Oncological treatment of renal cell carcinoma

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Locations of RCC
Risk factors

- Smoking
- Obesity
- Hypertension
- Long term dialysis
- Chemical substances: trichlor-acetylen, asbest, cadmium
- Occupational risk: leather and shoe industry, iron and steel industry, car sales and gas stations
- Drinking pilsen type beer?
Genetical abnormalities as reasons of RCC

- **Von Hippel-Lindau (VHL) syndrome**
  - Rare genetic disease, mutation of the VHL gene
  - In 50% of affected patients will develop RCC

- **Hereditary papillary RCC (HPRC)**
  - MET-kinase genetic mutations: papillary RCC of both sides

- **Birt-Hogg-Dubé syndrome**
  - Rare
Three classical signs

- Hematuria
  - 60%
- Abdominal pain
  - 40%
- Palpable resistency in the stomach
## T Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤7 cm in greatest dimension, limited to the kidney.</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤4 cm in greatest dimension, limited to the kidney.</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;4 cm but not &gt;7 cm in greatest dimension, limited to the kidney.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;7 cm in greatest dimension, limited to the kidney.</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor &gt;7 cm but ≤10 cm in greatest dimension, limited to the kidney.</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt;10 cm, limited to the kidney.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia.</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia.</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor grossly extends into the vena cava below the diaphragm.</td>
</tr>
<tr>
<td>T3c</td>
<td>Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava.</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland).</td>
</tr>
</tbody>
</table>
# Staging

<table>
<thead>
<tr>
<th>NX</th>
<th>Regional lymph nodes cannot be assessed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis.</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases in regional lymph node(s).</td>
</tr>
</tbody>
</table>

| M0  | No distant metastasis.                 |
| M1  | Distant metastasis.                    |

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1 or T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0 or N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Treatment of Stage I disease

- Radical nephrectomy
- Simple nephrectomy
- Partial nephrectomy (selected patients)
- EBRT (palliative)
- Arterial embolization (palliative)
- Clinical trials.
Treatment of Stage II disease

- Radical nephrectomy
- Nephrectomy before or after EBRT (selected patients)
- Partial nephrectomy (selected patients)
- EBRT (palliative)
- Arterial embolization (palliative)
- Clinical trials.
Treatment of Stage III disease

- Radical nephrectomy with renal vein and, as necessary, vena caval resection (for T3b tumors).
- Radical nephrectomy with lymph node dissection.
- Preoperative embolization and radical nephrectomy
- EBRT (palliative)
- Tumor embolization (palliative)
- Palliative nephrectomy.
- Preoperative or postoperative EBRT and radical nephrectomy
- Clinical trials involving adjuvant interferon-alpha.
Treatment of Stage IV disease

- Radical nephrectomy (for T4, M0 lesions).
- Cytoreductive nephrectomy
- Temsirolimus.
- Sunitinib
- Pazopanib
- Bevacizumab with or without interferon-alpha
- Everolimus (for patients who have previously been treated with sunitinib and/or sorafenib)
- Sorafenib
- Interferon-alpha
- IL-2
- Palliative EBRT.
Histological subtypes of renal cell cancer (RCC)

- Kidney cancers: 3% of solid tumors
- US data: new cases: 64,770, deaths: 13,570
- 80-85%: renal cell cancer, from this 75% clear cell

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear cell</th>
<th>Papillary type 1</th>
<th>Papillary type 12</th>
<th>Chromophob</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>T type</td>
<td>75%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>G gene</td>
<td>VHL</td>
<td>Met</td>
<td>FH</td>
<td>BHD</td>
<td></td>
</tr>
</tbody>
</table>

Renal Clear Cell Carcinoma (RCC)

- RCC: most of the kidney cancers
  - 33% of patients are metastatic in the time of diagnosis\(^1\)
  - Less than 10% of mRCC patients live longer than 5 years\(^2\)

- Limited OS benefit from traditional treatments
  - mRCC: usually chemoresistant\(^3\)
  - Few patients benefitting from cytokines\(^4\)

**Historical treatment**

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**Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma**

By Robert J. Motzer, Jannifar Boak, Barbara A. Murphy, Paul Russo, and Medhu Mazumdar

**Purpose:** To define outcome data and prognostic criteria for patients with metastatic renal cell carcinoma (RCC) treated with interferon-alfa as initial systemic therapy. The data can be applied to design and interpretation of clinical trials of new agents and treatment programs against this refractory malignancy.

