# VEGF Inhibition is the Best Option First Line Metastatic Renal Cell Carcinoma

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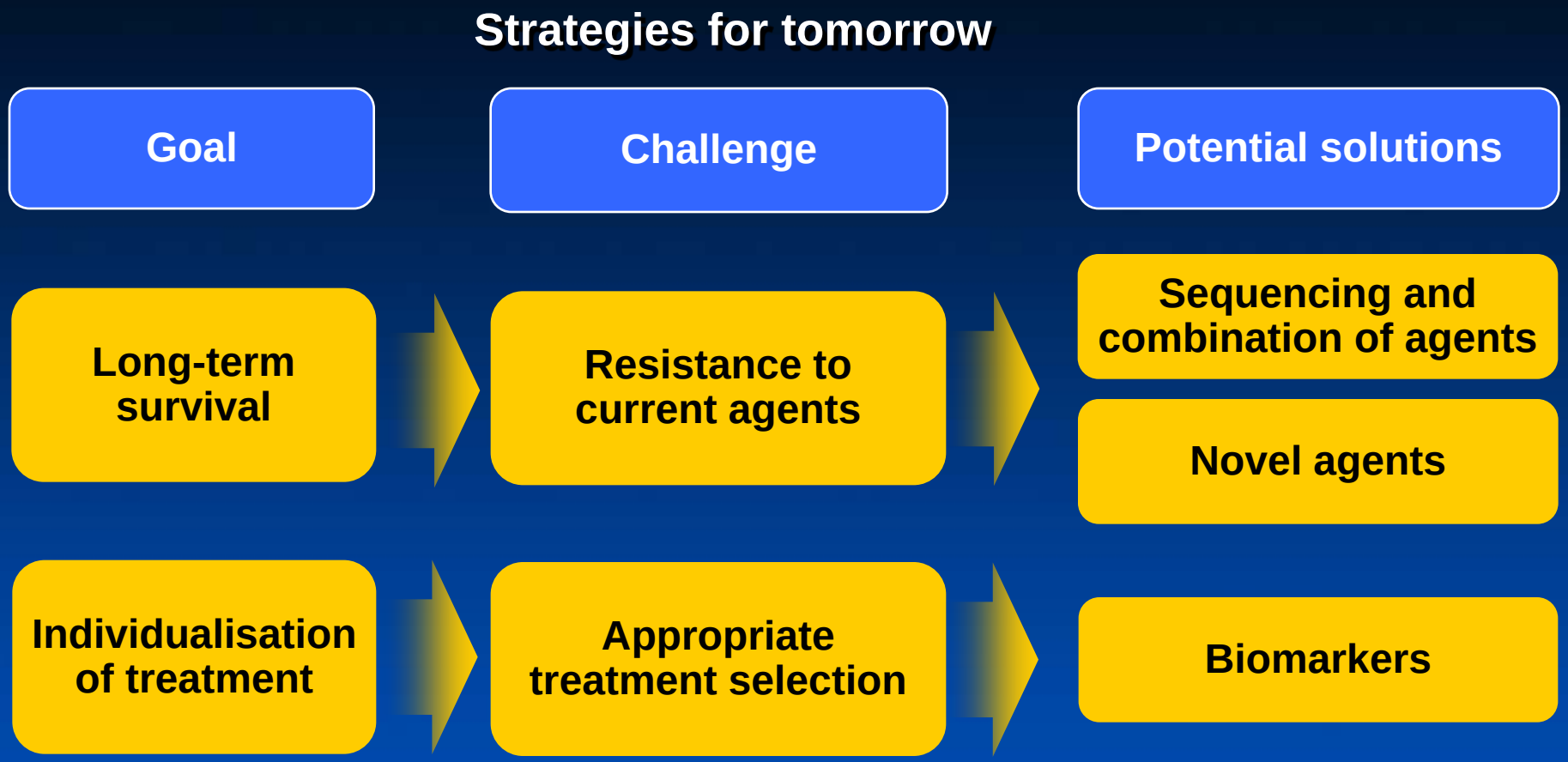
# Management of mRCC: Strategies for today

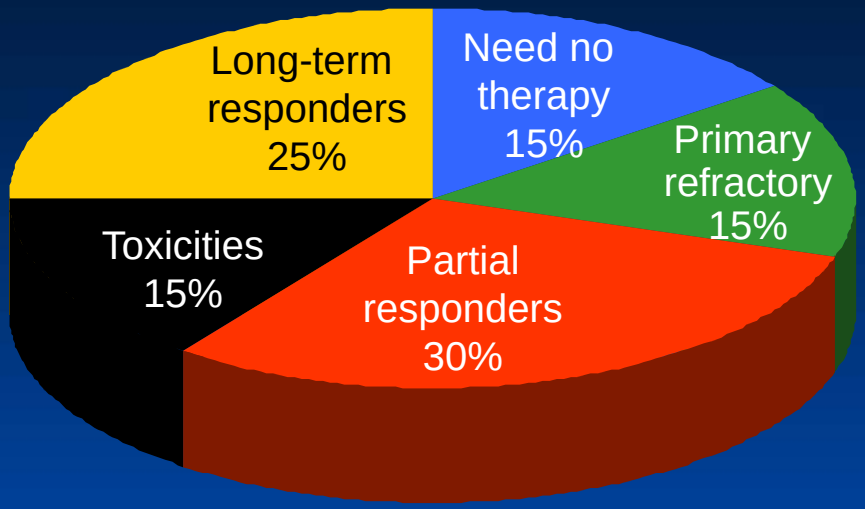
- How can we optimise outcomes with current therapies in the first-line treatment of mRCC?

# Management of mRCC: Strategies for today and tomorrow

- How can we achieve our goal of long-term survival in mRCC?



- Patients with mRCC are heterogeneous




**Predict risk of recurrence?**

**Choose appropriate therapy?**

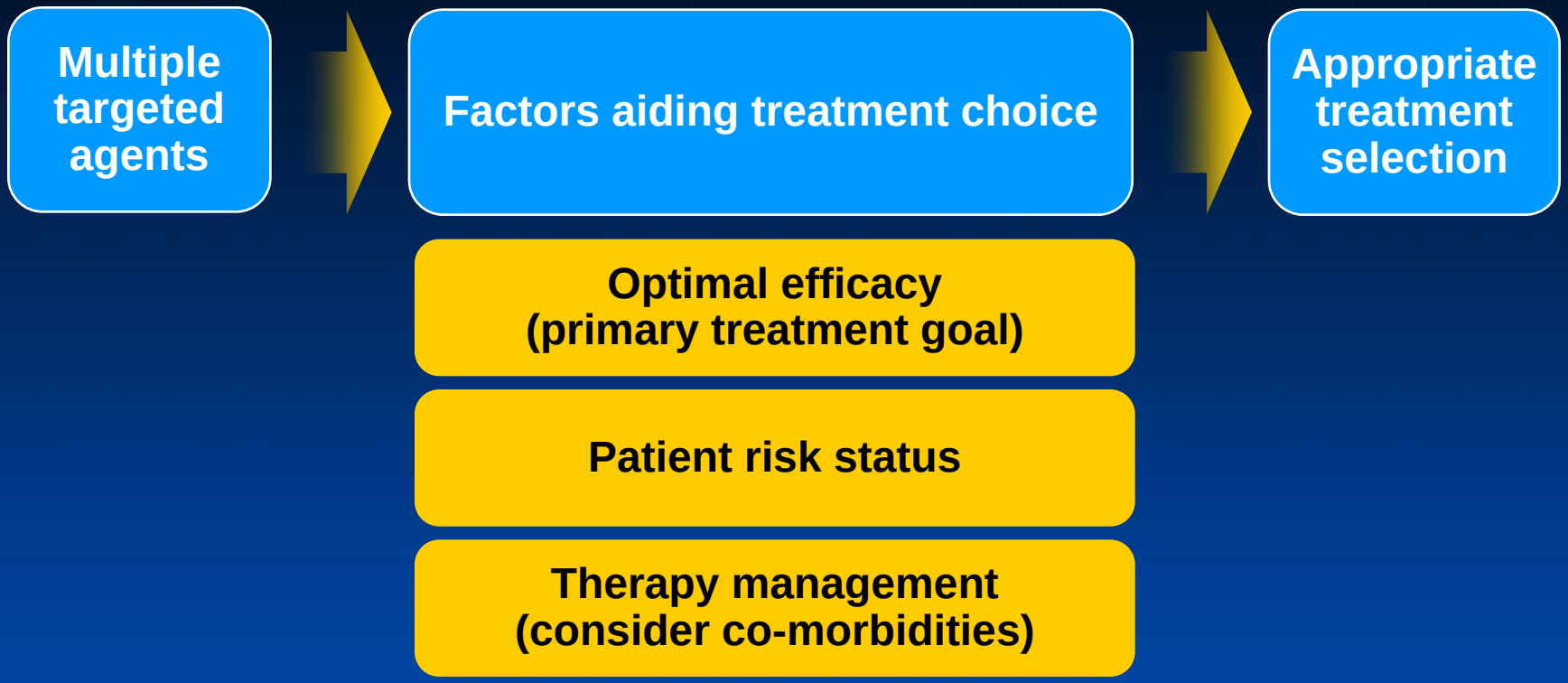
**Avoid toxicity?**

Srinivas, S. ASCO 2011 Education session

# Current options for maximising patient benefit with first-line agents

# Introduction

- Several targeted agents are now available for the treatment of mRCC




Schmidinger M, et al. *Cancer Invest* 2010; Oudard S, et al. *Cancer Treat Rev* 2011; Schmidinger M, et al. *J Cancer Res Clin Oncol* 2010

# Recommended targeted agents for first-line treatment of mRCC: Results from pivotal trials

| Agent | N | ORR (%) | Median PFS (months) | Median OS (months) |
|---|---|---|---|---|
| Sunitinib vs IFN-a[1] | 750 | 47 vs 12<br>P<0.001 | 11 vs 5<br>P<0.001 | 26.4 vs 21.8<br>P=0.051 |
| Bevacizumab + IFN-a vs IFN-a[2,3] | 649 | 31 vs 13<br>P=0.0001 | 10.2 vs 5.4<br>P<0.0001 | 23.3 vs 21.3<br>P=0.1291 |
| Bevacizumab + IFN-a vs IFN-a[4,5] | 732 | 26 vs 13<br>P<0.0001 | 8.5 vs 5.2<br>P<0.0001 | 18.3 vs 17.4<br>P=0.069 |
| *Pazopanib vs placebo[6,7] | 435 | 30 vs 3†<br>P<0.001 | 11.1 vs 2.8<br>P<0.0001 | 22.9 vs 20.5†<br>P=0.224 |
| Poor risk patients | | | | |
| Temsirolimus vs IFN-a[8*] | 626 | 8.6 vs 4.8<br>NS | 5.5 vs 3.1<br>P<0.001 | 10.9 vs 7.3<br>P=0.008 |

*Poor risk patients (modified MSKCC criteria); †Includes cytokine refractory and treatment-naïve patients

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

*Conditionally approved

# ‘Real world’ clinical experience with targeted agents: Sunitinib expanded-access programme

- International programme involving 4,564 patients with mRCC (treatment-naïve or cytokine-refractory)

| | Overall population | Brain metastases | ECOG PS ≥2 | Non-clear cell histology | Age ≥65 years |
|---|---|---|---|---|---|
| Evaluable patients (n) | 4,349 | 320 | 582* | 588 | 1,414 |
| PFS, months (95% CI) | 10.9 (10.3–11.2) | 5.6 (5.2–6.1) | 5.1 (4.2–5.5) | 7.8 (6.3–8.3) | 11.3 (10.7–12.3) |
| OS, months (95% CI) | 18.4 (17.4–19.2) | 9.2 (7.8–10.9) | 6.7 (6.0–7.9) | 13.4 (10.7–14.9) | 18.2 (16.6–19.8) |

*There were 503 patients with ECOG PS ≥2 evaluable for OS

Sunitinib demonstrated efficacy in subpopulations of interest

Gore ME, et al. *Lancet Oncol* 2009

# Efficacy in mRCC: ESMO/EAU treatment guidelines (2011)

| | Setting | Treatment |
|---|---|---|
| Treatment-naïve | Favourable or intermediate MSKCC risk status | Sunitinib[1,2]<br>Bevacizumab + IFN-α[1,2]<br>*Pazopanib[1,2] |
| | Poor MSKCC risk status | Temsirolimus[1,2] |
| Refractory | Prior cytokine | Sorafenib[1,2]<br>Pazopanib[1,2] |
| | Prior VEGFR-TKI | Everolimus[1,2] |
| | Prior mTOR | Clinical trials[1] |

