Immunotherapy for Kidney Cancer: Lessons Learned and Future Directions

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

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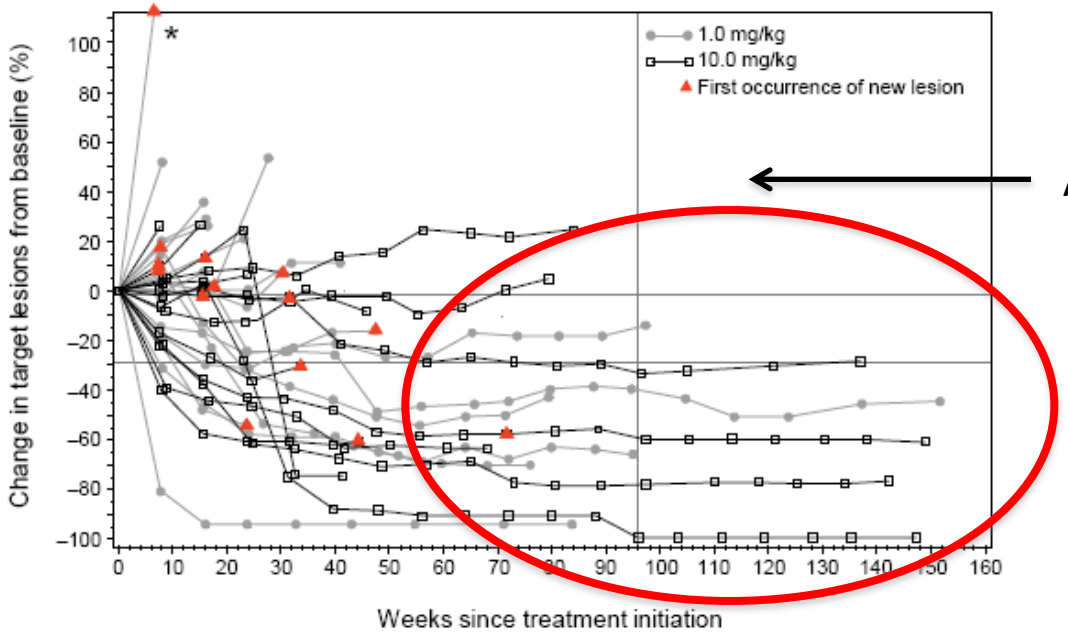
Phase I Nivolumab: RCC cohort (n=34)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% objective responses
  - Median PFS 7.3 months



All stopped therapy

Treatment - Free Survival (TFS)

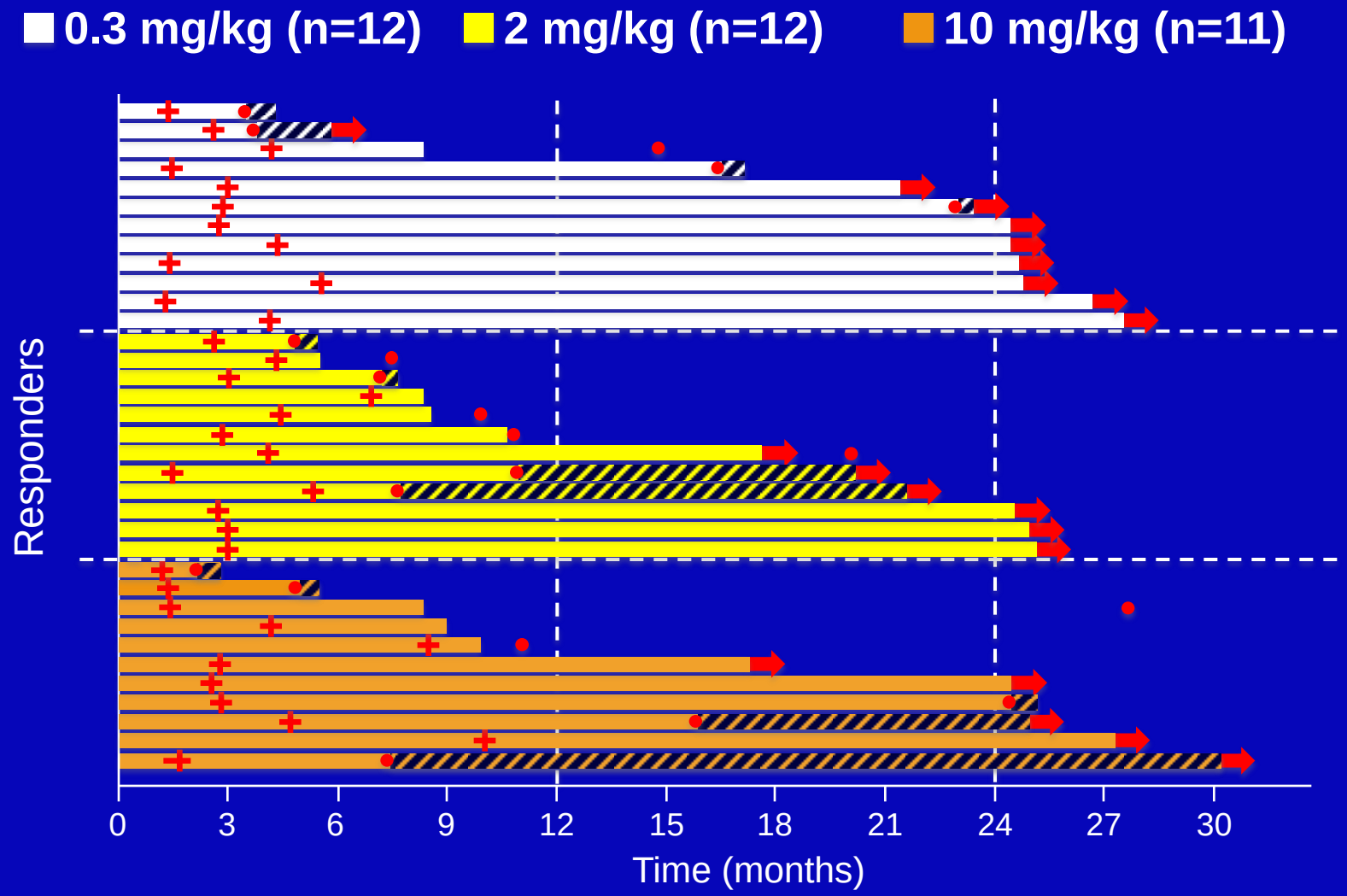
Drake ASCO 2013

PD-1 Pathway Blockade in RCC: Unanswered Questions

- Efficacy data
  - Will the clinical activity = improved OS?
  - How many responses are durable off therapy?
    - As seen with IL-2 and ipilimumab
- Predictive Biomarkers
  - Can we improve patient selection and move PD-1 pathway blockade to the first-line?
- Combination Therapy
  - Can we produce more durable responses?

Motzer et al, ASCO 2014

Nivo RCC Phase 2: Duration of response



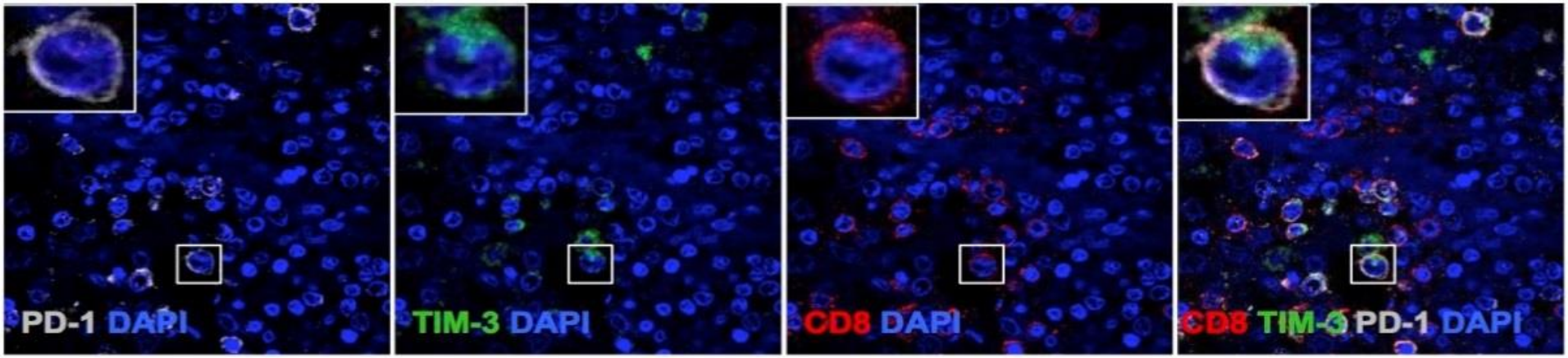
PD-1 Pathway Blockade in RCC: Unanswered Questions

- Efficacy data

- Predictive Biomarkers
  - Are they ready to guide clinical development?
  - Should we stratify patients on pivotal trials based on PD-L1 expression?
  - Can we develop a reliable response prediction model?
    - Incorporating tumor and immune infiltrate
    - Incorporating multiple platforms:
      - IHC + IF + Mutational signature + Gene Expression

