Clinical Perspectives-Tailoring Immunotherapy To The Patient

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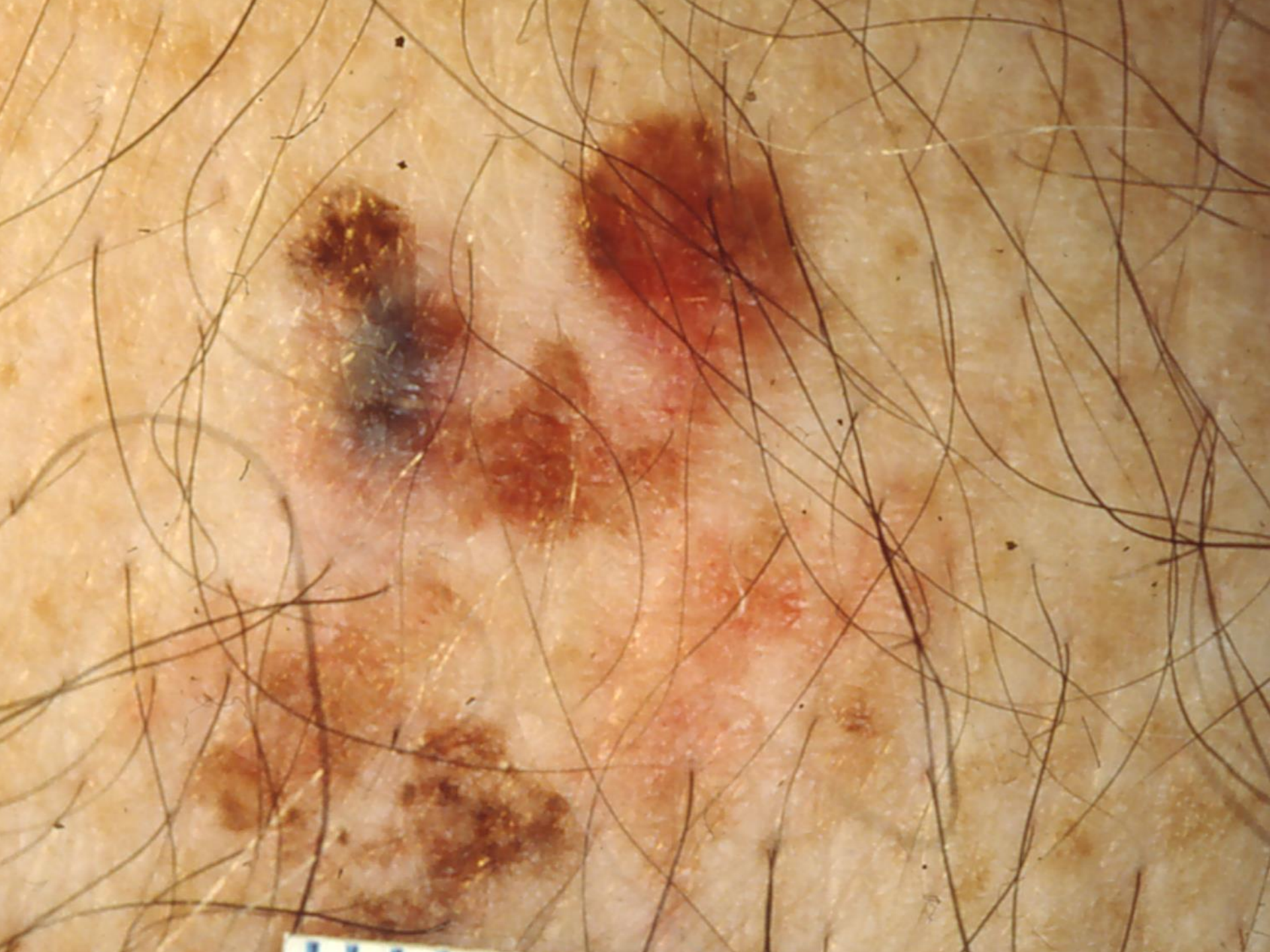
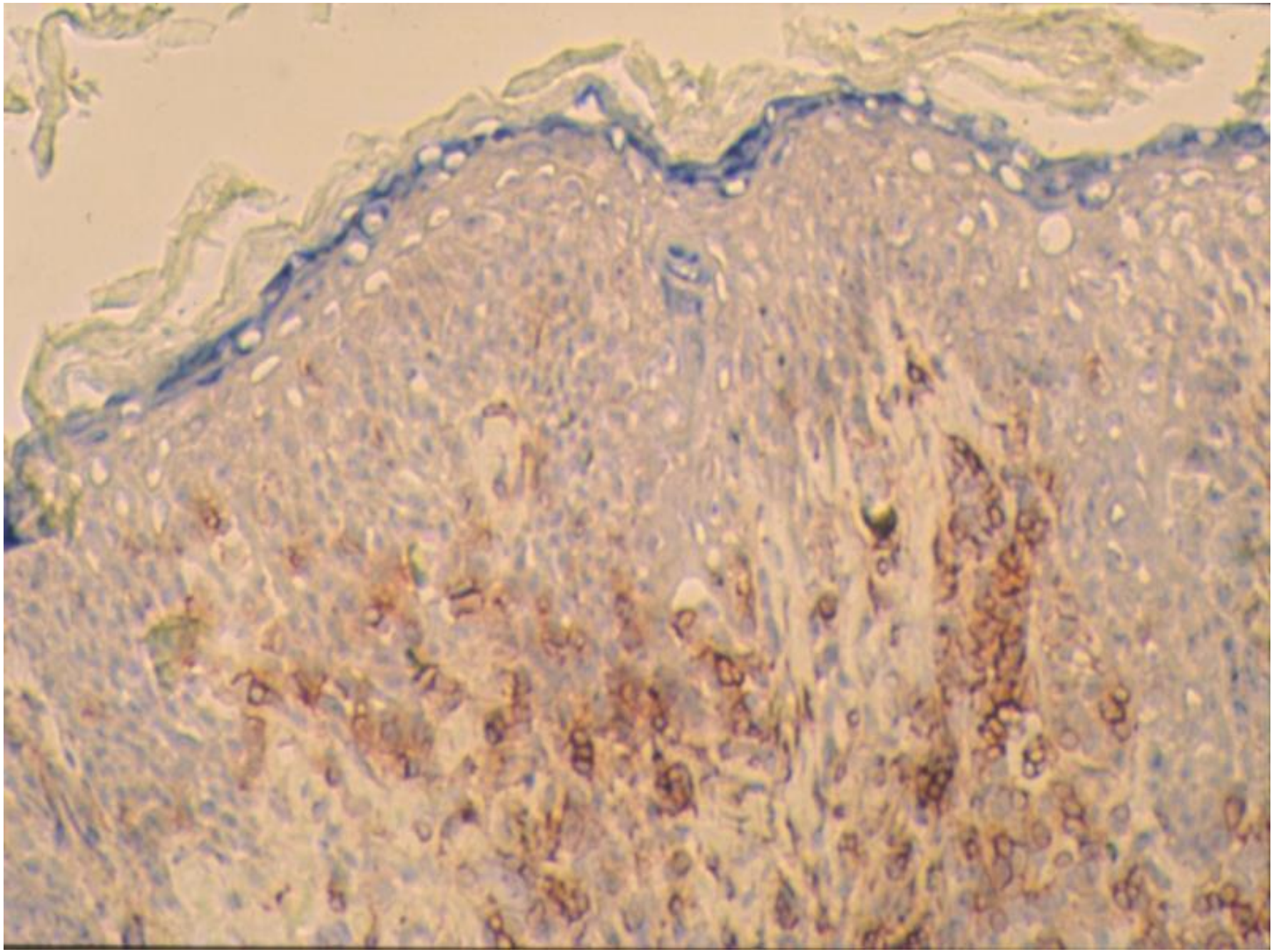
Clinical Perspectives In Immunotherapy

- **Where we are up to**
- **Current limitations-What we need to do**
- **Handling Side Effects**





What we have learnt about immunotherapy over the past 5 years

Inhibition of Physiologic Checkpoints is more effective than stimulation of the immune system by vaccines or cytokines

Recapitulating the Current Theories Underpinning anti Checkpoint Immunotherapy

The Ig Super Family of Co-stimulators and Checkpoint inhibitors

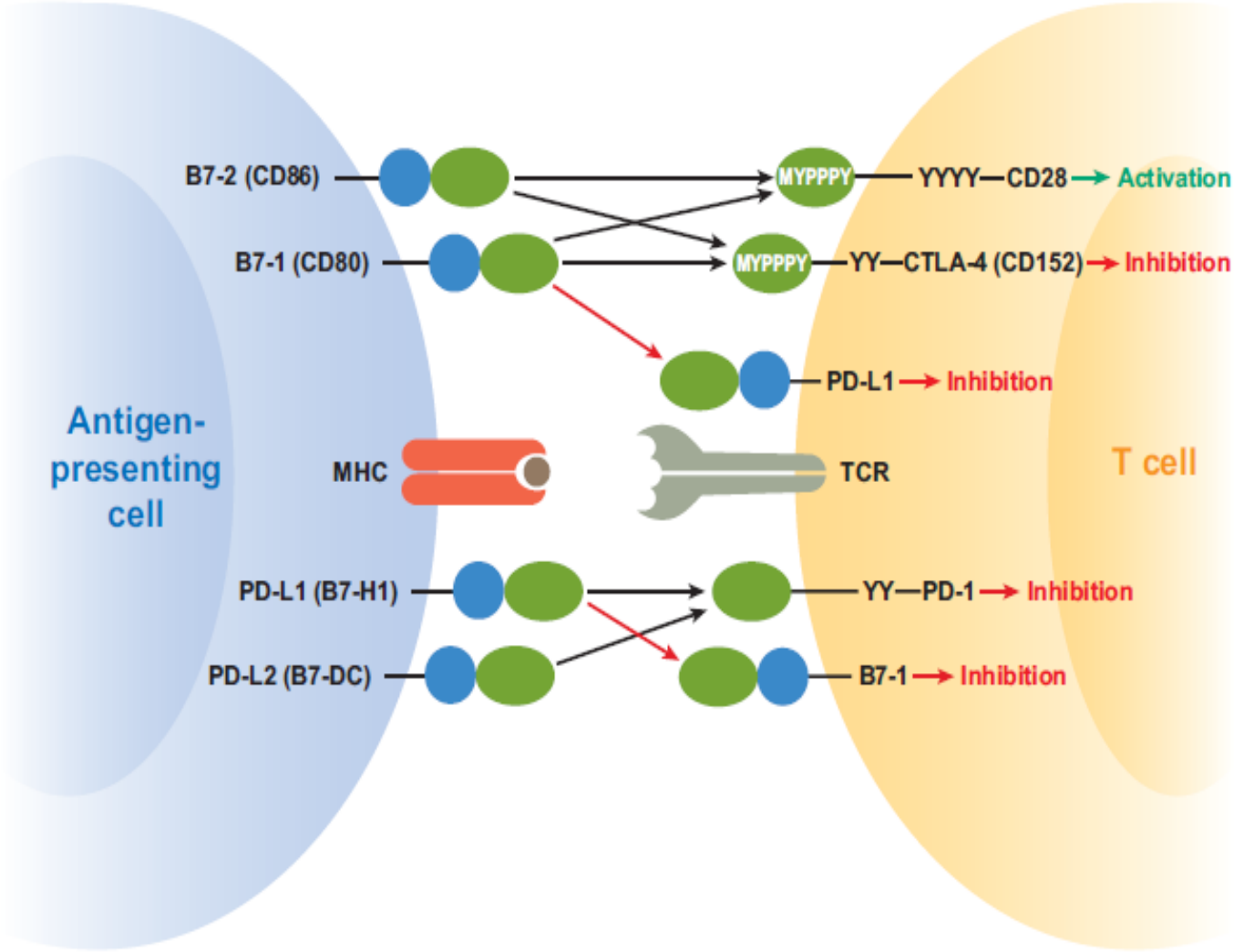
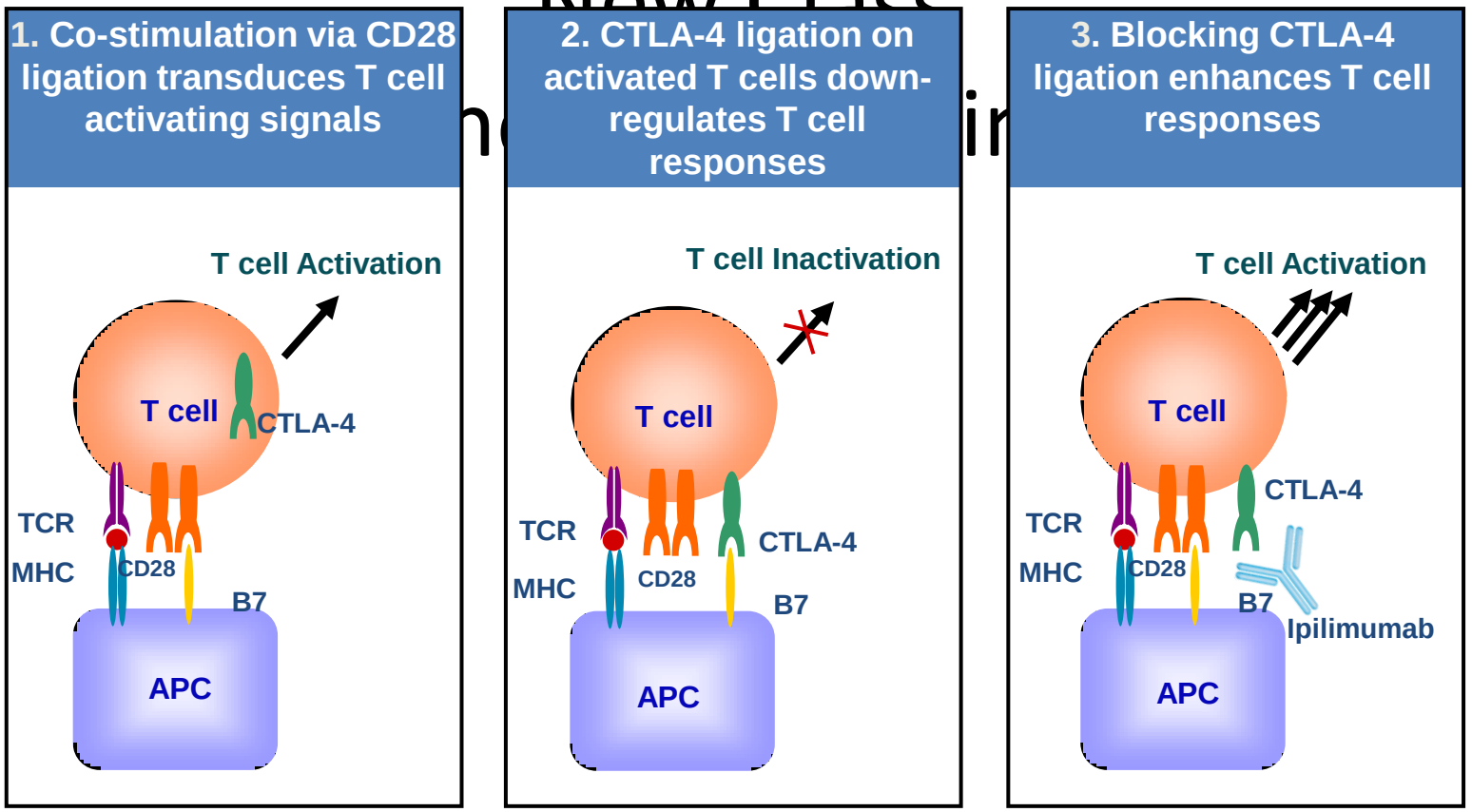


Figure 3

Arlene Sharp et al 2008

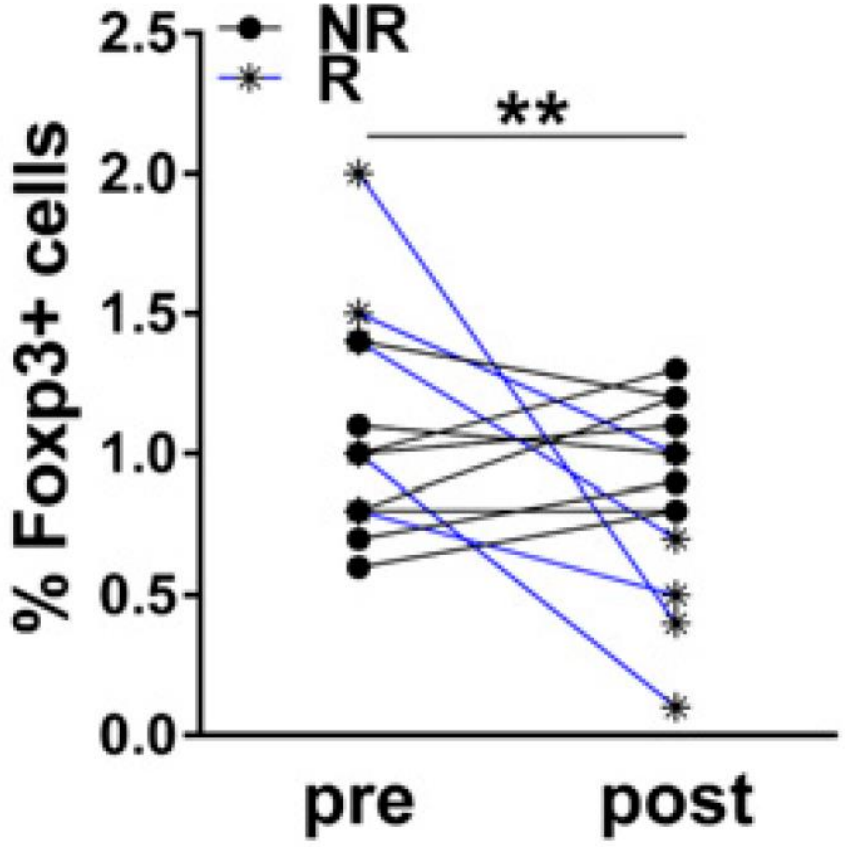
Ipilimumab (anti–CTLA-4): First in a New Class



