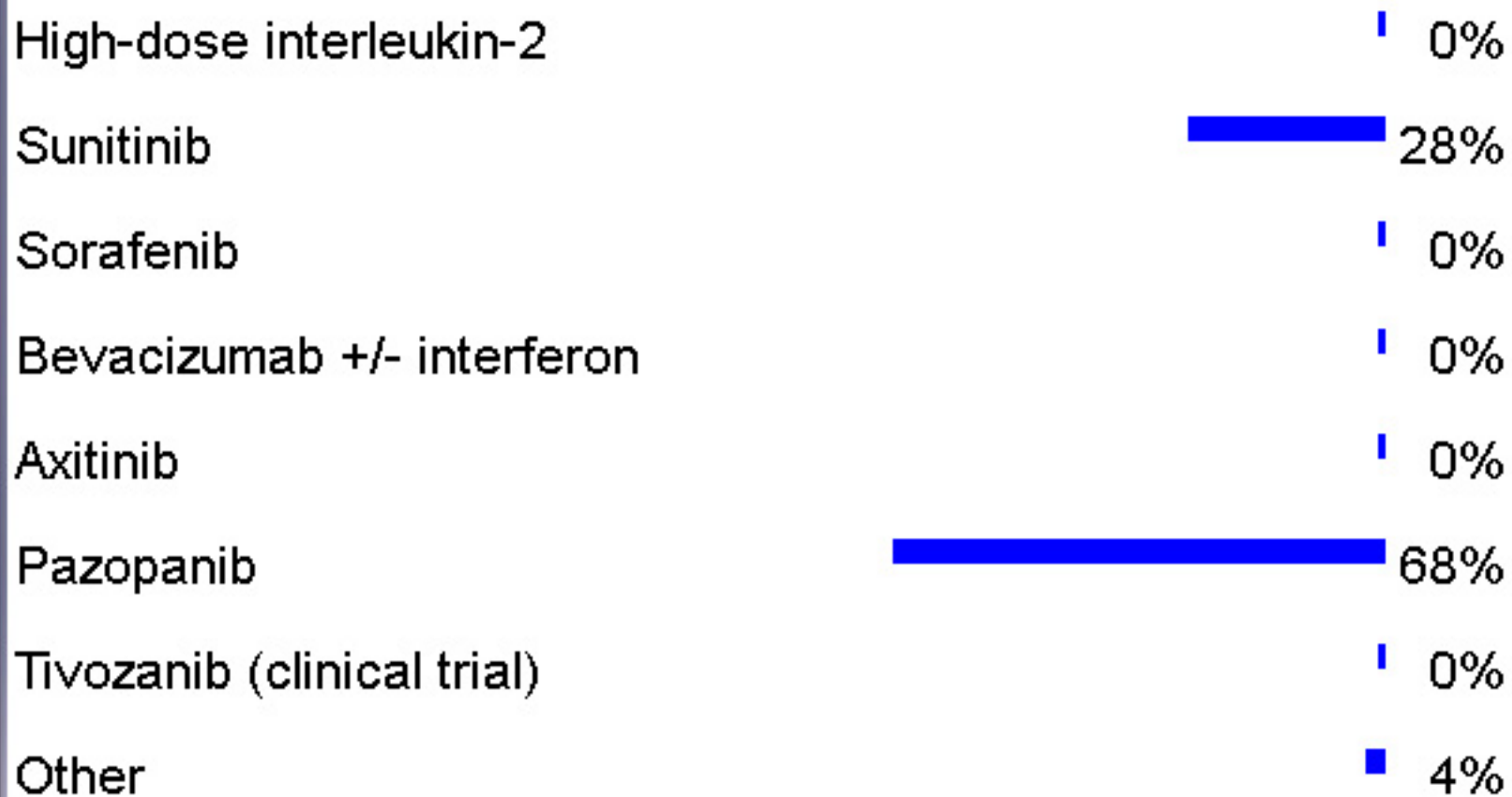
7. What is your likely initial systemic treatment for RCC in a younger (age 55), otherwise healthy patient with low-volume asymptomatic mets?



What is your likely initial systemic treatment for RCC in an elderly (age 78), otherwise healthy patient with low-volume asymptomatic mets?

1. High-dose interleukin-2
2. Sunitinib
3. Sorafenib
4. Bevacizumab +/- interferon
5. Axitinib
6. Pazopanib
7. Tivozanib (clinical trial)
8. Other

8. What is your likely initial systemic treatment for RCC in an elderly (age 78), otherwise healthy patient with low-volume asymptomatic mets?