*Conditionally approved

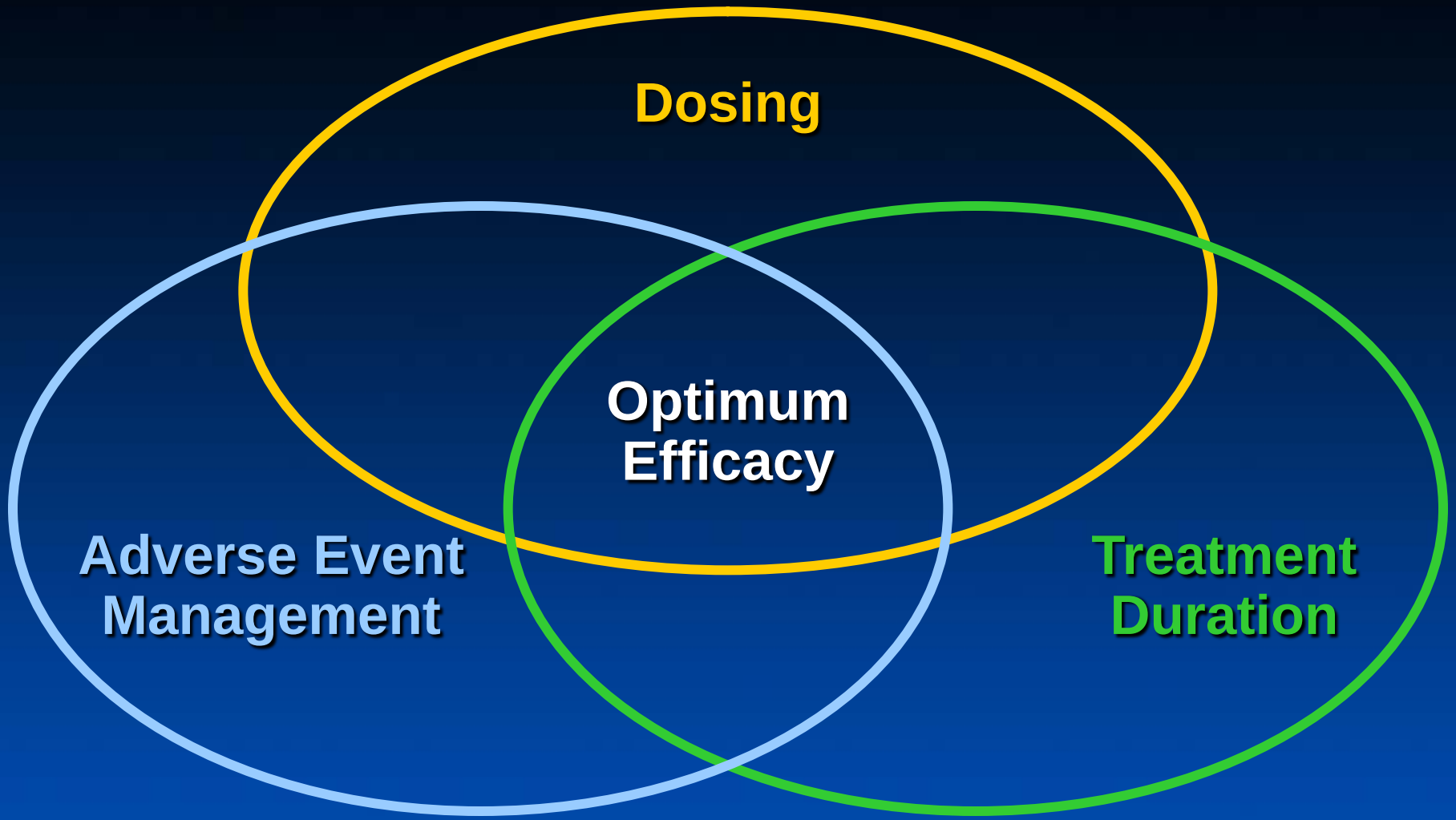
1. Ljungberg B, et al. 2010; http://www.uroweb.org; 2. Escudier B, et al. *Ann Oncol* 2010

# Appropriate treatment selection: Defining risk status in clinical trials

| MSKCC criteria | ARCC trial criteria |
| --- | --- |
| Karnofsky PS <80 | Karnofsky PS = 60/70 |
| Low serum hemoglobin | Low serum haemoglobin |
| High corrected calcium | High corrected calcium |
| High LDH | High LDH |
| Time from diagnosis to treatment <1 year | Time from diagnosis to randomization <1 year |
| | Multiple organ site of metastasis |

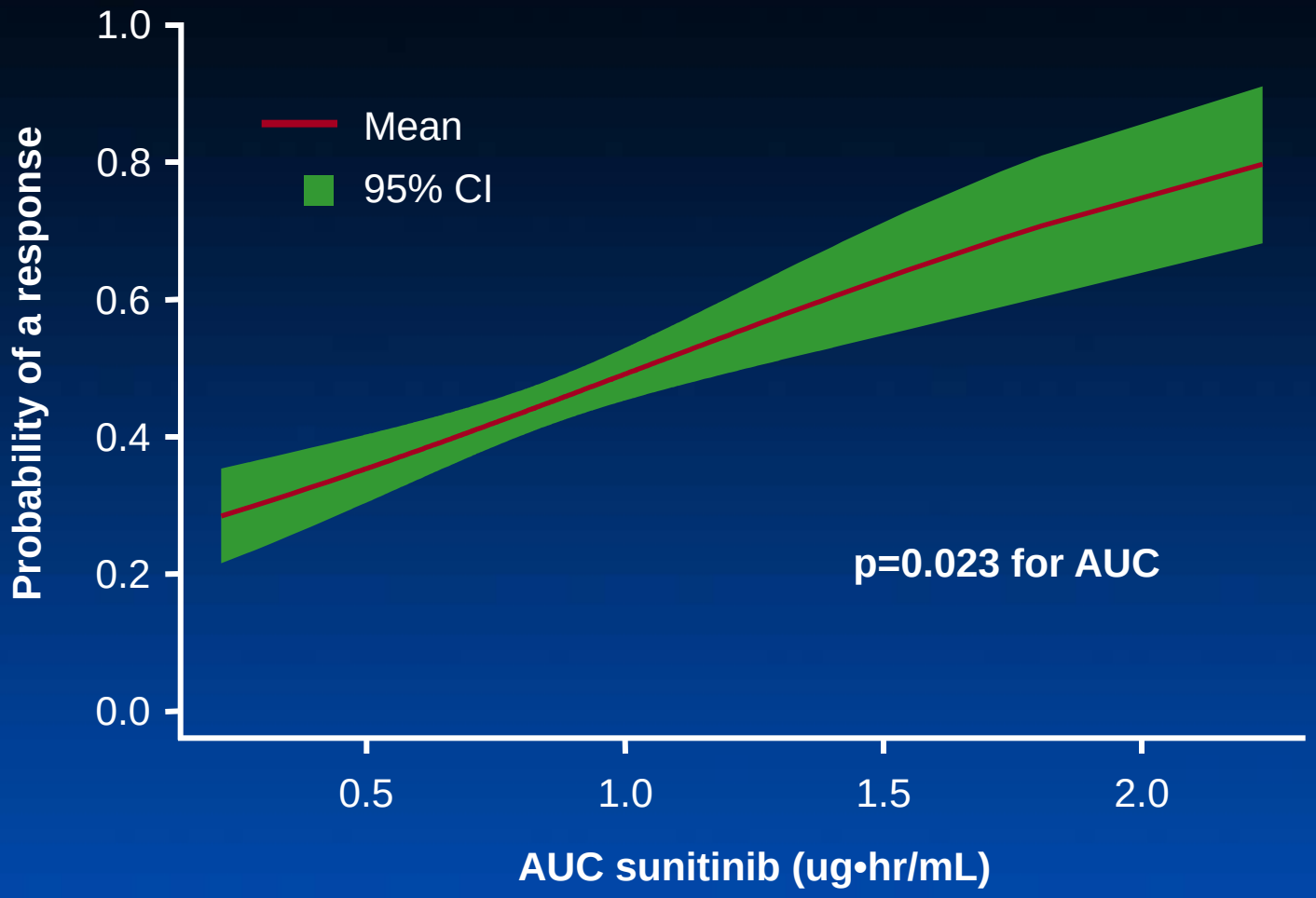
Motzer RJ, et al. *J Clin Oncol* 2002; Hudes G, et al. *N Engl J Med* 2007

# Effective therapy management




Ravaud A. *Ann Oncol* 2009

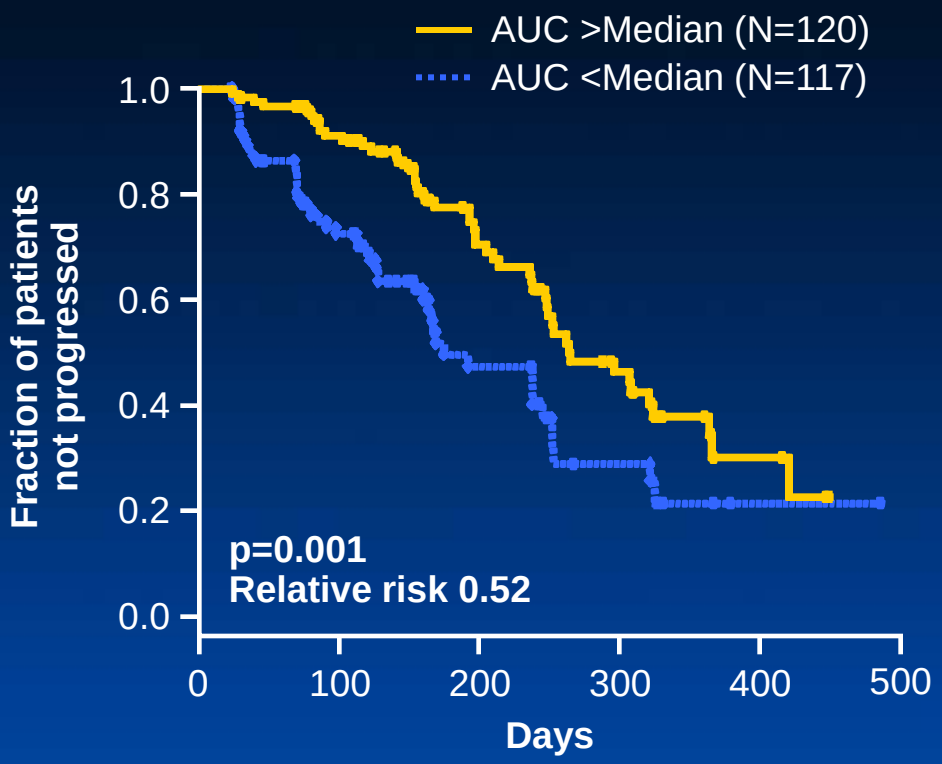
# Probability of a Tumour Response Increases with Mean Daily Sunitinib Exposure



