

# Renal Cell Carcinoma: Are Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?

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# Renal Cell Carcinoma: Are Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?

## Part I:

Which of the following approaches would you recommend?

- Radical nephrectomy followed by consideration of **adjuvant systemic therapy**
- Clinical trial of **neoadjuvant systemic therapy**

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- **Summary of the clinical case**
  - A 59-year-old male, PS:1, diabetes controlled by metformin
  - Symptoms: right flank pain, loss of appetite, 10 kg weight loss
  - CT scan: 10 cm mass arising from the upper pole of the right kidney. Extension into the right adrenal is suspected. No lymphadenopathy. No metastasis.
  - Stage :  $\geq T3N0M0$
  - Laboratory test: Hgb 11.9 g/dL, lactate dehydrogenase (LDH) 1.7 x upper limits of normal. Serum calcium and creatinine normal.

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- Nearly 60,000 patients were expected to be diagnosed with kidney cancer in the European Union (25 countries) in 2009<sup>1</sup>
- Despite significant improvements in treatment in 2009, 13,000 patients were expected to die from their disease
- One third with fully resected, localized disease will develop either a local or a distant recurrence, the majority of whom will succumb to distal metastases<sup>2</sup>
- Despite the significant risk, the current standard treatment after resection in these patients is surveillance

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## Part I: Why proposing a complementary treatment?

- Patients with T3 or higher locally advanced disease have a significant risk of recurrence:
  - 30 to 90 percent
- Precise definition of high-risk patients is imperative in order to:
  - propose appropriate treatment for pts who are most likely to benefit from adjuvant and neoadjuvant therapy
- Surgical resection may be technically more difficult in these cases and will not eliminate risk of recurrence

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## Part I: Definition of high-risk patients

### Two most extensively integrated stratification systems:

- Mayo Clinic stage (**SSIGN**)
  - TNM stage, Size, grade and necrosis system
- University of California-Los Angeles (UCLA) system (**UISS**)
  - PS, Fuhrman grade & TNM stage

### Prognostic factors affecting outcome of patients with renal cell carcinoma

Anatomic prognostic factors	Tumor size Tumor extension Adrenal involvement	Venous involvement Lymph node involvement Distant metastases
Histologic prognostic factors	Tumor grade Histologic subtype Sarcomatoid features	Necrosis Collecting system invasion
Clinical prognostic factors	Performance status Localized symptoms	Cachexia Platelet count

### Comparison of the clinical stage, size, grade, and necrosis (SSIGN) score and the University of California-Los Angeles integrated staging system (UISS)

Model	Parameters	Histology validation	External (n)	Patients	Limitations
SSIGN	TNM stage, size, grade, necrosis	CCRCC	Yes	2656	Reliance upon subjective variable of necrosis
UISS	ECOG-PS, Fuhrman grade, TNM stage	RCC	Yes	8249	Reduced predictive power in nonmetastatic patients

TNM=tumor size, metastasis, and nodal involvement staging system; CCRCC=clear-cell renal cell carcinoma; ECOG-PS=Eastern Cooperative Oncology performance status' RCC=renal cell carcinoma

Frank I, et al. *J Urol.* 2002;168(6):2395-2400. Leibovich BC, et al. *Cancer.* 2003;98(12):2566-2575.

# Renal Cell Carcinoma: Are Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?

## Part I: How will high-risk patients fail?

- **Locoregionally:**
  - Failure to achieve negative margins
  - Lymphadenopathy
- **Distantly:**
  - High rate of micrometastases

## Do we have any active therapy?

- That can provide cytoreduction
  - Tumor shrinkage
- That can prevent metastatic disease growth
- Can our current therapies fulfill these criteria?

# In Which Situation Could Neoadjuvant treatment Be Performed in RCC?

## ■ Two situations of interest:

### – Nonmetastatic RCC:

- Locally advanced disease (unresectable primary tumors)
  - Bulky regional lymph node metastases
  - Caval thrombi
- Hereditary forms of RCC (Von Hippel-Lindau disease)
- Anatomical or functional solitary kidney

### – Metastatic clear cell carcinoma:

- But talk in term of “presurgical therapy”

# Key Advantages Using Neoadjuvant Trials (With AA Drugs) in RCC

## ■ Disease down-staging

- Allowing less radical surgical approaches with possible benefits in terms of surgical morbidity and/or functionality
  - Radical nephrectomy → nephron-sparing surgery

## ■ Destroy tumor vasculature

- Might induced reduction mortality and the ability to treat high-risk surgical candidates

# Key Advantages Using Neoadjuvant Trials (With AA Drugs) in RCC

- **Evaluation of tumor sensitivity to treatment**
  - Interesting in patients selected for adjuvant therapy
    - Responders: maintenance of the same drug
    - Nonresponders: alternative therapy
- **Identification of molecular markers and imaging parameters of response**
  - Measurement of parameters prior to and after nephrectomy

# Summary of Neoadjuvant or Primary Treatment Prior Nephrectomy Clinical Trials

P Investigator	Clinical Stage	Nb pts	Drug	Primary Endpoints
Jonasch E, US	mRCC	50	BV + E	TTP/toxicity
Jonasch E, US	mRCC	45	SO	RR/toxicity/safety
Jonasch E, US	mRCC	50	SU	RR/toxicity/safety
Rathmell K, US	Locally advanced/mRCC	30	SO	Surgical procedure
Rini B, US	Unresectable primary T	50	SU	Surgical procedure
Powles T, UK	mRCC	40	SU	RR
Eisen T, UK	mRCC	50	SU	RR/toxicity/safety
Staehler F, Germany	mRCC (perioperative)	50	SU	RR/toxicity/safety
Oudard S, Fr	mRCC	100	SU	RR/pOR

