BIOMARKERS AND CLINICAL CHARACTERISTICS OF RESPONSE TO PD-1 IMMUNE CHECKPOINT BLOCKADE IN NON-SMALL CELL LUNG CANCER

Julie R. Brahmer, M.D., M.Sc.
Associate Professor of Oncology
Director of the Thoracic Oncology Program

JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

Disclosures

Julie R. Brahmer, M.D., M.Sc.

- Merck, Consultant/Advisor
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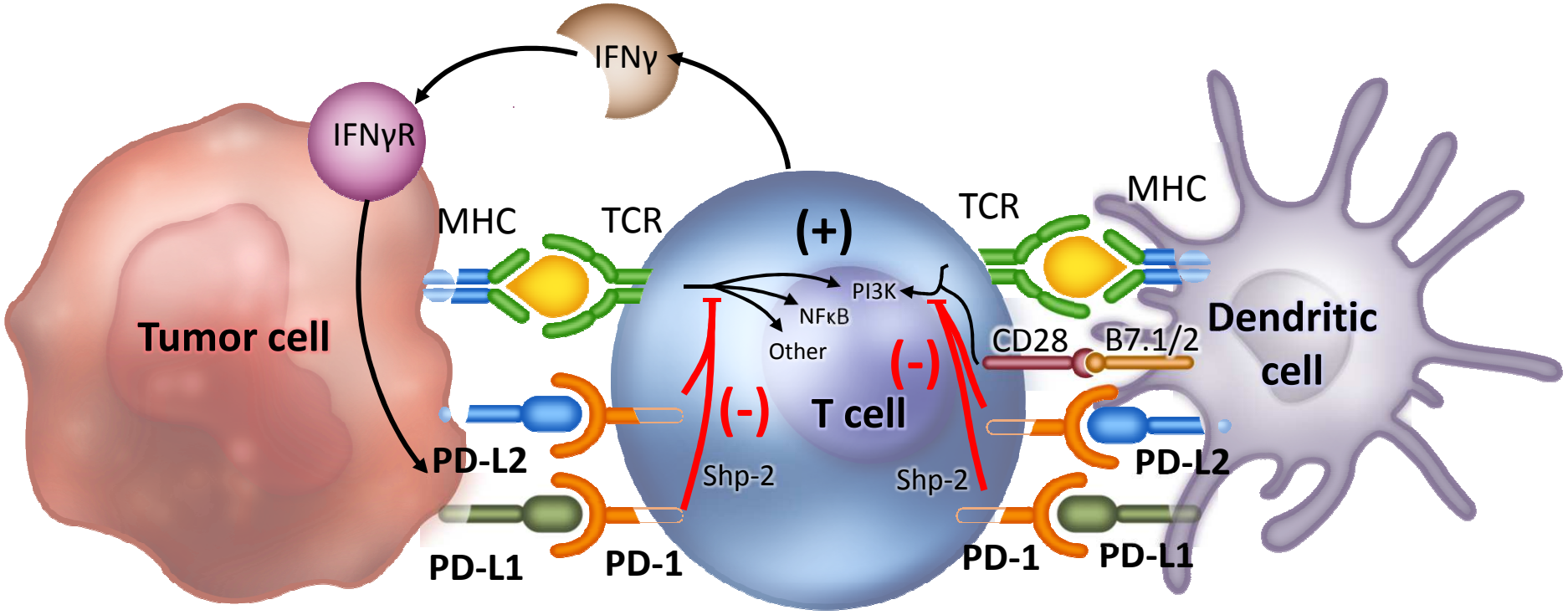
- Bristol Myers Squibb, Grant/Research Funding
- Merck, Grant/Research Funding
- AstraZeneca, Grant/Research Funding

Role of the PD-1 pathway in suppressing anti-tumor immunity



Tumor-specific T cell recognition in the periphery

Lymphocyte priming to tumor antigens

Pretreated NSCLC –Phase I Trials

Regimens	Subgroup, n		ORR[†], %	Median PFS (mo)	Median OS (mo)
Pembrolizumab[1] (N=217)	10 mg/kg q 3wk	126	21	2.5	8.2
Nivolumab[2] (N=129)	3 mg/kg q 2wk	37	24	1.9	14.9
MEDI4736[3] (N=155)	10 mg/kg q 2wk	150	15	NR	NR
MPDL-3280a[4] (N=53)	Multiple doses	53	23	NR	NR

1. Garon, et al. Poster. ASCO 2014 (abstr 8020). 2. Brahmer, et al. Poster. ASCO 2014 (abstr 8112). 3. Antonio S, et al. Poster. ESMO 2014 (abstr 7629) 4. Soria J et al Presentation ECC 2013.

Who is Most Likely to Respond?

Lessons From the Trials

Nivolumab ORR by Select Patient Characteristics

Subgroup	ORR, % (n/N) [95% CI][a]
Age	
<70 yr	17 (15/90) [10, 26]
≥70 yr	18 (7/39) [8, 34]
Sex	
Female	18 (9/50) [9, 31]
Male	17 (13/79), [9, 27]
ECOG PS	
0	11 (3/27) [2, 29]
1-2	19 (19/102) [12, 28]
Histology	
Squamous	17 (9/54) [8, 29]
Non-squamous	18 (13/74) [10, 28]

Subgroup	ORR, % (n/N) [95% CI][a]
Number of prior therapies	
<3	12 (7/59) [5, 23]
≥3	21 (15/70) [13, 33]
EGFR status	
Mutant	17 (2/12) [2, 48]
Wild-type	20 (11/56) [10, 32]
KRAS status	
Mutant	14 (3/21) [3, 36]
Wild-type	25 (9/36) [12, 42]

Brahmer J et al, ASCO 2014

Pembrolizumab Activity by Select Patient Characteristics

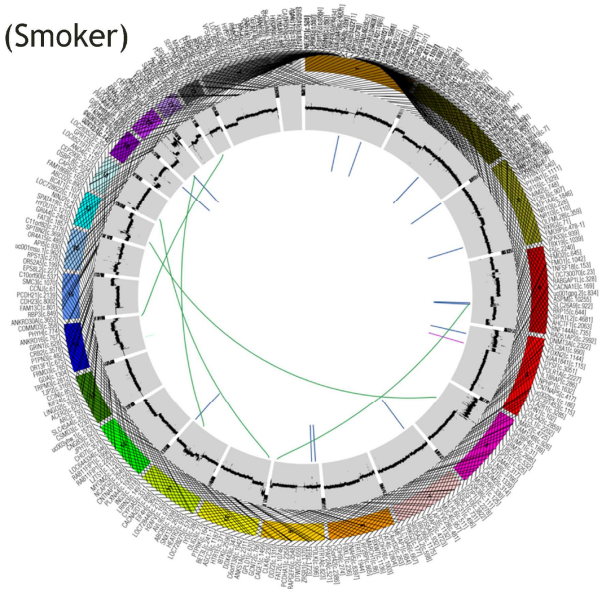
	N	ORR[a] % (95% CI)
Total	**236**	**21 (16-27)**
Previous treatment	236	
Treatment naive	42	26 (14-42)
Previously treated	194	20 (15-26)
Histology	230	
Nonsquamous	191	23 (17-29)
Squamous	39	18 (8-34)
Smoking history	230	
Current/Former	165	27 (20-34)
Never	65	9 (4-19)

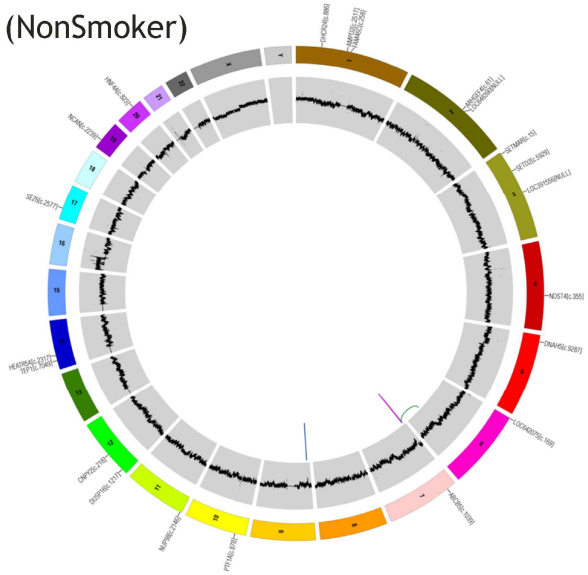
	N	ORR[a] % (95% CI)
Dose/schedule	236	
2 Q3W	6	33 (4-78)
10 Q3W	126	21 (14-29)
10 Q2W	104	21 (14-30)
PD-L1 expression[b]	236	
Positive	201	23 (18-30)
Negative	35	9 (2-23)
EGFR mutation	36	14 (5-30)
KRAS mutation	39	28 (15-45)
ALK rearrangement	6	17 (0-64)

[a]Includes confirmed and unconfirmed responses.
[b]As assessed using a prototype assay. Positive was defined as staining in ≥1% of tumor cells.
Analysis cutoff date: March 3, 2014.

