sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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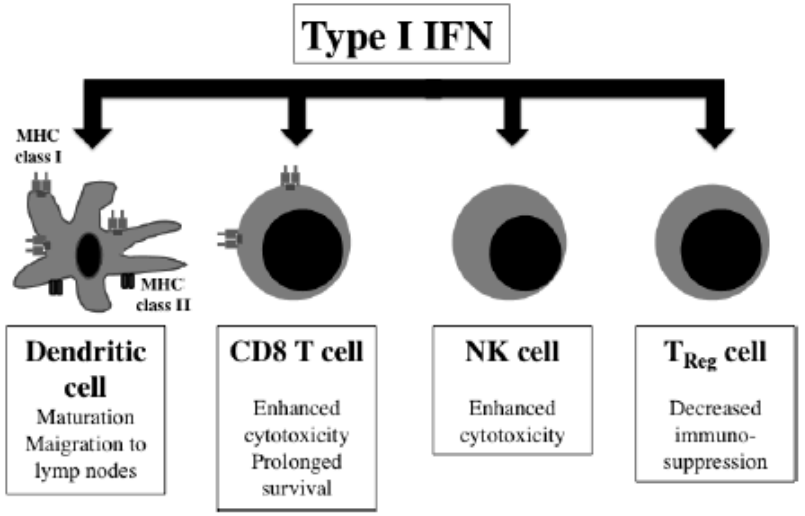
Disclosures

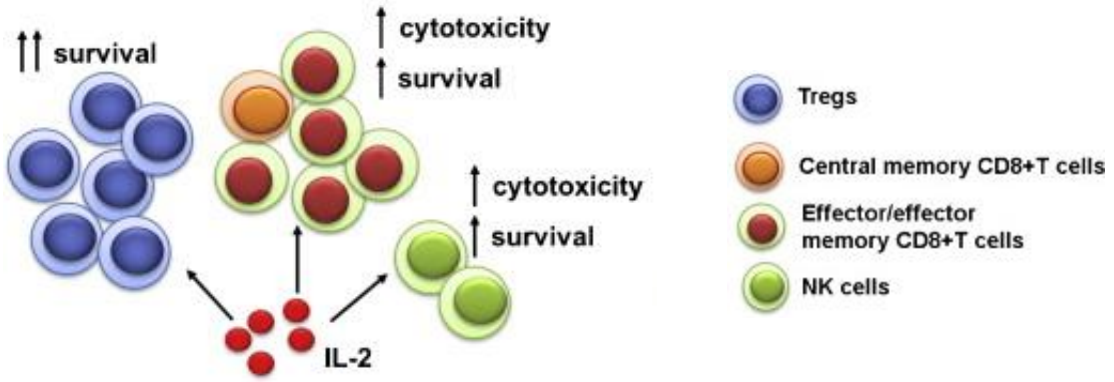
- I have no disclosures
- I will not be discussing non-FDA approved indications during my presentation.

FDA-approved Immunotherapies in Melanoma

- Cytokines
  - Interferon-α2b- Adjuvant therapy- high dose intravenous (I.V.) part, followed by subcutaneous (SQ)
  - Pegylated Interferon-Adjuvant therapy, SQ
  - Interleukin-2-Stage IV, I.V.



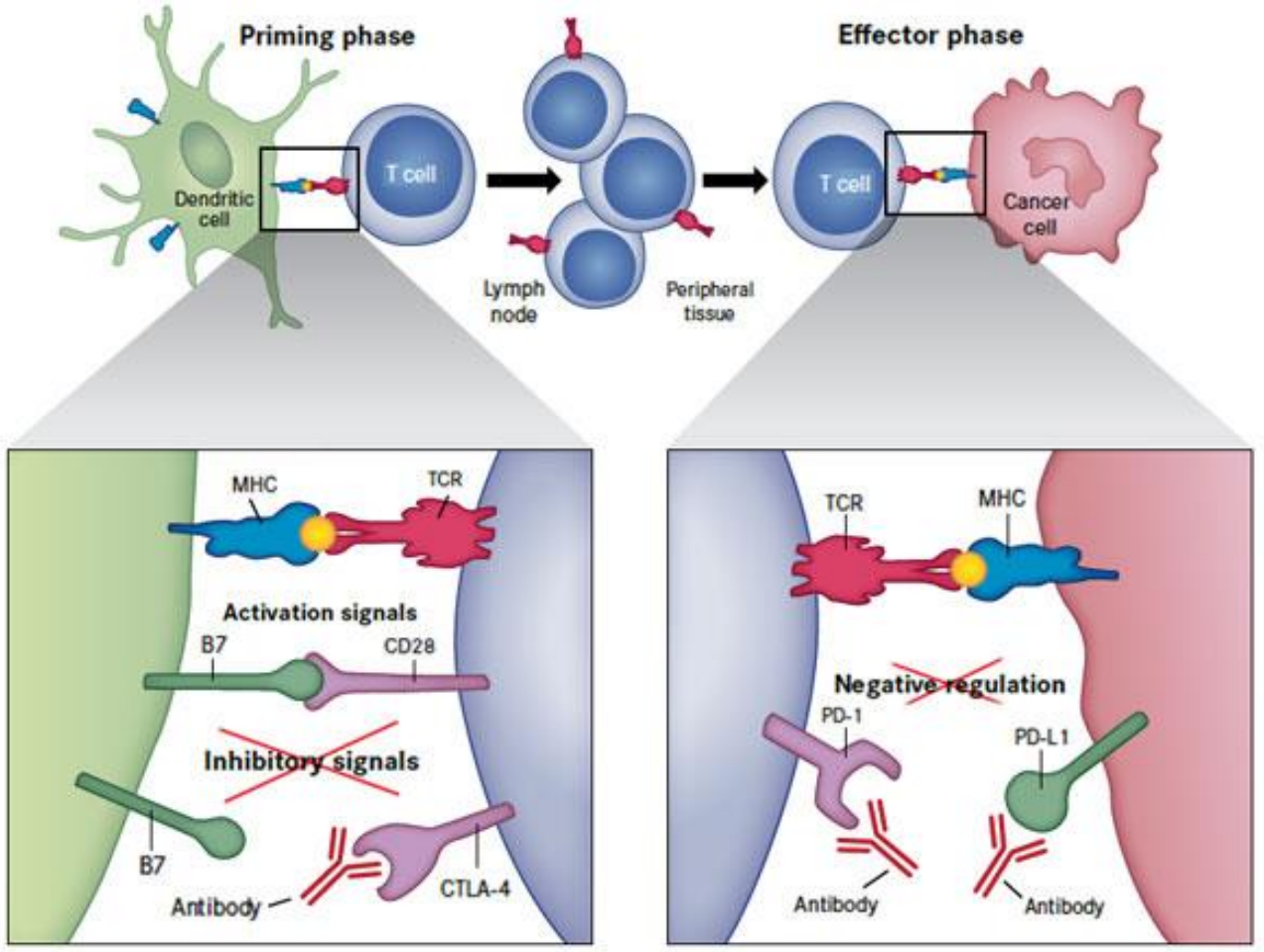
Numasaki et al. Immunotherapy 2016



Sim, Radvanyi Cytogfr 2014

FDA-approved Immunotherapies in Melanoma

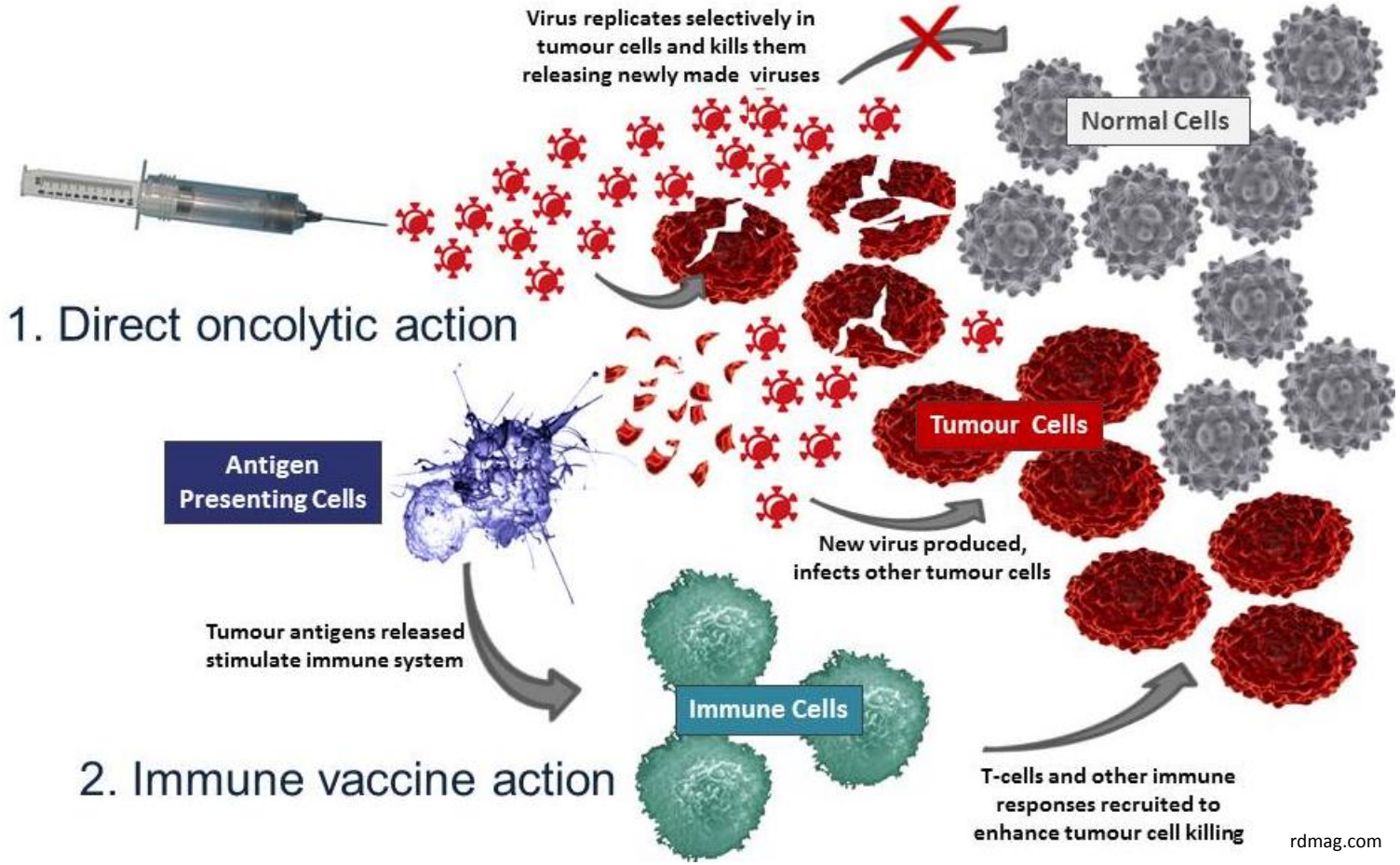
- Checkpoint inhibitors
  - Ipilimumab, adjuvant and nonresectable/Stage IV, I.V.- different dosing for adjuvant and nonresectable/Stage IV
  - Pembrolizumab, nonresectable/Stage IV, I.V.
  - Nivolumab, adjuvant and non resectable/Stage IV, I.V.
  - Ipilimumab in combination with nivolumab, Stage IV