- Combination Therapy

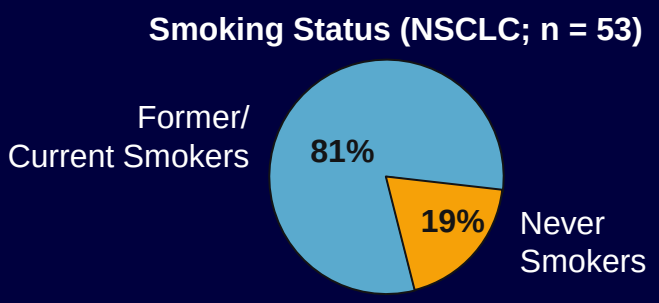
Towards a Multi-factor PD-1 Blockade Prediction Model: Tumor + Infiltrate

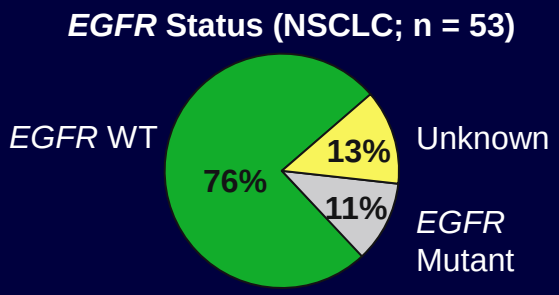


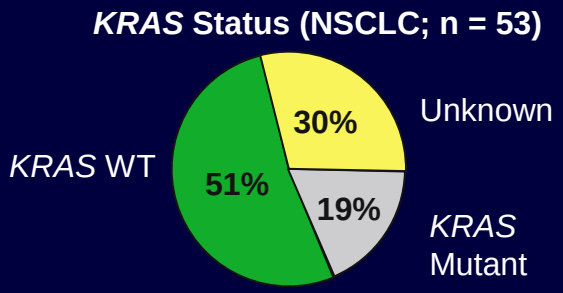
Representative confocal images of triple immunofluorescence labeling for CD8, PD-1 and TIM-3 in a FFPE clear cell RCC sample. A subset of T-cells co-expressing CD8, PD-1 and TIM-3 is identified.

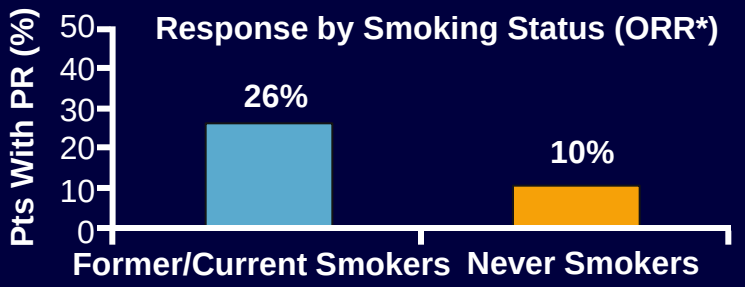
S Signoretti, with permission

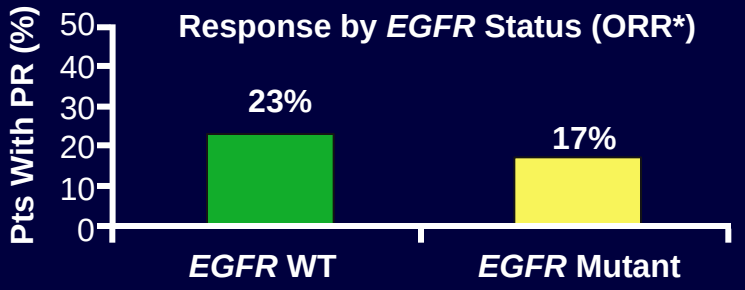
MPDL3280A Phase Ia: Response by Smoking and Mutational Status

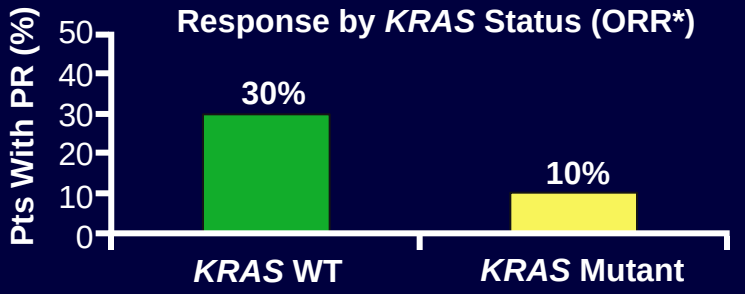












Horn L, et al. WCLC 2013. Abstract MO18.

RCC tumor grade and response to PD-1 Blockade

- Nivolumab Phase 1 RCC Trial
  - ORR = 29% (n=34)
  - ORR by tumor grade – based on path reports
    - Grade 1/2 – 18%
    - Grade 3/4 – 45% (9/20)
    - Grade 4 – 62% (5/8)

MPDL3280A: Efficacy by PD-L1 IHC (IC)

Efficacy-evaluable population with clear cell RCC

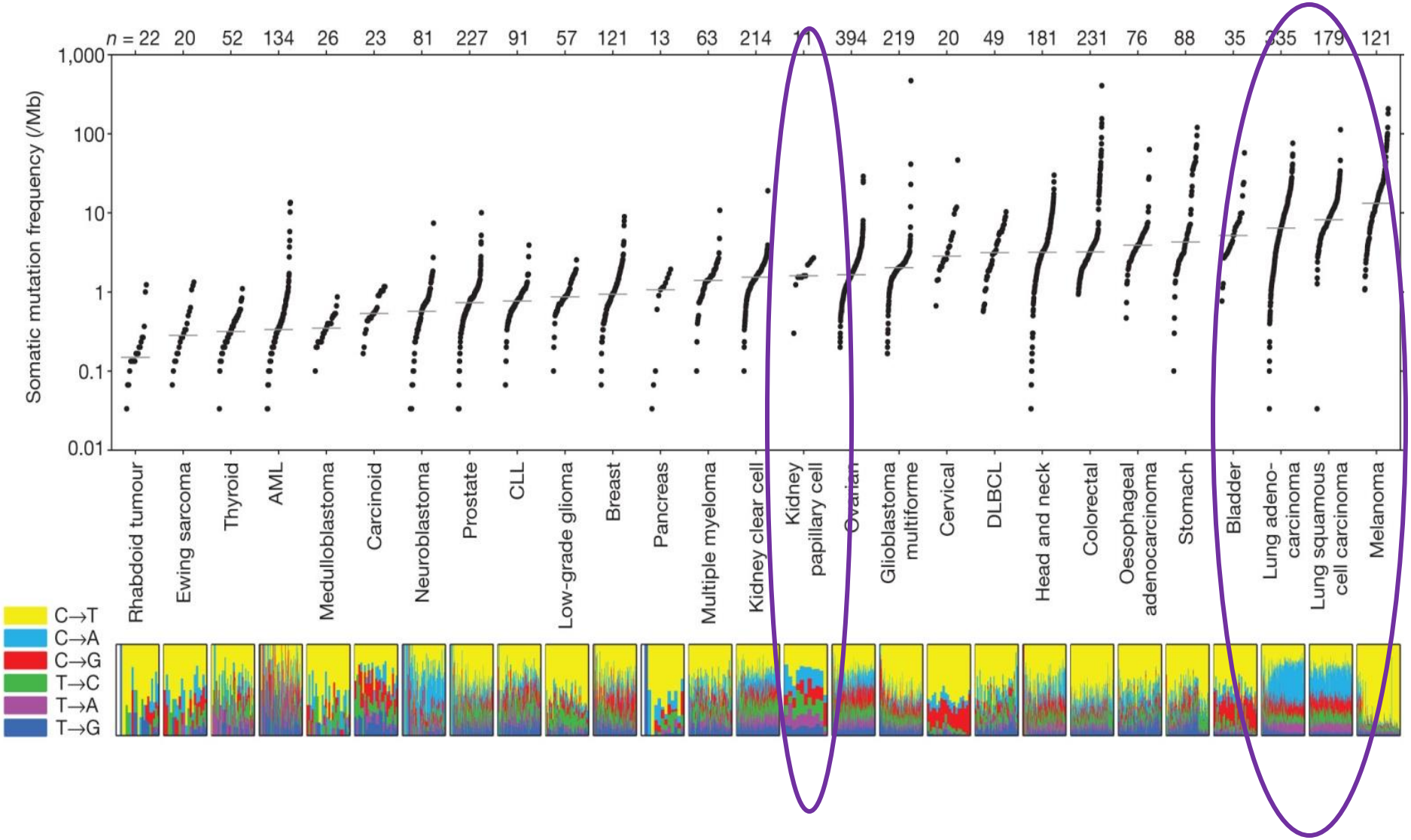
PD-L1 IHC (IC)[a] n = 62	ORR (95% CI), %
IHC 3 (n = 8)	38% (11-71)
IHC 2 (n = 12)	8% (0.4-35)
IHC 1 (n = 15)	20% (6-45)
IHC 0 (n = 21)	10% (2-30)

- 24-week PFS rate was 51% (95% CI: 38-63)
- 1 CR (IHC [IC] 3)
- ORR for Fuhrman grade 4 or sarcomatoid clear cell RCC (n = 18) was 22% (95% CI: 8, 47)

McDermott et al. ESMO, 2014.
IC, tumor-infiltrating immune cell.
[a] A PD-L1+ cohort of patients was enrolled. 6 patients had unknown PD-L1 IHC (IC) status.
Investigator-assessed confirmed ORRs per RECIST v1.1.
Patients dosed by Oct 21, 2013; data cutoff Apr 21, 2014.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% but < 10% of ICs are PD-L1+; IHC 1: ≥ 1 % but < 5% of ICs are PD-L1+; IHC 0: < 1% are PD-L1+.

