ICLIO National Conference

Immuno-Oncology Indications and Combinations

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9.30.16
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Association of Community Cancer Centers

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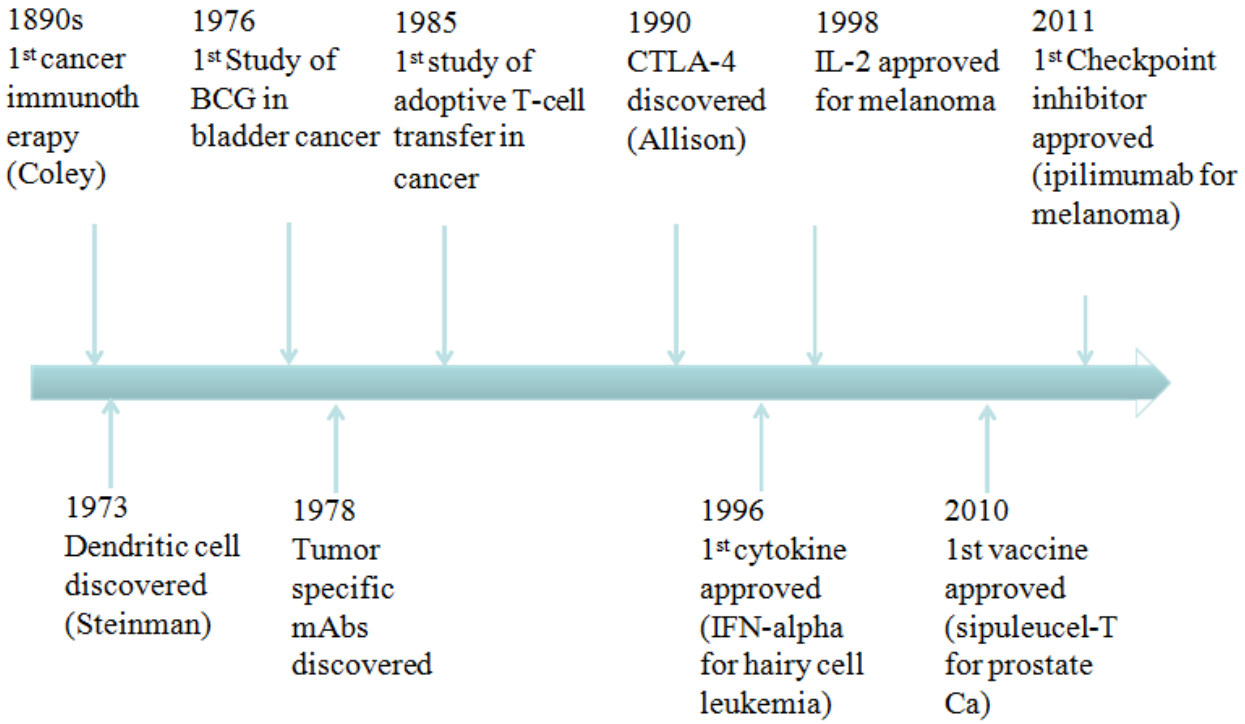
Disclosures

- Consultancy:
  - Amgen
  - Roche
- Research Grant Support to Institution:
  - Nektar
- Clinical Trial Support to Institution:
  - Novartis, MedImmune, Bristol-Myers Squibb, Pharmacyclics, Merck, BBI Therapeutics, Five Prime Therapeutics, Genentech, Corvus Pharmaceuticals, Delcath, Abbvie, Celldex, EMD Serono
  - I will discuss the investigational use of pembrolizumab and TVEC

Objectives

1. Review the current status of immunotherapy
2. Identify determinants of response
3. Discuss strategies to enhance efficacy

Cancer Immunotherapy: Timeline



FDA approved immunotherapy checkpoint inhibitors include ipilimumab, nivolumab, pembrolizumab, atezolizumab

- **Ipilimumab:** human, monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T cells.
  - Ipilimumab is indicated for the treatment of unresectable or metastatic melanoma

- **Nivolumab/pembrolizumab**: Human monoclonal antibodies directed against the programmed death-1 (PD-1) receptor of the T Cell. **Atezolizumab**: anti PD-L1
  - Nivolimumab has indications for melanoma, RCC, metastatic squamous or non- squamous non-small cell lung cancer (NSCLC), Hodkin's lymphoma.
  - Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic melanoma, NSCLC (PDL-1+), HNSCC
  - Atezolizumab is indicated for the treatment of patients with unresectable or TCC/bladder cancer

Features of Cancer Immunotherapy

Adaptable	**Ability to adapt the response beyond the initially targeted antigen**
Specific	**Ability to recognize and target only tumor cells**
Long Lasting	**Capacity for memory can result in durability of tumor responses**
Universal	**Potentially applicable to all cancers**

Cancer Immunotherapies: Different Approaches

Approach	Examples	Agents/Targets
Vaccines	Peptide, protein, DC, DNA, virus	
Immune Modulatory Antibodies	Checkpoint inhibitors	anti-CTLA-4 anti-PD-1/PD-L1
	Co-stimulatory Activators	anti-OX-40, anti-CD137, anti-GITR
Adoptive T cell therapy	T cells expanded from tumor infiltrating T cells (TIL)	
	T cells expressing tumor antigen specific transgenic TCRs	
	Chimeric antigen receptor (CAR) adoptive T cells	
Cytokines		IL-2, IFN-alpha, GM-CSF
Oncolytic Viruses		TVEC
Reversal of Immunosuppression	IDO- inhibitors	Epacadostat
	T-reg depletion	

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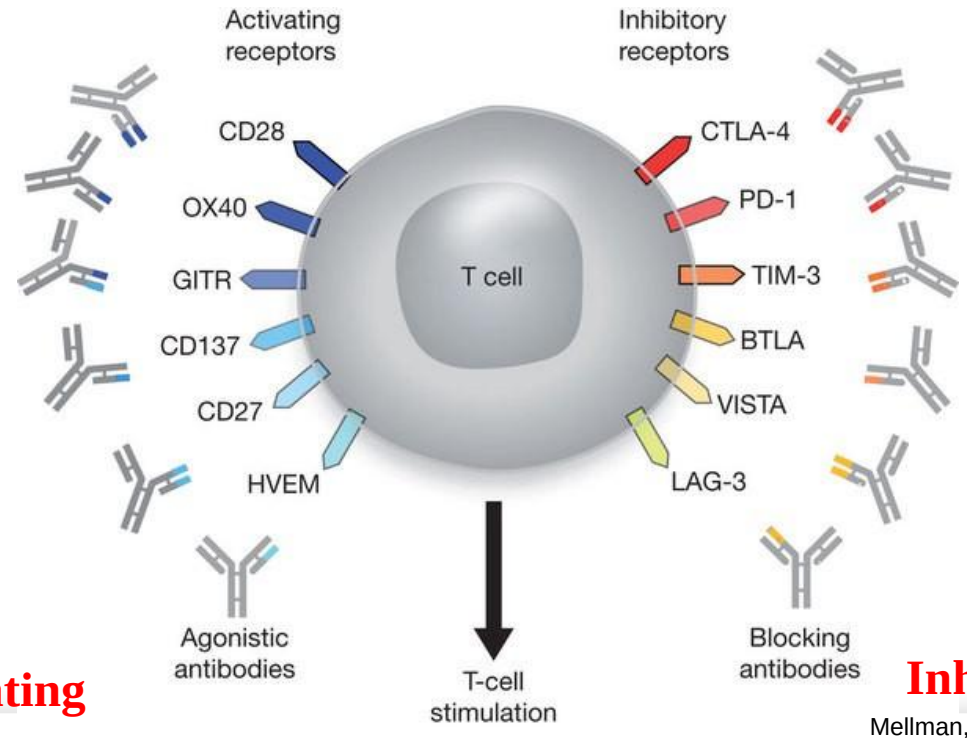
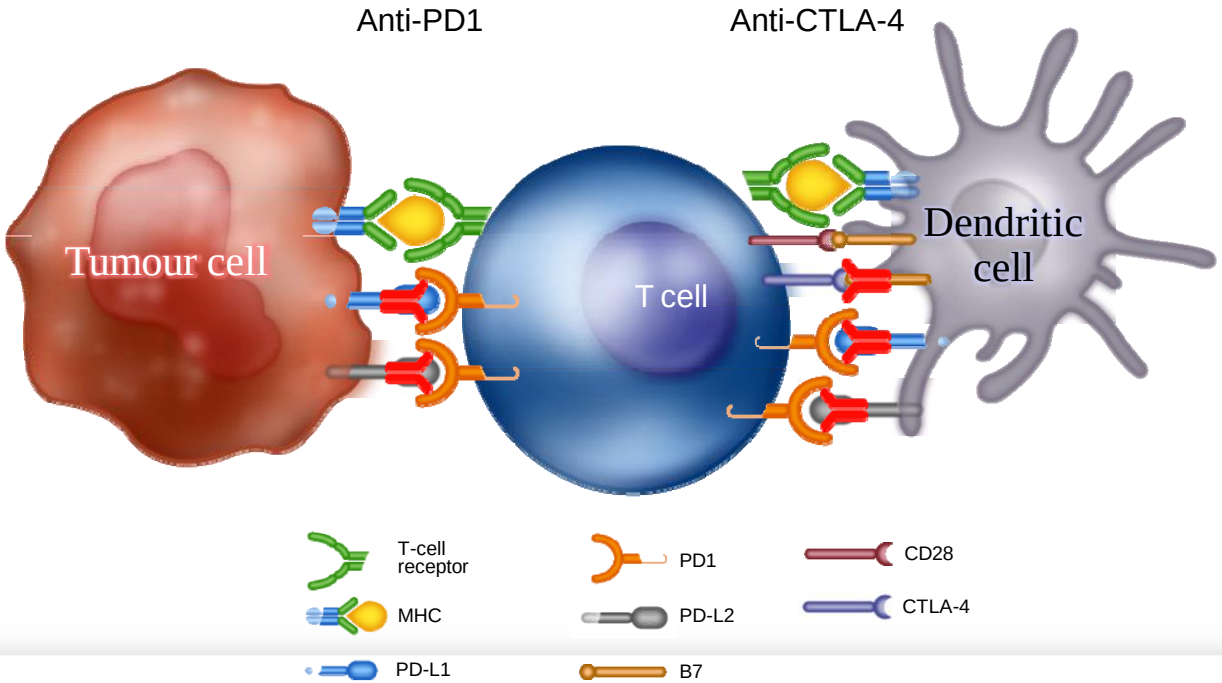
Immune Modulatory Receptors



Activating **Inhibiting**

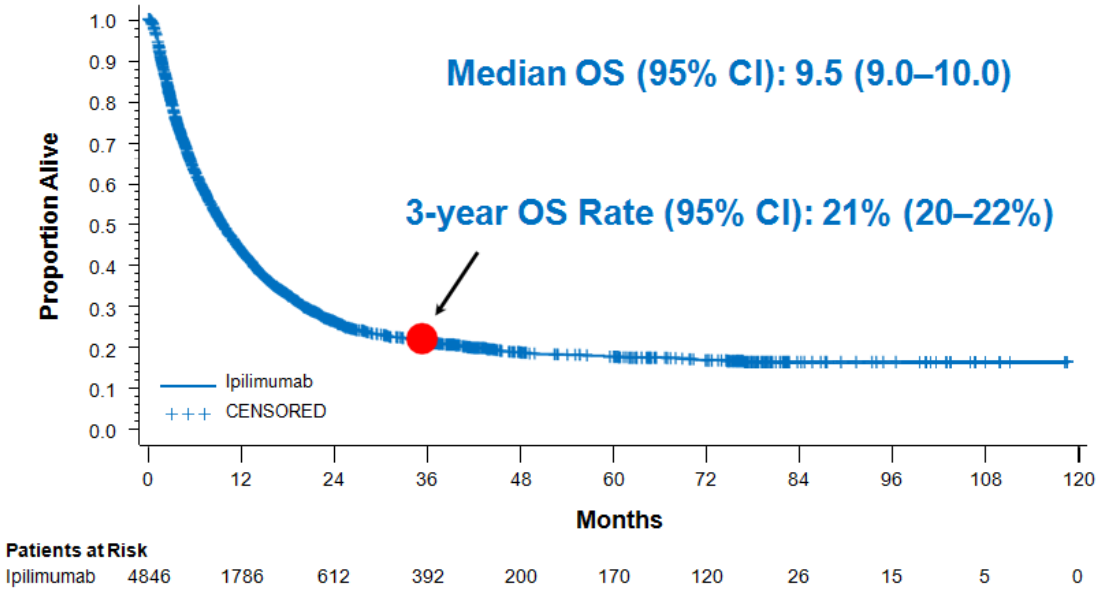
Mellman, *Nature*, 2011

Immune-checkpoint inhibition

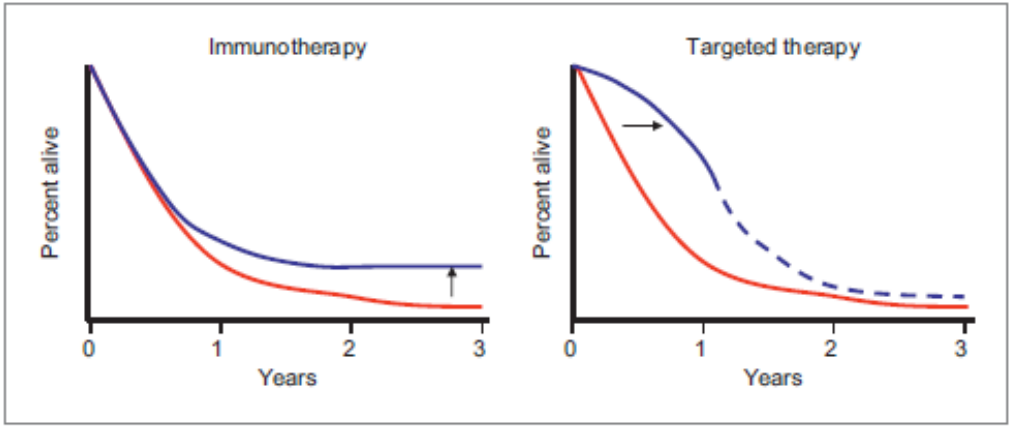


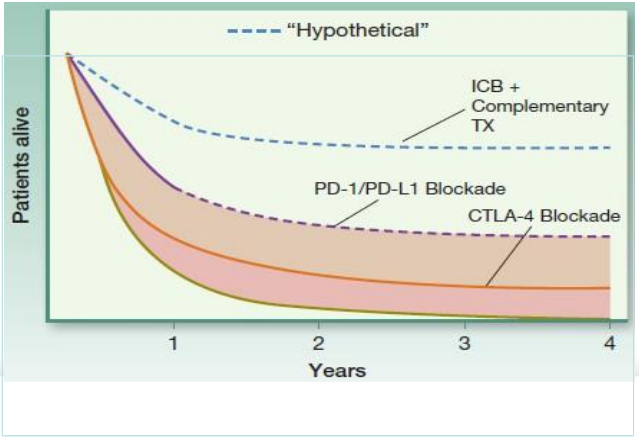
Adapted from Sznol M, et al. Presented at ASCO 2013: oral presentation CRA9006