BV: Bevacizumab; E: Erlotinib ; SO: Sorafenib ; SU: Sunitinib



# Members and Roles



- siRNA screens
- pshRNA screens
- Tumour genetic analyses
- Drug target identification
- Functional analysis of drug resistance genes



- pshRNA library technology



- Biomarker validation



- Bioinformatics
- Project administration



- Exon sequencing
- Bioinformatics



- Ex-vivo cell culture



- Cell line engineering for functional studies

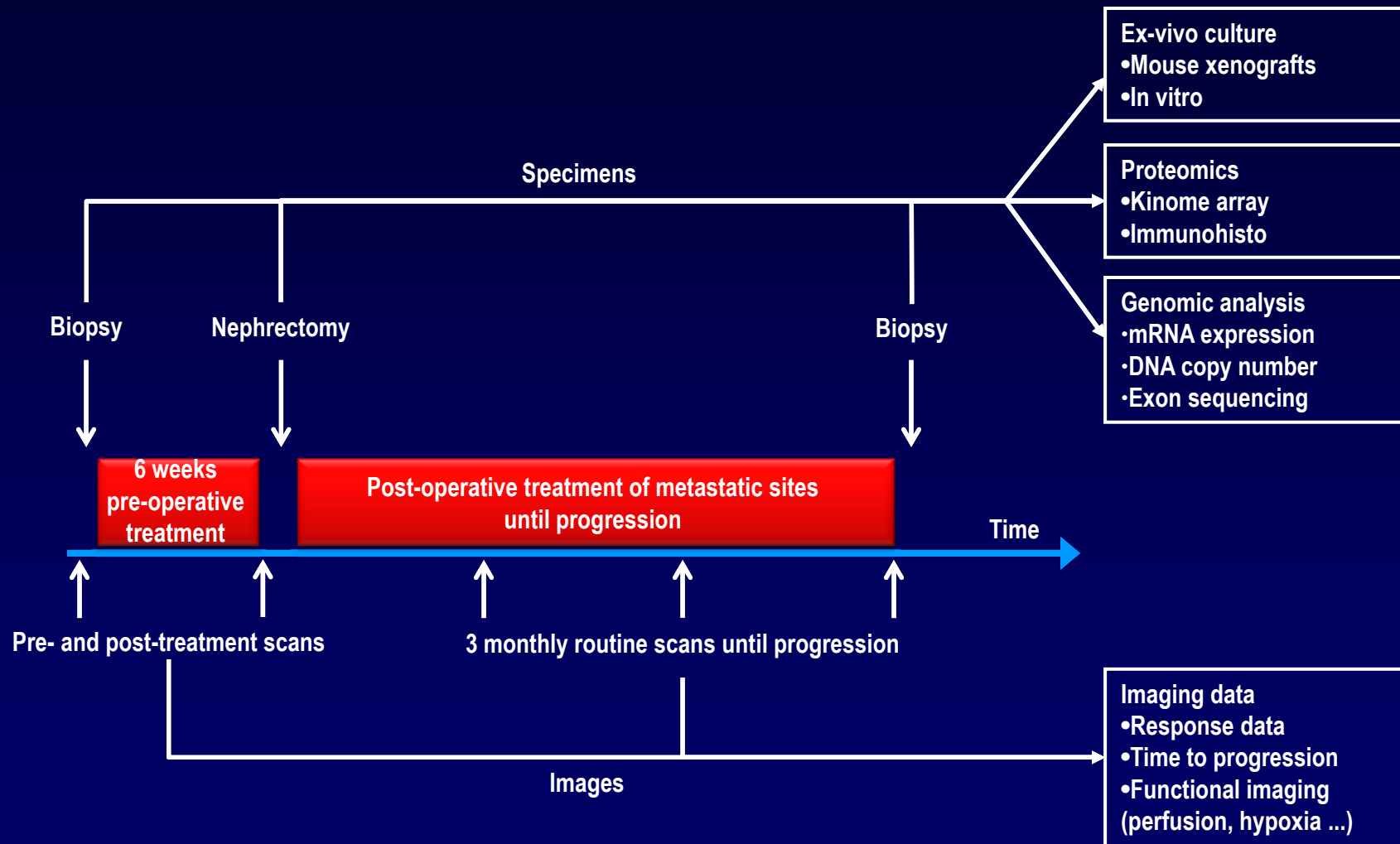


- Clinical trials
- Imaging data analysis



- Drug target validation
- Biomarker test development

# Pre-Nephrectomy Clinical Trials S- E-PREDICT

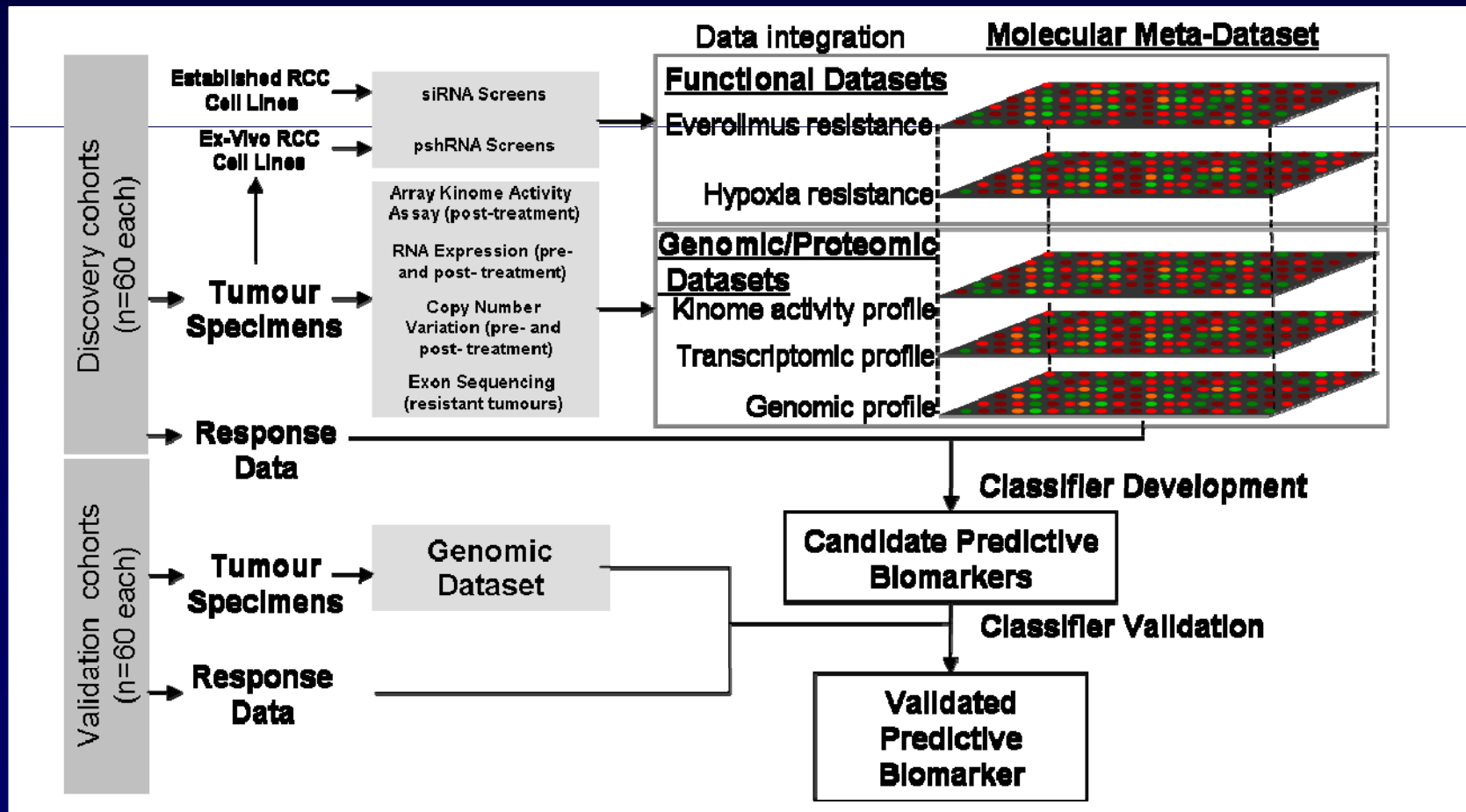


# Strategy

Method: Integration of

In vitro whole genome siRNA screens

Tumour genomic / transcriptomic data



# **Renal Cell Carcinoma: Are Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?**

## **Part I: Adjuvant or neoadjuvant systemic therapy?**

- **Prior studies have been completed and have shown there is no benefit to adjuvant immunotherapy in patients with RCC**
- **Studies are currently underway to evaluate the benefits of (neo)adjuvant antivascular therapy in high-risk patients**
- **No treatment has to be given outside a clinical trial**
  - **Only prospective trials +++**

# Renal Cell Carcinoma: Are Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?

## Part II:

Does nephrectomy increase the likelihood of benefit from tyrosine kinase inhibitors (TKIs)?

- Yes, definitely
- No, definitely
- Maybe, but I'm not sure

# **Metastatic RCC: Cytoreductive Nephrectomy?**

**In the era of antivasular therapy,  
is cytoreductive nephrectomy  
a necessity?**

# Metastatic RCC: Cytoreductive Nephrectomy?

- **Management of metastatic RCC**
  - Removal of the primary tumor (cytoreductive nephrectomy)
    - In retrospective studies: favorable feature?
- **Two prospective studies evaluated impact of nephrectomy (N) on outcome**

Clinical Trials	Design	Nb pts	Resp. rates (%)	Overall survival (months)	P value
SWOG-8949 <sup>1</sup>	N + IFNa vs IFNa alone	246	3.6 vs 3.3	11.1 vs 8.1	0.05