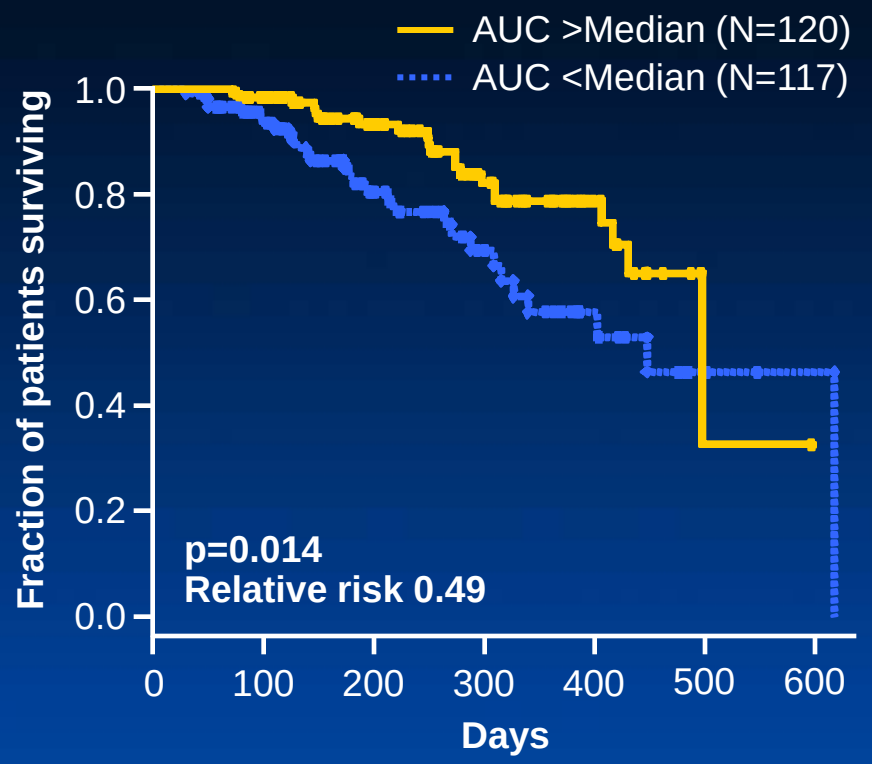

Source: Houk BE, et al. Cancer Chemother Pharmacol 2010, 66:357-371

# Higher Exposure to Sunitinib Is Associated with Longer Time to Progression and OS

## Time to Tumour Progression




## OS




Source: Houk BE, et al. Cancer Chemother Pharmacol 2010, 66:357-371

# Therapy management: Appropriate treatment duration

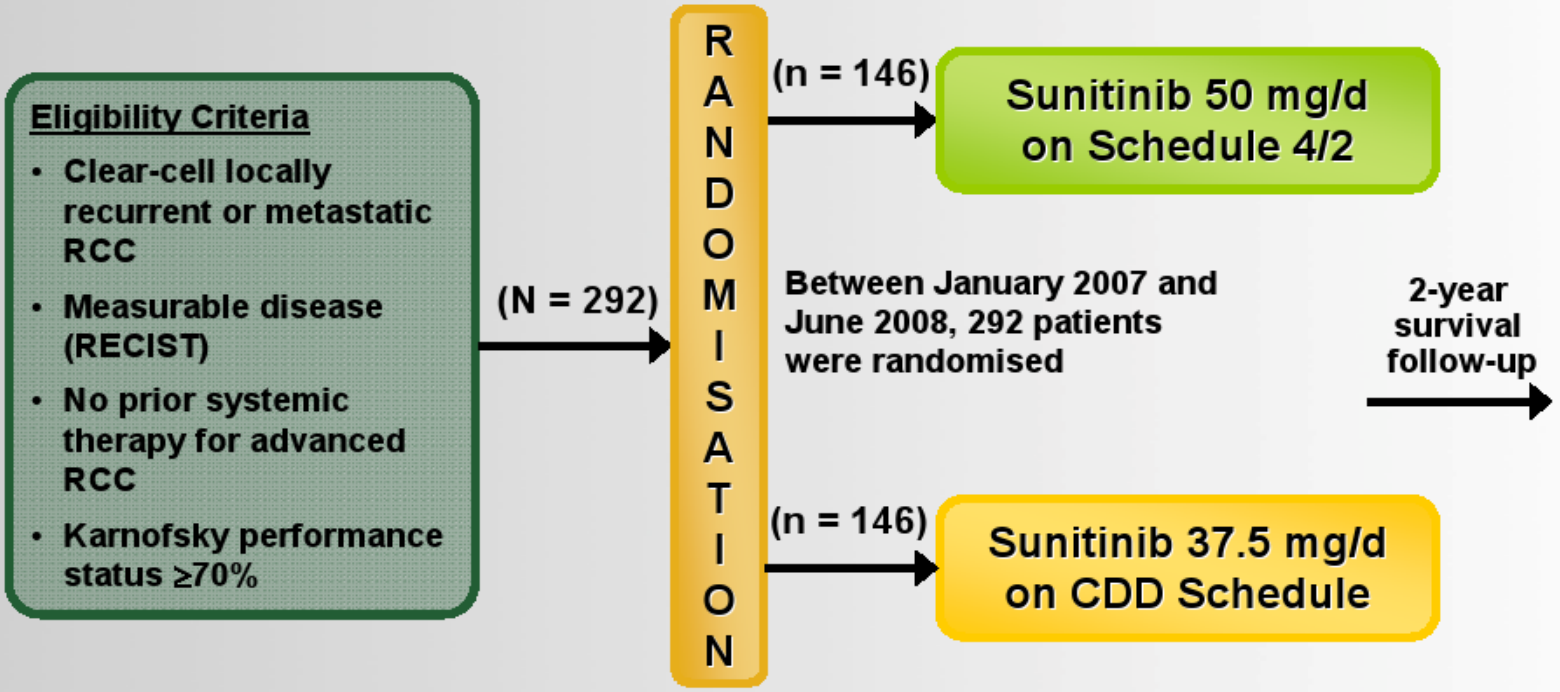
- Objective response may be increased by long-term exposure to targeted agents

| Analysis | Sunitinib N=374 | | IFN-α N=373 | | P-value |
|---|---|---|---|---|---|
| | Duration, months (range) | ORR, % | Duration, months (range) | ORR, % | |
| Interim | 6 (1–15) | 31 (26–36) | 4 (1–13) | 6 (4–9) | <0.001 |
| Final | | | | | |
| Invest. | 11 (<1–41) | 47 (42–52) | 4 (<1–40) | 12 (9–16) | <0.001 |
| Central | | 39 (34–44) | | 8 (6–12) | <0.001 |

Motzer *et al. N Engl J Med.* 2007;356:115–124
Motzer *et al. J Clin Oncol*. 2009;27:3584–3590
Figlin *et al. J Clin Oncol.2008;26(15S):Abstract 5024*

# What is the best dose or optimal schedule for VEGFR-targeted agents?

# Phase II EFFECT Study: Sunitinib 4/2 vs Continuous Dosing Schedule as First-line Therapy in mRCC




CDD, continuous daily dosing.

Motzer RJ et al. Presented at the 2011 Genitourinary Cancers Symposium (abstract LBA308).

# Phase II EFFECT Study: Sunitinib 4/2 vs Continuous Dosing Schedule as First-line Therapy in mRCC

| Endpoint | Sunitinib 50 mg/d Schedule 4/2 (n = 146) | Sunitinib 37.5 mg/d CDD schedule (n = 146) |
|---|---|---|
| ORR, % (95% CI) | 32.2 (24.7–40.4) | 28.1 (21.0–36.1) |
| *P* | .444 | |
| TTP, median (95% CI), months | 9.9 (7.0–13.4) | 7.1 (6.8–9.7) |
| HR (95% CI) | 0.77 (0.57–1.04) | |
| *P* | .090 | |
| OS, median (95% CI), months | 23.1 (17.4–25.4) | 23.5 (17.5–not reached) |
| HR (95% CI) | 1.09 (0.78–1.50) | |
| *P* | .615 | |
| PFS, median (95% CI), months * | 8.5 (6.9–11.1) | 7.0 (6.0–8.7) |
| HR (95% CI) | 0.77 (0.58–1.02) | |
| *P* | .070 | |

*PFS was estimated as a sensitivity analysis for TTP.

Motzer RJ et al. Presented at the 2011 Genitourinary Cancers Symposium (abstract LBA308).

# Conclusions

- In this randomized phase II mRCC trial, there was no statistically significant difference in TTP between the two treatment schedules
  - ORR and OS were similar
  - Grade 3/4 AE profiles were similar
  - No significant difference was observed in PRO between the two treatment arms; however, an 'on/off' effect was evident for Schedule 4/2
- There was a trend toward inferior TTP (and PFS) with continuous dosing, and Schedule 4/2 was statistically superior to continuous dosing in time to deterioration
- The treatment goal should be to adhere to the approved dose and schedule

# Individualized Dose/Schedule Strategy for Sunitinib in RCC patients to maximize dose and minimize time off Rx: Correlation with DCE-US data

## A single Centre Experience

Bjarnason et al: ESMO 2011

# Rationale for dose / schedule changes

- **Clinical observation:**
  - Pts referred as Sutent resistant taking 37.5 and 25 mg
  - Responded / stabilized when dose escalated to 50mg, and Rx schedule changed to 14 days on/ 7 days off
- **Individually maximize dose and course duration**
  - ↑ AUC associated with better response, PFS and OS
  - High inter-patient variability in pharmacokinetics (40-60%)
  - Ethnic differences in toxicity
  - Sunitinib steady state reached at 10-14 days
- **Minimize time off therapy**
  - Progression during Rx breaks
- **Minimize toxicity / Maximize overall duration of therapy**
  - Dose modifications done to keep dose limiting toxicity at ≤ grade-2

# Individualized Dose/Schedule Strategy: Maximize dose and minimize time off therapy

**Dose modifications done to keep dose limiting toxicity at ≤ grade-2**

**Pts seen on day 14 on first course to assess toxicity**

- **DL1: Starting dose: 50 mg, 28 days on / 14 days off:**
  - **Reduce off period to 7 days if minimum toxicity**

- **DL 2: 50 mg, 14 days on / 7 days off**
  - Individually increase # of days on treatment

- **DL 3: 50 mg, 7 days on / 7 days off**
  - Individually increase # of days on treatment

- **DL 4: 37.5 mg continuously**
  - Individualize 7 day breaks off Rx based on toxicity

- **DL 5: 25 mg continuously**
  - Individualize 7 day breaks off Rx based on toxicity

# Single Centre retrospective data: Patient characteristics for 172 pts

| | patient (%) |
|---|---|
| **Mean age = 60** | |
| **Males / Females** | 125 / 47 |
| **Heng prognostic group:** | |
| Favorable | 35 (20) |
| Intermediate | 102 ( 60) |
| Poor | 35 (20) |
| **Histology** | |
| Clear cell | 136 (79.1) |
| Papillary | 19 (11.1) |
| Chromophobe | 4 (2.3) |

| | patient (%) |
|---|---|
| **Nephrectomy** | |
| yes | 139 (80.8) |
| no | 33 (19.2) |
| **Line of Therapy** | |
| 1st | 103 (59.1) |
| 2nd | 53 (31.1) |
| 3rd | 13 (8.1) |
| 4th | 3 (1.7) |

**Imaging done q3 months**

# Median PFS based on Sunitinib dose/schedules used for the majority of time on Rx. N=172 RCC pts

| Schedule | pts | Median PFS Mo | 95% CI Mo | P for Pairs* |
|---|---|---|---|---|
| 25 / 37.5 mg cont | 62 | **11.9** | 8.3 – 19.0 | < 0.0001 |
| 50 mg 7-14/7 | 71 | **11.5** | 7.9 – 15.8 | < 0.0001 |
| 50 mg 28/14 | 39 | **4.9** | 3.4 – 6.9 | |

**Patient were only dose reduced (37.5 mg) if they did not tolerate the 50mg 7 / 7 schedule**

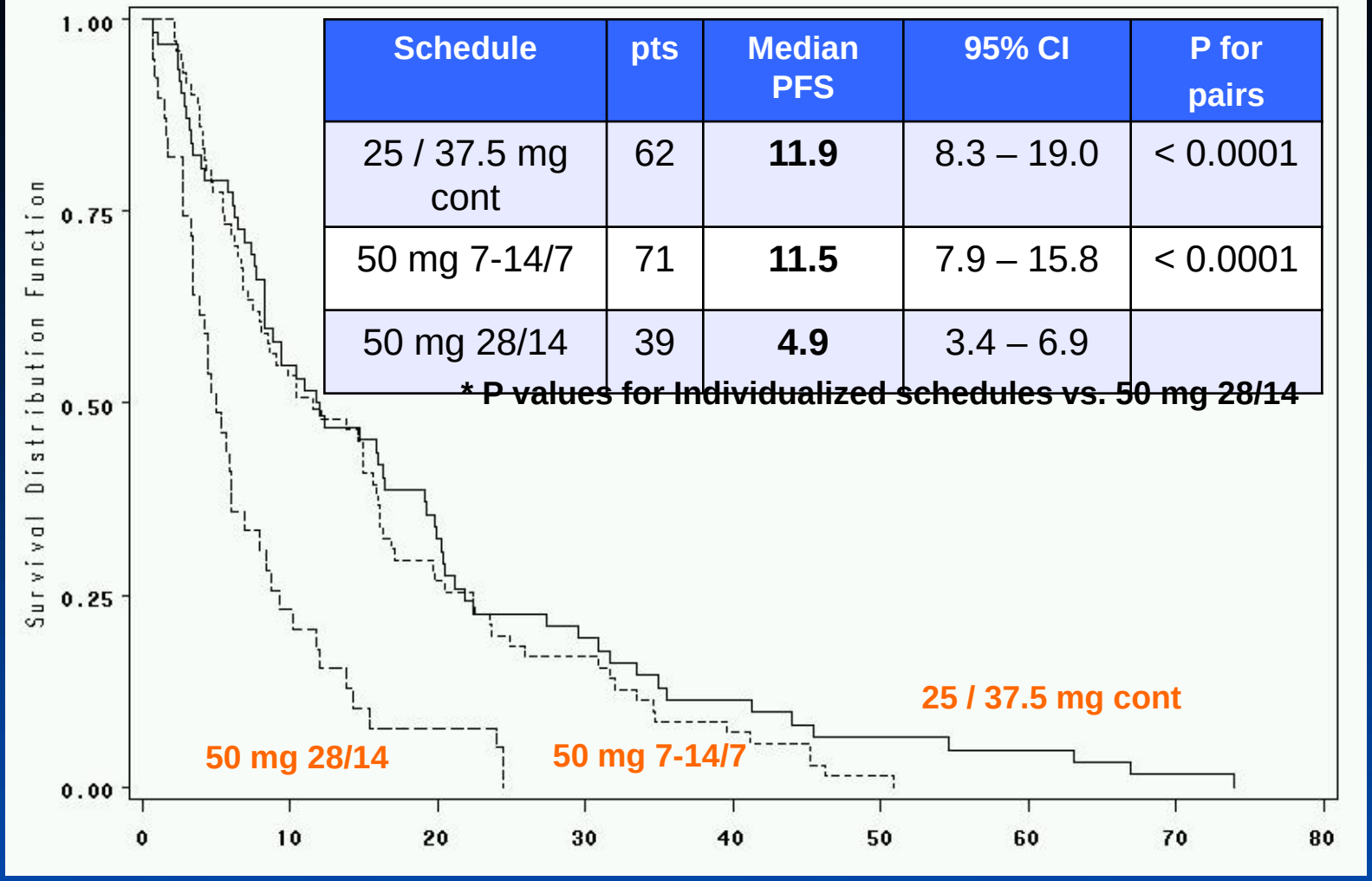
**The 71 (41.2%) patients that were maintained on 50 mg individualized 7-14/7 schedule would have been dose reduced to 37.5 if standard dosing criteria were used.**

**22.6% of patient remained on 50 mg 28/14**

# 172 RCC patients: Median PFS based on Sunitinib dose/schedules used for the majority of time on Rx.

| Schedule | pts | Median PFS | 95% CI | P for pairs |
|---|---|---|---|---|
| 25 / 37.5 mg cont | 62 | **11.9** | 8.3 – 19.0 | < 0.0001 |
| 50 mg 7-14/7 | 71 | **11.5** | 7.9 – 15.8 | < 0.0001 |
| 50 mg 28/14 | 39 | **4.9** | 3.4 – 6.9 | |

*** P values for Individualized schedules vs. 50 mg 28/14**



# 172 RCC patients: Response data

| Schedule | pts | PD % | PR % | SD % | PR and SD % |
|---|---|---|---|---|---|
| 25 / 37.5 mg cont | 62 | 17.7 | 21.0 | 61.3 | **82.3** |
| 50 mg 7-14/7 | 71 | 22.5 | 18.3 | 59.2 | **77.5** |
| 50 mg 28/14 | 39 | 35.9 | 15.4 | 48.7 | **64.1** |

# Planned confirmatory trial: Patient numbers and statistics

- Based on recent studies and the standard arm of the EFFECT trial (identical eligibility criteria as this study)
  - Median PFS of 8.5 month in patients treated using standard Sunitinib dosing criteria.
- Based on the retrospective data from Bjarnason, MD-Anderson and two Pfizer trials
  - Median PFS of 14 months with an individualized dosing strategy
- Number of patient required:
  - Setting H0: median PFS=8.5 months versus HA: median PFS=14 months,
    - alpha=0.05, a two-sided, single-arm non-parametric survival test would have over 90% power to detect this difference with a total of 99 patients on study
  - Accounting for a 10% loss to follow-up, we will aim to accrue a total of 110 patients.
  - If the true median PFS is 12 or 13 months, this trial design with a sample size of 99 patients would still have 67% and 81% power respectively to detect this difference.

