sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

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September 6, 2018

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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Disclosures

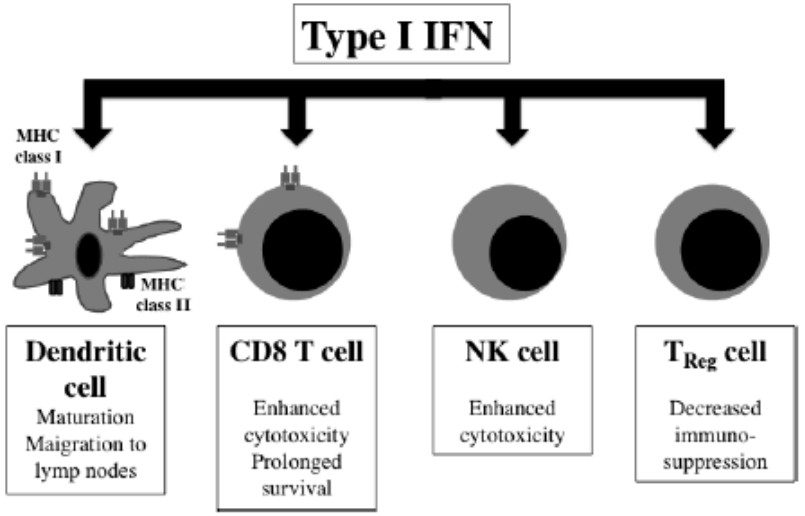
- Research Collaborations:
  - Bristol-Myers Squibb
  - Aperion Biologics
- Conflict of Interest: None
- I will be discussing non-FDA approved indications during my presentation.

Presentation Objectives

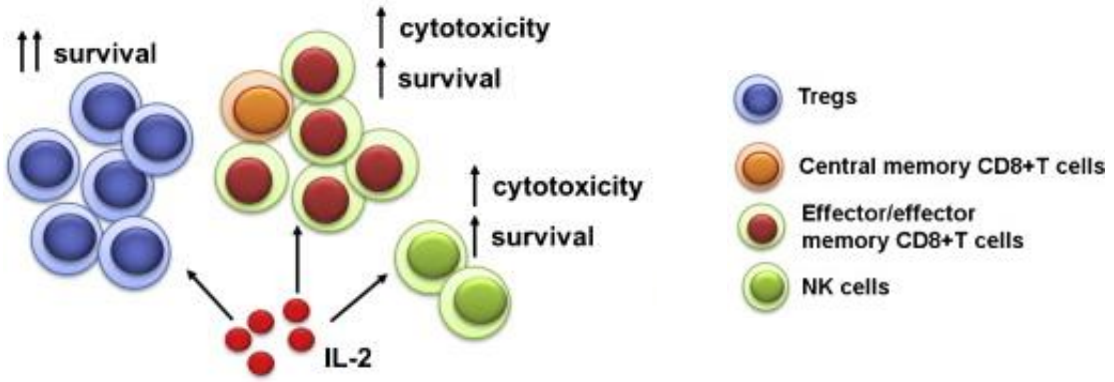
- Describe the rationale for common approaches to melanoma immunotherapy
- Identify the appropriate clinical management of common side effects of immunotherapy agents
- Be able to implement cancer immunotherapy for melanoma patients

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.



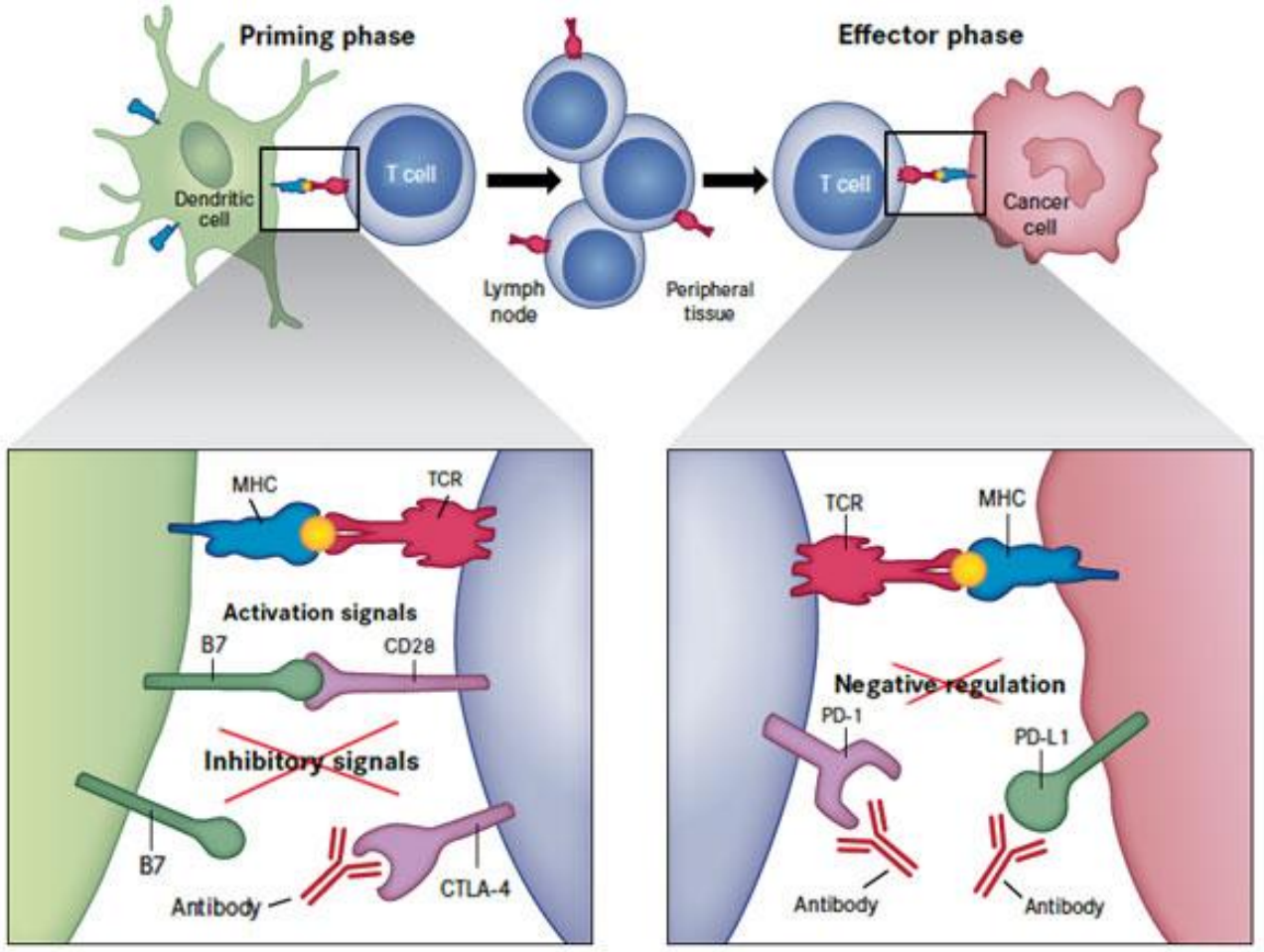
Numasaki et al. Immunotherapy 2016



Sim, Radvanyi Cytogfr 2014

FDA-approved Immunotherapies in Melanoma

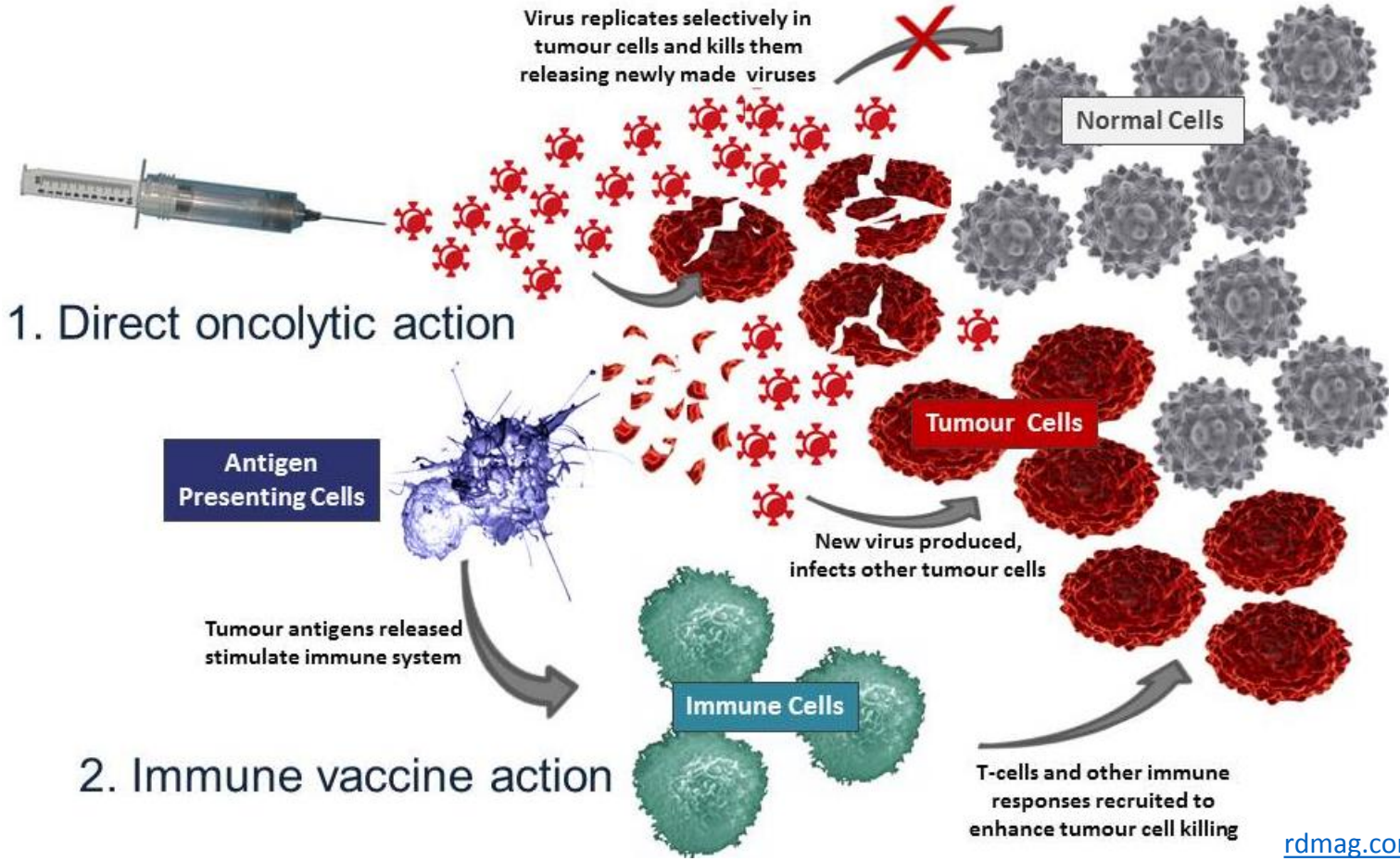
- Checkpoint inhibitors
  - Ipilimumab, adjuvant and nonresectable/Stage IV, I.V.- different dosing for adjuvant and nonresectable/Stage IV
  - Pembrolizumab, nonresectable/Stage IV, I.V.
  - Nivolumab, adjuvant and non resectable/Stage IV, I.V.
  - Ipilimumab in combination with nivolumab, Stage IV



Ribas NEJM 2012
Gordon et al Nature 2017

FDA-approved Immunotherapies in Melanoma

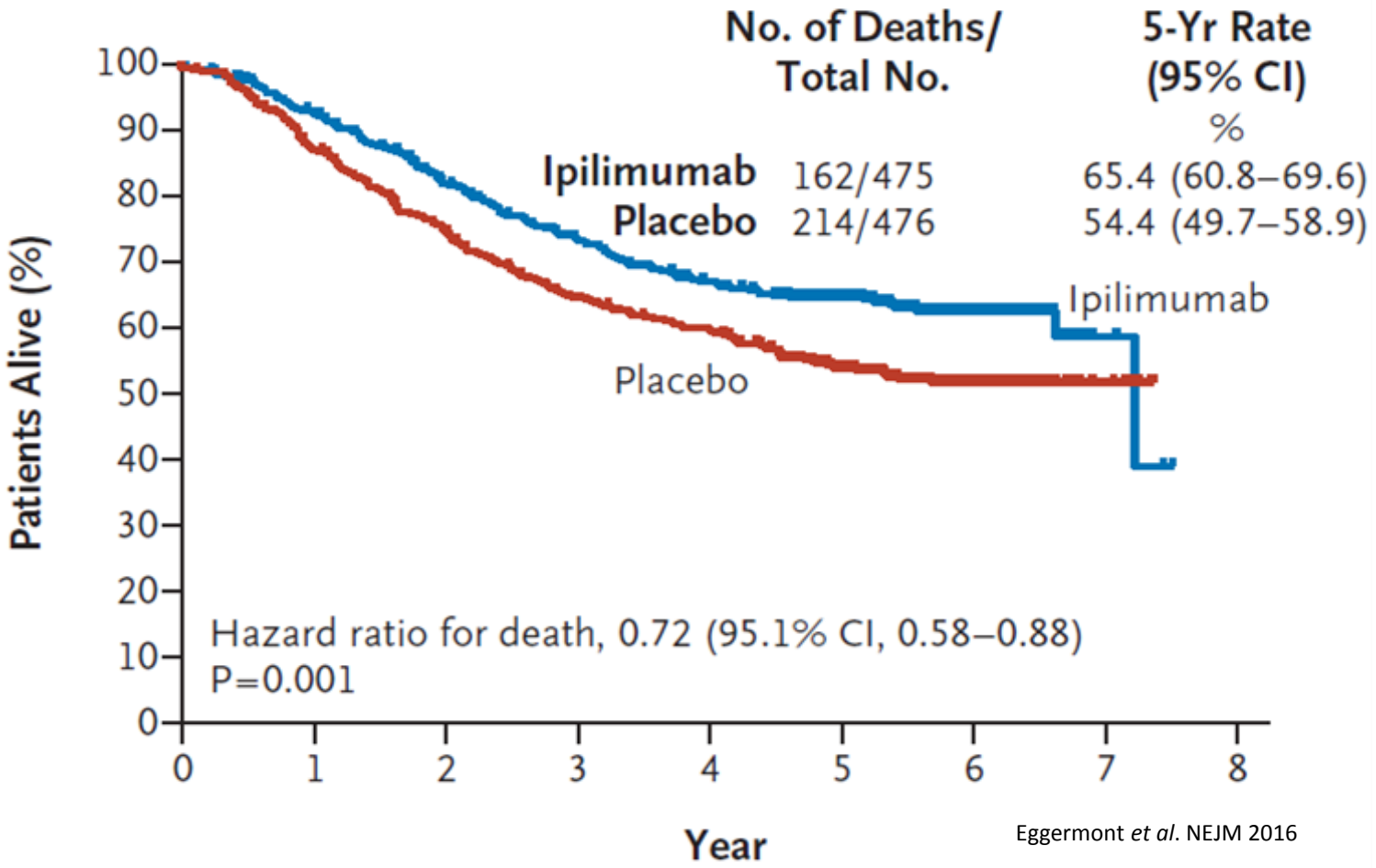
- Oncolytic Viruses
  - Talimogene Laharparepvec; TVEC - non resectable, intratumoral



