Novel Immunotherapeutic Approaches in mRCC

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Dana Farber Harvard Cancer Center
Harvard Medical School
Clinical Activity and Safety of Anti-Programmed Death-1 (PD-1) (Nivolumab; BMS-936558/MDX-1106/ONO-4538) in Patients With Previously Treated, Metastatic Renal Cell Carcinoma (mRCC): An Updated Analysis


1Beth Israel Deaconess Medical Center, Boston, MA; 2Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; 3Yale Cancer Center, New Haven, CT; 4Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women’s Hospital/Harvard Medical School, Boston, MA; 5Carolina BioOncology Institute, Huntersville, NC; 6University of Michigan, Ann Arbor, MI; 7Bristol-Myers Squibb, Princeton, NJ; 8Georgetown Lombardi Comprehensive Cancer Center, Washington DC
Anti-PD-1: Blocking T cell Suppression

Phase I Nivolumab: RCC cohort (n=34)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% ORR
  - 58% progression-free at 6 months
- Generally tolerable: fatigue, rash, pruritus, diarrhea; no MTD
  - 3 deaths: pneumonitis (non-RCC)
  - Grade 3-4 drug-related AEs occurred in 18%
Unanswered Clinical Questions

**Efficacy data**
- Is the clinical benefit a reflection of patient selection?
  - Or will SD pts = improved OS?
- How many responses are durable off therapy?
  - Like IL-2 and ipilimumab

**Toxicity**
- Will certain toxicities make combinations difficult?
  - (e.g. nephritis, hepatitis, pneumonitis)

**Biomarkers**
- Is PDL-1 expression predictive of response?
- Tumor heterogeneity
Phase III Nivolumab vs. Everolimus

Eligibility Criteria:
- mRCC with clear cell component
- 1 to 2 prior VEGF-targeted therapy
- Max=3 lines
- Stratification:
  - Regions
  - MSKCC risk

Randomization

Nivolumab
3mg/kg q2 weeks

Everolimus 10 mg PO QD

N=822

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, duration of response, OS in relation to PDL-1 status, safety, Patients-reported outcomes.

www.clinicaltrials.gov (NCT01668784)
Partial regression of metastatic RCC in a patient treated with 1 mg/kg nivolumab: durable benefit off therapy

• 48-year-old patient with low volume but poorly differentiated mRCC
• Developed progressive disease after sunitinib, sorafenib, and thoracic surgery
• Therapy held after 3 cycles due to near CR
• Response has continued for 3 years, while off therapy

Courtesy of M. Sznol, Yale Cancer Center
PD-1/PDL-1 Ab Data: Unanswered Clinical Questions

- **Efficacy data**
  - Is the clinical benefit a reflection of patient selection?
    - Or will SD pts = improved OS?
  - How many responses are durable off therapy?
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- **Toxicity**
  - Will certain toxicities make combinations difficult?
    - (e.g. nephritis, hepatitis, pneumonitis)

- **Biomarkers**
  - Is PDL-1 expression predictive of response?
  - Tumor heterogeneity
## Nivolumab-related adverse events

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tot Pop*†</td>
<td>RCC</td>
</tr>
<tr>
<td></td>
<td>N (%) of Patients, All Doses</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>220 (72)</td>
<td>29 (85)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>78 (26)</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Rash</td>
<td>41 (14)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (12)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31 (10)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (8)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Appetite ↓</td>
<td>24 (8)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hemoglobin ↓</td>
<td>18 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (5)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

*AEs occurring in ≥5% of the total population.
†Drug-related renal failure/nephritis occurred in 1% of the total population, with no grade 3-4 drug-related events, based on an analysis on July 3, 2012.
‡The most common grade 3-4 AEs were respiratory system disorders (2 patients) and hypophosphatemia (2 patients). An additional 10 grade 3-4 drug-related AEs (pruritus, rash macular, alanine aminotransferase, blood alkaline phosphatase increased, hypophosphataemia, muscular weakness, acute respiratory failure, cough, hypercapnia, hypoxia) were observed and one or more occurred in a single patient.
Pulmonary Complications with PD-1 Blockade
Established tumor on Day 7...
Combination therapy with irradiated RENCA and CTLA4 mAb had optimal efficacy
Phase 1 Study Combining Anti-PD-1 (Nivolumab) With Sunitinib or Pazopanib in Patients with Metastatic RCC

