

Case #1: The Emerging Role of Adjuvant and Neoadjuvant Therapy

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Case #1—Renal Cell Carcinoma

- **63-year-old male with left flank pain, night sweats and weight loss**
- **CT shows 11.5-cm renal mass. No liver or pulmonary metastases**
- **Hgb 11.0 g/dL, Ca, LDH & creatinine normal**

Case #1—Renal Cell Carcinoma

- **Surgery: Left radical nephrectomy**
- **Pathology: Fuhrman grade 3 renal cell carcinoma (RCC) with moderate (microscopic) tumor necrosis**
- **Involvement of left renal vein**
- **1 perinephric lymph node involved**

pT3 pN1 M0

Does the Patient Need Adjuvant Therapy?

- **Stratification of risk of recurrence**

Leibovich Score (Modified SSIGN)

- **Mayo Clinic Series having radical nephrectomy between 1970 and 2000**
- **1695 sporadic patients, M0, unilateral clear cell tumors. Complete data on 1671 patients**
- **Clinical and detailed pathologic review**
- **Mean follow up 7.1 years (median 5.4 range 0-31)**
- **Multivariate analysis**

Leibovich Score

Pathologic Feature

pT3

pN1

Tumor size >10 cm

Nuclear grade 3

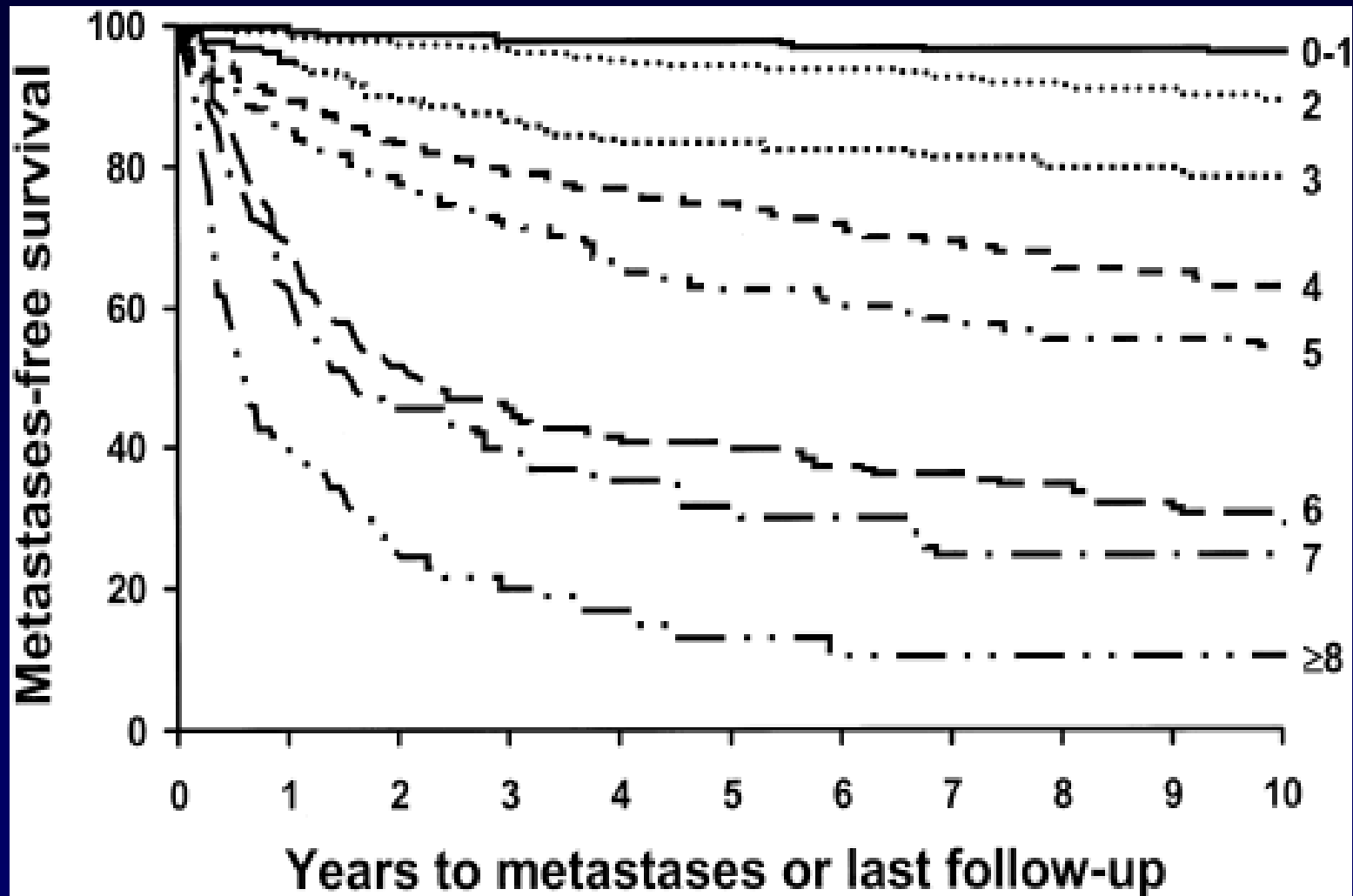
Histologic necrosis

Total score

Leibovich Score

Pathologic Feature	Leibovich Score
pT3	4
pN1	2
Tumor size >10 cm	1
Nuclear grade 3	1
Histologic necrosis	1
Total score 9 (Maximum = 10)	

Metastasis-Free Survival After RCC Resection



UCLA Integrated Staging System

Low risk	T1	Fuhrman grade 1-2	ECOG 0
Intermediate risk	T1	G 3-4	ECOG >0
	T2	G 1-4	ECOG 0-3
	T3	G1	ECOG 0-3
High risk	T3	G >1	ECOG >0
	T4	G 1-4	ECOG 0-3
Nod- positive disease			

UCLA Integrated Staging System

	5-Year Recurrence Free, %	Median Time to Recurrence, months	Site(s) of Recurrence
Low risk	90.4	28.9	75% Chest 37% Abdo
Intermediate risk	61.8	17.8	77% Chest 58% Abdo