Ipilimumab stimulates the immune system to destroy melanoma cells

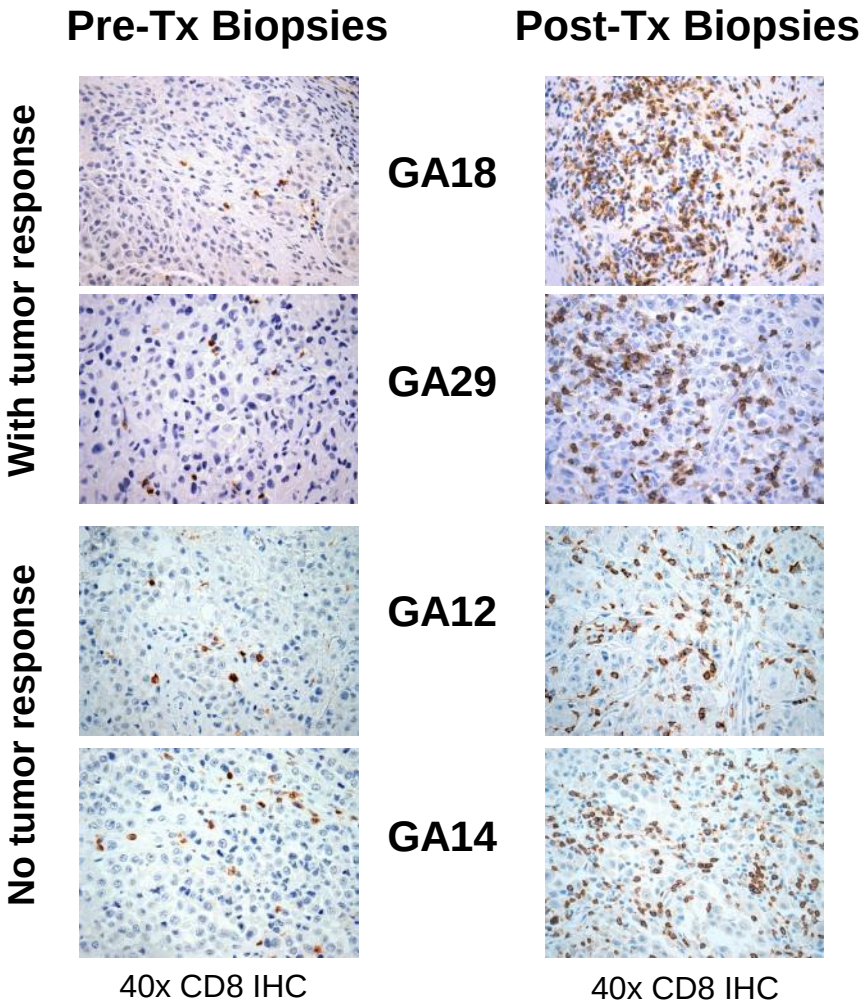
APC, antigen-presenting cell; CTL-A, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.
Adapted from Tarhini A, et al. *Cancer Biotherapy and Radiopharmaceuticlals.* 2010;25(6):601-613.

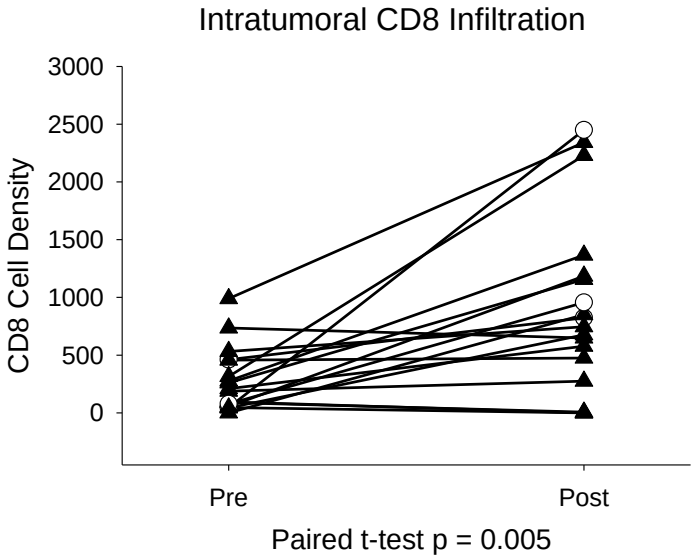
Ipilimumab Reduces Tregs in Responding Patients



Romano E et al. *Proc Natl Acad Sci U S A.* 2015;112(19):6140-6145.

Increase in TILs in Most Patients Treated with Anti-CTLA-4 (tremelimumab) Regardless of Tumor Response





CTLA-4 blockade brings T cells into tumors

Huang RR et al. *Clin Cancer Res.* 2011;17(12):4101-4109.

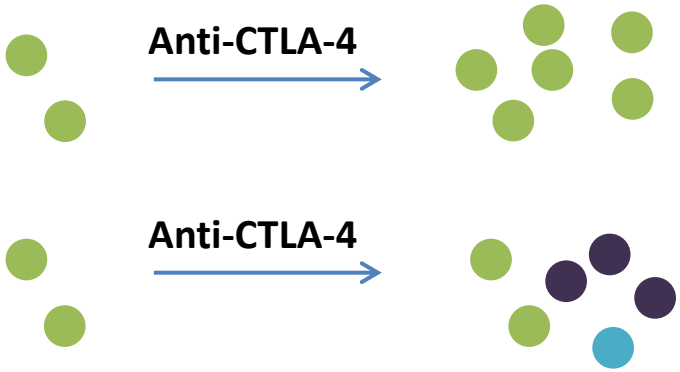
CTLA-4 Blockade Diversifies Peripheral T-cell Responses Without Expanding Pre-existing Ones

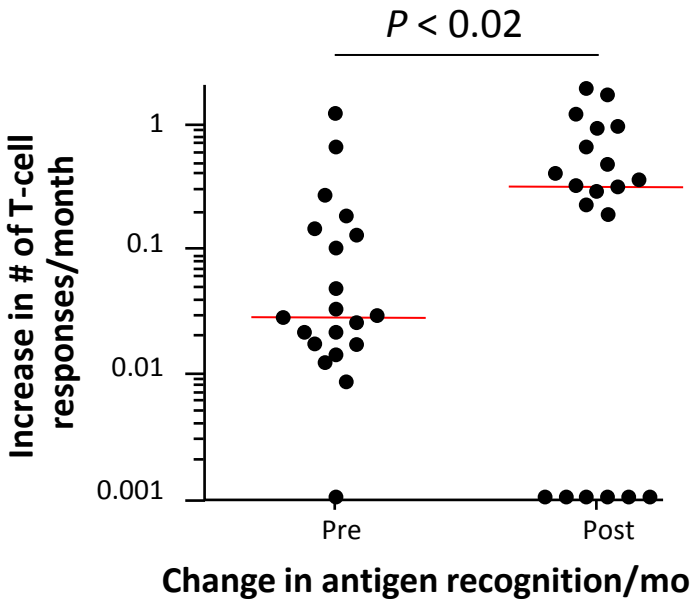
RESEARCH ARTICLE

IMMUNOTHERAPY

Anti–CTLA-4 therapy broadens the melanoma-reactive CD8$^+$ T cell response

Pia Kvistborg,[1]* Daisy Philips,[1] Sander Kelderman,[1] Lois Hageman,[1] Christian Ottensmeier,[2] Deborah Joseph-Pietras,[2] Marij J. P. Welters,[3] Sjoerd van der Burg,[3] Ellen Kapiteijn,[3] Olivier Michielin,[4] Emanuela Romano,[4] Carsten Linnemann,[1] Daniel Speiser,[4] Christian Blank,[1] John B. Haanen,[1†] Ton N. Schumacher[1*†]

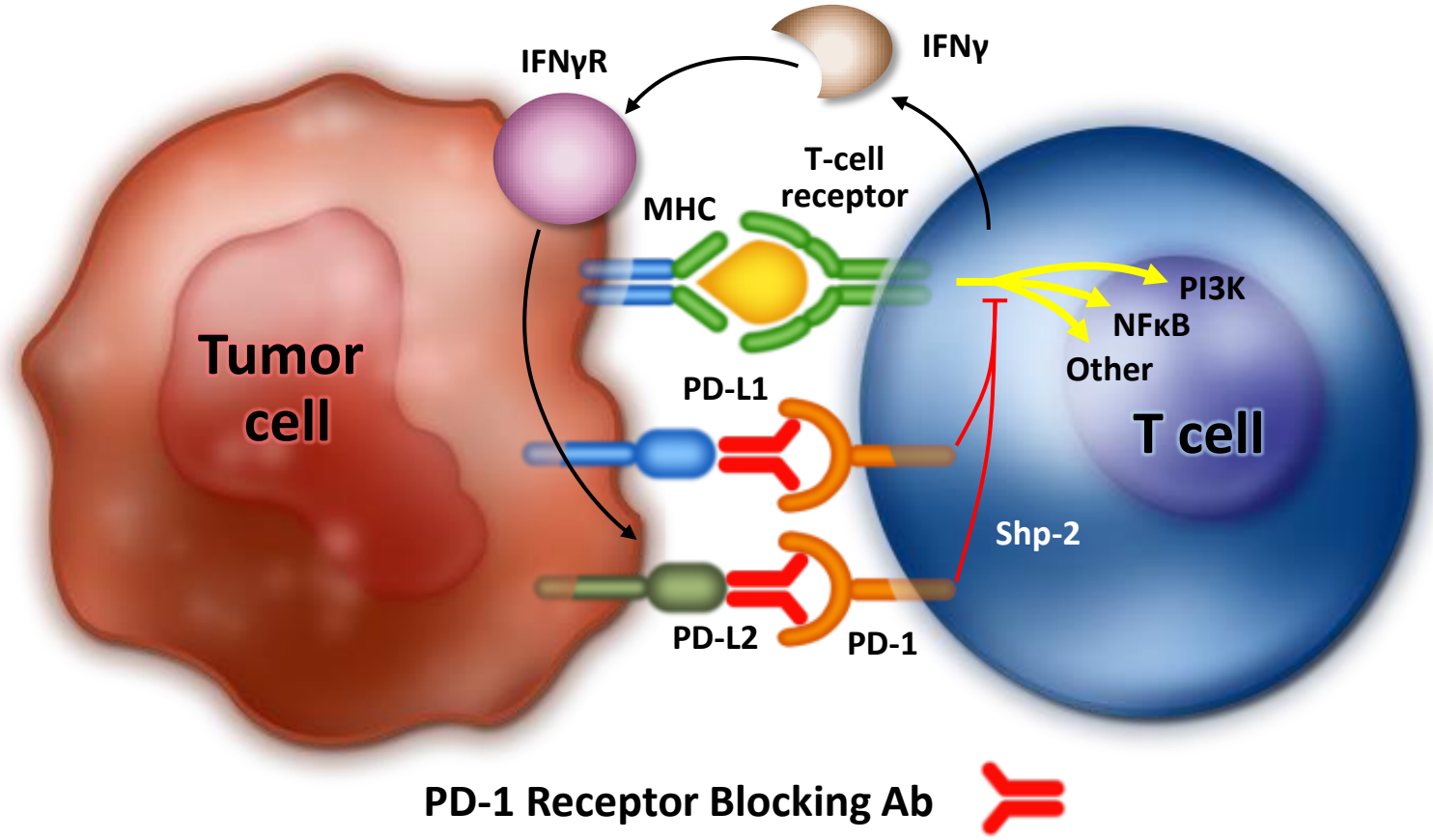




Kvistborg P et al. *Sci Transl Med.* 2014;6(254):254ra128.

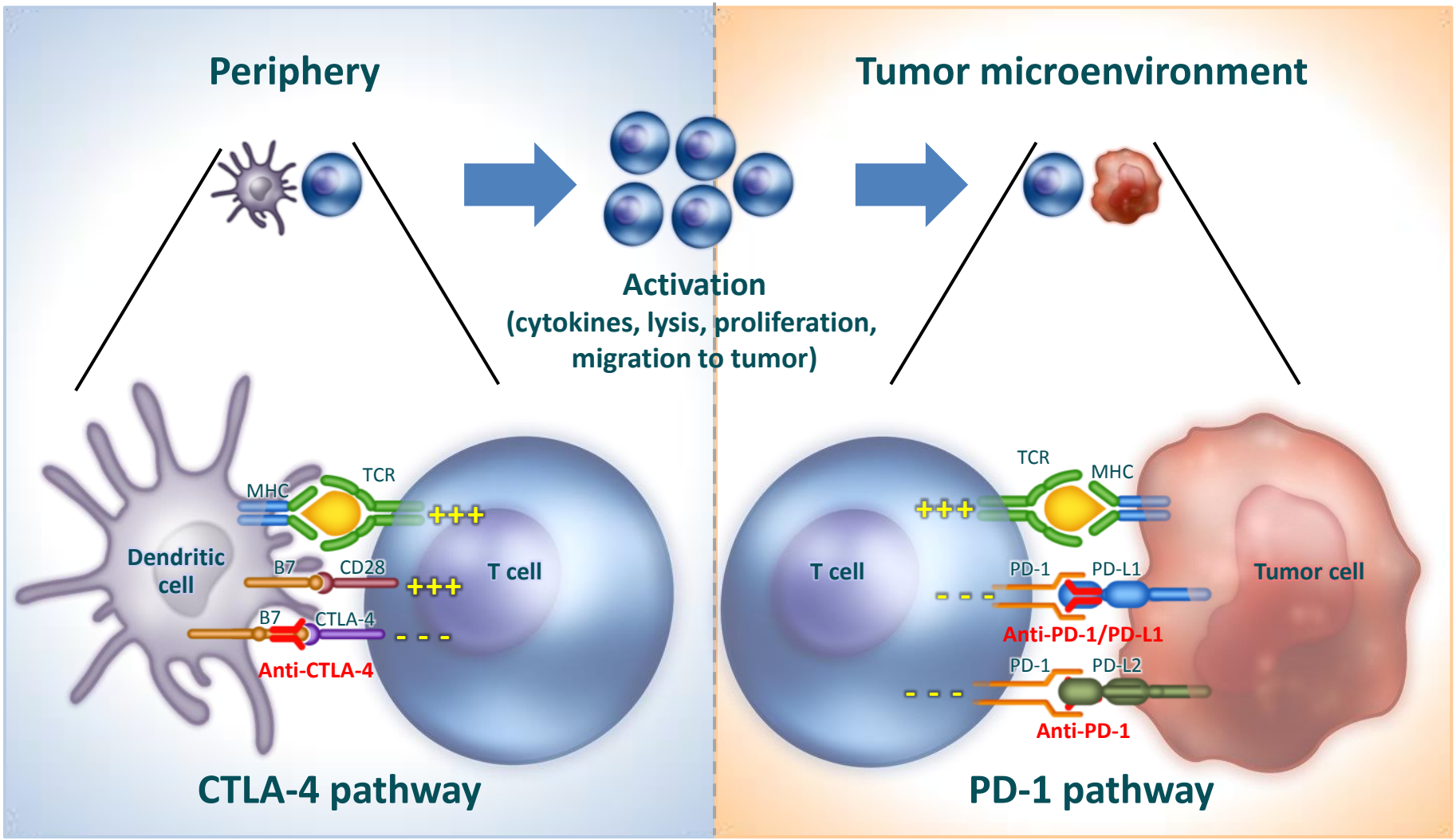
Anti-PD-1 Mechanism of Action

Overcoming Adaptive Immune Resistance



Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-64. Ribas A. *Cancer Discov.* 2015;5(9):915-919.

