Treatment of metastatic renal cell carcinoma (RCC): Present and future

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September 2014
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Biology of RCC

- New entities are coming (Vancouver classification)

  - Clear cell renal cell carcinoma
  - Multilocular clear cell renal cell neoplasm of low malignant potential
  - Papillary renal cell carcinoma
  - Chromophobe renal cell carcinoma
  - Hybrid oncocytic chromophobe tumour
  - Carcinoma of the collecting ducts of Bellini
  - Renal medullary carcinoma
  - MiT family translocation renal cell carcinoma
  - Xp11 translocation renal cell carcinoma
  - t(6;11) renal cell carcinoma
  - Carcinoma associated with neuroblastoma
  - Mucinous tubular and spindle cell carcinoma
  - Tubulocystic renal cell carcinoma
  - Acquired cystic disease–associated renal cell carcinoma
  - Clear cell papillary (tubulopapillary) renal cell carcinoma
  - Hereditary leiomyomatosis-associated renal cell carcinoma
  - Renal cell carcinoma, unclassified

Biology of RCC

- New entities are coming (Vancouver classification)
- Genomic classification has started…. 
Gene expression

- Clear Cell: 75%
- Papillary Type 1: 5%
- Papillary Type 2: 10%
- Chromophobe: 5%
- Oncocytoma: 5%

Genes:
- VHL
- cMET
- FH
- cMYC
- BHD

A lot of new genes: SEDT2, PBRM1, BAP 1, KMD61, NF2 …..
Some important genes on chromosome 3

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BAP1 and PBRM1 are mutually exclusive
BAP1 and PBRM1 are prognostic factors of survival

Biology of RCC

- New entities are coming (Vancouver classification)

- Genomic classification has started….

- Genomic signatures are coming
Development and Validation of a 16-gene signature in localized RCC

Development study*
Stage I-II-III ccRCC Surgery Alone
Cleveland Clinic (n=942)
RT-PCR analysis of 732 genes

Selection of Final Gene List and Algorithm

Standardization and Validation of Analytical Methods

Clinical Validation Study
Stage I-II-III ccRCC Surgery Alone
The French Consortium (n=626)
Test prediction of recurrence risk

* Rini et al., ASCO 2010

Escudier et al, ASCO 2014
Recurrence Score = - 0.45 x Vascular Group Score – 0.31 x Immune Response Score + 0.27 x Cell Growth/Division Score + 0.04 x Inflammation Score
Scaled to 0-100

Escudier et al, ASCO 2014
Recurrence Score quantified wide ranges of recurrence risks for each stage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>HR (95% CI)</th>
<th>$p$-value</th>
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<tbody>
<tr>
<td>RS</td>
<td>per 25 units</td>
<td>3.9 (2.6, 5.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Escudier et al, ASCO 2014
This score is better than current prognostic models

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>HR 95% CI</th>
<th>DF</th>
<th>LR ChiSq</th>
<th>P value</th>
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<tr>
<td>Leibovich Score</td>
<td>2</td>
<td>5.75</td>
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<td></td>
<td>0.057</td>
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<tr>
<td>Leibovich High vs Low</td>
<td>1.96</td>
<td>(0.72, 5.34)</td>
<td>2</td>
<td>5.75</td>
<td>0.057</td>
</tr>
<tr>
<td>Leibovich Int vs Low</td>
<td>2.59</td>
<td>(1.13, 5.95)</td>
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<tr>
<td>RS (per 25 units)</td>
<td>4.20</td>
<td>(2.76, 6.40)</td>
<td>1</td>
<td>41.01</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
What is the current treatment in mRCC?