rdmag.com

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



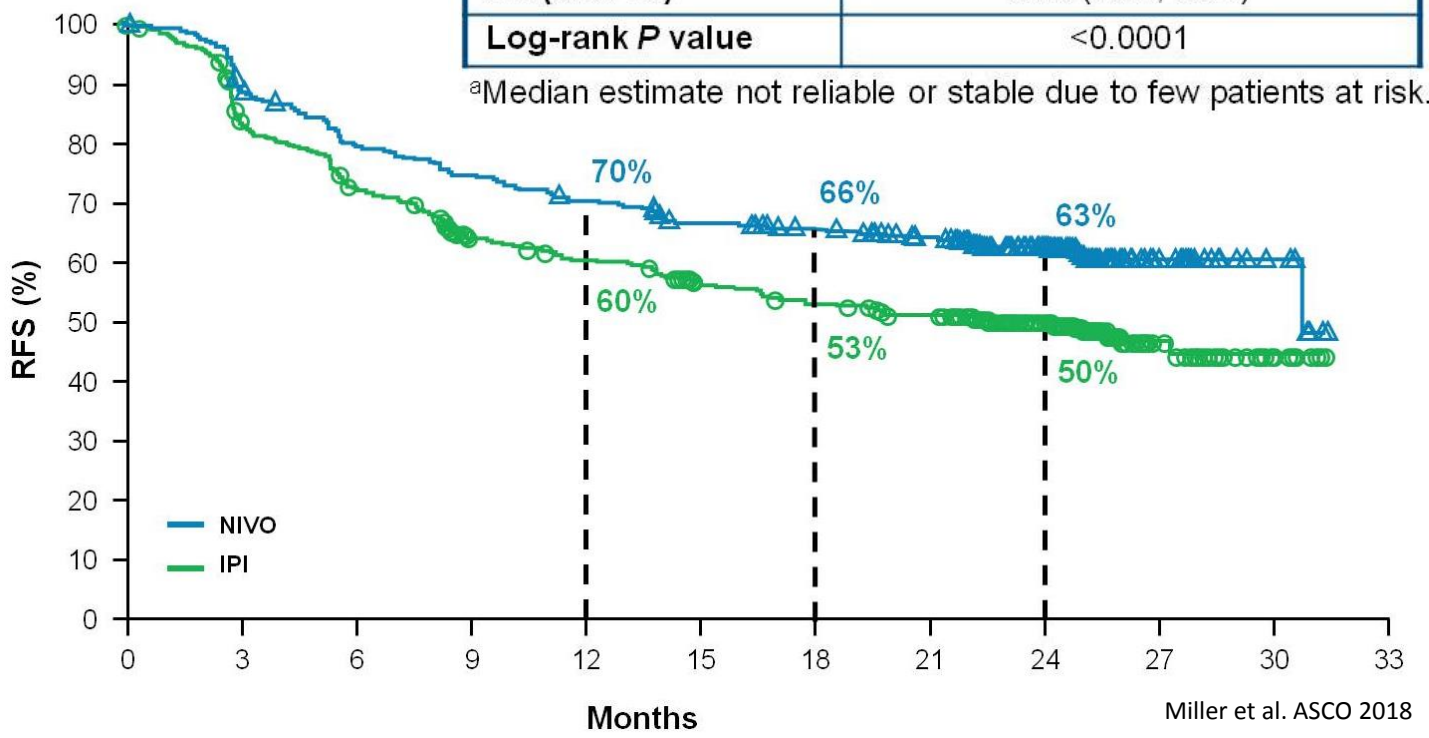
Eggermont *et al*. NEJM 2016

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	

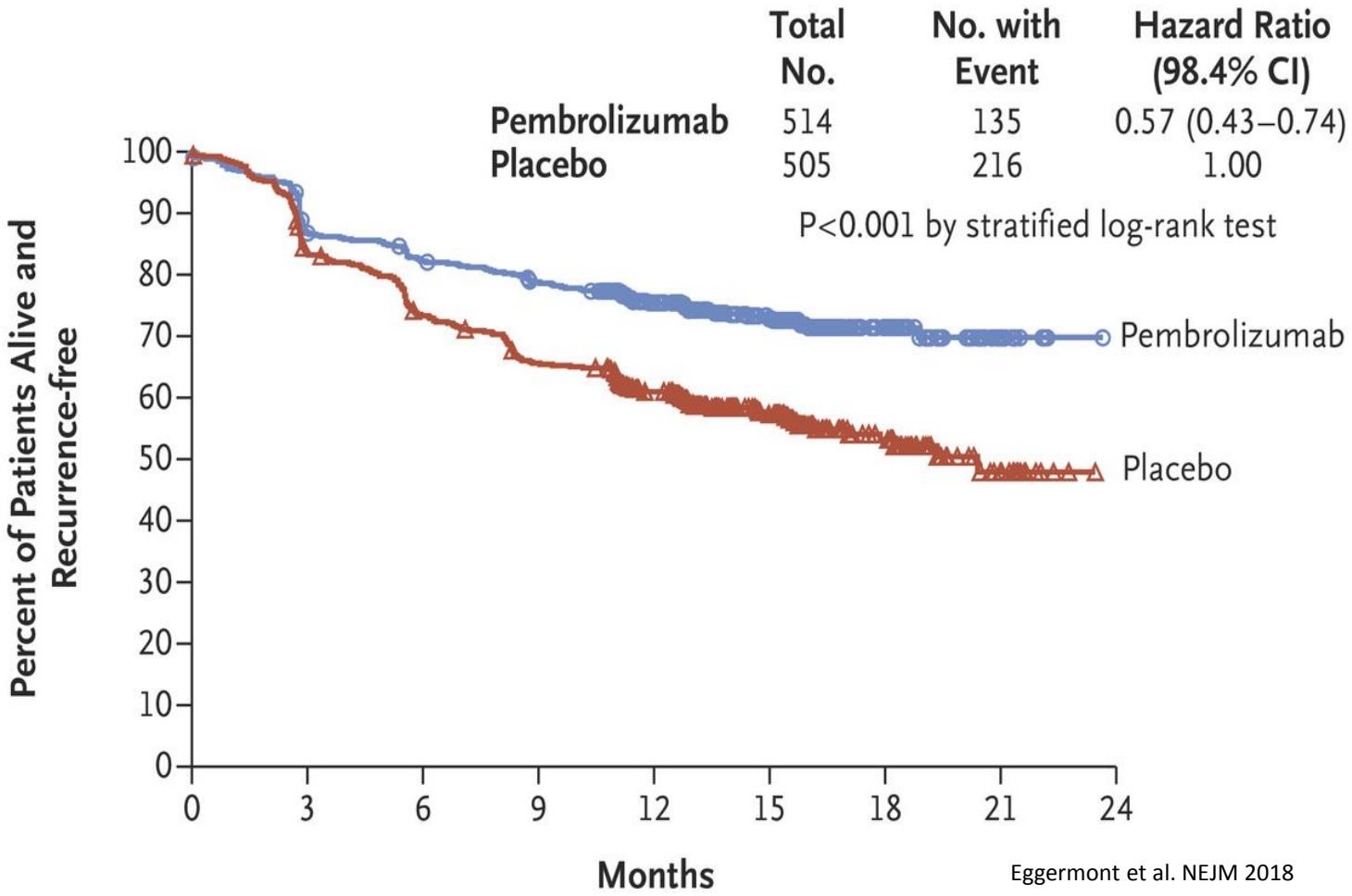
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

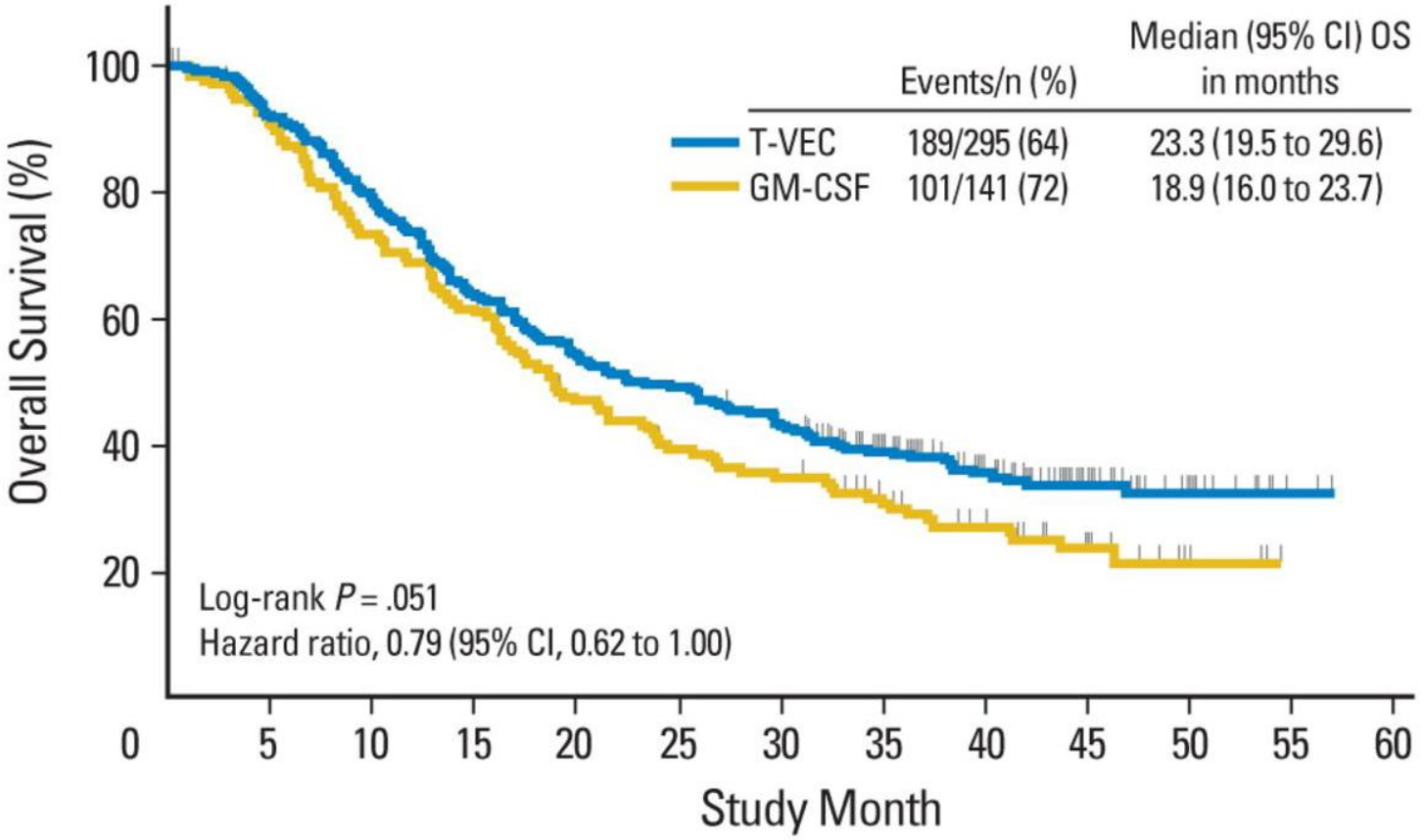
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)



Eggermont et al. NEJM 2018

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

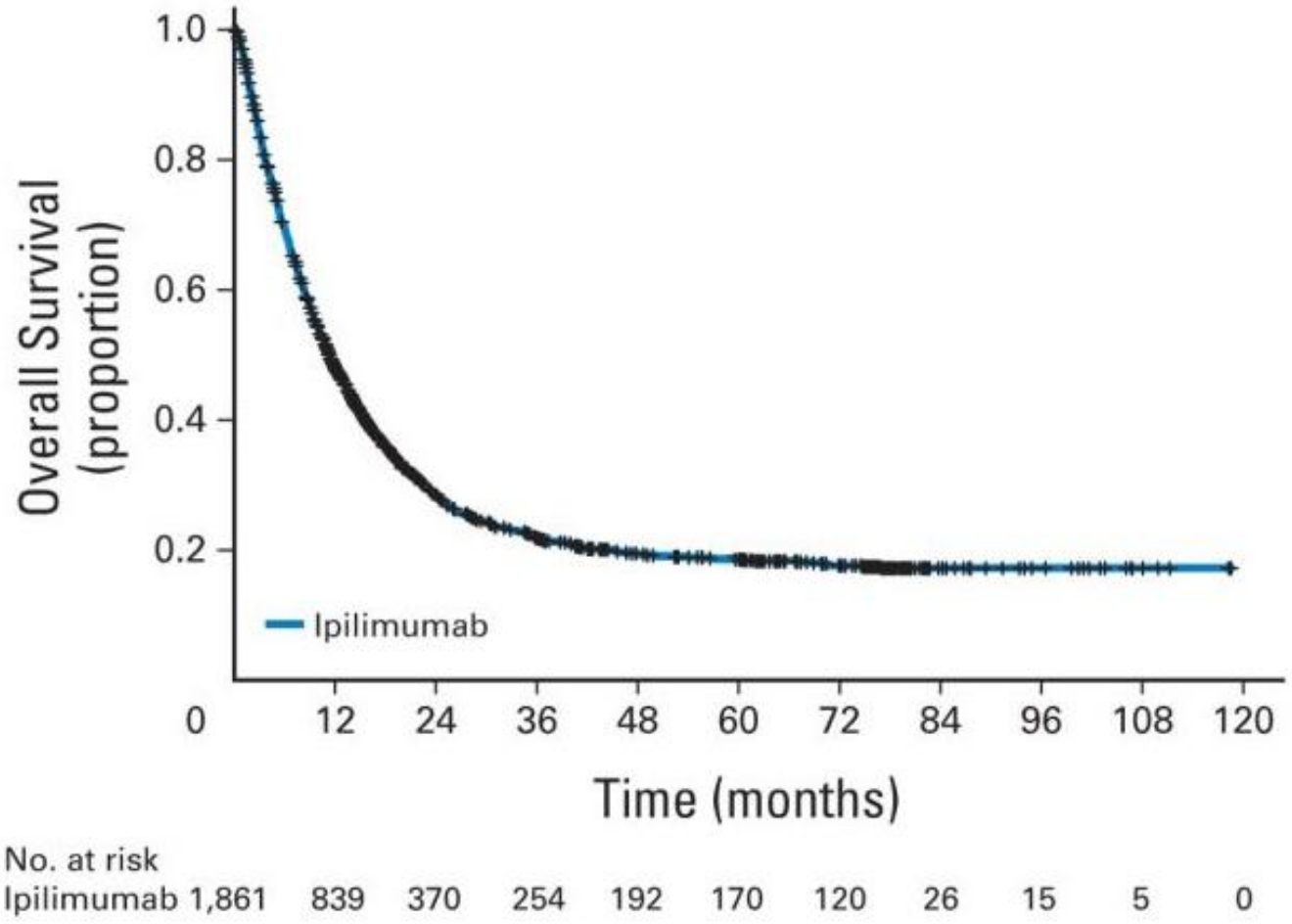
- Phase III Trial
  - NCT00769704
  - **Intralesional** T-VEC vs subcutaneous GM-CSF
  - T-VEC 10^6 pfu/mL, 10^8 pfu/mL 3 weeks after initial dose, then Q2W



