First-line Therapy for Renal Cell Carcinoma: Defining New Standards of Care from Phase III Trials

Joaquim Bellmunt
University Hospital del Mar & Dana-Farber Cancer Institute/Brigham and Women’s Hospital
Harvard Medical School
Renal Cell Carcinoma Epidemiology

- Europe estimated numbers of new cancer cases and deaths (thousands) for 2012*
  - 115.2 new cases / 49.0 deaths

- US estimates for 2013
  - 65,000 new cases/13,000 deaths.
  - 3.5% of all cancers

- 7th most common cancer in men, 9th most common in women
  - 85% or more: clear cell RCC
  - 2/1 Male/Female ratio
  - Smoking, obesity and hypertension are established risk factors

- Median age at diagnosis: 65 years (2000-2004)
- Median age at death: 71 years (2000-2004)
- 5-year survival has improved:
  - 50.9% in 1975-1977; 70.6% in 2002-2008

Advanced/Metastatic RCC

- ~20% of patients present with metastatic disease
- ~30% of individuals treated for localised disease experience recurrence with distant disease

- Metastatectomy: in highly selected cases of single/oligo metastases
- Cytoreductive nephrectomy in patients who present with metastatic disease:
  - Associated with an OS benefit in the cytokine era
  - Appropriate patient selection (good PS, limited disease burden, no brain mets)
## EMA and FDA Regulatory Approved Drugs for RCC

<table>
<thead>
<tr>
<th>Approval</th>
<th>Agent</th>
<th>EMA and FDA Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Interleukin-2</td>
<td>Metastatic</td>
</tr>
<tr>
<td>2005</td>
<td>Sorafenib</td>
<td>Advanced</td>
</tr>
<tr>
<td>2006</td>
<td>Sunitinib</td>
<td>Advanced</td>
</tr>
<tr>
<td>2007</td>
<td>Temsirolimus</td>
<td>Advanced</td>
</tr>
<tr>
<td>2009</td>
<td>Bevacizumab (+ IFN-α)</td>
<td>Metastatic</td>
</tr>
<tr>
<td>2009</td>
<td>Everolimus</td>
<td>After failure of sunitinib or sorafenib</td>
</tr>
<tr>
<td>2009</td>
<td>Pazopanib</td>
<td>Advanced</td>
</tr>
<tr>
<td>2012</td>
<td>Axitinib</td>
<td>Failure of prior systemic therapy</td>
</tr>
</tbody>
</table>
Treatment options for patients with mRCC* have been revolutionised in a short period of time...


*mRCC: metastatic Renal Cell Carcinoma
Downstream effects of *VHL* mutation

**VHL Gene Mutation**

- VHL Protein

**VHL Complex Disrupted**

- **HIF-a Accumulation**
  - VEGF
  - PDGF

**Downstream effects**

- **Angiogenesis**
- **Paracrine Growth Stimulation**
- **Autocrine Growth Stimulation**

**VHL**
- CUL2
- Elongin B
- Elongin C
- Mutant α-domain
- Rbx1
Reprinted from Rini B et al. Lancet 2009;373(9669):1119-1132, with permission from Elsevier
Choice of targeted agent in first-line treatment
First-line treatment of RCC: overview of pivotal trials leading to approval

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Response vs. IFN-α, %</th>
<th>Median Progression-free Survival vs. IFN-α, mo</th>
<th>Median Overall Survival vs. IFN-α, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib vs. IFN-α¹</td>
<td>750</td>
<td>47 vs. 12</td>
<td>11 vs. 5 P &lt;0.01</td>
<td>26.4 vs. 21.8 P = 0.051</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α vs. IFN-α²</td>
<td>649</td>
<td>31 vs. 12</td>
<td>10.4 vs. 5.5 P &lt;0.01</td>
<td>23.3 vs. 21.3 P = 0.1291</td>
</tr>
<tr>
<td>Pazopanib vs. placebo³</td>
<td>233</td>
<td>30 vs. 3</td>
<td>11.1 vs. 2.8 P &lt;0.01</td>
<td>NA</td>
</tr>
<tr>
<td>Temsirolimus vs. IFN-α⁴ (Poor Risk)</td>
<td>626</td>
<td>9 vs. 5</td>
<td>5.5 vs. 3.1 P &lt;0.01</td>
<td>10.9 vs. 7.3 P &lt; 0.01</td>
</tr>
</tbody>
</table>

