Understanding Checkpoint Inhibitors: Approved Agents, Drugs in Development and Combination Strategies

Tumor Immunology 101: A Navigation Guide to the Growing Field of Cancer Immunotherapy

Advances in Cancer Immunotherapy™ (ACI™)

August 7, 2015

Washington D.C.

Disclosures

- Consulting Fees
  - Genentech-Roche
  - Bristol-Myers Squibb
  - AztraZeneca/MedImmune
  - Pfizer, Novartis
  - Kyowa-Kirin
  - Amgen
  - Merus
  - Seattle Genetics
  - Immune Design
  - Prometheus
  - Anaeropharma
  - Astellas-Agensys
  - Immunova
  - Nektar
  - Neostem
  - Pierre-Fabre (not paid)
- Scientific Advisory Board
  - Symphogen
  - Lion Biotechnolgies
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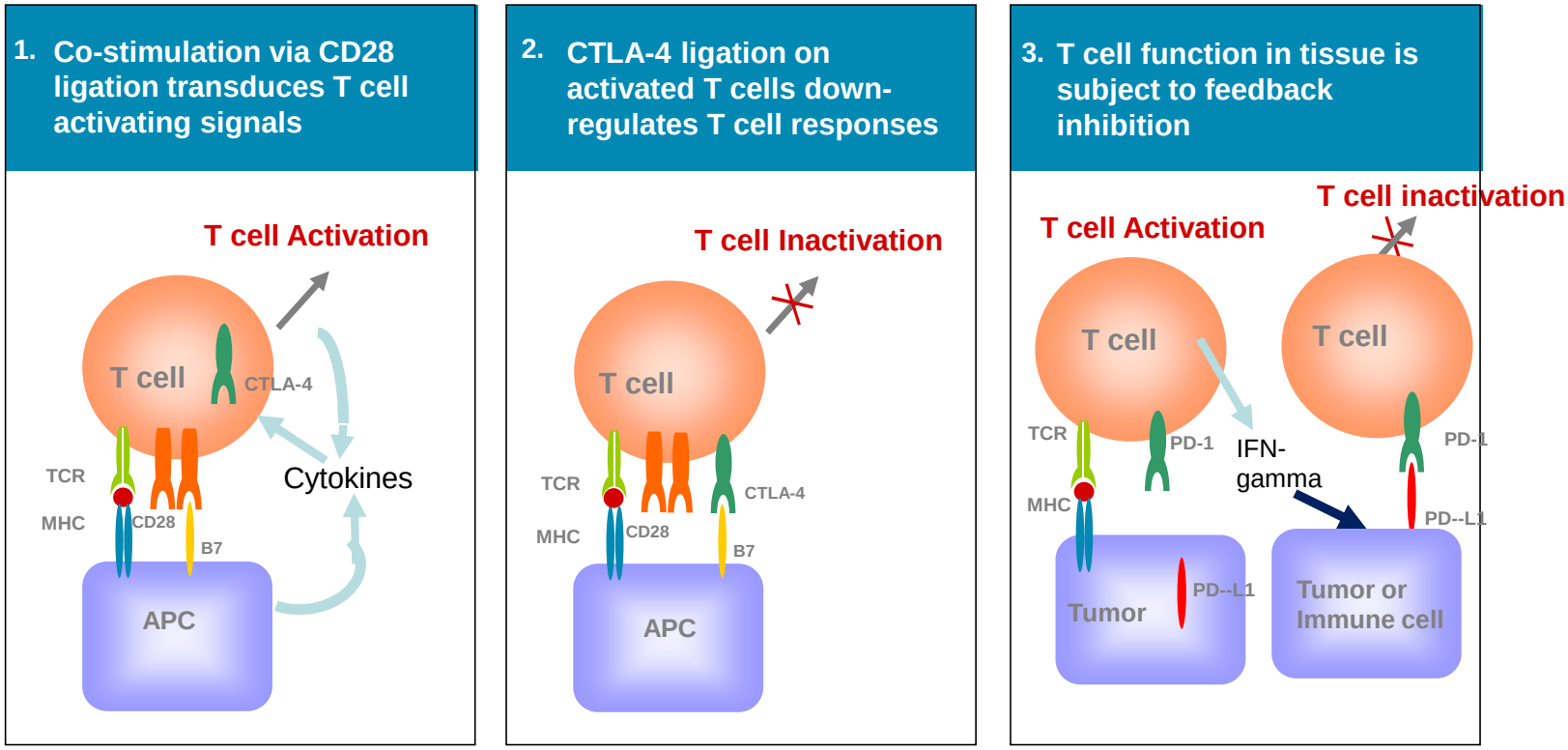
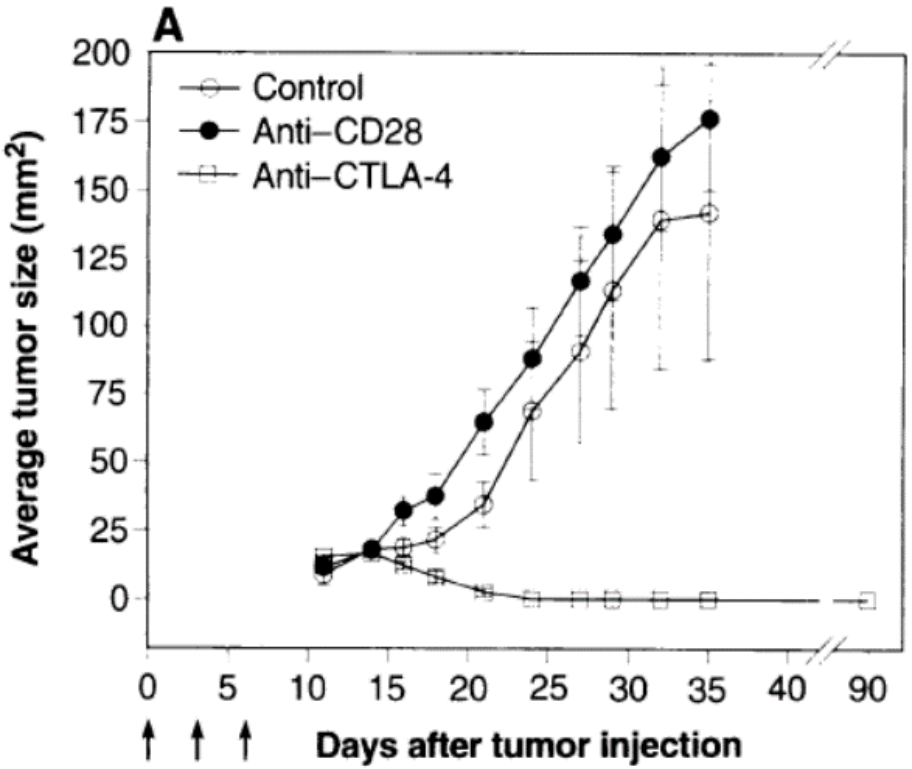
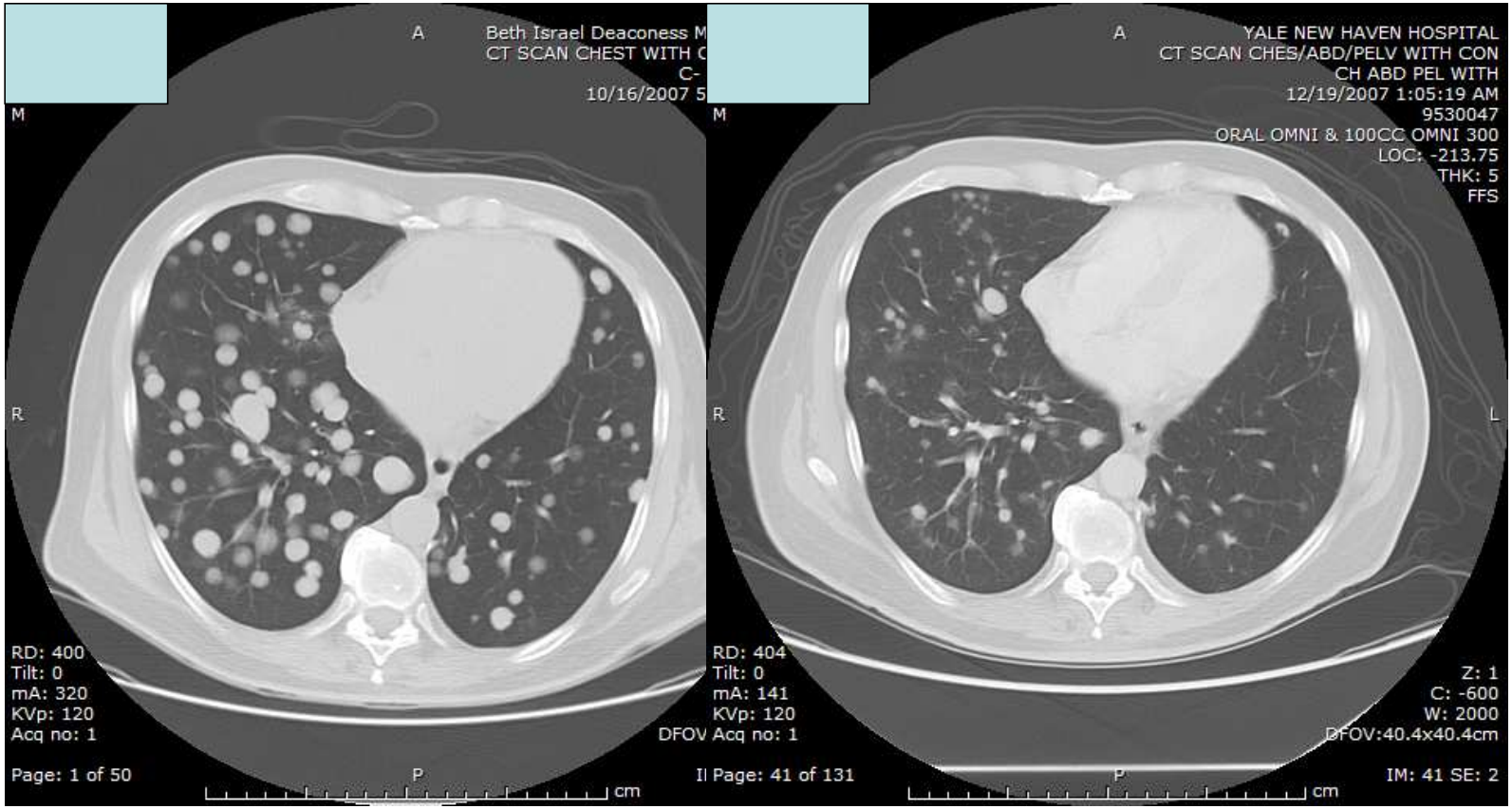
T-cell Activation, Proliferation, and Function is Controlled by Multiple Agonist and Antagonist Signals

