Immunotherapy: Myth or Reality?

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Harvard Medical School
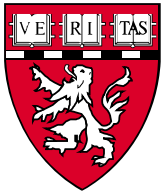
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

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David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc.,
Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc.,
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Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D.,
Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D.,
Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

ABSTRACT

BACKGROUND

Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples.

METHODS

From the Cancer Research UK London Research Institute (M. Gerlinger, A.J.R., S.H., D.E., E.G., P.M., N.M., A.S., B.P., S.B., N.Q.M., C.R.S., B.S.-D., G.C., G.S., J.D., C.S.), Royal Marsden Hospital De-

Intratumoral Heterogeneity (ITH) is an old story

Science AAAS

The Clonal Evolution of Tumor Cell Populations

Acquired genetic lability permits stepwise selection of variant sublines and underlies tumor progression.

Peter C. Nowell , 1976

"One may ultimately have to consider each advanced malignancy as an individual therapeutic problem**….**Immunotherapy becomes a leading candidate for the easiest means of destroying the remainder of the neoplastic clone**...it is more** feasible **to produce specific cytotoxic antiserums or lymphocytes against a particular tumor than to design a specific chemotherapeutic agent for each neoplasm."**

Heterogeneity – Burden or Asset?

◆**Development of a sufficiently large arsenal of molecularly targeted therapies is a technical and clinical challenge**

◆**Resistance to targeted therapies can develop due to clonal diversity and evolution**

*Immune-based therapy is uniquely suited to addressing the challenge of cancer heterogeneity*

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

Suzanne L. Topalian, M.D. , F. Stephen Hodi, M.D., Julie R. Brahmer, M.D.,
Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D.,
John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D.,
Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D.,
Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D.,
Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D.,
William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D.,
Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A.,
Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D.,
Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D.,
Jon M. Wigginton, M.D., and Mario Sznol, M.D.

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:
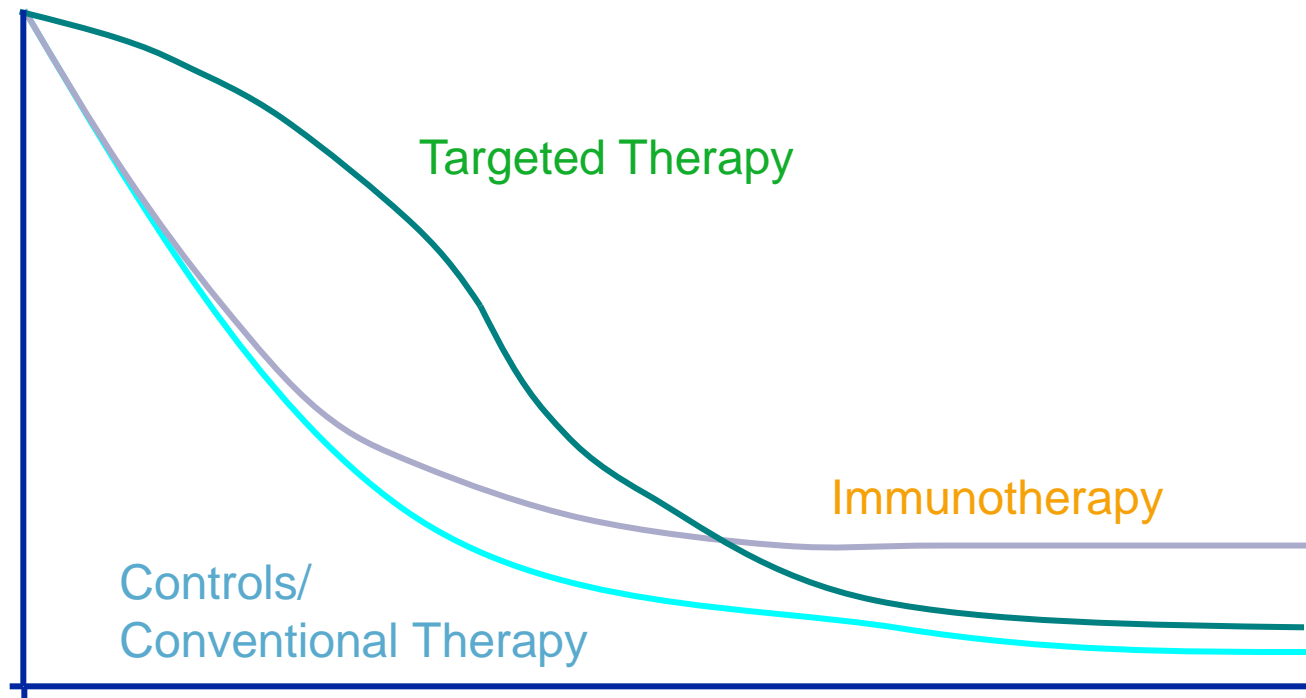 - 29% objective responses
  - Median PFS 7.3 months
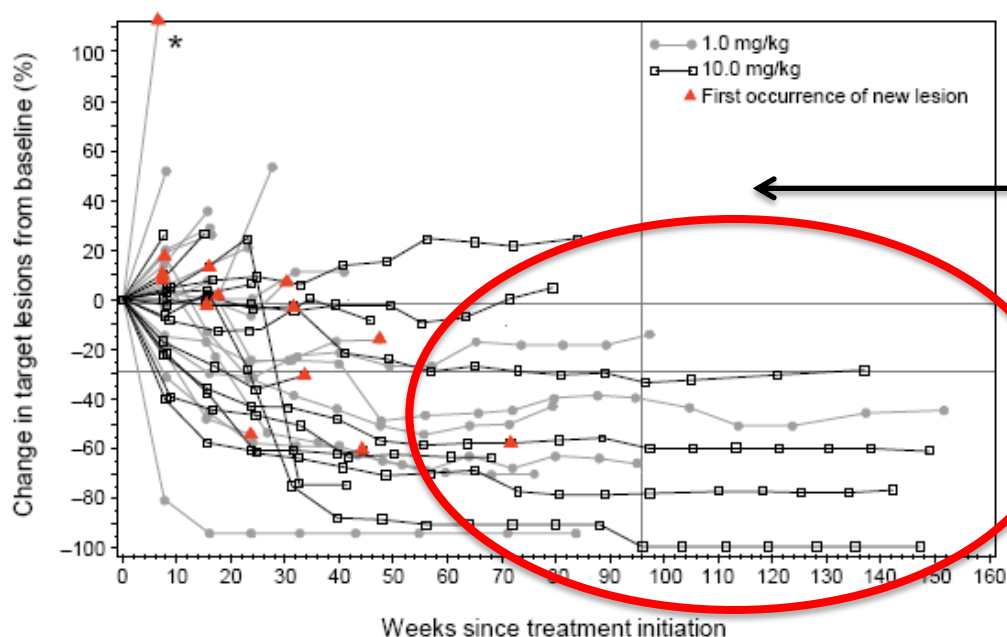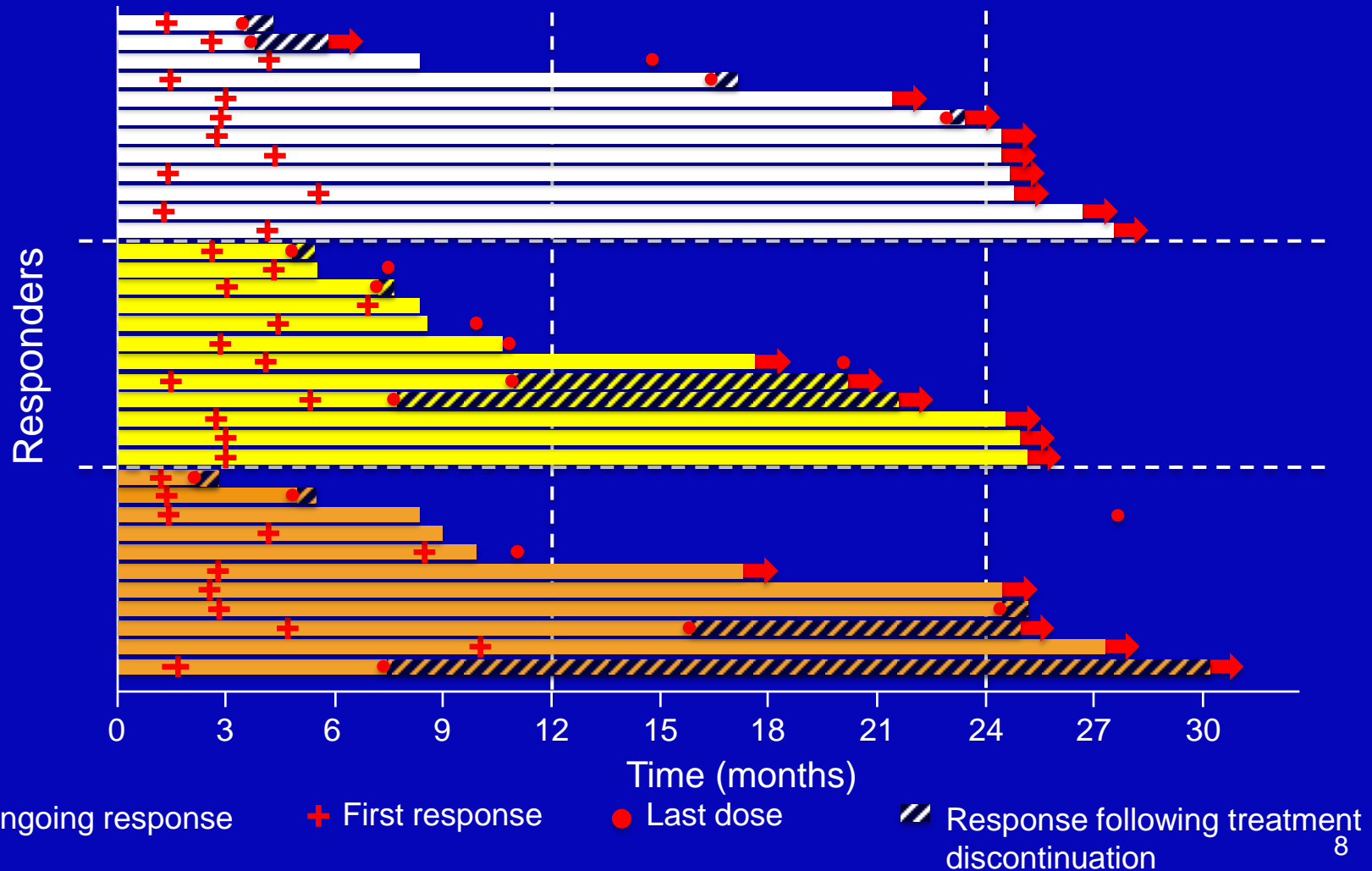

