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Therapeutic Approaches to Metastatic Melanoma

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Objectives

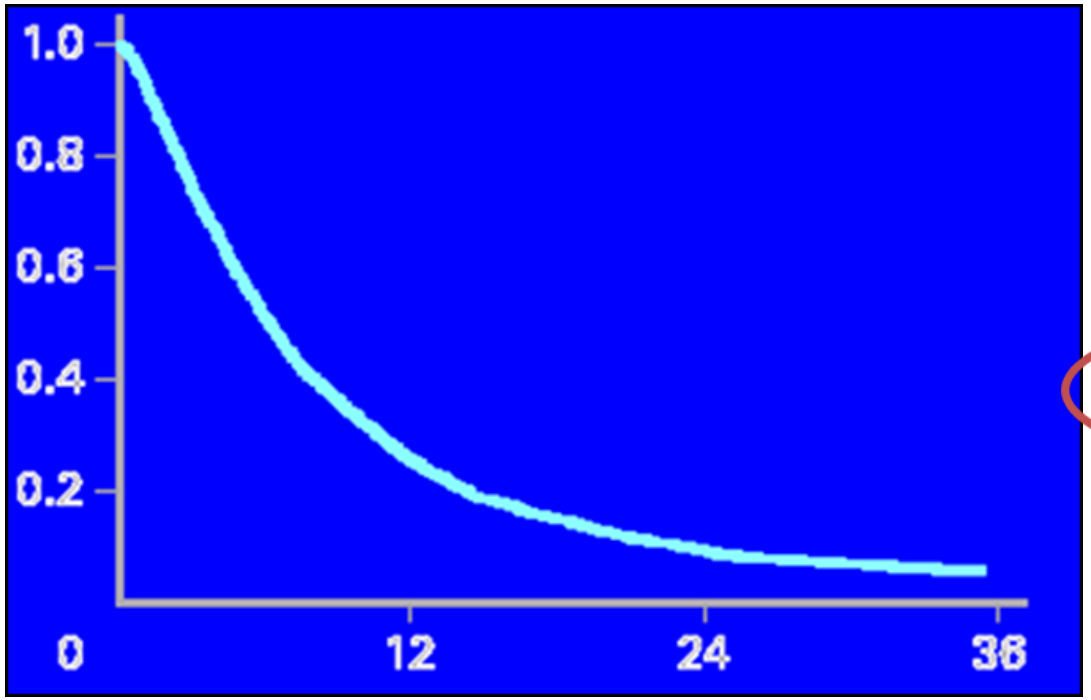
- Introduction and Background
- Questions I ask myself in the clinic
- Future Directions

The Transformed Landscape of Melanoma Therapy: Approved Drugs Before 2011

- **Dacarbazine (DTIC), 1970s**
  - Response rate: <10% in unselected stage IV melanoma patients
  - No proven impact on survival

- **High-dose IL-2, 1998**
  - Response rate: 16% in highly selected stage IV melanoma patients
  - Durable responses: ~5%
  - Rarely used outside of specialized centers
  - Not used outside USA

The Pre-PD-1 Era: Survival for Metastatic Melanoma

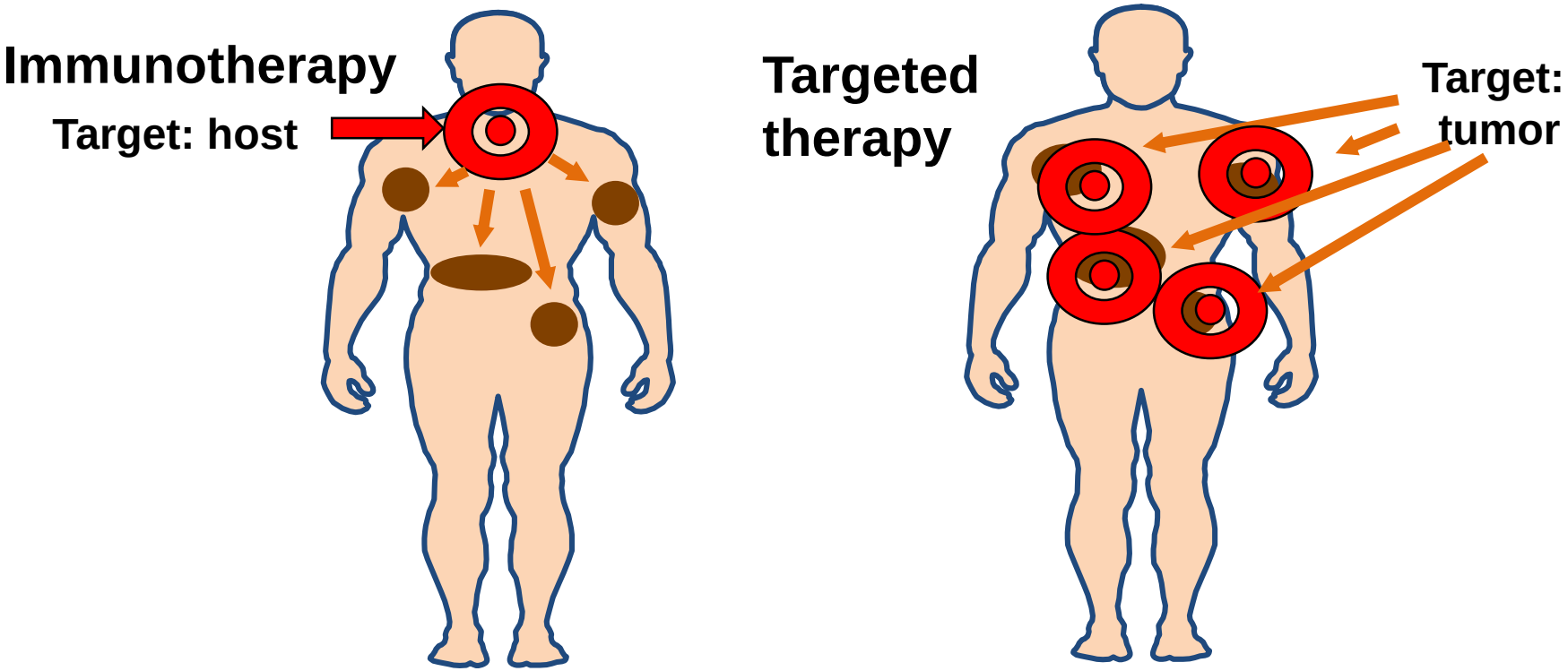


Adapted from Korn 2008

Survival data from 42 Phase II trials with over 2,100 stage IV patients[1]:
12 month OS: 25.5 %,
median OS: 6.2 mos

[1]Korn EL et al. J Clin Oncol 2008;26(4):527-34.

New Paradigm in the Treatment of Cancer



Courtesy Axel Hauschild, MD

My Options in 2017

- Clinical Trials
- Immunotherapy
- Targeted therapy

In 2017 Immunotherapy for Cancer = Checkpoint Inhibitors

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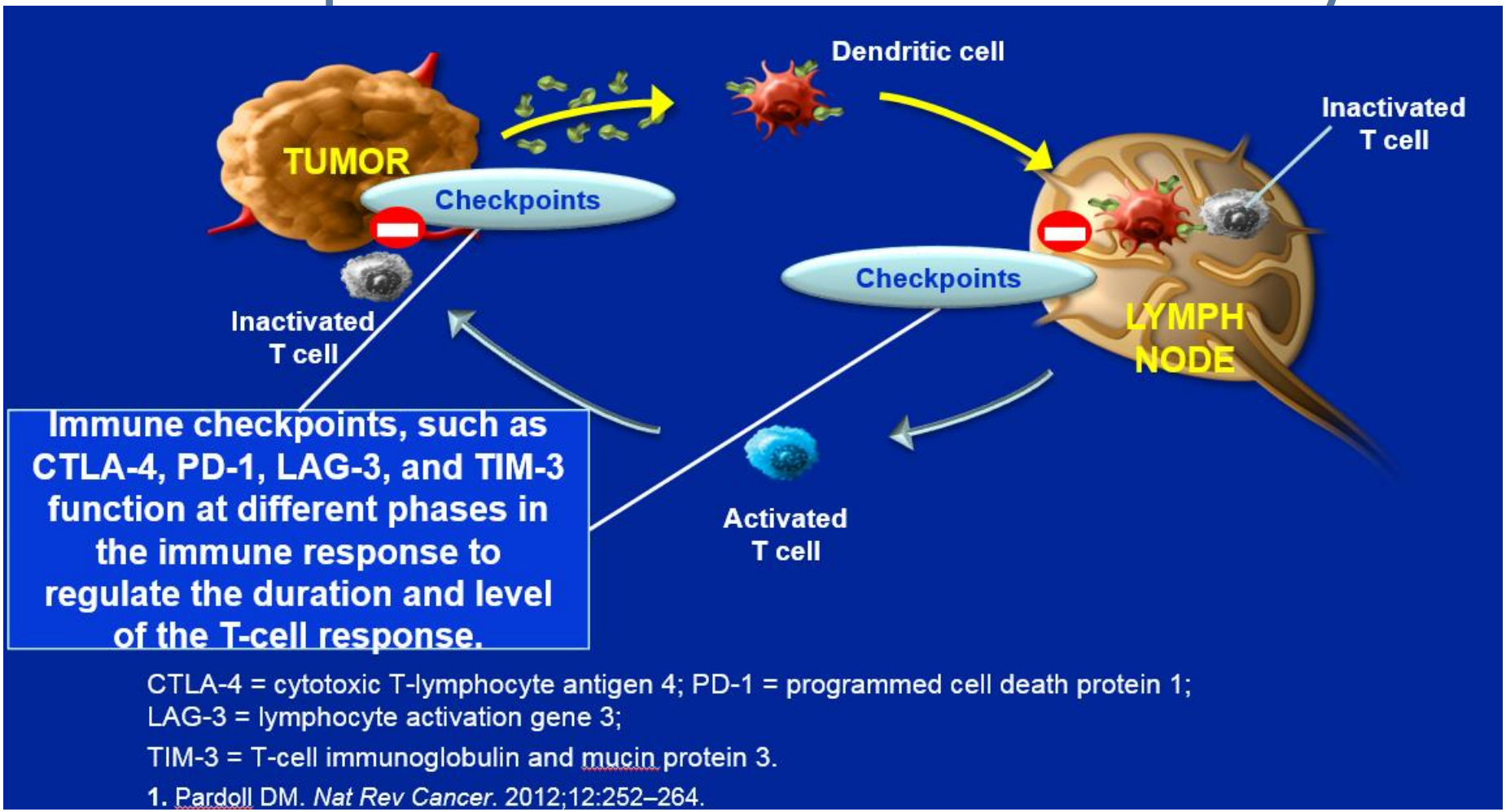
T-Cell Activity Is Regulated By Immune Checkpoints to Limit Autoimmunity[1]

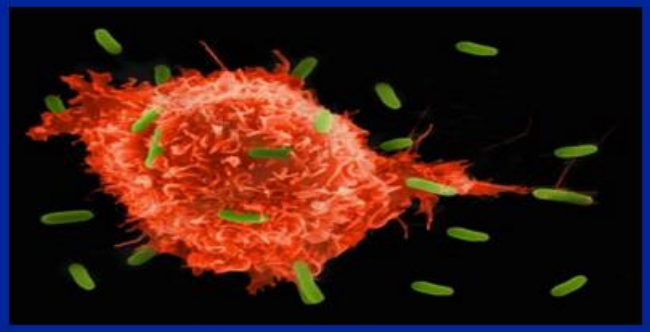


CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1;
LAG-3 = lymphocyte activation gene 3;
TIM-3 = T-cell immunoglobulin and mucin protein 3.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

What is a “Checkpoint Inhibitor”?

Checkpoint Inhibition



Immune System

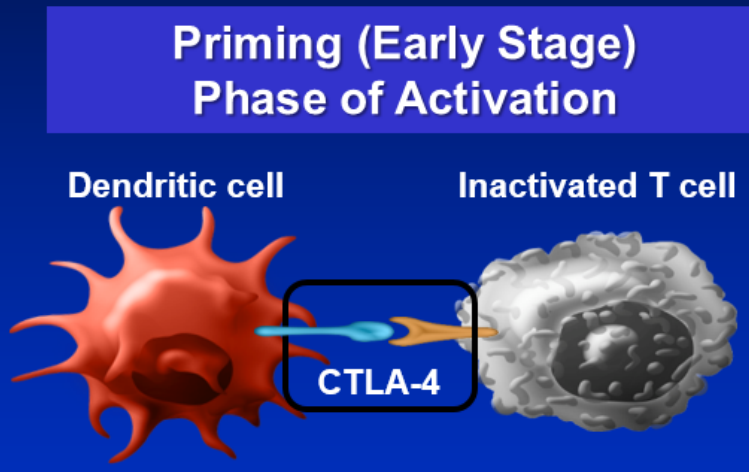
=

Cytokines

Antigens

Regulatory molecules
(CTLA-4, PD-1)

CTLA-4 Affects the Priming Phase of T-Cell Activation[1]

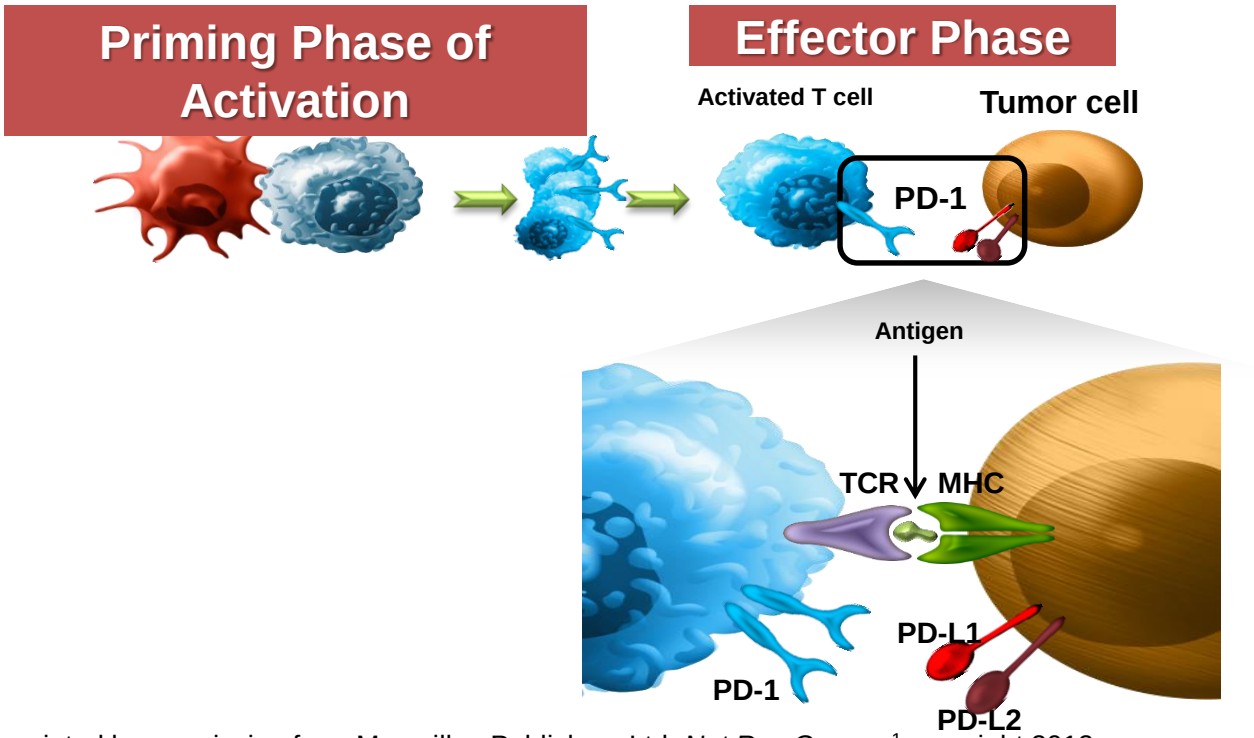


- In healthy tissues, CTLA-4 is thought to function as a dominant "off switch" broadly shutting down T-cell activity to prevent autoimmunity[1-3]

CTLA-4 = cytotoxic T-lymphocyte antigen 4.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264; **2.** Ribas A. *N Engl J Med*. 2012;366:2517–2519; **3.** Topalian SL et al. *Curr Opin Immunol*. 2012;24:207–212.

PD-1 affects Mainly the Effector Phase of T-cell Activity



- Emerging research has identified PD-1 as an immune checkpoint pathway that tumor cells may exploit to evade immune surveillance.
- Tumor cells may block immune responses via the PD-1 immune checkpoint pathway by expressing the dual PD-1 ligands, PD-L1 and PD-L2.

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PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64.

Overview

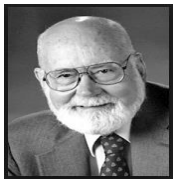
- Introduction and Background
- Questions I ask myself in the clinic
- Future Directions

Questions I Ask Myself in the Clinic

- What are my options for immunotherapy?
- Should I use PD-1 monotherapy or combination with CTLA-4?
- What are my options for targeted therapy?
- What should I choose between immunotherapy or targeted therapy for BRAF+ patients?

