Immunotherapy versus targeted treatments in metastatic renal cell carcinoma: The return game?

Sylvie NEGRIER MD, PhD
Centre Léon Bérard, Lyon
Université Lyon 1
IMMUNOTHERAPY:
A LONG AND WIDING ROAD!
WHERE DO WE COME FROM?

Immunotherapy in mRCC: IL2, IFN
The Cochrane Collaboration: Analysis of the literature on IL2 and IFN treatment in advanced disease (2004)

- 52 randomized studies identified
- 5,989 patients involved
- 685 partial or complete remissions reported: **11.4% [0-39%]**
- Gain in overall survival? Not demonstrated

(Coppin et al. Cochrane Database Syst Rev 2005)
Recombinant human IL2, recombinant human IFN, or both in metastatic renal cell carcinoma

by the French Immunotherapy Group

<table>
<thead>
<tr>
<th>Good prognosis</th>
<th>Intermediate prognosis</th>
<th>Poor prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only 1 metastatic site</td>
<td>60% of patients</td>
<td>25% of patients</td>
</tr>
<tr>
<td>15% of patients</td>
<td>Probability of response: 5-25%</td>
<td>Probability of progression under cytokines: &gt;70%</td>
</tr>
<tr>
<td>Probability of failure: 25-70%</td>
<td>Median survival time: 13 months</td>
<td>Median survival time: 5.5 months</td>
</tr>
<tr>
<td>Median survival time: 25 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BEST CANDIDATES

NO BENEFIT

NO BENEFIT

Cancer 2007;110:2468-77

Ann Oncol 2002;13:1460-8

Clin Cancer Res 2008;14:5907-12

Tenth European International Kidney Cancer Symposium
Lyon, France — 24-25 April 2015
Best candidates for cytokine treatment
Results from the randomized trial PERCY DUO

This subgroup 15 % of all metastatic patients

- **Response rate** = 20%
- **Median progression-free survival (95% CI: 8)** = 6.8 Months

Long responding patients at 3 years: **11/155 (7%)**

1% of the whole patient population

by the French Immunotherapy Group (Clin Cancer Res 2008;14:5907-11)
IN 2003, A TINY RAY OF HOPE APPEARED

A Randomized Trial of Bevacizumab, an Anti–Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer

The eminent Dr Escudier opened a new road

Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma

Bernard Escudier, M.D., Tim Eisen, M.D., Walter M. Stadler, M.D., Cezary Szczyl, M.D., Stéphane Oudard, M.D., Michael Siebels, M.D., Sylvie Negrier, M.D., Christine Chevream, M.D., Ewa Solska, M.D., Apurva A. Desai, M.D., Frédéric Rolland, M.D., Tomasz Demkow, M.D., Thomas E. Hutson, D.O., Pharm.D., Martin Gore, M.D., Scott Freeman, M.D., Brian Schwartz, M.D., Minghua Shan, Ph.D., Ronit Simantov, M.D., and Ronald M. Bukowski, M.D., for the TARGET Study Group*
Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Hazard Ratio = 0.821
(95% CI: 0.673 - 1.001)
p = 0.051 (Log-rank)

Motzer RJ 2007;356:115-24
Targeted agents currently approved for mRCC in Europe

- **Sunitinib (oral)**
  - Advanced/mRCC
  - 2006

- **Bevacizumab (+IFN-α) (IV)**
  - First-line mRCC
  - 2007

- **Everolimus (oral)**
  - Advanced RCC after VEGF-targeted therapy
  - 2008

- **Temsirolimus (IV)**
  - Advanced RCC with 3–6 prognostic risk factors
  - 2009

- **Sorafenib (oral)**
  - Advanced RCC after IFN-α/IL-2 or if unsuitable for IFN-α/IL-2
  - 2009

- **Pazopanib (oral)**
  - Advanced RCC
  - 2009

- **Axitinib (oral)**
  - Advanced RCC after sunitinib or a cytokine
  - 2010

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  - First-line mRCC
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  - 2014

- **Sorafenib (oral)**
  - Advanced RCC after IFN-α/IL-2 or if unsuitable for IFN-α/IL-2
  - 2014