# Individualized Dose/Schedule Adjustment for Toxicity

- **DL1: Starting dose: 50 mg, 28 days on / 14 days off**

- **DL 2: 50 mg, 14 days on / 7 days off**
  - Individually increase # of days on treatment

- **DL 3: 50 mg, 7 days on / 7 days off**
  - Individually increase # of days on treatment

- **DL 4: 37.5 mg 14 days on / 7 days off**
  - Individually increase # of days on treatment

- **DL 5: 25 mg 14 days on / 7 days off**
  - Individually increase # of days on treatment

# Efficacy of bevacizumab appears to be independent of baseline VEGF levels

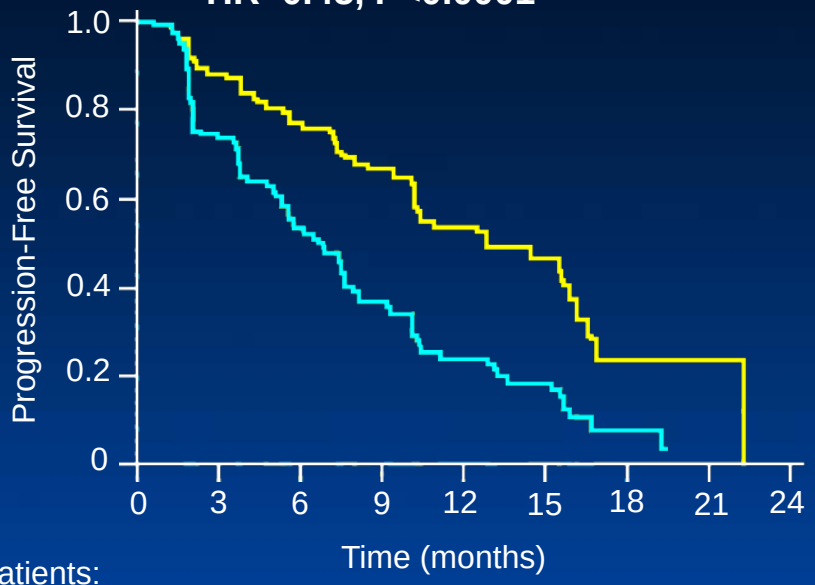
## ≤ Median baseline VEGF (N=191)

**Median PFS**

Bevacizumab + IFN = 12.9 months

IFN + placebo = 6.8 months

**HR=0.45, P<0.0001**




No. of patients:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bevacizumab + IFN | 97 | 86 | 73 | 52 | 37 | 17 | 3 | 1 | 0 |
| IFN + Placebo | 94 | 54 | 33 | 23 | 13 | 4 | 1 | 0 | 0 |

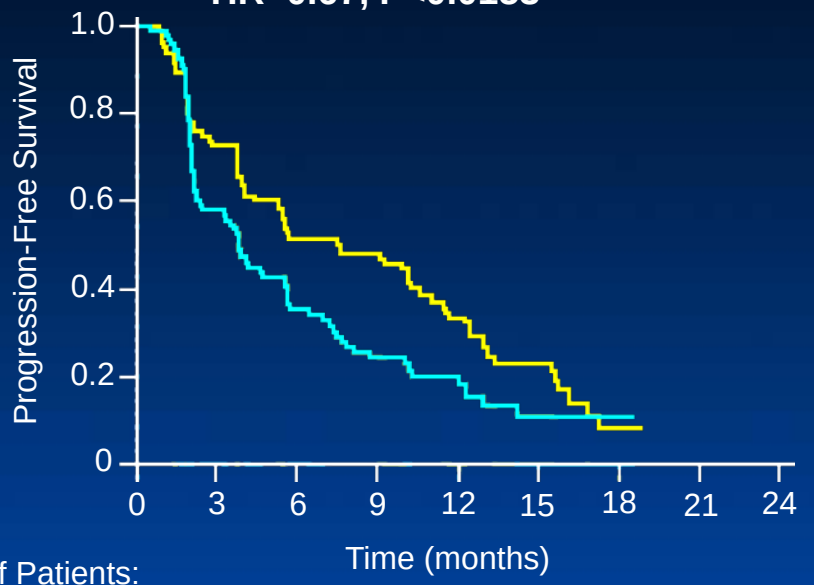
## ≥ Median baseline VEGF (N=191)

**Median PFS**

Bevacizumab + IFN = 7.6 months

IFN + placebo = 3.8 months

**HR=0.67, P<0.0153**

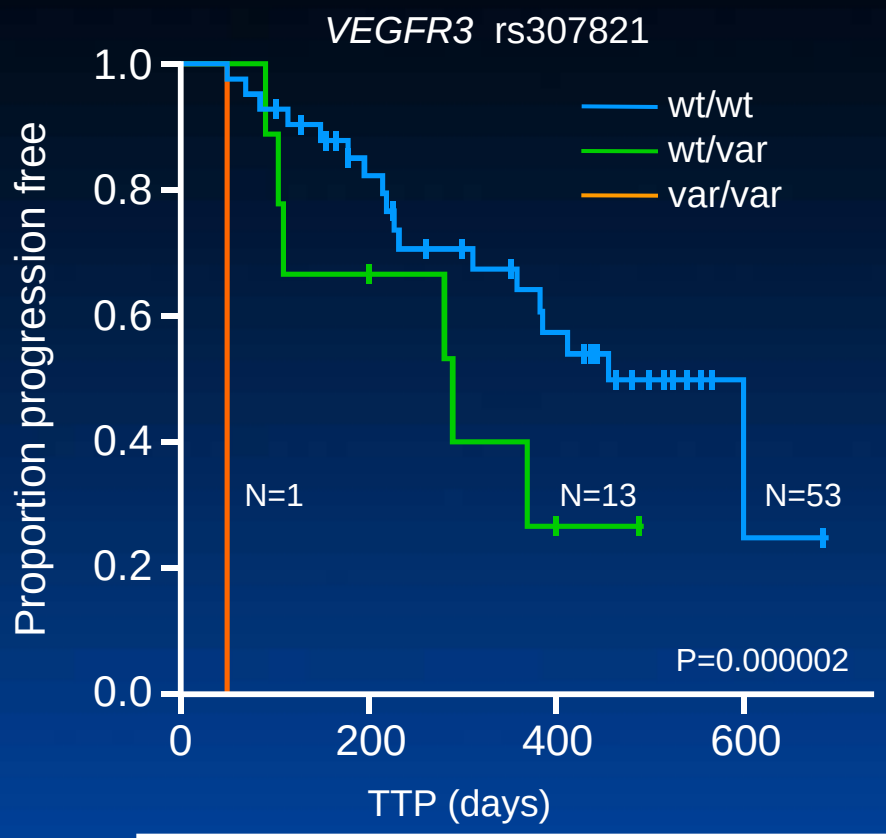


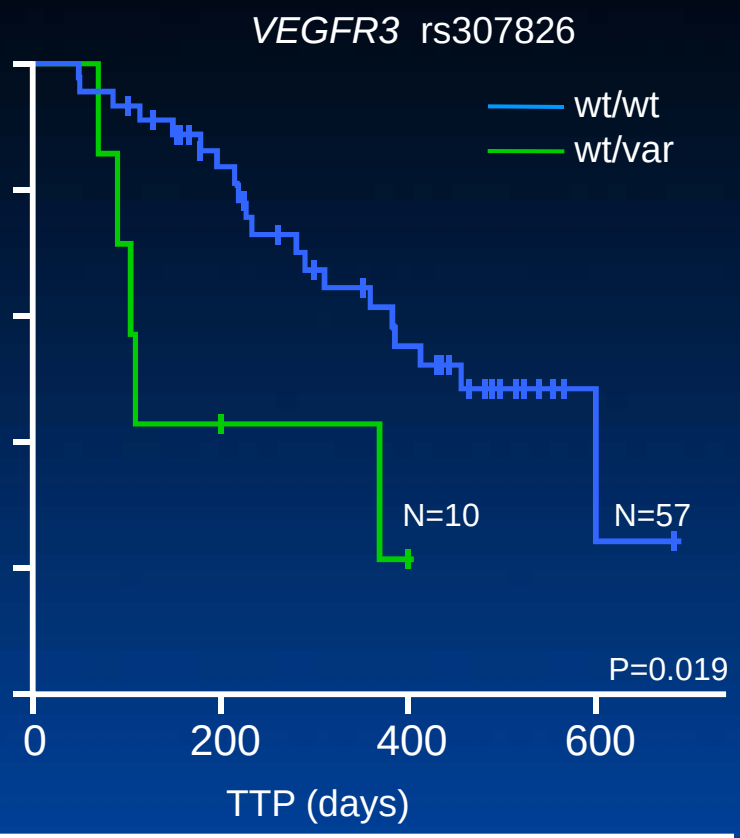

No. of Patients:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bevacizumab + IFN | 97 | 70 | 49 | 45 | 28 | 11 | 3 | 0 | 0 |
| IFN + Placebo | 94 | 69 | 50 | 35 | 18 | 12 | 3 | 0 | 0 |

Escudier B et al. *J Clin Oncol* 2008;26 (20 suppl; abstr 5025)

# VEGFR3 polymorphisms associated with differential response to sunitinib



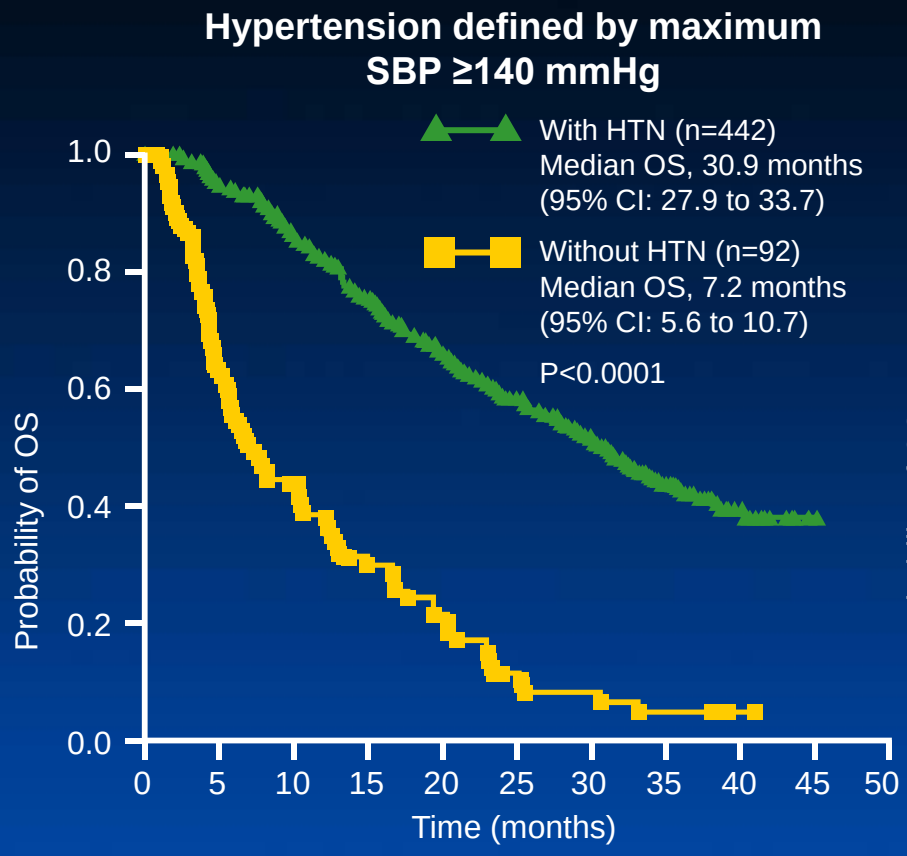

**Response**
**(PD vs CR+PR+SD)**

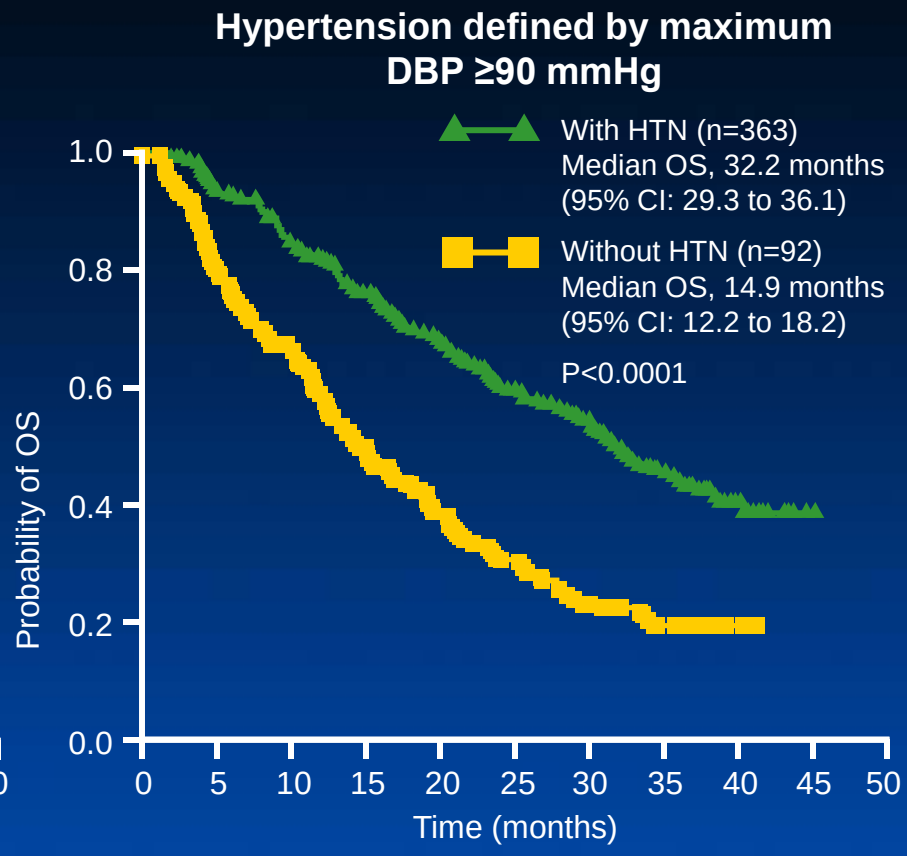
**VEGFR3** rs307821 **P=0.045** (Univariate)
**VEGFR3** rs307826 **P=0.028** (Univariate)