**Patients and Methods:** Four hundred sixty-three patients with advanced RCC administered interferon-alfa as first-line systemic therapy on six prospective clinical trials were the subjects of this retrospective analysis. Three risk categories for predicting survival were identified on the basis of five pretreatment clinical features by a stratified Cox proportional hazards model.

**Results:** The median overall survival time was 13 months. The median time to progression was 4.7 months. Five variables were used as risk factors for short survival: low Karnofsky performance status, high lactate dehydrogenase, low serum hemoglobin, high corrected serum calcium, and time from initial RCC diagnosis to start of interferon-alfa therapy of less than 1 year. Each patient was assigned to one of three risk groups: those with zero risk factors (favorable risk), those with one or two (intermediate risk), and those with three or more (poor risk). The median time to death of patients deemed favorable risk was 30 months. Median survival time in the intermediate-risk group was 14 months. In contrast, the poor-risk group had a median survival time of 5 months.

**Conclusion:** Progression-free and overall survival with interferon-alfa treatment can be compared with new therapies in phase II and III clinical investigations. The prognostic model is suitable for risk stratification of phase III trials using interferon-alfa as the comparative treatment arm.


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Medián OS: 13 hónap  
N = 463 pts

The PERCY QUATTRO Study: the end of immunotherapy

Median OS
Arm A: 14.9 month (95% CI: 11.7–19.2)
Arm B: 15.2 month (95% CI: 12.8–19.9)
Arm C: 15.3 month (95% CI: 13.3–20.0)
Arm D: 16.8 month (95% CI: 14.0–18.9)
“Pharmacoptosis”: Programmed death of IFN and IL-2
The 1971 hypothesis of Folkman
Theoretical bases of therapy

'Without vascularisation solid tumors remain in a dormant stage and their size not more than 2–3mm³; this is the size which is determined by the intratumorous diffusional capacity of oxygen and nutrients’
The tumor and its environment induces VEGF expression

EGF, IL-8, bFGF, Hypoxia, COX-2, NO, Oncogenes

Hypoxia $\uparrow$, COX-2 $\uparrow$, NO $\uparrow$, Oncogenes $\uparrow$

VEGF release

Binding to VEGF receptor
Activation of VEGF receptor

Overexpression (MMP, tPA, uPA, uPAr, eNOS, etc.)

Survival, Proliferation, Migration

Permeability

ANGIOGENESIS

IGF = insulin-like growth factor; PDGF = platelet-derived growth factor
Angiogenic switch

Small tumor (1–2mm)
• Avascular
• Hided

Bigger tumor
• Vascularised
• Metasztatic potential

Angiogenic „switch”
Overexpression of elements of Signal transduction (pl. VEGF)
Role of angiogenesis in tumor formation, growth and metastasis

Premalignant stage
Avascular tumor

Malignant tumor
Angiogenic switch

Tumor growth
Vascularised tumor

Vascular invasion
Tumor cell invasion

Dormant mikro-metastasis
Metastasis to distant organs

„Living“ metastasis
Secondary angiogenezis

Stages of tumorous progression: role of angiogenesis

Effect of anti-VEGF treatment on tumor vasculature

Early effect:
1. Decrease of tumorous microvasculature
2. Normalisation of remaining tumorous microvasculature

Long term effect:
3. Decrease of new tumorous microvasculature

References:
Scientific facts

- The RCC is a hypervascularised tumor$^{-3}$
  - Angiogenesis is needed for tumorous growth over 1-2 mm$^{3}$
- Inactivated VHL tumor suppressor gene$^{1-3}$
  - Overproduction of "hypoxia inducible factor" (HIF), transcription of HIF target genes
    - "Vascular endothelial growth factor" (VEGF)
    - "Transforming growth factor" (TGF)-α
    - "Platelet-derived growth factor" (PDGF)

RCC=renal cell carcinoma; mm=millimeter; VHL=von Hippel-Lindau; VEGFR-TKI=vascular endothelial growth factor receptor-tyrosine kinase.