Pooled Overall Survival Analysis of 4846 Melanoma Patients Treated with Ipilimumab



F-S. Hodi, MD – ECCO 2013

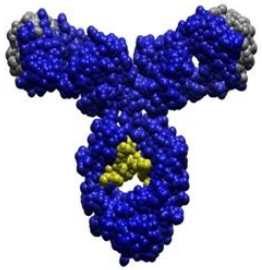




Ribas, Clin Can Res, 2012
Ott, Hodi, Robert, Clin Can Res, 2013

Non-Small Cell Lung Cancer

Comparison of Therapeutic Antibodies Blocking PD-1/PDL-1 Interaction



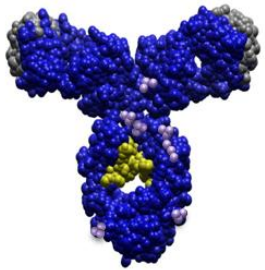
IgG1 wt

Examples: Curetech Anti-PD-1

ADCC intact →
Potential to deplete activated T cells and TILs and diminish activity

Blocks PD-1/PD-L2 interaction in lungs →
Potential for autoimmune pneumonitis

†at clinically relevant doses

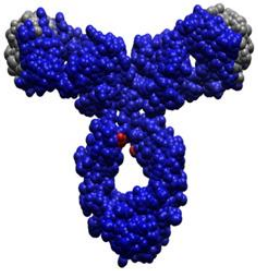


IgG4 hinge mutant

BMS Anti-PD-1
Merck Anti-PD-1

40% reduced ADCC† →
Potential to deplete activated T cells and TILs and diminish activity

Blocks PD-1/PD-L2 interaction in lungs →
Potential for autoimmune pneumonitis



IgG1 Engineered

Genentech Anti-PD-L1
MedI-4736

No ADCC† →
Decreased potential to deplete activated T cells and TILs

Leaves PD-1/PD-L2 interaction intact in lungs →
Decreased potential for autoimmune pneumonitis

Blocks PD-L1/B7.1 interaction → ***Potential for enhanced priming***

Courtesy of Dr. Herbst

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

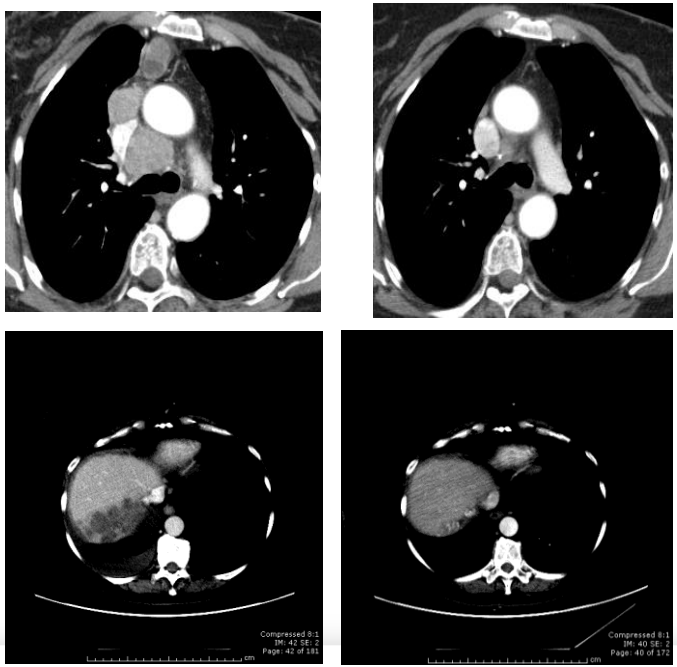
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M.

Tumor Type (dose, mg/kg)	No. Pts	OR (CR/PR) No. Pts (%)	SD ≥24 wk No. Pts (%)	PFS (mos,median)
NSCLC (1-10)	129	22 (17)	13 (10)	2.3
MEL (0.1-10)	107	33 (31)	7 (7)	3.7
RCC (1 or 10)	34	10 (29)	9 (27)	7.3

Immune Checkpoint Inhibitors

Anti-tumor activity consistent across the drug class

Agent	N	RR N (%)
NSCLC		
Nivolumab[1]	129	22 (17)
MK-3475[2,3]	33 129	7 (21) 25 (19)
MPDL3280A[4]	53	12 (23)
BMS 936559[5]	49	5 (10)
MEDI-4736[6]	6	3/6 (50)

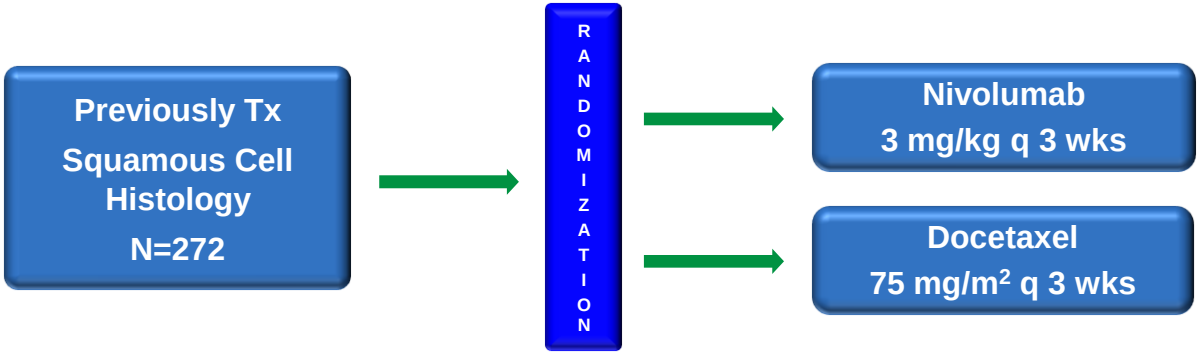


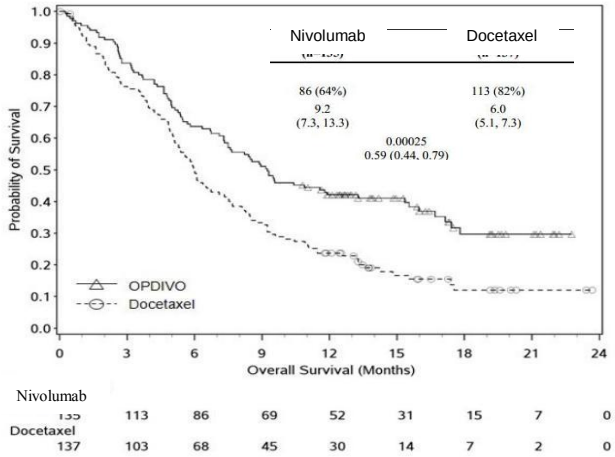
[1]Brahmer et. al. WCLC, 2013, [2]Garon et. al. WCLC 2013, [3]Ghandi et. al. AACR 2014, [4]Horn et. al. WCLC 2013, [5]Brahmer et. al. NEJM 2012, [6] Khleif et. al. WCLC 2013

Second line Phase III Trials

Trial	Agent	PD-L1 Status
Checkmate 057	Nivolumab vs. docetaxel (non-squamous)	Not required
Keynote 010	Pembrolizumab vs. docetaxel	PD-L1 positive
OAK	MPDL3280A vs. docetaxel	PD L1 positive
LUNG-MAP	MEDI4736 vs docetaxel	Not required

CheckMate -017, A Phase 3 Study of Opdivo (Nivolumab) Compared to Docetaxel in Patients with Second-Line Squamous Cell Non-small Cell Lung Cancer (BMS press release, January 2015)





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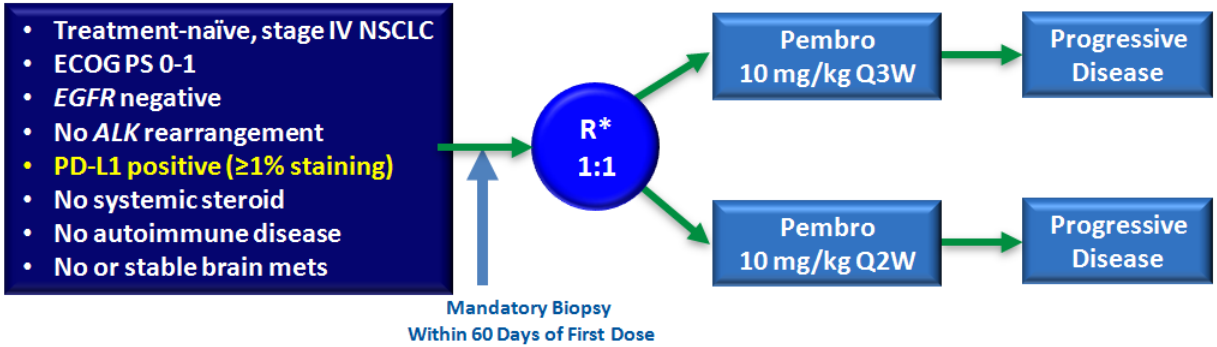
First Line Immunotherapy in Advanced NSCLC

KEYNOTE-001: Randomized Dose Comparison



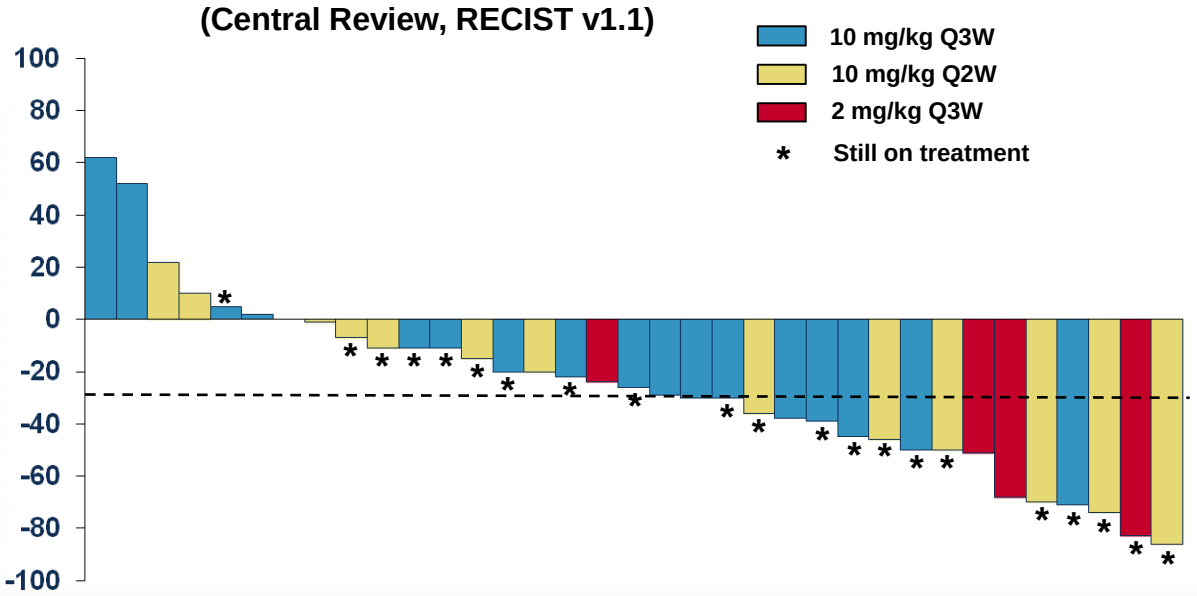
*First 11 patients were randomized to 2 mg/kg or 10 mg/kg Q3W

Objectives

- Evaluate safety, tolerability, and clinical activity of pembrolizumab
- Evaluate correlation between clinical activity of pembrolizumab and PD-L1 expression