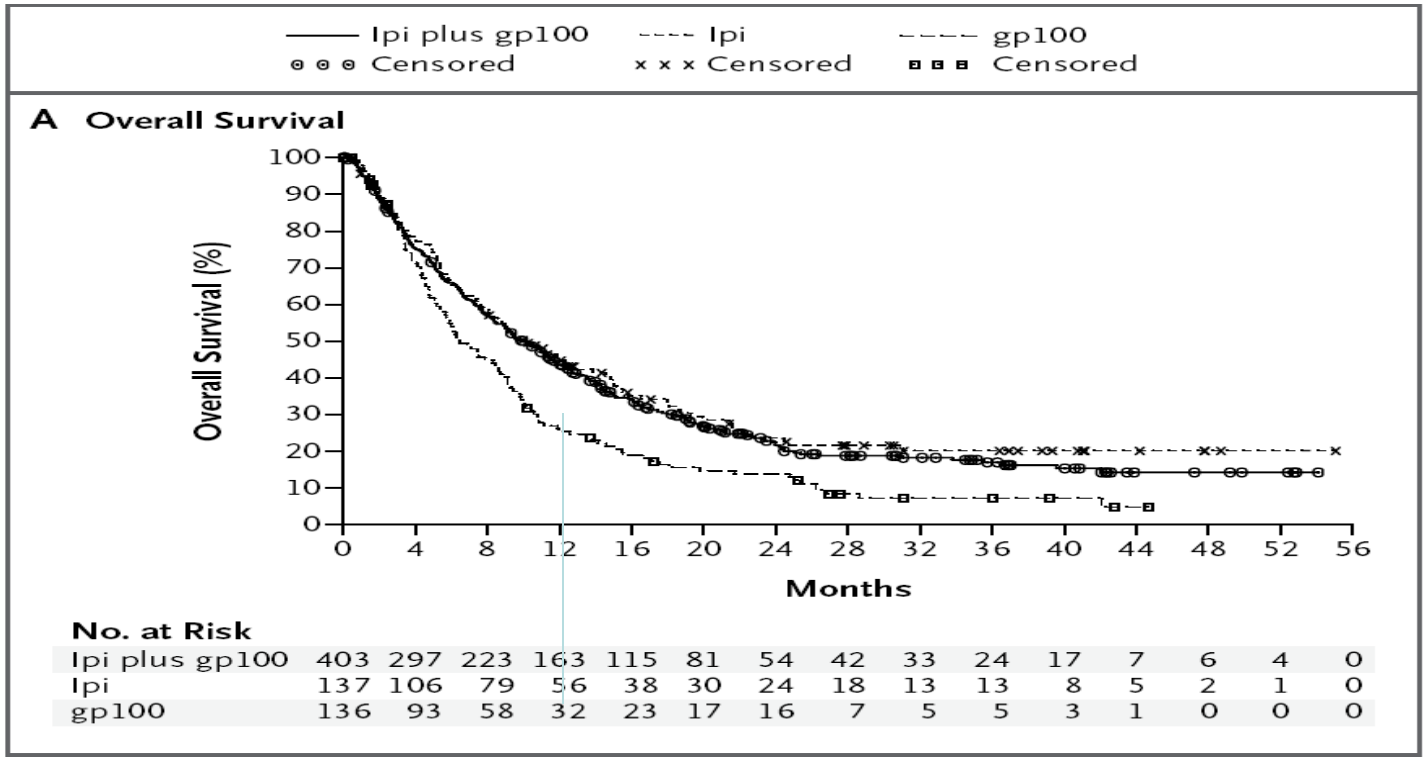



A
Control
Anti–CD28
Anti–CTLA-4
Average tumor size (mm²)
200
175
150
125
100
75
50
25
0
0
5
10
15
20
25
30
35
40
90
Days after tumor injection

Response to Ipilimumab 10 mg/kg x 2 doses



2 baseline brain mets regressed also:
No disease progression 7+ years



Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

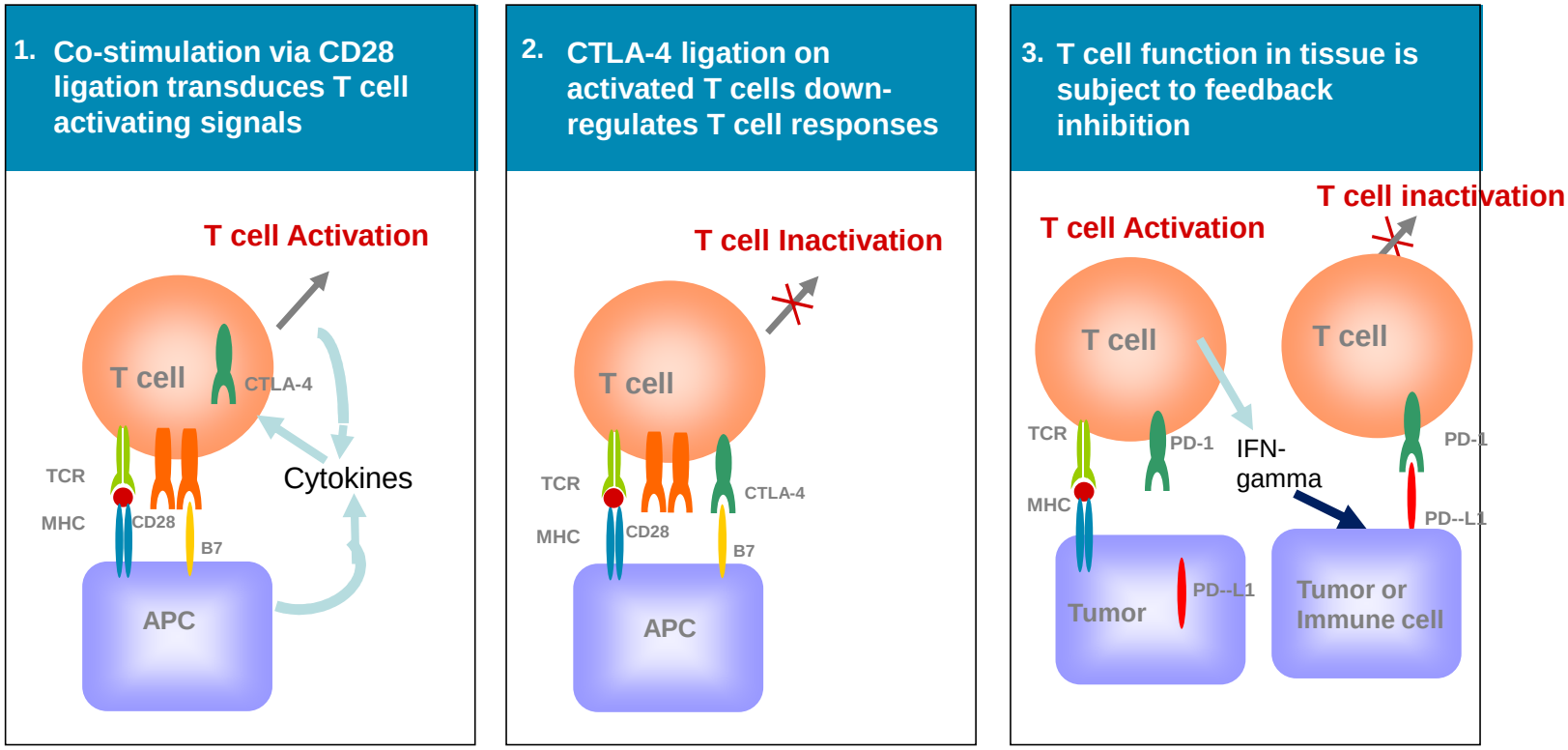
Anti-CTLA4, Other Clinical Activity

- Ovarian
- Lymphoma (PR in follicular lymphoma)
- Gastric-esophageal (2/18 with tumor regression)
- Pancreas (1/27 responding)
- Colon (1/46 PR)
- **RCC (9.8%)**
- NSCLC (+ chemotherapy)
- Prostate
- Mesothelioma

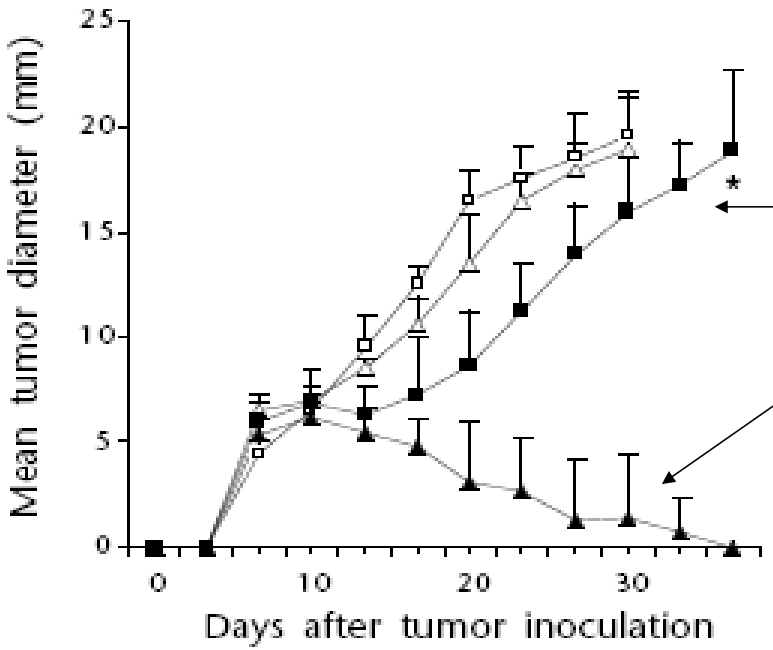
Key Aspects of Anti-CTLA4 Therapy

- **Can be associated with autoimmune adverse events**
  - **Any organ, but rash, colitis, hepatitis and endocrinopathies are most common**
  - **May require steroids +/- additional immunosuppressive agents**
- **Unique kinetics of response in some patients**
  - **SD with slow, steady decline in total tumor volume**
  - **Response after initial increase in total tumor volume**
  - **Response in index plus new lesions at or after the appearance of new lesions**
  - **Continued benefit after Rx of discordant progressing lesions**
- **Possibility of second response with re-induction after PD**

T-cell Activation, Proliferation, and Function is Controlled by Multiple Agonist and Antagonist Signals



B7-H1 (PD-L1) negates positive co-stimulation in tumor cells



Expression of checkpoint blocks effect of strong co-stimulation

+ B7.1
and B7-H1

+B7.1
Strong co-stimulation → tumor regression

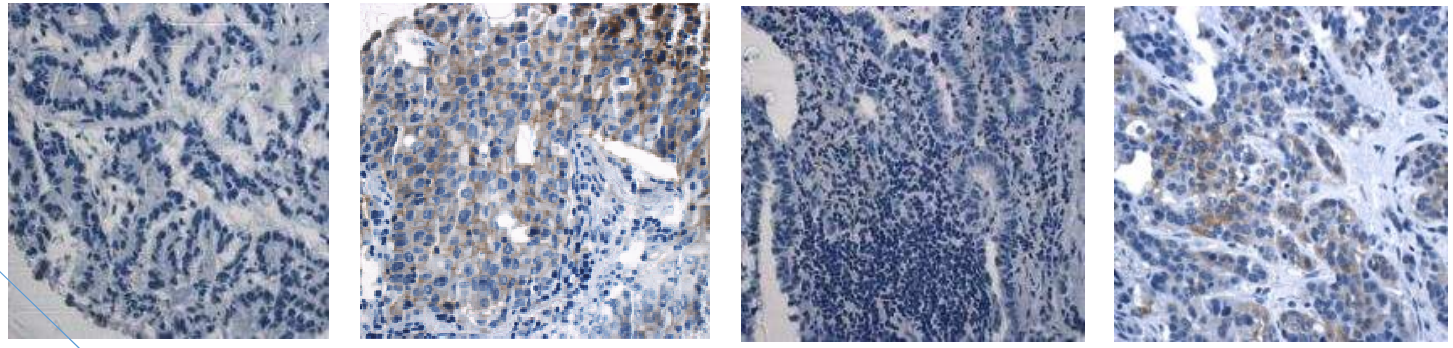
Open triangle – P815
Rectangles – P815/B7-H1
Closed triangle – P815/B7-1
Closed squares – P815/B7-1/B7-H1

22/22 human melanomas expressed B7-H1, 17/22 at 2-3+ intensity

Dong et al, Nat Med, 2002

Presence of PD-L1 or TILs[1]

PD-L1⁻/TIL⁻	PD-L1⁺/TIL⁺	PD-L1⁻/TIL⁺	PD-L1⁺/TIL⁻



45%	17%	26%	12%
Type 1	**Type 2**	**Type 3**	**Type 4**
45%	41%	13%	1%

NSCLC

Melanoma

Schalper and Rimm, Yale University

Taube et al

Table 2. Correlation of B7-H1 expression by melanocytes with the presence of immune cell infiltration.