Hypervascularity in RCC: Molecular Basis

- mTOR
- Angiogenesis
- VHL gene inactivated

Aberrantly activated PI3K/AKT/mTOR pathway

Survival
Growth and Proliferation
Metabolism
Angiogenesis

EGF, EGF-R, HER2, VEGF, VEGFR, PI3K, PTEN, mTOR, AKT, RAS, SOS, GRB, RAF, MEK, ERK, TSC1/2, PDGFR, PDGF, HIF1α, IGF-1R, IGF-1
Firts line treatment: scientific considerations

- Strategies of anti-angiogenesis\(^1-3\)
  - Anti-VEGF antibody (bevacizumab)
  - VEGFR-TKI (sunitinib)
  - „Mammalian target of rapamycin” (mTOR) inhibitor (temsirolimus)
  - Cytokine therapy

RCC=renal cell carcinoma; mm=millimeter; VHL=von Hippel-Lindau; VEGFR-TKI=vascular endothelial growth factor receptor-tyrosine kinase.

MSKCC risk factors

<table>
<thead>
<tr>
<th>MSKCC Criteria 2002⁴</th>
<th>0 risk factor = favorable prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Time from diagnosis to treatment</td>
<td>&lt;12 hónap</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt;LLN</td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;1.5 x ULN</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>&gt;10.0 mg/dL</td>
</tr>
</tbody>
</table>

1 or 2 risk factor = intermediate prognosis
≥3 risk factor = poor prognosis

KPS = Karnofsky PS; LDH = lactate dehydrogenase; LLN = lower limit of normal; MSKCC = Memorial Sloan-Kettering Cancer Center; ULN = upper limit of normal.

Prognosis of mRCC: MSKCC risk model (cytokin éra)

Median OS

- **favorable**: 19.9 months (n = 164)
- **intermediate**: 10.3 months (n = 348)
- **poor**: 3.9 months (n = 144)

mRCC prognosis: risk factor model: TKI era

*Prognostic factors: Time from diagnosis to treatment <1 év, KPS <80%, low hemoglobin, High corrected calcium, high neutrophil count, high platelet count

Mechanism of action: bevacizumab

- **Molecular target**
  - Monoclonal antibody against VEGF

- **Effects**
  - Block the binding of VEGF to its own receptor
  - Decrease the proliferation of endothelial cells
  - Decrease the VEGFR-induced proliferation of endothelial cells

Bevacizumab: Phase III studies in mRCC

**Patient population: mRCC, no previous treatment**

<table>
<thead>
<tr>
<th>CALGB 90206</th>
<th>BO17705 (AVOREN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 732</strong></td>
<td><strong>N = 649</strong></td>
</tr>
</tbody>
</table>

**Randomised**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CALGB 90206¹</th>
<th>AVOREN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α 9.0 MU TIW</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>13.1%</td>
<td></td>
</tr>
<tr>
<td><strong>PFS (median)</strong></td>
<td>4.9 months</td>
<td></td>
</tr>
<tr>
<td>IFN-α 9.0 MU TIW + Bevacizumab 10 mg/kg d1,15</td>
<td>25.5%</td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td>31%</td>
</tr>
<tr>
<td><strong>PFS (median)</strong></td>
<td>8.4 months</td>
<td>10.4 months</td>
</tr>
<tr>
<td>IFN-α 9.0 MU TIW + Bevacizumab 10 mg/kg d1,15 + Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td><strong>PFS (median)</strong></td>
<td></td>
<td>5.5 months</td>
</tr>
</tbody>
</table>

