Renal Cell Carcinoma Webinar

Tuesday, January 7, 2020
11 a.m.–12 p.m. EST

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

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The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC)

Brian I. Rini¹, Dena Battle², Robert A. Figlin³, Daniel J. George⁴, Hans Hammers⁵, Tom Hutson⁶, Eric Jonasch⁷, Richard W. Joseph⁸, David F. McDermott⁹, Robert J. Motzer¹⁰, Sumanta K. Pal¹¹, Allan J. Pantuck¹², David I. Quinn¹³, Virginia Seery⁹, Martin H. Voss¹⁰, Christopher G. Wood⁷, Laura S. Wood¹ and Michael B. Atkins¹⁴
# Webinar Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:00–11:05 a.m. EST</td>
<td>Welcome, Introductions and Overview</td>
</tr>
<tr>
<td>11:05–11:35 a.m. EST</td>
<td>Review of SITC Cancer Immunotherapy Guideline – Renal Cell Carcinoma</td>
</tr>
<tr>
<td>11:35-11:40 a.m. EST</td>
<td>Discussion</td>
</tr>
<tr>
<td>11:40–11:45 a.m. EST</td>
<td>Question and Answer Session</td>
</tr>
<tr>
<td>11:45-11:57 a.m. EST</td>
<td>Case Studies</td>
</tr>
<tr>
<td>11:57 a.m.–12:00 p.m. EST</td>
<td>Closing Remarks</td>
</tr>
</tbody>
</table>
How to Submit Questions

**Computer**

**Mobile Phone**
Webinar Faculty

Michael B. Atkins, MD  
Georgetown-Lombardi Comprehensive Cancer Center

Dena Battle  
KCCure

David McDermott, MD  
Beth Israel Deaconess Medical Center

Brian Rini, MD  
Vanderbilt University Medical Center
Previous standard-of-care treatment for aRCC

• Nephrectomy, if eligible
• Tyrosine kinase inhibitors (TKIs)
• mTOR inhibitors
• High-dose IL-2
Timeline of IO in RCC

Resurgence of interest in immunotherapy

Level of interest

- <1980s
- 1992
- 2000
- 2009
- 2013
- 2015
- 2018

- Vaccines
- HD IL-2
- IFN-α and IL-2 based regimens
- Targeted Therapies
- Bevacizumab + IFN-α
- Nivolumab
- Ipilimumab + Nivolumab, Pembrolizumab + axitinib, Avelumab + axitinib
## Current immunotherapy approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose Interleukin-2</td>
<td>1992</td>
<td>Metastatic RCC</td>
<td>600,000 International Units/kg (0.037 mg/kg) IV q8hr infused over 15 minutes for a maximum 14 doses, THEN 9 days of rest, followed by a maximum of 14 more doses (1 course)</td>
</tr>
<tr>
<td>Interferon-a + bevacizumab</td>
<td>2009</td>
<td>Clear cell RCC</td>
<td>IFN 9 MIU s.c. three times a week + bev 10 mg/kg Q2W</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>2015</td>
<td>Clear cell RCC refractory to prior VEGF targeted therapy</td>
<td>3mg/kg or 240mg IV Q2W or 480mg IV Q4W</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>2018</td>
<td>Clear cell RCC, treatment naïve</td>
<td>3mg/kg nivo plus 1mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing</td>
</tr>
<tr>
<td>Pembrolizumab + axitinib</td>
<td>2019</td>
<td>Advanced RCC, Treatment naïve</td>
<td>200 mg pembro Q3W + 5 mg axitinib twice daily</td>
</tr>
<tr>
<td>Avelumab + axitinib</td>
<td>2019</td>
<td>Advanced RCC, Treatment naïve</td>
<td>800 mg avelumab Q2W + 5 mg axitinib twice daily</td>
</tr>
</tbody>
</table>
Key clinical questions

1. How should checkpoint inhibitors be integrated into the **first-line** treatment of advanced clear cell renal carcinoma (accRCC)?
2. How should checkpoint inhibitors be integrated into treatment of **refractory** accRCC?
3. How should **adjuvant therapy** and related failures be managed within an IO-related treatment paradigm for patients with accRCC?
4. How should **treatment response** to immunotherapy be evaluated, monitored and managed in patients with accRCC?
5. What is the role of **biomarker** testing in patients with aRCC?
6. What is the role of immunotherapy in **non-clear cell** pathology?
7. How should immune-related **adverse events** be recognized and managed in patients with accRCC?
8. Are there populations of patients with accRCC who should not receive **immunotherapy**?
Key clinical questions

