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Principles and Application of Immunotherapy for Cancer: Advanced Melanoma

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Faculty Disclosures

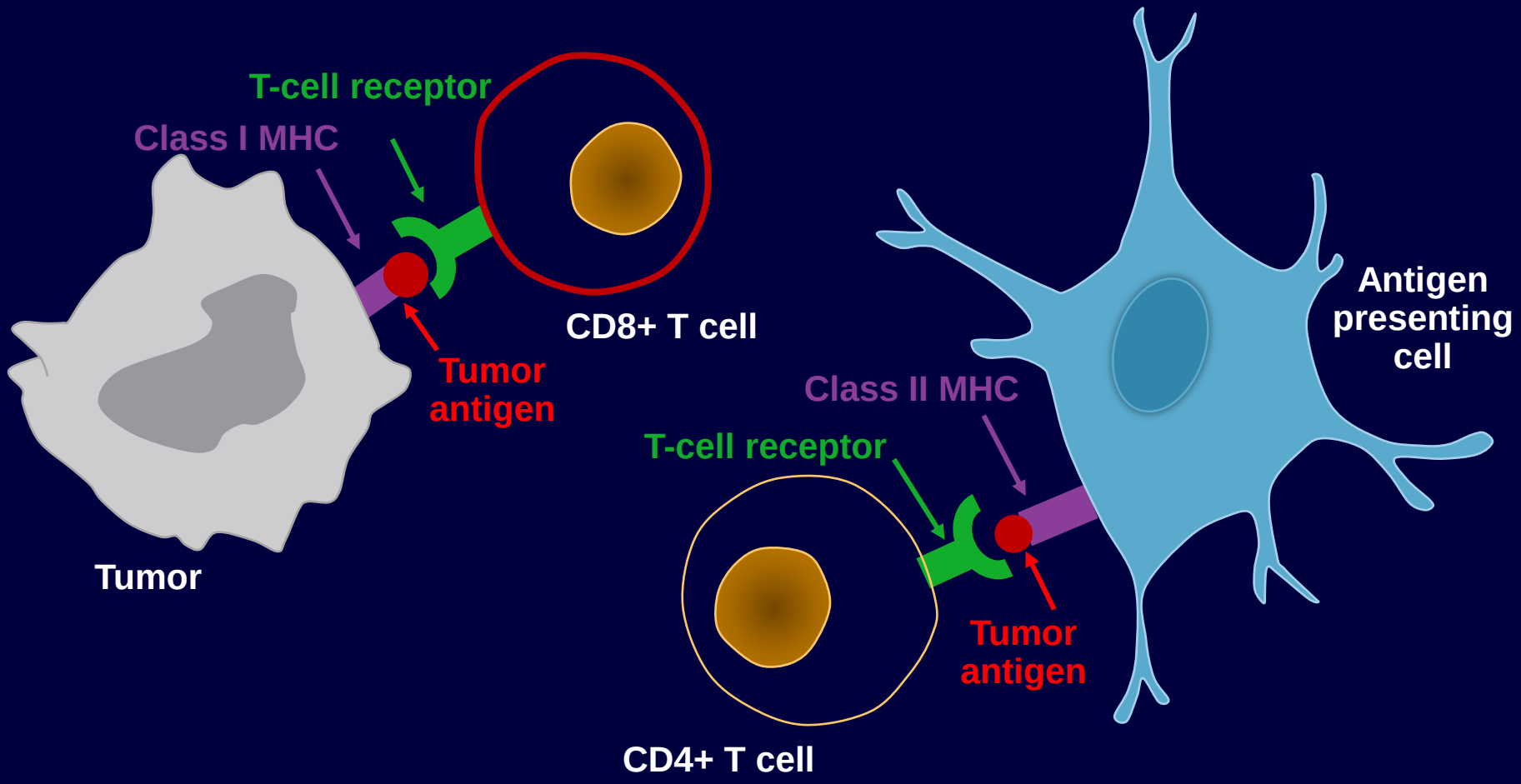
Jeffrey S. Weber, MD, PhD, has disclosed that he has served as a consultant for Bristol-Myers Squibb, Celldex, Genentech, GlaxoSmithKline, and Merck and has ownership interest in Altor, cCAM and Celldex.

Peg Esper, DNP, ANP-BC, AOCN, has no real or apparent conflicts of interest to report.

Agenda

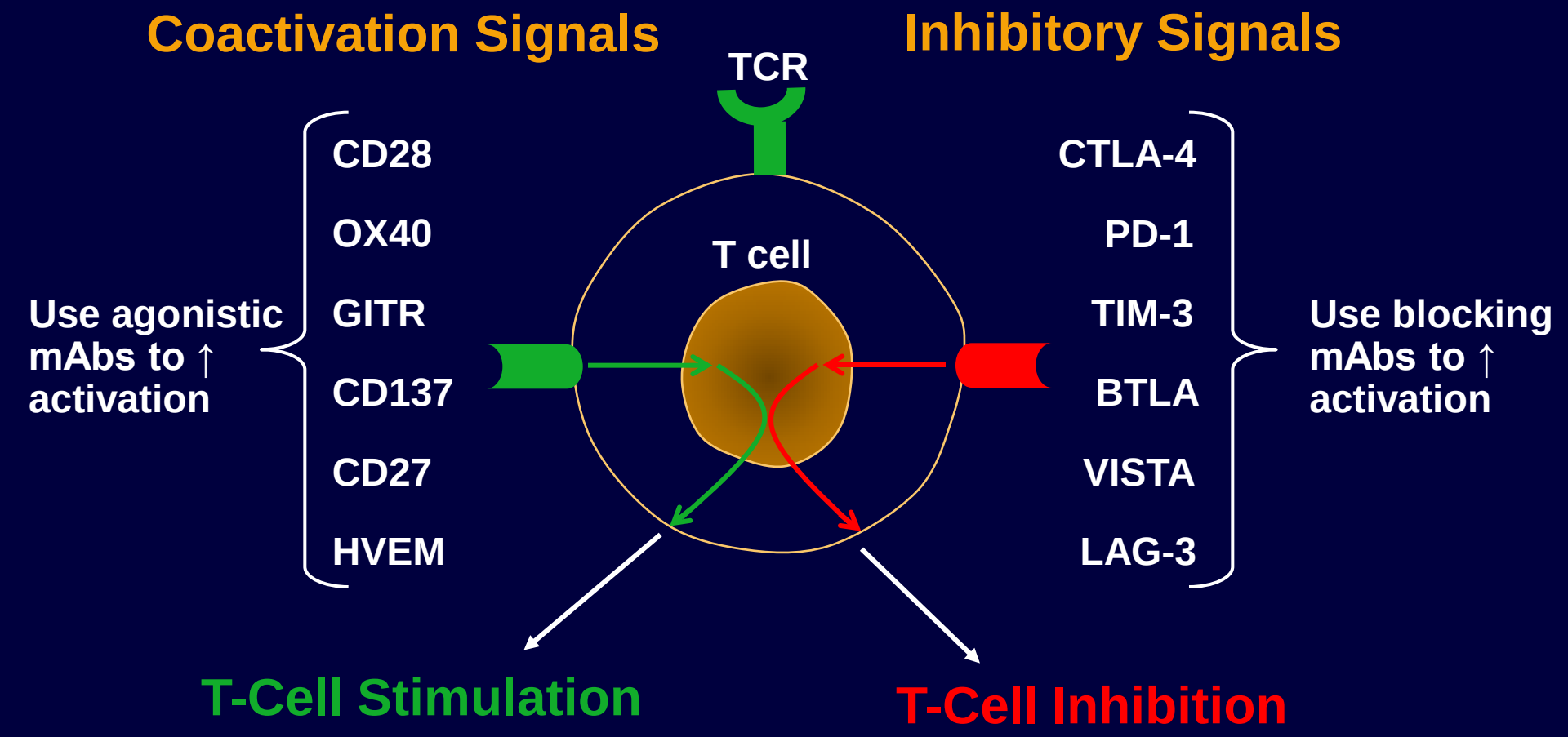
- Melanoma and the Immune System
  - Defining the role of the immune system in cancer
  - Tumor escape from immune surveillance
  - Harnessing the immune system for melanoma treatment
- Current Immunotherapy for Melanoma
  - Efficacy and safety of currently approved agents
  - Managing potential adverse events associated with immunotherapy
- Novel Agents and Immunotherapy Combinations

T-Cell Response: First Signal



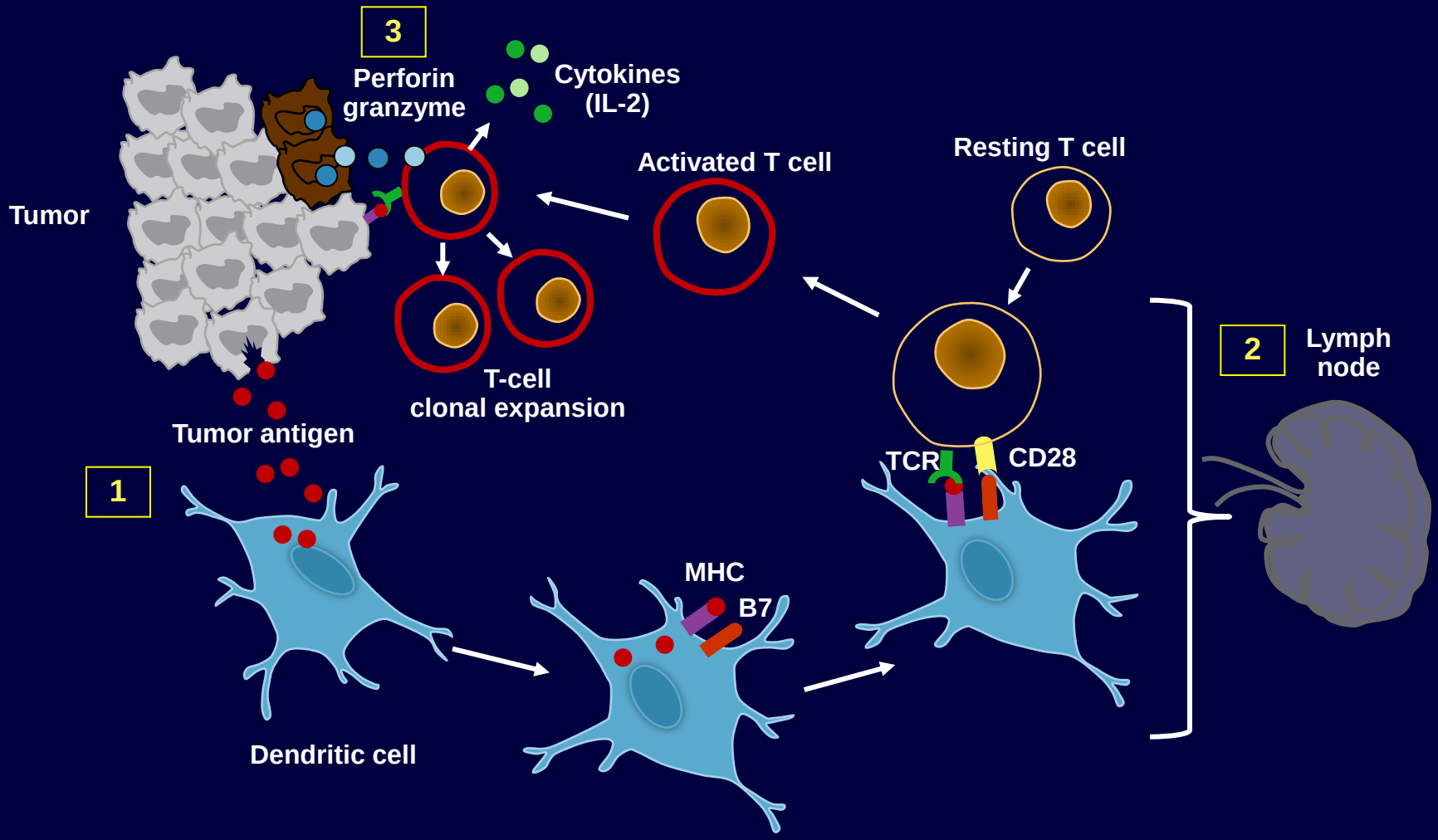
Snyder A, et al. Curr Opin Genet Dev. 2015;30C:7-16.

T-Cell Response: Accelerate or Brake?

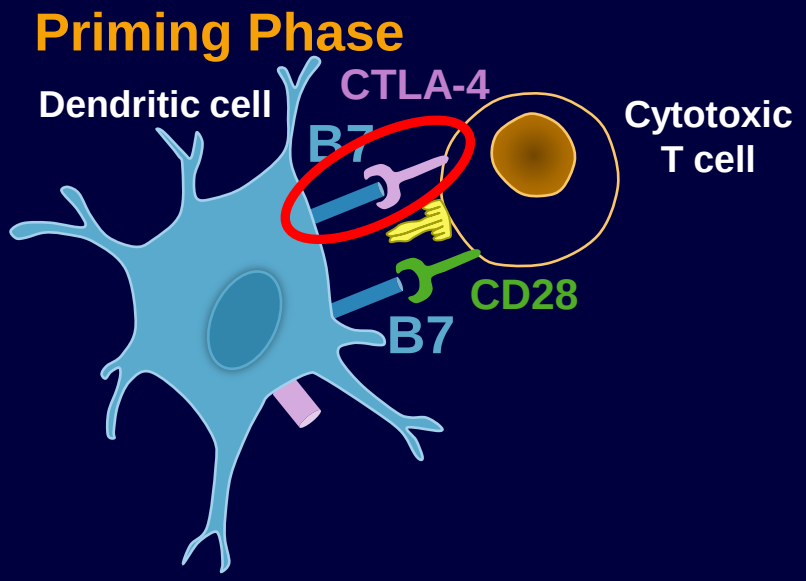


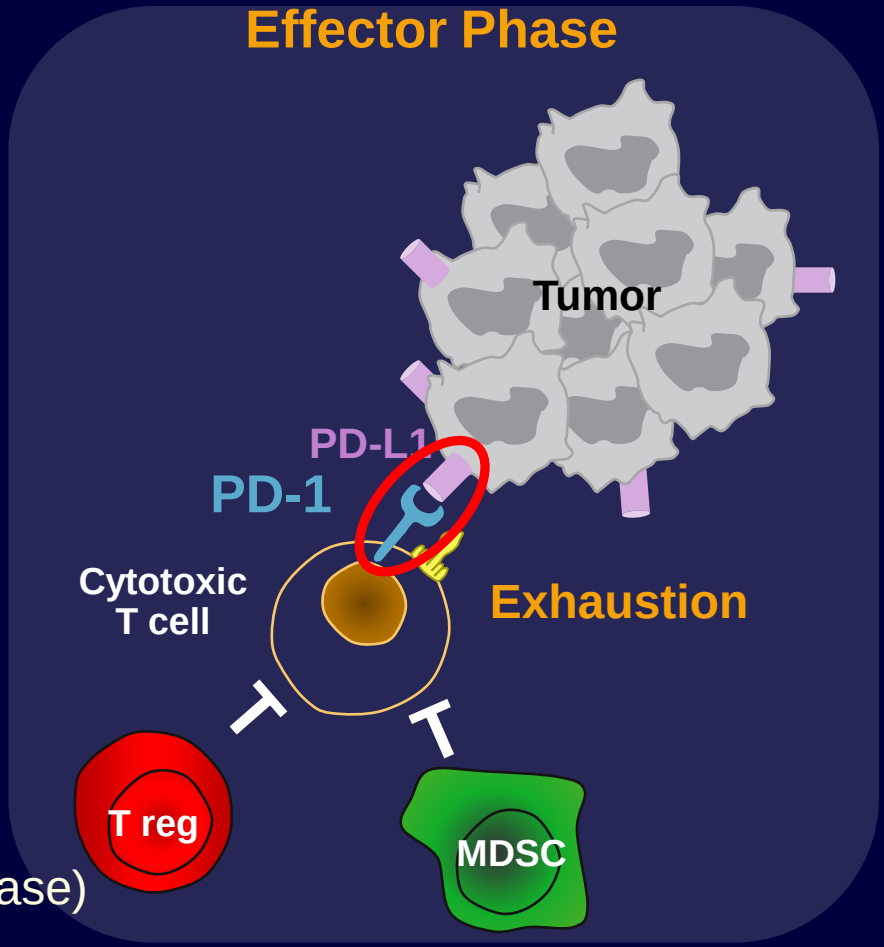
Adapted from Mellman I, et al. Nature. 2011;480:480-489.