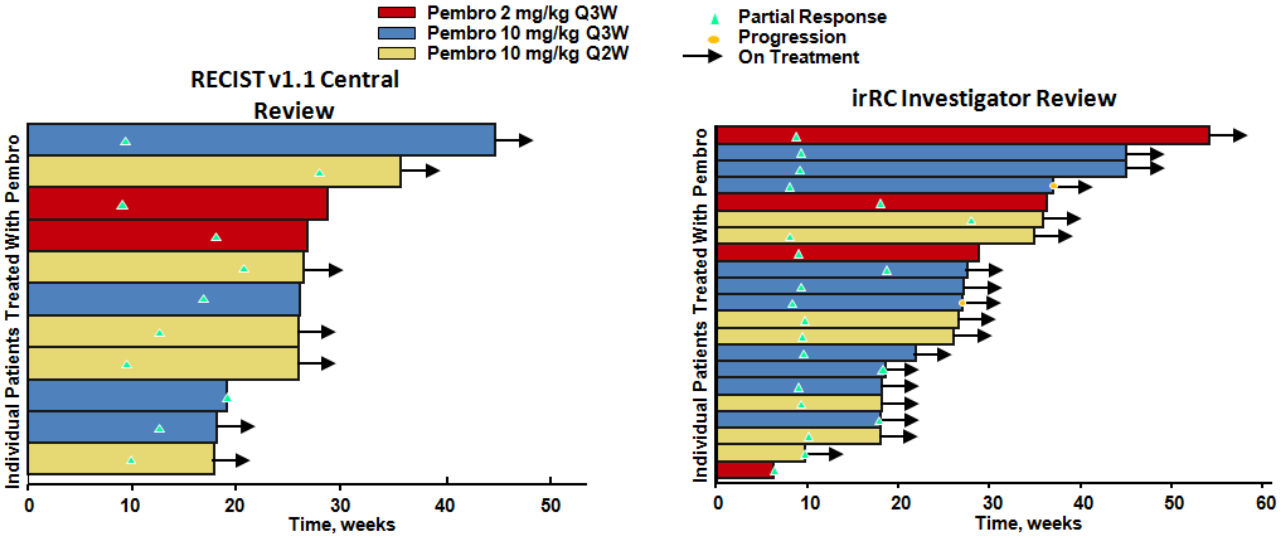
Balmanoukian SA, et al. Abstract #2

Maximum Percent Change from Baseline in Tumor Size in Evaluable Patients (N=35)



Rizvi NA et al. J Clin Oncol. 32(5s) Abstract 8007, 2014

Time to and Durability of Response



- 11 of 11 (100%) responses are ongoing
  - Median duration of response not reached (median follow-up, 36 weeks)
- 7 of 11 (64%) responders remain on treatment
  - Median duration of treatment: 27.1 weeks (range, 15.0+ – 48.3+)

- 19 of 21 (90%) responses are ongoing
  - Median duration of response not reached (median follow-up, 36 weeks)
  - 18 of 21 (86%) responders remain on treatment
  - Median duration of treatment: 27.1 weeks (range, 6.1 – 57.1+)

Rizvi NA et al. J Clin Oncol. 32(5s) Abstract 8007, 2014

First Line Immunotherapy in Advanced NSCLC

	Pembrolizumab	Nivolumab
Number of Patients	45	20
ORR	26%	30%
SD	38%	35%
PFS (median)	27 weeks	36 weeks

Gettinger SN et al. ASCO 2014 #8024

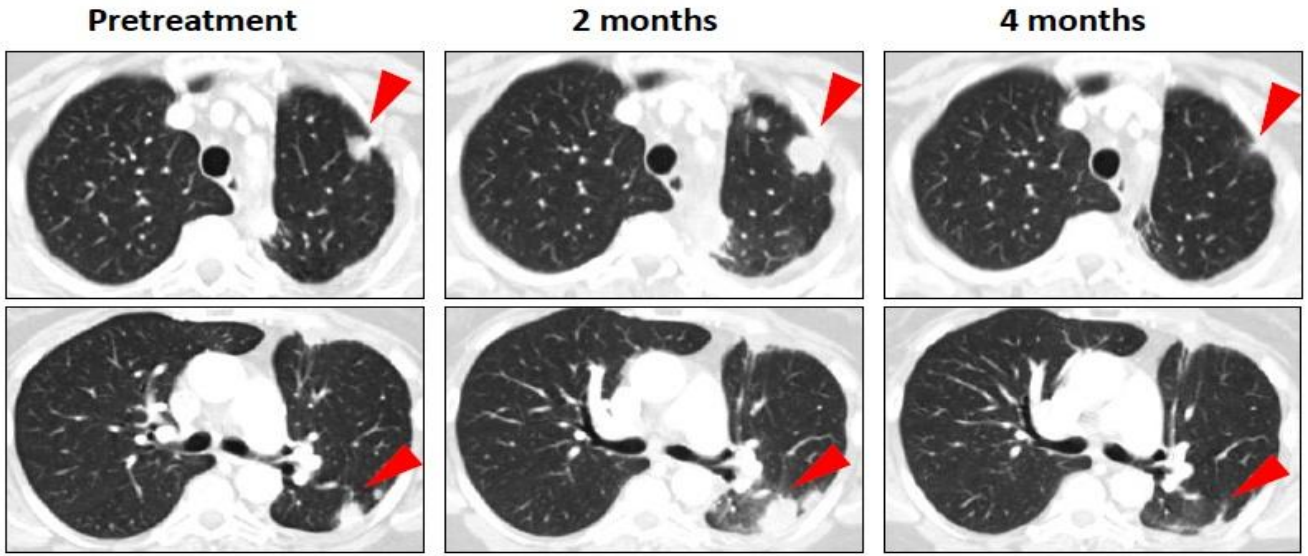
Ongoing Phase III Trials

Trial	Line of Therapy	Agent	PD-L1 Status
CheckMate 026	First	Nivolumab vs. investigator choice chemotherapy	PD-L1 positive 5% cutoff, PFS not met
Keynote 042/42	First	Pembrolizumab vs. investigator choice chemotherapy	PD-L1 positive
ARCTIC	Third Line	MEDI4736 vs. Chemotherapy	Not required
PACIFIC	Locally Advanced	Following concurrent chemo-RT vs. placebo	Not required

Phase III Trials in Development:

1) Maintenance therapy in advanced NSCLC
2) Adjuvant therapy

Pseudo-Progression



iRECIST

May occur in 7-10% of patients

Comparison: RECIST-irRC Criteria*

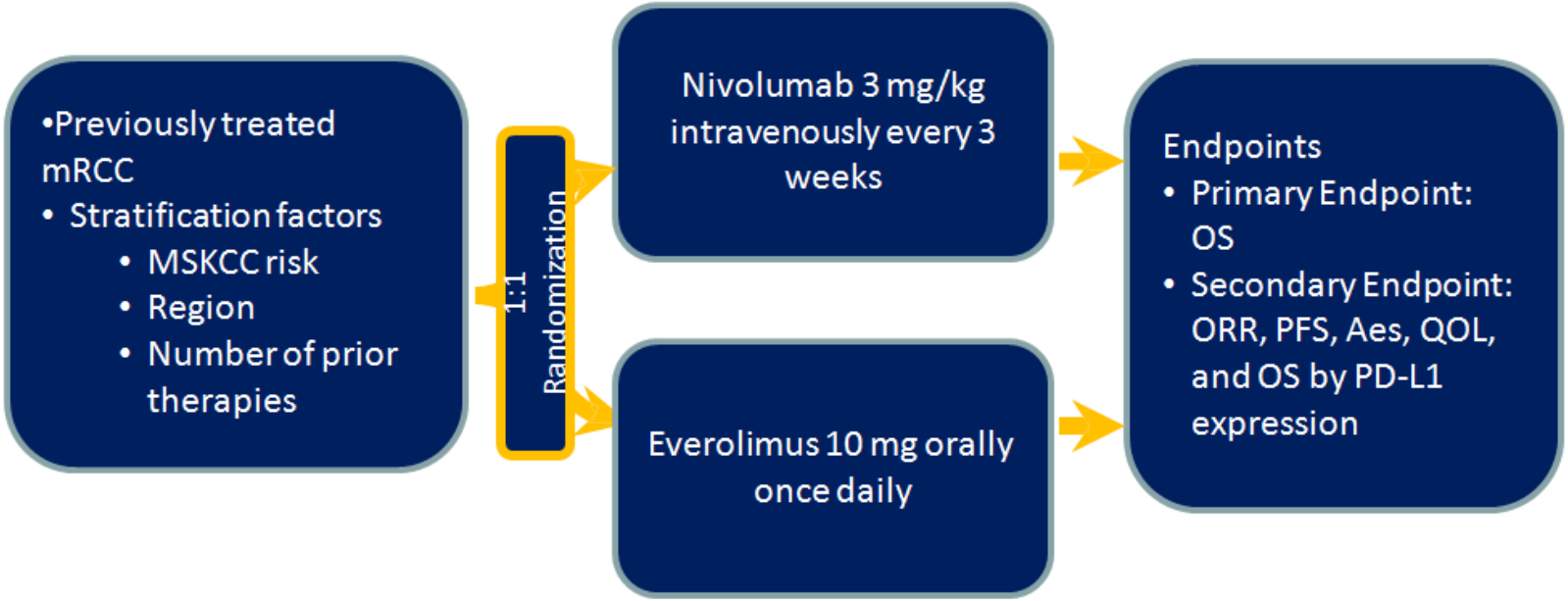
	RECIST	irRC
New, measurable lesions (i.e. ≥5 x 5 mm)	**Always represent PD**	**Incorporated into tumor burden**
New, nonmeasurable lesions (i.e. <5 x 5 mm)	**Always represent PD**	**Do not define progression (but preclude irCR)**
Non-index lesions	**Changes contribute to defining BOR of CR, PR, SD, and PD**	**Contribute to defining irCR (complete disappearance required)**
Complete Response (CR)	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to <10 mm in short axis	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
Partial Response (PR)	At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters	≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
Progressive Disease (PD)	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5 mm (two lesions increasing from 2 mm to 3mm, for example, does not qualify)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart

***Total Burden=SPD $_{\text{index lesions}}$ + SPD $_{\text{new, measurable lesions}}$**

Wolchok J et al Clin Can Res 19:7412-7420, 2009

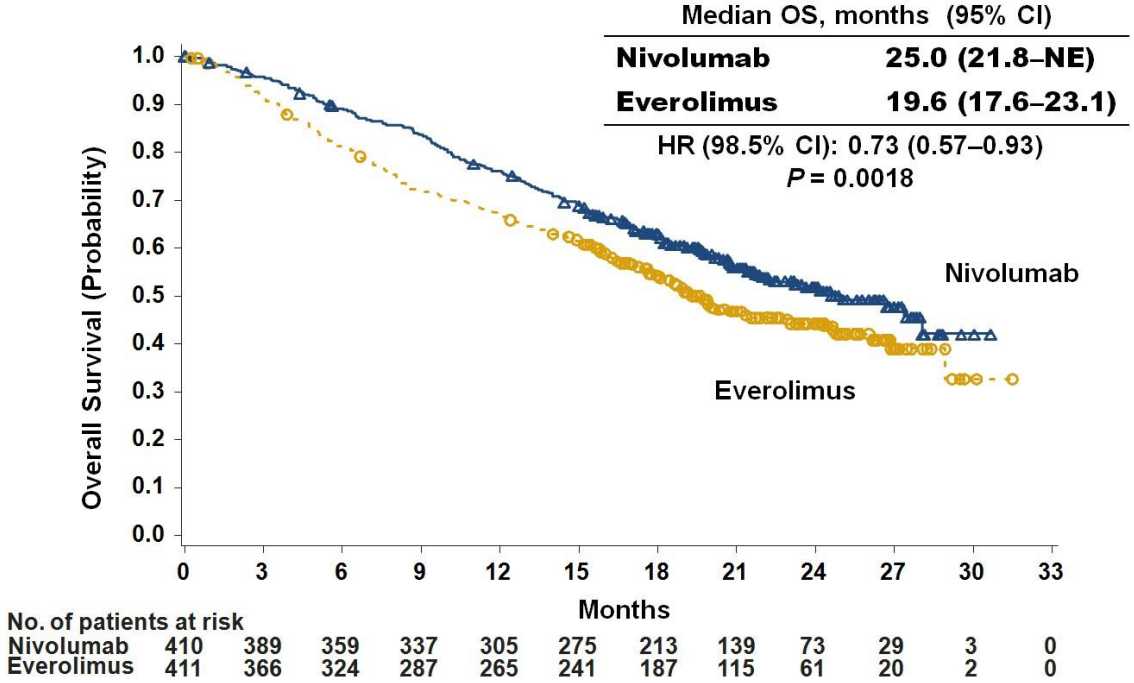
Renal Cell Carcinoma

Second and Third Line for RCC



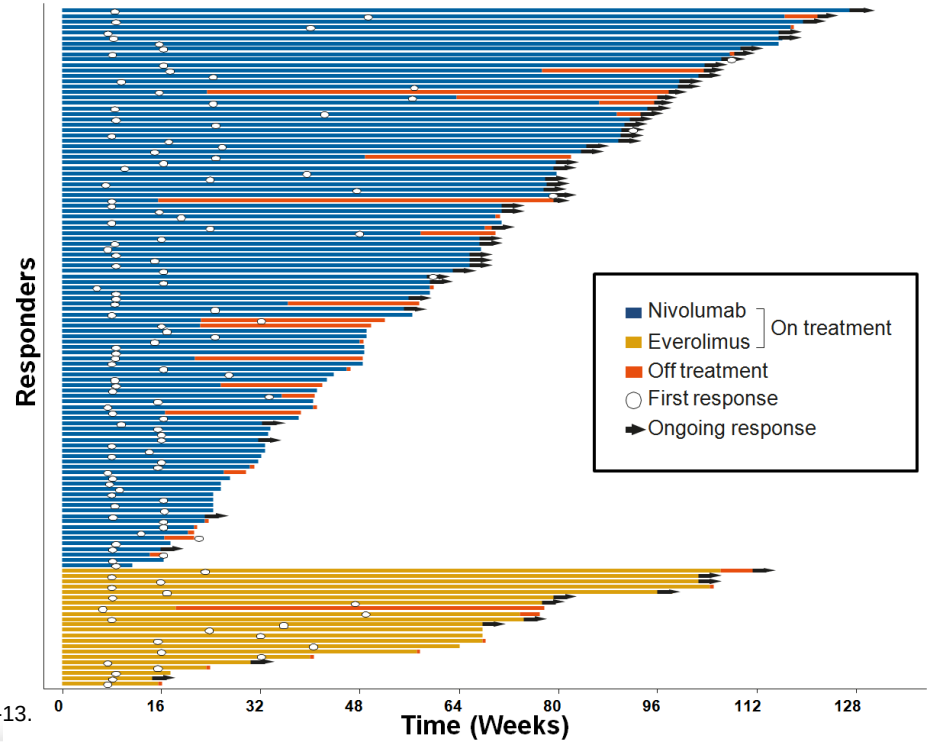
Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

