Perioperative Systemic Therapy for Localized Renal Cell Carcinoma: To Treat or Not to Treat

Brian I. Rini, M.D.
Department of Solid Tumor Oncology
Cleveland Clinic Taussig Cancer Institute
Glickman Urologic and Kidney Institute
Disclosures*

- Research Funding to Institution: Pfizer, Merck, GNE/Roche, Peloton, Aveo, Astra-Zeneca, BMS
- Consulting: BMS, Pfizer, GNE/Roche, Aveo, Novartis, Synthorx, Peloton, Compugen, Merck, Corvus, Exelixis
- Stock: PTC therapeutics

*Last 36 months
Perioperative Systemic Therapy in RCC

- Neoadjuvant therapy
  - VEGF TKI
  - I/O ongoing trials

- Adjuvant therapy
  - VEGF TKI results to date
  - S-TRAC in more depth
  - I/O ongoing trials
## Pre-surgical VEGF-Targeted Therapy in RCC

<table>
<thead>
<tr>
<th>Approach</th>
<th>Patient population</th>
<th>No. of pts/tumors with primary tumor shrinkage</th>
<th>Amount of primary tumor shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sunitinib (CCF)</strong></td>
<td>‘Unresectable’ RCC; 50mg continuous (n=29)</td>
<td>80%</td>
<td>22% 1.2 cm</td>
</tr>
<tr>
<td><strong>Sorafenib (UNC)</strong></td>
<td>≥T2 RCC; sorafenib 400 mg BID x 4–8 weeks prior to nephrectomy (n=25)</td>
<td>64%</td>
<td>9% 0.8 cm</td>
</tr>
<tr>
<td><strong>Pazopanib (CCF)</strong></td>
<td>Localized RCC to enable partial nephrectomy; 8 weeks (n=28)</td>
<td>93%</td>
<td>25% 1.8 cm</td>
</tr>
<tr>
<td><strong>Axitinib (MDACC)</strong></td>
<td>Localized RCC; 12 weeks (n=24)</td>
<td>100%</td>
<td>28% 3.1 cm</td>
</tr>
</tbody>
</table>
PADRES (Prior Axitinib as a Determinant of Outcome of REnal Surgery)

1) Imperative indication for nephron sparing surgery (preexisting CKD or solitary kidney/anatomically functionally solitary kidney or bilateral synchronous disease); and
2) complex renal lesion defined as RENAL score ≥10 or proximity to renal hilum, defined as <2 mm away from at least 2 renal hilar vessels-the main artery/vein or first order branches); and
3) radical nephrectomy would place patient on dialysis or leave patient with severe CKD (> stage IIIb)

Axitinib-5 mg po BID x 8 weeks (with titration to 7mg BID as tolerated at 4 weeks), then re-staging

Outcome measures
1) Assessment of Tumor Response (CT or MRI) after completion of axitinib therapy
   a) RECIST v1.1 response / change in maximal tumor diameter
   b) Change in R.E.N.A.L. Nephrometry Score
2) Ability to perform Partial Nephrectomy after TKI therapy with Negative Margins
3) Functional issues: avoidance of dialysis and severe CKD (stage 4, GFR <30 ml/min/1.73 m2)
4) Safety indices
   a) avoidance of major Complications: Clavien ≥ 3
   b) avoidance of need for multiple blood transfusion
Patients with locally advanced RCC (T2b-T4 &/or N1 & M0)
Age ≥ 18 year
ECOG 0-1

**Neoadjuvant therapy**

- Cohort 1: Durvalumab x1 dose (n=6)
- Cohort 2: Durvalumab+Tremelimumab x1 dose (n=6)
- Cohort 3: Durvalumab+Tremelimumab x1 dose (n=15)
- Cohort 4: Randomized-Durvalumab vs Durvalumab+Tremelimumab (n=9 each)

**Adjuvant dosing**

- Cohort 1 & 2: Durvalumab x1 dose
- Cohort 3: Durvalumab+Tremelimumab x1 dose, then Durvalumab for 1 year
- Cohort 4: no adjuvant dosing

- Peripheral blood
- Nephrectomy
- Peripheral blood
- Surgery can be done anytime after neoadjuvant therapy
- Adjuvant treatment 2-8 weeks after surgery
Frequencies of PD-L1 expression on M-MDSC and UC-MDSC in PBMC decreased significantly from pre- to post-neoadjuvant treatment (p < 0.01).
Cohort 2 and 3 have the Most Peripheral Clonal Expansion, And Cohort 2 Maintains Expansion of Tumor Clones

- Both cohort 2 and 3 show the most clonal expansion at Surgery. All 3 cohorts have greater than 75% of expanded clones being present in the tumor.

- At Follow-up cohort 2 has the most expansion overall and maintains expansion of TIL clones.