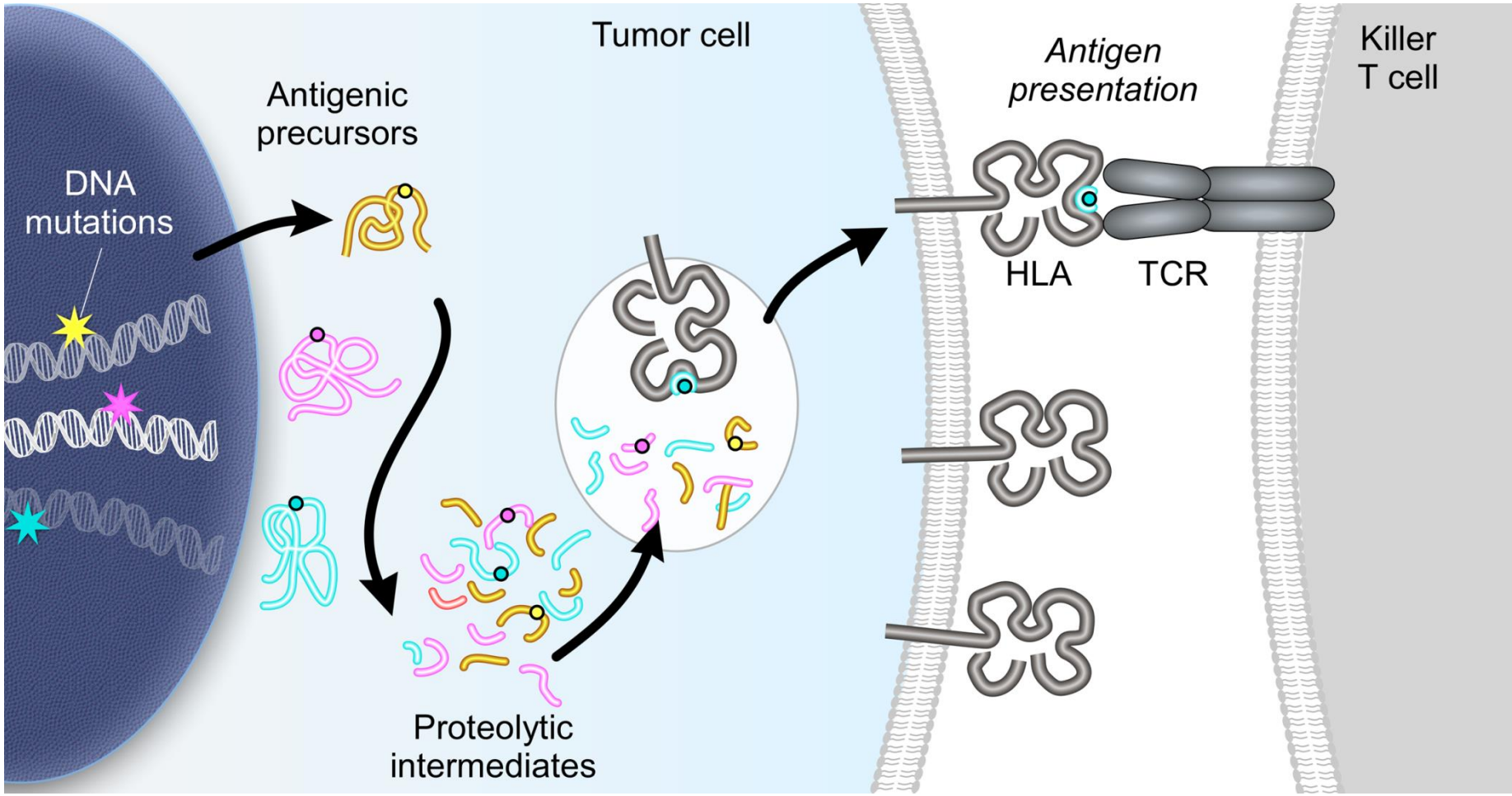
McDermott et al. KCS, 2014.

Somatic mutations by tumor type

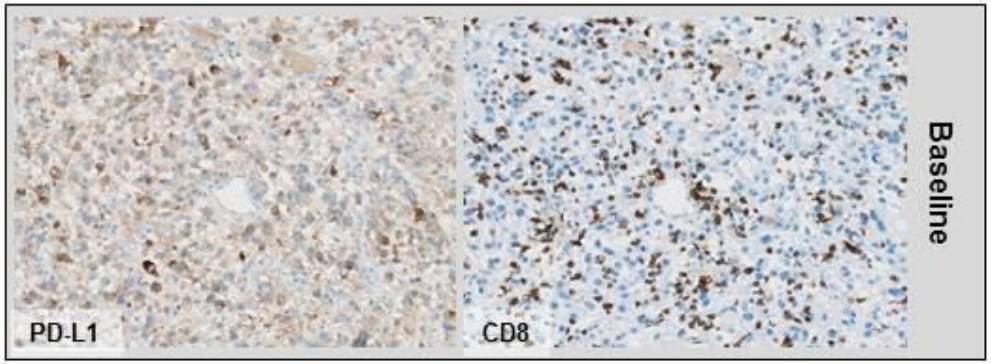


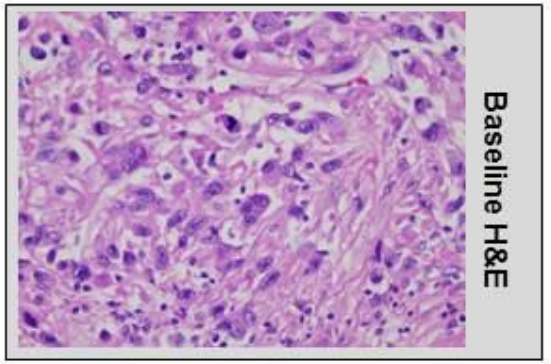
MS Lawrence *et al. Nature* **2013**

Somatic mutations have the potential to generate neoantigens

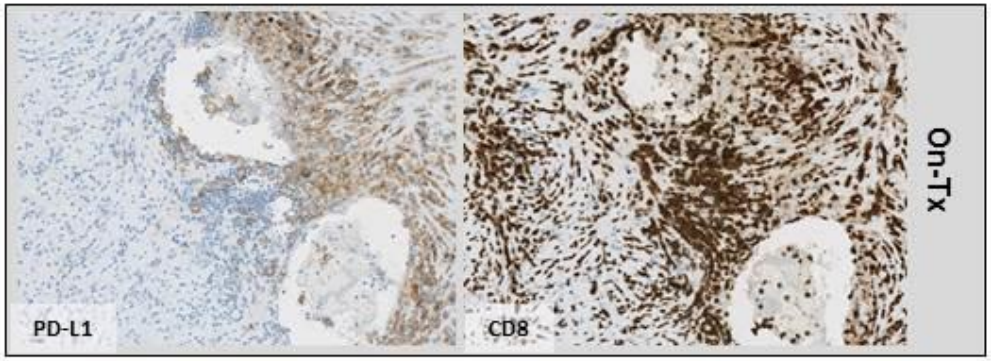


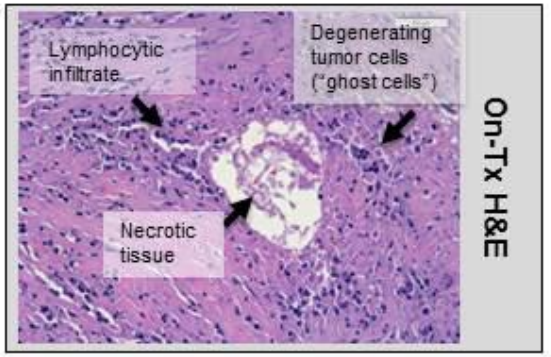
Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A