EORTC-30947 <sup>2</sup>	N + IFNa vs IFNa alone	85	19 vs 12	17 vs 7	0.03
Combined analysis <sup>3</sup>	N + IFNa vs IFNa alone	331	6.9 vs 5.7	13.6 vs 7.8	0.002

1. Flanigan RC, et al. *N Engl J Med.* 2001;345(23):1655-1659. 2. Mickish GH, et al. *Lancet.* 2001;358(9286):966-970.  
3. Flanigan RC, et al. *J Urol.* 2004;171(3):1071-1076.

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## Part II:

In the era of immunology, the benefit of cytoreductive nephrectomy may be due to several mechanisms<sup>1,2</sup>:

- Renal tumor cells may secrete proangiogenic growth factors (VEGF, PDGF, FGF and TGF)
- Renal tumor may act as an immunologic « sink » leading to the trapping of circulating antibodies and immune cells

# Prognostic Classification mRCC

## CYTOKINE ERA

MSKCC (463 patients)

Motzer, *JCO* 2002

- KS < 80 %
- Hb < N
- Ca > N
- Time < 1 year
- LDH > 1.5 N

Favorable group = 0

Intermediate-risk group = 1 or 2

Poor-risk group >3

## TARGETED-DRUG ERA

HENG (645 patients)

Heng, *JCO* 2009

- KS < 80 %
- Hb < N
- Ca > N
- Time < 1 year
- Platelets > N
- ANC > N

# Possibility of a Positive Impact of CN With Anti-VEGF Drugs?

Only limited and biased data available evaluating the impact on CN in the context of anti-VEGF drugs

Most of the patients in previous studies had undergone nephrectomy ( $\approx 90\%$ )

## ■ Motzer et al study<sup>1</sup>

Subgroup analysis (375 pts) of the phase III sunitinib trial (340 underwent CN)

– According to pts who did or did not undergo initial CN

- PFS: 11 mo (range 11-13 mo) vs 6 mo (range 4-11 mo),  $P = 0.09$
- Prior nephrectomy integrated in the nomogram of Motzer to evaluate the probability of 12-months PFS of pts receiving sunitinib<sup>2</sup>

## ■ Choueri et al study<sup>3</sup>

Analysis of 314 pts treated with AA (201 underwent CN)

– In univariate analysis, CN associated with median OS of 19.8 mo vs 9.4 mo for pts without CN ( $P = 0.0001$ )

1.Motzer RJ, et al. *J Clin Oncol*. 2007;25(18S): Abstract 5024. 2.Motzer RJ, et al. *Cancer* . 2008;113(7):1552-1558.