Ribas NEJM 2012
Gordon et al Nature 2017

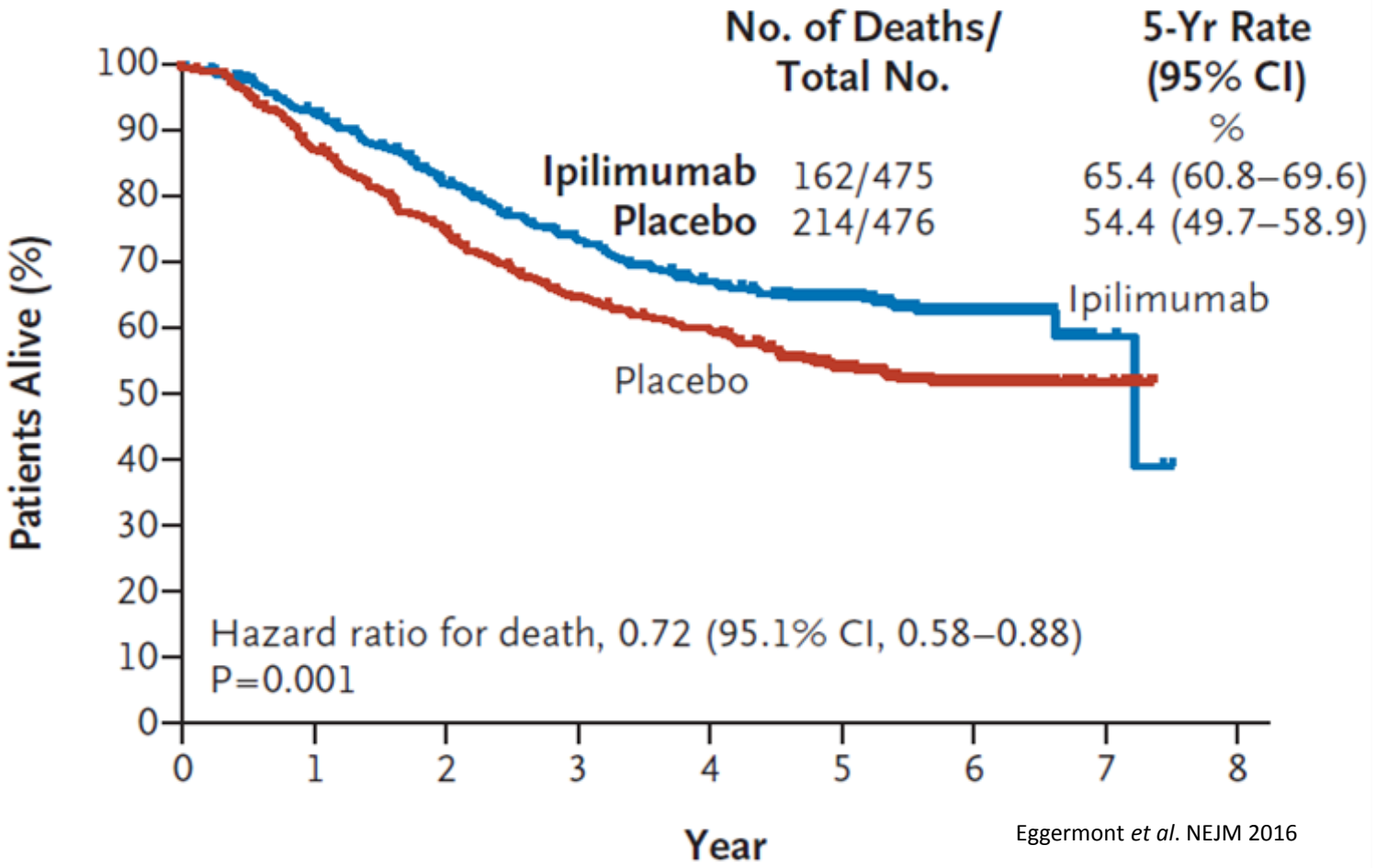
FDA-approved Immunotherapies in Melanoma

- Oncolytic Viruses
  - Talimogene Laharparepvec; TVEC - non resectable, intratumoral



Adjuvant Ipilimumab in High-Risk Stage III Melanoma

- EORTC 18071 phase III trial
  - NCT00636168
  - Adjuvant ipilimumab vs placebo
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 3 years



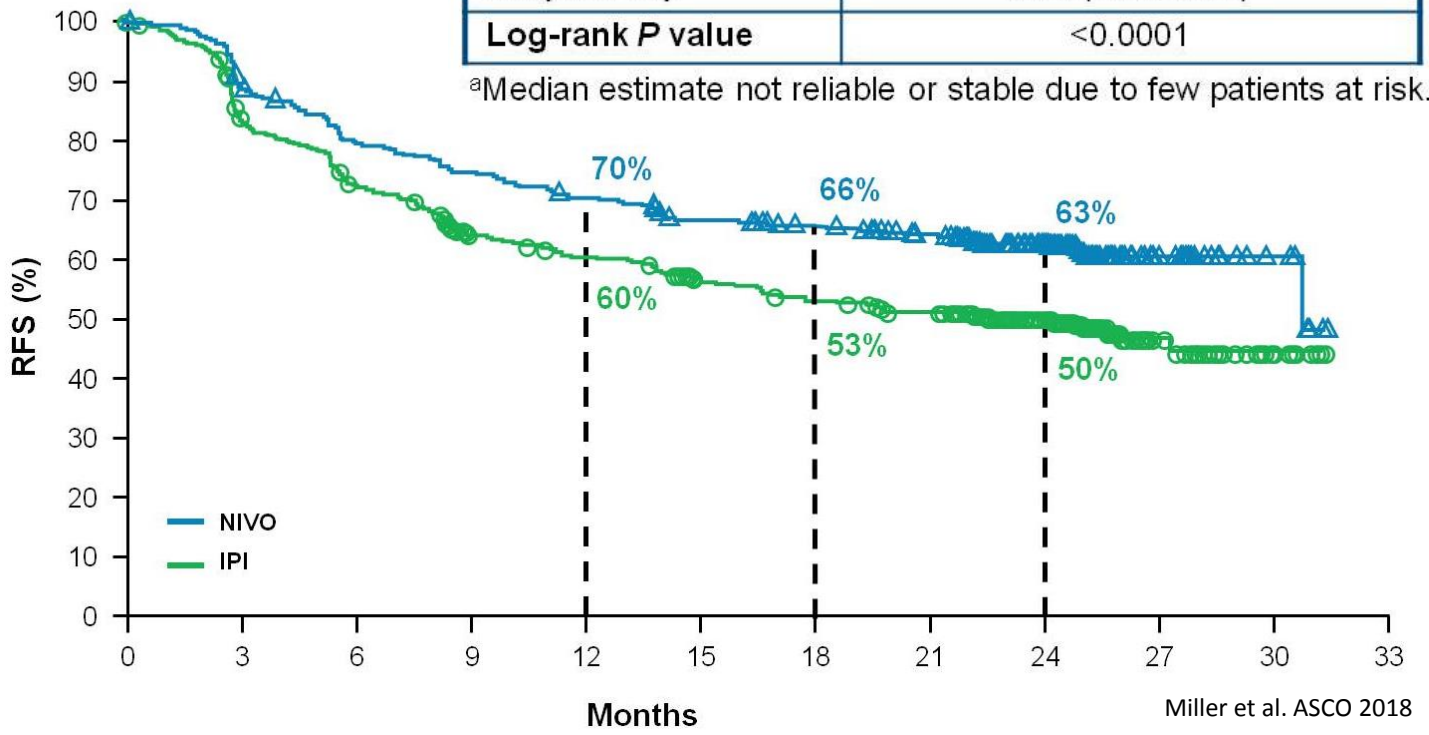
Eggermont *et al*. NEJM 2016

Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

- CheckMate 238 phase III trial
  - NCT02388906
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 1 year
  - Nivolumab 3mg/kg Q2W for four doses, then every 3 months for up to 1 year

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

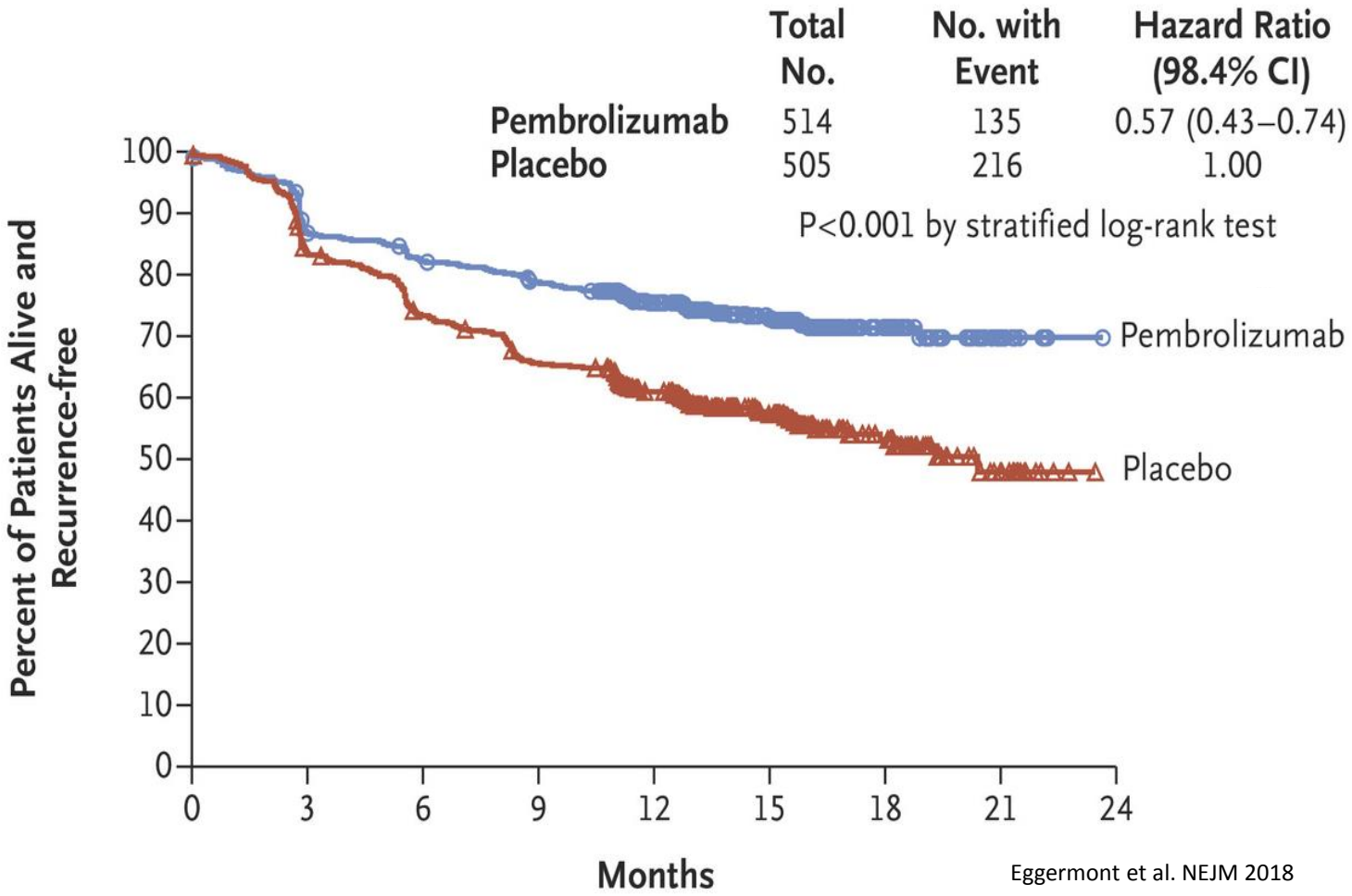
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