Biomarkers at baseline:
PD-L1 positive
CD8+ T cells present



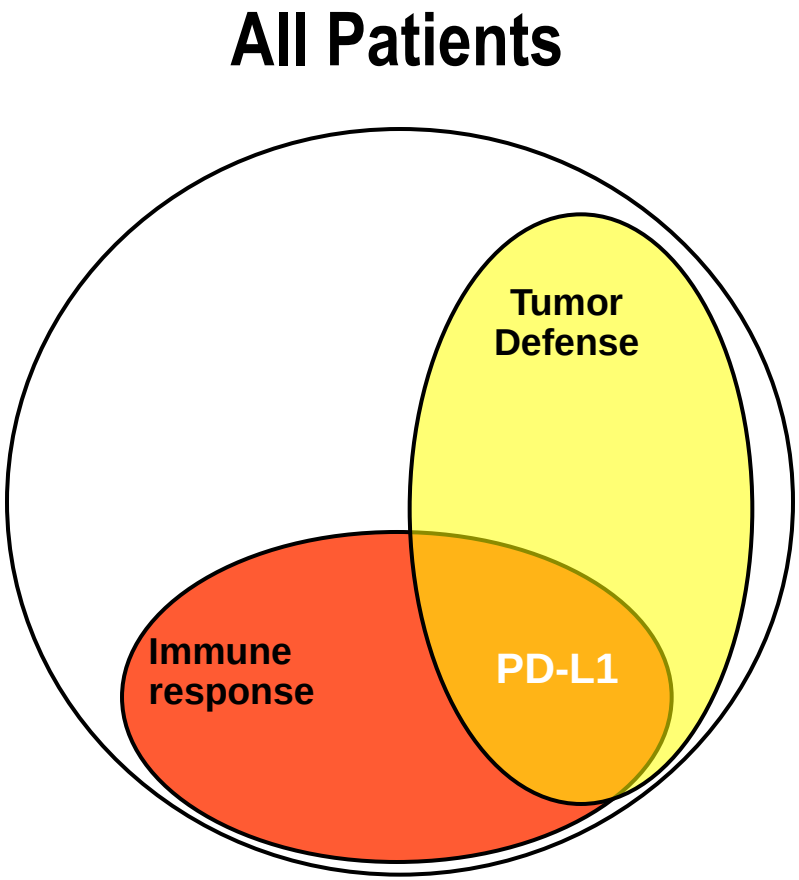


Biomarkers at week 4 post C1D1:
PD-L1 positive
Increased CD8+ T-cell infiltrate

On-treatment H&E:
dense lymphocytic infiltrate
and *no viable* tumor cells seen

Presented By John D. Powderly, MD at 2013 ASCO Annual Meeting

Immunotherapy Improvement Model



Biomarker +, responsive:
Single agents PD-1/PD-L1 Ab

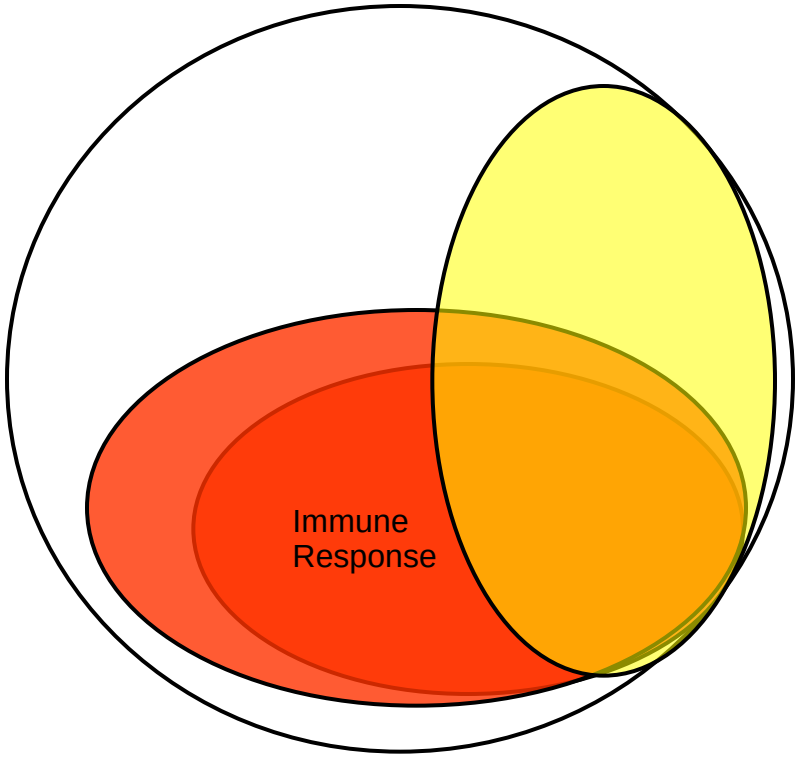
PD-1 Pathway Blockade in RCC: Unanswered Questions

- Efficacy data
- Predictive Biomarkers
- Combination Therapy
  - Which will improve durable response rate?
  - Will toxicities limit potential?

Immunotherapy Improvement Model

Biomarker+, Rx Sensitive:
Single agents PD-1/PD-L1 Ab

All Kidney Tumors



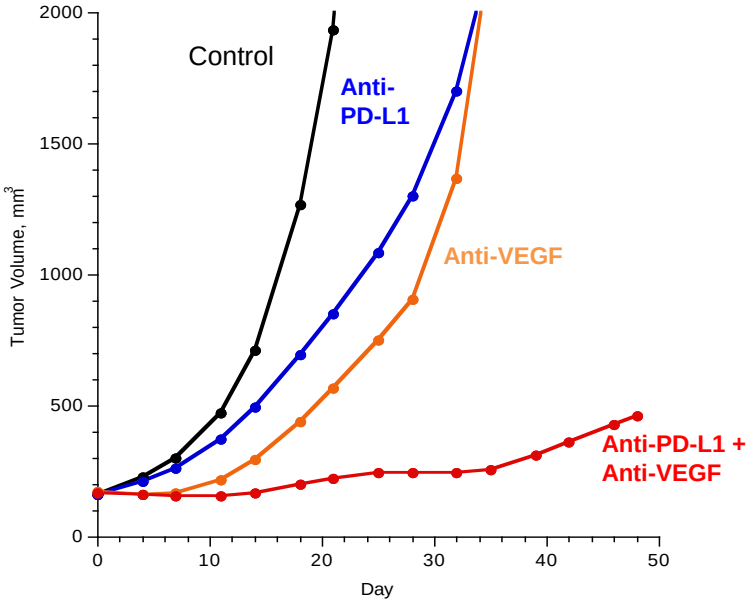
Biomarker Neg or Positive but Rx Resistant:
Combination Therapy

1) Elimination of Tregs: anti-GTR, CCR4
2) Inhibition of VEGF/MDSC: anti-VEGF, HDM2
3) Support effector T cells: IL-2,CD137 Ab, IL-21
4) Support DCs: GM-CSF
5) Other checkpoint inhibitors (CTLA4,TIM3 etc)

Rationale to Combine PD-L1 + VEGF Abs

- Anti-VEGF therapy has immunomodulatory properties
  - Increases trafficking of T cells into tumors[1,2]
  - Reduces suppressive cytokines and infiltrating Tregs and MDSCs[3,4]

Cloudman melanoma model[5]

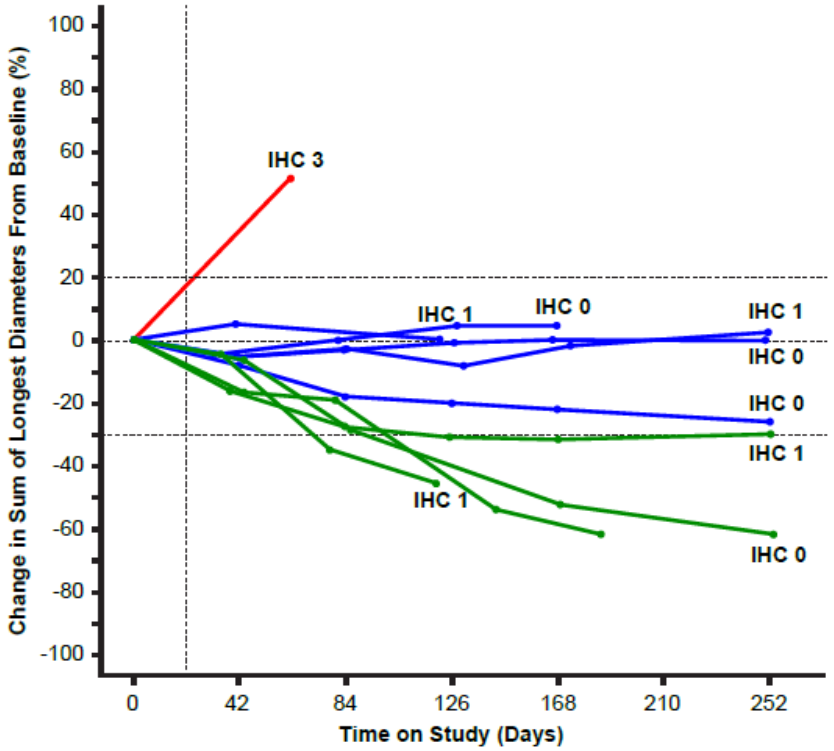


MDSC, myeloid-derived suppressor cell; Tregs; regulatory T cells . 1. Manning. *Clin Cancer Res.* 2007. 2. Shrimali. *Cancer Res.* 2010. 3. Kutsmartsev. *J Immunol.* 2008. 4. Roland. *PLOS One.* 2009. 5. Genentech, data on file.

