# Renal Cell Carcinoma: Status of Medical and Surgical Therapy

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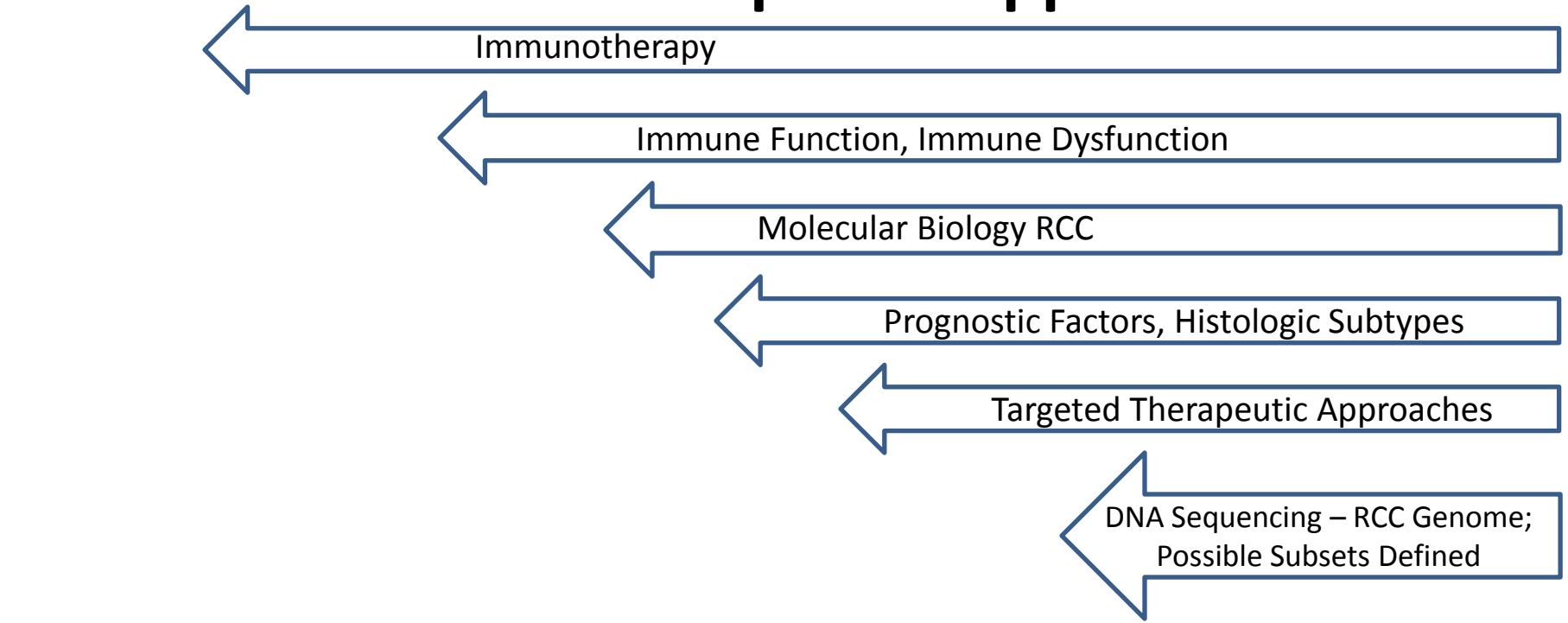
# Metastatic Renal Cell Carcinoma: Evolution of Current Therapeutic Approaches



# RCC Clinical Trial with Targeted Agents: Recent Developments

- Initial Phase – 2000 to 2010
  Defined the efficacy of Targeted Therapy

- Second Phase – 2010 to present
  Compared treatments with regard to efficacy and tolerability

- Next Phase – define new/novel treatments
  New targets/medications
  Improve patient outcomes
  Integration “genomic approaches”

