

EA8143 Study Update
*A Phase 3 RandOmized Study Comparing
PERioperative Nivolumab vs. Observation in
Patients with Localized Renal Cell Carcinoma
Undergoing Nephrectomy (PROSPER RCC)*

ECOG-ACRIN
cancer research group
Reshaping the future of patient care



Phase 3 Study of Perioperative Nivolumab in M0 RCC (EA8143, PROSPER RCC):

Neoadjuvant/adjuvant approach to priming the immune system before surgery

ECOG-ACRIN Team:

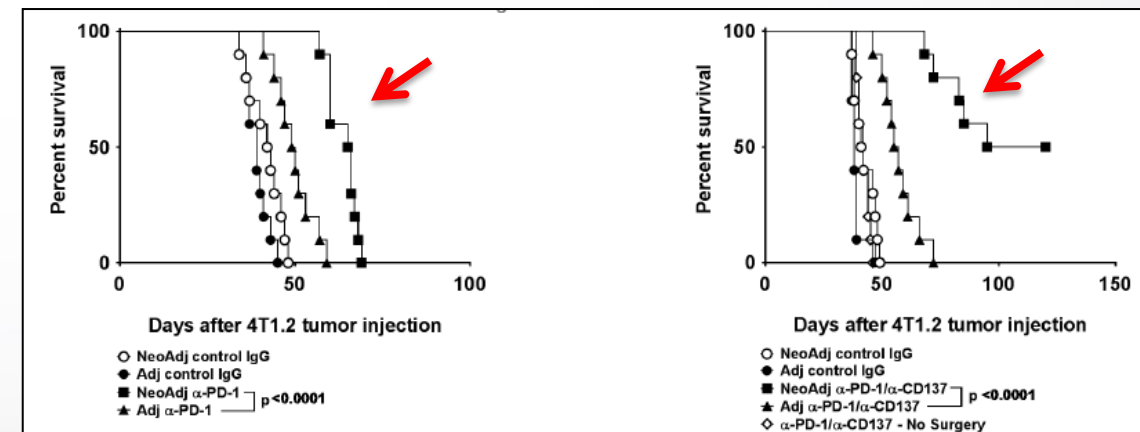
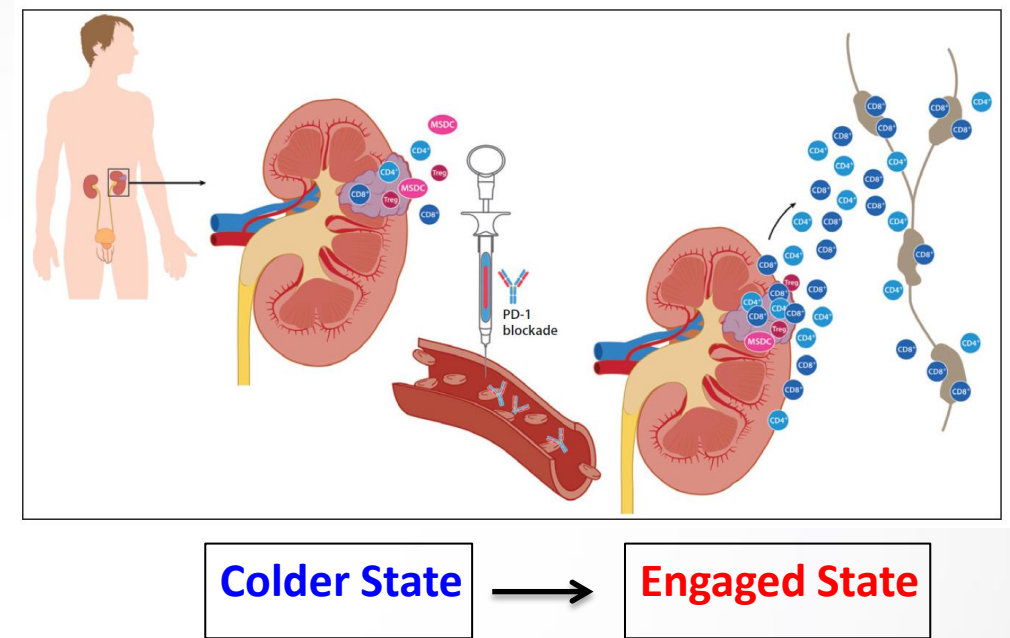
Lauren Harshman, Mohamad Allaf, Naomi Haas,
Judi Manola, Maneka Puligandla, Charles Drake, David McDermott,
Michael Carducci **on behalf of the NCTN PROSPER Team**

