Summary of Front-line mRCC Trials

Brian I. Rini, MD, FASCO
Vanderbilt University Medical Center
# First-line IO Combination Trials in mRCC

<table>
<thead>
<tr>
<th></th>
<th>CheckMate 214 (Ipi/Nivo)¹ (n=550 vs n=546)</th>
<th>KEYNOTE-426 (Axi/Pembro)² (n=432 vs n=429)</th>
<th>CheckMate 9ER (Cabo/Nivo)³ (n=323 vs n=328)</th>
<th>CLEAR (Len/Pembro)⁴ (N=355 vs n=357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR mOS, months</td>
<td>0.72</td>
<td>0.73</td>
<td>0.70</td>
<td>0.72</td>
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<tr>
<td></td>
<td>55.7 vs 38.4</td>
<td>45.7 vs 40.1</td>
<td>37.7 vs 34.3</td>
<td>NR vs 79% (est.)</td>
</tr>
<tr>
<td>Landmark OS 12 mo</td>
<td>83% vs. 78%</td>
<td>90% vs. 79%</td>
<td>86% vs. 76%</td>
<td>90% vs 79%</td>
</tr>
<tr>
<td>Landmark OS 24 mo</td>
<td>71% vs. 61%</td>
<td>74% vs. 66%</td>
<td>70% vs 60%</td>
<td>79% vs 70%</td>
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<tr>
<td>Landmark OS 12 mo</td>
<td></td>
<td>83% vs. 78%</td>
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<tr>
<td>Landmark OS 24 mo</td>
<td></td>
<td>71% vs. 61%</td>
<td></td>
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</tr>
<tr>
<td>HR mPFS, months</td>
<td>0.86</td>
<td>0.68</td>
<td>0.56</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>12.3 vs 12.3</td>
<td>60 vs 40</td>
<td>56 vs 28</td>
<td>71 vs 36</td>
</tr>
<tr>
<td>ORR, %</td>
<td>39 vs 32</td>
<td>60 vs 40</td>
<td>56 vs 28</td>
<td>71 vs 36</td>
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<tr>
<td>CR, %</td>
<td>12 vs 3</td>
<td>10 vs 4</td>
<td>12 vs 5</td>
<td>16 vs 4</td>
</tr>
<tr>
<td>Med f/u, months</td>
<td>67.7</td>
<td>42.8</td>
<td>32.9</td>
<td>33.7</td>
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<tr>
<td>Primary PD, %</td>
<td>18</td>
<td>11</td>
<td>6</td>
<td>5</td>
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<tr>
<td>Landmark PFS</td>
<td>30% (5 years)</td>
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</table>

- **Consistent OS benefit vs VEGF TKI**
- **More tumor shrinkage with TKI-containing regimens**
- **Less early PD with TKI-containing regimens**

1. Motzer et al. ESMO 2021
2. Rini et al. ASCO 2021

**CTLA-4 containing regimen perhaps with higher tail of the curve**
## Front-line IO-based Trials in mRCC: IMDC Favorable Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>OS HR</th>
<th>PFS HR</th>
<th>mPFS, mos</th>
<th>Landmark PFS</th>
<th>ORR</th>
<th>CR</th>
<th>Med f/u, months</th>
<th>Duration of response, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 214 (Ipi/Nivo)(^1) (n=125 vs n=124)</td>
<td>0.94</td>
<td>1.60</td>
<td>12.4 vs 28.9</td>
<td>63% vs 55% at 5 years</td>
<td>30% vs 52%</td>
<td>13% vs 6%</td>
<td>67.7</td>
<td>61.5 vs 33.2</td>
</tr>
<tr>
<td>KEYNOTE-426 (Axi/Pembro)(^2) (n=138 vs n=131)</td>
<td>1.17</td>
<td>0.76</td>
<td>20.7 vs 17.8</td>
<td>72% vs 73% at 3.5 years</td>
<td>69% vs 50%</td>
<td>12% vs 6%</td>
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<tr>
<td>CheckMate 9ER (Cabo/Nivo)(^3) (n=74 vs n=72)</td>
<td>0.94</td>
<td>0.58</td>
<td>24.7 vs 12.8</td>
<td>89% vs 88% at 15 months</td>
<td>66% vs 44%</td>
<td>12% vs 6%</td>
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<tr>
<td>CLEAR (Len/Pembro)(^4) (N=110 vs n=124)</td>
<td>1.22</td>
<td>0.41</td>
<td>28.1 vs 12.9</td>
<td>95% vs 92% (est.) at 15 months</td>
<td>68% vs 51%</td>
<td>10% vs 10%</td>
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<tr>
<td>HCRN(^5) (Nivo) (N=35)</td>
<td></td>
<td></td>
<td>32.5</td>
<td>58% (est.) at 2 years</td>
<td>21% vs 5%</td>
<td>11% vs 2%</td>
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</tr>
<tr>
<td>KEYNOTE-427(^6) (Pembro) (N=42)</td>
<td></td>
<td></td>
<td>9.7</td>
<td>19% at 2 years</td>
<td>11% vs 5%</td>
<td>2% vs 2%</td>
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</tbody>
</table>