All stopped therapy

Treatment - Free Survival (TFS)

Drake ASCO 2013

Meeting the goal of the patient

Adapted from Ribas A, et al. Clin Cancer Res. 2012;18:336-341.

Nivo RCC Phase 2: Duration of response

Making PD-1 Pathway Blockade Based Immunotherapy a Reality

- 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?

PD-L1 Expression and Response

Agent(s)	Tumor Type	n	RR (%) PD-L1 pos	RR(%) PD-L1 neg
Nivolumab[1]	Multiple Solid Tumors	42	36%	0%
MPDL3280A[2]	Kidney Cancer	47	20%	10%
Nivolumab[3]	Melanoma	34	44%	17%
Nivo/Ipi[4]	Melanoma	27	40%	47%

[1]Topalian et al, NEJM, 2012, [2]Cho et al ASCO 2013, [3]Grosso et al ASCO 2013, [4]Wolchok et al, NEJM 2013

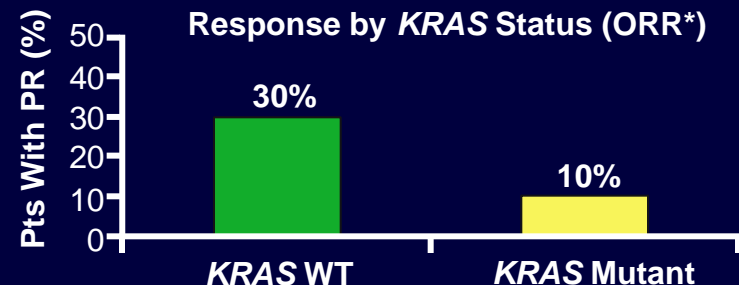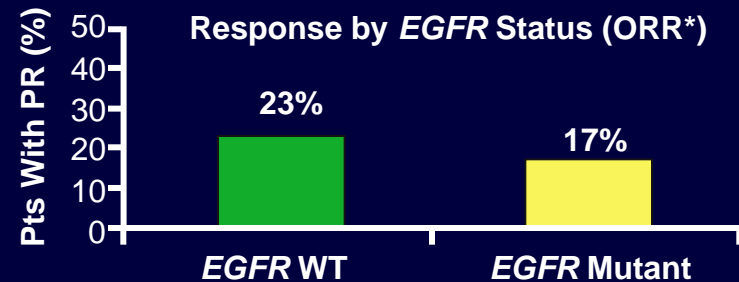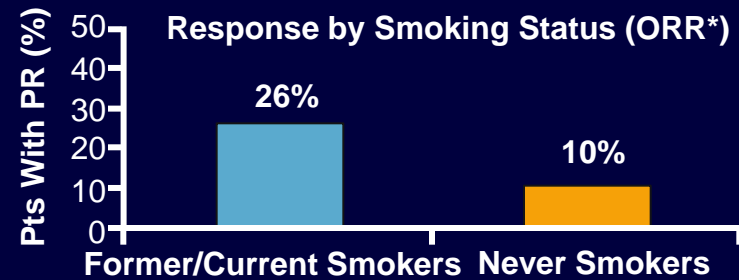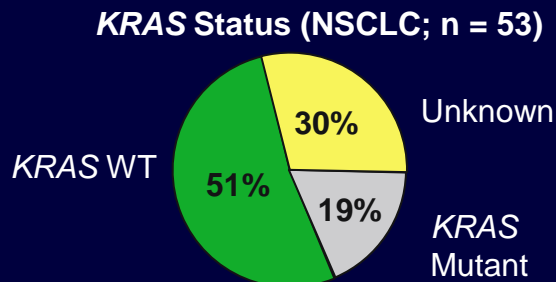# Making PD-1 Pathway Blockade Based Immunotherapy a Reality

- Efficacy data

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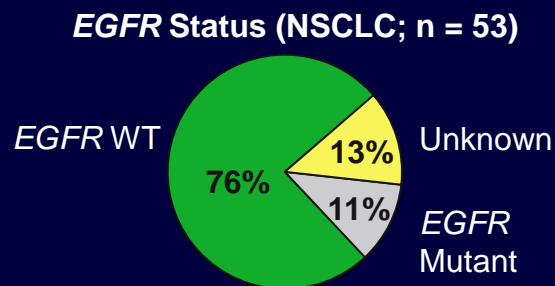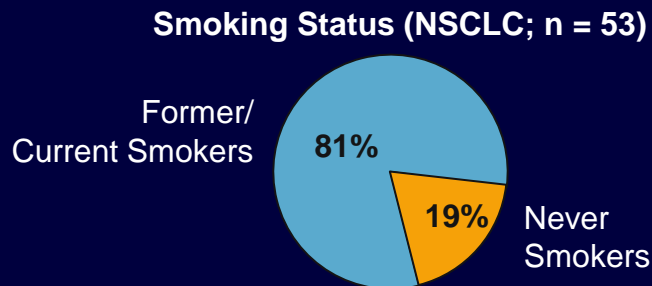 - Are they ready to guide clinical development?
  - Should we stratify patients on pivotal trials based on PD-L1 expression?
  - Can we develop a reliable response prediction (PRP) model?
    - Incorporating tumor and immune infiltrate
    - Incorporating multiple platforms:
      - IHC + IF + Mutational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

- Combination Therapy

Towards a Multi-factor PRP Model: Tumor + Infiltrate
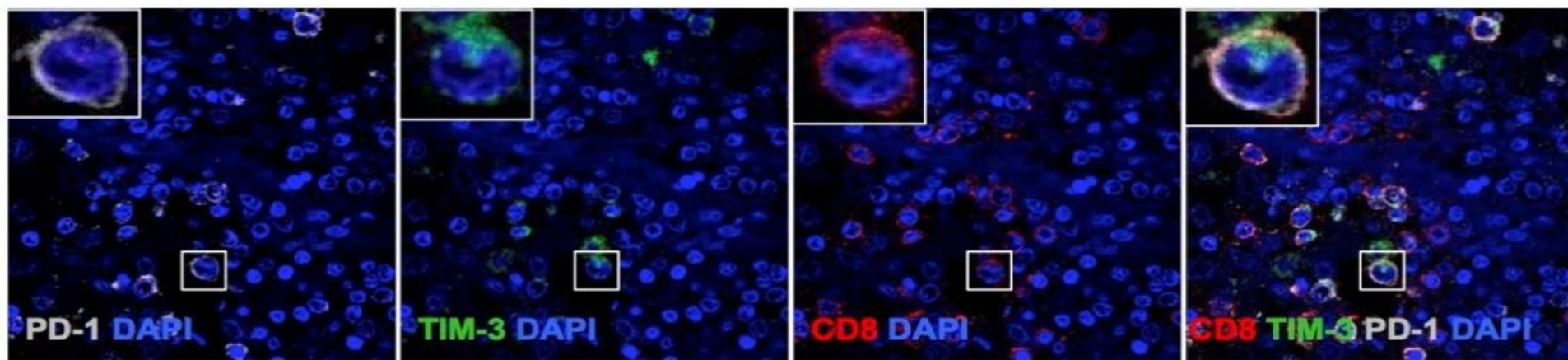
Representative confocal images of triple immunofluorescence labeling for CD8, PD-1 and TIM-3 in a FFPE clear cell RCC sample. A subset of T-cells co-expressing CD8, PD-1 and TIM-3 is identified.