Immuno-Oncology Timeline

Clinical Developments



2011
Regulatory approvals
FDA: Brentuximab aCD30
HD&AnLC Lymphoma
FDA Ipi Melanoma

2014
Regulatory approvals
FDA Nivo Melanoma
FDA Blinotumomab (BiTE) ALL
FDA Pembo Melanoma
Japan: Nivo melanoma

William Coley Mixed Toxins

Allogeneic BM transplantation

BCG Bladder Cancer

Hepatitis B Vaccine

First trial with IL-2

First trial Adoptive T cells in cancer

First trial with IFNα Melanoma

TNFa Isolated limb perfusion melanoma & sarcoma

Non-myelo-ablative chemoRx & adoptive T cell melanoma

Imiquimod VIN

HPV Vaccine in VIN

1882 1957 1967 1973 1974 1976 1983 1985 1991 1992 1995 1996 2002 2008 2009 2011- 2015

Burnett Cancer Immuno-surveillance

Steinman Dendritic Cells

Zinkernagel & Doherty MHCI Tcell recognition

Interferons cloned

Boon, Rosenberg Characterisation 1st Human Tumour Antigens

CTLA4 Identified

Sakaguchi Rediscovery of Tregs

Discovery of TLRs

Allison CTLA4 blockade enhances cancer

Chen & Pardoll PD-1 Ligands identified

Laboratory Discoveries

2015
Regulatory approvals
FDA Nivo Renal Cancer
FDA Daratumumab (aCD38) Myeloma
FDA Tvec melanoma
FDA Nivo NonSq NSCLC
FDA: pembro NSCLC
: FDA Ipi Nivo Combination Melanoma
: FDA: Nivo NSCLC
: Austr: Pembro: Melanoma

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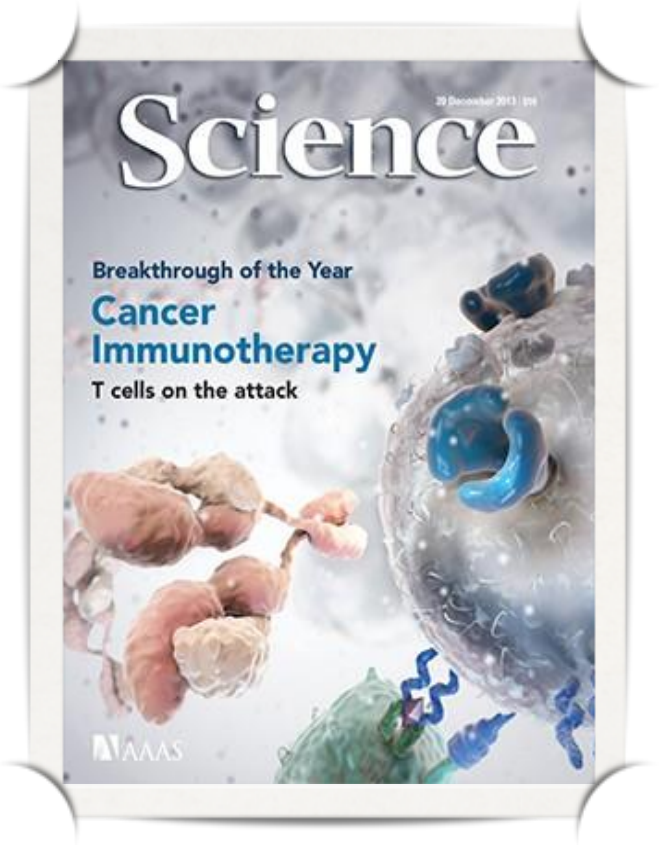
Rationale for targeting checkpoint pathways as a therapeutic option: Cancer Immunotherapy

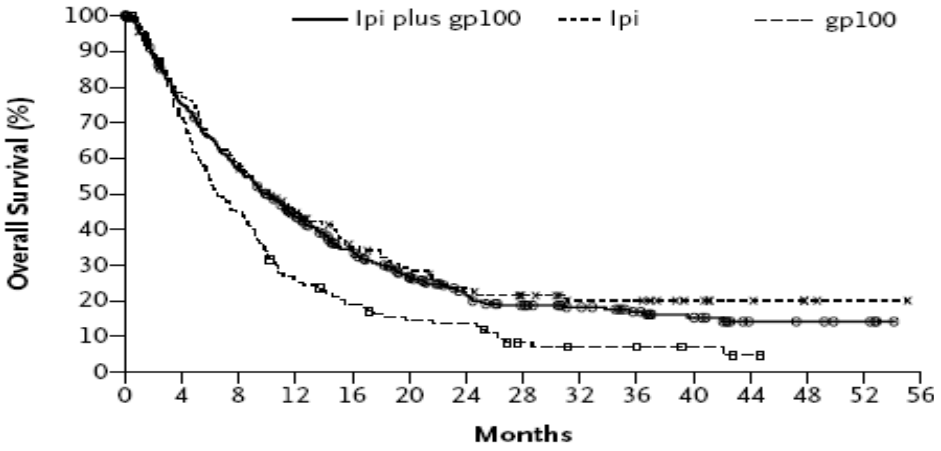


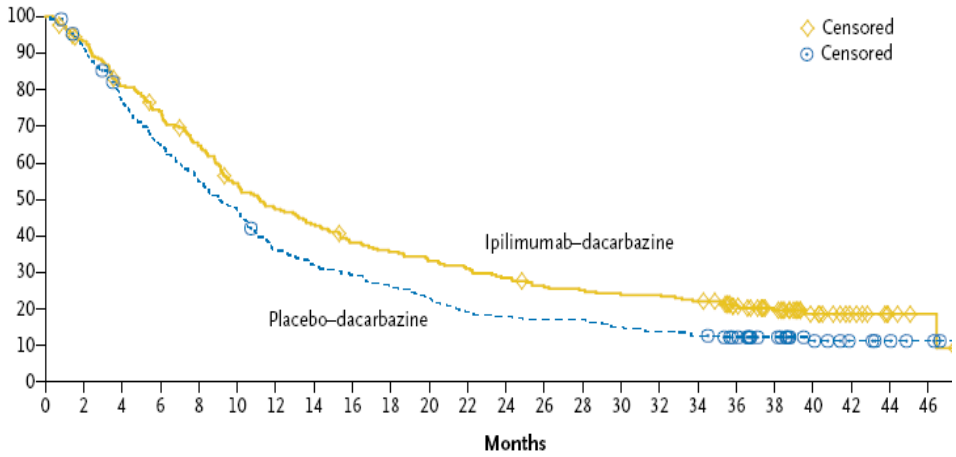
Checkpoint Inhibitors Approved for Melanoma

- Anti CTLA-4 antibody: ipilimumab
- Anti PD-1 inhibitors: pembrolizumab, nivolumab
- Combination anti CTLA-4 and anti-PD-1 (ipilimumab and nivolumab)

Clinical Results with Ipilimumab (2nd and 1st line)

Ipilimumab vs vaccine and Ipi + DTIC vs DTIC





HR: 0.66 and 0.68
Pre-treated pts
Ipi 3 mg/kg +/- gp100

Hodi FS, et al. *N Engl J Med.* 2010;363:711-23

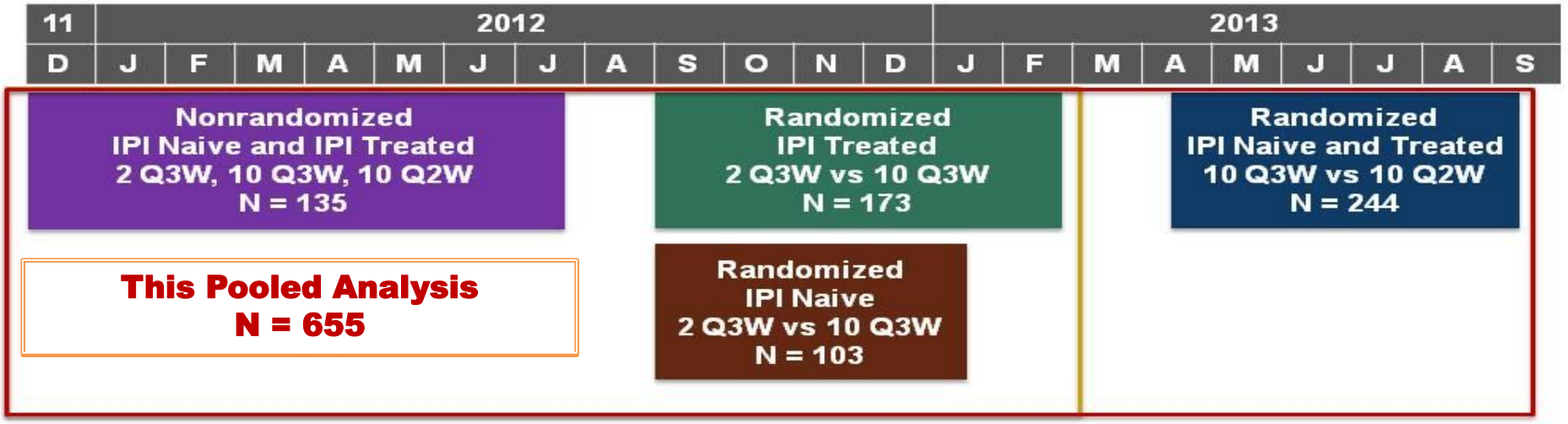
HR: 0.72
First line
Ipi 10 mg/kg + DTIC

Robert C, et al. *N Engl J Med*. 2011;364:2517-26.

Ipilimumab became the standard of care for advanced melanoma in 2011.

But can we do better?

KEYNOTE-001: Melanoma Cohorts



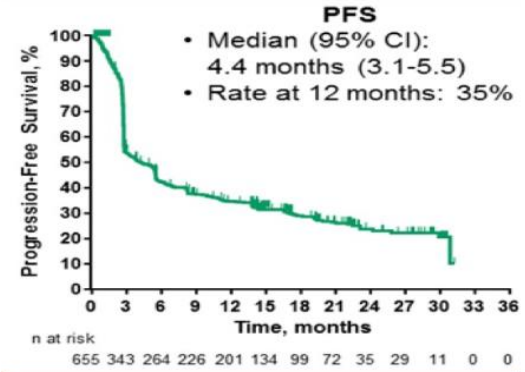
- IPI-T defined as unequivocal PD within 6 mo of first IPI dose
- BRAF inhibitor not required for *BRAF*-mutant melanoma
- IPI-T defined as confirmed PD within 24 wk of last IPI dose; ≥2 IPI doses required
- BRAF inhibitor required for IPI-T, but not IPI-N, *BRAF*-mutant melanoma

PRESENTED AT: ASCO Annual '15 Meeting

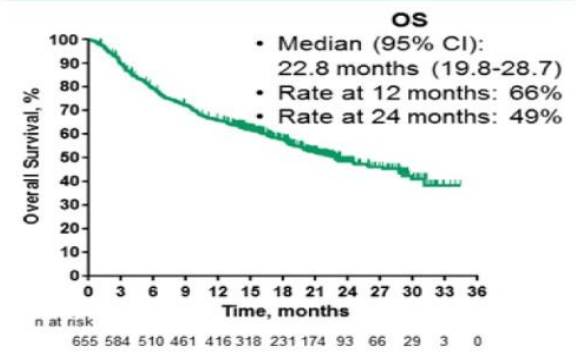
Presented By Adil Daud at 2015 ASCO Annual Meeting

KN-001: Pembrolizumab All Pts (n=655)

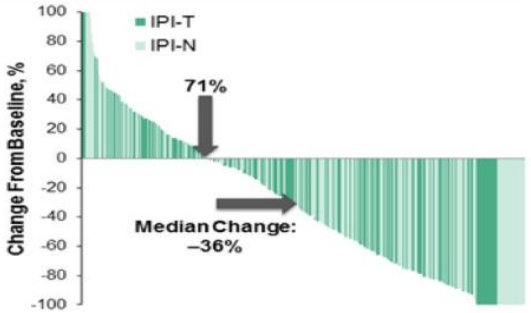
Progression-free Survival



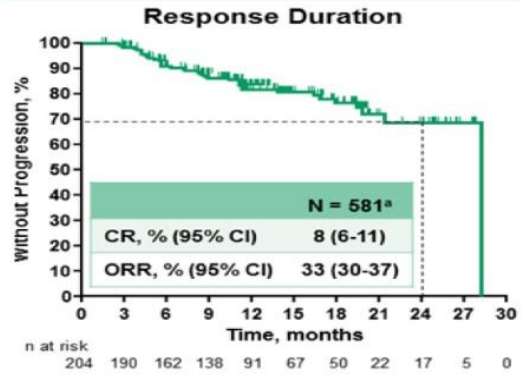
Overall Survival



Change From Baseline



Response Duration



Exposure and AEs Summary

Adverse Event, n (%)	IPI-T (n = 342)	IPI-N (n = 313)	Total (N = 655)
Duration of therapy, mean (range), weeks	31.9 (0.1-116.3)	35.1 (0.1-123.1)	33.4 (0.1-123.1)
No. of doses, median (range)	8 (1-59)	11 (1-58)	10 (1-59)
Any grade treatment related	82%	85%	83%
Grade 3-4 treatment related	14%	14%	14%
Treatment-related death	0%	0%	0%
Discontinuation due to treatment-related AE	4%	4%	4%

KEYNOTE-001: **Pembrolizumab** in **Total Population** (n=655)

A. Daud. Presented May 30, 2015.

PRESENTED AT: ASCO Annual '15 Meeting

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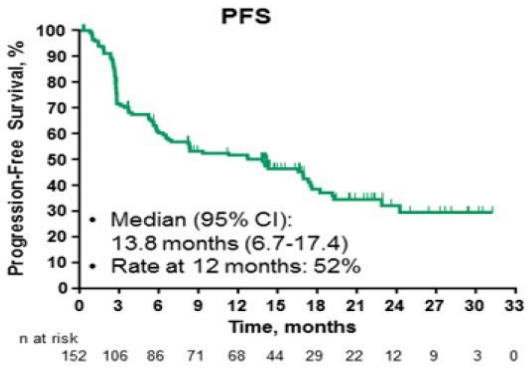
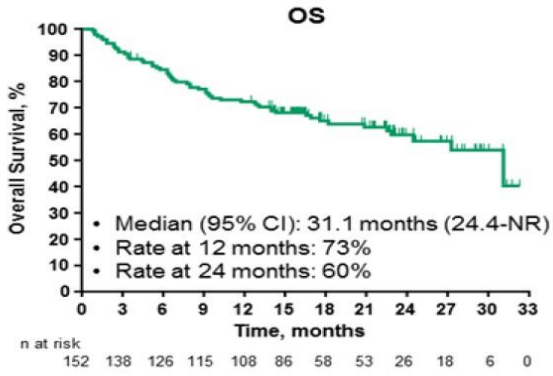
KN-001: Pembrolizumab first line (n=133)

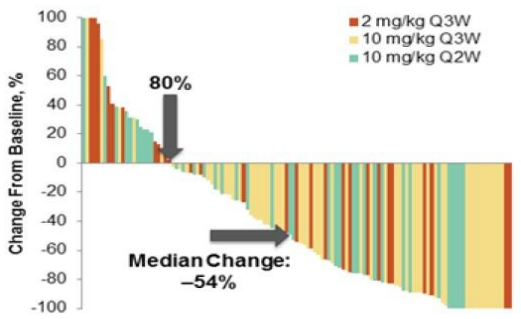
Progression-free Survival



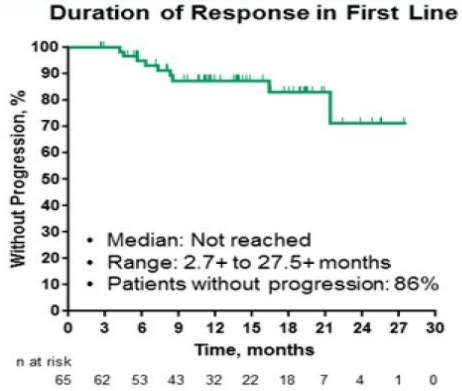
Overall Survival



Change From Baseline



Response Duration



Efficacy as First-Line Therapy

	Total (N = 133)	*BRAF*^{V600} Wild Type (n = 109)	*BRAF*^{V600} Mutant (n = 22)
Complete response, % (95% CI)	13.5 (8.2-20.5)	12.8 (7.2-20.6)	18.2 (5.2-40.3)
ORR, % (95% CI)	45.1 (36.5-54.0)	45.0 (35.4-54.8)	50.0 (28.2-71.8)
DCR, % (95% CI)	60.9 (52.1-69.2)	60.6 (50.7-69.8)	63.6 (40.7-82.8)

A. Daud. Presented May 30, 2015.

KEYNOTE-001: **Pembrolizumab** in **First Line (1L) Population** (n=133)