- **OS HR**: Overall Survival Hazard Ratio
- **PFS HR**: Progression-Free Survival Hazard Ratio
- **mPFS**: Median Progression-Free Survival
- **ORR**: Objective Response Rate
- **CR**: Complete Response Rate
- **Med f/u, months**: Median Follow-up, months
- **Duration of response, mos**: Duration of response, months

**Key Observations**
- **Inconsistent OS effects**: Across trials, the OS effects vary widely, with no clear advantage for any treatment regimen.
- **Enhanced tumor shrinkage endpoints**: Keynote-426 demonstrated significant tumor shrinkage, a novel endpoint that may better reflect clinical benefit.
- **A subset of favorable risk RCC is immune-responsive**: A specific subset of patients with favorable risk renal cell carcinoma (RCC) appears to respond well to IO-based therapies, highlighting the potential for personalized treatment strategies.

*1. Motzer et al. ESMO 2021  
2. Rini et al. ASCO 2021  
3. Apollo et al. ASCO 2021  
5. Atkins et al. ASCO GU 2022  
6. McDermott et al. JCO 2021*
Sarcomatoid histology is the best biomarker for Ipi/Nivo

- ORR 61% / 23% CR
Patient groups defined by clinical characteristics (IMDC) display heterogeneous biology

Motzer et al. *Cancer Cell* 2020
**Key Eligibility Criteria**
- ECOG 0 or 1
- Newly diagnosed mccRCC
- No prior systemic therapy
- Available tumor tissue for RNA-sequencing/cluster prediction
- Clusters 3/6/7 will be excluded

**Simon’s Minimax Two-Stage Design**

- **Nivolumab/Cabozantinib (N=26)**
  - $H_0$: ORR $\leq 55\%$
  - $H_A$: ORR $> 55\%$
  - Stage I (N=12) $\geq 7/12$ responders
  - Stage II (N=14) $\geq 18/26$ responders

- **Ipilimumab/Nivolumab (N=28)**
  - $H_0$: ORR $\leq 40\%$
  - $H_A$: ORR $> 40\%$
  - Stage I (N=16) $\geq 7/16$ responders
  - Stage II (N=12) $\geq 15/28$ responders

- **Primary Endpoint**: ORR $> 60\%$

**OPTimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC) (NCT 05361720)**
How long does a TKI need to be continued?: Tide A Study design

75 Pts
- Diagnosis of mRCC
- Measurable disease
- ECOG 0-1
- No bulky or symptomatic disease
- No hepatic metastases.

36 weeks of

Avelumab 800 mg Q2W
Axitinib 5mg BID

24 weeks of

Tumor evaluation

PR

PD

STOP

Avelumab 800 mg Q2W

Until PD

Eudract CT number: 2019-004098-23
ClinicalTrials.gov Identifier: NCT04698213

Iacovelli et al. Presented at ASCO GU 2020 TPS762

PR: partial response
PD: progression of disease
SD: stable disease
Brian Rini, MD
@brian_rini

Last one... what would be most convincing endpoint to adopt triplets?

- Significant OS benefit: 75.8%
- 12 month PFS increase: 2.5%
- Doubling of CR rate: 14.2%
- 10% more PD-free at 5 yrs: 7.5%

120 votes • Final results
Assume no OS benefit of triplet vs doublet in mRCC. What magnitude of absolute PFS benefit vs doublets is required to adopt triplets?