Garon E et al, ESMO 2014

Tobacco exposure and PD-1 response in NSCLC





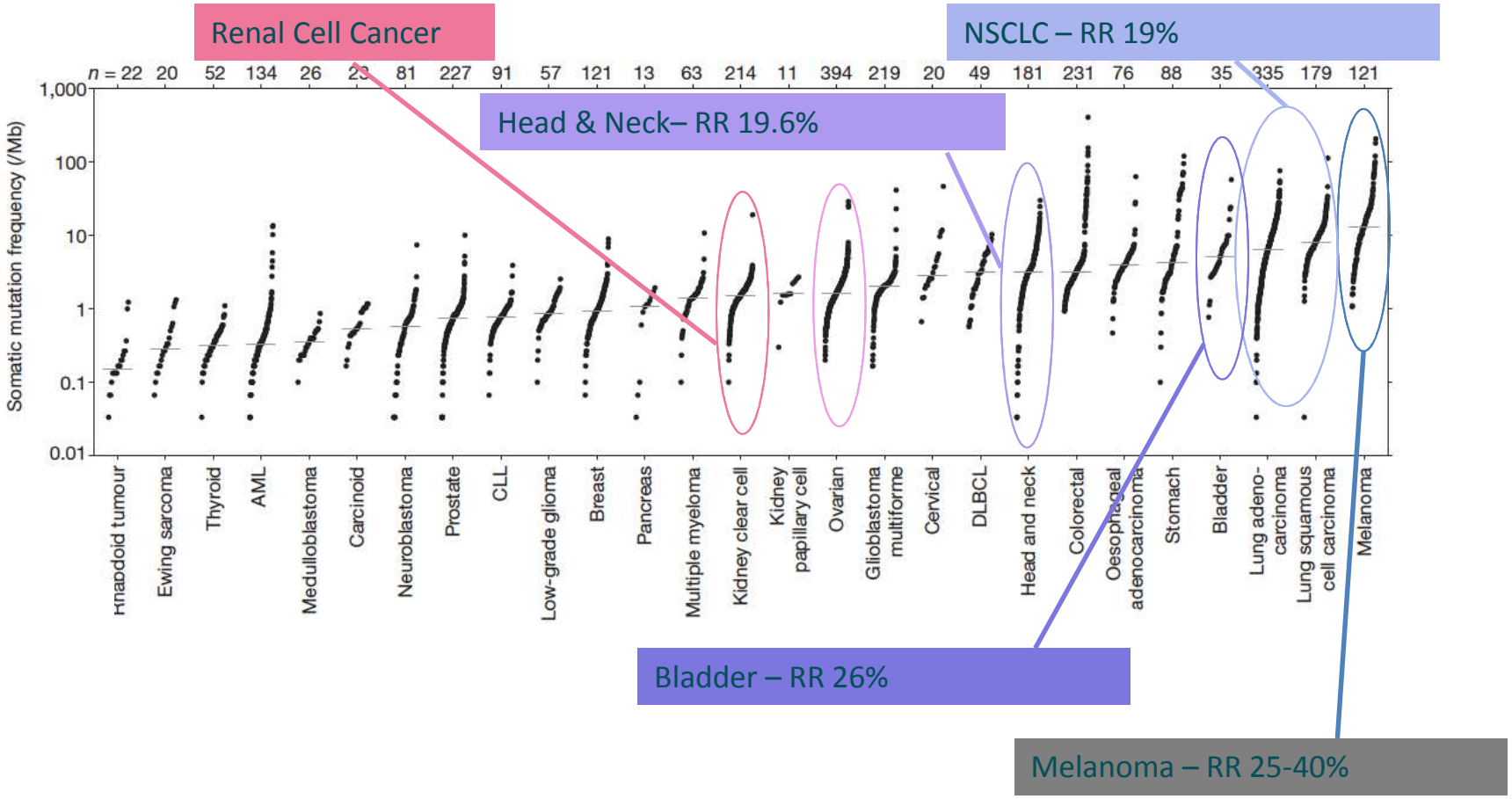
Govindan et al., *Cell* 2012

	Smokers or Ex-smokers	Never smokers	
Pembrolizumab	33/129 (26%)	5/60 (8%)	Garon et al, ASCO 2014
MPDL3280A	11/43 (26%)	1/10 (10%)	Soria et al, WCLC 2013
Nivolumab	20/75 (26%)	0/13 (0%)	Hellman et al, ESMO 2014

? Potential surrogate marker for mutational density?

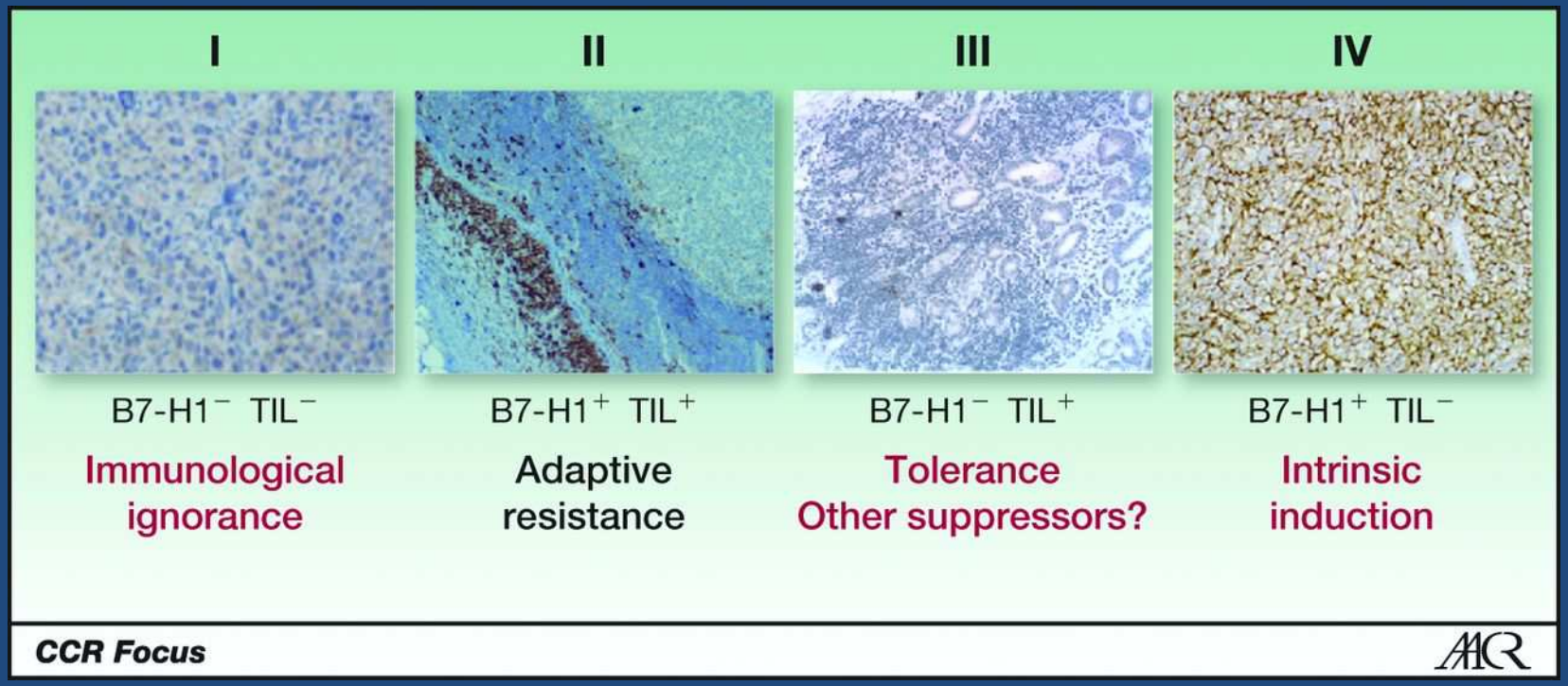
Adapted from Rizvi N ,2014

Can mutation burden help select for patients more likely to respond to immunotherapy ?