**Poor risk factors in advanced untreated RCC: MSKCC criteria**

<table>
<thead>
<tr>
<th>MSKCC Criteria</th>
<th>Risk Group by No. of Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky Performance Status &lt;80%</td>
<td>Favourable 0</td>
</tr>
<tr>
<td>Time from diagnosis to treatment with IFN-α &lt;12 months</td>
<td>Intermediate 1 or 2</td>
</tr>
<tr>
<td>Haemoglobin &lt;LLR</td>
<td>Poor 3-5</td>
</tr>
<tr>
<td>LDH &gt;1.5 x ULR</td>
<td></td>
</tr>
<tr>
<td>Corrected serum calcium &gt;10.0 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

IFN = interferon; KPS = Karnofsky PS; LDH = lactate dehydrogenase; LLR = lower limit of laboratory’s reference range; MSKCC = Memorial Sloan-Kettering Cancer Center; ULR = upper limit of laboratory’s reference range.

Phase III trial of temsirolimus and IFN-α: overall survival in poor prognosis RCC

**Median OS, months (95% CI)**

- IFN (n = 207): 7.3 (6.1–8.8)
- Temsirolimus (n = 209): 10.9 (8.6–12.7)
- Temsirolimus + IFN (n = 210): 8.4 (6.6–10.3)

Phase III trial sunitinib vs. IFN-α: PFS
independent central review

HR = 0.538 95% CI (0.439, 0.658)  
P < .00001

Sunitinib
Median: 11.0 months
(95% CI: 10.7–13.4)

IFN-α
Median: 5.1 months
(95% CI: 3.9–5.6)

Pazopanib vs. Sunitinib
Pazopanib vs. sunitinib for 1st-line treatment of clear-cell mRCC (COMPARZ)

Phase III study

Eligibility criteria:
- Metastatic RCC or mRCC
- Clear-cell histology
- No prior systemic therapy
- Measurable disease

N=1110

Randomisation

Pazopanib 800 mg/day

Sunitinib 50 mg/day (Schedule 4/2)

Primary Endpoint: PFS (non-inferiority)
Secondary Endpoints: OS, ORR, safety, QoL

Motzer R et al. ESMO 2012 oral presentation; Abst LBA8_PR;
Primary endpoint: progression-free survival (independent review)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557</td>
<td>8.4 mo (8.3, 10.9)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
<td>9.5 mo (8.3, 11.1)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 1.047 (0.898, 1.220)

The upper bound of 95% CI hazard ratio < 1.25 indicates pazopanib is non-inferior compared to sunitinib

Relative risk in adverse events AE occurrence ≥10% in either arm; 95% CI for RR does not cross 1

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair colour change</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Serum ALT increased</strong></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td></td>
</tr>
<tr>
<td><strong>Serum AST increased</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Taste alteration</td>
<td></td>
</tr>
<tr>
<td><strong>LDH increased</strong></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine increased</td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td></td>
</tr>
<tr>
<td><strong>Hand-foot syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
</tr>
<tr>
<td><strong>Serum TSH increased</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mucositis</strong></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of ESMO. Motzer R et al. ESMO 2012 oral presentation; Abst LBA8_PR
Potent VEGFr inhibitors- tivozanib and axitinib in first-line treatment
Reported potencies of tivozanib and axitinib compared to other TKIs

Approximate: adjustment in consideration of 2.3% BSA

More potent

Less potent

Tivozanib\(^2,3\) (AV-951)  Axitinib\(^*,1\) (AG13736)

Note: Reported potencies* are either biochemical- or cell-based IC\(_{50}\)s (nM); cell-based data are shown when available.

*Axitinib data for VEGFR-2 are from an ELISA assay; all other axitinib data are from an immunoprecipitation assay.

In addition, Chow LQM, Eckhardt SG reported an axitinib IC\(_{50}\) of 1.2, 0.25, and 0.29 nM for VEGFR-1, -2, and -3 (J Clin Oncol 2007;25(7):884-895).

