Is Immune Therapy the Holy Grail in Metastatic Kidney Cancer?”

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New Frontiers in Urologic Oncology  
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Is Immune Therapy the Holy Grail in Metastatic Kidney Cancer?

No, it is not.

Did I let Phil write my presentation title?

Yes, I did.

Do we need a Holy Grail?

It would solve some problems.
These are not very specific to RCC

Contemporary Immune therapy

- Cytokines
- Checkpoint inhibitors
- Vaccines
- Cellular therapy
Opportunities for RCC

RCC has features that show immune susceptibility

- Slow pattern of growth, for some
- Antigen load is intermediate
  SET2D: May amplify existing mutanome
- Proven response patterns
- Integration with targeted drugs (VEGFR, mTOR)

Challenges

- Responses may be slow
- Sequencing with VEGFR, debulking
- Subtypes – new development needed
- Coordinating with other diseases translational efforts
On-label/ off-label

Green:
US-FDA indication in RCC

Blue:
RCC specific trials accrual-completed

*/Red:
No US-FDA indication or no RCC pivotal trial
Contemporary Immune therapy

Opportunities for RCC

Cytokines

Interferon
IL-2

Engineered IL-2 cytokines

Activating antibodies

* / ALT-801
* / ALK-4230
* / NKTR-214

* / OX-40 ligand
MOXR0916, RG7888
Opportunities for RCC

Contemporary Immune therapy

Checkpoint inhibitors

*PD-1*

Nivolumab

*/ Pembrolizumab*

*/ Atezolizumab*

*/ Darvelumab*

*/ Avelumab*

*/ Ipilimumab*

*/ Tremilimumab*
Opportunities for RCC

Contemporary Immune therapy

*/ Immatics IMA-901

Vaccines

ARGOS

*/ ADAPT (AGS-003)
Opportunities for RCC

Contemporary Immune therapy

- TIL
- CAR-T

Cellular therapy
Contemporary Immune therapy

Combinations

- Cytokines
- Checkpoint inhibitors
- Vaccines
- Cellular therapy
- Targeted drugs
IL-2 aldesleukin (Proleukin™)

- 1992 approval in RCC
- Label describes ORR from phase II studies from over 20 years ago
- Newer series have higher response rates.

Responders

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Ever-treated

Evolving patient selection
Less fit
Not-clear cell type
Convenience factor
IL-2: The label

- 600,000 IU/kg/dose
- One dose every 8 hours, x 14 doses (or omit)
- Inpatient management only

- Two courses of 14 doses, 9-16 days apart:
  - Week 1 and 3 or
  - Week 1 and 4

- Evaluate response ~ 8-9 weeks.
- Repeat – 1-3 courses
IL-2: Still works

4/2016 ← ← ← 12/2013

45 y/o. Off treatment now 2+ years
1/12 or 1/6 or 1/3: Still not most.

*Patient selection* means fewer are treated.
ASCO 2016: #4555 Chow et al from UK: High dose Interleukin 2 (HD IL2) as 1\textsuperscript{st} line treatment in metastatic renal cell carcinoma (mRCC): A 10-year single centre experience.

<10% papillary + at least one of:

a) >50% alveolar and or > 50% solid architecture
b) <50% granular cytoplasm or >50% clear cell features

### Table

<table>
<thead>
<tr>
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<th>FAVOURABLE N=123</th>
<th>OTHER N = 21</th>
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<tr>
<td>Number</td>
<td>83</td>
<td>33</td>
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<tr>
<td>Papillary &lt;10%</td>
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<td>✓</td>
</tr>
<tr>
<td>Alveolar &gt;50%</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Granular &lt;50%</td>
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<tr>
<td>ORR %</td>
<td>51</td>
<td>39</td>
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<tr>
<td>CRR %</td>
<td>23</td>
<td>21</td>
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MCC 17099 “PROCLAIM”
IL-2 RCC database

Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival Probability

<table>
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<tr>
<th>CR</th>
<th>PD</th>
<th>PR</th>
<th>SD</th>
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<tr>
<td>11</td>
<td>116</td>
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<td>6</td>
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</tbody>
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Months Follow-Up

CR, n=11, mOS=NR
PR, n=17, mOS=NR
SD, n=41, mOS=49.6
PD, n=116, mOS=32.6
The lymphocyte

IL-2 receptor

IL-2

Alpha CD25

Beta CD 122

Gamma CD 132

The lymphocyte
IL-2 receptor: intermediate affinity

The T or NK lymphocyte
The regulatory lymphocyte

IL-2 receptor: high affinity

The alpha chain
Inhibits the off-rate of the IL-2

IL-2

Alpha CD25

Beta CD 122

Gamma CD 132

The regulatory lymphocyte
High dose IL-2

Both are ligated

Undesirable?
Low or very low dose IL-2

Desirable for Graft-vs-host?
Engineered IL-2: NKTR-214

CD25 is sterically blocked

Desirable – More effector?
NKTR-214, an Engineered Cytokine with Biased IL2 Receptor Binding, Increased Tumor Exposure, and Marked Efficacy in Mouse Tumor Models