Tumor Immunology: Overview



Dampening the Immune System in Cancer





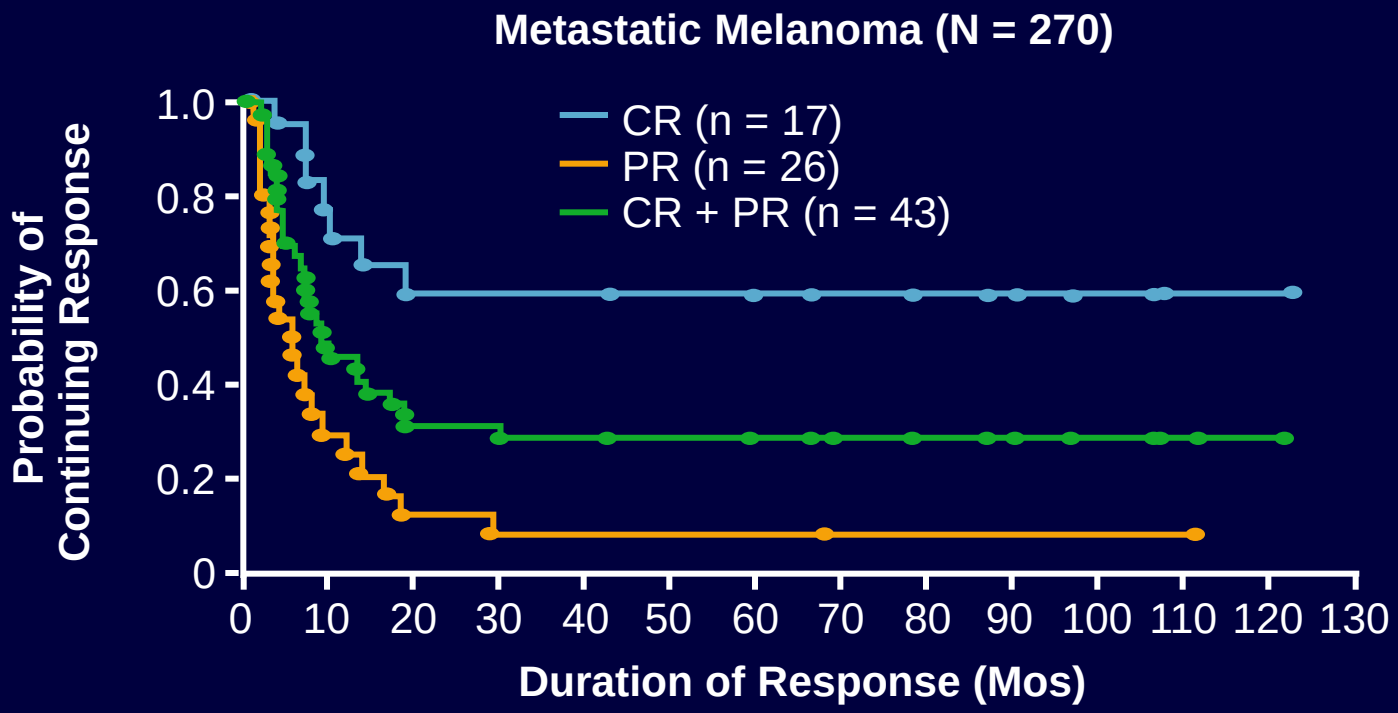
- Negative immune regulators
  - Inhibitory receptors
  - Suppressive cells
  - Suppressive enzymes (IDO, arginase)

Ribas A. N Engl J Med. 2012;366:2517-2519. Spranger S, et al. J Immunother Cancer. 2013;1:16.

Immunotherapy for Melanoma

High-Dose IL-2 Therapy: Durable Responses Seen

- High-dose IL-2 produces durable responses in 16% of pts with advanced melanoma
- Few relapses in pts responding for over 2.5 yrs (likely cured)
- FDA approval in 1998 for melanoma



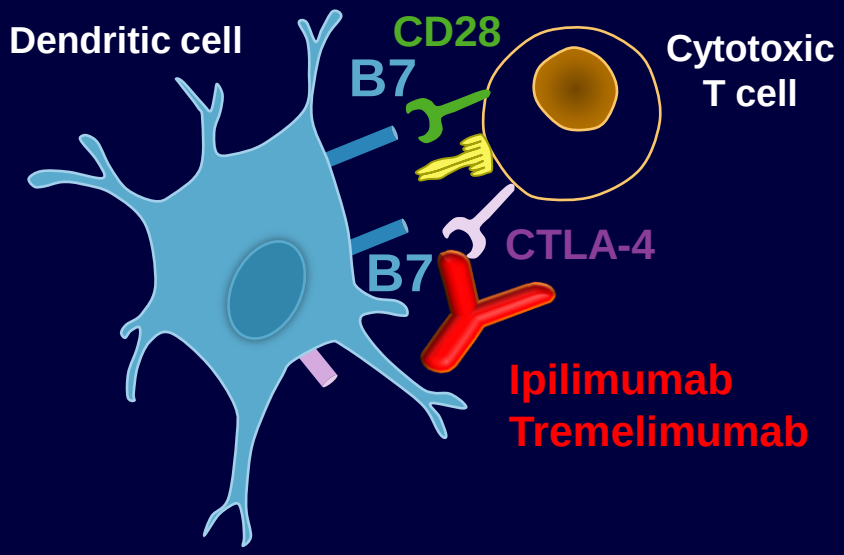
Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116.

High-Dose IL-2 Therapy in Melanoma

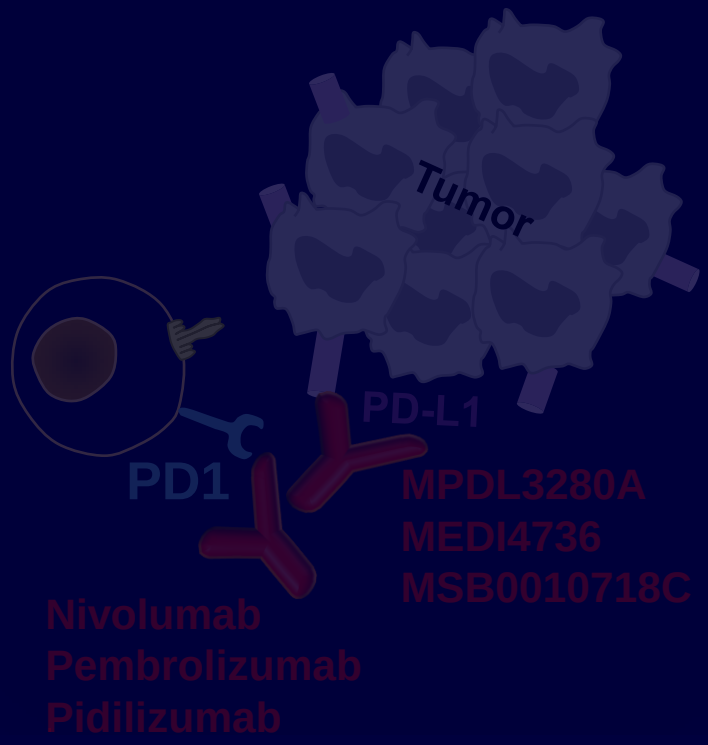
- High-dose IL-2 appears to benefit pts, but:
  - Toxic
  - Complex; must be delivered as an inpatient regimen
- Use remains limited to selected pts treated at experienced centers
- Efforts to develop more tolerable regimens unsuccessful
- Efforts to better select pts who might benefit from high-dose IL-2 therapy have produced modest advances
- Proof of principle that immunotherapy can produce durable benefit in pts with cancer, but newer immunotherapies are needed

Blocking Immunologic Checkpoints

Priming: T-Cell Activation in the Lymph Node

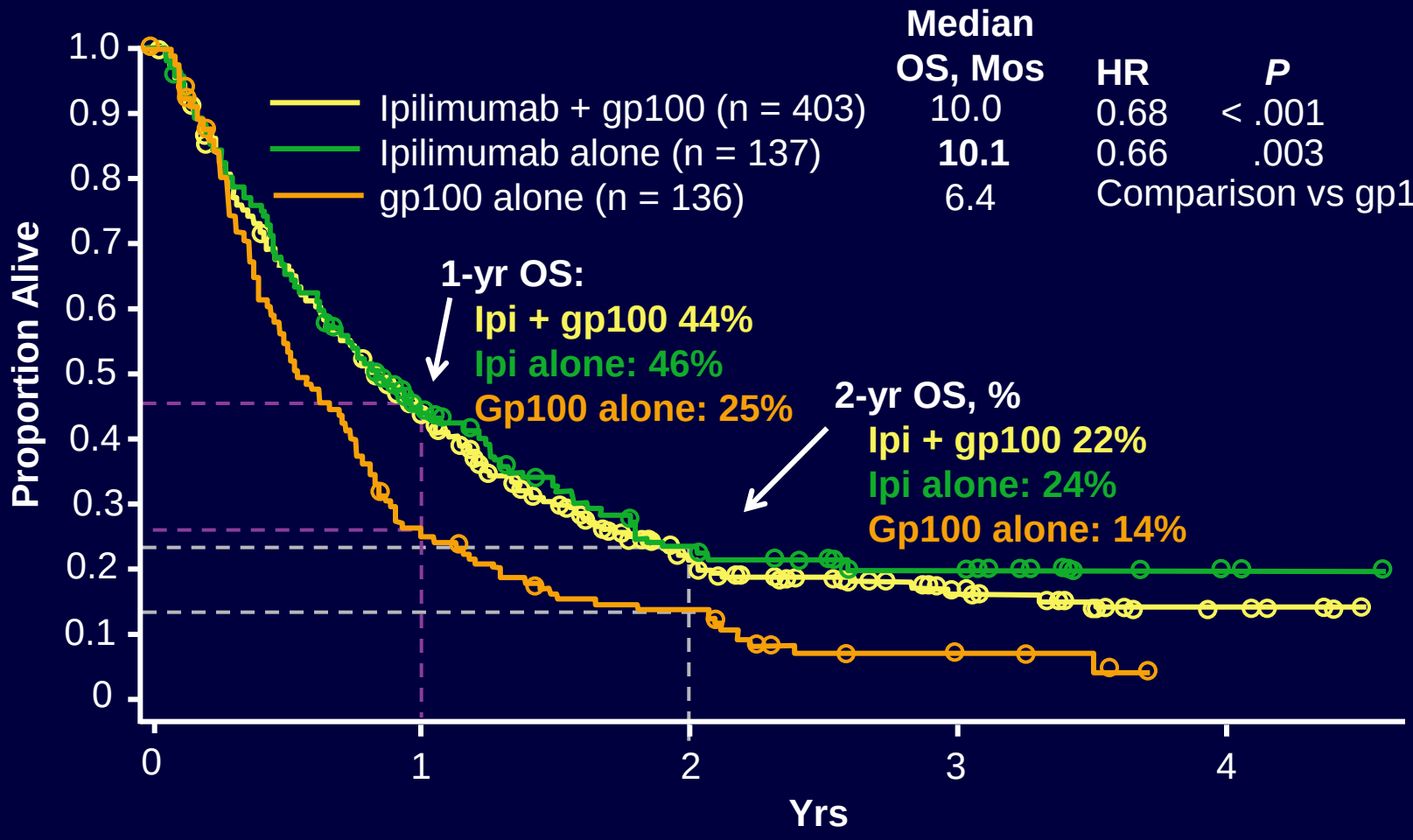


Effector Phase: Peripheral Tissues



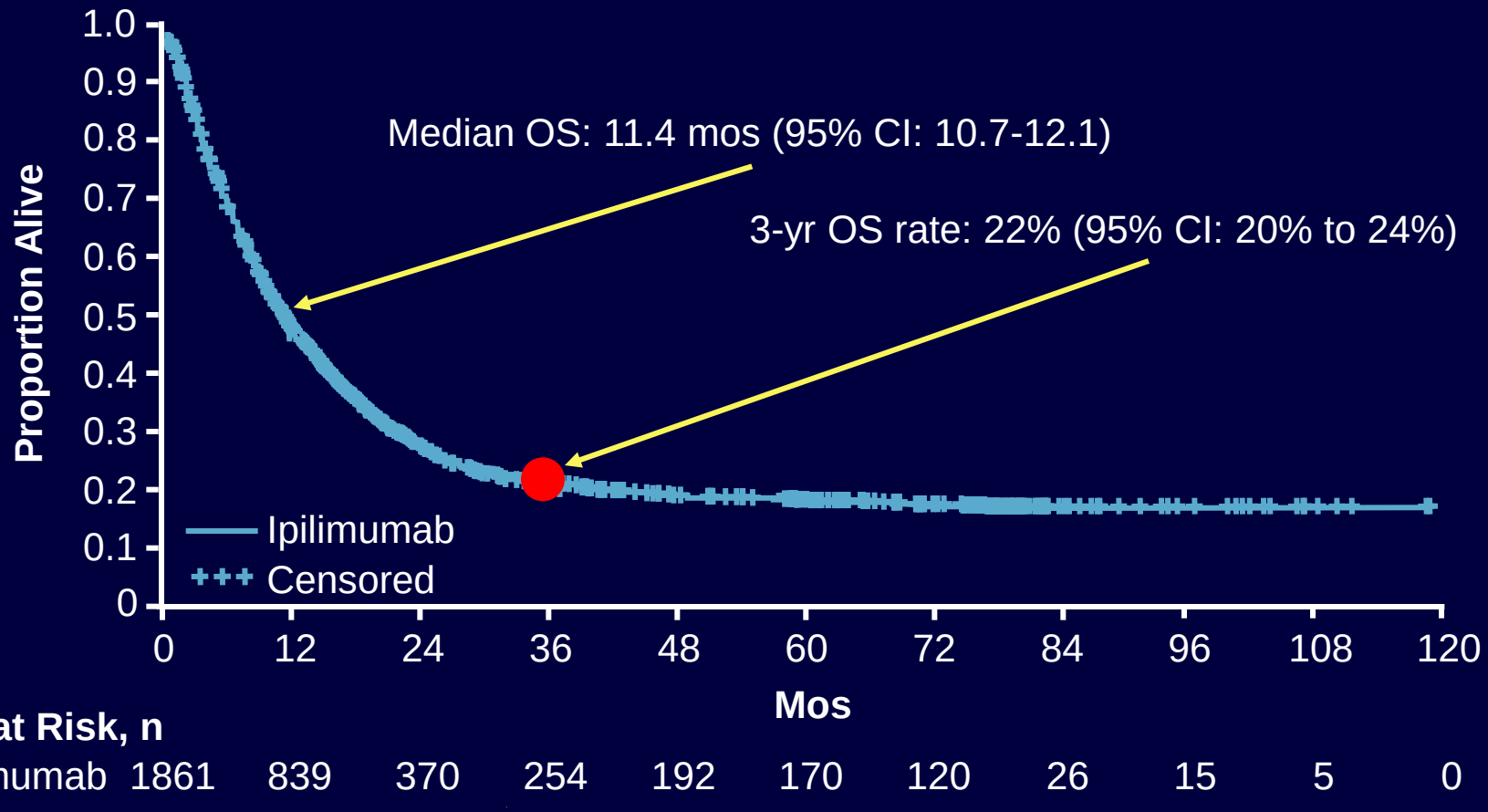
Ribas A. N Engl J Med. 2012;366:2517-2519. Spranger S, et al. J Immunother Cancer. 2013;1:16.