- VEGF inhibition is key
  - In first line
  - In second line
  - In third line

- mTOR inhibition is active
  - In second and third line
  - In first line in poor risk patients

- Third line recommendations do exist
Risk assessment is important in mRCC: IMDC classification

- Six risk factors:
  - Karnofsky performance status < 80%
  - Haemoglobin < lower limit of normal
  - Time from diagnosis to treatment < 1 year
  - Corrected calcium > upper limit of normal
  - Platelets > upper limit of normal
  - Neutrophils > upper limit of normal
If patient has 0 factors: Favorable Prognosis

If patient has 1-2 factors: Intermediate Prognosis

If patient has 3-6 factors: Poor Prognosis
IMDC Prognostic Factors

Overall survival (%)

Time since start of treatment (months)

Favorable 43 mons
Intermediate 23 mons
Poor 8 mons

Log rank p<0.0001

Heng et al Lancet Oncology 2013
IMDC in non-clear cell RCC

Kroeger et al, Cancer 2013
IMDC in 2nd-line targeted therapy

- Favorable 35.3 mons
- Int 16.6 mons
- Poor 5.4 mons

Ko et al. GU Cancers Symposium 2014
Role of nephrectomy?
While expecting data from randomized trials...

3245 mRCC patients

- 676/1658 (41%) No nephrectomy
- 982/1658 (59%) Cytoreductive Nephrectomy

2569 (79%) patients with nephrectomy

EXCLUDED 1587 (49%) w/ nephrectomy prior to metastases

Heng et al, GU ASCO 2014
Cytoreductive nephrectomy benefit?

Overall Survival vs. Months Since Initiation of Targeted Therapy
IMDC prognostic factors are useful

<table>
<thead>
<tr>
<th># of IMDC Criteria Met</th>
<th>No CN OS months (N)</th>
<th>CN OS months (N)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92% (65/71) patients had CN, insufficient number to compare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22.5 (n=72)</td>
<td>30.4 (n=178)</td>
<td>0.0024</td>
</tr>
<tr>
<td>2</td>
<td>10.2 (n=143)</td>
<td>20.2 (n=253)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>10.0 (n=113)</td>
<td>15.9 (n=106)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>5.4 (n=103)</td>
<td>6.0 (n=67)</td>
<td>0.1664</td>
</tr>
<tr>
<td>5</td>
<td>3.6 (n=36)</td>
<td>2.8 (n=14)</td>
<td>0.5044</td>
</tr>
<tr>
<td>6</td>
<td>25% (3/12) patients had CN, insufficient number to compare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### ESMO 2014 guidelines

#### First line

<table>
<thead>
<tr>
<th>Histology and setting</th>
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</table>
COMPARZ study

- Sunitinib versus Pazopanib

- Locally advanced or metastatic RCC, with clear cell component histology
- No prior systemic therapy

n=876

Pazopanib 800 mg/day

Sunitinib 50 mg/day (Schedule 4/2)

Motzer et al, NEJM 2013
Sunitinib vs Pazopanib: COMPARZ

PFS independent

PFS investigator

OS

Response rate

Sunitinib vs Pazopanib: COMPARZ

PFS independent

PFS investigator

OS

Response rate
PISCES Design

Stratification factors:
• ECOG PS (0 vs 1)
• Metastatic sites (1 vs ≥ 2)

Period 1

1:1

n = 169

Pazopanib
800 mg OD

Sunitinib
50 mg 4/2\(^a\)

Period 2

Pazopanib
800 mg OD

Sunitinib
50 mg 4/2\(^a\)

Double-blind phase

Time (weeks)

0 10 12 22

Escudier et al, JCO 2014
Patient preference in PISCES

Pazopanib Preferred
Sunitinib Preferred
No Preference

Percent of Patients

Escudier et al, JCO 2014
<table>
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<th>Standard</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear-cell</td>
<td>Poor risk</td>
<td><strong>Temsirolimus [II, A]</strong></td>
<td>Sunitinib [II, B] Sorafenib [III, B]</td>
</tr>
</tbody>
</table>
## ESMO 2014 guidelines

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<th>Risk group</th>
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<th>Option</th>
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</thead>
<tbody>
<tr>
<td>Non Clear-cell</td>
<td></td>
<td></td>
<td>Temsirolimus [III, B]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sunitinib [III, B]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sorafenib [III, B]</td>
</tr>
</tbody>
</table>

Escudier , Porta, Schmidinger et al Ann Oncol 2014
When to stop therapy?

- What to do if CR occurs?
How to deal with CRs?

