The Therapeutic Landscape in Advanced Renal Cell Carcinoma

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What best describes the change in median overall survival (OS) for renal cell carcinoma (RCC) over the last 15 years?
Progress in the Treatment of RCC: Systemic Therapies

Cytotoxic chemotherapy experiments performed

High-dose Interleukin 2 (IL-2) FDA approved

Interferon-alpha (IFN-α) shows improved survival versus hormonal therapy

Sorafenib: First targeted therapy licensed in the US. Sunitinib followed, then both licensed in the EU

Temsirolimus and bevacizumab + IFN licensed

TARGET: first evidence of progression-free survival (PFS) benefit with targeted therapy

Everolimus and pazopanib licensed

Elucidation of Angiogenesis Pathways Has Led to the Development of Therapies That Affect the Vascular Endothelial Growth Factor (VEGF) Axis

CNS, central nervous system; WBC, white blood cells

As Well as the Mammalian Target of Rapamycin (mTOR) Pathway

Survival in Metastatic RCC (mRCC)

- Median OS has dramatically improved in mRCC:
  - Medical Research Council study with IFN (1999): 8.5 months
  - Crecy study (2000): 10 months
  - Pazopanib pivotal trial (2010): 22 months
  - COMPARZ study (2012): 29 months
  - SWITCH study (2014): 31 months

- Median OS mainly improved in good, intermediate and poor prognostic groups

# Survival According to Risk Groups

<table>
<thead>
<tr>
<th></th>
<th>MSKCC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>IKCWG&lt;sup&gt;2&lt;/sup&gt;</th>
<th>IMDC&lt;sup&gt;3&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Year</td>
<td>1999</td>
<td>2011</td>
<td>2013</td>
</tr>
<tr>
<td>Good</td>
<td>19.9</td>
<td>26.9</td>
<td>43.2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10</td>
<td>11.5</td>
<td>22.5</td>
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<tr>
<td>Poor</td>
<td>3.9</td>
<td>3.9</td>
<td>7.8</td>
</tr>
</tbody>
</table>

MSKCC, Memorial Sloan Kettering Cancer Center; IKCWG, International Kidney Cancer Working; IMDC, International Metastatic Renal-Cell Carcinoma Database Consortium

After treating a patient with metastatic RCC, at the time of disease progression on first-line VEGF tyrosine-kinase inhibitor (TKI), what would be your choice of second-line therapy?
EAU/ESMO Treatment Algorithm for mRCC Therapy$^{1,2}$


$^a$Level of evidence I, A (European Society for Medical Oncology [ESMO]) / 1b European Association of Urology [EAU]

$^b$Level of evidence II, A (ESMO) / 1b (EAU)
Relapse or stage IV medically or surgically unresectable predominant clear-cell histology

**1-st line**
- Clinical trial
- Pazopanib\(^1\)
- Sunitinib\(^1\)
- Bevacizumab + IFN-α\(^1\)
- Temsirolimus\(^a\)
- High-dose IL-2\(^b\)
  - Sorafenib\(^\dagger\)

\(^{\dagger}\) selected patients

**2-nd line**

Prior VEGF-TKI
- Clinical trial
- Axitinib\(^1\)
- Everolimus\(^1\)
- Sunitinib\(^2\text{A}\)
- Bevacizumab\(^2\text{A}\)
- Sorafenib\(^2\text{A}\)
- Temsirolimus\(^2\text{B}\)
- Pazopanib\(^3\)
- IL-2\(^2\text{B}\)

Prior cytokine
- Clinical trial
- Pazopanib\(^1\)
- Sunitinib\(^1\)
- Sorafenib\(^1\)
- Axitinib\(^1\)
- Bevacizumab\(^2\text{A}\)
- Temsirolimus\(^2\text{A}\)
- IL-2\(^2\text{B}\)

\(^a\) Category 1 for poor-prognosis patients; category 2B for selected patients of other risk groups
\(^b\) Patients with excellent PS and normal organ function

What is the preferred sequence of targeted agents?

1. TKI → mTOR → TKI

2. TKI → TKI → mTOR

3. TKI → TKI → TKI
Adaptive Resistance to VEGF Inhibition

Early phase: response to anti-VEGFR2 treatment
- No angiogenesis
- Hypoxia
- Cancer cells
- VEGF

Late phase: evasion to anti-VEGFR2 treatment
- Reactivation of angiogenesis
- VEGF
- FGFs and others
- Cancer cells
- Endothelial cells

What About Third-Line Therapy?
GOLD: Dovitinib vs Sorafenib After TKI and mTOR

- mRCC with clear-cell histology
- Measurable disease
- 2 prior therapies 1 TKI and 1 mTOR
- Progressive disease within 6 months of last targeted therapy

N = 564 1:1

Primary endpoint: PFS
Secondary endpoints: OS, ORR, safety, QoL

Dovitinib 500mg 5 days on/ 2 days off + best supportive care (BSC)

Sorafenib 400 mg twice daily + BSC

GOLD: Dovitinib Did Not Achieve Improved PFS Over Sunitinib (Independent Review)

Median PFS
- Dovitinib (n = 284): 3.7 months (95% CI: 3.5-3.9)
- Sorafenib (n = 286): 3.6 months (95% CI: 3.5-3.7)

HR: 0.86 (95% CI: 0.72-1.04) P = .063

PFS was not better between a VEGFR inhibitor Sorafenib and a dual FGFR-VEGFR inhibitor dovitinib

Cabozantinib Is Active in RCC (n = 21)

Number of prior systemic agents

- 1
- 2-4
- >4

Prior Tx:

† V(3), C, M, O
† V(3), M
† V, M, C(2), O
† V, M
† V, M, G, O

% Change from Baseline

‡ cPRs

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

METEOR: Phase III Study of Second-Line Treatment With Cabozantinib vs Everolimus in mRCC

Eligibility:
- mRCC with clear-cell component
- One prior VEGF-targeted therapy

- Primary endpoint: PFS
  - Study assumes median PFS of 5 months for everolimus and 7.5 months for cabozantinib. This provides for a HR of 0.67 and 90% power and requires 259 PFS events among the first 375 patients randomized.