3.Choueri TK, et al. Presented at: 2010 Genitourinary Cancer Symposium; March 5-7, 2010:San Francisco. California. Abstract 311.

# Possibility of a Positive Impact of CN With Anti-VEGF Drugs?

Only limited and biased data available evaluating the impact on CN in the context of anti-VEGF drugs

Most of the patients in previous studies had undergone nephrectomy ( $\approx 90\%$ )

- Heng et al study<sup>1</sup>

- Analysis of 645 pts treated with anti-VEGF therapy-naïve mRCC (532 underwent CN)

- In univariate analysis, CN associated with median OS of 27 mo vs 11 mo for pts without CN ( $P < 0.0001$ )

# CARMENA Study

Study design N = 576  
Study centers: initiated in France

Clear-cell histology (biopsy)  
Resectable renal tumor  
ECOG PS 0 or 1  
Good organ function  
Measurable metastasis  
No brain metastasis

Noninferiority trial

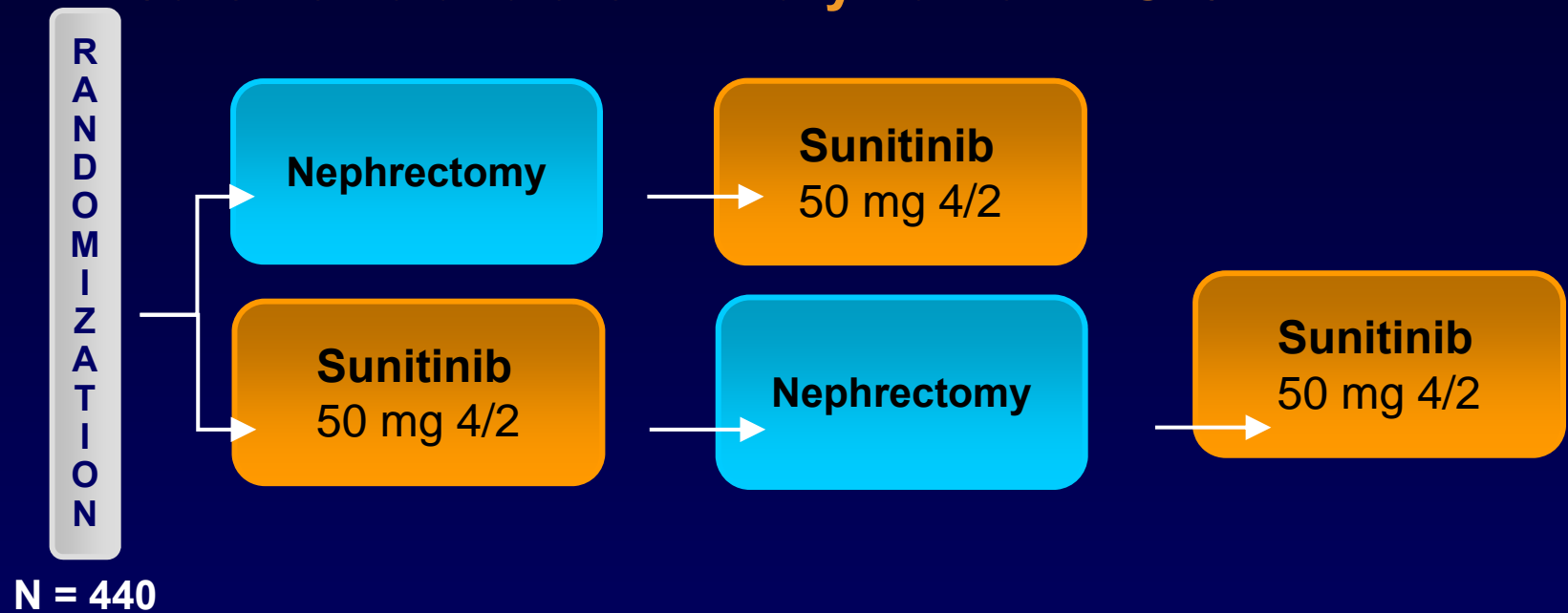
R  
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Nephrectomy + sunitinib 50 mg  
4 weeks ON/ 2 weeks OFF

Sunitinib 50 mg 4 weeks ON/ 2  
weeks OFF

- **Primary objective : absence of difference in OS**
- Secondary objectives:
  - % pts not starting sunitinib within 6 PO weeks
  - Nb nephrectomy in sunitinib arm
  - Nb nonresectable tumors
  - Morbidity mortality of nephrectomy
  - Time to second-line treatment

# Sunitinib Followed by Nephrectomy in Case of Nonprogressive Metastases Followed by Sunitinib vs Nephrectomy Followed by Sunitinib in Patients With Synchronous Metastatic Renal Cell Carcinoma and the Primary Tumor *In Situ*



## Study Objective:

- Does pretreatment with sunitinib result in improved surgical and clinical outcome for patients with metastatic RCC when compared to nephrectomy first followed by sunitinib?
- Primary endpoint: PFS

# Renal Cell Carcinoma: Are Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?

## Part III:

The patient undergoes right radical nephrectomy.