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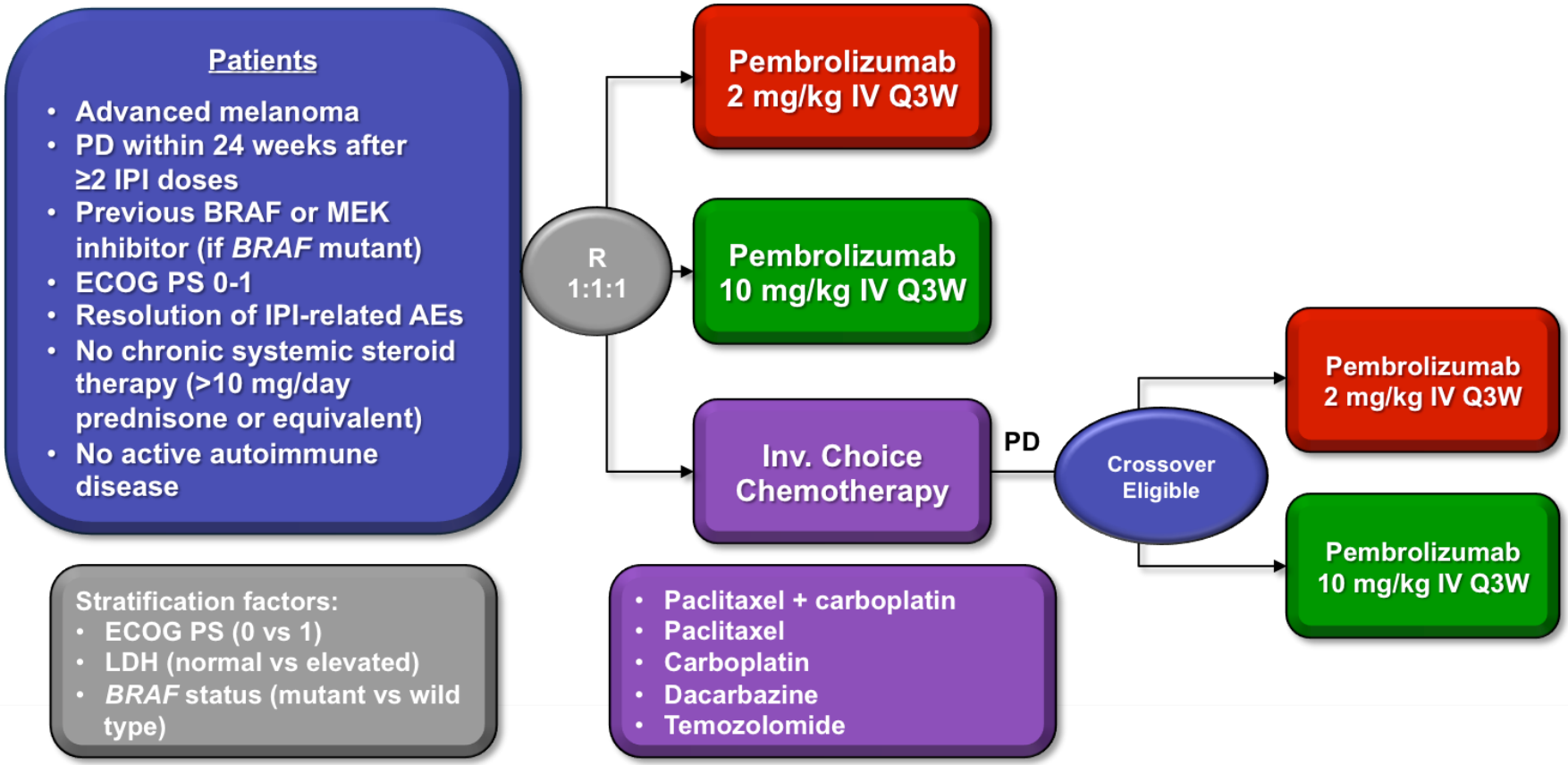
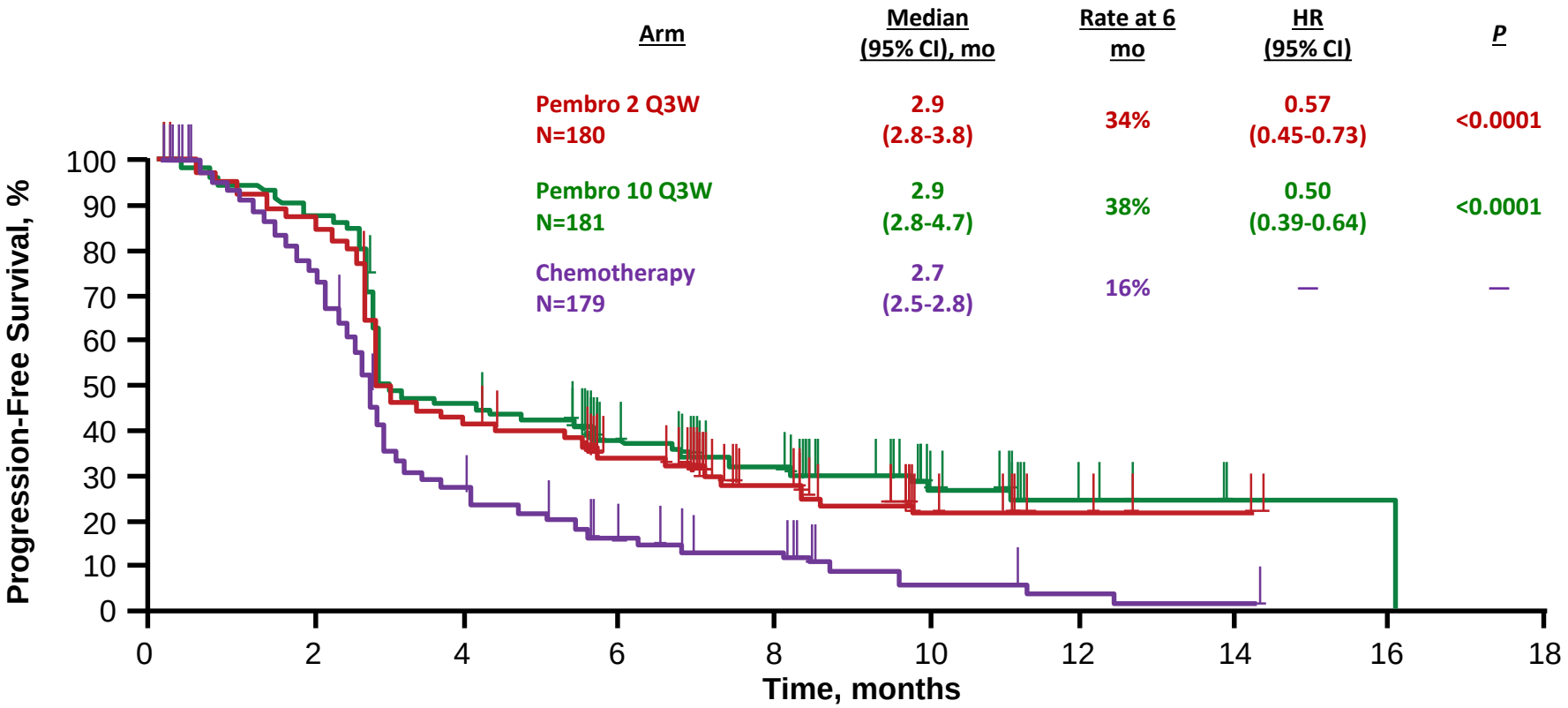
KEYNOTE-002 (NCT01704287):
Pembrolizumab post ipilimumab



- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

Keynote 002: Progression-Free Survival

(Post ipilimumab, RECIST v1.1, Central Review)

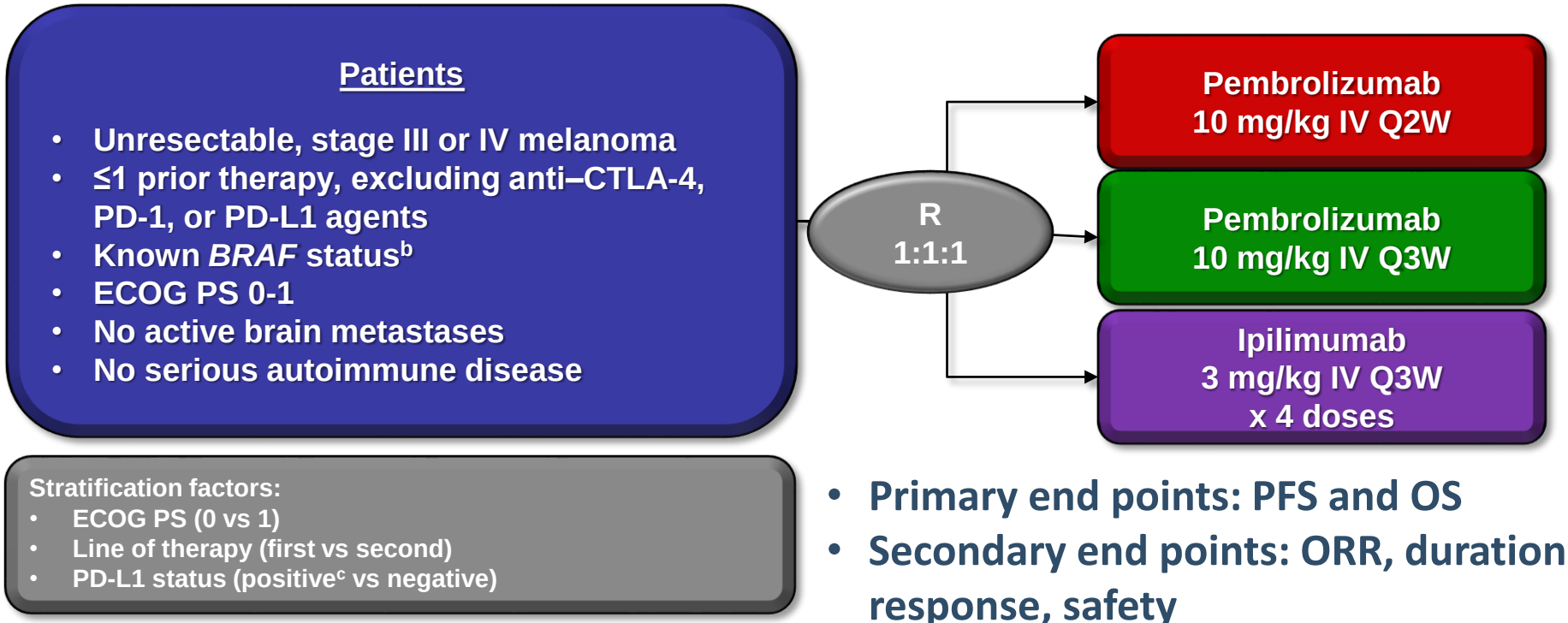


Analysis cut-off date: May 12, 2014.

Ribas A, et al. SMR 2014

After ipilimumab, anti-PD-1 is better than chemotherapy.

Keynote-006 Pembro vs Ipilimumab



- **Primary end points: PFS and OS**
- **Secondary end points: ORR, duration of response, safety**

[a]Patients enrolled from 83 sites in 16 countries.

[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

[c]Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

Baseline Characteristics

Characteristic	Pembrolizumab Q2W N = 279	Pembrolizumab Q3W N = 277	Ipilimumab N = 278
Age, median (range), years	61 (18-89)	63 (22-89)	62 (18-88)
Men	161 (58%)	174 (63%)	162 (58%)
ECOG PS 0	196 (70%)	189 (68%)	188 (68%)
Elevated LDH	81 (29%)	98 (35%)	91 (33%)
BRAF^{V600} mutant	98 (35%)	97 (35%)	107 (38%)
PD-L1 positive[a]	225 (81%)	221 (80%)	225 (81%)
M1c disease	179 (64%)	189 (68%)	178 (64%)
1 previous therapy	96 (34%)	92 (33%)[b]	97 (35%)

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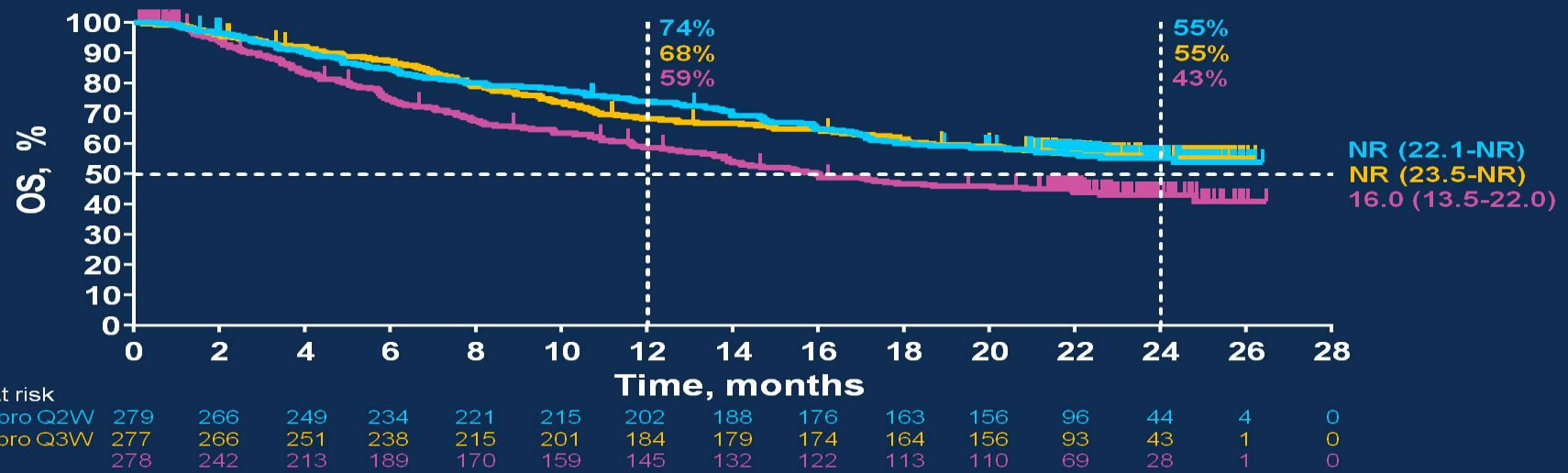
[a]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).
[b]1 patient had 2 lines of previous therapy.
Final analysis data cutoff date: Dec 3, 2015.

Presented By Jacob Schachter at 2016 ASCO Annual Meeting

Overall Survival

Arm	Events, n	HR (95% CI)	*P*
Pembro Q2W	122	0.68 (0.53-0.87)	0.00085
Pembro Q3W	119	0.68 (0.53-0.86)	0.00083
Ipi	142	—	—



No. at risk

Pembro Q2W	279	266	249	234	221	215	202	188	176	163	156	96	44	4	0
Pembro Q3W	277	266	251	238	215	201	184	179	174	164	156	93	43	1	0
Ipi	278	242	213	189	170	159	145	132	122	113	110	69	28	1	0

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Final analysis data cutoff date: Dec 3, 2015.

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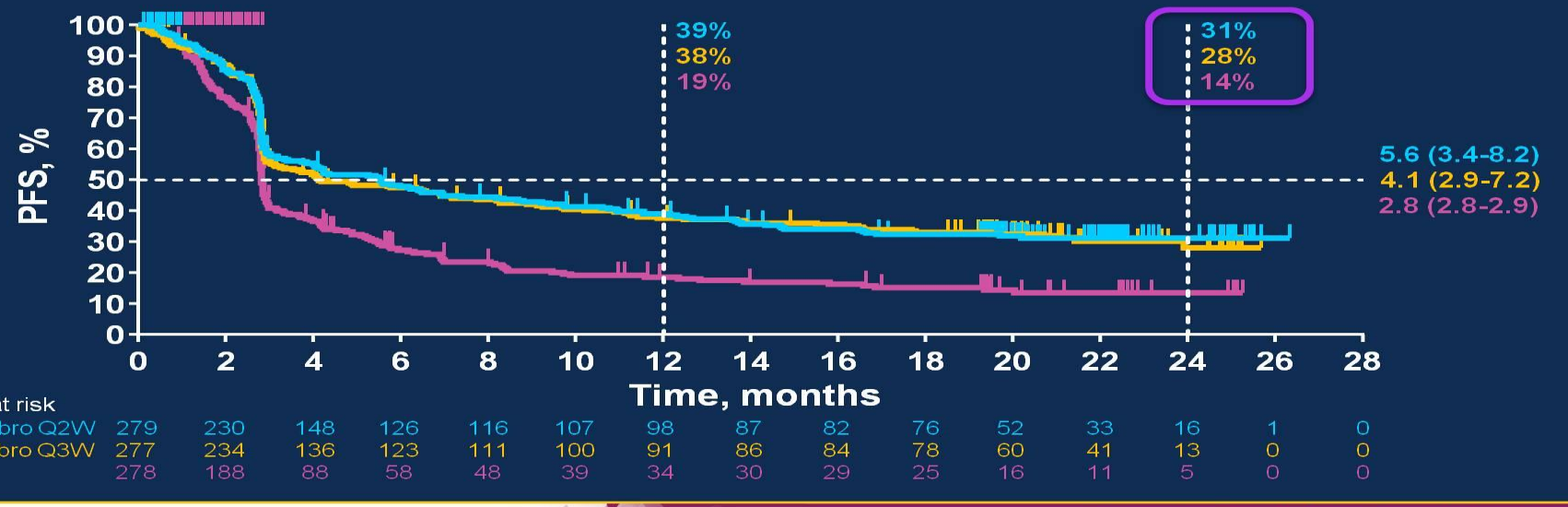
Progression-Free Survival[a]

Arm	Events, n	HR (95% CI)	P[b]
Pembro Q2W	181	0.61 (0.50-0.75)	<0.00001
Pembro Q3W	183	0.61 (0.50-0.75)	<0.00001
Ipi	202	—	—



No. at risk

Pembro Q2W	279	230	148	126	116	107	98	87	82	76	52	33	16	1	0
Pembro Q3W	277	234	136	123	111	100	91	86	84	78	60	41	13	0	0
Ipi	278	188	88	58	48	39	34	30	29	25	16	11	5	0	0

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[a]Assessed per RECIST v1.1 by independent central review.
[b]*P* values are nominal only because no statistical alpha was applied to the comparison at final analysis.
Final analysis data cutoff date: Dec 3, 2015.