Garcia-Donas JG, et al. ESMO 2010

# Hypertension as a biomarker of improved efficacy during sunitinib treatment

- Hypertension associated with improved response, PFS and survival

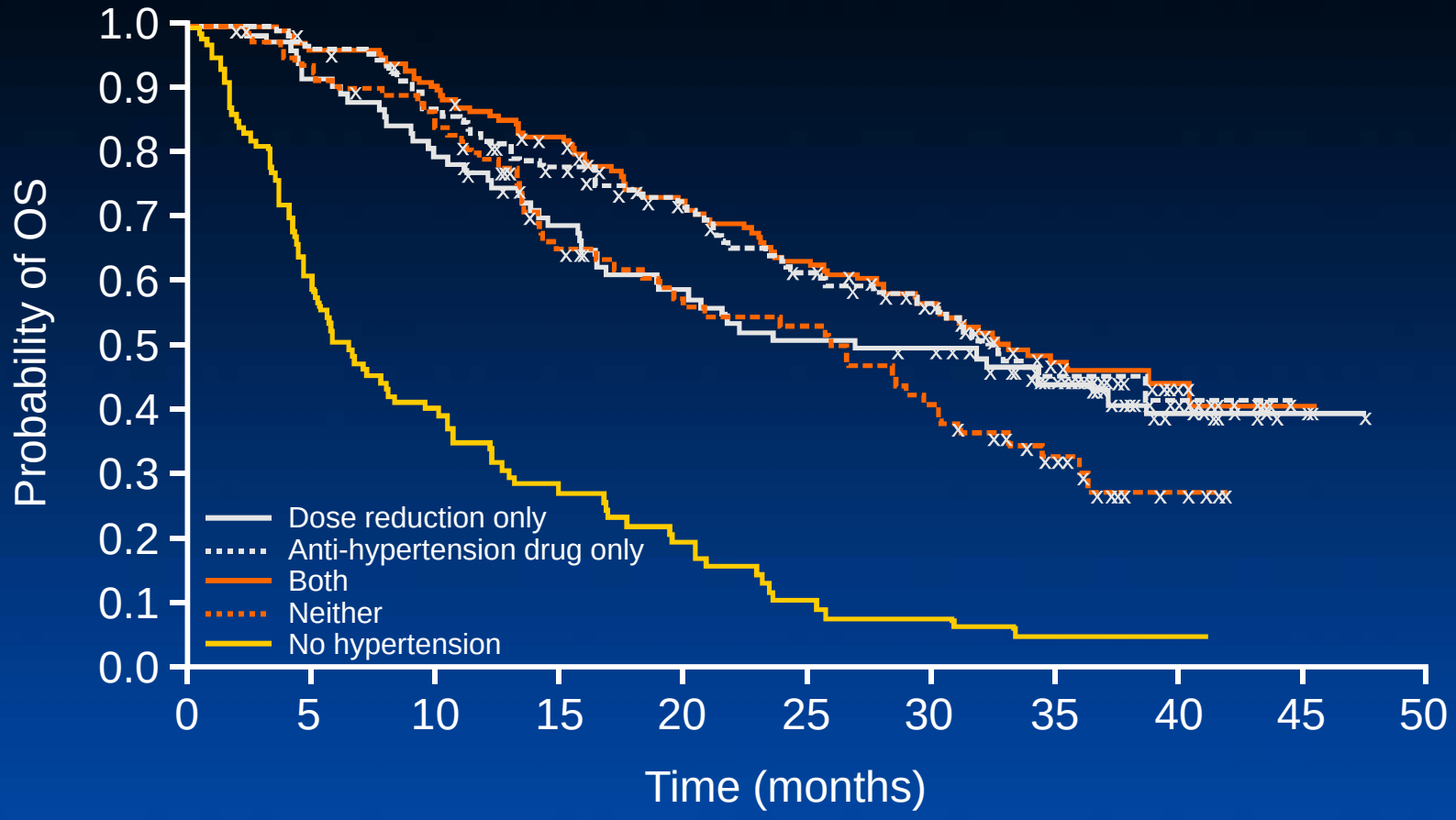



**Do you escalate to hypertension?**

Rini B, et al. *J Natl Cancer Inst* 2011

# Control of blood pressure did not diminish the effect of sunitinib




Rini B, et al. *J Natl Cancer Inst* 2011

# Therapy management: Adverse event management

Key adverse events associated with targeted agents

| VEGFR-targeted therapy | mTOR inhibitors |
| --- | --- |
| Fatigue/asthenia<br>Skin toxicities<br>Gastrointestinal symptoms<br>Stomatitis<br>Hypertension | Metabolic abnormalities (e.g. hyperglycaemia)<br>Fatigue/asthenia<br>Rash<br>Anaemia<br>Pneumonitis (rarely) |

Motzer RJ, et al. *N Engl J Med 2007*; Escudier B, et al. *N Engl J Med 2007*; Escudier B, et al. *Lancet* 2007; Rini B, et al. *J Clin Oncol* 2008; Hudes G, et al. *N Engl J Med* 2007; Sternberg C, et al. *J Clin Oncol* 2010; Motzer RJ, et al. *Lancet* 2008; Schmidinger and Bellmunt. *Cancer Treat Rev* 2010

# Adverse-event management

**Prior to treatment**

- Patient education about potential adverse events
- Assess and stabilise baseline co-morbidities

**During treatment**

- Monitor patients frequently
- Prompt adverse event management
  - Standard medical intervention
  - Consider dose reductions/ interruptions

Schmidinger M, et al. *Cancer Invest* 2010

# Conclusions

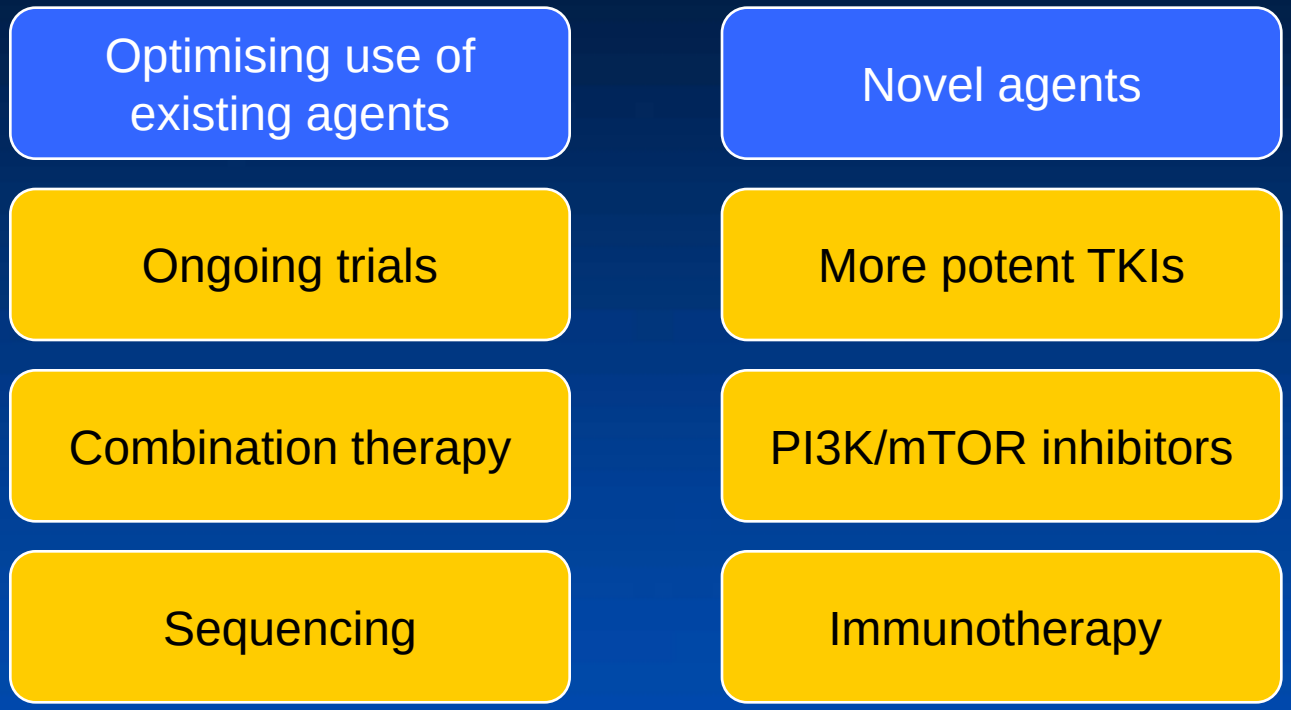
- Targeted agents have significantly improved patient outcomes in mRCC
  - In some patients, it is now possible to achieve long-term survival with targeted agents, such as sunitinib and temsirolimus
- To maintain patients on currently available agents and thus derive optimal clinical benefit, we need to:
  - Select treatment appropriately according to patient risk status
  - Manage the chosen therapy effectively through:
    - Optimising dose
    - Maximising treatment duration
    - Prompt and effective adverse-event management

# Novel agents and approaches for the treatment of mRCC

This presentation contains data on agents not currently approved

# Can we further improve clinical outcomes for patients with mRCC?

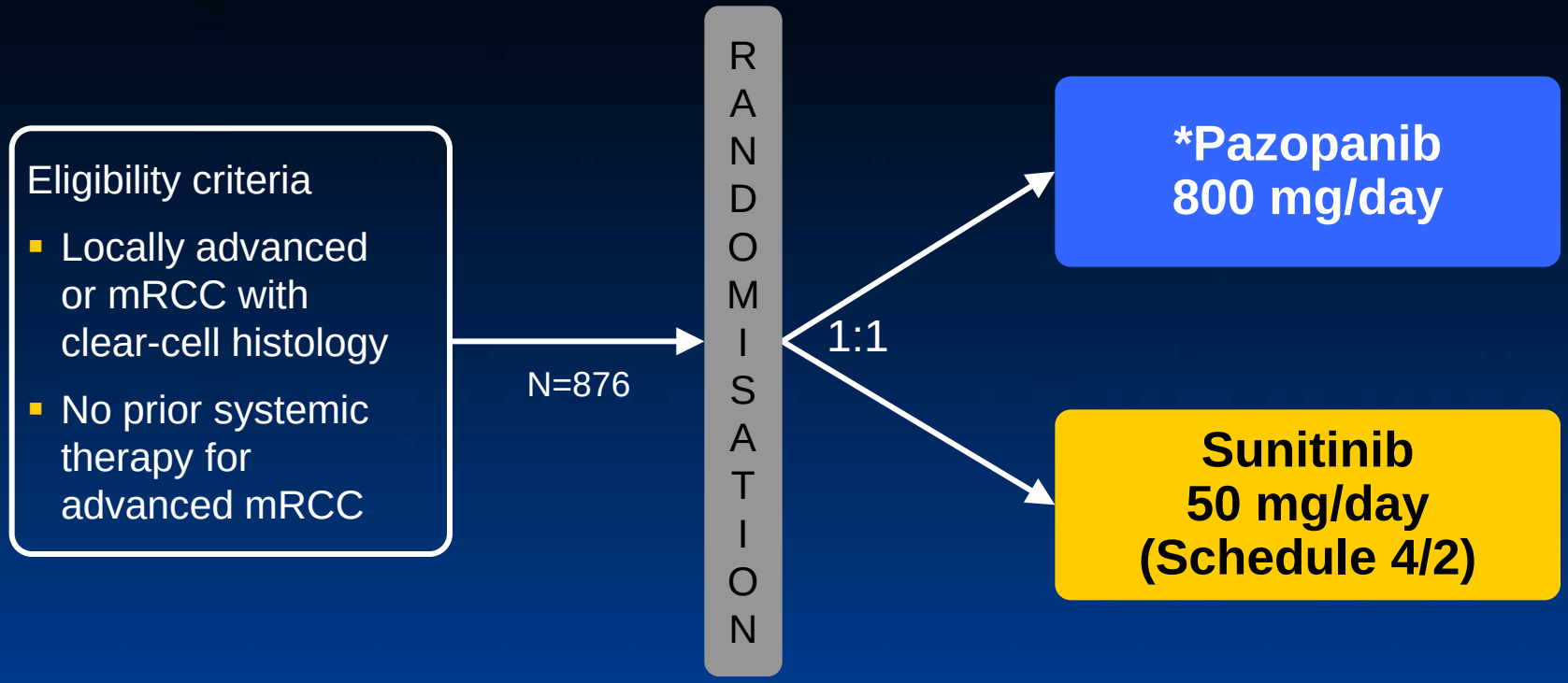
- Targeted agents have significantly improved patient outcomes in mRCC
- However, resistance to targeted agents eventually develops and some patients do not respond to treatment
- Several approaches are being assessed to try to improve patient outcomes



# Optimising use of existing agents

Is there an optimal TKI for first line treatment?