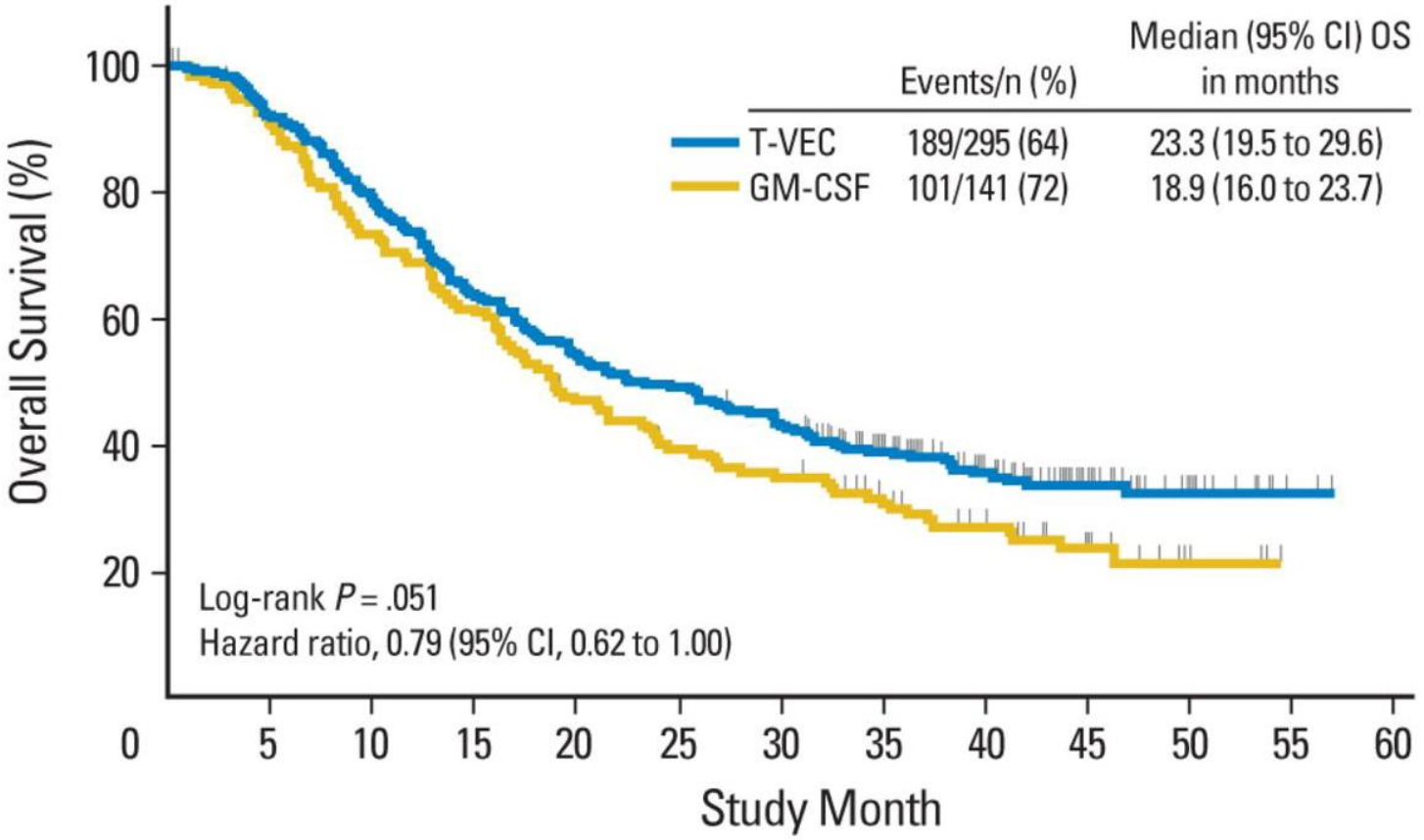
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)



Eggermont et al. NEJM 2018

Talimogene laherparepvec (T-VEC) in Stage III/IV Melanoma

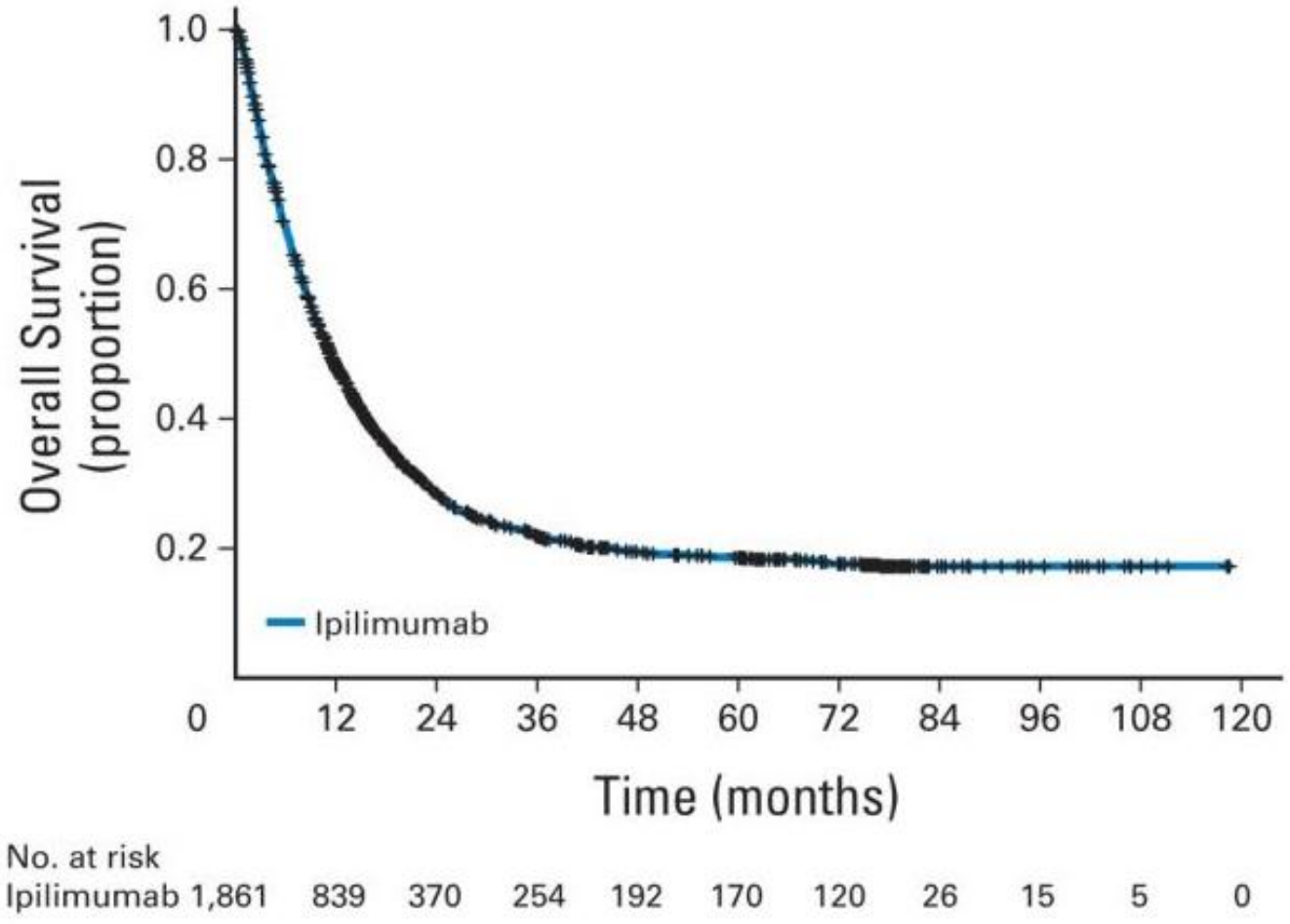
- **Phase III OPTiM Trial**
  - Oncolytic, genetically-engineered herpes virus
  - **Intralesional** T-VEC 10^6 pfu/mL, 10^8 pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF



Andtbacka, Kaufman et al. JCO 2015

Ipilimumab in Stage III/IV Melanoma

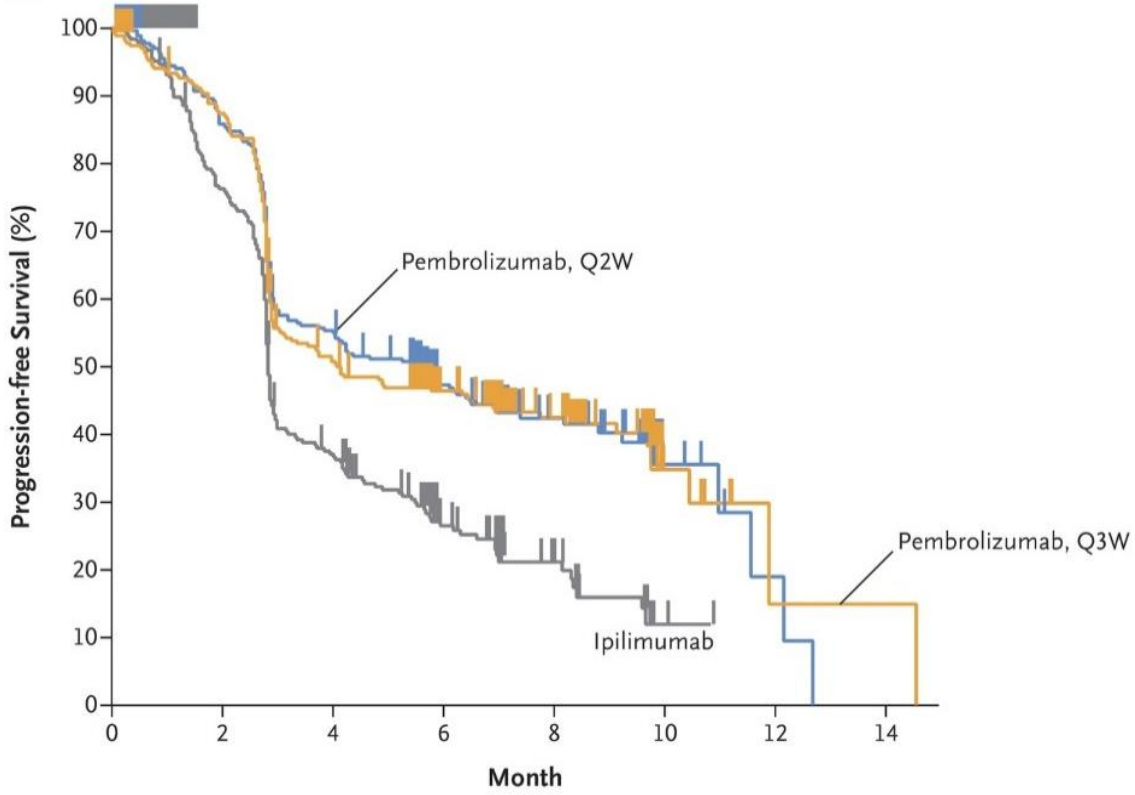
- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)