Pathology shows pure clear cell carcinoma with direct invasion of the adrenal gland, Fuhrman’s grade 3. No involvement of the renal vein, but 1 perinephric lymph node contains metastatic clear cell carcinoma (T3aN1M0).

**Which of the following would you recommend postoperatively?**

- Observation only
- Clinical trial of adjuvant targeted therapy (SORCE, ASSURE, S-TRAC)
- Adjuvant vaccine therapy
- Adjuvant bevacizumab–based therapy

# Renal Cell Carcinoma: Are Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?

## Part III: Which treatment has proven to be active in an adjuvant setting?

### Randomized adjuvant clinical trials in renal cell carcinoma

Author	Treatment	n	Outcome
<i>Non-cytokine adjuvant trials that did not demonstrate improvement with intervention</i>			
Kjaer et al	Radiotherapy vs observation	72	OS: 50% vs 62% (NS)
Pizzocaro et al	Medroxyprogesterone acetate vs observation	136	Relapse: 33% vs 34% (NS)
Adler et al	BCG + hormonotherapy vs hormonotherapy alone	43	PFS: 82% vs 48% (NS)
Galligioni et al	BCG vs observation	120	DFS: 63% vs 72% (NS)
<i>Cytokine adjuvant trials that did not demonstrate improvement with intervention</i>			
Messing et al	IFN vs observation	283	OS: 5.1 yrs vs 7.4 yrs (NS)
Clark et al	High-dose IL-2 vs observation	69 (closed early)	OS (NS)
Pizzocaro et al	IFN- $\alpha_{2b}$ vs observation	247	OS at 5 years: 66.5% vs 66.0% (NS)
Atzpodien et al	IL-2 + IFN- $\alpha_{2a}$ + 5-FU vs observation	203	OS at 5 years: 76% vs 58% ( $P = 0.0278$ )
Passalacqua	IFN- $\alpha$ + IL-2 vs observation	310	DFS at 5 years: 0.73 vs 0.73 (NS)

Rodriguez AR, et al. *Expert Opin Pharmacother.* 2007;8(17):2979-2990.

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## Part III: Which treatment has proven to be active in an adjuvant setting?

### Randomized adjuvant clinical trials in renal cell carcinoma

Author	Treatment	n	Outcome
Completed autologous vaccine trials			
Jocham et al, 2004	Autologous tumor vaccine vs observation	533	PFS< per-protocol analysis: 77% vs 68% ( $P = 0.02$ ) (no placebo, not blinded, lost of FU)
Doehn et al, 2007 (update of Jocham et )	Autologous tumor vaccine	352	PFS and OS significant in favor of vaccine group (PFS favors vaccine, $P = 0.024$ by intent to treat)
Wood et al, 2008	Autologous HSP-P96 vaccine vs observation	728	Recurrence-free survival HR = 0.922 ( $P = 0.502$ , NS) Intermediate risk $P = 0.052$

**Conclusions: immunotherapy concepts may have a benefit in a subgroup of pts but the data from the phase III remain largely negative**

# Licensed Targeted Agents for Metastatic RCC: Summary of Efficacy in First-Line Setting

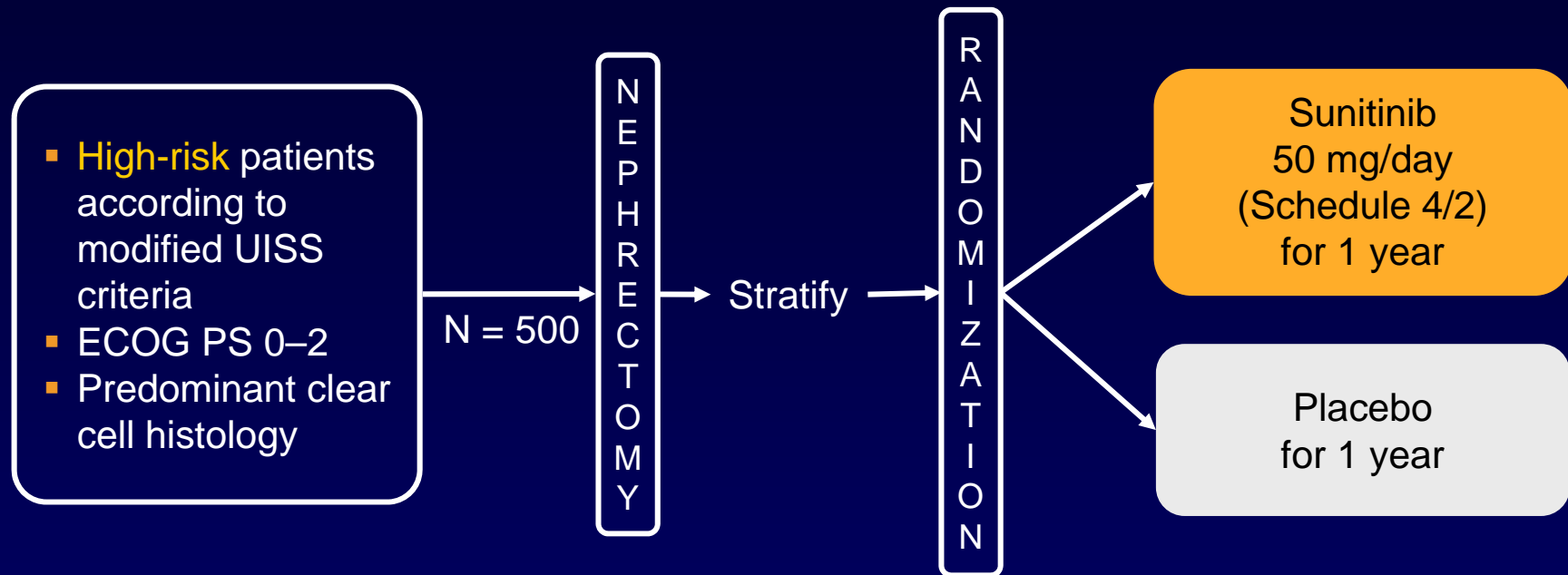
Agent	N	ORR (%)	Median PFS (months)	Median OS (months)
Sunitinib vs IFN- $\alpha$ <sup>1</sup>	750	47 vs 12 <i>P</i> <0.001	11 vs 5 <i>P</i> <0.001	26.4 vs 21.8 <i>P</i> = 0.051
Bevacizumab + IFN- $\alpha$ vs IFN- $\alpha$ <sup>2,3</sup>	649	31 vs 13 <i>P</i> = 0.0001	10.2 vs 5.4 <i>P</i> <0.0001	23.3 vs 21.3 <i>P</i> = 0.1291
Pazopanib <sup>4</sup>	435	32 vs 3 <i>P</i> = 0.01	11.1 vs 2.8 <i>P</i> <0.0000001	Not yet Determined
Sorafenib vs IFN- $\alpha$ <sup>5</sup>	189	5.2 vs 8.7	5.7 vs 5.6 <i>P</i> = 0.504	Not reported
Temsirolimus vs IFN- $\alpha$ <sup>6</sup>	626	8.6 vs 4.8 NS	5.5 vs 3.1 <i>P</i> <0.001	10.9 vs 7.3 <i>P</i> = 0.008
Poor-risk patients (modified MSKCC criteria)				