- Multicenter
- Retrospective analysis

- Patient developing CR
  - With VEGFR-TKI alone
  - With VEGFR-TKI plus local treatment

- Double radiological review
Patient characteristics

Table 1. Patient Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TKI alone</td>
<td>36</td>
<td>56</td>
</tr>
<tr>
<td>TKI plus local treatment</td>
<td>28</td>
<td>44</td>
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<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>60</td>
<td>94</td>
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<tr>
<td>Papillary</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td>64</td>
<td>100</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>36</td>
<td>56</td>
</tr>
<tr>
<td>Cytokine</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Local treatment: surgery/radiotherapy</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Prior TKI</td>
<td>2</td>
<td>3</td>
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<tr>
<td>TKI achieving CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>59</td>
<td>92</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>5</td>
<td>8</td>
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<tr>
<td>Prognostic group (French classification)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Intermediate</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>No. of metastatic sites before TKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>≥ 3</td>
<td>15</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; TKI, tyrosine kinase inhibitor.
CRs with TKIs alone

CR with VEGFR TKI alone (n=36)

- TKI discontinuation (n=16; 44%)
  - Relapse (n=7/16; 44%)

- TKI discontinuation after additional cycles (n=12; 33%)
  - Medianion of TKI after CR obtention = 3.9 months (range 1.06–32.5)
  - Relapse (n=4/12; 33%)

- TKI continuation (n=8; 22%)
  - Relapse (n=1/8; 13%)
Should we continue TKIs if CR?

- Only half of the patients relapse at 18 months
- Rechallenge is almost always active

Thus, current attitude in France:
- If CR with systemic treatment only, continue for 2-3 months to confirm CR and stop
- If CR with systemic + local treatment, stop after local treatment
When to stop therapy?

- What to do if CR occurs?
- Is it possible to propose drug holiday?
Drug holiday is feasible

- In selected patients
- Preliminary experience reported:
  - Sadeghi et al, Cancer. 2012 Jul 1;118(13):3277-82
  - Update at ASCO 2014 (Mital et al, ASCO 2014)
- 112 patients, with period of drug cessation > 3 months

Mital et al, ASCO 2014
Patient population

- 75% male/ 25% female
- Median age at diagnosis: 56
- 95% clear cell histology
- 19% pts. had received prior systemic therapy
- By Heng criteria, 48% pts. were favorable, 48% intermediate and 4% poor risk.

Mital et al, ASCO 2014
Results

- For the first treatment break: (n=112)
  - Median duration on first line: 13.5 months
  - Median duration of break: 16.8 months

- For second break (n=68)
  - Median duration on first line: 16.1 months
  - Median duration of break: 9.5 months

Mital et al, ASCO 2014
When to switch to second line?

- RECIST progression is not a good choice
- When VEGF inhibition is interrupted, tumor growth increases
Change in tumor growth rate

Ferté et al, Eur Urol 2013
Distribution of TGR in Sorafenib-treated patients according to treatment periods

Ferté et al, Eur Urol 2013
When to switch to second line?

- RECIST progression is not a good choice
- When VEGF inhibition is interrupted, tumor growth increases
- Thus, switching should be proposed if second line treatment is active enough (and available)….
  - Primary refractory disease
  - New site of disease associated with RECIST PD
  - Rapidly progressive disease
## ESMO 2014 guidelines

### Second line

<table>
<thead>
<tr>
<th>Histology and setting</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Pazopanib [II, A]</td>
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</table>

Escudier , Porta, Schmidinger et al Ann Oncol 2014
### ESMO 2014 guidelines

#### Second line

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<tbody>
<tr>
<td></td>
<td>Post TKIs</td>
<td><strong>Axitinib [I, B]</strong> Everolimus [II, A]</td>
<td><strong>Sorafenib [II, A]</strong></td>
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</table>

Escudier, Porta, Schmidinger et al Ann Oncol 2014
## ESMO 2014 guidelines

### Third line

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<th>Histology and setting</th>
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<th>Option</th>
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<tbody>
<tr>
<td>Clear-cell</td>
<td>Post 2 TKIs</td>
<td>Everolimus [II, A]</td>
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</tr>
<tr>
<td>Histology and setting</td>
<td>Risk group</td>
<td>Standard</td>
<td>Option</td>
</tr>
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<td>-----------------------</td>
<td>-----------------------------</td>
<td>------------------------</td>
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</tr>
<tr>
<td>Clear-cell</td>
<td>Post 2 TKIs</td>
<td>Everolimus [II, A]</td>
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<tr>
<td></td>
<td>Post TKI and mTOR</td>
<td>Sorafenib [I, B]</td>
<td>Other TKI [IV, B]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rechallenge [IV, B]</td>
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</table>
The future of RCC treatment