Ipilimumab, gp100, or Both: OS in Advanced Melanoma



Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Analysis From Phase II and Phase III Trials of Ipilimumab Show OS Plateau at 3 Years



Pts at Risk, n

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

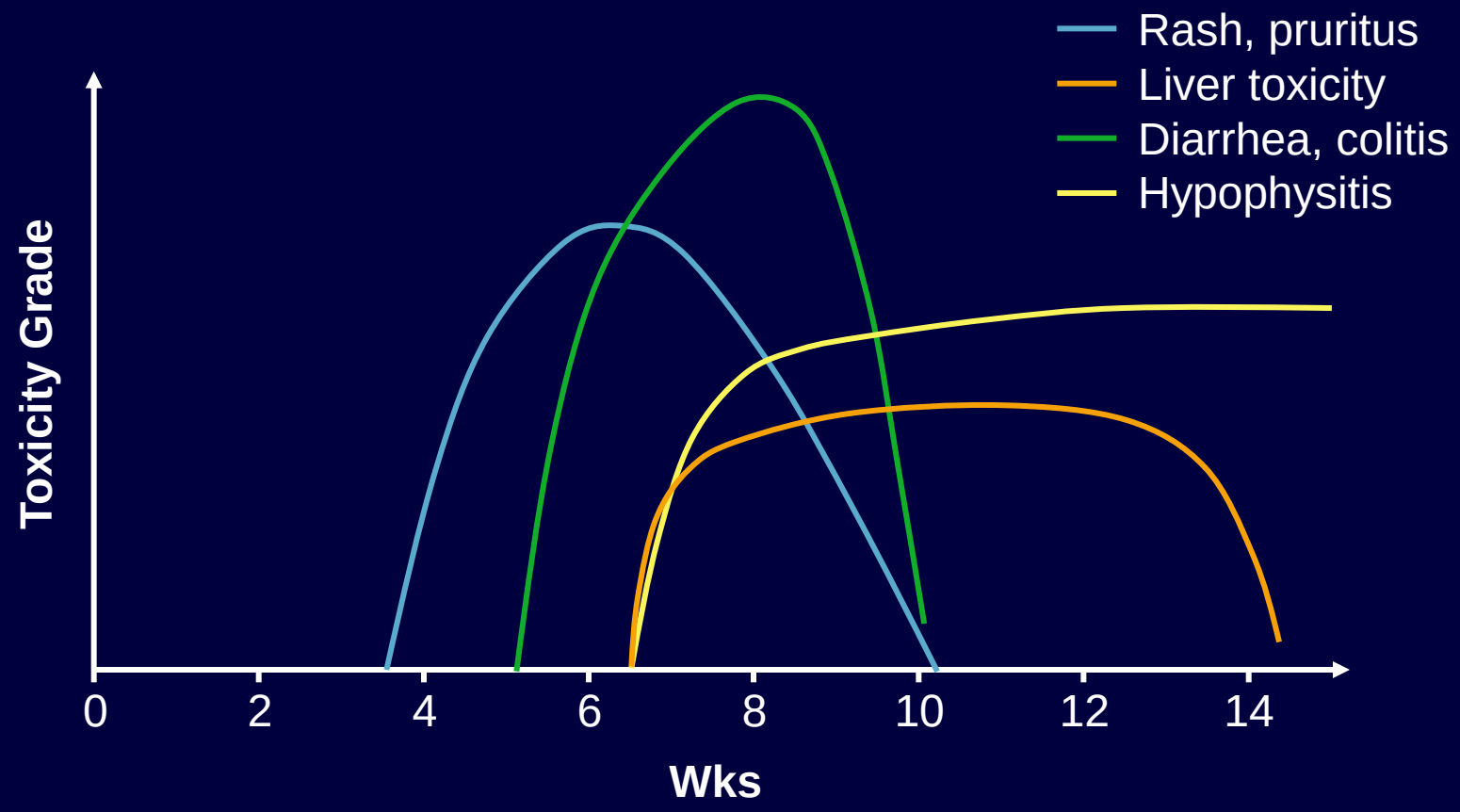
Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.
Schadendorf D, et al. J Clin Oncol. 2015 [Epub ahead of print].

Ipilimumab, gp100, or Both in Advanced Melanoma (MDX010-20): irAEs

irAE, %	All Grades (Grade 3/4)		
	Ipi + gp100 (n = 380)	Ipi + Placebo (n = 131)	gp100 + placebo (n = 132)
Any	**58** (9.7/0.5)	**61** (12.2/2.3)	**32** (3.0/0)
Dermatologic	40 (2.1/0.3)	44 (1.5/0)	17 (0/0)
Gastrointestinal	32 (5.3/0.5)	29 (7.6/0)	14 (0.8/0)
Endocrine	4 (1.1/0)	8 (2.3/1.5)	2 (0/0)
Hepatic	2 (1.1/0)	4 (0/0)	5 (2.3/0)

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

Kinetics of Appearance of irAEs with Ipilimumab



Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Ipilimumab: Key to Optimal Patient Management

- First Dose: baseline assessment; review medical history, check standard of care lab values including LFTs, TFTs
- Subsequent doses: before each infusion or as needed, check lab values including AST, ALT, total bilirubin, and thyroid function
- Conduct thorough assessment of immune-mediated symptoms
- Educate on importance of detecting and prompt reporting of symptoms
  - Discuss key points about immune-mediated adverse events and importance of prompt medical intervention
  - Confirm patient's ability to verbalize important symptoms
  - Emphasize that symptoms may be intermittent and can occur wks to mos after treatment is complete

Ipilimumab: Managing Immune-Related Adverse Events

System	Symptoms	Management
GI tract	Diarrhea Abdominal pain Dark, bloody stools	Moderate enterocolitis: hold ipilimumab, administer antidiarrheal. Persistent diarrhea (> 1 wk): systemic corticosteroids. 7+ stools/day: start methylprednisone, permanently discontinue ipilimumab. Consider infliximab for corticosteroid-refractory pts.
Skin	Rash (± itching) Blistering/peeling Oral sores	Moderate/nonlocalized rash: hold ipilimumab, start topical or systemic corticosteroids. Severe dermatitis: permanently discontinue ipilimumab, start corticosteroids.
Liver	Jaundice Nausea/vomiting	Assess ALT/AST, bilirubin, and thyroid function before each dose and as necessary. Hold ipilimumab if ALT/AST > 2.5 x but ≤ 5 x ULN; permanently discontinue if AST/ALT > 5 x ULN or bilirubin > 3 x ULN. The immunosuppressant mycophenolate can be used for hepatotoxicity in corticosteroid-refractory pts.
CNS	Weakness in extremities Numbness/tingling Sensory changes	Moderate neuropathy: hold ipilimumab. New or worsening neuropathy: permanently discontinue ipilimumab. Consider corticosteroids.
Endocrine	Headaches Fatigue Behavior/mood changes Menstruation changes Dizziness/light-headedness	Moderate endocrinopathy: hold ipilimumab, start corticosteroids. Endocrine abnormalities can be difficult to detect, due to nonspecific symptoms. Consider having an endocrinologist follow the pt.
Eyes	Vision problems Irritation	Monitor for redness suggesting uveitis; treat with topical steroidal eye drops.

Ipilimumab adverse reaction management guide.
Available at: https://www.hcp.yervoy.com/pdf/rems-management-guide.pdf

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Skin		
Liver		
CNS		
Endoc		
	Dizziness/light-headedness	
Eyes	Vision problems Irritation	Monitor for redness suggesting uveitis; treat with topical steroidal eye drops.

Principles of Managing irAEs:

- **Hold ipilimumab**
- **Initiate steroids therapy (1–2 mg/kg of prednisone or equivalent daily)**
- **Consider infliximab (if gastrointestinal toxicity) or mycophenolate (if hepatotoxicity) if steroids do not resolve symptoms**

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Ipilimumab adverse reaction management guide.
Available at: https://www.hcp.yervoy.com/pdf/rems-management-guide.pdf

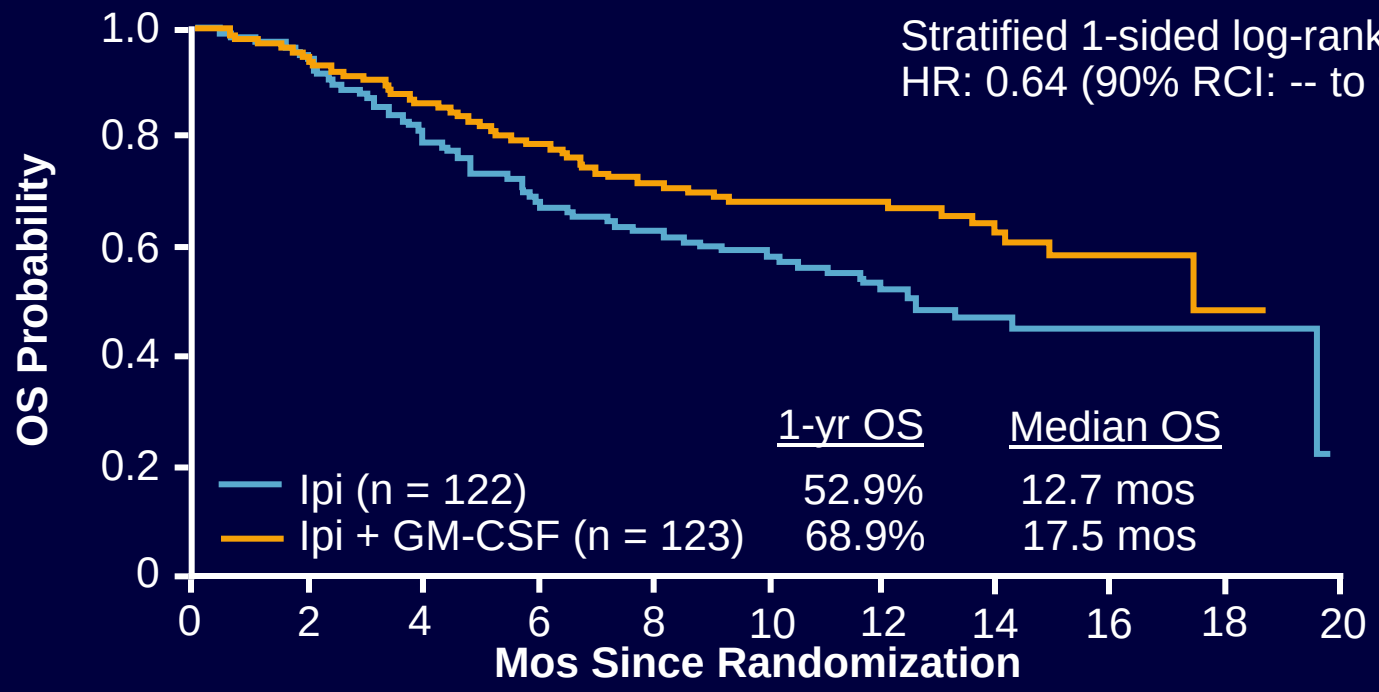
Ipilimumab in Melanoma: Current Issues

- Dose: 3 mg/kg or 10 mg/kg?
  - Phase III results pending in patients with metastatic melanoma[1]
- Schedule: maintenance therapy or not?
- Role in the adjuvant setting?
  - EORTC 18071: ipilimumab 10 mg/kg vs placebo[2]
  - E1609: ipilimumab 3 or 10 mg/kg vs IFN[3]
- In combinations?
  - Bevacizumab, other immunotherapies (GM-CSF, IFN, IL-2, **PD-1 antibodies, and T-Vec**), and radiation therapy
  - High toxicity when combined with BRAF inhibitors[4]

1. ClinicalTrials.gov. NCT01515189. 2. Eggermont A, et al. ASCO 2014. LBA9008. 3. ClinicalTrials.gov. NCT01274338. 4. Ribas A, et al. N Engl J Med. 2013;368:2861365-1366.

OS: Ipi + GM-CSF vs Ipi Alone

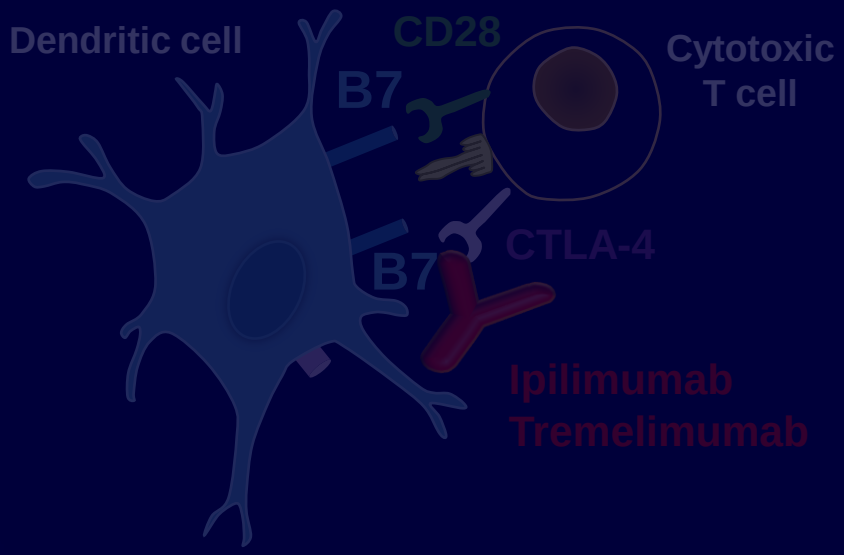
- Phase II trial: pts randomized to receive ipilimumab 10 mg/kg IV on day 1 ± GM-CSF 250 µg SQ on days 1 to 14 of a 21-day cycle



Hodi S, et al. JAMA. 2014;312:1744-1753.

