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
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ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

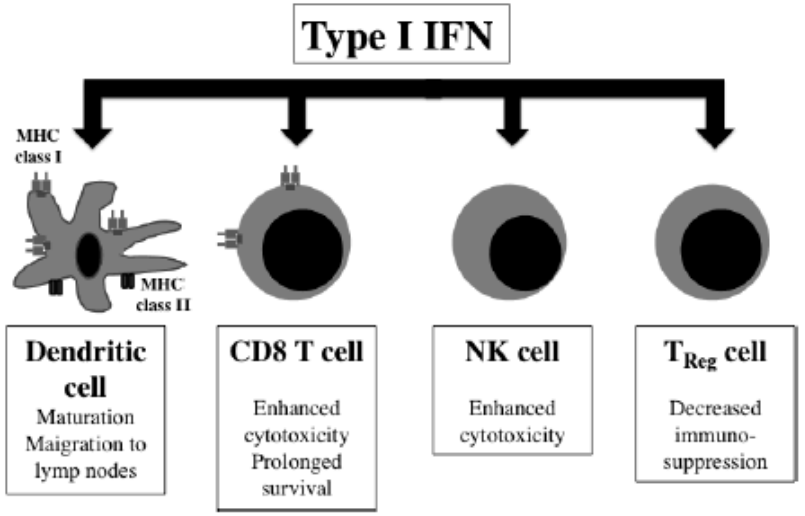
Disclosures

- Disclosures: Research funding: Roche/Genentech, BMS, Merck, Array, Astrazeneca, Incyte, Amgen, Morhptek, GSK, Regeneron, Polynoma, AbbVie Stemcentrx, EMD Serono, Tesaro, Nektar Therapeutics, Janssen, Iovance, Novartis; Consulting/Honoraria: Roche/Genentech, Merck, Regeneron, Array.
- I will not be discussing non-FDA approved indications during my presentation.

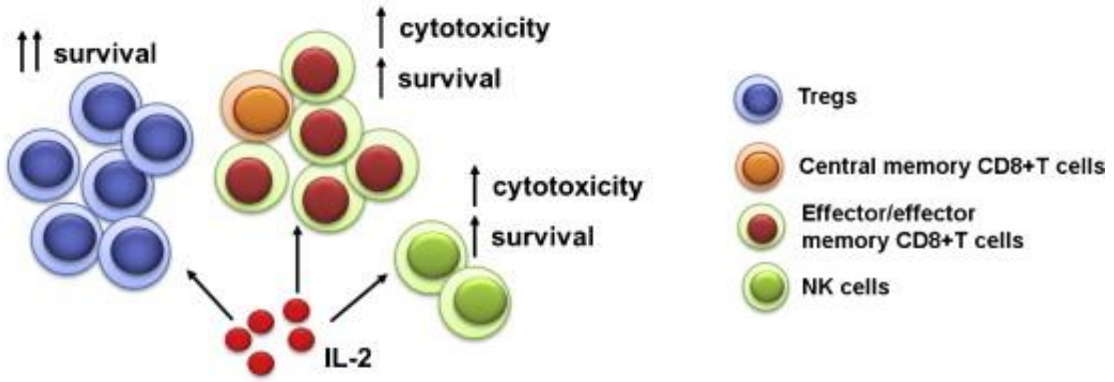
FDA-approved Immunotherapies in Melanoma

Cytokines

- High-dose Interferon
  - Adjuvant therapy
  - High dose I.V., followed by SQ
  - Treatment for up to one year
- Pegylated Interferon
  - Adjuvant therapy
  - SQ only
  - Longer duration than high dose interferon
- Interleukin-2
  - Stage IV
  - I.V., significant toxicities
  - Long term survival