# Renal Call Carcinoma Clinical Trials 2000 2010: Defined Efficacy

| Agent (s) | Publication | Trial Description | Patient Nos. | |
|---|---|---|---|---|
| | | | Naive | Prior Rx |
| Bevacizumab | 2003 | Phase 2 randomized | - | 116 |
| | 2007 (vs. IFN) | Phase 3 randomized | 649 | - |
| | 2008 (vs. IFN) | Phase 3 randomized | 732 | - |
| Sunitinib | 2005/2006 | Phase 2 | - | 163 |
| | 2007 (vs. IFN) | Phase 3 randomized | 750 | - |
| Sorafenib | 2006 (vs. PLC*) | Phase 3 randomized | - | 903 |
| | 2009 (vs. IFN) | Phase 2 randomized | 189 | - |
| Temsirolimus | 2007 (± IFN) | Phase 3 randomized | 626 | - |
| Everolimus | 2009 (vs. PLC) | Phase 3 randomized | - | 416 |
| Pazopanib | 2010 | Phase 2 Randomized Discontinuation | 155 | 70 |
| | 2010 (vs. PLC) | Phase 3 randomized | 290 | 145 |

Treatment naive patients – 2791; treatment refractory patients – 1813; total patients – 4604

*PLC : placebo

# Renal Call Carcinoma Clinical Trials 2010 – Present: Define "Optimal Therapy" & Tolerability

| Agent (s) | Publication Date (Comparator Arm) | Trial Description | Patient Nos. | |
|---|---|---|---|---|
| | | | Naive | Prior Rx |
| Bevacizumab + IFNα | 2012 (vs. TEMSR + Bev) | Phase 3 randomized | 791 | - |
| Axitinib | 2012 (vs. sorafenib) | Phase 3 randomized | - | 723 |
| | 2013 (vs. sorafenib) | Phase 3 randomized | 288 | - |
| | 2012 | Phase 2 randomized | 213 | - |
| Temsirolimus | 2012 (vs. sorafenib) | Phase 3 randomized | - | 512 |
| Tivozanib | 2012 (vs. sorafenib)) | Phase 3 randomized | 362 | 155 |
| Pazopanib | 2012 (vs. sunitinib) | Phase 3 Randomized | 1110 | - |

Treatment naive patients – 2551; treatment refractory patients – 1290; total patients – 3841

*PLC : placebo

# Current Standards for Clear Cell mRCC Therapy

| Setting | | Category 1 | Alternative |
|---|---|---|---|
| **1st-Line Therapy** | **Good or intermediate risk*** | **Sunitinib<br>Bevacizumab + IFN<br>Pazopanib** | HD IL-2 |
| | **Poor risk*** | **Temsirolimus** | Sunitinib |
| **2nd-Line Therapy** | **Prior cytokines** | **Sorafenib<br>Pazopanib<br>Axitinib** | Sunitinib or<br>Bevacizumab |
| | **Prior VEGFR inhibitors** | **Everolimus<br>Axitinib** | **Clinical Trials** |
| | **Prior mTOR inhibitor** | **Clinical Trials; Axitinib** | |

* MSKCC or Heng Criteria

# Current Approaches RCC Therapy

1. VEGFR inhibitors:
    - Diverse spectrum clinical, biochemical & toxic effects
    - Efficacy may correlate with potency of VEGFR inhibition
    - Efficacy & plasma levels may be related
    - Dosing based on target plasma level is a consideration
    - Hypertension may be a clinical surrogate for plasma drug levels
    - Axitinib and tivozanib may be “cleaner TKIs” & have a better TI
2. mTOR inhibitors:
    - May be inferior to anti-VEGFR TKI’s in treatment naïve patients
    - Most clear cell RCC tumors do not express activated mTOR kinase
    - Current use is in TKI refractory patients or non-clear cell RCC
    - Identification of RCC that are mTOR dependent would be of interest

# Results of New mRCC Treatment Paradigm

- Improved clinical benefit:
  - Increased frequency of tumor regression
  - Delayed disease progression
  - Survival : appears improved, confounding effect sequential therapy recognized, eg, TIVO-1 trial
- Quality of life indicators – improved
- Multiple treatment alternatives available
- Cost versus benefits – appear acceptable
- Are we utilizing the correct surrogate endpoints to demonstrate clinical benefit?
  - OS: “gold standard”
  - PFS: do improvements always translate into OS benefit?
  - PRO: a work in progress