# 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

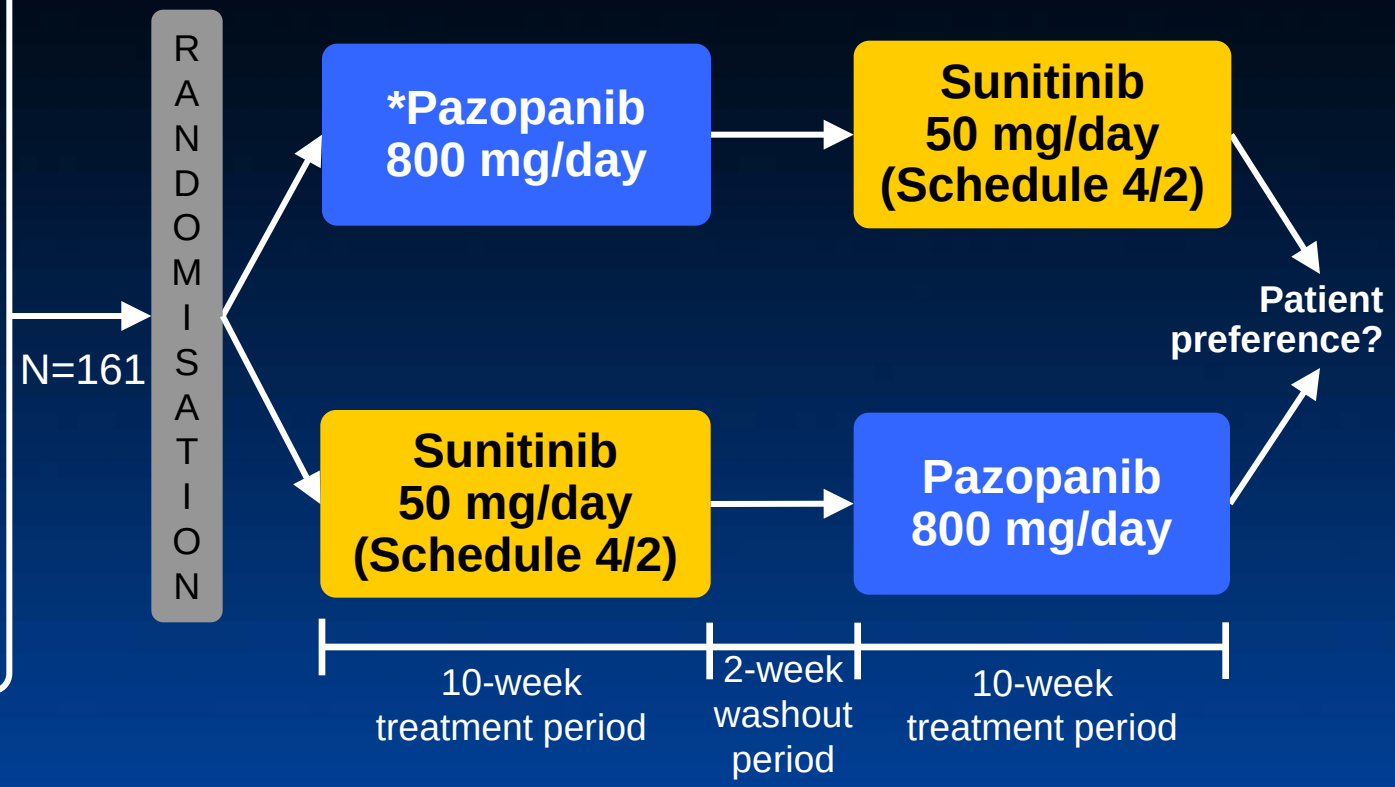
*Conditionally approved

www.clinicaltrials.gov (NCT00720941)

# Phase III patient preference study of sunitinib vs pazopanib (PISCES)

**Eligibility criteria:**

- Locally advanced or mRCC of any histology
- Non-measurable disease permitted if metastatic disease confirmed
- No prior systemic therapy for advanced or mRCC
- ECOG PS 0 or 1




- Primary endpoints: Patient preference (questionnaire)
- Secondary endpoints: Reason for patient preference; fatigue; dose modifications and time to dose modification; safety/tolerability

*Conditionally approved

www.clinicaltrials.gov (NCT01064310)

# Optimising use of existing agents

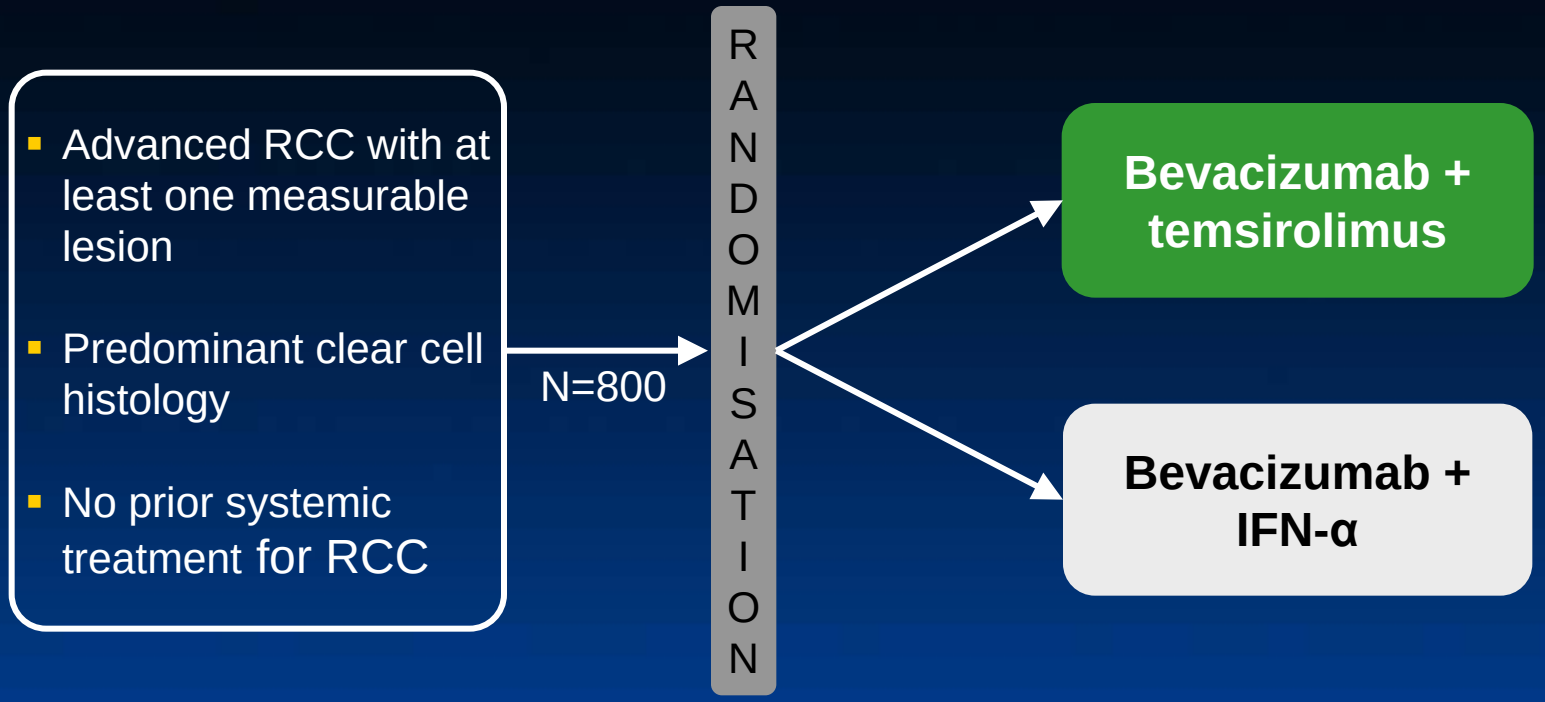
Combination and sequencing of therapy

# Combination therapy may be limited by toxicity profiles

| Combination | N | Frequently reported grade 3/4 AEs |
|---|---|---|
| Bevacizumab + sunitinib | 26 | Hypertension/MAHA (60%)<br>Proteinuria (36%)<br>Elevated lipase (28%) |
| Bevacizumab + sunitinib | 38 | Hypertension/MAHA (47%)<br>Fatigue (24%)<br>Thrombocytopenia (18%)<br>Proteinuria (13%) |
| Bevacizumab + everolimus | 80 | Proteinuria (26%)<br>Mucositis/stomatitis (15%)<br>Fatigue (12%) |
| Bevacizumab + temsirolimus | 80 | Grade 3 or worse (77%)<br>Grade 4 (13%)<br>Discontinuation rate for toxicity (42%) |

Feldman DR, et al. *J Clin Oncol* 2009; Rini B, et al. *Clin Cancer Res* 2009; Hainsworth JD, et al. *J Clin Oncol* 2010; Negrier S, et al. *Lancet Oncol* 2011

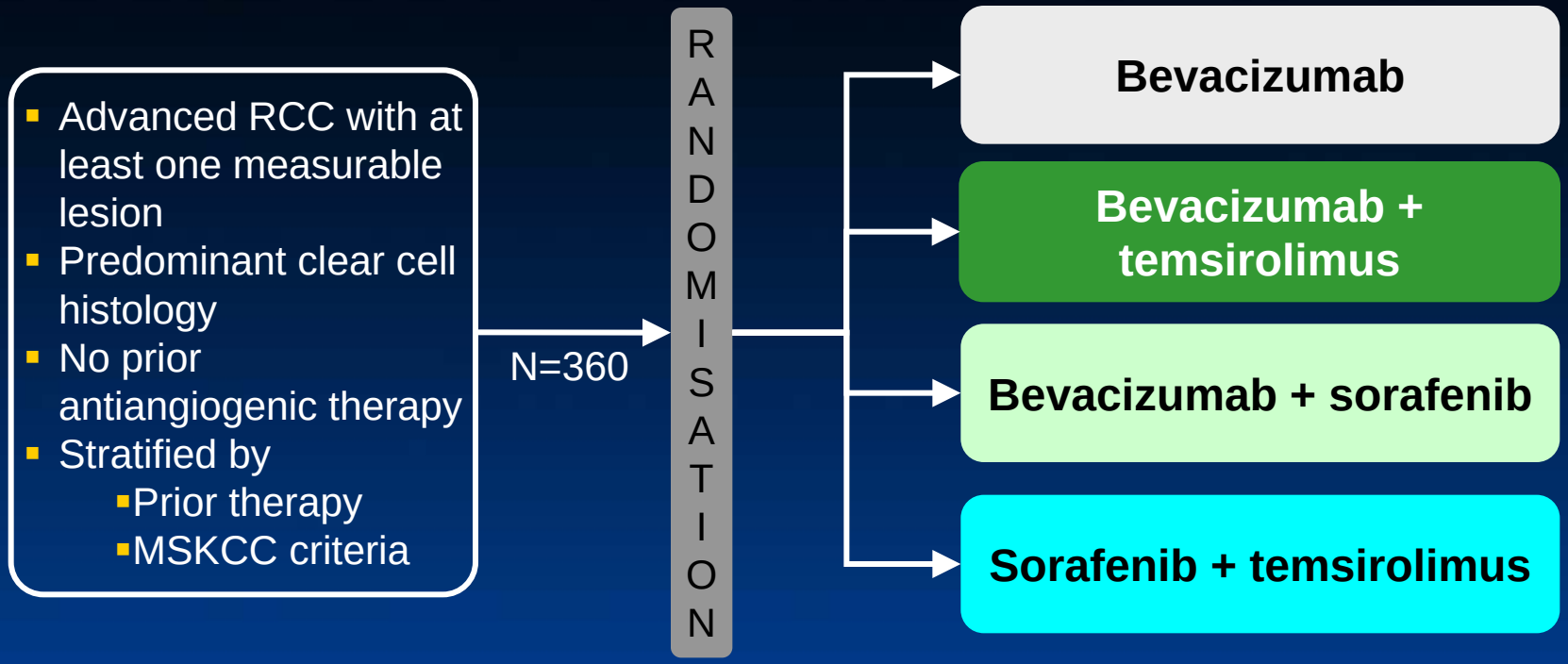
# Ongoing phase III combination studies in the first-line setting: INTORACT




- Primary endpoint: tumour measurements and survival status
- Secondary endpoints: safety, investigator-assessed PFS, ORR, survival

www.clinicaltrials.gov (NCT00631371)