Histology	Total	Number of cases/total cases (%)				*P**
		B7-H1⁺†		B7-H1⁻		
		TIL⁺‡	TIL⁻	TIL⁺	TIL⁻	
Benign nevi	40	14/14 (100)	0/14 (0)	4/26 (15)	22/26 (85)	<0.0001
Primary melanomas (in situ or invasive)	54	19/19 (100)	0/19 (0)	15/35 (43)	20/35 (57)	<0.0001
Metastases	56	23/24 (96)	1/24 (4)	7/32 (22)	25/32 (78)	<0.0001
All	150	56/57 (98)	1/57 (2)	26/93 (28)	67/93 (72)	<0.0001

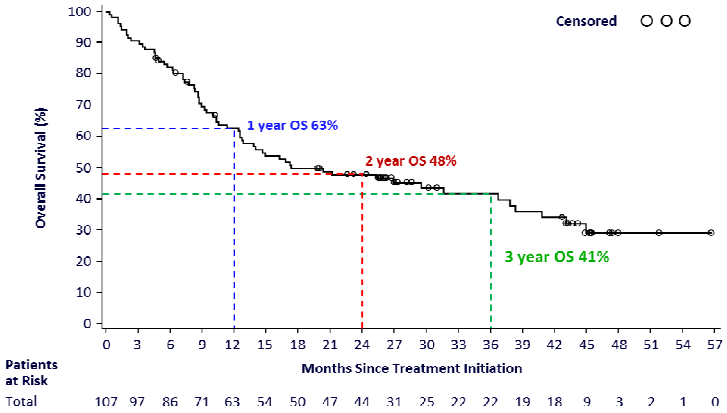
*Fisher's exact test, two-sided, was conducted on the 2 × 2 matrix defined by B7-H1 (±) expression and TIL (±) for each lesion type. †More than 5% melanocytes with membranous expression on IHC. ‡Including mild, moderate, and severe lymphocyte infiltrates and their associated histiocytes/macrophages.

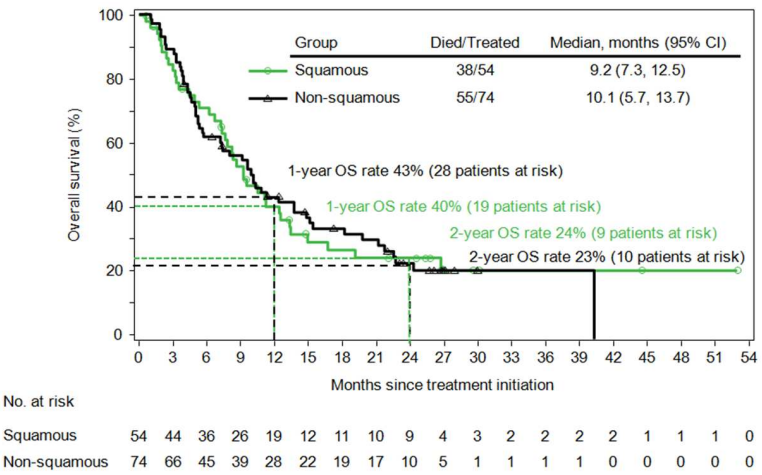
Clinical Activity of Nivolumab (anti-PD-1) (Phase 1 Multi-Dose Trial)

Dose mg/kg	ORR % (n/N)	Estimated Median DOR Weeks (Range)	Stable Disease Rate ≥24 Wks % (n/N)	Median PFS Months (95% CI)
NSCLC	**17 (22/129)**	**74 (6+, 134+)**	**10 (13/129)**	**2 (2, 4)**
MEL[a]	**31 (33/107)**	**104 (18, 117+)**	**7 (7/107)**	**4 (13, 44)**
RCC[a]	**29 (10/34)**	**56 (37, 127+)**	**27 (9/34)**	**7 (4, 13)**

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival
[a]1 CR was noted in MEL and 1 CR was noted in RCC.

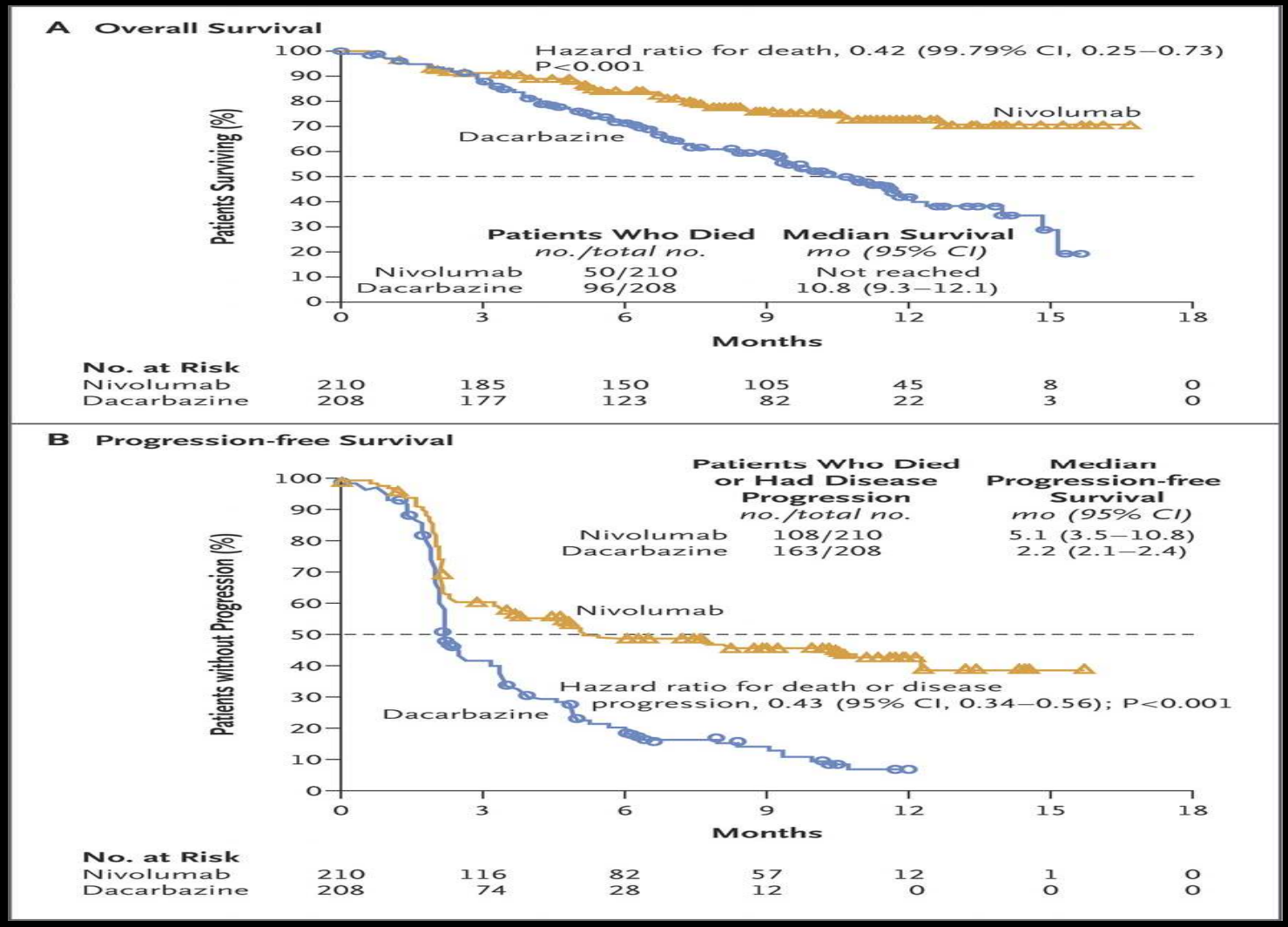
- 30/65 (46%) responses were evident at first tumor evaluation (8 weeks)
- 42/65 (65%) responses were ongoing >1 year
- No OR in CRPC or CRC





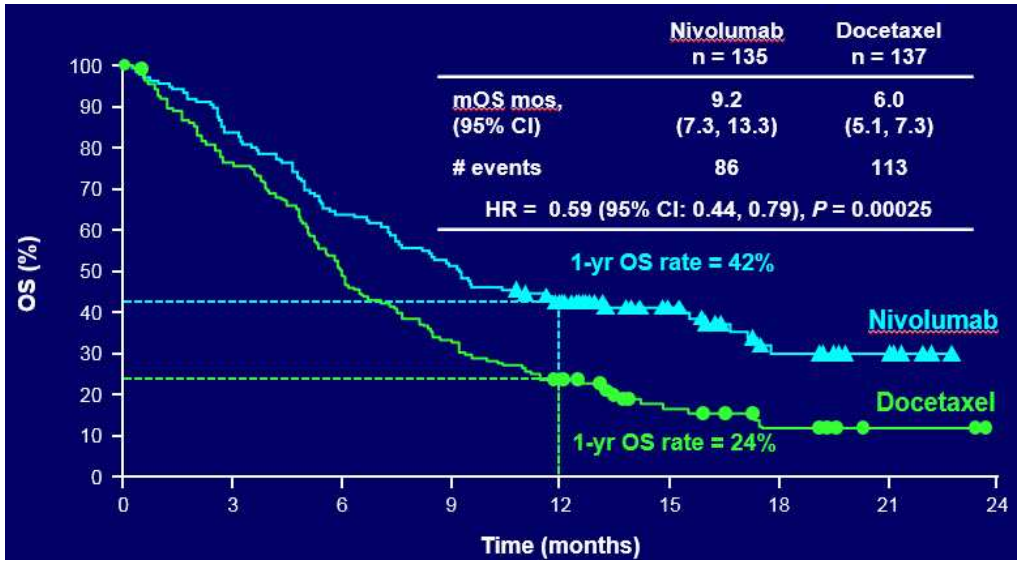
Robert C et al. N Engl J Med 2014. DOI:
10.1056/NEJMoa1412082

The NEW ENGLAND JOURNAL of MEDICINE

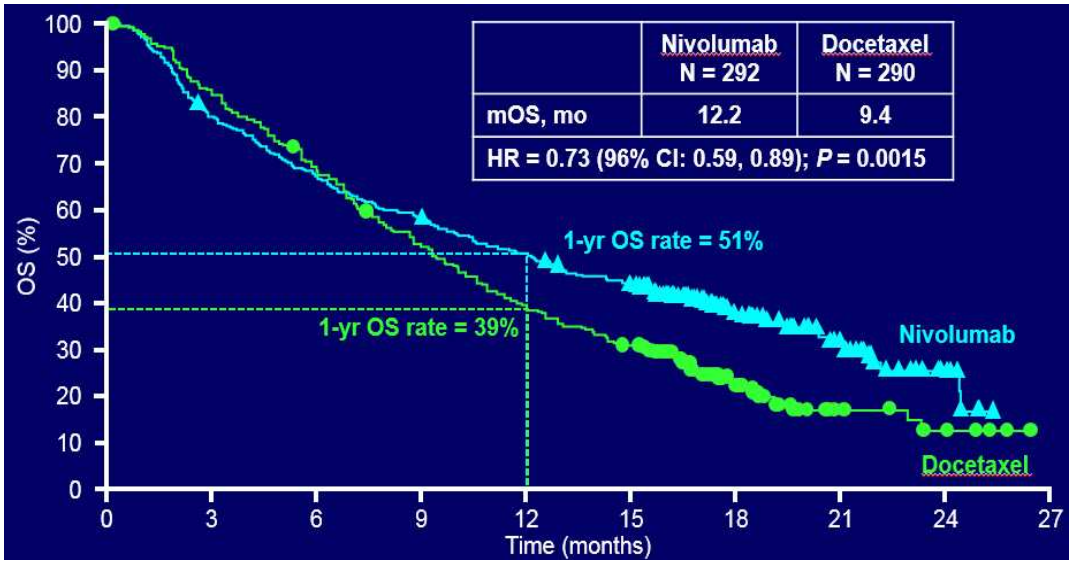


Randomized phase III trials of nivolumab vs. docetaxel in NSCLC

Trial 17: Squamous Cell Carcinoma



Trial 57: Non-Squamous Cell Carcinoma



Spectrum of PD-1/PD-L1 Antagonist Activity

Active

- **Melanoma**
- **Renal cancer (clear cell and non-clear cell)**
- **NSCLC – adenocarcinoma and Squamous cell**
- Small cell lung cancer
- Head and neck cancer
- Gastric and GE junction
- **Mismatch repair deficient tumors (colon, cholangiocarcinoma)**
- Bladder
- Triple negative breast cancer
- Ovarian
- Glioblastoma
- Hepatocellular carcinoma
- Thymoma
- Mesothelioma
- Cervical
- **Hodgkin Lymphoma**
- Diffuse large cell lymphoma
- Follicular lymphoma
- T-cell lymphoma (CTCL, PTCL)
- **Merkel Cell**