1. Axitinib FDA Oncologic Drugs Advisory Committee briefing document. 12/7/2011;

Courtesy of Eisen T. 2012
Axitinib for first-line metastatic RCC: overall efficacy and pharmacokinetic analyses from a randomised Phase II study

**Study Design**

- **Lead-in period (Cycle 1)**
  - Axitinib 5 mg BID (4 wks)

- **During Cycle 1 (subset of patients)**
  - ABPM^c
  - 6-h PK sampling^d

**Randomisation criteria**^a^
- BP ≤150/90 mm Hg
- ≤2 concurrent anti-HTN medications
- No grade 3 or 4 axitinib-related toxicities
- No dose reduction

**Randomisation**^ RANDOMISE^ 1:1

- **Arm A**
  - Axitinib 5 mg BID + Axitinib dose titration^b^ (blinded therapy)

- **Arm B**
  - Axitinib 5 mg BID + Placebo dose titration^b^ (blinded therapy)

- **Arm C**
  - Axitinib ≤5 mg BID (no dose titration)

---

^a For at least 2 consecutive weeks

^b Titrated stepwise to 7 mg BID and then to a maximum of 10 mg BID if criteria for randomisation to dose titration were met

^c Ambulatory blood pressure monitoring performed at baseline and on Cycle 1 Days 4 and 15

^d 6-hr PK sampling performed on Cycle 1 Day 15

Rini B *et al.* J Clin Oncol 2012;30(15S):Abst 4503
**Clinical efficacy of axitinib for first-line metastatic RCC**

<table>
<thead>
<tr>
<th></th>
<th>Arm C Not Eligible for Dose Titration</th>
<th>Arms A + B Eligible for Dose Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong>&lt;sup&gt;a&lt;/sup&gt; (N = 213)</td>
<td><strong>mPFS, mo</strong>&lt;sup&gt;b&lt;/sup&gt; 14.5 (11.5, 17.4)</td>
<td><strong>mPFS, mo</strong> 14.5 (11.0, 19.3)</td>
</tr>
<tr>
<td><strong>ORR</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>48% (41%, 55%)</td>
<td>43% (34%, 53%)</td>
</tr>
<tr>
<td><strong>ORR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>48% (41%, 55%)</td>
<td>43% (34%, 53%)</td>
</tr>
<tr>
<td><strong>ORR</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>59% (49%, 70%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes 10 patients who discontinued study treatment prior to decision for dose titration

<sup>b</sup> As of April 30, 2012

CI, confidence interval; mPFS, median progression-free survival

Rini B *et al.* J Clin Oncol 2012;30(15S):Abst 4503
Late-Breaking Abstract No. 348

Axitinib versus sorafenib as first-line therapy in patients with metastatic renal cell carcinoma (mRCC)

TE Hutson\textsuperscript{1}, J Gallardo\textsuperscript{2}, V Lesovoy\textsuperscript{3}, S Al-Shukri\textsuperscript{4}, VP Stus\textsuperscript{5}, A Bair\textsuperscript{6}, B Rosbrook\textsuperscript{6}, P Bycott\textsuperscript{6}, J Tarazi\textsuperscript{6}, S Kim\textsuperscript{6}, NJ Vogelzang\textsuperscript{7}

\textsuperscript{1}GU Oncology Program, Baylor Sammons Cancer Center, Dallas, TX and US Oncology Research, Houston, TX; \textsuperscript{2}Instituto de Terapias Oncológicas, Providencia, Santiago, Chile; \textsuperscript{3}Kharkiv Regional Clinical Center of Urology and Nephrology, Kharkiv, Ukraine; \textsuperscript{4}Department of Urology, Saint-Petersburg State Medical University, Saint-Petersburg, Russian Federation; \textsuperscript{5}Department of Urology, Municipal Institution “Dnipropetrovsk’ Regional Clinical Hospital n.a. I.I. Mechnikov”, Dnipropetrovsk, Ukraine; \textsuperscript{6}Clinical Development, Pfizer Oncology, San Diego, CA; \textsuperscript{7}Comprehensive Cancer Centers of Nevada, Las Vegas, NV, and US Oncology Research, Houston, TX
Study Design*

Previously untreated metastatic RCC

Randomisation stratified by ECOG PS (0 vs. 1)

Axitinib 5 mg BID† (n=192)

Sorafenib 400 mg BID (n=96)

---

* ClinicalTrials.gov: NCT00920816.
† Titrated stepwise to 7 mg BID and then 10 mg BID in patients without grade 3 or 4 (CTCAE v3.0) axitinib-related AEs for a consecutive 2-week period, unless BP >150/90 mmHg.
Progression-free survival (IRC assessment)

Stratified by ECOG PS; assuming proportional hazards, HR <1 indicates a reduction in favour of axitinib and HR >1 indicates a reduction in favour of sorafenib.

