Pieter de Mulder Lecture

From cytokines to targeted therapies to immunotherapy: 30 years of progress in advanced RCC

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Rome, Italy
Born: May 28th 1949 and Died April 7th 2007

Pieter de Mulder
Phase II Trials prior to modern therapies for RCC at MSKCC


**High-Dose IV Bolus IL-2 Therapy: (n=255; 7 clinical trials)**

- FDA Approval 1992
- 15% RR with durable responses in a small % of patients
- MDR - 54 months
- But: **Significant toxicity and cost!**
- Application limited to selected patients treated at a few centers

6 PR with response durations of 43+ to 85+ mos. Median survival 15.8 mos

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Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in advanced RCC

- September 1987 until March 1989
- Interleukin-2 administered $3 \times 10^6$ U/m$^2$/day CI (or 9 mU, international unit) on days 1-5, 13-17, 21-24, and 28-31 (18 doses per cycle).
- Patients on the LAK treatment arm underwent leukapheresis after 1st IL-2 infusion on days 8-10 and LAK cell reinfusion on days 13-15

Lower dose but given by continuous infusion (CI) rather than by bolus as is current regimen

Lam TM et al., Cancer 1995 Sep 1;76(5):824-32
Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in advanced RCC (n=71)

No differences between treatment arms with regard to response ($p = 0.61$)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td>45</td>
<td>47</td>
<td>33</td>
<td>68</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td>CR</td>
<td>CR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td>IL-2</td>
<td>IL-2+LAK</td>
<td>IL-2</td>
<td>IL-2</td>
</tr>
<tr>
<td><strong>Prior therapy</strong></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sites of disease</td>
<td></td>
<td>Lung</td>
<td>Lung</td>
<td>Lung, skin</td>
<td>Lung, mediastinum</td>
</tr>
<tr>
<td>Duration of response</td>
<td></td>
<td>5+ yr</td>
<td>5+ yr</td>
<td>2 mo</td>
<td>3.5 mo</td>
</tr>
</tbody>
</table>

CR: complete response; PR: partial response; IL-2: interleukin-2; LAK: lymphokine-activated killer cells.

Law TM et al., Cancer 1995 Sep 1;76(5):824-32
# Multicenter US Randomized Trial (n=71)

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
<th>IL-2</th>
<th>IL-2 + LAK</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>36</td>
<td>35</td>
<td>71</td>
</tr>
<tr>
<td>Male:Female (%)</td>
<td>31/5 (86/14)</td>
<td>24/11 (69/31)</td>
<td>55/16 (77/23)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>53 (33–68)</td>
<td>53 (30–68)</td>
<td>53 (30–68)</td>
</tr>
<tr>
<td>Median performance status (range)</td>
<td>80 (80–90)</td>
<td>90 (80–90)</td>
<td>90 (80–90)</td>
</tr>
<tr>
<td>Prior therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>30 (83)</td>
<td>31 (89)</td>
<td>61 (86)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>9 (25)</td>
<td>2 (6)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>2 (6)</td>
<td>4 (11)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0</td>
<td>2 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Sites of metastatic disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>26 (72)</td>
<td>26 (74)</td>
<td>52 (73)</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>16 (44)</td>
<td>16 (46)</td>
<td>32 (45)</td>
</tr>
<tr>
<td>Mediastinal lymph nodes</td>
<td>13 (36)</td>
<td>11 (31)</td>
<td>24 (34)</td>
</tr>
<tr>
<td>Liver</td>
<td>7 (19)</td>
<td>12 (34)</td>
<td>19 (27)</td>
</tr>
<tr>
<td>Bone</td>
<td>9 (25)</td>
<td>5 (14)</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Peripheral lymph nodes</td>
<td>7 (19)</td>
<td>1 (3)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Skin</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Total no. of evaluable sites: median (range)</td>
<td>2 (1–5)</td>
<td>2 (1–4)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Treatment center (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emory University</td>
<td>12 (33)</td>
<td>11 (31)</td>
<td>23 (32)</td>
</tr>
<tr>
<td><strong>Memorial Hospital</strong></td>
<td><strong>11 (30)</strong></td>
<td><strong>9 (26)</strong></td>
<td><strong>20 (28)</strong></td>
</tr>
<tr>
<td>University of Chicago</td>
<td>7 (19)</td>
<td>9 (26)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>Duke University</td>
<td>4 (11)</td>
<td>4 (11)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Wadley Institutes</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

