

Adjuvant and Neoadjuvant Strategies for RCC in the Era of Targeted Therapy

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Key Areas of Trials Activity

- **Risk Stratification**
- **Adjuvant Trial Data So Far**
- **Neo-adjuvant vs Adjuvant Approaches**
- **2nd line metastatic**

Risk Stratification Models

UISS	TN Stage	ECPG PS	Grade	
SSIGN	TN Stage	Size	Grade	Necrosis

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)
Tumour + BCG v Obs	43	Adler	DFS (NS)
	120	Galligioni	DFS 63 v 72%
IFN v Obs	283	Messing	OS 5.1 v 7.4 yrs (NS)
HD IL-2 v Obs	69	Clark	RFS 76 v 65% (NS)
Aut. Tum. Vacc. v Obs	553*	Jocham	PFS 77 v 68% (p=0.02)
IL-2 + IFN v Obs	303	Passalacqua	RFS & OS (NS)
HSPCC-96 v Obs	818**	Wood	RFS & OS (NS)
Atzpodien v Obs	309	Aitchison	RFS & OS (NS)

2 Key Differences Between Targeted Therapies & Immunotherapy

1. Targeted therapies effective in the primary tumour

- Immunotherapy rarely shrinks the primary
- TKIs may provide rapid palliative benefit

2. No evidence that nephrectomy improves TKI outcome

Nephrectomy & Targeted Therapy

- Existing nephrectomy data relate to immunotherapy, not targeted therapy
- Targeted therapy is safe & effective **IRRESPECTIVE** of whether nephrectomy is performed
- Is there any benefit in performing a nephrectomy in patients with mRCC?

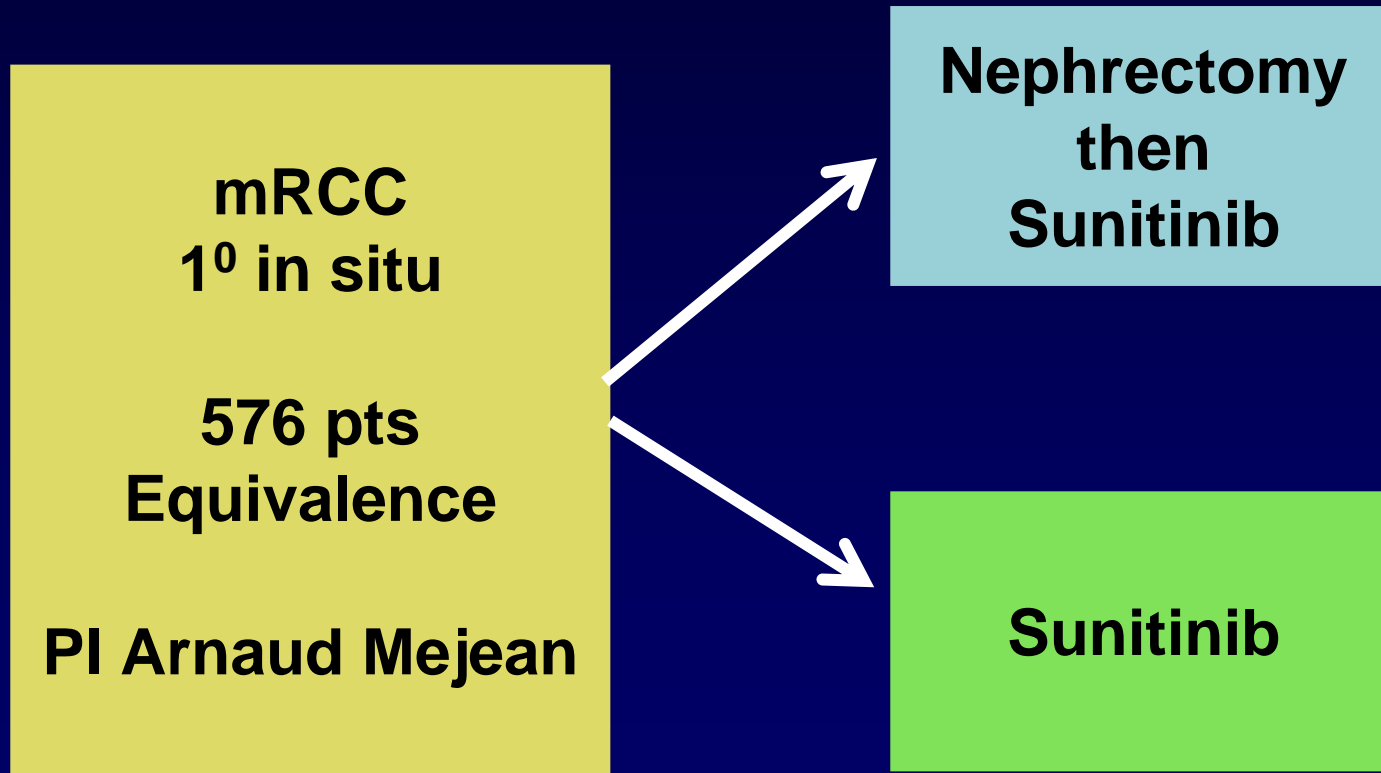
Concerns About Using Targeted Therapy Before Nephrectomy