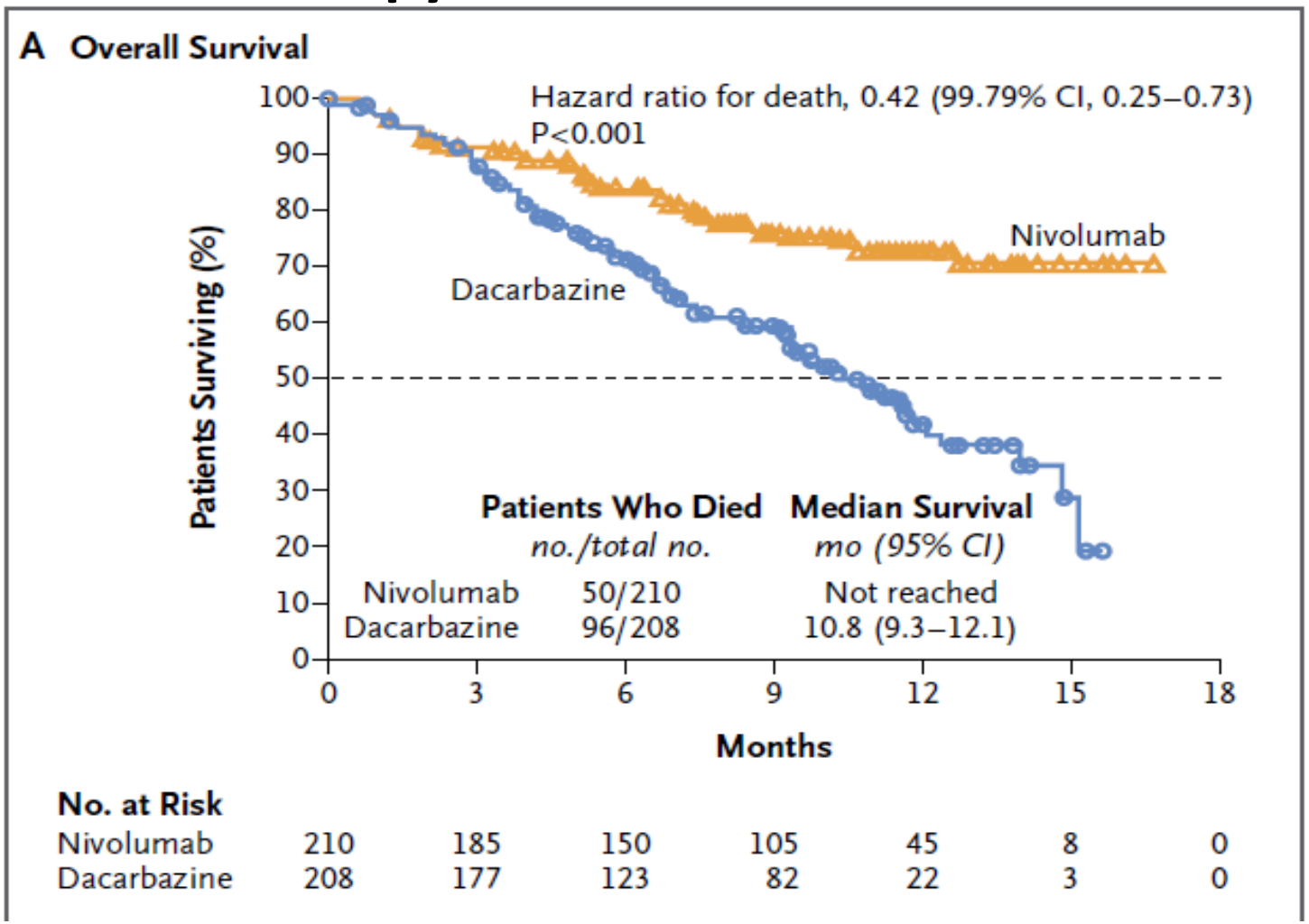
Combining Two Distinct Pathways:



Wolchok J et al. *J Clin Oncol.* 2013;31(15 suppl):abstract 9012.

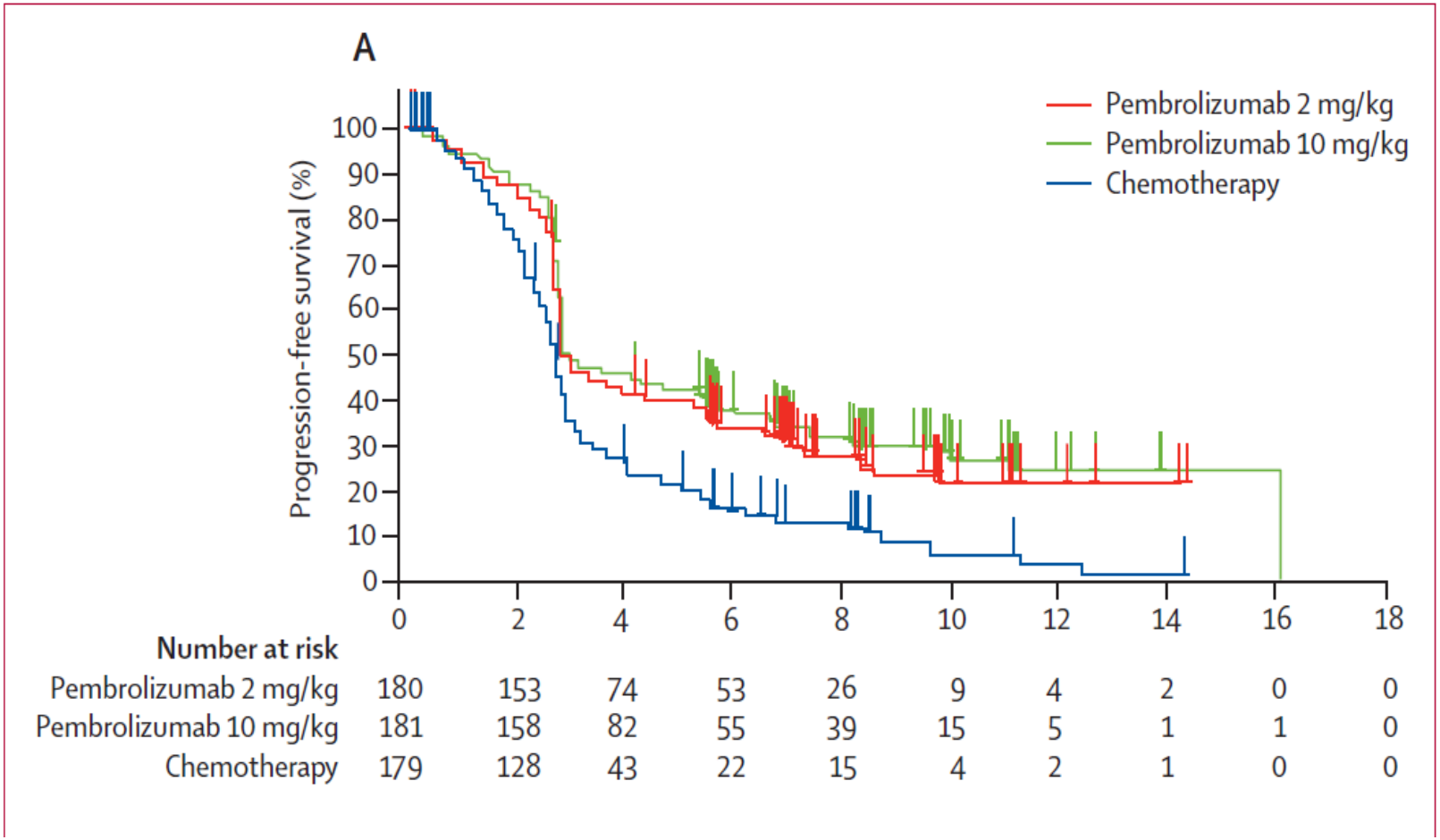
These theories have served us well!

Nivolumab Anti PD1 is better than DTIC in first line therapy of melanoma



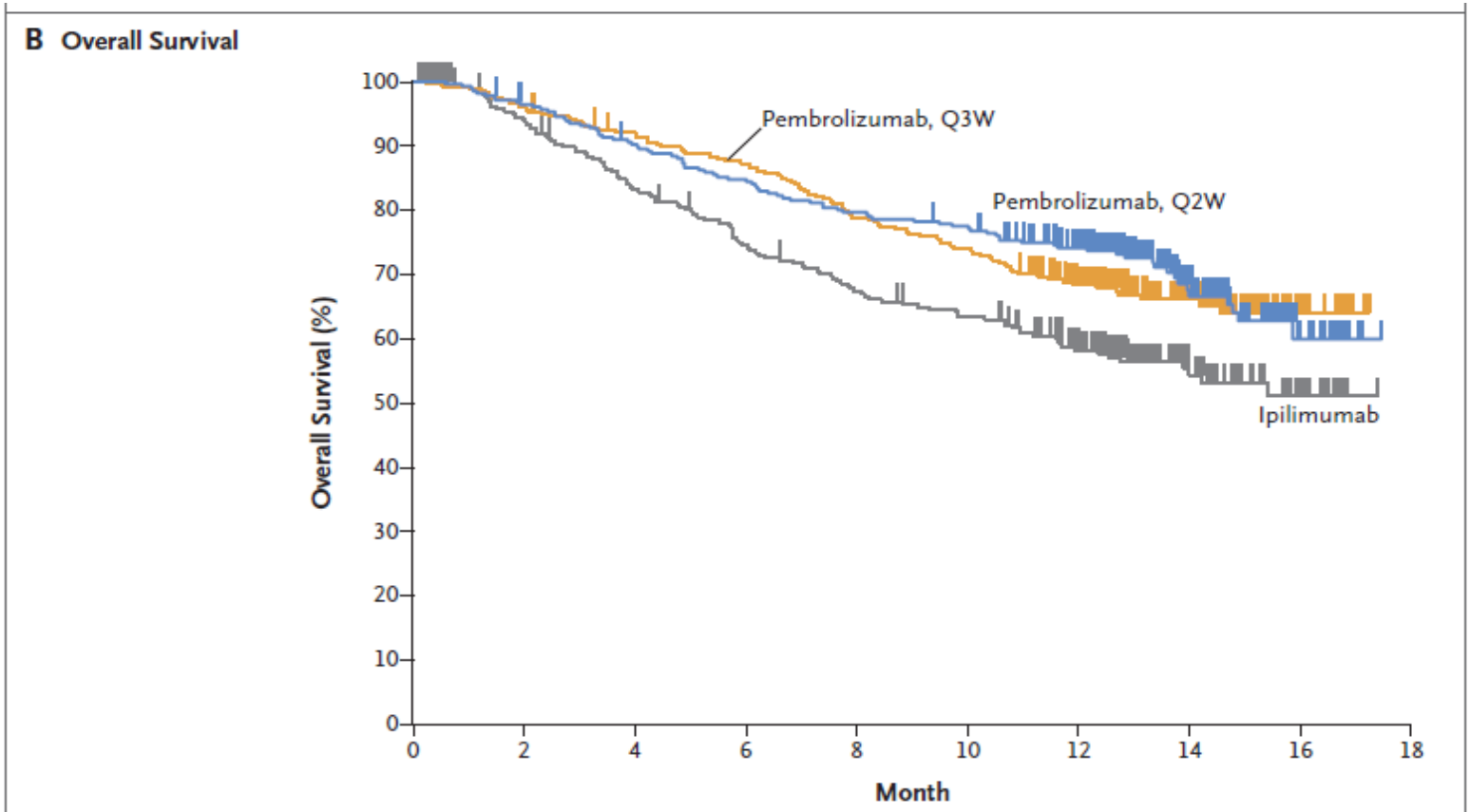
Robert et al NEJM 2015

Pembrolizumab Anti PD1 is better than chemotherapy in Second Line Therapy (Merck 002 trial)



Ribas et al. Lancet Oncology 2015

Anti PD1 is better than Ipilimumab in Treating Metastatic Melanoma



No. at Risk

Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.

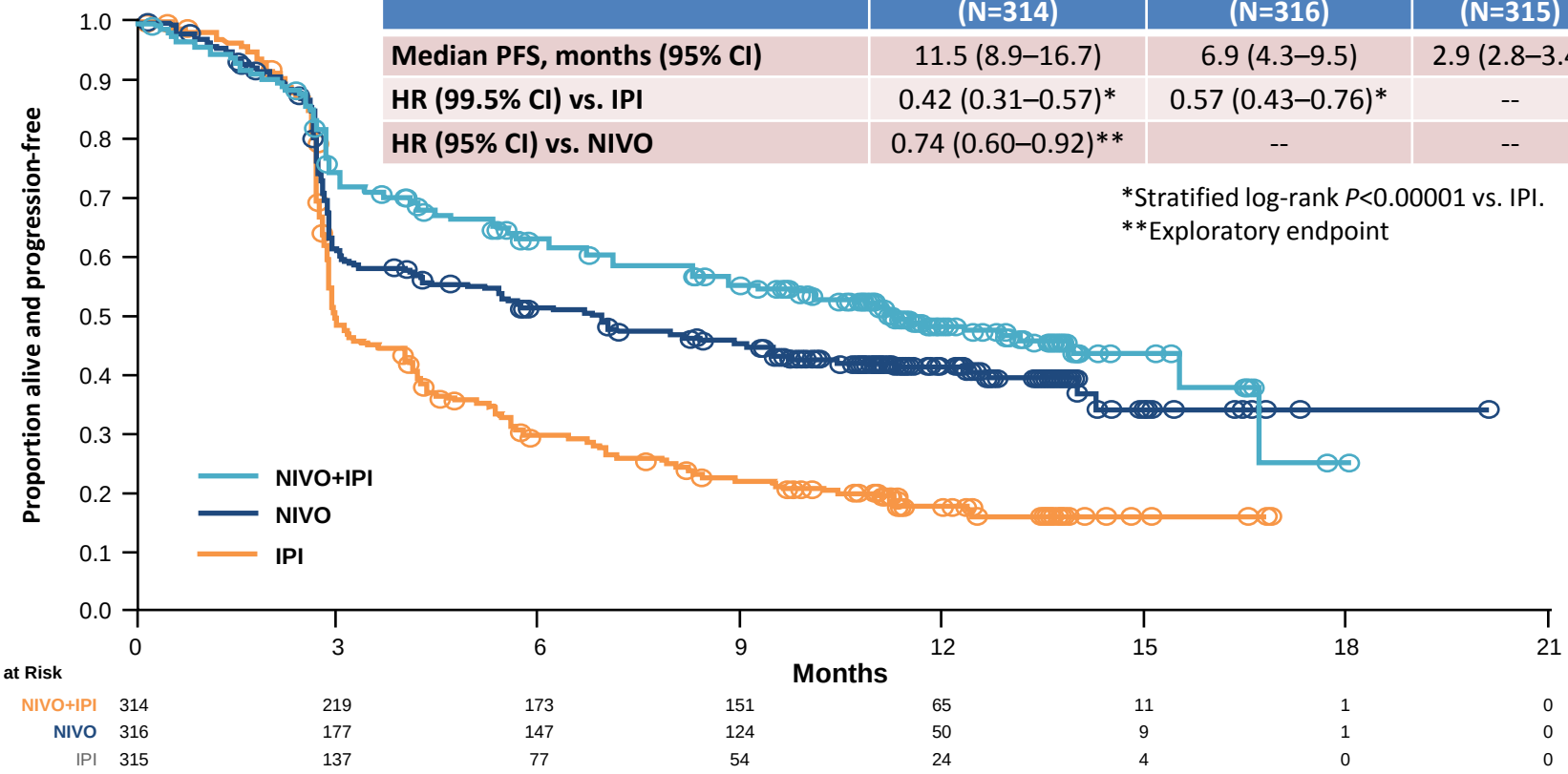
Shown are rates of progression-free survival as of September 3, 2014 (Panel A), and overall survival as of March 3, 2015 (Panel B), in the intention-to-treat population among patients receiving pembrolizumab every 2 weeks (Q2W) or every 3 weeks (Q3W) or ipilimumab.

Combinations of Nivolumab and Ipilimumab appear more effective than either alone

CheckMate 067: PFS (Co-Primary Endpoint)

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank *P*<0.00001 vs. IPI.
**Exploratory endpoint

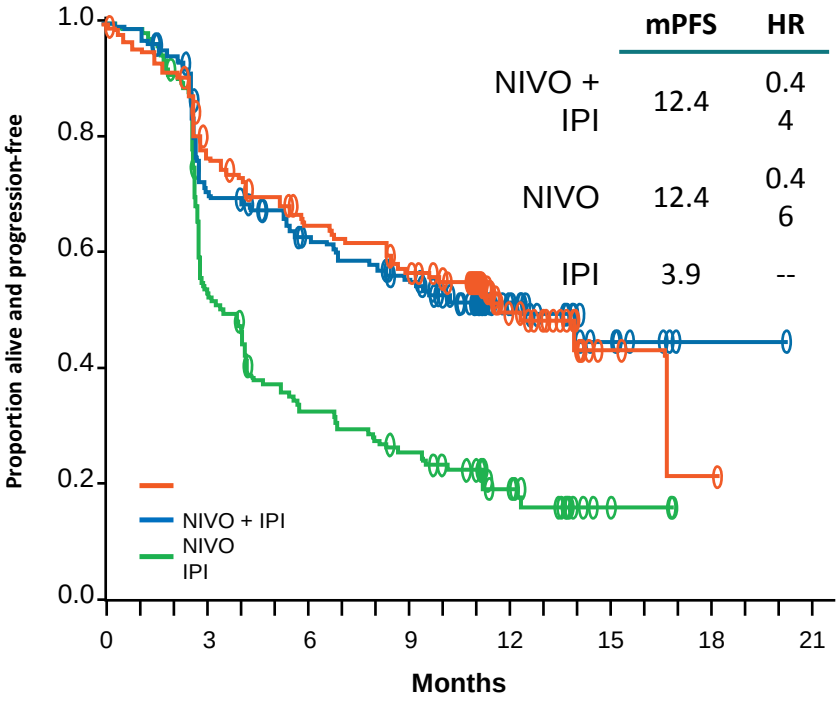


Both NIVO+IPI and NIVO alone showed a significantly greater PFS than IPI alone

Larkin J et al. Oral presentation at ECC 2015. Abstract 3303.