Minimal to no activity:

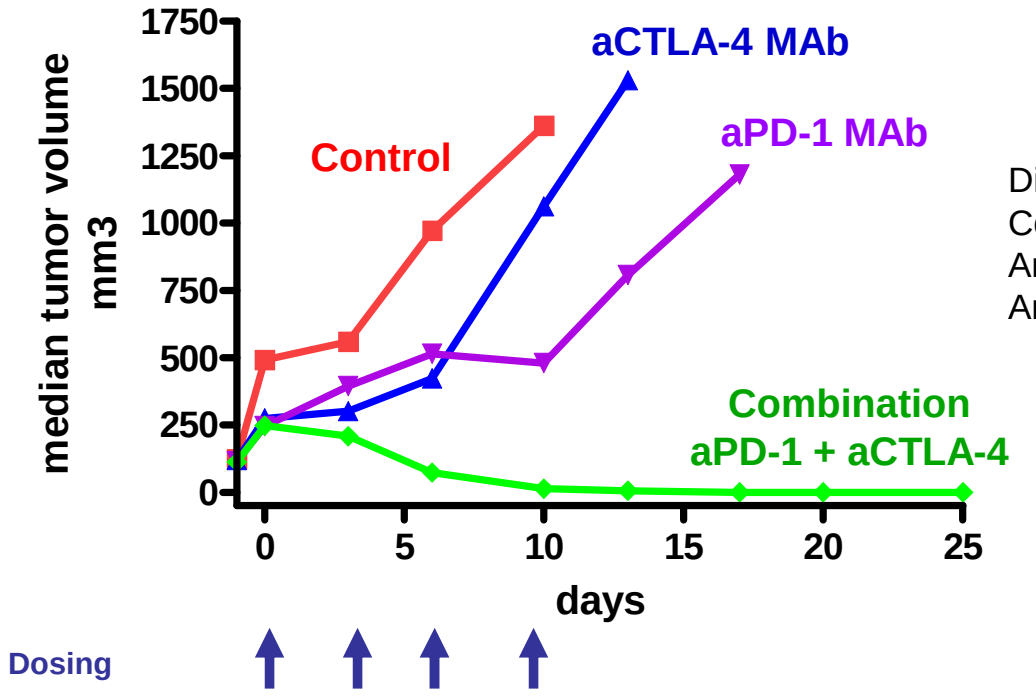
- Prostate cancer
- MMR+ Colon cancer
- Myeloma
- Pancreatic Cancer

Major PD-1/PD-L1 antagonists

- Nivolumab (anti-PD-1)
- Pembrolizumab (anti-PD-1)
- Atezolizumab (MPDL3280, anti-PD-L1)
- MEDI-4736 (anti-PD-L1)

Synergistic Activity with Anti-PD-1 and Anti-CTLA-4 Antibodies

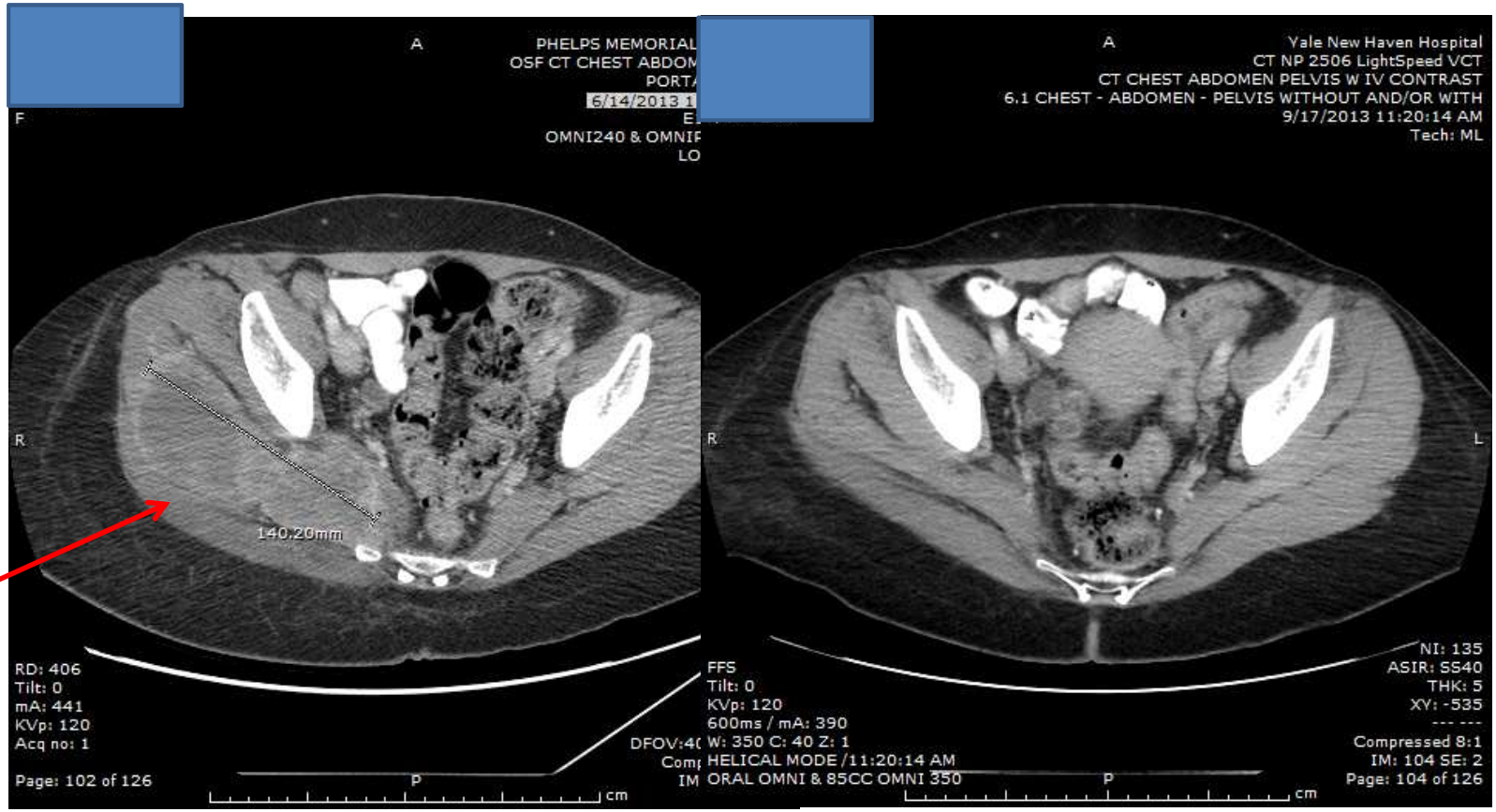
Combination of Non-Efficacious Doses of anti-PD1 and anti-CTLA-4 Antibodies is Efficacious in Mouse Model



Different roles in T cell Differentiation-
Compensatory upregulation
Anti-CTLA4 elimination of tumor Treg
Anti-CTLA4 induced tumor T cell infiltration

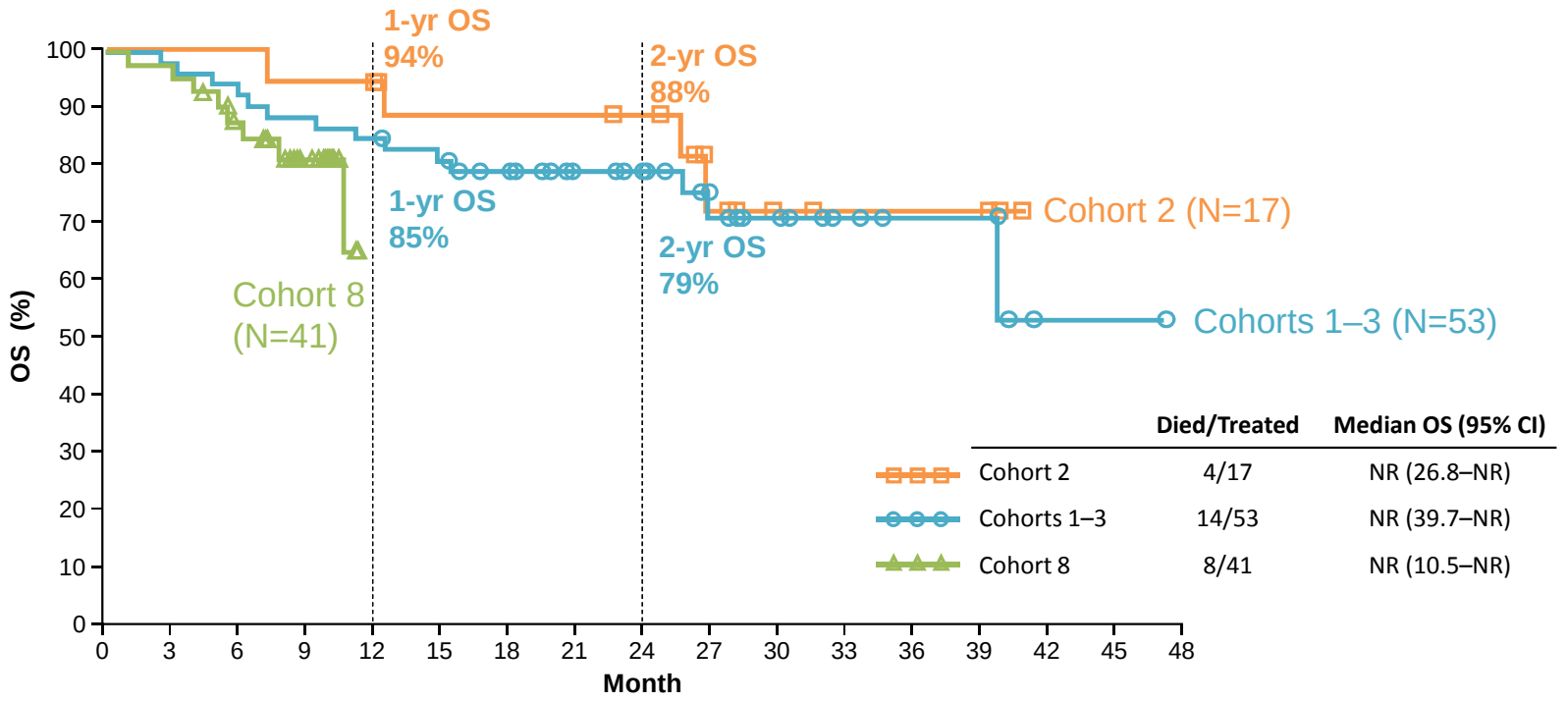
Provided by Alan Korman, BMS

Cohort 8, Ipilimumab + nivolumab, response at 12 weeks



Prior therapy with HD-IL2, multiple resections, Vemurafenib, and RT;
LDH > 2000 at baseline; LDH nearly normal within 3 weeks

Overall Survival



	Died/Treated	Median OS (95% CI)
Cohort 2	4/17	NR (26.8–NR)
Cohorts 1–3	14/53	NR (39.7–NR)
Cohort 8	8/41	NR (10.5–NR)

Patients at Risk

Cohort 2 (Nivo 1 + Ipi 3)	17	17	17	16	16	14	14	14	13	7	4	3	3	3	0	0	0
Cohorts 1–3	53	52	49	47	45	42	37	30	25	16	11	7	5	5	1	1	0
Cohorts 8 (Nivo 1 + Ipi 3)	41	40	31	16	0	0	0	0	0	0	0	0	0	0	0	0	0

- **Cohort 8 uses the same dosing schedule that is being tested in the phase 3 trial (CA209-067)**

JUNE 2014 data analysis.