MPDL3280A + Bevacizumab: Summary of Phase Ib Results

Safety and efficacy of patients in Arm A

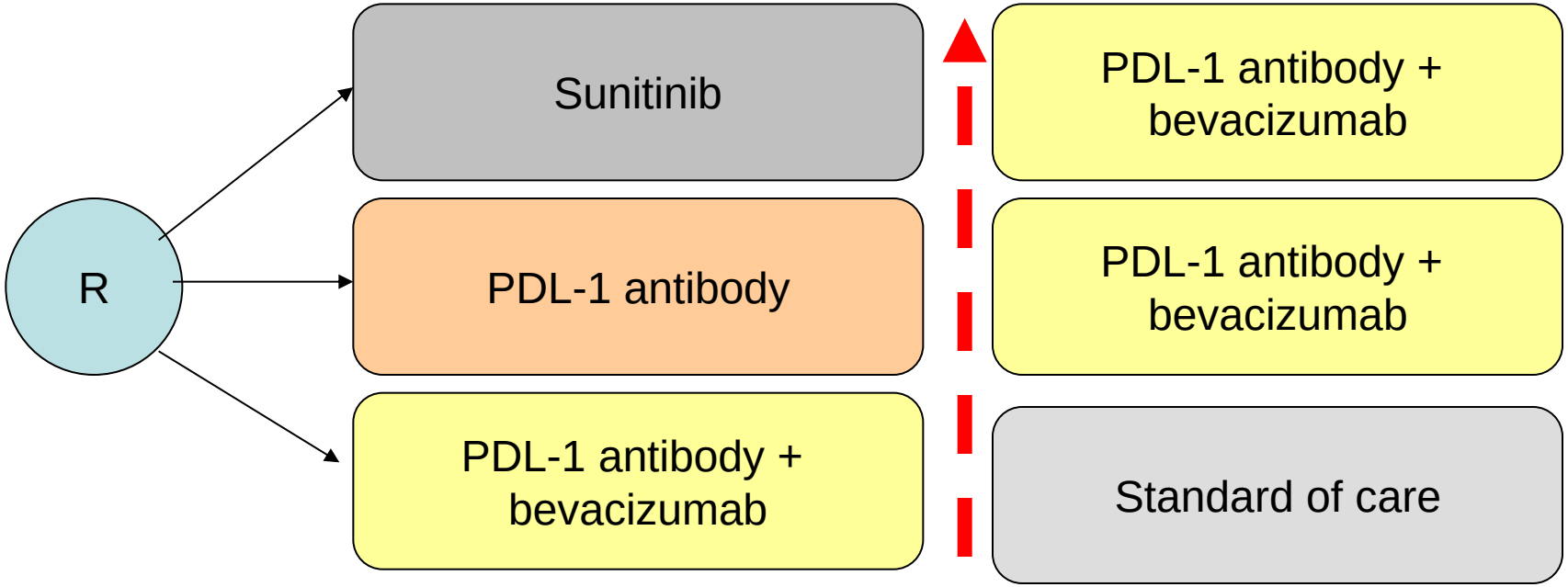
- Safety
  - Treatment-related Grade 3 AEs occurred in 3% of patients (1 case of neutropenia)
  - No Grade 4 AEs or deaths were attributed to MPDL3280A
- Efficacy in patients with 1L clear cell RCC
  - 4 of 10 patients demonstrated an objective response
  - Additionally, 4 of 10 patients experienced SD ≥ 24 weeks
  - Responding patients included 2 with IHC (IC) 1, 1 with IHC (IC) 0 and 1 with IHC (IC) unknown
  - 9 of 10 patients with mRCC remain on study treatment



Lieu et al. ESMO, 2014.
Patients dosed by Apr 7, 2014; data cutoff Jul 7, 2014; Unconfirmed best responses by RECIST v1.1.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% and < 10% of ICs are PD-L1+. IHC 1: ≥ 1% and < 5% of ICs are PD-L1+; IHC 0: < 1% ICs are PD-L1+.

McDermott et al. KCS, 2014.

RAPID: A Randomised phase II study investigating anti PDL-1 alone or in combination with bevacizumab in mRCC

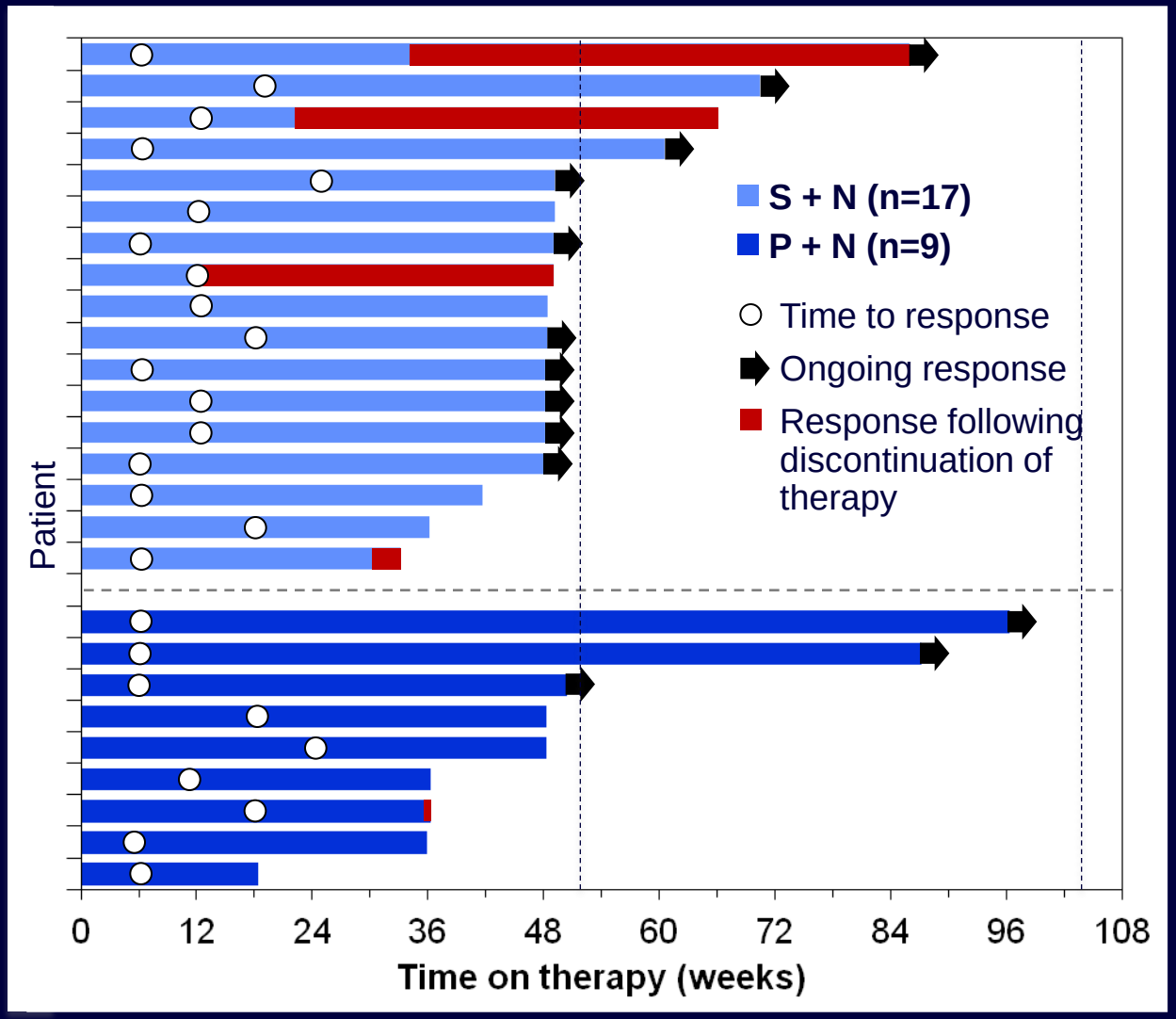


Eligibility
Metastatic clear cell renal cancer
Measurable disease (RECIST v1.1)
Archived or fresh tissue available
PDL-1 +ve and – ve patients eligible
No previous therapy for metastatic disease

Primary endpoint
Progression free survival

N=300 in 40 sites

PD-1 Ab + VEGF TKI = more efficacy?



Responders at first assessment (6 weeks):
S + N = 7/17 (41.2%)
P + N = 5/9 (55.6%)

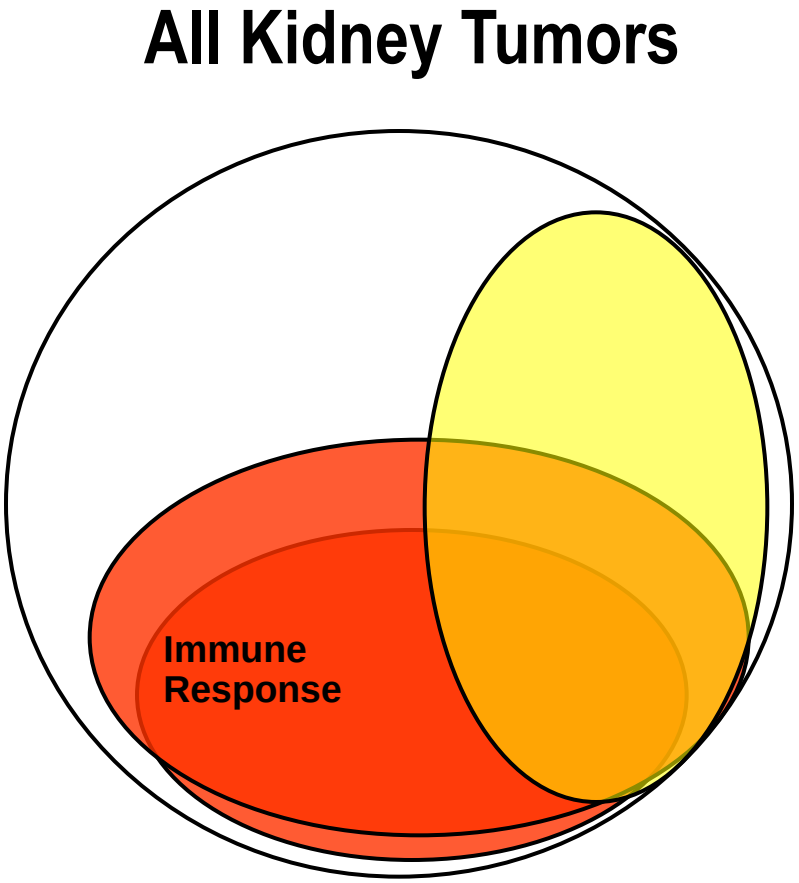
Ongoing responders:
S + N = 10/17 (58.8%)
P + N = 3/9 (33.3%)