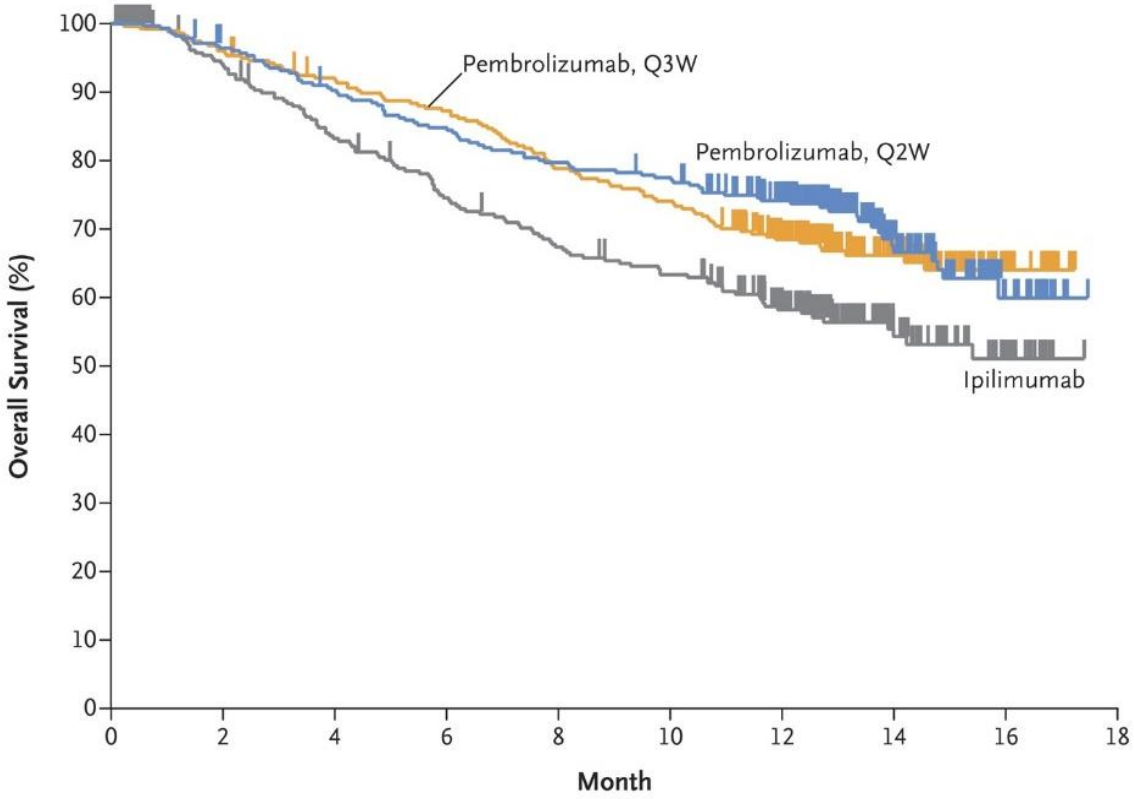


Schadendorf et al. JCO 2015

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial



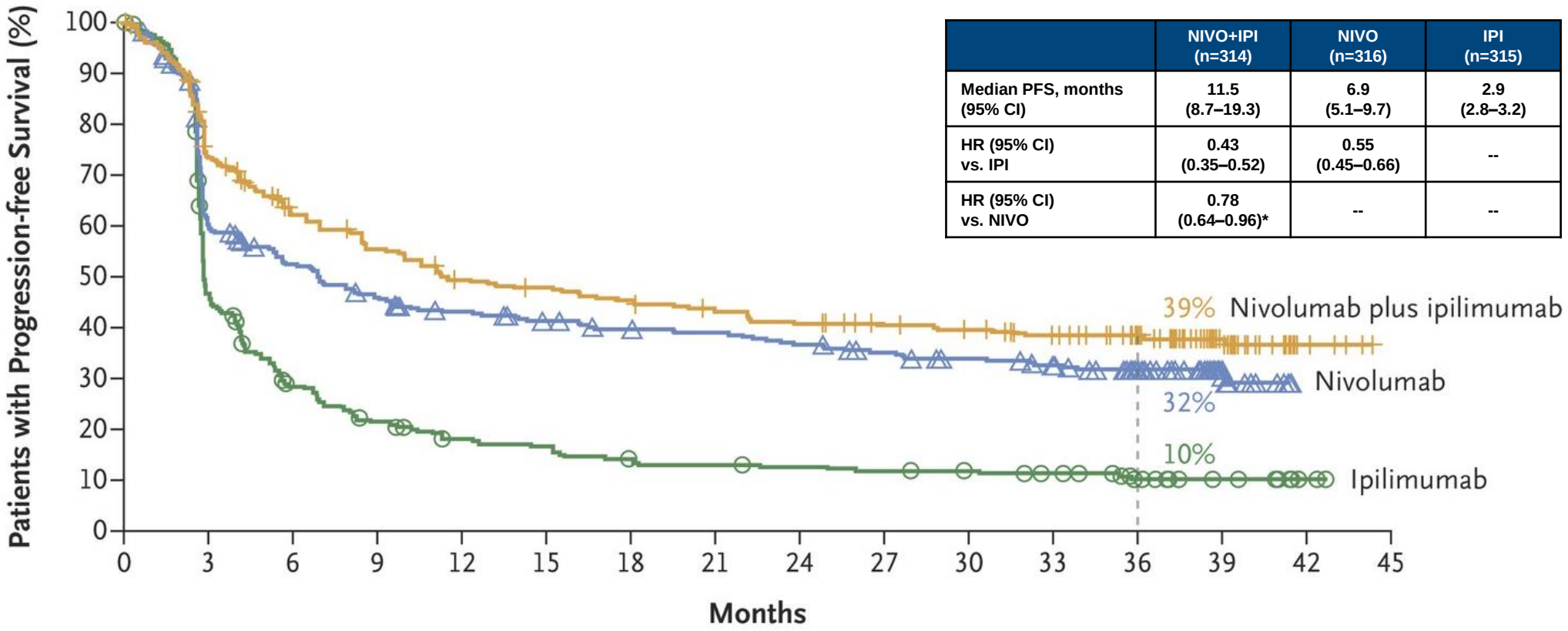


Robert et al. NEJM 2015

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

Phase III CheckMate 067 Trial

	NIVO+IPI (n=314)	NIVO (n=316)	IPI (n=315)
Median PFS, months (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–9.7)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.43 (0.35–0.52)	0.55 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.78 (0.64–0.96)*	--	--



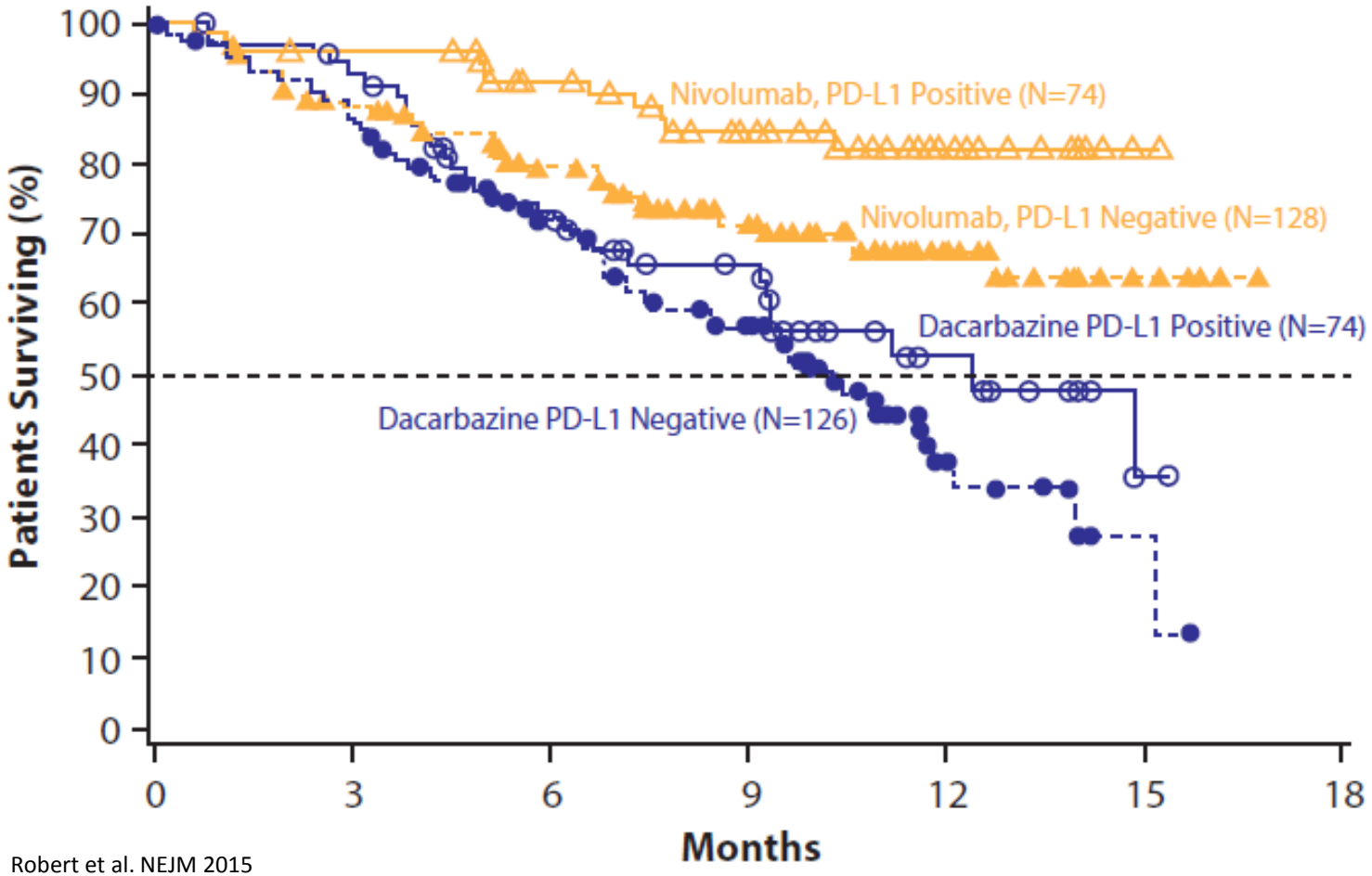
Wolchok et al. NEJM 2017

Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41-65)	55 (43-66)	49 (38-61)
Clinical benefit rate, % (95% CI)[c]	59 (47-70)	60 (48-71)	52 (40-64)