Nivolumab is Superior for OS



Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

Durability of Response



Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

Bladder Cancer

FDA approved the use of atezolizumab

LETTER

doi:10.1038/nature13904

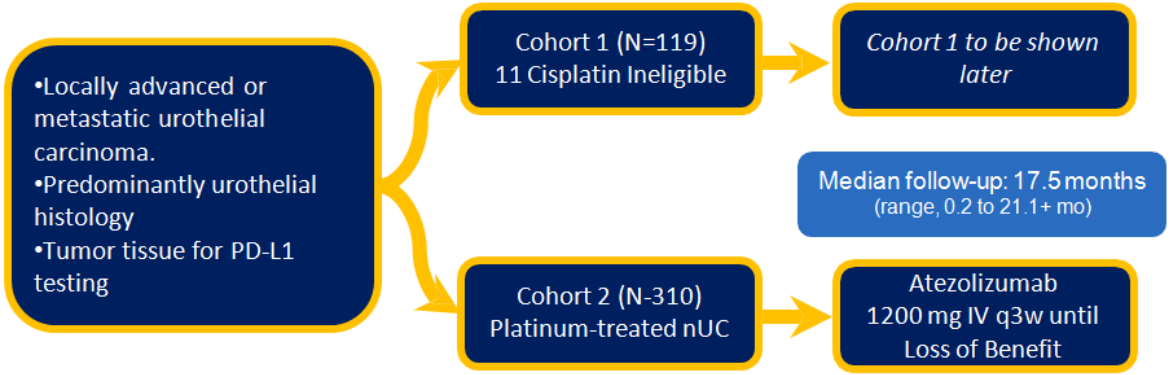
MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles[1], Joseph Paul Eder[2], Gregg D. Fine[3], Fadi S. Braiteh[4], Yohann Loriot[5], Cristina Cruz[6], Joaquim Bellmunt[7], Howard A. Burris[8], Daniel P. Petrylak[2], Siew-leng Teng[3], Xiaodong Shen[3], Zachary Boyd[3], Priti S. Hegde[3], Daniel S. Chen[3] & Nicholas J. Vogelzang[9]

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer

Imvigor210 Study Design



Co-primary endpoints:

ORR (confirmed) per RECIST v1.1 by central review

ORR per immune-modified RECIST by investigator

Key secondary endpoints

DOR, PFS, OS, safety

Key exploratory endpoints

Intratumoral biomarkers

Cohort 2-Specific Inclusion Criteria

- Progression during/following platinum (no restrictions on # prior lines of therapy)
- ECOG PS 0-1
- CrCl ≥ 30 mL/min

Dreicer R et al. IMvigor210: Atezolizumab in platinum-treated mUC. ASCO2016

Atezolizumab Response Rates (by PD-L1 status)

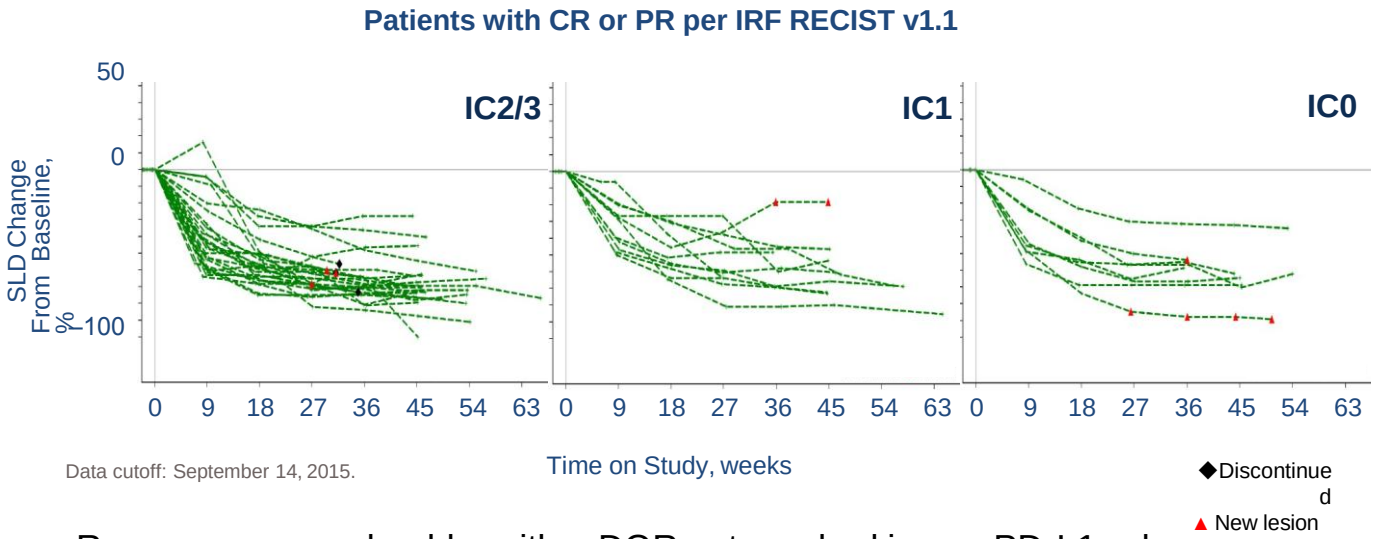
	IC2/3 n = 100	IC1/2/3 n = 207	All[a] N = 310	IC1 n = 107	IC0 n = 103
ORR: confirmed IRF RECIST v1.1 (95% CI)	28% (19, 38)	19% (14, 25)	16% (12, 20)	11% (6, 19)	9% (4, 16)
CR rate: confirmed IRF RECIST v1.1 (95%CI)	**15%** **(9, 24)**	**9%** **(6, 14)**	**7%** **(4, 10)**	**4%** **(1, 9)**	**2%** **(0, 7)**

- Responses were seen in all IC subgroups, but ORR was enriched with higher PD-L1 status
- Complete responses accounted for nearly half of the observed responses
  - CRs were observed in all PD-L1 subgroups, with the highest rate in IC2/3 patients

[a] Includes 46 patients with missing/unevaluable responses. [b] CR + PR + SD ≥ 24-wk rate per IRF RECIST v1.1. Treated patients had measurable disease at baseline per investigator- assessed RECIST v1.1. Data cutoff: Mar. 14, 2016.

Dreicer R et al. IMvigor210: Atezolizumab in platinum-treated mUC. ASCO 2016

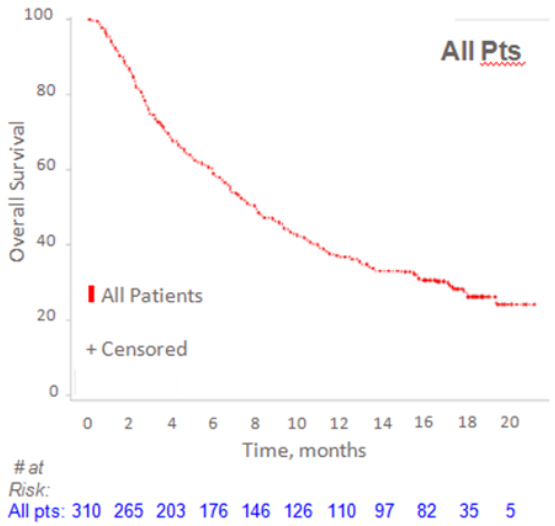
Duration of Response to Atezolizumab



- Responses were durable, with mDOR not reached in any PD-L1 subgroup (range, 2.0+ to 13.7+ mo)
- Ongoing responses were seen in 38 of 45 responding patients (84%)
- Median follow-up time: 11.7 mo (range, 0.2+ to 15.2 mo)

Hoffman-Censits et al. GU ASCO 2016. Abstr 355.

Overall Survival with Atezolizumab



Subgroup	Median OS (95% CI)		
	IC2/3	IC0/1	All
All pts (N = 310)	11.9 mo (9.0, 17.9)	6.7 mo (5.4, 8.0)	7.9 mo (6.7, 9.3)

Subgroup	12-mo OS (95% CI)		
	IC2/3	IC0/1	All
All pts (N = 310)	50% (40, 60)	31% (24, 37)	37% (31, 42)

- Longer OS observed in patients with higher PD-L1 IC status
- mPFS (2.1 mo per RECIST v1.1; 2.6 mo per imRECIST) underscores a disconnect between PFS and OS

NE, not estimable. Data cutoff: Mar. 14, 2016.

Median follow-up (range):
All Pts: 17.5 mo (0.2 to 21.1+ mo)

Dreicer R et al. IMvigor210: Atezolizumab in platinum-treated mUC. ASCO2016

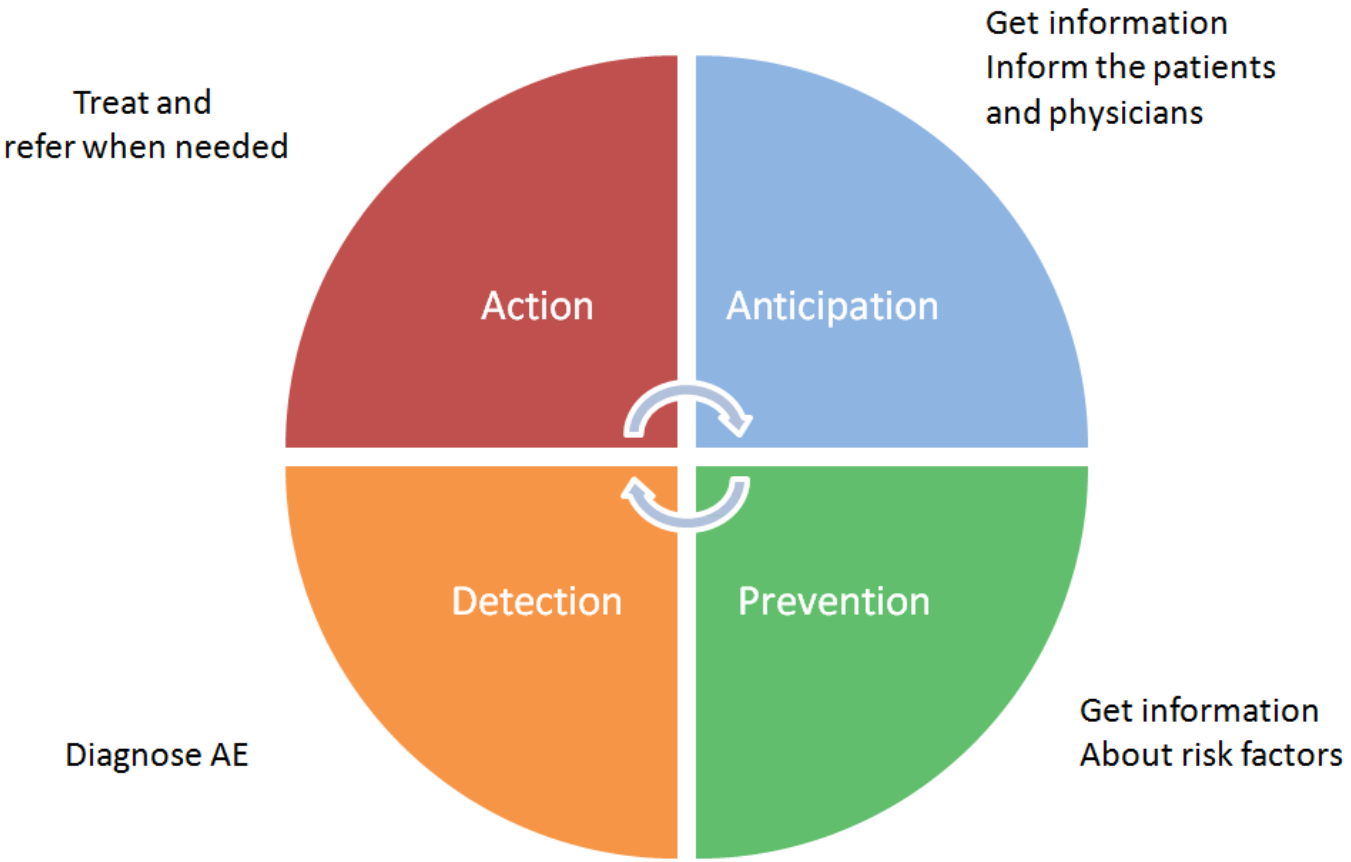
Toxicities

Treatment Related Adverse Events

- Fatigue is the most common AE (24%)
- Grade 3-4 AEs are uncommon (6-12.6%)