- 3 months: 2.2%
- 6 months: 14.5%
- 9 months: 16.7%
- Would not adopt w/o OS: 66.7%
COSMIC-313 Study Design

**Advanced RCC (N~840)**
- No prior systemic therapy*
- Clear cell component
- Intermediate or poor risk per IMDC criteria
- Measurable disease per RECIST v1.1
- Karnofsky Performance Status ≥70%

**Stratification**
- IMDC risk
- Region

**R1:1**

**Cabo+Nivo+lpi**
- Cabo 40 mg PO QD
- Nivo 3 mg/kg IV Q3W ×4
- Ipi 1 mg/kg IV Q3W ×4

**Cabo**
- Cabo 40 mg PO QD
- Nivo 3 mg/kg IV Q3W ×4
- Ipi 1 mg/kg IV Q3W ×4

**Pbo+Nivo+lpi**
- Pbo PO QD
- Nivo 480 mg IV Q4W

**Pbo**
- Pbo PO QD
- Nivo 480 mg IV Q4W

**Tumor assessment every 8 weeks per RECIST v1.1‡**
- Treatment until loss of clinical benefit or intolerable toxicity§
- No crossover allowed

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*One prior systemic adjuvant therapy allowed for completely resected RCC and if recurrence occurred ≥6 months after the last dose of adjuvant therapy; adjuvant PD-1 or PD-L1 inhibitor in combination with a CTLA-4 inhibitor not permitted. †Nivolumab given for a maximum of 2 years. ‡Tumor assessment (RECIST v1.1) at week 10, then every 8 weeks through week 50, then every 12 weeks thereafter. §Discontinuation of one agent did not mandate discontinuation of all agents.

Toni K. Choueiri
COSMIC313: PFS Final Analysis (PITT Population)

<table>
<thead>
<tr>
<th></th>
<th>No. of Events</th>
<th>Median PFS mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabo+Nivo+Ipi</td>
<td>116</td>
<td>NR (14.0–NE)</td>
</tr>
<tr>
<td>Pbo+Nivo+Ipi</td>
<td>133</td>
<td>11.3 (7.7–18.2)</td>
</tr>
</tbody>
</table>

Hazard ratio 0.73 (95% CI 0.57–0.94); p=0.013

Number at Risk

Cabo+Nivo+Ipi 276 234 170 145 119 98 69 37 19 10 1 0
Pbo+Nivo+Ipi 274 185 136 115 98 69 37 19 10 1 0

Data cut-off: Aug 23, 2021
COSMIC313: PFS by IMDC Risk Group (PITT Population)

### Intermediate

- **Cabo+Nivo+Ipi (N=209)**
  - No. of Events: 79
  - Median PFS mo (95% CI): NR (16.9–NE)

- **Pbo+Nivo+Ipi (N=208)**
  - No. of Events: 103
  - Median PFS mo (95% CI): 11.4 (7.6–17.3)

**HR 0.63 (95% CI 0.47–0.85)**

### Poor

- **Cabo+Nivo+Ipi (N=67)**
  - No. of Events: 37
  - Median PFS mo (95% CI): 9.5 (7.8–17.3)

- **Pbo+Nivo+Ipi (N=66)**
  - No. of Events: 30
  - Median PFS mo (95% CI): 11.2 (4.0–NE)

**HR 1.04 (95% CI 0.65–1.69)**

PFS per RECIST v1.1 by BIRC. IMDC risk group is per IxRS.

Toni K. Choueiri
## Treatment Exposure and Discontinuation (Safety Population)

<table>
<thead>
<tr>
<th></th>
<th>Cabo+Nivo+Ipi (N=426)</th>
<th>Pbo+Nivo+Ipi (N=424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of exposure of study treatment (range), mo</td>
<td>10.9 (0.2–28.5)</td>
<td>10.3 (0.1–28.1)</td>
</tr>
<tr>
<td>Median average daily dose (range) of Cabo or Pbo, mg</td>
<td>23.2 (3.6–40.0)</td>
<td>36.1 (0.8–40.0)</td>
</tr>
<tr>
<td>Median Nivo infusions (range) received, no</td>
<td>10 (1–27)</td>
<td>9 (1–27)</td>
</tr>
<tr>
<td>Doses of Ipi received, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Any dose hold due to an AE, %</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Any dose reduction of Cabo or Pbo due to an AE, %</td>
<td>54</td>
<td>20</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any study treatment</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>Cabo or Pbo</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Nivo</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Ipi</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>All treatment components (due to the same AE)</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