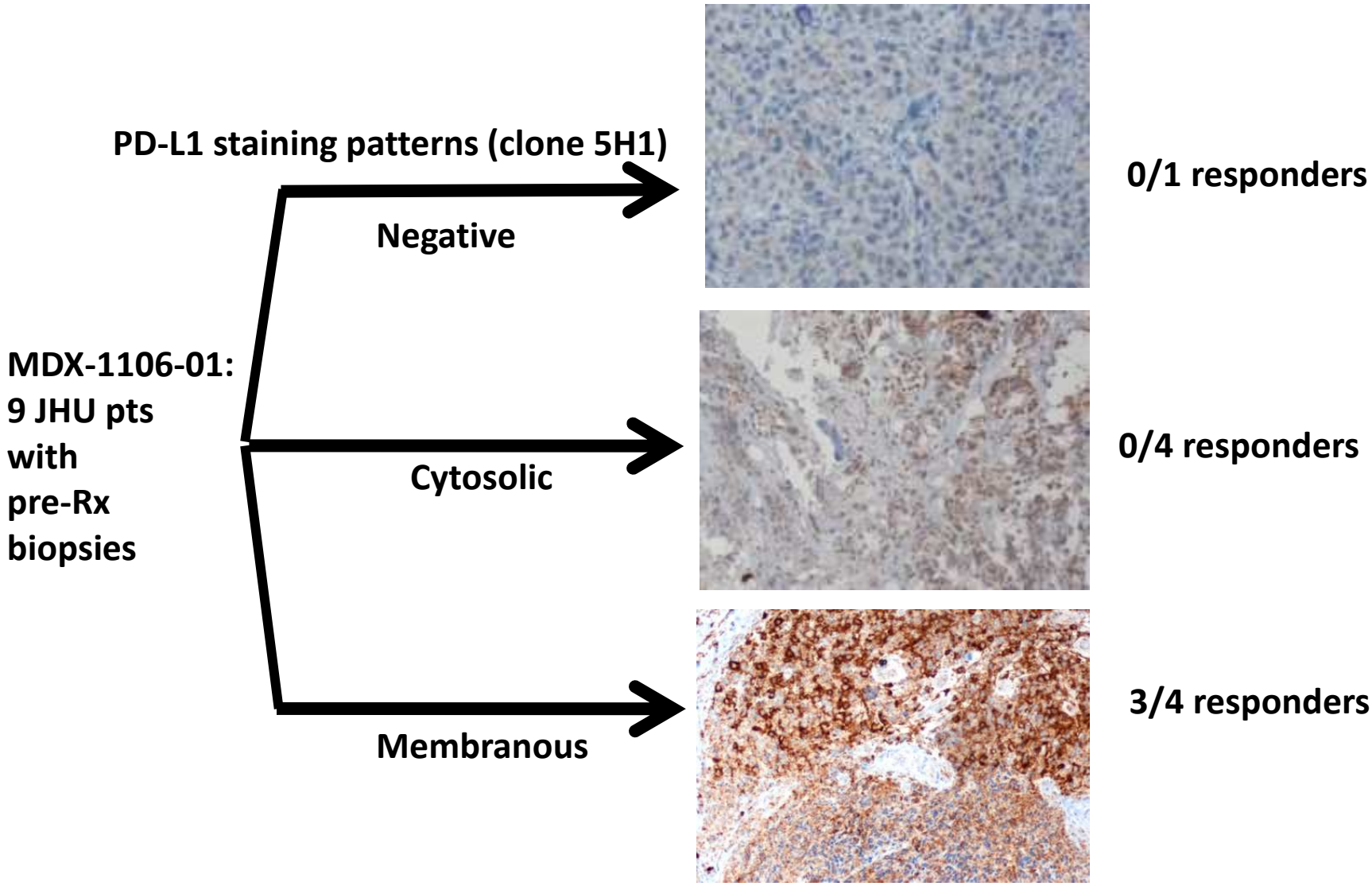
Adapted from Alexandrov et al., *Nature* 2013

PD-L1 (B7-H1) Expression and Inflammation: Implications for Mechanisms and Therapy



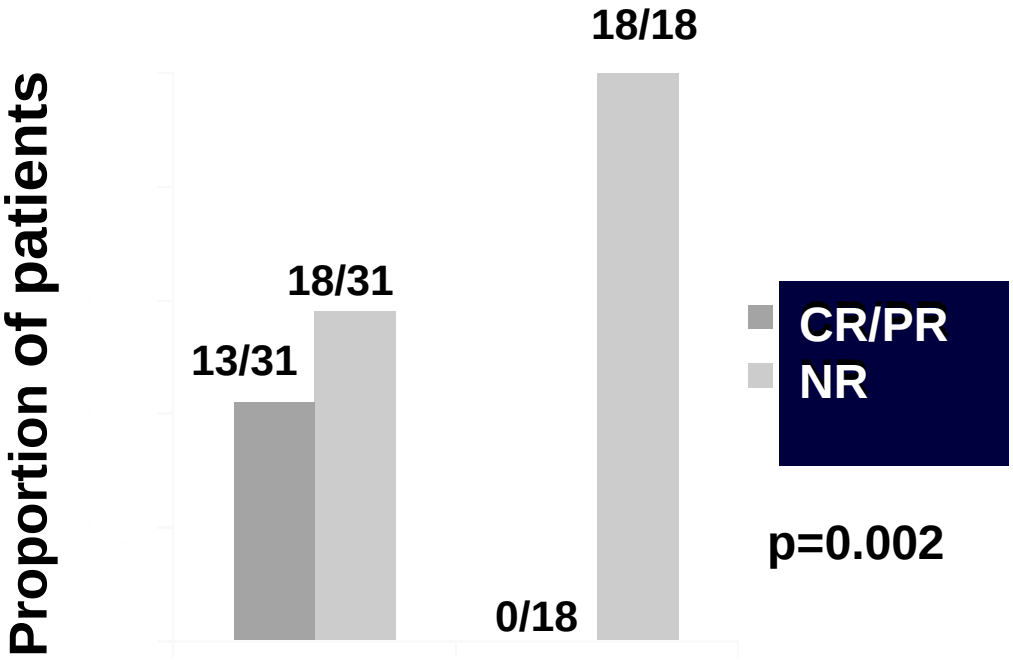
Sznol M , and Chen L Clin Cancer Res 2013;19:1021-1034

Expression of PD-L1: Required for Clinical Response to PD-1 Blockade? Initial Information from the First in Human Trial of Nivolumab