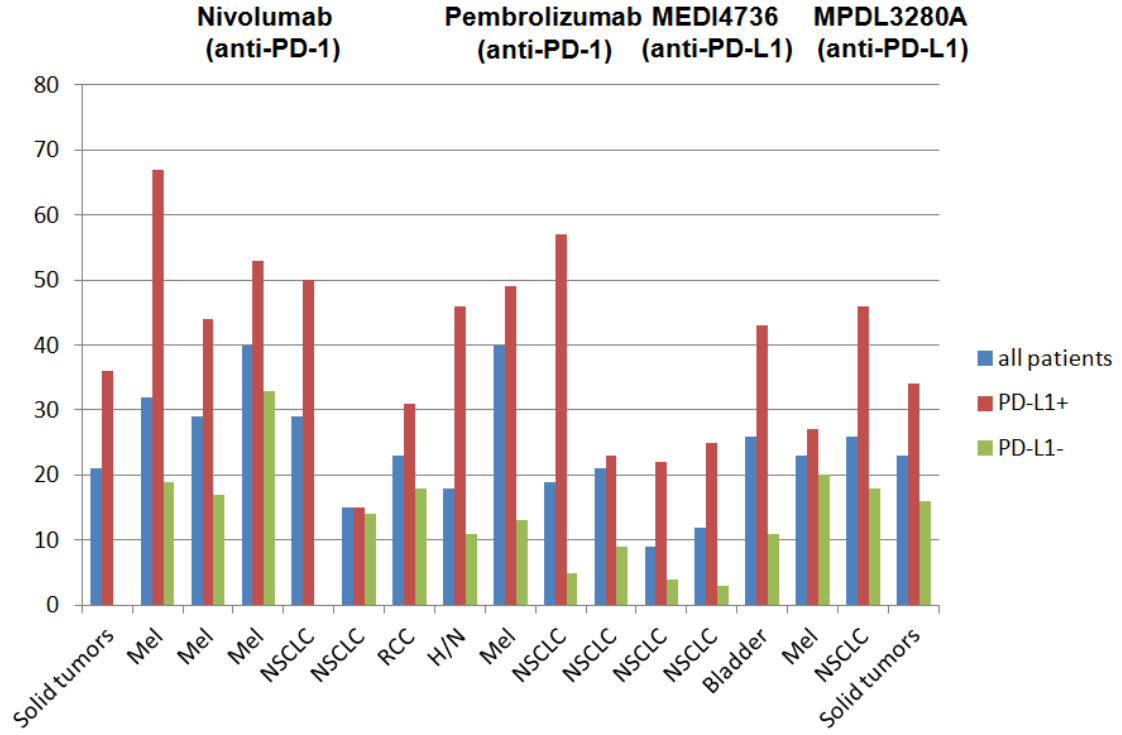
System	Immune Related Adverse Events
Gastrointestinal	Colitis (Diarrhea, perforation)
Renal	Acute Interstitial Nephritis (Increased serum Creatinine)
Pulmonary	Pneumonitis (dyspnea, cough)
Dermatologic	Dermatitis (Lichenoid/ spongiotic dermatitis, rash), Vitaligo
Hepatic	Hepatitis (elevated LFTs)
Neurologic	Central and Peripheral (Aseptic Meningitis, Guillan-Barre Syndrome, Myasthenia Gravis
Endocrine	Hypophysitis, thyroiditis, adrenal insufficiency
Ocular	Uveitis, Iritis

Risk management



Biomarkers of Response

Identifying Predictor(s) of Response

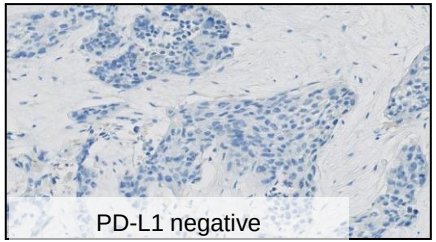


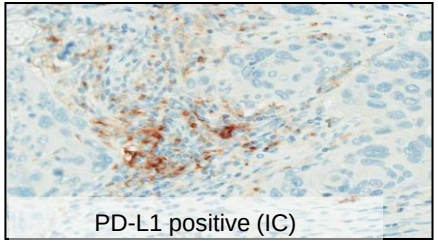
Responses are higher in PD-L1+ tumors but seen in PD-L1- tumors

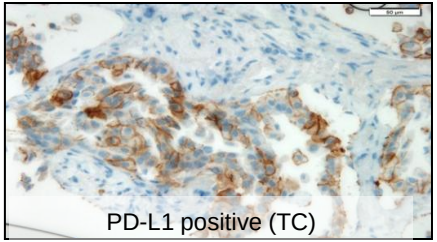
Lipson, Taube, et al. Semin Oncol. In press.

Identifying Predictor(s) of Response

Challenges


PD-L1 negative


PD-L1 positive (IC)


PD-L1 positive (TC)

PD-L1 IHC Expression By Various Assays				
Tumor	**GNE**	**DAKO 28-8**	**Merck CC23**	**5H1**
Melanoma	40%	45%	71%	42%
NSCLC	45-50%	49%	45% (25% if ≥50% Staining)	
Renal	20%			24%
Bladder		21%		28%
Head And Neck		31%		46%
Glioblastoma		25%		100%

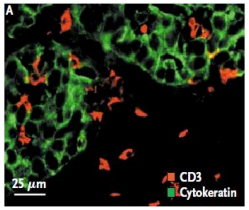
- No validated assay
- Variable cut off levels for positivity

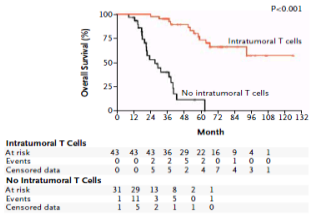
Identifying Predictor(s) of Response

Tumor-Infiltrating Lymphocytes (TIL cells)

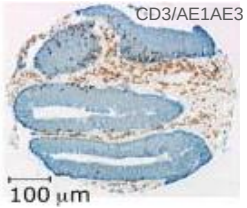
The presence of TIL cells at diagnosis correlates with improved clinical outcomes

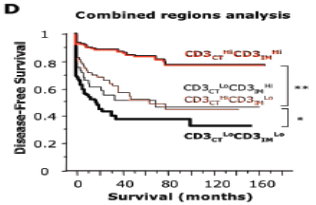
Ovarian



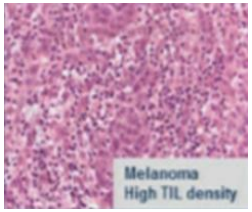


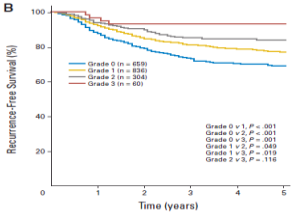
Colon



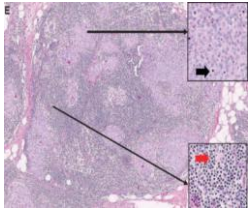


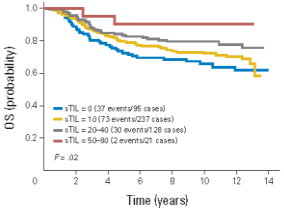
Melanoma





Breast

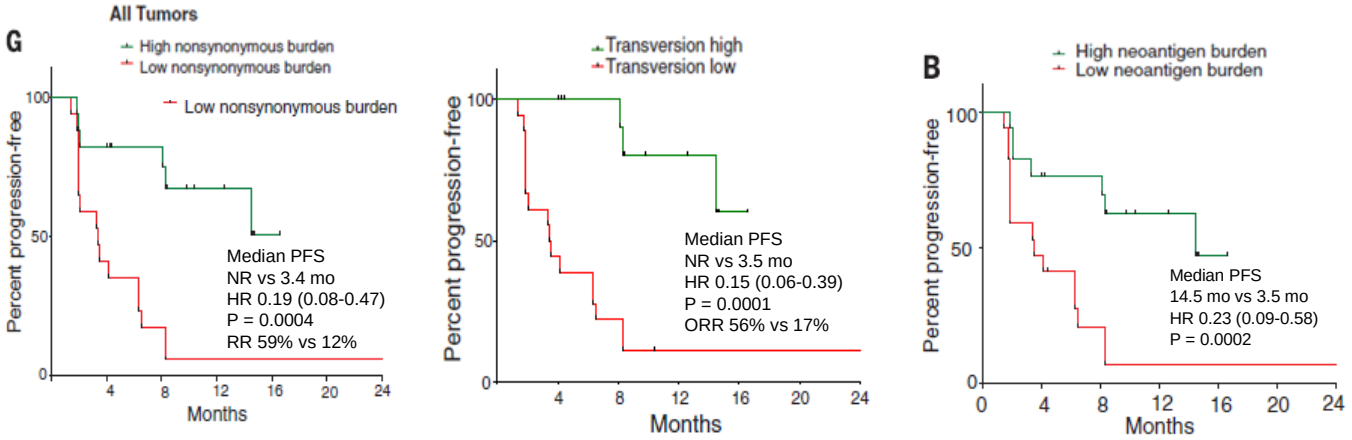




Zhang L et al. NEJM 348:203-13, 2003
Galon J et al. Science 313: 1960-4, 2006
Azimi F et al. J Clin Oncol 30: 2678-83, 2012
Adams S et al. J Clin Oncol 2014 [Epub ahead of print]

Identifying Predictor(s) of Response

Mutational Burden

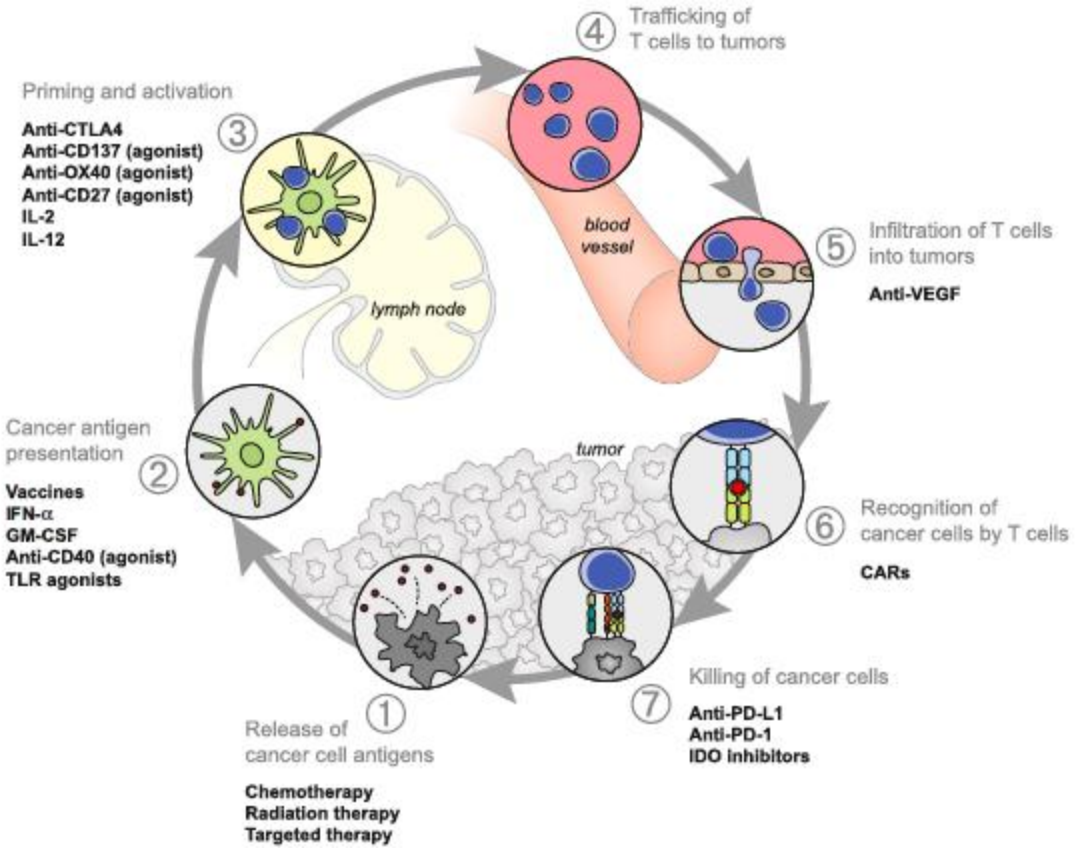


- Median values used to determine high vs low
- No mutations or copy number alterations in CD274 (PDL-1 gene)
- Smoking history did not discriminate for responders
- Molecular smoking signature correlated with mutational burden