S Signoretti, with permission

MPDL3280A Phase Ia:
Response by Smoking and Mutational Status

Smoking Status (NSCLC; n = 53)
- Former/Current Smokers 81%
- Never Smokers 19%

Response by Smoking Status (ORR*)
- Former/Current Smokers: 26%
- Never Smokers: 10%

EGFR Status (NSCLC; n = 53)
- EGFR WT 76%
- Unknown 13%
- EGFR Mutant 11%

Response by EGFR Status (ORR*)
- EGFR WT: 23%
- EGFR Mutant: 17%

KRAS Status (NSCLC; n = 53)
- KRAS WT 51%
- Unknown 30%
- KRAS Mutant 19%

Response by KRAS Status (ORR*)
- KRAS WT: 30%
- KRAS Mutant: 10%

Horn L, et al. WCLC 2013. Abstract MO18.
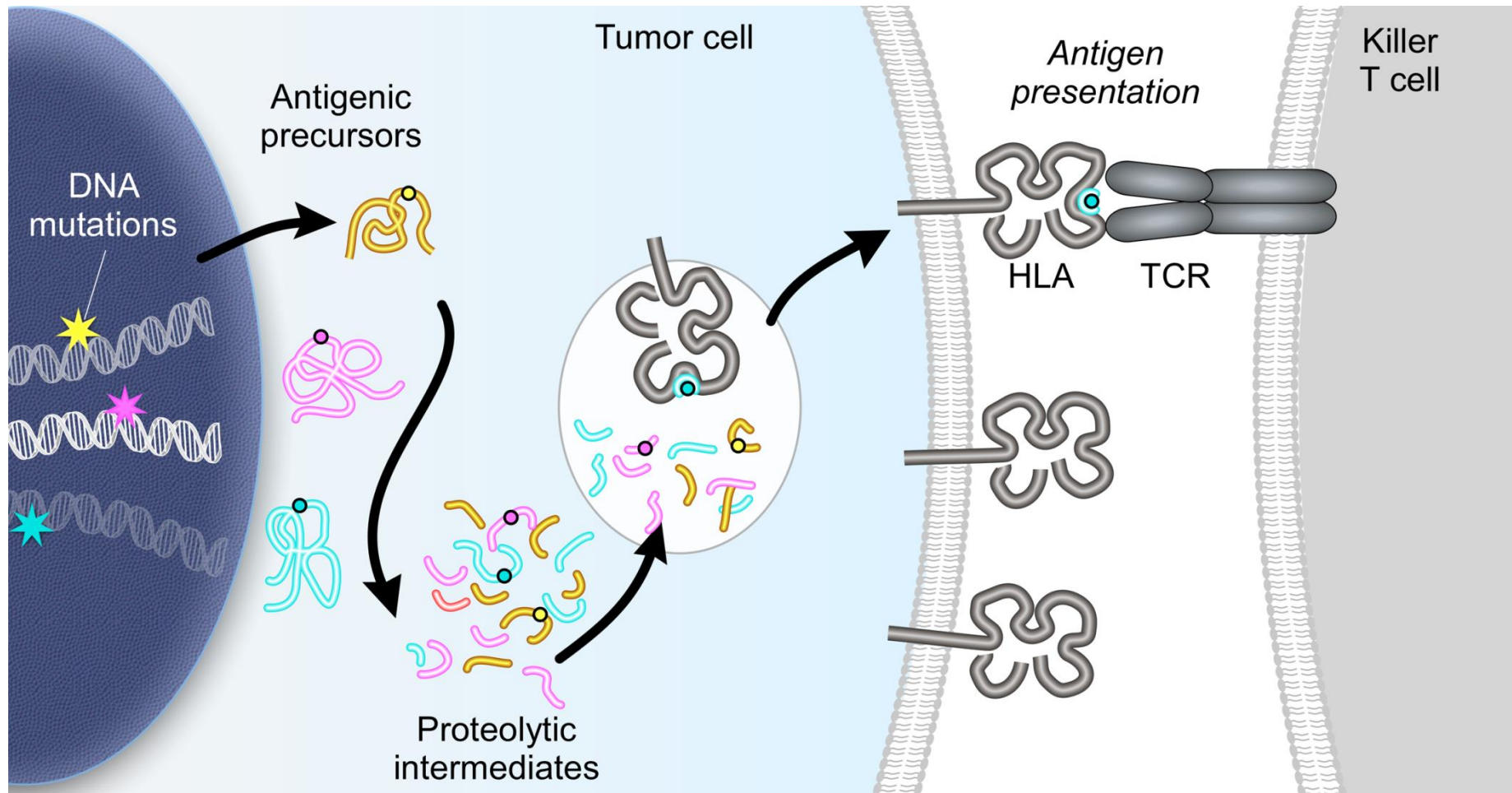
Tumor grade and response to PD-1 Blockade in RCC

- Nivolumab Phase 1 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)

Somatic mutations by tumor type

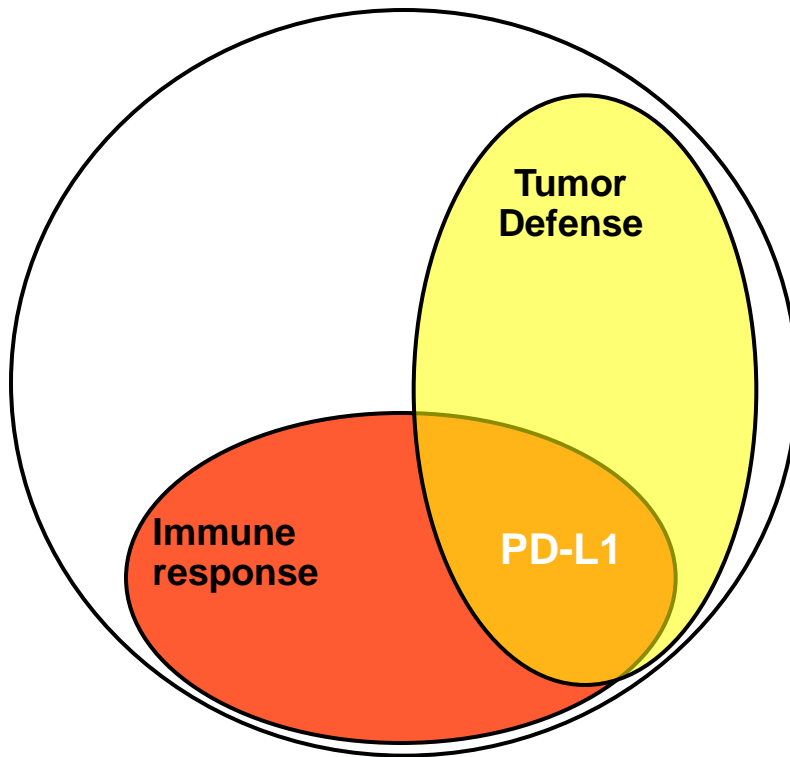MS Lawrence *et al. Nature* **2013**
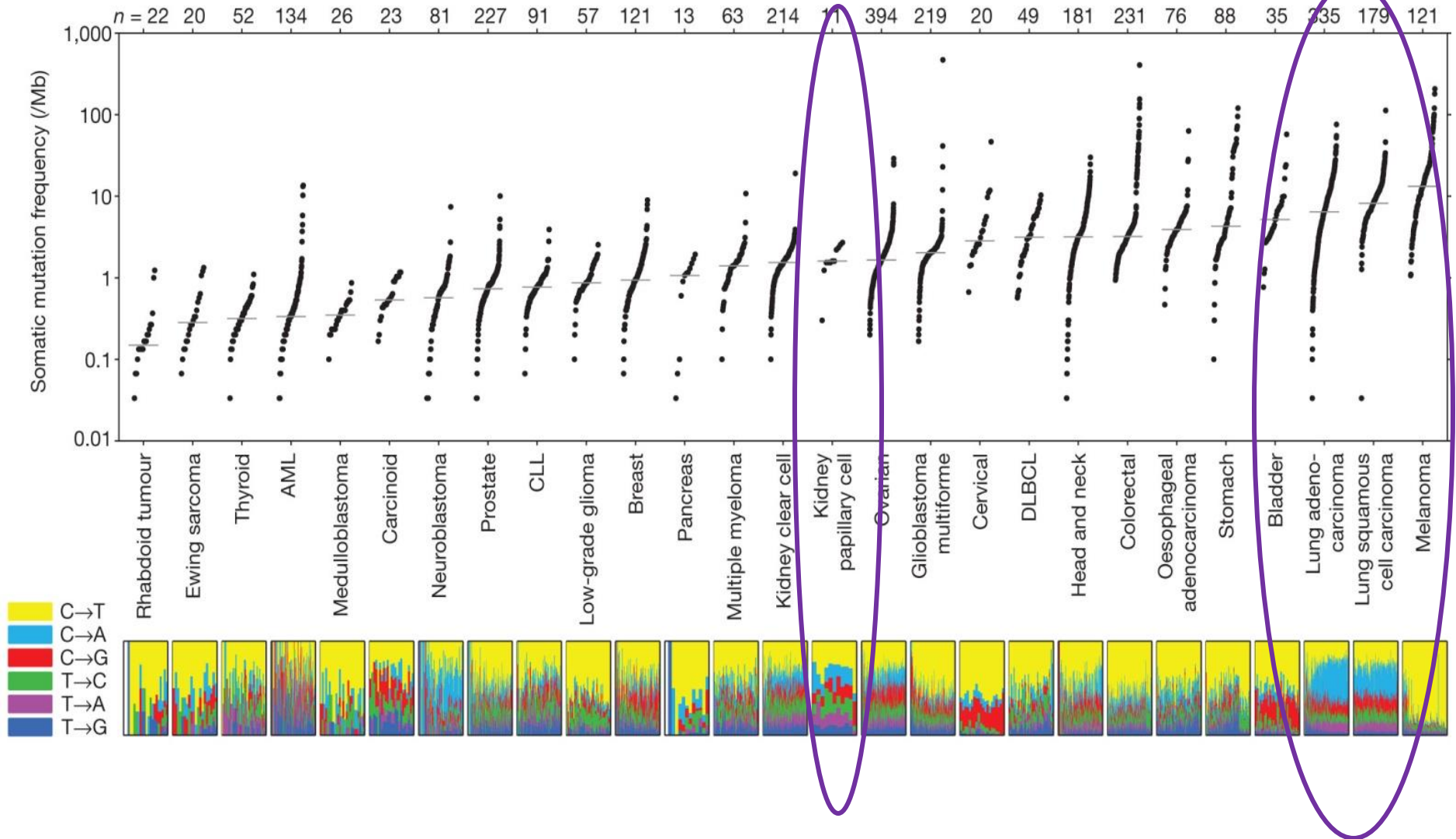
Somatic mutations have the potential to generate neoantigens