Andtbacka, Kaufman et al. JCO 2015

Ipilimumab in Stage III/IV Melanoma

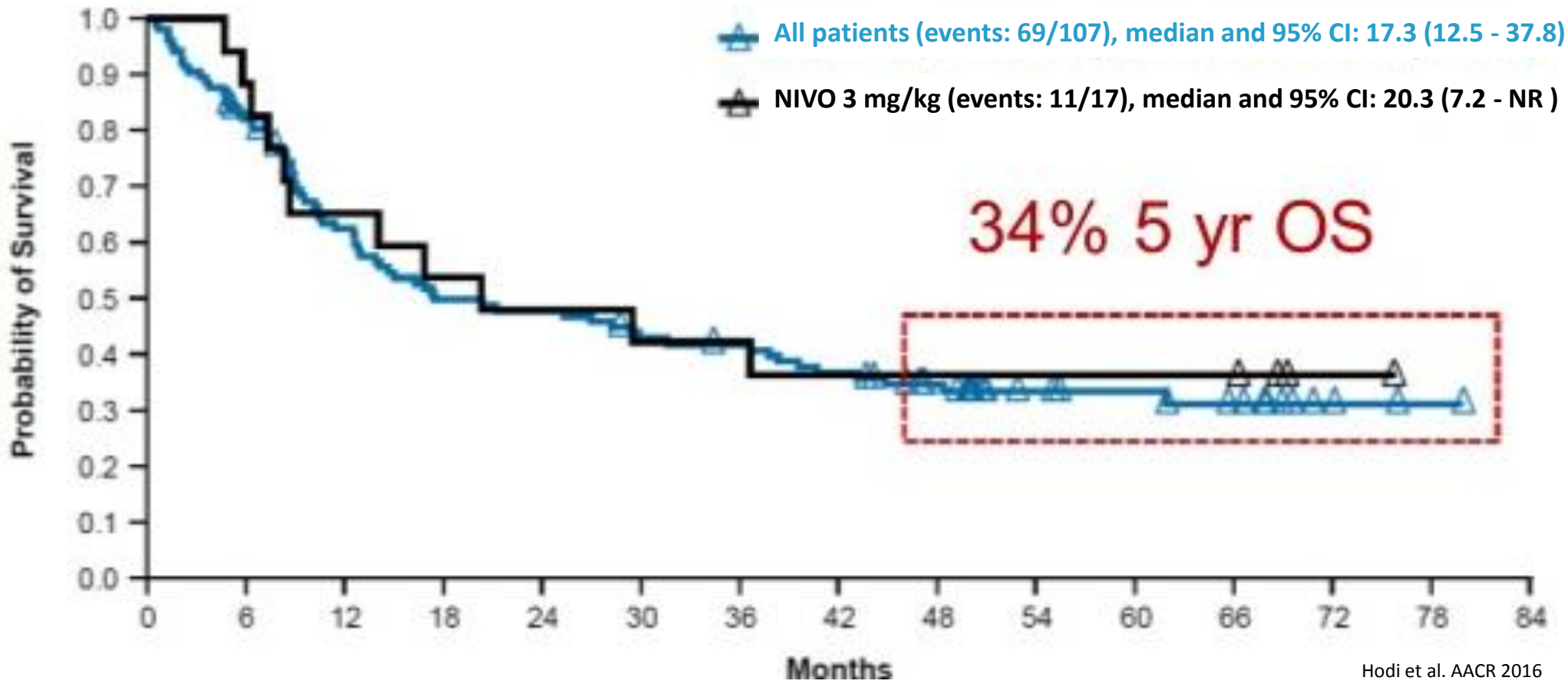
- Pooled OS data from 10 phase II/III trials
  - NCT01024231
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706



Schadendorf et al. JCO 2015

Nivolumab in Stage III/IV Melanoma

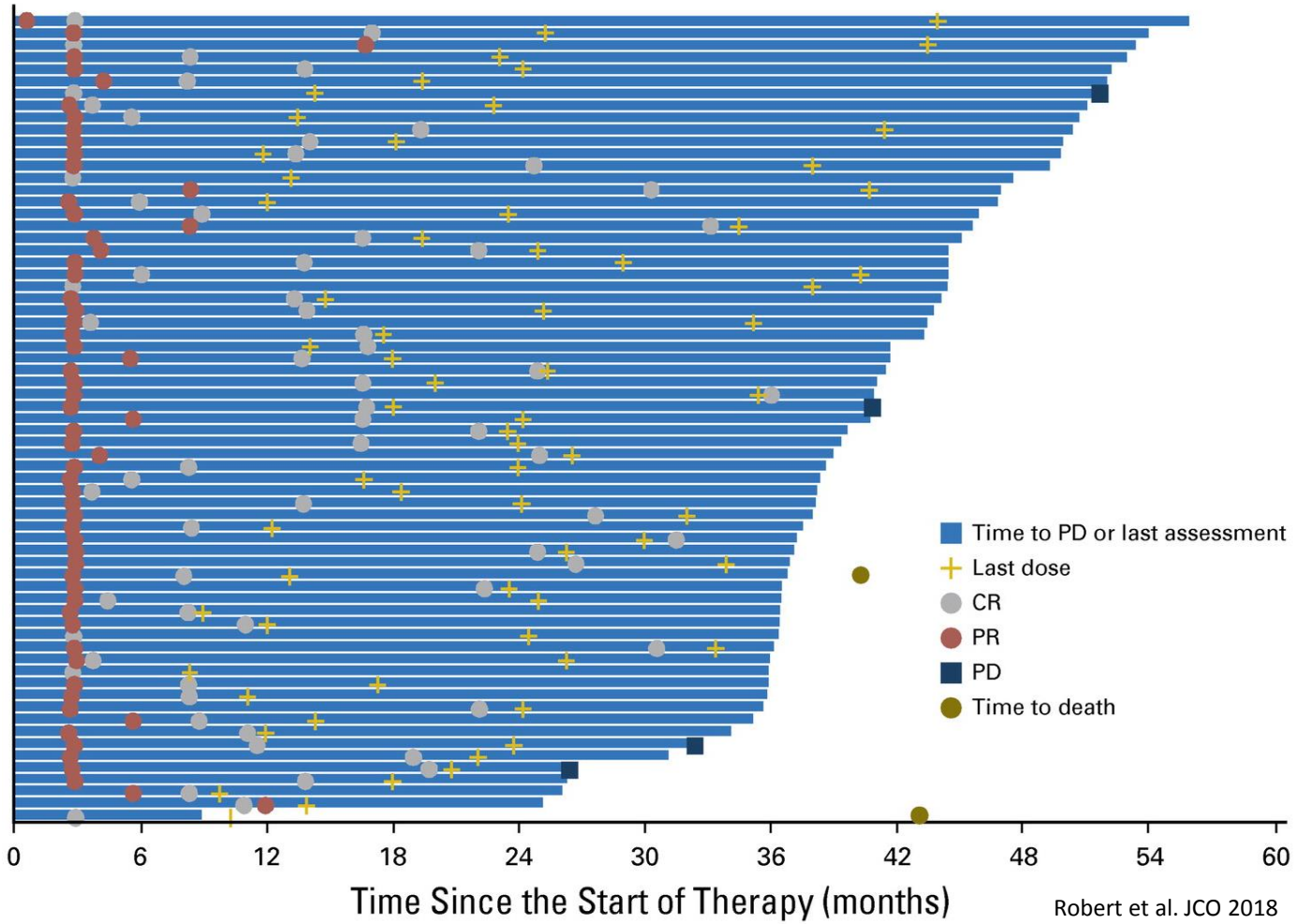
Extended Analysis from CA209-003 Phase I Trial



Hodi et al. AACR 2016

Pembrolizumab in Stage III/IV Melanoma

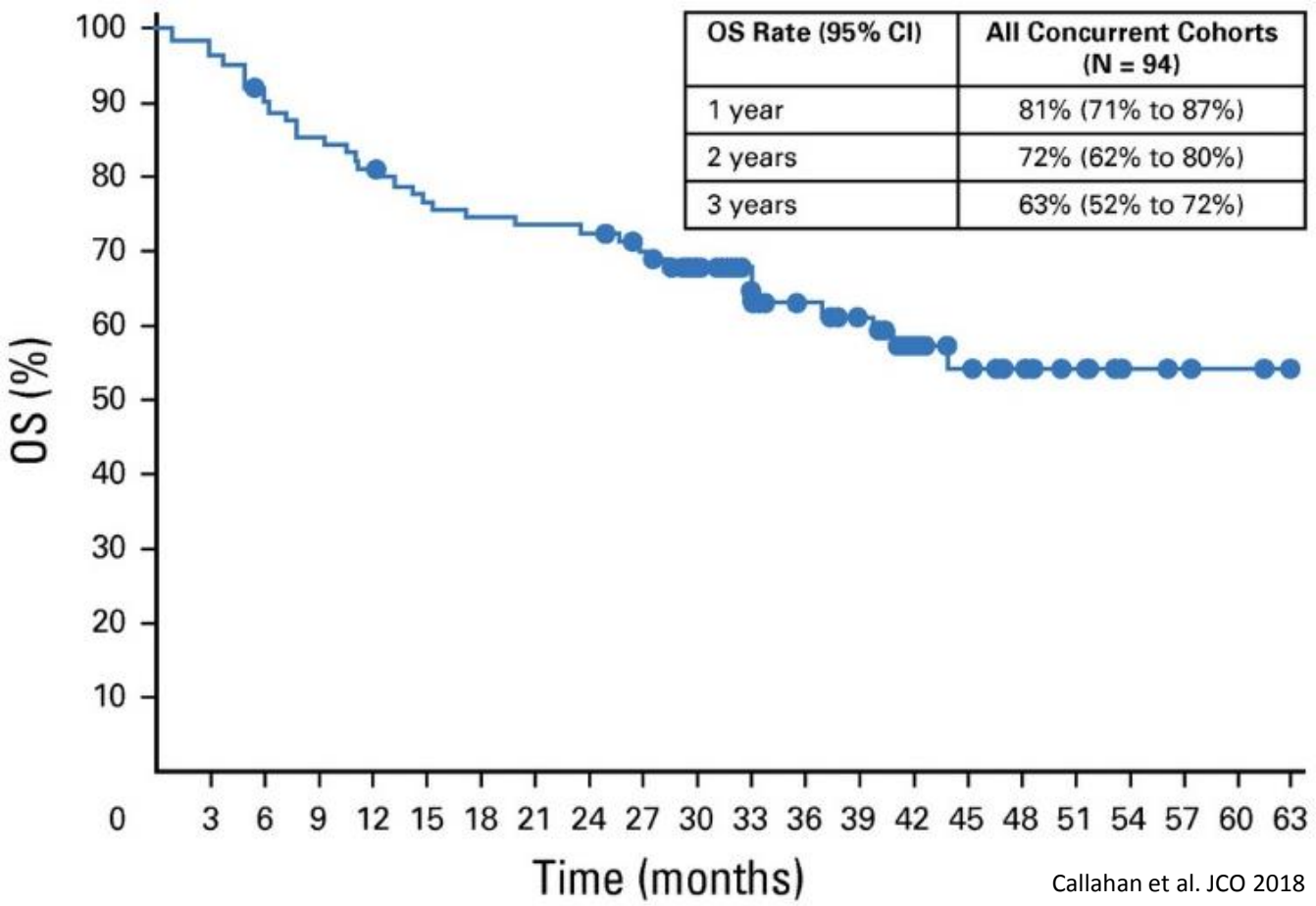
- Phase 1 KEYNOTE-001 Trial
  - NCT01295827
  - Pembrolizumab 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W
  - Durable responses in complete responders patients who discontinued pembrolizumab



Robert et al. JCO 2018

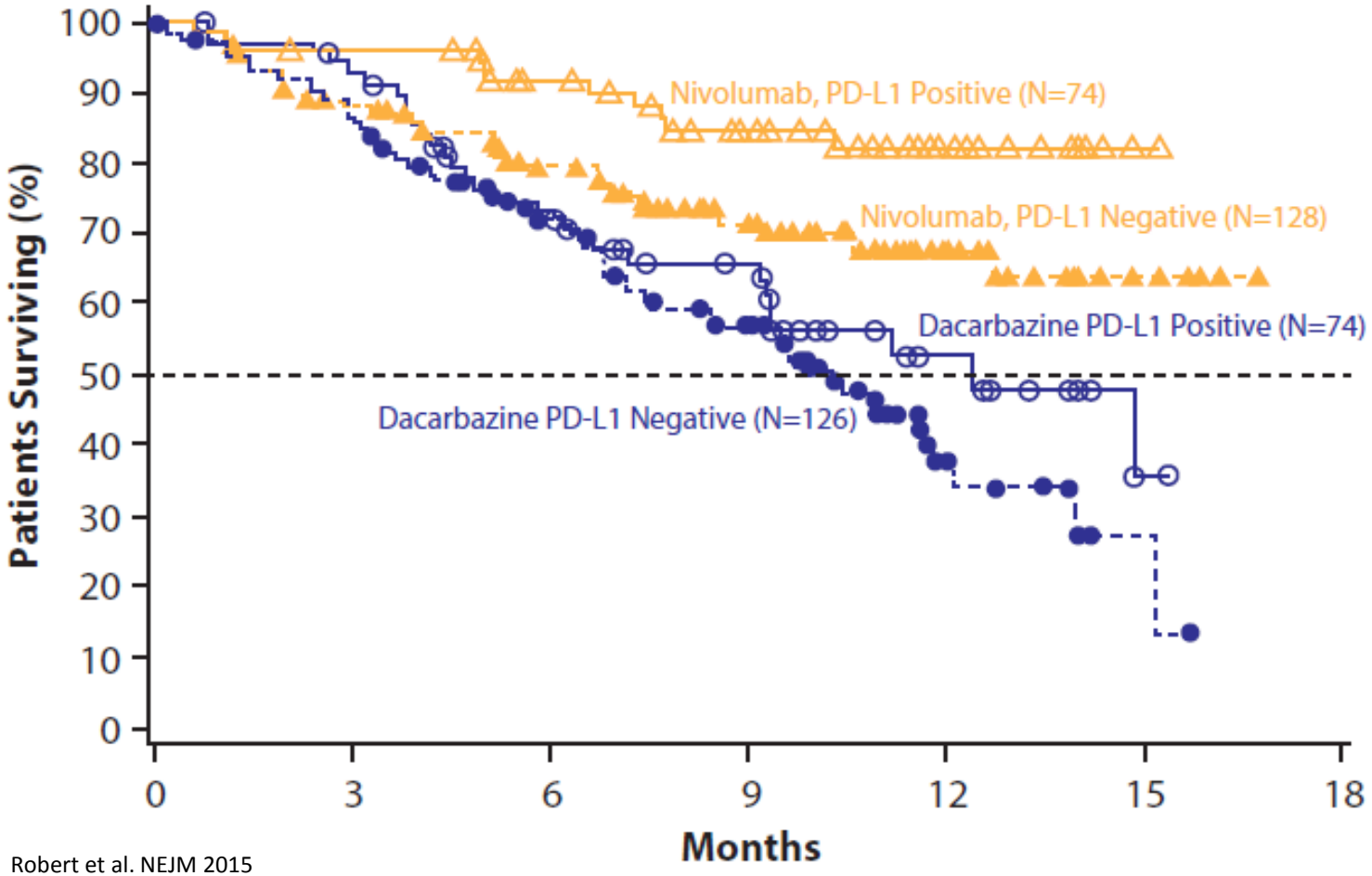
Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

- Phase 1b CA209-004 Trial
  - NCT01024231
  - Nivolumab + ipilimumab Q3W for 4 doses, then nivolumab Q3W for 4 doses, then nivolumab + ipilimumab Q12W for 8 doses



Callahan et al. JCO 2018

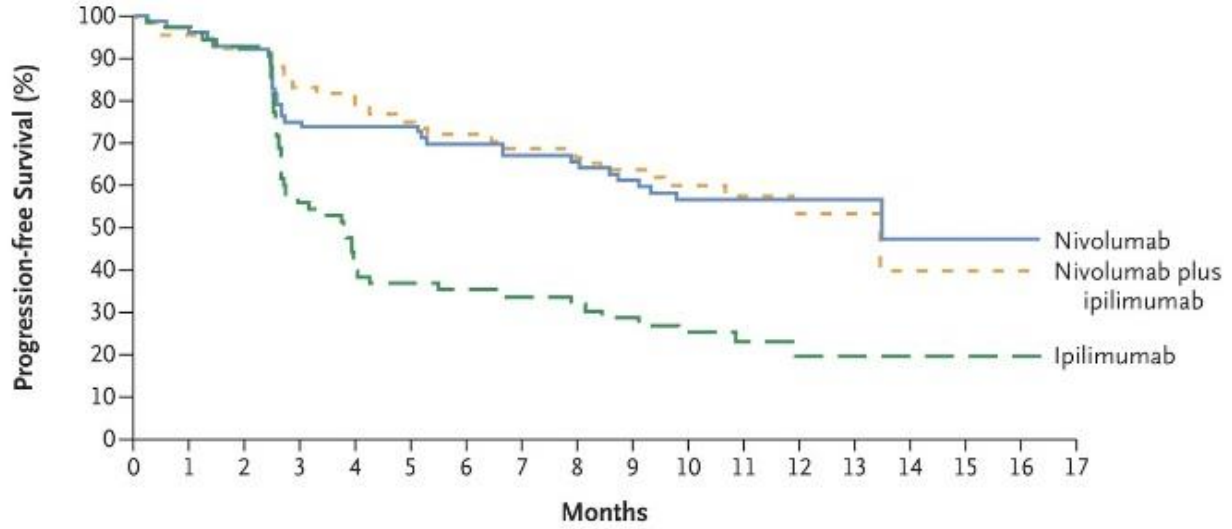
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