Metastatic RCC (Prior Pazopanib) → Arm S Escalation
Sunitinib + Nivolumab → MTD
Arm S Expansion
Sunitinib + Nivolumab

Metastatic RCC (Prior Sunitinib) → Arm P Escalation
Pazopanib + Nivolumab → MTD
Arm P Expansion
Pazopanib + Nivolumab

Nivolumab + Ipilimumab Arms Opening

NCT01472081
Primary end points:
Safety, Tolerability, MTD
PD-1/PDL-1 Ab Data: Unanswered Clinical Questions

• Efficacy data
  – Is the clinical benefit a reflection of patient selection?
    • Or will SD pts = improved OS?
  – How many responses are durable off therapy?
    • Like IL-2 and ipilimumab

• Toxicity
  – Will certain toxicities make combinations difficult?
    • (e.g. nephritis, hepatitis, pneumonitis)

• Biomarkers
  – Is PDL-1 expression predictive of response?
  – Tumor heterogeneity
Increased PD-L1 Expression in RCC Diminishes Survival

![Graph showing the relationship between Tumor PD-L1 expression and cancer-specific survival.](image)

- **Negative** PD-L1 expression is associated with higher cancer-specific survival compared to **Positive** expression.
- **N=306 Patients**

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Thompson, Kwon et al PNAS 2004
Correlation of PD-L1 expression in pre-treatment tumor biopsies with clinical outcomes

PD-L1 expression by IHC in 61 pretreatment tumor biopsies across tumor types from 42 patients

- **CR/PR**
- **Non-responders**
  - P=0.006

**Proportion of Patients**

- CR/PR: 17/17
- Non-responders: 16/25

**PD-L1 (+)**
- Patient samples: 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, 2 CRPC

**PD-L1 (-)**

- **RCC**
  - *2 patients still under evaluation*

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Topalian et al NEJM, 2012

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*Analysis was not pre-planned and based on a subset of patients

2 patients still under evaluation
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D.,
David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc.,
Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc.,
Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc.,
Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D.,
Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D.,
Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

ABSTRACT

Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples.

METHODS

From the Cancer Research UK London Research Institute (M. Gerlinger, A.J.R.,
S.H., D.E., E.G., P.M., N.M., A.S., B.P.,
S.B., N.Q.M., C.R.S., B.S.-D., G.C., G.S.,
J.D., C.S.). Royal Marsden Hospital De-
Response to IL-2 may be associated with tumor expression of PD-L1 and B7H-3 (VISTA)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>RR</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-L1 Tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=95)</td>
<td>19%</td>
<td>0.012</td>
</tr>
<tr>
<td>Positive (n=18)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td><strong>PD-L3 Tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=28)</td>
<td>10.7%</td>
<td>0.075</td>
</tr>
<tr>
<td>Positive (n=85)</td>
<td>29.4%</td>
<td></td>
</tr>
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</table>

Bailey, et al, ASCO 2013
IHC performed at Mayo Clinic by Kwon, Leibovich, et al.
High levels of innate immune signals, chemokines for T cell recruitment
But, negative immune regulators dominate

Gajewski, Curr Opin Immun 2011
Unanswered Questions

• Is PD-L1 expression uniform and stable in an individual tumor and from primary to metastasis?

• Are factors other than PD-L1 expression more reliable predictive markers of efficacy?

• Is predictive marker expression influenced by prior VEGF pathway therapy and does it predict for response to this therapy?

• Is PD-1 blockade better applied in the treatment naïve or VEGF pathway resistant setting?

• What are the mechanisms of resistance to PD-1 pathway blockade?

• What strategy is optimal for improving the efficacy of PD-1 blockade in RCC – combination with T cell agonists, other checkpoint inhibitors or VEGF pathway inhibitors?
Phase II PD-1 Ab RCC Study

Eligibility: metastatic clear cell RCC, no prior systemic rx

Assess:
- T cell infiltrate
- PD-L1 expression

Baseline primary tumor biopsy

Randomize

VEGF TKI X → Biopsy → PD-1 Ab Y

Serum samples at baseline, dose 4 and at time of progression (Tregs, MDSCs, sPD-L1)

Primary EP: DCR Landmark

Secondary endpoints:
- Safety
- Correlatives
  - CD8 T cell infiltration of kidney
  - CD8/Treg ratio, CD4/Treg ratio
  - Tumor PD-L1 expression
## PD-1/PD-L1 Pathway Agents in Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Agent</th>
<th>Structure</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplimune/GSK</td>
<td>AMP-224</td>
<td>Fc fusion protein to PD-L2</td>
<td>Phase I</td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>Nivolumab</td>
<td>Fully human, IgG 4 Ab</td>
<td>Phase III RCC, others solid tumors</td>
</tr>
<tr>
<td>Curetech/Teva</td>
<td>CT-011</td>
<td>Humanized monoclonal</td>
<td>Phase II melanoma, RCC</td>
</tr>
<tr>
<td>Genentech/Roche</td>
<td>MPDL3280A</td>
<td>PDL-1 Ab</td>
<td>Phase I</td>
</tr>
<tr>
<td>Merck</td>
<td>MK-3475</td>
<td>Humanized, IgG 4 ab</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR=47% in melanoma</td>
<td></td>
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## Investigational Immunotherapy

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Class</th>
<th>Development Phase</th>
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</thead>
<tbody>
<tr>
<td>Blockade of T-cell regulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTLA-4 Antibody</td>
<td>Ipilimumab</td>
<td>Fully human IgG1 mAb</td>
<td>FDA approved (melanoma)</td>
</tr>
<tr>
<td>PD-1 Antibody</td>
<td>Nivolumab</td>
<td>Fully human mAb</td>
<td>Phase III (RCC, Lung, Melanoma)</td>
</tr>
<tr>
<td>Inhibition of tumor induced T-cell function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β Antibody</td>
<td>GC1008</td>
<td>mAb</td>
<td>Phase I</td>
</tr>
<tr>
<td>T-cell activation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD-137</td>
<td>BMS-663513</td>
<td>mAb</td>
<td>Phase I</td>
</tr>
<tr>
<td>Targeted Cytokines</td>
<td>IL-21</td>
<td>Recombinant molecule</td>
<td>Phase 2 (melanoma)</td>
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<td>Dendritic cell activation</td>
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<tr>
<td>Toll-like receptor</td>
<td>HYB2055</td>
<td>TLR9 agonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Activated Dendritic Cells</td>
<td>AGS-003</td>
<td>Dendritic cell immunotherapy</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
Immunotherapy Improvement Model

All patients and tumors

**Immune responsiveness**
Elimination of Tregs/MDSC
CTLA4Ab
PD1 Ab
CD137 agonist Ab, IL-15, IL-21

**Tumor Responsiveness**
PDL1 Ab
Combination therapy (VEGF TKI)
Earlier therapy – front-line, adjuvant (ECOG)

**Focus Response**
AGS-003
PD-1 Ab + DC Vaccine (DFHCC SPORE Project 5)

**Selection**
Identify the patients in the overlap through translational research

Slide courtesy of M Atkins
Achieving the Dr Eisen’s Dream through “Targeted Immunotherapy”

"Bummer of a birthmark, Hal"
Phase III Perioperative PD-1 Blockade (E1812)

- Primary endpoint: Recurrence-free survival (RFS)
- 81% power to detect 25% reduction in survival hazard
- \( \uparrow \) RFS 4.9 yrs to 6.5 yrs
- \( \uparrow \) OS 6.4 yrs to 8.5 yrs

Gr3/4 T1b, T2-T3 RCC No Mets

Randomization

PD-1 Ab Y

2:1

IV Placebo q 2 wks x 2 cycles

n=975 all histologies (85% clear cell)

Stratify: intermediate high vs. very high risk, clear cell vs. non-clear cell histology, ECOG PS: 0 vs. 1

PD-1 Ab Y

Nephrectomy

IV Placebo q 3 wks x 17 Cycles
PD-1 inhibition: RCC Efficacy and Biomarker Discovery Studies

**Advanced or Metastatic RCC after Anti-Angiogenic Therapy (N=150)**
- BMS-936558: 0.3 mg/kg q3 wks
- BMS-936558: 2 mg/kg q3 wks
- BMS-936558: 10 mg/kg q3 wks

Primary Endpoint = Progression-free survival
www.clinicaltrials.gov (NCT01354431)

**Advanced or Metastatic RCC after Anti-Angiogenic Therapy (N=60)**
- BMS-936558: 0.3 mg/kg q3 wks
- BMS-936558: 2 mg/kg q3 wks
- BMS-936558: 10 mg/kg q3 wks

**Treatment-Naïve Advanced or Metastatic RCC (N=20)**
- BMS-936558: 10 mg/kg q3 wks

Primary Endpoint = Immunomodulatory Activity
www.clinicaltrials.gov (NCT01358721)