Making Immunotherapy a Reality

All Patients

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

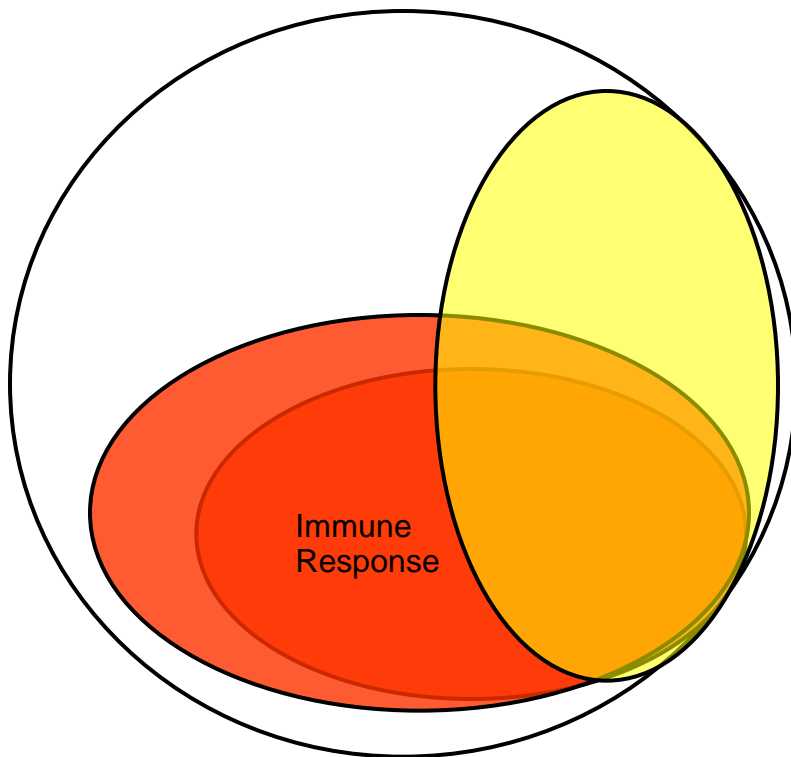Tumor
Defense

Immune
response

PD-L1

Making Immunotherapy a Reality

- Efficacy data

- Predictive Biomarkers

- Combination Therapy
  - Which will improve durable response rate?
  - Will toxicities limit potential?

Making Immunotherapy a Reality

All Kidney Tumors

Immune
Response

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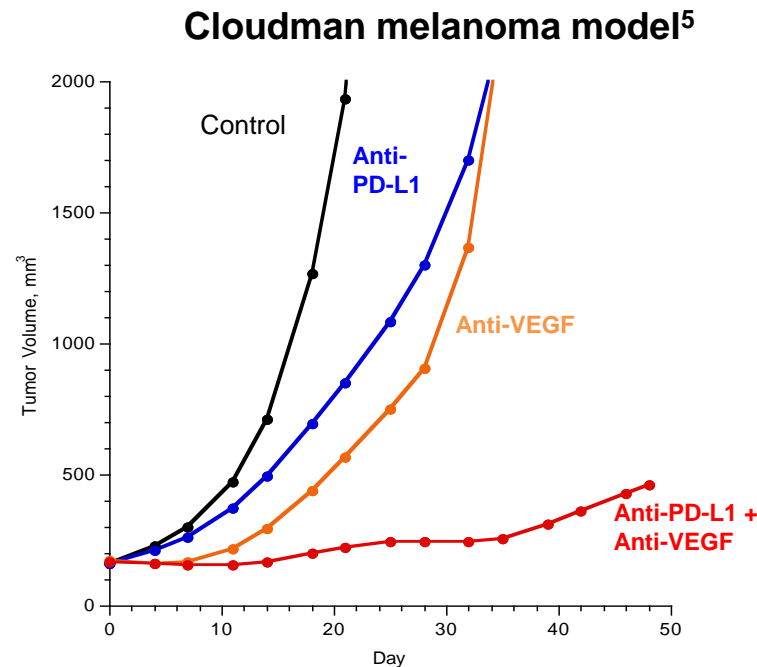**Single agents** **PD-1/PD-L1 Ab**

Biomarker+, Rx Resistant:
Combination Therapy

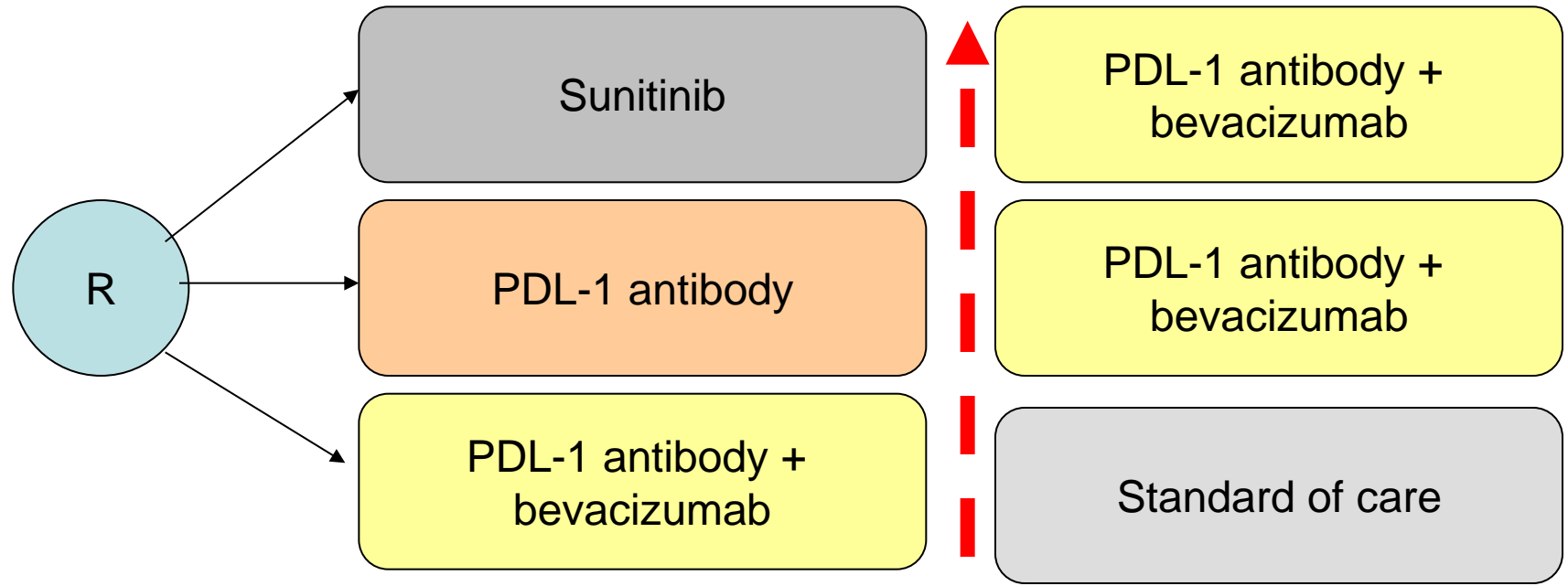**1) Elimination of Tregs: anti-GTR, CCR4**
2) Inhibition of VEGF/MDSC: anti-VEGF, HDM2
3) Support effector T cells: IL-2,CD137 Ab, IL-21
4) Support DCs: GM-CSF
5) Other checkpoint inhibitors (CTLA4,TIM3 etc)

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.