PFS by PD-L1 Expression Level (1%)

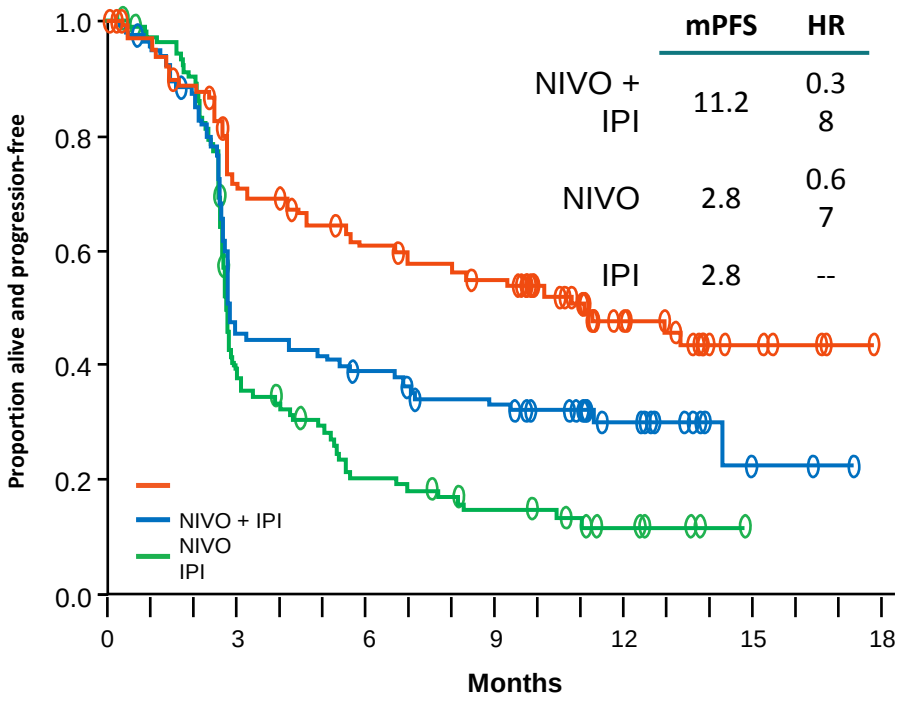
PD-L1 ≥1%*



	mPFS	HR
NIVO + IPI	12.4	0.44
NIVO	12.4	0.46
IPI	3.9	--

No. at Risk								
NIVO + IPI	155	113	91	78	32	4	1	
NIVO	171	115	97	83	34	7	1	0
IPI	164	83	47	36	16	3		

PD-L1 <1%*



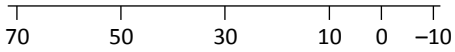
	mPFS	HR
NIVO + IPI	11.2	0.38
NIVO	2.8	0.67
IPI	2.8	--

No. at Risk							
NIVO + IPI	123	82	65	57	26	6	0
NIVO	117	50	42	34	13	2	0
IPI	113	39	19	12	5	0	

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

CheckMate 067: ORR in Patient Subgroups

	ORR (Patients)	Unweighted ORR Difference vs Ipilimumab (95% CI)
Total population	57.6% (314) 43.7% (316)	38.6% (31.3-45.2) 24.6% (17.5-31.4)
BRAF		
Wild type	53.3% (212) 46.8% (218)	35.6% (26.8-43.6) 29.1% (20.5-37.1)
Mutant	66.7% (102) 36.7% (98)	44.7% (31.5-55.6) 14.7% (2.0-26.8)
M stage		
M1c	51.4% (185) 38.9% (185)	37.1% (27.9-45.4) 24.6% (15.8-33.0)
Baseline LDH		
≤ULN	65.3% (199) 51.5% (196)	40.6% (31.1-48.9) 26.8% (17.3-35.6)
>ULN	44.7% (114) 30.4% (112)	35.2% (24.1-45.2) 20.8% (10.5-30.7)
>2× ULN	37.8% (37) 21.6% (37)	37.8% (20.0-53.9) 21.6% (6.3-37.2)
Age, years		
≥65 and <75	57.4% (94) 48.1% (79)	39.5% (25.8-51.0) 30.1% (16.0-42.8)
≥75	54.3% (35) 43.6% (39)	27.0% (5.3-45.8) 16.3% (–4.1-35.2)
PD-L1 expression level		
<5%	54.8% (210) 41.3% (208)	36.9% (28.0-45.0) 23.5% (14.8-31.8)
≥5%	72.1% (68) 57.5% (80)	50.7% (35.0-62.8) 36.2% (21.0-49.0)



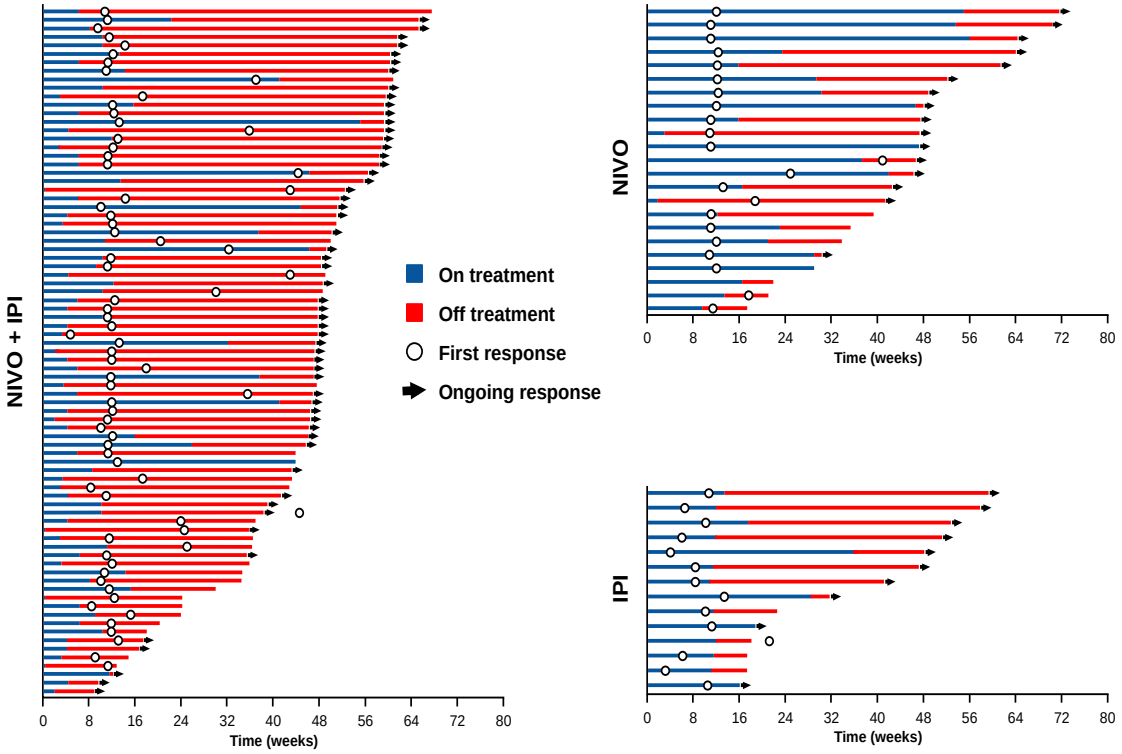
Nivolumab or nivolumab + ipilimumab better ⟷ Ipilimumab better

Nivolumab + ipilimumab — Nivolumab

Larkin J et al. Oral presentation at ECC 2015. Abstract 3303.

CheckMate 067: Durability of Response in Patients Who Discontinued Due to Toxicity

- 68% (81/120), 85% (23/27), and 30% (14/47) of patients who discontinued NIVO+IPI, NIVO, and IPI, respectively, due to drug-related toxicity, experienced a complete or partial response

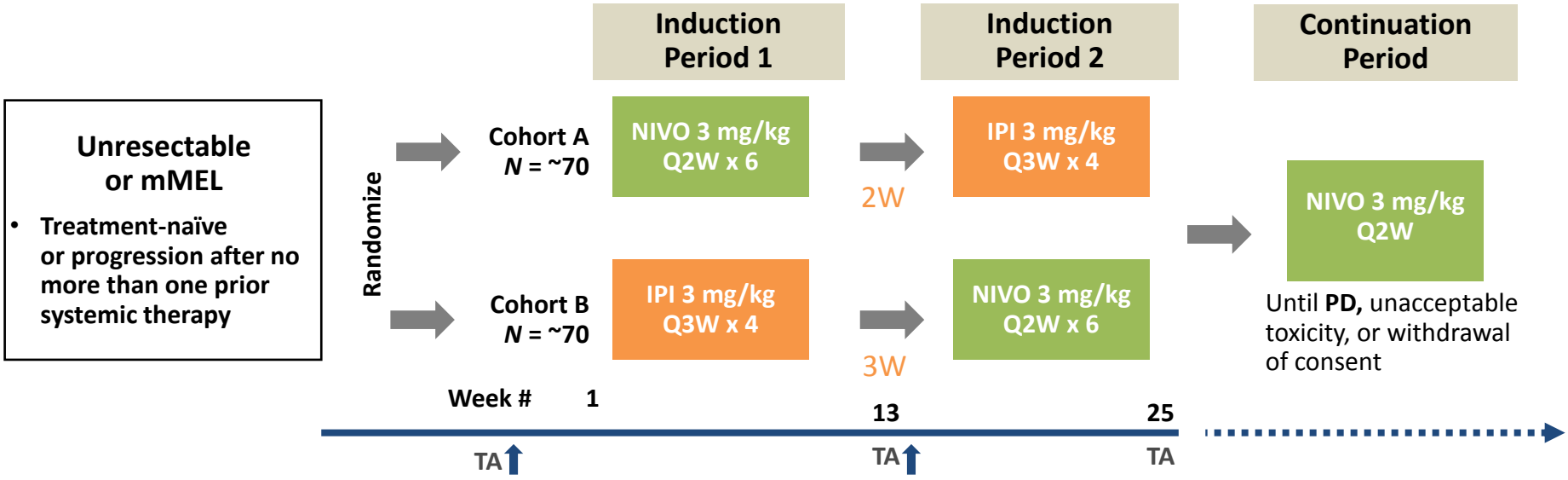


Larkin J et al. Oral presentation at ECC 2015. Abstract 3303.

How Do We Progress From Here?

- Should we sequence treatment with the agents to reduce toxicity?

064 study. Randomized, Open-Label, Phase 2 Study Evaluating the Safety and Efficacy of NIVO and IPI Sequentially with Planned Switch



Primary endpoint: Incidence of treatment-related Grade 3-5 AEs during induction periods in both cohorts

Secondary endpoints: Confirmed ORR at Week 25* and progression rates (Week 13 and Week 25)

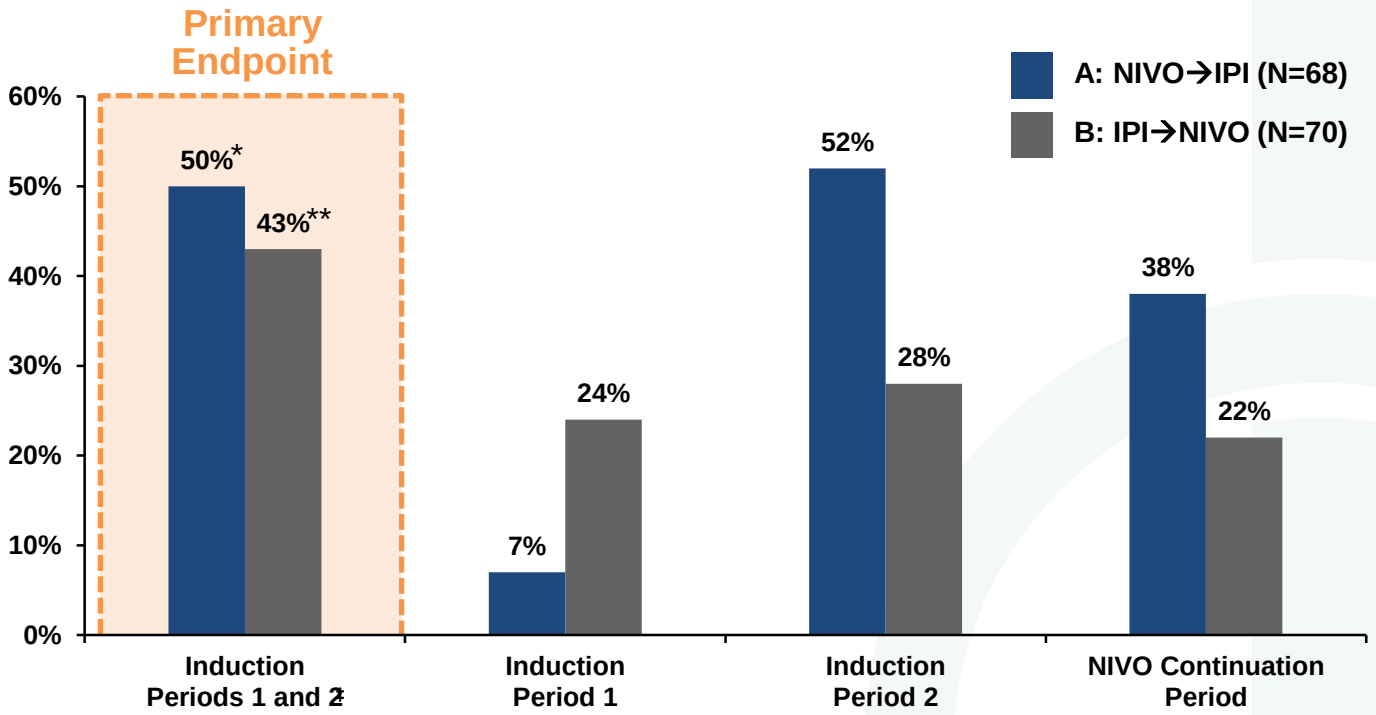
Exploratory endpoints: Safety and tolerability during the different treatment periods, pharmacodynamic immune biomarkers, OS

TA = tumor assessment; ⇑ = biopsy timepoint; **PD** = progressive disease.

* By modifed RECIST v 1.1. Week 25 scan reflected back to baseline for determining response, with confirmation at Week 33. Database lock; May 22, 2015.

Hodi FS et al. Oral presentation at ECC 2015. 23LBA.

CheckMate 064: Treatment-Related Grade 3-4 AEs



- There were no study drug-related deaths in either cohort
- Treatment-related Grade 3-4 AEs leading to discontinuation Cohort A: **24%**, Cohort B: **27%**

*95% CI: 37.6%–62.4%. **95% CI: 31.1%–55.3%. [‡]AEs are counted only once for both induction periods.
Hodi FS et al. Oral presentation at ECC 2015. 23LBA.

Appears no benefit in sequencing Nivolumab and Ipilimumab?

	CheckMate 064[1] (N = 138)		CheckMate 067[2] (N=945)
	NIVO with planned switch to IPI (n = 68)	**IPI with planned switch to NIVO** (n = 70)	**NIVO + IPI** (n = 314)
ORR, %	41.2	20	58
Treatment-related Grade 3-4 AEs, %	50	43	55

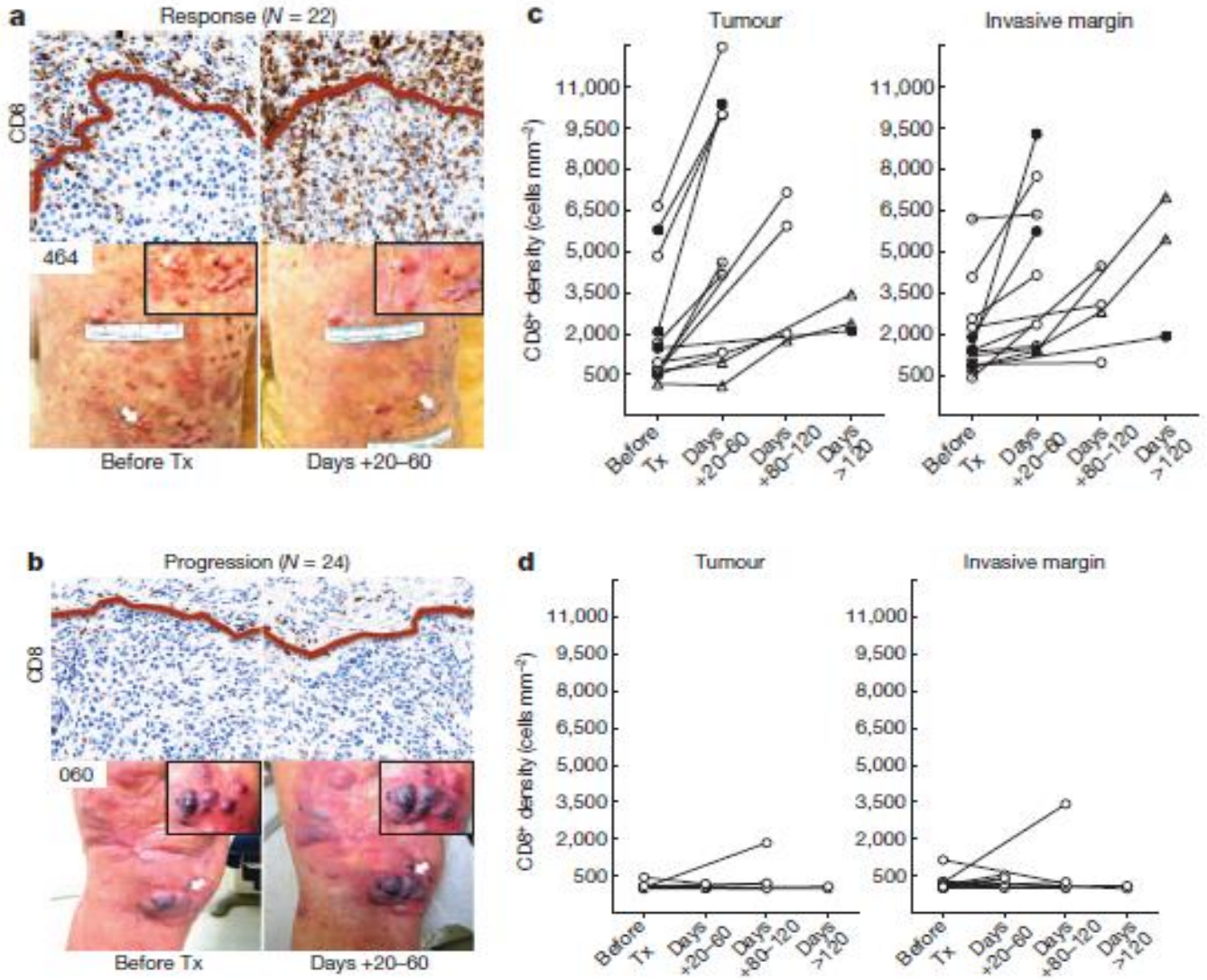
1. Hodi FS et al. Oral presentation at ECC 2015. 23LBA. 2. Larkin J et al. Oral presentation at ECC 2015. Abstract 3303.