Nivo + IPI: Response to Treatment

	NIVO (N=316)	NIVO + IPI (N=314)	IPI (N=315)
ORR, % (95% CI)*	**43.7** (38.1–49.3)	**57.6** (52.0–63.2)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.00001	<0.00001	--
Best overall response — %			
Complete response	8.9	11.5	2.2
Partial response	34.8	46.2	16.8
Stable disease	10.8	13.1	21.9
Progressive disease	37.7	22.6	48.9
Unknown	7.9	6.7	10.2
Duration of response (months)			
Median (95% CI)	NR (11.7, NR)	NR (13.1, NR)	NR (6.9, NR)

*By RECIST v1.1.

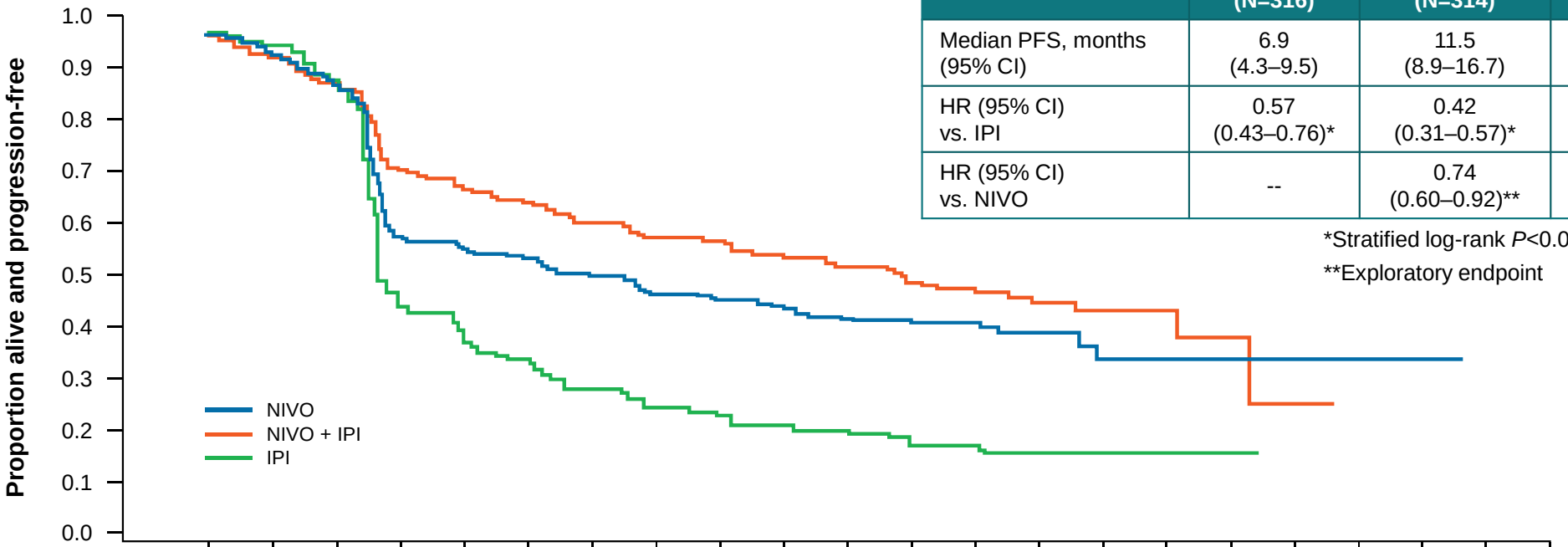
NR, not reached.

Nivo/Ipi vs. Ipi vs Nivo: Co-primary Endpoint: PFS (Intent-to-Treat)

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

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

**Exploratory endpoint



Number at Risk																						
NIVO	316	292	271	170	160	147	136	132	124	124	106	86	50	38	14	9	6	2	1	1	1	0
NIVO + IPI	314	293	275	208	191	173	164	163	151	151	137	116	65	54	18	11	7	2	1	0	0	0
IPI	315	285	265	118	95	77	68	63	54	54	47	42	24	17	7	4	3	0	0	0	0	0

PRESENTED AT: ASCO Annual '15 Meeting

Adverse Events from Immune Checkpoint Inhibitors

- Generally do not induce cytokine like effects
- Autoimmunity can affect any organ system
  - But skin, GI, liver, and endocrine organs most common
  - Multiple organ systems can be affected (concurrently or serially)
- Incidence/severity anti-CTLA-4 > PD-1/PD-L1 antagonists
- Dose-relationship for anti-CTLA-4; not evident for active range of anti-PD-1/PD-L1
- Re-challenge with same agent often (but not always) leads to recurrent toxicity
- High grade AE to one class does not preclude safe administration of the other class
- Vast majority of events (except endocrine) completely reversible over time

N Engl J Med 2015;373:23-34.
DOI: 10.1056/NEJMoa1504030

Ipi/Nivo versus Nivo versus Ipi, Larkin et al, NEJM

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

Unusual Immune Checkpoint Adverse Events

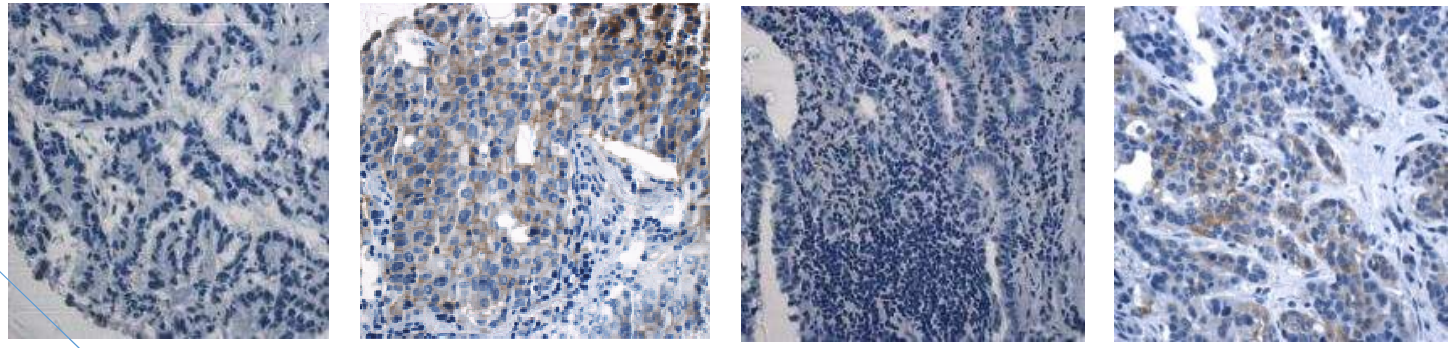
- Systemic inflammatory syndrome (first dose)
- Severe arthritis
- Myositis
- Pneumonitis
- Nephritis
- Bowel perforation
- Meningitis
- Myasthenia Gravis
- Ascending polyneuropathy (Guillan-Barre)
- Uveitis
- Thrombocytopenia (ITP)
- Dry eye syndrome
- Lichen planus
- Alopecia areata
- Insulin-dependent diabetes mellitus

Principles of AE Management

- Onset of adverse effects not predictable for individuals
- Close follow-up of patients, and timely management necessary to minimize morbidity
- Set of basic clinical decisions
  - Autoimmune or other cause?
  - Hold or continue treatment?
  - When to start steroids?
  - Dose? Duration?
  - PO or IV?
  - Inpatient versus outpatient?
  - When to start second-line immune suppressive?

Presence of PD-L1 or TILs[1]

PD-L1⁻/TIL⁻	PD-L1⁺/TIL⁺	PD-L1⁻/TIL⁺	PD-L1⁺/TIL⁻



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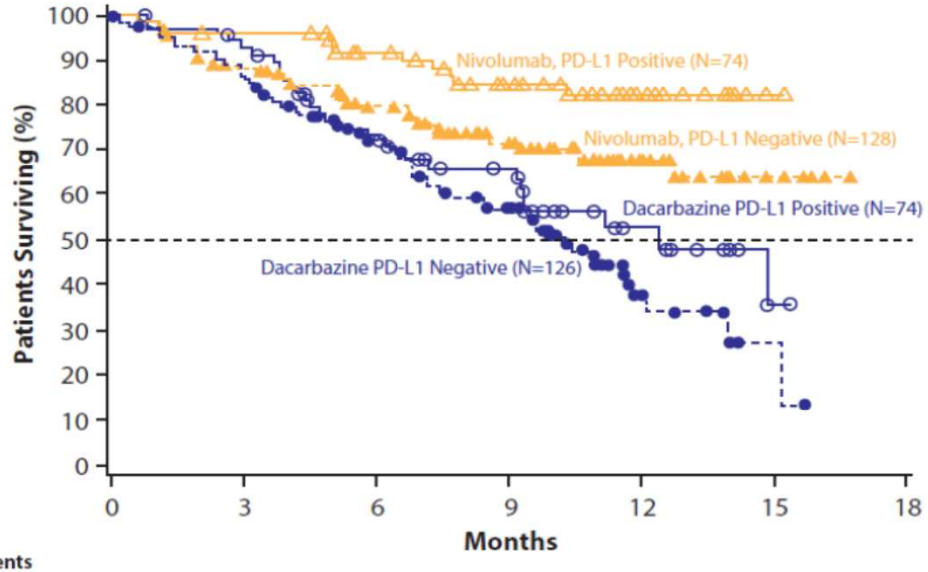
Robert C et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1412082

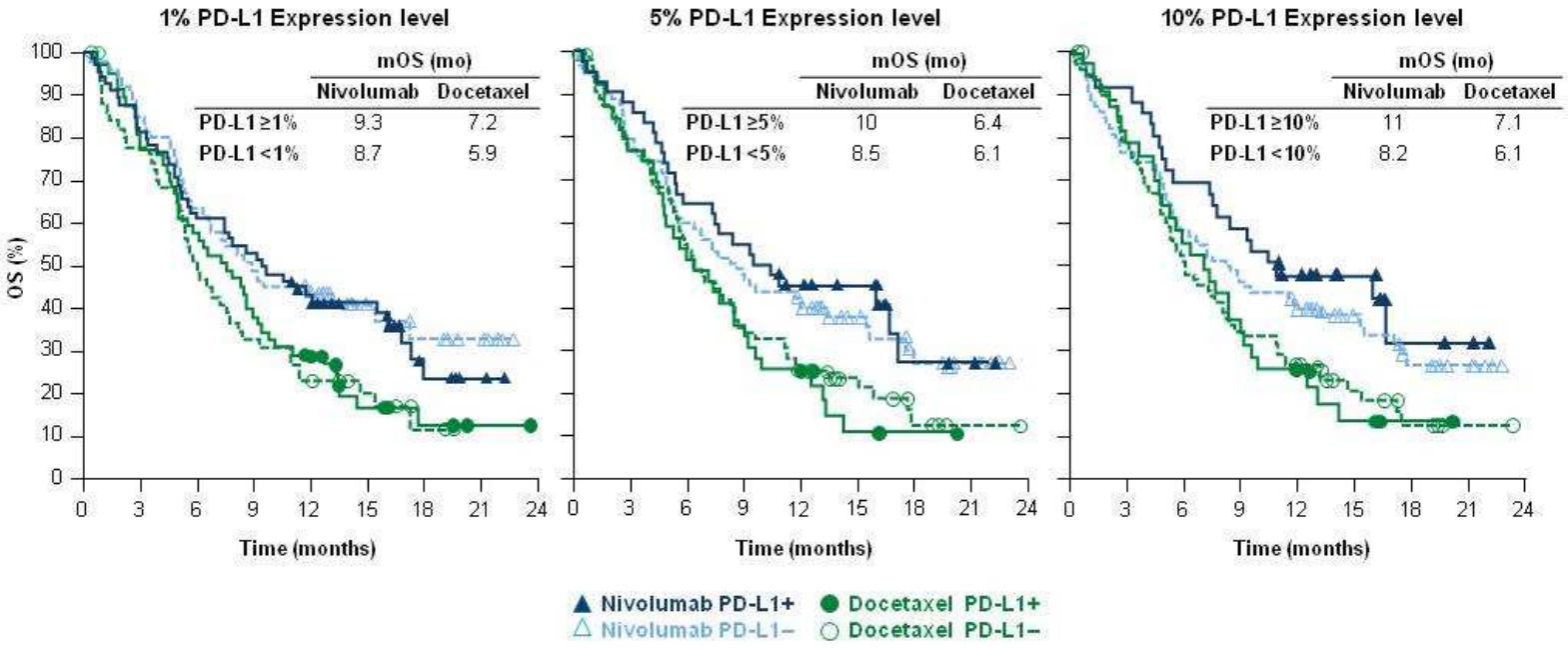
Figure S3 Kaplan-Meier curve for overall survival by treatment group and PD-L1 status subgroup. The median overall survival was not reached in the nivolumab group, regardless of PD-L1 status (n=74, PD-L1 positive; n=128, PD-L1 negative). In the dacarbazine group, median overall survival was 12.4 months (95% CI, 9.2–N.A.) and 10.2 months (95% CI, 7.6–11.8) in the PD-L1 positive (n=74) and PD-L1 negative (n=126) subgroups respectively