Median follow-up: S + N2, 91 weeks; S + N5, 53 weeks; P + N, 76.5 weeks

Amin, et al ASCO 2014

Immunotherapy Improvement Model

Biomarker +, Rx Sensitive:
Single agents PD-1/PD-L1 Ab



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3) Support effector T cells:
IL-2,CD137 Ab, IL-15, IL-21
4) Support DCs: GM-CSF
5) Other checkpoint inhibitors
CTLA4, LAG3, TIM3 etc

Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC)

H. Hammers, E.R. Plimack, J.R. Infante, M.S. Ernstoff, B. Rini, D.F. McDermott, A. Razak, S.K. Pal, M.H. Voss, P. Sharma, C. Kollmannsberger, D. Heng, J. Spratlin, Y. Shen, J.F. Kurland, P. Gagnier, A. Amin

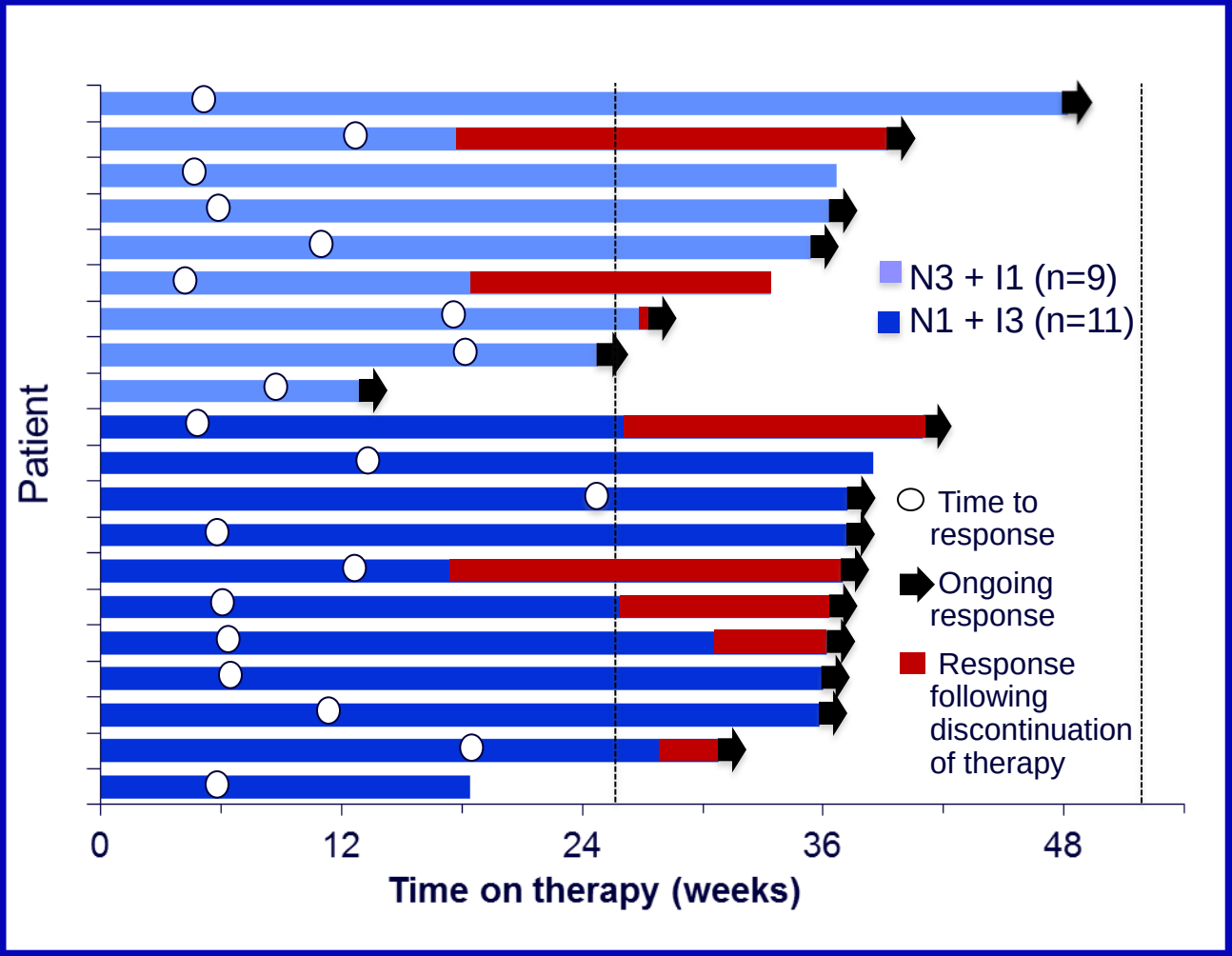
Treatment-related select AE categories

Category, n (%)	N3 + I1 (n=21)		N1 + I3 (n=23)	
	All	Grade 3-4	All	Grade 3-4
Endocrinopathy	3 (14.3)	0	8 (34.8)	0
Gastrointestinal disorder	6 (28.6)	1 (4.8)	9 (39.1)	4 (17.4)
Hepatic	1 (4.8)	0	9 (39.1)	6 (26.1)
Infusion reaction	2 (9.5)	0	2 (8.7)	0
Pulmonary	1 (4.8)	0	2 (8.7)	0
Renal disorder	2 (9.5)	0	3 (13.0)	0
Skin disorder	8 (38.1)	0	9 (39.1)	0

- **No high-grade pulmonary AEs, including pneumonitis, were observed**

Hammers, et al ASCO 2104

PD-1 + CTLA-4 Blockade = more efficacy?



Responders at first assessment (6 weeks):
N3 + I1 = 4/9 (44.4%)
N1 + I3 = 6/11 (54.5%)

Ongoing responders:
N3 + I1 = 7/9 (77.8%)
N1 + I3 = 9/11 (81.8%)

Patients discontinuing treatment (not due to progression) who continued to respond:
N3 + I1 = 3/9 (33.3%)
(23.3, 16.4, & 0.3 weeks)

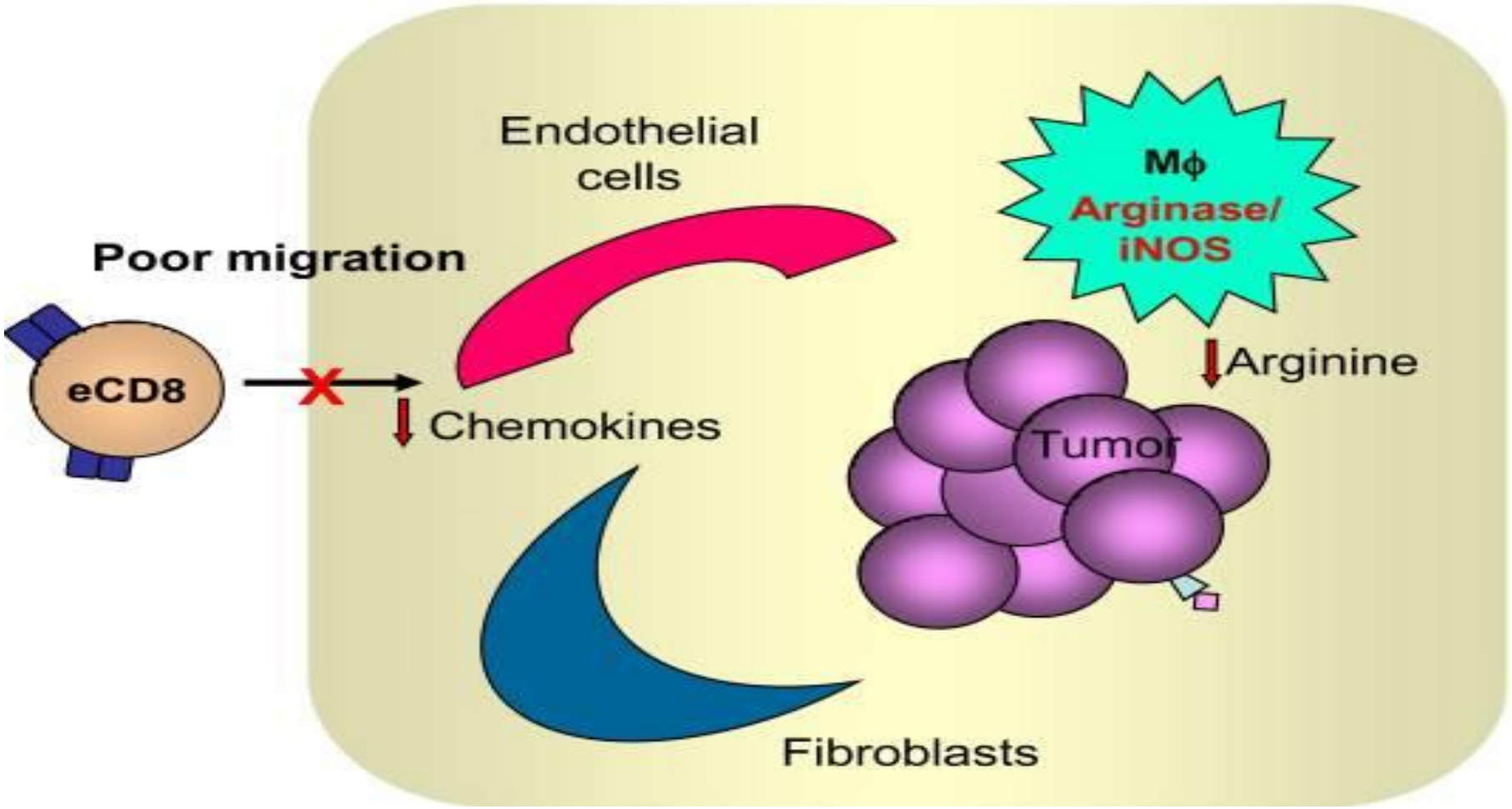
N1 + I3 = 5/11 (45.5%)
(17, 22, 12.3, 7.2 & 4.1 weeks)