Tawbi et al. ASCO 2017

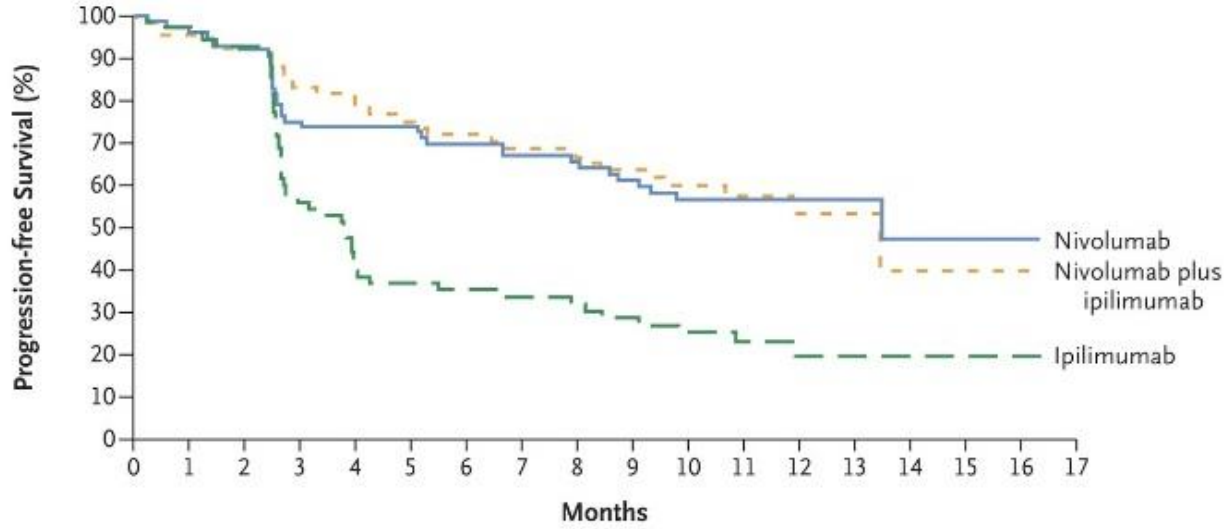
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



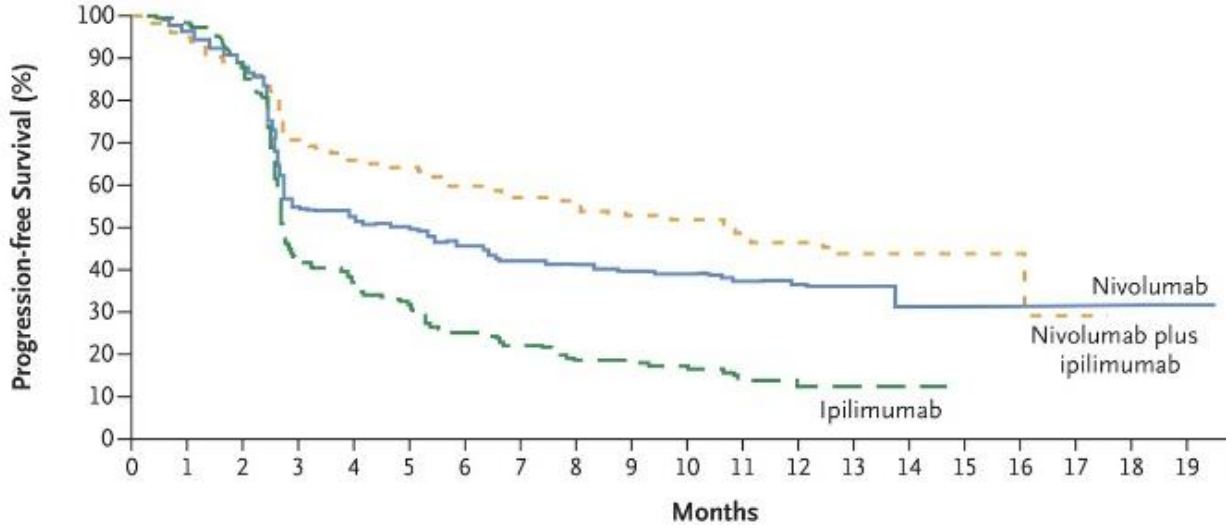
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

Importance of Tumor PD-L1 Status between Combination Checkpoint Blockade and Monotherapy



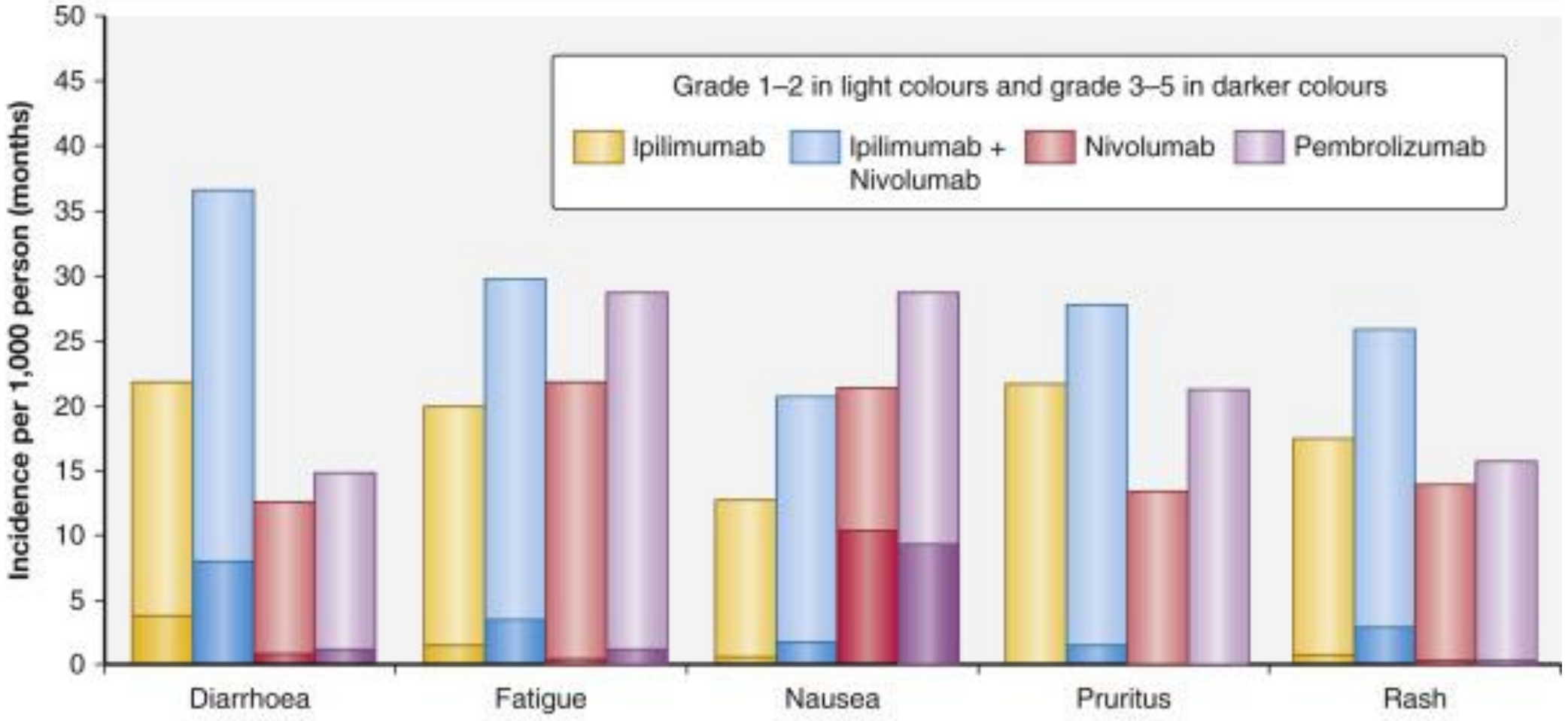
Tumor PD-L1 Positive Patients



Tumor PD-L1 Negative Patients

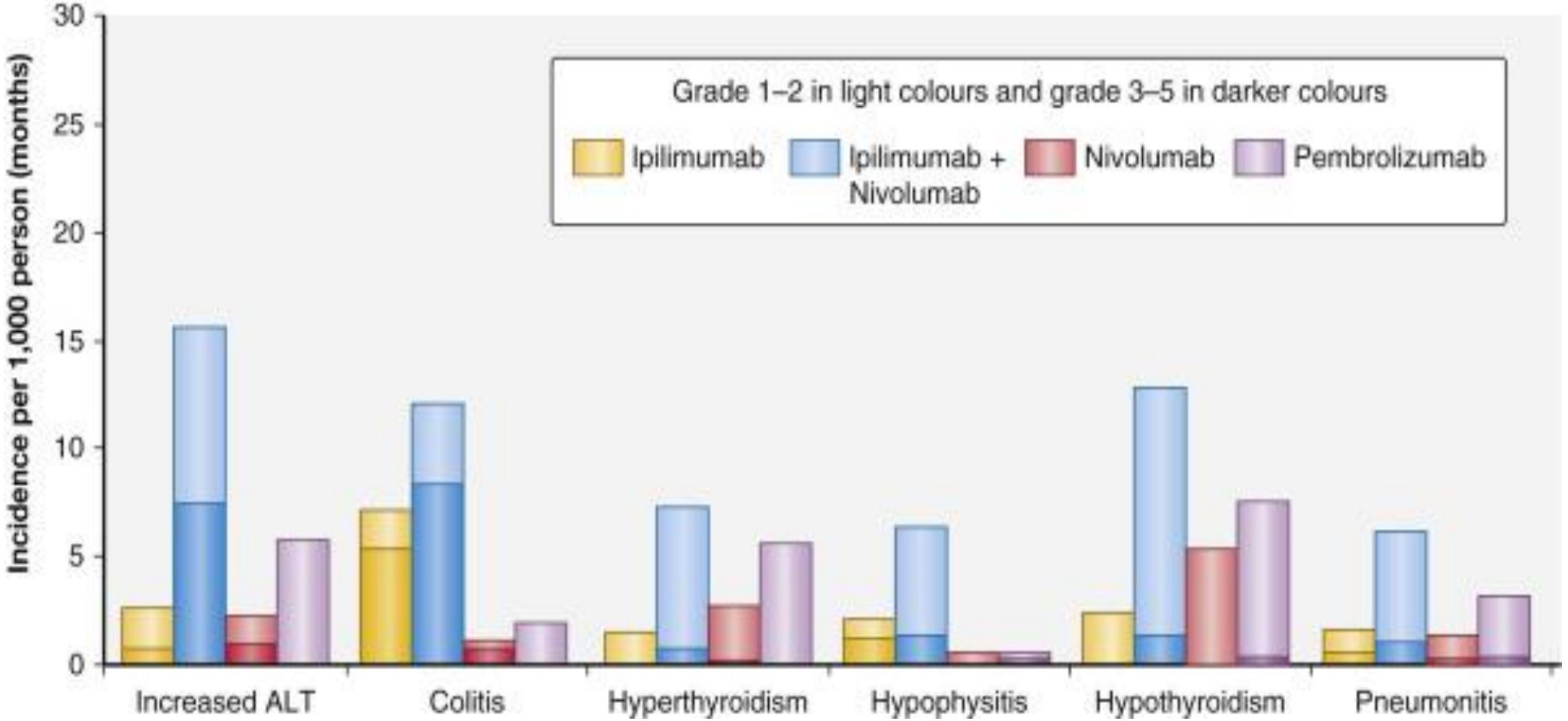
Larkin et al. NEJM 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