**AVOREN: PFS**

- **Probability of progression**
- **Time (months)**
- **Bevacizumab + IFN**
  - HR=0.63; p<0.0001
- **IFN + placebo**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Bevacizumab + IFN</th>
<th>IFN + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab + IFN</td>
<td>327</td>
<td>322</td>
</tr>
<tr>
<td>IFN + placebo</td>
<td>196</td>
<td>137</td>
</tr>
</tbody>
</table>

Mechanism of action: sunitinib

- **Molecular targets**
  - TKI
  - VEGFR, PDGFR, KIT, FLT3, CSF-1R, RET

- **Effects**
  - Blocks the signal transduction of target molecules
  - Decrease vascularisation and endothelial proliferation

1st line sunitinib vs. IFN-α: Phase 3 trial design

**Inclusion criteria**
- Older than 18 years
- mRCC
- Clear cell histology
- No previous systemic treatment
- Measurable disease by RECIST
- ECOG PS 0 or 1
- Adequate organ functions

- 101 australian, brasilian, canadian, european and USA center

**Sunitinib**
- 50 mg/day, per os
- 4 weeks on, 2 weeks off

**IFN-α**
- 3 MU sc. TIW week 1,
- 6 MU sc. TIW week 2
- 9 MU sc. TIW after week 3

**Primary endpoint: PFS**

RECIST = response evaluation criteria in solid tumors; SC = subcutaneously; TIW = three times weekly.

Sunitinib vs. IFN-α: efficacy data

<table>
<thead>
<tr>
<th>Response</th>
<th>Sunitinib (n=375)</th>
<th>IFN-α (n=375)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>ORR</td>
<td>176</td>
<td>47</td>
</tr>
<tr>
<td>CR</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>PR</td>
<td>165</td>
<td>44</td>
</tr>
<tr>
<td>SD</td>
<td>150</td>
<td>40</td>
</tr>
<tr>
<td>PD</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>

Sunitinib vs. IFN-α: PFS

HR = 0.538
95% CI (0.439, 0.658)

\( P < 0.00001 \)

**Primary endpoint**

**Sunitinib vs. IFN-α: OS**

**Median Survival Times**
- **Sunitinib (n = 375)**: Median = 26.4 months (95% CI: 23.0–32.9)
- **IFN-α (n = 375)**: Median = 21.8 months (95% CI: 17.9–26.9)

**HR = 0.821**
(95% CI: 0.673–1.001)

**P = 0.051 (logrank)**

**Total deaths**
- **Sunitinib**: 190
- **IFN-α**: 200

**Time, months**
- 0 3 6 9 12 15 18 21 24 27 30 33 36

**Probability of OS (%)**
- 1.0 1.0
- 0.9 0.9
- 0.8 0.8
- 0.7 0.7
- 0.6 0.6
- 0.5 0.5
- 0.4 0.4
- 0.3 0.3
- 0.2 0.2
- 0.1 0.1
- 0.0 0.0

**nDeath/nRisk**
- **Sunitinib**: 0 / 375 44 / 326 38 / 283 48 / 229 42 / 180 14 / 61 4 / 2
- **IFN-α**: 0 / 375 61 / 295 46 / 242 52 / 187 25 / 149 15 / 53 1 / 1

Sunitinib vs. IFN-α: OS of patients not receiving post-study treatment

HR = 0.647
(95% CI: 0.483–0.870)
P = 0.0033 (logrank)

*Includes 20 patients who crossed over to sunitinib on study.