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

R

→ Sunitinib

→ PDL-1 antibody

→ PDL-1 antibody + bevacizumab

PDL-1 antibody + bevacizumab

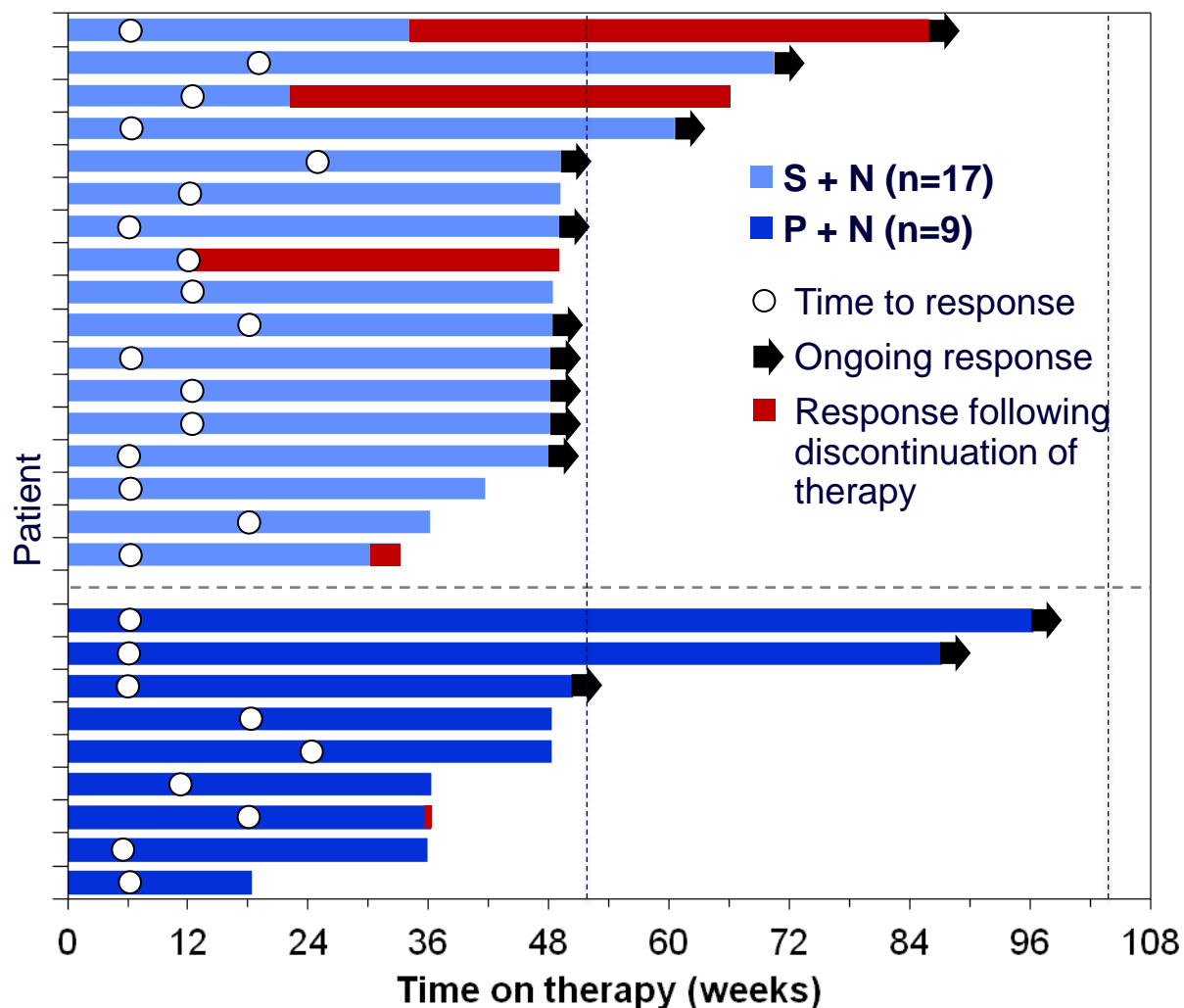PDL-1 antibody + bevacizumab

Standard of care

PD

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=150 in 40 sites

PD-1 Ab + VEGF TKI = more efficacy?

Chart axes: Patient (y-axis) vs Time on therapy (weeks) (x-axis, 0–108)

Legend:
- S + N (n=17)
- P + N (n=9)
- ○ Time to response
- ➤ Ongoing response
- ■ Response following discontinuation of therapy

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
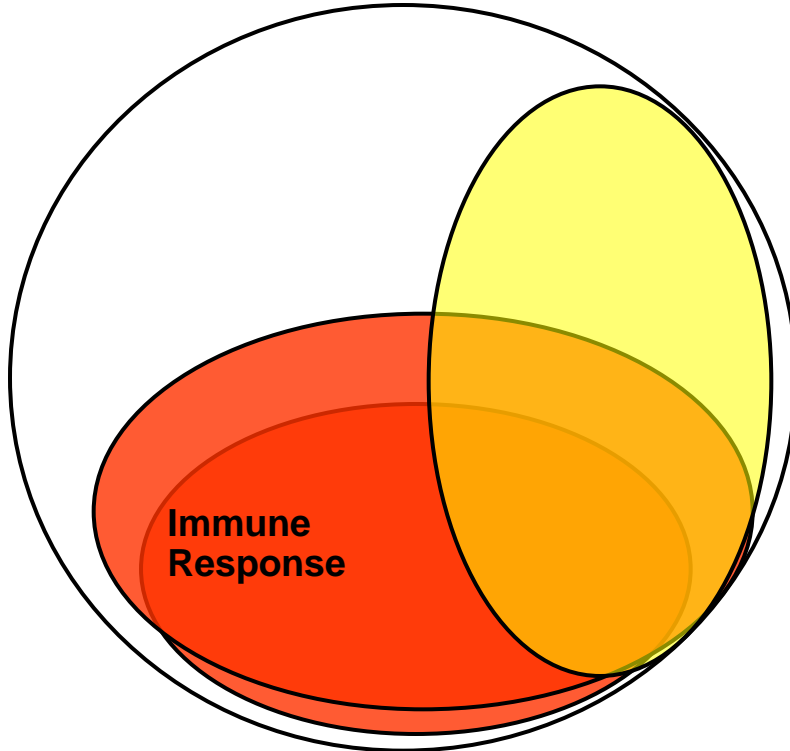
Amin, et al ASCO 2014

Making Immunotherapy a Reality

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

All Kidney Tumors

Biomarker +, Rx Resistant:
<u>Combination Therapy</u>

1) Elimination of Tregs: anti-GTR, CCR4
2) Inhibition of VEGF/MDSC: VEGF RTK, HDM2
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