1.Motzer RJ, et al. *J Clin Oncol* 2009;27(22):3584-3590. 2.Escudier B, et al. *Lancet*. 2007;370(9605):2103-211.  
3.Escudier B, et al. *J clin Oncol*. 2009;27(15S): Abstract 5020. 4.Sternberg CN, et al. *J Clin Oncol*. 2010;28(6):1061-1068.  
5.Escudier B, et al. *J Clin Oncol*. 2009;27(8):1280-1289. 6.Hudes G, et al. *N Engl J Med*. 2007;356(22):2271- 2281.

# Ongoing/Planned Adjuvant RCC Phase III Studies

	N	Population/Design	Primary endpoint	Study start
<b>ASSURE (ECOG)</b>	<b>1940</b>	<b>Placebo vs sunitinib vs sorafenib, 1 year</b>	<b>DFS</b>	<b>2006</b>
<b>SORCE (MRC)</b>	<b>1650</b>	<b>Placebo vs sorafenib 1 year vs sorafenib 3 year</b>	<b>DFS</b>	<b>2007</b>
<b>S-TRAC (Pfizer)</b>	<b>500</b>	<b>Placebo vs sunitinib 1 year</b>	<b>DFS</b>	<b>2007</b>
<b>Everest (SWOG)</b>	<b>1218</b>	<b>Placebo vs everolimus 1 year</b>	<b>DFS</b>	<b>Q3 2010?</b>
<b>PROTECT (GSK)</b>	<b>1500</b>	<b>Placebo vs pazopanib 1 year</b>	<b>DFS</b>	<b>Q4 2010</b>

# S-TRAC: Sunitinib Phase III Trial in Adjuvant Renal Cancer Treatment



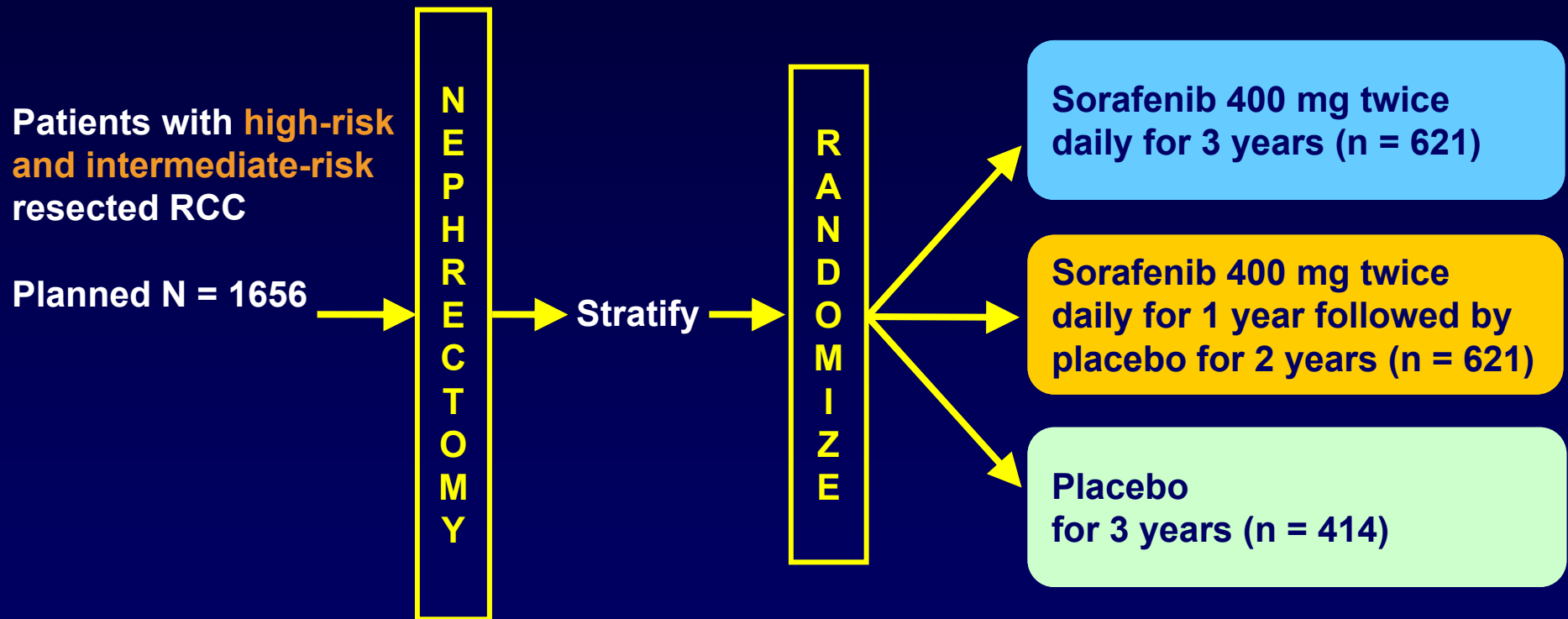
1. T3 N0 or NX, M0, Fuhrman's grade  $\geq 2$  and ECOG general status  $\geq 1$ , or
2. T4 N0 or NX, M0, any Fuhrman's grade, and any ECOG status, or
3. Any T, N1-2, M0, any Fuhrman's grade, and any ECOG general status