CURRENT LIMITATIONS OF ANTI PD1/PD-L1 TREATMENTS -The Task ahead

- 30% do not respond , 20% SD only
- Most responses are partial and not complete
- Relapse rates at 2 years ~40 %

Responses to checkpoint inhibitors depend on TILs

Responses to anti PD1 depends on T cells
Tumeh et al Nature 2014



Can we use Immuno-profiling to target therapies to individual patients

FOUR GROUPS OF MELANOMA PATIENTS BASED ON TIL and PD-L1 EXPRESSION

- Group 1. PD-L1+, TIL + ~30% (Type 1)
- Group 2 PD-L1-,TIL + ~20% (Type4)
- Group 3 PD-L1+, TIL- ~5% (Type 3)
- Group 4 PD-L1-,TIL- ~42% Type 2)

- Jason Madore et al Pigment cell and Mel Res

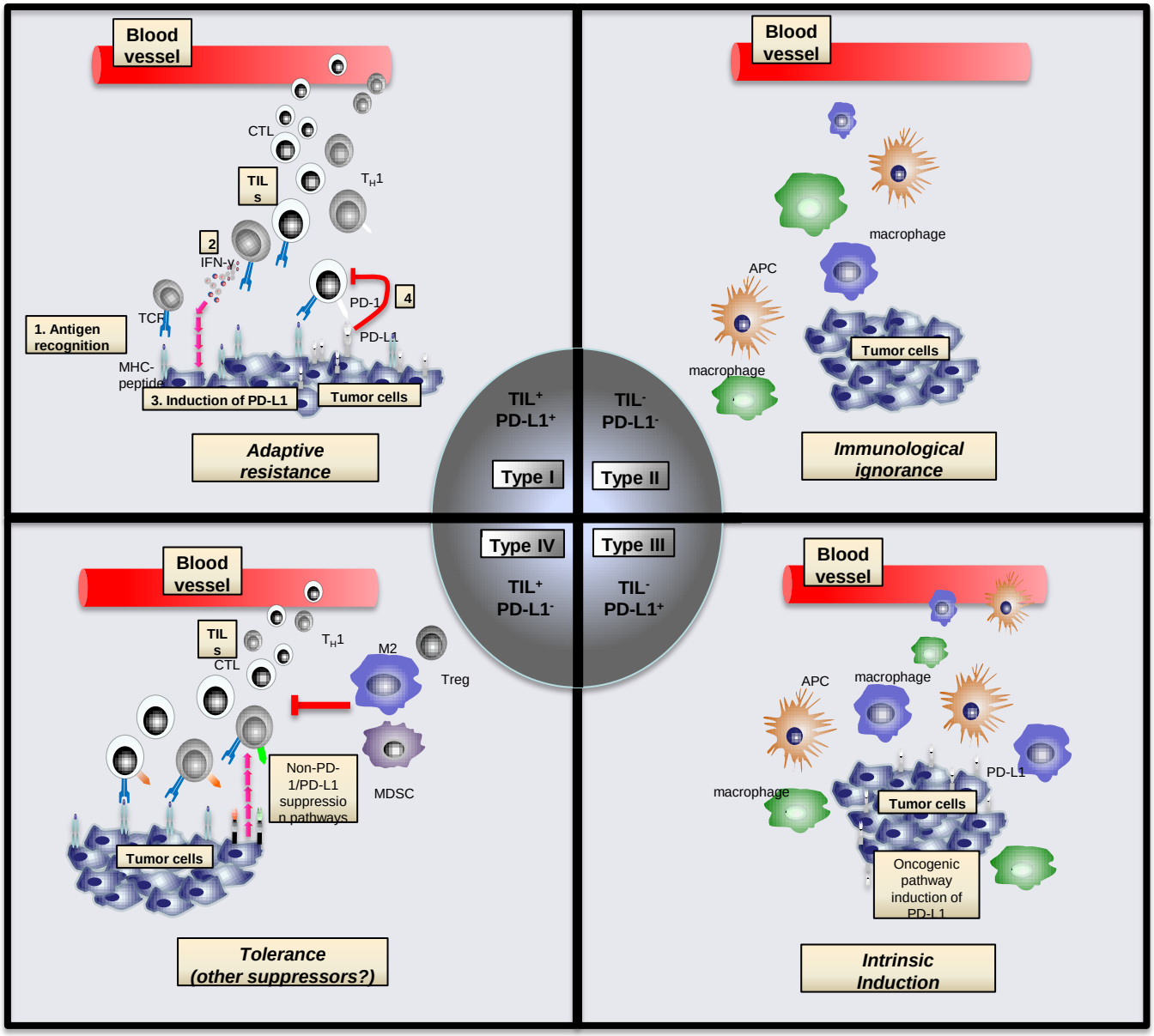
Classification of cancers depending on T cell infiltration and PD-L1 expression

35%

40%

20%

5%



Classification adapted from Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. Clinical Cancer Research 2013;19 (5): 1021-34.

Teng MW, Ngiow SF, Ribas A, Smyth MJ. Cancer Res 2015

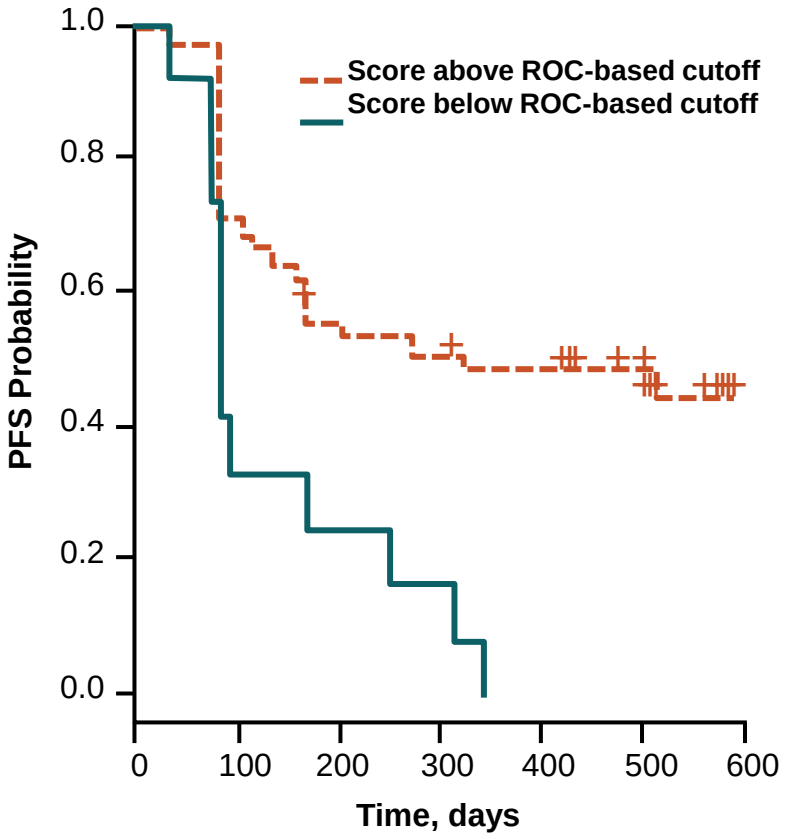
Taube et al

Future Immuno-Profiling

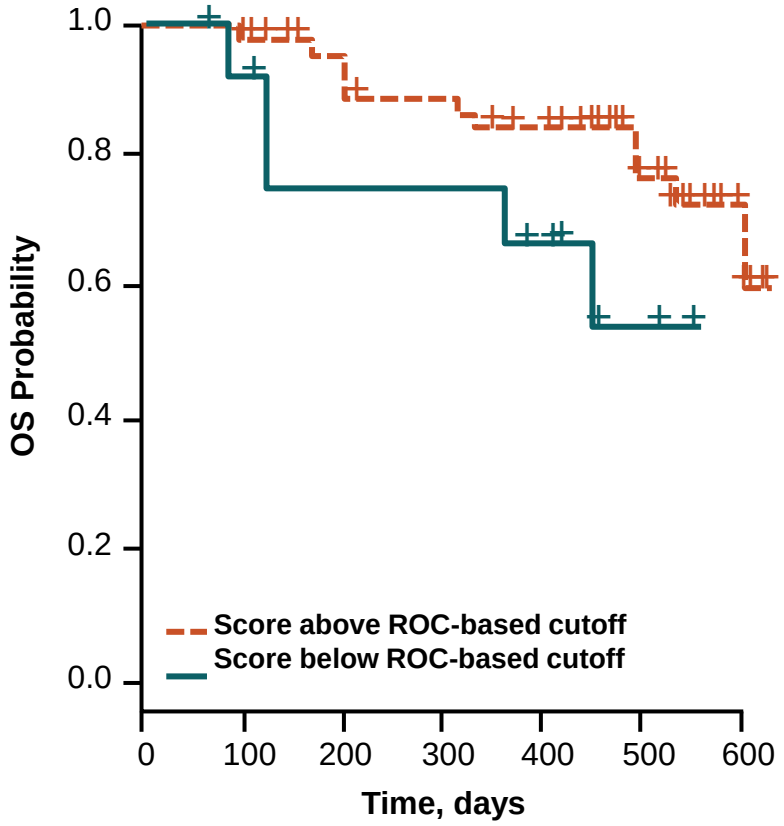
- Can we make it more mechanistic?
- ?Whole genome sequencing combined with Nano string profiling of the tumor.eg mutation rate and sites
- ? Multi parameter profiling of lymphocytes in the circulation for adhesion factors, chemokine receptors ,subsets etc(Fazekas et al)

PFS and OS in Patients With Melanoma and IFNγ Signature Score Above and Below the Cutoff

PFS by RECIST v1.1



Overall Survival



Ribas et al 2015

PRESENTED AT: ASCO Annual '15 Meeting

Focusing On Type 2. What Induces T Cell Responses into Tumors?

- Type 1 Interferon gene signatures associated with TILs (Gajewski and Colleagues)
- May depend on activation of STING pathway in CD103 DC and cross presentation in LNs
- Practical application in combination with Oncolytic viruses

  or radiotherapy

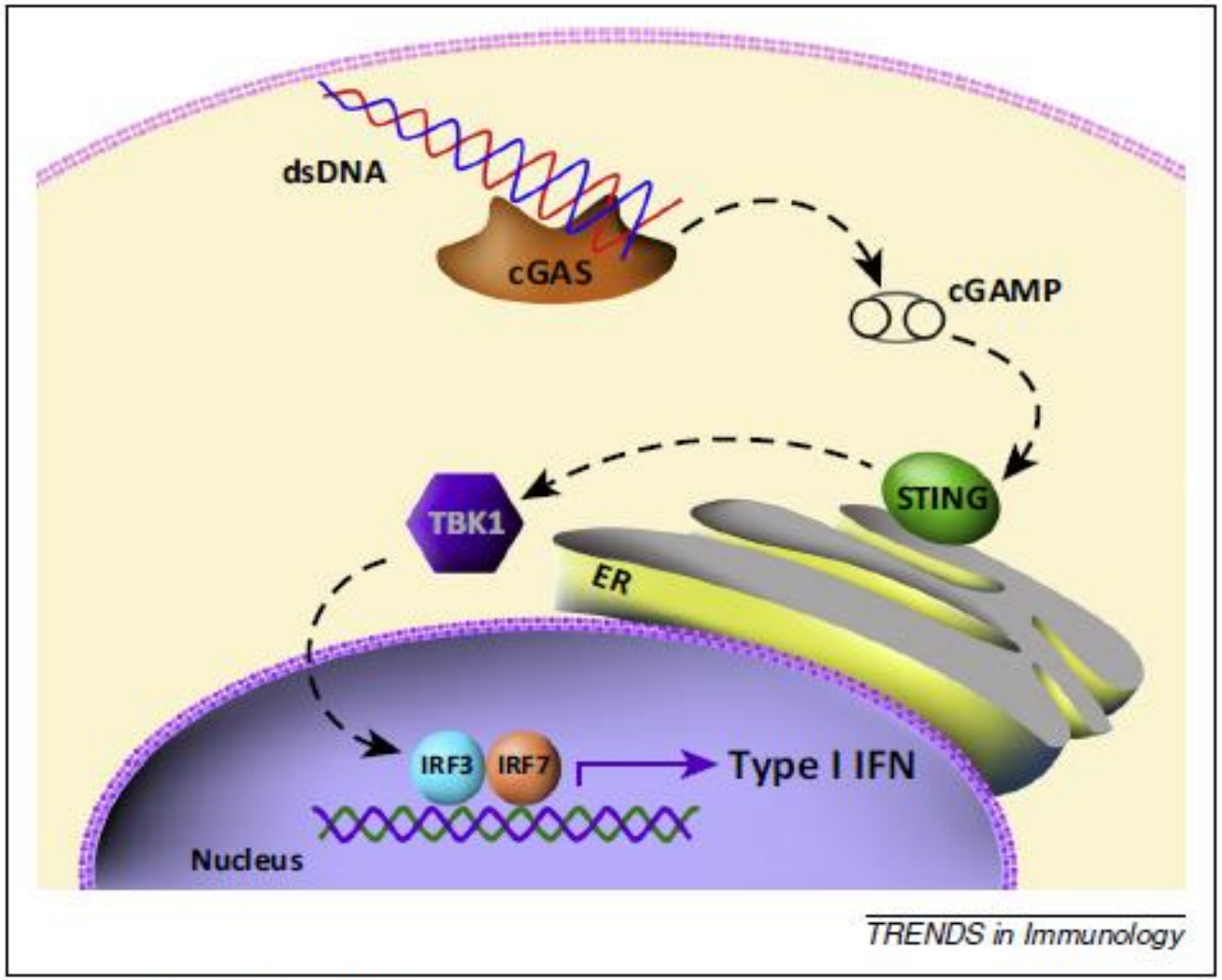


Figure 1. Model for STING (stimulator of interferon genes) pathway activation by cytosolic double-stranded (ds) DNA. The appearance of DNA in the cytosol

