Ideal Sequence for Advanced Kidney Cancer Treatment

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Disclosures

I am a Consultant for Astellas, Aveo, Bristol-Myers Squibb, Eisai, Exelixis, Genentech, Ipsen, Novartis, Pfizer and Roche.
Background

- RCC incidence and deaths are in excess of 60,000 and 20,000 per year
- Incidence had been rising by about 2% per year, likely secondary to more sophisticated imaging approaches
- Localized disease currently managed by surgery alone (adjuvant treatment not common)
- Metastatic disease treated with either:
  - Surgery (if limited sites) or
  - Systemic therapy (more common)

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Histologies of RCC

- **Clear cell**
- **Papillary**
- **Chromophobe**
- **Sarcomatoid (10-15%)**

Other (~5%):
- Collecting Duct
- Unclassified
- Xp11.2 Translocation
Canonical Pathway in Clear Cell RCC

Kim WY, Kaelin WG. J Clin Oncol 2004

2019 Nobel Prize
Targets and Targeted/Immune Therapy for RCC

Debates in RCC Therapy

- Is HD IL-2 appropriate for everyone?
- Sunitinib or sorafenib?
- Everolimus or sorafenib?
- Cabozantinib, nivolumab or lenvatinib/everolimus?

First Line Debate

1992

2005
- Temsirolimus for poor risk?

2007

2009
- Axitinib or everolimus?

2011

2015

2018

2020
- Nivo/mpi or cabozantinib or axitinib/pembrolizumab?

Second Line Debate
Heng/IMDC risk validated in patients getting VEGF-TKIs.
A Banner Year for Immunotherapy in RCC

ESMO 2017: Nivolumab/Ipilimumab vs Sunitinib

ASCO GU 2018: Bevacizumab/Atezolizumab

ESMO 2018: Axitinib/Avelumab vs Sunitinib

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CheckMate 214: Study design

Patients
- Treatment-naïve advanced or metastatic clear-cell RCC
- Measurable disease
- KPS ≥70%
- Tumor tissue available for PD-L1 testing

Randomize 1:1
Stratified by
- IMDC prognostic score (0 vs 1–2 vs 3–6)
- Region (US vs Canada/Europe vs Rest of World)

Treatment
Arm A
3 mg/kg nivolumab IV + 1 mg/kg ipilimumab IV Q3W for four doses, then 3 mg/kg nivolumab IV Q2W

Arm B
50 mg sunitinib orally once daily for 4 weeks (6-week cycles)

Treatment until progression or unacceptable toxicity
OS: IMDC intermediate/poor risk

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>42 (37–47)</td>
<td>27 (22–31)</td>
</tr>
<tr>
<td>Confirmed BOR, %</td>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Complete response</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Partial response</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Stable disease</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Unable to determine/not reported</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

**Hazard ratio (99.8% CI), 0.63 (0.44–0.89)**

\[ P < 0.0001 \]
# ORR and PFS: IMDC **favorable** risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 249^a</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed ORR,(^b) % (95% CI)</td>
<td>29 (21–38)</td>
<td>52 (43–61)</td>
</tr>
<tr>
<td>PFS,(^c) median (95% CI), months</td>
<td>15.3 (9.7–20.3)</td>
<td>25.1 (20.9–NE)</td>
</tr>
</tbody>
</table>

- **Confirmed ORR:**
  - NIVO + IPI: 29 (21–38)
  - SUN: 52 (43–61)
  - *P* = 0.0002

- **PFS:**
  - NIVO + IPI: 15.3 (9.7–20.3)
  - SUN: 25.1 (20.9–NE)
  - HR (99.1% CI) 2.18 (1.29–3.68)
  - *P* < 0.0001

\(^a\) SUN and NIVO + IPI: No crossover allowed.
\(^b\) ORR includes PD-L1 positive PD-L1 positive cases.
\(^c\) No crossover allowed.
### Patient disposition: All treated patients