Blocking Immunologic Checkpoints

Priming: T-Cell Activation in the Lymph Node



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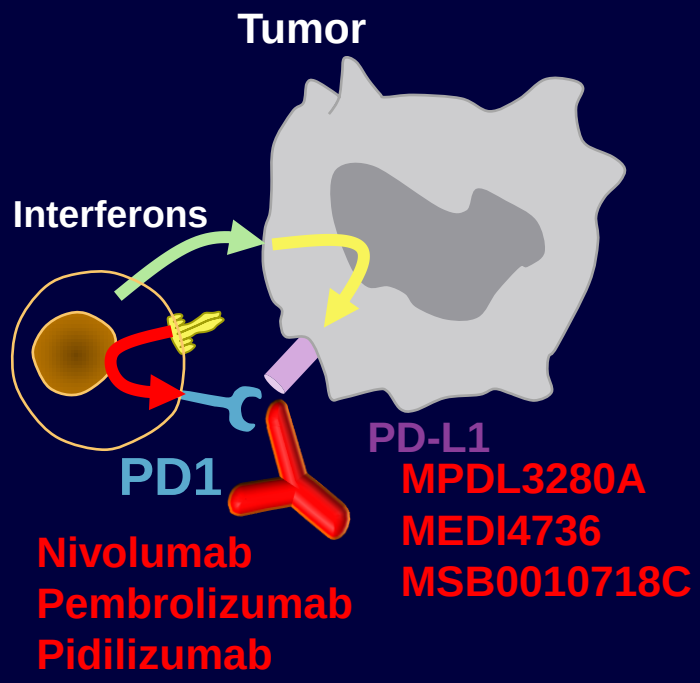
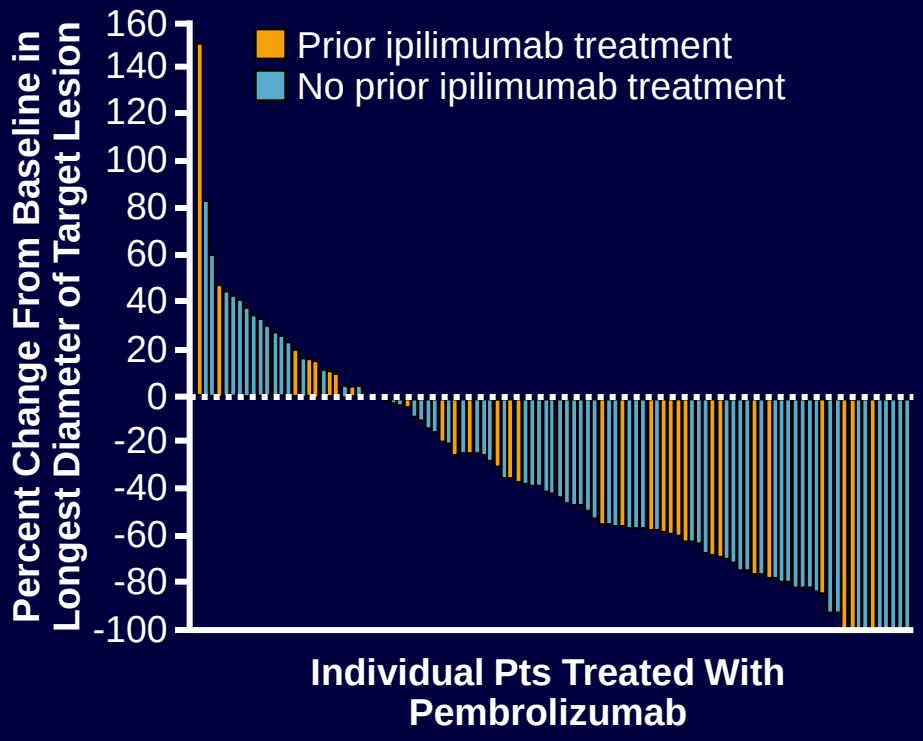
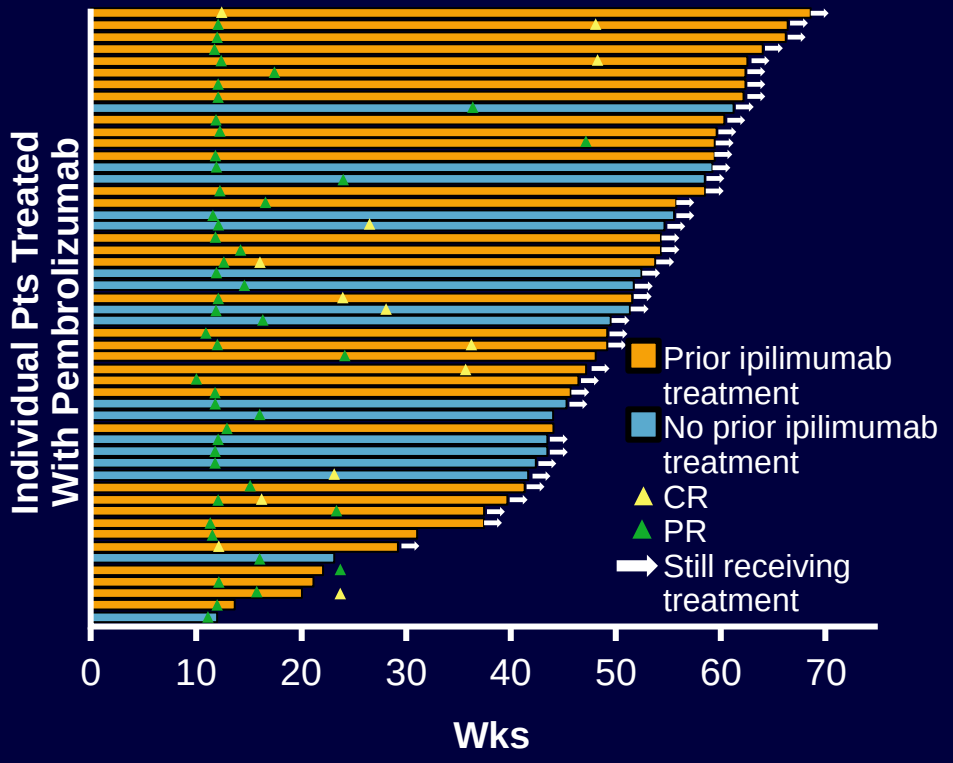


Ribas A. N Engl J Med. 2012;366:2517-2519. Spranger S, et al. J Immunother Cancer. 2013;1:16.

Phase I (KEYNOTE-001): Pembrolizumab Leads to Frequent and Durable Responses

- ORR is 37%; 81% with response continue to receive treatment





Hamid O, et al. N Engl J Med 2013;369:134-144.

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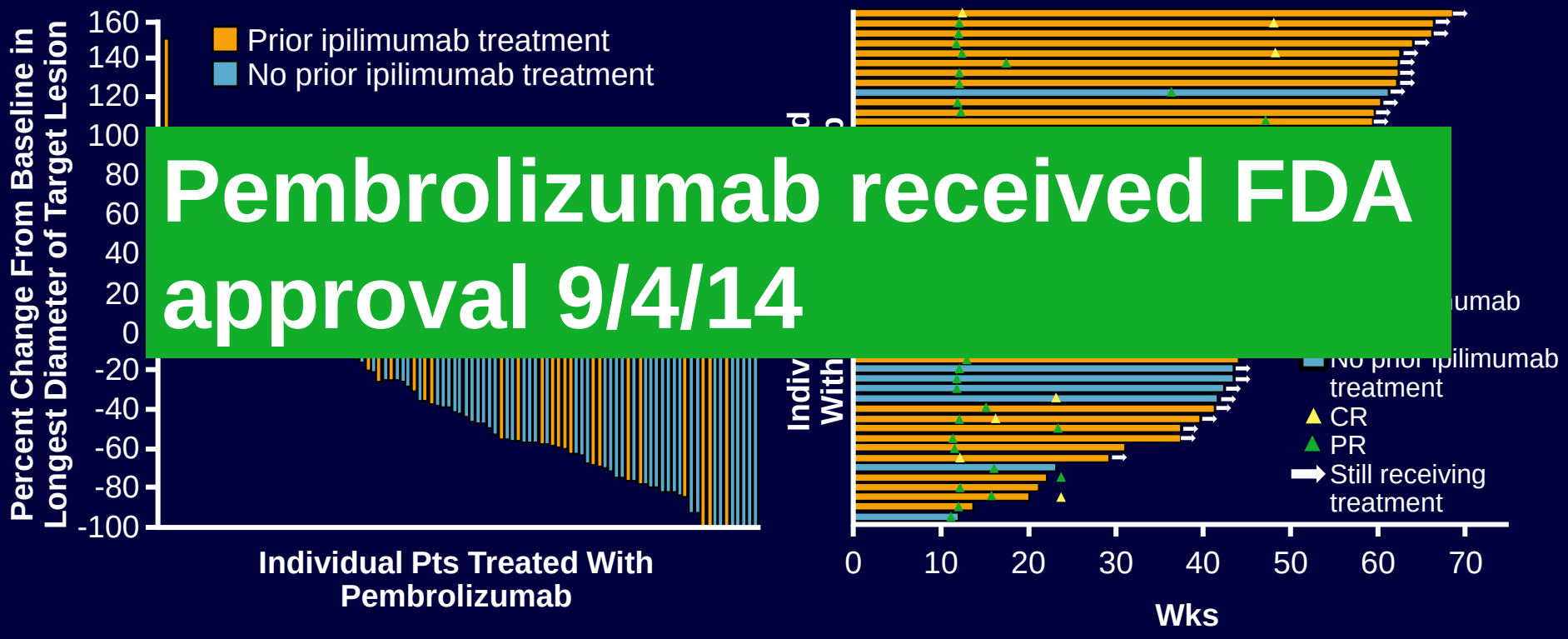
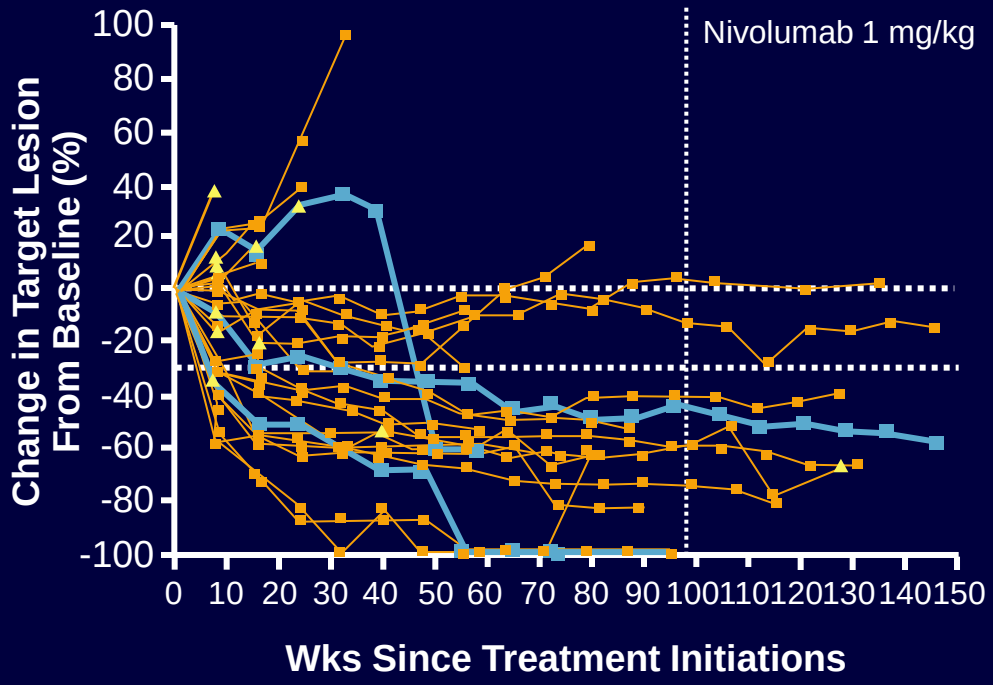


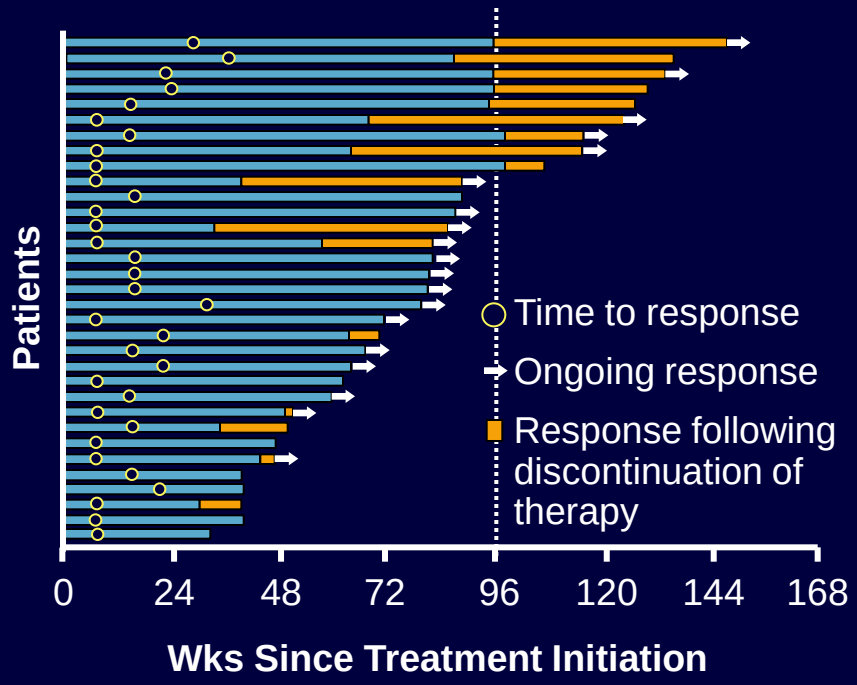
Pembrolizumab received FDA approval 9/4/14

Hamid O, et al. N Engl J Med 2013;369:134-144.

Phase I: Nivolumab Leads to Frequent and Durable Responses

- ORR is 31%; 58% with response ongoing at time of analysis





Topalian SL, et al. J Clin Oncol. 2014;32:1020-1030.

Phase I: Nivolumab Leads to Frequent and Durable Responses

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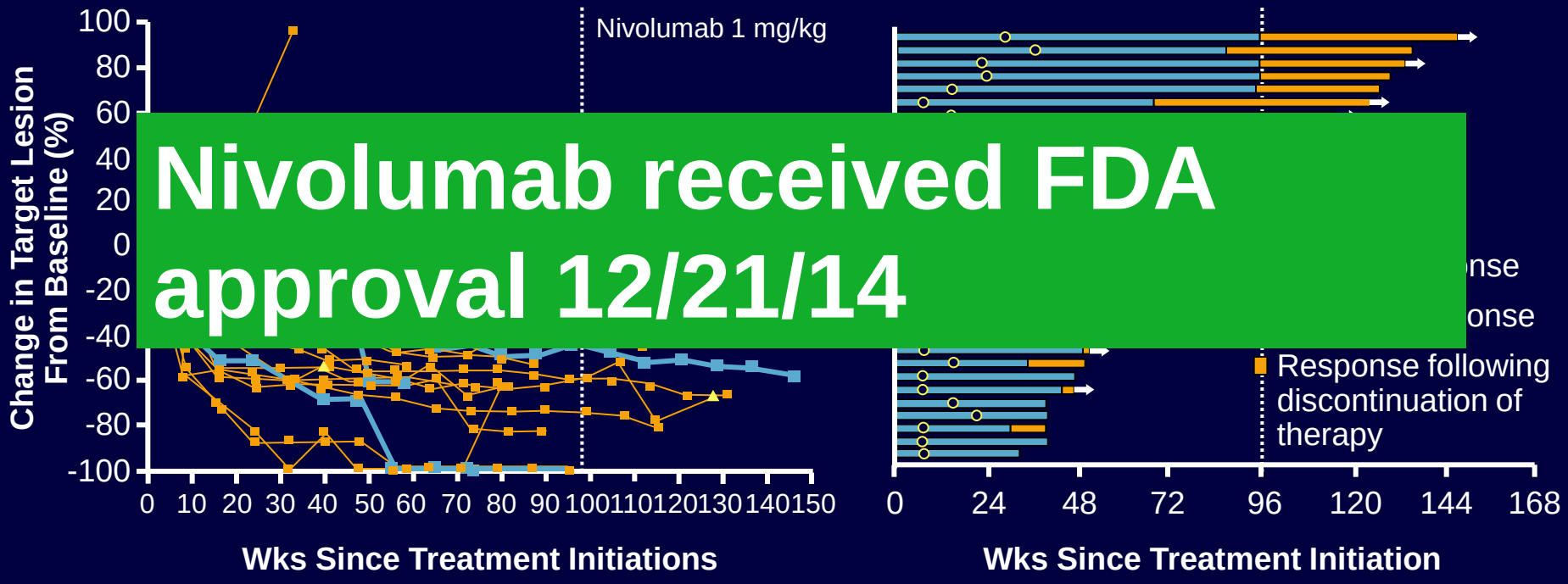


Nivolumab received FDA approval 12/21/14

Topalian SL, et al. J Clin Oncol. 2014;32:1020-1030.