Numasaki et al. Immunotherapy 2016

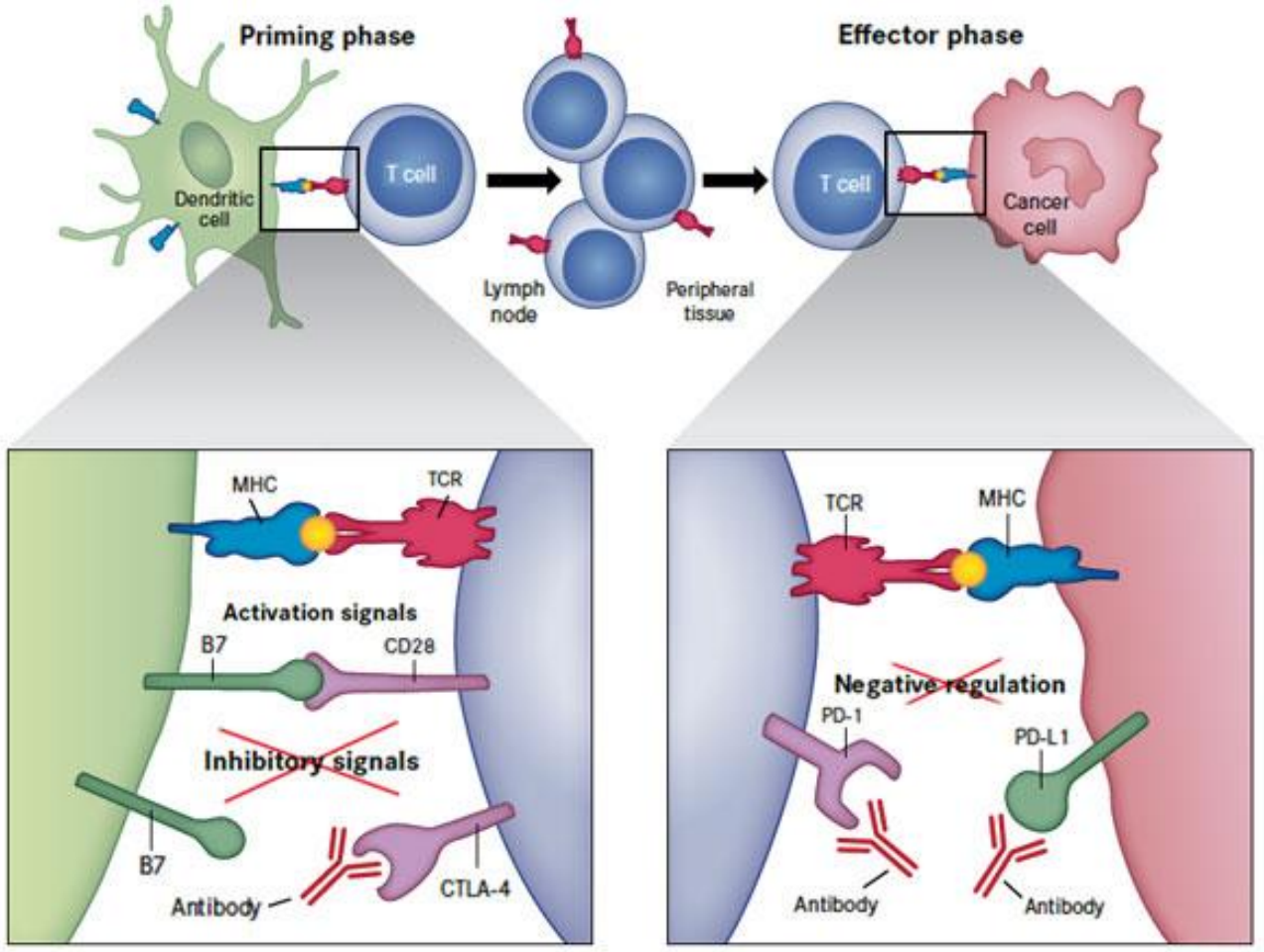


Sim, Radvanyi Cytogfr 2014

FDA-approved Immunotherapies in Melanoma

Immune 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

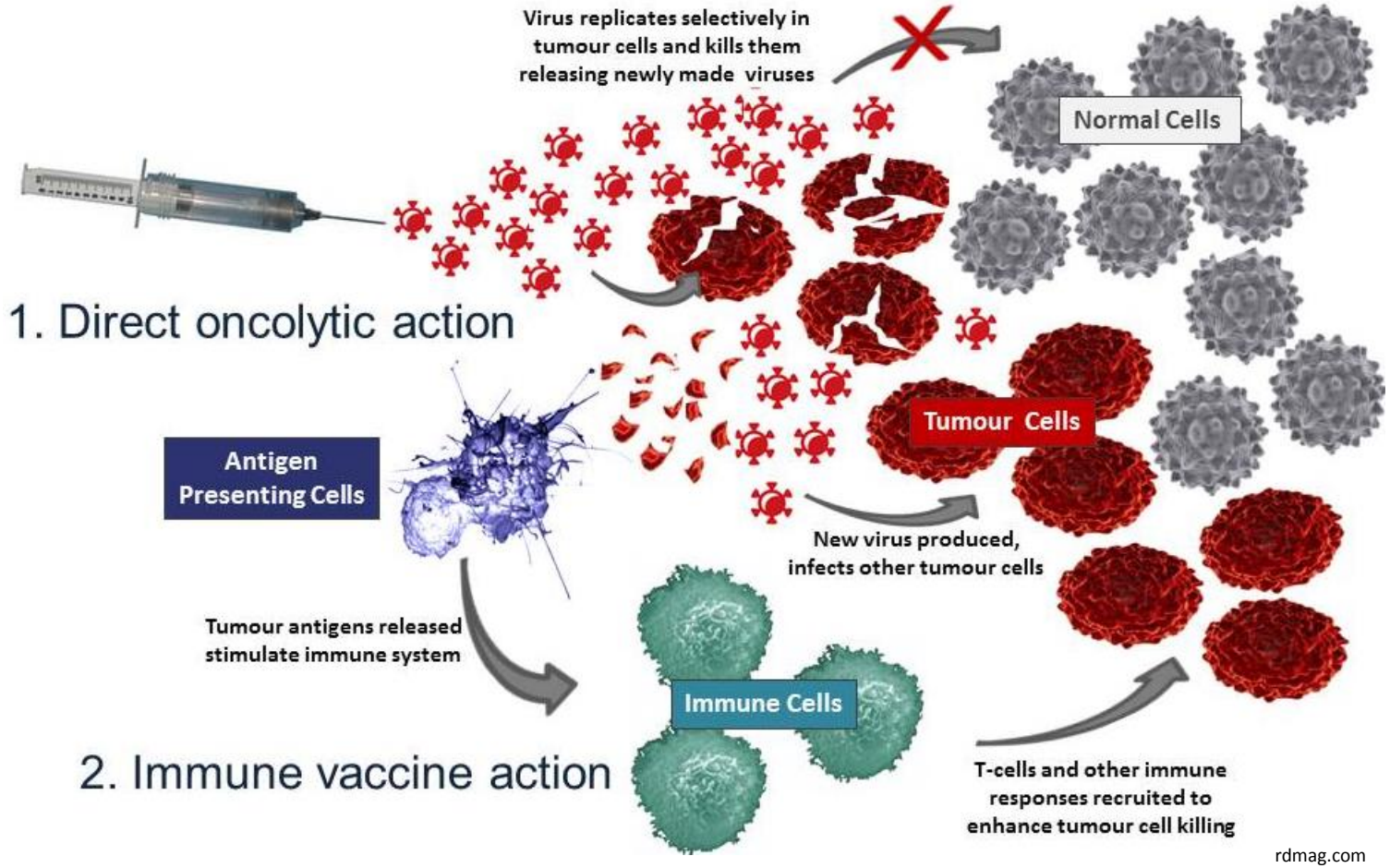


Ribas NEJM 2012
Gordon et al Nature 2017

FDA-approved Immunotherapies in Melanoma

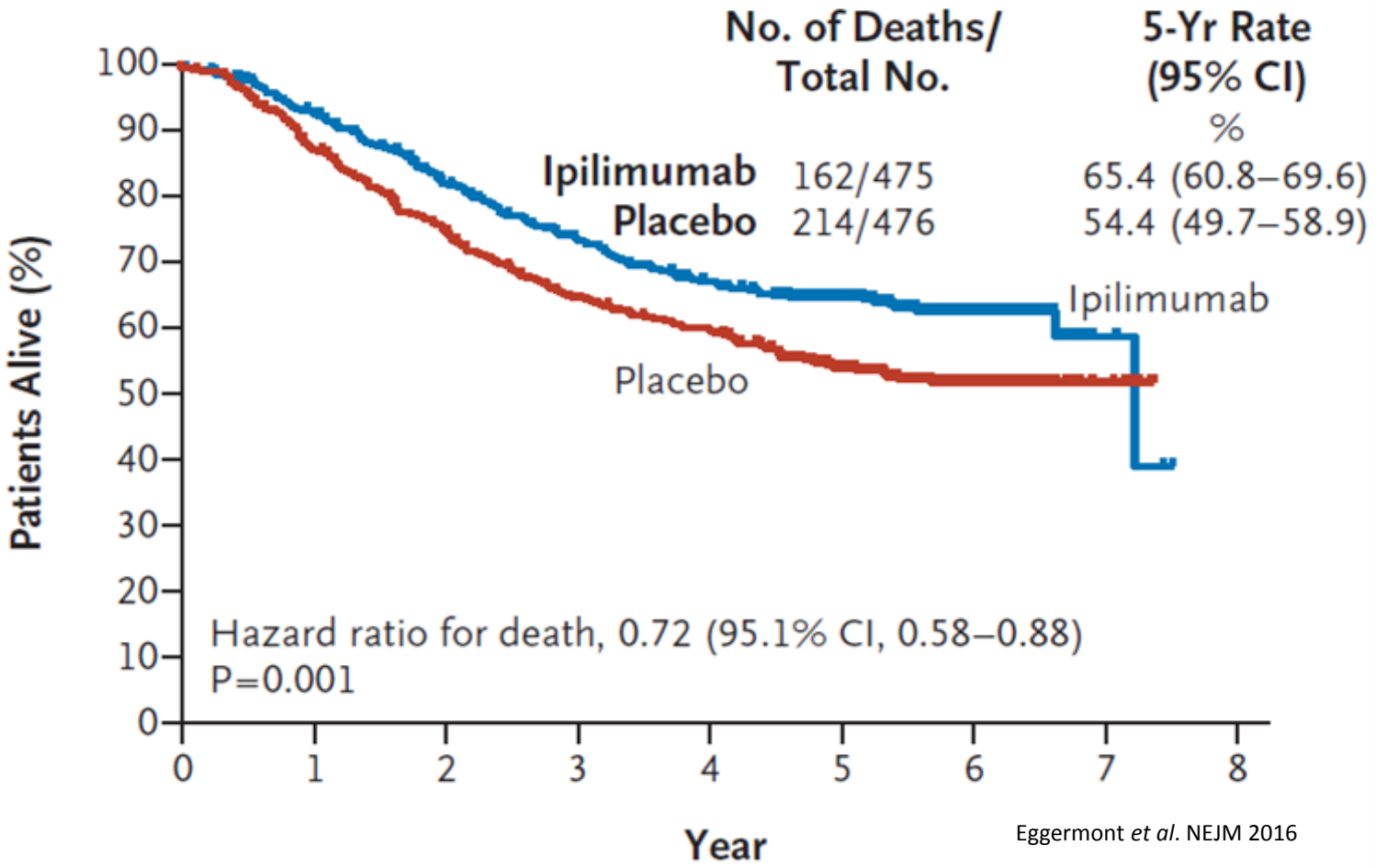
Oncolytic Viruses

- Talimogene Laharparepvec
  - T-VEC
  - Non resectable, intratumoral/Intralesional



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



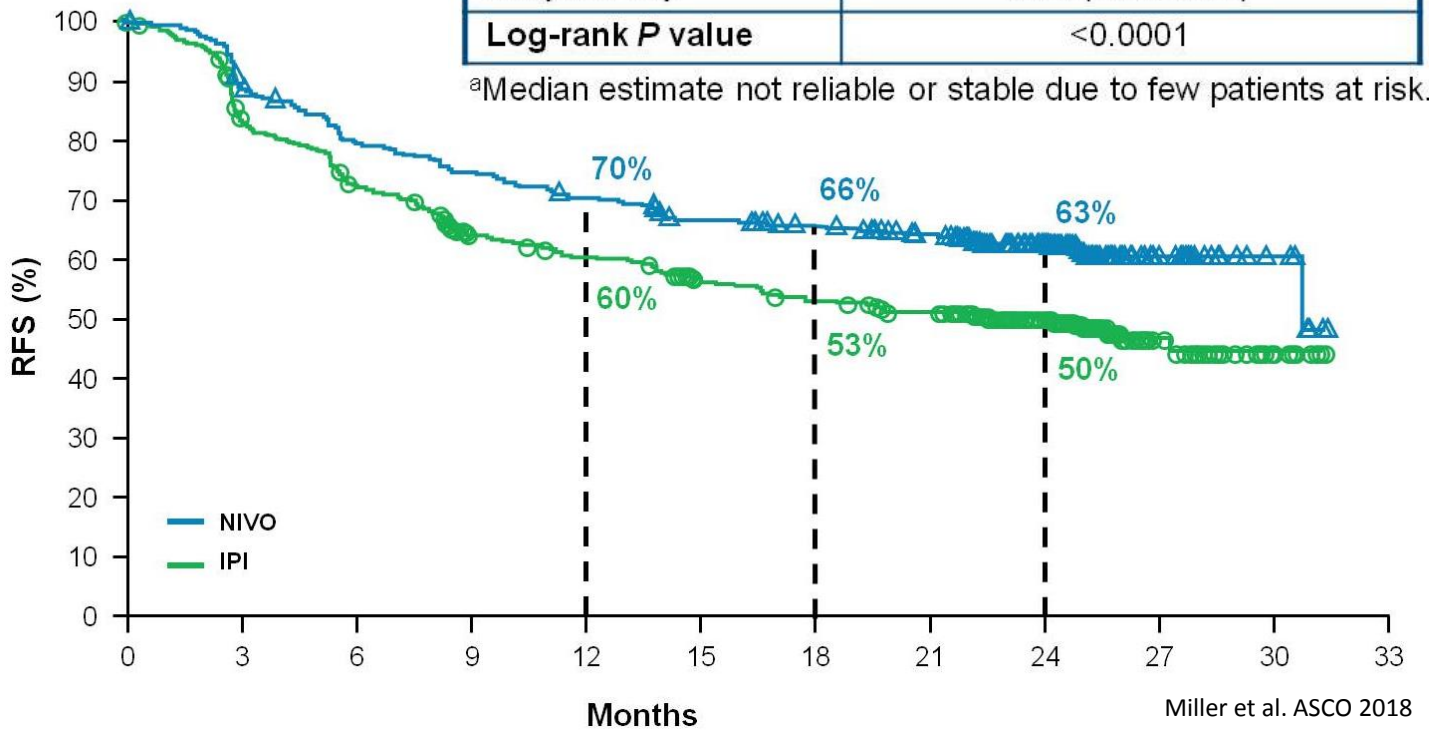
Eggermont *et al*. NEJM 2016

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
  - Nivolumab 3mg/kg Q2W 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	

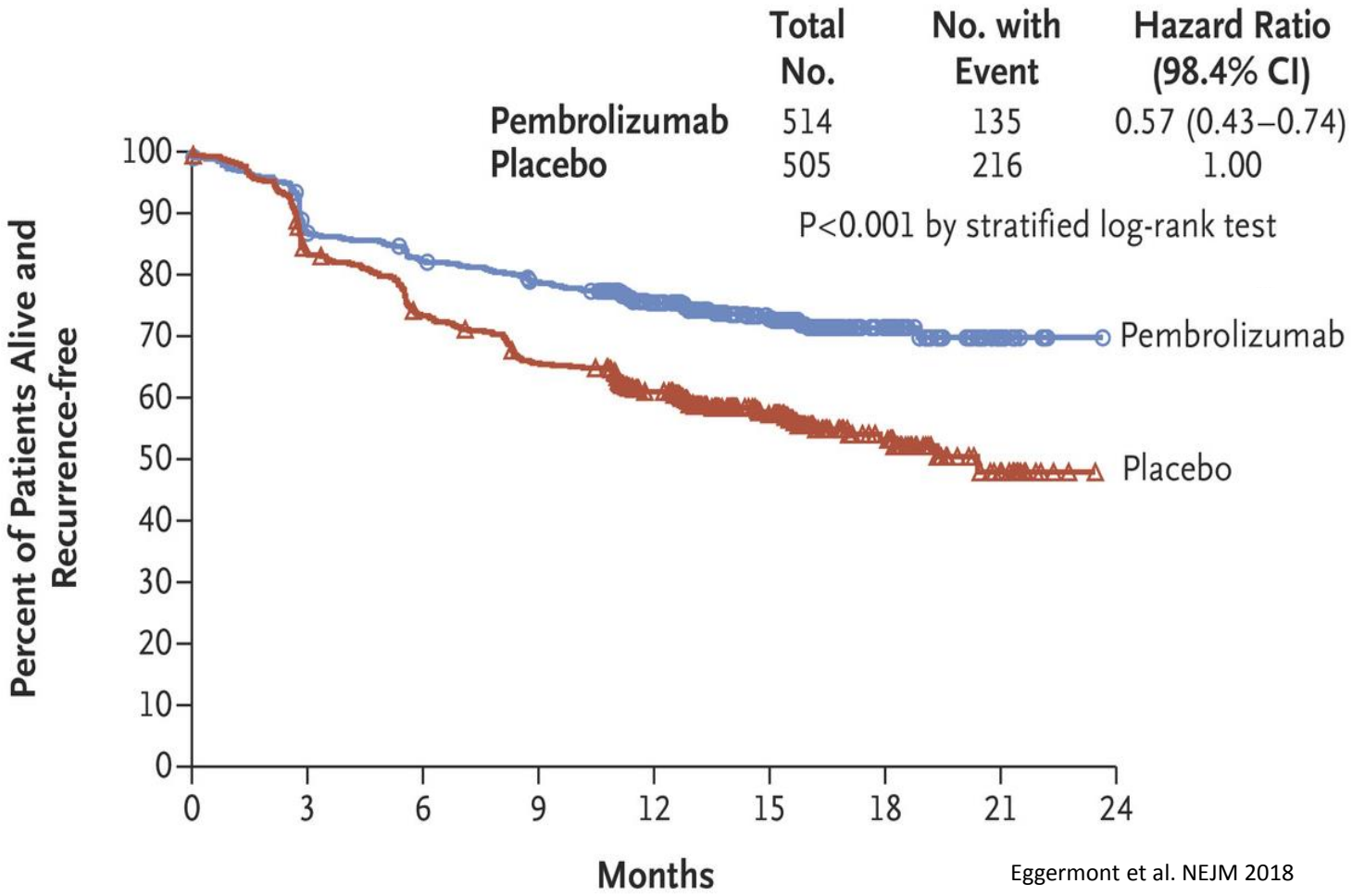
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

