Targeted and immunotherapy in RCC
Treatment options

- Surgery (radical VS partial nephrectomy)
- Thermal ablation therapy
- Surveillance
- Immunotherapy
- Molecular targeted therapy
Molecular targeted therapy
Targeted therapy

- Antagonists of the Vascular Endothelial Growth Factor Pathway (VEGF)

- Inhibitors of the Mammalian Target of Rapamycin (mTOR)
VHL

- Short arm of chromosome 3
- Von Hippel-Lindau protein (VHL)
- Association with elongins B and C and Cullin 2 (CUL2) → protein complex
- Delivery to and degradation of certain cellular proteins by the ubiquitin system
Proteins targeted for ubiquitin-mediated degradation: hypoxia-inducible factor (HIF)

Cells with intact VHL function: HIF levels are primarily controlled by ambient oxygen tension
In normoxic conditions:

- Hydroxylation of key proline residues on HIF
- Association with the protein complex
- Degradation
- Hypoxia impedes prolyl hydroxylation of HIF and its subsequent degradation

- Mutations in VHL interfere with its binding to either HIF or elongin/CUL2 → HIF accumulation even under normoxia
Upregulation of proangiogenic and growth factors:

- VEGF
- Platelet-derived growth factor (PDGF)
- Transforming growth factor-α
- Glucose transporter 1 (Glu1)
- Erythropoietin (EPO)
**VHL Protein: Normal and Aberrant Function**

**Normoxia and Normal VHL Protein Function**
- VHL Protein
- hp
- HIFα
- Ubiquitin attachment
- Proteasome
- HIFα degradation

**Hypoxia or Abnormal VHL Protein Function**
- VHL Protein
- HIFα
- Constitutively expressed HIFα translocates into the nucleus
- Induction of hypoxia-inducible genes (e.g., VEGF, PDGF)

HIF = hypoxia-inducible factor; hp = hydroxyproline; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor.
Inhibitors of the Mammalian Target of Rapamycin:

- mTOR: key intracellular protein
- Component of several signaling cascades $\rightarrow$ growth factors
- Regulating translation and stability of HIF-1$^\alpha$
- mTOR inhibitors: block in HIF-1$^\alpha$ translation
Antagonists of the Vascular Endothelial Growth Factor Pathway

- **Bevacizumab (Avastin):**
  - Humanized monoclonal antibody against circulating VEGF
  - First VEGF pathway antagonist used in clinical trials
AVOREN study: Bevacizumab + IFN-α VS INF-α monotherapy

• Overall response was higher in the combination group

• Median PFS increased from 5.4 m with IFN-α to 10.2 m with bevacizumab + IFN-α

• No benefit was seen in poor-risk patients

• Overall toxicity was greater for combination group

Number of patients at risk
Placebo plus interferon alfa 322 137 59 15 0 0
Bevacizumab plus interferon alfa 327 196 107 18 0 0
### Table 7.1: MSKCC (Motzer) criteria [87]*

<table>
<thead>
<tr>
<th>Risk factors**</th>
<th>Cut-off point used</th>
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</thead>
<tbody>
<tr>
<td>Karnofsky PS</td>
<td>&lt; 80</td>
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<tr>
<td>Time from diagnosis to treatment</td>
<td>&lt; 12 months</td>
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<tr>
<td>Haemoglobin</td>
<td>&lt; Lower limit of laboratory reference range</td>
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<tr>
<td>LDH</td>
<td>&gt; 1.5 times the upper limit of laboratory range</td>
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<tr>
<td>Corrected serum calcium</td>
<td>&gt; 10.0 mg/dL (2.4 mmol/L)</td>
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</table>

* The Metastatic Renal Cancer Database Consortium (IMDC) risk model is also widely used in this setting [326].
** Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three or more risk factors.

LDH = lactate dehydrogenase; PS = performance status.
Bevacizumab is not widely used as a single agent in the initial therapy for mccRCC

Role in patients who have failed standard therapy in combination with interferon
Tyrosine kinase inhibitors (TKI)

- **Sunitinib (sutent):**
  - Oral tyrosine kinase (TK) inhibitor
  - Anti-tumour and anti-angiogenic activity
  - Simultaneous targeting of VEGF and PDGF pathways is likely to act synergistically
  - Widely used in the initial management of mccRCC
Sunitinib VS INF-α: (first line monotherapy)

- Significantly longer PFS for sutent
- Overall survival was greater
EFFECT trial: Sunitinib 50 mg/day (4 weeks on/2 weeks off) VS continuous uninterrupted dose of 37.5 mg/day