NCTN Champions:

Toni Choueiri, Primo Lara, Daniel Heng, Anil Kapoor, Brad Leibovich
Brian Shuch, Dror Michaelson and **Many Others!**

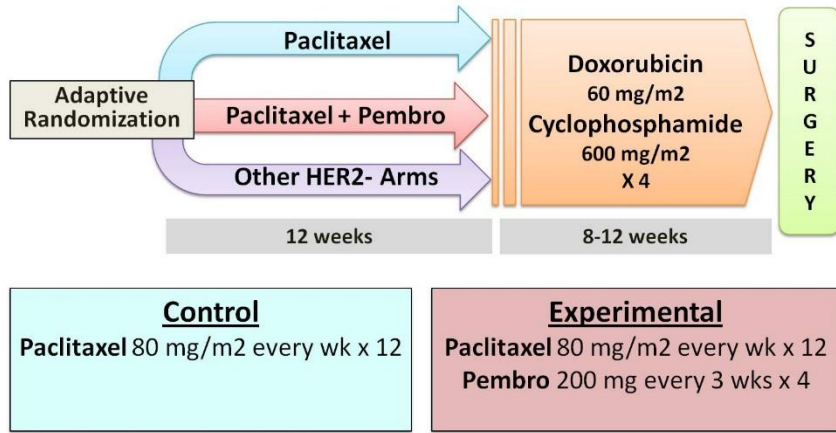
Disrupting Practice: Pre-surgical Priming with anti-PD-1

- 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



Proof of efficacy in other solid tumors: TNBC & Lung Cancer

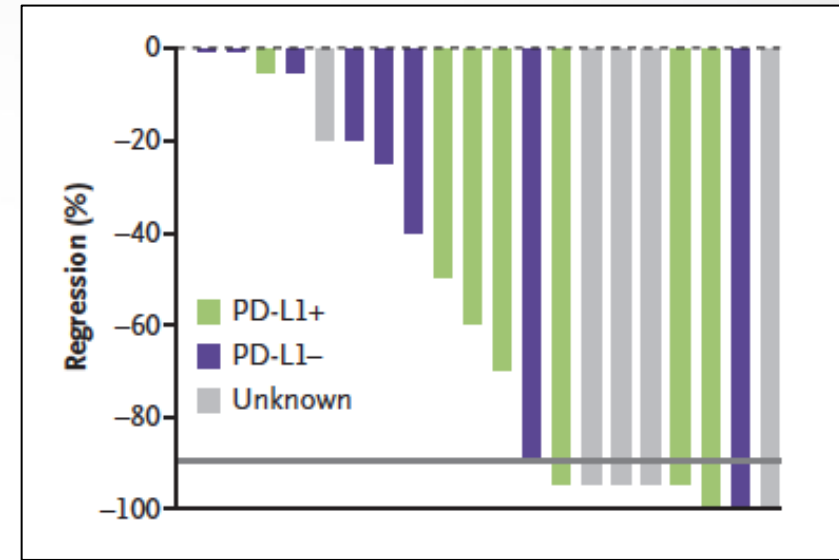
I-SPY 2 TRIAL Schema: HER2- Signatures



12

Nanda ASCO 2017

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



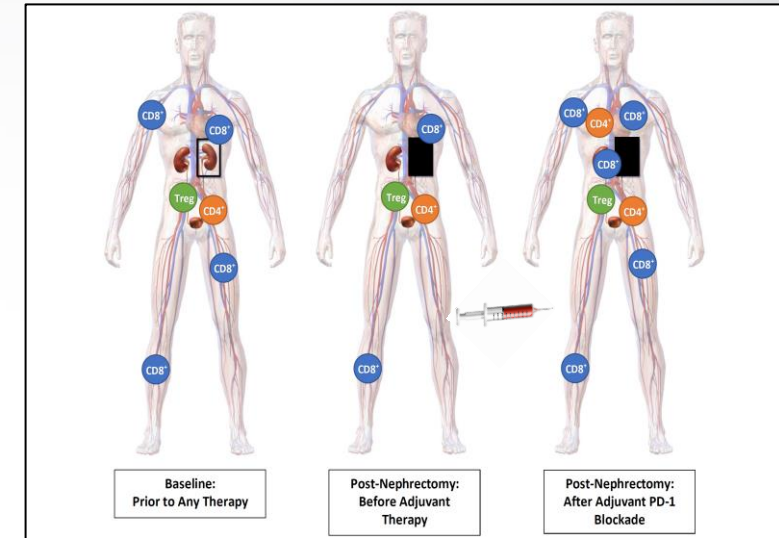
Forde NEJM 2018

- 2 doses of preoperative nivolumab in M0 NSCLC
- 45% experienced major pathologic response (MPR \leq 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

