Innovaciones en el tratamiento del cáncer renal

Enrique Grande

12, 13 Y 14 DE JULIO 2017 · SANTANDER
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Pza. Italia, 1 39005 Santander
The enriched inflammatory environment of RCC
Available agents are expanding across the three eras of aRCC treatment

Immunotherapy and renal cancer: a long love story

Immunotherapy works in renal cancer: High-Dose IL-2 was approved for Metastatic RCC in 1992

- The recommendation for the use of high-dose bolus interleukin-2 (IL-2) is based upon its ability to induce durable, high-quality remissions in a minority of patients

PERCY Quattro trial: is there any better 'old' immunotherapy for RCC?


- MPA: Median 14.9 months [11.7–19.2]
- IFN: Median 15.2 months [12.8–19.9]
- IL-2: Median 15.3 months [13.3–20.0]
- IFN + IL-2: Median 16.8 months [14.0–18.9]
Most updated CheckMate-025 overall survival

**Median OS, months (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</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

**No. at risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>410</th>
<th>390</th>
<th>359</th>
<th>337</th>
<th>305</th>
<th>276</th>
<th>251</th>
<th>225</th>
<th>204</th>
<th>171</th>
<th>129</th>
<th>80</th>
<th>38</th>
<th>5</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>411</td>
<td>367</td>
<td>325</td>
<td>289</td>
<td>268</td>
<td>247</td>
<td>214</td>
<td>183</td>
<td>162</td>
<td>130</td>
<td>103</td>
<td>61</td>
<td>32</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Everolimus</td>
<td>411</td>
<td>367</td>
<td>325</td>
<td>289</td>
<td>268</td>
<td>247</td>
<td>214</td>
<td>183</td>
<td>162</td>
<td>130</td>
<td>103</td>
<td>61</td>
<td>32</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Plimack ER et al at the 15th International Kidney Cancer Symposium; November 4–5, 2016; Miami, FL, USA
CheckMate-025: Change in QoL assessments by FKSI-DRS


- Significant improvement ($P<0.05$) from baseline in FKSI-DRS for nivolumab.
- Significant improvement ($P<0.05$) in FKSI-DRS mean change from baseline scores between nivolumab and everolimus arms.
- Significant deterioration ($P<0.05$) from baseline in FKSI-DRS for everolimus.
Can we combine antiangiogenics with novel IOs?
The promising for synergistic activity of novel IOs plus antiangiogenics

Summary of the activity of novel IOs in combination with antiangiogenics in phase I trials

<table>
<thead>
<tr>
<th></th>
<th>Nivo + Sun</th>
<th>Nivo + Pazo</th>
<th>Pembro + Axi</th>
<th>Pembro + Lenva</th>
<th>Pembro + Pazo</th>
<th>Avelumab + Axi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Amin ASCO 2014</td>
<td>Amin ASCO 2014</td>
<td>Atkins ESMO 2016</td>
<td>Taylor ESMO 2016</td>
<td>Chowdhury ASCO 2017</td>
<td>Choueiri ASCO 2017</td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>20</td>
<td>52</td>
<td>13</td>
<td>26</td>
<td>55</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>52</td>
<td>45</td>
<td>71.2</td>
<td>69.2</td>
<td>36</td>
<td>58.2</td>
</tr>
<tr>
<td>Complete Resp (%)</td>
<td>3</td>
<td>0</td>
<td>5.8</td>
<td>0</td>
<td>NR</td>
<td>5.5</td>
</tr>
<tr>
<td>mPFS (m)</td>
<td>11.4</td>
<td>7.3</td>
<td>15.1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Toxicity</td>
<td>GI, ALT, AST</td>
<td>ALT, AST, GI, Ebandocrinopathy</td>
<td>Diarrhoea, Fatigue</td>
<td>ALT, AST, Fatigue</td>
<td>ALT, AST, amylase,lipase</td>
<td>Myocarditis</td>
</tr>
</tbody>
</table>
But let’s wait until phase III data....
Immotion 150: a phase II study of atezolizumab with or without bevacizumab vs sunitinib in first line mRCC

- The coprimary endpoints are PFS (RECIST v1.1 by IRF) in ITT and PD-L1+ patients
- IMmotion150 was designed to be hypothesis generating and inform the trial design of the Phase III study IMmotion151
- Amendments included:
  - Based on Phase 1a data, the definition of PD-L1 positivity was revised from ≥ 5% to ≥ 1% of IC expressing PD-L1
  - In addition to ITT patients, PD-L1+ patients were included in the coprimary endpoint of IRF-assessed PFS, after interim analyses

Atkins M, et al. Oral presentation at ASCO 2017
Immotion 150: a phase II study of atezolizumab with or without bevacizumab vs sunitinib in first line mRCC

Atkins M, et al. Oral presentation at ASCO 2017

Atezo, atezolizumab; bev, bevacizumab.
PFS measured by independent review facility.