High risk	41.9	9.5	45% Chest 68% Abdo
Node-positive disease	36	Not stated	59% Chest 76% Abdo

Comparison of SSIGN & UISS

- 388 patients treated between 1986 and 2000—
median follow up 56 months
- Independent pathology review
- Predictive accuracy compared with receiver
operating characteristics curves (ROC)

Comparison of SSIGN & UISS

SSIGN Score	10-Year CSS*	UISS Group	10-Year CSS
0-2	96%	Low	100%
3-4	78%	Intermediate	73%
5-6	43%	High	62%
7-9	26%		
≥10	0%		
AUC	0.83	AUC	0.76

*CSS – Cancer Specific Survival AUC – Area under curve

Ficarra V, et al. *BJU Int.* 2009;103(2):165-170.

Adjuvant Therapy?

- **What is the evidence to support adjuvant therapy?**

Adjuvant Treatments for RCC

Treatment	N	Author	Outcome
RT v Obs	72	Kjaer	OS 50% v 62% (NS)
MPA v Obs	136	Pizzocaro	Relapse 33% v 33% (NS)
Tumor + BCG v Obs	43	Adler	DFS (NS)
	120	Galligioni	DFS 63% v 72%
IFN v Obs	283	Messing	OS 5.1 yrs v 7.4 yrs (NS)
HD IL-2 v Obs	69	Clark	Relapse 76% v 65% (NS)
Aut. Tum. Vacc. v Obs	553*	Jocham	PFS 77% v 68% ($P = .02$)
IL-2 + IFN v Obs	303	Passalacqua	RFS & OS (NS)
G250Ab v Placebo	612		Awaiting analysis
HSPCC-96 v Obs	818	Wood	RFS & OS (NS)
Atzpodien v Obs - Hydra	315		Awaiting analysis

*174 lost at randomization

Is There Effective Therapy for Advanced Disease?

- Tyrosine kinase inhibitors—
sunitinib, sorafenib, temsirolimus,
everolimus
- Monoclonal antibody—
bevacizumab
- Biological response modifiers—
interferon alpha, interleukin-2

Rationale for Adjuvant Trials in RCC: In the Era of Tyrosine Kinase Inhibitors (TKIs)

- **Poor prognosis for selected groups after nephrectomy**
- **No proven adjuvant treatment**
- **Efficacy of TKIs in advanced disease setting**
- **TKIs are suitable for prolonged adjuvant use**
 - **Oral**
 - **Well tolerated**