- Median time to progression (TTP) with sunitinib 50 mg was numerically longer than the 37.5 mg arm (9.9 months vs. 7.1 months)
- No significant differences in OS
- Toxicity was comparable in both arms
Side effects:

- Gastrointestinal events: diarrhea
- Dermatologic manifestations: rash, hand-foot syndrome
- Constitutional symptoms: fatigue and asthenia
- Hypertension
- Bone marrow suppression
- Hypothyroidism
- **Sorafenib (Nexavar):**

- Oral multikinase inhibitor
Sorafenib VS INF- Alfa:

- In patients with previously untreated mRCC, sorafenib was not superior to IFN-α.
Although sorafenib is FDA-approved for the treatment of advanced kidney cancer, its precise role remains to be determined.
- **Pazopanib (Votrient):**
  - oral angiogenesis inhibitor
Pazopanib VS placebo in treatment-naïve mRCC patients and cytokine-treated patients:

Significant improvement in PFS and tumor response was observed.
COMPARZ trial: **Pazopanib VS sunitinib**

- Pazopanib was not associated with significantly worse PFS or OS compared to sunitinib
- Different toxicity profiles (increased incidence of hepatotoxicity with pazopanib)
- QoL was better with pazopanib
- Pazopanib better tolerated than sunitinib by the majority of patients
Axitinib (Inlyta):

- Oral selective second-generation inhibitor of VEGFR-1, -2, & -3
AXIS trial: Axitinib VS sorafenib as a second line treatment:

- Improved PFS compared to sorafenib
- Second-line setting in patients with advanced RCC
- Axitinib is not approved for first-line therapy
- **Cabozantinib:**
  - Oral inhibitor of tyrosine kinases
METEOR (Phase 3)
- 650 patients with clear cell RCC who have received and progressed on at least one VEGFR TKI
- Randomized, open-label trial; no crossover permitted
- ~200 sites predominantly in W. Europe, North America, Australia

Enrollment completed in November 2014

Endpoints:
- **Primary:** Progression-Free Survival, conducted once 259 events from the first 375 patients enrolled have occurred
  - Statistical modeling assumptions for primary endpoint: 5.0 months for everolimus, 7.5 months for cabozantinib
  - Designed to provide 90% power to detect a hazard ratio (HR) of 0.667 with a two-sided alpha of 0.05
- **Secondary:** Overall Survival and Objective Response Rate

Study initiated in May 2013, FPI August 2013.
**METEOR trial: Cabozantinib VS everolimus in patients with ccRCC failing one or more VEGF-targeted therapy:**

- Cabozantinib delayed PFS compared to everolimus in VEGF targeted therapy refractory disease by 42%
- OS results show a strong trend favoring cabozantinib
mTOR inhibitors

- Everolimus (Afinitor):
  - Oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease
RECORD-1 study: **Everolimus + best supportive care (BSC)** vs. **placebo + BSC** in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF targeted therapy):

Initial data showed a median PFS of **4.0 months** vs. **1.9 months** for everolimus and placebo, respectively.
Final overall survival analysis for the RECORD-3 study of first-line everolimus followed by sunitinib vs. first-line sunitinib followed by everolimus in mRCC

higher median PFS for first-line treatment in the sunitinib group

Sunitinib Still Standard First-Line Treatment in Metastatic RCC
- Temsirolimus

- Temsirolimus is not recommended in patients with VEGF TKI refractory disease
INTORSECT trial: **Temsirilimus** vs. **sorafenib** in patients who had previously failed sunitinib

- No benefit in PFS was observed
- Significant OS benefit for sorafenib
Immunotherapy
IFN-α combined with bevacizumab:

- Bevacizumab + IFN-α increased response rates and PFS in first-line therapy compared with IFN-α monotherapy
- **Interleukin-2:**
  - Complete and durable responses have been achieved with high-dose bolus IL-2
  - The toxicity of IL-2 is substantially greater than that of IFN-α
Immunology

Foreign (or self) antigen

Antigen Presenting Cell (APC)

Antigen-specific T cell receptor

MHC/antigen complex

CD4 helper T cell

Cytokines

B Cell

CD8 cytotoxic T cell

Infected cells (displays foreign T cell epitope on its surface) or self (i.e., loss of self tolerance)

Whole self antigen

Production of pathogenic self-reactive antibodies

Free pathogen clearance by specific antibody

Cell death
Signal 1

Signal 2

Antigen
PD-1 : programmed cell death protein 1
PD-L1 : Programmed death-ligand 1
PD-1 : programmed cell death protein 1
PD-L1 : Programmed death-ligand 1
Co-stimulation via CD28: T-cell activation
CTLA-4 blocks co-stimulation: No T-cell activation
Ipilimumab blocks CTLA-4: T-cell activation