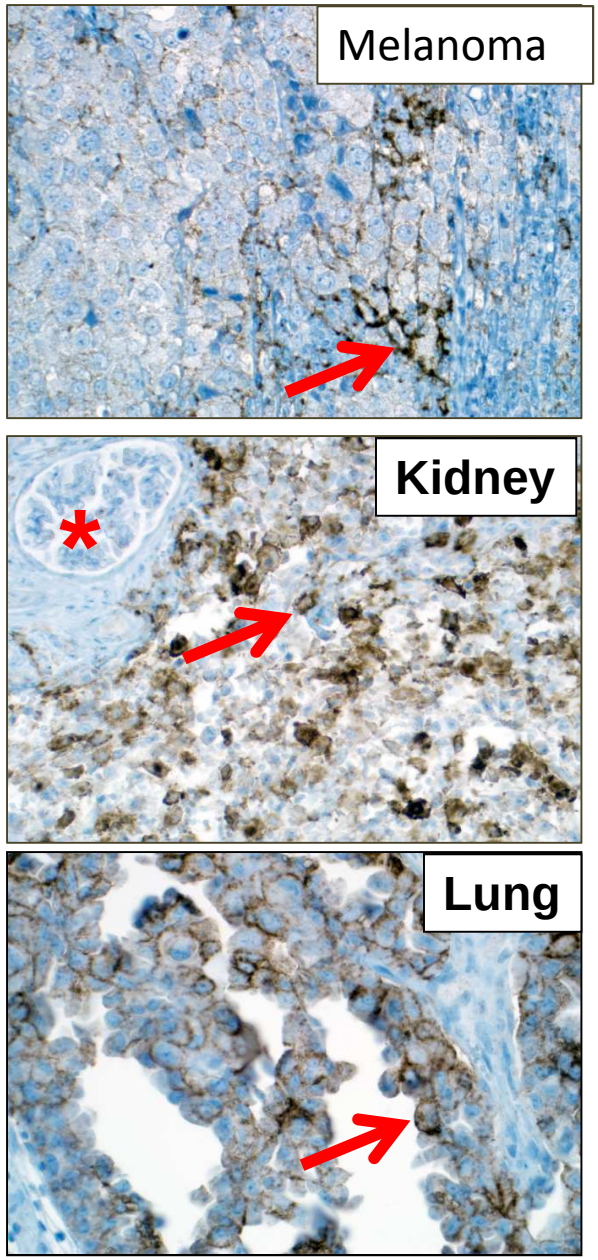


J. Taube and S. Topalian, Brahmer J et al JCO 2010

Preliminary molecular marker studies: Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical response to anti-PD-1



49 patients include 20 with melanoma,13 NSCLC, 7 colon, 6 kidney, and 3 prostate cancer.



*** Normal renal glomerulus**

Topalian S and Taube J, 2013

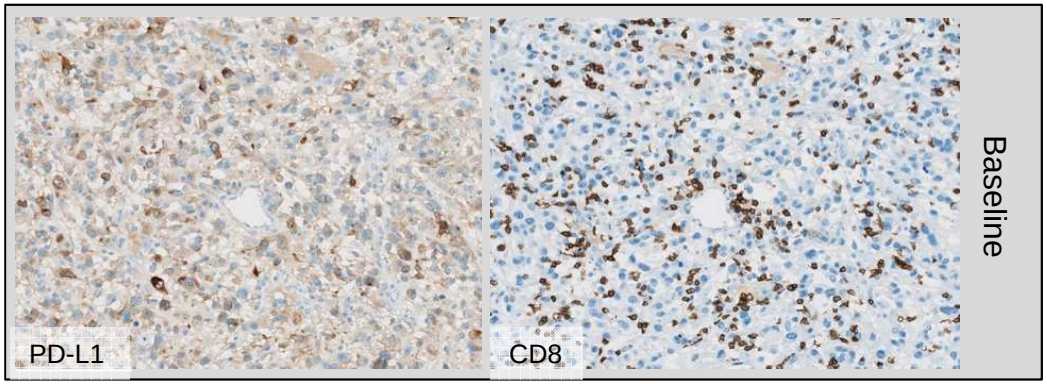
Relationship Between PreRx Tumor Microenvironment and Clinical Response to Nivolumab

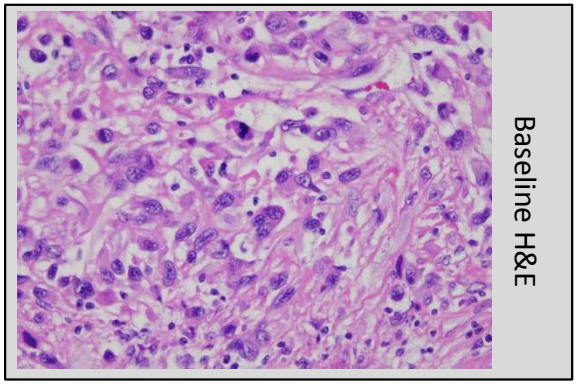
Pathologic parameter (number of patients analyzed)	All patients*n* (%)	Objective response[b]			Clinical benefit[c]		
		No*n* (%)	Yes*n* (%)	*P* value[d]	No*n* (%)	Yes*n* (%)	*P* value[d]
Tumor PD-L1 expression ($n = 41$)[e]							
Absent	18 (44)	17 (94)	1 (6)	0.025	17 (94)	1 (6)	0.005
Present	23 (56)	14 (61)	9 (39)		12 (52)	11 (48)	
Immune cell infiltrate PD-L1 expression ($n = 41$)[e]							
Absent	18 (44)	16 (89)	2 (11)	0.142	16 (89)	2 (11)	0.038
Present	23 (56)	15 (65)	8 (35)		13 (57)	10 (43)	

- Included NSCLC, RCC, melanoma, CRPC, Colon CA tumors
- PD-L1 positivity defined as $\geq$ 5% membranous staining by IHC 5H1 Ab
- Presence of TIL, PD-L2 expression, CD4:CD8 ratio, CD 20 B-cell, lymphoid aggregates, necrosis, small sample size, or time from Bx to treatment was NOT associated with response

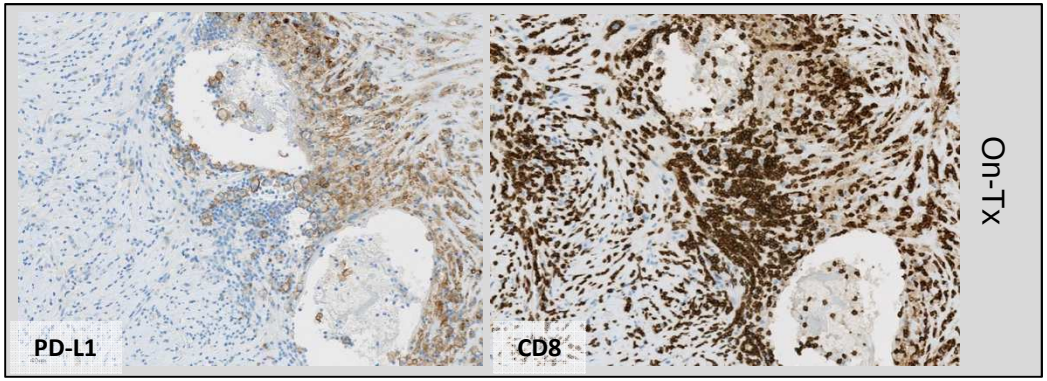
Taube JM et al Clin Cancer Res, 2014

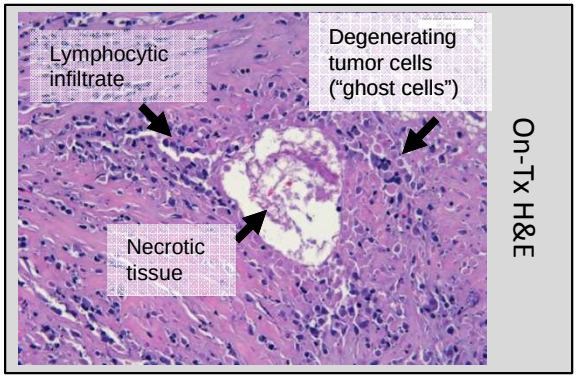
Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A