- Check point inhibitors

- cMET inhibitors
PD-1 Blockade as a Strategy for Cancer Immunotherapy

Naive T Cell

Activated T Cell

Exhausted T Cell

Reinvigorated T Cell

• T-cell clonal expansion
• Cytokine secretion
• Effector functions
• Tumour-directed migration

Signal 1

TCR
AG
MHC

CD28
B7

Signal 2

PD-1

PD-L1

BMS-936558

APC or Tumour cell

APC or Tumour cell

APC or Tumour cell


AG, antigen; APC, antigen presenting cell; MHC, major histocompatibility complex; PD-1, programmed death-1; TCR, T-cell receptor.
Promising efficacy in RCC

Figure 3. Percent change in tumor burden in RCC patients*

*Patients treated at the 10 mg/kg dose
Ongoing phase 3

Key Eligibility Criteria:
- Advanced or metastatic cc RCC
- Progression on or after most recent therapy and within 6 months of study enrollment
- One or 2 previous anti VEGF
- No mTOR inhibitor

Randomize

Nivolumab
3 mg/kg IV Q2 wk s

Everolimus
10 mg PO QD

n = 822

Primary endpoint: Overall Survival
First line data are limited

Archival nephrectomy specimen

Fresh tissue biopsy from a metastasis (baseline)

Fresh tissue biopsy from a metastasis (C2D8)

Arm 1
Nivolumab 0.3 mg/kg IV Q3W

Arm 2
Nivolumab 2 mg/kg IV Q3W

Arm 3
Nivolumab 10 mg/kg IV Q3W

Arm 4
Nivolumab 10 mg/kg IV Q3W

Treat until progression or intolerable toxicity

Treatment-naïve mRCC (clear cell) (n=24)
• KPS ≥70%

mRCC (clear cell) after antiangiogenic therapy (n=67)
• 1-3 prior therapies
• Progressed from most recent therapy within 6 months
• KPS ≥70%

Choueiri et al, ASCO 2014
Are treatment naive patients better candidates?

| | Previously treated (n=67) |
|---|---|---|---|
| | Nivolumab 0.3 mg/kg (n=22) | Nivolumab 2.0 mg/kg (n=22) | Nivolumab 10 mg/kg (n=23) |
| Objective response rate, n (%) ; (95% CI)<sup>a</sup> | 2 (9) (1.1-29.2) | 5 (23) (7.8-45.4) | 5 (22) (7.5-43.7) |
| Best response, n (%) | | | |
| Partial response (PR) | 2 (9) | 5 (23) | 4 (17) |
| Unconfirmed PR | 0 | 0 | 1 (4) |
| Stable disease (SD) | 5 (23) | 6 (27) | 8 (35) |
| Progression-free survival rate, % (95% CI) | 24 weeks | 18 (6-36) | 32 (14-51) | 49 (27-68) |

Choueiri et al, ASCO 2014
Are treatment naive patients better candidates?

<table>
<thead>
<tr>
<th></th>
<th>Previously treated (n=67)</th>
<th>Treatment-naïve (n=23)</th>
<th>All (N=90)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, n (%)(^a); (95% CI)</strong></td>
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<td></td>
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<tr>
<td>Nivolumab 0.3 mg/kg (n=22)</td>
<td>2 (9) (1.1-29.2)</td>
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<td>Nivolumab 2.0 mg/kg (n=22)</td>
<td>5 (22) (7.5-43.7)</td>
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<tr>
<td>Nivolumab 10 mg/kg (n=23)</td>
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<td><strong>Best response, n (%)</strong></td>
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<td>5 (23)</td>
<td>6 (27)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>Progression-free survival rate, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>18 (6-36)</td>
<td>32 (14-51)</td>
<td>45 (24-64)</td>
</tr>
</tbody>
</table>

No signal that first line efficacy will be better
Biomarker to select patients?