Adapted from Lebbé et al. ESMO 2008
Binding of PD-L1 to PD-1 receptor downregulates T-cell effector functions

Antibody-mediated blockage of the binding of PD-L1 protein to PD-1 receptor restores T-cell effector functions
Immune checkpoint blockade:

- Monoclonal antibodies target and block:
  - Inhibitory T-cell receptor Programmed Death-1 (PD-1)
  - Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)-signalling

- To restore tumor specific T cell immunity
- Pembrolizumab and **nivolumab** target the PD-L1 receptor

- Atezolizumab and durvalumab block the ligand, PD-L1

- Ipilumimab targets CTLA-4
Nivolumab (opvido)

- Humanized IgG4 anti-PD-1 monoclonal antibody
Nivolumab (opvIdo)

CheckMate-025 Study

Patients with ADVANCED RCC previously treated with a prior anti-angiogenic systemic therapy*

OPDIVO monotherapy 3 mg/kg IV every 2 weeks (n=410)

EVEROLIMUS 10 mg qd po (n=411)

PRIMARY ENDPOINT OVERALL SURVIVAL

TREATMENT CONTINUED UNTIL DISEASE PROGRESSION OR UNACCEPTABLE TOXICITY

Study Type: Multicenter, Open-label, Randomized
CheckMate-025 study

- **Nivolumab**:
  - No. of Patients: 410
  - Median Overall Survival (95% CI): 25.0 (21.8–NE) months
  - No. of Deaths: 183

- **Everolimus**:
  - No. of Patients: 411
  - Median Overall Survival (95% CI): 19.6 (17.6–23.1) months
  - No. of Deaths: 215

Hazard ratio, 0.73 (98.5% CI, 0.57–0.93), P=0.002

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 months</td>
<td>305</td>
<td>213</td>
</tr>
<tr>
<td>24 months</td>
<td>275</td>
<td>139</td>
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<td>12 months</td>
<td>337</td>
<td>115</td>
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<tr>
<td>6 months</td>
<td>359</td>
<td>73</td>
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<td>3 months</td>
<td>389</td>
<td>29</td>
</tr>
<tr>
<td>1 month</td>
<td>410</td>
<td>3</td>
</tr>
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</table>

No events observed at 1 month for Everolimus group.
CheckMate-025 study

### A Subgroup Analyses of Overall Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Nivolumab no. of events/total no.</th>
<th>Everolimus no. of events/total no.</th>
<th>Unstratified Hazard Ratio for Death (95% CI)</th>
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<tbody>
<tr>
<td>Overall</td>
<td>183/410</td>
<td>215/411</td>
<td>0.76 (0.62–0.92)</td>
</tr>
<tr>
<td>MSKCC prognostic score</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>45/145</td>
<td>52/148</td>
<td>0.89 (0.59–1.32)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>101/201</td>
<td>116/203</td>
<td>0.76 (0.58–0.99)</td>
</tr>
<tr>
<td>Poor</td>
<td>37/64</td>
<td>47/60</td>
<td>0.47 (0.30–0.73)</td>
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<tr>
<td>Previous antiangiogenic regimens</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>128/294</td>
<td>158/297</td>
<td>0.71 (0.56–0.90)</td>
</tr>
<tr>
<td>2</td>
<td>55/116</td>
<td>57/114</td>
<td>0.89 (0.61–1.29)</td>
</tr>
<tr>
<td>Region</td>
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<td></td>
</tr>
<tr>
<td>United States or Canada</td>
<td>66/174</td>
<td>87/172</td>
<td>0.66 (0.48–0.91)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>78/140</td>
<td>84/141</td>
<td>0.86 (0.63–1.16)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>39/96</td>
<td>44/98</td>
<td>0.78 (0.51–1.20)</td>
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<tr>
<td>Age</td>
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</tr>
<tr>
<td>&lt;65 yr</td>
<td>111/257</td>
<td>118/240</td>
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<tr>
<td>≥65 to &lt;75 yr</td>
<td>53/119</td>
<td>77/131</td>
<td>0.64 (0.45–0.91)</td>
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<td>≥75 yr</td>
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<td>1.23 (0.66–2.31)</td>
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<tr>
<td>Sex</td>
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<td></td>
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</tr>
<tr>
<td>Female</td>
<td>48/95</td>
<td>56/107</td>
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<tr>
<td>Male</td>
<td>135/315</td>
<td>159/304</td>
<td>0.73 (0.58–0.92)</td>
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</table>
CheckMate-025 study