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Tumor Response[a]

Characteristic	Pembro Q2W N = 279	Pembro Q3W N = 277	Ipilimumab N = 278
ORR, % (95% CI)	37% (30%-42%)	36% (30%-42%)	13% (10%-18%)
Best overall response			
Complete response (CR)	33 (12%)	36 (13%)	14 (5%)
Partial response	70 (25%)	64 (23%)	23 (8%)
Stable disease	30 (11%)	30 (11%)	43 (15%)
NonCR/NonPD[b]	12 (4%)	14 (5%)	9 (3%)
Progressive disease (PD)	107 (38%)	115 (42%)	137 (49%)
Not evaluable[c]	19 (7%)	15 (5%)	50 (18%)
No assessment[d]	8 (3%)	3 (1%)	2 (<1%)

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[a]Assessed per RECIST v1.1 by independent central review. [b]Patients without measurable disease per central review at baseline who did not experience CR or disease progression. [c]Target lesion not captured by postbaseline scan or for who a target lesion was surgically removed. [d]No postbaseline scan performed or scans not able to be evaluated. Final analysis data cutoff date: Dec 3, 2015.

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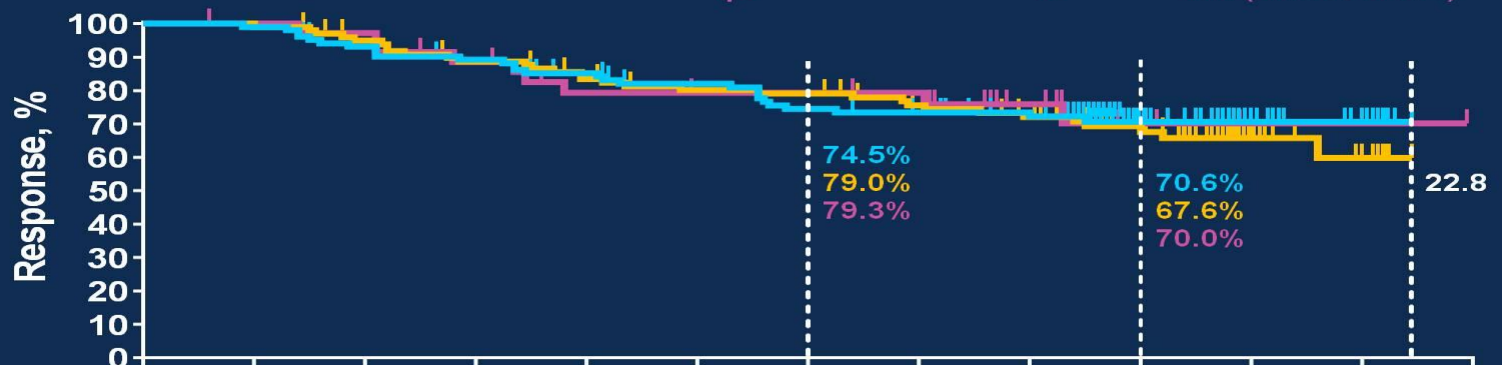
Duration of Response[a]

Arm	Responders, n	Median (range), mo	Ongoing Response[b]
Pembro Q2W	103	NR (1.8 to 22.8+)	69 (67%)
Pembro Q3W	100	NR (2.0 to 22.8+)	60 (60%)
Ipi	37	NR (1.1+ to 23.8+)	23 (62%)



No. at risk

Pembro Q2W	103	102	94	89	82	76	69	66	62	32	17	9	0
Pembro Q3W	100	100	92	85	78	73	72	65	60	41	13	8	0
Ipi	37	36	34	30	25	24	24	23	16	9	4	3	0

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[a]Assessed per RECIST v1.1 by independent central review.
[b]Patients without progression, death, or new anticancer therapy.
Final analysis data cutoff date: Dec 3, 2015.

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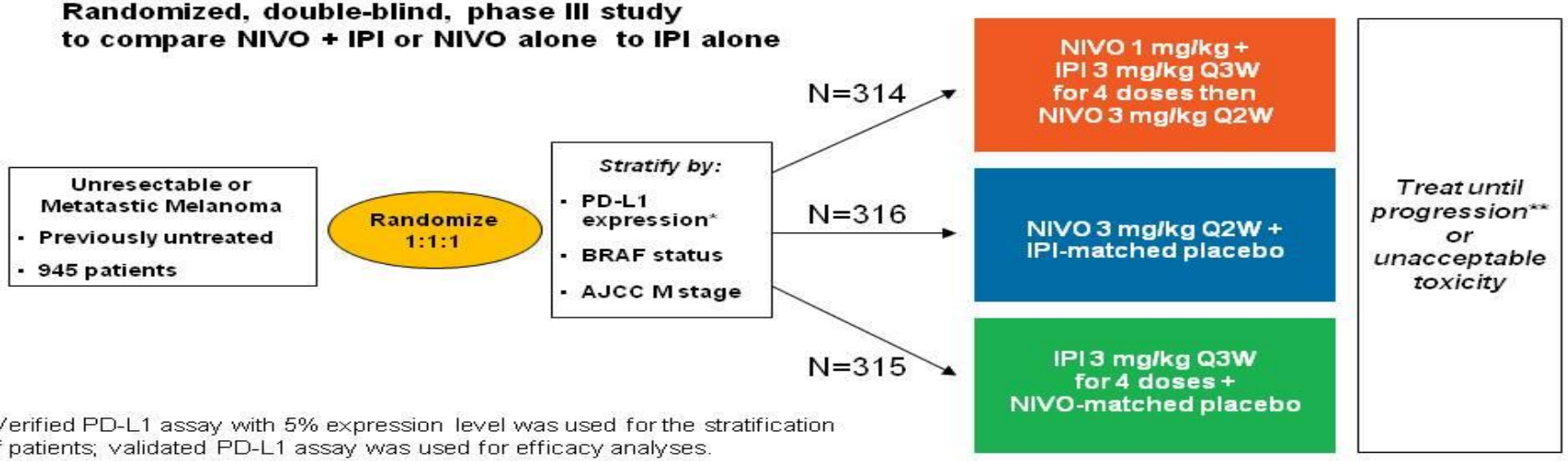
Anti-PD-1 is better than ipilimumab front line and has less toxicity.

Questions I Ask Myself in the Clinic

- What are my options for immunotherapy?
- Should I use PD-1 monotherapy or combination with CTLA-4?
- What are my options for targeted therapy?
- What should I choose between immunotherapy or targeted therapy for BRAF+ patients?

CA209-067: Study Design



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

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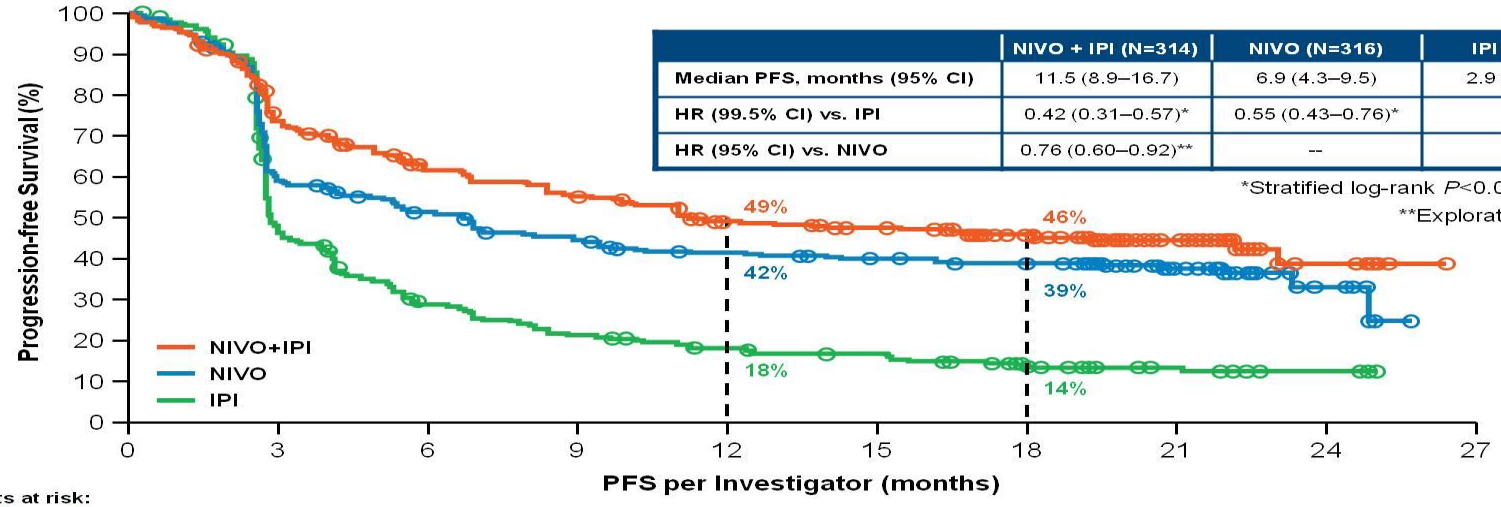
Presented By Jedd Wolchok at 2015 ASCO Annual Meeting

Progression-Free Survival (Intent-to-Treat Population)



	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)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

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

**Exploratory endpoint

Number of patients at risk:

Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

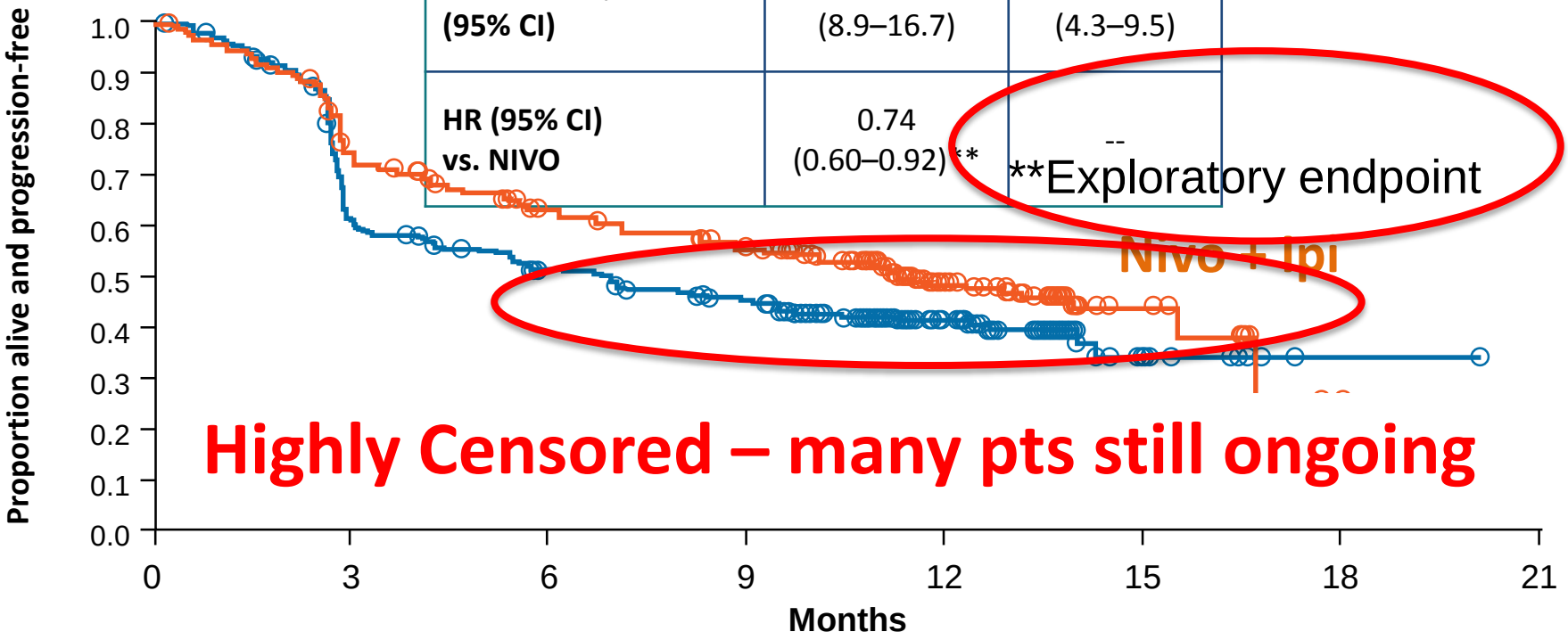
Database lock Nov 2015

6

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

Checkmate 067: Progression-Free Survival
N= 945

	NIVO + IPI (N=314)	NIVO (N=316)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--



Wolchok J, et al. ASCO 2015; Larkin J, et al. *NEJM* 2015

Safety Summary

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

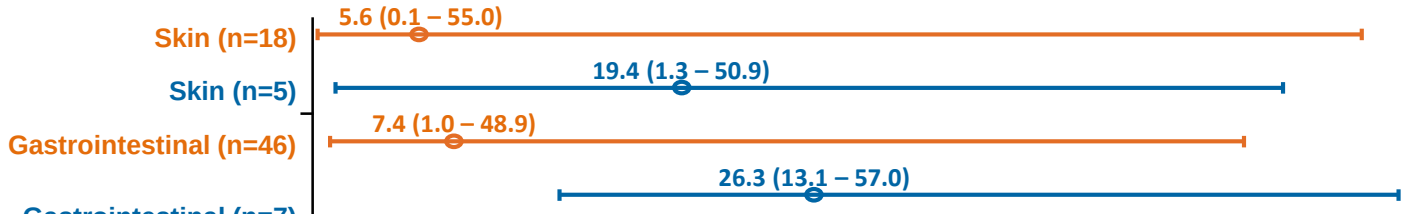
- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs



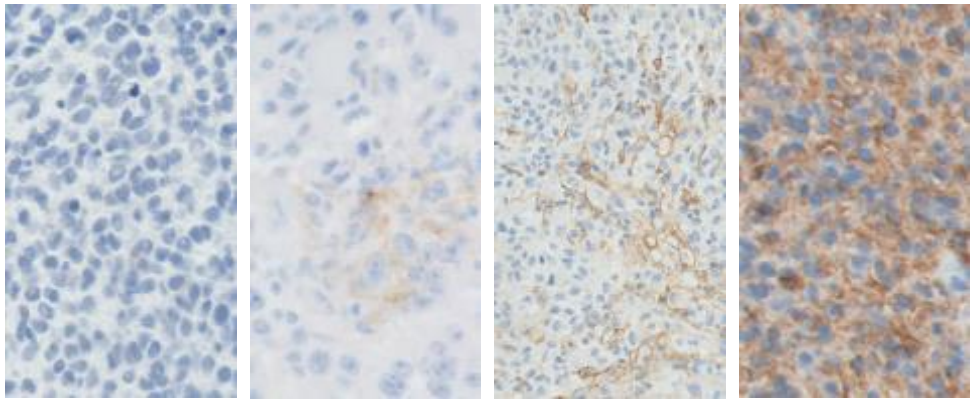
Toxicity Earlier

Longer Time to Resolution

Circles represent medians; bars signify ranges

Larkin J, et al. ECC 2015

Keynote 001 Pembrolizumab
PD-L1 Expression and Response



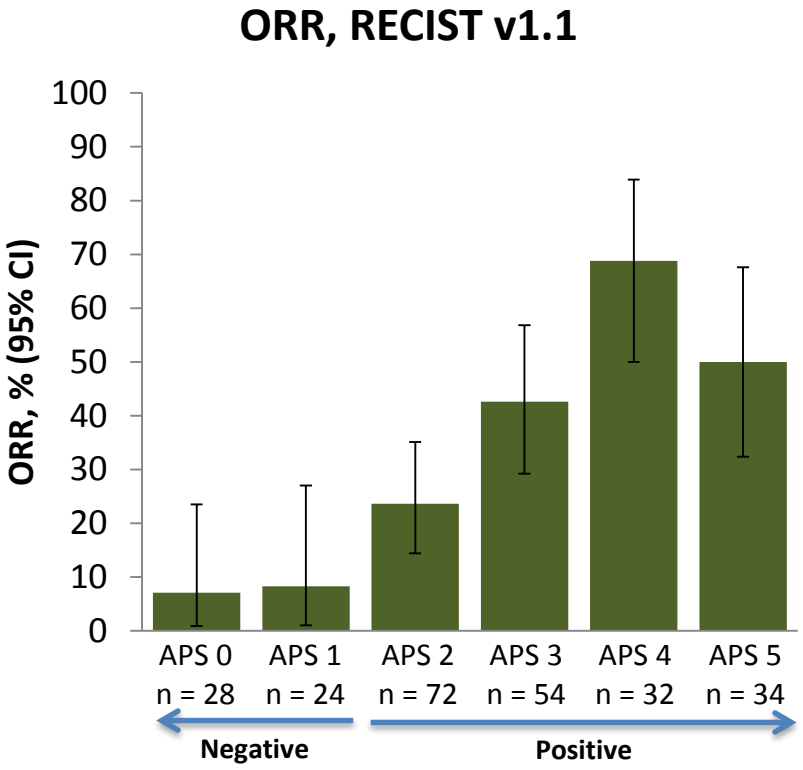
PD-L1 Negative
0% Staining
APS = 0

PD-L1 Positive
1-10% Staining
APS = 2

PD-L1 Positive
10-33% Staining
APS = 3

PD-L1 Positive
66-100% Staining
APS = 5

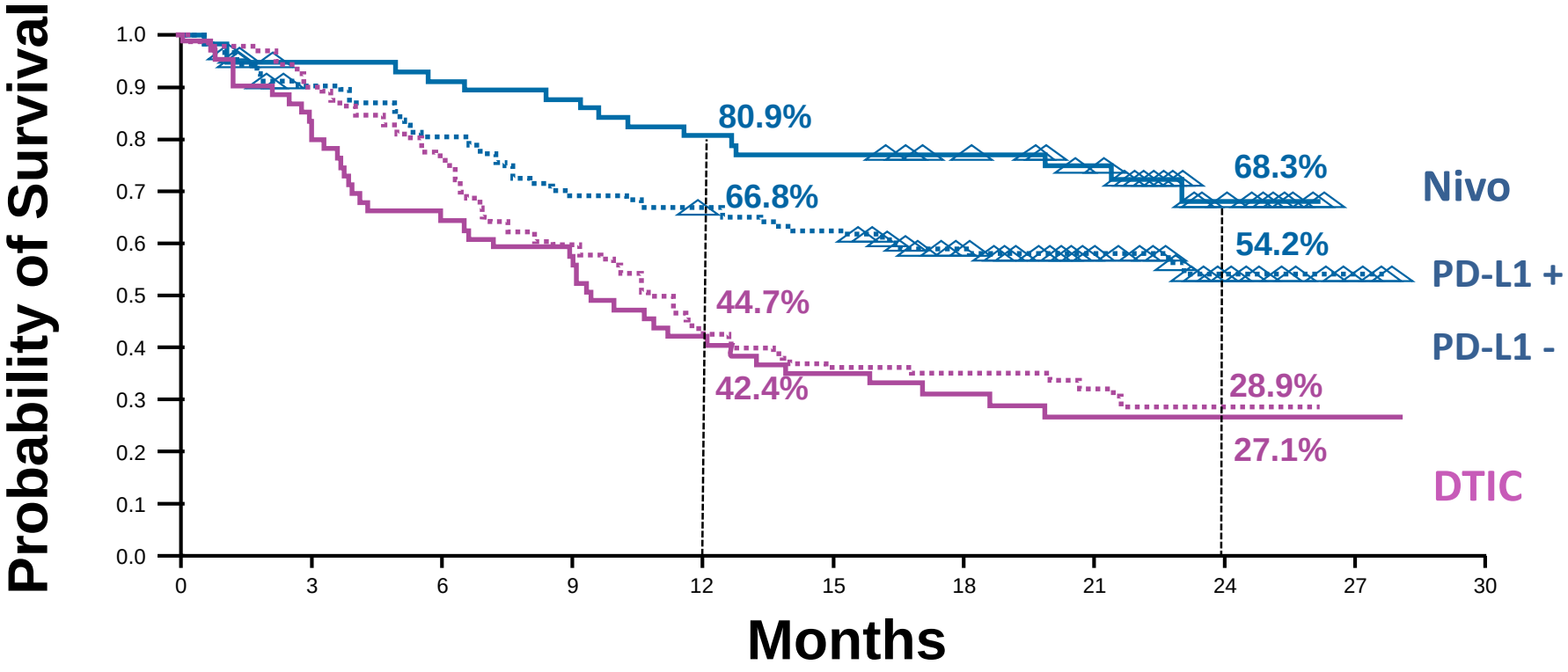
APS, Allred proportion score.
Analysis cut-off date: October 18, 2014.



Daud A, et al. ASCO 2015

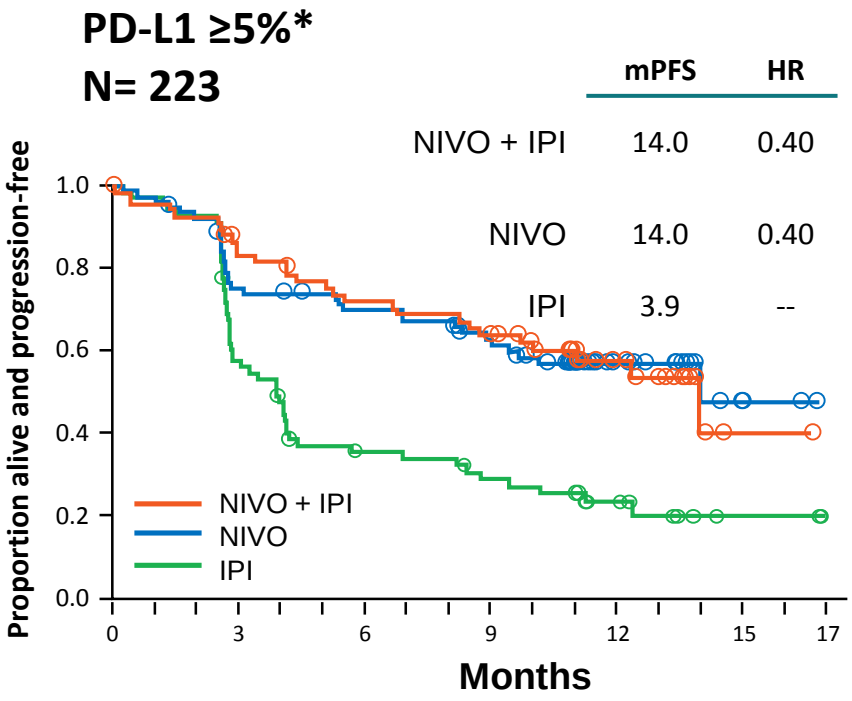
Phase III: Nivolumab versus DTIC

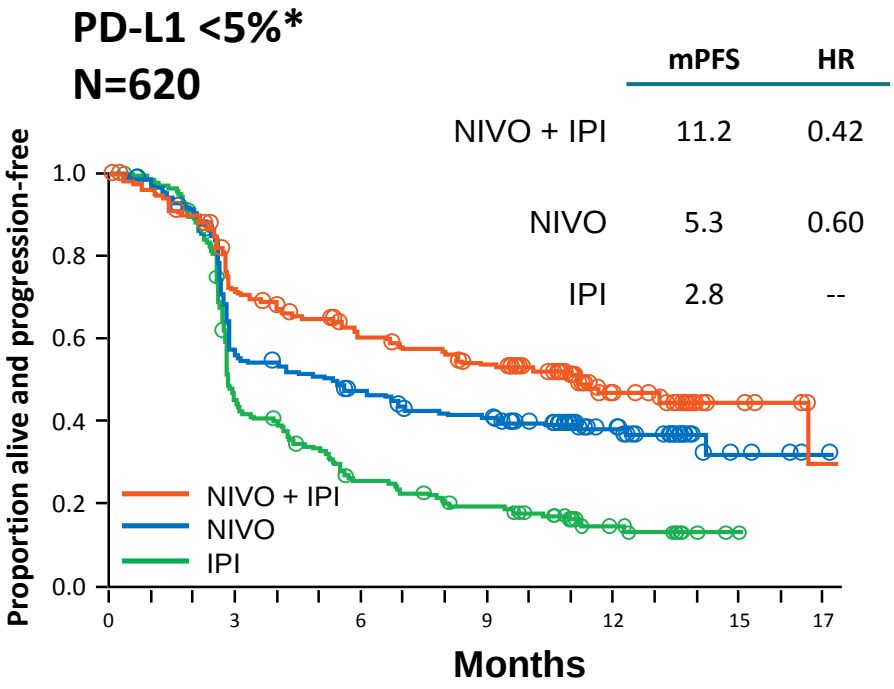
Overall Survival by PD-L1 Status



Atkinson V, et al. SMR 2015

Checkmate 067: PFS by PD-L1 Expression

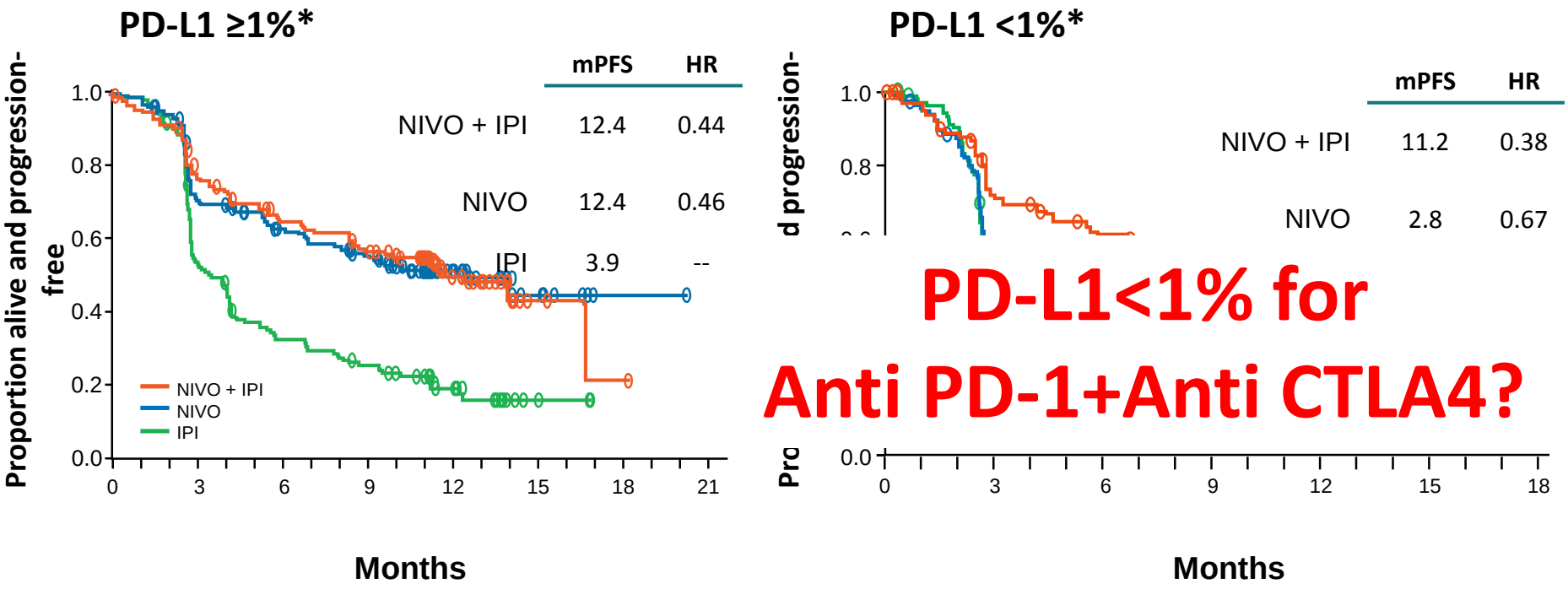




*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100

Wolchok J, et al. ASCO 2015; Larkin et al. NEJM 2015

Checkmate 067: PFS by PD-L1 Expression (1%)

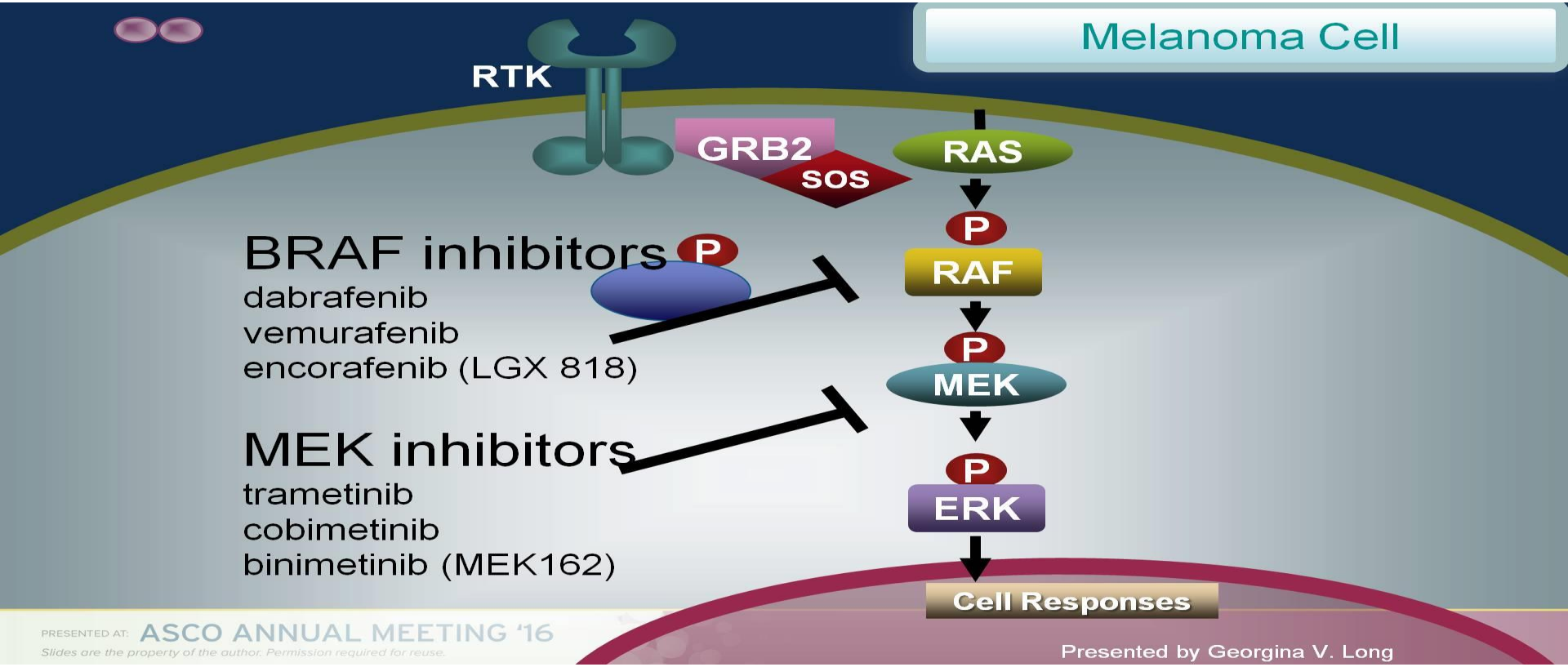


*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Wolchok J, et al. ASCO 2015; Larkin et al. *NEJM* 2015

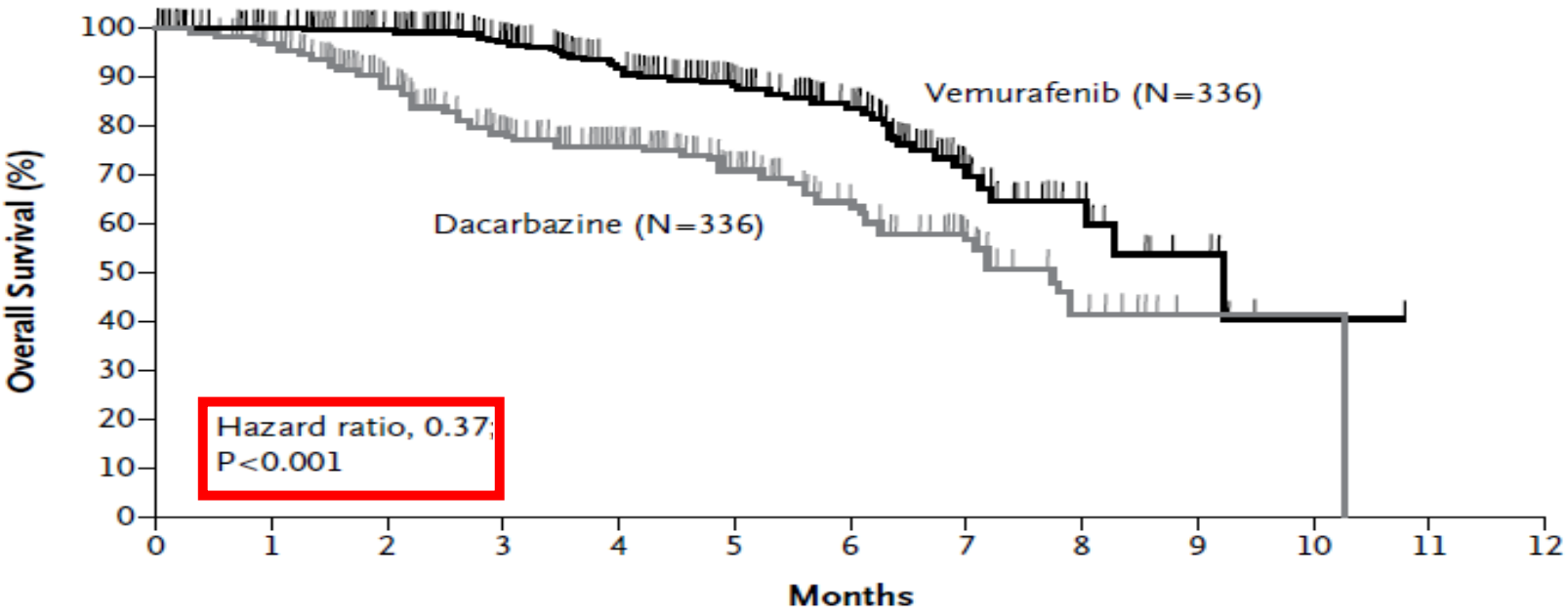
Questions I Ask Myself in the Clinic

- What are my options for immunotherapy?
- Should I use PD-1 monotherapy or combination with CTLA-4?
- What are my options for targeted therapy?
- What should I choose between immunotherapy or targeted therapy for BRAF+ patients?