# Improving Outcomes in mRCC Patients

- Continued development of novel targeted agents
- VEGFR TKIs with improved therapeutic indicies: ?tivozanib
- Dose Intensification-based on biomarkers: ?hypertension
- Combination therapy ± immunotherapy
- Back to biology:
    1) Consider concept of clonal tumor evolution
    2) VEGFR TKI resistance – novel approaches
    3) Treatment based on tumor biology

# Next Generation RCC Clinical Trials

- Have we reached a “therapeutic plateau” with TKI and mTOR inhibitors?
- New and novel targets:
  - Immune checkpoint regulators: PD-1 Mab
  - Vaccines: peptide based, dendritic cells

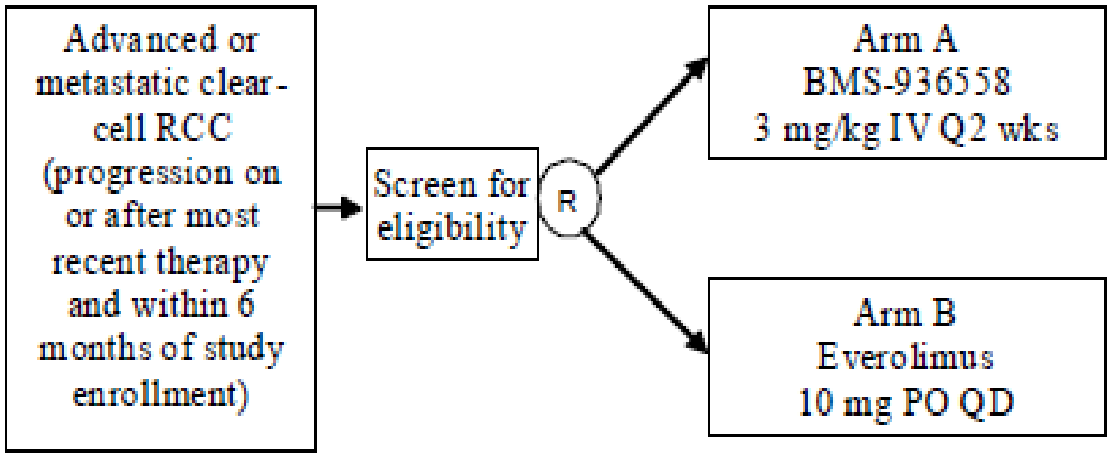
  } Immunotherapy based

  - cMet inhibitors: carbozantinib
  - FGFR inhibitors: divotinib

  } Multikinase inhibitors

  - Ang-2 inhibitors
  - ?Combinations
- Trials in pre-defined patient subsets – refine current patient selection
  - Clinically defined groups: risk group, histology,
  - Biomarker defined groups:, genetically defined subsets, IL-6, LDH
- Continued focus on clinical trials with optimal design