<table>
<thead>
<tr>
<th>MSKCC risk group</th>
<th>Nivolumab</th>
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<th>Everolimus</th>
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<th>ORR Difference</th>
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<tbody>
<tr>
<td></td>
<td>ORR, %</td>
<td>95% CI</td>
<td>ORR, %</td>
<td>95% CI</td>
<td>(95% CI)</td>
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<tr>
<td>Favorable</td>
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<td>17-32</td>
<td>8</td>
<td>4-13</td>
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<tr>
<td>Intermediate</td>
<td>25</td>
<td>19-32</td>
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<td>2-9</td>
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<tr>
<td>Poor</td>
<td>27</td>
<td>17-38</td>
<td>3</td>
<td>0.3-9</td>
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<table>
<thead>
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<th>No. of sites of metastases</th>
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<th>Everolimus</th>
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<th>ORR Difference</th>
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<tbody>
<tr>
<td></td>
<td>ORR, %</td>
<td>95% CI</td>
<td>ORR, %</td>
<td>95% CI</td>
<td>(95% CI)</td>
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<tr>
<td>1</td>
<td>32</td>
<td>22-45</td>
<td>9</td>
<td>3-18</td>
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<tr>
<td>≥2</td>
<td>24</td>
<td>19-29</td>
<td>5</td>
<td>3-8</td>
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<table>
<thead>
<tr>
<th>Bones metastases</th>
<th>Nivolumab</th>
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<tr>
<td></td>
<td>ORR, %</td>
<td>95% CI</td>
<td>ORR, %</td>
<td>95% CI</td>
<td>(95% CI)</td>
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<tr>
<td>Yes</td>
<td>26</td>
<td>17-38</td>
<td>6</td>
<td>2-14</td>
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<tr>
<td>No</td>
<td>25</td>
<td>20-30</td>
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<thead>
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<th>Liver metastases</th>
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<tr>
<td></td>
<td>ORR, %</td>
<td>95% CI</td>
<td>ORR, %</td>
<td>95% CI</td>
<td>(95% CI)</td>
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<td>21</td>
<td>14-30</td>
<td>3</td>
<td>1-10</td>
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<td>27</td>
<td>22-32</td>
<td>6</td>
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<th>Prior therapy</th>
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<th>Everolimus</th>
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<tr>
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<td>95% CI</td>
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<td>95% CI</td>
<td>(95% CI)</td>
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<tr>
<td>Pazopanib</td>
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<table>
<thead>
<tr>
<th>Months of first-line therapy</th>
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<th>Everolimus</th>
<th></th>
<th>ORR Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ORR, %</td>
<td>95% CI</td>
<td>ORR, %</td>
<td>95% CI</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>26</td>
<td>18-35</td>
<td>5</td>
<td>2-11</td>
<td></td>
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<tr>
<td>≥ 6</td>
<td>25</td>
<td>20-30</td>
<td>5</td>
<td>3-9</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior anti-angiogenic therapies</th>
<th>Nivolumab</th>
<th></th>
<th>Everolimus</th>
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<th>ORR Difference</th>
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<tr>
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<td>95% CI</td>
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<td>(95% CI)</td>
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<tr>
<td>1</td>
<td>24</td>
<td>20-29</td>
<td>5</td>
<td>3-9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>19-38</td>
<td>5</td>
<td>2-11</td>
<td></td>
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</tbody>
</table>

Higher levels of PD-L1 expression are associated with poorer survival. A benefit was observed with nivolumab irrespective of PD-L1 expression.
CheckMate-025 study

Kaplan–Meier Curve for Progression-free Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
<th>No. of Progression Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>410</td>
<td>4.6 (3.7–5.4)</td>
<td>318</td>
</tr>
<tr>
<td>Everolimus</td>
<td>411</td>
<td>4.4 (3.7–5.5)</td>
<td>322</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.88 (95% CI, 0.75–1.03)  
P = 0.11

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>410</th>
<th>230</th>
<th>145</th>
<th>116</th>
<th>81</th>
<th>66</th>
<th>48</th>
<th>29</th>
<th>11</th>
<th>4</th>
<th>0</th>
<th>0</th>
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</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Everolimus</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Nivolumab

- Durable responses
- Well tolerated
- No progression free survival benefit despite OS advantage
### Summary of evidence