- **Median duration of response (DOR) for N3 + I1 was 31 weeks**
- **Median DOR was not reached in the N1 + I3 arm at 40.1 weeks follow-up**

Current PD-1 Pathway Trials in RCC

Trial	Sponsor	Status	NCT #
Nivolumab vs. Everolimus Phase III	BMS	Enrolled	01844505
Phase I/II Pazopanib + Pembro	GSK	Enrolling	02014636
Phase II PD-L1 vs. Bev/PD-L1 vs. Sunitinib	Genentech	Enrolling	01984242
Phase I Axitinib + Pembro	Pfizer	Enrolling	02133742
Nivo/Ipi vs. Sunitinib Phase III	BMS	Coming Soon	02231749
PD-1 Adjuvant Trial	NCI/Coop	In Development	

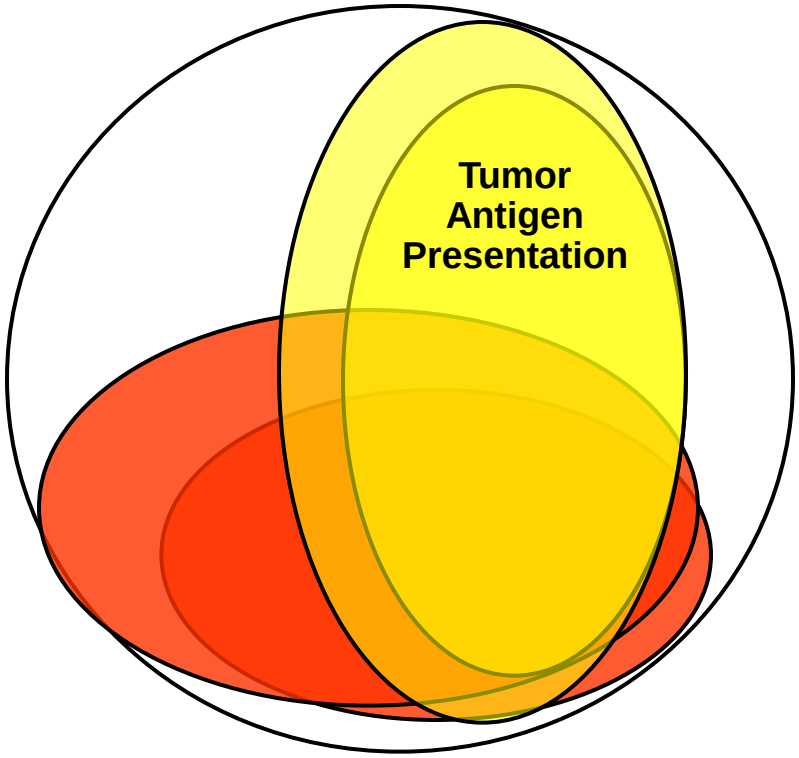
Non-Inflamed Tumor



High expression of vascular markers, macrophages, fibroblasts +
Low inflammation and chemokines, few lymphocytes =
Poor effector cell trafficking

Gajewski, Curr Opin Immun 2011

Immunotherapy Improvement Model



Non-Inflamed Tumors (Biomarker neg)

Induce Antitumor Immunity

1) Enhance Antigen Expression:

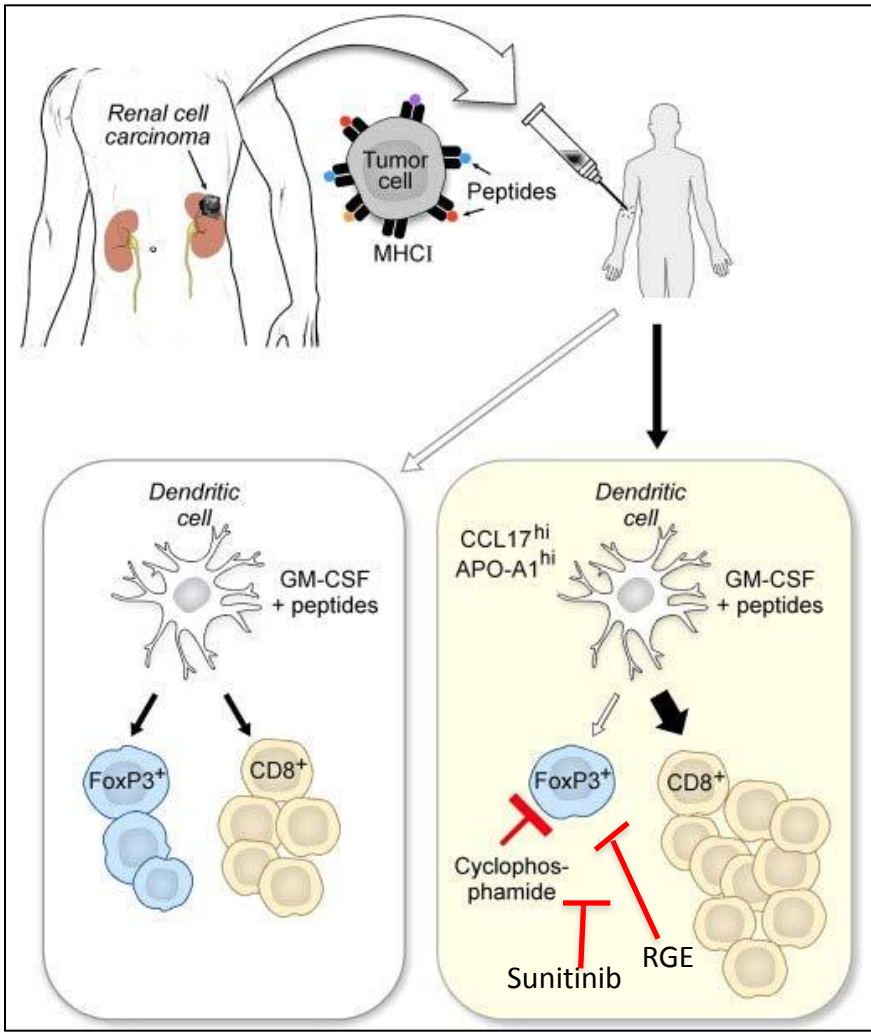
- Demethylating Agents
- SBRT, IT IFN

2) Focus Immune Response:

- **DC Vaccines**
- **Neo-antigen based vaccines**

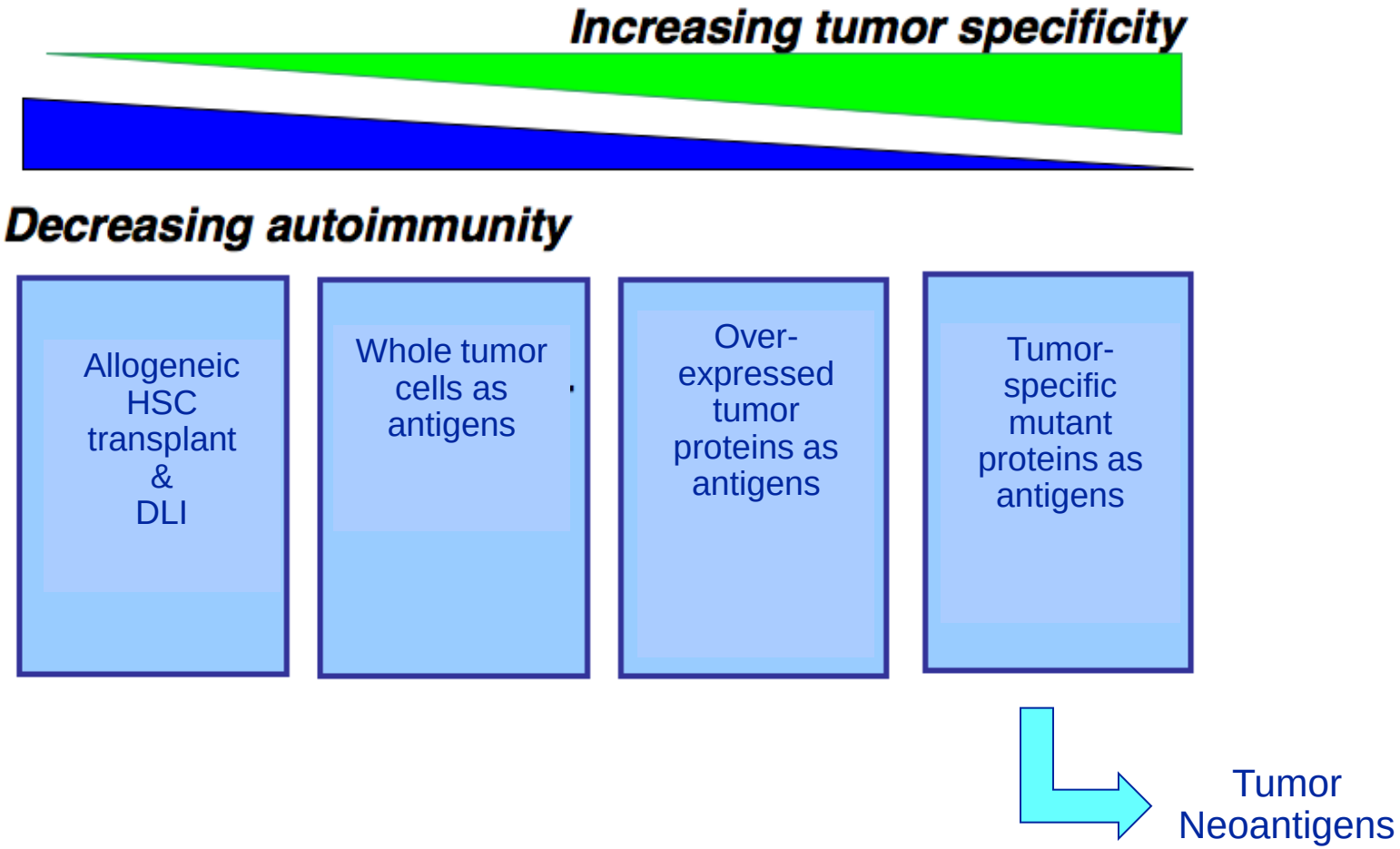
RCC Vaccine Approaches

- IMA901:
  - Multiple tumor associated peptide vaccine + GM-CSF
- Dendritic Cell (DC) Vaccines
  - AGS-003: autologous DC vaccine + sunitinib

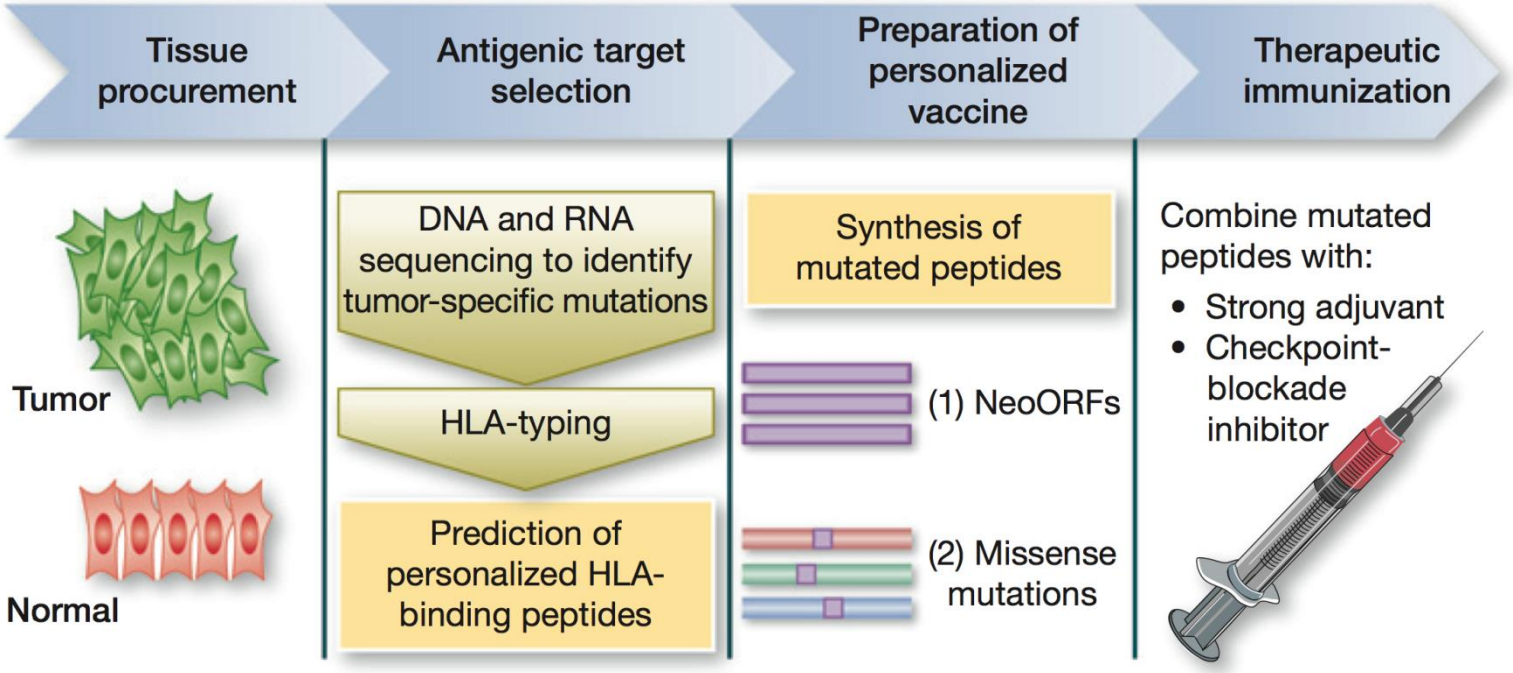


Adapted from Dranoff Cancer Cell 2012

The specificity of antigens underlying tumor immunotherapy



Developing NeoVax: based on multiple coding mutations unique to each pt tumor



- *Safety, feasibility*
- *immune activity*
- *clinical activity*

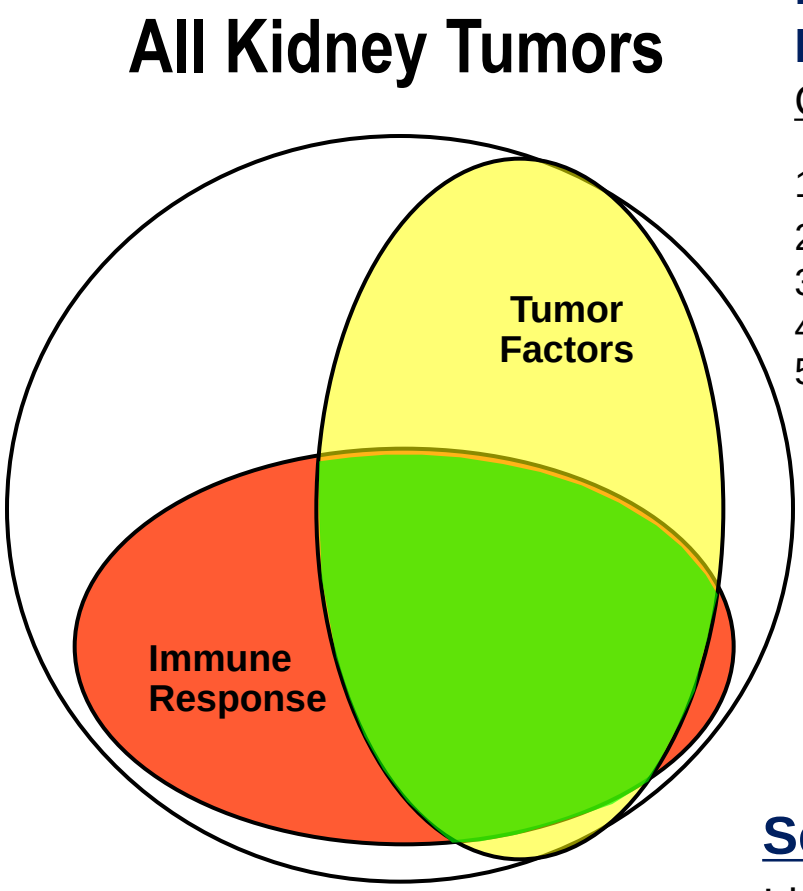
High-risk melanoma,
IND (Wu CJ); PI (Ott PA)
NCT 01970358

Hacohen et al, Can Imm Res 2013

Neoantigen Based Vaccine Summary

- Next-generation sequencing capabilities now enable systematic mining of the genome for potential neoantigens
- Tumor neoantigens are a potentially important class of immunologic targets against which tumor-specific responses can be generated
- Further characterization of the immunogenicity of neoantigens and association with clinical response is in progress
- Phase I clinical trials to test a personalized cancer neoantigen vaccine are planned – Cathy Wu (DFCI)
  - Melanoma – Patrick Ott (PI)
  - RCC – Toni Choueiri (PI)

Immunotherapy Improvement Model



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5) Other checkpoint inhibitors (PDL2, LAG3, TIM3 etc)

Non-Inflamed Tumors (PD-L1 neg)
Induce Antitumor Immunity
1) Enhance Antigen Expression:
   - Demethylating Agents
   - SBRT, IT IFN
2) Focus Immune Response:
   - DC Vaccines
   - NeoAntigen Based

Selection

Identify the patients in the overlap through translational research

Immunotherapy for Kidney Cancer: Lessons Learned

- Single agent activity of PD-1 pathway blockade in RCC is more limited than in melanoma
  - "Treatment-Free Survival" in the community
- Predictive biomarkers require refinement to expand application (e.g. first line, adjuvant settings)
  - Tumor grade, mutational load may add value?
- Combinations improve outcomes but increase toxicity
  - Management algorithms need to be refined
- Vaccine strategies in late stage trials
  - Neoantigen vaccination worthy of further study

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