IRC = independent radiology committee; mPFS = median progression-free survival

With permission by TE Hutson. Genitourinary Cancers Symposium 2013:Abstr LBA348
First-Line RCC Conclusions

- Sunitinib, pazopanib, bevacizumab (plus IFN) and tivozanib show improved PFS in phase III trials
- Pazopanib shows similar efficacy, a differentiated safety profile, and higher quality of life scores compared to sunitinib
- Tivozanib improves PFS compared to sorafenib
  - Benefit compared to other VEGFR TKIs undefined. Less OS
- Axitinib is active, but phase 3 trial in first line did not meet primary endpoint of superiority over sorafenib

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557</td>
<td>8.4 mo (8.3, 10.9)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
<td>9.5 mo (8.3, 11.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.047 (0.898, 1.220)</td>
<td></td>
</tr>
</tbody>
</table>
Exploring the role of second-line therapy after failure of anti-VEGF
Everolimus Phase III trial vs. placebo
Study Design and conduct

- N = 416

Stratification
- Prior VEGFR-TKI: 1 or 2
- MSKCC risk group: favourable, intermediate, or poor

Randomisation

2:1

Everolimus 10 mg/day + best supportive care (BSC)
(n = 277)

Upon Disease Progression

Study Unblinded

Placebo + BSC
(n = 139)

Safety interim analysis

Second interim analysis data cut-off: October 15, 2007, N = 410

End of double-blind analysis data cut-off: February 28, 2008

- 416 patients randomised between December 2006 and November 2007
- Analysis cut-off: February 28, 2008, based on 266 PFS events
- Second interim analysis based on cut-off: October 15, 2007, efficacy boundary crossed with 410 patients/191 PFS events, complete study unblinded on February 28, 2008

1. Motzer RJ et al. ASCO-GU 2009:Abst 278;
Everolimus vs. placebo: results

**Progression-free survival**

- **Central radiology review**

  - Hazard ratio = 0.33
  - 95% CI [0.25, 0.43]
  - Medians PFS
    - Everolimus: 4.90 mo
    - Placebo: 1.87 mo
  - Log rank $P$ value < 0.001

  - **Graph**: Progression-free survival (Everolimus, Placebo)

**Overall survival**

- Hazard ratio = 0.87
- 95% CI [0.65, 1.71]
- Kaplan-Meier Medians
  - Everolimus: 14.78 mo
  - Placebo: 14.39 mo
- Log rank $P$ value 0.177

  - **Graph**: Overall survival (Everolimus, Placebo)

**Number of Patients at Risk**

- **Everolimus**
  - Feb 2008 Data Cutoff: 277
  - Nov 2008 Data Cutoff: 267
  - Analysis on Feb 2008 Data Cutoff: 277
- **Placebo**
  - Feb 2008 Data Cutoff: 139
  - Nov 2008 Data Cutoff: 131
  - Analysis on Feb 2008 Data Cutoff: 139

**Number of Patients at Risk**

- **Everolimus**
  - Feb 2008 Data Cutoff: 277
  - Nov 2008 Data Cutoff: 277
  - Analysis on Nov 2008 Data Cutoff: 277
- **Placebo**
  - Feb 2008 Data Cutoff: 139
  - Nov 2008 Data Cutoff: 139
  - Analysis on Nov 2008 Data Cutoff: 139

**Adapted from Motzer RJ et al.** Lancet 2008;372(9637):449-456
Phase III trial of axitinib as 2nd-line therapy for mRCC

Patients after disease progression to 1 prior systemic first-line treatment (N=540)

- Primary endpoint: Compare PFS of patients receiving axitinib vs. sorafenib in mRCC after disease progression to 1 prior systemic first-line regimen containing 1 of the following agents: Sunitinib, bevacizumab + IFN-α, temsirolimus or cytokine(s)
- Secondary endpoint: OS, ORR, evaluate safety and tolerability, DR, compare symptoms severity

Accessed at www.clinicaltrials.gov
Axitinib vs. sorafenib 2nd-line Phase 3 study - progression-free survival

Stratified HR 0.665 (95% CI: 0.544-0.812)
P<0.0001 (log-rank, 1-sided)

Median PFS | 95% CI
---|---
Axitinib | 6.7 months | 6.3 – 8.6
Sorafenib | 4.7 months | 4.6 – 5.6

Adapted from Rini B et al. J Clin Oncol ASCO 2011;30(15_suppl):4503
Only prior sunitinib: mTOR inhibitor (everolimus) or VEGF TKI (axitinib) ?

<table>
<thead>
<tr>
<th></th>
<th>RECORD-1 (everolimus) (N=43, 13% of all pts)</th>
<th>AXIS (axitinib) (N=194, 26% of all pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>1-2%</td>
<td>11%</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>4.6(^1)</td>
<td>4.8</td>
</tr>
<tr>
<td>FKSI scores</td>
<td>Minimal impact vs. placebo(^2)</td>
<td>Similar to sorafenib(^3)</td>
</tr>
<tr>
<td>(disease-related symptoms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to AEs(^4)</td>
<td>14%</td>
<td>9%</td>
</tr>
</tbody>
</table>

4. Updated Package Inserts for everolimus and axitinib (accessed May 13 2012)
# Targeted agents selected toxicities

<table>
<thead>
<tr>
<th></th>
<th>VEGF TKI</th>
<th>Bevacizumab</th>
<th>mTOR inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/Asthenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea/mucositis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hand Foot Skin Reaction</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Thyroid abnormalities</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heme toxicities (minimal overall)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperlipidemia/Hyperglycemia</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea/pneumonitis</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis/bleed/CHF</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients with mRCC and PD on 1st-line sunitinib (N=512)

Stratification factors:
- Duration of sunitinib therapy (≤ or >6 mo)
- MSKCC risk group
- Histology (clear cell or non–clear cell)
- Nephrectomy status

Tensirolimus (mTOR) vs. sorafenib (VEGF TKI) as 2nd line: INTORSECT* Study Design

- Tensirolimus 25 mg IV weekly† (n=259)
- Sorafenib 400 mg oral BID† (n=253)

Primary end point: PFS (per IRC)

Treat until PD, unacceptable toxicity, or discontinuation for any other reason

*ClinicalTrials.gov Identifier: NCT00474786
†Dose reductions were allowed: temsirolimus (to 20 mg then 15 mg), sorafenib (to 400 mg/day then every other day).

Hutson TE et al. ESMO 2012
Progression-Free Survival (IRC Assessment)

Median PFS, months 95% CI
Temsiorimus 4.28 4.01, 5.43
Sorafenib 3.91 2.80, 4.21

P = 0.1933 (log-rank)
Stratified HR: 0.87
(95% CI: 0.71, 1.07)

CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; PFS, progression-free survival.

Courtesy of ESMO. Hutson TE et al. ESMO 2012
Overall survival

- **Sorafenib**
  - Median OS: 16.64 months
  - 95% CI: 13.55, 18.72

- **Temsirolimus**
  - Median OS: 12.27 months
  - 95% CI: 10.13, 14.80

**P = 0.014 (log-rank)**

**Stratified HR: 1.31**

(95% CI: 1.05, 1.63)

**Patients at risk, n**
- **Sorafenib**: 253, 158, 74, 34, 13, 0
- **Temsirolimus**: 259, 132, 54, 22, 8, 0

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Courtesy of ESMO. Hutson TE et al. ESMO 2012
Second-line option after progression on VEGF first-line treatment

- **PROGRESSION**
  - **Sunitinib or Pazopanib**
  - **mTOR (Everolimus)**
  - **VEGF TKI (Axitinib)**
Optimal scenario is exposure to both TKI and mTOR in 2nd and 3rd lines

1st Line

Sunitinib
Pazopanib

Progression

2nd Line

Axitinib
Everolimus

Progression

3rd Line

Everolimus
Axitinib

Longer progression free survival (and overall survival)
# Treatments for clear-cell mRCC