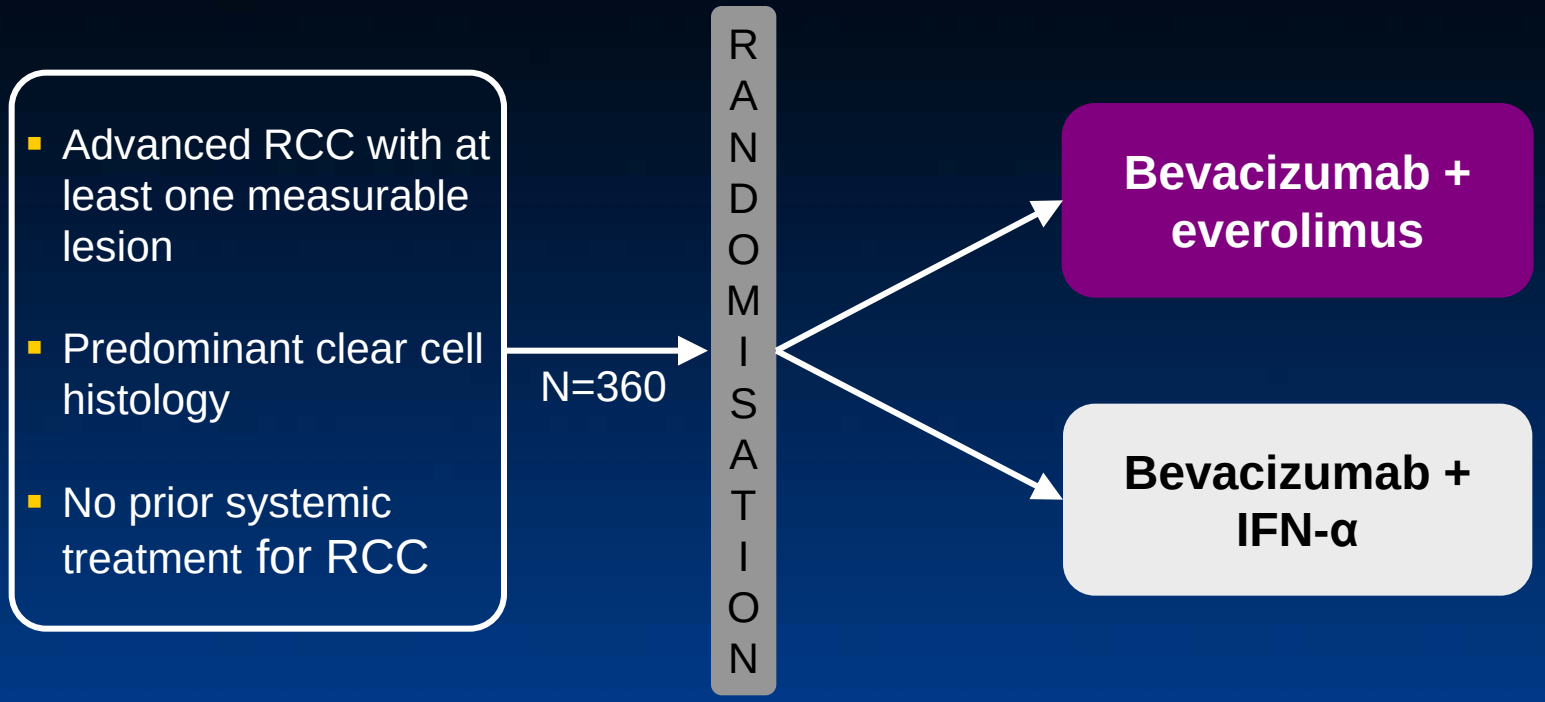
# Phase II study of VEGF, RAF kinase and mTOR combination therapy: BeST




- Primary endpoint: PFS
- Secondary endpoints: Safety, OS, ORR, number and percentage of patients with SD at 6 months

www.clinicaltrials.gov (NCT00378703)

# Phase II combination study: RECORD-2




- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, response duration, safety, QoL

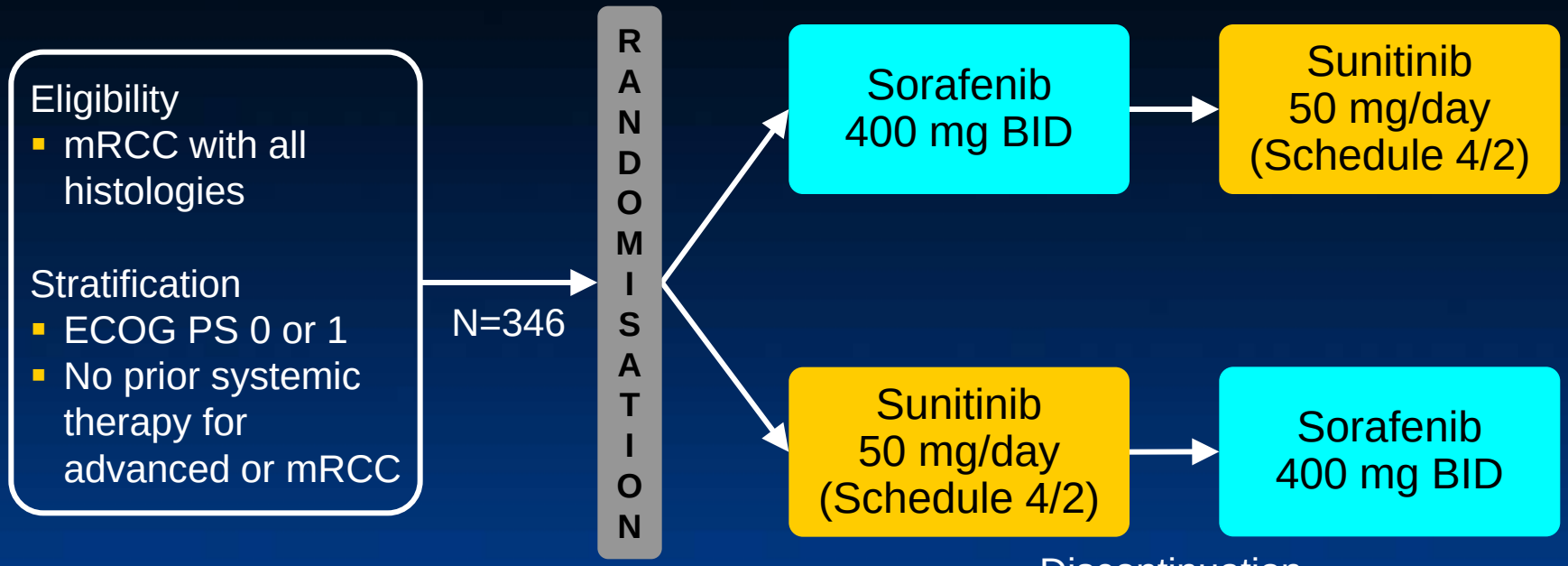
www.clinicaltrials.gov (NCT00719264)

# Sequential therapy with current agents

- Sequencing of therapy is commonly performed in clinical practice
  - May enable resistance to individual agents to be overcome
  - Less toxicity than combination therapy
- For patients who have progressed following a tyrosine kinase inhibitor, everolimus is currently recommended as second-line treatment
- The optimal sequence remains to be determined
  - Ongoing trials may provide further information

Ljungberg B, et al. *Eur Urol* 2010; Escudier B, et al. *Ann Oncol* 2010

# SWITCH: Phase III sequential study of sorafenib and sunitinib

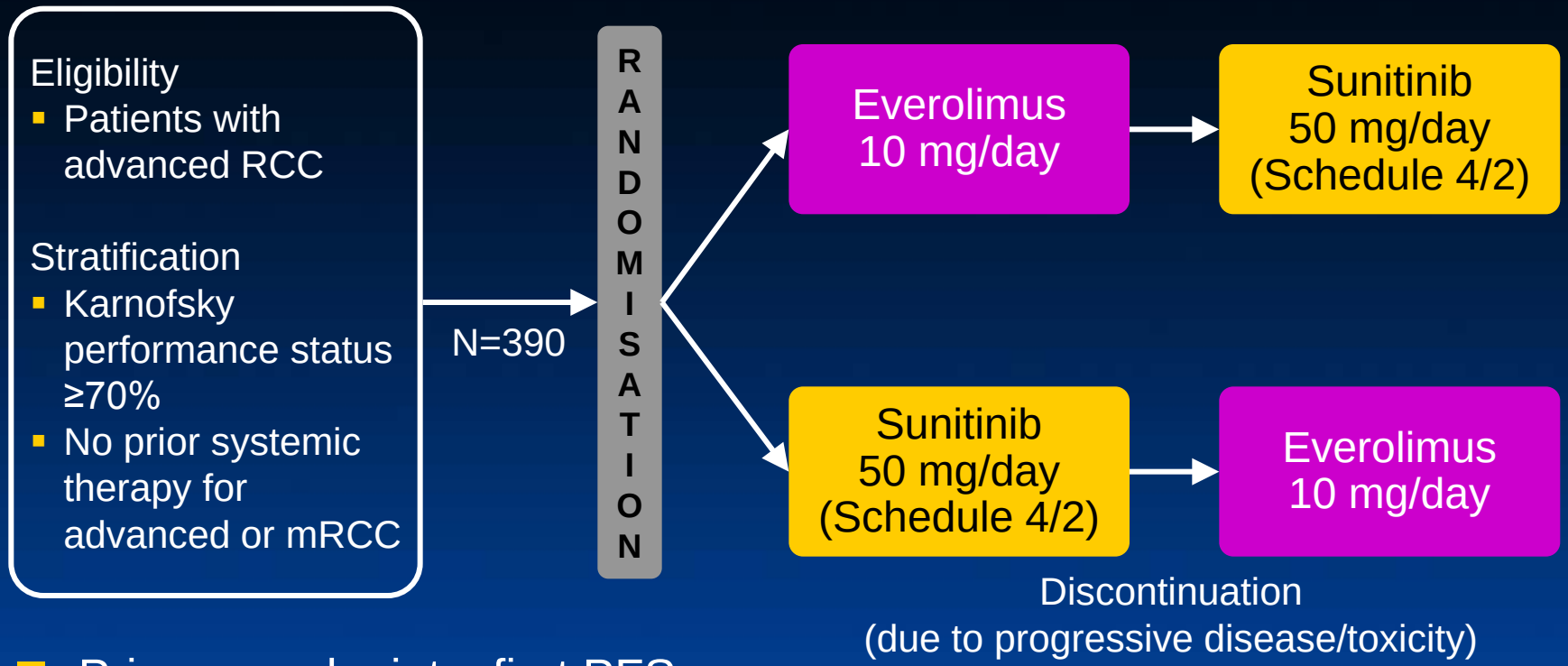



- Primary endpoints: overall PFS
- Secondary endpoints: total time to progression, OS, disease control rate and cardiotoxicity

Study being conducted in Germany

www.clinicaltrials.gov (NCT00732914)

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



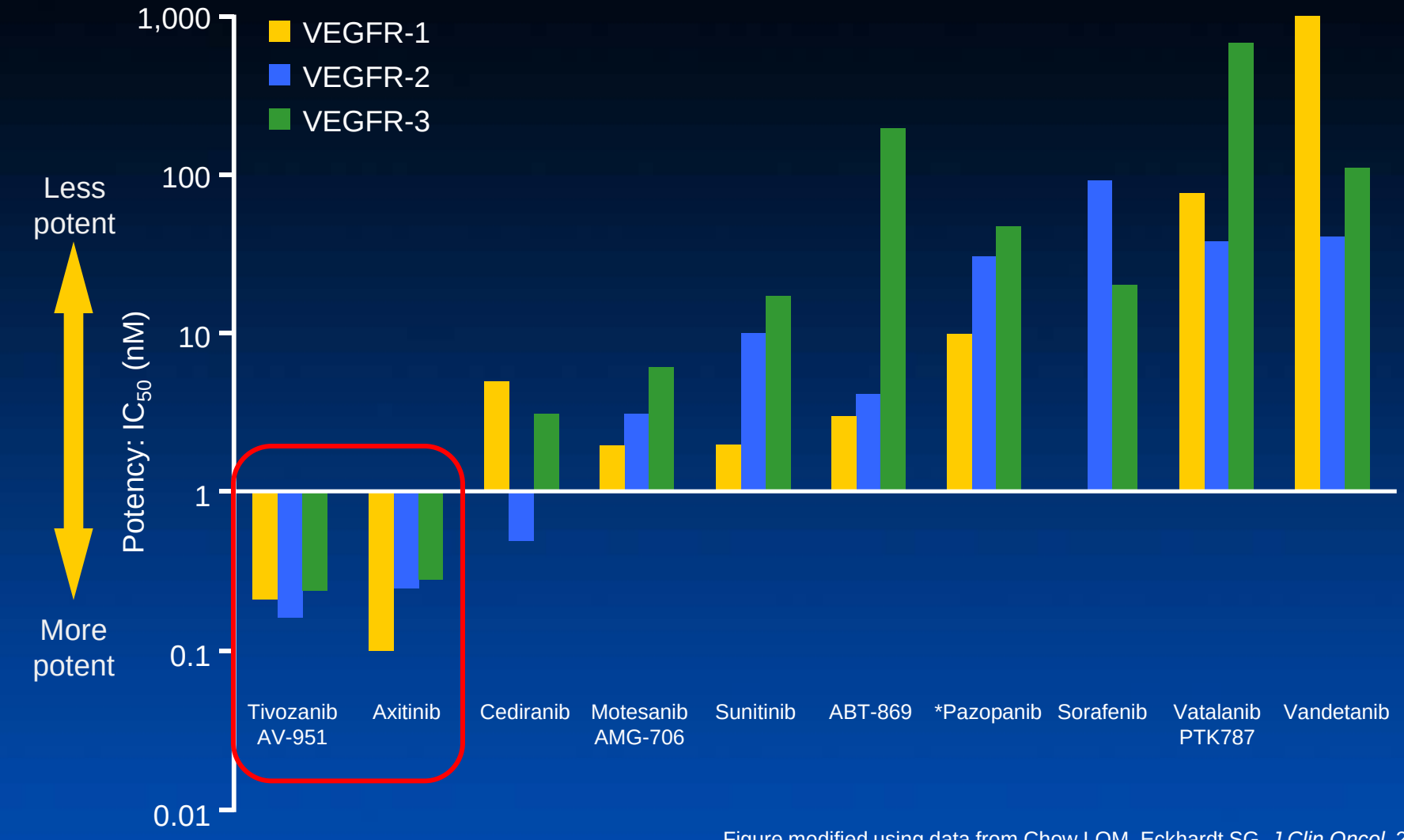

- Primary endpoints: first PFS
- Secondary endpoints: second PFS, ORR, duration of response, patient-reported outcomes, OS

www.clinicaltrials.gov (NCT00903175)