Rizvi NA et al. Science 348:124-8, 2015

Combinations

Combined Immunomodulation

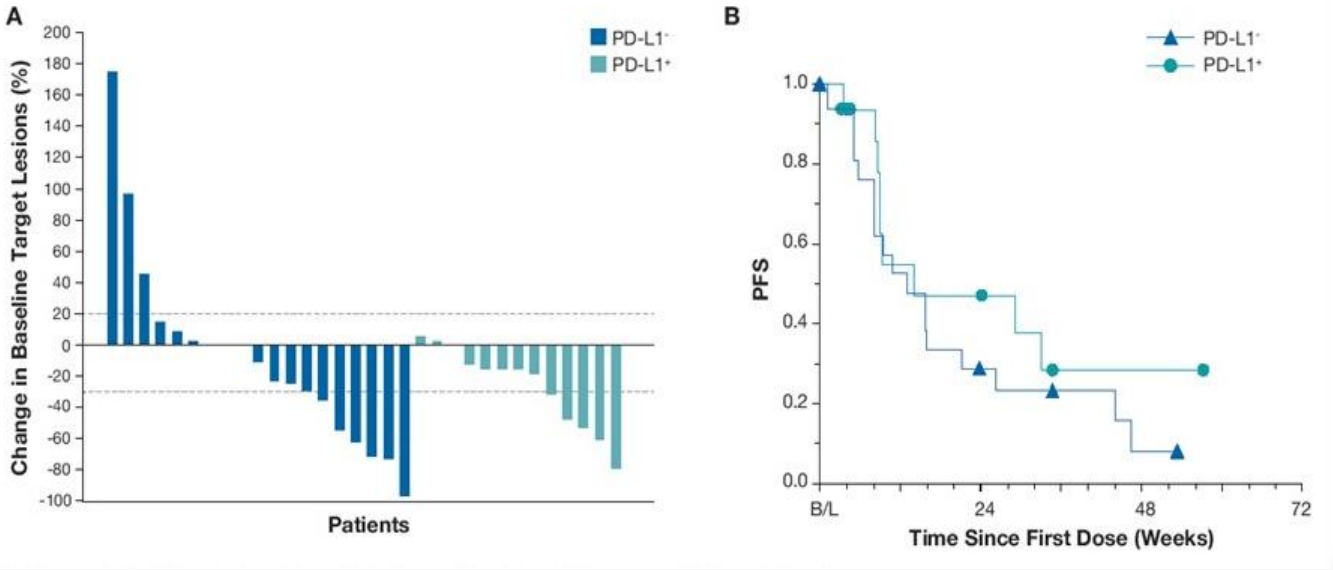


Chen DS, et al. Immunity. 2013;39:1-10

Combined Immunomodulation

Phase I Trial of Ipilumumab and Nivolumab in First Line NSCLC N=49

ORRs: 8/49 (16%); PFS: 14 -16 wks



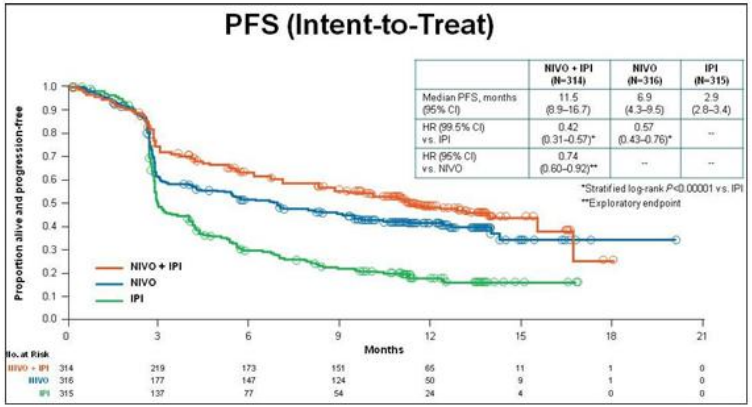
Treatment related Grade 3 or 4 AE (49%); Discontinuation (35%)

Antonia SJ, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8023)

Ipi+Nivo vs. Ipi *or* Nivo vs. Ipi in Melanoma

Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

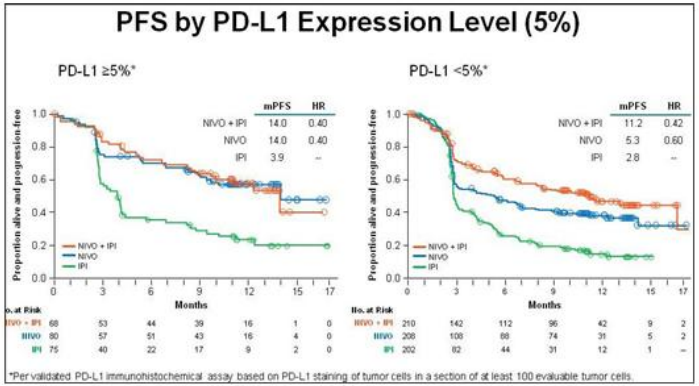
PFS (Intent-to-Treat)



	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

PFS by PD-L1 Expression Level (5%)



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

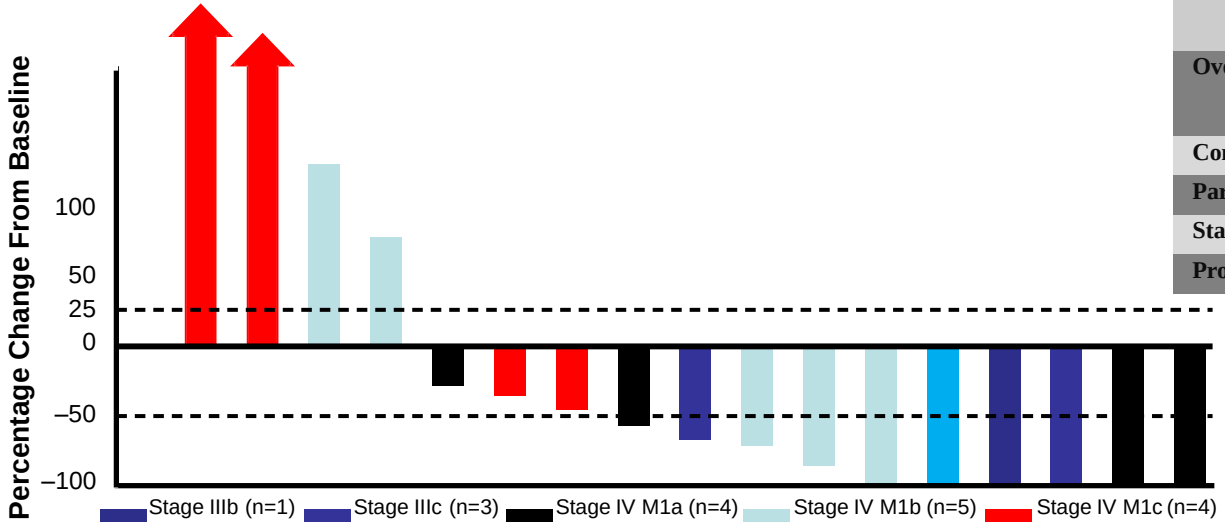
Safety Summary

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	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

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

T-Vec + Ipi in Unresected Stage IIIB-IV Melanoma: Max Change in Tumor Burden

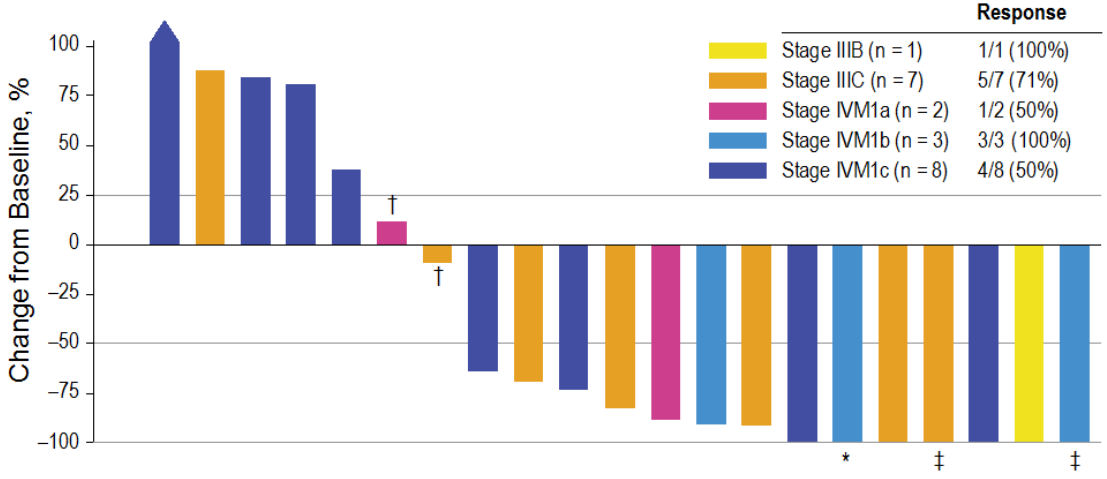


Investigator-Assessed	Responses, n (%) (N = 18*)
Overall response	10 (56) (95% CI: 31-79)
Complete response	6 (33)
Partial response	4 (22)
Stable disease	3 (17)
Progressive disease	5 (28)

*Only patients who received both T-Vec and ipilimumab. CR, CRu, and PD included.
† One patient with PD not shown in the plot because tumor burden could not be accurately calculated (missing post-baseline data)
· Percentage change from baseline: 538
§ Percentage change from baseline: 265

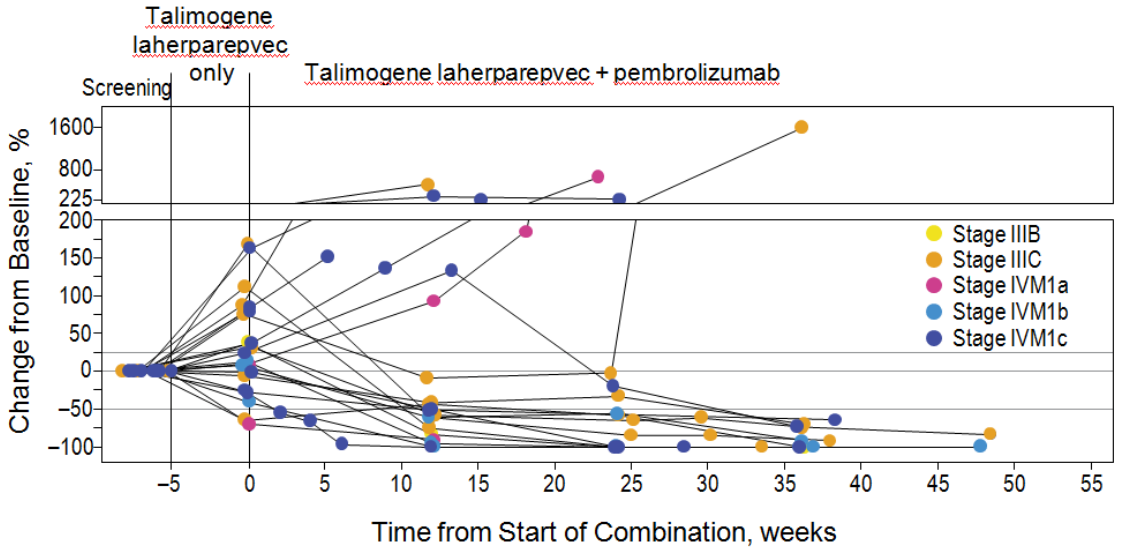
Puzanov I, et al. ASCO 2014

T-VEC+pembrolizumab: Best Change in Tumor Burden



Safety analysis set includes all subjects who received at least one dose of talimogene laherparepvec or pembrolizumab
*no complete response due to presence of nonmeasurable lesions
17 patients were PD-L1 positive
†2 patients with PD-L1 negative
‡2 patients with PD-L1 indeterminate

T-VEC+pembrolizumab: Change in Tumor Burden Over Time



Median tumor follow-up time from first dose: 41 weeks

Top Questions about Immune Checkpoint Inhibitors

- Anti- PD1 vs. Anti-PDL1?
- Ideal schedule/duration of therapy?
- Will/should PDL1 status guide treatment?
- Sequencing/Maintenance Therapy?
- Optimal Combinations?
- Mechanisms of Resistance?

Summary

- Immune checkpoint inhibitors represent a new class of agents that are showing great promise for the treatment of patients with advanced cancer.
- Immune checkpoint inhibitors have a distinct toxicity profile and response assessment that must be taken into account in treating patients with these agents.
- Immune checkpoint inhibitors represent one of several strategies targeting the immune system for therapeutic benefit.