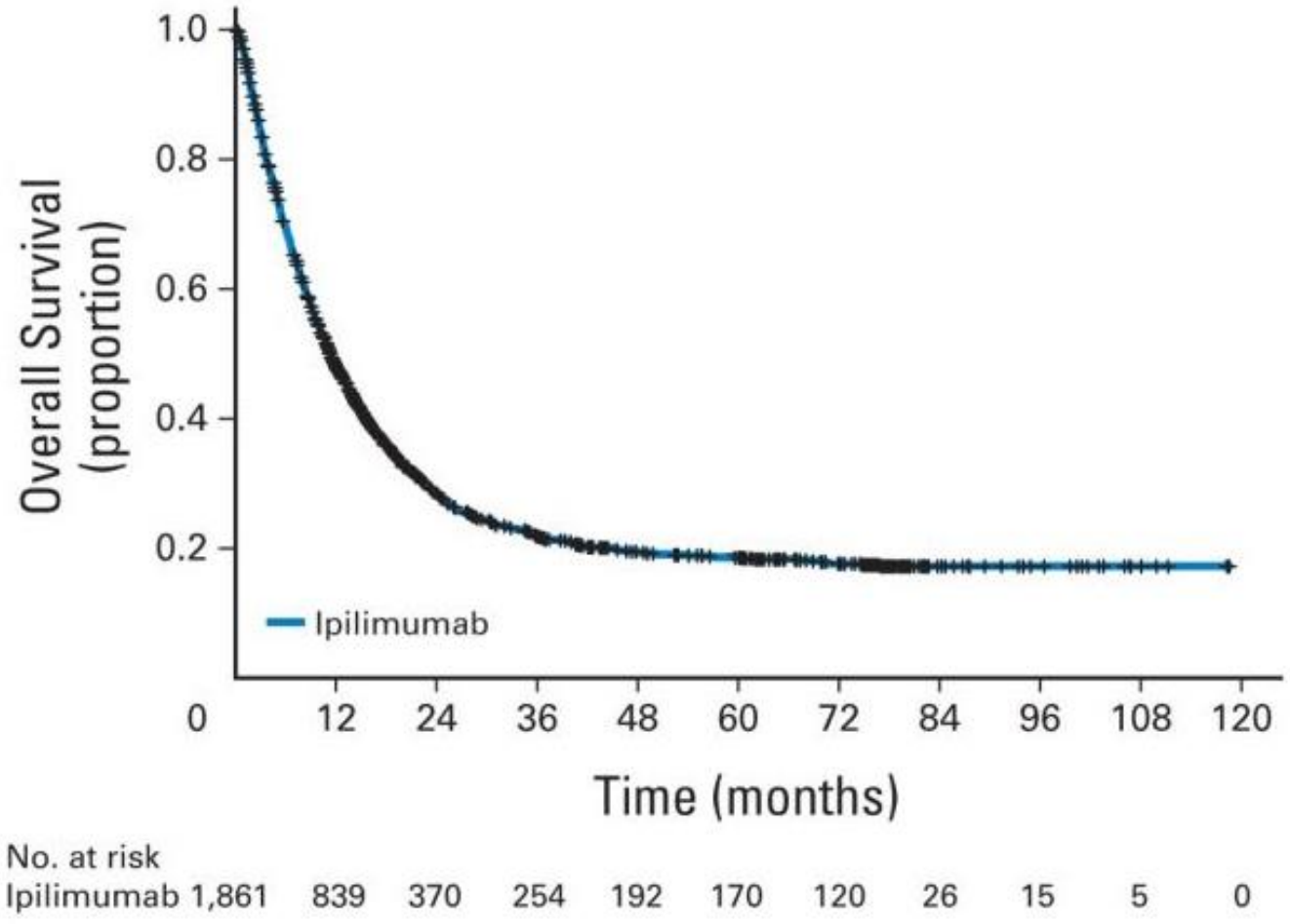
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)



Eggermont et al. NEJM 2018

Ipilimumab in Stage III/IV Melanoma

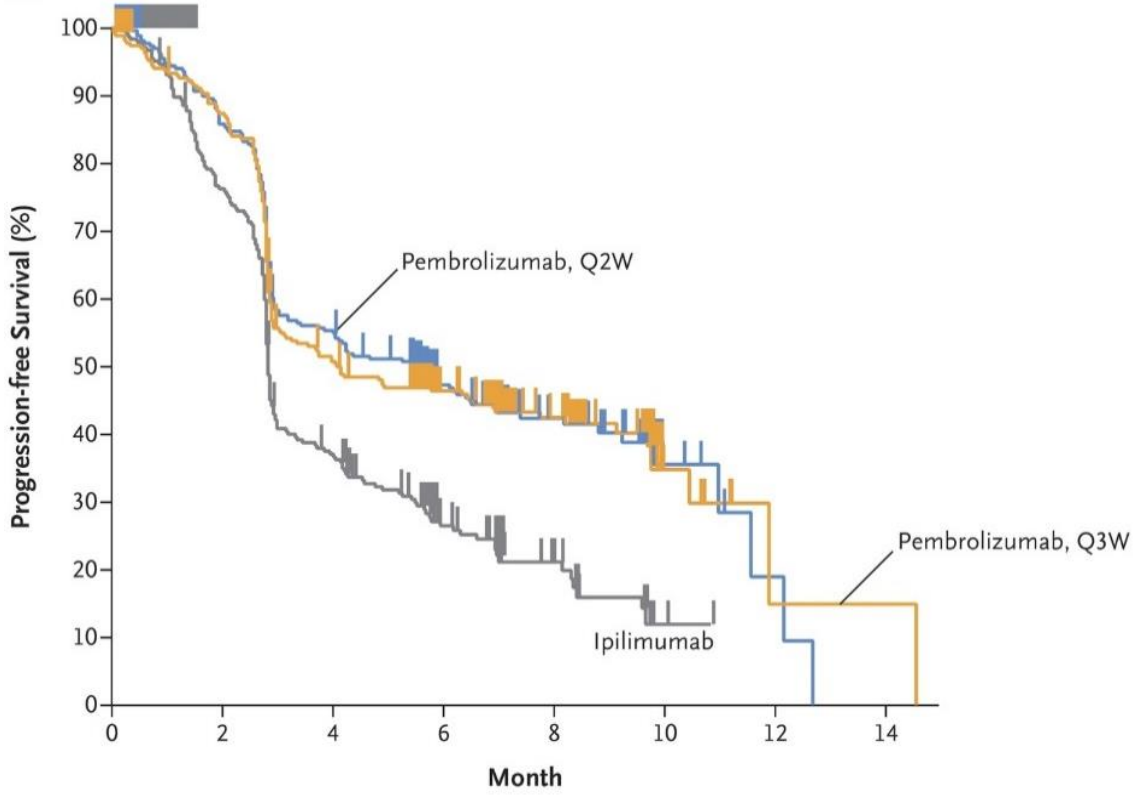
- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)