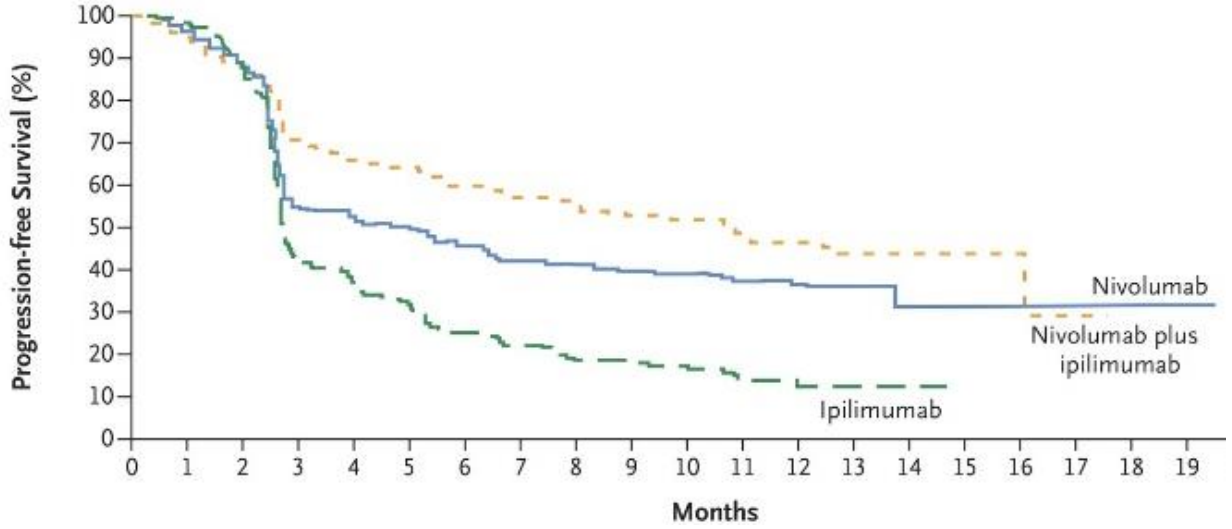
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

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



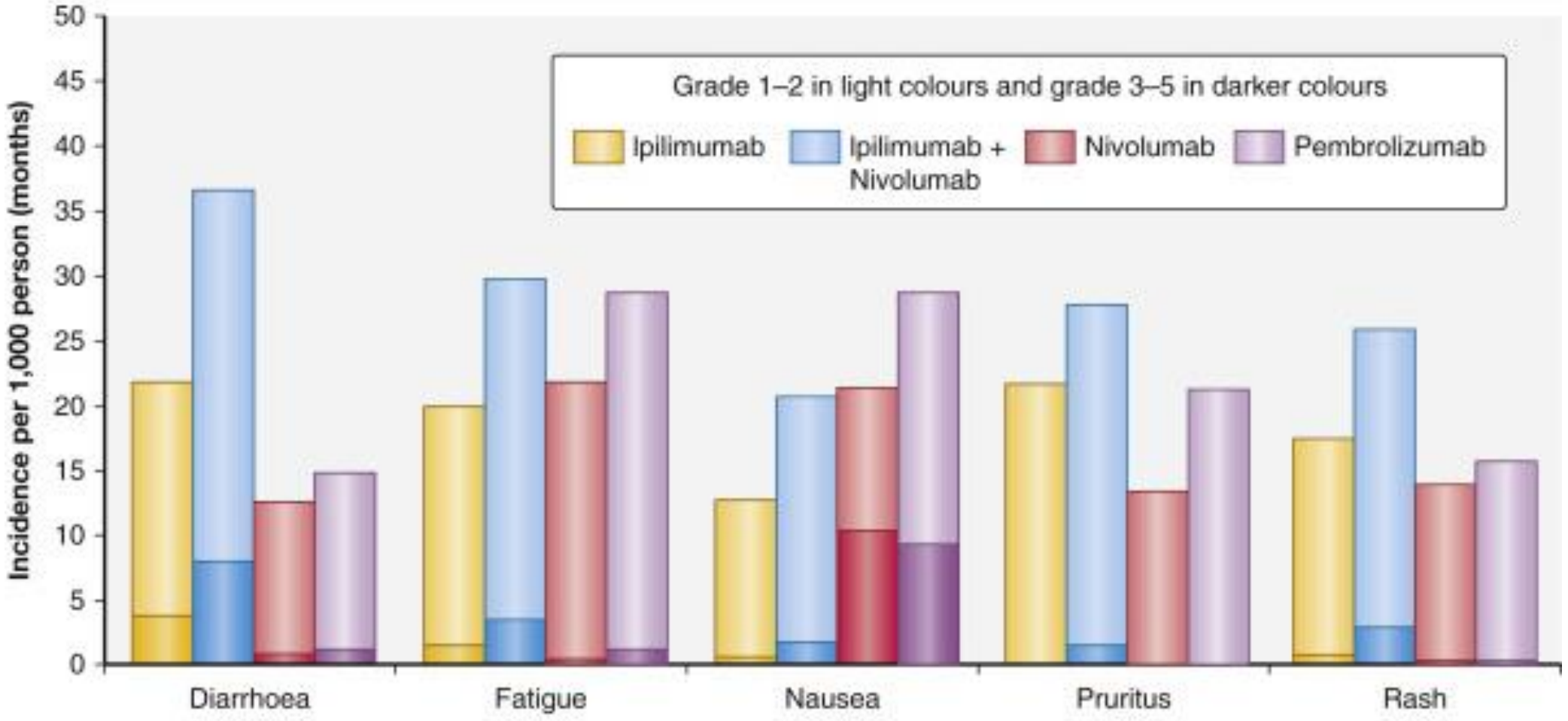
Tumor PD-L1 Positive Patients



Tumor PD-L1 Negative Patients

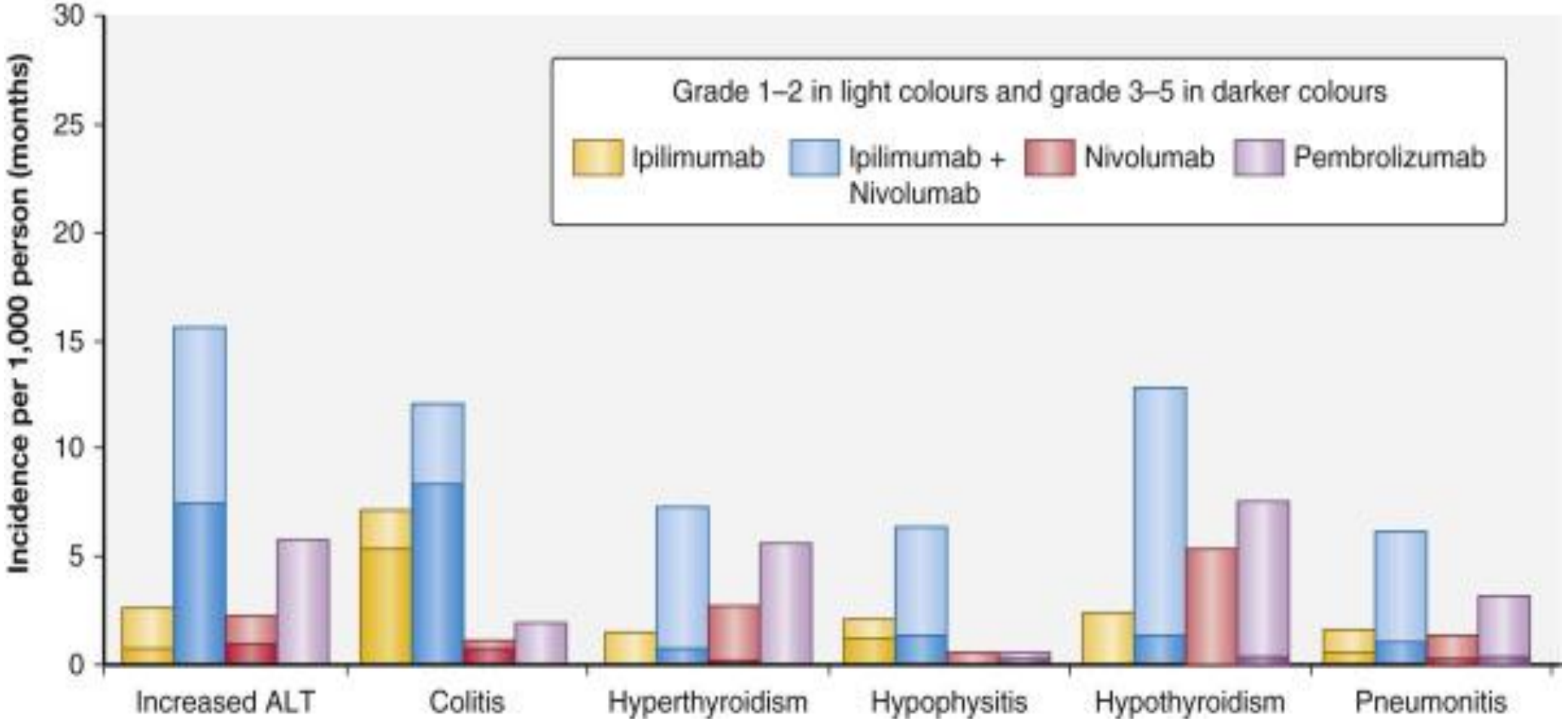
Larkin et al. NEJM 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



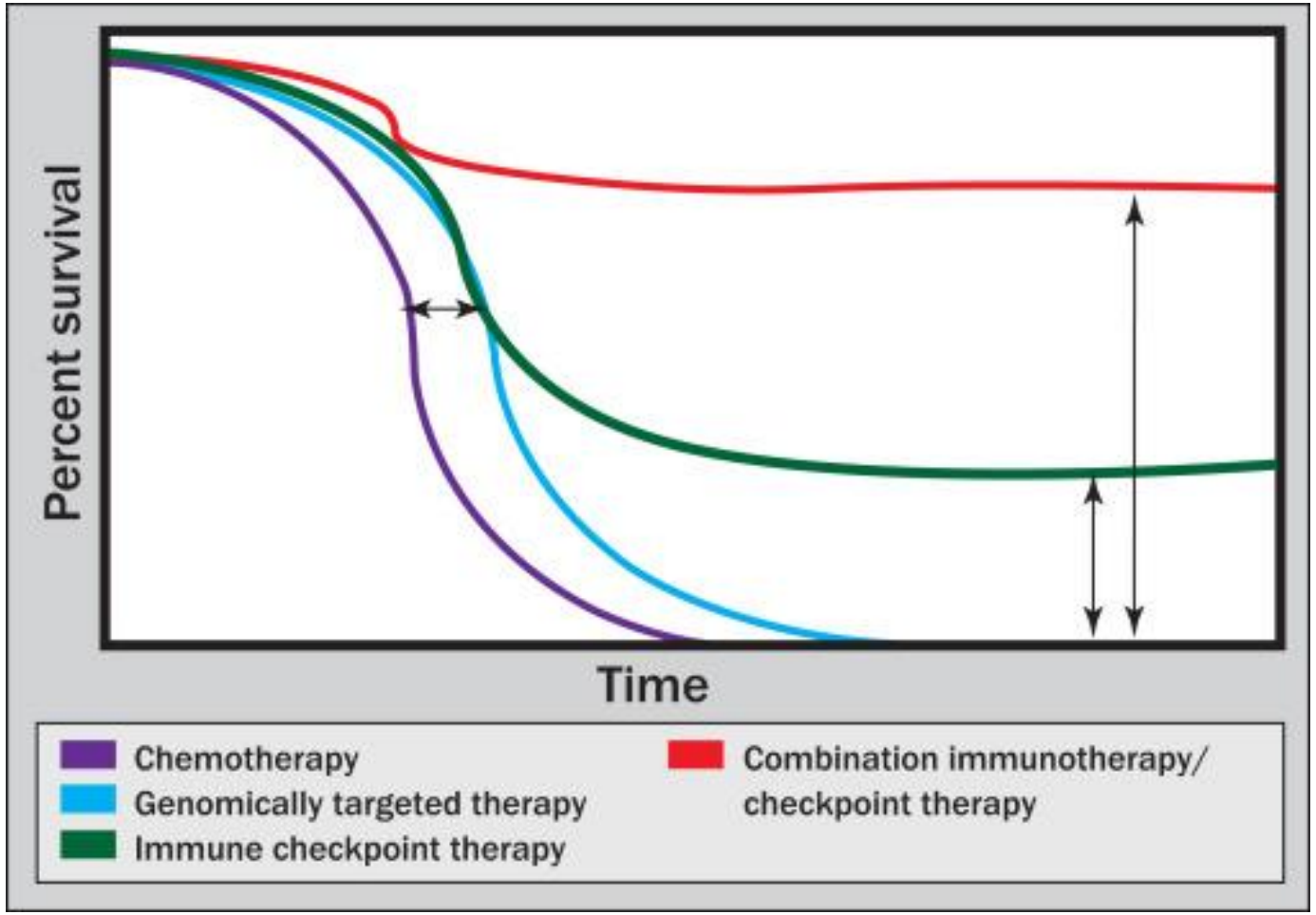
Emens et al. Eur J Cancer 2017

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

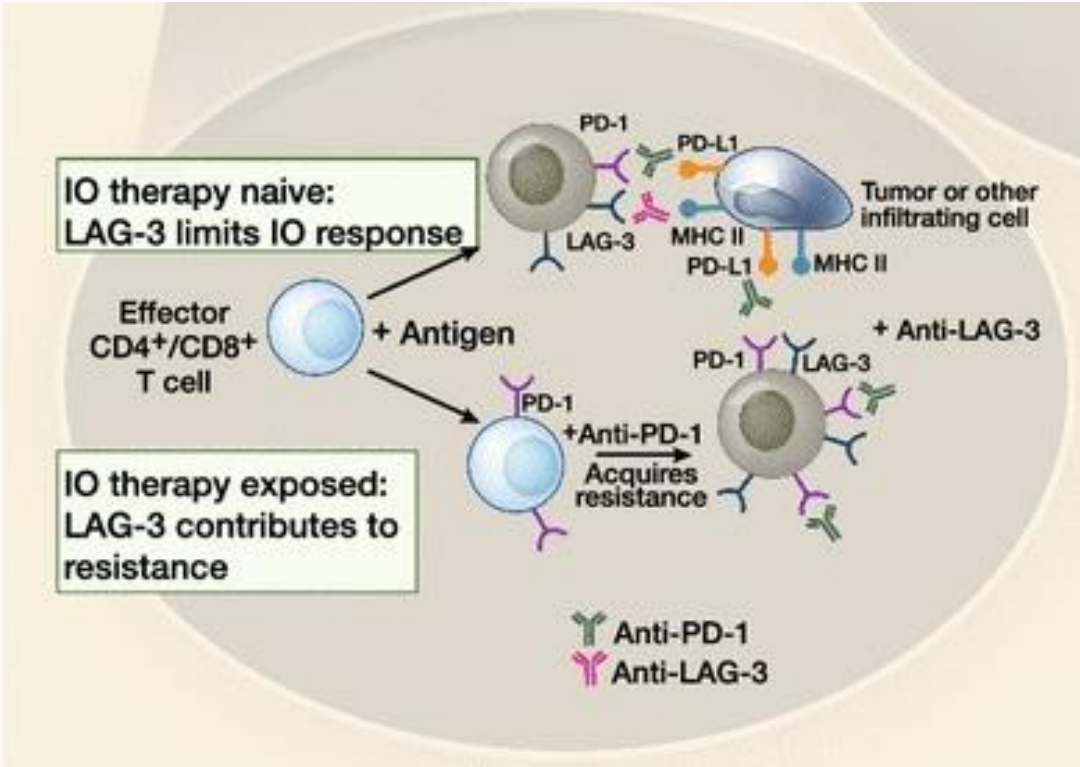
Developmental Immunotherapeutic Strategies for Melanoma