# Phase 3 Trial BMS-936558 vs. Everolimus in Patients with mRCC who have received prior Anti-Angiogenic Therapy



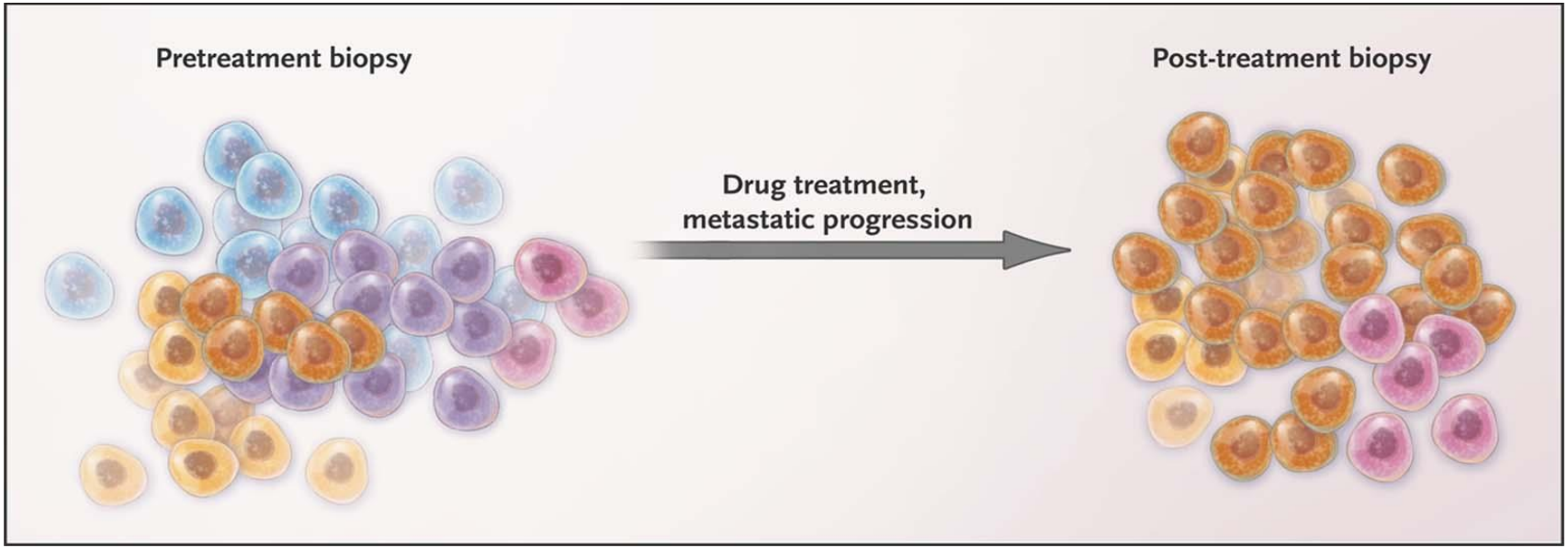

Patients Eligible:

- RCC with clear cell component
- Must have received one or two prior anti-angiogenic Rx's: sunitinib, sorafenib, pazopanib, axitinib, tivozanib and bevacizumab
- Prior cytokine Rx, cytotoxic Rx, or vaccine therapy allowed
- Must have received ≤ three prior treatment regimens for mRCC

Study endpoints:

