Phase 3 Perioperative Nivolumab in M0 RCC (PROSPER RCC, ECOG –ACRIN 8143)

The strong case for a neoadjuvant/adjuvant approach to priming the immune system before surgery

Lauren C. Harshman MD
Overview

• Room for improvement even with S-TRAC’s positive results?

• Trial design considerations

• PROSPER RCC (EA8143) rationale and synopsis
Current Controversy: ASSURE vs. S-TRAC in M0 RCC

**ASSURE: No DFS or OS Benefit**
- 2016: Still no established systemic perioperative therapy
- Controversial benefit to 1 year of adjuvant VEGF blockade:
  - Negative: 1 yr of sunitinib or sorafenib (ASSURE) did not increase DFS or OS
  - Positive: 1 yr of sunitinib (S-TRAC) increased DFS in higher risk disease, OS data maturing
  - Quality of life may be integral to the decision: ~30% treatment discontinuations due to tox
  - Await outcomes of several other adjuvant TKI and mTOR inhibitor studies but move latest IO agents forward

**S-TRAC: DFS benefit; OS not mature**

N. Haas

A. Ravaud
Moving Beyond the TKIs: Bring Nivolumab Forward to the Perioperative Setting

- Survival benefit and unparalleled tolerability of nivolumab in treatment refractory metastatic setting
- Makes sense to move the success of PD-1 blockade forward into the M0 space

<table>
<thead>
<tr>
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<th>Median OS, months (95% CI)</th>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>25.0 (21.8–NE)</td>
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<tr>
<td>Everolimus</td>
<td>19.6 (17.6–23.1)</td>
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HR (98.5% CI): 0.73 (0.57–0.93)

\( P = 0.0018 \)

Sharma et al ESMO 2015, Motzer NEJM 2015
Perioperative PD-1 Blockade Approaches

• **Neoadjuvant (presurgical):**
  - Duration considerations:
    • Balance adequate number of doses for sufficient efficacy with delays to curative surgery
    • Worth it for an effective systemic therapy but not all will be responders
  - Science Science Science: tissue and sera to study for pharmacodynamic and predictive markers

• **Adjuvant (postsurgical):**
  - Standard paradigm, most feasible
  - If using PD-1/L1 blockade: is there enough antigen post surgery to drive response?
  - Much less opportunity for science given lack of comparative tissue or sera

• **Neoadjuvant plus adjuvant combination:** potential sweet spot
  - Are both necessary for success and feasibility?
Perioperative Approaches for M0 disease

• Combinations
  - Monotherapy is rarely sufficient to eradicate cancer but may be it is just enough for micrometastases
  - Must balance tolerability and quality of life with the clinical gains

• Selected populations would be ideal
  - Higher risk stage
  - Biomarker driven: PD-L1 positive
  - Inflammatory (“hot”) tumors only
  - Mutation/immune/cytokine signatures
Phase 3 RCC study: tumor PD-L1 did not pan out

- Prognostic but not predictive in VEGF-treatment refractory setting
- Dynamic nature and potential heterogeneity among sites make it unlikely to be a reliable marker
Design considerations: short and sweet

• Ensure feasibility but not at the expense of inefficacy

• Maximize efficacy:
  - Priming when bulk of tumor in place
  - Choice of agent may matter: Is full PD-1 blockade better than PD-L1 blockade or vice versa?

• Minimize patient resources: i.e., aim for a higher degree of clinical benefit

• Shorten duration of trials and time to an answer
Rationale for Pre-Nephrectomy Anti-PD-1 Priming

- Ongoing but unsuccessful anti-tumor T cell response in the primary tumor, tumor microenvironment, and draining lymph nodes
- Post-PD-1 blockade anti-tumor CD8 T cells may preferentially expand in these areas → can then traffic to distant sites → potential to eradicate micrometastases now and later (memory)
- Nephrectomy will remove the majority of these effector cells and cytokines: induce less potent response?
- Campbell lab has shown significant decrease in circulating PD-1+ cells (the army) after nephrectomy

Woo Cancer Res 2012, C Drake personal comm.
Neoadjuvant Better than Adjuvant Immunotherapy ... in Mice

- Short course of neoadjuvant immunotherapy improved survival compared to adjuvant therapy
- May be explained by ability to increase gp70 tumor specific CD8+ T cells that were proliferating, had an effector/memory phenotype, and produced IFNγ and TNF in peripheral blood and distant organs
- Primary tumor required for expansion of tumor specific T cells → did not observe same magnitude of tumor-specific T cell expansion with adjuvant therapy
- Elevated tumor specific CD8+ T cells in blood early after Neo predicted greater survival

Liu...Smyth, Teng Cancer Discovery 2016
**PROSPER RCC: Phase III Study of Perioperative PD-1 Blockade Non-metastatic RCC---Optimizing for Success**