IL-2: interleukin-2; LAK: lymphokine-activated killer.
Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in advanced RCC (n=71)

Lesser toxicity but inpatient ICU administration

Median survival 13 mos (95% CI 9-18 mos); p= 0.47

3 alive and free of disease at 63+, 69+ and 75+ mos: 2 with CR and 1 SD treated with IL-2+IFN α and surgery
Kidney cancer is not a single disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear cell</th>
<th>Papillary type 1</th>
<th>Papillary type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)¹</td>
<td>75%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Hereditary mutations¹</td>
<td>VHL</td>
<td>MET</td>
<td>FH</td>
<td>BHD</td>
<td>BHD</td>
</tr>
<tr>
<td>Sporadic mutations²</td>
<td>VHL (89%)</td>
<td>MET (13%)</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
</tr>
</tbody>
</table>

FLCN, folliculin; BHD, Birt-Hogg-Dubé; FH, fumarate hydratase; MET, mesenchymal epithelial transition factor; VHL, von Hippel-Lindau.

Features of clear cell RCC biology

- Disruption of VHL gene\(^1\)
- Activation of mTOR signaling\(^1\)
- Characterized by:
  - Metabolic derangements\(^1\)
  - Molecularly distinct phenotypes\(^2\)
  - Marked inter- and intratumor heterogeneity\(^3\)

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Metastatic RCC is a VEGF-driven disease

VEGF-A expression in ~5000 tissue specimens

VEGF-A expression is 3.2-fold higher in kidney malignancies than in normal tissue


VEGF, vascular endothelial growth factor.
NGS Genomic alterations in clear cell RCC

Frequently mutated genes identified in RCC samples by both Sato et al.\(^2\) and The Cancer Genome Atlas\(^3\)

*Selective deep sequencing of frequently mutated tumor suppressors in additional samples in the study by Sato et al. (n = 240).
Effects on survival of BAP1 and PBRM1 mutations in sporadic RCC: a retrospective analysis with independent validation

Figure 1. Kaplan-Meier curves of overall survival
HR=hazard ratio. (A) UTSW cohort and (B) TCGA cohort.

Intra-tumoural heterogeneity: A key challenge in the validation of genetic biomarkers

Sites of core biopsies and regions harvested from nephrectomy and metastasectomy

Metastatic RCC is a VEGF-driven heterogeneous disease

- The “trunk” of the tumor harbors the ubiquitous founding driver mutations
- The sprouting “branches” carry heterogeneous mutations

ccRCC, clear-cell RCC; VHL, von Hippel–Lindau.

From cytokines to targeted therapies: 30 years of progress in advanced RCC

- **1980**: Cytokines (IL-2 and IFN-α)
- **1990**: High-dose IL-2 approval based on phase II data
- **2000**: VHL tumour suppressor gene isolated
- **2010**: Bevacizumab + IFN-α
- **2020**: Chromatin remodelling gene mutations

Key therapies:
- Sunitinib
- Sorafenib
- Temsirolimus
- Everolimus
- Axitinib
- Pazopanib
From cytokines to targeted therapies: 30 years of progress in advanced RCC