- Statistically only expanded clones at surgery shows a significant p-value between groups (Kruskal Wallis test p=0.04)
• Need the **trifecta**: presurgical priming with PD-1 blockade necessary for enhanced efficacy
• 2 neoadjuvant doses may not be sufficient → further engage with adjuvant administration
• Biopsy will allow critical insights into tumor response and resistance mechanisms as well of proof of RCC

Urology PI: Allaf; PIs: Harshman/McDermott, MANY OTHERS
Neoadjuvant Therapy in RCC

• Neoadjuvant TKI can shrink tumors and is potentially useful in specific clinical circumstances (e.g. hilar tumor in a solitary kidney)

• Neoadjuvant IO is an opportunity for correlate science
Adjuvant Therapy in RCC
ASSURE

Sunitinib vs Sorafenib vs Placebo

Haas NB et al/ Lancet 2016
S-TRAC

Sunitinib vs Placebo

No. at Risk
Sunitinib: 309, 225, 173, 153, 144, 119, 53, 10, 3, 0
Placebo: 306, 220, 181, 150, 135, 102, 37, 10, 2, 0

Hazard ratio, 0.76 (95% CI, 0.59–0.98)
P = 0.03

Survival Distribution Function

Median OS, years
Sunitinib: NR
Placebo: NR

P = 0.938*
HR 1.014 (95% CI, 0.716–1.435)

PROTECT

**A** 600 mg

**B** 800 mg

**C** ITT

Motzer R et al J Clin Oncol 2017
## TKI Adjuvant Trials: Analysis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>N</th>
<th>Histology</th>
<th>Stage</th>
<th>Starting Dose</th>
<th>Minimum Dose</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSURE</strong></td>
<td>1943</td>
<td>79% ccRCC</td>
<td>≥pT1b, G3-4, or N+</td>
<td>50 or 37.5 mg (Su)</td>
<td>25mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sunitinib Sunitinib Sorafenib Placebo</td>
<td></td>
<td>99% ccRCC</td>
<td>≥pT3b or N+</td>
<td>50mg</td>
<td>37.5mg</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>S-TRAC</td>
<td>615</td>
<td>ccRCC</td>
<td>pT2 (3-4), or ≥pT3, or N+</td>
<td>600mg</td>
<td>400mg</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>PROTECT</strong></td>
<td>1538</td>
<td>ccRCC or mostly ccRCC</td>
<td>≥pT1b, G3-4, or N+</td>
<td>50 or 37.5 mg (Su)</td>
<td>25mg</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Ravaud A. NEJM 2016; Haas NB Lancet 2016; Motzer R JCO 2017
Longer DFS was observed in patients achieving higher $C_{\text{trough}}$ quartiles and those achieving $C_{\text{trough}} > 20.5 \, \mu g/mL$.
### Adjuvant Sunitinib in RCC

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The standard of care is doing nothing which neither docs nor patients like.</td>
<td></td>
</tr>
</tbody>
</table>
Disease-Free Survival (years)

3-year DFS rate: 64.9%
5-year DFS rate: 59.3%

Proportion Disease-Free

Median DFS, y (95% CI)
- Sunitinib 6.8 (5.8–NR)
- Placebo 5.6 (3.8–6.6)

P=0.030*
HR 0.761 (95% CI, 0.594–0.975)

No. at risk
- Sunitinib: 309, 225, 173, 153, 144, 119, 53, 10, 3, 0
- Placebo: 306, 220, 181, 150, 135, 102, 37, 10, 2, 0

* Two-sided P value from log-rank test stratified by UISS high-risk group.
Adjuvant Sunitinib in RCC

**Pros**
- The standard of care is doing nothing which neither docs nor patients like.
- There is a DFS benefit to sunitinib - which may be durable (?)

**Cons**
- The DFS benefit of sunitinib is relatively small (5% ish more pts disease-free or 1+ year of median benefit)
Common Treatment-Emergent Adverse Events*

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Sunitinib (n=306)</th>
<th>Placebo (n=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>99.7</td>
<td>48.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56.9</td>
<td>3.9</td>
</tr>
<tr>
<td>PPE</td>
<td>50.3</td>
<td>15.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>34.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>33.7</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>33.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>26.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>26.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Hair color change</td>
<td>22.2</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20.9</td>
<td>4.9</td>
</tr>
</tbody>
</table>

* In ≥20% of patients. Grade 5 events occurred in 5 (1.6%) and 5 (1.6%) of patients in the sunitinib placebo arms; no grade 5 AEs in either arm were considered treatment-related. PPE, palmar-plantar erythrodysesthesia syndrome
# Adjuvant Sunitinib in RCC

## Pros

- The standard of care is doing nothing which neither docs nor patients like.
- There is a DFS benefit to sunitinib - which may be durable (?)
- There is likely an adequate window of exposure that balances benefit and risk.
- You can always discontinue drug for a particular patient.

