Why perioperative therapy might cure kidney cancer

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Directory of Abramson Cancer Center Kidney and Prostate Cancer Clinical Trial Programs
My Disclosures

- Pfizer - correlative and clinical trial support for E2805
- Merck - advisory board
- Roche - consultant
What is perioperative therapy?

• Additional treatment before, during or after surgery
• Usually in the case of kidney cancer limited to the kidney area
Guidelines that Doctors and Nurses Use for treating your cancer

NCCN Guidelines Version 1.2020
Kidney Cancer

INITIAL WORKUP
- H&P
- CBC, comprehensive metabolic panel
- Urinalysis
- Abdominal & pelvic CT (or MRI)
- Chest x-ray
- If clinically indicated
  - Bone scan
  - Brain MRI
  - Chest CT
  - Consider needle biopsy
- If urothelial carcinoma suspected (eg, central mass), consider urine cytology, ureteroscopy or percutaneous biopsy
- If multiple renal masses or <45 y, consider genetic evaluation
- Suspicious mass

STAGE
- Stage I (T1a)
- Stage I (T1b)
- Stage II
- Stage III
- Stage IV

PRIMARY TREATMENT
- Partial nephrectomy (preferred)
- Ablative techniques
- Active surveillance
- Radical nephrectomy (if nephron-sparing not indicated or feasible)

ADJUVANT TREATMENT
- Surveillance
- Clinical trial or Surveillance
- Clear cell histology:
  - Clinical trial (preferred)
  - Surveillance
- Adjuvant sunitinib (category 3)
- Non-clear cell histology:
  - Surveillance

FOLLOW-UP
- (category 2B)
- Follow-up See KID-2
- Relapse or Progression, See KID-3
Surveillance

• Stage I- every 6 months for year one, then annually for up to 5 years
• Stage II- every 3-6 months for 3 years, then annually for at least 2 more years
• Preferred imaging is CT or MRI of abdomen and CT of chest
The drugs we have used in perioperative clinical trials

- VEGF TKIs (Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors)
  - Sunitinib (Sutent)
  - Axitinib (Inlyta)
  - Pazopanib (Votrient)
  - Sorafenib (Nexavar)

- Immune Checkpoint Inhibitors
  - Ipilimumab (Yervoy) +Nivolumab (Opdivo)
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)
  - Atezolizumab (Tecentriq)
Metastatic RCC Therapy:

Mechanisms:
Angiogenesis
Metabolism
Immunomodulation
Epigenetics

Cell stimuli (e.g., growth factors)

Cell growth/survival

Inactivated VHL tumor suppressor gene

Hypoxia

VEGF

PDGF

VEGFR

PDGFR

Tumor

Endothelial Cell

HIFα

HIFα

HIFα

HIFα

MK-6482

Bevacizumab

Temsirolimus

Everolimus

PI3K

AKT

mTOR

Sunitinib

Sorafenib

Pazopanib

Axitinib

Lenvatinib

Cabozantinib

Adapted from Rini BI, et al. Lancet.
VEGF-TKIs are very active in kidney cancer that has spread

- Broadly efficacious: 80% achieve clinical benefit in metastatic disease
- Little data about best sequence
- However, not a panacea: ~20% non-responders

But the use of VEGF TKIs is controversial in the adjuvant setting
One trial of the 5 conducted has shown improved in DFS.
No improvement in OS in any of the 5 VEGF Adjuvant trials

1yr sunitinib, sorafenib, pcb

1 yr sunitinib, pcb

1 yr pazopanib, pcb

<3 yr axitinib, pcb

ASSURE
Haas, Lancet 2016

S-TRAC Ravaud
NEJM 2016

PROTECT
Motzer JCO 2017

ATLAS Quinn
Annals Oncol 2018

Sorafenib, pcb

SORCE 3y
Eisen ESMO 2019

SORCE 1y
Eisen ESMO 2019
Patients who have higher drug levels of pazopanib in their bodies might benefit but it is difficult to determine who those patients might be.

Sternberg C, PROTECT, Clin Cancer Res 2018
Patients on the adjuvant VEGF TKI trials had worse (or less well tolerated) side effects than those patients who participated in clinical trials for advanced disease.

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>&gt;3 pts with side effects</th>
<th>&gt;3</th>
<th>&gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>ASSURE (all)</td>
<td>63%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>S-TRAC (all)</td>
<td>56.9%</td>
<td></td>
</tr>
<tr>
<td>Pazopanib</td>
<td>PROTECT (600 mg dose)</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATLAS (all)</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>SORCE (all)</td>
<td></td>
<td>57%</td>
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</table>
What Is Being Tested in the remaining VEGF TKI trials?

<table>
<thead>
<tr>
<th>Current/Recent Adjuvant RCC Trials</th>
<th>Design / risk criteria Different Populations!</th>
<th>Reporting?</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST (SWOG)</td>
<td>Can an mTor inhibitor for 1 year cure kidney cancer (cc and non ccRCC)? Everolimus vs placebo</td>
<td>2020?</td>
</tr>
</tbody>
</table>
What Is Being Tested in the Immune Checkpoint Inhibitor Perioperative trials?