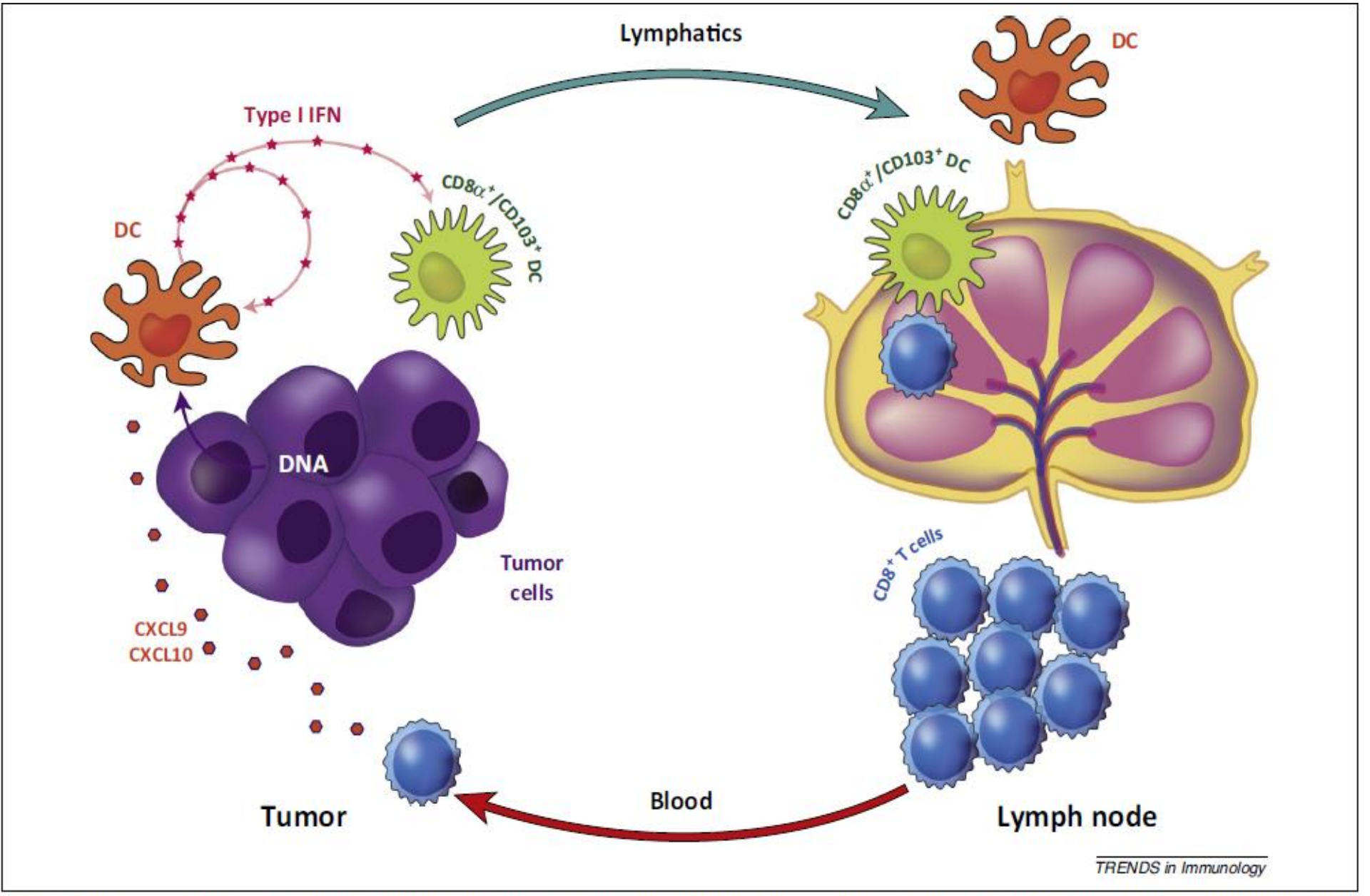
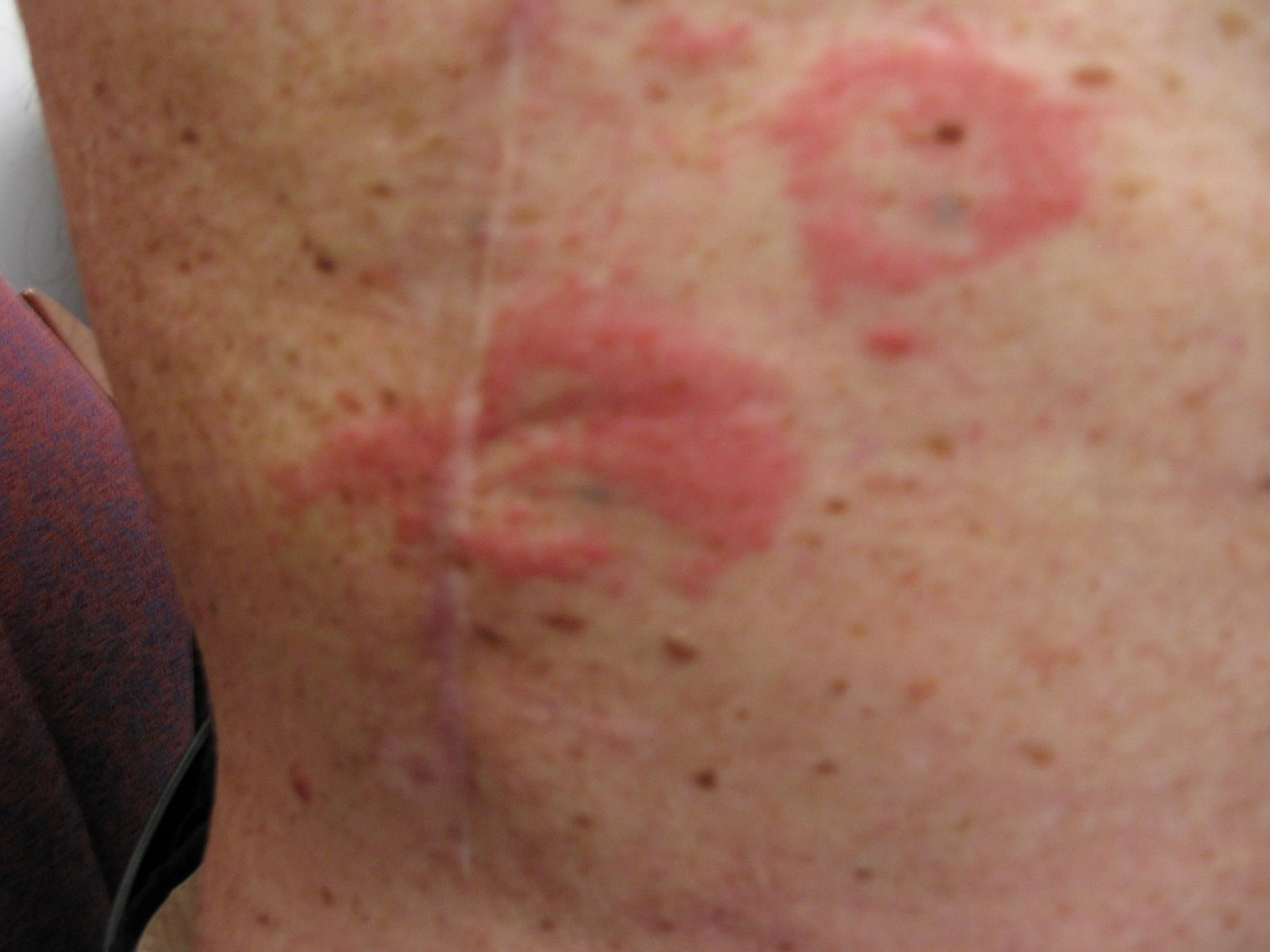


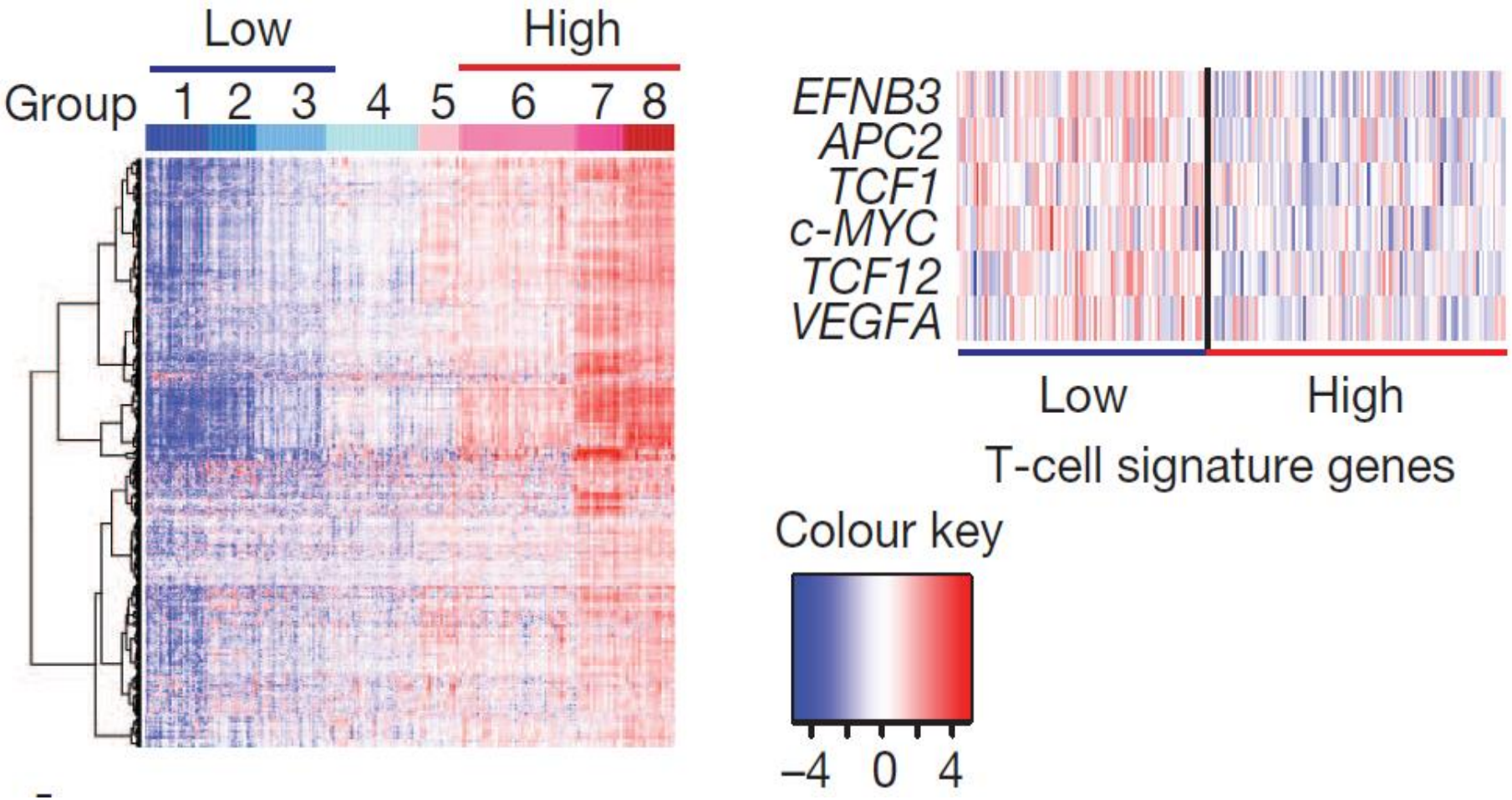
Figure 2. Working model for innate immune sensing leading to spontaneous antitumor T cell responses *in vivo*. Tumor-derived DNA, presumably generated during tumor

Are Type 2 (TIL-,PD-L1-)responses due to Inhibitory cytokines?

- Melanoma can release high levels of inhibitory cytokines
- Beta Catenin pathway in melanoma possibly one inhibitory factor(Spranger etal Nature 2015)