Number of Patients at Risk							
Nivolumab, PD-L1 Positive	74	69	56	39	18	1	0
Nivolumab, PD-L1 Negative	128	108	88	63	26	7	0
Dacarbazine, PD-L1 Positive	74	64	44	30	11	1	0
Dacarbazine, PD-L1 Negative	126	107	78	52	11	2	0

	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

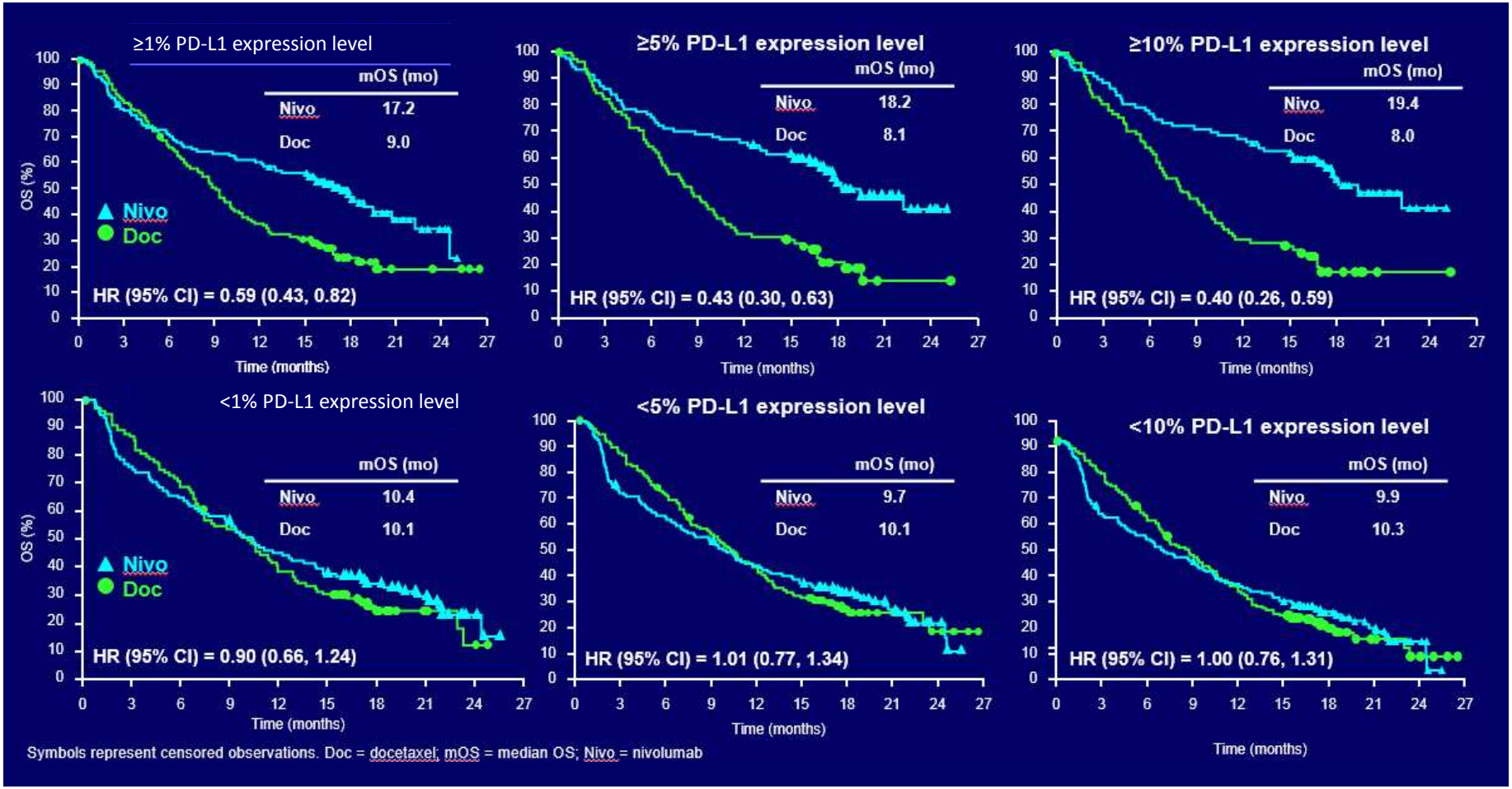
OS by PD-L1 Expression



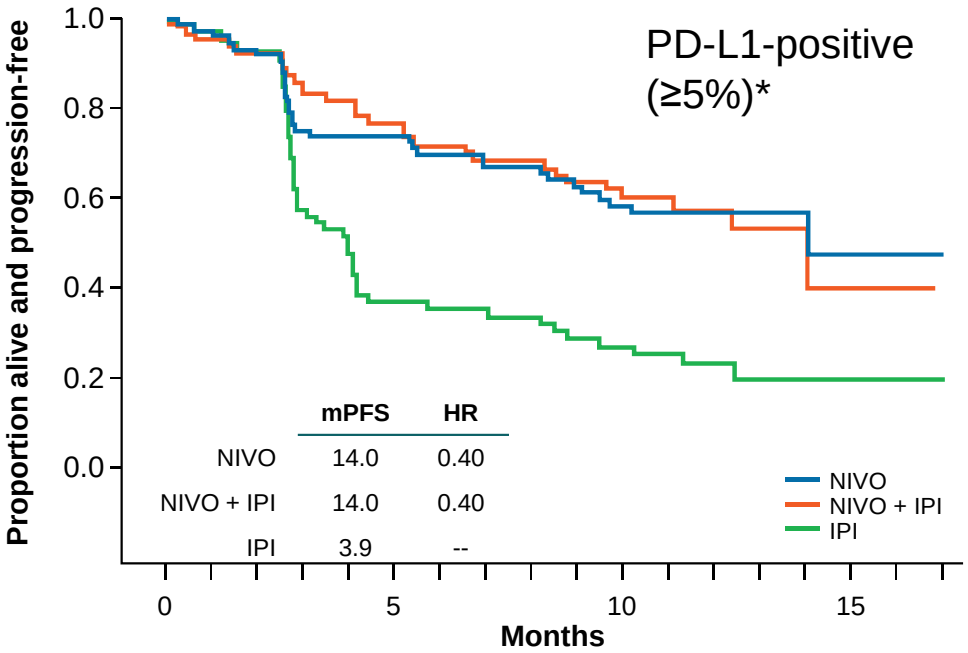
PRESENTED AT: ASCO Annual '15 Meeting

Presented By David Spigel at 2015 ASCO Annual Meeting

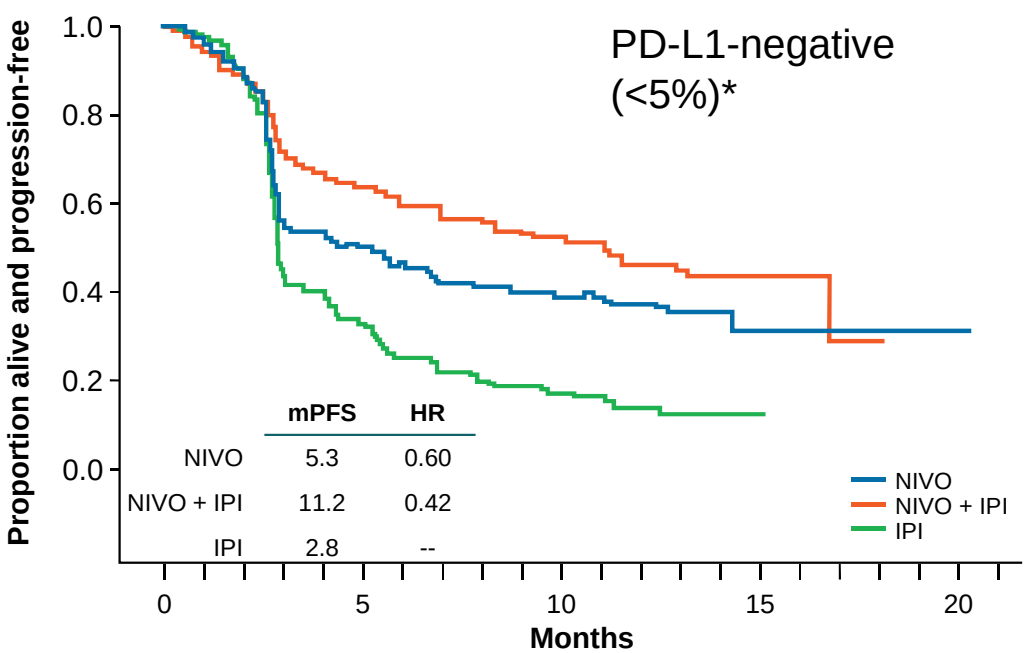
Overall Survival by PD-L1 Expression: Nivo vs Docetaxel in Lung AdenoCa



PFS by PD-L1 Status (5% Cutoff)