– Does leaving the kidney tumor in, when immune therapy is started, make the Immune checkpoint inhibition therapy work better?
– Does Immune checkpoint inhibition cure high risk kidney cancer?
– Does immune checkpoint inhibition cure low volume resected metastatic disease?
– Does immune checkpoint inhibition delay relapse of cancer?
– Can we identify immune or other profiles which could predict benefit to these agents?
Completed Phase 3 RCC single agent IO Adjuvant Studies

**IMmotion010**
- High risk or limited M1 NED
- Post nephrectomy ≤12 wks
- Clear cell or sarcomatoid
- Stratification Factors:
  - T2/T3a vs. >T3b
  - PD-L1 (IC0 vs IC1/2/3)
  - Region (US/Canada vs ROW)

Randomize

1:1 N=664

Atezolizumab 1200mg IV Q3 wks x 16 cycles

Placebo IV Q3 wks x 16 cycles

**KEYNOTE 564**

NCT03142334

Patients (N=950)
- RCC with clear cell component
- Post-nephrectomy (total/partial) with intermediate to high risk of recurrence
  - pT2, grade 4 or sarcomatoid, N0, M0
  - pT3, any grade, N0, M0
  - pT4, any grade, N0, M0
  - pT any stage, any grade, N0, M0
- Postnephrectomy (total/partial) plus complete resection of metastasis
- M1 NED

Randomize 1:1

1:1 N=950

Pembrolizumab 200mg Q3W x17 cycles

Placebo Q3W x17 cycles

Safety and survival follow-up

Allow limited resectable M1 disease that would be rendered NED
Ongoing
Checkmate -914(BMS)
Nivolumab + Ipilimumab vs Placebo

• High risk or limited M1 NED
• Post nephrectomy ≤12 wks
• Clear cell or sarcomatoid

Nivo 3mg/kg and Ipi 1 mg/kg IV every 6 weeks for 24 wks

Placebo IV every 6 weeks for 24 weeks

Open at LHV Allentown
And MSKCC
Disrupting Practice: Pre-surgical Priming with anti-PD-1

- Ongoing but unsuccessful anti-tumor T cell response in the primary tumor, tumor ME, and draining nodes

- Post-PD-1 blockade anti-tumor CD8 T cells may preferentially expand in these areas and traffic to distant sites and develop into memory cells (mice)

- Nephrectomy may remove the majority of these effector cells and cytokines → less potent response?

- Short course of neoadjuvant immunotherapy increased survival compared to adjuvant ...in MICE
  - Primary tumor required for T cell expansion

- Two ongoing phase 2 studies of neoadjuvant nivolumab in M0 RCC: safe, no surgical delays, target is hit

Woo...Drake Cancer Res 2012, MacFarlane CIR 2013, Liu Cancer discovery, Harshman Kidney 2017
Proof of efficacy in other solid tumors: TNBC & Lung Cancer

- Tripling of estimated pCR rate in TNBC: 60 vs. 20%
- Near tripling in HR+/HER2 neg: 34 vs. 13%

Nanda ASCO 2017

2 doses of preoperative nivolumab in M0 NSCLC
45% experienced major pathologic response (MPR ≤10% viable tumor cells)
Primary tumors with MPR: increased infiltrating lymphocytes and macrophages consistent with immune mechanism of response
PD-L1 expression didn’t predict response

Forde NEJM 2018
EA8143 PROSPER RCC: Adjuvant Therapy with a Twist

- Need the **trifecta**: presurgical priming with PD-1 blockade necessary for enhanced efficacy
- 1 neoadjuvant dose may not be sufficient → further engage with adjuvant therapy
- No Placebo—patients really do care about this!

Urology PI: Allaf; PIs: Harshman/McDermott, MANY OTHERS
Conclusions

• No OS benefit in any of the 5 reported adjuvant VEGF trials
• No DFS benefit in 4 large adjuvant VEGF TKI trials/ DFS Benefit in 1 trial led to FDA approval of adjuvant sunitinib
• Adjuvant VEGF TKI inhibitors are associated with severe side effects in more than half of all patients so we need to really understand who should be offered this therapy
• Pharmacokinetic/ pharmacogenomic analyses may help to determine benefit to VEGF TKI adjuvant therapy
• Current immune checkpoint inhibitor trials are ongoing and we are hopeful
• Surveillance Clinical trial participation or adjuvant sunitinib remain choices for patient with kidney cancer at high risk for recurrence
Role of Cytoreduction

- Benefit for nephrectomy in the metastatic setting?
- 5.8 month overall survival benefit in the immunotherapy era
  - Combined analysis: SWOG 8949 and EORTC 30947
  - No difference in response
  - Acceptable toxicity
- True for targeted agents?
  - Need? (can shrink primary tumor)
  - Toxicity?

Harshman Future Drugs 2007, Adapted from Flanigan J Urol 2004
Cytoreductive Nephrectomy in the Targeted Therapy Era

**Nephrectomy needed?**
- CARMENA Trial
  - N=576
  - Non-inferiority trial
  - Primary Objective: OS

**Sequence?**
- EORTC Trial
  - N=440
  - Nephrectomy after sunitinib only if no PD in metastatic dz
  - Primary Objective: PFS
Cytoreductive Nephrectomy in the Targeted Therapy Era

Nephrectomy needed?

Nephrectomy

Sunitinib 50 mg 4/2

Sunitinib 50 mg 4/2

N=576

CARMENA Trial

- Non-inferiority trial
- Primary Objective: OS
Hypertension associated with:
- Increased tumor shrinkage
- Prolonged time to progression
- Increased overall survival

Controlling BP did not diminish effect

• On-therapy marker of effectiveness
Combination VEGF TKI and immune checkpoint inhibition has improved overall survival and led to first-line approval.
Phase II Immotion 150:

- Atezolizumab + bevacizumab
- Atezolizumab
- sunitinib

305 pts
mccRCC
PFS
PDL1
3 | Association between tumor mutations and clinical outcome. a, TMB and TNB are plotted by response group (CR and PR vs. SD (stable disease) and PD (progressive disease)) for each treatment arm. No apparent difference was observed between response groups in the sunitinib (two-tailed t
Exploratory analyses of angiogenesis and immune-associated genes and PFS in IMmotion150.