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



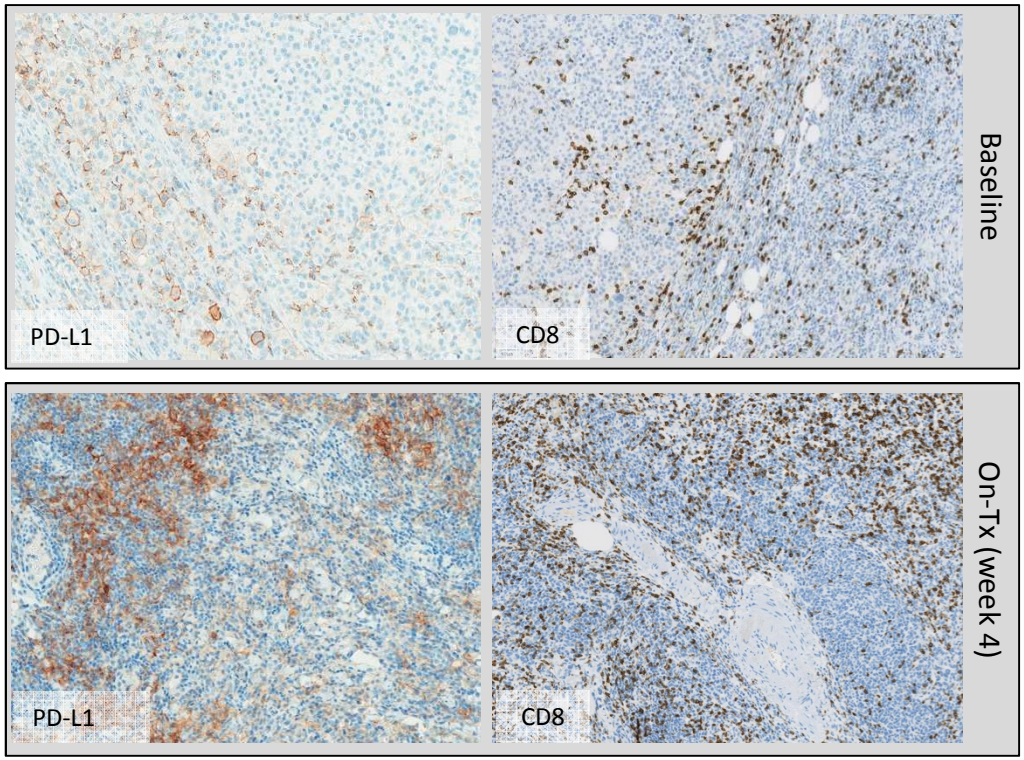


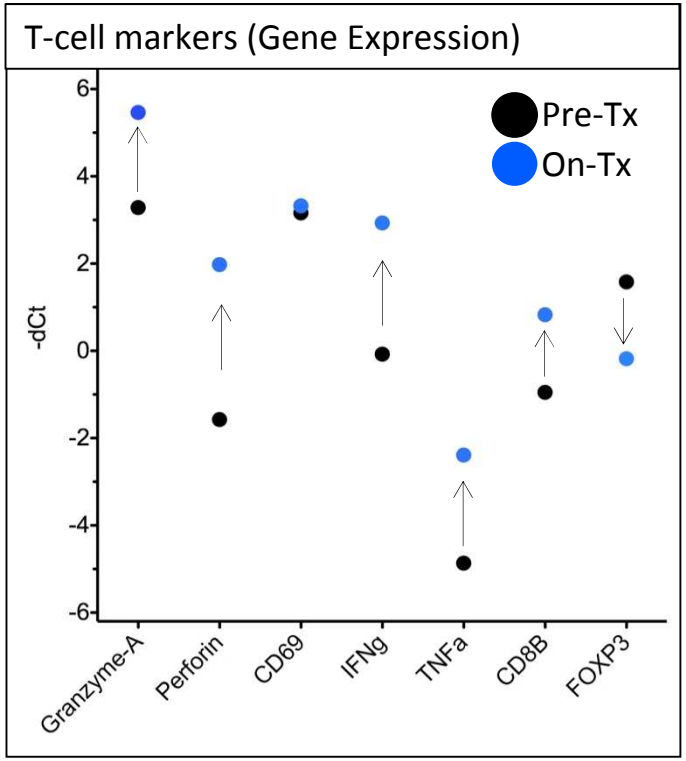
Biomarkers at week 4 post C1D1:
PD-L1 positive
Increased CD8+ T-cell infiltrate

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

Carolina BioOncology Institute (Powderly). ASCO 2013

MPDL3280A Leads to Increased T-cell Activation in PD-L1– Positive Patient Responding to Treatment





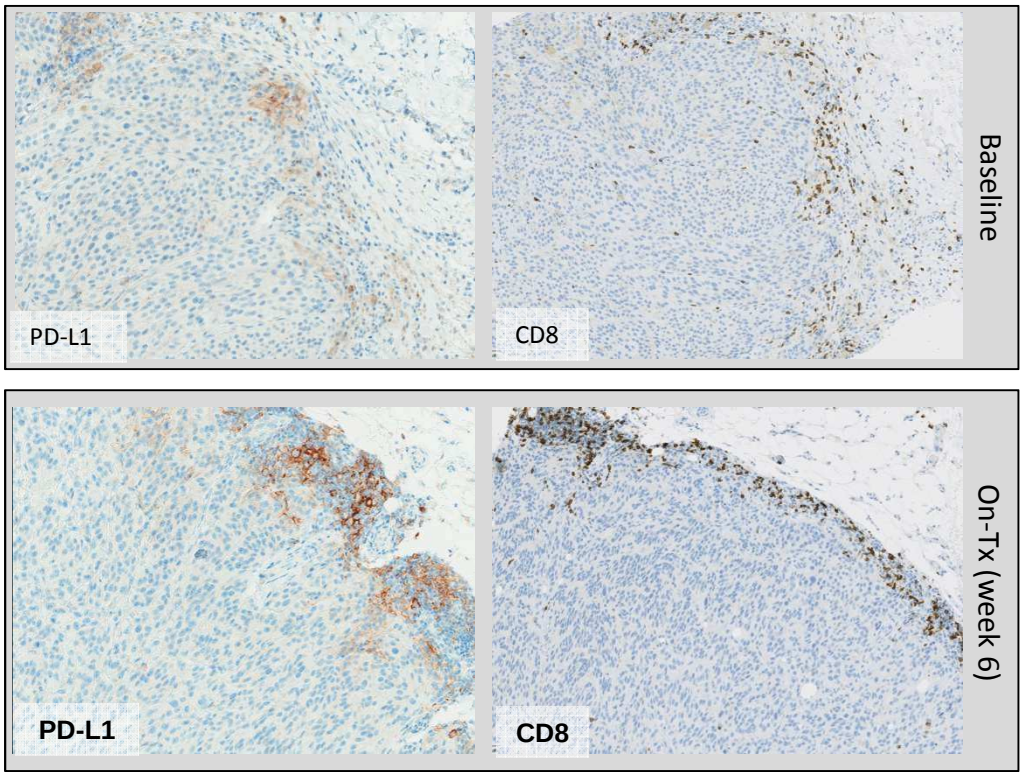
Possible MoA of response to MPDL3280A:

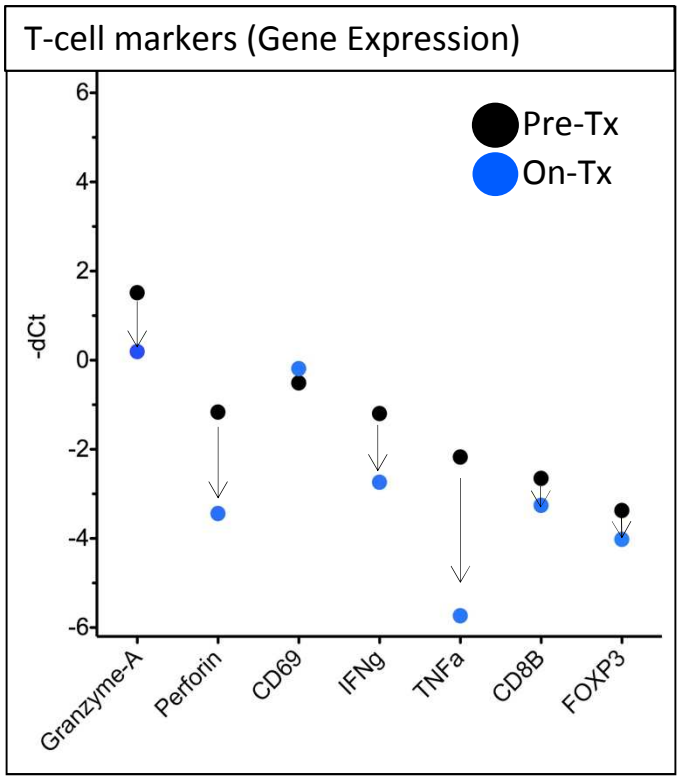
- Pre-existing intra-tumoral CD8+ T cells
- Increased trafficking or proliferation of intra-tumoral CD8+ cells
- Increased T-cell activation and cytotoxicity (e.g., Granzymes and Perforin production)

Powderly J et al ASCO 2013

Yale Cancer Center (Kluger/Herbst).

PD-L1–Negative Patient Not Responding to MPDL3280A Exhibits Low Frequency of Intratumoral T cells





Possible MoA of resistance:

- CD8+ T cells remain at the edge of the tumor (possible impaired trafficking)
- No increase in T-cell cytotoxicity
- No T-cell recognition of cancer antigens in this patient

Powderly J et al ASCO 2013

Massachusetts General Hospital (Lawrence/Hodi).