Data cut-off: Jan 31, 2022
Toxicity limited drug delivery

**Proportion of patients receiving 4 doses of ipilimumab**
- CM214 (Nivo/Ipi): 79%
- COSMIC-313 (Nivo/Ipi/Pbo): 73%
- COSMIC-313 (Nivo/Ipi/Cabo): 58%

**Proportion of patients receiving >40 mg of prednisone or equivalent**
- CM214 (Nivo/Ipi): 29%
- COSMIC-313 (Nivo/Ipi/Pbo): 35%
- COSMIC-313 (Nivo/Ipi/Cabo): 58%
More shrinkage with triplet but less deep responses

Cabo+Nivo+Ipi (N=258)
232/258 (90%) patients had any reduction
142/258 (55%) patients had reduction ≥30%

Pbo+Nivo+Ipi (N=251)
187/251 (75%) patients had any reduction
114/251 (45%) patients had reduction ≥30%

However, look at proportions of patients in “deep response” categories.
The #UromigosLive Poll Q1: Please reply w a comment on who you’d offer to. @brian_rinl will be discussing on Sat w @TiansterZhang @montypal et al; link below for livestream info. If you could use the triplet combo (cabo/nivo/ipl) for 1L #kidneycancer (I/P risk), would you? (2/8)

Yes, I would  
No I wouldn’t  

93 votes · 4 days left

The #UromigosLive Poll Q2: The data for 1L therapy has marinated for some time. Among approved available options, in Sep 2022, what is your preferred 1L therapy for pts w int/poor risk disease? @KidneyCancer @kidneycan @IKCCorg @ACTION4KC (3/8)

Nivo/Ipi  
Cabo/Nivo  
Axi/Pembro  
Len/Pembro

106 votes · 4 days left
- Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC = clear cell renal cell carcinoma.
- The treatment arms are the HIF triplet (MK-6482 + pembrolizumab + lenvatinib), the CTLA4 triplet (MK-1308A + lenvatinib), and the doublet (pembrolizumab + lenvatinib). Note: MK-1308A is a coformulation of pembrolizumab and MK-1308
- Global Study- ~225 sites, 33 countries
## Front-line IO-based Trials in mRCC: 1 vs 2 vs 3 drugs in IMDC Int/Poor

<table>
<thead>
<tr>
<th>Comparator</th>
<th>None</th>
<th>Sunitinib</th>
<th>Ipi/Nivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS HR</td>
<td>NA</td>
<td>0.68</td>
<td>I: 0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 0.44</td>
</tr>
<tr>
<td>PFS HR</td>
<td>NR</td>
<td>0.73</td>
<td>I: 0.59</td>
</tr>
<tr>
<td></td>
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<td>P: 0.36</td>
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<tr>
<td>mPFS, mos.</td>
<td>6.9</td>
<td>11.6</td>
<td>13.8</td>
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<td>I: 17.5</td>
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<tr>
<td></td>
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<td></td>
<td>P: 9.9</td>
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<tr>
<td>Landmark PFS</td>
<td>24% at 2 years</td>
<td>31% at 5 years</td>
<td>51% at 15 months</td>
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<td></td>
<td></td>
<td></td>
<td>I: 55%</td>
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<td>P: 44%</td>
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<tr>
<td>ORR</td>
<td>40%</td>
<td>42%</td>
<td>57%</td>
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<td></td>
<td>51%</td>
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<td>72%</td>
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<td>43%</td>
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<td>11%</td>
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<td>9%</td>
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<td>14%</td>
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<td>Primary PD</td>
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<td>19%</td>
<td>7%</td>
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<td>8%</td>
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<tr>
<td>Med f/u, mos</td>
<td>35.9</td>
<td>67.7</td>
<td>42.8</td>
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<td>33.7</td>
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<td>20.2</td>
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</tbody>
</table>

Conclusions

- IO-based doublets are initial standards of care.
  - IO and TKI monotherapy in select patients
  - Duration of TKI/therapy in general is undefined as de-intensification efforts are needed

- We lack clinically useful/validated biomarkers upon which to individualize therapy.

- Triplets are being tested but may be unlikely to be effective in unselected patients if toxicity limits drug delivery.