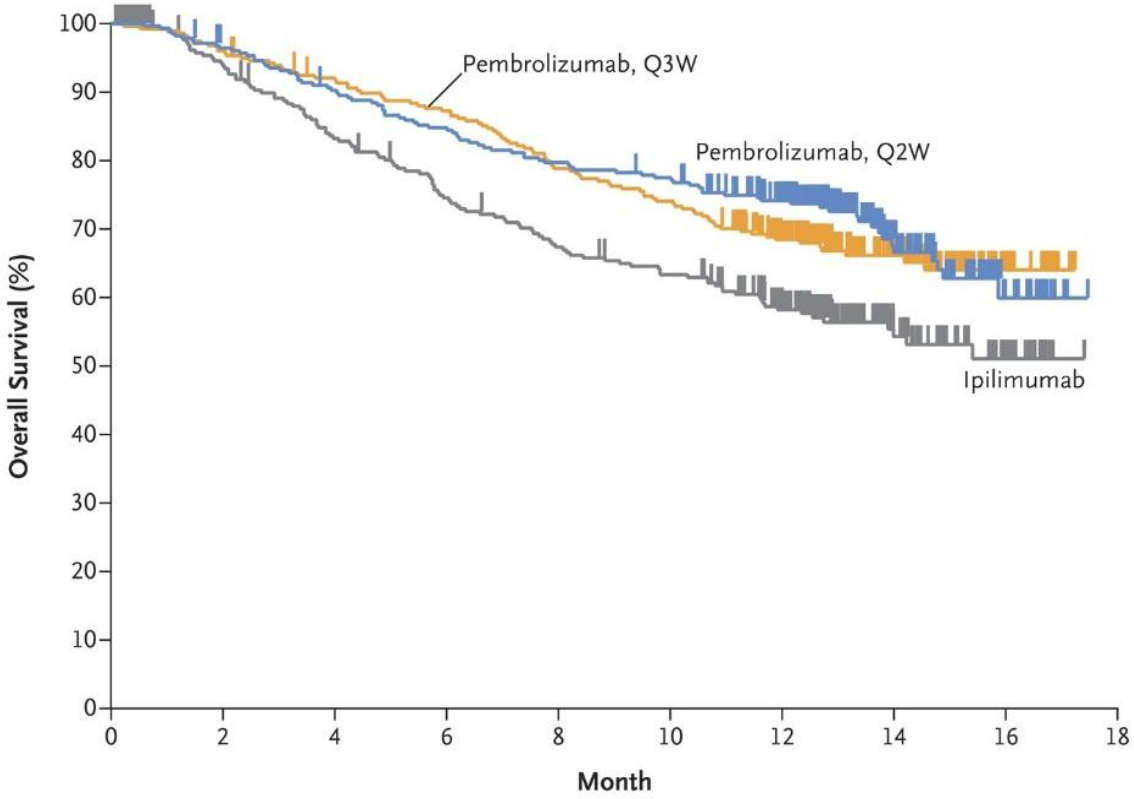


Schadendorf et al. JCO 2015

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial

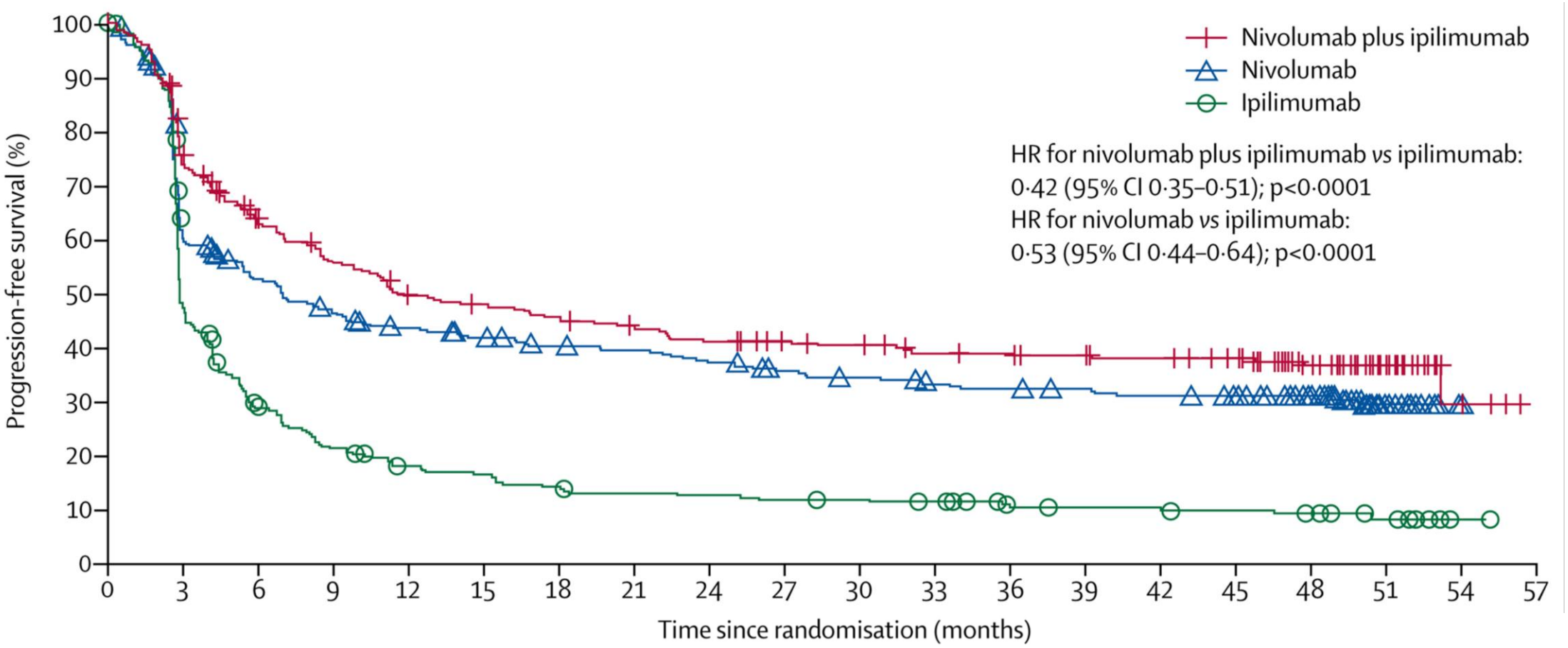




Robert et al. NEJM 2015

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

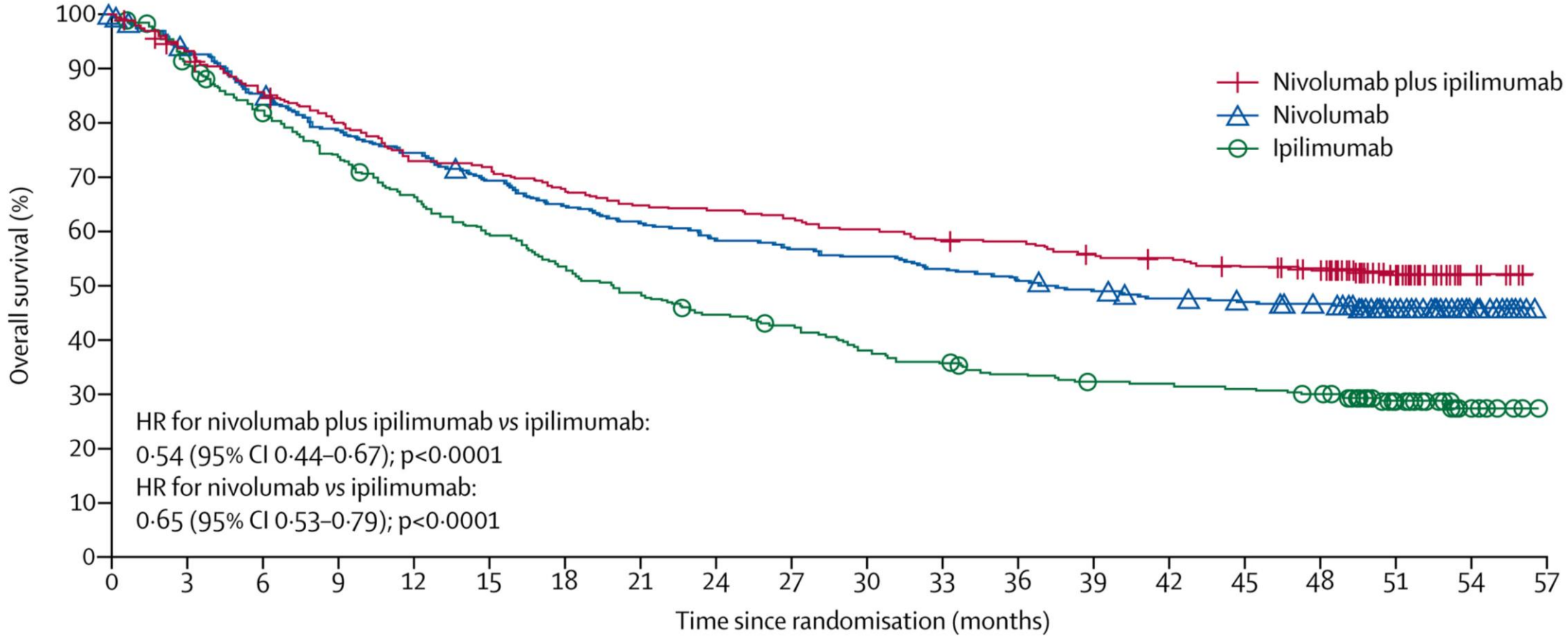
Phase III CheckMate 067 Trial



Hodi et. al. Lancet Oncol 2018

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

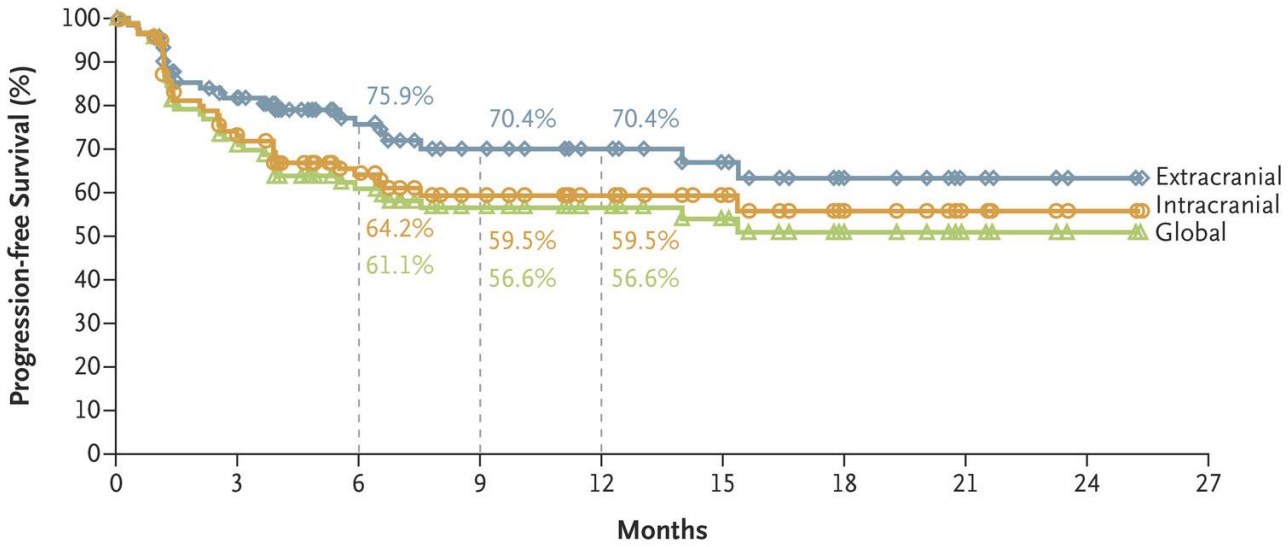
Phase III CheckMate 067 Trial



Hodi et. al. Lancet Oncol 2018

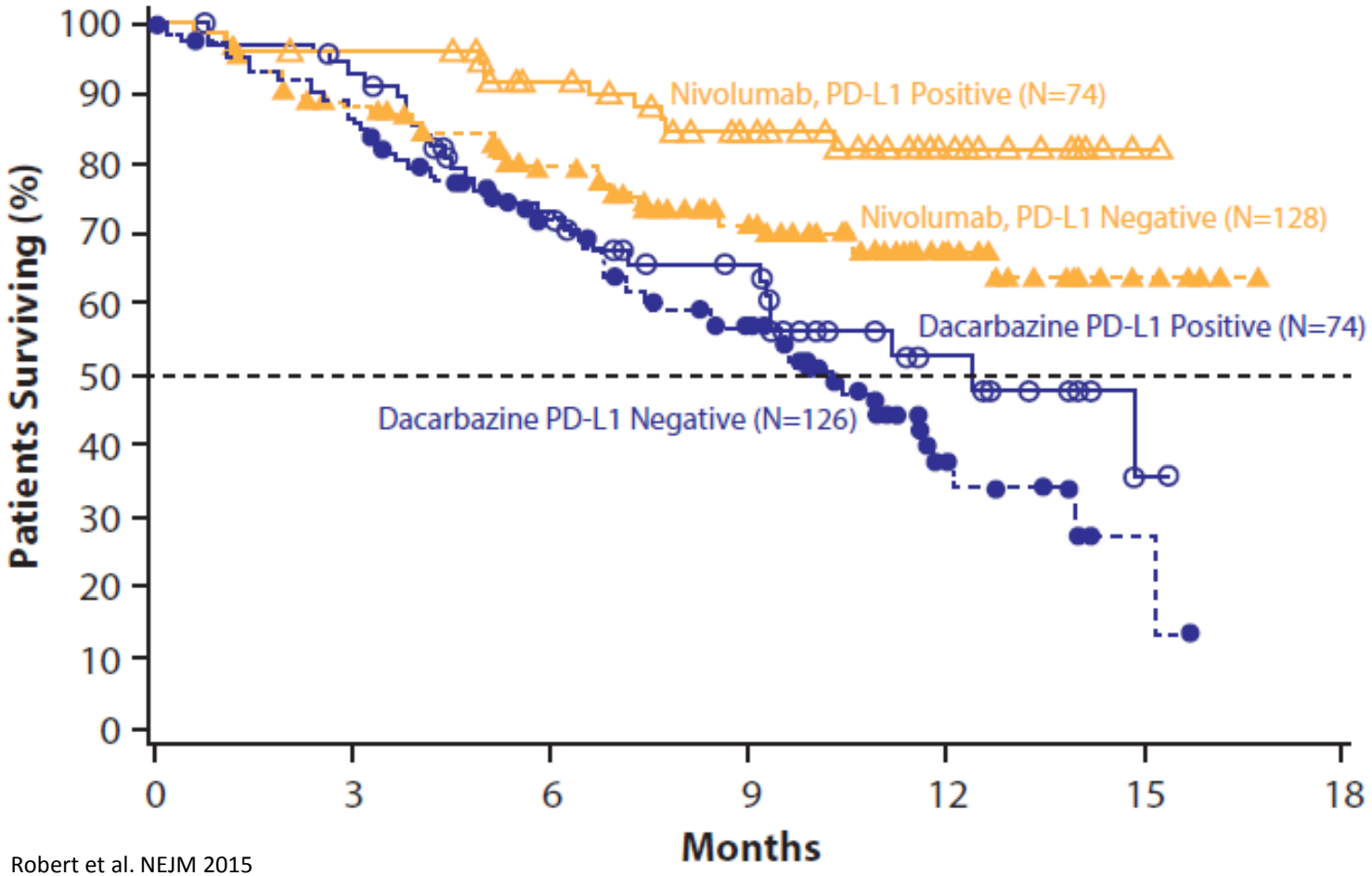
Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)