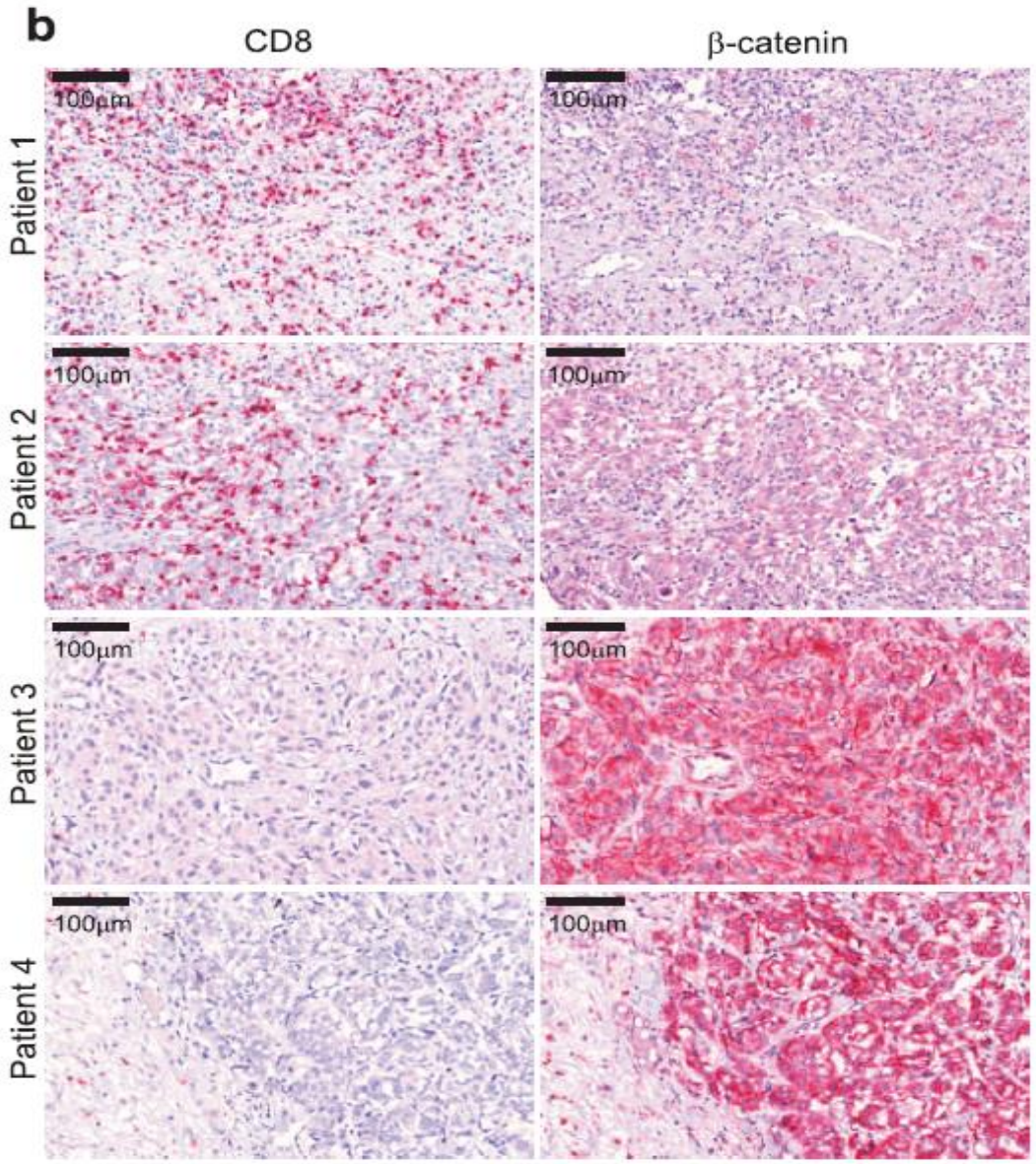


Gajewski-TCGA data mining shows low TILs in high Beta Catenin melanoma

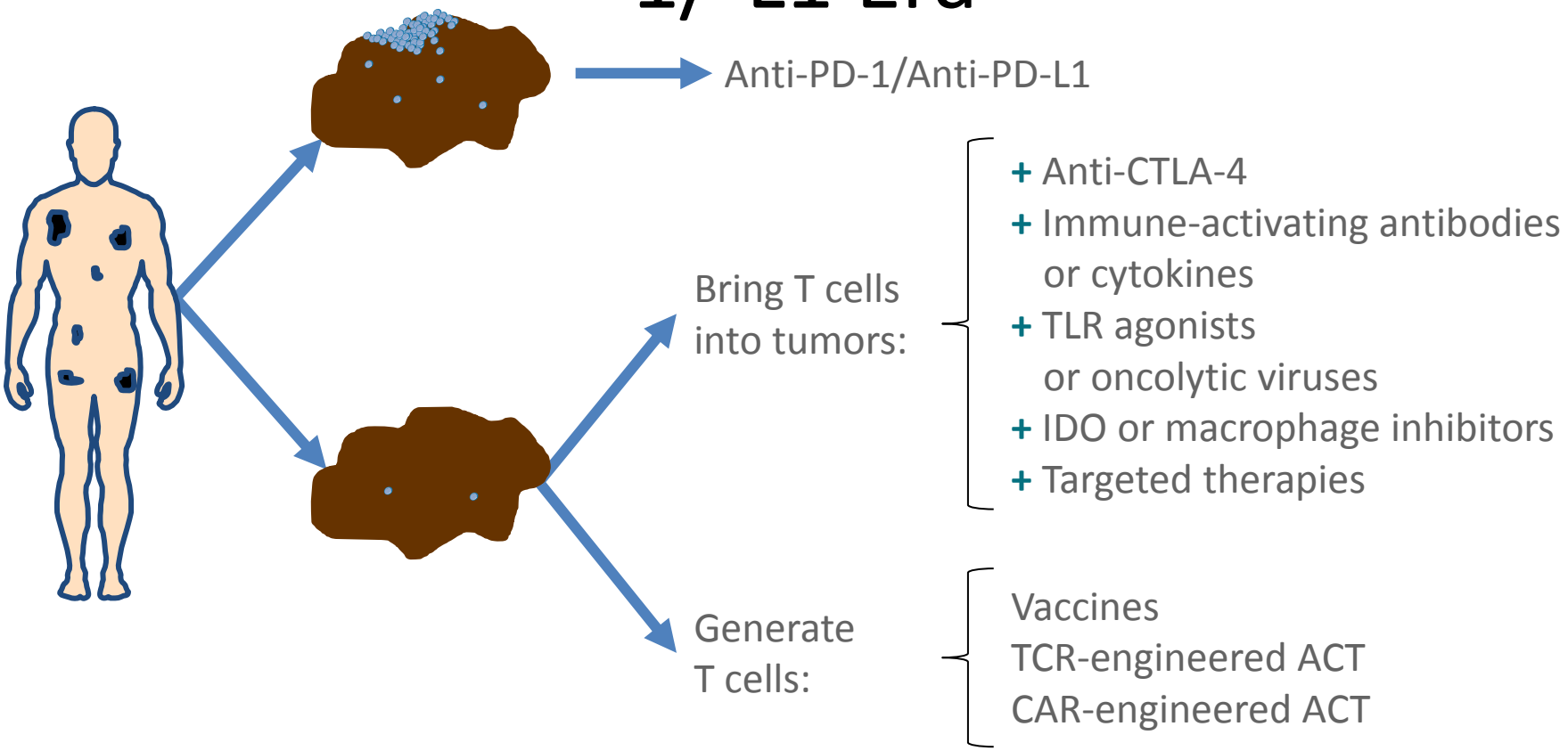


Spranger et al 2015

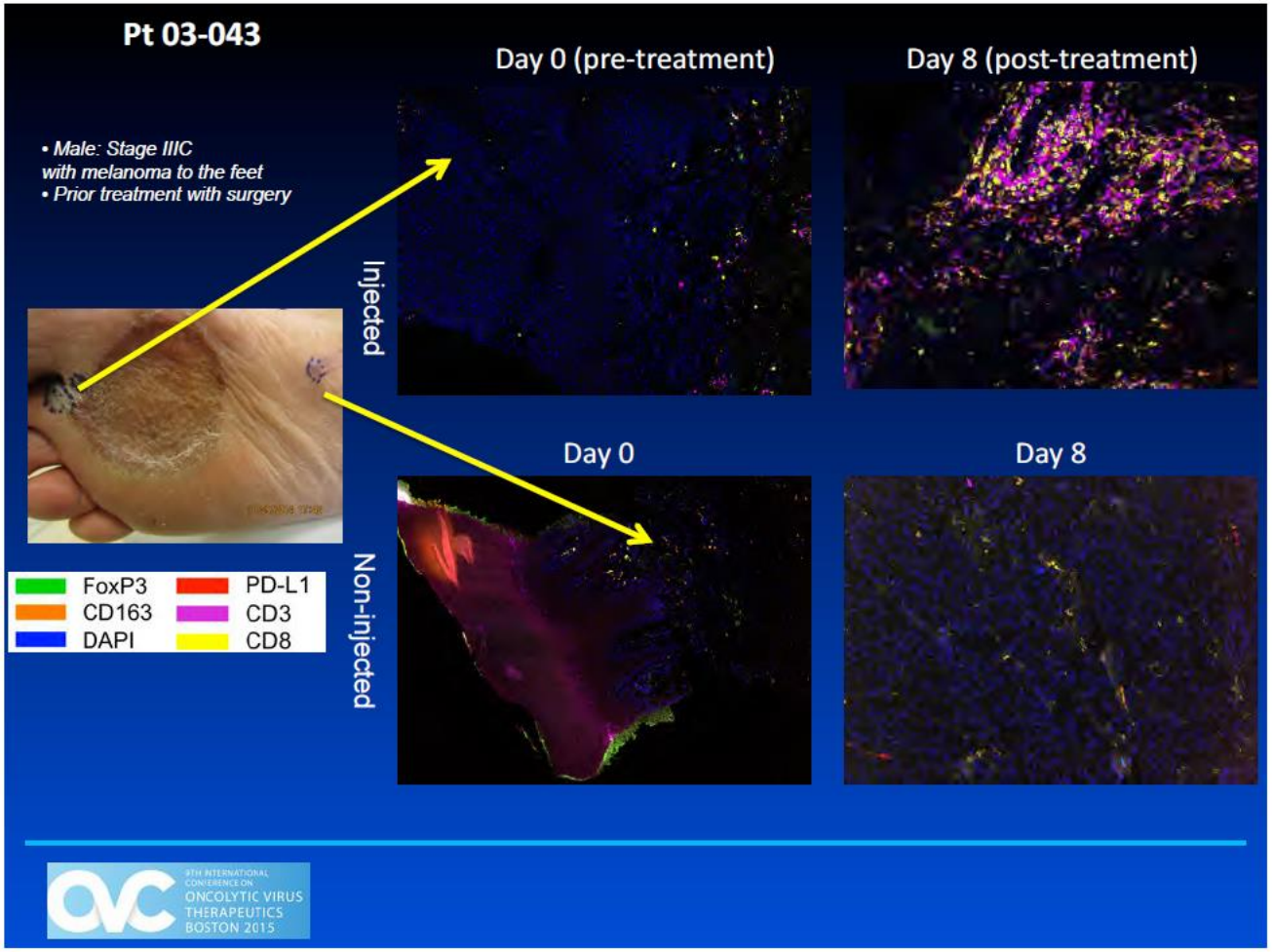
B Catenin Levels Inversely related to TIL in melanoma (Spranger et al 2015)



Management of Cancer in the Anti-PD-1/-L1 Era

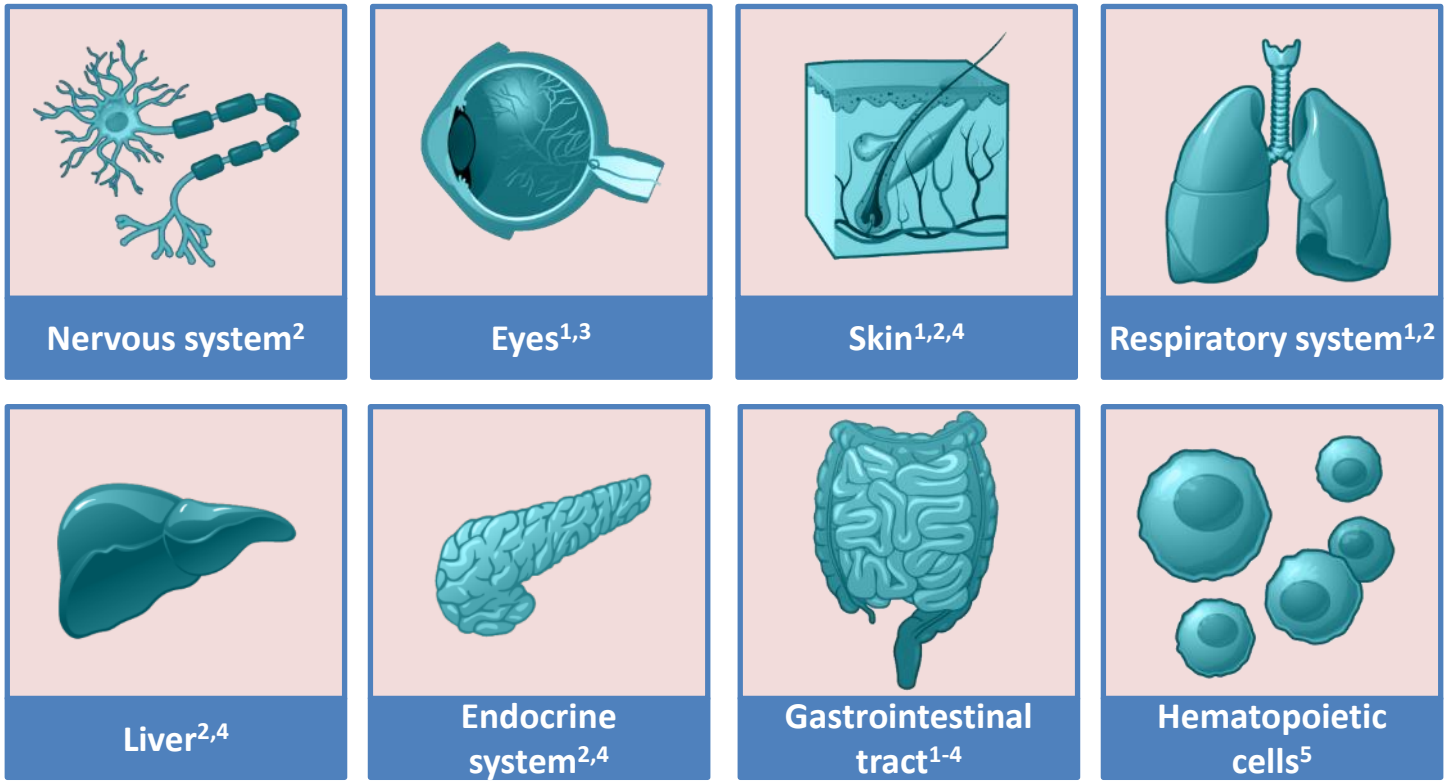


Intralesional Coxackie A21 Increases TILs In Melanoma (Daren Shafren)



What About the Problem of Auto Immune Side Effects

Immune-Mediated Adverse Reactions

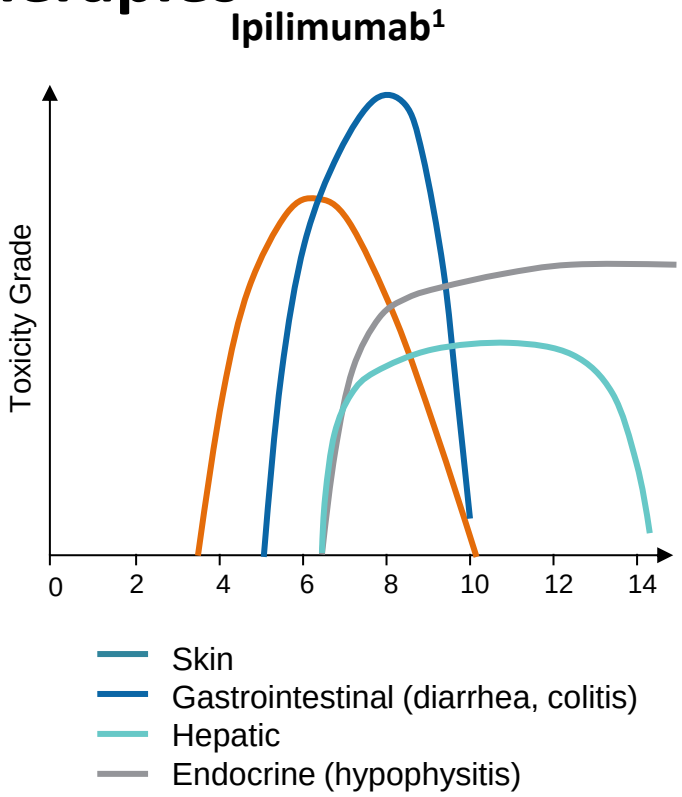


Immune activation, as a result of modulating T-cell activity, may lead to immune-mediated adverse reactions that affect certain organ systems[1]

1. Amos SM et al. *Blood*. 2011;118(3):499-509. 2. Chow LQ. *Am Soc Clin Oncol Educ Book*. 2013:280-285. 3. Robinson MR et al. *J Immunother*. 2004;27(6):478-479. 4. Phan GQ et al. *Proc Natl Acad Sci U S A*. 2003;100(14):8372-8377. 5. Lin TS et al. *J Clin Oncol*. 2010;28(29):4500-4506.

Early Diagnosis and Appropriate Management Are Essential for I-O Therapies

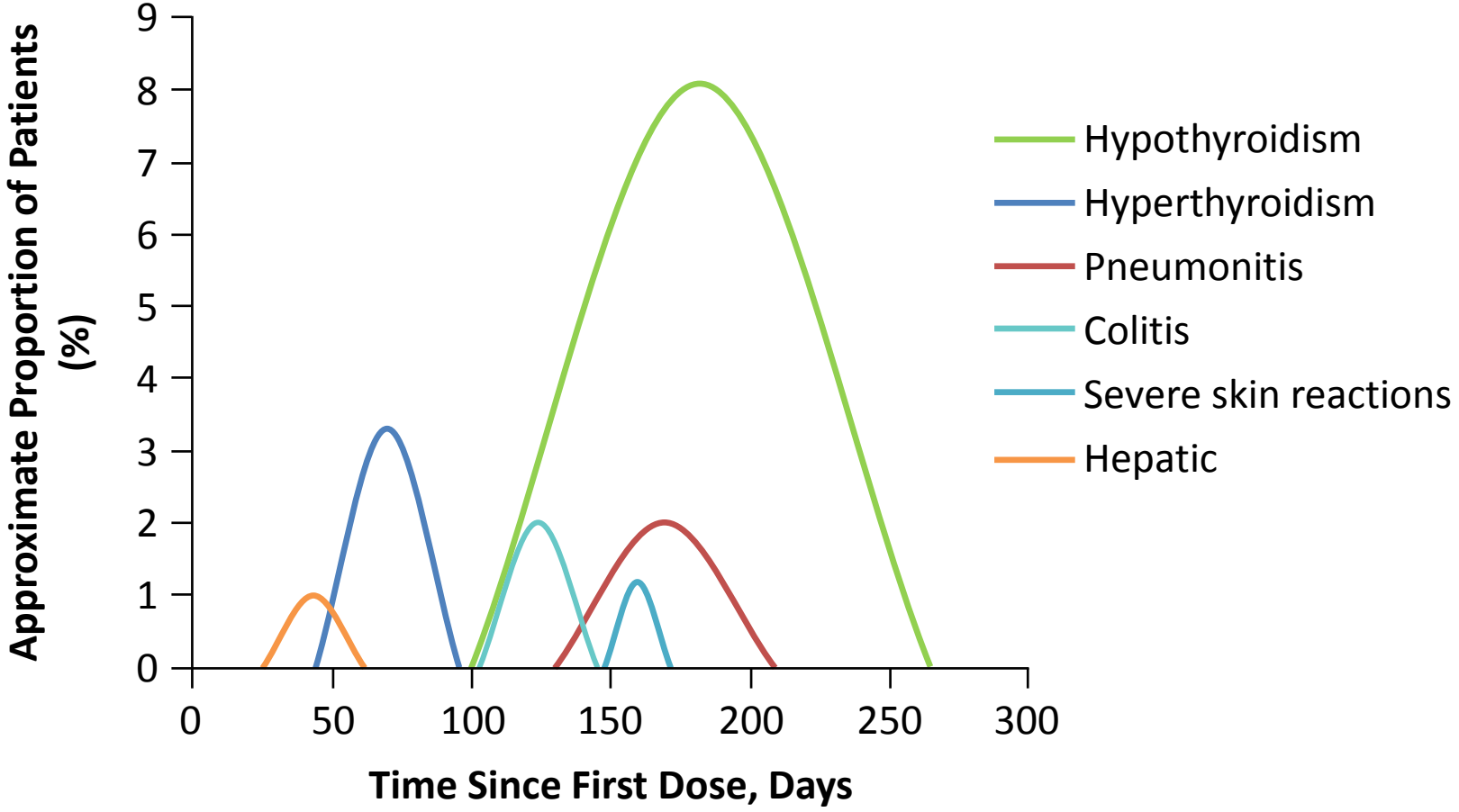
- Frequent monitoring and early recognition[1]
- Patient education and assessment for appropriate signs/symptoms[2,3]
- Most AEs grade 1–2[1,4-11]
  - In rare cases, AEs can be serious or life-threatening
- imARs are well-characterized, medically manageable, and typically reversible using established algorithms[12]



imAR=immune-mediated adverse reactions.

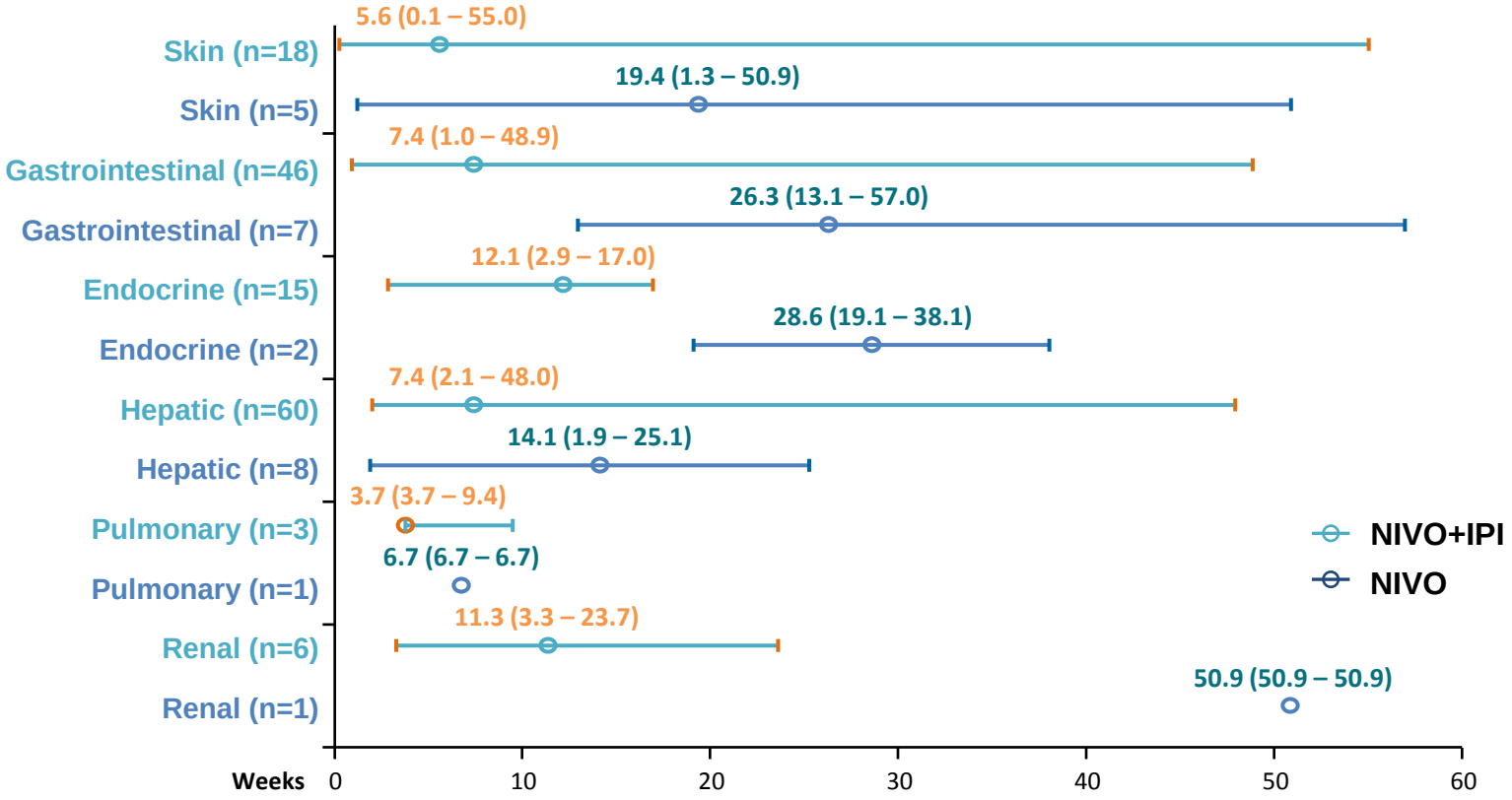
1. Weber J, et al. *J Clin Oncol.* 2012;30:2691–2697. 2. Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at www.yervoy.co.uk/. 3. Bristol-Myers Squibb. YERVOY (ipilimumab) SmPC. Updated July 2013. http://www.ema.europa.eu. 4. Brahmer *J Semin Oncol*. 2014;41:126–132. 5. Nivolumab investigator brochure Version 12, July 21, 2013. 6. Brahmer J, et al. Poster presented at ASCO 2014. Abstract 8112; 7. Garon E, et al. Poster presented at ASCO 2014. Abstract 8020. 8. Soria J, et al. Presented at ECC 2013. Abstract 3408. 9. Brahmer J, et al. Poster presented at ASCO 2014. Abstract 8021. 10. Gettinger S, et al. Poster presented at ASCO 2014. Abstract 8024. 11. Rizvi N, et al. Poster presented at ASCO 2014. Abstract 8007. 12. Chin K, et al. Poster presented at ESMO 2008. Abstract 87P.