Overall PROSPER Study Objective

- To examine whether the addition of perioperative nivolumab to radical or partial nephrectomy can improve clinical outcomes in patients with locally advanced renal cell carcinoma (RCC)

**Adjuvant
Only**



**Neoadjuvant
Priming
Followed by
Adjuvant**

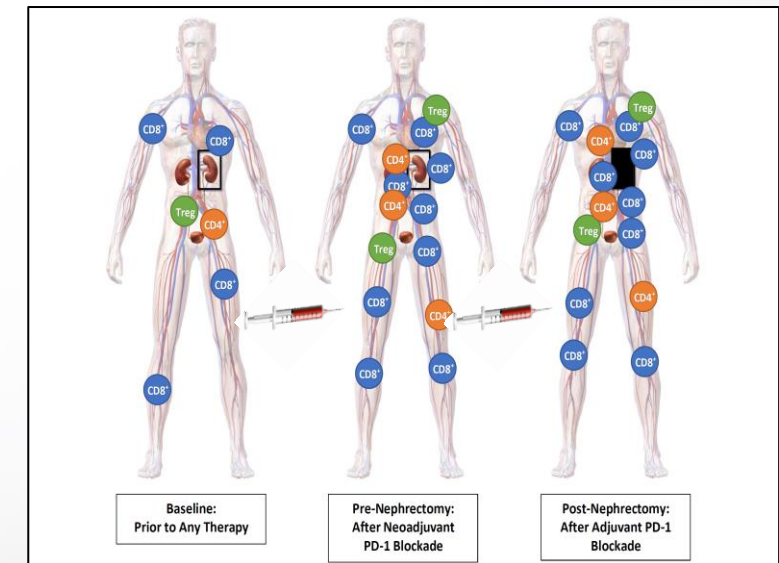
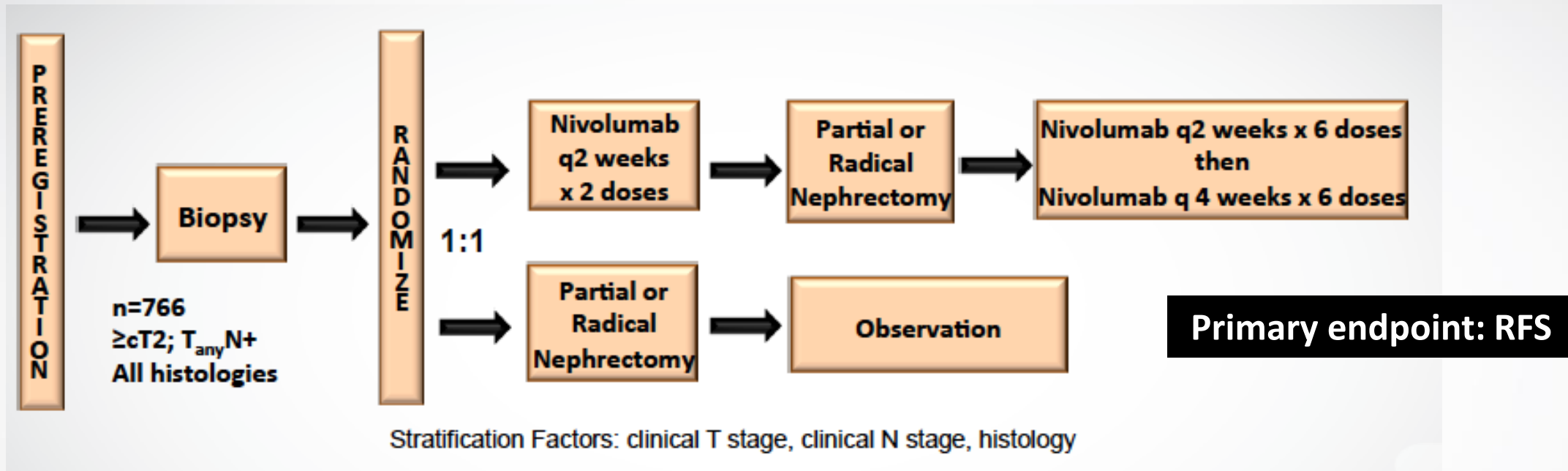