Chronic infection
Persistent antigen stimulation

Exhausted T cell
Immune Response

↓ Proliferation
↓ Cytokines (IFN-γ)
↓ Cytotoxicity
Biomarker to select patients?

- Proliferation
- Cytokines (IFN-γ)
- Cytotoxicity
Response according to PD-L1 status by IHC

- 56 evaluable fresh pretreatment biopsies:
  - Minimum of 100 tumor cells (DAKO assay; antibody 28-8)
  - PD-L1+ specimens defined by plasma membrane staining on ≥5% of tumor cells
  - 18 of 56 (32%) samples were PD-L1+

- 81% (22/27) of matched fresh specimens showed a <5% increase in tumor membrane PD-L1 expression from baseline to C2D8

Response rate:

<table>
<thead>
<tr>
<th></th>
<th>PD-L1(+)</th>
<th>PD-L1(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>0.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Response rate: 4/18 (22%) 3/38 (8%)
Monotherapy or combination?

**Previously treated or treatment naïve**

- **Arm N3 + I1**
  - Nivolumab 3 mg/kg IV +
  - Ipilimumab 1 mg/kg IV
  - Q3W x4

- **Arm N1 + I3**
  - Nivolumab 1 mg/kg IV +
  - Ipilimumab 3 mg/kg IV
  - Q3W x4

**Continuous**

- Nivolumab 3 mg/kg IV
- Q2W

**Including patients who received prior pazopanib**

- **Arm S Escalation**
  - Sunitinib 50 mg\(^b\) +
  - Nivolumab 2 mg/kg
  - (planned escalation to 5 mg/kg\(^c\)) Q3W

**Including patients who received prior sunitinib**

- **Arm P Escalation**
  - Pazopanib 800 mg/d +
  - Nivolumab 2 mg/kg
  - (planned escalation to 5 mg/kg\(^c\)) Q3W

**Amin et al, ASCO 2014**

- **Arm P Expansion**
  - Pazopanib + Nivolumab Q3W

**Hammers et al, ASCO 2014**

- **Arm S Expansion**
  - Sunitinib + Nivolumab Q3W
Combination Nivoliumab + Ipilimumab

+1st occurrence of new lesion

Time since first dose (weeks)

Nivo3 + Ipi1 (n=20)

Time since first dose (weeks)

6 0 12 18 24 30 36 42 48

Nivo1 + Ipi3 (n=22)

Change in baseline (%)

-100.00
-80.00
-60.00
-40.00
-20.00
0.00
20.00
40.00
60.00
80.00
100.00

Change in baseline target lesions (%)

N3 + I1 (n=20)  N1 + I3 (n=22)
Is there any ideal combination?

|                         | ARM S  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sunitinib + nivolumab</td>
</tr>
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Is there any ideal combination?

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c-Met pathway

WG Jiang et al. 2005
cMET expression in clear cell RCC

Good Prognosis CC  Poor Prognosis CC  Normal

HGF expression for probe 3082 7q21.1

MET expression for probe 4233 7q31

Courtesy of Bin Teh
Cabozantinib is active in RCC (n = 21)

*V=VEGF pathway inhibitor; M=mTOR inhibitor; C=cytokine; G=gemcitabine; O=other

Choueiri et al, ASCO 2012
METEOR study

Key Eligibility Criteria:
• Advanced or metastatic cc RCC
• Progression on or after most recent therapy and within 6 months of study enrollment
• One or 2 previous anti VEGF
• No mTOR inhibitor

n = 650

Primary endpoint: PFS
Conclusions

1. Biology of RCC is moving rapidly
2. VEGF inhibition remains key
3. mTOR inhibition is active in poor risk patients, and after VEGF failure
4. New strategies start to be better defined:
   - Drug holiday
   - Management of CR
   - Switching strategies
5. New pathways are under exploration and might change the next ESMO guidelines
THANK YOU........

My colleagues: Laurence ALBIGES, Yohann LORIOT, Christophe MASSARD, Karim FIZAZI

My research nurse: Stephane LEBORGNE

My assistant: Catherine CORNUAULT