Cancer Immunotherapies: Different Approaches

Approach	Examples	Agents/Targets
Vaccines	Peptide, protein, DC, DNA, virus	
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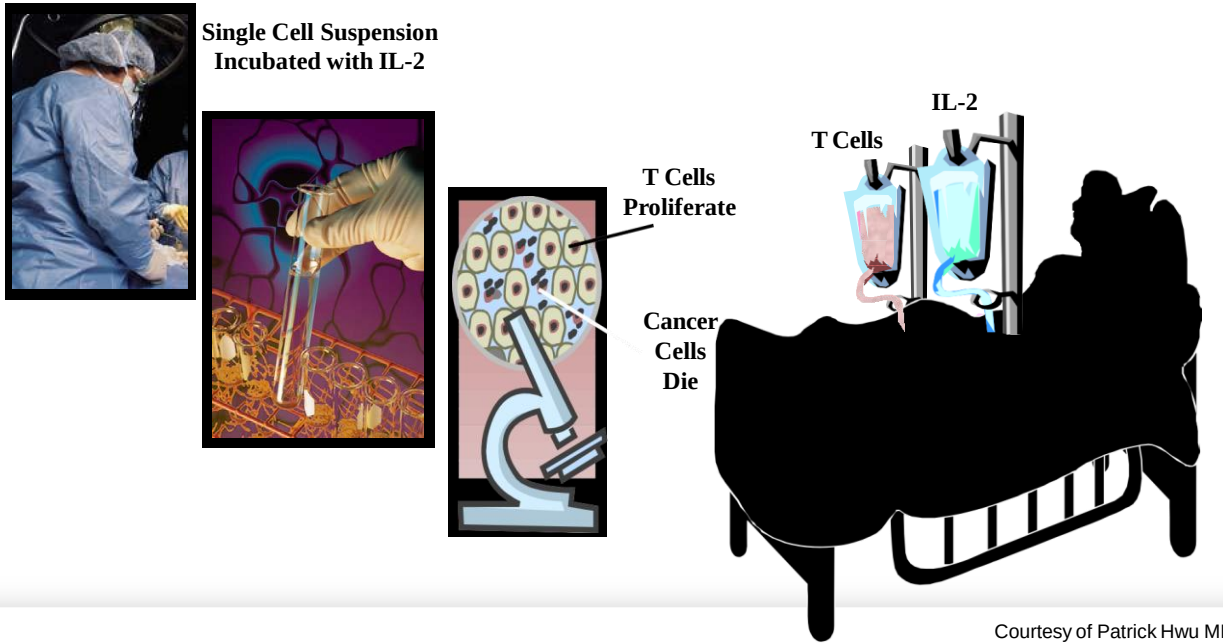
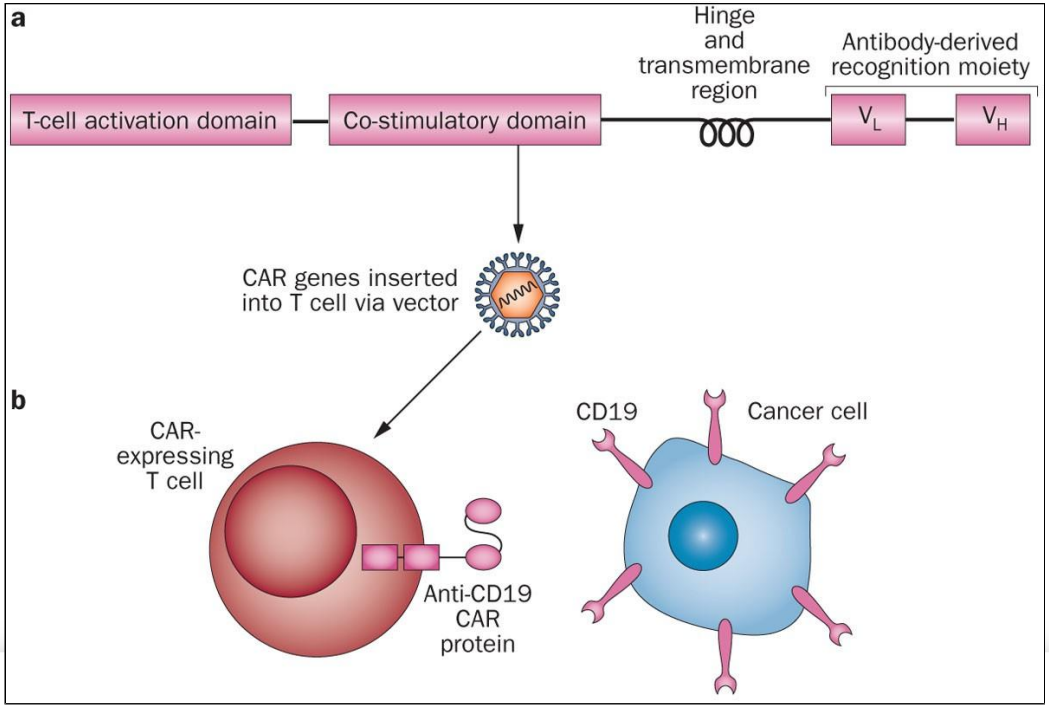
Cytokines		IL-2, IFN-alpha, GM-CSF
Oncolytic Viruses		TVEC
Reversal of Immunosuppression	IDO- inhibitors T-reg depletion	Epacadostat

Adoptive Cell Therapy (ACT) with Antigen Specific T-cells



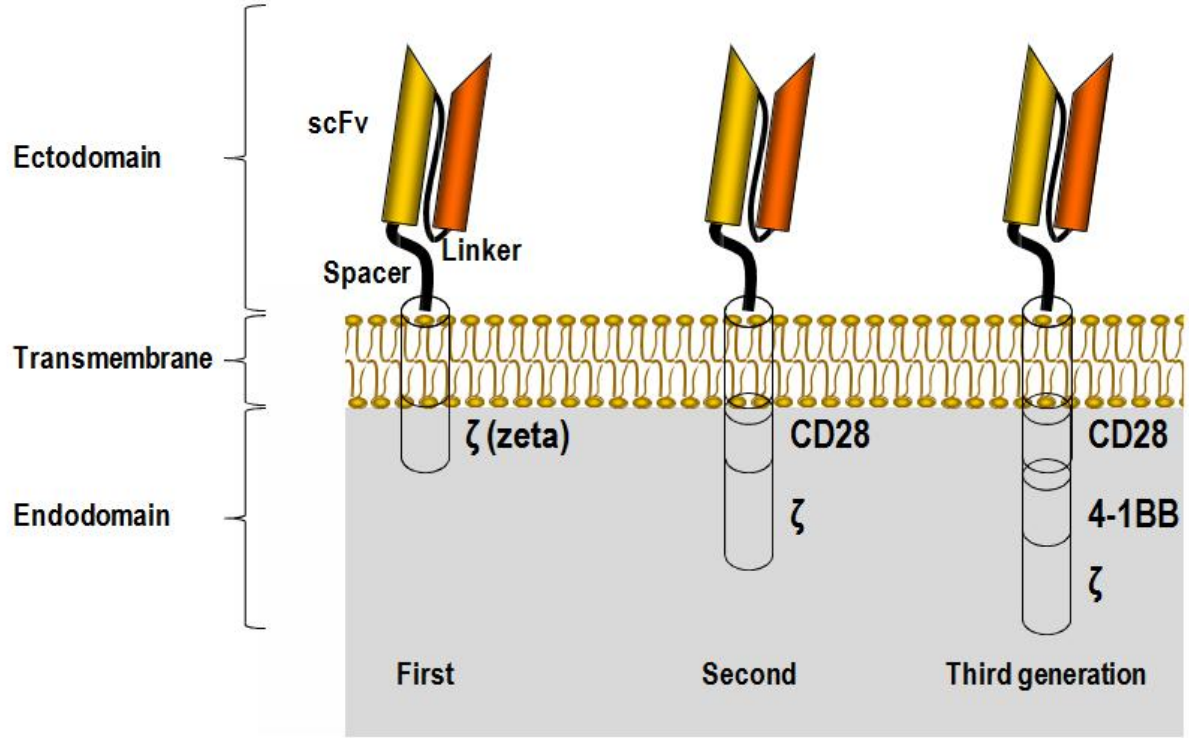
Courtesy of Patrick Hwu MD, PhD – MD Anderson Cancer Center

Chimeric Antigen Receptor (CAR) T cells Targeting CD19 in B Cell Cancers

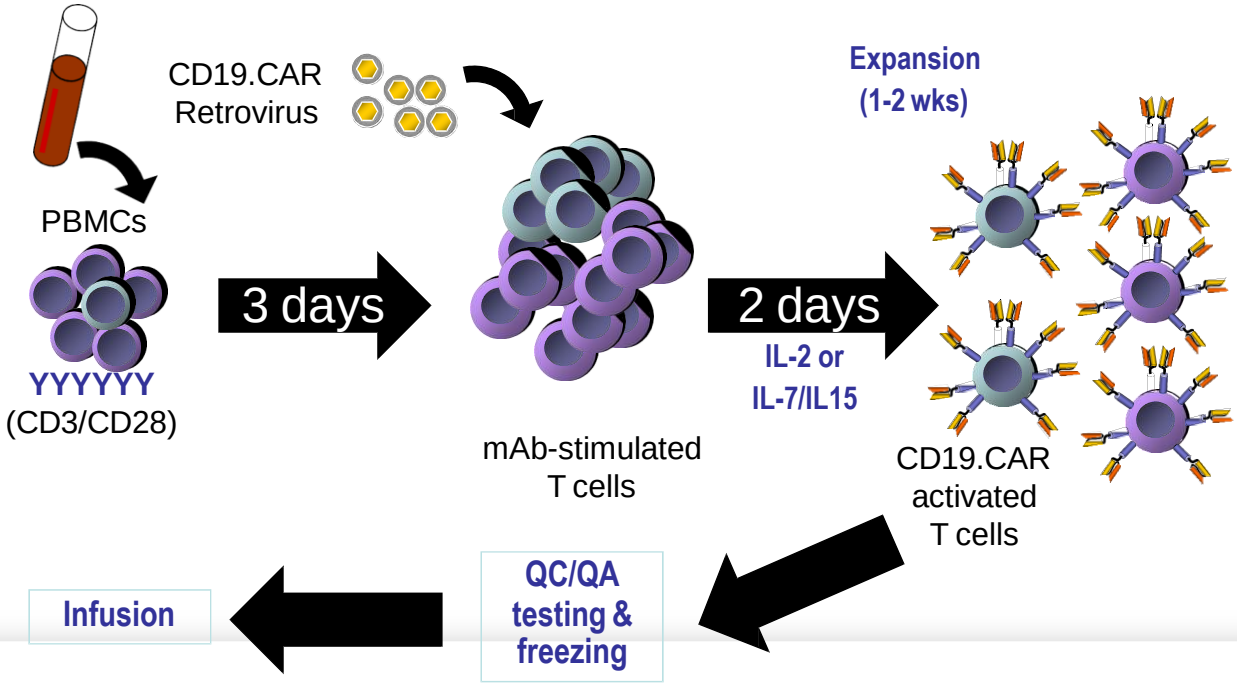


Kochenderfer and Rosenberg. Nat Rev Clin Oncol. 2013

First vs. later generation CARs



CAR-T cell manufacture



CD19.CAR-T cell therapy can be highly effective…

Non-Hodgkin Lymphoma/Chronic Lymphocytic Leukemia

Reference	Center	N	Efficacy
Kochenderfer, JCO 2015	NCI	30 (adult/peds)	53% CR 27% PR
Porter, Blood (ASH) 2014	UPenn	15 (adult)	29% CR 29% PR
Savoldo, JCI 2011	BCM/HMH	6 (adult)	33% SD

Acute Lymphoblastic Leukemia

Reference	Center	N	Efficacy
Maude, NEJM 2014	UPenn	30 (adult/peds)	90% CR
Davila, SciTM 2014	MSKCC	15 (adult)	88% CR
Lee, Lancet 2015	NCI	21 (peds/AYA)	67% CR (ITT)

Questions?

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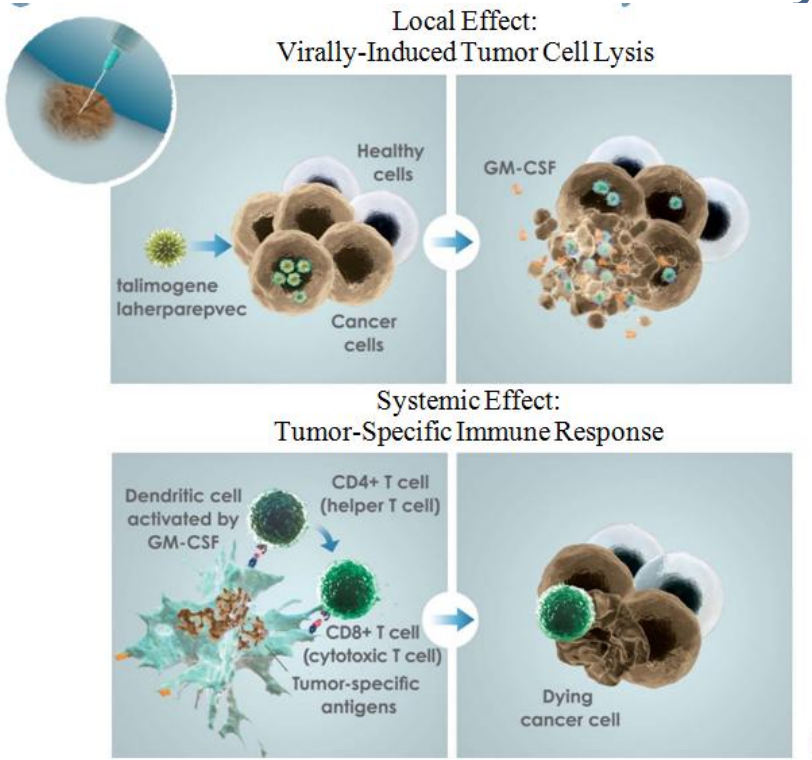
Reversal of Immunosuppression	IDO- inhibitors	Epacadostat
	T-reg depletion	

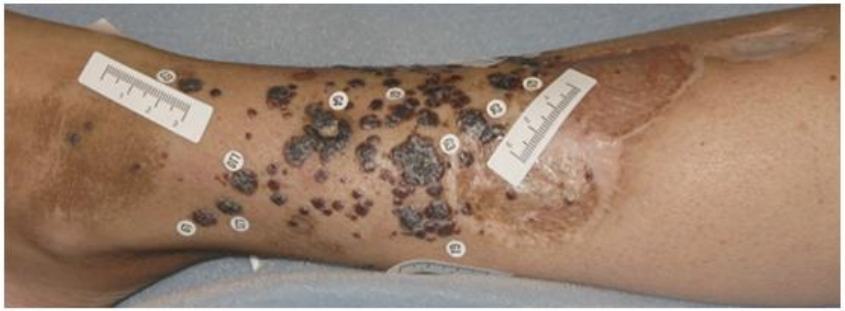
T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects



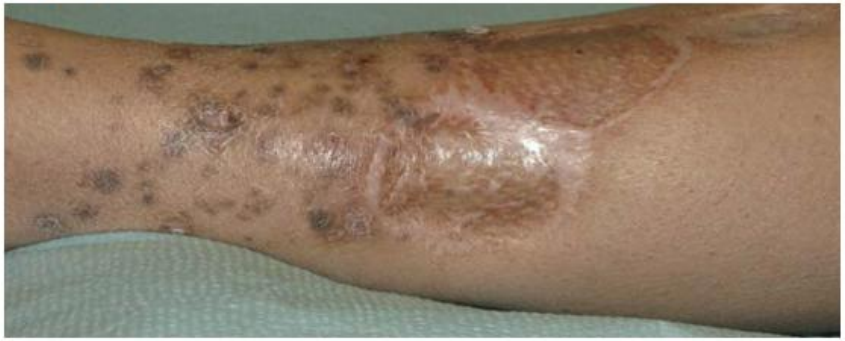
Kaufman et al. ASCO 2014

T-VEC Responses in Injected And Uninjected Lesions

Cycle 1

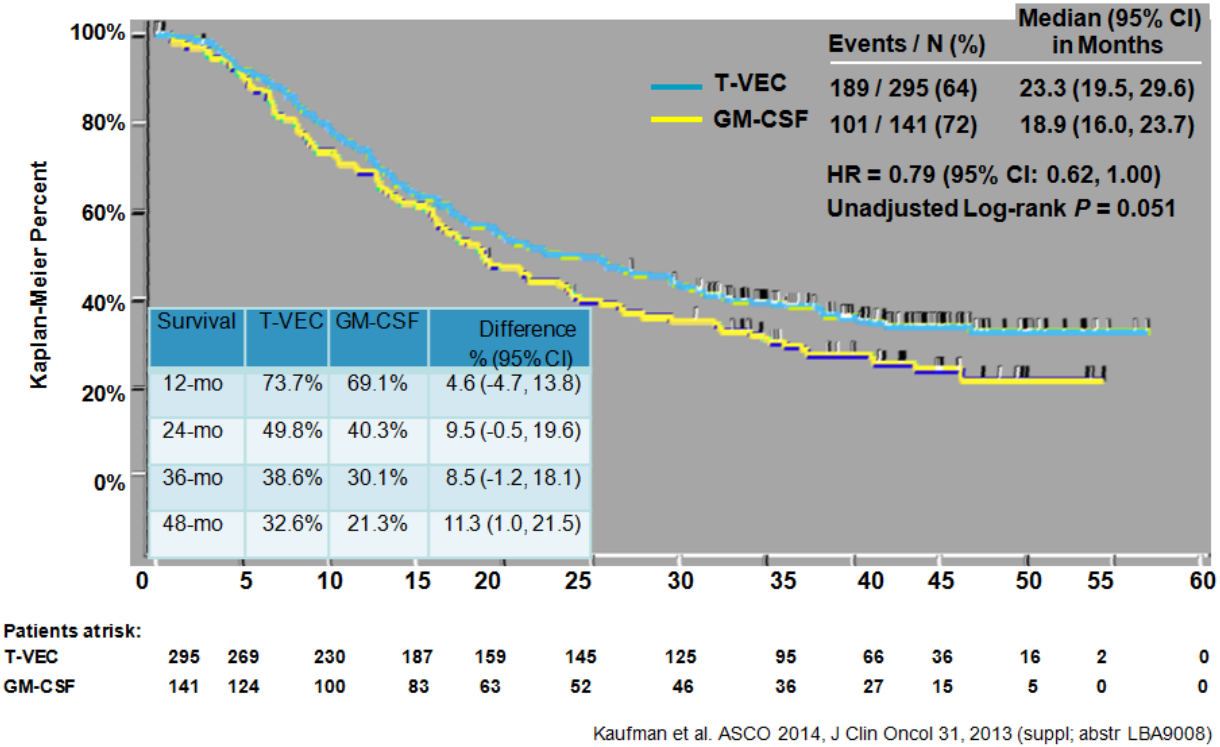


Cycle 13



Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

Primary Overall Survival



Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

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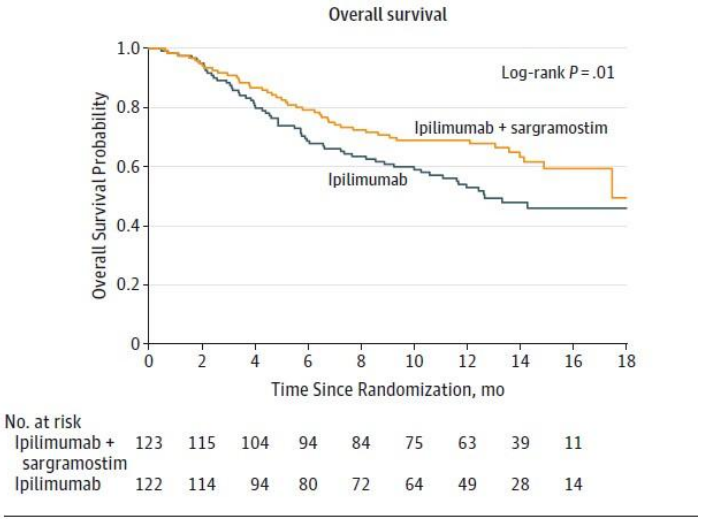
Ipilimumab + sargramostim in Advanced Melanoma



Treatment-Related Grades 3-5 Toxicity by Toxicity Category		
Gastrointestinal[b]	19 (16.1)	32 (26.7)
Investigations	17 (14.4)	18 (15.0)
Dermatology or other skin related	13 (11.0)	14 (11.7)
Metabolic	13 (11.0)	11 (9.2)
Constitutional symptoms	10 (8.5)	8 (6.7)
Musculoskeletal	8 (6.8)	8 (6.7)
Endocrine	4 (3.4)	9 (7.5)
Neurology	4 (3.4)	0
Vascular disorders	3 (2.5)	5 (4.2)
Infection or febrile neutropenia	2 (1.7)	4 (3.3)
Blood or bone marrow	1 (0.8)	1 (0.8)
Cardiac disorders	1 (0.8)	1 (0.8)
Hepatobiliary disorders	1 (0.8)	1 (0.8)
Immune system disorders	1 (0.8)	5 (4.2)
Injury, poisoning, and procedure complications	1 (0.8)	0
Neutrophil count	0	1 (0.8)
Pulmonary[b]	0	9 (7.5)
Renal or genitourinary	0	1 (0.8)
Any toxicity (with worst)[b]	53 (44.9)	70 (58.3)

Hodi, *JAMA*, 2014

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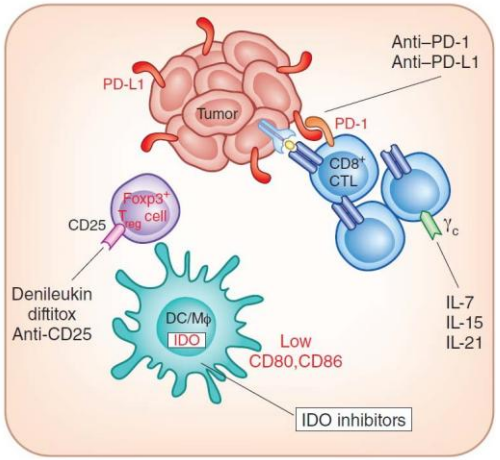
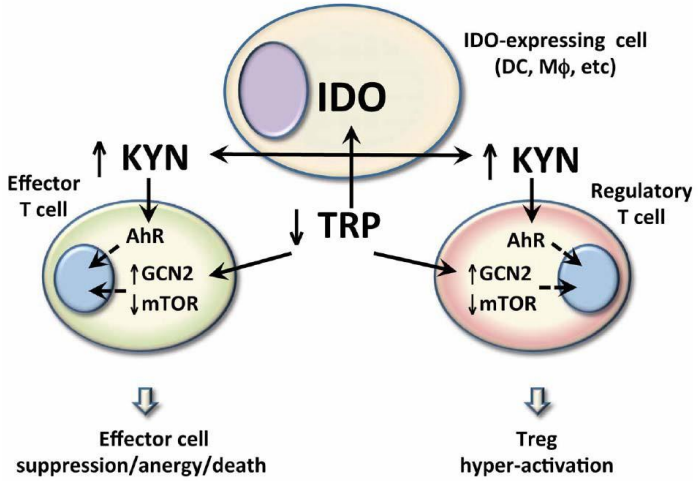
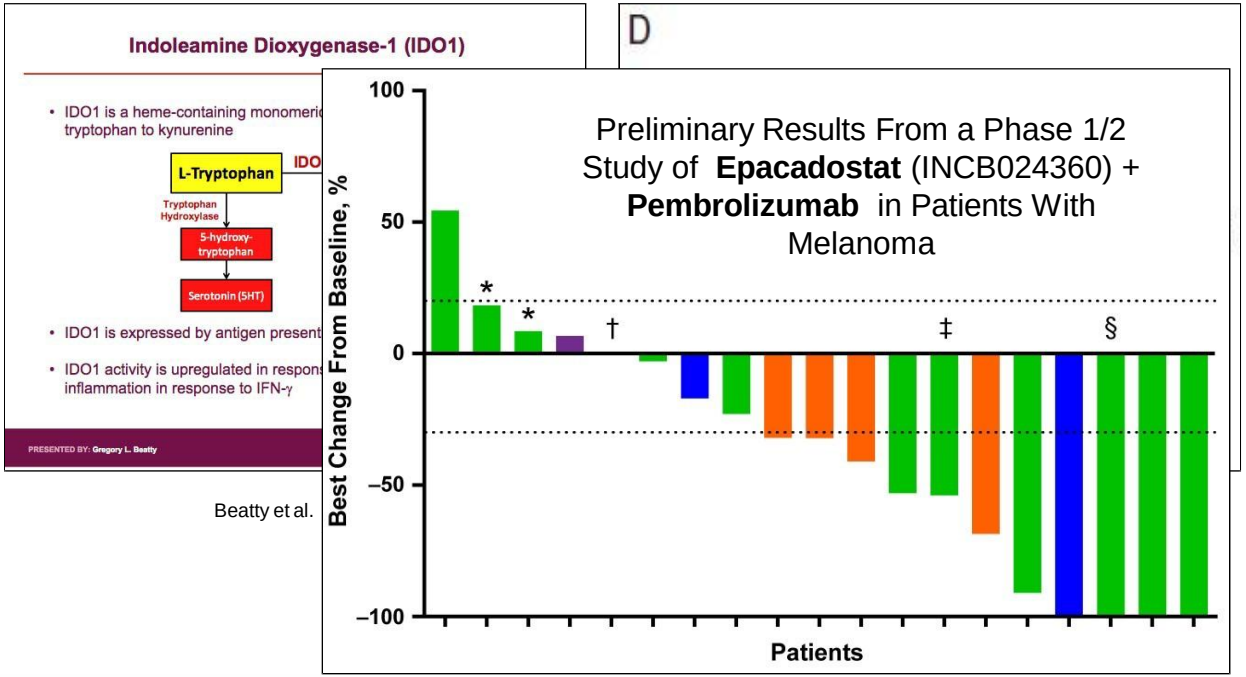
Reversal of Immunosuppression





Sheridan *Nature Biotechnol*. 2015

IDO inhibitor epacadostat + pembrolizumab



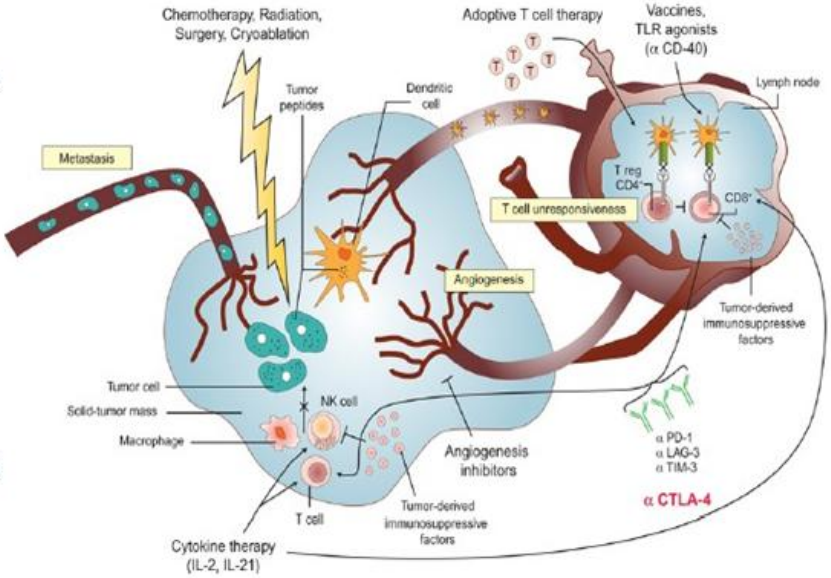
Beatty et al.

RECIST response = 55%, no increase in toxicity from pembrolizumab alone

Hamid et al. SMR 2015

Potential immunotherapy combinations

- Future is likely in combinatio
  - **Multiple checkpoints**
    - (PD-1 + CTLA-4, LAG3 etc.)
  - **Small Molecules Inhibitors**
    - (VEGFi or iNOS modulation + PD-L1)
  - **Radiation**
  - **Chemotherapy**
    - (Cyclophosphamide to deplete T_{reg} prior to checkpoint blockade)
  - **Costimulatory receptors** (OX 40, CD137, GITR, CD40)
  - **Novel Vaccines**
  - **Adoptive Cell Therapy**



Grosso and Jure-Kunkel, Cancer Immunity, 2013

Questions?

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