KEYNOTE-001: Pembrolizumab AE Profile

Grade 3/4 AEs in ≥ 1 Pt, %	Pembro 2 mg/kg (n = 89)	Pembro 10 mg/kg (n = 84)
Fatigue	6	0
Amylase increase	1	0
Anemia	1	0
Autoimmune hepatitis	1	0
Confusion	1	0
Diarrhea	0	1
Dyspnea	0	1
Encephalopathy	1	0
Hypophysitis	1	0
Hypoxia	0	1
Muscular weakness	1	0
Muscoloskeletal pain	0	1
Pancreatitis	0	1
Peripheral motor neuropathy	1	0
Pneumonitis	1	0
Rash	0	1
Rash maculopapular	0	1

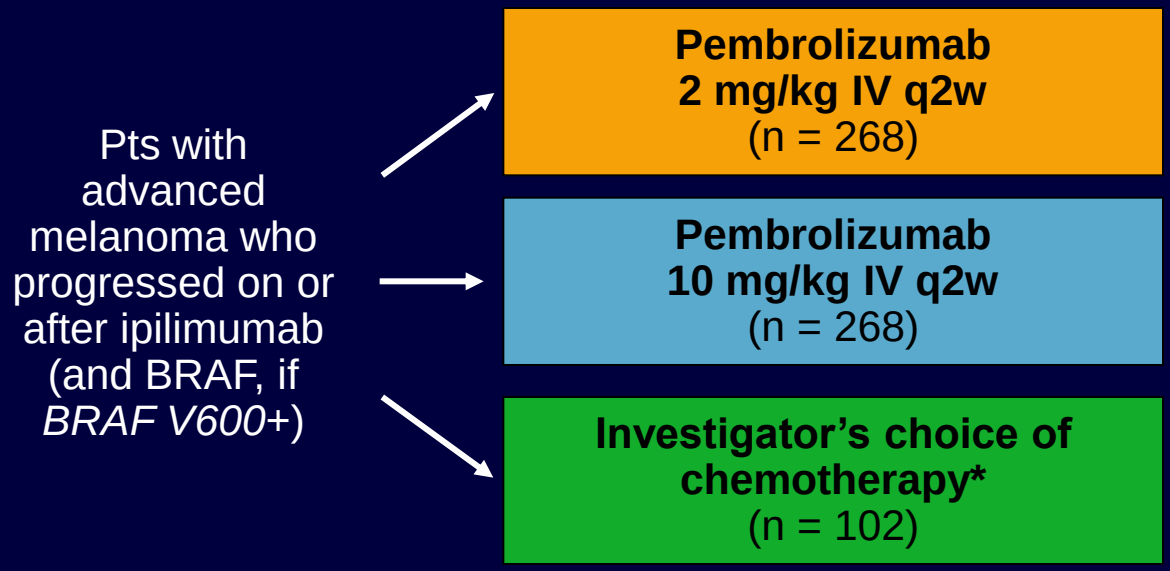
Robert C, et al. Lancet 2014;384:1109-1117.

Nivolumab AE Profile

Grade 3/4 AEs, %	Nivolumab (N = 107)
Any AE	22.4
Lymphopenia	2.8
Fatigue	1.9
Diarrhea	1.9
Nausea	0.9
Abdominal pain	1.9
Dry mouth	0.9
Vomiting	0.9
Hyperuricemia	0.9
Hypophosphatemia	0.9
Blood thyroid-stimulating hormone increased	0.9
Hemoglobin decreased	0.9
Platelet count decreased	0.9
Hypothyroidism	0.9

Topalian SL, et al. J Clin Oncol. 2014;32:1020-1030.

KEYNOTE-002: Phase II Trial of Pembro vs Chemotherapy in Ipi-Refractory Pts



Pts with PD confirmed by independent central review could cross over to pembrolizumab treatment after the first 3-mo assessment

*Carboplatin + paclitaxel, paclitaxel alone, dacarbazine, or temozolomide.

- Primary endpoint: PFS, OS
- Secondary endpoints: ORR, DoR

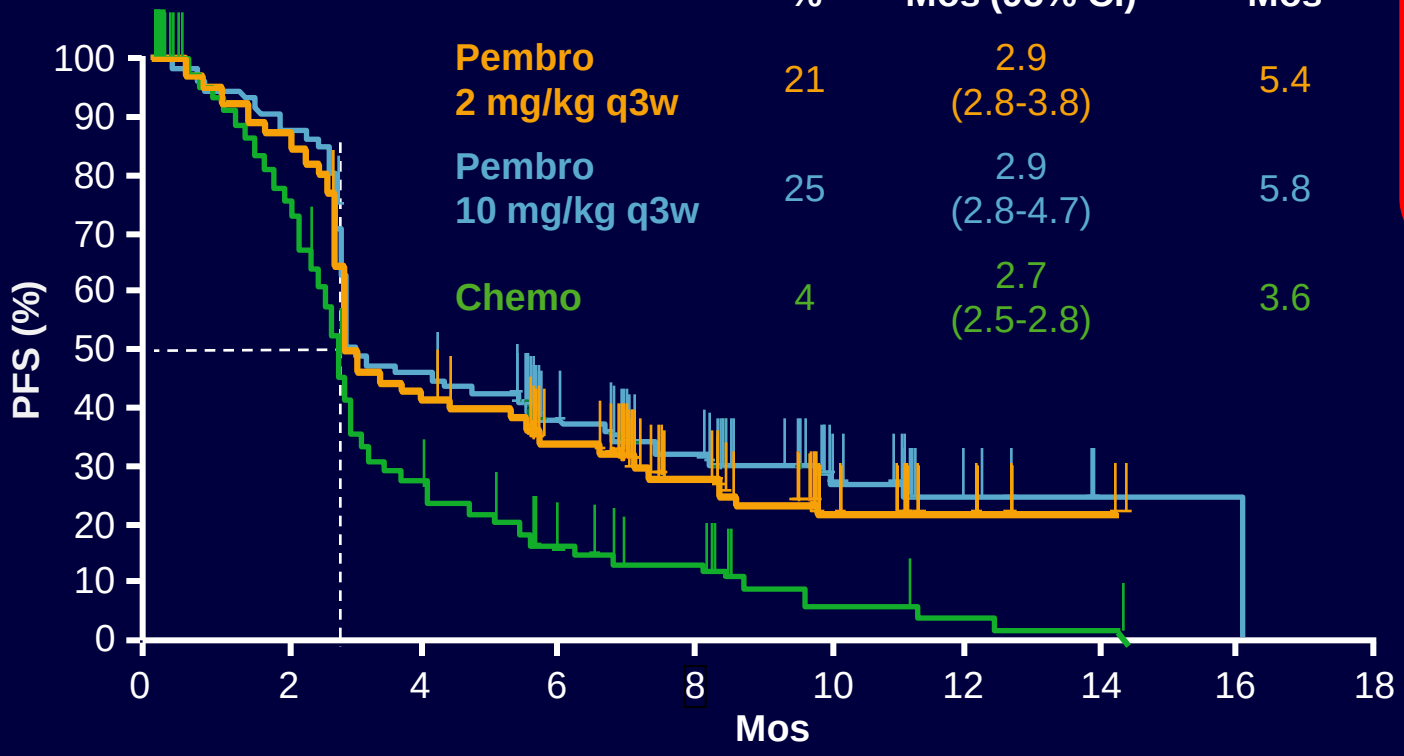
Ribas A, et al. SMR 2014. November 16, 2014.

KEYNOTE-002: Pembrolizumab vs Chemotherapy in Ipi-Refractory Melanoma

- An international, randomized phase II study in pts with advanced melanoma with PD within 24 wks after ≥ 2 Ipi doses

Arm	ORR, %	Median PFS, Mos (95% CI)	Mean PFS, Mos	PFS HR (95% CI)	PFS *P* value
Pembro 2 mg/kg q3w	21	2.9 (2.8-3.8)	5.4	0.57 (0.45-0.73)	< .0001
Pembro 10 mg/kg q3w	25	2.9 (2.8-4.7)	5.8	0.50 (0.39-0.64)	< .0001
Chemo	4	2.7 (2.5-2.8)	3.6		

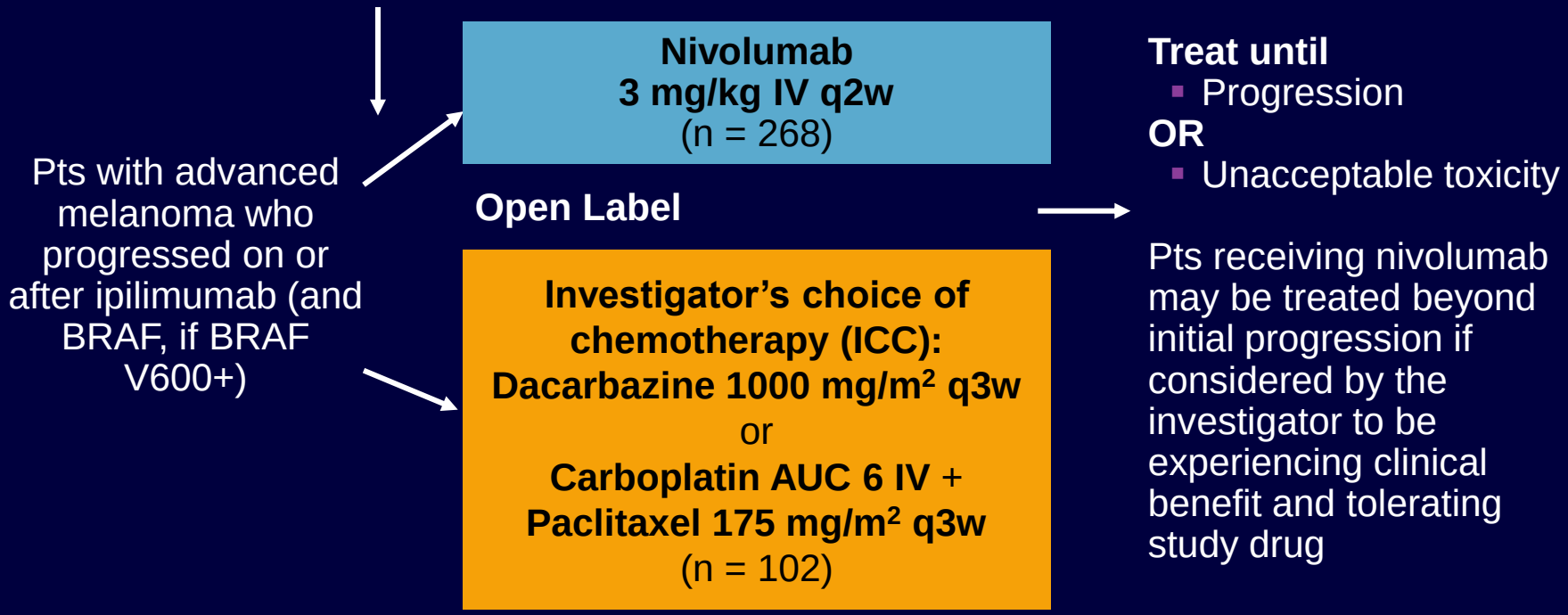
Pembro vs Chemo



Ribas A, et al. SMR 2014. November 16, 2014.

Checkmate-037: Phase III Trial of Nivolumab vs Chemotherapy in IPI-Refractory Pts

Stratified by PD-L1 expression (+ vs - or indeterminate); BRAF wt vs V600 mutant; best overall response prior to anti–CTLA-4 (clinical benefit vs no clinical benefit)*



*Positive: ≥ 5% tumor cell surface staining cutoff by immunohistochemistry.

Weber JS, et al. Lancet Oncol. 2015;16:375-384.

Targeting T Cells With Nivolumab Leads to Higher Response Rate vs Chemotherapy

Treatment	N	CR + PR, n	ORR,* % (95% CI)	Best Overall Response,* %				
				CR	PR	SD	PD	UNK
Central review†								
Nivolumab	120	38 (4 CR)	32 (24-41)	3	28	23	35	10
ICC	47	5 (0 CR)	11 (4-23)	0	11	34	32	23

*Confirmed response.
†Independent radiology review committee based on RECIST 1.1.

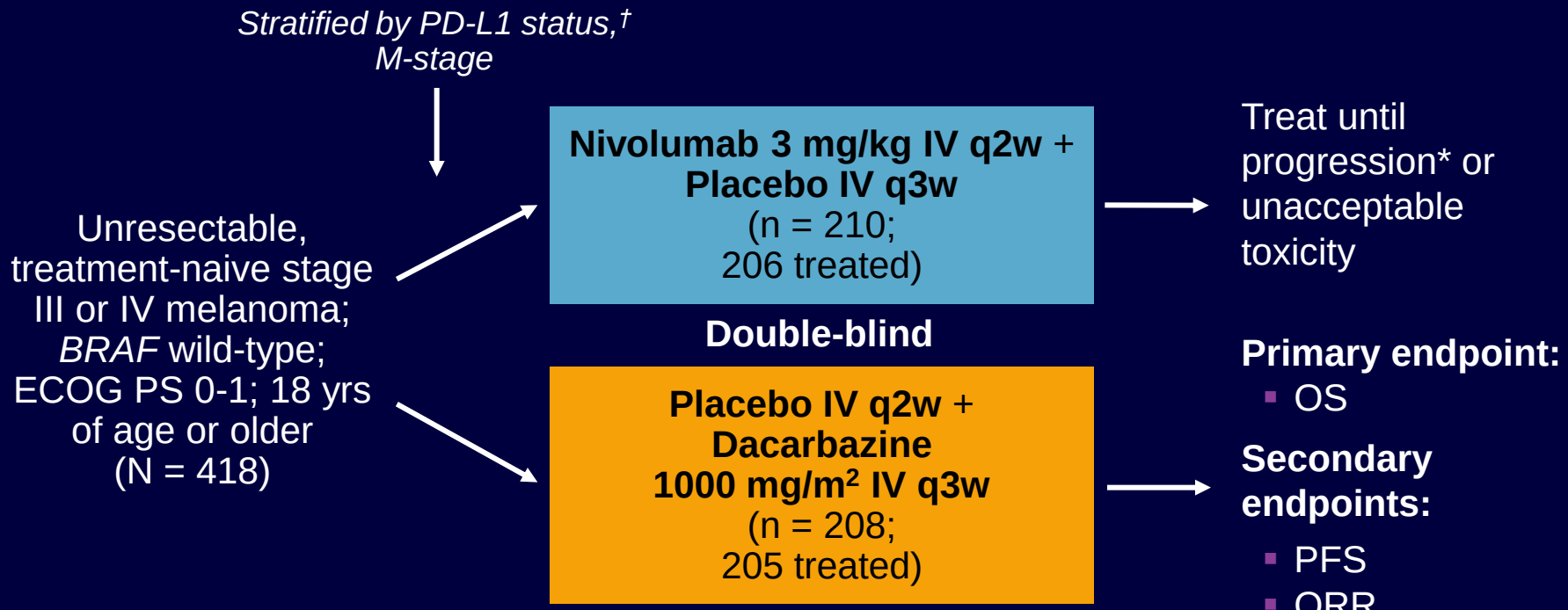
Weber JS, et al. Lancet Oncol. 2015;16:375-384.