Tawbi et al. NEJM 2018

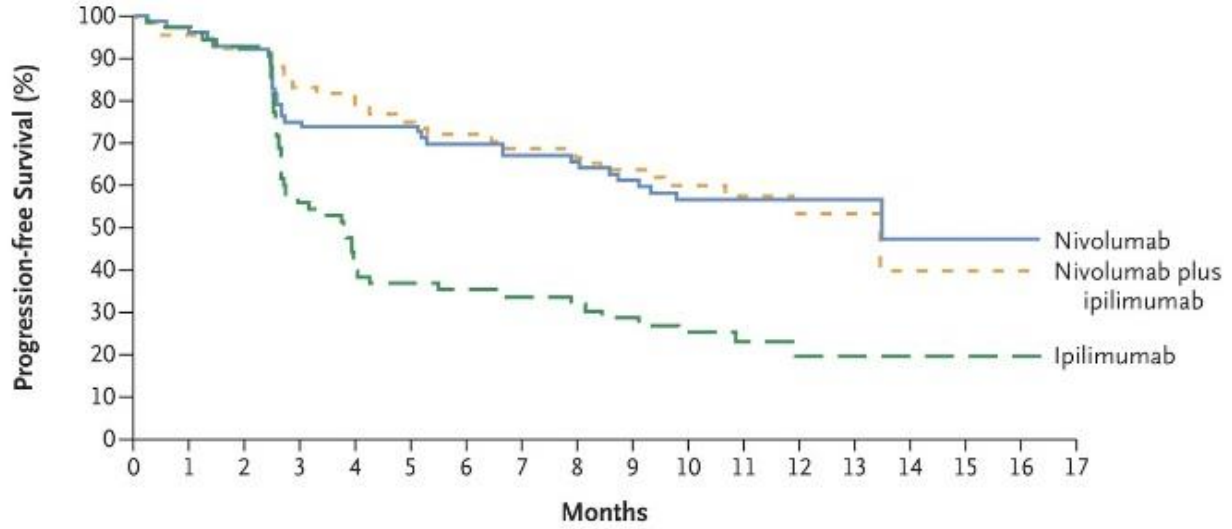
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



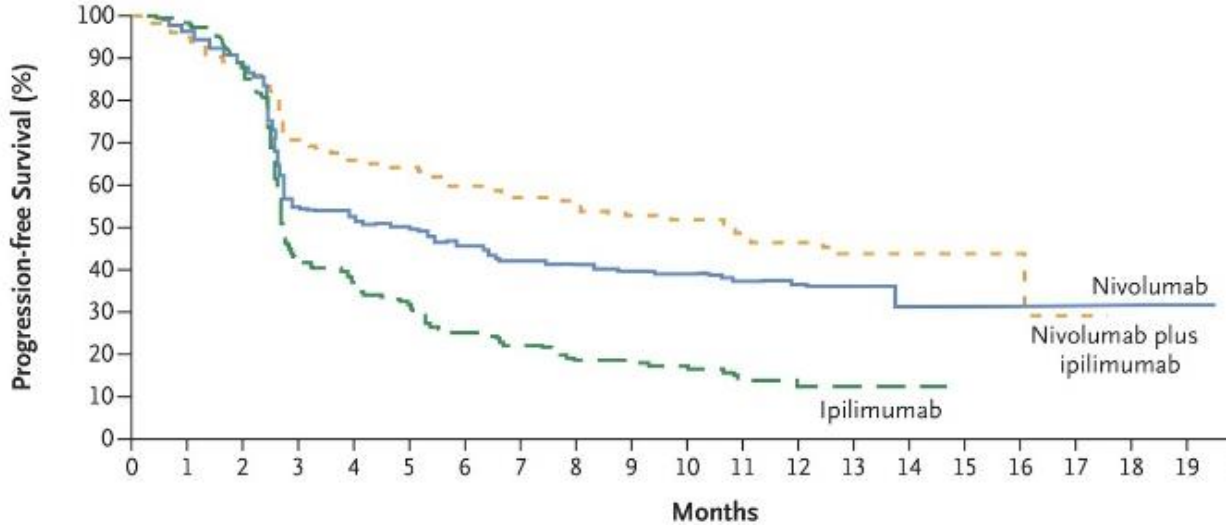
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

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



Tumor PD-L1 Positive Patients

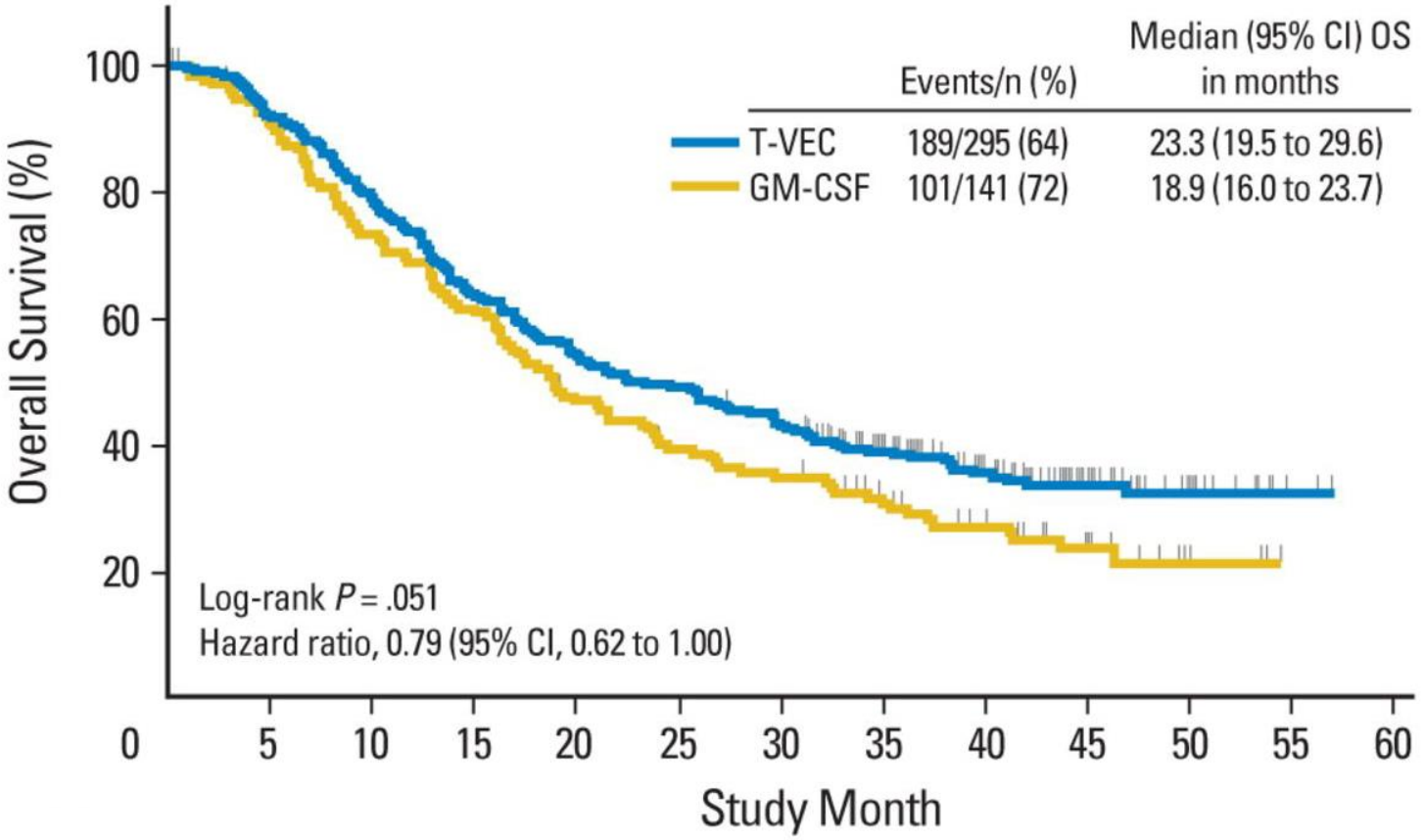


Tumor PD-L1 Negative Patients

Larkin et al. NEJM 2015

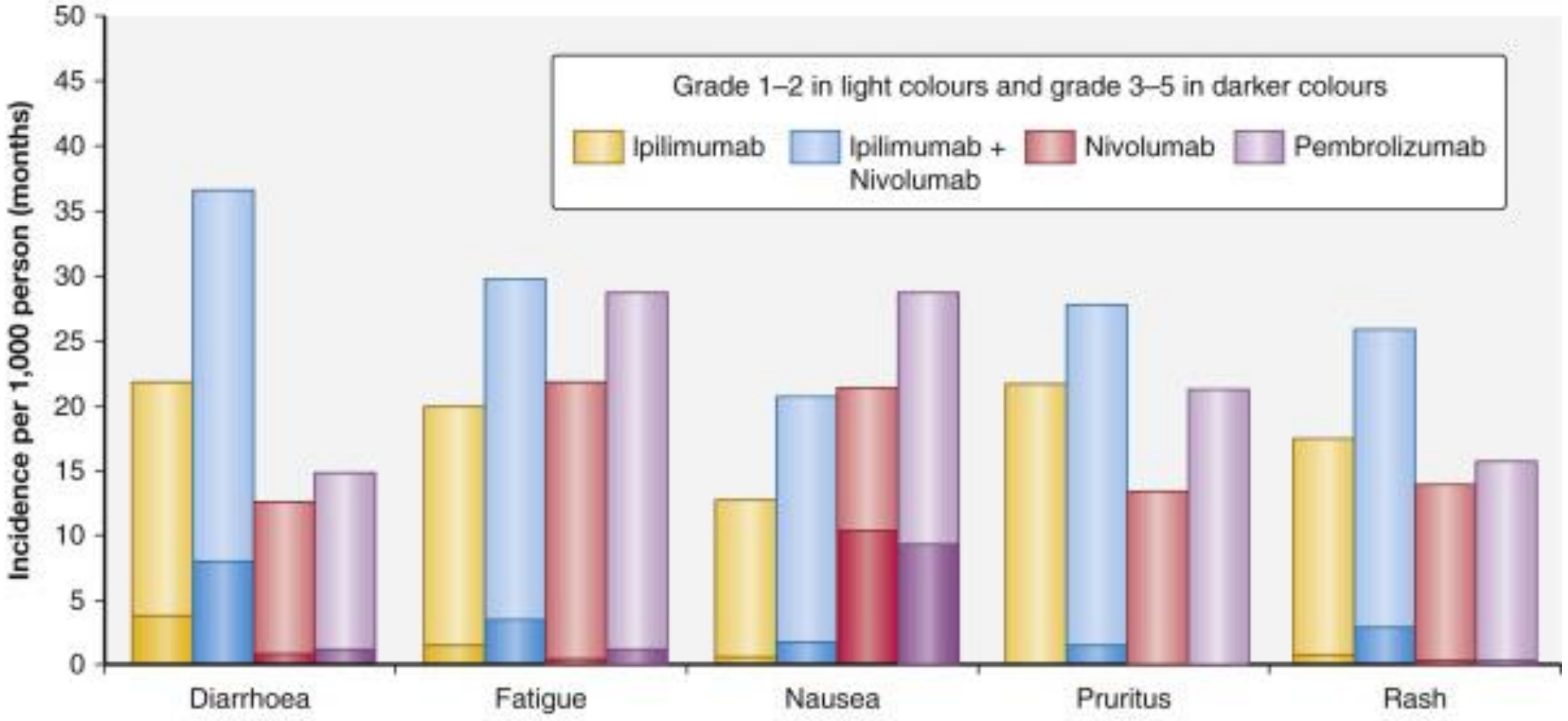
Talimogene laherparepvec (T-VEC) in Stage III/IV Melanoma