- Primary: overall survival
- Secondary: PFS, ORR

# Changes in Clonal Composition over Time & Changes in Clonal-Mutation Prevalence




Aparicio S, Caldas C. N Engl J Med 2013;368:842-851

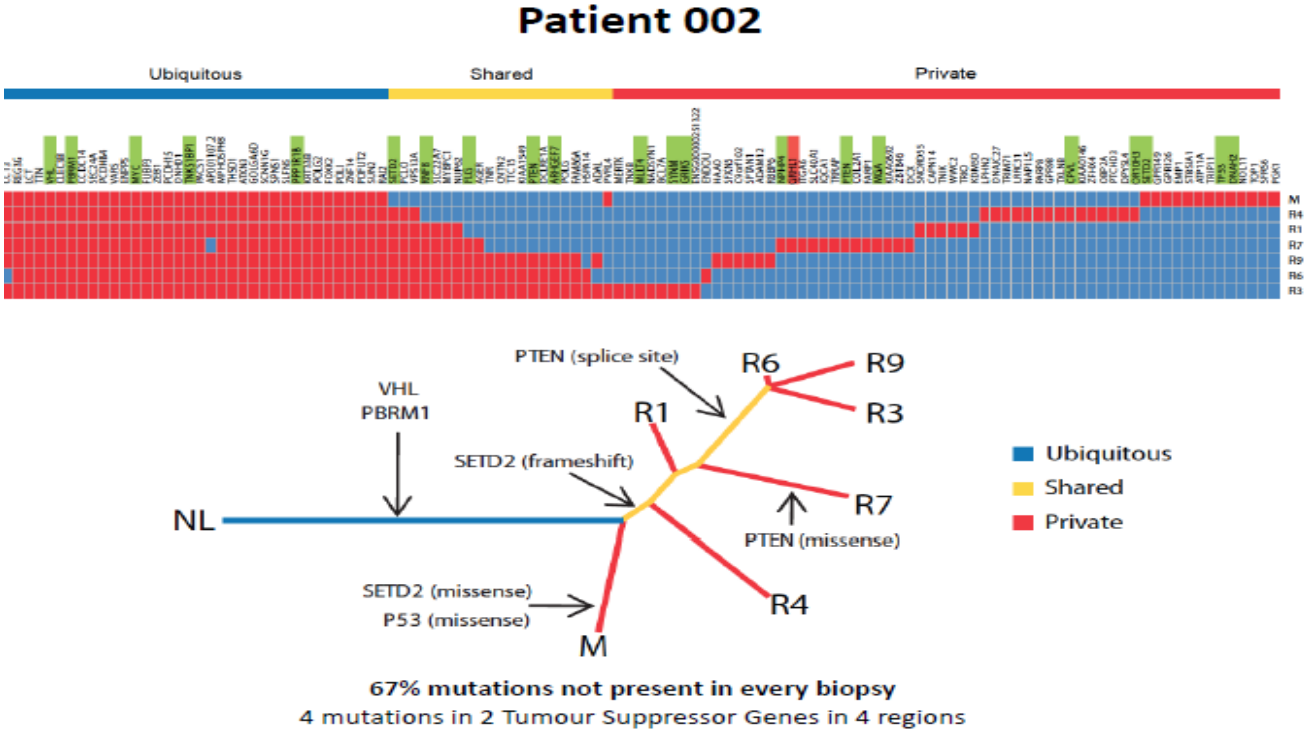
# VHL Genotype in Primary & Metastatic CCRCC

- 10 paired specimens from patients with metastatic clear cell CA utilized
  - Paraffin embedded specimens
  - Genomic DNA from microdissected specimens
  - Paired tumor/metastatic tissue (#10) & normal adjacent tissue (#6) analyzed
  - 3 exons of the VHL gene sequenced (PCR-based amplification)
  - Results independently validated (Transgenomic)

- In 4/10 (40%) patients, the VHL genotype differed between the primary & metastatic lesion
  - VHL mutation in the primary & metastasis was also identical
  - In normal adjacent tissue VHL was always WT

Vazari S, et al Frontiers in Oncology, 2012

# Intratumor Heterogeneity and Evolution Revealed by Multiregion Sequencing




- Intratumor heterogeneity examined
- 4 primary RCC from patients with mRCC examined
- Performed exome sequencing & chromosome analysis, IMH, mutational functional analysis, profiling mRNA
- Results:
  - 63 to 69% somatic mutations not detectable across tumor regions
  - Intratumor heterogeneity observed in mTOR kinase mutation
- Tumor heterogeneity may result in tumor adaptation & therapy failure

Marco Gerlinger, et al: NEJM 2012; 366: 883

# Clonal Evolution and Therapy for mRCC: Implications

- Clinical documentation of response variability:
  - a) Metastases
  - b) Primary tumor
- Suggests clinical relevance of tumor subclones and mutations:
  - a) Intratumoral heterogeneity of mutations recognized
  - b) Even among early “driver” mutations subclonality may occur
  - c) Suggests that multiple assessments of tumors will be required
- Clonal heterogeneity constitutes a molecular phenotype:
  - a) Assessment may guide therapy
  - b) Genomic heterogeneity may prove to be prognostic
- Monitoring and profiling of clonal evolution in RCC may be necessary:
  - a) Characterization of clonal heterogeneity in tumors
  - b) Monitoring of plasma DNA may be less invasive
  - c) Development of a tumor “barcode”

# Emergence of Treatment Resistance in mRCC: Major Challenge

- Clonal tumor evolution in response to the selective pressure of therapy
- Determining resistance mechanisms:
  - a) Role of clonal evolution
  - b) Identification of mutations that drive resistance
  - c) Identification of therapy that can bypass target responsible for resistance
- Approaches to resistance:
  - a) Target alternate pathways, e.g., FGFR, immune check points, cMet, etc.
  - b) Development of new agents active versus mutant protein
  - c) Use of combinations to inhibit bypass pathway
  - d) Will combinations delay emergence of resistance
- Large-scale DNA sequencing of the RCC genome will provide insights into the clonality of tumor cells and possibly define new targets and therapeutic approaches.