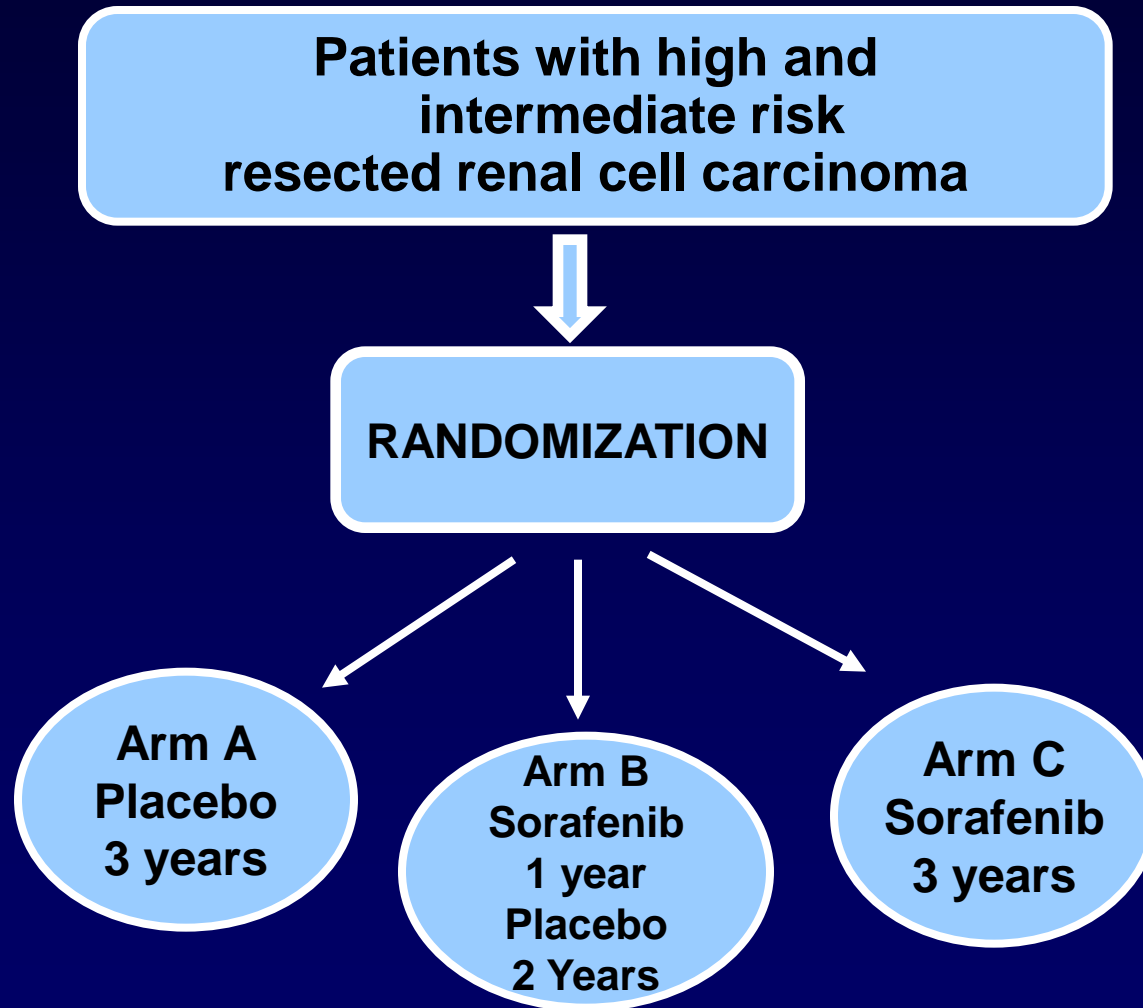
Adjuvant Trials with Targeted Therapies for RCC

Treatment	n	Sponsor	Status
cG250 vs placebo	612	Wilex	Awaiting analysis
Sorafenib vs placebo Sunitinib vs placebo	1332	ECOG	Recruiting
Sorafenib vs placebo Sorafenib 1 vs 3 years	1656	MRC/EORTC	Recruiting
Sunitinib vs placebo	290	Pfizer	Recruiting

SORCE

A Phase III Randomized, Double-Blind Controlled Study Comparing **S**orafenib with Placebo in Patients with **R**esected Primary Renal **C**ell Carcinoma at High or Intermediate Risk of Relapse

SORCE Trial Design



SORCE Outcome Measures

- **Primary:**
 - Disease-free survival (DFS) (ie, time from randomization to first evidence of local recurrence or distant metastases or death from RCC)
- **Secondary:**
 - RCC-specific survival time (ie, time to death from RCC)
 - Overall survival
 - Toxicity
 - Biologic characteristics of resected primary RCC (VHL, VEGFR2, FGF2, B-RAF, MEK, ERK)
 - Cost effectiveness
 - Corroboration of Leibovich Prognostic Score

SORCE Research Questions

- **Question 1:**

Does at least one year of treatment with sorafenib increase DFS compared to treatment with placebo?