- **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



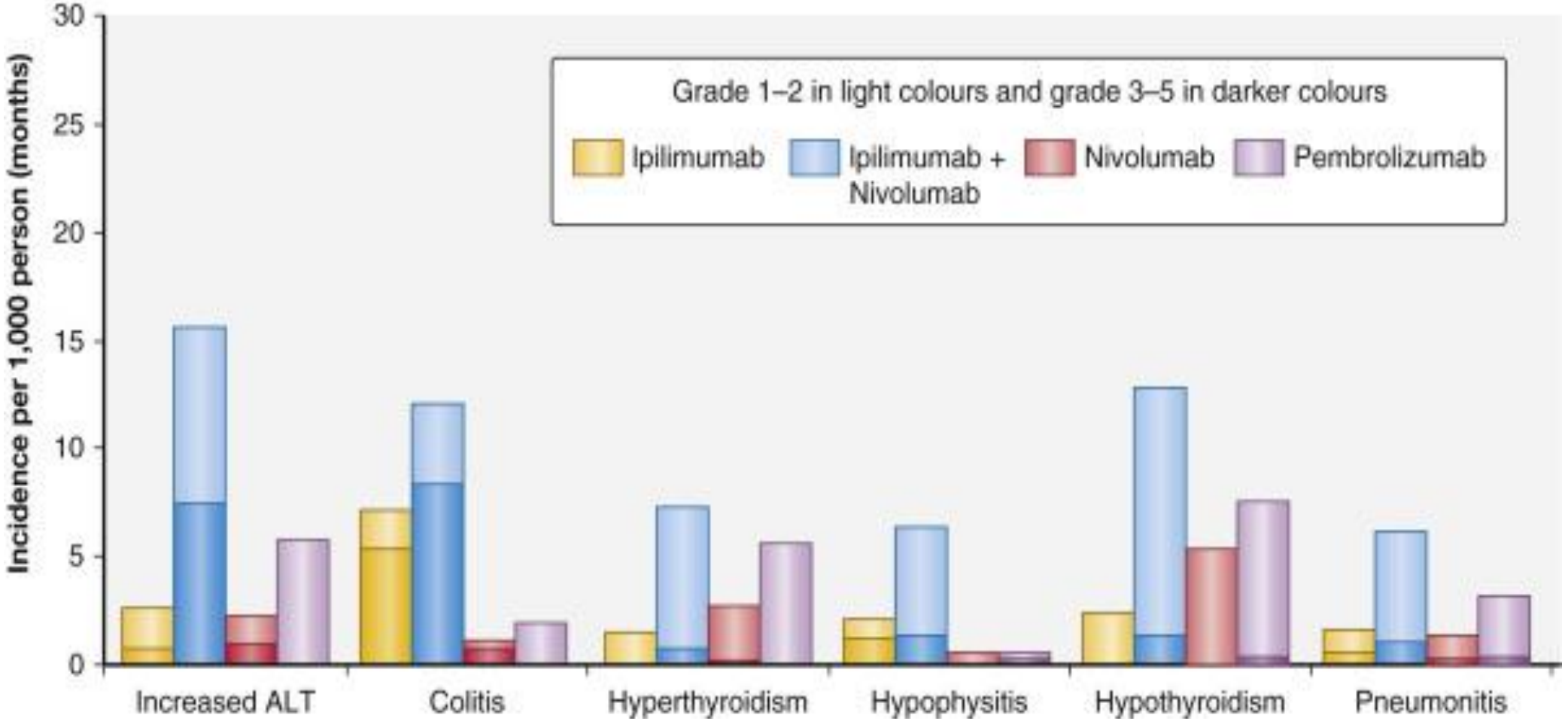
Andtbacka, Kaufman et al. JCO 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



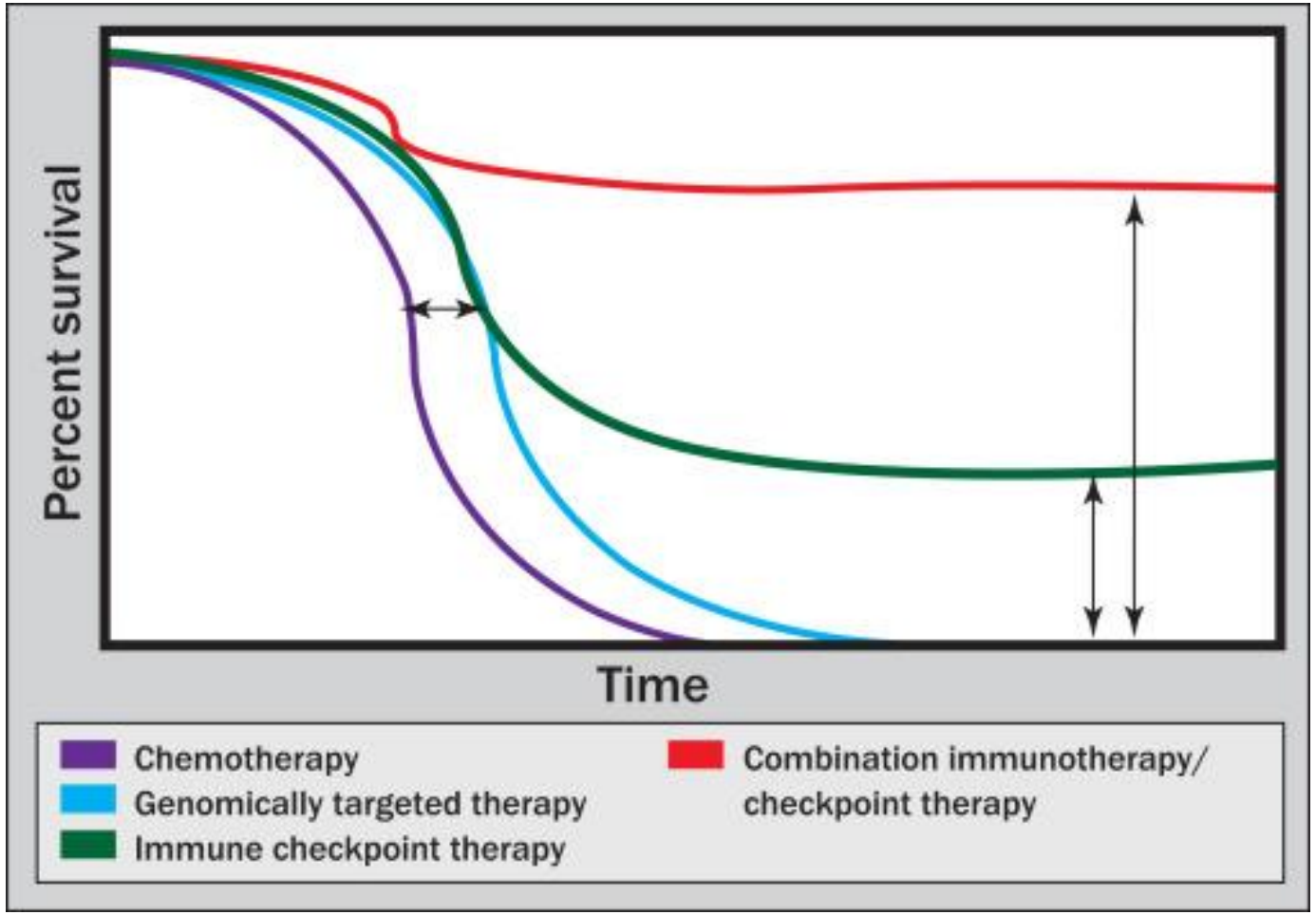
Emens et al. Eur J Cancer 2017

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

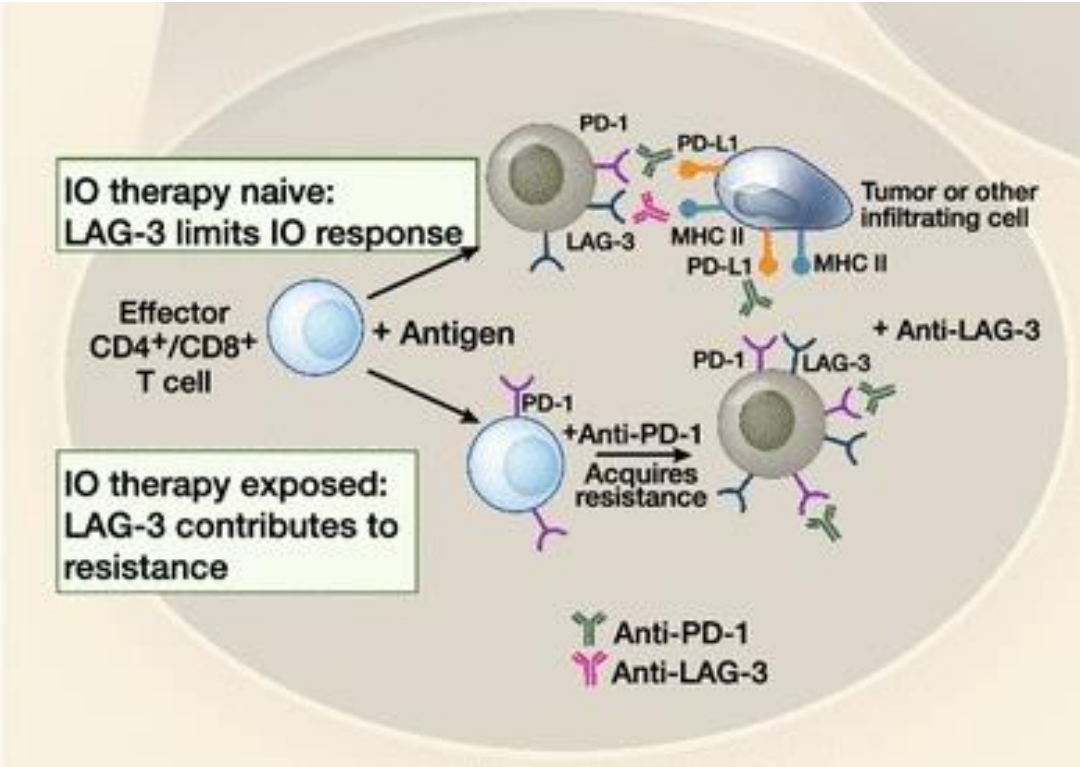
Developmental Immunotherapeutic Strategies for Melanoma