1. How should checkpoint inhibitors be integrated into the first-line treatment of advanced clear cell renal carcinoma (accRCC)?
2. How should checkpoint inhibitors be integrated into treatment of refractory accRCC?
3. How should adjuvant therapy and related failures be managed within an IO-related treatment paradigm for patients with accRCC?
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5. What is the role of biomarker testing in patients with aRCC?
6. What is the role of immunotherapy in non-clear cell pathology?
7. How should immune-related adverse events be recognized and managed in patients with accRCC?
8. Are there populations of patients with accRCC who should not receive immunotherapy?
# Summary of front-line phase 3 trials

<table>
<thead>
<tr>
<th></th>
<th>CheckMate 214</th>
<th>KEYNOTE-426</th>
<th>JAVELIN 101</th>
<th>IMmotion151</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Ipilimumab + Nivolumab</td>
<td>Pembrolizumab + Axitinib</td>
<td>Avelumab + Axitinib</td>
<td>Atezolizumab + Bevacizumab</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>OS, PFS, ORR in int/poor risk</td>
<td>OS, PFS</td>
<td>PFS, OS in PD-L1+</td>
<td>PFS in PD-L1+; OS</td>
</tr>
<tr>
<td><strong>mPFS, months</strong></td>
<td>9.7 vs 9.7</td>
<td>15.1 vs 11.1</td>
<td>13.8 vs 8.4</td>
<td>11.2 vs 8.4</td>
</tr>
<tr>
<td><strong>ORR (ITT), %</strong></td>
<td>41% vs 34%</td>
<td>59% vs 36%</td>
<td>51% vs 26%</td>
<td>37% vs 33%</td>
</tr>
<tr>
<td><strong>12 month survival (ITT)</strong></td>
<td>83% vs 77%</td>
<td>90% vs 78%</td>
<td>86% vs 83%</td>
<td>63% vs 60%</td>
</tr>
</tbody>
</table>

IIT: Intent-to-Treat; PFS: progression-free survival; ORR: overall response rate; OS: overall survival

Tannir, ASCO GU 2019.  
CheckMate 214

**Intermediate/poor risk**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months (95% CI)</th>
<th>HR (95% CI), 0.66 (0.54–0.80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO+IPI</td>
<td>NR (35.6–NE)</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>SUN</td>
<td>26.6 (22.1–33.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Favorable risk**

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months (95% CI)</th>
<th>HR (95% CI), 1.22 (0.73–2.04)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO+IPI</td>
<td>NR (NE)</td>
<td>P = 0.4426</td>
</tr>
<tr>
<td>SUN</td>
<td>NR (NE)</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>425</td>
<td>422</td>
</tr>
<tr>
<td>6</td>
<td>399</td>
<td>388</td>
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<tr>
<td>12</td>
<td>372</td>
<td>353</td>
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<td>18</td>
<td>348</td>
<td>318</td>
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<tr>
<td>24</td>
<td>332</td>
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<td>30</td>
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<td>36</td>
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<td>236</td>
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<td>42</td>
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<td>48</td>
<td>270</td>
<td>207</td>
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<td>54</td>
<td>253</td>
<td>194</td>
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<td>60</td>
<td>233</td>
<td>179</td>
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<td>66</td>
<td>183</td>
<td>144</td>
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<tr>
<td>72</td>
<td>90</td>
<td>75</td>
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<td>78</td>
<td>34</td>
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<tr>
<td>84</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Tannir, ASCO GU 2019.
KEYNOTE-426

KEYNOTE-426: OS in the ITT Population

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

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts w/ Event</td>
<td>432</td>
<td>417</td>
<td>378</td>
<td>256</td>
<td>136</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>12</td>
<td>16</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Pembro + Axi</td>
<td>13.7%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>13.7%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
<td>22.6%</td>
</tr>
</tbody>
</table>