REACT: Efficacy and Safety of Everolimus

	Everolimus (n = 1,367)
Partial response	1.7%
Stable disease	51.6%
Grade 3 or 4 adverse event	
Anemia	13.4%
Fatigue	6.7%
Dyspnea	6.5%
Hyperglycemia	5.5%
Stomatitis	5.4%
Pneumonia	4.2%
Pneumonitis	2.7%

- In the REACT study, safety findings and tumor responses were consistent with those observed in RECORD-1.

Best Response with Everolimus/Temsirolimus in Relation to Pneumonitis

	No. of patients	Stable Disease	Progressive Disease
Pneumonitis	14	85.7%	14.3%
No Pneumonitis	32	43.8%	56.3%

RECORD-3: A Phase II Study of Everolimus as First- and Second-Line Treatments for Metastatic RCC

Trial Identifier: NCT00903175 Target Accrual: 460 (Closed)



- **Primary endpoint:** Progression-free survival after first-line therapy (noninferiority)

CALGB 90802: A Phase III Trial of Everolimus with or without Bevacizumab for Advanced RCC

Trial Identifier: NCT01198158

Target Accrual: 700 (Open)

Metastatic, unresectable RCC, some clear cell histology

Treated with ≥ 1 prior VEGF TKI, progressed/intolerant to therapy

No active brain metastases



Everolimus +
Bevacizumab

Everolimus +
Placebo

- **Primary endpoint:** Overall survival
- **Secondary endpoint:** Progression-free survival, objective response rate, toxicity

www.clinicaltrials.gov. Accessed September 2012.

Faculty Case: Dr Motzer

- A 70-year-old man
- 2008:
- Nephrectomy: conventional clear cell type RCC
 - pT3b tumor grossly extended into renal vein(s) or vena cava
 - Mets: right adrenal, left psoas muscle, left inguinal nodes
- Sunitinib: PR 18 months
 - Dose reduction to 37.5 mg for fatigue and hand-foot reaction
- At progression: Everolimus: SD 6 months
 - Grade 1 fatigue, weight loss, dyspnea on exertion, rash, chills, nausea, vomiting, bleeding gums and myalgias
 - Bilateral pulmonary infiltrates but no respiratory symptoms

Faculty Case: Dr Hutson

- A 67-year-old man s/p sunitinib, tivozanib (trial)
- On Phase II trial of everolimus for 11 months

Faculty Case: Dr Motzer

- A 43-year-old woman
- 2008: Laparoscopic radical nephrectomy with lymph node dissection
 - Type II papillary RCC
- 2009: Subphrenic, peritoneal and hepatic nodules
 - Biopsy: RCC Rx: Sunitinib 50 mg (4 weeks on/2 weeks off)
 - Progression after 2 cycles
- Temsirolimus for 2 years – stable disease
 - Grade 1 nausea, fatigue, headache, cough, mucositis, hypercholesterolemia, epistaxis, bilateral pedal edema and skin rash

Faculty Case: Dr Motzer

- A 70-year-old man
- 2004: Right radical nephrectomy for clear cell RCC
- CT/MRI: Bilateral adrenal metastases
- RCC confirmed by needle biopsy
- Tivozanib (trial): PR for 30 months then progressed
 - Tolerated tivozanib well (mild abdominal pain and myalgia)

Faculty Case: Dr Hutson

- A 65-year-old man with mRCC
- On front-line Phase III trial:
 - Axitinib 2 mg po BID (dose reduced due to toxicity)
 - Near CR at 20 months on therapy

Faculty Case: Dr Motzer

- A 64-year-old man
- 2007: Left nephrectomy clear cell RCC
 - Mets to lung
 - Hypertension; on 1 antihypertensive
 - Sunitinib for 2 years: Dose reduction because of hand-foot syndrome
 - Progression in lung and bone
- Axitinib (trial)
 - PR: 23 four-week cycles
 - Hypertension worse
 - Required dose reduction for Grade 3 diarrhea

Faculty Case: Dr Hutson

- A 65-year-old woman with hematuria
 - 10-cm renal mass with renal vein involvement
 - Pulmonary metastases too numerous to count
 - Retroperitoneal nodes, liver metastases
- Sunitinib: cytopenias, hospitalizations (neutropenia, thrombocytopenia)