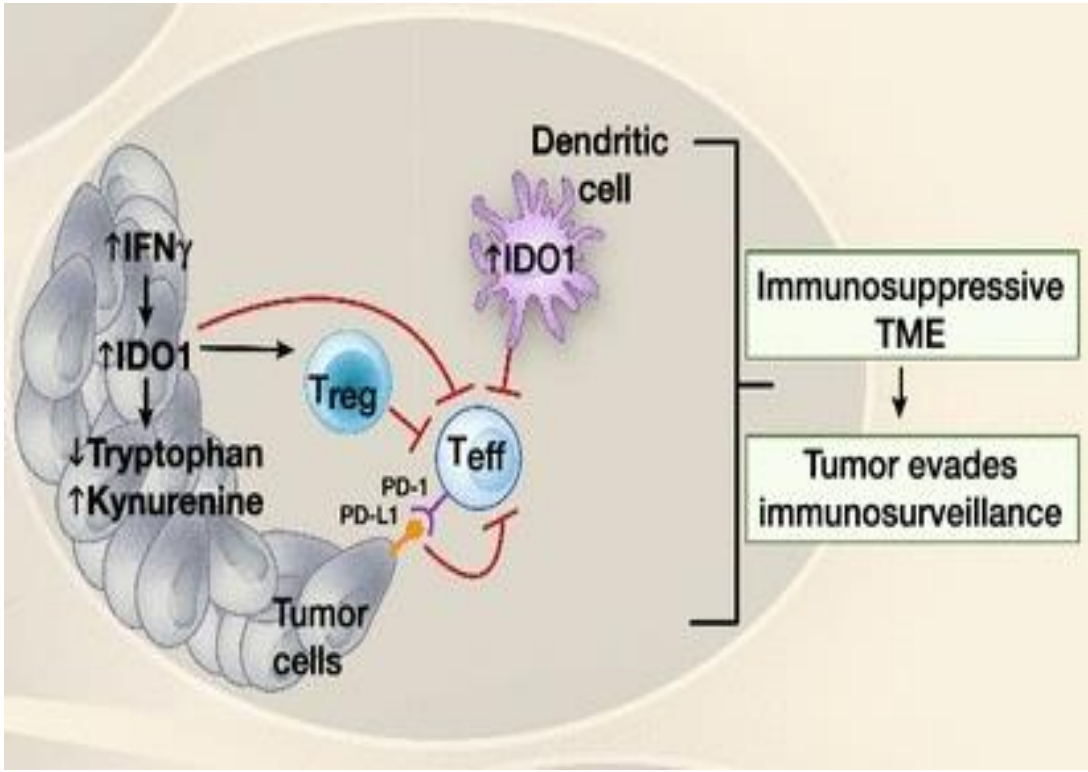


Atkins, Semi. Oncology 2015

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

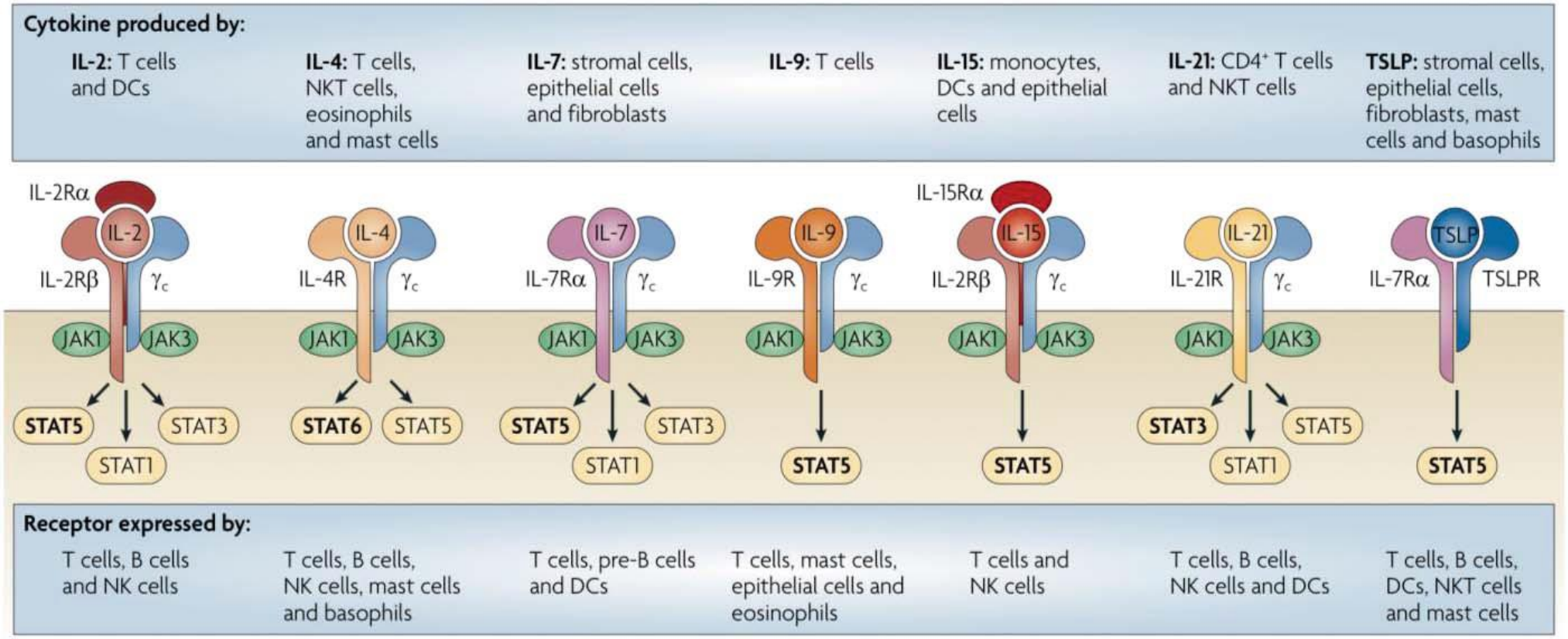
A UWCCC Clinical Trial (IND being prepared) with collaboration from Apeiron, NMS and NCI

- 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

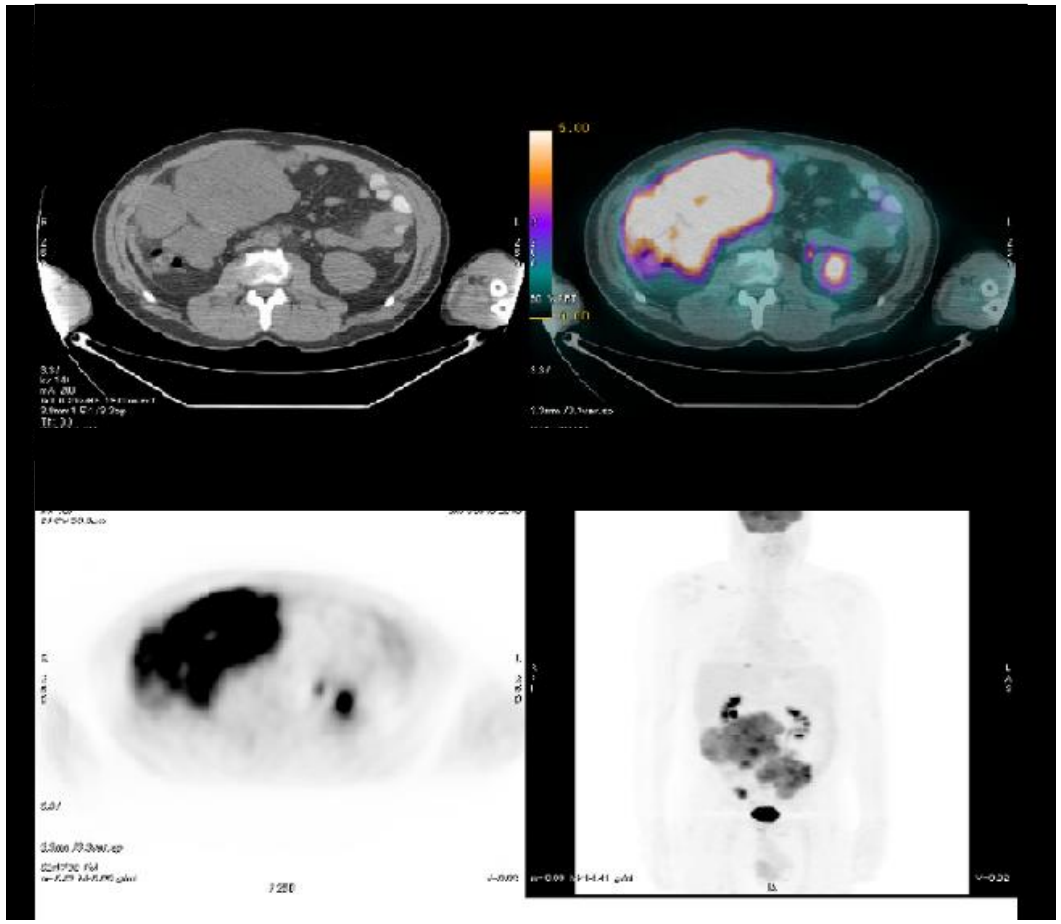
Ryan J. Sullivan[1], Michael B. Atkins[2], John M. Kirkwood[3], Sanjiv S. Agarwala[4], Joseph I. Clark[5], Marc S. Ernstoff[6], Leslie Fecher[7], Thomas F. Gajewski[8], Brian Gastman[9], David H. Lawson[10], Jose Lutzky[11], David F. McDermott[12], Kim A. Margolin[13], Janice M. Mehnert[14], Anna C. 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

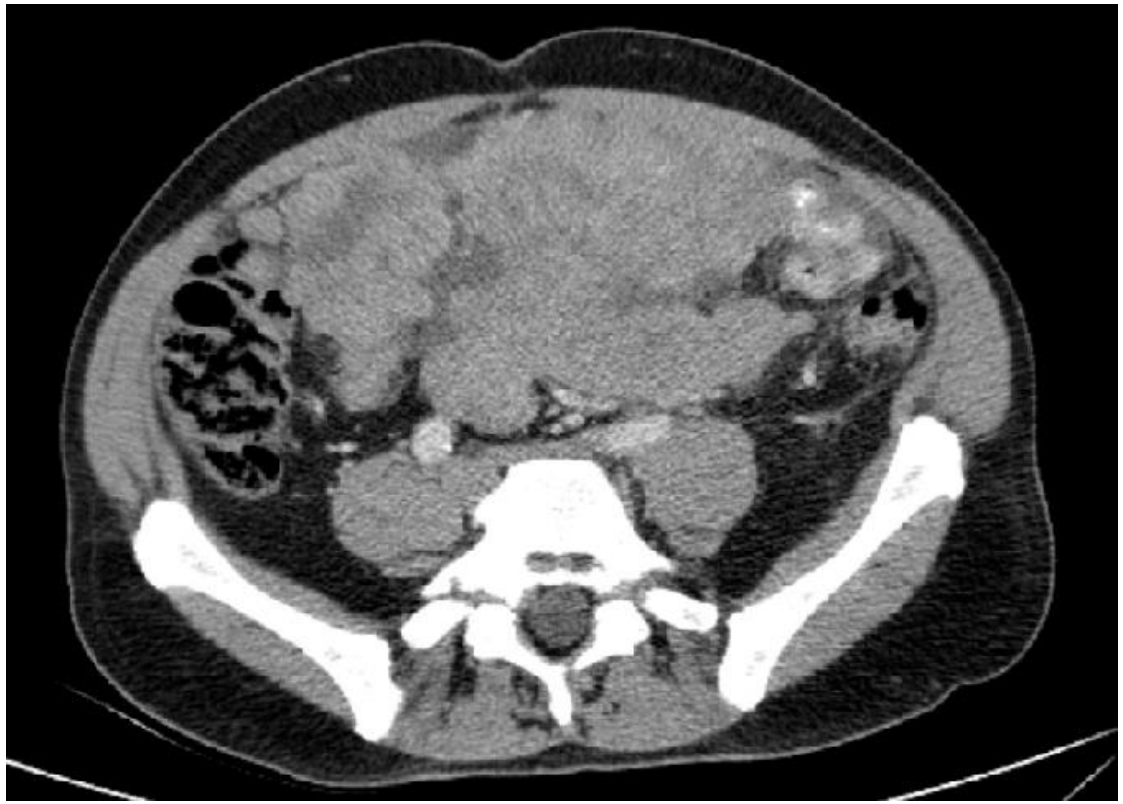
- 56 yo male developed abdominal pain in summer of 2013. Previous history of a 5.5 mm, ulcerated melanoma on the thigh treated with wide excision and negative SLN biopsy in 2007. Symptoms were progressive and subsequent imaging demonstrated findings concerning for metastatic disease with lung, intraabdominal and retroperitoneal disease. Biopsy of a lung lesion was pathologically consistent with metastatic melanoma. Tumor was wild type for BRAF.