Presented By Georgina Long at 2016 ASCO Annual Meeting

Vemurafenib Improves Overall Survival in Previously Untreated Stage IV BRAF V600 Mutant Melanoma



No. at Risk

Dacarbazine	336	283	192	137	98	64	39	20	9	1	1	0	0
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1	0	0

Chapman, et al. N Engl J Med. 2011;364:2507

MAPK Pathway Targeted Therapy

BRAFi (dabrafenib)

PFS HR, 0.37 vs DTIC[1]

Hyperproliferative skin AEs

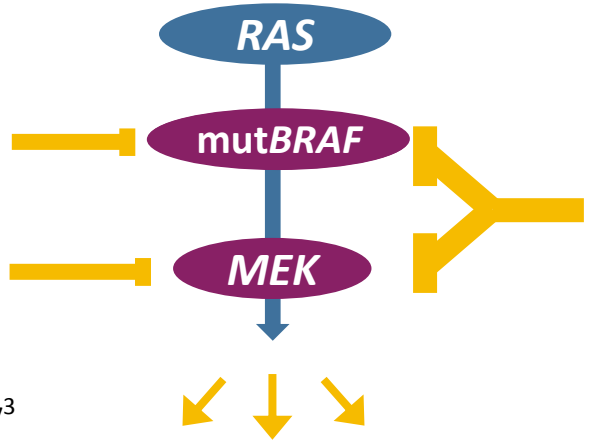
BRAFi (vemurafenib)

PFS HR, 0.38 vs DTIC[2]

Hyperproliferative skin AEs

MEKi (trametinib)

PFS HR, 0.45 vs chemotherapy[3]



BRAFi + MEKi ph III studies

+ trametinib (D + T)

PFS HR, 0.67 vs dabrafenib[4]

OS HR, 0.71 vs dabrafenib[4]

PFS HR, 0.56 vs vemurafenib[5]

OS HR, 0.69 vs vemurafenib[5]

Vemurafenib + cobimetinib

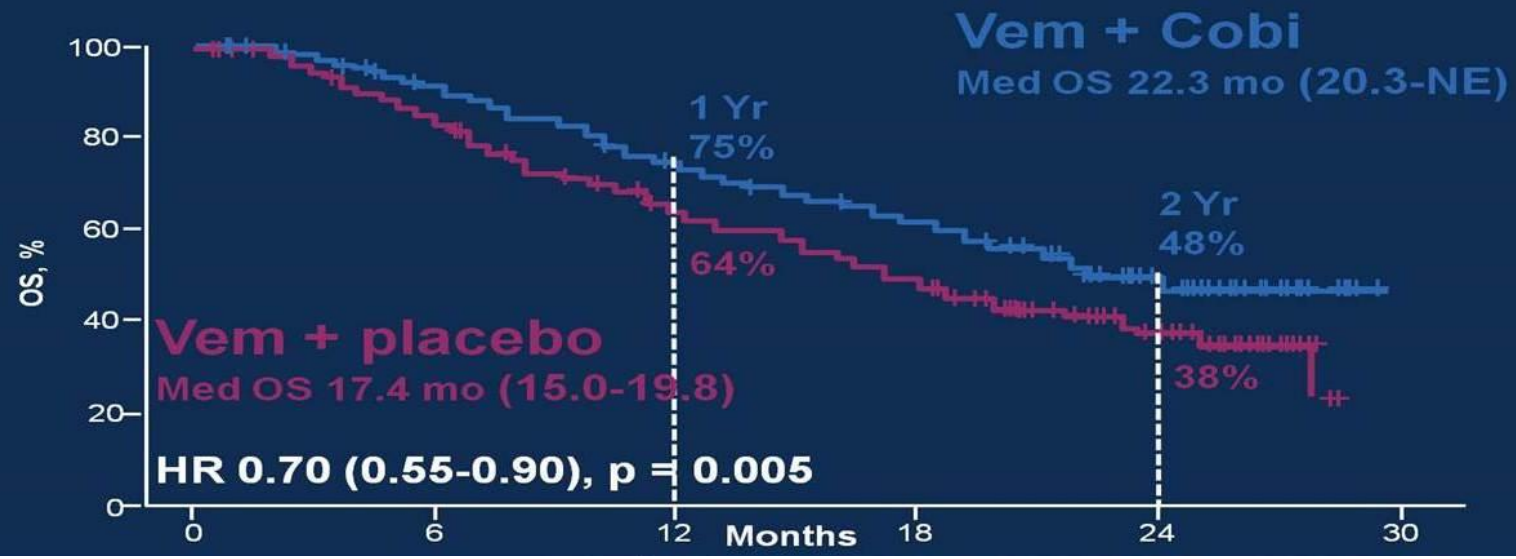
PFS HR, 0.58 vs vemurafenib[6]

OS HR, 0.70 vs vemurafenib[6]

Decreased hyperproliferative skin AEs[4,5,6]

1. Hauschild A, et al. *Lancet.* 2012;380(9839):358-365.
2. McArthur GA, et al. *Lancet Oncol*. 2014;15(3):323-332.
3. Flaherty KT, et al. *N Engl J Med.* 2012;367(2):107-114.
4. Long GV, et al. *Lancet.* 2015;386(9992):444-451.
5. Robert C, et al. *N Engl J Med.* 2015;372(1):30-39.
6. Atkinson V, et al. Presented at: Society for Melanoma Research 2015 Congress.

coBRIM: Overall Survival

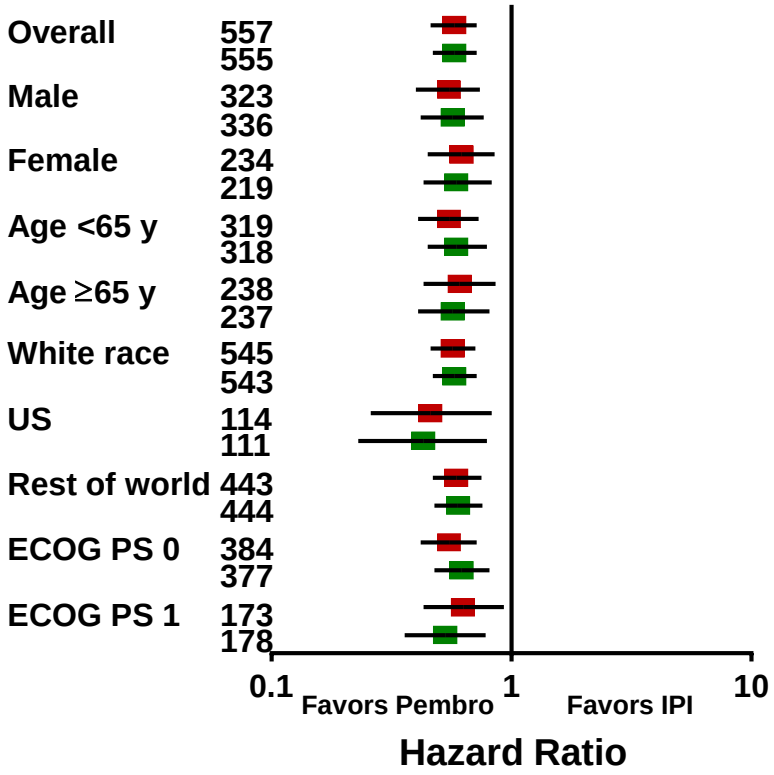


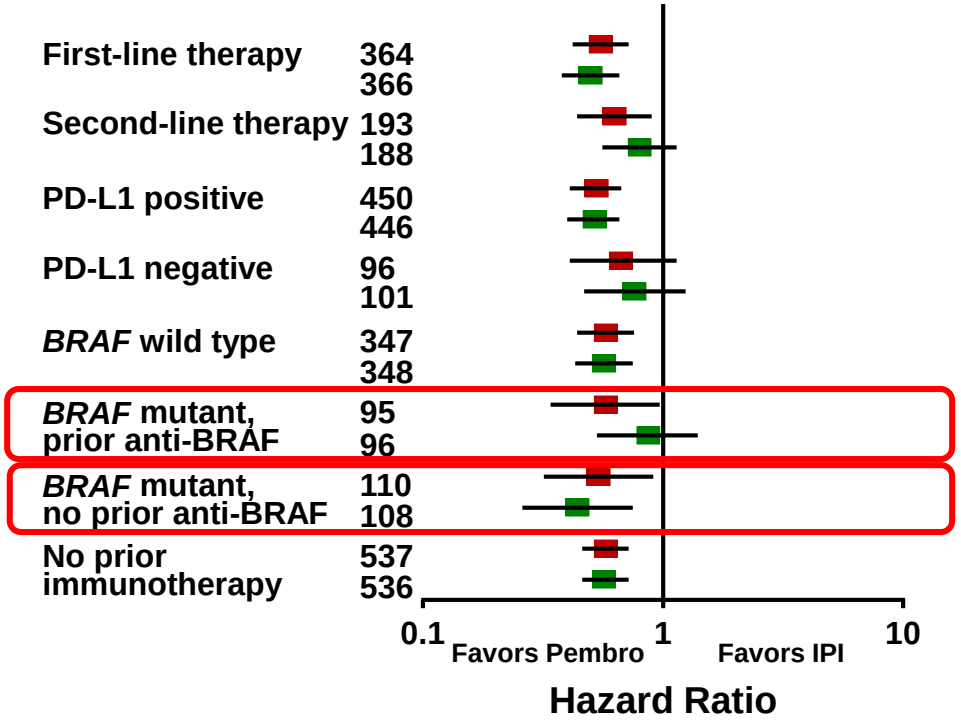
Atkinson V, et al. SMR 2015

Questions I Ask Myself in the Clinic

- What are my options for immunotherapy?
- Should I use PD-1 monotherapy or combination with CTLA-4?
- What are my options for targeted therapy?
- What should I choose between immunotherapy or targeted therapy for BRAF+ patients?

Phase III KEYNOTE-006:
PFS in Prespecified Subgroups





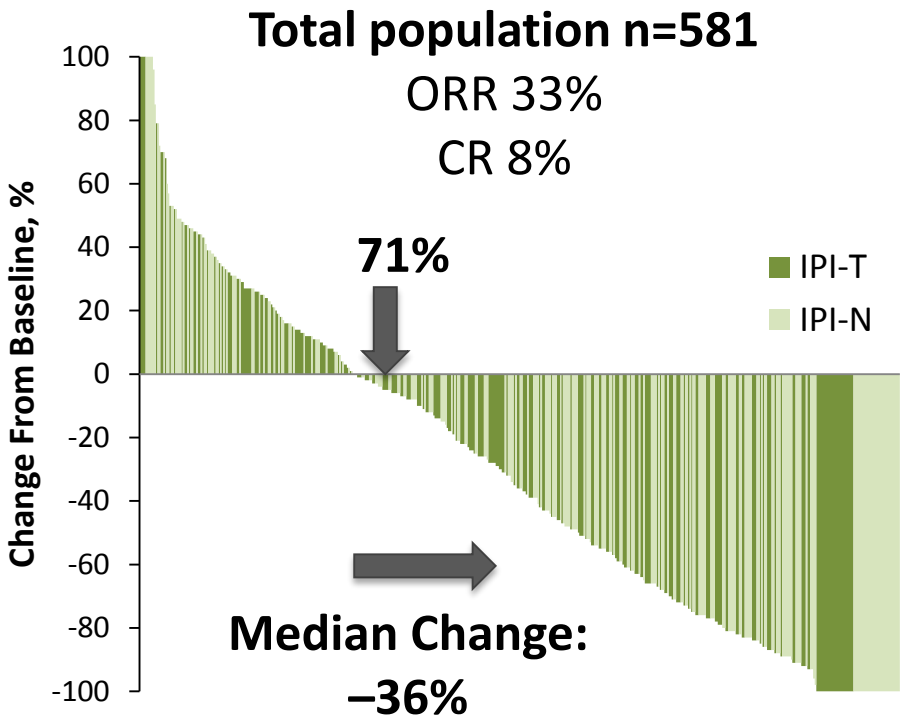
Pembrolizumab Q2W vs ipilimumab

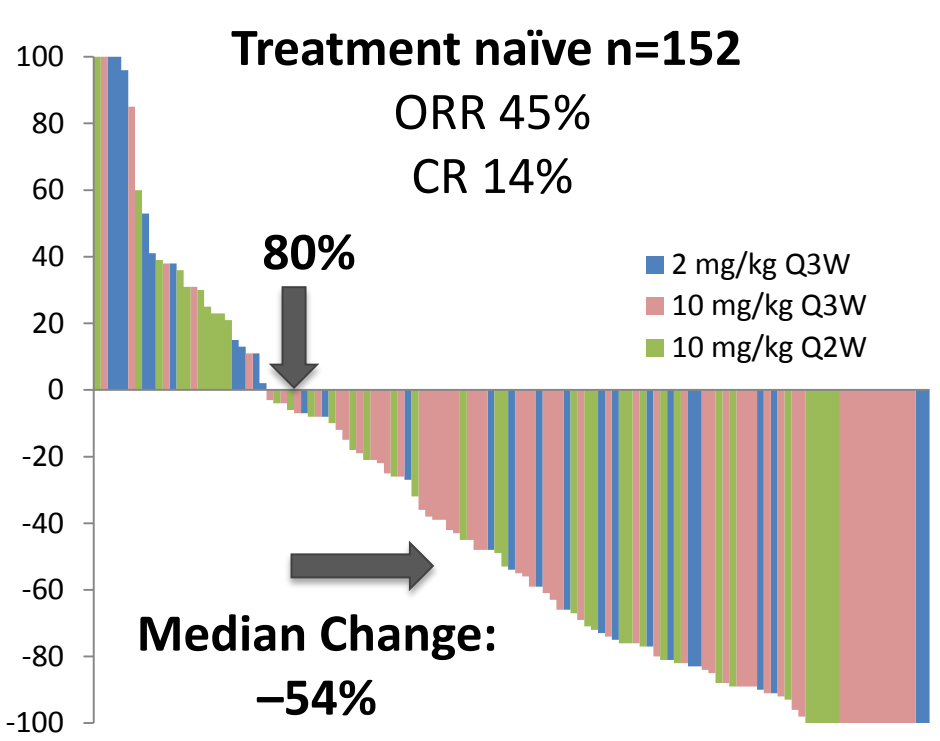
Pembrolizumab Q3W vs ipilimumab

Analysis cut-off date: September 3, 2014.