Cytokines IL-2 and IFN-α

High-dose IL-2 FDA approval based on phase II data

VHL tumour suppressor gene isolated

Temsirilimus + IFN-α

Bevacizumab + IFN-α

Temsiroliusm + IFN-α

Sorafenib + IFN-α

Sunitinib + IFN-α

Everolimus + IFN-α

Pazapinib + IFN-α

Axitinib + IFN-α

VHL tumour suppressor gene isolated

Chromatin remodelling gene mutations

1980

1990

2000

2010

2020

Lenvatinib + everolimus

Cabozantinib

Nivolumab

Axitinib

Pazopanib

Sunitinib

Sorafenib

Everolimus

Bevacizumab

Temsiroliusm

Temsirilimus + IFN-α

Sorafenib + IFN-α

Sunitinib + IFN-α

Everolimus + IFN-α

Pazapinib + IFN-α

Axitinib + IFN-α

VHL tumour suppressor gene isolated

Chromatin remodelling gene mutations

1980

1990

2000

2010

2020

Lenvatinib + everolimus

Cabozantinib

Nivolumab
Targeted therapies have improved OS in mRCC

Before VEGF-targeted therapies (IFN-α)

- 0 risk factor (n = 80)
- 1 or 2 risk factors (n = 269)
- 3, 4 or 5 risk factors (n = 88)

Favourable: Median survival 30 months
Intermediate: 14 months
Poor: 5 months

VEGF-targeted therapies

- Risk group
- No. factors
- Median survival
- Favourable 0 43 months
- Intermediate 1-2 23 months
- Poor 3-6 8 months

*Risk factors for survival included anaemia, thrombocytosis, neutrophilia, hypercalcaemia, KPS <80%, and <1 year from diagnosis to treatment.

Pathways and Current Drugs in Metastatic Renal Cell Carcinoma

AKT, protein kinase B; FGFR, fibroblast growth factor receptor; HIF, hypoxia-inducible factor; MET, hepatocyte growth factor receptor; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; PD-1, programmed cell death protein 1; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PD-L1/2, programmed cell death ligand 1/2; PI3K, phosphatidylinositol-3-kinase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VHL, von Hippel–Lindau.

Sunitinib vs. IFN-α: progression-free survival in the treatment-naïve population

Italian Sunitinib Expanded Access Program: (n=521)

Median PFS: 9.1 months (95% CI: 7.9–11.0)

Median OS: 27.2 months (95% CI: 22.5–36.5)

Phase III Pazopanib in Locally Advanced and/or Metastatic Renal Cell Carcinoma

Subjects with advanced RCC
(N = 435)

Randomization
2:1

Pazopanib 800 mg qd
(n = 290)

Placebo
(n = 145)

Stratification
ECOG PS 0 vs 1
Prior nephrectomy Y vs. N
Rx naïve vs 1 cytokine pre-treated

Option to receive pazopanib via an open-label study at progression (VEG107769)

Pazopanib vs placebo: progression-free survival in the treatment-naïve population

In the treatment-naïve population, PFS was significantly greater with pazopanib vs placebo (p<0.001)

**Key Eligibility Criteria**
- Advanced/metastatic RCC
- Clear-cell histology
- No prior systemic therapy
- Measurable disease (RECIST 1.0)
- KPS ≥70
- Adequate organ function

**Stratification factors**
- KPS 70/80 vs. 90/100
- Prior nephrectomy
- Baseline LDH >1.5 vs. ≤1.5 × ULN

**Primary endpoint**
- PFS

**Secondary endpoints**
- OS
- ORR
- Time to response
- Duration of response
- Safety
- Health outcomes analysis

**COMPARZ Study design (n=1110)**

- **Randomised 1:1 Open Label**
- **Pazopanib 800 mg qd Continuous dosing**
- **Sunitinib 50 mg qd 4 wk on/2 wk off**

COMPARZ TRIAL: Pazopanib is non-inferior to sunitinib for efficacy
PFS independent review

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557</td>
<td>8.4 (8.3–10.9)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
<td>9.5 (8.3–11.1)</td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td>1.05 (95% CI 0.90–1.22)</td>
</tr>
</tbody>
</table>

**PISCES: Study Design**

**Period 1**
- **Pazopanib 800 mg OD**
- **Sunitinib 50 mg 4/2**

**Period 2**
- **Sunitinib 50 mg 4/2**
- **Pazopanib 800 mg OD**

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

*a 4 weeks on treatment → 2 weeks matching placebo → 4 weeks on treatment.*

ECOG PS, Eastern Cooperative Oncology Group performance status

Phase 3 METEOR study: PFS and Response in All 658 Patients

**Progression-Free Survival per IRC**

- Cabozantinib (N=330): 7.4 mo
- Everolimus (N=328): 3.9 mo

HR 0.51 (95% CI 0.41-0.62), p<0.0001

**Objective Response Rate**

<table>
<thead>
<tr>
<th></th>
<th>Cabozantinib (N=330), %</th>
<th>Everolimus (N=328), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR per IRC (95% CI)</td>
<td>17 (13, 22)</td>
<td>3 (2, 6)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>ORR per Investigator (95% CI)</td>
<td>24 (19, 29)</td>
<td>4 (2, 7)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

Cut-off for PFS and ORR: May 22, 2015

Confirmed responses per RECIST version 1.1. All responses were partial responses.

Phase 3 METEOR study: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Cabozantinib (N=330)</th>
<th>Everolimus (N=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS mo (95% CI)</td>
<td>21.4 (18.7-NE)</td>
<td>16.5 (14.7-18.8)</td>
</tr>
<tr>
<td>No. of Deaths</td>
<td>140</td>
<td>180</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.66 (95% CI 0.53-0.83), P=0.0003</td>
<td></td>
</tr>
</tbody>
</table>

34% reduction in the risk of death

Cut-off: Dec 31, 2015

Cancer cells may express tumor-specific antigens due to the presence of mutations. These antigens may induce an immune response. Upregulation of PD-L1 in the tumor microenvironment enables cancers to evade T-cell-mediated killing. Inhibition of the PD-L1/PD-1 and PD-L1/B7.1 interaction may restore antitumor T-cell activity.

# Nivolumab Phase 3 Checkmate-025 study: progression-free survival and antitumor activity

## PFS per investigator

![Graph showing progression-free survival per investigator with Nivolumab and Everolimus.](chart)

**HR = 0.88 (95% CI 0.75–1.03, p = 0.11)**

### Table: Median PFS per Investigator

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (mo)</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>4.6 (3.7–5.4)</td>
<td>318</td>
</tr>
<tr>
<td>Everolimus</td>
<td>4.4 (3.7–5.5)</td>
<td>322</td>
</tr>
</tbody>
</table>

## Antitumour activity per investigator

### Table: Objective response rate

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table: Odds ratio

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.98 (3.68–9.72)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table: Best overall response

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>34</td>
<td>55</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

### Table: Median time to response

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.5 (1.4–24.8)</td>
<td>3.7 (1.5–11.2)</td>
</tr>
</tbody>
</table>

### Table: Median duration of response

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.0 (0–27.6+)</td>
<td>12.0 (0–22.2+)</td>
</tr>
</tbody>
</table>

Nivolumab Phase 3 Checkmate-025 study: Overall Survival

- Minimum follow-up was 14 months

**Overall Survival (Probability)**

- **Nivolumab**: 25.0 (21.8–NE)
- **Everolimus**: 19.6 (17.6–23.1)

**HR = 0.73 (98.5% CI 0.57–0.93, p=0.0018)**

**27% reduction in the risk of death**
Checkmate-025 study: Updated Overall Survival

Median OS, months (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>26.0</td>
<td>(22.2–29.6)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>19.7</td>
<td>(17.6–22.3)</td>
</tr>
</tbody>
</table>

HR (95% CI) 0.73 (0.61–0.88), P=0.0006

Minimum follow-up was 26 months at the database lock on May 11, 2016

Plimack E, et al. IKCS, 2016
Treatment beyond progression

Tumor Burden change post-PD
A total of 142/153 pts treated with nivolumab beyond PD had tumor measurements pre- and post-PD

50% had a reduction in tumor burden post-progression and 14% (n = 20) had a ≥30% reduction in tumor burden

Escudier B et al. Poster presentation at ASCO 2016. 4509.
First line combination trials: closed

**Checkmate214**
Phase III

- **Sunitinib**
  - 50 mg/day 4/2
  - n=1071
  - Co-Primary endpoint: PFS, OS

- **Nivolumab + ipilimumab**
  - 3mg/kg IV + 1mg/kg IV every 3 weeks X4
  - then Nivolumab 3mg/kg IV every 2 weeks

**IMmotion151**
Phase III

- **Sunitinib**
  - 50 mg/day 4/2
  - n=830
  - Co-Primary endpoint: PFS, OS

- **Atezolizumab + bevacizumab**
  - 1200 mg IV + 15 mg/kg IV every 3 weeks

**ADAPT**
Phase III

- **Sunitinib**
  - n=450
  - Primary endpoint: OS

**Personalized immunotherapy + VEGFR inhibition**

- **AGS-003 + sunitinib**
  - 8 injections in first year followed by quarterly boosters + sunitinib

**Co-primary endpoint: PFS, OS**

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1. NCT02231749
2. NCT02420821
3. NCT01582672
First line combination ongoing trials

**Javelin renal 101**
Phase III

- **Sunitinib**
  - 50 mg/day 4/2
  - n=583
- **Avelumab + axitinib**
  - 10mg/kg IV every 2 weeks + 5mg PO BD
- **Primary endpoint**: PFS

**Lenvatinib + everolimus or pembrolizumab**
Phase III

- **Sunitinib**
  - 50 mg/day 4/2
  - n=735
- **Lenvatinib + pembro**
  - 20 mg/day + 200 mg (IV) every 3 weeks
- **Lenvatinib + everolimus**
  - 18 mg/day + 5 mg/day
- **Primary endpoint**: PFS

**KEYNOTE 426**
Phase III

- **Sunitinib**
  - 50 mg/day 4/2
  - n=840
- **Axitinib + pembro**
  - 5 mg BID + 200 mg (IV) every 3 weeks
- **Co-Primary endpoint**: PFS, OS

1. NCT02684006
2. NCT02811861
3. NCT02853331
The immuno-oncology landscape

Classes of immuno-oncology therapeutics

## ESMO RCC guidelines update 2016

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Standard recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST LINE</strong></td>
<td></td>
</tr>
<tr>
<td>Good or intermediate risk</td>
<td>Sunitinib, Bevacizumab + IFN, Pazopanib</td>
</tr>
<tr>
<td>Poor risk</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td><strong>SECOND LINE</strong></td>
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<tr>
<td>Post-TKIs</td>
<td><strong>Cabozatinib, Nivolumab</strong>&lt;br&gt;Options: Axitinib, Everolimus, Sorafenib</td>
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<tr>
<td><strong>THIRD LINE</strong></td>
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<tr>
<td>Post two TKIs</td>
<td><strong>Cabozatinib, Nivolumab</strong>&lt;br&gt;Option: Everolimus</td>
</tr>
<tr>
<td>Post TKI/ Nivolumab</td>
<td><strong>Cabozatinib</strong>&lt;br&gt;Options: Axitinib, Everolimus</td>
</tr>
<tr>
<td>Post TKI / Cabozatinib</td>
<td>Nivolumab&lt;br&gt;Options: Everolimus, Axitinib</td>
</tr>
<tr>
<td>Post TKI and mTOR</td>
<td>Sorafenib, Nivolumab, Cabozatinib&lt;br&gt;Options: Other TKI or re-challenge</td>
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</tbody>
</table>
From cytokines to targeted therapies to immunotherapy: 30 years of progress in advanced RCC

We have made great progress!