*P values are for descriptive purposes only and not adjusted for multiple comparisons.
Challenges ahead in RCC
Challenges in RCC to face shortly

- Molecular Biomarkers should be mandatory in the future
- Non clear cell histologies
- Would cytoreductive nephrectomy still be needed?
- Defining the role of adjuvant therapy
- Phase III trials that may change the game in the next couple of years
- Role of TKI after IOs
Challenges in RCC to face shortly

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Immotion 150: activity of atezolizumab + bevacizumab in patients expressing >1% PD-L1

Atezo: 5.5 mo (3.0, 13.9)
Sunitinib: 7.8 mo (3.8, 10.8)
Atezo + bev: 14.7 mo (8.2, 25.1)

Atezo, atezolizumab; bev, bevacizumab.
PFS measured by independent review facility.

<table>
<thead>
<tr>
<th></th>
<th>Stratified HR (95% CI)</th>
<th>P Value^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + bev vs sunitinib</td>
<td>0.64 (0.38, 1.08)</td>
<td>0.095</td>
</tr>
<tr>
<td>Atezo vs sunitinib</td>
<td>1.03 (0.63, 1.67)</td>
<td>0.917</td>
</tr>
</tbody>
</table>

Atkins M, et al. Oral presentation at ASCO 2017
Immotion 150: Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

McDermott D, et al. IMmotion150 biomarkers: AACR 2017
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Immotion 150: Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

Sunitinib

<table>
<thead>
<tr>
<th>Angiogenesis (High vs Low)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n = 44)</td>
<td>0.31</td>
<td>(0.18, 0.55)</td>
</tr>
<tr>
<td>Low (n = 45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atezolizumab + Bevacizumab

<table>
<thead>
<tr>
<th>Angiogenesis (High vs Low)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n = 45)</td>
<td>0.90</td>
<td>(0.54, 1.51)</td>
</tr>
<tr>
<td>Low (n = 43)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atezolizumab

<table>
<thead>
<tr>
<th>Angiogenesis (High vs Low)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n = 42)</td>
<td>0.74</td>
<td>(0.42, 1.28)</td>
</tr>
<tr>
<td>Low (n = 44)</td>
<td></td>
<td></td>
</tr>
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McDermott D, et al. IMmotion150 biomarkers: AACR 2017
Immotion 150: Transcriptome Map of Angiogenesis and Immune-Associated Genes in RCC Tumors

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Sunitinib

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<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-effector (High vs Low)</td>
<td>1.31</td>
<td>(0.77, 2.23)</td>
</tr>
</tbody>
</table>

Atezolizumab + Bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-effector (High vs Low)</td>
<td>0.50</td>
<td>(0.30, 0.86)</td>
</tr>
</tbody>
</table>

Atezolizumab

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-effector (High vs Low)</td>
<td>0.83</td>
<td>(0.48, 1.45)</td>
</tr>
</tbody>
</table>

McDermott D, et al. IMmotion150 biomarkers: AACR 2017
Challenges in RCC to face shortly

• Molecular Biomarkers should be mandatory in the future
• Non clear cell histologies
• Would cytoreductive nephrectomy still be needed?
• Defining the role of adjuvant therapy
• Phase III trials that may change the game in the next couple of years
• Role of TKI after IOs
Our own experience with atezo + beva in 1st Line mRCC with sarcomatoid component

<table>
<thead>
<tr>
<th>March 2016</th>
<th>August 2016</th>
<th>March 2017</th>
</tr>
</thead>
</table>

- 60 y.o. male
- Nephrectomy due to left kidney primary tumor in February 2016
- Sarcomatoid 35% component
- Recruited for Immotion 151 trial
- Started atezo + bev May 2016

Enrique Grande. *unpublished data
Our own experience with atezo + beva in 1st Line mRCC with sarcomatoid component

- 65 y.o. woman
- Nephrectomy due to left kidney primary tumor in 2013
- 15% sarcomatoid component
- Recruited for Immotion 151 trial
- Started atezo + beva July 2016
Challenges in RCC to face shortly

- Molecular Biomarkers should be mandatory in the future
- Non clear cell histologies
- **Would cytoreductive nephrectomy still be needed?**
- Defining the role of adjuvant therapy
- Phase III trials that may change the game in the next couple of years
- Role of TKI after IOs
Is Cytoreductive nephrectomy still needed with novel IOs?

Deferring CN may improve response to IOs due to:

- Development of immune responses against patient specific antigens/private mutations
- Higher mutational load
- Increased exposure to heterogeneity of mutations
- Higher possibility of immune response against multiple clones

Challenges in RCC to face shortly

- Molecular Biomarkers should be mandatory in the future
- Non clear cell histologies
- Would cytoreductive nephrectomy still be needed?
- **Defining the role of adjuvant therapy**
- Phase III trials that may change the game in the next couple of years
- Role of TKI after IOs
STRACT Trial: Disease-Free Survival By Blinded Independent Central Review

Median DFS, y (95% CI)
- Sunitinib: 6.8 (5.8–NR)
- Placebo: 5.6 (3.8–6.6)

P=0.030*  
HR 0.761 (95% CI, 0.594–0.975)

Disease-Free Survival (years)