- A comparison of Arm A vs Arm B plus Arm C

- **Question 2:**

If the answer to question 1 is Yes, does an additional two years of sorafenib (Arm C) increase DFS?

- **Question 3:**

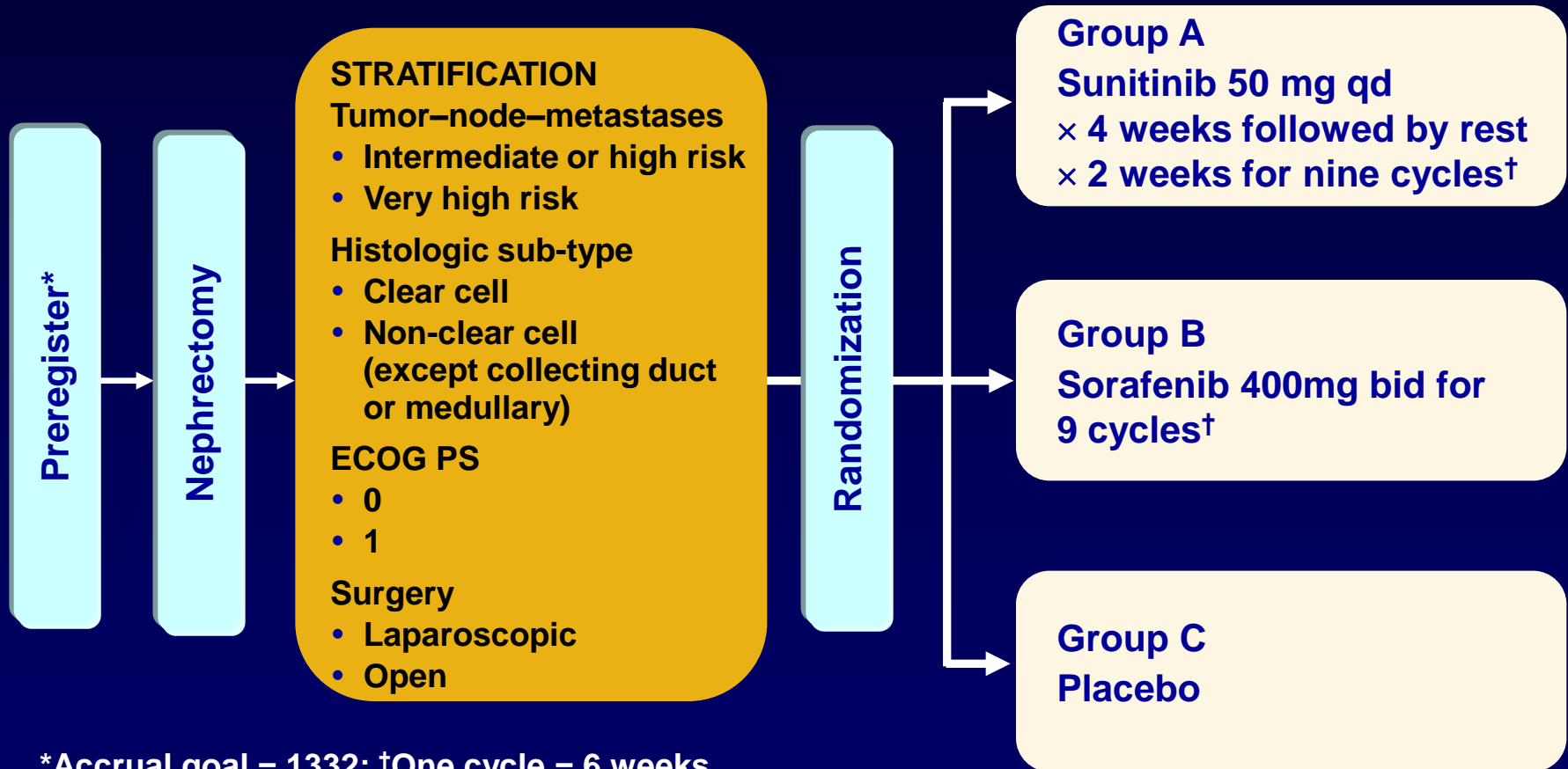
Which biologic parameters predict benefit from sorafenib?