- **Pazopanib (oral)**
  - Advanced RCC
  - 2014

- **Axitinib (oral)**
  - Advanced RCC after sunitinib or a cytokine
  - 2015

IFN-α, interferon-alpha; IL-2, interleukin-2; IV, intravenous; mRCC, metastatic renal cell carcinoma; VEGF, vascular endothelial growth factor

<table>
<thead>
<tr>
<th>Histology and setting</th>
<th>Risk group</th>
<th>Standard</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear-cell first line</td>
<td>Good or intermediate risk</td>
<td>Sunitinib [I, A]</td>
<td>High-dose IL2 [III, C]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab + IFN-α [I, A]</td>
<td>Sorafenib [II, B]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib [I, A]</td>
<td>Bevacizumab + IFN [III, A]</td>
</tr>
<tr>
<td></td>
<td>Poor risk</td>
<td>Temsirolimus [II, A]</td>
<td>Sunitinib [II, B]</td>
</tr>
<tr>
<td>Clear-cell second line</td>
<td>Post cytokines</td>
<td>Axitinib [I, A]</td>
<td>Sorafenib [III, B]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib [I, A]</td>
<td>Sunitinib [III, A]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib [II, A]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axitinib [I, B]</td>
<td>Sorafenib [II, A]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Everolimus [II, A]</td>
<td></td>
</tr>
<tr>
<td>Clear-cell third line</td>
<td>Post 2 TKIs</td>
<td>Everolimus [II, A]</td>
<td>Other TKI [IV, B]</td>
</tr>
<tr>
<td></td>
<td>Post TKI and mTOR</td>
<td>Sorafenib [I, B]</td>
<td>Rechallenge [IV, B]</td>
</tr>
</tbody>
</table>

**Effect of targeted therapies on survival in mRCC: a notable gain**

**IL2/IFN trials: overall survival**

**good and intermediate prognosis patients**

Median overall survival: **20.89 months**

[95% CI: 17.57 – 24.11]

**Phase III study of So-Su vs. Su-So (SWITCH): overall survival**

<table>
<thead>
<tr>
<th></th>
<th>Median (one-sided 95% CI) OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>So-Su</td>
<td>31.5 (+21.3, &lt;36.9)</td>
</tr>
<tr>
<td>Su-So</td>
<td>30.2 (+26.6, &lt;50.1)</td>
</tr>
</tbody>
</table>

HR: 1.00 (one-sided 95% CI: 0.90)

*P* value for superiority: 0.49

by the French Immunotherapy Group

Intention-to-treat population.

Michel MS et al. ASCO-GU 2014;abstr 393.
Targeted therapy limitations

- Tumour resistance due to adaptive and evasive mechanisms eventually appears and overcomes the targeted treatment effect

- Long lasting complete remissions are uncommonly seen

- Improvements by use of sequential targeted therapies were done but came to an end

The potential of cure by targeted treatments is very unlikely
Adjuvant phase III trial (ASSURE/ECOG E2805)
1 943 patients

D’après Haas NB et al., abstr. 403, actualisé
The new Immunotherapy
TARGETED IMMUNOTHERAPY

Built on increased knowledge and better comprehension of underlying mechanisms of tumour development

New tools became available: **Immune Checkpoint Inhibitors**
Antibodies directed against:
- **CTLA4**
- **PD1** or **PDL1**

New Immunotherapy versus old Immunotherapy

- IL2 is a growth factor for T lymphocytes and NK cells. Giving high-doses IL2 induces a non specific proliferation and activation of the immune system.

- Immune checkpoint Inhibitors induce the blockade of immunosuppressive functions.