# Effects on survival of *BAP1* and *PBRM1* mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation

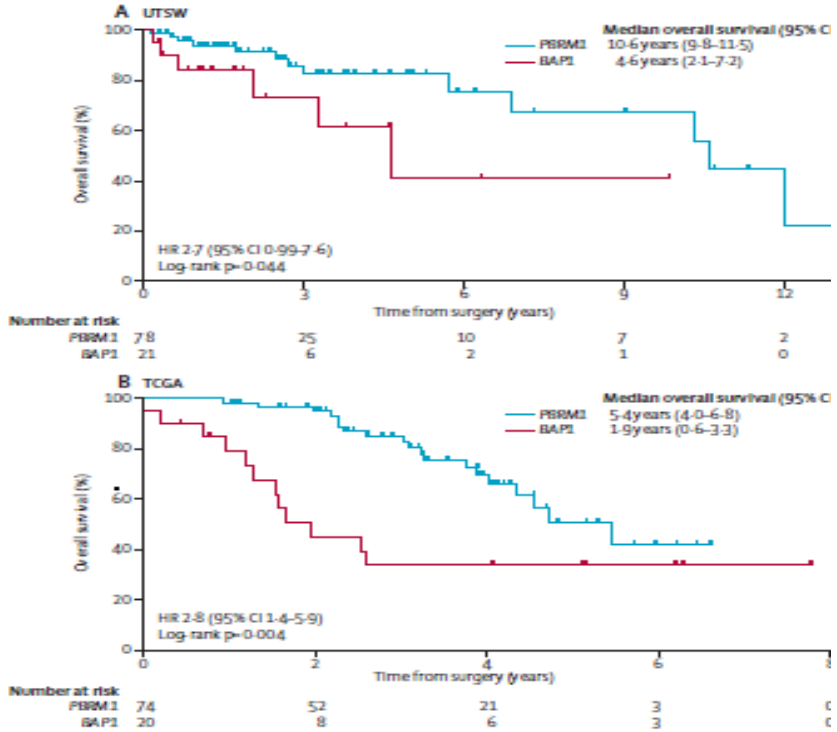
Payal Kapur*, Samuel Peña-Llopis*, Alana Christie, Leah Zhrebker, Andrea Pavía-Jiménez, W Kimryn Rathmell, Xian-Jin Xie, James Brugarolas

PBRM1 (polybromo 1):

1) Gene encoding an SW1/SNF chromatin-remodeling complex
2) Truncating mutations described in 41% CCRCC
3) Low grade tumors noted

BAP1 (BRCA 1 associated protein-1)

1) Mutations in 15% CCRCC
2) High grade tumors reported




Kapur et al: Lancet Oncology 2013

# Treatment Approach Based on Molecular Profile

| Setting | Tumor Characteristic | Therapy |
|---|---|---|
| Treatment Naive | VHL -/-, BAP-1 WT, PD-L1 - | VEGF Inhibitor |
| | mTOR activation | mTOR Inhibitor |
| | PDL1+, ± other | Anti-PD1 Therapy |
| | VHL-/-, BAP-1 mutant, PDL1- | VEGF Inhibitor + "Other Agent" |
| | C-Met +, ± other | Met inhibitor |
| | Other mutation: PBRM1 ± Other | ?Specific Inhibitor<br>?Observation |