- **Surgical / Anaesthetic Safety**
- **Wound Healing**
- **Bleeding & Thrombosis**

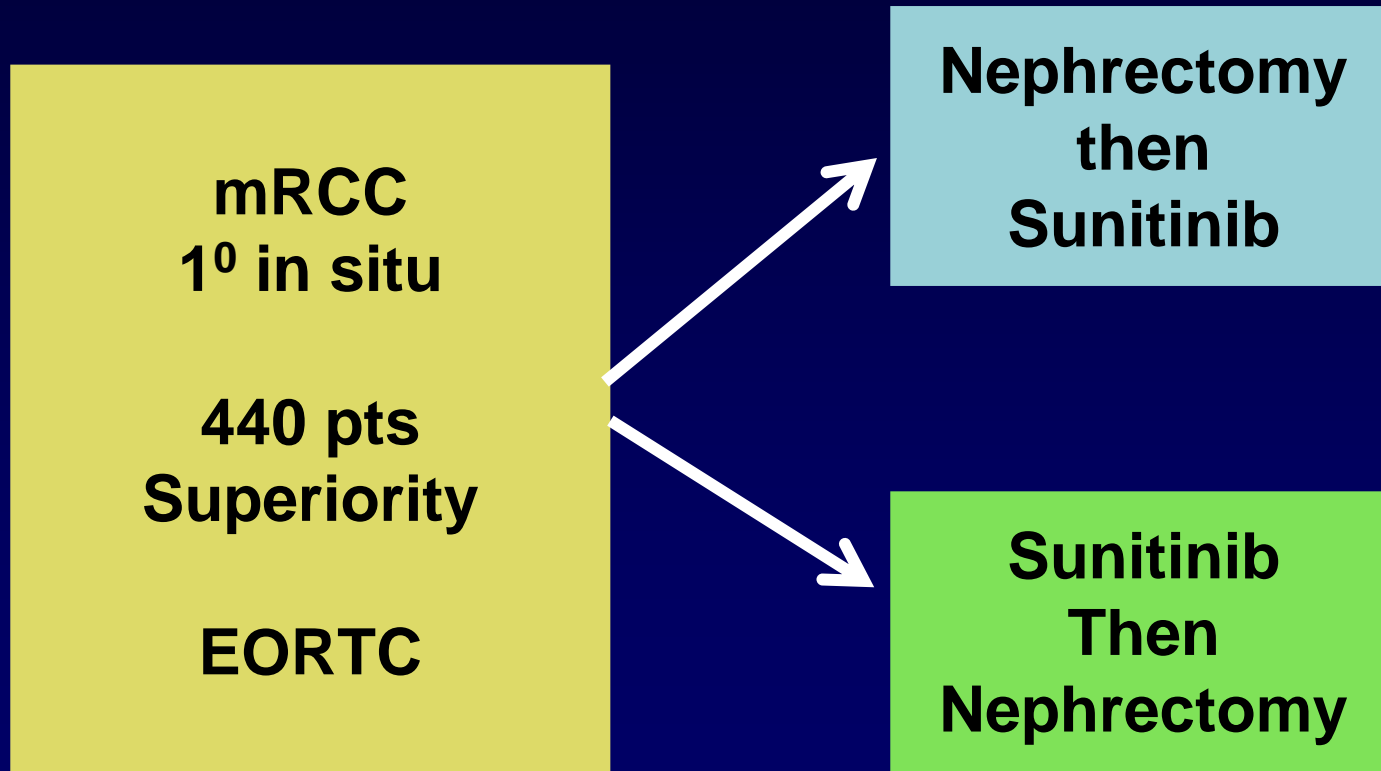
Ongoing Neoadjuvant Studies

- 11 clinical trials listed on clinicaltrials.gov
- Phase II
- Aim to recruit 10-110 patients
- Agents:
 - Sunitinib
 - Sorafenib
 - Bevacizumab