Nivolumab vs Pembrolizumab in Ipilimumab-Refractory Patients

Comparison	Nivolumab (Checkmate-037)	Pembrolizumab (KEYNOTE-002)
Number of patients (IPI-R)	120 (preliminary subset)	180
FDA Approved Schedule	3 mg/kg IV every 2 weeks	2 mg/kg IV every 3 weeks
ORR, % (95% CI)	32 (24-41)	21 (15-28)
Grades 3-4 drug related toxicities, %	5	8

Weber JS, et al. Lancet Oncol. 2015;16:375-384. Ribas A, et al. SMR 2014. November 16, 2014.

Phase III CA209-066 First-line Nivolumab vs Chemotherapy Trial: Study Design



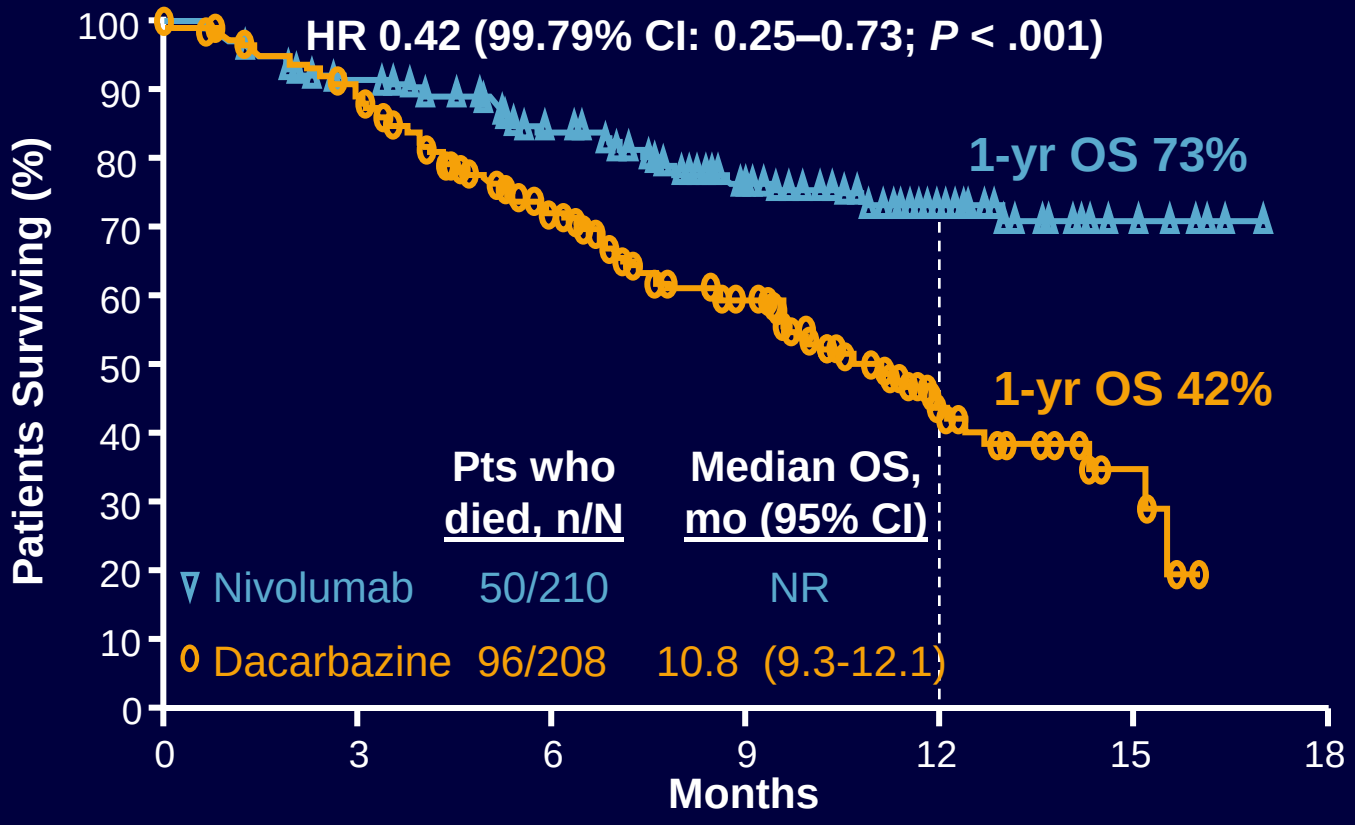
†PD-L1 positive: ≥ 5% tumor cell surface staining.

*Pts may be treated beyond initial RECIST v1.1–defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.

Robert C, et al. N Engl J Med. 2015;372:320-330.

OS: First-line Nivolumab vs Chemotherapy

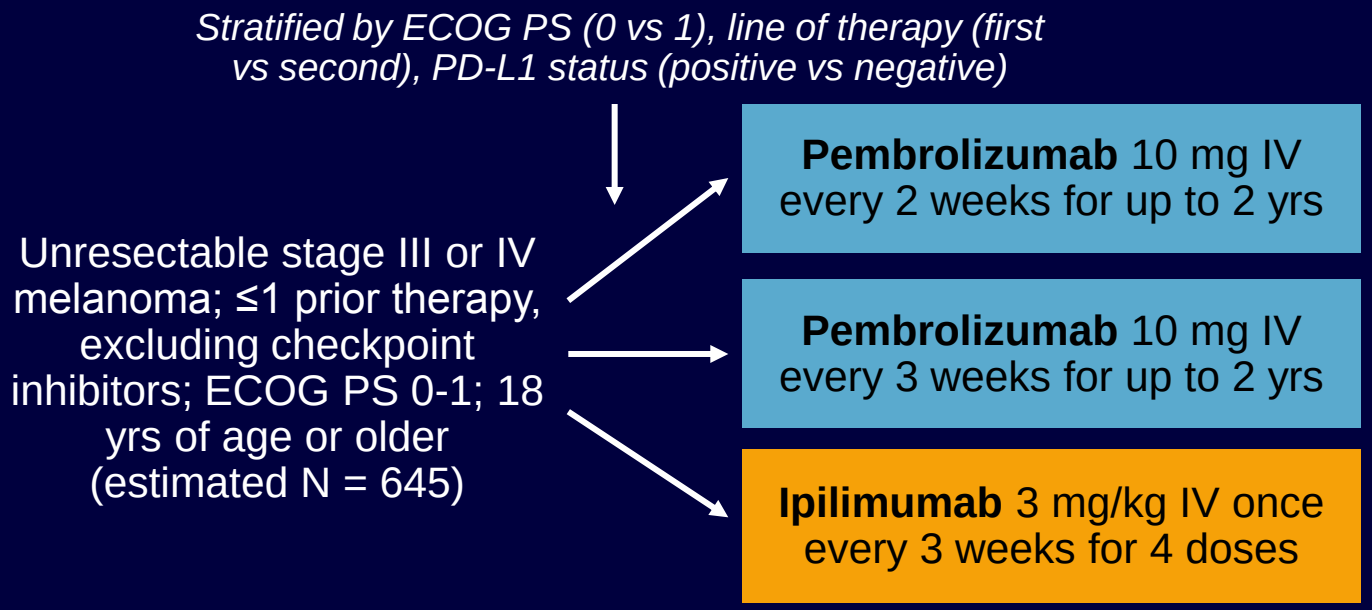
- Objective response rate: 40% with nivolumab vs 13.9% with chemo (P <.001)
- Significantly better OS with nivolumab vs dacarbazine



Robert C, et al. N Engl J Med. 2015;372:320-330.

KEYNOTE-006: Analysis of Pembro vs Ipi Trial Design

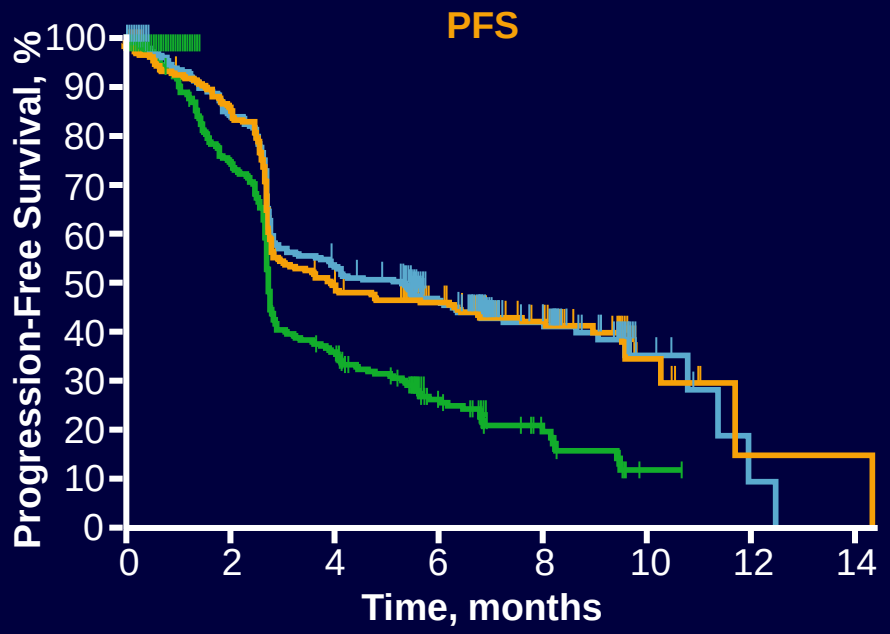
- A multicenter, randomized, controlled phase III study

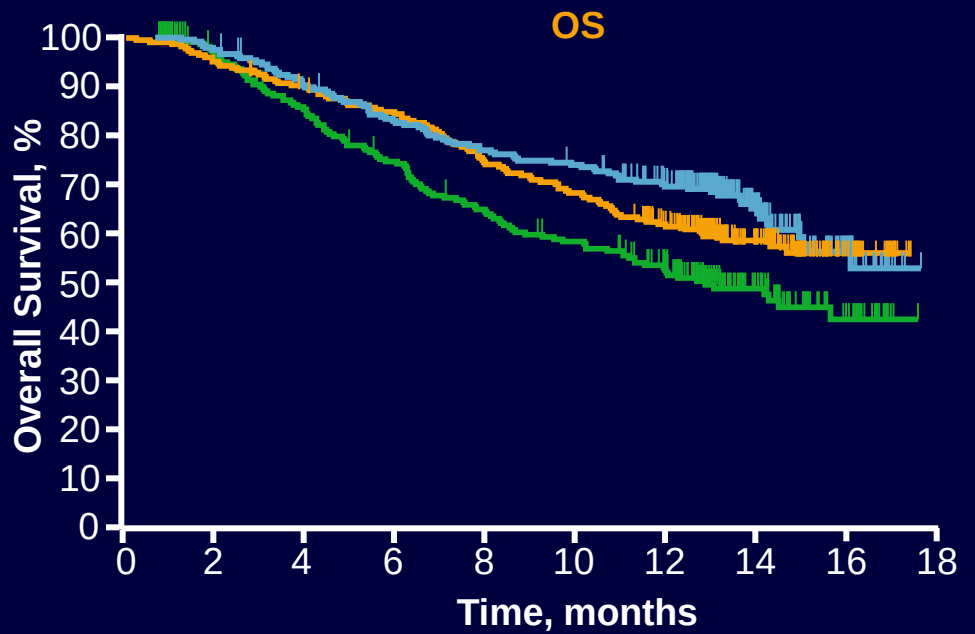


- Primary endpoint: PFS, OS
- Secondary endpoint: ORR, DoR, Safety

Robert C, et al. N Engl J Med. 2015;372:2521-2532.

KEYNOTE-006: Survival Efficacy at First Interim Analysis of Pembro vs Ipi





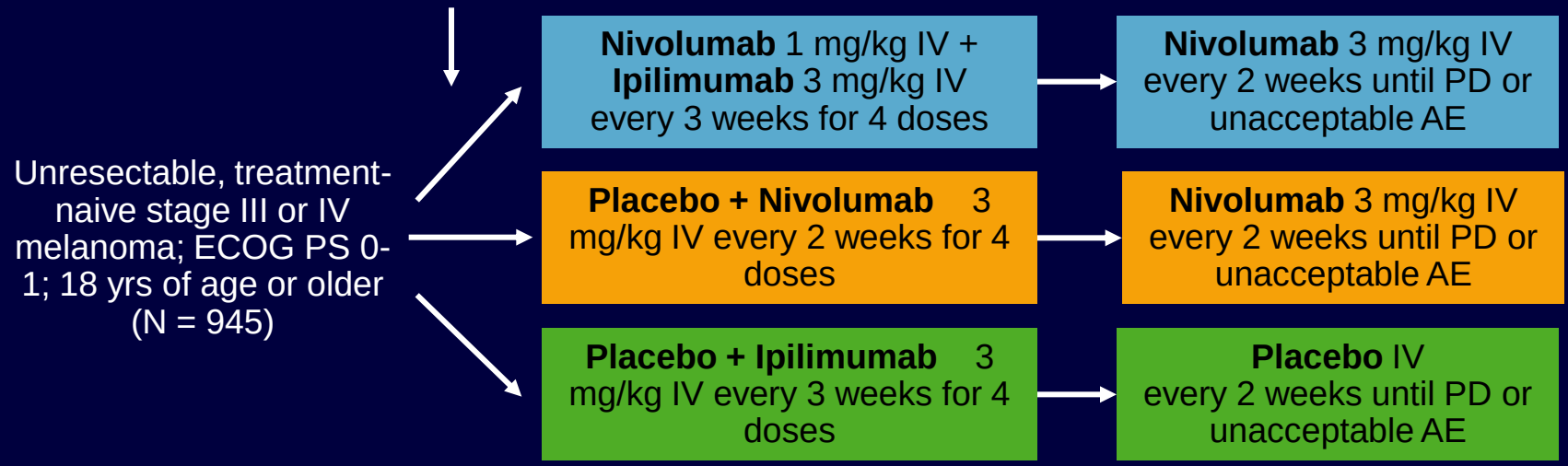
Treatment Arm	Median PFS (95% CI), mo	Rate at 6 mo, %	HR (95% CI)	*P*	Median OS (95% CI), mo	Rate at 12 mo, %	HR (95% CI)	*P*
Pembrolizumab Q2W	5.5 (3.4-6.9)	47.3	0.58 (0.46-0.72)	<.00001	NR (NR-NR)	74.1	0.63 (0.47-0.83)	.00052
Pembrolizumab Q3W	4.1 (2.9-6.9)	46.4	0.58 (0.47-0.72)	<.00001	NR (NR-NR)	68.4	0.69 (0.52-0.90)	.0036
Ipilimumab	2.8 (2.8-2.9)	26.5	—	—	NR (12.7-NR)	58.2	—	—

Robert C, et al. N Engl J Med. 2015;372:2521-2532.