Pretreated NSCLC –Phase I Trials Activity by PD-L1 Staining

Regimens	Subgroup, n		ORR[†], %	Median PFS (mo)	Median OS (mo)
Pembrolizumab[1] (N=217)	10 mg/kg q 3wk	126	21	3.25	8.2
	PD-L1+	201	23	2.75	NR
	PD-L1 -	35	9	2.5	NR
Nivolumab[2] (N=129)	3 mg/kg q 2wk	37	24	1.9	14.9
	PD-L1 +	33	15	3.6	7.8
	PD-L1 -	35	14	1.8	10.5
MEDI4736[3] (N=155)	10 mg/kg q 2wk	150	15	NR	NR
	PD-L1 +	47	26	NR	NR
	PD-L1 -	74	10	NR	NR

1. Garon, et al. Presentation. ESMO 2014 ..2. Brahmer, et al. Poster. ASCO 2014 (abstr 8112). 3. Antonio S, et al. Poster. ESMO 2014 (abstr 7629).

PD-L1 as a biomarker in NSCLCs

Drug	Nivolumab			Pembrolizumab			MPDL3280A			MEDI4736
Assay	28-8			22C3						SP263
Cells scored	Tumor cell membrane			Tumor cell (and stroma)			Infiltrating immune cells			Tumor cell membrane
Tissue	Archival			Recent			Arch./Recent			Arch./Recent
Setting	1st line	2L ++		1st line	2L ++		2L ++			2L ++
Cut-point	5%	1%	5%	1%	1%	50%	1%	5%	10%	NR
ORR in PD-L1 +	31% N=26	13% N=38	15% N=33	26-47% N=45	19-23% N=177	37% N=41	31% N=26	46% N=13	83% N=6	26% N=47
ORR in PD-L1 -	10% N=21	17% N=30	14% N=35	???	9-13% N=40	11% N=88	20% N=20	18% N=40	18% N=40	10% N=74

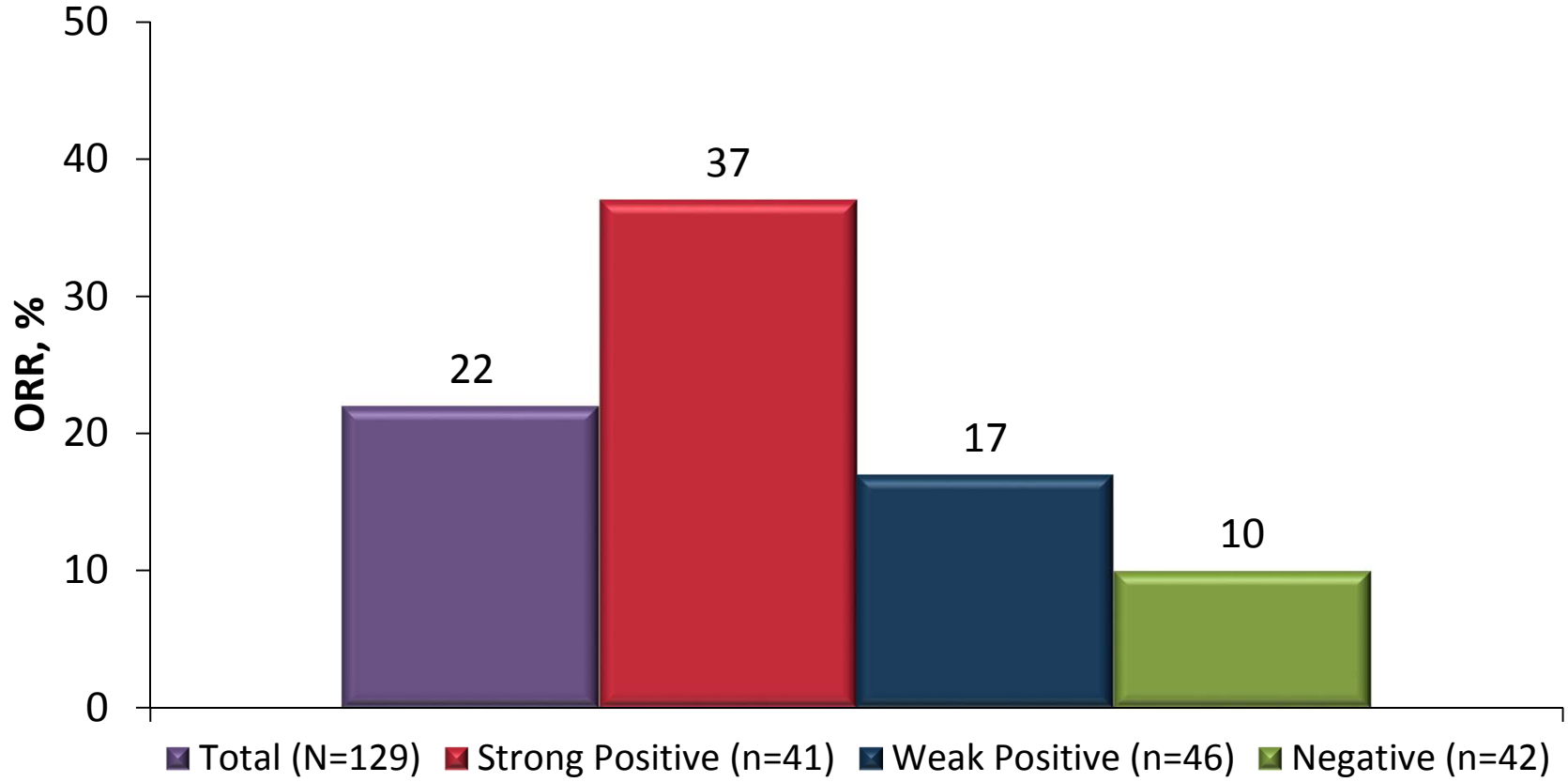
NIVO
Topalian, NEJM 2012
Grosso, ASCO 2013, #3016
ASCO 2014, #8112
Rizvi, CSMTO 2014

Pembro
Daud, AACR 2014
Ghandi, AACR 2014
Rizvi, ASCO 2014, #8009
Garon, ESMA 2014

MPDL3280A
Hamid, ASCO 2013, #9010
Herbst, ASCO 2013, #3000
Powderly, ASCO 2013, #3001
Spigel, ASCO 2013, #8008

MEDI4736
Segal, ASCO 2014, #3002
Brahmer, SITC 2014

Pembrolizumab Response Rate by Level of PD-L1 Expression (RECIST 1.1, Central Review)



Clinical trial assay

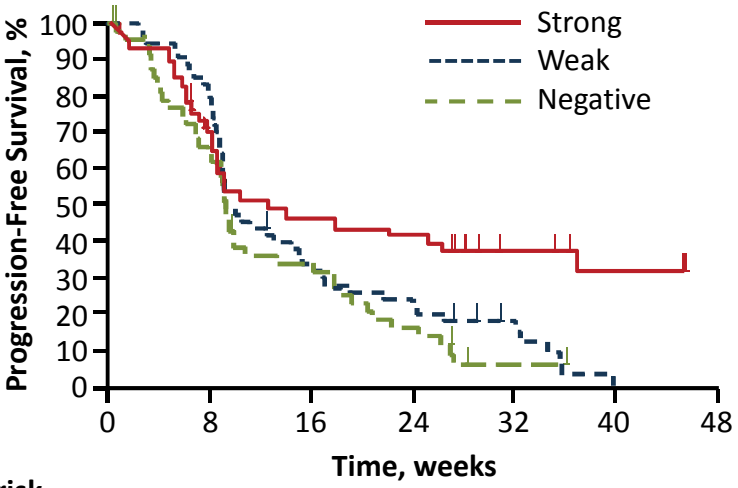
- Strong PD-L1 expression: defined as ≥50% membranous staining in tumor cells
- Weak PD-L1 expression: defined as 1-49% membranous staining in tumor cells

[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria.
Analysis cut-off date: March 3, 2014.