Immune Response

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**

PD-1 + CTLA-4 Blockade = more efficacy?
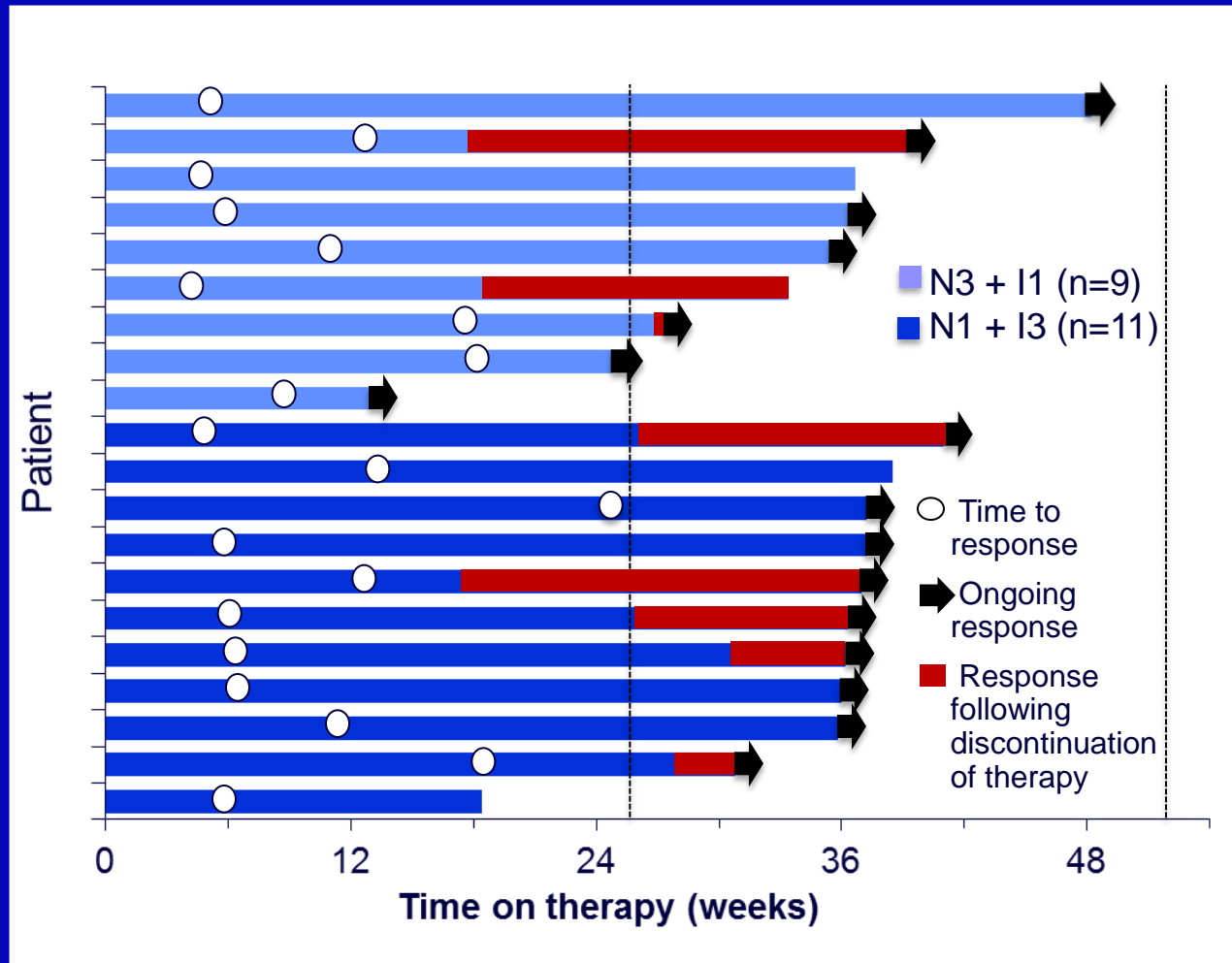
Responders at first assessment (6 weeks):
N3 + I1 = 4/9 (44.4%)
N1 + I3 = 6/11 (54.5%)

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	

Making Immunotherapy a Reality
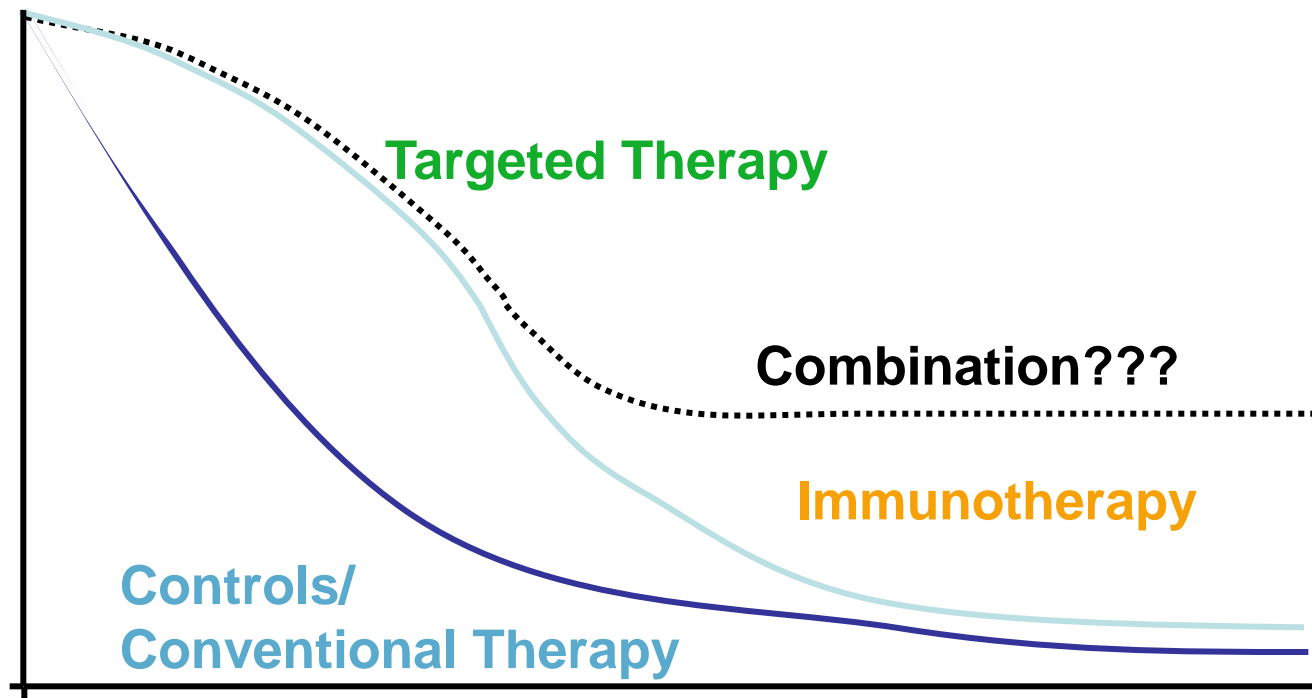
Non-Inflamed Tumor
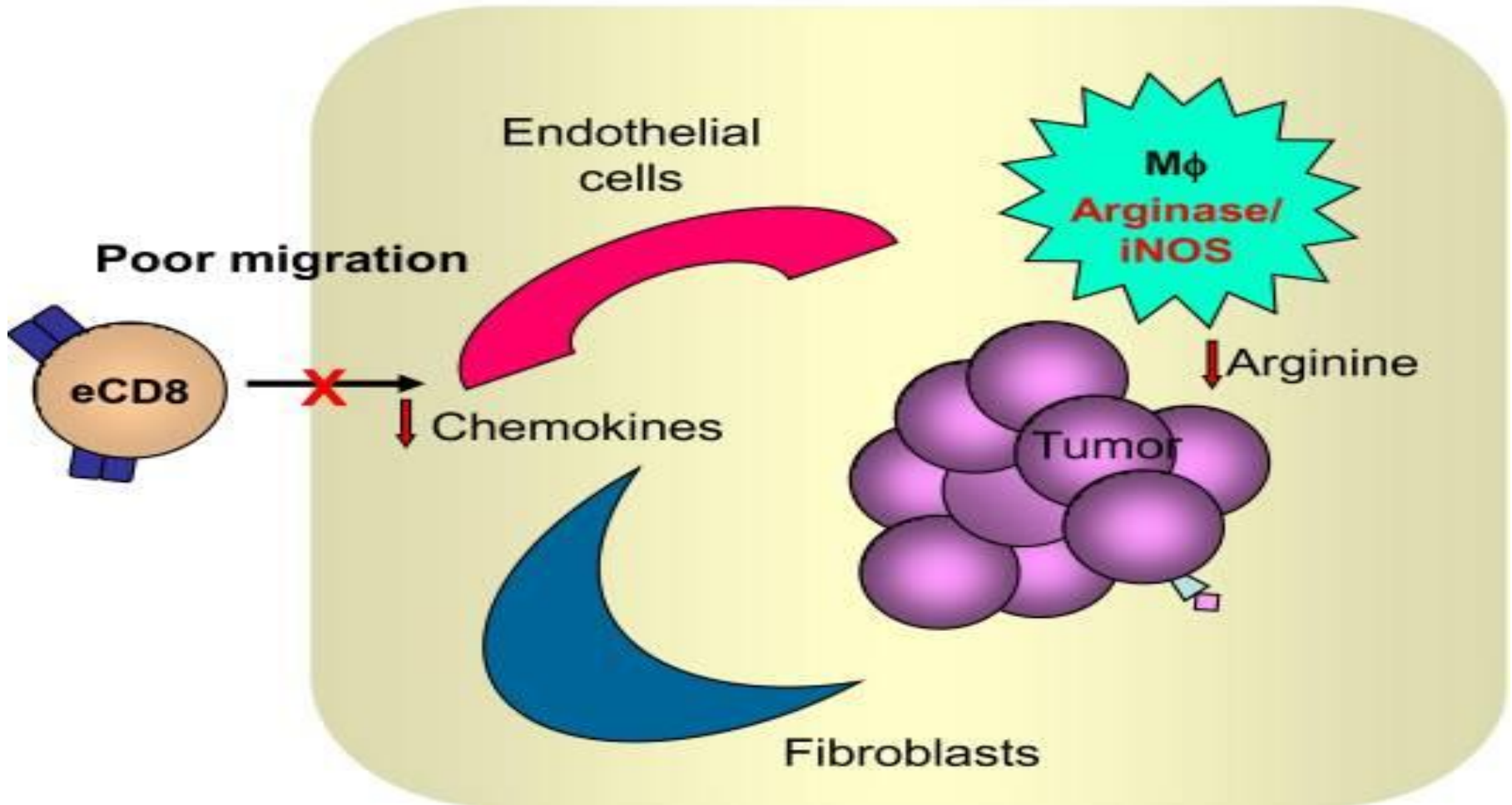
High expression of vascular markers, macrophages, fibroblasts +
Low inflammation and chemokines, few lymphocytes =
Poor effector cell trafficking