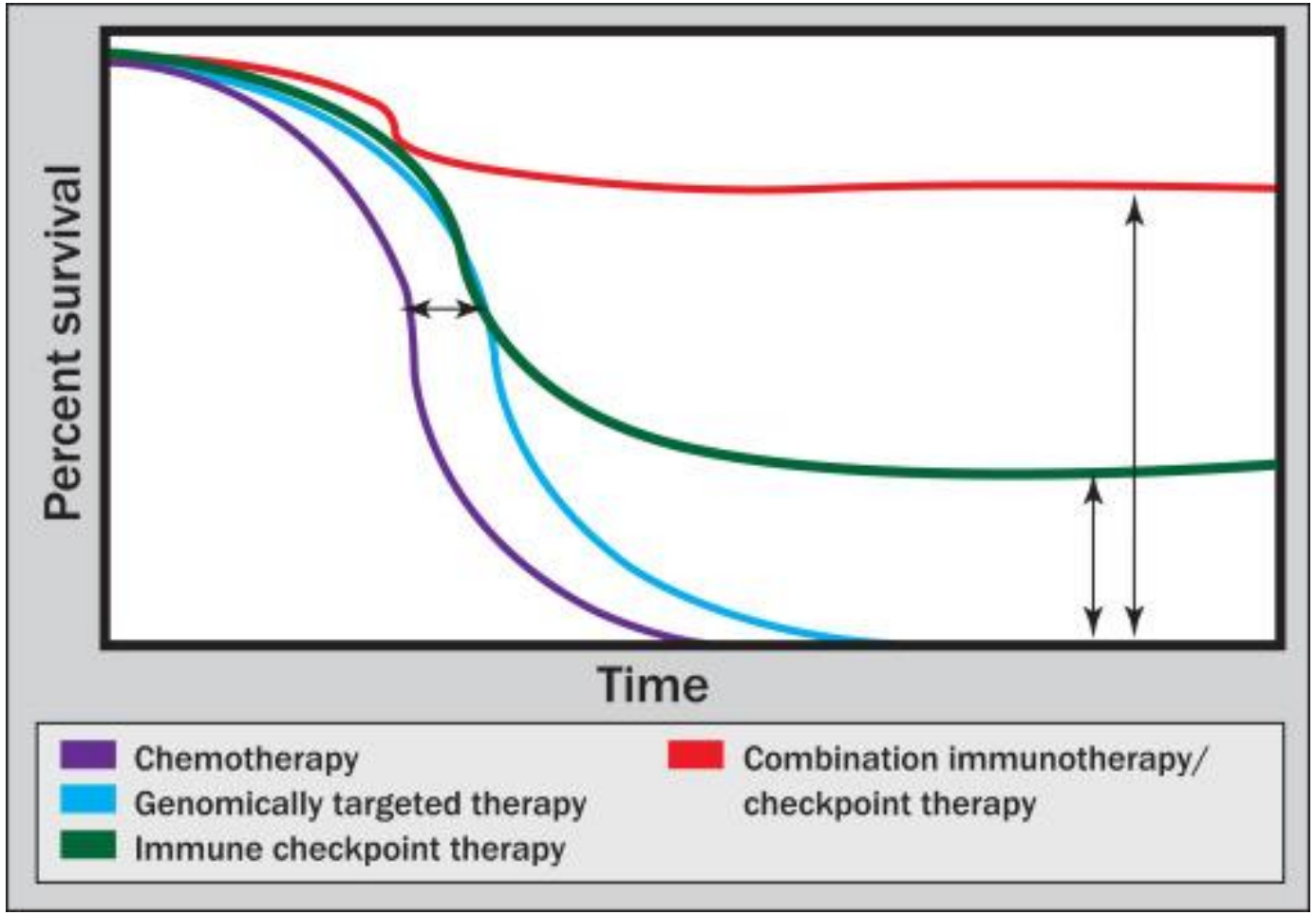
Emens et al. Eur J Cancer 2017

Treatment of Immune-Related AEs

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Puzanov et al. JITC 2017

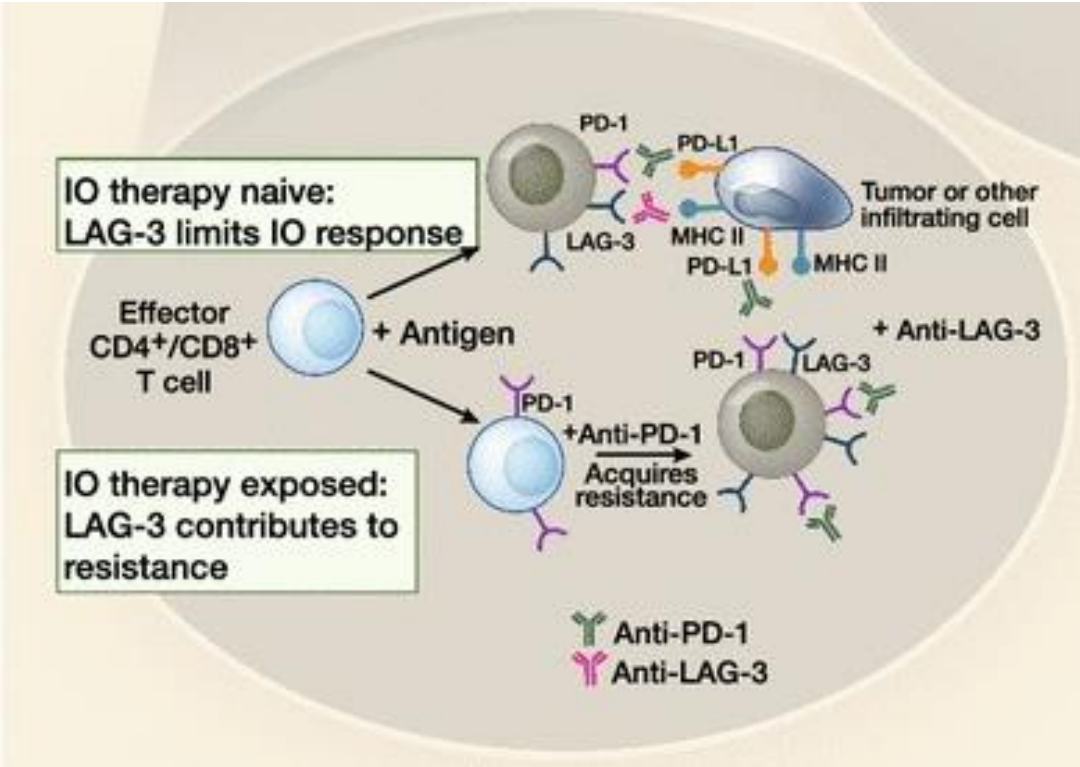
Developmental Immunotherapeutic Strategies for Melanoma

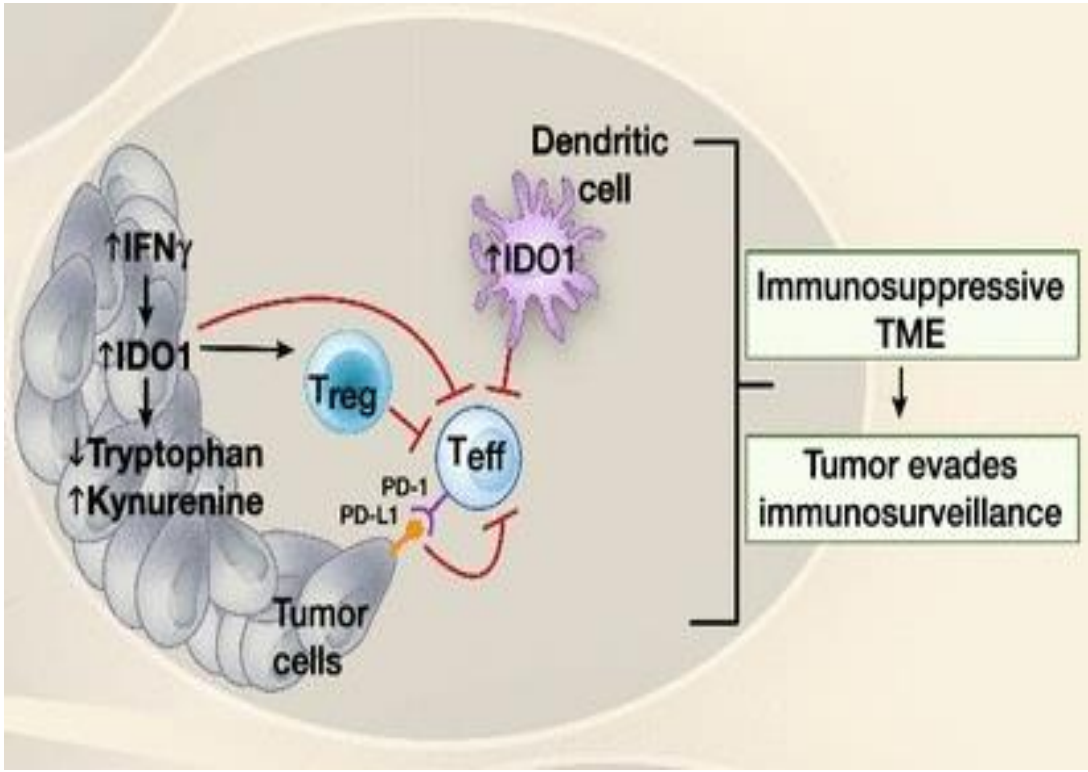


Atkins, Semi. Oncology 2015

Developmental Immunotherapeutic Strategies for Melanoma

Targeting New Immune Checkpoints





Ascierto, McArthur J Transl Med 2017

Pilot Study: Radiotherapy (RT) + Intratumoral Immunocytokine (IT-IC) + Ipilimumab + Nivolumab for Advanced Melanoma