KEYNOTE-001: Phase I

RECIST Response (v1.1)





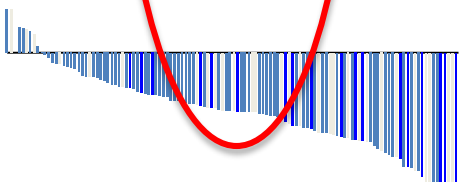
Analysis cut-off date: October 18, 2014; Median follow up 21 mo

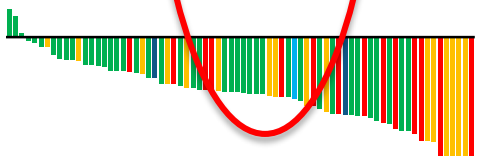
Daud A, et al. ASCO 2015

BRAF Inhibitors

Second line

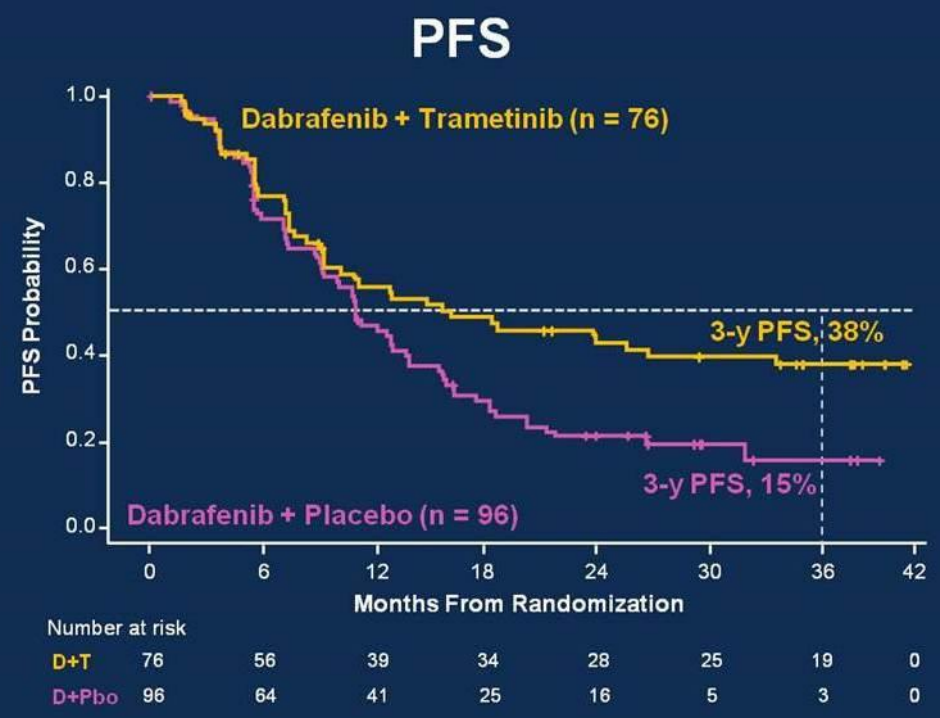
	Vemurafenib[1]			Dabrafenib[2]		
Phase	1	2	3	1	2	3
RR	56%	57%	57%	56%	59%	59%
PFS		6.7	6.9	5.5	6.3	6.9
OS	13.8	15.9	13.6		13.1	18.2

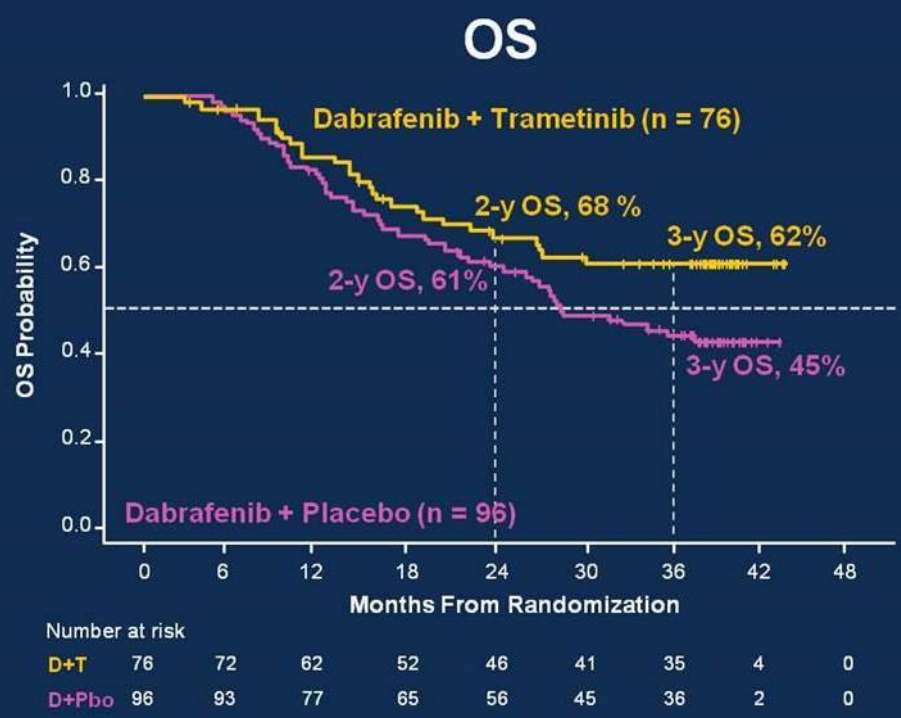




1. Chapman PB, *et al. N Engl J Med* 2011;364:2507–2516 (updated Chapman *et al.* ASCO 2012); Sosman JA, *et al. N Engl J Med* 2012;366:707–714;
2. Hauschild A, *et al. Lancet* 2012;380:358–365 (updated Hauschild *et al.* ASCO 2013); Ascierto PA, *et al. J Clin Oncol* 2013; 31:3205–3211.

COMBI-d: Normal LDH[a] and < 3 Disease Sites[b]

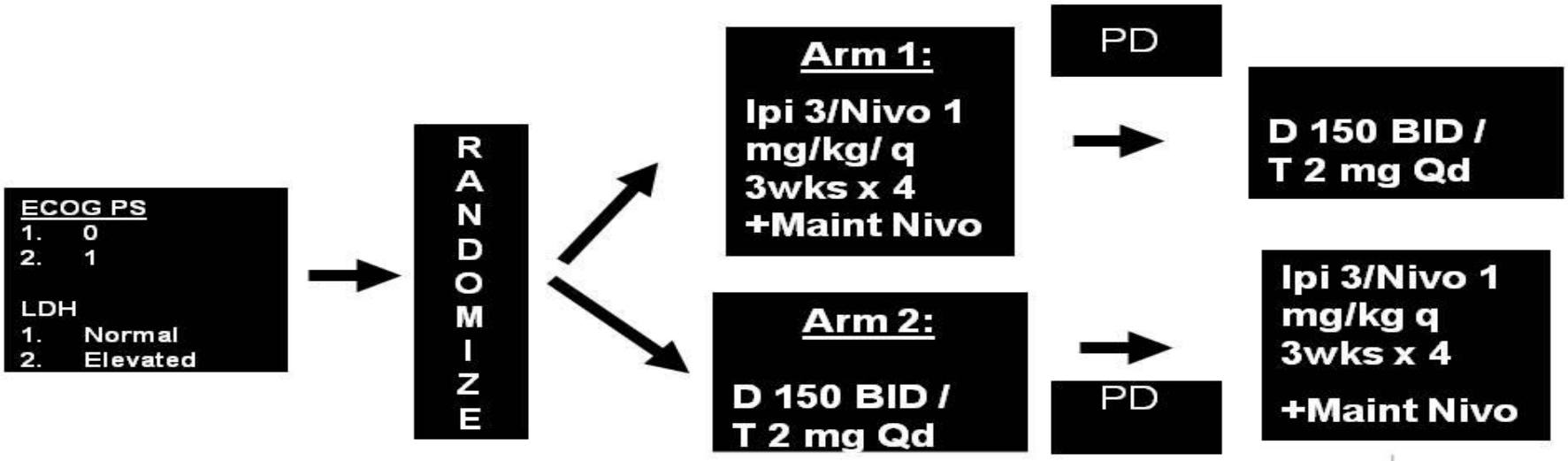




[a] Baseline LDH ≤ ULN; [b] Any organ at baseline with ≥ 1 metastasis could be counted as a single disease site; +, censored.

Presented by Keith Flaherty, ASCO 2016

EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo



ECOG and SWOG protocol – Atkins, Chmielowski
Anticipated opening 6/2015

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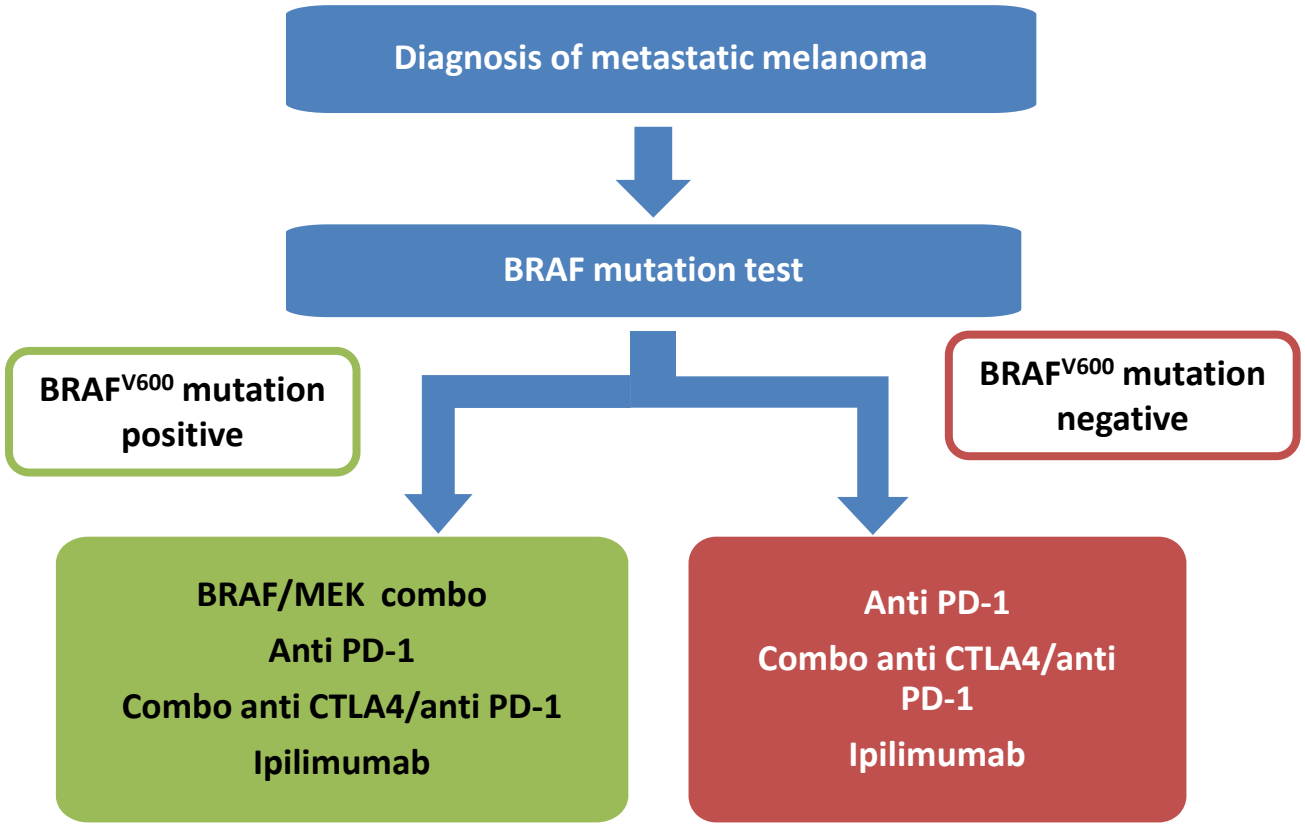
PRESENTED AT: ASCO Annual '15 Meeting

Presented By Michael Atkins at 2015 ASCO Annual Meeting

How I Treat Metastatic Melanoma



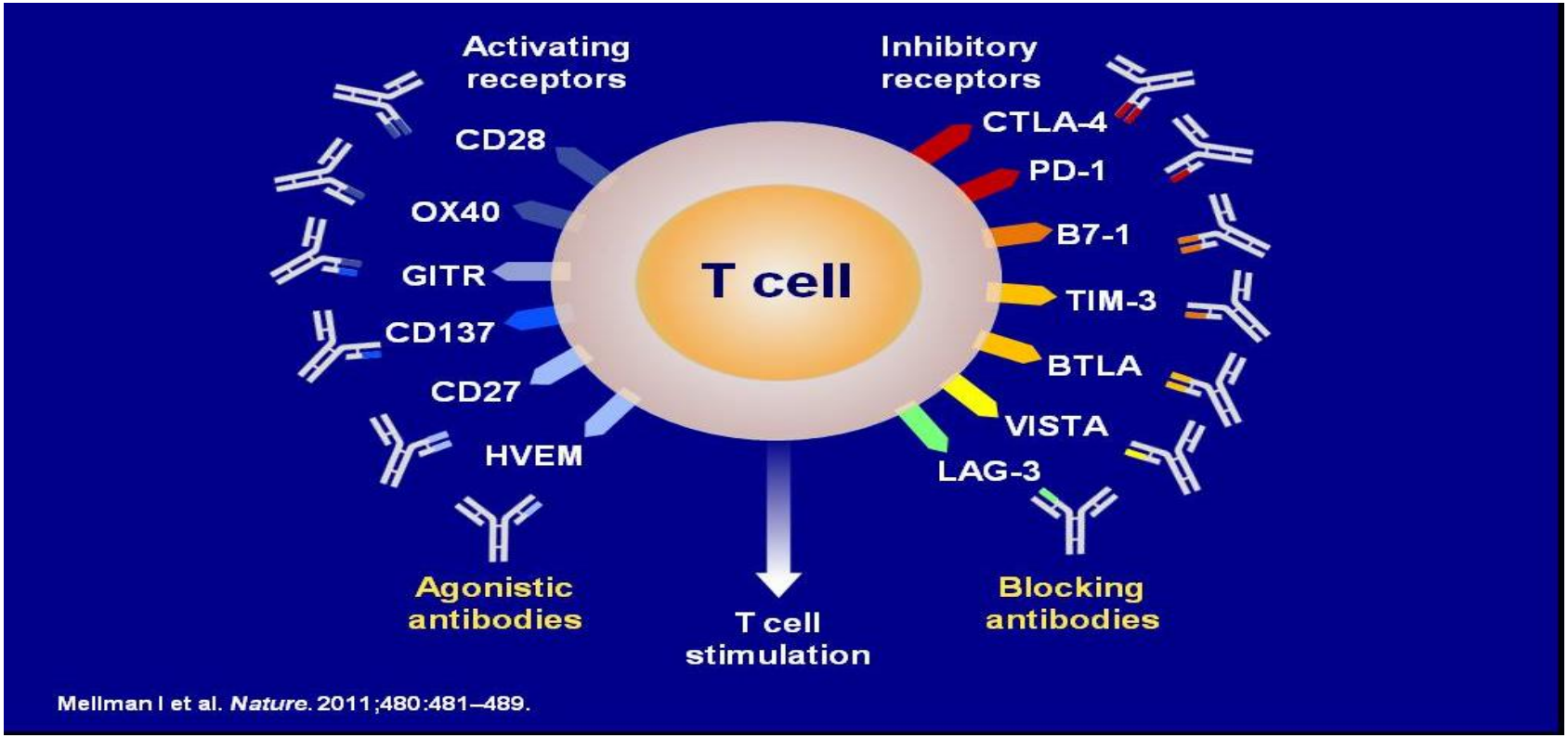
Overview

- Introduction and Background
- Questions I ask myself in the clinic
- Future Directions

How Can Immunotherapy be Optimized and Improved?

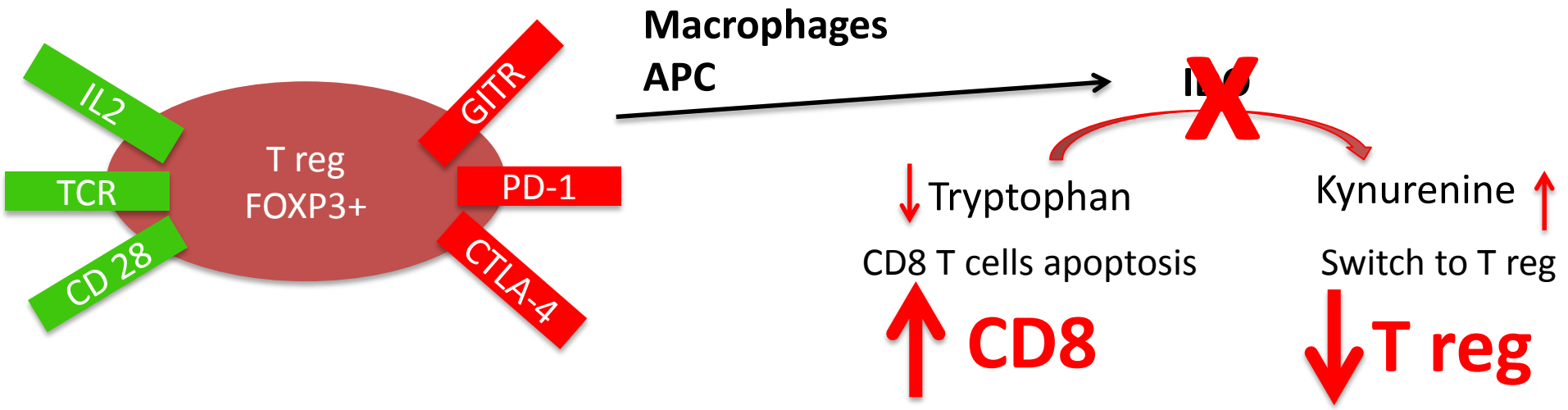
- Addition of other checkpoint modulators
- BRAF/MEK Combination
- Reduce toxicity of combination therapy
  - Lower dose ipilimumab
- Can we “injure” the tumor to render it more vulnerable to systemic immune attack?
  - Oncolytic therapy
  - Radiation/Chemotherapy