- The PD1 / PDL1 system plays a major role in tumour invasiveness and the “homing” of metastases.
PD1/PDL1 receptors

- **PD1** expressed on T & B lymphocytes, NK cells, highly expressed by TIL and Treg lymphocytes

- **PDL1** expressed on T & B lymphocytes, dendritic cells, macrophages and by a number of **tumour cells**
PDL1 expression in RCC

Variable in absence of standard analysis process

- **In clear cell RCC** *
  - 24% on paraffin-embedded samples
  - 44% on frozen tissues
    with 10 % on tumour cells vs 50% on TIL

- **In other histologic subtypes** **
  - Chromophobe 5%
  - Papillary 10%
  - Xp11 translocation 43%

*Thomson Clin Cancer Res 2006, **Choueiri Ann Oncol 2014
Results of ICPI in pre-treated mRCC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total pts</th>
<th>RCC pts</th>
<th>RR</th>
<th>SD at 24 weeks</th>
<th>PFS at 24 weeks</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>296</td>
<td>34</td>
<td>27%</td>
<td>27%</td>
<td>56%</td>
<td>Mc Dermott JCO2015</td>
</tr>
<tr>
<td>Nivolumab/3 doses</td>
<td>168</td>
<td>168</td>
<td>24%</td>
<td>41%</td>
<td>≈ 35%</td>
<td>Motzer JCO 2014</td>
</tr>
<tr>
<td>BMS936559</td>
<td>207</td>
<td>17</td>
<td>12%</td>
<td>41%</td>
<td>53%</td>
<td>Topalian NEJM 2012</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>171</td>
<td>53</td>
<td>13%</td>
<td>32%</td>
<td>53%</td>
<td>Brahmer NEJM 2012</td>
</tr>
</tbody>
</table>

Response rates: 12 to 27%
Median PFS: 4 to 6 months

same range than 2nd line targeted therapies: axitinib, everolimus?
(A) Progression-free and (B) overall survival by Nivolumab treatment arm

PFS not different from other 2d line treatments?

OS looks promising
Median OS 18 to 25.5 months


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Treatment optimisation

• Combination may be a way of progress
• If TKI + ICPI combination looks hazardous
  
  (*Rini Cancer 2011; Amin ASCO GU 2015*)

Some look promising:

- Nivolumab + Ipilimumab (*Hammers ASCO 2014*)
- MPDL3280A + Bevacizumab (*Sznol ASCO GU 2015*)
Immunotherapy: Hopes and pitfalls

Hopes:

• To achieve long lasting remissions (cures?) in advanced situations

• To increase survival and thus reduce mortality after surgery for localised disease by adjuvant treatment
Immunotherapy: Hopes

• To achieve long lasting remissions (cures?) in advanced situations

• The apparent gain in OS, despite the moderate benefit in PFS, can be explained by the duration of efficacy
Immunotherapy: Hopes

• To increase survival and thus reduce mortality after surgery for localized disease by adjuvant treatment

• Due to its mechanisms of action, immunotherapy represents a better tool to treat residual or microscopic disease than angiogenesis TKI

• Some promising results obtained in adjuvant melanoma
Immunotherapy: Pitfalls

- Limited number of responses and limited gain in median PFS (RR < 30%, median PFS 6-8 months)

- Relapses are seen after initial remissions

Motzer JCO 32 @ 2014
Why a limited number of patients are able to respond?

1) Tumour immune suppressor effects:
- Immuno-suppressive cytokines: IL6, IL10, TGF, VEGF
- Immuno-suppressive receptors: FASLr, PDL1
- Attraction of immuno-suppressive cells: Treg, macrophages, myeloid-derived suppressor cells...
Why a limited number of patients are able to respond?

2) Absence of non-self antigens

Analysis of presence of neo-antigens in advanced melanoma and effect of anti-CTLA4 treatment

Immunotherapy: Pitfalls

Why do some responding patients relapse?

• Tumour plasticity and heterogeneity:
  - Tumours cells that do not express recognized antigens proliferate
  - Increase level of immuno-suppressive receptors or ligands
Immunotherapy, the return game?

Yes, Immunotherapy is back

The interest of active angiogenesis inhibitors in advanced RCC remains

- The initial (even short-lived) tumour growth inhibition is observed in $\approx 80\%$ of patients
- A good situation to favor antigen presentation and immune activation?
How to improve the results in the future?

• **Patient selection:**
  - Presence of the target?
  - Presence of neo-antigens?
  - Other immune status parameters?

• **Patient preparation:**
  - To induce a « good » immune status and target expression?

   The work on treatment strategy is just beginning

   **Combination: how and when?**
Immunotherapy, the return game?

• The game is not over
• But players make progress
• Efforts must continue

Immunotherapy in 2015:
The road is not so winding!