Garon E et al, ESMO 2014

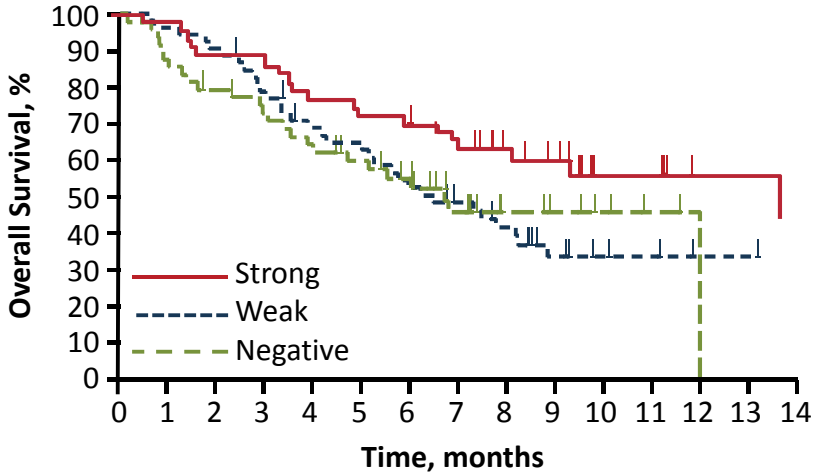
Pembrolizumab Kaplan-Meier Estimates of Survival by PD-L1 Staining Status

PFS (RECIST v1.1, Central Review)



n at risk							
Strong	44	28	18	17	9	6	3
Weak	53	43	17	12	6	0	0
Negative	49	30	15	7	1	0	0

OS



	44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
	53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
	49	42	38	34	29	26	21	14	8	6	4	2	0	0	0

- PFS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.52; 95% CI, 0.33-0.80)
- OS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.59; 95% CI, 0.35-0.99)

[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression.
Strong PD-L1 positivity defined as staining in ≥50% of tumor cells, and weak PD-L1 positivity as staining in 1-49% of tumor cells. Negative staining is no PD-L1 staining in tumor cells.
Data cut-off: March 3, 2014.

Garon E et al ESMO 2014

Issues with Assay Methodology

- Bx type - Excisional versus core versus FNA
- **Addressing heterogeneity** – multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment – effect of other therapies
- Primary versus metastatic disease
- Antibody and staining conditions
- Frozen versus FFPE tissue
- Automated versus 'manual' read
- **Defining a positive result (cut-offs):**
  - Cell type expressing PD-L1 (immune cell versus tumor or both)
  - Presence or absence of T-cells near PD-L1 expression
  - Location of expression – cell surface versus intracellular
  - intensity
  - Distribution - patchy versus diffuse, intratumoral versus peripheral
  - percent of cells 'positive'

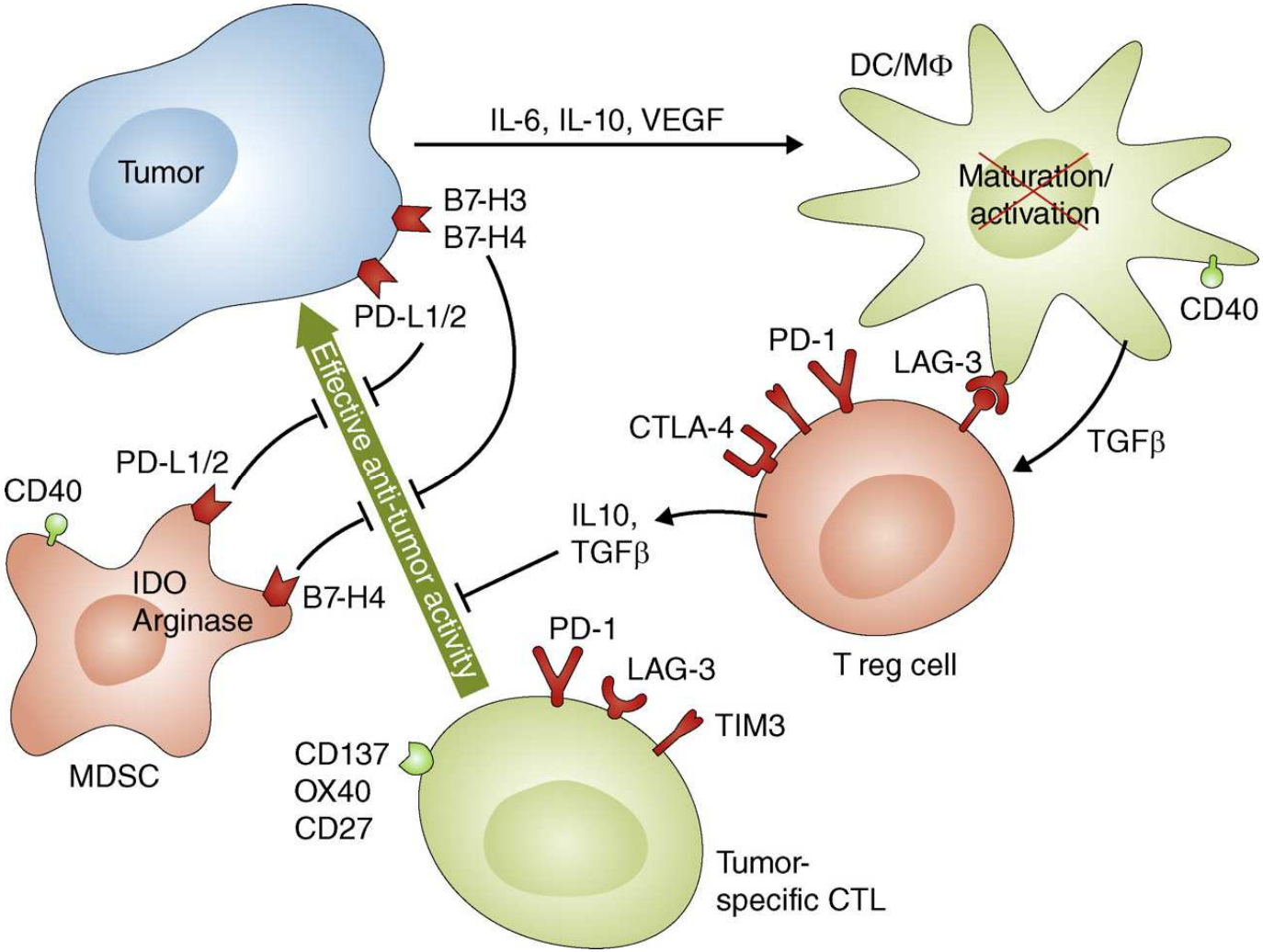
Mario Sznol, AACR 2014

Multiple Current Trials of PD-1 or PD-L1 inhibitors in Stage 4 NSCLC

- **First Line Trials – PD-L1 + disease (ds)**
  - Chemo vs. PD-1 Ab (Pembro and Nivo trials ongoing)
- **Second Line Trials**
  - Nivolumab vs. docetaxel in either Squam or Nonsquam – both trials completed enrollment
  - Pembrolizumab vs. docetaxel in PD-L1 positive ds
  - MPDL-3280a vs. docetaxel
- **Beyond 2nd Line**
  - MEDI-3476 vs. dealers choice chemotherapy
  - MPDL-3280a in PD-L1 positive ds
  - Phase 1s of combination therapies or expansion cohorts ongoing with other PD-L1 Abs

How Can We Increase the Response Rate in Those Less Likely to Respond?

Multiple immune inhibitory and co-stimulatory pathways in the tumor microenvironment are targets of therapeutic manipulation by antibodies or drugs.