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in metastatic RCC.</td>
<td>1b</td>
</tr>
<tr>
<td>IL-2 monotherapy may have an effect in selected cases (good PS, ccRCC, lung metastases only).</td>
<td>2</td>
</tr>
<tr>
<td>IL-2 has more side-effects than IFN-α.</td>
<td>2-3</td>
</tr>
<tr>
<td>High dose IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL-2.</td>
<td>1b</td>
</tr>
<tr>
<td>Bevacizumab plus IFN-α is more effective than IFN-α treatment-naïve, low-risk and intermediate-risk tumours.</td>
<td>1b</td>
</tr>
<tr>
<td>Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy.</td>
<td>1b</td>
</tr>
<tr>
<td>Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy.</td>
<td>1b</td>
</tr>
<tr>
<td>Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.</td>
<td>1b</td>
</tr>
</tbody>
</table>
Therapeutic strategies and recommendations (EUA 2016)

- Therapy for treatment-naïve patients with clear-cell mRCC:
  - Sunitinib and bevacizumab plus IFN-α as first-line treatment options
  - COMPARZ study demonstrated that pazopanib and sunitinib have similar efficacy and different toxicity profiles ➔ another first-line option
Sequencing targeted therapy:

- Following progression of disease with one or more lines of VEGF-targeted therapy:
  - Nivolumab and cabozantinib should be considered a new standard of care in patients of all risk categories.
Treatment after progression of disease with mTOR inhibition:

- Limited data addressing this issue
- In view of the efficacy of VEGF-targeted therapy in renal cancer, a switch to VEGF-targeted therapy is advised
Treatment after two VEGF-targeted therapies:

- Nivolumab and cabozantinib as third-line treatment upon failure of 2 VEGF-targeted therapies
Combination of targeted agents:

- VEGF targeted therapy and mTOR inhibitors
- Results have all been negative
- No combinations of targeted agents are currently recommended
Non-clear-cell renal cancer:

- No standard treatment available
- Patients should be treated in the framework of clinical trials
Figure 7.1: Recommendations for patients with metastatic ccRCC who have failed one or more lines of VEGF targeted therapy

- **Recommend with OS advantage**
- **Recommend without OS**
- **Recommend if other options not available**

**First line**
- Sunitinib
- Pazopanib

**Second line**
- Nivolumab
- Cabozantinib
- Cabozantinib

**Third line**
- Axitinib
- Nivolumab
- Everolimus-axitinib

**Fourth line**
- Everolimus

4th line therapy should focus on drugs not previously given, especially nivolumab or cabozantinib.
Sorafenib no more indicated

- OS advantage > Everolimus
- Impressive PFS and trend towards OS advantage
- First TKI to have superior PFS compared with everolimus

>> Sorafenib (PFS)
= Sorafenib (OS)

Everolimus > placebo in terms of PFS
Everolimus < cabozantinib and nivolumab
Nivolumab
Significant OS advantage
Good tolerability

Cabozantinib
Significant PFS advantage

Axitinib

Everolimus
Second line

Everolemus should not be recommended (side effects)
using both drugs in sequence in the second and third lines following VEGF targeted therapy

- **Sunitinib**
  - **Nivolumab**
    - **Cabozantinib**
      - **Nivolumab**
        - **Axitinib**
          - **Everolimus**
        - **Everolimus/axitinib**
      - **Cabozantinib**
    - **Axitinib**
      - **Everolimus**
      - **Nivolumab**
  - **Everolimus**

**Recommendations**:
- Recommend with OS advantage
- Recommended without OS
- Recommended if other options not available

**Fourth-line therapy** should focus on drugs not previously given, especially nivolumab or cabozantinib.
Nivolumab versus Cabozantinib: Comparing Overall Survival in Metastatic Renal Cell Carcinoma

- OS for nivolumab will remain superior for longer treatment timeframes in clinical practice as opposed to cabozantinib given the reports on tolerability issues with this latter treatment.
Using both drugs in sequence in the second and third lines following VEGF targeted therapy:

- **Sunitinib, Pazopanib** → **Nivolumab**
  - **First line**
  - **Second line**
    - Cabozantinib
    - Axitinib
    - Everolimus
  - **Third line**
    - Cabozantinib
    - Nivolumab
    - Everolimus/axitinib
  - **Fourth-line therapy** should focus on drugs not previously given, especially nivolumab or cabozantinib

- **Recommend with OS advantage**
- **Recommended without OS**
- **Recommended if other options not available**
Neoadjuvant therapy in the management of locally advanced renal cell carcinoma:

- Primary tumor shrinkage, with the majority of the effect occurring early in the treatment phase
- Downstage unresectable tumors and potentially ease surgical resection
- In select patients, it may facilitate nephron-sparing approaches
- Lacks consistent benefit in patients with IVC tumor thrombus
At present, we do not recommend the routine use of neoadjuvant therapy in patients who otherwise have resectable disease.