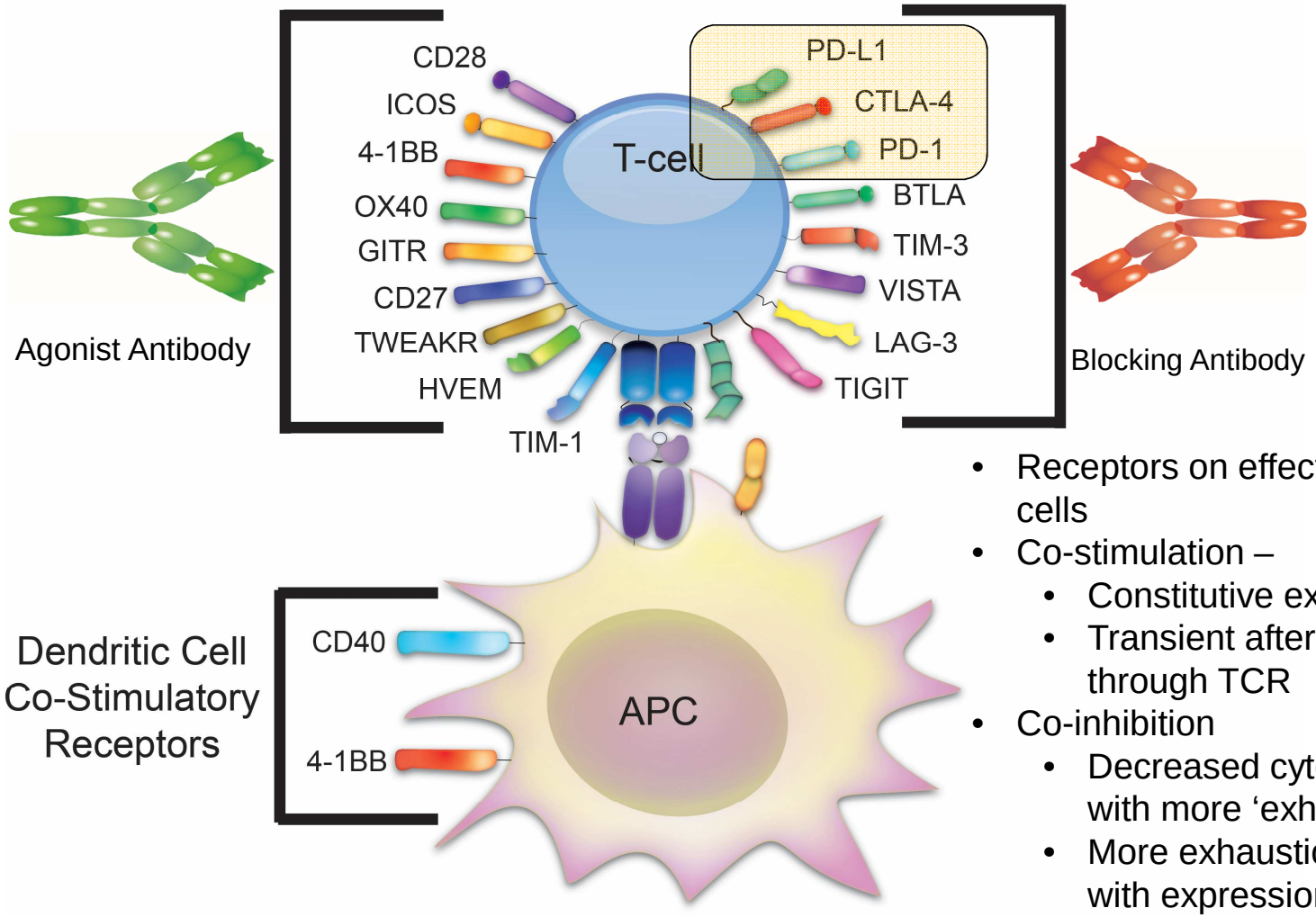
Number at Risk					
NIVO	80	54	38	4	0
NIVO + IPI	68	47	34	1	0
IPI	75	24	16	2	0



Number at Risk					
NIVO	208	98	63	5	1
NIVO + IPI	210	123	88	9	
IPI	202	59	26	1	

- **Similar results were obtained using a 1% cutoff.**

*Per validated PD-L1 immunohistochemical assay with positivity defined as ≥5% of tumor cells showing PD-L1 staining in a section of at least 100 evaluable tumor cells.

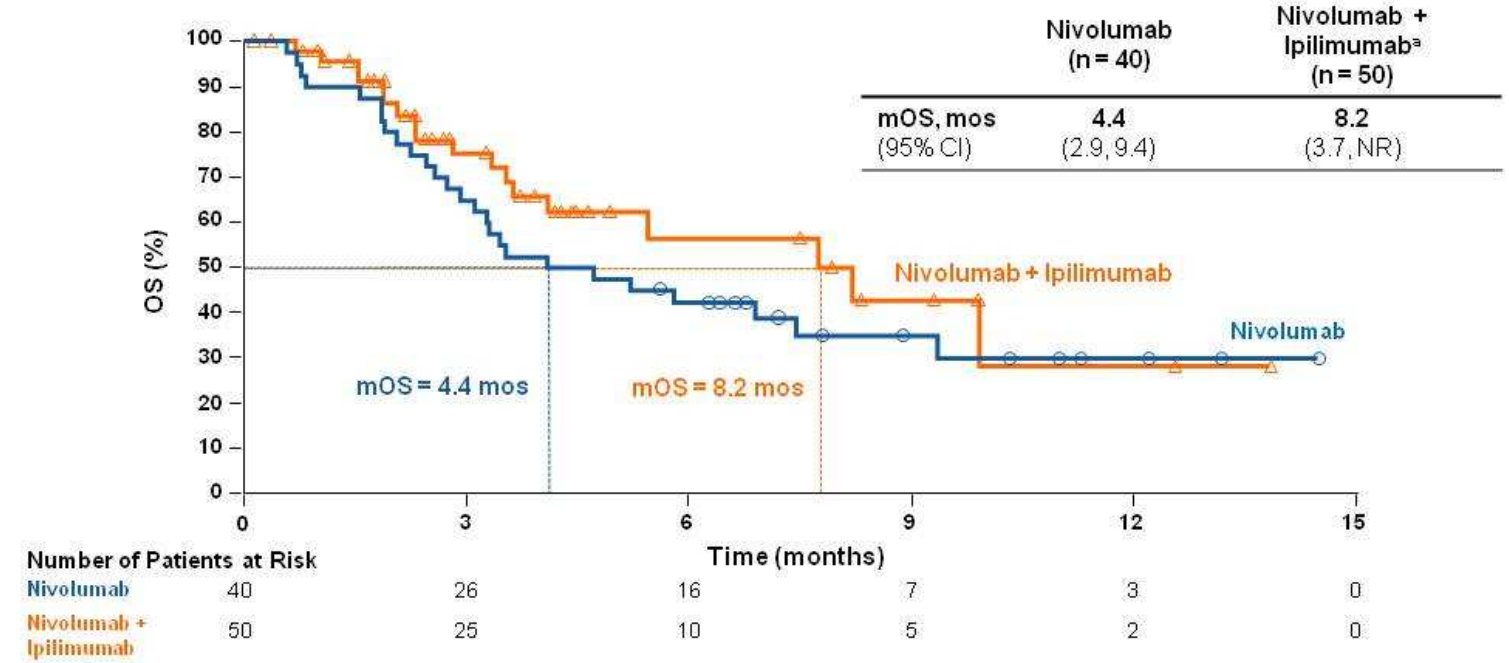


- Receptors on effector T, Treg, NK cells
- Co-stimulation –
  - Constitutive expression or
  - Transient after activation through TCR
- Co-inhibition
  - Decreased cytokine production with more ‘exhaustion’
  - More exhaustion associated with expression of multiple co-inhibitory receptors

Ai M., **Curran M.** Immune checkpoint combinations from mouse to man. *Cancer Immunology Immunotherapy*, 2015.

Nivo + Ipi in Small Cell Lung Cancer

Overall Survival



	Nivolumab (n = 40)	Nivolumab + Ipilimumab[a] (n = 50)
mOS, mos (95% CI)	4.4 (2.9, 9.4)	8.2 (3.7, NR)

Number of Patients at Risk						
Nivolumab	40	26	16	7	3	0
Nivolumab + Ipilimumab	50	25	10	5	2	0

[a]Combined data for nivolumab 1 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 cohorts

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Scott Antonia at 2015 ASCO Annual Meeting

Update of Nivo+Ipi in mRCC, Hammers et al, ASCO 2015

	N3 + I1 n = 47	N1 + I3 n = 47
OS, mos (range)	NR (3.5 – 18.4+)	NR (1.1 – 18.4+)
Overall ORR[a], n (%)	**18 (38)**	**20 (43)**
Stable disease, n (%)	19 (40)	18 (38)
Median DOR[b], wks (range)	NR (4.1+ – 67.1+)	53.9 (6.1+ – 66.0+)
Median PFS, wks (range)	30.3 (4.7+ – 72.6+)	36.0 (4.1+ – 77.9+)
PFS, 24 wks, % (95% CI)	53 (37 – 67)	64 (47 – 77)

Anti-tumor effects of blocking multiple co-inhibitory molecules

Anti-TIM3 Antibody Promotes T Cell IFN-γ–Mediated Antitumor Immunity and Suppresses Established Tumors

Shin Foong Ngiow[1,2], Bianca von Scheidt[1], Hisaya Akiba[3], Hideo Yagita[3], Michele W. L. Teng[1,2], and Mark J. Smyth[1,2]

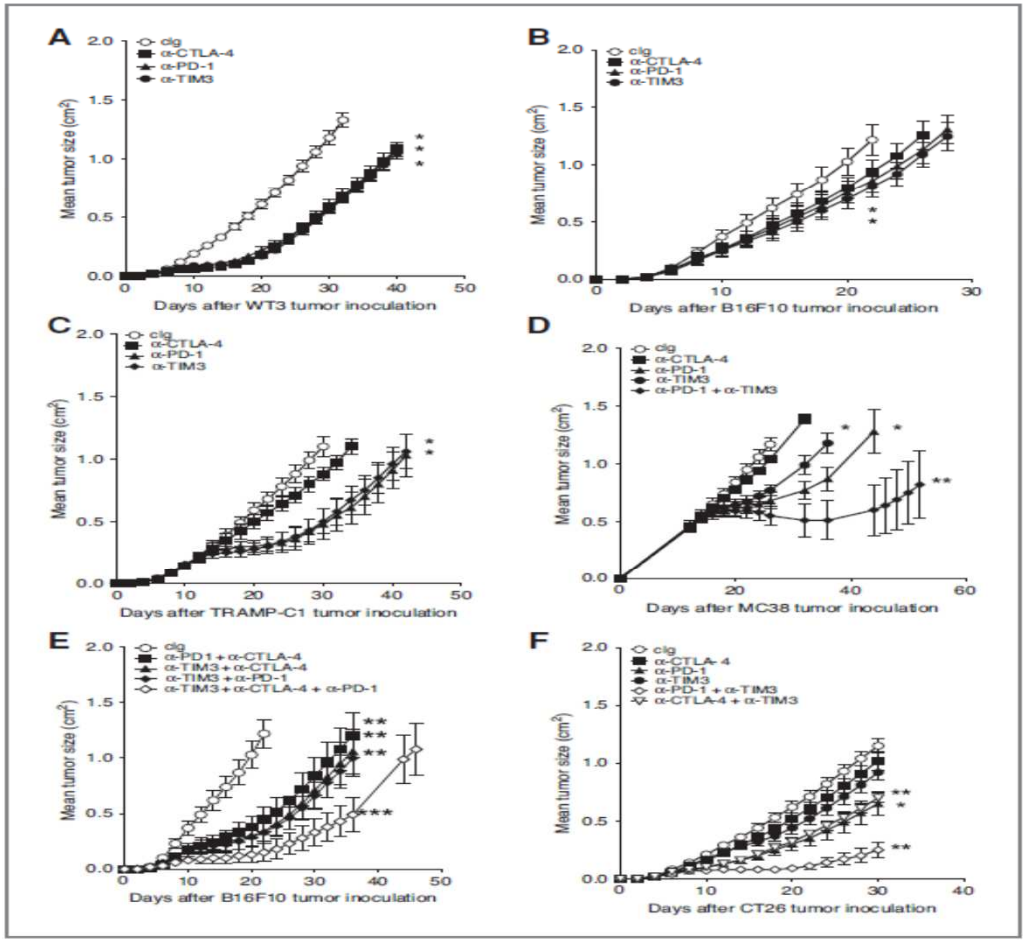
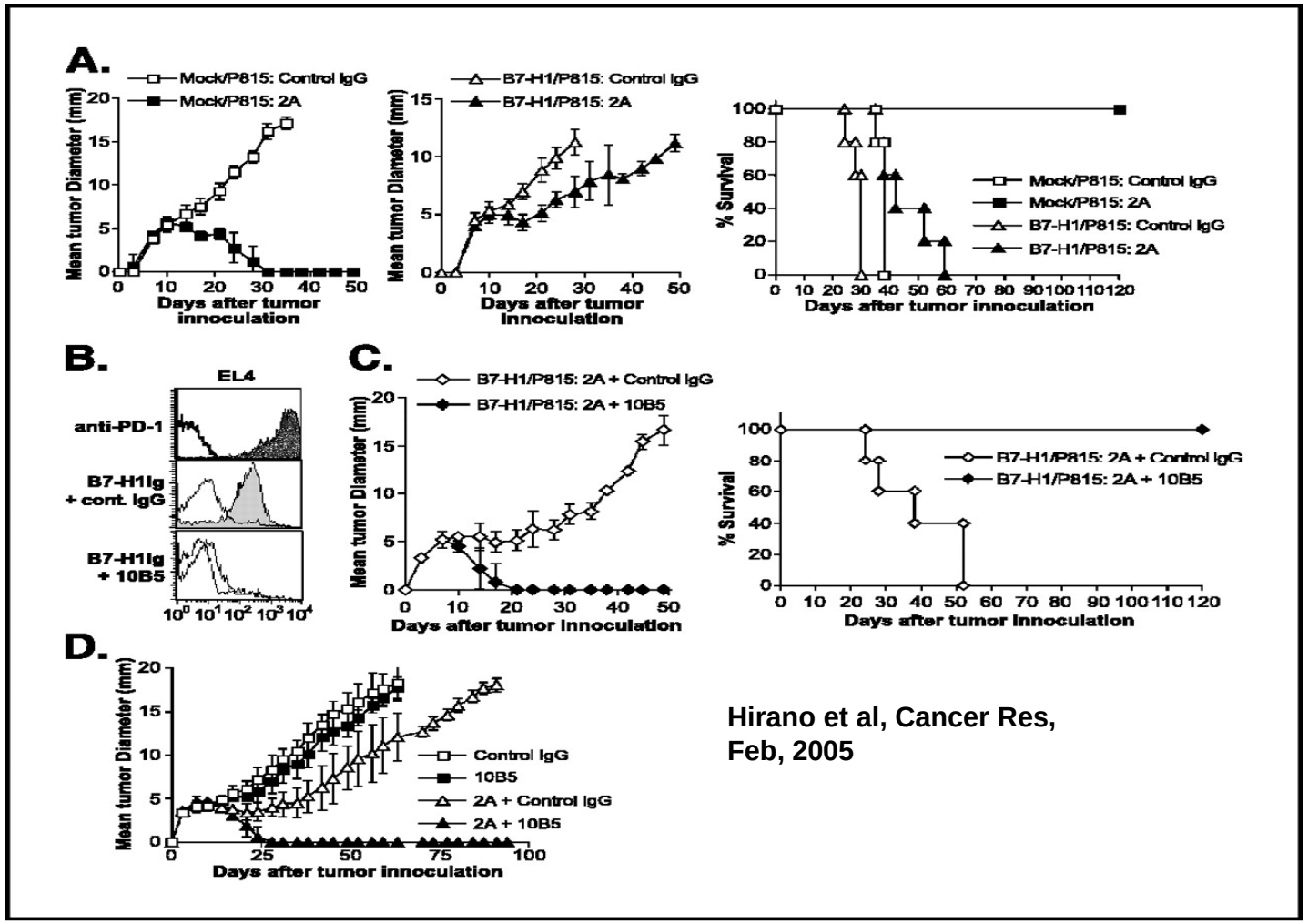