Time to Development of Side Effects During Treatment With Pembrolizumab



Robert C, et al. Manuscript submitted:

CheckMate 067: Time to Onset of Grade 3–4 Treatment-Related Select AEs



Majority of Grade 3–4 AEs, with the exception of endocrinopathies, resolved within 4 weeks with the use of immune modulators according to established guidelines

Circles represent medians; bars signify ranges.
Larkin J et al. Oral presentation at ECC 2015. Abstract 3303.

CheckMate 067: Safety Summary

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

* One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).
Wolchok JD et al. Oral presentation at ASCO 2015. Abstract LBA1.

More Aggressive Algorithms Are Needed For Combination Therapies

Teamwork with other specialist essential!

New Initiatives Needed In Prevention And Management Of Autoimmune side Effects!

- Cortico steroids are a very blunt instrument with their own problems
- Are all the side effects due to deletion or inhibition of T regs?
- ? Prevent IBD with Mabs to alpha 4 Beta 7 Integrins as in ulcerative colitis
- Do T reg subsets change during treatment?
- Are ILC3 cells in the gut deleted?

The Immune Response — Learning to Leave Well Enough Alone

James T. Rosenbaum, M.D.

NEJM Dec 2015

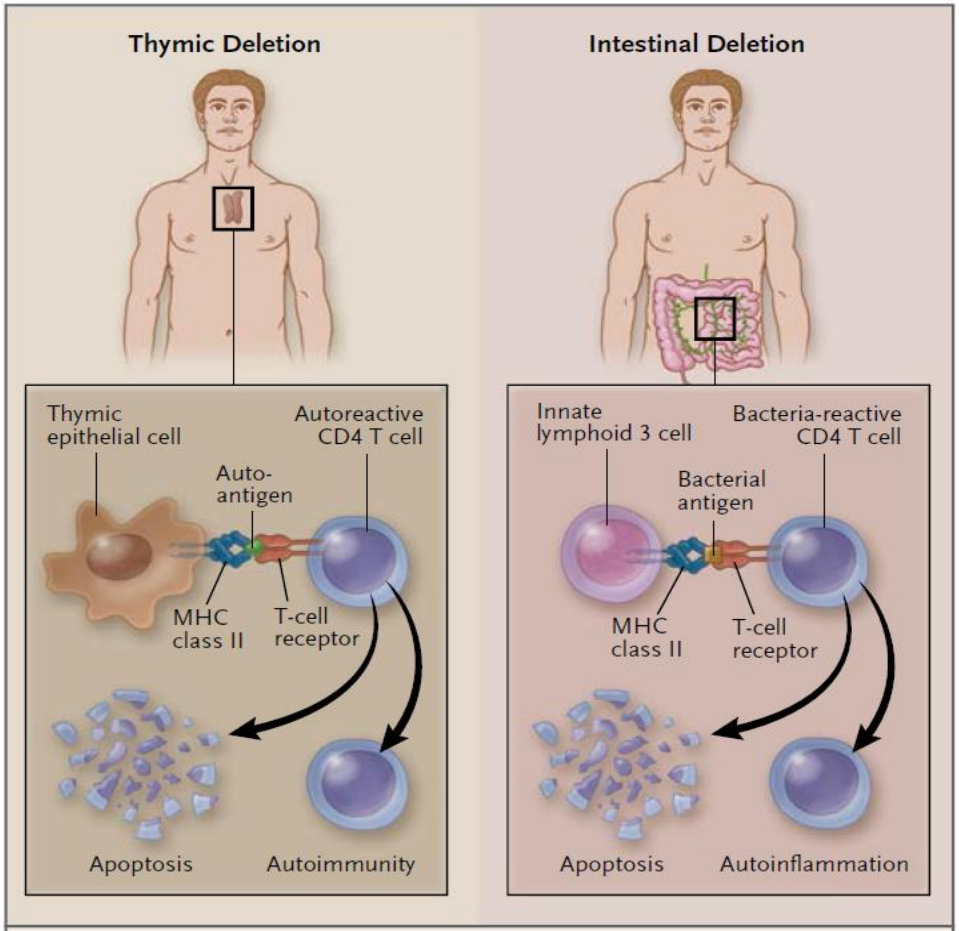


Figure 1. Autoimmunity and Autoinflammation.

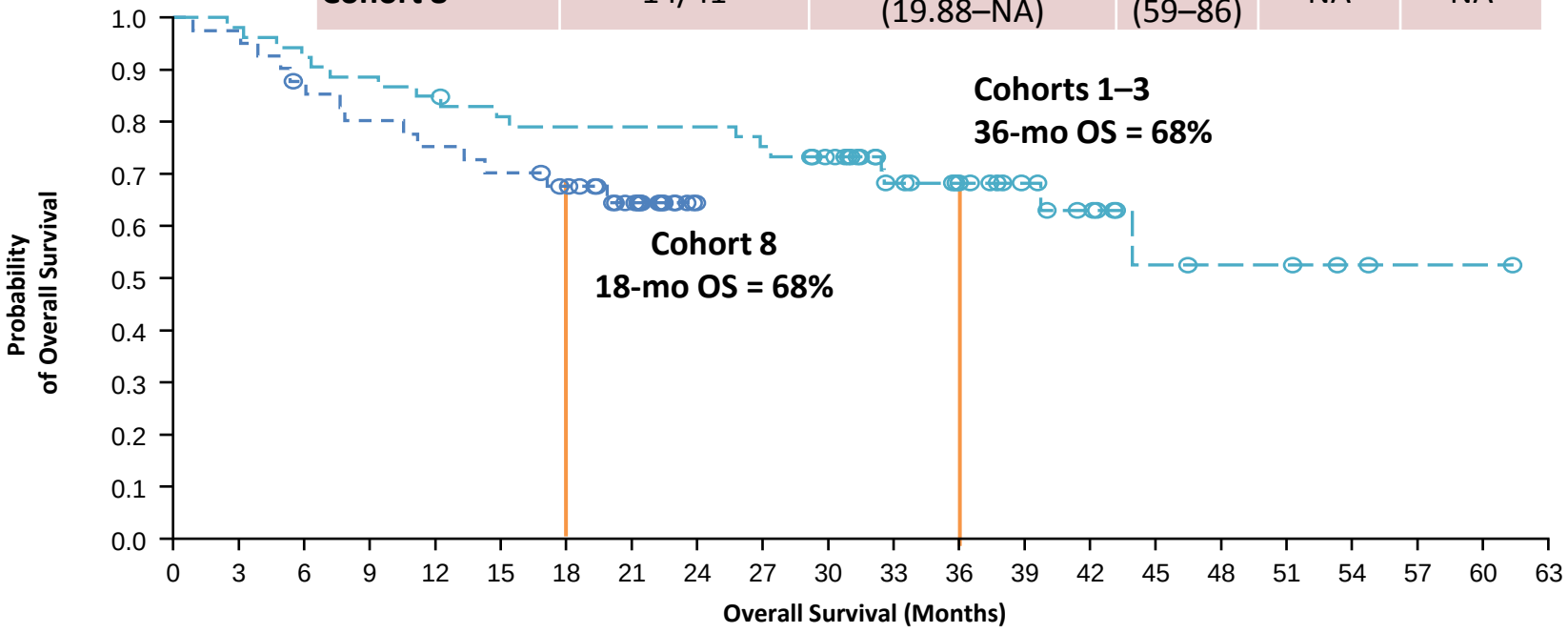
The thymus is responsible for deleting autoreactive T cells that have the potential to cause autoimmune disease. Medullary epithelial cells or dendritic cells in the thymus present antigen in association with a cell-surface molecule known as MHC class II. The antigen is recognized by the T-cell receptor. If the recognition is strong, the autoreactive T cell is killed by means of apoptosis. The failure to delete autoreactive cells potentially results in autoimmunity. ILC3 cells (a subset of innate lymphoid cells) in the lamina propria of the intestine or in the mesenteric lymph node perform a

Conclusions

- **It is a wonderful story with impressive results**
- **The science of Oncology is undergoing a rapid switch to incorporate this new modality**
- **Plenty of scope for new ideas**
- **Management of Side Effects as part of a team with other specialists essential**
- **New intiatives needed in management of side effects**

CA209-004: Phase 1 Study of Nivolumab plus Ipilimumab in Patients with Ac

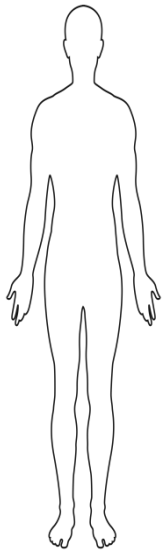
	Died/Treated, n/N	Median OS, mo (95% CI)	OS rate, % (95% CI)		
			12 mo	24 mo	36 mo
Cohorts 1–3	18/53	NA (39.75–NA)	85 (72–92)	79 (65–88)	68 (53–79)
Cohort 8	14/41	NA (19.88–NA)	75 (59–86)	NA	NA



Cohorts 1–3	53	52	49	47	45	42	41	41	41	39	35	26	21	14	10	5	4	4	2	1	1	0
Cohort 8	41	40	35	32	30	28	25	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Sznol M et al. Poster presentation at SMR 2015.

Methods: NanoString Analysis of 19 Biopsies (Discovery Set) and 62 Biopsies (Validation Set) From KEYNOTE-001 (NCT01295827)

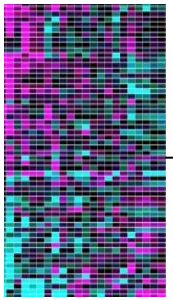


FFPE Tumor Tissue Collected At Baseline Before Receiving Pembrolizumab

RNA

NanoString Platform

Gene Expression Data

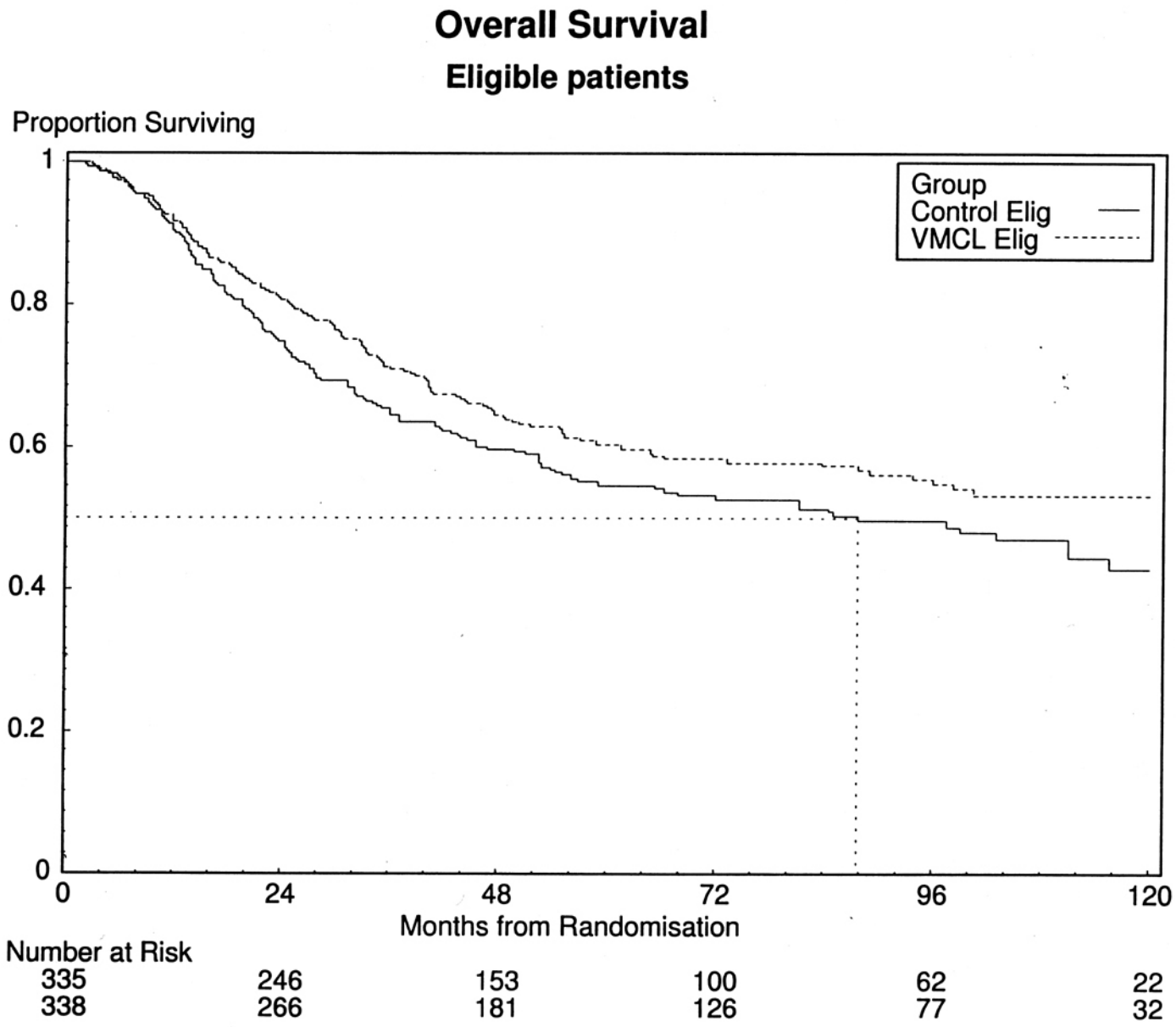


400-680 Genes On Custom Platform - Immune Focused -

Discover Genes & Signatures Associated With Anti–PD-1 Response

- Most samples yield >20 ng of usable RNA per slide
- 50 ng of RNA required for 1 assay

IMMUNOTHERAPY WITH VMCL VACCINE



Management of Immune-Related ARs Associated with Nivolumab Plus

	GRADE 1*	GRADE 2*	GRADE 3-4*
Severity (NCI CTCAE v4)	**Diarrhea:** <4 stools per day over baseline **Colitis:** Asymptomatic	**Diarrhea:** 4–6 stools/day over baseline; IV fluids indicated <24 hours; not interfering with ADL **Colitis:** Abdominal pain, blood in stool	**Diarrhea:** *Grade 3:* ≥7 stools/day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL **Colitis:** *Grade 3:* Severe abdominal pain, medical intervention indicated, peritoneal signs *Grade 4:* life-threatening, perforation
Management	**Treatment:** Continue treatment **Symptomatic Treatment:** Administer	**Treatment:** Withhold treatment until Grade 0-1 **Symptomatic Treatment:** Administer **Steroids:** If symptoms persist >5 days or recur • 0.5–1 mg/kg/day prednisone equivalents†	**Treatment:** Permanently discontinue **Steroids:** • 1–2 mg/kg/day prednisone equivalents‡ **Gastrointestinal (GI) Tests:** • Consider lower GI endoscopy
Follow-up	**Close monitoring for worsening symptoms** **Educate patient to report worsening immediately** **If symptoms worsen or persist** • Treat as Grade 2 or 3-4	**If improved** • Resume treatment • If steroids have been administered, taper steroids over at least 1 month before resuming treatment **If symptoms worsen or persist >3 to 5 days with steroids** • Treat as Grade 3-4	**If symptoms persist >3 to 5 days, or recur after improvement** • Add non-corticosteroid immunosuppressive medication

* Grades correspond to those listed in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

† Consider prophylactic antibiotics for opportunistic infections.

‡ Add prophylactic antibiotics for opportunistic infections.

ADL=activities of daily living; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Bristol-Myers Squibb. Immune-Mediated Adverse Reactions Management Guide. Available at: http://www.opdivoyervoyhcp.com/. Accessed December 2, 2015.