T-Cell Immune Checkpoints

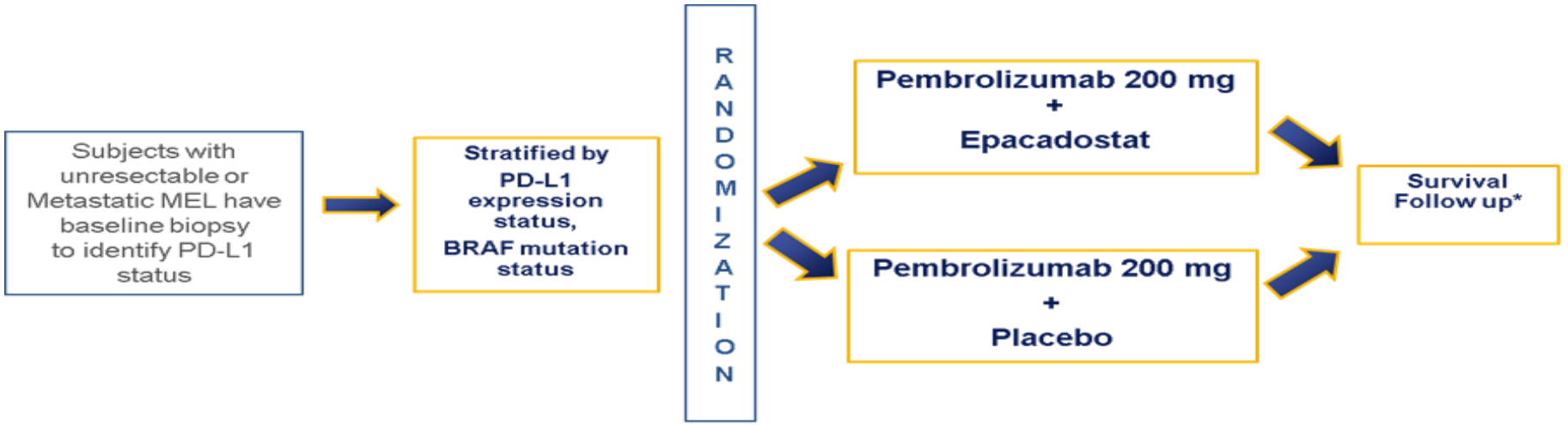


Presented By Scott Gettinger at 2014 ASCO Annual Meeting

IDO and T Cells



KEYNOTE 252//ECHO 501:Trial Design



Pembrolizumab in Combination With Dabrafenib and Trametinib for BRAF-Mutant Advanced Melanoma: Phase 1/2 KEYNOTE-022 Study

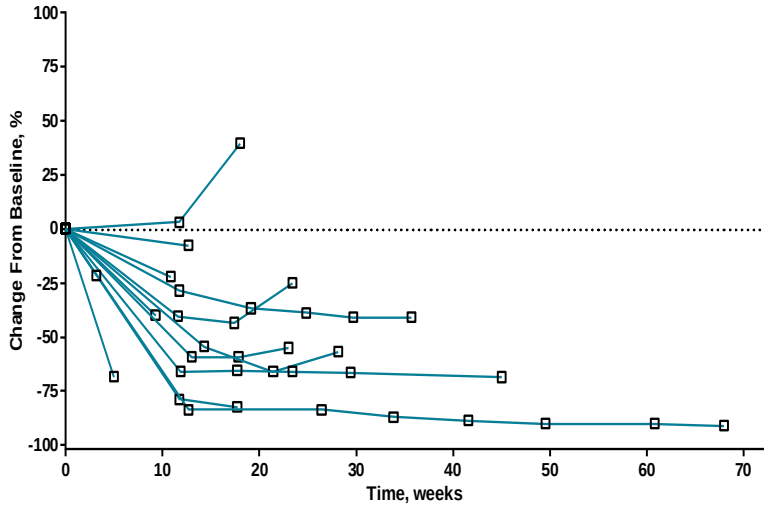
Ribas A[1]; Hodi FS[2]; Lawrence D[3]; Atkinson V[4]; Starodub A[5]; Carlino MS[6]; Fisher R[7]; Long GV[8]; Miller, Jr. WH[9]; Huang Y[10]; Diede SJ[11]; Ebbinghaus S[11]; Hamid O[12]

Figure 2. Part 2: dose expansion.

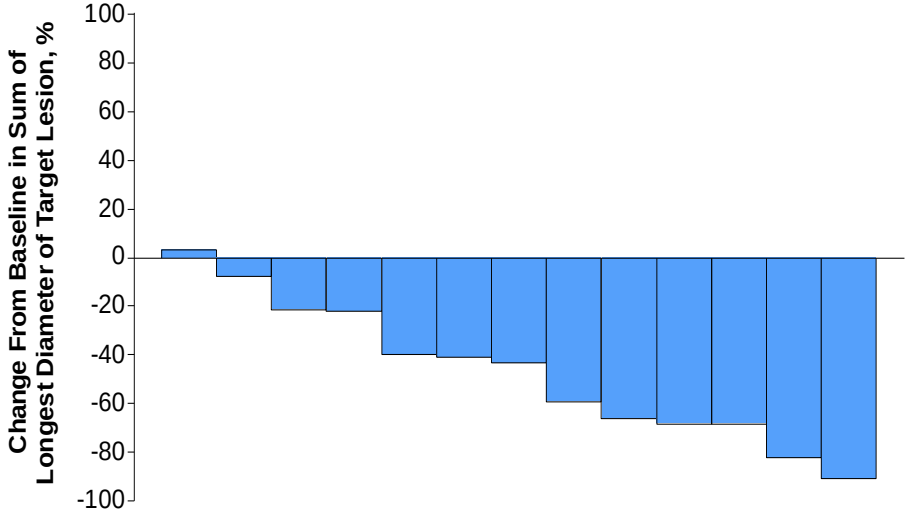
BID = twice daily; Q3W = once every 3 weeks; QD = once daily.

KEYNOTE 022: Pembrolizumab in Combination With Dabrafenib and Trametinib

Longitudinal Change From Baseline in Tumor



Maximum Percentage Change From Baseline in Tumor

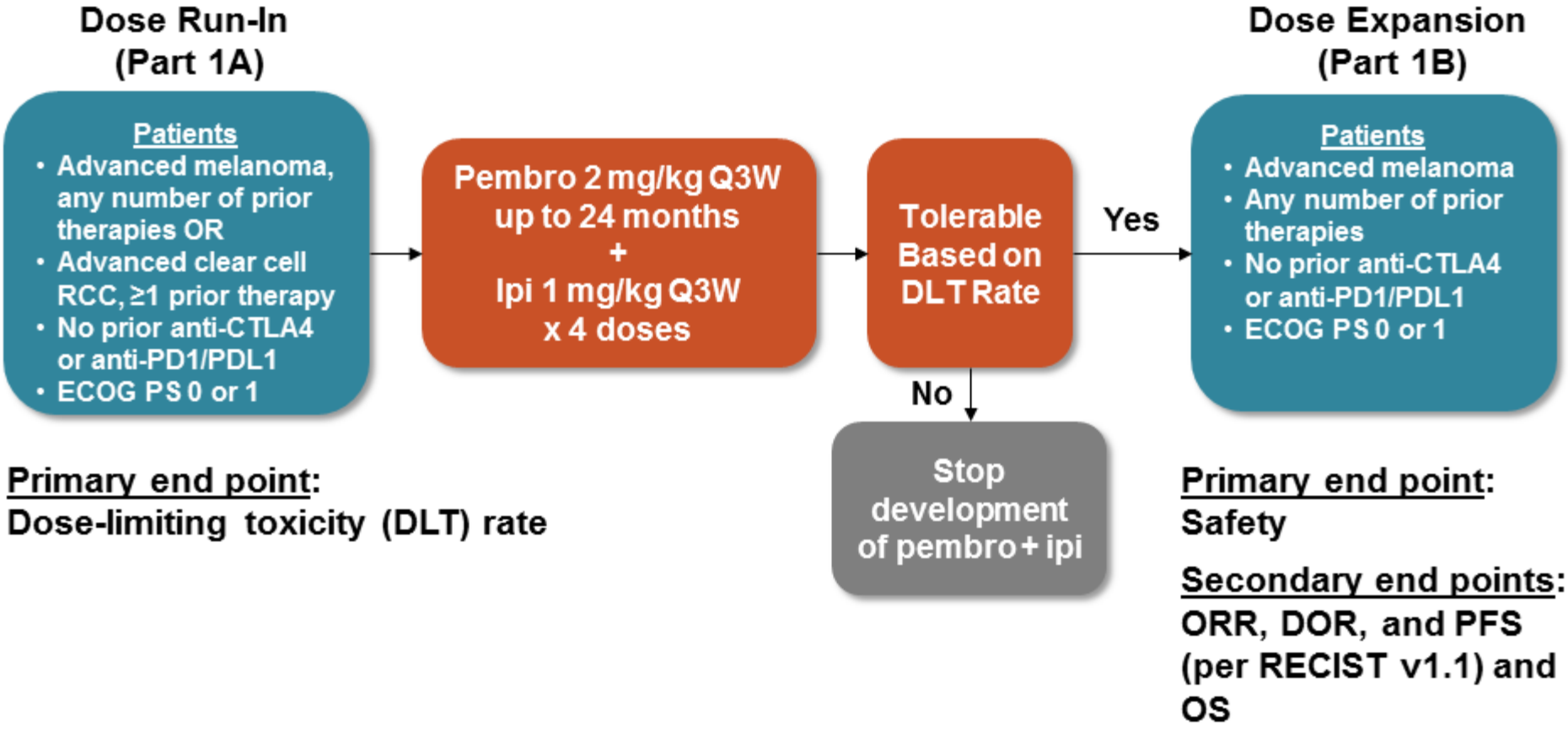


[a]Assessed in all patients who received ≥1 dose of study treatment (n = 13). [b]Only patients with measurable disease per RECIST v1.1 by investigator review at baseline and ≥1 post-baseline tumor assessment were included (n = 13). [c]In patients with confirmed response only. Data cutoff date

Ribas A, et al. *J Clin Oncol*. 2016;34(suppl): Abstract 3014.

G V Long et al. SMR 2015.

KEYNOTE-029: Study Design



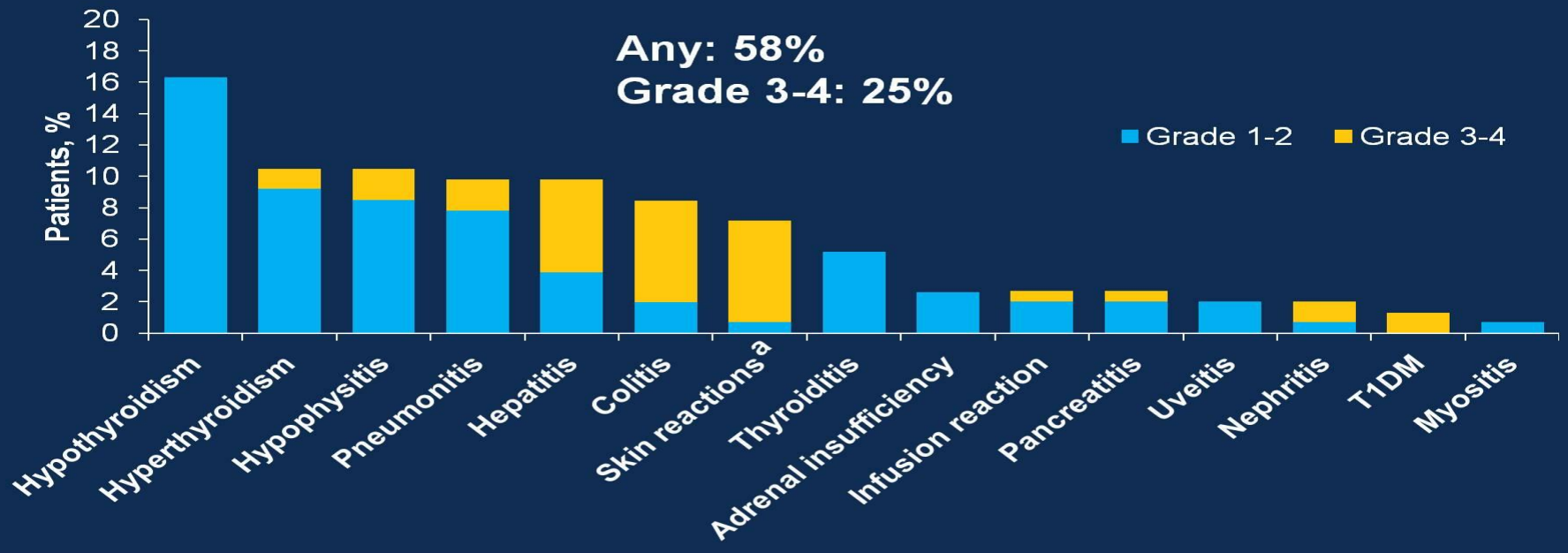
Primary end point:
Dose-limiting toxicity (DLT) rate

Primary end point:
Safety

Secondary end points:
ORR, DOR, and PFS (per RECIST v1.1) and OS

ClinicalTrials.gov identifier NCT02089685.

Immune-Mediated AEs: Incidence



PRESENTED AT: ASCO ANNUAL MEETING '16

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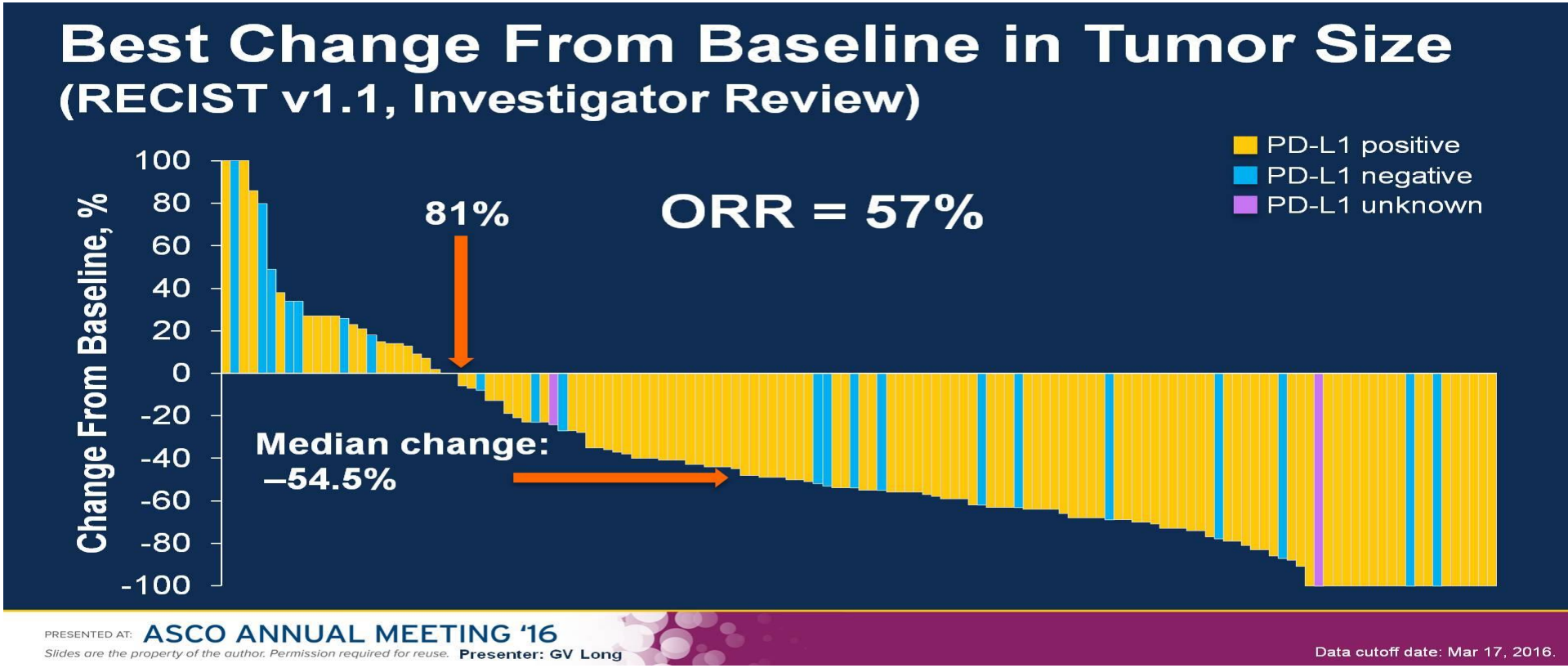
[a]Includes grade 3 rash (n = 6), grade 3 drug reaction (n = 3), grade 3 pemphigoid (n = 1), and grade 2 exfoliative dermatitis (n = 1)
Data cutoff date: Mar 17, 2016.

Presented By Georgina Long at 2016 ASCO Annual Meeting



Presented By Georgina Long at 2016 ASCO Annual Meeting

Intralesional Oncolytic Therapy
"Injuring the Tumor"

- TVEC (FDA approved)
- PV-10
- IL-12
- HF-10
- Cavatak

MASTERKEY-265 Phase 3 Study Design

N = 660

- Unresectable stage III or IV melanoma
- Treatment naive
- Injectable lesions
- No clinically active brain mets
- No active herpetic skin lesions or prior complications from herpetic infection

T-VEC intralesional
- Up to 4 mL per treatment
- 1st dose 10^6 PFU/mL
- Then 10^8 PFU/mL Q2W

R

1:1

N = 330

T-VEC Intralesional

Pembrolizumab 200mg IV Q3W

N = 330

T-VEC placebo Intralesional

Pembrolizumab 200mg IV Q3W

SAFETY FOLLOW-UP

30 (+7) days after end of treatment

Treatment until whichever occurs first:
- CR or PD per irRC-RECIST
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

T-VEC: talimogene laherparepvec

Summary & Conclusions

- Checkpoint inhibitors and MAPK targeted agents have revolutionized the treatment of advanced melanoma.
- First line immunotherapy in the US is either anti-PD-1 monotherapy or combination with anti-CTLA4.
- BRAF+ patients may receive targeted therapy or immunotherapy.
- Future directions will exploit adding new agents and lowering toxicity of combinations

Questions?

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Thank you for participating in the ICLIO Webinar. Presentation slides and archived recording will be available at accc-iclio.org

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Association of Community Cancer Centers