Pazopanib vs. placebo in the first and second line treatment of mRCC

Inclusion criteria
- Locally advanced or mRCC
- Primarily clear cell histology
- Measurable disease (≥1 lesion)
- 1 previous systemic treatment (cytokine based)

Primary endpoint: PFS
No OS data available yet

2:1

Pazopanib 800 mg/day

Placebo

Open-label extension study (Pazopanib 800 mg; N = 71)

*N Patients with no prior treatment were also permitted to enroll in the study

### Pazopanib* vs Placebo: tumor response: independent review

<table>
<thead>
<tr>
<th></th>
<th>Pazopanib* (n=290)</th>
<th>Placebo (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (&lt;1)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PR (30)</td>
<td>87</td>
<td>5</td>
</tr>
<tr>
<td>SD (38)</td>
<td>110</td>
<td>59</td>
</tr>
<tr>
<td>PD (18)</td>
<td>51</td>
<td>58</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>88† (30)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Pazopanib vs. placebo: PFS

Every ITT patient

Hazard ratio = 0.46
95% CI (0.34, 0.62)
P value <0.0000001

Median PFS
- Pazopanib: 9.2 months
- Placebo: 4.2 months

Patients not receiving prior therapy

Hazard ratio = 0.40
95% CI (0.27, 0.60)
P value <0.0000001

Median PFS
- Pazopanib: 11.1 months
- Placebo: 2.8 months

Mechanism of action: sorafenib

- **Molecular targets**
  - TKI
  - Like sunitinib — VEGFR, PDGFR, RAF, KIT, FLT3

- **Effects**
  - Inhibits downstream signal transduction
  - Decreases vascularisation and endothelial cell proliferation

**Sorafenib vs. IFN-α in first line: Phase II**

**Inclusion criteria:**
- Clear cell histology
- No prior systemic therapy
- ECOG PS 0 or 1
- Every MSKCC prognostic groups

**Randomisation:**
1:1
N = 189

**Stratification:** MSKCC prognostic categories

**1. period**
- Sorafenib 400 mg BID (n = 97)
- IFN-α 9 MU TIW (n = 92)

**Progression**

**2. period**
- Sorafenib 600 mg BID (n = 44)
- Sorafenib 400 mg BID (n = 50)

*BID = twice daily*  
Sorafenib vs. IFN: Median PFS

Median PFS (121 events/189 patients)
- **Sorafenib** = 5.7 months
- **IFN** = 5.6 months

Hazard Ratio = 0.883

\[ p = 0.504 \text{ (log-rank test)} \]

The PI3K/AKT/mTOR signal transduction pathway in the tumor: aberrant activation

- mTOR activity often increased in cancer cells:
  - Increased EGFR, IGF-1R, and VEGFR signal transduction\(^1,2\)
  - Appearance of function modifying mutationse.g. in PI3K, Ras/Raf, erbB receptors, and Abl\(^2-4\)
  - Loss of function of negative regulators (e.g. PTEN és TSC1/2)\(^3\)

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Temsirilimus phase III study on RCC patients with poor prognosis

Inclusion criteria
- Locally advanced or mRCC
- Primarily clear cell histology
- 3/6 poor risk sign
  - LDH >1.5 x ULN
  - Hgb < LLN
  - Corrected Ca++ >10
  - KPS <70
  - DFI <1 year
  - Multiple organ metastases

Primary endpoint: OS

RANDOMISATION

N = 626

- IFN 3 MU-18 MU (n = 207)
- TEM 25 mg QW (n = 209)
- IFN 6 MU + TEM 15 mg QW (n = 210)

*Modified MSKCC poor risk; †Stratification by country and nephrectomy status.
DFI = disease-free interval.

Tems atirolimus vs. IFN: OS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IFN Arm 1 (n=207)</th>
<th>TEMSR Arm 2 (n=209)</th>
<th>TEMSR + IFN Arm 3 (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mos)</td>
<td>7.3</td>
<td>10.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Arm 2:Arm 1</td>
<td>Arm 3:Arm 1</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank p</td>
<td>0.0069</td>
<td>0.6912</td>
<td></td>
</tr>
</tbody>
</table>


*Modified MSKCC poor risk; †Stratification by country and nephrectomy status.
# Toxicity profiles of drugs used in first line (Grade 3/4)