Role of Surgery in TKI Therapy



Role of Surgery in TKI Therapy



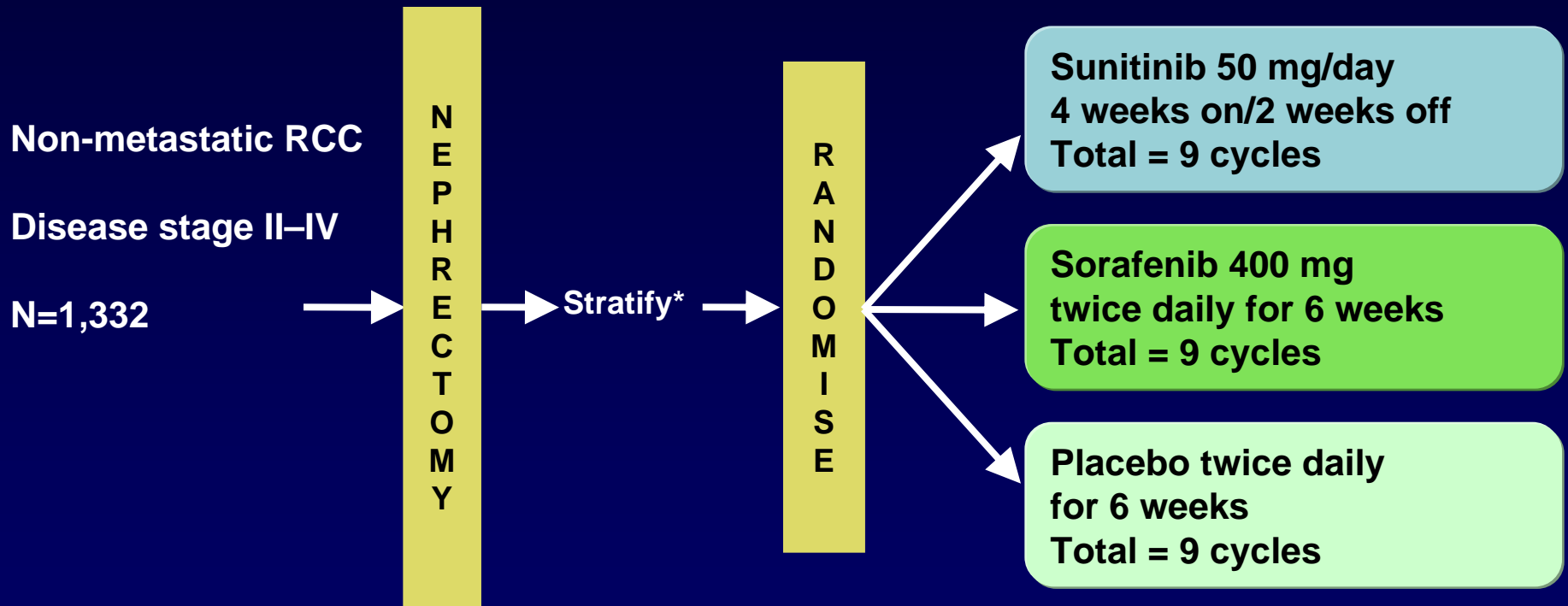
Rationale for Adjuvant Trials in RCC in the Era of TKIs

- **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	830	Wilex	Awaiting Analysis
Sorafenib vs placebo Sunitinib vs placebo	1,332	ECOG	Recruiting
Sorafenib vs placebo Sorafenib 1 vs 3 years	1,656	MRC/EORTC	Recruiting
Sunitinib vs placebo	228	Pfizer	Recruiting