Checkmate-067: Nivo + Ipi vs Nivo vs Ipi for First-line Treatment of Melanoma

- A randomized, double-blind phase III study

Stratified by tumor PD-L1 status (positive vs negative/indeterminate), BRAF mutation status (V600 mutation–positive vs wild-type), and AJCC metastasis stage (M0, M1a, or M1b vs. M1c)



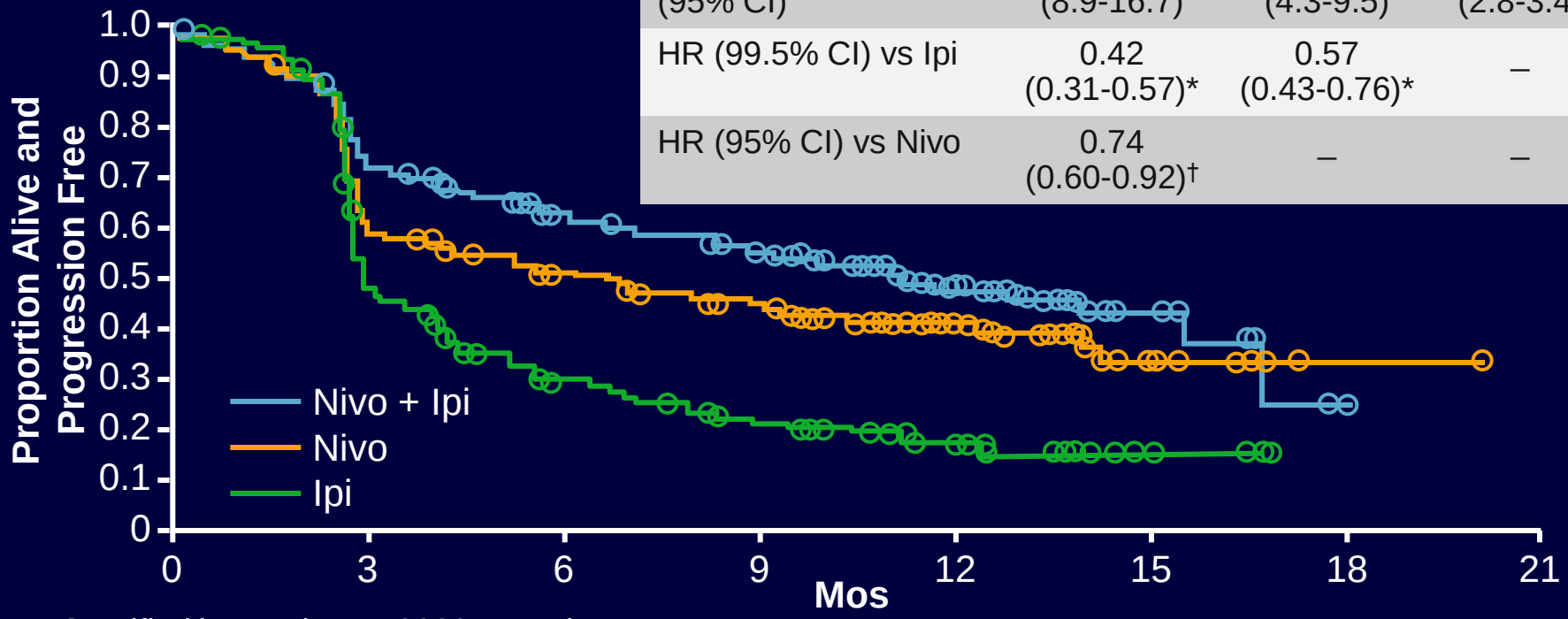
All patients receive injections 2 out of every 3 weeks

- Primary endpoint: OS, PFS
- Secondary endpoint: ORR, OS by PD-L1, Safety

Larkin J, et al. N Engl J Med. 2015;373:23-34.

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone

	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mos (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 $P < .00001$ vs Ipi.
†Exploratory endpoint. Study not powered to detect a statistical difference between Nivo + Ipi and Nivo.

Larkin J, et al. N Engl J Med. 2015;373:23-34.

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone

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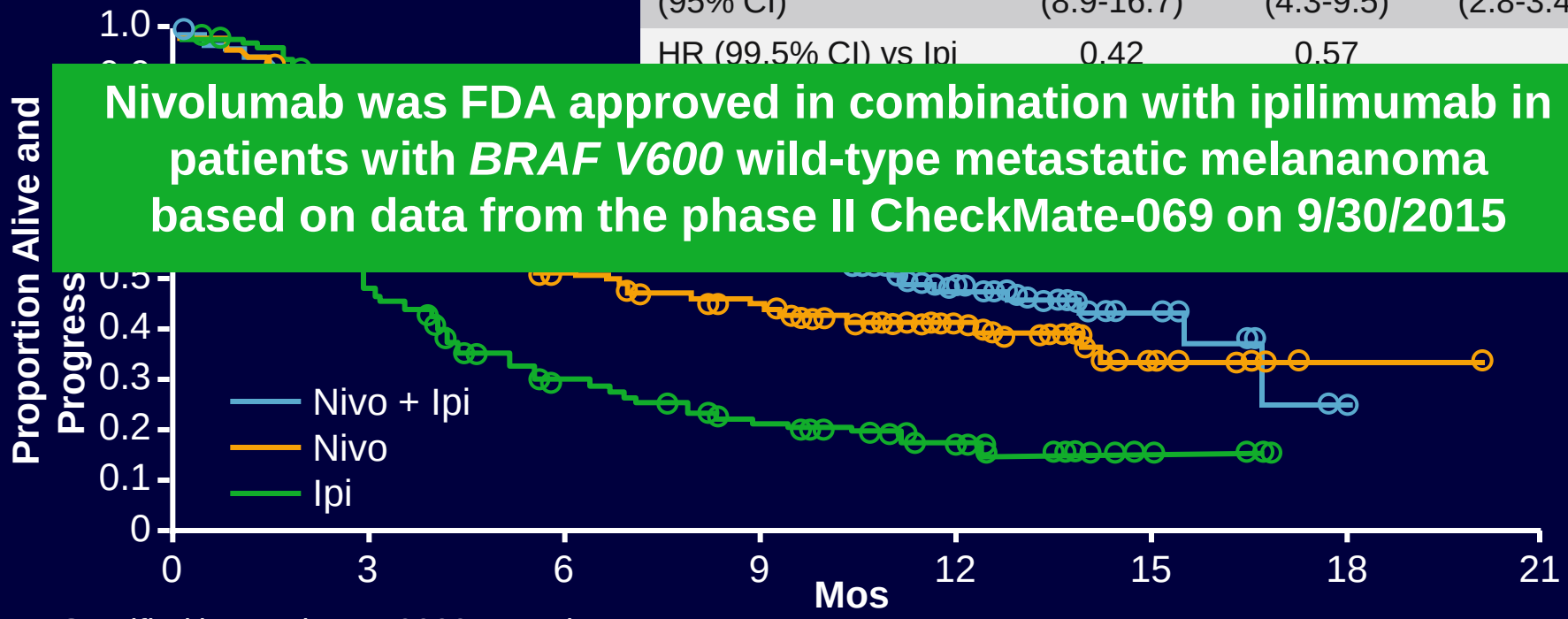
HR (99.5% CI) vs Ipi	0.42	0.57	

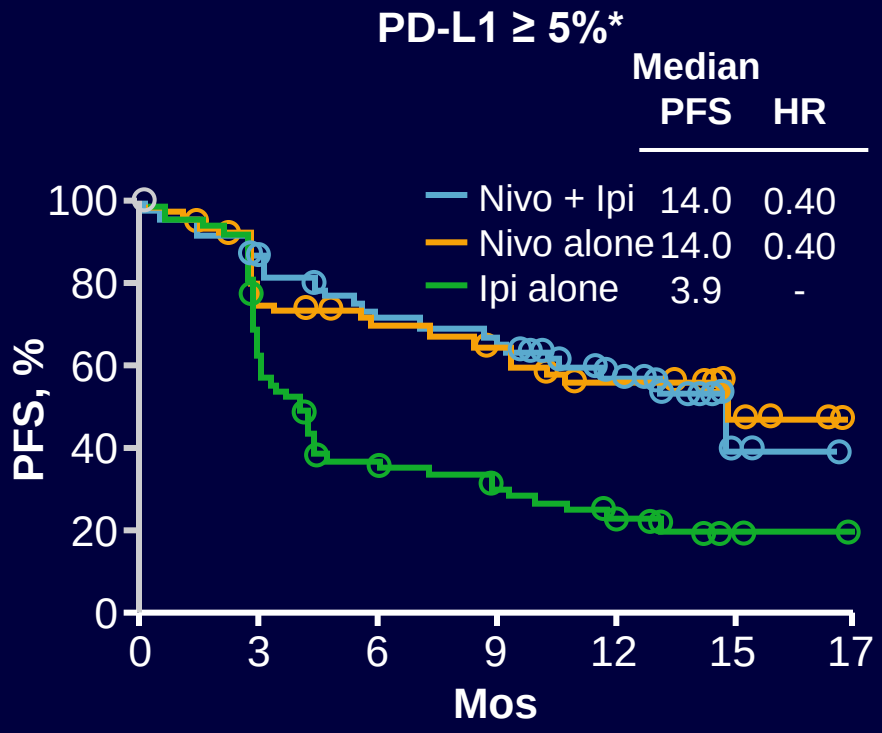
Nivolumab was FDA approved in combination with ipilimumab in patients with *BRAF V600* wild-type metastatic melananoma based on data from the phase II CheckMate-069 on 9/30/2015

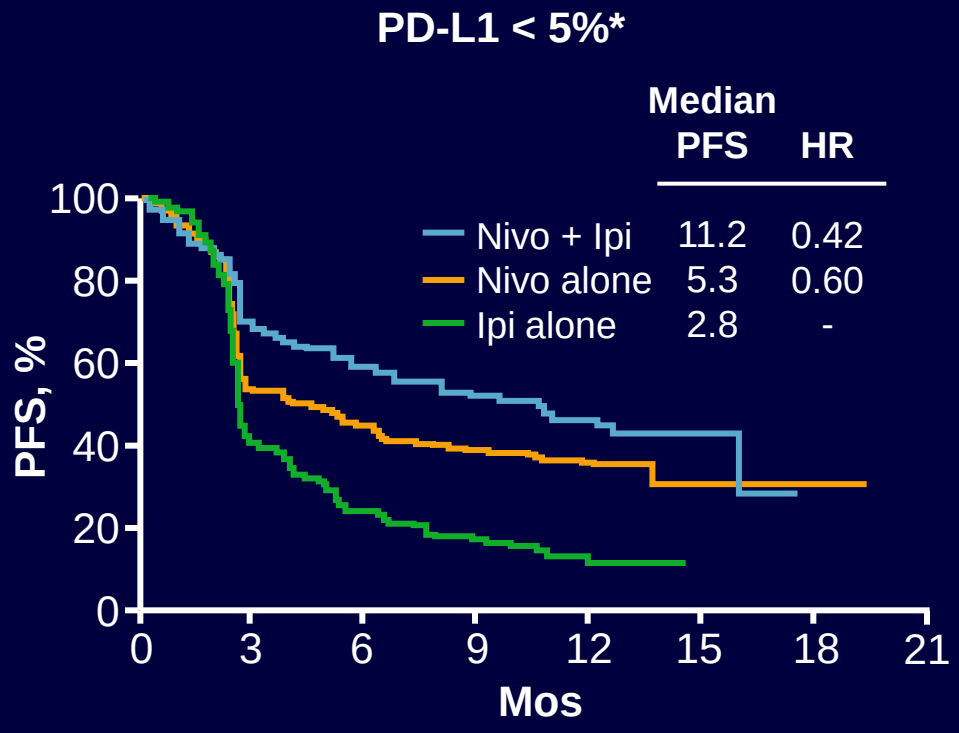


*Stratified log-rank $P < .00001$ vs Ipi.
†Exploratory endpoint. Study not powered to detect a statistical difference between Nivo + Ipi and Nivo.

Larkin J, et al. N Engl J Med. 2015;373:23-34.

CheckMate 067: Nivo + Ipi Provides Most Benefit for PD-L1^{lo}, Similar to Nivo for PD-L1^{hi}





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

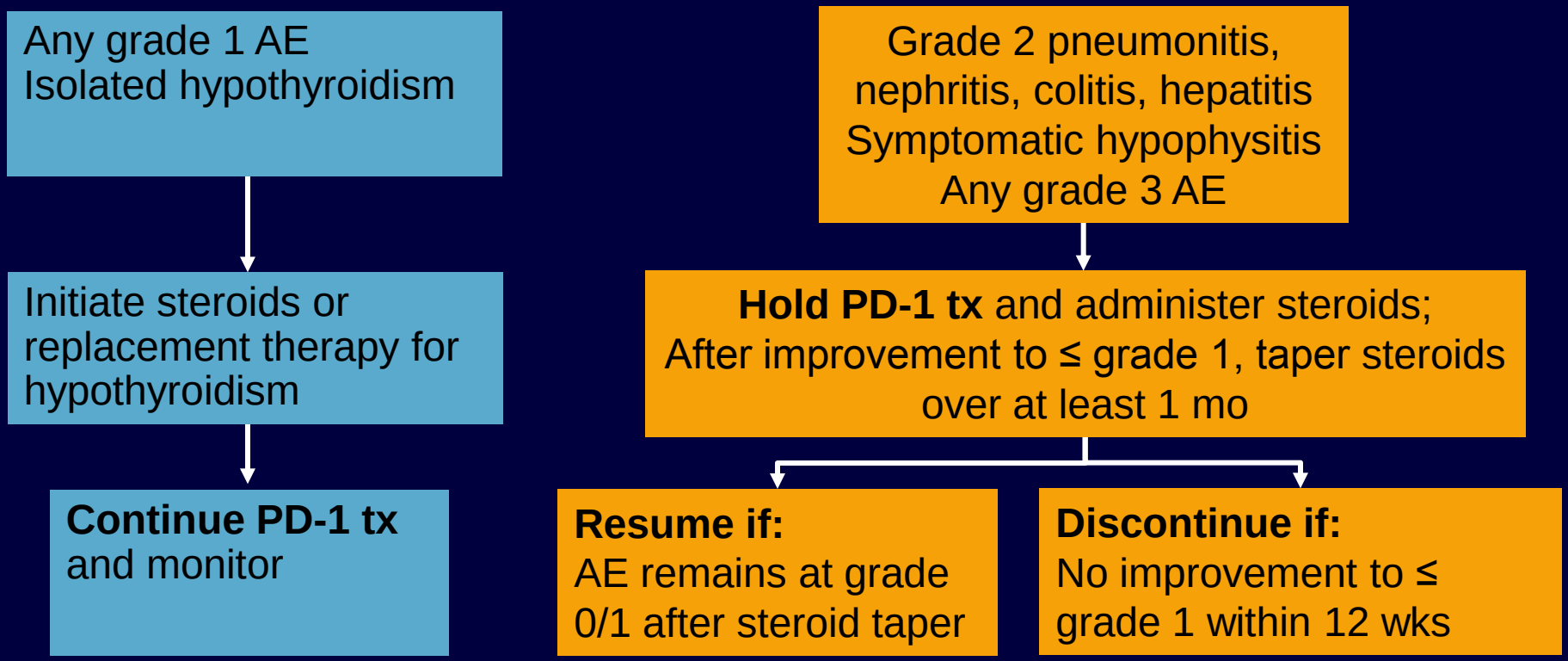
Larkin J, et al. N Engl J Med. 2015;373:23-34.