Gajewski, Curr Opin Immun 2011

Making Immunotherapy a Reality

All Kidney Tumors
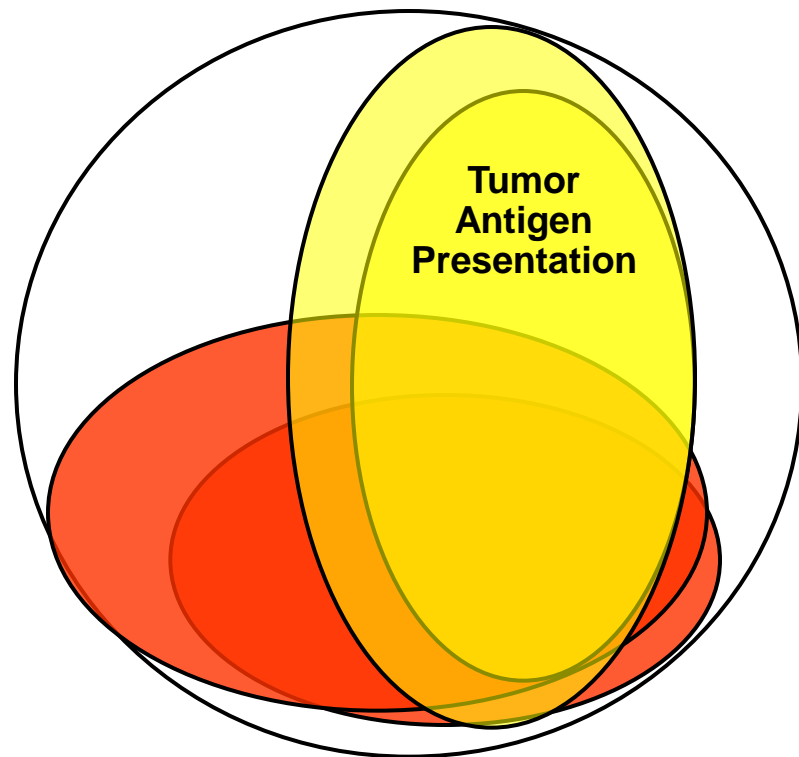
Non-Inflamed Tumors (Biomarker neg)
Induce Antitumor Immunity
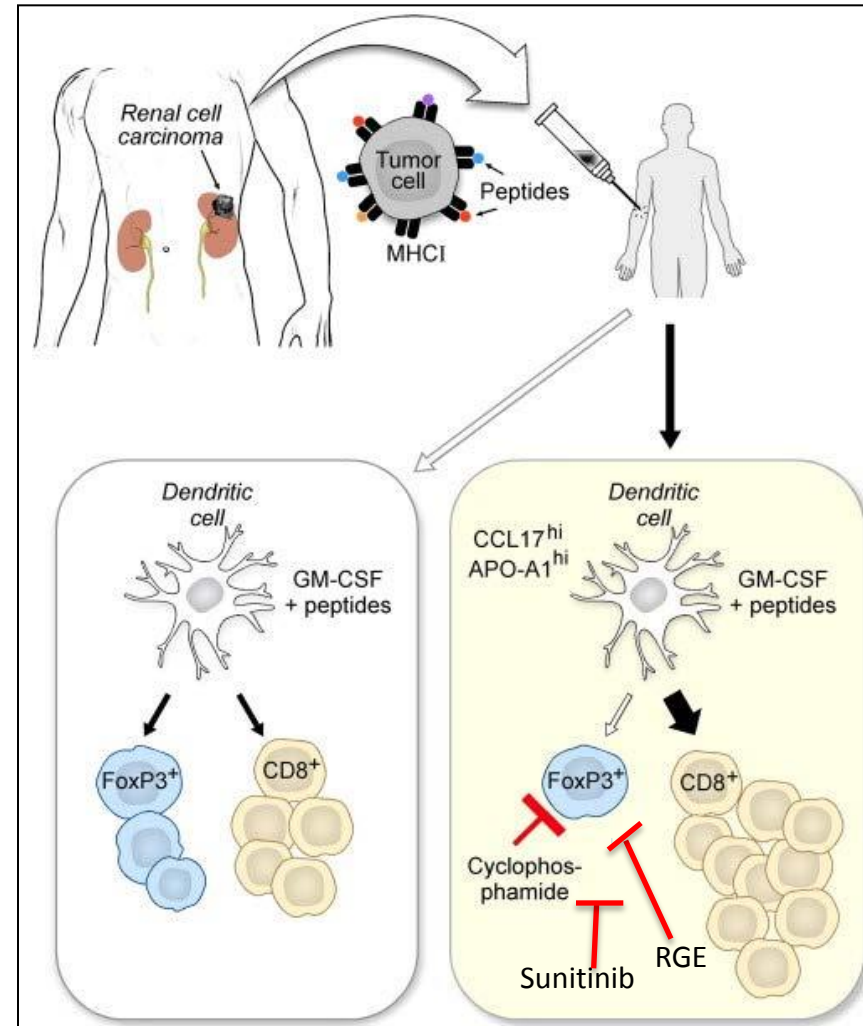1) Enhance Antigen Expression:
Demethylating Agents
SBRT, IT IFN
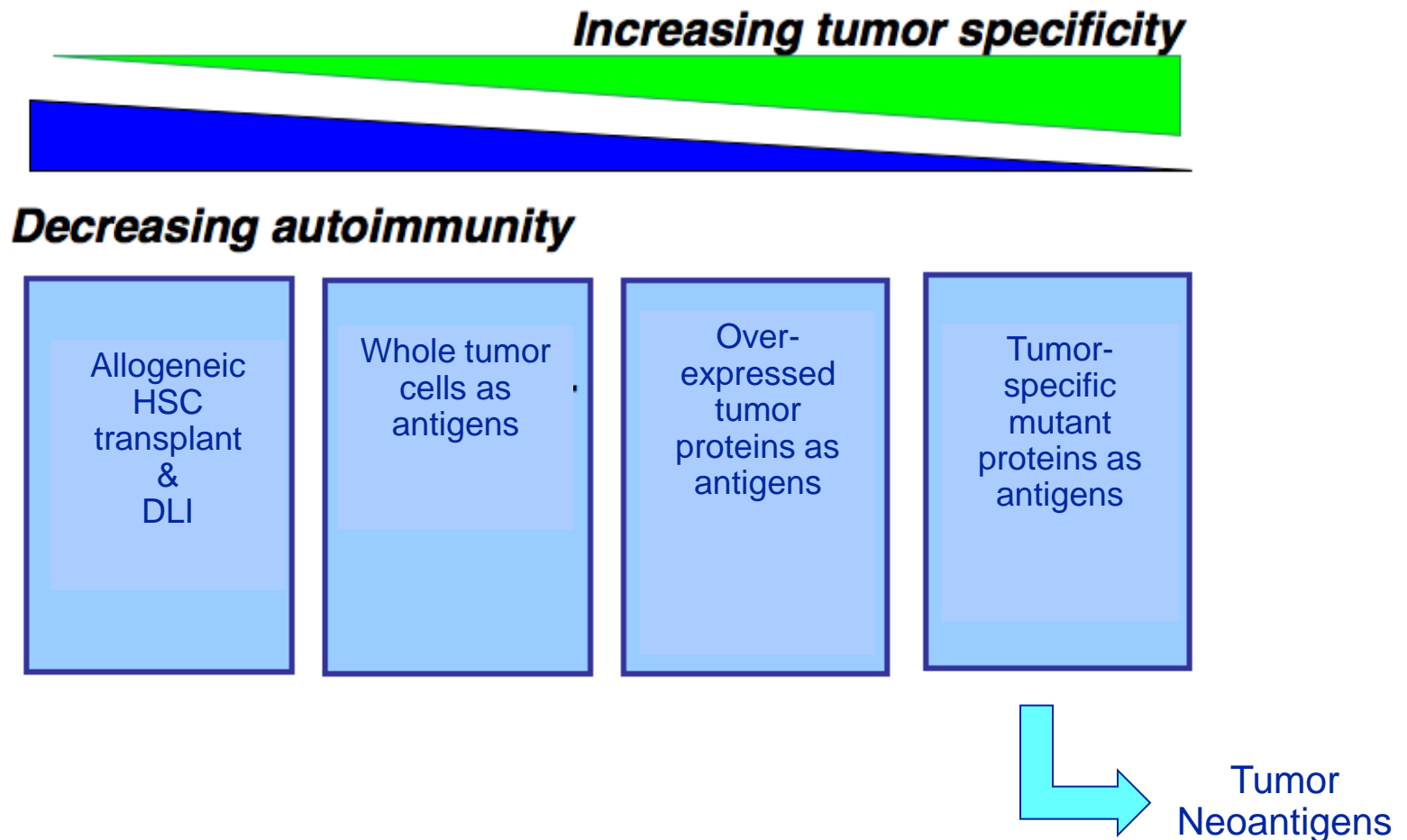**2) Focus Immune Response:**
DC Vaccines
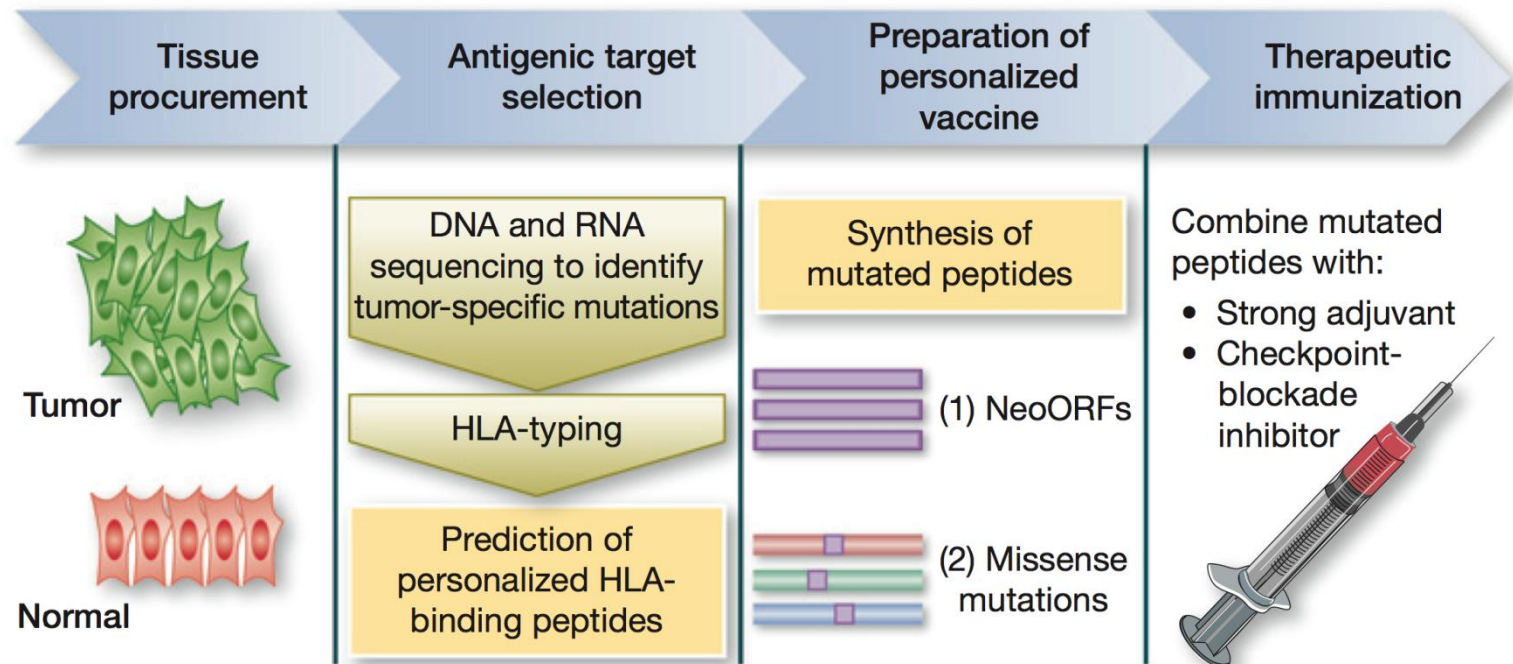**Neo-antigen based vaccines**