- **Question 4:**

Corroboration of Leibovich risk model

ECOG 2805 (ASSURE): Study Design

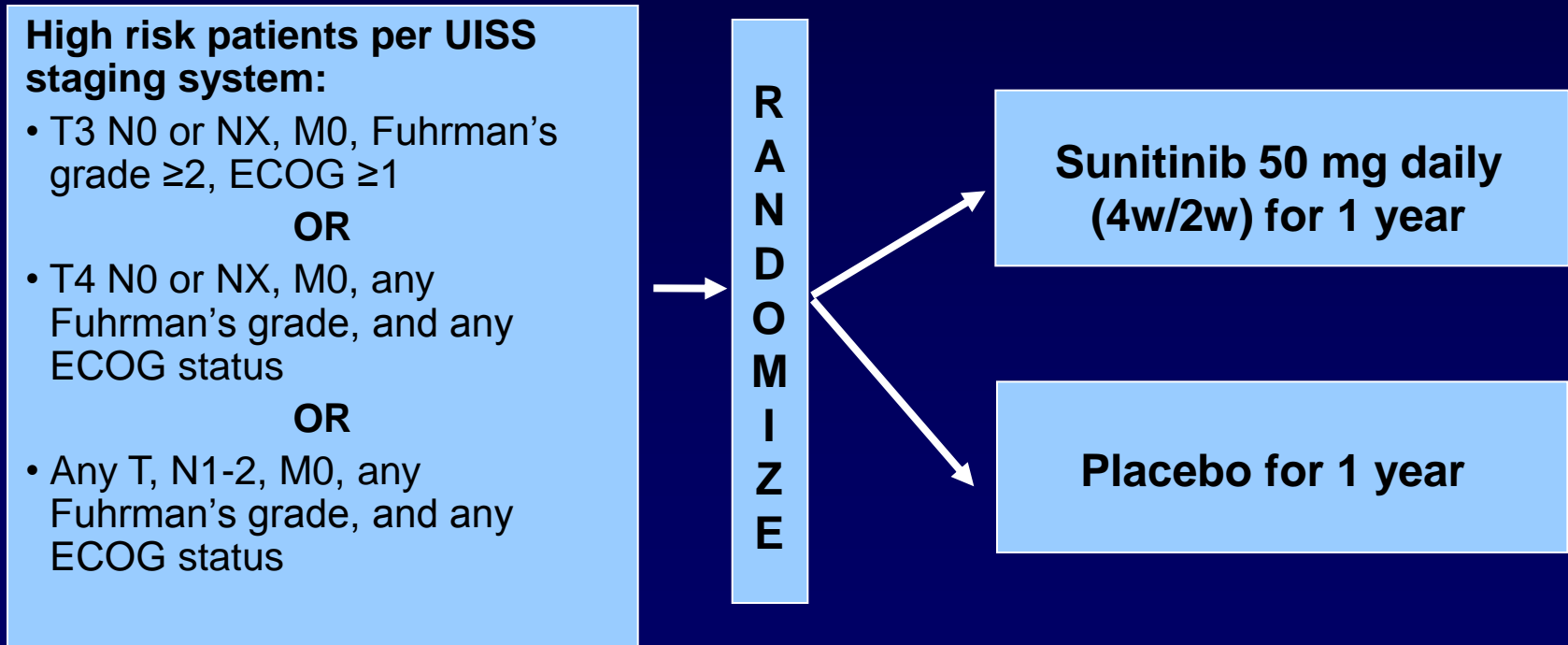
Primary objective: DFS



*Accrual goal = 1332; †One cycle = 6 weeks
ECOG = Eastern Cooperative Oncology Group
ECOG PS = ECOG Performance Status

S-TRAC

- **Primary endpoint: DFS**
- **Secondary endpoints: RFS, OS, safety, patient-related outcomes, association of molecular markers with DFS and OS**



Adjuvant Trial Desirables

- **Innovative trial design**
 - **Multiple questions in a trial**
- **Translational component**
 - **Identification of patients who will benefit**
- **Health economic component**
- **Meta-analysis**
- **Validation & extension of prognostic models**

Neoadjuvant Therapy?

- **What is the evidence to support neoadjuvant therapy?**

Neoadjuvant Phase II – In Progress

- **Sunitinib**
- **Bevacizumab**
- **Everolimus**

Neoadjuvant Therapy?

- **No phase III data**
- **Beware complications and wound healing problems**
- **Other trials in progress**

Summary and Choice of Therapy

- Little evidence to support adjuvant therapy as standard treatment
- Neoadjuvant therapy is interesting but 'experimental'

Where there is clinical uncertainty – patients should be considered for clinical trials