Adapted: Atkins M: KCA Chicago Symposium, 2012

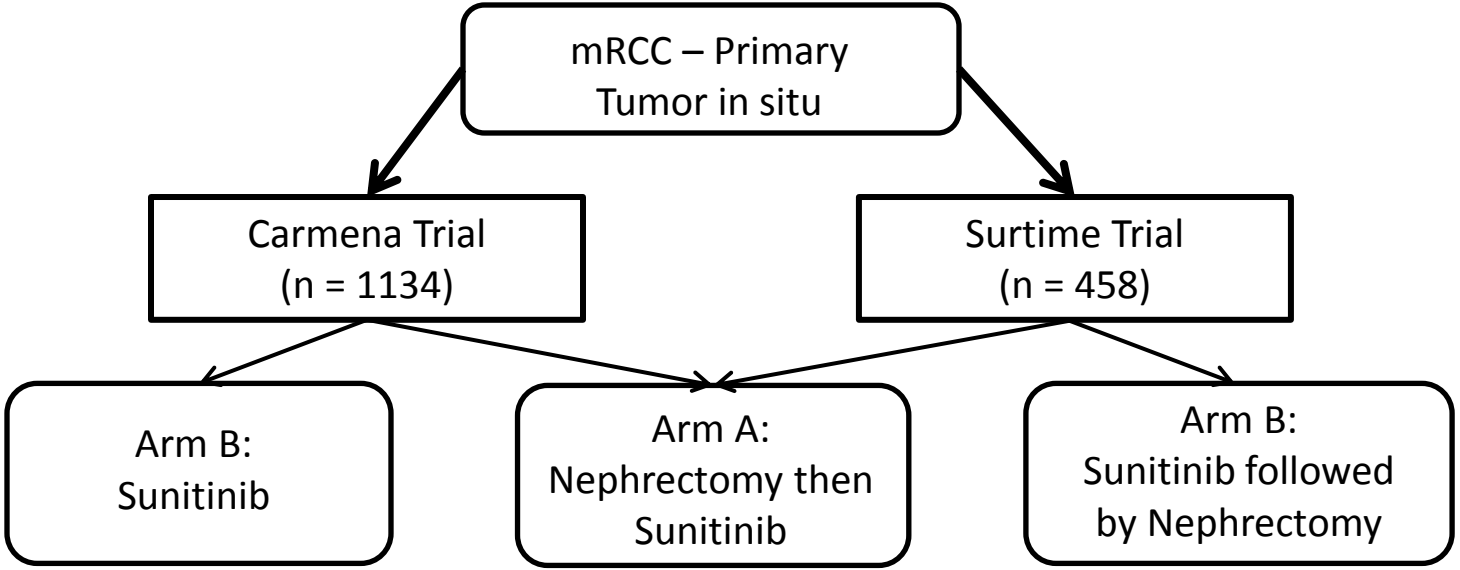
# Surgery in Renal Cell Carcinoma

- Localized disease:
    - Small renal masses
    - Non-surgical ablative techniques
    - Observation
- Locally advanced/metastatic disease:
    - Cytoreductive nephrectomy
    - Neoadjuvant therapy
- Adjuvant therapy

# Cytoreductive Nephrectomy: 2013

- Remains the paradigm of choice in the current targeted therapy:
  - Trials from the cytokine era
  - Retrospective analysis
- Patient selection is a major issue
- Prospective trials are in progress, may clarify the issue