Figure H. Patel/JHU

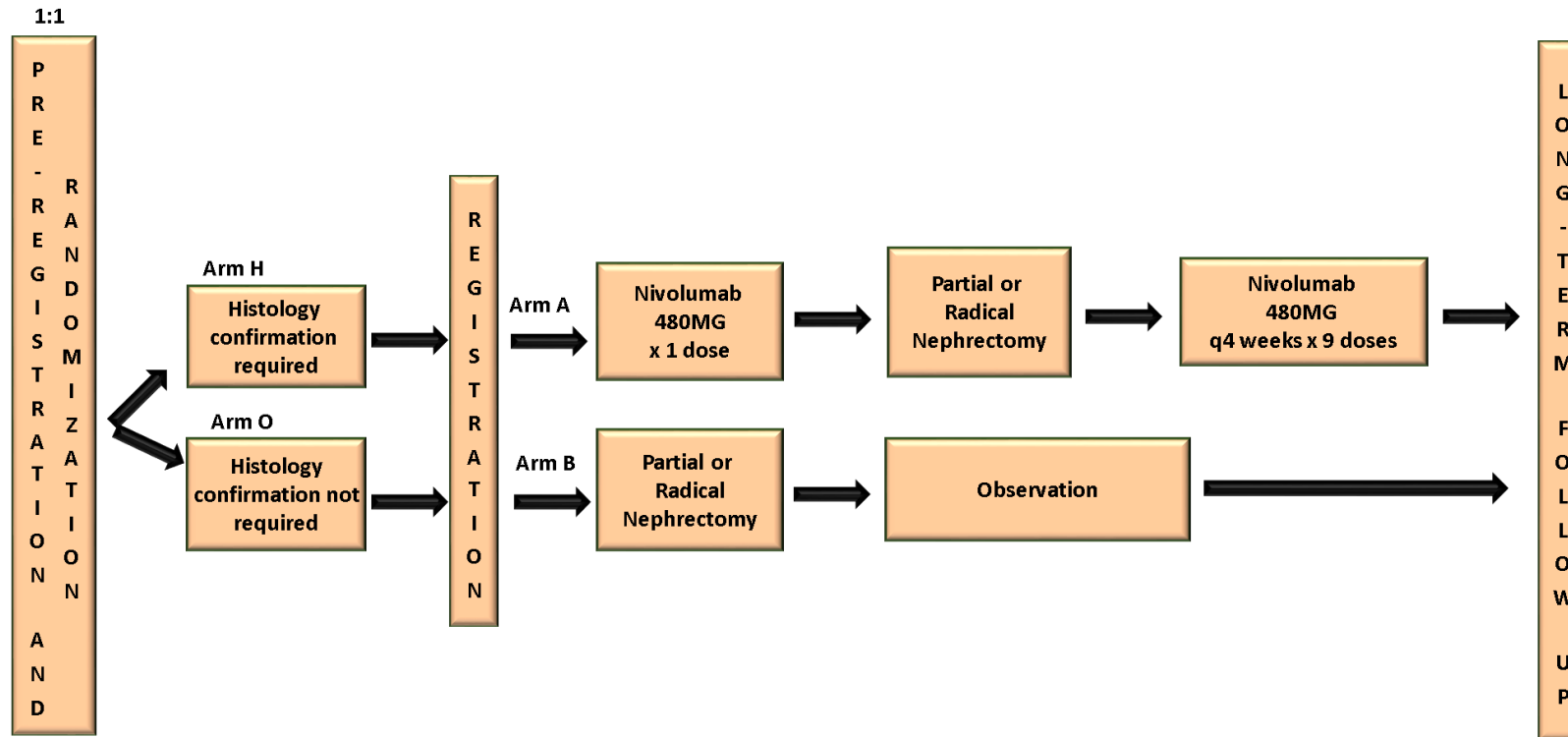
EA8143 PROSPER RCC: Adjuvant Therapy with a Twist



- Need the trifecta: presurgical priming with PD-1 blockade necessary for enhanced efficacy
- 2 neoadjuvant doses may not be sufficient → further engage with adjuvant therapy
- Biopsy before or after consent; Note: non-diagnostic biopsy is considered a good faith effort