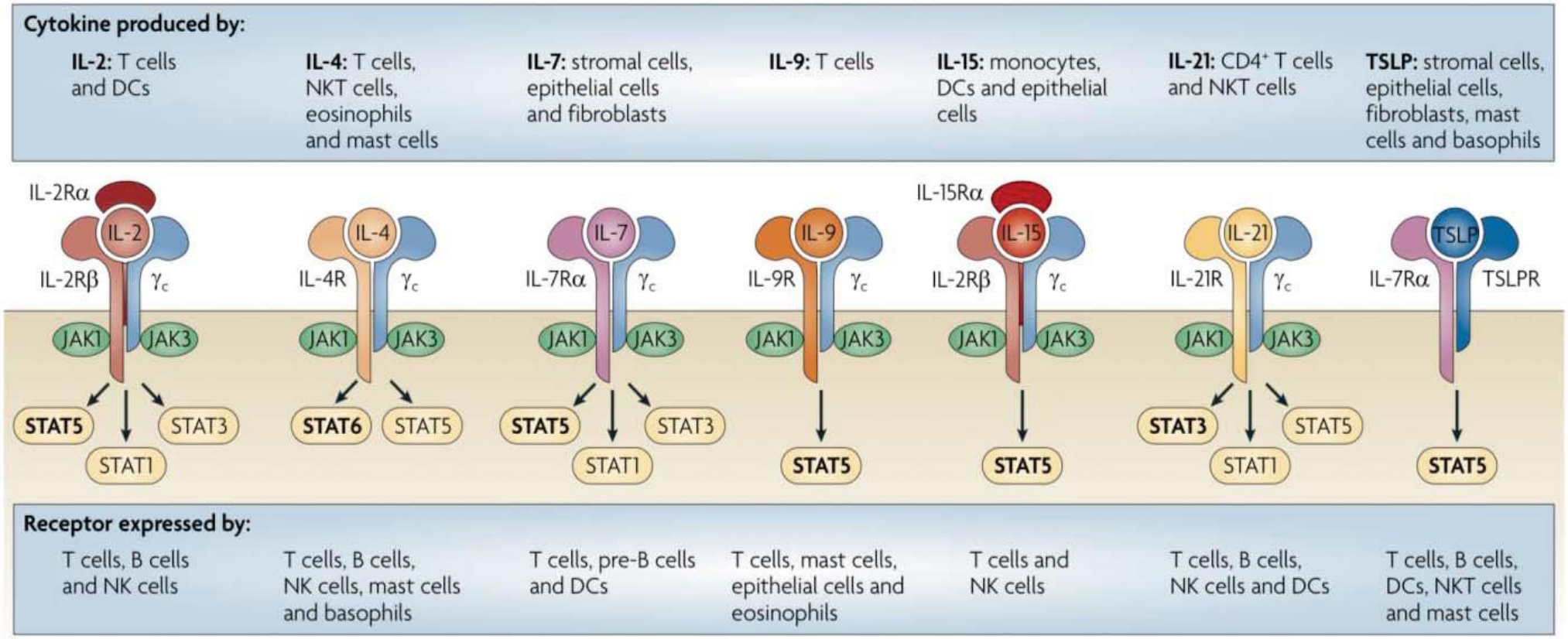
A UWCCC Clinical Trial (IND being prepared) with collaboration from Apeiron, NMS and NCI

- Goals:
  - First in human Phase-1 testing of IT-IC with an IC that can bind to tumor and mediate ADCC
  - First in human IT-IC of such an IC immunologically timed after local RT
  - First in human testing of this in combination with anti-CTLA4 and/or anti-PD1
  - Toxicity/Tolerance/Anti-tumor effects
  - Serial biopsies of the same lesions, to look for the changes seen in murine tumors

Protocol Chairs: Mark Albertini, M.D.
Radiation Oncology Co-Chair: Zachary Morris, M.D., Ph.D
Laboratory Co-Chair: Jacqueline A. Hand, Ph.D
Pathology Co-Chair: Erik Ranheim, M.D., Ph.D.
NCI Grant (R35 CA197078-01) PI: Paul M. Sondel, M.D., Ph.D.

Developmental Immunotherapeutic Strategies for Melanoma

Cytokine-based Strategies



Lee, Margolin Cancers 2011
Rochman et al. Nat Rev Immunol 2009

Resources

Sullivan et al. Journal for ImmunoTherapy of Cancer (2018) 6:44
https://doi.org/10.1186/s40425-018-0362-6

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

Ryan J. Sullivan[1], Michael B. Atkins[2], John M. Kirkwood[3], Sanjiv S. Agarwala[4], Joseph I. Clark[5], Marc S. Ernstoff[6], Leslie Fecher[7], Thomas F. Gajewski[8], Brian Gastman[9], David H. Lawson[10], Jose Lutzky[11], David F. McDermott[12], Kim A. Margolin[13], Janice M. Mehnert[14], Anna C. Pavlick[15], Jon M. Richards[16], Krista M. Rubin[1], William Sharfman[17], Steven Silverstein[18], Craig L. Slingluff Jr[19], Vernon K. Sondak[20], Ahmad A. Tarhini[21], John A. Thompson[22], Walter J. Urba[23], Richard L. White[24], Eric D. Whitman[25], F. Stephen Hodi[26] and Howard L. Kaufman[1*]

Case Study 1

75 y/o Caucasian male with PMH of stage IIB desmoplastic melanoma of the left temple status post Mohs resection in October 2017 followed by adjuvant XRT in January 2018 developed metastatic disease based on PET CT in June 2018 for which he was started on Nivo/Ipilimumab and completed 4 cycles on August 31, 2018 was admitted with syncope, anemia and melanotic stools. About a week prior to presentation, he was diagnosed with Clostridium difficile colitis and started on oral Flagyl. At presentation, Hb was 8.5 down from 13.8, about 2 weeks ago and elevated INR > 10, due to warfarin therapy for history of DVT and PAF. He denied any abdominal pain, nausea or vomiting. He received vitamin K and FFP. EGD showed diffuse gastric mucosal oozing of blood with no esophagitis and varices or ulceration. Mucosal areas of bleeding were ablated. He was started on PPI. He was discharged home on high dose PO vancomycin after melanotic stools and diarrhea improved. He was readmitted few days later with non-resolving diarrhea, hypotension, AKI and severe acidosis. He was transferred to the ICU. CT showed likely enteritis. C Diff returned negative. Sigmoidoscopy with biopsy was scheduled with possible colectomy to follow.

Case Study 1

What should you do next?

1. Proceed with colectomy
2. Start high-dose steroids
3. Start Infliximab
4. Watch and wait
5. Recommend hospice

Would you start this patient back on immunotherapy?

Yes or No

Immunotherapy Related Colitis

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death

- Incidence of diarrhea/colitis is much higher in patients receiving CTLA-4-blocking antibodies compared with PD(L)-1
- Frequency of diarrhea appears to be dose-dependent

	Nivo/Ipi		**Nivo**		**Ipi**	
	G3/4 (%)	Any grade (%)	G3/4 (%)	Any grade (%)	G3/4 (%)	Any grade (%)
Diarrhea	9	45	9	21	6	34
Colitis	8	13	1	2	5.3-8	7.6-11

CTCAE v5.0 – November 27, 2017, page 26

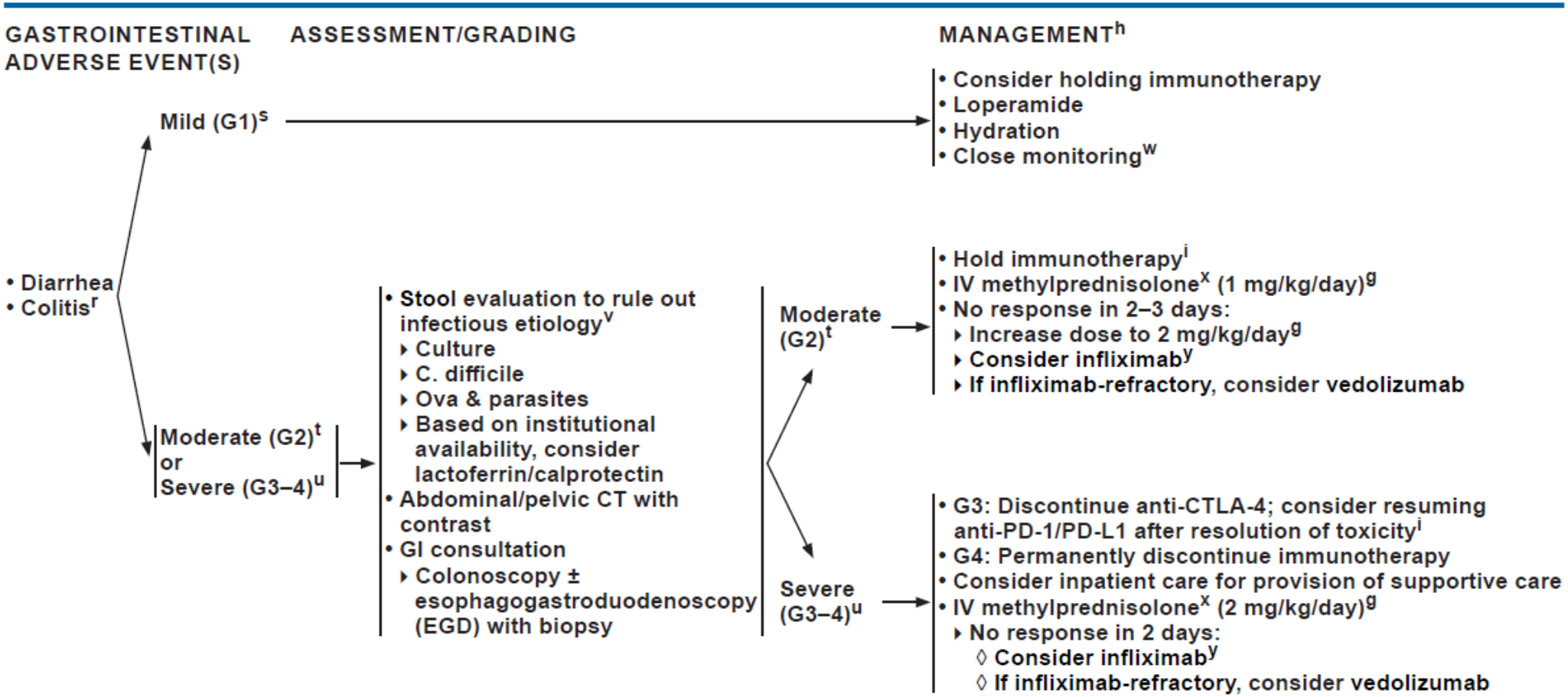
Wolchok JD et al; Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma; N Engl J Med. 2017;377(14):1345. CheckMate067
Hodi FS et al; Improved survival with ipilimumab in patients with metastatic melanoma; N Engl J Med. 2010;363(8):711.