# Current Trials: Cytoreductive Nephrectomy mRCC

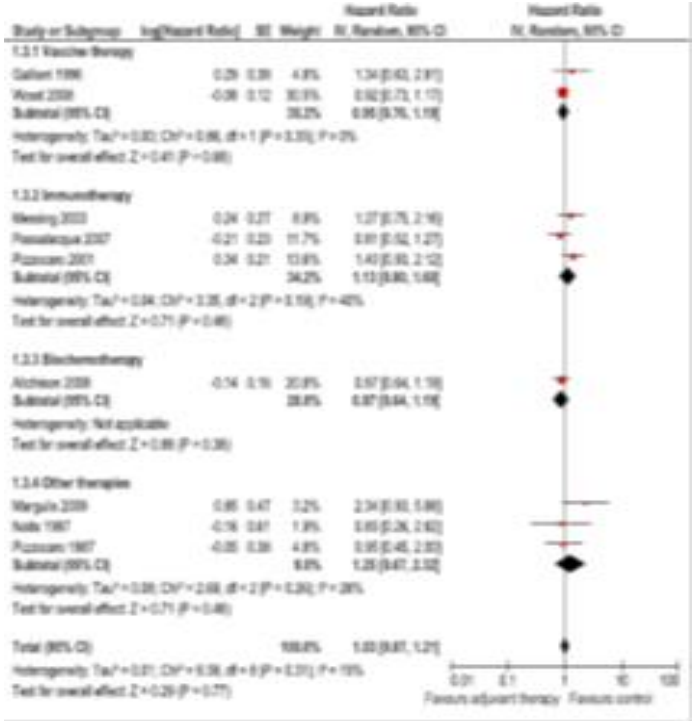



**Carmena Endpoints:**
Primary Endpoint: OS (non-Inferiority design)
Secondary Endpoints: ORR, PFS, CBR
Morbidity, compliance

**Surtime Endpoints:**
Primary Endpoint: PFS
Secondary Endpoints: OS, ORR,
Morbidity, Early PD

# Meta-analysis Adjuvant Therapy: RCC

- 10 randomized controlled studies with 2609 patients
- Interventions: cytokines, vaccines, biochemotherapy, hormone therapy
- Endpoints:  overall survival, disease free survival
- No benefit for any intervention identified



Scherr et al, BMC Cancer 2012

# Current Generation RCC Adjuvant Trials

| Trial | Interventions | No. Patients | Patients Eligible | Final Analysis Estimate |
|---|---|---|---|---|
| ARISER | Rencarex vs PLC | 864 | CCRCC | Oct, 2012: negative |
| S-TRAC | Sunitinib vs. PLC | 720 | Predom. CCRCC | June, 2017 |
| SORCE | Sorafenib(1 or 3 yrs.) vs. PLC | 1656 | RCC: CCRCC or non-CCRCC | Accrual completed 2013 |
| ASSURE | Sorafenib, sunitinib, PLC | 1923 | RCC: CCRCC or non-CCRCC | April, 2016 |
| PROTECT | Pazopanib vs. PLC | 1500 | CCRCC or Predom. CCRCC | April, 2017 |
| EVEREST | Everolimus vs. PLC | 1170 | RCC: CCRCC or non-CCRCC | Oct, 2021 |
| ATLAS | Axitinib vs. PLC | 592 | Predom. CCRCC | May, 2019 |

Patients to be investigated: 8425

PLC – placebo; CCRCC – clear cell RCC; non-CCRCC - non-clear cell RCC

# Summary

- Current treatment paradigm with the various TKI's represents a significant advance in therapy for CCmRCC
- Continued development of following necessary:
    - Therapy vs. novel targets
    - Integration of immune therapy
    - Personalized approaches: use of data from RCC genome analysis
- Significant surgical advances past 10 years
- Evaluation of the role of post-surgical adjuvant therapy now underway
- Next major advances in therapy for RCC:
    - Emphasis on "personalized (precision) approaches"
    - Understanding tumor resistance
    - Development of combinations
    - Define a role for adjuvant therapy

# French Wine Auction: Can this be True?

**Élysée Palace to Put Wine Up for Bid**
**By STEVEN ERLANGER**
**Published: April 30, 2013**
PARIS — The dreaded phantasm of economic austerity has finally knocked its bony fingers on the door of the Élysée Palace, which announced on Tuesday that it would auction off 1,200 bottles of its finest wines, renew its cellar with “more modest” vintages and return the surplus to the state budget.

# Non-inferiority Clinical Trials

- Recent examples:

  COMPARZ: Sunitinib vs. Pazopanib

  Ongoing: Carmena Trial
- A non-inferiority trial tries to show a new intervention is not ‘inferior’ to a standard one, or, more precisely, is ‘not unacceptably worse’ than the intervention used as the control.
- This design does not demonstrate equivalence
- Non-inferiority is different from equivalence which attempts to demonstrate two treatments are the same or ‘not unacceptably different’ from each other. In a non-inferiority trial, by contrast, the aim is to show that a new therapy is not unacceptably worse than an older or standard one.
- Will this trial design using an open label approach involving surgery in one of the arms be informative?

  Possibly