<table>
<thead>
<tr>
<th>AE (%)</th>
<th>Sunitinib(^1,2)</th>
<th>Bev + IFN-α(^3)</th>
<th>Sorafenib(^4)</th>
<th>Pazopanib(^5)</th>
<th>Temsirolimus(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase III 1st line</td>
<td>Phase III 1st line</td>
<td>Phase II 1st line</td>
<td>Phase III 1st line</td>
<td>Phase III* 1st line</td>
</tr>
<tr>
<td>Anorexia</td>
<td>–</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4</td>
<td>10</td>
<td>–</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>–</td>
<td>&lt;1</td>
<td>0</td>
<td>–</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Hand-foot szindróma</td>
<td>5</td>
<td>–</td>
<td>11</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>&lt;1</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12</td>
<td>4</td>
<td>–</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8</td>
<td>2</td>
<td>–</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tretament interruption due to AE</td>
<td>19</td>
<td>28</td>
<td>11</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

*Poor prognostic patients based on MSKCC criteria (+ metasztatically involved organs)

Hand-foot skin reaction
NCCN Guidelines: 1st line treatment

Relapse or metastatic disease or irresectable Clear cell histology

Level 1 evidence*

- Sunitinib
- Bevacizumab + IFN-α
- Pazopanib
- Temsirolimus (for patients with poor prognosis)

* Level 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

† Poor prognosis patients, defined as those with ≥3 predictors of short survival.

NCCN = National Comprehensive Cancer Network; RT = radiation therapy.
Everolimus: Post-TKI Therapy (RECORD-1)

Inclusion criteria
- Metastatic clear cell RCC
- Progression on sunitinib, or sorafenib, or 6 months after finishing sunitinib/sorafenib treatment
- Measurable disease (RECIST)
- Karnofsky PS ≥70%
- Adequate bone marrow, liver and kidney function

Stratification
- Prior VEGFR-TKI: 1 vs 2
- MSKCC risk: good, intermediate, poor

Randomization
- Everolimus 10 mg qd + BSC (n=277)
- Placebo + BSC (n=139)

Primary endpoint
- Progression free survival (PFS)

Secondary endpoints
- Objective response rate (ORR), Overall survival (OS), Toxicity (AE-s), Quality of life (QoL)

RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors; PS=performance status; VEGFR-TKI=vascular endothelial growth factor receptor tyrosine kinase inhibitors; MSKCC=Memorial Sloan-Kettering Cancer Center; qd=every day; BSC=best supportive care. IFN-α=interferon alfa.

PFS improved in every MSKCC risk groups, independently from the type of previous VEGFR-TKI therapy

Everolimus (median PFS: 4.90 months)
Placebo (median PFS: 1.87 months)
Hazard Ratio = 0.33
95% CI: 0.25, 0.43
Log-Rank P Value <0.001

The real evaluation of OS is biased by the cross-over of 81% of placebo treated patients to everolimus arm after progression.

TARGET: Phase III, sorafenib vs. placebo, 2nd line

Inclusion criteria
- Histologically confirmed non-resectable or metastatic disease
- Clear cell histology
- Measurable disease
- Failure of at least one prior therapy
- ECOG PS 0 or 1
- Good organ functions
- No brain metastasis
- Poor prognostic group excluded

1:1 randomisation n~905

Stratification MSKCC criteria Country

Sorafenib 400 mg bid
ORR 10%
SD 74%
PFS 5.5 months

Priary endpoint
- PFS (P=0.01)
- OS (P=0.04)

Secondary endpoint
- ORR

Placebo*
ORR 2%
SD 53%
PFS 2.8 months

*Crossover initiated 6/05.

TARGET: OS analysis

TARGET: 561 death
OS analysis defined by protocol

- 216/452 patient receiving placebo changed to sorafenib
- 61% of patients of placebo arm has received sorafenib

TARGET: pre-planned secondary analysis†: data of censored sorafenib receiving patients excluded

- HR = 0.78*
- 95% CI: 0.62–0.97
- P=0.0287*

OS

Final analysis

Sorafenib 17.8 hó
Placebo 15.2 hó

Censored analysis

Sorafenib 17.8 hó
Placebo 14.3 hó

*Non-significant (P=0.146); †Planned analysis prior to unblinding of the OS data; O’Brien-Fleming threshold for statistical significance α=0.037.