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Level 1*</th>
<th>&gt; Level 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Good or intermediate risk</td>
<td>Pazopanib</td>
<td>High-dose IL-2 Sorafenib</td>
</tr>
<tr>
<td>line</td>
<td></td>
<td>Sunitinib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab + IFN-α</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Poor risk</td>
<td>Temsirolimus (Sunitinib)**</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Prior cytokine</td>
<td>Sorafenib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>(or 3&lt;sup&gt;rd&lt;/sup&gt;)</td>
<td></td>
<td>Pazopanib</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Line</td>
<td>Prior VEGF-TKI</td>
<td>Everolimus or Axitinib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Prior mTOR</td>
<td>Axitinib</td>
<td></td>
</tr>
</tbody>
</table>


Adapted from Molina AM and Motzer RJ. Clin Genitourin Cancer 2008;6(Suppl 1):S7-S13;
Please also refer to Escudier B et al. Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 (Suppl 7):vii65-vii71
New Agents
MSKCC led Phase 3 of dovitinib (TKI258)* vs. dorafenib as third-line therapy for mRCC

Patients after disease progression to 1 prior VEGF and 1 prior mTOR systemic treatment (N=550)

Primary endpoint: Compare PFS
Secondary endpoint: OS, ORR, safety, quality of life

Dovitinib*
Sorafenib

1:1

*TKI258 is potent inhibitor of FGFR-1, -2, -3, VEGFR & PDGFR
FGF mediates escape from anti-angiogenesis therapy (Casanovas. Cancer Cell October 2005)

Accessed at www.clinicaltrials.gov
BMS-936558 (anti-PD-1, MDX-1106): A monoclonal antibody that increases immune surveillance against tumours

Figure 1. PD-1 blockade as a strategy for cancer immunotherapy

Ag, antigen; APC, antigen-presenting cell; MHC, major histocompatibility molecule; PD-1, programmed death-1; TCR, T-cell receptor

We have a bright sunrise on the horizon for immunotherapy trials in oncology

- PD1/PDL1 inhibitors
- AGS-003 (ADAPT Trial)
- IMA901/GM-CSF-301
  - Phase 3 trial
  - (HLA-A*02-positive)
  - HLA-A*02-positive (TUMAPs)
MSKCC led Phase 3 of anti-PD1 antibody (BMS) vs. everolimus following VEGF-targeted therapy for renal cell carcinomas

Patients after disease progression to 1 or 2 prior VEGF systemic treatment (N=860)

Primary endpoint: Compare Overall Survival
Secondary endpoint: PFS, ORR, safety, quality of life

Accessed at www.clinicaltrials.gov
Combinations
Assessing mTOR plus anti-VEGF combination therapy in first-line; INTORACT* Study Design

Patients with previously untreated advanced RCC (N=791)

Stratification factors:
- MSKCC risk group
- Nephrectomy status

April 2008–October 2012

1:1

Treat until PD, unacceptable toxicity, or discontinuation for any other reason

Temsorilimus + Bevacizumab (n=400)

Bevacizumab (+ interferon-alfa) (n=391)

*ClinicalTrials.gov Identifier: NCT00631371

MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma

Rini B et al. ESMO 2012
Progression-free survival

Median PFS, months 95% CI
TEM + BEV 9.1 8.1, 10.2
IFN + BEV 9.3 9.0, 11.2

1-sided $P=0.759$ (log-rank)
Stratified HR: 1.07
(95% CI: 0.89, 1.28)

Patients at risk, n
TEM + BEV 400 316 256 208 161 120 95 76 59 48 31 26 21 14 9 4 3 2 1 1
IFN + BEV 391 280 230 196 167 138 114 92 78 68 60 42 32 26 22 16 12 9 6 2 2

BEV, bevacizumab; CI, confidence interval; HR, hazard ratio; IFN, interferon alfa; IRC, Independent Review Committee; PFS, progression-free survival; TEM, temsirolimus

Courtesy of ESMO. Rini B et al. ESMO 2012
Conclusions (RCC)

- Standard of care for advanced RCC has dramatically changed in era of targeted therapy
- Both VEGF and mTOR are important therapeutic targets in RCC
- Standard front line therapy for most patients is VEGF TKI, likely pazopanib or sunitinib based on tolerability and QOL vs. minor efficacy difference
- Standard second line therapy for most patients is everolimus or axitinib
- Combination therapy appears to add toxicity but not necessarily efficacy
- Adjuvant therapy remains under investigation
Thank you!