NKTR-214, an Engineered Cytokine with Biased IL2 Receptor Binding, Increased Tumor Exposure, and Marked Efficacy in Mouse Tumor Models


Phase 1 just getting started

Works better with CTLA-4

Retards growth of B16 F10 melanoma
Engineered IL-2: ALK4230

CD25 is on the Cytokine already

Desirable – Level field
Engineered IL-2: ALK4230

CD25 is on the Cytokine already

regulatory lymphocyte

Desirable – Level field

Effector lymphocyte
“Circularly permuted IL-2 and IL-2Rα that is selective for the intermediate-affinity IL-2 receptor”

Both drive expansion of NK cells, however, a greater proportion of CD25+ NK cells with ALK 4232- than IL-2

Unlike IL-2, ALK 4230 does not effectively expand highly suppressive ICOS+ T_{reg}s

Contemporary Immune therapy

- Cytokines
- Checkpoint inhibitors
- Vaccines
- Cellular therapy

Tumor
Antibody Checkpoint inhibitors

- CTLA-4
- PD-1
- PD-L1

Checkpoint inhibitors

• CTLA-4:
  – Ipilimumab + nivolumab vs sunitinib

• PD-1
  – Nivolumab vs everolimus, 2\textsuperscript{nd} line (details)
  – Nivolumab + sunitinib
  – Nivolumab + pazopanib
  – Pembrolizumab + axitinib
Checkpoint inhibitors

- PD-L1
  - Bevacizumab/atezolizumab vs sunitinib
  - Avelumab/axitinib vs sunitinib ("Javelin")
  - Darvelumab study
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma


Clear Cell RCC
Prior therapy with VEGF

Nivolumab 3mg/kg 2w

Everolimus 10 mg

Sunitinib 488 (59)
Pazopanib 250 (30)
Axitinib 101 (12)

<table>
<thead>
<tr>
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<th>med PFS</th>
<th>events</th>
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<tr>
<td>Nivolumab</td>
<td>4.6 (3.7–5.4) mo</td>
<td>318</td>
</tr>
<tr>
<td>Everolimus</td>
<td>4.4 (3.7–5.5)</td>
<td>322</td>
</tr>
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</table>
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma


Clear Cell RCC
Prior therapy with VEGF

Nivolumab 3mg/kg 2w
Everolimus 10 mg

Nivolumab

Everolimus

med. OS # dec.
Nivolumab 25.0 (21.8–NE) mo 183
Everolimus 19.6 (17.6–23.1) 215

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

OS
Nivolumab

OS: PD-L1 < 1%

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

OS: **PD-L1 at least 1%**

Under 1% is favorable

**Median OS**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td>27.4 (21.4–NE)</td>
<td>21.2 (17.7–26.2)</td>
</tr>
</tbody>
</table>

“Same difference”
Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma


<table>
<thead>
<tr>
<th>PD-L1 expression level</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1%</td>
<td>181 (24)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>575 (76)</td>
</tr>
<tr>
<td>≥5%</td>
<td>85 (11)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>671 (89)</td>
</tr>
<tr>
<td>Patients without quantifiable PD-L1 expression — no. (%)</td>
<td>65 (8)</td>
</tr>
</tbody>
</table>
Nivolumab

Mechanism:
- PD-1 (programmed death) checkpoint protein on lymphocytes
- Antibody blocks ligation of ligands – PD-L1 (in some tumors) and PD-L2
- Lymphocyte behavior is changed: Tumor is attacked.
Nivolumab

August 2012 < ------------ June 2012 (prior sorafenib, LD IL-2, IFN)
April 2016  < ------------

HD IL-2 for lung nodules (regressed); skin nodules resected

Jan 2015  < ------------
Immatics IMA-901
- Sunitinib
- Sunitinib + cyclophosphamide/ 9 peptides (HLA-A2 only)
- No OS difference (ESMO 2015)

ARGOS Adapt
- Sunitinib ➔ everolimus ➔ next
- with or without: autologous DC vaccine – loaded with mRNA from the primary tumor
Cellular therapy

- CAR (chimeric antigen receptor)-T cells:
  - One day, but not today
  - RCC is does not have a prominent antigen to target
Cellular therapy

• TIL cells
  – RCC was an original development target
  – Negative trial for IL-2/LAK vs IL2 (next slide)
  – I think it will come around again.

  Tumor sample excision → Isolate lymphocytes, growth with IL-2 → Select relevant clones → Massive expansion → Reinfusion and IL-2 combination

181 patients
97 had RCC
54 had melanoma
(30 had other diagnoses)

1:1 randomization HD-IL-2 vs HD-IL+ LAK

Follow up at + 63 months median.

“Our results suggest a trend toward increased survival when IL-2 is given with LAK cells in patients with melanoma, but no trend was observed for patients with renal cell cancer.”
Summary – straightened out

- Cytokines
- Checkpoint inhibitors
- Targeted drugs
- Vaccines
- Radiation therapy
- Immunologic XRT
- Marker analysis
- Cellular therapy

THANK YOU