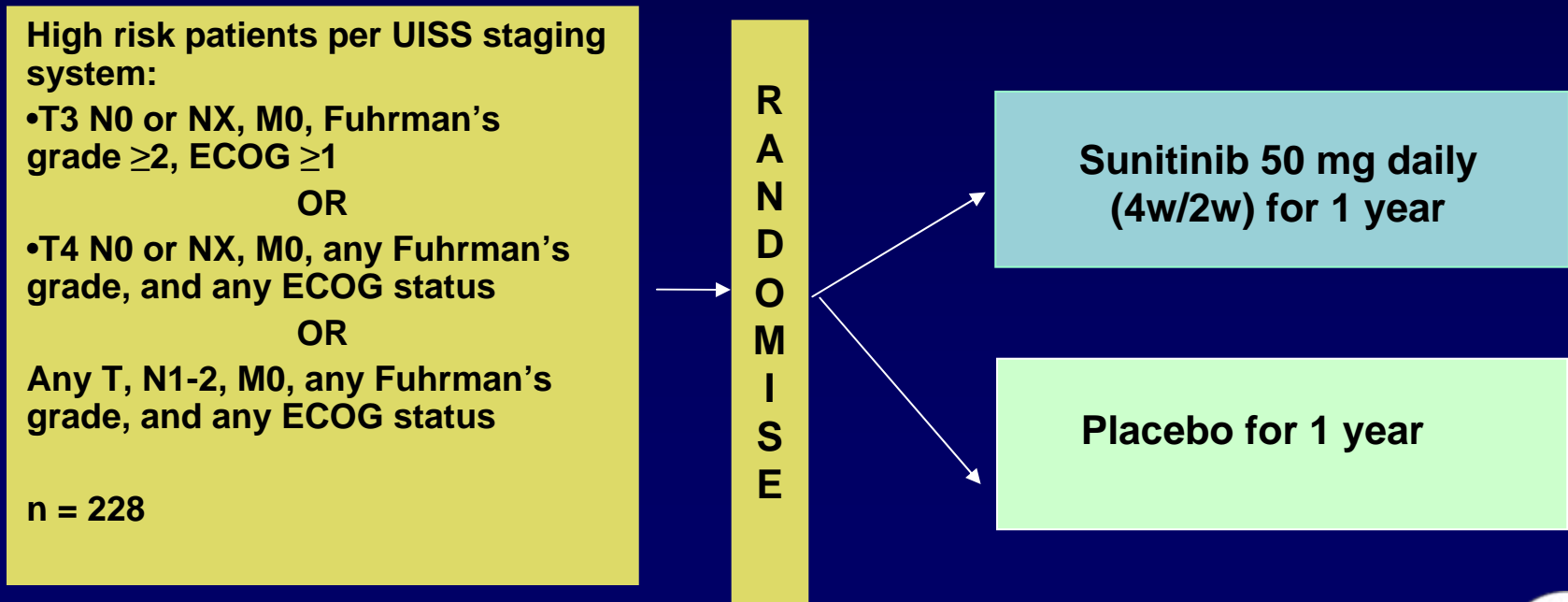
ECOG ASSURE Phase III Trial: Adjuvant Sorafenib Sunitinib Unfavourable Renal Cell Carcinoma



- **Primary endpoint: Disease-free survival at 5 years**
- **Duration: 1 year**

S-TRAC

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

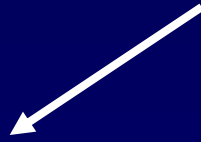


SORCE

Patients with high and intermediate risk
resected renal cell carcinoma



RANDOMISATION



Placebo
3 years



Sorafenib
1 year
Placebo
2 Years



Sorafenib
3 years

Practical Issues in Adjuvant Studies

- How rigorously should metastatic disease be excluded?
- Should the balance of QoL v Efficacy be different from advanced disease studies

Adjuvant Trial Desirables

- **Innovative Trial Design**
 - Multiple questions in a trial
 - Multi-stage – drop the losers
- **Translational Component**
 - Identification of patients who will benefit
- **Health Economic Component**
- **Metanalysis**
- **Validation & Extension of Prognostic Models**

Design Issues for the Next Study

- **Emerging data may change standard of care**
- **Improving technology may change adjuvant population**
- **Multiple treatment strategies**
- **Limited patient accrual potential**
- **Long timescale for design conduct and analysis**

Design Proposals for the Next Study

- Answer to trial 1 before starting trial 3
- Answer to trial 2 before starting trial 4
 - Very demanding if only 2 types of question asked
 - May need multiple tracks



T1: AvBvC				
T2: 1v2v3				
T3: BvDvE				
T4: B1vB3vF				

Design Requirements for the Next Study

- Rapid accrual
- Large studies
- Realistic event assumptions

**Large
International
Collaborations**

Thank you