<table>
<thead>
<tr>
<th>Treatment discontinuation, %</th>
<th>NIVO + IPI N = 547</th>
<th>SUN N = 535</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment discontinuation, %</td>
<td>77</td>
<td>82</td>
</tr>
</tbody>
</table>

**Reasons for treatment discontinuation, %**

<table>
<thead>
<tr>
<th>Reason</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>42</td>
<td>55</td>
</tr>
<tr>
<td><strong>Study drug toxicity</strong></td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Adverse event unrelated to study drug</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

**Median duration of therapy (95% CI), months**

- NIVO + IPI: 7.9 (6.5–8.4)
- SUN: 7.8 (6.4–8.5)

**Median doses received (range), no.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>14 (1–63)</td>
<td>NA</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>4 (1–4)</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Median daily dose (range), mg/day**

- NIVO + IPI: NA
- SUN: 31 (14–50)

- In the NIVO + IPI arm, 79% of patients received all four doses of IPI
- Median follow-up was 25.2 months
## Treatment-related adverse events: All treated patients

<table>
<thead>
<tr>
<th>Event, %</th>
<th>NIVO + IPI N = 547</th>
<th>SUN N = 535</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–5</td>
</tr>
<tr>
<td>Treatment-related adverse events in ≥25% of patients</td>
<td>93</td>
<td>46</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Palmar-plantar erythrodynesesthesia syndrome</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Treatment-related AEs leading to discontinuation, %

<table>
<thead>
<tr>
<th>Event</th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| <sup>a</sup>Two patients had grade 5 cardiac arrest. <sup>b</sup>Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. <sup>c</sup>Cardiac arrest (n = 2), heart failure, multiple organ failure

60% of patients treated with NIVO + IPI required systemic corticosteroids for an adverse event

### Treatment-related deaths

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;sup&gt;b&lt;/sup&gt;n = 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;sup&gt;c&lt;/sup&gt;n = 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Banner Year for Immunotherapy in RCC

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ESMO 2018: Axitinib/Avelumab vs Sunitinib

ASCO GU 2019: Axitinib/Pembrolizumab vs Sunitinib
KEYNOTE-426 Study Design

**Key Eligibility Criteria**
- Newly diagnosed or recurrent stage IV clear-cell RCC
- No previous systemic treatment for advanced disease
- Karnofsky performance status ≥70
- Measurable disease per RECISTv1.1
- Provision of a tumor sample for biomarker assessment
- Adequate organ function

![Diagram showing study design and patient assignment](image)

- N = 432
- Pembrolizumab 200 mg IV Q3W for up to 35 cycles + Axitinib 5 mg orally twice daily\(^a\)

- N = 429
- Sunitinib 50 mg orally once daily for first 4 wks of each 6-wk cycle\(^b\)

**Stratification Factors**
- IMDC risk group (favorable vs intermediate vs poor)
- Geographic region (North America vs Western Europe vs ROW)

**End Points**
- **Dual primary**: OS and PFS (RECIST v1.1, BICR) in ITT
- **Key secondary**: ORR (RECIST v1.1, BICR) in ITT
- **Other secondary**: DOR (RECIST v1.1), PROs, safety

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\(^a\) Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.

\(^b\) Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.

BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.

KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab + Axitinib N = 432</th>
<th>Sunitinib N = 429</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>62 yrs (30-89)</td>
<td>61 yrs (26-90)</td>
</tr>
<tr>
<td>Male</td>
<td>308 (71.3%)</td>
<td>320 (74.6%)</td>
</tr>
<tr>
<td>Region of enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>104 (24.1%)</td>
<td>103 (24.0%)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>106 (24.5%)</td>
<td>104 (24.2%)</td>
</tr>
<tr>
<td>Rest of world</td>
<td>222 (51.4%)</td>
<td>222 (51.7%)</td>
</tr>
<tr>
<td>IMDC risk category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>138 (31.9%)</td>
<td>131 (30.5%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>238 (55.1%)</td>
<td>246 (57.3%)</td>
</tr>
<tr>
<td>Poor</td>
<td>56 (13.0%)</td>
<td>52 (12.1%)</td>
</tr>
<tr>
<td>Sarcomatoid features</td>
<td>51/285 (17.9%)</td>
<td>54/293 (18.4%)</td>
</tr>
<tr>
<td>PD-L1 CPS $\geq 1^a$</td>
<td>243/410 (59.3%)</td>
<td>254/412 (61.7%)</td>
</tr>
<tr>
<td>$\geq 2$ metastatic organs</td>
<td>315 (72.9%)</td>
<td>331 (77.2%)</td>
</tr>
<tr>
<td>Previous nephrectomy</td>
<td>357 (82.6%)</td>
<td>358 (83.4%)</td>
</tr>
</tbody>
</table>

*Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells $\times$ 100.

Data cutoff date: Aug 24, 2018.
Subsequent Anticancer Therapy Among Patients Who Discontinued Study Therapy

<table>
<thead>
<tr>
<th></th>
<th>Pembro + Axi n = 176</th>
<th>Sunitinib n = 242</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any subsequent therapy</td>
<td>88 (50.0%)</td>
<td>147 (60.7%)</td>
</tr>
<tr>
<td>Any PD-1 or PD-L1 inhibitor</td>
<td>8 (4.5%)</td>
<td>91 (37.6%)</td>
</tr>
<tr>
<td>Any VEGF or VEGFR inhibitor</td>
<td>78 (44.3%)</td>
<td>86 (35.5%)</td>
</tr>
<tr>
<td>Any other therapy</td>
<td>21 (11.9%)</td>
<td>26 (10.7%)</td>
</tr>
</tbody>
</table>

Patients may have received more than one subsequent therapy overall or within a category. Data cutoff date: Aug 24, 2018.
Overall Survival

12-mo rate
89.9%
78.3%

18-mo rate
82.3%
72.1%

HR 0.53 (95% CI 0.38-0.74)
P < 0.0001

No. at Risk
432
429

417
401

378
341

256
211

136
110

18
20

18
0

0

Data cutoff date: Aug 24, 2018.
Confirmed Objective Response Rate

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Pembro + Axi N = 432</th>
<th>Sunitinib N = 429</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>25 (5.8%)</td>
<td>8 (1.9%)</td>
</tr>
<tr>
<td>PR</td>
<td>231 (53.5%)</td>
<td>145 (33.8%)</td>
</tr>
<tr>
<td>SD</td>
<td>106 (24.5%)</td>
<td>169 (39.4%)</td>
</tr>
<tr>
<td>PD</td>
<td>47 (10.9%)</td>
<td>73 (17.0%)</td>
</tr>
<tr>
<td>NE(^a)</td>
<td>8 (1.9%)</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>NA(^b)</td>
<td>15 (3.5%)</td>
<td>28 (6.5%)</td>
</tr>
</tbody>
</table>

Response Duration

<table>
<thead>
<tr>
<th></th>
<th>N = 256</th>
<th>N = 153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range), mo</td>
<td>NR</td>
<td>15.2</td>
</tr>
<tr>
<td>(1.4+ to 18.2+)</td>
<td>(1.1+ to 15.4+)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Patients who had ≥1 post-baseline imaging assessment, none of which were evaluable per RECIST v1.1 by BICR.  \(^b\)Patients who did not have ≥1 post-baseline imaging assessment. Data cutoff date: Aug 24, 2018.
Treatment-Related Adverse Events: Incidence ≥20%

- Diarrhea
- Hypertension
- PPE
- Fatigue
- Hypothyroidism
- Nausea
- Decreased appetite
- Dysgeusia
- ALT increased
- AST increased
- Stomatitis
- Mucosal inflammation
- Dysphonia
- Thrombocytopenia

Incidence, %

Grade 1-2
Grade 3-5

Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.
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ASCO GU 2018: Bevacizumab/Atezolizumab

ESMO 2018: Axitinib/Avelumab vs Sunitinib

ASCO GU 2019: Axitinib/Avelumab vs Sunitinib

What is the role of VEGF-TKIs alone?
CABOSUN

Metastatic renal cell carcinoma
• No prior systemic trx
• Clear cell histology
• Measurable disease
• Intermediate/poor risk

1:1 Randomization

Primary endpoint of progression free survival.

Cabozantinib

Sunitinib

PFS per IRC and Overall Survival

Data cutoff: PFS, Sep 15, 2016; OS, July 1, 2017; IRC, Independent Review Committee; IMDC, International Metastatic RCC Database Consortium.

### Overall Survival (OS)
- **HR=0.80 (95% CI: 0.53-1.21); p=0.29 (2-sided)**
- Median OS: Cabozantinib **26.6 mo**, Sunitinib **21.2 mo**

### Subgroup Analyses of PFS per IRC

- **Median PFS**
  - Cabozantinib (N=79): 8.6 mo
  - Sunitinib (N=78): 5.3 mo

- **HR=0.48 (95% CI: 0.31-0.74), p=0.0008 (2-sided)**

- **No. of Events**
  - Cabozantinib: 43
  - Sunitinib: 49

### Time Since Randomization (Months)

- **Probability of PFS**

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**Choueiri et al ESMO 2017**
# Algorithm incorporating emerging first-line options

<table>
<thead>
<tr>
<th>Treatment</th>
<th>First-Line</th>
<th>Second-Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good risk</td>
<td>Axitinib/Pembrolizumab</td>
<td>Cabozantinib</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib*</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Intermediate/Poor-risk</td>
<td>Considering Nephrectomy</td>
<td>Nivolumab/Ipilimumab</td>
</tr>
<tr>
<td></td>
<td>Not Considering Nephrectomy</td>
<td>Nivolumab/Ipilimumab Axitinib/Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib*</td>
<td>Nivolumab</td>
</tr>
</tbody>
</table>

* For special populations (e.g., good-risk, bony metastatic disease, IO intolerant)
Optimizing Sequencing: ALLIANCE PDIGREE Trial

PIs: Tian Zhang, MD, Toni Choueiri, MD
RCC Cadre Leader: Dan George, MD

Nivo/Ipi x 4 doses

Primary Endpoint: OS
N=1044

CR (~10%)
Pd (~20%)

Randomization

1:1

Nivolumab

Cabo/Nivo

Cabozeratinib

mRCC
- Metastatic RCC (clear cell)
- IMDC intermediate or poor risk
- Archival tissue available (biopsy not required)
Optimizing Sequencing: Using the Most Potent TKIs in Upfront Combination

Cabozantinib with Atezolizumab

Dose Escalation

- UC (including renal pelvis, ureter, bladder, urethra) after prior platinum-based therapy, or
- RCC (clear cell, non-clear cell) with or without prior systemic anticancer therapy

Define Recommend Dose

RCC with clear cell histology who have not received prior systemic anticancer therapy

UC with progression on or after platinum-containing chemotherapy

UC not eligible for cisplatin-based chemo and no prior platinum-based chemotherapy

UC eligible for cisplatin-based chemotherapy with no prior platinum-based chemotherapy

Study Co-Chairs: Pal (COH)/Agarwal (Huntsman)

Dose Expansion in ncRCC

NCT03170960: A Phase 1b Dose-Escalation Study of Cabozantinib (XL184) Administered in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors
COSMIC-021: Cabo/Atezo Dose Escalation Cohort

40 mg cabozantinib + 1200 mg atezolizumab
60 mg cabozantinib + 1200 mg atezolizumab

Confirmed complete response
Confirmed partial response

nccRCC

ncc, non-clear cell
Where do gaps exist?

Second-line therapy?

Non-Clear Cell?

Need something that goes beyond current targeted therapy strategies and immunotherapy!
Optimizing Sequencing: Agents Outside of the VEGF/IO Axis

A Phase 1 Trial of SGN-CD70A in Patients With CD70-Positive, Metastatic Renal Cell Carcinoma

Sumanta K. Pal, MD; Andres Forero-Torres, MD; John A. Thompson, MD; John C. Morris, MD; Saurabh Chhabra, MD; Christopher J. Holmes, MD; Nicholas J. Vogelzang, MD; Thomas Boyd, MD; Paulo G. Bergerot, MD; Jacob J. Adashek, BA; Hong Li, PhD; Xuesong Yu, PhD; Elaina M. Gartner, MD; Anne-Sophie Carret, MD; and David C. Smith, MD

BACKGROUND: Cluster of differentiation 70 (CD70) is frequently expressed in renal cell carcinoma (RCC) and has immunomodulatory properties. An antibody-drug conjugate targeting CD70, SGN-CD70A, was developed to treat patients with CD70-positive RCC.

METHODS: The objective of this phase 1, open-label, dose-escalation, multicenter study was to evaluate the safety and tolerability of SGN-CD70A and establish its maximum tolerated dose in patients with CD70-positive, metastatic RCC (mRCC). All subtypes of RCC were permitted, and no limit was set on the number of prior therapies. Safety assessments consisted of monitoring and recording all adverse events (AEs) and dose-limiting toxicities (DLTs). Treatment response was assessed by radiographic tumor evaluation according to the Response Evaluation Criteria for Solid Tumors, version 1.1. A model-based, modified continual-reassessment method was used to estimate the probabilities of DLT and response.

RESULTS: The maximum tolerated dose was determined to be 30 μg/kg, with thrombocytopenia as the DLT. The most common AEs were fatigue (67%), anemia (61%), and thrombocytopenia (58%). Of 18 enrolled patients, 1 achieved a partial response and 13 achieved stable disease, for a clinical benefit rate of 78%. Limitations of the study included the heavily pretreated nature of patients, receipt of a median of 4 prior lines of therapy (range, 1-8 prior lines of therapy), and diminishing response potential.

CONCLUSIONS: The modest antitumor activity of SGN-CD70A does not support its development in mRCC. However, given the high disease control rate in a heavily pretreated population and the modest toxicity profile, CD70 remains of interest because of its immunomodulatory properties. Cancer 2019;125:1124-1132. © 2019 American Cancer Society.

KEYWORDS: antibody-drug conjugate, cluster of differentiation 70 (CD70), kidney cancer, phase 1, renal cell carcinoma, SGN-CD70A.
Optimizing Sequencing: Agents Outside of the VEGF/IO Axis

Figure 2. Tumor size is illustrated over time (N = 18). Diamonds indicate response assessments that occurred after the last dose. CP indicates clinical progression; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Median progression-free survival is illustrated in patients with metastatic renal cell carcinoma who received SGN-CD70A (N = 18). CI indicates confidence interval; PD, progressive disease.

Randomized, phase II study ongoing now (CANTATA) of a glutaminase inhibitor
Primary endpoint is progression-free survival (recall median estimate is 7.4 mos in METEOR)
Optimizing Sequencing: Targeting the Microbiome

Summary:
- 20 patients with mRCC
- Receiving VEGF-TKIs
- Median of 2 prior lines of therapy
- Objective: To determine association between bacteriomic profile and presence or absence of diarrhea

Pal SK et al CCR 2015
Microbiome in Renal Cell Carcinoma

Summary:
• 121 pts with RCC
• 239 pts with NSCLC
• Antibiotic use associated with inferior outcome in pts receiving checkpoint inhibitors
• Similar trends in NSCLC and RCC pts

Derosa L et al Ann Oncol 2018 (RCC Investigators: DeRosa, Albiges, Escudier)
Microbiome in Renal Cell Carcinoma

Summary:
- 60 pts with NSCLC
- 40 pts with RCC
- Baseline and serial stool collections after checkpoint inhibitor initiated
- Specific bacterial species associated with response

Routy B et al Science 2017 (RCC Investigators: DeRosa, Albige, Escudier)
Microbiome in Renal Cell Carcinoma

- Patients with mRCC receiving standard of care nivolumab.
  - Bacteriomic profiling
  - n = 30
  - C1D1

- No diarrhea
  - C3D1

- Development of diarrhea

Courtesy of Nazli Dizman, MD. Unpublished data. Do not distribute.
Microbiome in Renal Cell Carcinoma

A. PCO2 (21.5% of total variation)

B. PCO2 (16.3% of total variation)

- Bacteroides
- Barnesiella
- Phascolarctobacterium
- Faecalibacterium
- Anaerorhabdus
- Lactonifactor

- Nivolumab P
- Nivolumab R

Unclassified Clostridiales
Unclassified Ruminococcaceae
Bifidobacterium, Blautia,
Dorea, Asaccharobacter,
Coprococcus, Lachnospira,
Anaerostipes, Roseburia

Courtesy of Nazli Dizman, MD. Unpublished data. Do not distribute.
## Treatment Arms

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Number of Patients</th>
<th>Dose</th>
<th>CBM588</th>
<th>Nivolumab/Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>10</td>
<td>None</td>
<td>3 mg/kg</td>
<td>3 mg/kg / 1 mg/kg</td>
</tr>
<tr>
<td>Arm 2</td>
<td>20</td>
<td>60 mg tid</td>
<td>3 mg/kg</td>
<td>3 mg/kg / 1 mg/kg</td>
</tr>
</tbody>
</table>

![Graph](image)
Can we better target non-clear cell RCC?

- Clear cell
- Papillary
- Chromophobe
- Other (~5%): Collecting Duct, Unclassified, Xp11.2 Translocation
- Sarcomatoid (10-15%)
Beyond TCGA: Genomics of Papillary RCC

- TCGA
  - 73% of pts M0
  - 3% of pts M1
  - Remainder unknown

- FMI cohort
  - 61% of pts M1
  - 21% of pts stage III
  - 13% of pts stage I-II
## Beyond TCGA: Genomics of Papillary RCC

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>169</td>
<td>39</td>
<td>108</td>
<td>22</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>60 (19–88)</td>
<td>60 (30–88)</td>
<td>59 (19–85)</td>
<td>61 (25–76)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>40 (24)</td>
<td>10</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>129 (76)</td>
<td>29</td>
<td>82</td>
<td>18</td>
</tr>
<tr>
<td>Median TMB, mutations/Mb (range)</td>
<td>2.7 (0–13.5)</td>
<td>2.7 (0.9–9.0)</td>
<td>2.7 (0–13.5)</td>
<td>2.7 (0–8.1)</td>
</tr>
<tr>
<td>Site of origin for sequenced sample (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>102</td>
<td>26</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>Metastasis</td>
<td>67</td>
<td>13</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Clinical stage (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>14</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Stage II</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Stage III</td>
<td>36</td>
<td>9</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Stage IV</td>
<td>103</td>
<td>20</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

TMB = tumor mutational burden.
Beyond TCGA: Genomics of Papillary RCC

- TCGA
  - 73% of pts M0
  - 3% of pts M1
  - Remainder unknown

- FMI cohort
  - 61% of pts M1
  - 21% of pts stage III
  - 13% of pts stage I-II

Pal SK et al European Urology 2018
The Previous Approach

Lump into a single clinical trial

- Chromophobe
- Papillary
- Sarcomatoid
Clinical Management of Non-Clear Cell RCC: ESPN

- **mRCC**
  - Non-clear cell histology
  - ECOG PS 0-1
  - Measurable disease
  - Adequate organ function
  - No prior systemic therapy
  - No uncontrolled brain metastasis

- **Randomization**
  - Sunitinib (Standard schedule)
  - Everolimus (Standard schedule)

- **Crossover**
  - Sunitinib (Standard schedule)
  - Everolimus (Standard schedule)

- **Histologies permitted:** Papillary, chromophobe, unclassified, translocation (Xp11.2) and clear-cell with ≥ 20% sarcomatoid features
- **Projected sample size:** 108 patients

### Clinical Management of Non-Clear Cell RCC: ESPN

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Everolimus Median, mos (95% CI)</th>
<th>Sunitinib Median, mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>14.9 (7.1, 22.7) n=13</td>
<td>16.6 (5.9, NA) n=14</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>25.1 (4.7, NA) n=6</td>
<td>31.6 (14.2, NA) n=6</td>
</tr>
<tr>
<td>Unclassified</td>
<td>NA n=6</td>
<td>15.4 (NA) n=4</td>
</tr>
<tr>
<td>Translocation</td>
<td>8.1 (5.5, 23) n=4</td>
<td>16.2 (8.8, NA) n=3</td>
</tr>
<tr>
<td>Sarcomatoid w/ clear-cell</td>
<td>11.1 (2.0, NA) n=6</td>
<td>7.0 (5.4, 10.4) n=6</td>
</tr>
</tbody>
</table>

**Are these numbers just too small?**

Clinical Management of Non-Clear Cell RCC: ESPN

- What other data might guide us?

mRCC
- Non-clear cell histology
- ECOG PS 0-1
- Measurable disease
- Adequate organ function
- No prior systemic therapy
- No uncontrolled brain metastasis

ESPN

Sunitinib (Standard schedule)
Everolimus (Standard schedule)

Randomization

Crossover

Sunitinib (Standard schedule)
Everolimus (Standard schedule)

Clinical Management of Non-Clear Cell RCC: RECORD-3

- What other data might guide us?

Clinical Management of Non-Clear Cell RCC: RECORD-3

- What other data might guide us?

mRCC
- Non-clear cell (papillary, chromophobe and undifferentiated)
- N=108 (study completed accrual)

ASPEN

Sunitinib (Standard schedule)

Everolimus (Standard schedule)

Crossover

The Previous Approach

Lump into a single clinical trial

- ASPEN
- ESPN
- RECORD-3

Across all studies, pts did better with sunitinib v everolimus

How does this apply across subtypes?
A Better Approach

Understand disease biology

- Chromophobe
- Papillary
- Sarcomatoid

Apply rationally selected drugs

- Papillary
- Sarcomatoid
Clinical Management: Focus on Papillary RCC

- PI3K
- Akt/PKB
- Ras
- TSC1/2
- Raf
- mTOR
- S6K1
- 4E-BP1
- eIF-4E
- Sunitinib
- Pazopanib
- Axitinib
- Sorafenib
- Lenvatinib
- Temsirolimus
- Everolimus
Clinical Management: Focus on Papillary RCC

- PI3K
- Akt/PKB
- Ras
- TSC1/2
- Raf
- mTOR
- S6K1
- 4E-BP1
- elF-4E
- Savolitinib
- Temsirolimus
- Everolimus
- Sunitinib
- Pazopanib
- Axitinib
- Sorafenib
- Lenvatinib
- MET
- VEGFR
- Ras
- Raf
- PI3K
- Akt/PKB
- TSC1/2
Savolitinib in PRCC (n=111)

Choueiri T …. Pal SK (JCO 2017)
Clinical Management: Focus on Papillary RCC

- PI3K
- Akt/PKB
- Ras
- Raf
- mTOR
- S6K1
- 4E-BP1
- eIF-4E
- PI3K
- Raf
- TSC1/2
- Sunitinib
- Pazopanib
- Axitinib
- Sorafenib
- Lenvatinib
- Temsirolimus
- Everolimus
- Savolitinib
- Crizotinib
**Clinical Management: Focus on Papillary RCC**

## Crizotinib in Type 1 PRCC

<table>
<thead>
<tr>
<th>Best response (RECIST V1.1)</th>
<th>PRCC1 MET+, N=4</th>
<th>PRCC1 MET-, N=16</th>
<th>PRCC1 MET?, N=3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best response (RECIST v1.1), N (%):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed CR</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>2 (50.0)</td>
<td>1 (6.3)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (25.0)</td>
<td>12 (75.0)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (25.0)</td>
<td>3 (17.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td><strong>Treatment ongoing/stopped</strong></td>
<td>0 / 4</td>
<td>3 / 13</td>
<td>1 / 2</td>
</tr>
<tr>
<td><strong>Treatment duration (months):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.9 (9.3)</td>
<td>5.3 (6.0)</td>
<td>20.6 (16.7)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>11.1 (1.5 – 23.9)</td>
<td>3.4 (1.9 – 26.8)</td>
<td>30.3 (1.4 – 30.3)</td>
</tr>
</tbody>
</table>

- Not all Type 1 pts were characterized as having abnormalities in MET
- Emphasizes need for understanding MET status

Schoffski P, Albiges L. Eur J Cancer 2017
Clinical Management: Focus on Papillary RCC

- PI3K
- Akt/PKB
- Ras
- TSC1/2
- Raf

**mTOR**

- S6K1
- 4E-BP1
- eIF-4E

**Targeted Agents**
- Sunitinib
- Pazopanib
- Axitinib
- Sorafenib
- Lenvatinib
- Temozolomide
- Everolimus
- Savolitinib
- Crizotinib
- Cabozantinib
Clinical Management: Focus on Papillary RCC

Cabozantinib in mRCC (clear cell)

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>21.4 (18.7-NE)</td>
<td>140</td>
</tr>
<tr>
<td>Everolimus</td>
<td>16.5 (14.7-18.8)</td>
<td>180</td>
</tr>
<tr>
<td>HR</td>
<td>0.66 (95% CI, 0.53-0.83)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>.00026</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Management: Focus on Papillary RCC

Cabozantinib in PRCC

- RENCA reflects ccRCC; ACHN reflects PRCC
- Cabozantinib and crizotinib may be more active in PRCC
- Preclinical models are being devised

Courtesy of Jeremy Jones, PhD
Clinical Management: Focus on Papillary RCC

- What is the optimal strategy for MET inhibition?
- Need comparative data!
Clinical Management: SWOG 1500 for mPRCC

- PI: S. Pal (City of Hope)
- Translational PI: B. Shuch (Yale)
  - BISQFP funding for genomic characterization

- Requires 41 pts/arm → 164 pts total
- Assuming 10% ineligibility → 180 pts total

NCT02761057: A Randomized, Phase II Efficacy Assessment of Multiple MET Kinase Inhibitors (Cabozantinib [NSC #761968], Crizotinib [NSC #749005], Savolitinib [NSC #785348], and Sunitinib [NSC #736511]) in Metastatic Papillary Renal Carcinoma (PAPMET)
A role for genomic profiling in every patient with PRCC?

Thank you!

City of Hope / Beckman Research Institute
- Tanya Dorff, MD (Section Chief, GU Oncology)
- Ravi Salgia, MD (Chair, Medical Oncology)
- GU Fellows: Paulo Bergerot, MD; Cris Bergerot, PhD; Nazli Dizman, MD; Nicholas Salgia

- Thank you do Dr. Morgan, Mortimer, Cristea, Margolin, Salehian and the exceptional COH faculty and nurses (Barb/Lani/Esmerelda) for over a decade of great teaching!

@montypal