Rini, ASCO 2019
JAVELIN 101

A Patients with PD-L1–Positive Tumors

- **Avelumab + Axitinib**
  - Median Progression-free Survival (95% CI): 13.8 (11.1–NE)
  - Stratified hazard ratio for disease progression or death: 0.61
    (95% CI: 0.47–0.79)
  - P < 0.001

- **Sunitinib**
  - Median Progression-free Survival (95% CI): 7.2 (5.7–9.7)

No. at Risk

- Avelumab + Axitinib: 270
  - 227
  - 205
  - 154
  - 120
  - 76
  - 53
  - 32
  - 23
  - 13
  - 3
  - 1
  - 0

- Sunitinib: 290
  - 210
  - 174
  - 119
  - 85
  - 49
  - 35
  - 16
  - 13
  - 5
  - 0

B Overall Population

- **Avelumab + Axitinib**
  - Median Progression-free Survival (95% CI): 13.8 (11.1–NE)

- **Sunitinib**
  - Median Progression-free Survival (95% CI): 8.4 (6.9–11.1)

No. at Risk

- Avelumab + Axitinib: 442
  - 364
  - 321
  - 250
  - 193
  - 127
  - 94
  - 57
  - 42
  - 24
  - 8
  - 1
  - 0

- Sunitinib: 444
  - 329
  - 271
  - 192
  - 144
  - 90
  - 64
  - 29
  - 20
  - 8
  - 2
  - 0

IMmotion151

A

Median progression-free survival in the PD-L1 positive population, months (95% CI)

- Atezolizumab plus bevacizumab group: 11.2 (8.9–15.0)
- Sunitinib group: 7.7 (6.8–9.7)

HR 0.74 (95% CI 0.57–0.96); p=0.0217

12-month progression-free survival: 49% (95% CI 41–56)

12-month progression-free survival: 38% (95% CI 31–45)

D

Median overall survival in the ITT population, months (95% CI)

- Atezolizumab plus bevacizumab group: 33.6 (29.0–NE)
- Sunitinib group: 34.9 (27.8–NE)

HR 0.93 (95% CI 0.76–1.14); p=0.4751

24-months overall survival: 63% (95% CI 58%–67%)

24-months overall survival: 60% (95% CI 56%–65%)

Are IMDC risk categories relevant in the era of IO-based combination therapy?

- Not relevant: 59%
- Still provide information that may influence treatment choice: 41%
First-line treatment

**Recommendations for:**
Treatment naïve, ECOG 0, ccRCC patient with “favorable” risk per IMDC, who is determined to need systemic therapy and has no contraindication to receiving either an IO or an anti-VEGF therapy

- Pembrolizumab + axitinib
- Nivolumab + ipilimumab
- TKI monotherapy
- Either avelumab/axitinib or HD IL-2

Percent committee recommending
First-line treatment

Recommendations for: Treatment naïve, ECOG 0 ccRCC patient with “intermediate/poor” risk per IMDC, who is determined to need systemic therapy and has no contraindication to receiving either an IO or an anti-VEGF therapy

- Nivolumab + ipilimumab
- Pembrolizumab + axitinib
- ICI monotherapy

Percent Committee Recommending
First-line treatment

When to give a treatment-naïve patient IO monotherapy over an IO-based doublet:

- History of autoimmune disease
- Over 80 years of age
- History of vascular disease
- Poor performance status
- Liver metastases with mild increase in LFTs
- Never recommend monotherapy
Key clinical questions

1. How should checkpoint inhibitors be integrated into the first-line treatment of advanced clear cell renal carcinoma (accRCC)?

2. How should checkpoint inhibitors be integrated into treatment of refractory accRCC?

3. How should adjuvant therapy and related failures be managed within an IO-related treatment paradigm for patients with accRCC?

4. How should treatment response to immunotherapy be evaluated, monitored and managed in patients with accRCC?

5. What is the role of biomarker testing in patients with aRCC?

6. What is the role of immunotherapy in non-clear cell pathology?

7. How should immune-related adverse events be recognized and managed in patients with accRCC?

8. Are there populations of patients with accRCC who should not receive immunotherapy?
CheckMate 025

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>410</td>
<td>411</td>
</tr>
<tr>
<td>Median Overall Survival (95% CI)</td>
<td>25.0 (21.8–NE)</td>
<td>19.6 (17.6–23.1)</td>
</tr>
<tr>
<td>No. of Deaths</td>
<td>183</td>
<td>215</td>
</tr>
</tbody>
</table>

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

Motzer, NEJM 2015.
Second-line treatment

Recommendations for:
A previously treated, ECOG 0, clear cell mRCC patient with “favorable” risk whose tumors progressed on front-line therapy with sunitinib

- Nivolumab monotherapy
- Nivolumab + ipilimumab
Second-line treatment

After progression on nivolumab/ipilimumab:

- Cabozantinib
- Axitinib
- HD IL-2
Second-line treatment

After progression on IO/TKI combination:

- [Green] Cabozantinib
- [Blue] Nivolumab + ipilimumab
- [Gray] Levatinib + everolimus
Key clinical questions

1. How should checkpoint inhibitors be integrated into the first-line treatment of advanced clear cell renal carcinoma (accRCC)?

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8. Are there populations of patients with accRCC who should not receive immunotherapy?
Sunitinib

• FDA-approved for RCC treatment post-nephrectomy in high-risk patients

• 50 mg/day

• Common AEs include diarrhea, palmar-plantar erythrodysesthesia, hypertension

Ravaud, NEJM 2016.
### Adjuvant treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment arms</th>
<th>Primary outcome</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 914</td>
<td>Nivolumab + Ipilimumab vs. placebo</td>
<td>DFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>IMmotion010</td>
<td>Atezolizumab vs. placebo</td>
<td>DFS</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>KEYNOTE-564</td>
<td>Pembrolizumab vs. placebo</td>
<td>Safety, efficacy, DFS</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>PROSPER RCC</td>
<td>Perioperative nivolumab vs. nephrectomy alone</td>
<td>RFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>RAMPART</td>
<td>Durvalumab vs. durvalumab + tremelimumab vs. active monitoring</td>
<td>DFS and OS</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
Adjuvant treatment

Would you recommend nivolumab/ipilimumab combination to a patient with aRCC who received prior adjuvant IO within last 6 months?

- Yes: 67%
- No: 33%
Adjuvant treatment

Would you recommend IO/TKI combination to a patient with aRCC who received prior adjuvant IO or sunitinib within last 6 months?

Yes: 67%
No: 33%
Adjuvant treatment

Treatment recommendation for RCC that progressed ≥6 months following adjuvant PD-1/PD-L1 monotherapy

Nivolumab + ipilimumab

47%

Pembrolizumab + axitinib

47%
Adjuvant treatment

**Recommendations for:**
Patients whose disease has progressed >6 months following completion of adjuvant sunitinib
Key clinical questions

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8. Are there populations of patients with accRCC who should not receive immunotherapy?
Evaluating response

Which endpoints are most important to you in evaluating a treatment for patients with advanced RCC?

Committee ranking:
1. Landmark overall survival (OS)
2. Complete response (CR) rate
3. Median progression free survival (PFS)
4. Treatment free survival (TFS)
5. Overall response rate (ORR)
6. Disease control rate (DCR)
7. Quality of life
8. Cost effectiveness
Monitoring patients

What do you routinely monitor in advanced ccRCC patients treated with immunotherapy?
Monitoring patients

**Recommendations for:**
An aRCC patient on anti-PD-1 monotherapy (e.g. nivolumab) who experiences RECIST-defined PD (e.g. in maintenance phase of ipilimumab/nivolumab or on nivolumab monotherapy)

Repeat scans in 4-12 weeks and continue nivolumab if the patient is clinically well, until additional progression is documented.

75%
Monitoring patients

**Recommendations for:** How long to continue therapy in a patient with a CR or near CR after ipilimumab plus nivolumab induction and 6-9 months of maintenance nivolumab therapy

- Stop therapy at this point
- Treat patient for a given number of cycles after best response
- Treat indefinitely
Monitoring patients

**Recommendations for:**
In the absence of limiting toxicity, patient receives axitinib/IO combination therapy. At month 9 they have a CR/near CR/over 80% response.
Monitoring patients

When to stop immunotherapy treatment

- Patient demonstrates CR
- Confirmed or symptomatic progression
- Two years of therapy without PD

Percent Committee Recommending
Key clinical questions

1. How should checkpoint inhibitors be integrated into the first-line treatment of advanced clear cell renal carcinoma (accRCC)?
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8. Are there populations of patients with accRCC who should not receive immunotherapy?
Biomarkers in aRCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>OS by PD-L1 status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 025</td>
<td>Nivolumab vs everolimus</td>
<td>&lt;1%: 27.4 vs 21.2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1%: 21.8 vs 18.8 mo</td>
</tr>
<tr>
<td>CheckMate 214</td>
<td>Nivolumab/ipilimumab vs sunitinib</td>
<td>&lt;1%: 80% vs 75% (@ 12 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1%: 86% vs 66% (@ 12 mo)</td>
</tr>
<tr>
<td>KEYNOTE-426</td>
<td>Pembrolizumab/axitinib vs sunitinib</td>
<td>&lt;1%: HR=0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥1%: HR=0.54</td>
</tr>
<tr>
<td>IMmotion151</td>
<td>Atezolizumab/bevacizumab vs sunitinib</td>
<td>≥1%: HR=0.68</td>
</tr>
</tbody>
</table>

The majority of the committee does not utilize PD-L1 testing in patients before immunotherapy, as the data is not conclusive.
Biomarkers in aRCC

Biomarker testing in newly diagnosed ccRCC

Yes    No
Studies in sarcomatoid histology

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 214</td>
<td>Nivolumab + ipilimumab vs sunitinib</td>
<td>Median: 31.2 vs 13.6 months</td>
</tr>
<tr>
<td>KEYNOTE-426</td>
<td>Pembrolizumab + axitinib vs sunitinib</td>
<td>12-month: 83.4% vs 79.5%</td>
</tr>
<tr>
<td>JAVELIN RENAL 101</td>
<td>Avelumab + axitinib vs sunitinib</td>
<td>12-month: 83% vs 67%</td>
</tr>
<tr>
<td>IMmotion151</td>
<td>Atezolizumab + bevacizumab vs sunitinib</td>
<td>Median: 21.7 vs 15.4 months</td>
</tr>
</tbody>
</table>
Sarcomatoid RCC

Recommendations for:
First-line treatment for patients with sarcomatoid RCC irrespective of IMDC risk factors

- Nivolumab + ipilimumab
- Pembrolizumab + axitinib
- Avelumab + axitinib
Key clinical questions

1. How should checkpoint inhibitors be integrated into the first-line treatment of advanced clear cell renal carcinoma (accRCC)?
2. How should checkpoint inhibitors be integrated into treatment of refractory accRCC?
3. How should adjuvant therapy and related failures be managed within an IO-related treatment paradigm for patients with accRCC?
4. How should treatment response to immunotherapy be evaluated, monitored and managed in patients with accRCC?
5. What is the role of biomarker testing in patients with aRCC?
6. What is the role of immunotherapy in non-clear cell pathology?
7. How should immune-related adverse events be recognized and managed in patients with accRCC?
8. Are there populations of patients with accRCC who should not receive immunotherapy?
KEYNOTE-427 cohort B

Figure 1. Study Design

- **Patients**
  - Recurrent or advanced/metastatic disease
  - Measurable per RECIST v1.1
  - No prior systemic therapy
  - Karnofsky Performance Status Scale score ≥70%

- **Cohort A**
  - ccRCC (N = 110)

- **Screen for eligibility**

- **Cohort B**
  - nccRCC* (N = 165)

- **Pembrolizumab**
  - 200 mg Q3W

- **Response assessed at**
  - week 12, Q6W until week 54, and Q12W thereafter

*nccRCC diagnosis confirmed by central pathology

ccRCC, clear cell renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks.

Lee, ASCO 2019.
KEYNOTE-427 cohort B

Figure 3. Maximum Change From Baseline in Target Lesions by BICR

- Any decrease: 56.3%
- Decrease ≥30%: 37.6%
- Decrease ≥60%: 23.6%
- Decrease ≥80%: 12.1%
- CR of target lesions: 4.2%

Lee, ASCO 2019.
Non-clear cell pathology

• Papillary or unclassified RCC:
  • Single-agent anti-PD-1
  • Nivolumab/ipilimumab possibly for unclassified

• Chromophobe RCC:
  • IO-based monotherapy
  • TKI
Non-clear cell pathology

Recommendations for:
Patient with non-clear cell RCC whose disease progressed on frontline VEGFR TKI
Key clinical questions

1. How should checkpoint inhibitors be integrated into the first-line treatment of advanced clear cell renal carcinoma (accRCC)?
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### Adverse events in accRCC

<table>
<thead>
<tr>
<th></th>
<th>CheckMate 214</th>
<th>KEYNOTE-426</th>
<th>Javelin RENAL 101</th>
<th>IMmotion151</th>
<th>CheckMate 025</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any TRAE</strong></td>
<td>93%</td>
<td>98.4%</td>
<td>95.4%</td>
<td>91%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>Grade 3-4 TRAE</strong></td>
<td>46%</td>
<td>63%</td>
<td>56.7%</td>
<td>40%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>TRAE leading to discontinuation of both drugs</strong></td>
<td>22%</td>
<td>10.7%</td>
<td>7.6%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Treatment-related deaths</strong></td>
<td>1.5%</td>
<td>0.9%</td>
<td>0.7%</td>
<td>1.1%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Most common TRAE</strong></td>
<td>Fatigue (37%)</td>
<td>Diarrhea (54.3%)</td>
<td>Diarrhea (62.2%)</td>
<td></td>
<td>Fatigue (33%)</td>
</tr>
<tr>
<td><strong>Most common grade 3-4 TRAE</strong></td>
<td>Increased lipase (10%)</td>
<td>Hypertension (22.1%)</td>
<td>Hypertension (25.6%)</td>
<td>Hypertension (14%)</td>
<td>Fatigue (2%)</td>
</tr>
</tbody>
</table>
Adverse events in aRCC

- When to hold PD-1 monotherapy
  - Do not hold unless grade 3+ toxicity
  - Hold for worrisome grade 2 toxicities

50%

50%
Adverse events in aRCC

Management of clinically-significant grade 3 irAEs on PD-1 monotherapy

- Hold therapy and start high dose oral steroids with 4-6 wk taper (72%)
- Other (28%)
Adverse events in aRCC

When to hold nivolumab + ipilimumab for any grade irAE

- Hold for grade 2, treat with immunosuppressives as needed, resume nivolumab monotherapy
- Hold for grade 1-2 and see if they worsen before resuming
Adverse events in aRCC

Stable disease on nivolumab + ipilimumab, but discontinued due to grade 3+ irAE

50%

Wait until grade ≤1 and prednisone <10mg/d, then PD-1 monotherapy maintenance

50%

Observe patient off all therapy until progression
Adverse events in aRCC

When to hold IO/TKI combination therapy due to grade 3 toxicity that could result from either drug

- Give steroids and hold IO, but continue axitinib
- Hold both drugs and observe
- Hold both drugs and give steroids
- Hold axitinib for 2-3 days and check for improvement

Percent Committee Recommending

0 10 20 30 40 50 60
Adverse events in aRCC

When to hold IO/TKI combination therapy for any grade irAE

- Hold axitinib for grade 1-2 to see if they worsen before resuming
- Do not hold unless grade 3+
Key clinical questions

1. How should checkpoint inhibitors be integrated into the **first-line** treatment of advanced clear cell renal carcinoma (accRCC)?
2. How should checkpoint inhibitors be integrated into treatment of refractory accRCC?
3. How should **adjuvant therapy** and related failures be managed within an IO-related treatment paradigm for patients with accRCC?
4. How should **treatment response** to immunotherapy be evaluated, monitored and managed in patients with accRCC?
5. What is the role of **biomarker** testing in patients with aRCC?
6. What is the role of immunotherapy in **non-clear cell** pathology?
7. How should immune-related **adverse events** be recognized and managed in patients with accRCC?
8. Are there populations of patients with accRCC who **should not receive immunotherapy**?
Excluded patient populations

**Recommendations for:**
The general factors to consider when determining NOT to give nivolumab/ipilimumab combination therapy in patients with aRCC
Excluded patient populations

**Recommendations for:**
The general factors to consider when determining NOT to give IO/TKI combination therapy in patients with aRCC
Excluded patient populations

• Other considerations:
  • Active autoimmune disease requiring medication
  • Receiving steroid dosing (for any reason) > 10mg per day prednisone equivalent
  • Significant burden and/or pace of disease
  • History of controlled HIV or hepatitis infection
Key clinical questions

1. How should checkpoint inhibitors be integrated into the first-line treatment of advanced clear cell renal carcinoma (accRCC)?
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Guidelines process

In accordance with the National Academy of Medicine’s Standards for Developing Trustworthy Clinical Practice Guidelines
1. Committee with range of relevant specialties
2. Systematic literature search
3. Survey development and completion
4. Manuscript draft
5. In-person meeting
6. Open comment period
Patient and tumor reviewed by multidisciplinary team
Staging confirmed including pathology and imaging*

Need for systemic therapy?
Yes
No

Candidate for immunotherapy?
Yes
No

Clear Cell Pathology
Non-Clear Cell Pathology

IMDC Risk: Favorable
IMDC Risk: Intermediate/Poor
Sarcomatoid component

Recommended: Axitinib/Pembrolizumab
Other Options: Ipilimumab/Nivolumab

Recommended: Ipilimumab/Nivolumab
Axitinib/Pembrolizumab
Other Options: Anti-PD-1 monotherapy

Recommended: Ipilimumab/Nivolumab
Axitinib/Pembrolizumab
Other Options: Anti-PD-1 monotherapy

Recommended: Anti-PD-1 monotherapy
Other Options: Anti-VEGF TKI

Recommendations post-treatment with:
- ipilimumab/nivolumab: TKI (cabozantinib, axitinib, lenvatinib/everolimus), HD-IL2
- axitinib/pembrolizumab: cabozantinib, lenvatinib/everolimus, HD-IL2

Notes: 1) Clinical Trials are always an option for any patient, in any category. 2) This recommendation may change as data matures.
Questions and Answer Session

Submit your questions

Computer

Mobile Phone

Q: Has the webinar started?
A: Yes, thank you for joining today!
Case study 1

• The patient is a 67yo male, former smoker
• In 2016, he presented with gross hematuria, work-up reveal a left renal mass (11cm)
• The patient underwent a laparoscopic nephrectomy, pathology clear cell renal cell carcinoma, grade 3
• The patient has been followed with regular CT scan, ECOG PS - 0
• In September 2019, CT scan reveals new lung lesions – incisional biopsy +RCC, sarcomatoid differentiation present
• Labs – CBC, Chem 20 – WNL

• How would you treat this patient?
Case study 2

• 73F presents with liver and lung mets after nephrectomy for clear cell RCC 10 months prior. IMDC intermediate risk (time to mets; anemia)

• Patient begins axitinib at 5mg BID and pembrolizumab 200mg IV q3 weeks

• Pt presents at 3 weeks for second dose. No fatigue or diarrhea. LFTs as follows:

<table>
<thead>
<tr>
<th></th>
<th>AlkPhos</th>
<th>ALT (ULN 54)</th>
<th>AST (ULN 40)</th>
<th>TBil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>90</td>
<td>24</td>
<td>24</td>
<td>0.4</td>
</tr>
<tr>
<td>3 wks after starting therapy</td>
<td>102</td>
<td>163</td>
<td>121</td>
<td>0.7</td>
</tr>
</tbody>
</table>

• Next steps?
  1. Hold axi; recheck LFTs in 3 days
  2. Hold axi and pembro; recheck LFTS in 3 days
  3. Continue both drugs and see patient in 3 weeks
  4. Hold both drugs and start prednisone 60mg/d
Questions and Answer Session

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Additional Resources from SITC

Cancer Immunotherapy Guidelines:
www.sitcancer.org/guidelines

Free Online Courses (CE) for Healthcare Providers:
www.sitcancer.org/clinician

Webinar Recording and Slides:
After the webinar, you will receive an email with more information
Continuing Education Credits

• Continuing Education Credits are offered for Physicians, PA’s, NP’s, RN’s and Pharmacists

• You will receive an email following the webinar with instructions on how to claim credit

• Questions and comments: connectED@sitcancer.org

Thank you for attending the webinar!

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

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