# Novel agents

Tyrosine kinase inhibitors in development:
Axitinib and Tivozanib

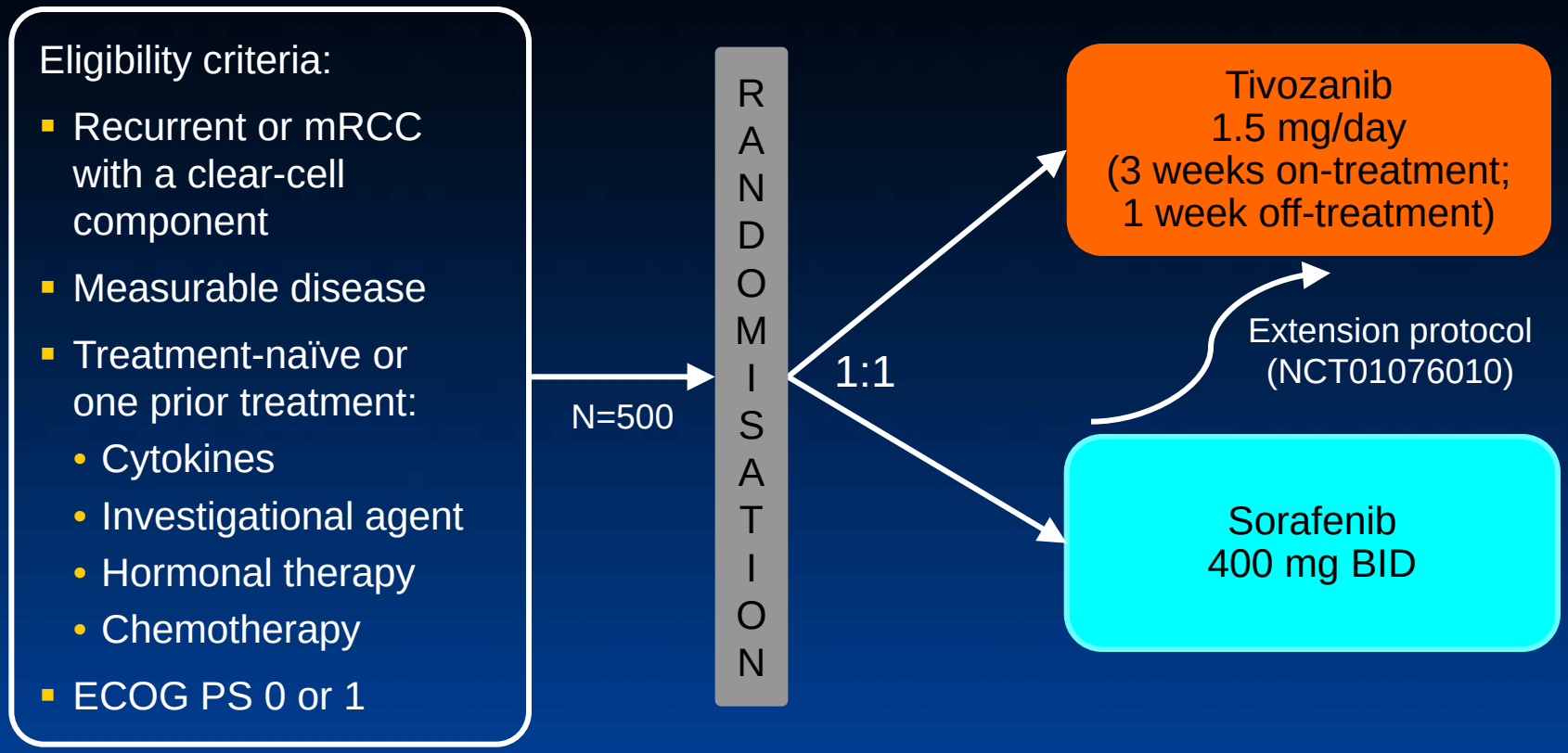
# Relative potency of VEGF-targeting TKIs




*Conditionally approved

Figure modified using data from Chow LQM, Eckhardt SG. *J Clin Oncol*. 2007
Eskens FALM, et al. AACR 2008. Abstract LB-201; Hu-Lowe DD, *Clin Cancer Res* 2008

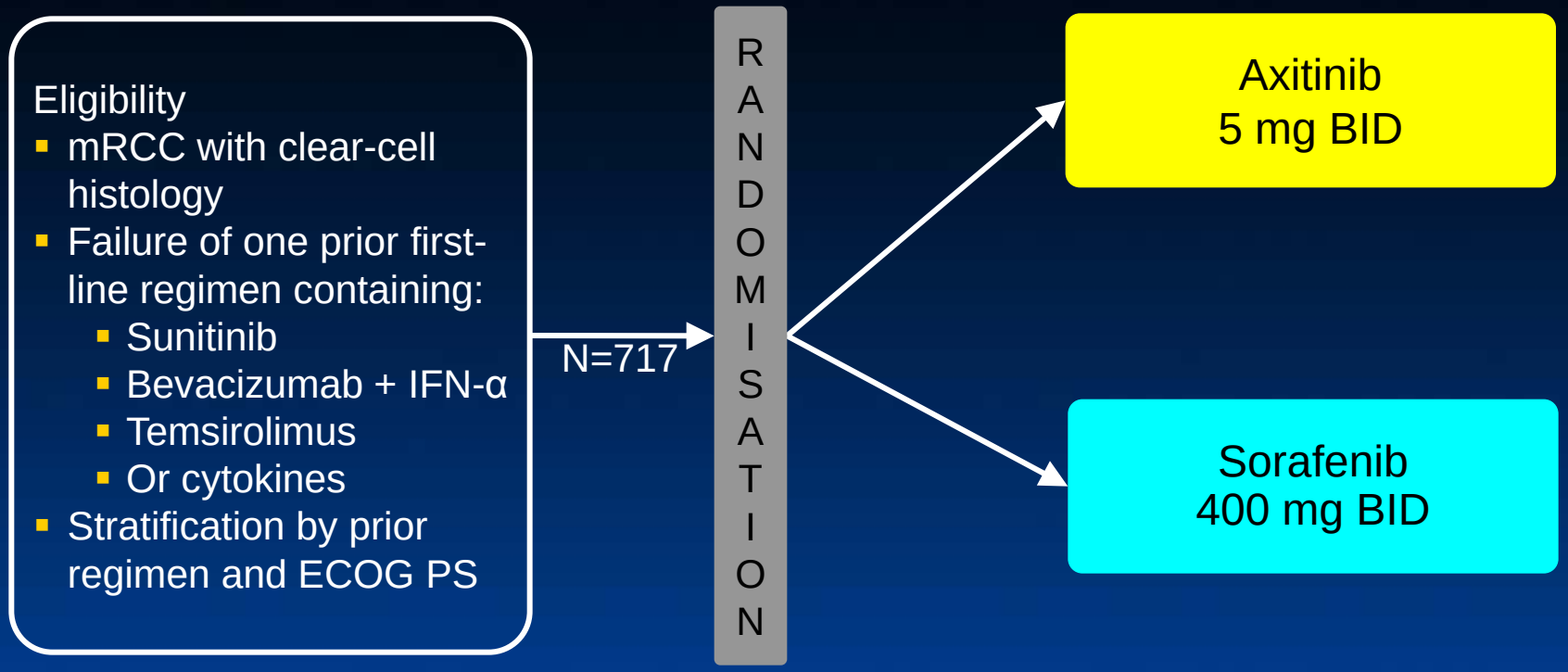
# Phase III study of tivozanib vs sorafenib in first- or second-line setting (TIVO-1)




- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, duration of response, safety and tolerability, kidney-specific symptoms and health outcome measurements, pharmacokinetics

www.clinicaltrials.gov (NCT01030783)

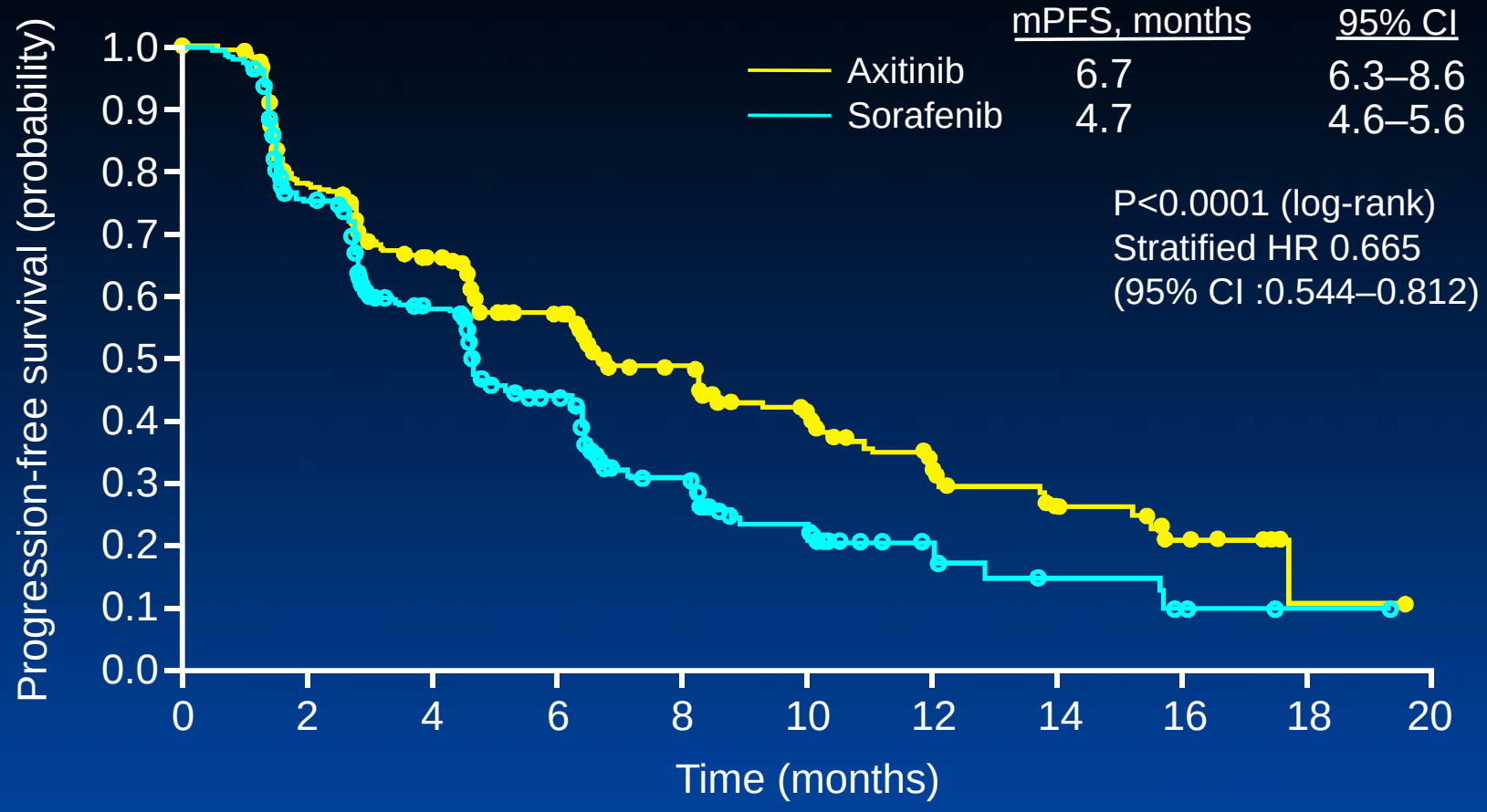
# Phase III study of axitinib versus sorafenib in second-line (AXIS)




- Primary endpoints: PFS
- Secondary endpoints: OS, ORR, safety and tolerability, duration of response, patient-reported outcomes

Rini B, et al. ASCO 2011

# AXIS: Axitinib significantly prolonged PFS versus sorafenib




Subjects at risk, n

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Axitinib | 361 | 256 | 202 | 145 | 96 | 64 | 38 | 20 | 10 | 1 | 0 |
| Sorafenib | 362 | 224 | 157 | 100 | 51 | 28 | 12 | 6 | 3 | 1 | 0 |

Rini B, et al. ASCO 2011

# Phase III study of first- and second-line axitinib versus sorafenib in mRCC patients (1051)

**Eligibility Criteria:**

- Histologically-confirmed mRCC with clear cell component
- Measurable disease
- No prior systemic first-line therapy or RECIST-defined progressive disease following one prior systemic first-line regimen for mRCC containing sunitinib, cytokines, or both

N=447
2:1

RANDOMISATION

Axitinib
5 mg BID

Sorafenib
400 mg BID

- Stratification (first line):
  - ECOG PS (0 vs. 1)
- Stratification (second line):
  - ECOG PS (0 vs. 1)
  - Prior therapy (sunitinib vs. cytokine)

**Primary endpoint:** PFS

**Secondary endpoints:** OS, response rate, safety and tolerability, duration of response, kidney specific symptoms and health status

www.clinicaltrials.gov (NCT00920816)

# Conclusions

- Despite the clinical benefits observed with current targeted agents, challenges remain to further improve patient outcomes
- Evidence demonstrates sequential therapy is the preferred treatment strategy
  - Ongoing trials will offer further evidence regarding the optimal sequencing of current and future agents
- Novel agents in clinical development may also provide further treatment options
  - Axitinib has demonstrated efficacy as second-line treatment for mRCC and supports sequencing of TKI to TKI
  - Many new agents are currently in phase 3 development