Pazopanib vs. placebo: 2nd line

Inclusion criteria

- Locally advanced or mRCC
- Primarily clear cell histology
- Measurable disease (≥1 lesion)
- 1 prior systemic treatment (cytokine based)*

Primary endpoint: PFS

Randomization

2:1

Pazopanib 800 mg/day

Placebo

Open-label extension study (Pazopanib 800 mg; N = 71)

*N: Patients with no prior treatment were also permitted to enroll in the study

Pazopanib PFS on cytokine pretreated patients

HR = 0.54
95% CI (0.35, 0.84)
$P$ value <0.001

Median PFS
Pazopanib: 7.4 hónap
Placebo: 4.2 hónap

**Relative potencies of VEGF TKI-s**

- VEGFR-1
- VEGFR-2
- VEGFR-3

Potency: IC₅₀ (nM)

Less potent

More potent

AXIS: Fázis III, axitinib vs. sorafenib, 2nd line

Inclusion criteria:
mRCC with clear cell histology
Failure of one prior treatment:
  - Sunitinib
  - Bevacizumab + IFN-α
  - Temsirolimus
  - Or cytokin

Stratification: Prior treatment, ECOG PS

Primary endpoint: PFS
Secondary endpoint: OS, ORR

Randomisation:
- N=717

Axitinib
5 mg BID

Sorafenib
400 mg BID

Rini B, et al. ASCO 2011
AXIS: Az axitinib szignifikánsan megnyújtja a PFS-t

![Graph showing progression-free survival (PFS) for axitinib and sorafenib treatments.](image)

**Progressziómentes túlélés**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Betegszám</th>
<th>mPFS, hónap</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>361</td>
<td>6.7</td>
<td>6.3–8.6</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>362</td>
<td>4.7</td>
<td>4.6–5.6</td>
</tr>
</tbody>
</table>

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

Rini B, et al. ASCO 2011
## PFS and prior treatments

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Axitinib (n=361)</th>
<th>Sorafenib (n=362)</th>
<th>HR</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines (n=251)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>12.1</td>
<td>6.5</td>
<td>0.464</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Investigator</td>
<td>12.0</td>
<td>8.3</td>
<td>0.636</td>
<td>0.005</td>
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<tr>
<td>Sunitinib (n=389)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>4.8</td>
<td>3.4</td>
<td>0.741</td>
<td>0.011</td>
</tr>
<tr>
<td>Investigator</td>
<td>6.5</td>
<td>4.5</td>
<td>0.636</td>
<td>0.0002</td>
</tr>
<tr>
<td>Temsirolimus (n=24)</td>
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<td></td>
</tr>
<tr>
<td>IRC</td>
<td>10.1</td>
<td>5.3</td>
<td>0.511</td>
<td>0.142</td>
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<tr>
<td>Investigator</td>
<td>2.6</td>
<td>5.7</td>
<td>1.210</td>
<td>0.634</td>
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<tr>
<td>Bevacizumab (n=59)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IRC</td>
<td>4.2</td>
<td>4.7</td>
<td>1.147</td>
<td>0.637</td>
</tr>
<tr>
<td>Investigator</td>
<td>6.5</td>
<td>4.5</td>
<td>0.753</td>
<td>0.213</td>
</tr>
</tbody>
</table>

*One-sided log-rank test stratified by ECOG PS

Rini B, et al. ASCO 2011
The ORR of axitinib is better

<table>
<thead>
<tr>
<th>Best tumor response, %</th>
<th>Axitinib</th>
<th>Sorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response*</td>
<td>19.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>49.9</td>
<td>54.4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>21.6</td>
<td>21.0</td>
</tr>
<tr>
<td>Not defined</td>
<td>6.1</td>
<td>11.6</td>
</tr>
</tbody>
</table>

Risk ratio (95% CI) 2.1 (1.4–3.0)