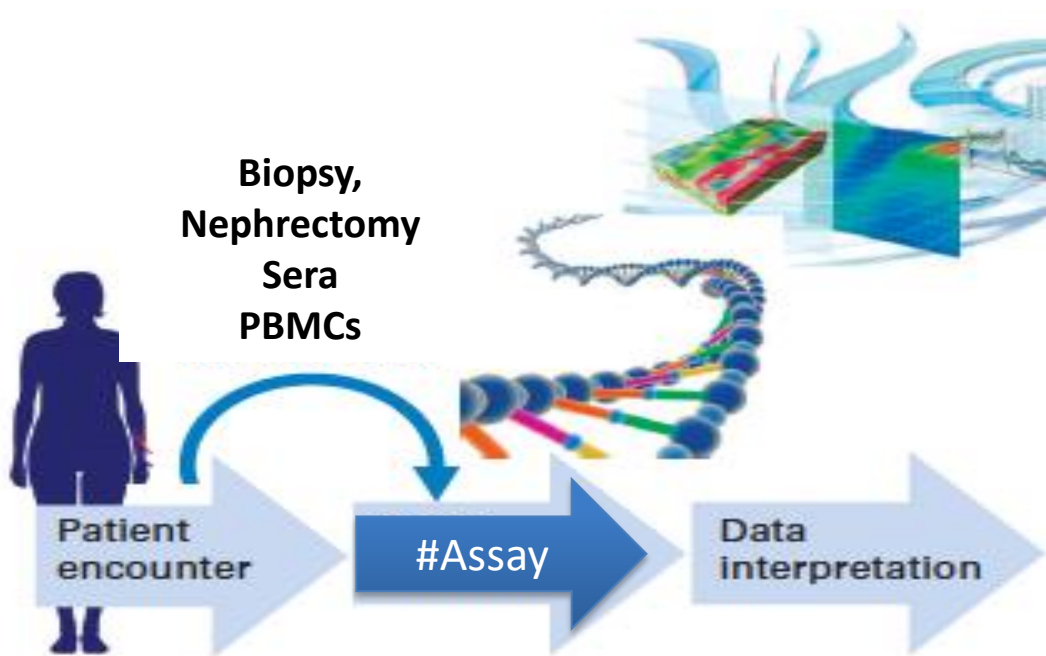
Urology PI: Allaf; PIs: Harshman/McDermott, MANY OTHERS

PROSPER: Revised Design—Amendment 4: Key Changes



- Limit biopsy to only Arm A – patients receiving nivolumab (encouraged in Arm B/control)
- Liberalizing the past/current cancer eligibility criteria
- Allow bilateral renal masses if can be resected/thermal ablation at the same time or within 12 weeks
- Allow M1 if resectable at same time/within 12 weeks and patient rendered NED
- Change neoadjuvant nivolumab dose to 1 and adjuvant doses to every 4 weeks

PROSPER Biobank & Potential for Discovery/Precision Medicine



IHC & Multiplex immunofluorescence (IF)



Whole exome & transcriptome sequencing
Mutational burden & neoantigen load



T cell proliferation (neoantigen response)
Nanostring platform (predictive immune signatures)



Cytokine signatures



RCC Organoids

To Name A Few

Quality of Life Studies



David Cella MD

- Especially germane when we think about the adjuvant sunitinib controversy....and factor in drug related and financial toxicity and increased clinic visits
- If you increase time to disease recurrence but not overall survival/cures, the quality of life of the patient during the adjuvant therapy holds even more weight...but patient specific

Imaging Correlatives: ACRIN Collaboration

- PROSPER “ScanBank”
- Untapped opportunity here: open to proposals
- Bi-RADs, Pi-RADs, why not Ki-RADs? (Singer)



Rajan Gupta MD
PROSPER Radiology Chair



Eric Singer MD
Urologist
Ki-RADs Lead

Closing thoughts on the PROSPER Neoadjuvant/Adjuvant Strategy

- Strong preclinical evidence that the mechanism behind PD-1 blockade relies on antigen—so **priming the immune system** when there's a greater burden of tumor antigen present **makes sense**
- **Change is good**--A little “hard work” upfront may mean a significant difference in survival for our patients
- The possible science and potential discovery with the addition of neoadjuvant priming is **priceless**



The logo icon consists of two light blue horizontal bars on the left, followed by three dark blue horizontal bars stacked vertically on the right.

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