CheckMate 067: Treatment-Related AEs Associated With Nivo and Ipi

Select Treatment-Related AEs, %	Nivo + Ipi (n = 313)		Nivo (n = 313)		Ipi (n = 311)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Any select AE	88	40	62	8	74	19
Skin	59	6	42	2	54	3
▪ Pruritus	33	2	19	0	35	< 1
▪ Rash	28	3	22	< 1	21	2
▪ Maculopapular rash	12	2	4	< 1	12	< 1
Gastrointestinal	46	15	20	2	37	12
▪ Diarrhea	44	9	19	2	33	6
▪ Colitis	12	8	1	< 1	12	9
Hepatic	30	19	6	3	7	2
▪ ALT increase	18	8	4	1	4	2
▪ AST increase	15	6	4	1	4	< 1
Endocrine	30	5	14	< 1	11	2
▪ Hypothyroidism	15	< 1	9	0	4	0
Pulmonary	7	1	2	< 1	2	< 1
▪ Pneumonitis	6	1	1	< 1	2	< 1

Larkin J, et al. N Engl J Med. 2015;373:23-34.

PD-1/PD-L1 Inhibition: Managing Treatment-Related Adverse Events



Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.

PD-1/PD-L1 Inhibition: Managing Treatment-Related Adverse Events

Grade 3/4 pneumonitis
Grade 3/4 nephritis
Grade 3/4 infusion-related reaction
Any life-threatening or grade 4 AE
Any severe or grade 3 recurrent AE

Hepatitis associated with

- AST/ALT > 5 x ULN
- AST/ALT ≥ 50% ↑ from baseline lasting ≥ 1 wk*
- Total bilirubin > 3 x ULN

→ **Initiate steroid therapy**

→ **Permanently discontinue PD-1 tx**

*In pts with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.

Patient Education on Novel Therapies

- Patient education should include information on:
  - Adverse reaction profiles that differs from standard chemotherapy
  - Early recognition of irAEs essential for effective treatment
  - irAEs are infrequent, treatable and respond well to steroids
  - Who and when to call for adverse reactions
- Evaluate pt and caregiver for continued educational needs related to the therapy and disease process
- Reinforce teaching points at every point of contact, office and treatment visits, and phone contact

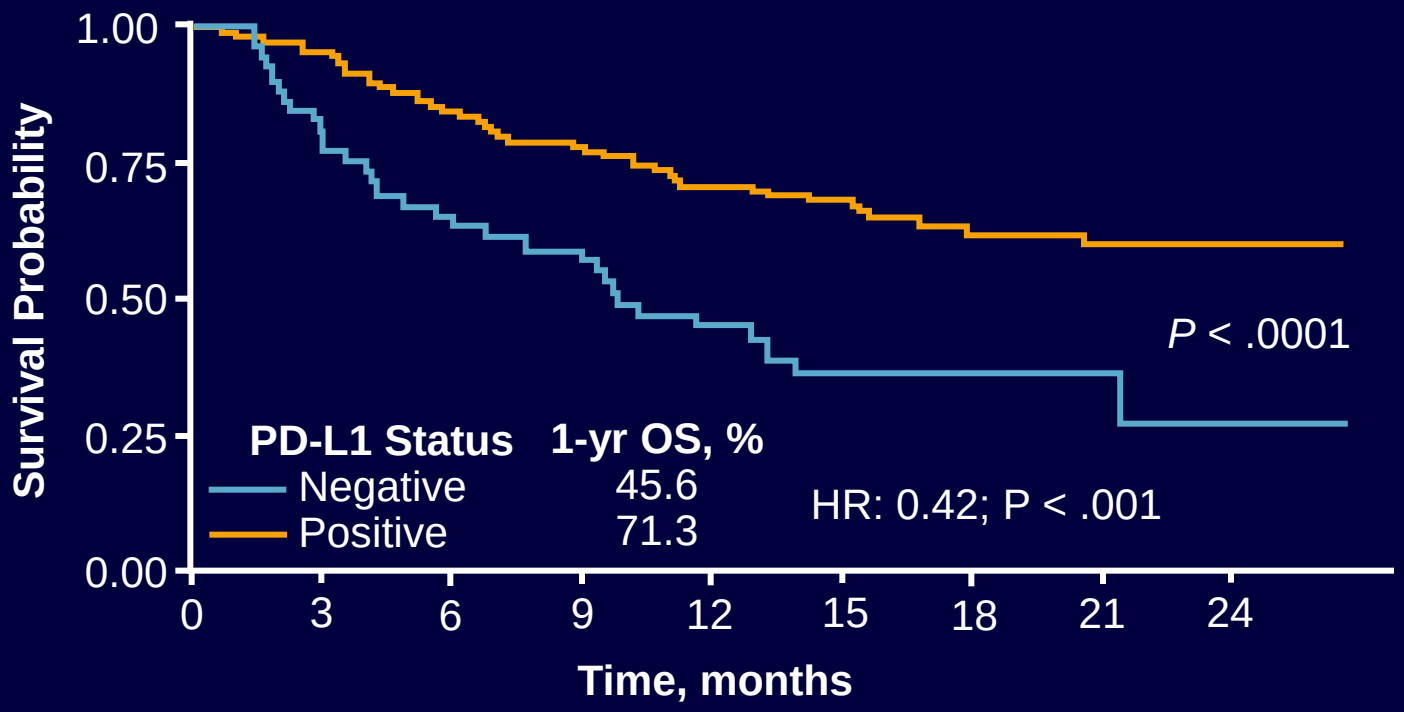
Future Directions

ORR by PD-L1 Expression in Pts With Solid Tumors

Rx Antibody	Tumor type	N	PD-L1 + RR, n/N (%)	PD-L1 - RR, n/N (%)
Nivolumab[1]	Solid tumors	42	9/25 (36)	0/17 (0)
Nivolumab[2]	Solid tumors	38	7/16 (44)	3/18 (17)
MPDL3280A[3]	Solid tumors	103	13/36 (36)	9/67 (13)
Nivolumab[4]	Melanoma	44	8/12 (67) 9/23 (39)	6/32 (19) 5/21 (24)
Pembrolizumab[5]	Melanoma	125	41/83 (49)	4/30 (13)
Ipi/Nivo[6]	Melanoma	27	4/10 (40)	8/17 (47)
Ipi/Nivo[7]	Melanoma	56	8/14 (57)	17/42 (40)

1. Topalian SL, et al. N Engl J Med. 2012;366:2443-2454. 2. Grosso J, et al. ASCO 2013. Abstract 3016. 3. Herbst RS, et al. ASCO 2013. Abstract 3000. 4. Weber JS, et al. ASCO 2013. Abstract 9011. 5. Kefford R, et al. ASCO 2014. Abstract 3005. 6. Callahan. ASCO 2013. Abstract 3003. 7. Sznol M, et al. ASCO 2014. LBA9003.

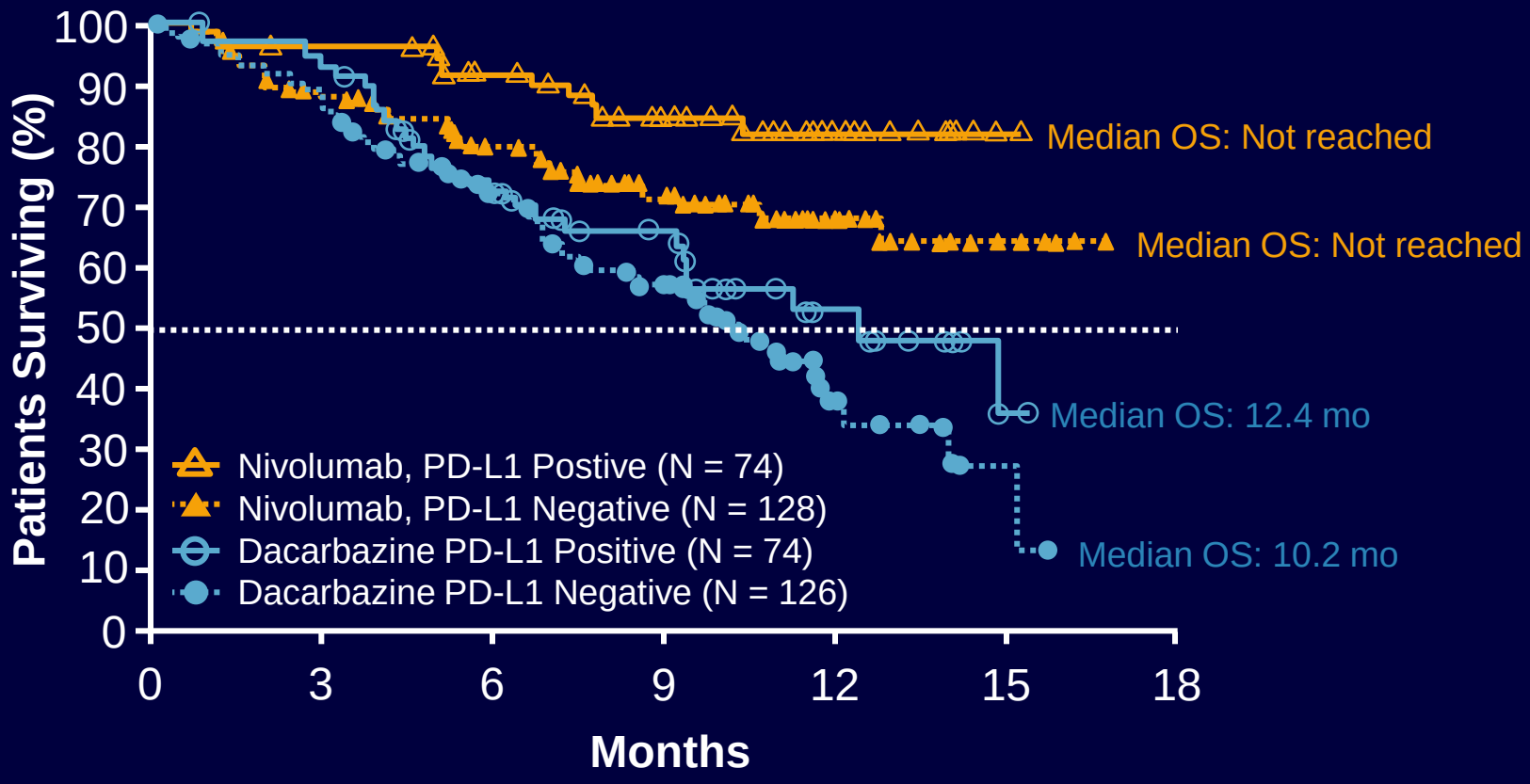
OS Appears to Favor PD-L1+ Tumors Treated With Pembrolizumab*



*Based on tumor PD-L1 expression by IHC

Joseph R, et al. SMR 2014. Abstract LBA34.

Nivo Improved OS vs Dacarbazine Regardless of PD-L1 status

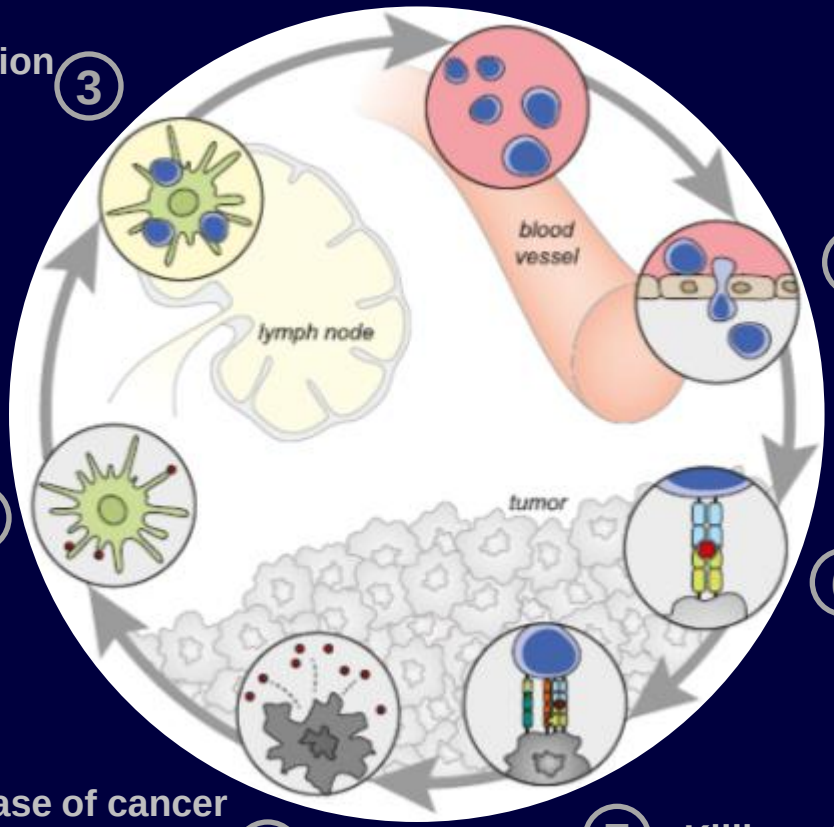


Robert C, et al. N Engl J Med. 2015;372:320-330.

Issues With PD-L1 as a Biomarker

- PD-L1 negativity an unreliable biomarker in certain settings
  - Assays are technically difficult, imperfect; results may differ depending on the antibody/assay (tumor vs immune cells)
  - Expression cut-off, tumor heterogeneity, and inducible gene = sampling error (false negative)
  - Archived tissue different than recent biopsy
- May be more useful in determining which tumors rather than which pts to treat
- PD-L1 expression may be less relevant for combination therapies
- PD-L1 expression may be constitutive (no immune infiltrate)

A Roadmap of Immunotherapy-Tumor Interactions



1 Release of cancer cell antigens
Chemotherapy
Radiation therapy
Targeted therapy

2 Cancer antigen presentation
Vaccines
IFN-α
GM-CSF
Anti-CD40 (agonist)
TLR agonists

3 Priming and activation
Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12

4 Trafficking of T cells to tumors

5 Infiltration of T cells into tumors
Anti-VEGF

6 Recognition of cancer cells by T cells
CARs

7 Killing of cancer cells
Anti-PD-L1
Anti-PD-1
IDO inhibitors

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

Conclusions

- Immunotherapy for melanoma induces responses of long duration and results in prolonged OS
- Novel patterns of response with checkpoint protein inhibition require new types of response criteria that accommodate progression followed by regression
- Immune-related adverse events are a unique spectrum of adverse events with checkpoint protein inhibition that require learning new ways to manage toxicity
- The best is yet to come!

Thank You!

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