*Axitinib vs. sorafenib: P = 0.0001

Rini B, et al. ASCO 2011
## Results of treatment of cytokin refrakter mRCC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>ORR (%)</th>
<th>Median PFS/TTP (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (vs. placebo)(^1)</td>
<td>903</td>
<td>10 vs. 2</td>
<td>5.5 vs. 2.8</td>
<td>17.8 vs. 15.2</td>
</tr>
<tr>
<td>Pazopanib (vs. placebo)(^4)</td>
<td>202</td>
<td>29 vs. 3</td>
<td>7.4 vs. 4.2</td>
<td>NA</td>
</tr>
<tr>
<td>Sunitinib(^2)</td>
<td>106</td>
<td>34</td>
<td>8.3</td>
<td>23.9(^4)</td>
</tr>
<tr>
<td>Sunitinib(^3)</td>
<td>63</td>
<td>40</td>
<td>8.7</td>
<td>16.4</td>
</tr>
<tr>
<td>Axitinib(^5)</td>
<td>52</td>
<td>44</td>
<td>15.7</td>
<td>29.9</td>
</tr>
</tbody>
</table>

* Date presented are not from comparative trials!

NCCN Guidelines: 2nd line treatments

Clear cell histology

- Clinical study
- **Sunitinib** (1* after cytokine treatment, 2A† after other TKI treatment)
- **Sorafenib** (1 after cytokine treatment, 2A after other TKI treatment)
- **Pazopanib** (1 after cytokine treatment, 3§ after other TKI treatment)
- **Everolimus** (1 after TKI treatment)

Level 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

† Level 2A: Uniform NCCN consensus based on lower-level evidence, including clinical experience, that the recommendation is appropriate.

§ Level 3: Recommendation is based on any level of evidence but reflects major disagreement.

## Europen mRCC treatment landscape

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Treatment</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prior treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSKCC: good or intermediate</td>
<td>Sunitinib Bevacizumab + IFNα Pazopanib</td>
<td>HD IL-2</td>
</tr>
<tr>
<td>MSKCC: poor</td>
<td>Temsirolimus Sunitinib</td>
<td></td>
</tr>
<tr>
<td><strong>Second-line patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine refracter</td>
<td>Sorafenib Pazopanib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>VEGF/VEGFR TKI refracter</td>
<td>Everolimus</td>
<td>Sequential TKI or VEGF inhibitor</td>
</tr>
</tbody>
</table>
Treatment of mRCC in Hungary
Improving PFS in the 1st line treatment of mRCC

- Best supportive care: Kane 2006, 2–3 months
- INF-α alone: Multiple studies, 3–5 months
- INF-α + IL-2+5-FU: Gore ASCO 2008, 5.3 months
- Temsirolimus: Hudes 2007, 5.5 months
- Sorafenib: Nexavar PI, 5.7 months
- Bevacizumab + INF-α: CALGB 90206 ASCO 2009, 8.4 months
- Bevacizumab + INF-α: AVOREN ASCO 2009, 10.4 months
- Sunitinib: Figlin ASCO 2008, 11.0 months
- Pazopanib: Pazopanib ASCO 2009, 11.1 months

From 2005 until recently

Improving OS in the 1st line treatment of mRCC

Best supportive care\(^1\)
- Kane 2006: 7–9 months

Temsiozilimus\(^2\)
- IFN: 7.3 months
- Temsirolimus: 10.9 months

IFN-\(\alpha\) + IL-2 + 5-FU\(^4,5\)
- Gore ASCO 2008: 18.5 months
- IFN: 18.7 months

CALGB\(^6\)
- Bevacizumab + IFN: 17.4 months

AVOREN\(^7\)
- Bevacizumab + IFN: 21.3 months

Sunitinib\(^8\)
- Figlin ASCO 2008: 26.4 months

From 2004 until recently

Primary goal in the treatment of mRCC: improving efficacy

- Before targeted therapies the ORR was low (~2–13%), and median OS was 13.3 months
- Effect of targeted therapies:
  - In contrast to palliation we can count on long OS
  - Comparing to cytokine based therapies PFS and OS significantly increased