- Secondary endpoints: OS, ORR
  - Assumes a median OS of 15 months for everolimus and 20 months for cabozantinib. This provides for a HR of 0.75 and 80% power and requires 413 events.

- Exploratory endpoints: Patient-reported outcomes, biomarkers, safety, pharmacokinetic (PK)

Would histopathology (papillary rather than clear cell) cause you to change your treatment recommendation for a patient with metastatic RCC?
Kidney Cancer Is Not a Single Disease

- Clear cell
- Papillary type 1
- Chromophobe
- Hybrid
- Oncocytoma
- Papillary type 2
- TFE3
- Angiomyolipoma
- Oncocytic
- Clear/chromophobe

Pathology and Gene Expression

Clear cell
- VHL

Papillary type 1
- Met

Chromophobe

Hybrid
- FLCN

Oncocytoma

Papillary type 2
- FH fumarate hydrase

TFE3
- TFE3, TFEB, MITF

Angiomyolipoma
- TSC1, TSC2

Oncocytic
- SDHB, SDHC, SDHD succinate dehydrogenase

Clear/chromophobe
- PTEN

True or false: Biomarkers that can assist in the determination of best sequence of therapies for metastatic RCC have recently been identified.
Treatment Will Be Guided by Genomics

Clear-cell RCC

Prognosis and Treatment Will Be Based on Genomic Classification

**BAP1 and PBRM1 Are Prognostic of OS Survival Shorter for BAP1 Mutated Tumors**

University of Texas Southwestern Medical Center (UTSW) cohort (n = 145)

BAP1 and PBRM1 mutations are largely mutually exclusive high-risk BAP1 mutated; favorable PBRM1-mutant

The Cancer Genome Atlas (TCGA) cohort (n = 327)

True or false: Novel immunotherapies will soon have an important role in the treatment of mRCC.
Targeted Immunotherapy Will Be Part of Our Treatment Strategy

CheckMate 214: Phase III Study of Nivolumab in Combination With Ipilimumab in First-Line mRCC

Eligibility:
- Patients with advanced RCC
- Treatment-naive

Primary endpoints: PFS, OS
Secondary endpoints: Overall response rate (ORR), adverse event rate

*Nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks for 4 doses then nivolumab 3 mg/kg

RAPID: Phase II Study of MPDL3280A as Monotherapy or in Combination With Bevacizumab vs Sunitinib in Untreated Advanced RCC

• **Eligibility**
  - Locally advanced or metastatic RCC with clear-cell and/or sarcomatoid component
  - Previously untreated with any systemic therapy
  - Karnofsky PS ≥70

**Randomization**

- MPDL3280A 1200 mg IV q3w + bevacizumab 15 mg/kg IV q3w
- MPDL3280A 1200 mg IV q3w
- Sunitinib 50 mg/day 4/2

**Primary endpoints:** PFS per RECIST v.1.1 via central ICR assessment

**Secondary endpoints:** PFS using investigator assessment per immune-related criteria, ORR, duration of response, OS, duration of response and PFS in patients progressing on sunitinib and MPDL alone arms who subsequently cross over to combination, safety, PK of MPDL3280A alone and in combination with bevacizumab

www.clinicaltrials.gov (NCT01984242)

CheckMate 025: Phase III Study of Nivolumab (Anti-PD-1) vs Everolimus in Locally Advanced Metastatic RCC With Prior Anti-Angiogenic Therapy\textsuperscript{1,2}

**Eligibility:**
- Advanced or metastatic RCC with clear-cell component
- Received prior anti-angiogenic therapy
- Progression on or after most recent therapy (within 6 months of study enrolment)
- Karnofsky PS ≥70

**Randomization:** 1:1

- **Nivolumab**
  - 3 mg/kg IV every 2 weeks
- **Everolimus**
  - 10 mg orally daily

**Treatment until disease progression or unacceptable toxicity**

**Primary endpoint:** OS
- HR of 0.76 (32% increase in median OS) required for positive study outcome
- Assumes a 4-month improvement in median OS from 14 to 18 month

**Secondary end points:** PFS, ORR, duration of response, duration of OS in PDL1-positive vs PDL1-negative subgroups, safety, disease-related symptom progression rate

Upcoming Results of RCC Clinical Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial Name</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>2015</td>
<td>SORCE</td>
<td>IMPRINT</td>
<td>proteasome</td>
<td>pembrolizumab</td>
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<tr>
<td>2016</td>
<td>ASSURE</td>
<td>PROTECT</td>
<td>S-TRAC</td>
<td>Axitinib</td>
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<tr>
<td>2017</td>
<td>RAPID</td>
<td>MPDL3280 +/- bevacizumab</td>
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<td>Adjuvant</td>
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<tr>
<td>2018</td>
<td>METEOR</td>
<td>TRC105 + axitinib</td>
<td>CheckMate 025 (nivolumab vs everolimus)</td>
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<tr>
<td>2018</td>
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Nephrectomy

1st Line

2018

Adjuvant

2015 2016 2017 2018