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

Increasing tumor specificity

Decreasing autoimmunity

| Allogeneic HSC transplant & DLI | Whole tumor cells as antigens | Over-expressed tumor proteins as antigens | Tumor-specific mutant proteins as antigens |

Tumor Neoantigens

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

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

- Safety, feasibility
- immune activity
- clinical activity

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)

Making Immunotherapy a Reality

All Kidney Tumors

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

Biomarker +, Resistant:
Combination Therapy

1) Elimination of Tregs: CTLA4 Ab, anti-GTR
2) Inhibition of MDSC (VEGF TKI, HDM2 Antagonists)
3) Support effector T cells: IL-2,CD137 Ab, IL-15, IL-21
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5) Other checkpoint inhibitors (PDL2, LAG3, TIM3 etc)
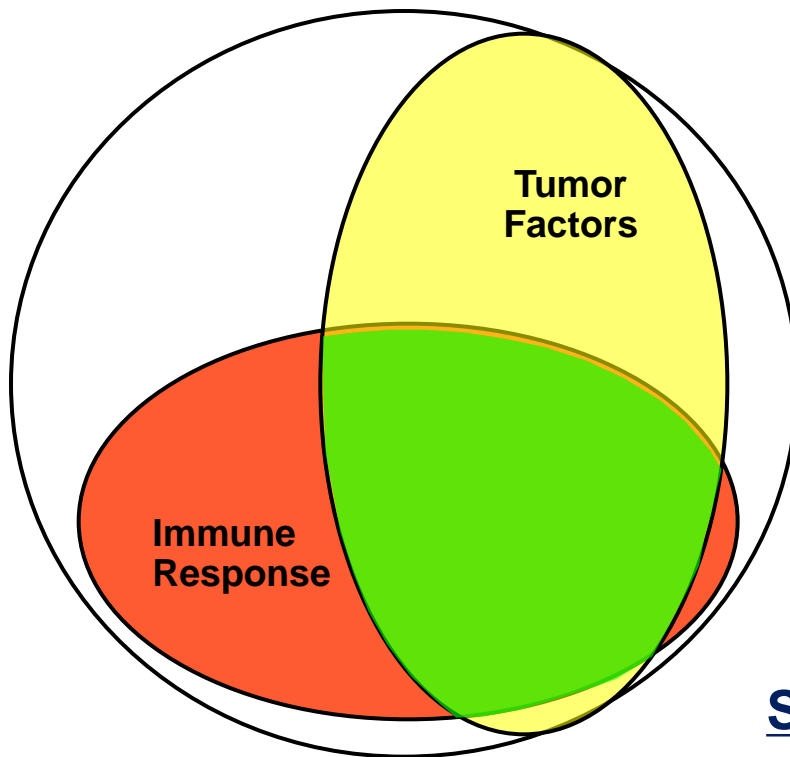
Non-Inflamed Tumors (PD-L1 neg)
Induce Antitumor Immunity
1) Enhance Antigen Expression:
　　　　Demethylating Agents
　　　　SBRT, IT IFN
2) Focus Immune Response:
　　　　DC Vaccines
　　　　NeoAntigen Based

Selection

Identify the patients in the overlap
through translational research

Making Immunotherapy a Reality for Patients with RCC

- Until we develop better tools, immunotherapy is the best method for achieving the patient's goal
  - "Treatment-Free Survival"

- ITH may be associated with relatively increased activity of immunotherapy
  - Mutational load = predictive biomarker?

- ITH generates neoantigens that could be used as immunotherapies?

Acknowledgements

◆ **DF/HCC Colleagues**
- **Sabina SIgnoretti**
- **Toni Choueiri**
- **Cathy Wu**
- **Lauren Harshman**
- **Gordon Freeman**
- **Arlene Shape**
- **Mike Atkins (GLCCC)**
- **Steve Hodi**

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- **Chuck Drake (JHU)**
- **Hans Hammers (JHU)**
- **Bob Motzer (MSKCC)**
- **Asim Amin (Carolinas)**