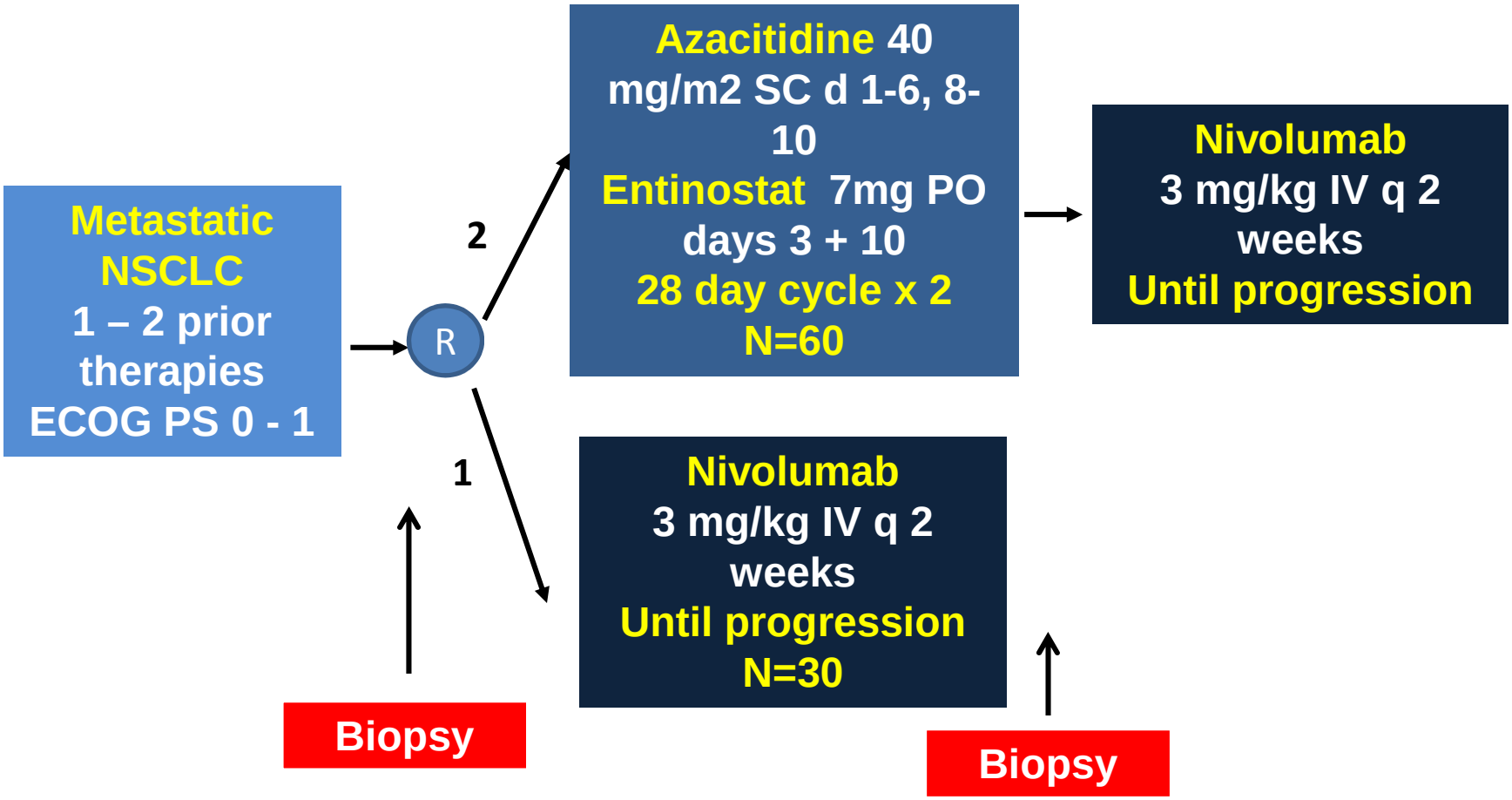


Pardoll D , and Drake C J Exp Med 2012;209:201-209

How does one turn a non-inflamed, PDL1 negative tumor into a immune responsive tumor?

- SRS
- Molecularly targeted therapy
- Tumor based vaccine
- CAR T cells or other modified T cells
- Epigenetic therapy

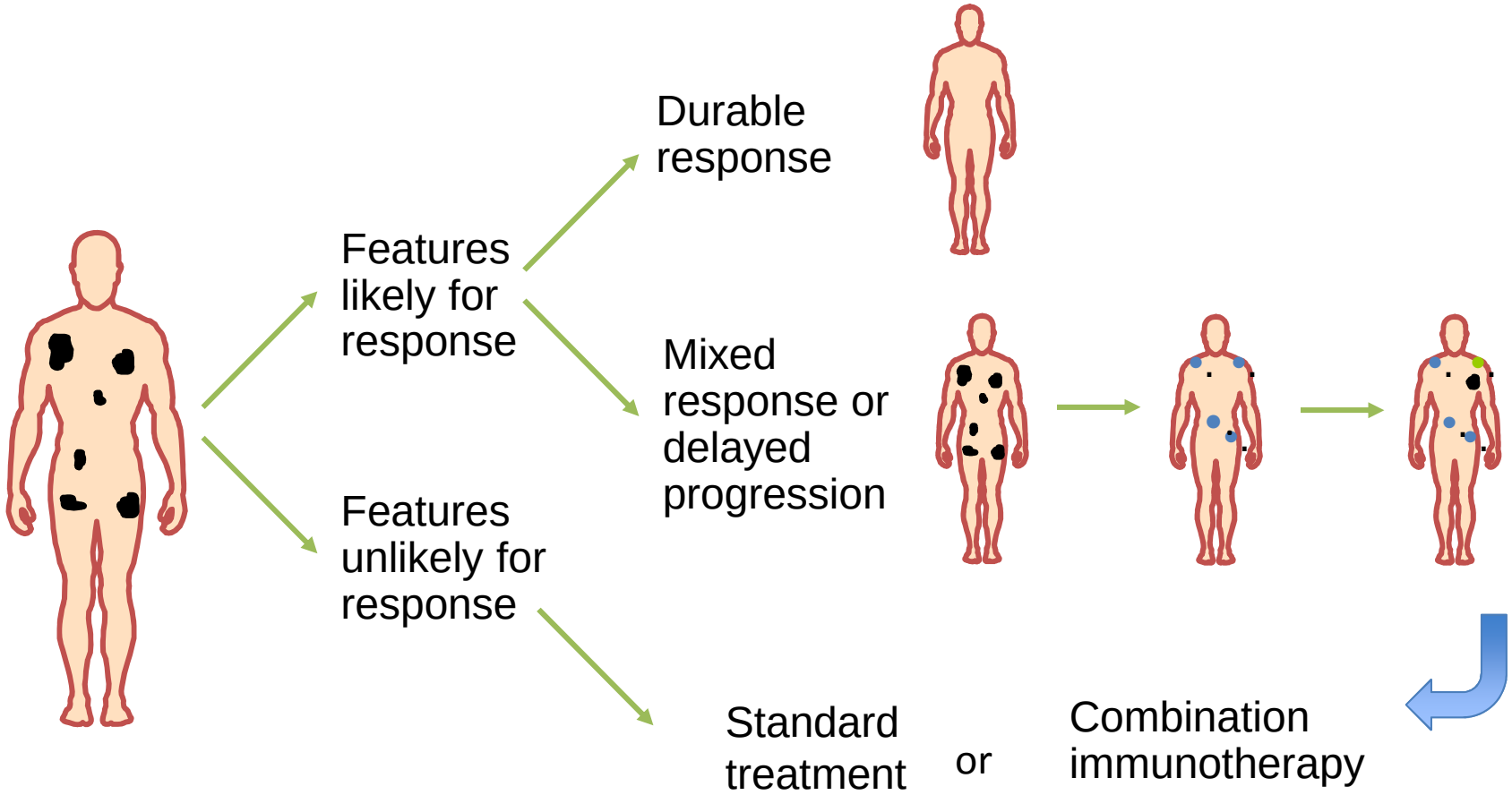
Epigenetic Priming of Immunotherapy



Primary endpoint – PFS rate at 32 weeks

Secondary endpoints – RR, PFS, TTP, OS, safety, lab correlates

Cancer Management in the Anti–PD-1/PD-L1 Era – The need for Personalized Immunotherapy



Adapted from Rizvi N, LALCA 2014

Conclusions

- PD-1/PD-L1 checkpoint inhibitors have promising activity in NSCLC
- Patient selection (biomarker) is being evaluated
- While PD-L1 positivity may be associated with a higher likelihood of response, it is not the complete answer
- Smoking status may predict response just as well
- The future of immunotherapy in NSCLC may be in determining the mechanism of immune evasion in each patient

Lessons and Take Home Messages

- Key points
  - Former or Current Smokers with lung cancer have a higher RR to PD-1 checkpoint blockade
  - PD-L1 positive tumors are associated with higher RR to PD-1 checkpoint blockade
  - PD-L1 positivity is not the perfect biomarker of response
- Potential impact on the field
  - Continued investigation for a biomarker of response to checkpoint blockade is needed
- Lessons learned
  - Biomarkers of response are needed
  - Cross validation of current PD-L1 testing techniques is needed if used for patient selection in the clinic