Case Study 1: Initial imaging

PET/CT Oct 2013



CT Nov 2013



Case Study 1

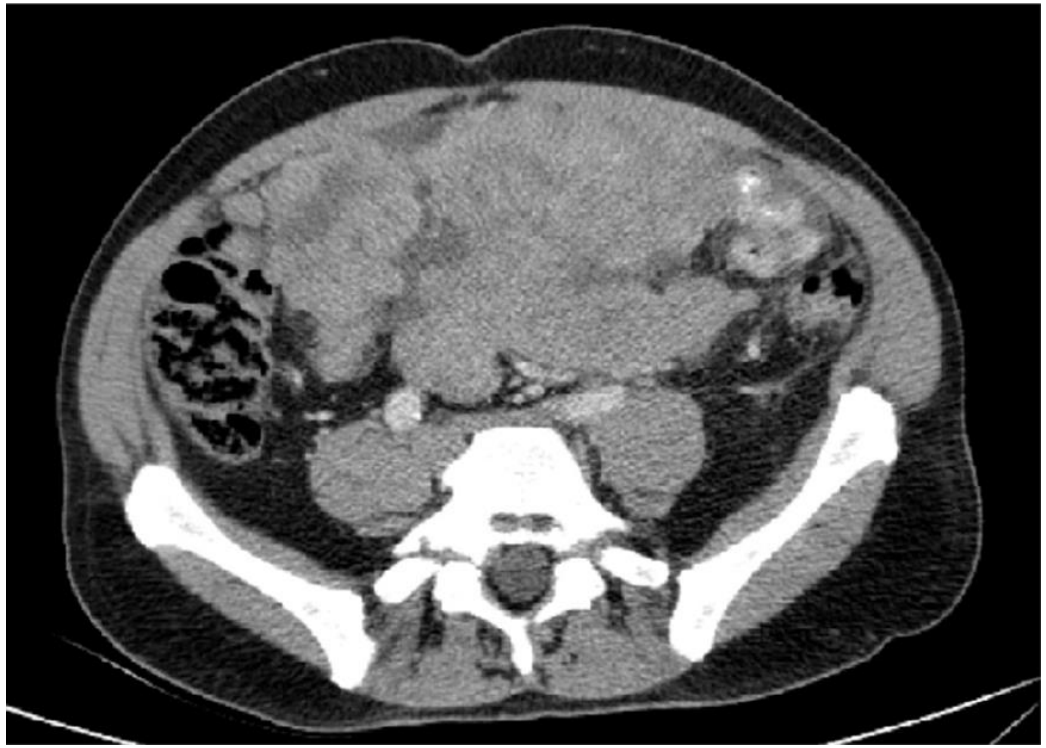
- He was started on a clinical trial of ipilimumab/nivolumab in Nov. 2013. He received 4 infusions and presented to ED with progressive N/V for one week. Found to have elevated LFTs (>15x ULN) and ARF. Started on high dose steroids with rapid improvement in symptoms and lab values. Follow up scans in Jan 2014 demonstrated a 90% reduction in tumor burden.

- Steroids tapered but had new and persistent elevation of blood glucose levels and was subsequently diagnosed with insulin-dependent diabetes.

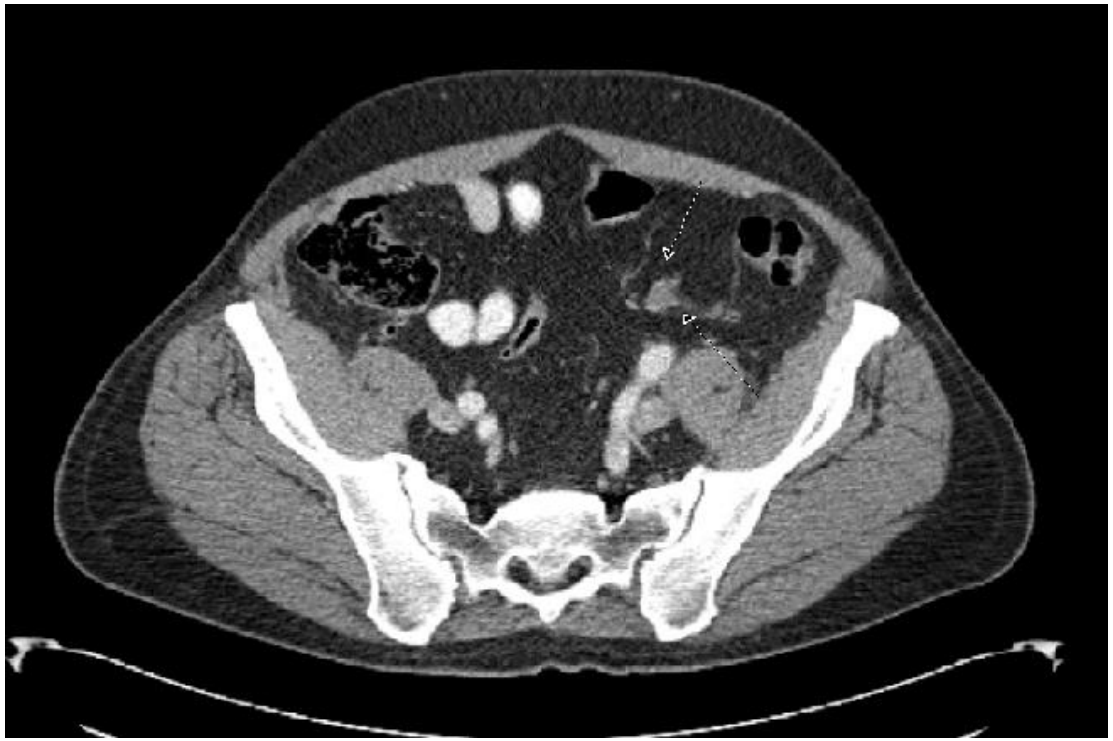
- Received no further treatment since Dec 2013.

Case Study 1: Follow up imaging

CT Nov 2013



CT Nov 2017



Case study 2

- 76 yo recently retired male in good health who had witnessed seizure in 3/17. MRI of the brain demonstrated seven CNS lesions consistent with metastatic disease. CT of body demonstrated two lung nodules. Underwent craniotomy with resection of the two larger masses that were pathologically consistent with metastatic melanoma.

Case study 2

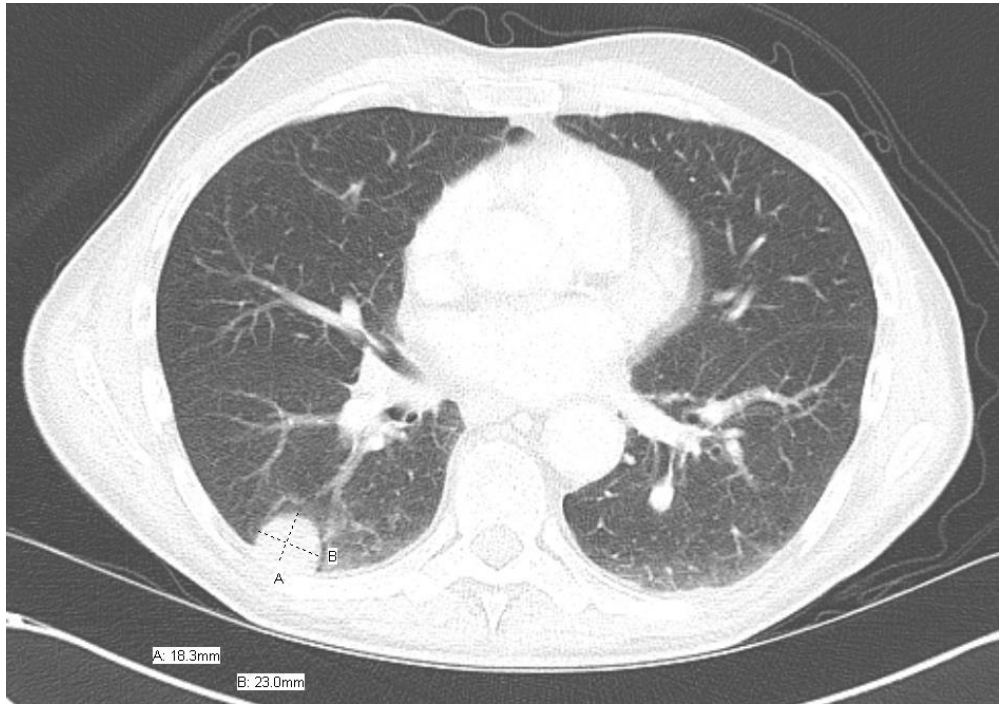
- Question 1: How would recommend treating the additional CNS disease?

- Question 2: What would you recommend for systemic therapy? Do you wait for BRAF results before starting therapy?

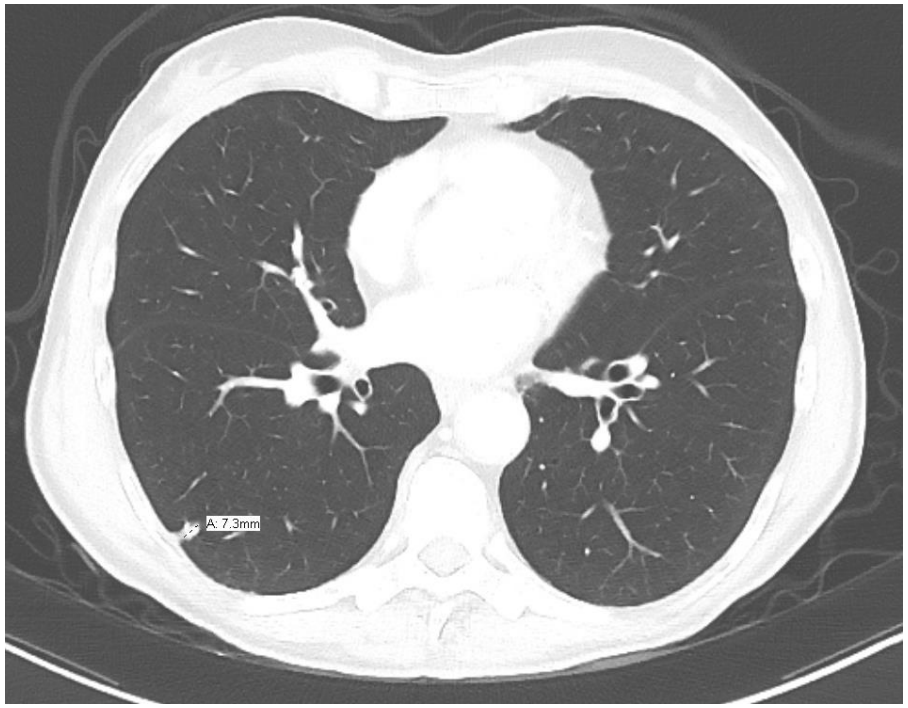
Case study 2

- He was weaned off steroids and started on single-agent pembrolizumab in 4/17. He has had an excellent radiographic response and has tolerated well with vitiligo as the main toxicity.

April 2017



Oct 2018



Case study 2

- Question 3: How long do you treat with PD1 antibody in this patient?