- **Clinical stage:** ≥T2 (7cm renal mass) or T\textsubscript{any}N+

**Randomize**

- 1: 1

**Nivolumab**

- q 2 wks
- x 2 doses

**Resection**

- Nivolumab q2 wks x 3 mos then q4 wks x 6 mo

**Observation**

**N=766**

- **Mandatory Biopsy**

**Stratify by:** cT2 or >cT2, cN0 or cN+, histology

- Need the trifecta: accept presurgical priming with PD-1 blockade is necessary for efficacy
- 2 neoadjuvant doses for feasibility but may not be sufficient
  - need adjuvant therapy
- 2 arm is more feasible than a 3 arm study
- Monotherapy: no proven combination; nivolumab established safe and effective in tx refractory disease
- Target a higher risk but unselected population: there is no validated predictive marker at present

**Approved by NCI on 10/21/15:**
- High Priority Question
- FDA Approval: Move Forward 9/12/16
- CIRB Approval 10/16
PROSPER RCC (EA8143): Phase III Perioperative PD-1 Blockade

Clinical stage: ≥T2 (7cm renal mass) or T\textsubscript{any}N+

1:1 Randomize

N=766

Mandatory Biopsy

*Stratify by: cT2 or >cT2, cN0 or cN+, histology

Nivolumab q 2 wks × 2 doses → Resection → Observation

Nivolumab q 2 wks × 3 mos then q 4 wks × 6 mo

Overall Survival
Clear cell RFS
Safety
Tolerability
Quality of Life

• Primary endpoint: 14.4% absolute benefit in RFS
  - 84.2% power to increase from 55.8% → 70.2% at 5 yrs; HR 0.70
• Secondary endpoint OS: 5 yr OS: 78.7% to 87.3%; HR 0.77
• Mandatory presurgical biopsy: ensure correct diagnosis and correlative science

EA8143 PI: Harshman
EA8143 Team Science: Major Opportunity for Forward Progress through Biomarker Discovery & Science

- Inflamed vs. non-inflamed tumors—pre-existing intratumoral T cells predict benefit?
- Does priming increase trafficking and proliferation of CD8+ T cells to the tumor?
- Will tumor PD-L1 expression adaptively increase after nivo (local TILs on the attack)?
- Whole exome sequencing:
  - Identify neoepitope signatures
  - Characterize mutational patterns and frequency
- Nanostring: predictive gene expression patterns
- T cell proliferation assays to detect neoantigen response
- Cytokine signatures
- WELCOME INVOLVEMENT & PROPOSALS
Closing arguments re: Neoadjuvant/Adjuvant Strategy

• Strong preclinical evidence that the mechanism behind PD-1 blockade relies on antigen—so priming the immune system when greater burden of antigen is present makes sense

• The possible science and potential discovery with the addition of neoadjuvant priming is priceless

• There is no point in enhancing the feasibility of a negative approach

• Change is good--A little “hardwork” upfront may mean a significant difference in survival for patients
WE WANT YOU!

On the PROSPER RCC Team

- Opening via CIRB and NCTN Intergroup mechanism.
- Please contact us—welcome correlative proposals and involvement on many levels

Meeting at KCA:
5pm Friday
Nov 4
Marco Island Room
(3rd Fl)

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Acknowledgements

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- Brian Shuch MD
- Dan George MD

Kidney Cancer Association

Many Others!
Current Controversy: ASSURE vs. S-TRAC in M0 RCC

ASSURE: No DFS or OS Benefit

- pT1b (high risk UISS), pT2-T4 or N+
- Clear cell and non-clear cell
- No central review of imaging
- Majority dose reduction in starting dose of sunitinib
- 34-44% treatment discontinuation

S-TRAC: DFS benefit; OS not mature

- Targeted higher risk: pT3-4 or N+
- Clear cell disease only
- Central review of imaging
- All started at full dose sunitinib: Dose matters?
- 28.1% treatment discontinuation for toxicity
Adjuvant Sunitinib: the jury is still out...

• With a high frequency of treatment discontinuations for toxicity in both studies and evidence of decreased quality of life during that year, imperative to await evidence of overall survival benefit too.
  – Delayed/Late treatment may produce similar outcomes

• Await outcomes of the other adjuvant TKI and mTOR inhibitor studies

• Meta-analyses of outcomes data (Bex ESMO 2016)

• Meta-analyses of tissue/serum data to identify biomarkers to identify and select the patients who need the added systemic therapy (Harshman ASCO News 2017)

HOWEVER, WE SHOULD NOT WAIT FOR THESE RESULTS.
WE NEED TO MOVE FORWARD WITH TESTING OF THE NEWER IMMUNONCOLOGIC AGENTS