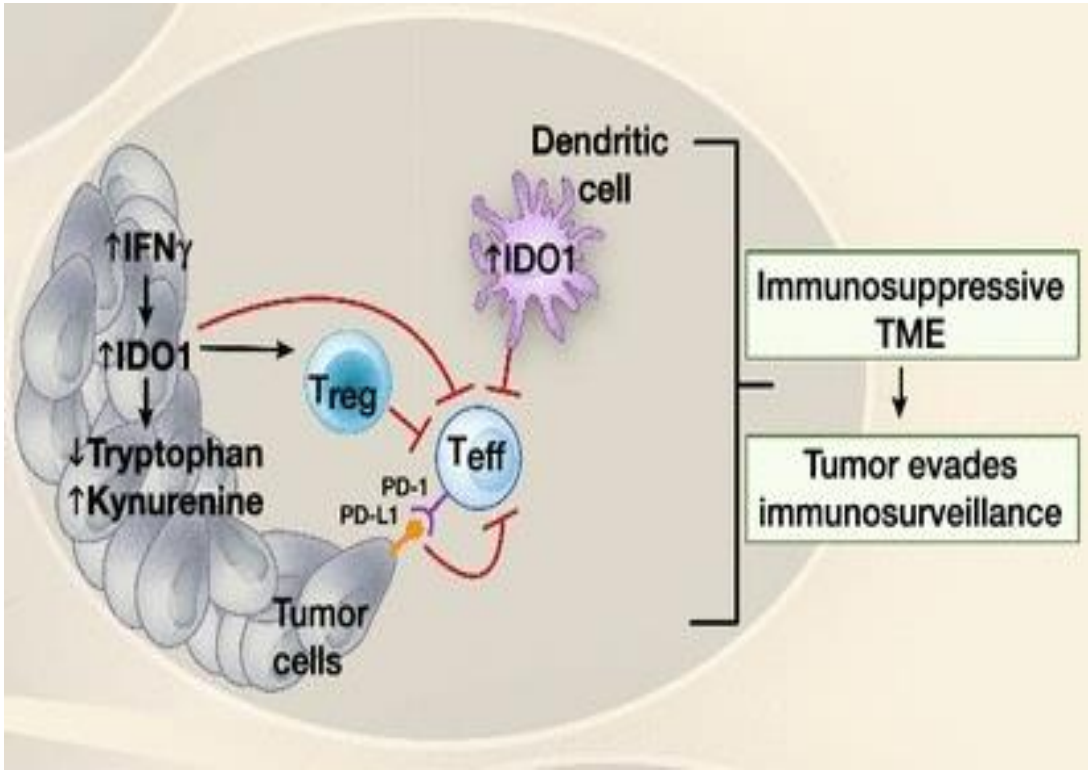


Atkins, Semi. Oncology 2015

Developmental Immunotherapeutic Strategies for Melanoma

Targeting New Immune Checkpoints

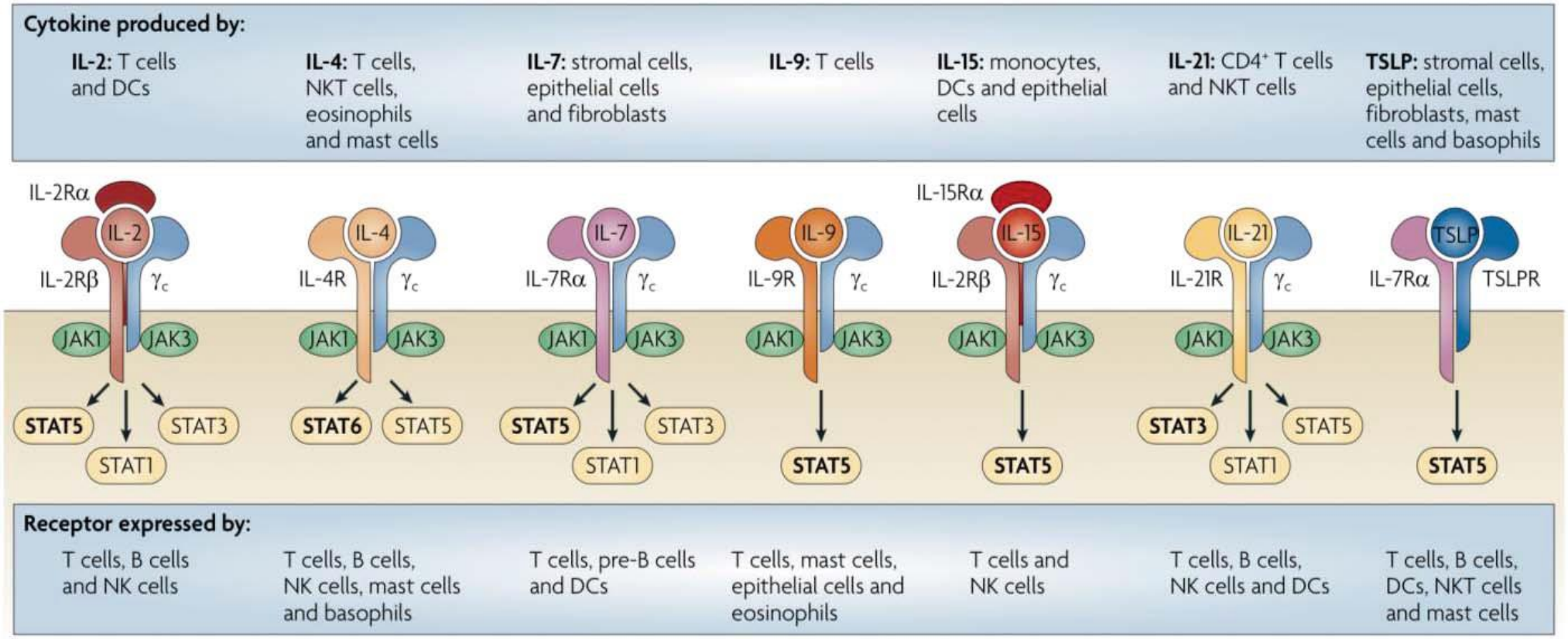




Ascierto, McArthur J Transl Med 2017

Developmental Immunotherapeutic Strategies for Melanoma

Cytokine-based Strategies



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

Case #1: Metastatic Melanoma BRAF Mutant

- 49 y/o male melanoma patient
- Presented with biopsy confirmed mediastinal LN involvement; melanoma had $BRAF^{V600E}$ mutation

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.

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

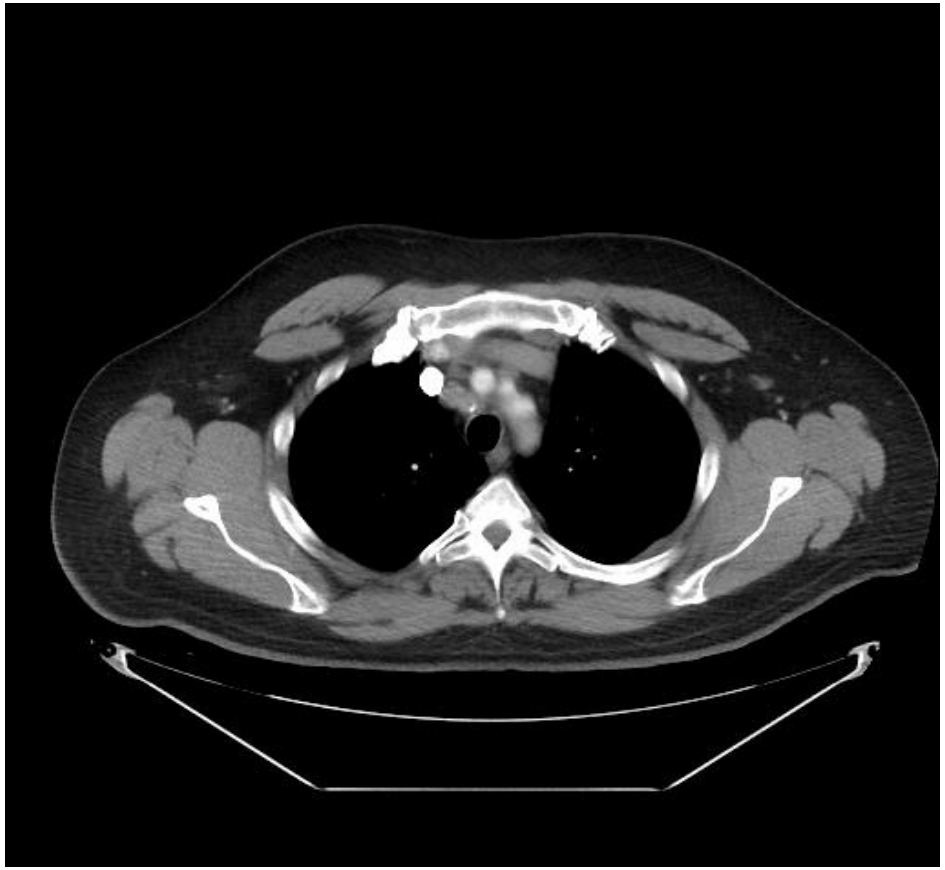
An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

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*]

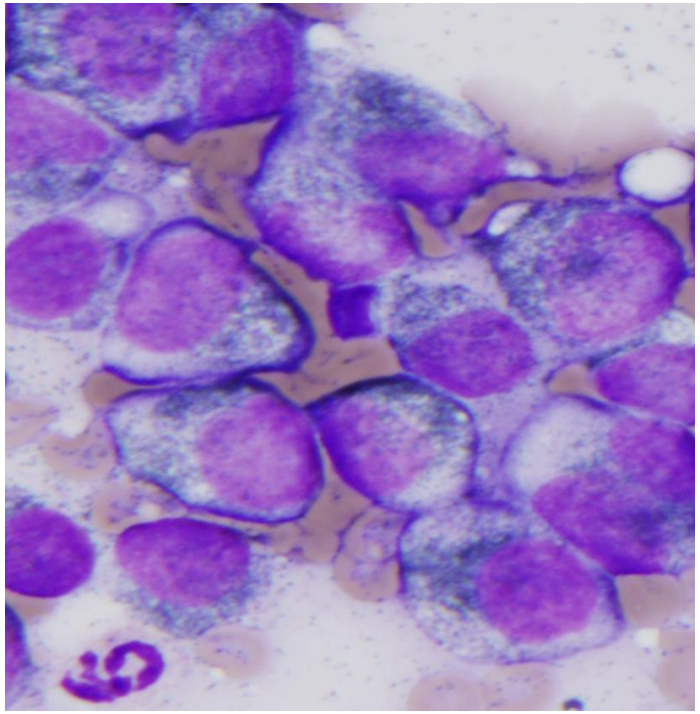
Case #1: Metastatic Melanoma BRAF Mutant

- 49 y/o male melanoma patient
- Presented with biopsy confirmed mediastinal LN involvement; melanoma had $BRAF^{V600E}$ mutation

- Cytology following fine needle aspiration of mediastinal lymph node



Courtesy of Dr. Meghan Lubner



Courtesy of Dr. Erik Ranheim

Case #1: Treatment Options

- Immunotherapy
  - Pembrolizumab
  - Nivolumab
  - Nivolumab + ipilimumab
  - High-dose IL-2
  - Ipilimumab 3 mg/kg x 4
- Targeted Therapy
  - Dabrafenib + Trametinib
  - Vemurafenib + Cobimetinib
  - Encorafenib + Binimetinib
  - Vemurafenib
  - Dabrafenib
  - Trametinib

What is the best sequencing of treatment for patients with advanced BRAF V600 mutant melanoma?

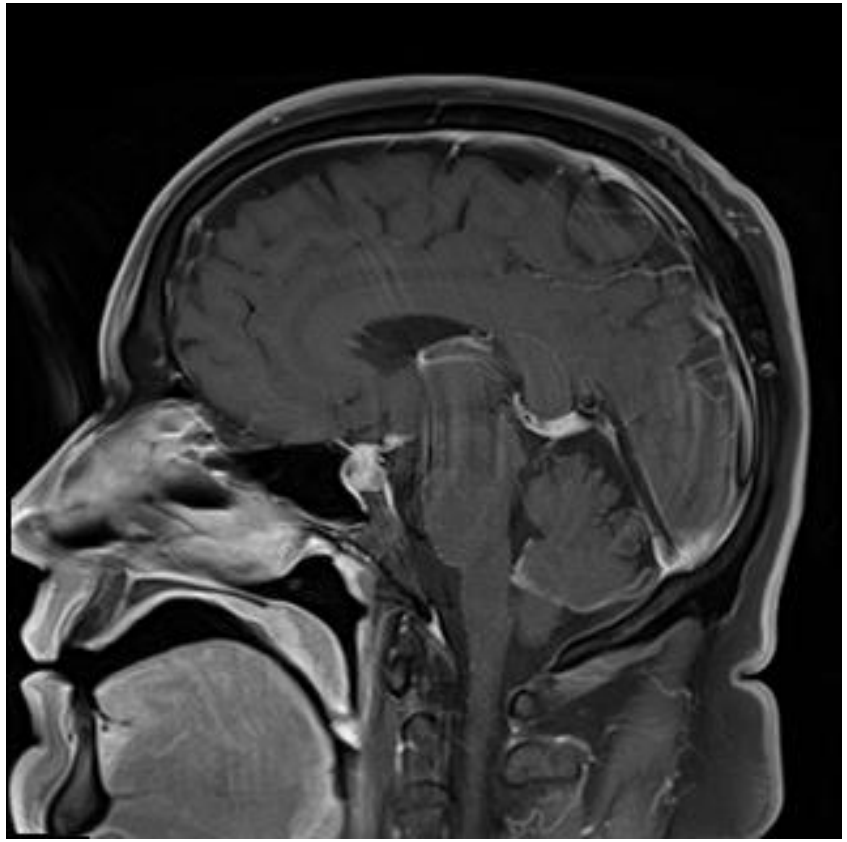
- EA6134: A Randomized Phase III Trial of Dabrafenib + Trametinib followed by Ipilimumab + Nivolumab at Progression vs Ipilimumab + Nivolumab followed by Dabrafenib + Trametinib at Progression in Patients with Advanced BRAFV600 Mutant Melanoma

Case #1: Metastatic Melanoma BRAF Mutant

- Initial Therapy
  - Ipilimumab and nivolumab
  - Tolerated therapy with minimal side effects for the first 2 cycles
- Presented with significant headaches as well as nausea with vomiting 12 days after cycle #3 of ipilimumab and nivolumab

2 Weeks after cycle #3 of Ipi/Nivo

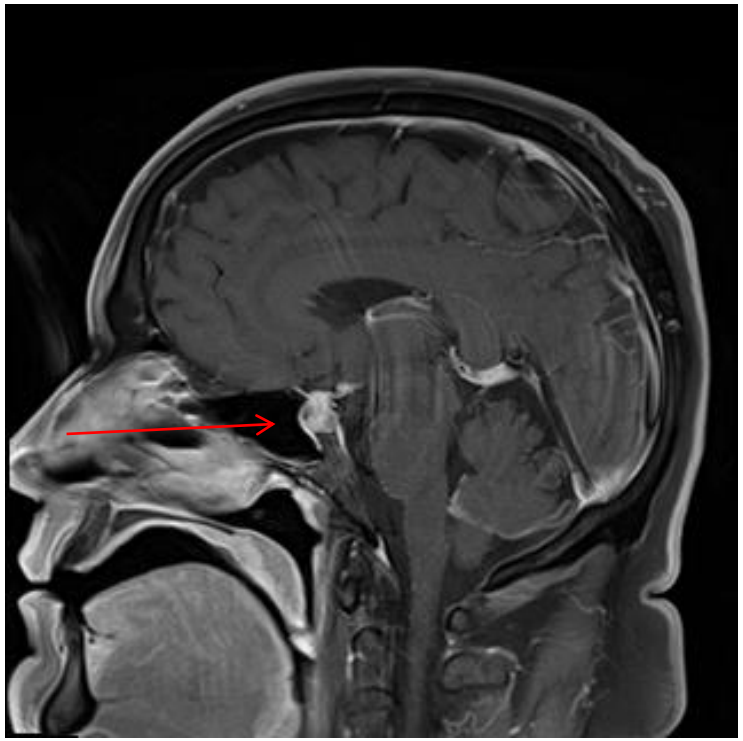
- Comprehensive laboratory studies including cortisol, TSH, T3, T4, testosterone