NCCN Recommendations

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Management of Immunotherapy-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion



NCCN Guidelines

Package Inserts for Nivolumab (Opdivo®) and Pembrolizumab (Keytruda®)

Table 1: Recommended Dose Modifications for Nivolumab (Opdivo)

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue

Table 1: Recommended Dose Modifications for Adverse Reactions
[see Warnings and Precautions (5.1-5.9)]

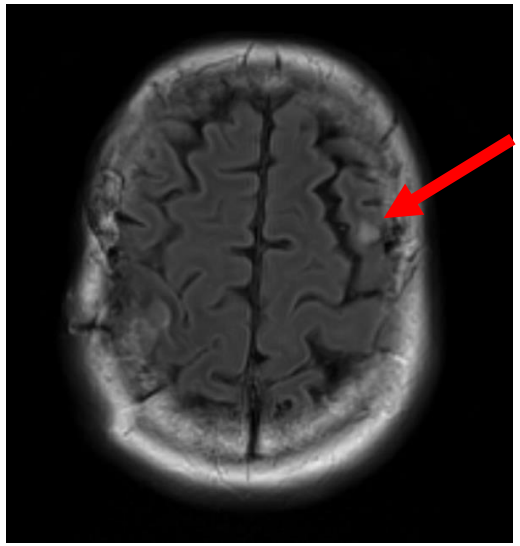
Adverse Reaction	Severity*	Does Modification for Pembrolizumab (Keytruda)
Immune-mediated colitis	Grades 2 or 3	Withhold[†]
	Grade 4	Permanently discontinue

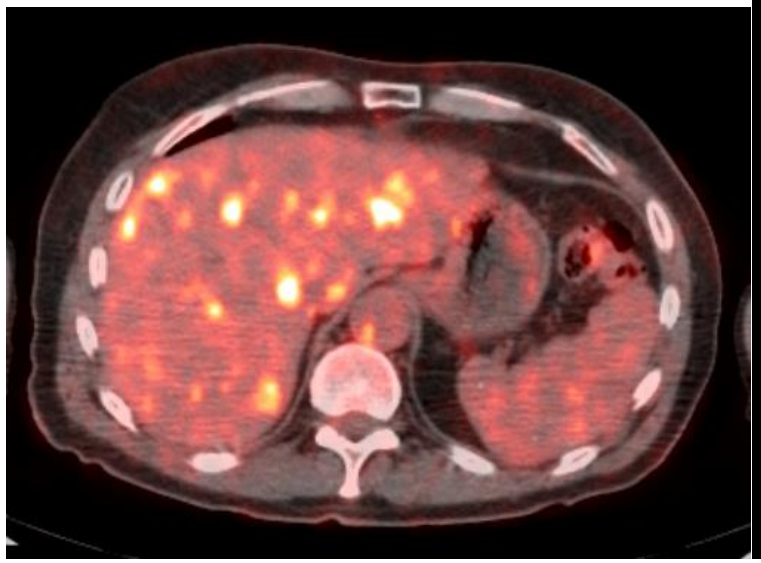
Adapted from Opdivo and Keytruda Package Inserts

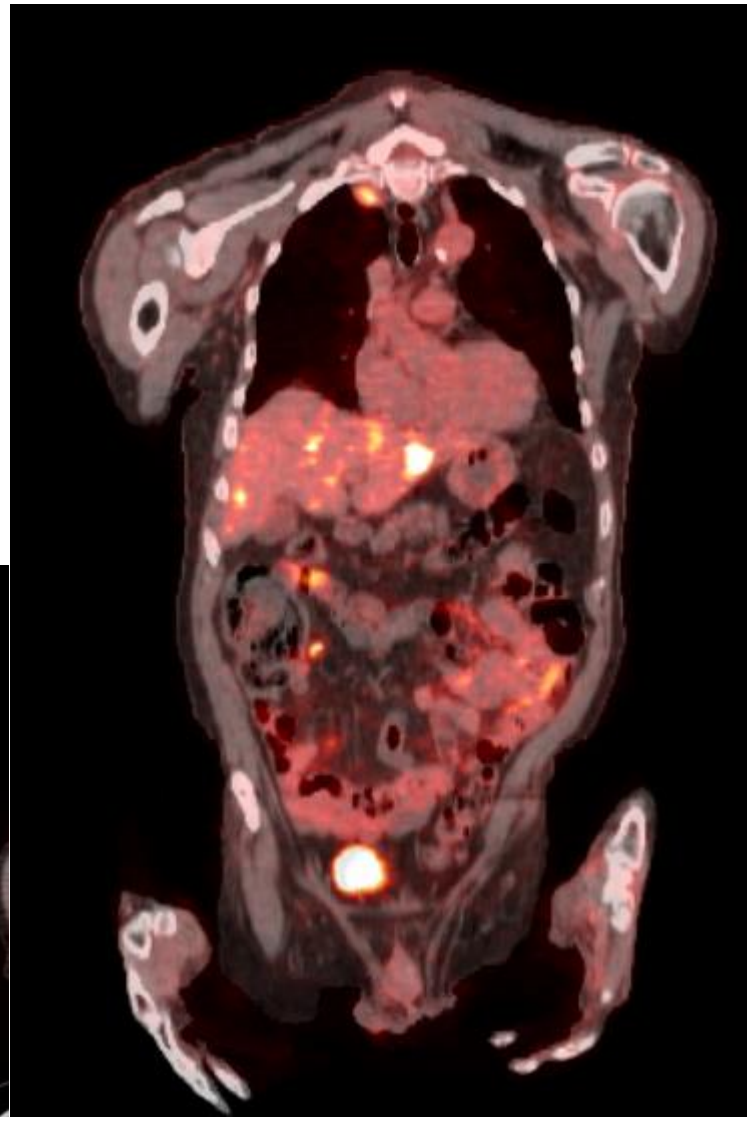
Case study 2

76 y/o Caucasian male presented with left hand weakness and was found to have a right superior frontal lobe lesion. He underwent resection on August 9th 2013 and was diagnosed with metastatic melanoma, BRAF (V600K). Received SRS in October 2013, followed by oral Mekinist which was discontinued in November 2013 due to side effects (rash, transient visual symptoms and anemia). He then developed left upper extremity weakness in late May 2014. MRI brain showed right frontal lobe lesion which was resected in August 2014 and was consistent with metastatic melanoma. Restaging PET/CT in October 2014 showed multiple liver metastases which were biopsy confirmed for metastatic melanoma. He received 4 cycles of ipilimumab (Yervoy®) with systemic evidence of response (regressing hepatic metastases) but had new CNS changes (pseudoprogression vs. radiation necrosis). He received 4 cycles of bevacizumab (Avastin) with improvement in his left-sided weakness. But, he progressed in liver and developed a new left frontal lobe lesion (6 mm).

Case study 2



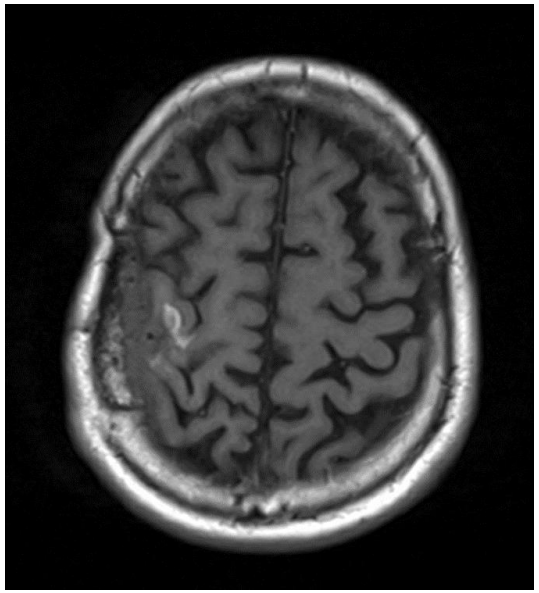


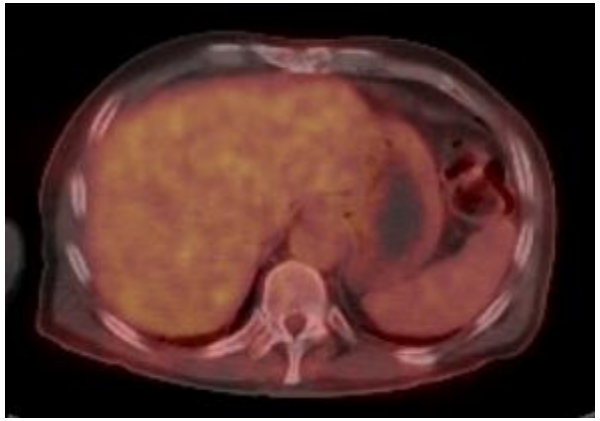


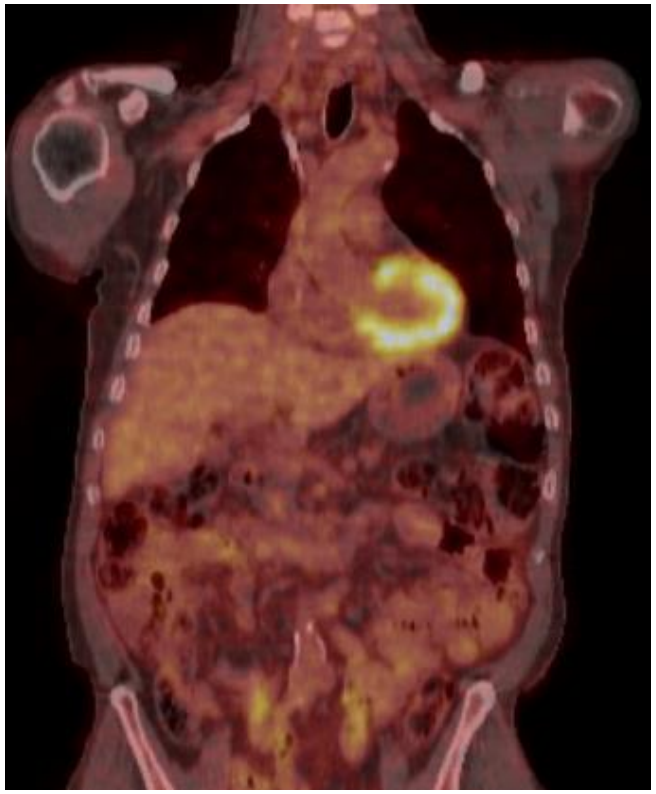
What should you do next?

1. Systemic chemotherapy
2. Radiation to brain and liver
3. Surgical resection of brain met
4. Hospice care
5. Anti-PD-1 therapy

Case study 2







He was started on (pemprolizumab) Keytruda and subsequent imaging demonstrated complete regression of the hepatic lesions and resolution of the left frontal lobe lesion; off therapy since 15 March 2016.

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

The NEW ENGLAND JOURNAL of MEDICINE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., et al.

THE LANCET Oncology

ARTICLES | VOLUME 17, ISSUE 7, P976-983, JULY 01, 2016

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

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Published: June 03, 2016 • DOI: https://doi.org/10.1016/S1470-2045(16)30053-5 • Check for updates

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer