Practical Management Pearls for Immunotherapy for the Treatment of Renal Cell Carcinoma

December 17, 2021
11:00 a.m. – 12:00 p.m. ET
Webinar faculty

**Brian Rini, MD** – Vanderbilt University Medical Center
Expert Panel Chair

**Hans Hammers, MD, PhD** – UT Southwestern

**Tom Hutson, DO, PharmD** – Charles A. Sammons Cancer Center, Baylor
Learning objectives

• Appraise and classify kidney-specific considerations for immunotherapy agents and combinations and associated toxicities/irAEs

• Appropriately manage toxicities/irAEs associated with immunotherapy and combinations in RCC

• Determine optimal sequencing of immunotherapies and combinations for advanced RCC

• Consider the integration of immunotherapies into treatment plans for early-stage RCC
Webinar outline

- Development of the guideline
- Treatment selection – all
- Adjuvant immunotherapy – Dr. Hammers
- Patient selection – Dr. Hutson
- Toxicity – Dr. Hammers
- Emerging data – Dr. Hutson
- Key takeaways
Development of the guideline

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*
Development of the guideline

• Developed according to the Institute of Medicine’s Standards for Developing Trustworthy Clinical Practice Guidelines
• Panel consisted of 18 experts in the field
• Recommendations are based upon published literature evidence, or clinical evidence where appropriate
• Consensus was defined at 75% approval among voting members
Webinar outline

• Development of the guideline
• Treatment selection
• Adjuvant immunotherapy
• Patient selection
• Toxicity
• Emerging data
• Key takeaways
## Immunotherapy combinations for first-line treatment of metastatic RCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pembrolizumab + Axitinib</th>
<th>Avelumab + Axitinib</th>
<th>Nivolumab + Ipilimumab</th>
<th>Nivolumab + Cabozantinib</th>
<th>Pembrolizumab + Lenvatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control arm</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
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<tr>
<td>Efficacy population</td>
<td>ITT</td>
<td>ITT</td>
<td>IMDC intermediate/poor-risk</td>
<td>ITT</td>
<td>ITT</td>
</tr>
<tr>
<td>PFS (combination vs control arm)</td>
<td>15.4 months vs 11.1 months</td>
<td>13.8 months vs 8.4 months</td>
<td>11.2 months vs 8.3 months</td>
<td>16.6 months vs 8.3 months</td>
<td>23.9 months vs 9.2 months</td>
</tr>
<tr>
<td>ORR (combination vs control arm)</td>
<td>60% vs 40%</td>
<td>51.4% vs 25.7%</td>
<td>41.9% vs 26.8%</td>
<td>55.7% vs 27.1%</td>
<td>71% vs 36.1%</td>
</tr>
<tr>
<td>OS (combination vs control arm)</td>
<td>Median OS: NR vs 35.7 months; HR = 0.68</td>
<td>Median OS: NE in either arm; HR = 0.8</td>
<td>Median OS: 48.1 months vs 26.6 months; HR = 0.65</td>
<td>Median OS: NR in either arm; HR = 0.6</td>
<td>Median OS: NR in either arm; HR = 0.66</td>
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<tr>
<td></td>
<td>24-month OS rates: 74.4% vs 65.5%</td>
<td>4-year OS rates: 50% vs 35.8%</td>
<td>12-month OS rates: 85.7% vs 75.6%</td>
<td>24-month OS rates: 79.2% vs 70.4%</td>
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</table>
RCC Immunotherapy Treatment Algorithm
1. Patient and tumor reviewed by multidisciplinary team
   - Staging confirmed including pathology and imaging

2. Need for systemic therapy?
   - Yes
     - Candidate for Immunotherapy?
       - No
         - Observation and/or Local Therapy
       - Yes
         - VEGFR TKI

3. Clear Cell Pathology
   - IMDC Risk: Favorable
   - IMDC Risk: Intermediate/Poor
   - Sarcomatoid component

4. Non-Clear Cell Pathology
   - Papillary
   - Chromophobe
   - Undifferentiated

5. Initial Therapy Treatment Recommendations
   - IMDC Risk: Favorable
     - Recommended: Anti-VEGF TKI/checkpoint inhibitor combination
     - Other Options: Ipilimumab/nivolumab, Anti-PD-1 monotherapy
   - IMDC Risk: Intermediate/Poor
     - Recommended: Ipilimumab/nivolumab
     - Anti-VEGF TKI/checkpoint inhibitor combination
     - Other Options: Nivolumab/cabozantinib, Ipilimumab/nivolumab, Axitinib/pembroliozumab
   - Sarcomatoid component
     - Recommended: Nivolumab/cabozantinib
     - Ipilimumab/nivolumab
     - Axitinib/pembroliozumab
     - Anti-PD-1 monotherapy
   - Papillary
     - Options: Nivolumab/cabozantinib, Lenvatinib/everolimus, Pembrolizumab/lenvatinib, Axitinib, Cabozantinib
   - Chromophobe
     - Options: Nivolumab/cabozantinib, Lenvatinib/everolimus, Pembrolizumab/lenvatinib
   - Undifferentiated
     - Options: Nivolumab/ipilimumab, Anti-VEGF TKI/checkpoint inhibitor combination, Anti-PD-1 monotherapy

6. Recommendations post-treatment with:
   - Ipilimumab/nivolumab TKI (cabozantinib, axitinib, lenvatinib/everolimus)
   - Cabozantinib/nivolumab: lenvatinib/everolimus, Ipilimumab/nivolumab, axitinib, tivozanib
   - Lenvatinib/pembroliozumab: cabozantinib, ipilimumab/nivolumab, tivozanib, everolimus
   - Axitinib/pembroliozumab: cabozantinib, lenvatinib/everolimus, Ipilimumab/nivolumab, tivozanib
Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

• In addressing preliminary issues surrounding frontline management of RCC, the Expert Panel recommends initiating systemic therapy first rather than cytoreductive nephrectomy in patients presenting with mRCC with:
  • IMDC poor risk categorization (80%)
  • Brain metastases (67%)
  • Large tumor burden outside primary kidney lesion (60%)


• Given the current data, the Expert Panel felt that all patients without a contraindication to immunotherapy should receive an IO-based regimen in the first line.

Note: Cytoreductive nephrectomy is still considered a preferable option for patients with the majority of their tumor burden confined to their primary and no other IMDC risk factors besides presenting with stage IV disease.
Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

• For first-line VEGF TKI + checkpoint inhibitor combination therapy for RCC, the Expert Panel recommends:
  • Lenvatinib + Pembrolizumab (47%)
  • Cabozantinib + Nivolumab (29%)
  • Axitinib + Pembrolizumab (24%)

• For a 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, the Expert Panel recommends:
  • VEGF TKI + checkpoint inhibitor combination (60%):
    • Pembrolizumab + axitinib (18%)
    • Nivolumab + cabozantinib (18%)
    • Pembrolizumab + lenvatinib (24%)
  • Nivolumab + ipilimumab (29%)
  • Pazopanib (6%)
  • Pembrolizumab or nivolumab monotherapy (6%)

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

• For a 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, the Expert Panel recommends:
  • Nivolumab + ipilimumab (77%)
  • VEGF TKI + checkpoint inhibitor combination (23%):
    • Pembrolizumab + lenvatinib (11%)
    • Pembrolizumab + axitinib (6%)
    • Nivolumab + cabozantinib (6%)

• For a treatment naïve, ECOG ≥ 1 ccRCC patient with “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, the Expert Panel recommends:
  • Nivolumab + ipilimumab (47%)
  • VEGF TKI + checkpoint inhibitor combination (23%):
    • Pembrolizumab + lenvatinib (17%)
    • Pembrolizumab + axitinib (11%)
    • Nivolumab + cabozantinib (11%)
  • Pembrolizumab or nivolumab monotherapy (6%)

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

- In determining when to give a treatment-naïve patient IO monotherapy over an IO-based doublet therapy, the Expert Panel recommends IO monotherapy for:
  - Patients with a history of autoimmune disease that is not potentially life threatening and is not currently on immunosuppressive agents (56%)
  - Elderly patients over 80 years of age (50%)
  - Patients with a history of vascular disease such as stroke, recent ischemic cardiac disease without coronary artery bypass grafting (39%)
  - Patients with poor performance status (28%)
  - Patients with IMDC favorable risk (6%)
  - Patients with liver metastases with mildly increased LFTs (6%)
  - 17% of the Expert Panel would never recommend IO monotherapy over an IO-based doublet therapy.

Expert Panel recommendations for first-line treatment of advanced clear cell RCC*

Expert Panel recommendations the treatment of refractory advanced clear cell RCC*

• For patients with accRCC who were previously treated with a VEGFR TKI, the Expert Panel recommends single agent anti-PD-1 immunotherapy based on evidence from CheckMate 025 (Category 1).

• For a previously treated, ECOG 0, clear cell mRCC patient with “favorable” risk whose tumors progressed on front-line therapy with sunitinib, the Expert Panel recommends:
  • Treat with a checkpoint immunotherapy (100%). The Expert Panel was split on the specific treatment recommendations:
    • Ipilimumab plus nivolumab immunotherapy if the patient can tolerate the combination (63%)
    • Nivolumab monotherapy (37%)

  *Note: As standard of care shifts to immunotherapy regimens in the first line setting, this situation will be unlikely to occur in the future and the use of VEGFR TKI monotherapy as first-line therapy will be limited to those patients who are perceived to be unable to receive a checkpoint inhibitor based treatment regimen.*

• In treating patients with disease progression after nivolumab/ipilimumab combination therapy, the Expert Panel recommends cabozantinib (72%). Other options are axitinib (22%) or high dose IL-2 (6%).

Expert Panel recommendations the treatment of refractory advanced clear cell RCC*

- For a patient who has progressed after axitinib + pembrolizumab combination therapy, the Expert Panel recommends:
  - Cabozantinib (65%), Lenvatinib + everolimus (23%), Ipilimumab + nivolumab (12%)
- For a patient who has progressed after cabozantinib + nivolumab combination therapy, the Expert Panel recommends:
  - Lenvatinib + everolimus (64%), Ipilimumab + nivolumab (12%), Axitinib (12%), Tivozanib (6%), Clinical trial enrollment (6%)
- For a patient who has progressed after lenvatinib + pembrolizumab combination therapy, the Expert Panel recommends:
  - Cabozantinib (76%), Ipilimumab + nivolumab (12%), Tivozanib (6%), Everolimus (6%)
- The Expert Panel also acknowledged that no data existed for the use of nivolumab/ipilimumab in patients with disease progression on an IO/TKI combination or for the use of an IO/TKI combination in patients with disease progression on front-line nivolumab/ipilimumab, and suggested that clinical trials to obtain such data would be useful.

Expert Panel recommendations on the treatment of non-clear cell RCC*

Expert Panel recommendations on the treatment of non-clear cell RCC*

• For first-line treatment for patients with papillary RCC, the Expert Panel recommends:
  • Nivolumab + cabozantinib (35%), Cabozantinib (35%), Nivolumab + ipilimumab (18%), Single agent anti-PD1 (12%)

• For first-line treatment for patients with chromophobe RCC, the Expert Panel recommends:
  • VEGF TKI + checkpoint inhibitor (42%)
    • Nivolumab + cabozantinib (24%), Pembrolizumab + lenvatinib (18%)
  • Lenvatinib + everolimus (41%), Cabozantinib (12%), Sunitinib or pazopanib (6%)

Expert Panel recommendations on the treatment of non-clear cell RCC*

• For first-line treatment for patients with undifferentiated RCC, the Expert Panel recommends:
  • VEGF TKI + checkpoint inhibitor combination (54%):
    • Nivolumab + Cabozantinib (30%), Pembrolizumab + Lenvatinib (18%), Pembrolizumab + Axitinib (6%)
  • Nivolumab + Ipilimumab (46%)
  • For patients with nccRCC whose disease has progressed on frontline VEGFR TKI, the Expert Panel recommends anti-PD-1 monotherapy with nivolumab (56%) or TKI therapy, specifically cabozantinib (22%).

How to selection anti-PD-(L)1 combinations for first-line therapy?

When to add targeted therapy vs immunotherapy?
Webinar outline

• Development of the guideline
• Treatment selection
• Adjuvant immunotherapy
• Patient selection
• Toxicity
• Emerging data
• Key takeaways
KEYNOTE-564 supporting FDA approval of adjuvant pembrolizumab
Webinar outline

• Development of the guideline
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• Key takeaways
Expert Panel Recommendations on combination therapy in special patient populations

• When determining NOT to give nivolumab/ipilimumab combination therapy in patients with aRCC, the Expert Panel felt that the most influential factors to consider were:
  • History of potentially life threatening autoimmune condition and/or need for immunosuppressive therapy (94%), Poor performance status (50%), Advanced patient age and IMDC risk stratification (39%)

• When determining NOT to give IO/TKI combination therapy in patients with aRCC, the Expert Panel felt that the most influential factors to consider were:
  • History of potentially life threatening autoimmune condition and/or need for immunosuppressive therapy (72%), Recent history of cardiovascular co-morbidities (39%), Advanced patient age (33%), Poor performance status (33%)
Expert Panel Recommendations on combination therapy in special patient populations

• Currently active autoimmune disease requiring medication would be considered a reason not to provide combination immunotherapy to an intermediate/poor risk patient with metastatic RCC (mRCC) (94% Expert Panel agreement). Additionally, the Expert Panel recommends:
  • Do not treat patients receiving steroid dosing (for any reason) > 10 mg per day prednisone or equivalent (75%).
  • Do not recommend excluding patients from treatment due to significant burden/pace of disease requiring rapid tumor burden reduction (56%).