Proportion Disease-Free

No. at risk
- Sunitinib: 309 225 173 153 144 119 53 10 3 0
- Placebo: 306 220 181 150 135 102 37 10 2 0
## Current adjuvant studies recruiting patients

<table>
<thead>
<tr>
<th></th>
<th>PROSPER</th>
<th>Immotion010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active therapy</strong></td>
<td>Nivolumab</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td><strong>Duration of therapy</strong></td>
<td>~10 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td><strong>Control arm</strong></td>
<td>Observation</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Biopsy needed</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Neoadjuvant Rx</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Correlative studies</strong></td>
<td>Enhanced with neoadjuvant component/tissue</td>
<td>Limited to postoperative/nephrectomy specimens</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>ccRCC or ncRCC</td>
<td>ccRCC and sarcomatoid</td>
</tr>
<tr>
<td><strong>Risk groups</strong></td>
<td>cT2-4, cN+</td>
<td>pT2 (G3-4), pT3a (G4), pT3b-4, pN+, NED after M1</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>RFS (investigator)</td>
<td>DFS (Independent)</td>
</tr>
</tbody>
</table>
Challenges in RCC to face shortly

- Molecular Biomarkers should be mandatory in the future
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- Defining the role of adjuvant therapy
- **Phase III trials that may change the game in the next couple of years**
- Role of TKI after IOs
Ongoing Phase III trials of combinations of immunotherapies with VEGFR inhibitors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary endpoint</th>
<th>Estimated patient enrolment</th>
<th>Trial</th>
<th>ClinicalTrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab-lenvatinib vs everolimus-lenvatinib vs sunitinib¹</td>
<td>PFS</td>
<td>735</td>
<td>CLEAR</td>
<td>NCT02811861</td>
</tr>
<tr>
<td>Nivolumab-ipilimumab vs sunitinib¹</td>
<td>PFS and OS</td>
<td>1070</td>
<td>CheckMate 214</td>
<td>NCT02231749</td>
</tr>
<tr>
<td>Nivolumab-cabozantinib vs nivolum-ipilimumab-cabozantinib vs sunitinib²</td>
<td>PFS</td>
<td>1014</td>
<td>CheckMate 9ER</td>
<td>NCT03141177</td>
</tr>
<tr>
<td>Atezolizumab-bevacizumab vs sunitinib¹</td>
<td>PFS and OS²</td>
<td>900</td>
<td>IMmotion151</td>
<td>NCT02420821</td>
</tr>
<tr>
<td>Avelumab-axitinib vs sunitinib¹</td>
<td>PFS</td>
<td>583</td>
<td>JAVELIN Renal 101</td>
<td>NCT02684006</td>
</tr>
<tr>
<td>Pembrolizumab-axitinib vs sunitinib¹</td>
<td>PFS and OS</td>
<td>840</td>
<td>KEYNOTE-426</td>
<td>NCT02853331</td>
</tr>
<tr>
<td>Autologous dendritic-cell immunotherapy-sunitinib vs sunitinib¹</td>
<td>OS</td>
<td>450</td>
<td>ADAPT</td>
<td>NCT01582672</td>
</tr>
</tbody>
</table>
Challenges in RCC to face shortly

- Molecular Biomarkers should be mandatory in the future
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TIVO-3: Phase 3 trial of Tivozanib vs. Sorafenib as 3rd or 4th line

Eligibility:
- Subjects with recurrent metastatic RCC who have failed 2 or 3 prior systemic regimens, one of which includes a VEGFR TKI
- Clear Cell Component
- Excluded >3 prior regimens

Stratification factors:
- ECOG PS (0 vs 1)
- Prior therapy with PD-1/PDL-1 (Y/N)

Randomization:
- Tivozanib: 1.5 mg (3 wk on/1 wk off)
- Sorafenib: 400 mg orally twice daily

N=322

Primary end point: PFS based on BICR
Secondary end points: ORR, OS, Safety

EudraCT Number: 2015-003607-30
McTigue M, et al. PNAS 2012
Immunosun trial: SOGUG-2016-A- IEC(REN)-10  (SOG058028)

- Clear Cell Renal Cell Carcinoma patients with stage IV that have failed to at least one prior line of systemic treatment based of immunotherapy either alone or in combination (antiPD-1, anti-PDL1 o rantiCTLA4)

  Sunitinib 50mg 4/2

- Radiologic progression by RECIST 1.1
- Unacceptable toxicity
- Consent withdrawal

PI Enrique Grande
My personal view of the future treatment of mRCC

Enrique Grande

VHL/angiogenesis driven biomarker

TKI w/wo IOs

Immune positive signature

IOs w/wo TKI or IOs doublets

AXL, MET or FGFR aberrations

Targeted agent

TSC, PTEN, PI3K, mTOR mutations

mTOR inhibitors w/wo lenvatinib
Muchas gracias

ONCOPROMESAS VS ONCOSAURIOS

ASIMILANDO LOS PROGRESOS EN ONCOLOGÍA

egrande@oncologiahrc.com