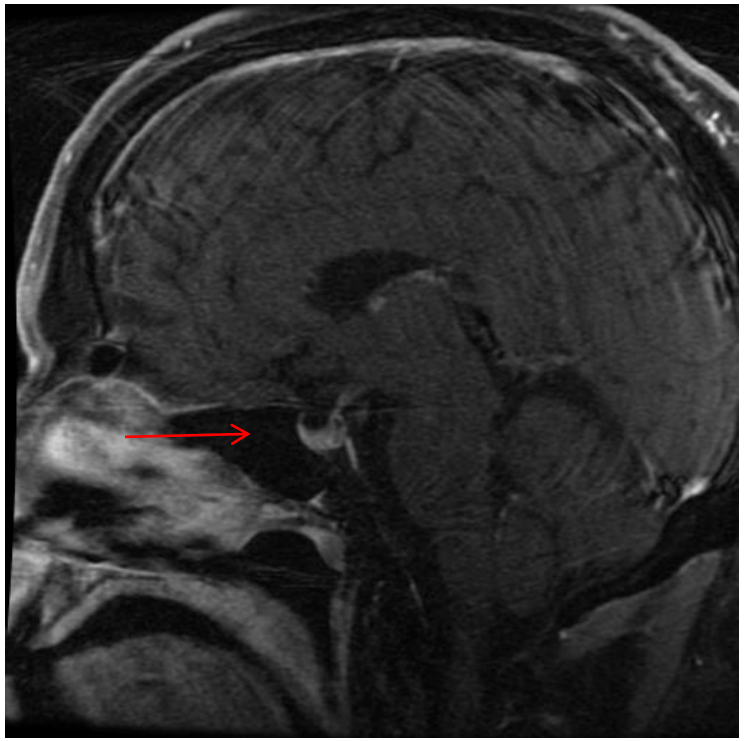
Courtesy of Dr. Meghan Lubner

Management

- Methylprednisolone 1 mg/kg IV twice daily followed by transition to oral prednisone with a prolonged taper
- GI Prophylaxis: omeprazole
- PJP Prophylaxis: bactrim
- Fungal prophylaxis: clotrimazole
- Levothyroxine

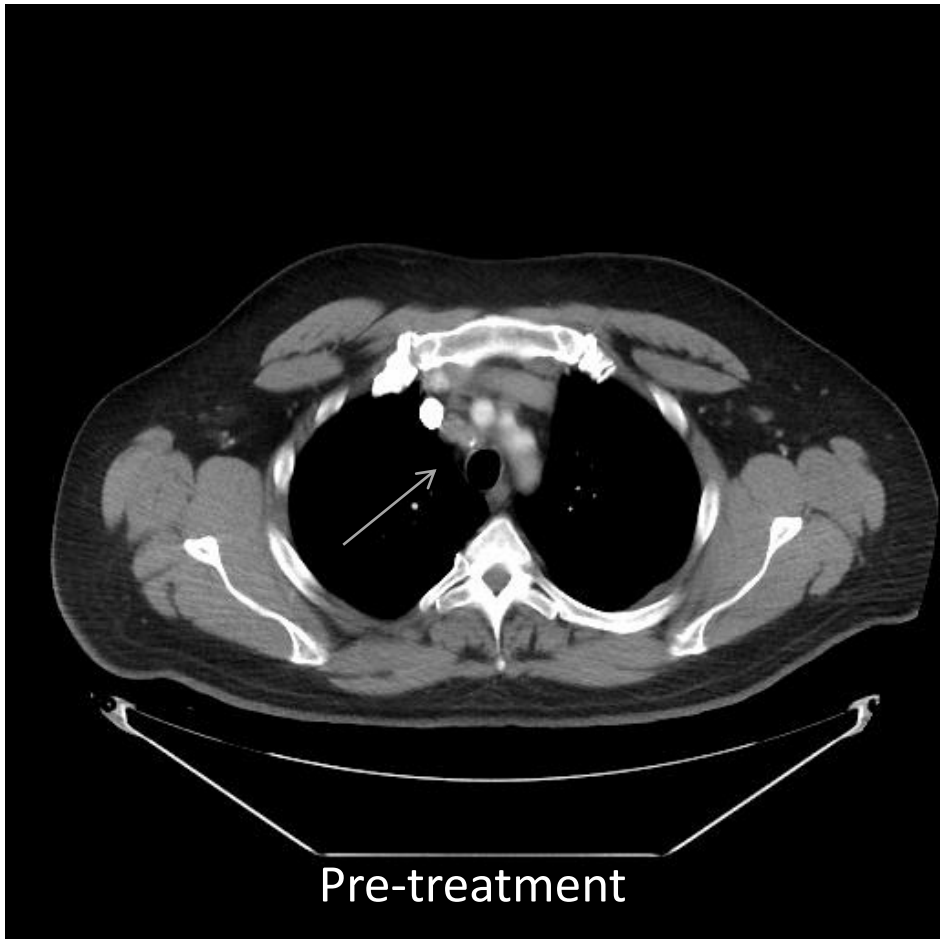


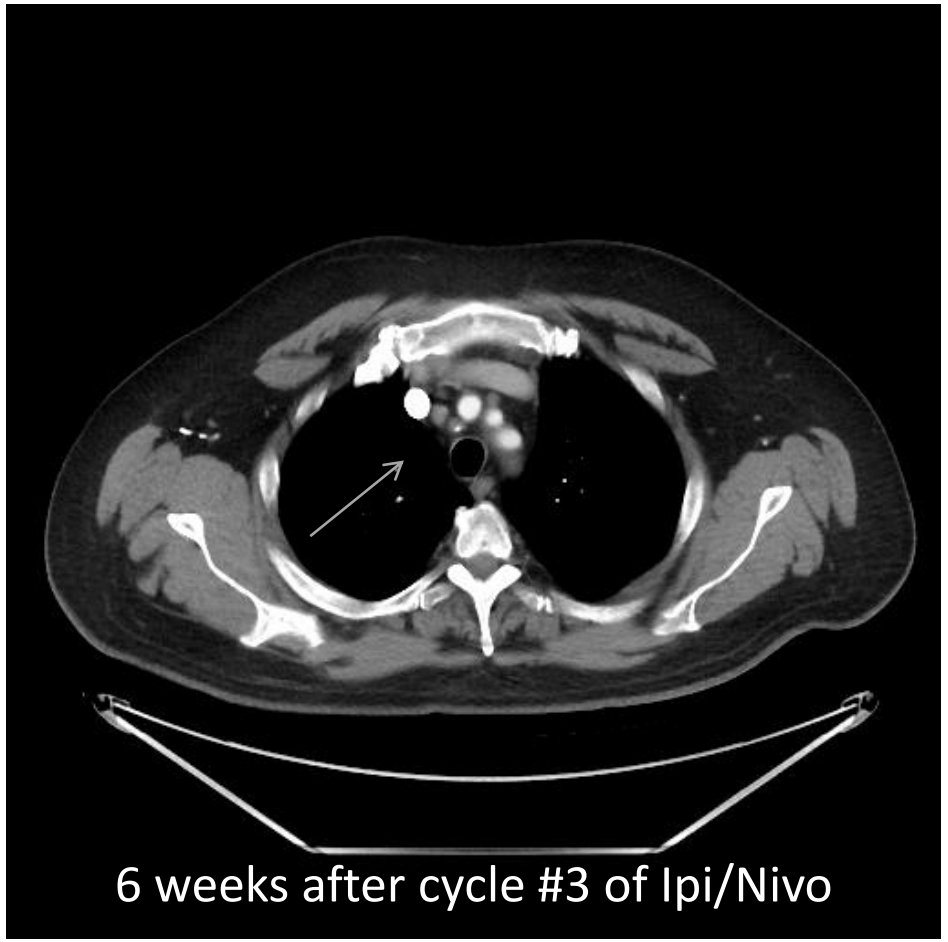
2 weeks after cycle #3 of Ipi/Nivo



6 weeks after cycle #3 of Ipi/Nivo

Courtesy of Dr. Meghan Lubner





Courtesy of Dr. Meghan Lubner

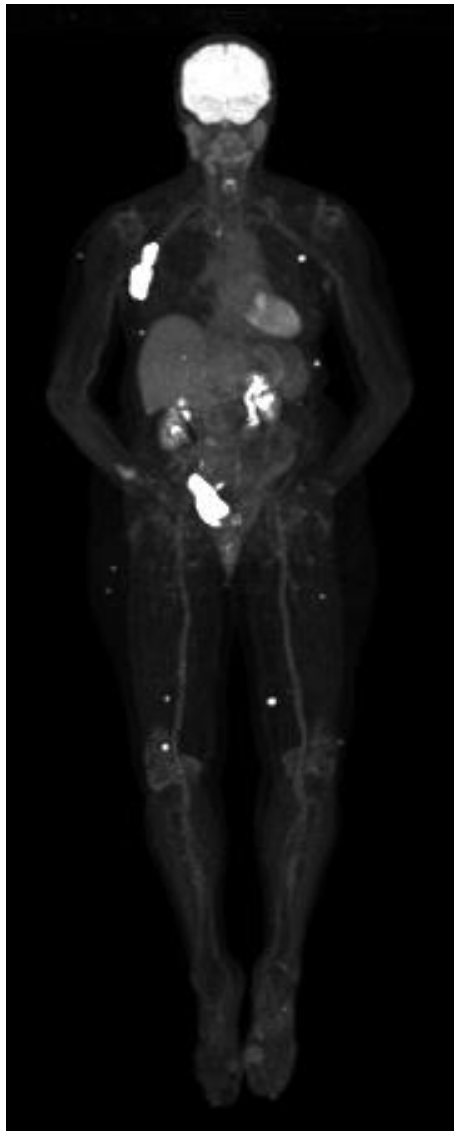
Clinical Status 2.5 years after cycle #3 Ipi/Nivo

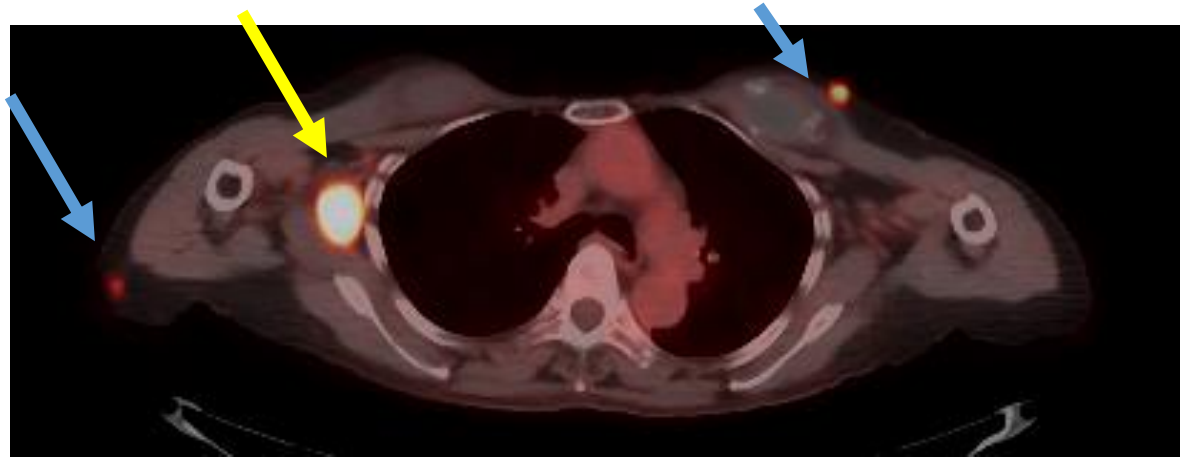
- CT scans stable and without evidence for progression
- Remains on hydrocortisone 10 mg in the AM and 5 mg in the PM as well as replacement levothyroxine

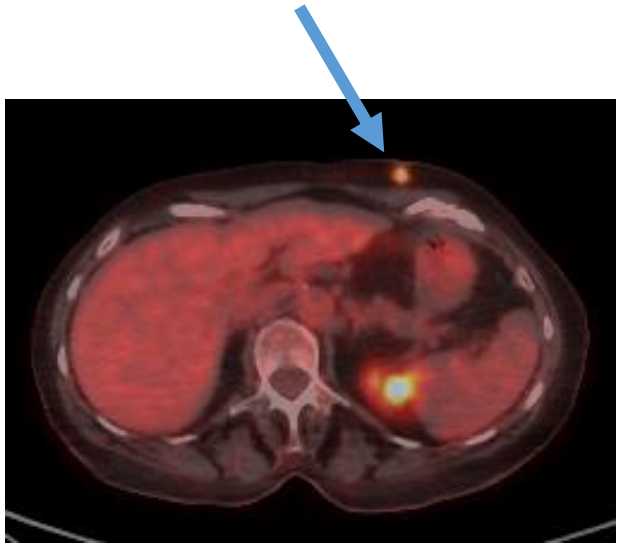
Case #2: Metastatic Melanoma BRAF Mutant

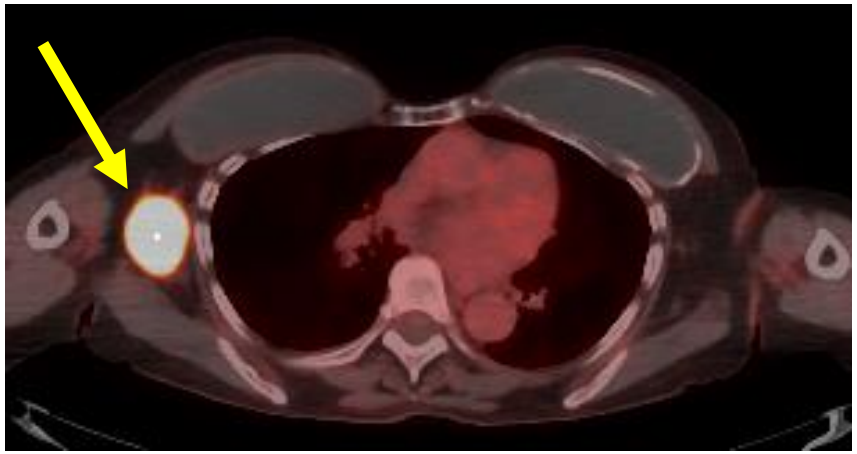
- 76 y/o female patient
- H/o stage IIC ovarian cancer
- Diagnosis of metastatic melanoma of unknown primary after presenting with enlarged bilateral axillary lymph nodes
- Ultrasound-guided core needle biopsies of right and left axillary lymph nodes revealed metastatic melanoma
- BRAF mutation in codon 600 of the BRAF gene was detected (V600E mutation)

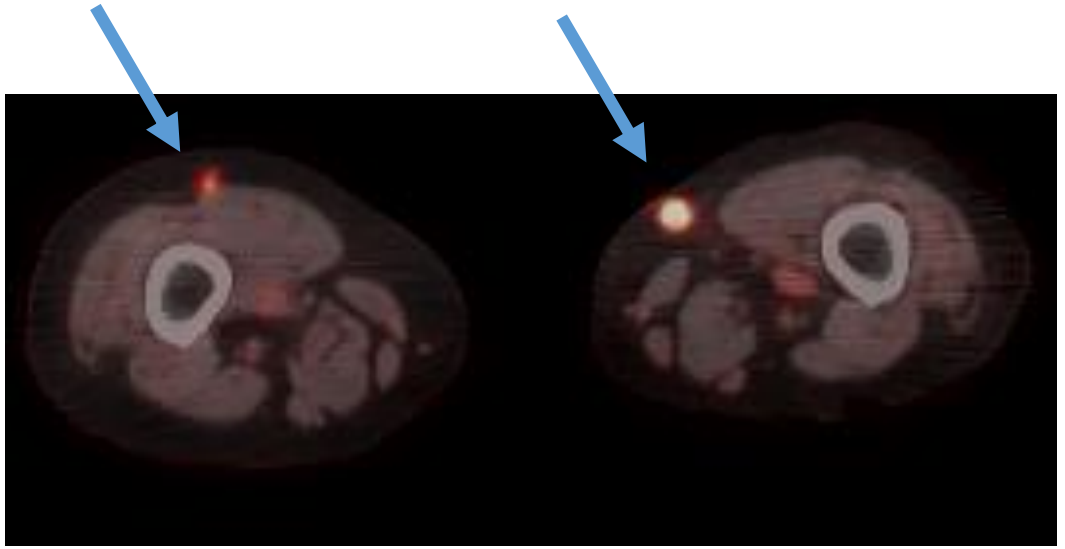
Pre-Treatment



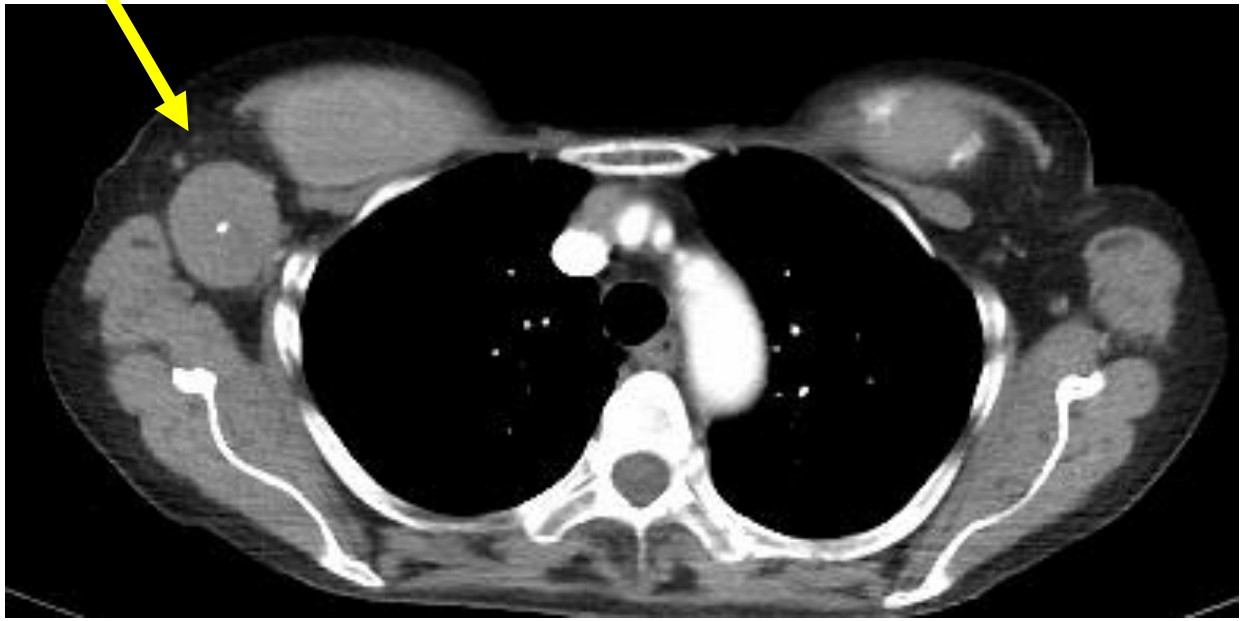


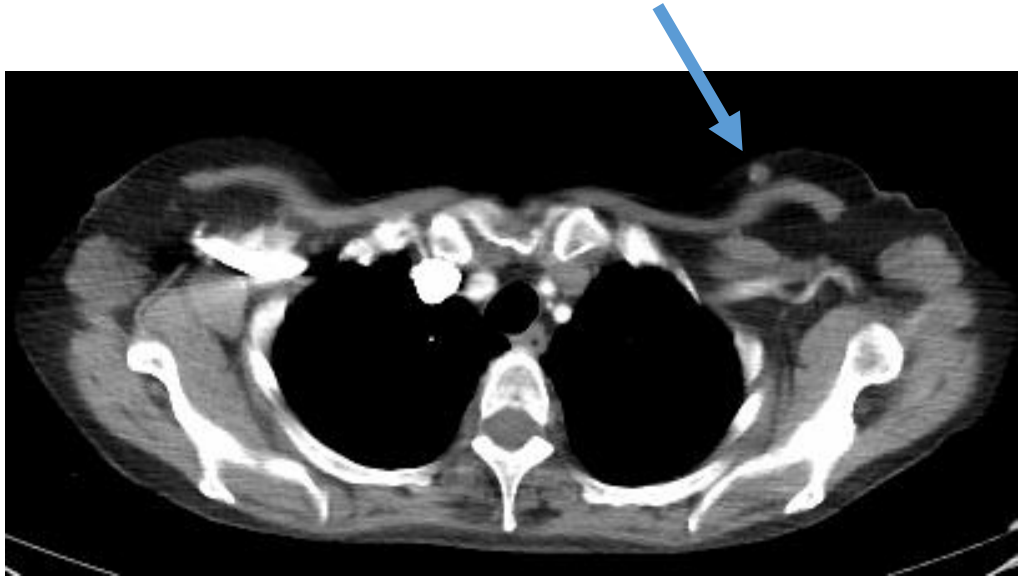


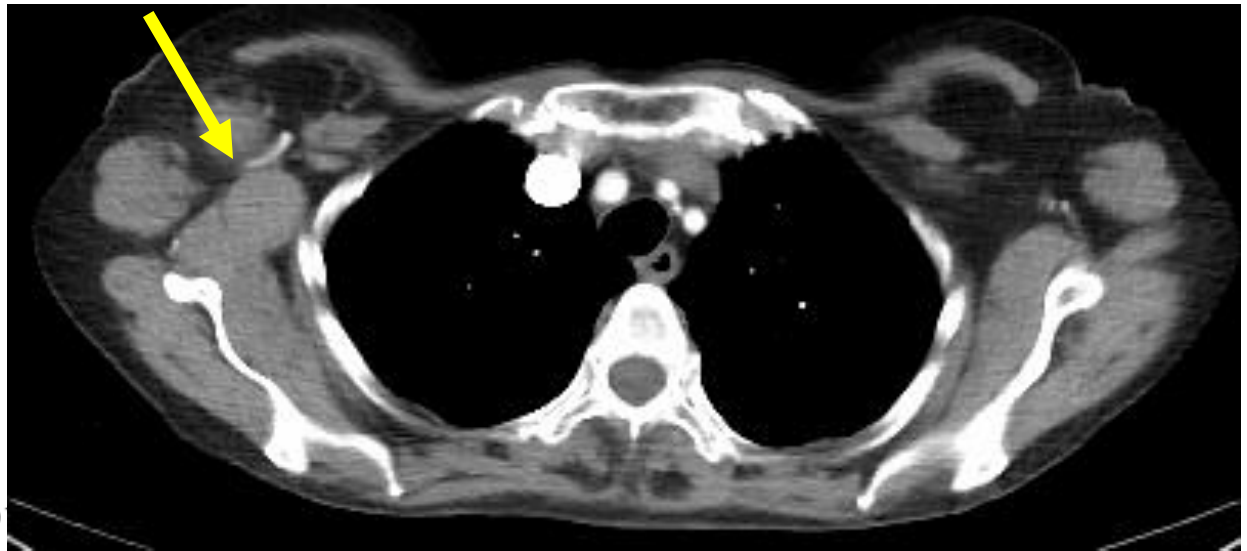


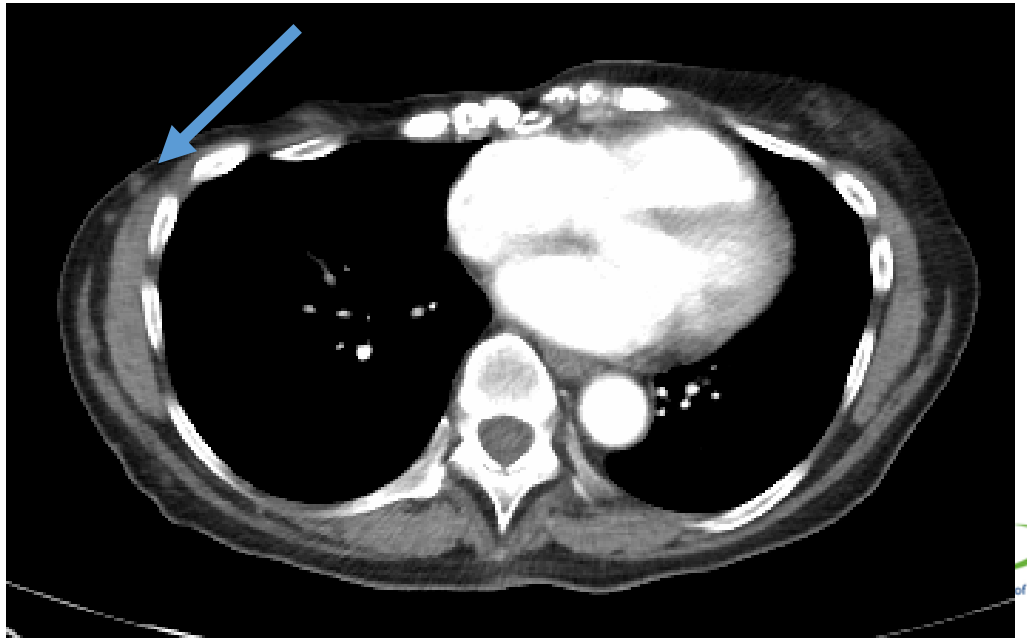


Pre-Treatment

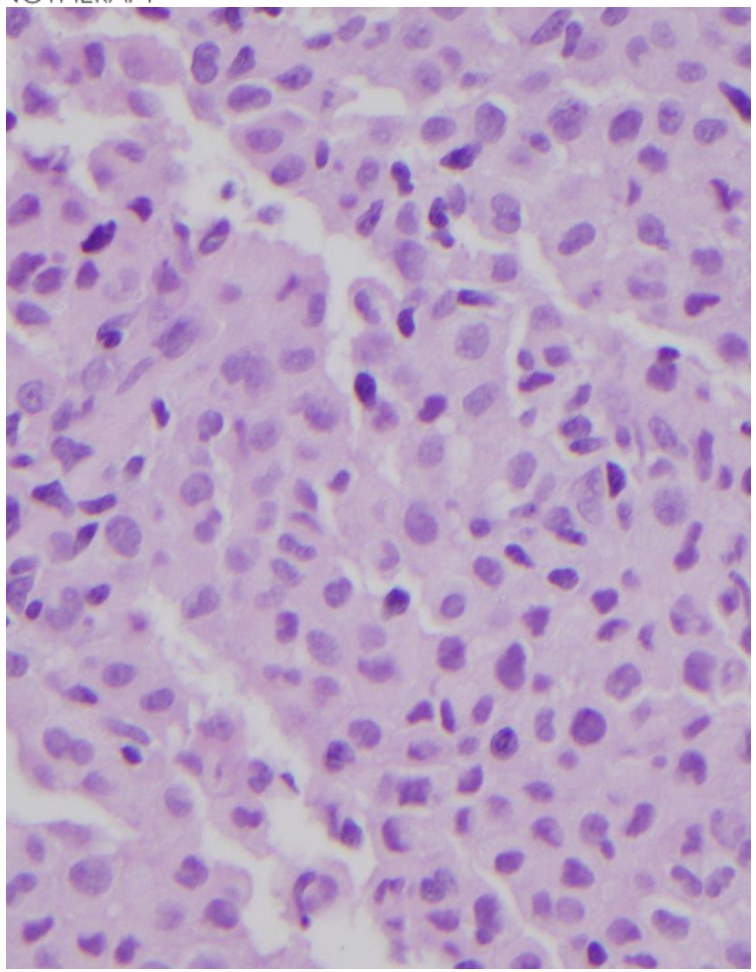




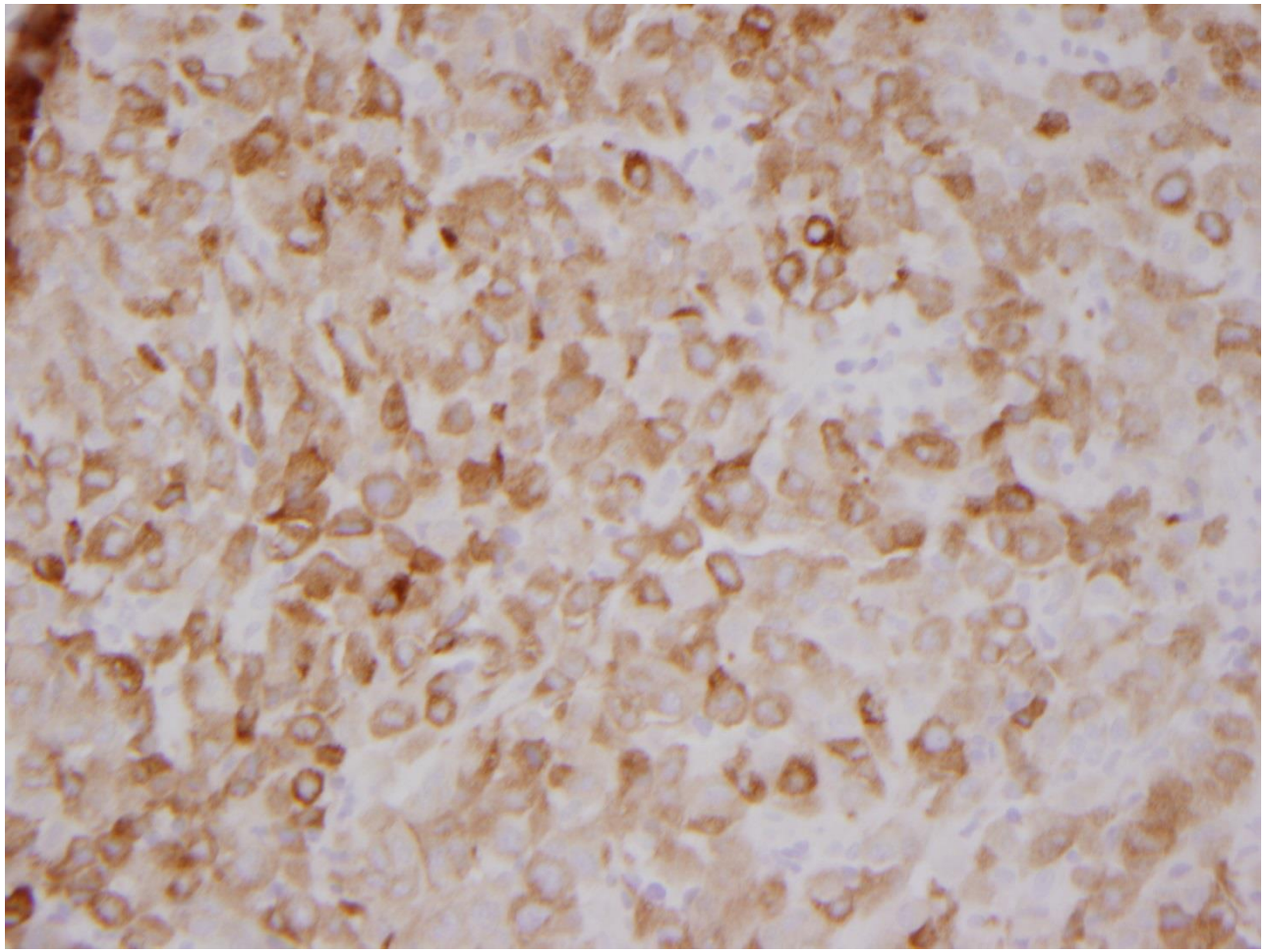




Ultrasound guided core needle biopsy of right axillary lymph node



Hematoxylin and Eosin stain



Immunostains for Melanoma Cocktail (HMB 45 and Melan A)

Courtesy of Dr. Erik Ranheim

Case #2: Treatment Options

- Immunotherapy
  - Pembrolizumab
  - Nivolumab
  - Nivolumab + ipilimumab
  - High-dose IL-2
  - Ipilimumab 3 mg/kg x 4
  - Talimogene laherparepvec (TVEC)
  - Experimental intralesional treatment
- Targeted Therapy
  - Dabrafenib + Trametinib
  - Vemurafenib + Cobimetinib
  - Encorafenib + Binimetinib
  - Vemurafenib
  - Dabrafenib
  - Trametinib

Can predictive biomarkers assist with treatment decisions?

PD-L1 Immunohistochemistry

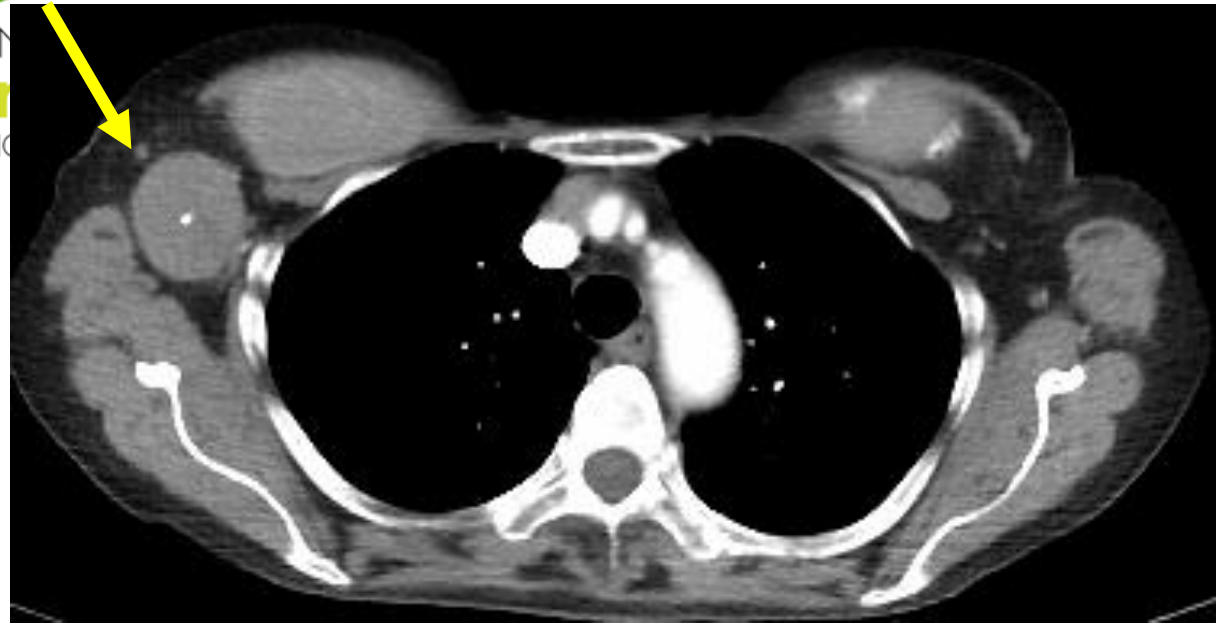
- PD-L1 immunohistochemistry was performed and was positive in less than 1% of tumor cells

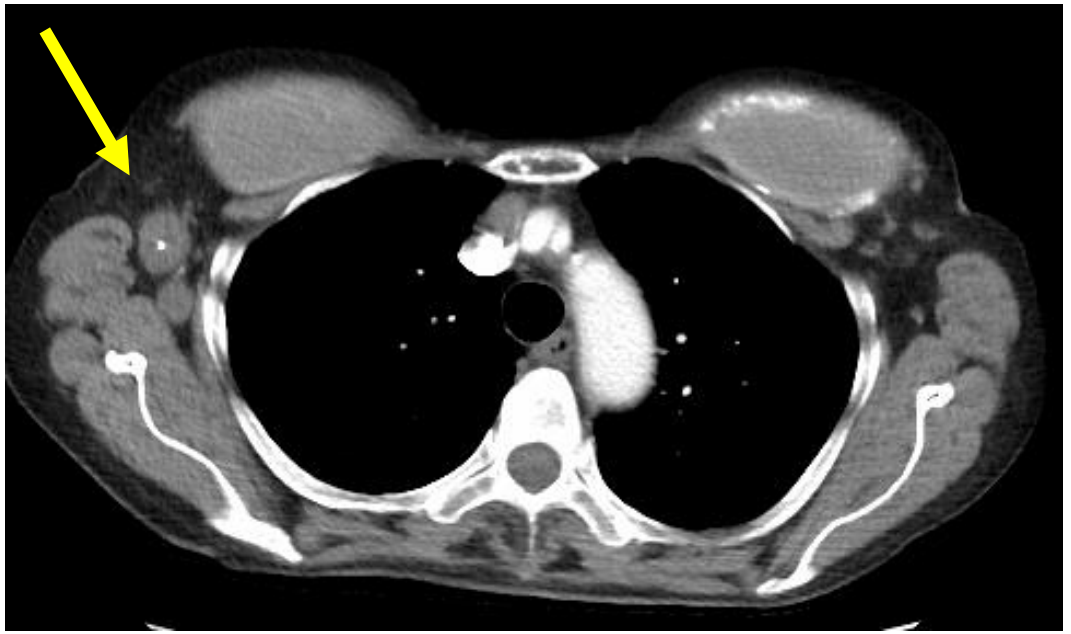
Case #2 Management

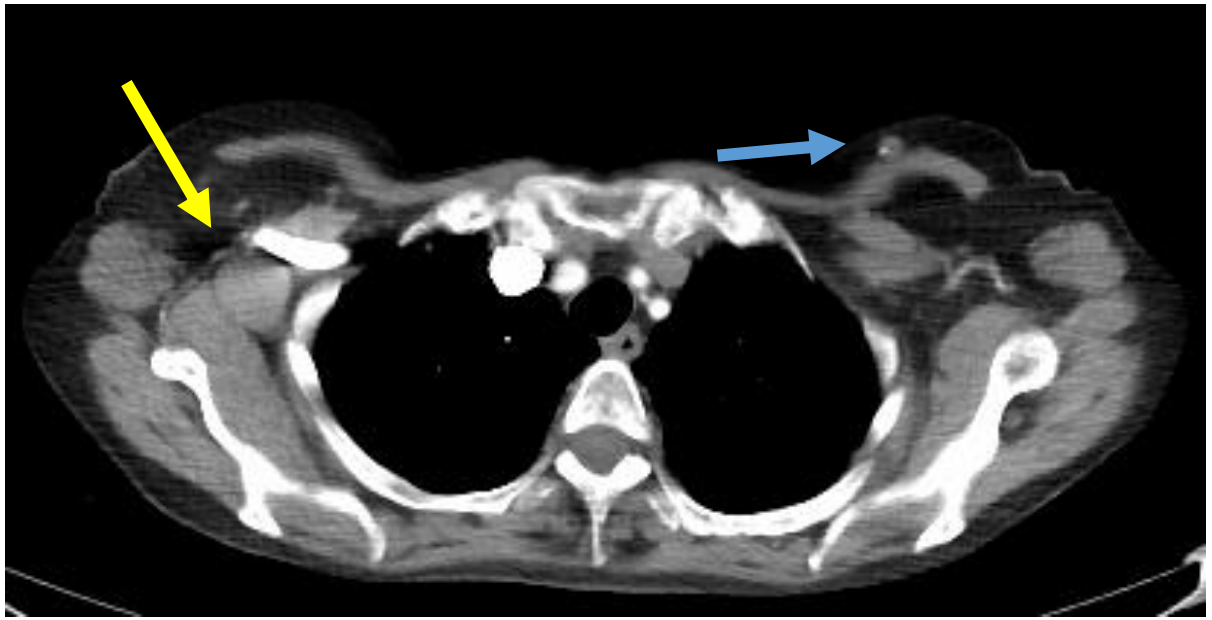
- Treatment with pembrolizumab with repeat disease assessments every 3 months
- No significant treatment-associated toxicity
- Significant anti-tumor response
- Treatment stopped after cycle 26 (approx. 18 months of treatment) due to separate medical and social considerations

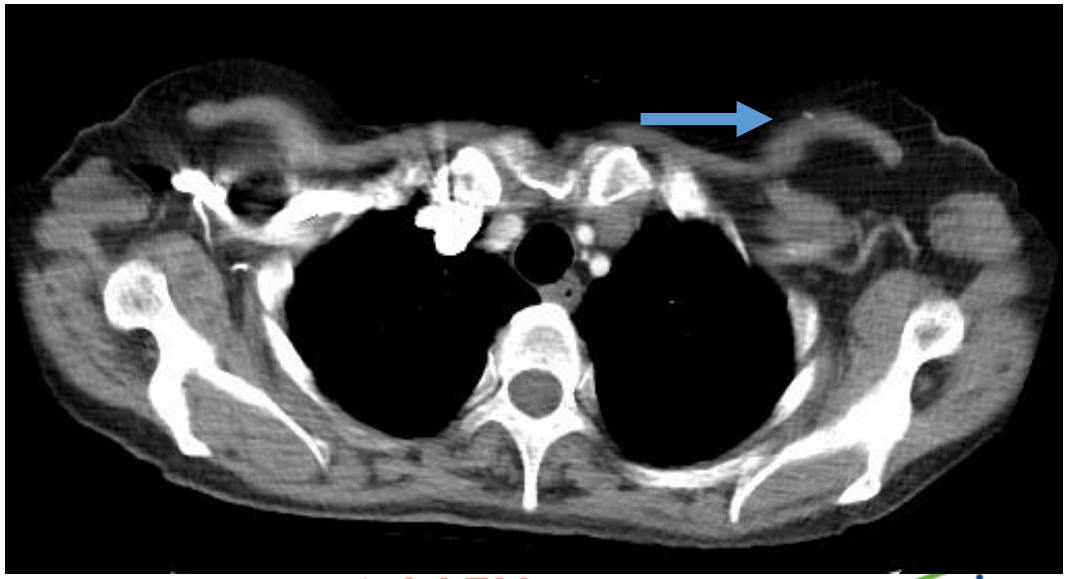
Pre-Treatment

2+ weeks after cycle #4 of pembrolizumab



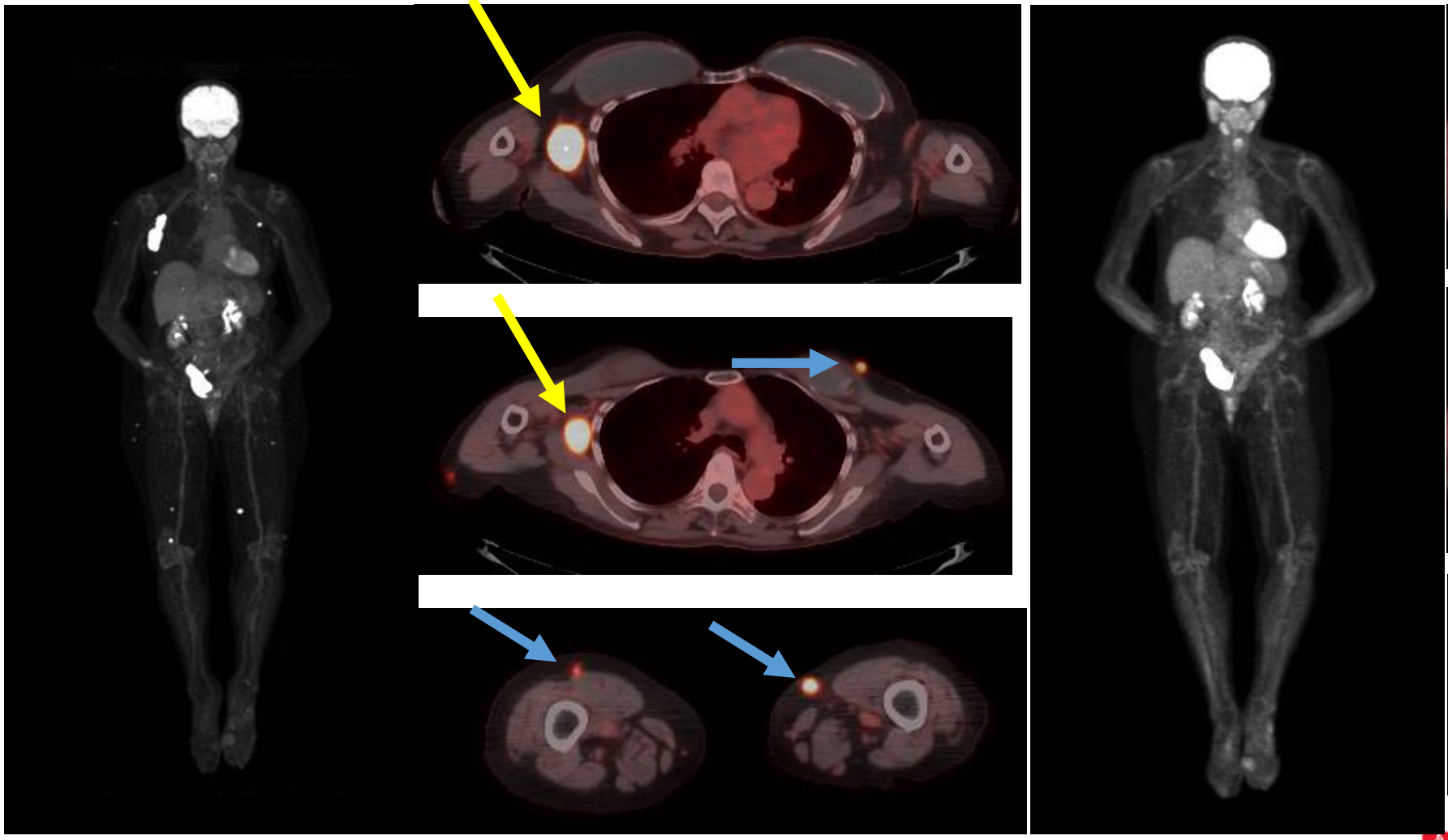


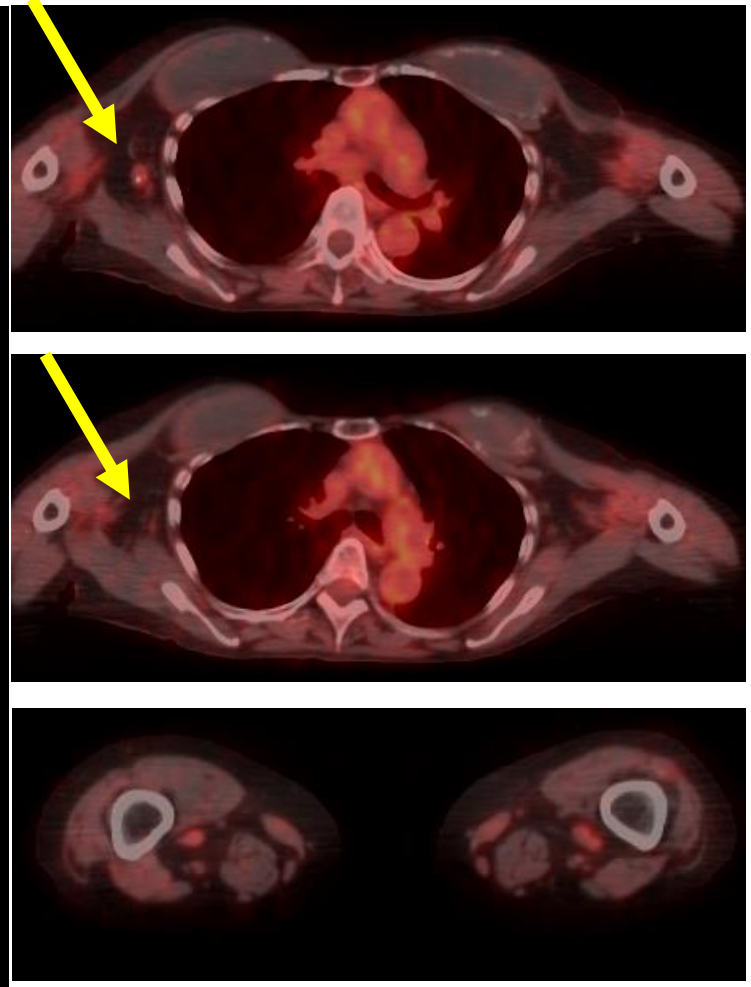




Pre-Treatment

2+ weeks after cycle #24 of pembrolizumab





Clinical status after stopping Pembrolizumab

- Remains without evidence of disease progression when last seen 7 months after stopping pembrolizumab

Take-Home Points:
Melanoma Immunotherapy

- Laboratory insights have changed the standard of care for metastatic melanoma patients.
- Immunotherapy can achieve durable responses and improve survival in metastatic melanoma, even after managing immune-related adverse events.
- Awareness of possible immune-related adverse events is essential following immunotherapy.
- Improved biomarkers of response and improved biomarkers of toxicity are needed for patients treated with immune checkpoint blockade.
- Enthusiasm is present to study treatment combinations with immune checkpoint blockade.