• Specific to VEGFR TKI/checkpoint inhibitor combination therapy, the Expert Panel recommends NOT treating patients with aRCC who:
  • Currently have active autoimmune disease requiring immunosuppressive medication (87%), Require corticosteroid use > 10 mg/d prednisone equivalent (53%), Have poor performance status (20%)
Expert Panel Recommendations on special patient populations

• Specific to checkpoint inhibitor monotherapy, the Expert Panel recommends NOT treating patients with aRCC who:
  • Currently have active autoimmune disease requiring immunosuppressive medication (93%), Require corticosteroid use > 10 mg/d prednisone equivalent (67%)

• For patients with advanced RCC who currently have controlled HIV and/or a history of hepatitis C or B infection, the Expert Panel would NOT recommend AGAINST using checkpoint inhibitor-based therapy (89%).
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Top 3 most common adverse events associated with ICI/TKI combos

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<tbody>
<tr>
<td><strong>Most Common AEs (any grade)</strong></td>
<td>• Diarrhea • Hypertension • Fatigue</td>
<td>• Diarrhea • Hypertension • Fatigue</td>
<td>• Diarrhea • Palmer-plantar erythrodesia • Hypertension</td>
<td>• Diarrhea • Hypertension • Hypothyroidism</td>
</tr>
<tr>
<td><strong>Most common AEs (Grade 3 or higher)</strong></td>
<td>• Hypertension • Elevated ALT • Diarrhea</td>
<td>• Hypertension • Diarrhea • Palmer-plantar erythrodesia</td>
<td>• Hypertension • Diarrhea • Palmer-plantar erythrodesia</td>
<td>• Hypertension • Diarrhea • Fatigue</td>
</tr>
</tbody>
</table>
Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Julie R Brahmer, Hamzah Abu-Sbeih, Paolo Antonio Ascierto, Jill Brufsky, Laura C Cappelli, Frank B Cortazar, David E Gerber, Lamya Hamad, Eric Hansen, Douglas B Johnson, Mario E Lacouture, Gregory A Masters, Jarushka Naidoo, Michele Nanni, Miguel-Angel Perales, Igor Puzanov, Bianca D Santomasso, Satish P Shanbhag, Rajeev Sharma, Dimitra Skondra, Jeffrey A Sosman, Michelle Turner, Marc S Ernstoff
Expert Panel recommendations for immune-related adverse events

• Regarding when to hold IO/TKI combination therapy due to grade 3 toxicity (e.g. diarrhea, LFT abnormalities) that could be from either drug, the Expert Panel recommends:
  • Hold axitinib for 2–3 days to see if toxicity improves (56%)
  • Hold both drugs and give steroids (22%)
  • Hold both drugs to see if toxicity improves (17%)
  • Give steroids and hold the IO component, but continue axitinib (6%)

• Regarding when to hold IO/TKI combination therapy due to any grade irAEs, the Expert Panel was split in their recommendations:
  • Hold axitinib treatment for grade 1 or 2 toxicities (diarrhea, arthritis, LFT abnormalities) to see if they worsen before resuming (60%)
  • Do not hold treatment unless the patient is experiencing a grade 3 toxicity (33%)
Practical pearls for managing immunotherapy toxicity

Initial dosing intervals of ICIs
• Pembrolizumab (+ axitinib or lenvatinib) dosing = every 3 or 6 weeks
• Nivolumab (+ ipilimumab or cabozantinib) dosing = every 2 or 4 weeks

Other considerations for immunotherapy regimens
• Lenvatinib + Pembrolizumab – no limiting liver toxicity
• VEGF TKI toxicities are dose-dependent (lenvatinib vs axitinib)
• Ipilimumab + Nivolumab
  • Higher frequency of use of steroids
  • Important to address with patients
  • Ipilimumab can drive specific immune-mediated adverse events (hepatitis, colitis, etc)
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Immunotherapy trials for RCC expected to report outcomes in 2022

Advanced or metastatic RCC

- **COSMIC-313**: Triple combination of cabozantinib + nivolumab + ipilimumab

Adjuvant trials

- **CheckMate 914**: Nivolumab + ipilimumab vs. placebo as adjuvant therapy
- **IMmotion010**: Atezolizumab vs. placebo as adjuvant therapy for 1 year
- **PROSPER RCC**: Perioperative nivolumab vs. nephrectomy alone
- **RAMPART**: Durvalumab monotherapy vs. durvalumab + tremelimumab vs. no intervention (active monitoring) as adjuvant therapy for 1 year
Case Studies in Immunotherapy for the Treatment of Renal Cell Carcinoma
January 20, 2021, 11 a.m. – 12 p.m. ET

Case Studies in Immunotherapy for the Treatment of Hepatocellular Carcinoma
January 10, 2021, 6:30 – 7:30 p.m. ET

Practical Management Pearls for Immunotherapy for the Treatment of HNSCC
January 13, 2021, 6:30 – 7:30 p.m. ET

Learn more and register at:
https://www.sitcancer.org/CPG-webinars

The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)
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