## Cons

- The DFS benefit of sunitinib is relatively small (5% ish more pts disease-free or 1+ year of median benefit)
- Adequate drug exposure is required - which can be associated with more toxicity
If you were able to get treatment to prevent recurrence of your kidney cancer, what would be important for you? (n=452)

- Prolonged OS: 63%
- DFS: 60%
- Toxicity: 43%
- Insurance coverage: 37%
- Efficacy Data: 37%
- Recommendation: 35%
- Optimized Surveillance: 33%

Battle et al, JCO sup, Abs. #644, 2018
## Targeted Therapy Adjuvant Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of RCC</th>
<th>Risk of Recurrence (Assessment System)</th>
<th>Stratification by Risk?</th>
<th>Surgery</th>
<th>Eligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE (NCT003265898)</td>
<td>Clear cell or non clear cell RCC</td>
<td>Intermediate high/very high risk (modified UISS)</td>
<td>Yes</td>
<td>Radical or partial nephrectomy with no evidence of residual macroscopic disease on postoperative CT scan</td>
<td>• pT1b N0 M0 G3-4&lt;br&gt;• pT2 N0 M0 G(any)&lt;br&gt;• pT3 N0 M0 G(any)&lt;br&gt;• pT4 N0 M0 G(any)&lt;br&gt;• pT(any) N+(fully resected) M0 G(any)</td>
</tr>
<tr>
<td>S-TRAC (NCT00375674)</td>
<td>Clear cell RCC</td>
<td>High risk (UISS)</td>
<td>Yes</td>
<td>Kidney tumor removed with no evidence of residual macroscopic disease</td>
<td>• pT3-4 N0 M0&lt;br&gt;• pT4 N0 M0&lt;br&gt;• pT(any) N1 M0</td>
</tr>
<tr>
<td>PROTECT (NCT01235962)</td>
<td>Predominantly clear cell RCC</td>
<td>Intermediate-high/very high risk (modified UISS)</td>
<td>No</td>
<td>Radical or partial nephrectomy</td>
<td>• pT2 N0 M0 G3-4&lt;br&gt;• pT3-4 N0 M0&lt;br&gt;• pT(any) N1 M0</td>
</tr>
<tr>
<td>ATLAS (NCT01599754)</td>
<td>Predominantly clear cell RCC</td>
<td>high risk (UISS)</td>
<td>No</td>
<td>Kidney tumor removed with no evidence of residual macroscopic disease or metastatic disease</td>
<td>• pT3-4 N0 M0 PS 0-1&lt;br&gt;• pT3-4 Nx M0 PS 0-1&lt;br&gt;• pT(any) N1 M0</td>
</tr>
<tr>
<td>SORCE (NCT00492258)</td>
<td>Clear cell or nonclear cell RCC</td>
<td>Intermediate or high risk (SSIGN)</td>
<td>Unknown</td>
<td>Kidney tumor removed with no evidence of residual macroscopic disease on postoperative CT scan</td>
<td>• SSIGN score 3-11</td>
</tr>
<tr>
<td>EVEREST (NCT01120249)</td>
<td>Clear cell or nonclear cell RCC</td>
<td>Intermediate-high/very high risk (modified UISS)</td>
<td>Yes</td>
<td>Postnephrectomy with clear surgical margins and no evidence of residual disease</td>
<td>• pT1b N0 M0 G3-4&lt;br&gt;• pT2-4 N1-3 M0</td>
</tr>
</tbody>
</table>
# I/O Adjuvant Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>N</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG Prosper</td>
<td>Neo/adjuvant nivolumab vs BSC</td>
<td>766</td>
<td>DFS</td>
</tr>
<tr>
<td>ImMOTION 110</td>
<td>Atezolizumab vs placebo</td>
<td>664</td>
<td>DFS</td>
</tr>
<tr>
<td>KEYNOTE 564</td>
<td>Pembrolizumab vs Placebo</td>
<td>950</td>
<td>DFS/OS</td>
</tr>
<tr>
<td>BMS Checkmate</td>
<td>Ipi/Nivo vs. placebo</td>
<td>800</td>
<td>DFS/OS</td>
</tr>
<tr>
<td>RAMPART</td>
<td>Durva vs. Durva/Treme vs. observation</td>
<td>1,750</td>
<td>DFS/OS</td>
</tr>
</tbody>
</table>
Conclusions

• Neoadjuvant VEGF-targeted therapy has activity against primary clear cell RCC tumors and may lead to enhanced feasibility of resection, but is still investigational at present
  – Likely to be most useful in specific surgical circumstances yet to be defined

• Adequately dosed VEGF-targeted therapy can prolong DFS at a cost of toxicity in high risk patients.

• Neo/adjuvant I/O trials are ongoing and likely to change this landscape.