- Primary endpoint: disease-free survival
- Secondary endpoints: overall survival, safety, tolerability, patient-related outcomes

PIs: Jean-Jacques Patard, MD, PhD. Alain Ravaud, MD, PhD  
UISS = UCLA Integrated Staging System

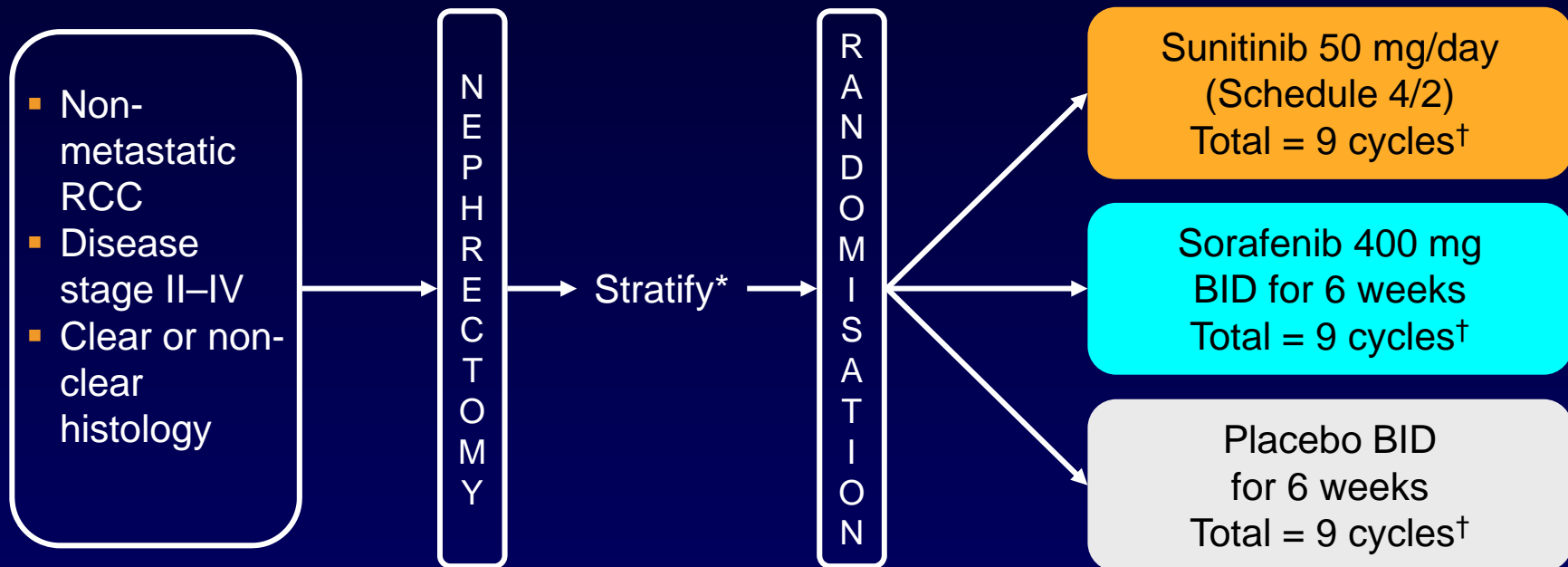
[www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00375674)

# SORCE Phase III Trial: Sorafenib in Patients With Resected Primary Renal Cell Carcinoma



- 1<sup>o</sup> end point: Disease-free survival
- 2<sup>o</sup> end points: RCC-specific survival time, toxicity, QOL and biomarkers
- Duration: 1 vs 3 years

# ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Cell Cancer (Phase III Trial)



- Duration: 1 year
- Primary endpoint: disease-free survival

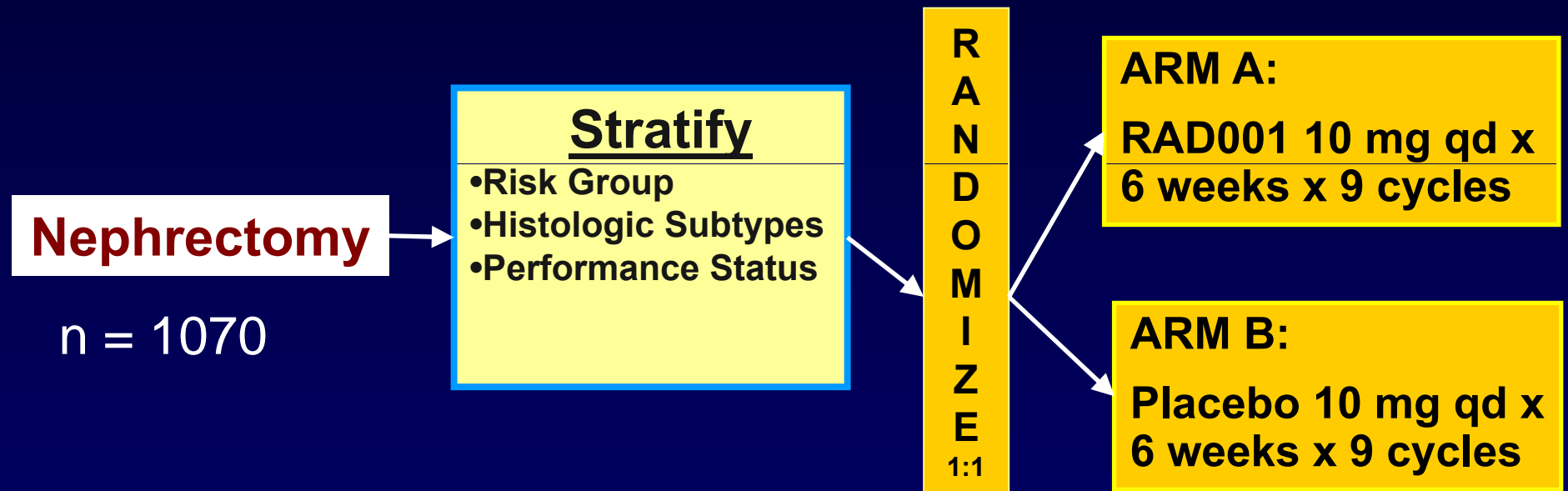
\*UISS (II-V); histology; ECOG PS; type of nephrectomy  
†Biopsy at recurrence

PIs: NS Balzer-Haas, CJ Kane, CG Wood, MAS Jewett

[www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00326898)

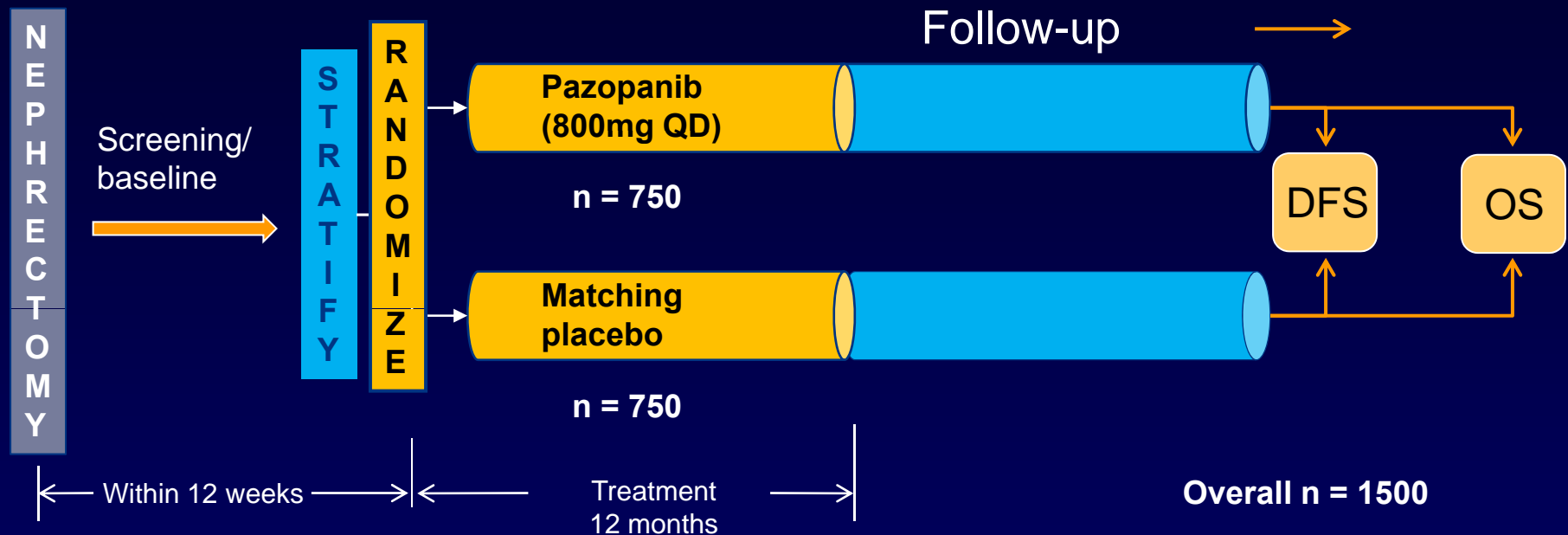
# EVEREST Trial: Phase III Study of Adjuvant Everolimus After Nephrectomy for Renal Carcinoma

Christopher Ryan MD, Primo Lara MD, SWOG



- Primary Objective: DFS
- Secondary Objective: OS, Safety, Biomarkers, PK
- Expected FPFV: Fourth Quarter 2010

# PROTECT Trial: Phase III Comparing Pazopanib vs Placebo After Nephrectomy for Renal Carcinoma



- **Key design/statistical features:**

- Primary endpoint: DFS; secondary endpoints: OS, safety, QoL
- 1:1 randomization
- 85% power to assess 30% improvement in DFS vs placebo (HR 0.77)
- Two interim analyses for DFS at 30% (futility only) and 75% (futility and superiority) of final information

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## Part III:

The patient undergoes right radical nephrectomy. Pathology shows pure clear cell carcinoma with direct invasion of the adrenal gland, Fuhrman’s grade 3. No involvement of the renal vein, but 1 perinephric lymph node contains metastatic clear cell carcinoma (T3aN1M0).

**Which of the following would you recommend postoperatively?**

- Observation only **NO**
- Clinical trial of adjuvant targeted therapy (SORCE, ASSURE, S-TRAC) **YES**
- Adjuvant vaccine therapy **NO**
- Adjuvant bevacizumab–based therapy **NO**

## **Conclusion: Clinical Case Adjuvant or Neoadjuvant Strategies Ready for “Prime Time”?**

- **T3NOMO : no neoadjuvant treatment**
- **Perform nephrectomy**
- **Keep frozen tissues**
- **Include this patient in an adjuvant clinical trial**
- **No treatment outside a clinical trial**