Figure 6. Comparative effect of anti-TIM3 against experimental tumors. Groups of B6 mice ($n = 5$) were inoculated subcutaneously with (A) WT3 (5×10^5), (B and E) B16F10 (1×10^5), (C) TRAMP-C1 (5×10^5), (D) MC38, and (F) CT26. On days 3, 7, 11, and 15 (A, B, E, and F), days 10, 14, 18, and 22 (C), or days 14, 18, 22, and 26 (D) after tumor inoculation, mice were intraperitoneally treated with either clg, anti-TIM3, anti-CTLA-4, anti–PD-1, or their combination (100 μg) as indicated. Tumor sizes are represented as the mean ± SEM. A–D and F, statistical differences in tumor sizes between mice treated with clg and single mAb therapy were determined by a Mann–Whitney test (*, $P < 0.05$). D–F, statistical differences in tumor sizes between mice treated with single mAb therapy or a dual combination were determined by a Mann–Whitney test (**, $P < 0.05$). E, statistical differences in tumor sizes between mice treated with dual mAb therapy or triple combination were determined by a Mann–Whitney test (***, $P < 0.05$).

Cancer Res; 71(10); 3540–51. ©2011 AACR.

Anti-tumor Synergy of Immune Co-Stimulation (Anti-CD137) and Blockade of Co-inhibition (Anti-PD-1)



Hirano et al, Cancer Res, Feb, 2005

Abstract # 410

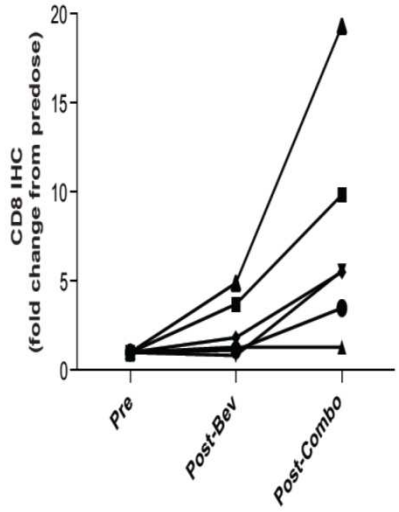
Phase 1b evaluation of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) in patients (pts) with metastatic renal cell carcinoma (mRCC)

Mario Sznol,[1] David F. McDermott,[2] Suzanne Jones,[3] James W. Mier,[2] Daniel Waterkamp,[4] Bo Liu,[4] Jeffrey Wallin,[4] Roel Funke,[4] Johanna Bendell[3]

[1]Yale Cancer Center, New Haven, CT, USA, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]Sarah Cannon Research Institute, Nashville, TN, USA, [4]Genentech, Inc, South San Francisco, CA, USA

ASCO GU 2015

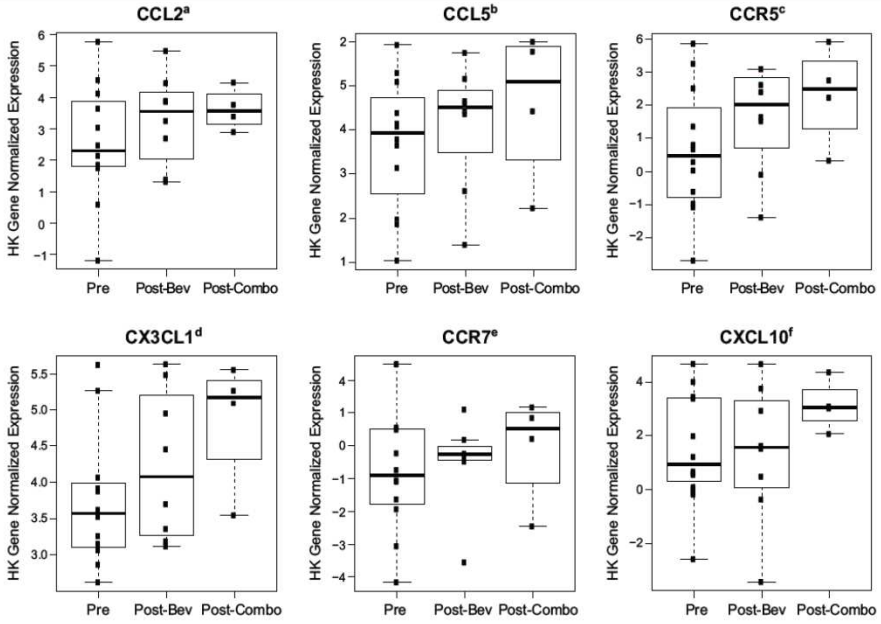
Figure 7. CD8 Staining in the Tumors of Patients With RCC After Treatment With MPDL3280A + Bevacizumab



IHC, immunohistochemistry.

- The increase in CD8+ cells was greatly enhanced in patients after treatment with MPDL3280A + bevacizumab

Figure 8. Chemokine Expression in the Tumors of Patients With RCC After Treatment With MPDL3280A + Bevacizumab



HK, housekeeping gene.

[a] CCL2 is generally produced by tissue injury or infection and serves as a chemoattractant for monocytes, T cells and dendritic cells.

[b] CCL5 is a chemoattractant for T cells, eosinophils and basophils.

[c] CCR5 is the receptor for CCL5.

[d] CX3CL1 is a potent chemoattractant for T cells and monocytes and is primarily expressed in endothelial cells.

[e] CCR7 is a chemoattractant for T cells and stimulates dendritic cell maturation.

[f] CXCL10 is secreted by monocytes, endothelial cells and fibroblasts in response to IFNγ and serves as a chemoattractant for immune cells.

Interventions

Agonist Ab
Inhibitory Ab
Vaccines
Cytokines
Cell therapy
Small molecule signaling

Non-Immunotherapy
VEGF/VEGFRi
RT
Molecular targets
ChemoRx

Antigen Presenting Cell or Tumor	T-lymphocyte	Function (excluding Treg)
Peptide-MHC	T cell receptor	Signal 1
CD80/CD86 (B7.1, B7.2)	CD28/CTLA-4	Stimulatory/inhibitory
CEACAM-1 and TIM-3	CEACAM-1	inhibitory
CD70	CD27	stimulatory
LIGHT	HVEM	stimulatory
HVEM	BTLA, CD160	inhibitory
PD-L1 (B7-H1)	**PD-1** and CD80	Inhibitory (Th1)
PD-L2 (B7-DC)	PD1 and ?	Inhibitory (Th2) or stimulatory
OX40L	OX40	stimulatory
4-1BBL	CD137	stimulatory
CD40	CD40L	Stimulatory to DC/APC
B7-H3	?	Inhibitory or stimulatory
B7-H4	?	inhibitory
PD-1H (Vista)	?	inhibitory
GAL9	TIM-3	inhibitory
MHC class II	LAG-3	inhibitory
B7RP1	ICOS	stimulatory
MHC class I	KIR	Inhibitory or stimulatory
GITRL	GITR	stimulatory
CD48	2B4 (CD244)	inhibitory
HLA-G, HLA-E	ILT2, ILT4; NKG2a	inhibitory
MICA/B, ULBP-1, -2, -3, and -4+-	NKG2D	Inhibitory or stimulatory
CD200	CD200R	inhibitory
CD155	TIGIT/CD226	Inhibitory/stimulatory

Other Inhibitory Factors
IDO
Treg
MDSC
Macrophages
TGF-beta
IL-10?
Adenosine

In our melanoma gene expression database, high levels of:
CEACAM-1
B7-H3
CD200
CD155 (PVR)

PD-1/PD-L1 Combinations in Development

- Ipilimumab (anti-CTLA-4)
- Tremelimumab (anti-CTLA-4)
- Bevacizumab
- IFNs – RCC/melanoma
- IL-21 – terminated?
- IL-2 (proposed)
- anti-LAG3
- anti-KIR
- peptide vaccines
- Oncolytic viruses (Tvec)
- Anti-OX40 (proposed)
- Anti-CD27
- Anti-CD137
- Treg inhibitors – mogamulizumab
- IDOi
- Adoptive Cell Therapy
- Dabrafenib +/- Trametinib
- Vemurafenib +/-Cobimetinib
- RT
- HDACi
- CSF1-R antagonists
- CD3 or IL-2-bispecifics

CTLA-4 Combinations in Development

- IL-2
- Interferon
- GM-CSF
- Anti-CD27
- IDOi
- Bevacizumab
- Sunitinib
- Dabrafenib+-trametinib
- Tvec
- ACT
- IL-21
- Anti-PD-1/Anti-PD-L1
- Chemotherapy
- RT
- Vaccines

Rituximab, Signaling Ab

Conclusions

- Single agent checkpoint inhibitors are effective in subsets of many different malignancies (anti-PD-1/anti-PD-L1 > anti-CTLA-4)
- For a subset of patients, a single agent appears to be sufficient for durable response
  - But no reliable method to identify this subset
- Combinations should be addressed to underlying immunobiology of tumor-host relationship
  - But no reliable method to assess
  - Multiple combinations possible
- Ipilimumab-nivolumab provides proof of concept of potential increased activity in multiple tumor types
- Combinations may produce increased autoimmunity but should be manageable in most patients