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

sitc Society for Immunotherapy of Cancer

Disclosures

PERSONAL

- AstraZeneca/MedImmune Data Safety Monitoring Board
- eTHERNA – Advisor
- CellDex – DSMB
- Bristol-Myers Squibb-Travel

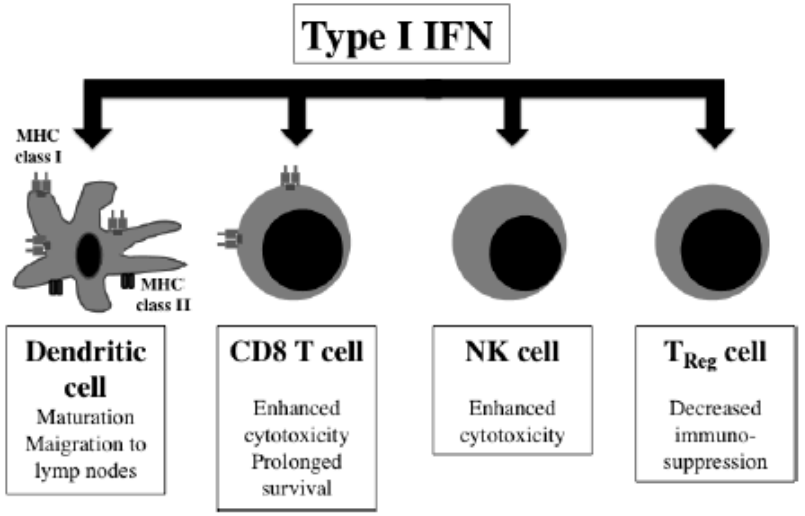
INSTITUTIONAL

- Bristol-Myers Squibb -International I-O Network
- AstraZeneca/MedImmune – Sponsored Research Agreement (OX40)

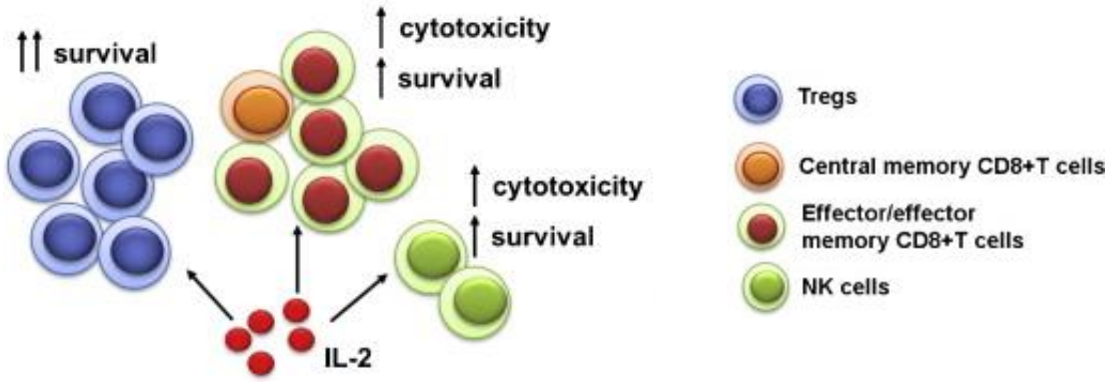
I will be discussing non-FDA approved indications during my presentation.

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.



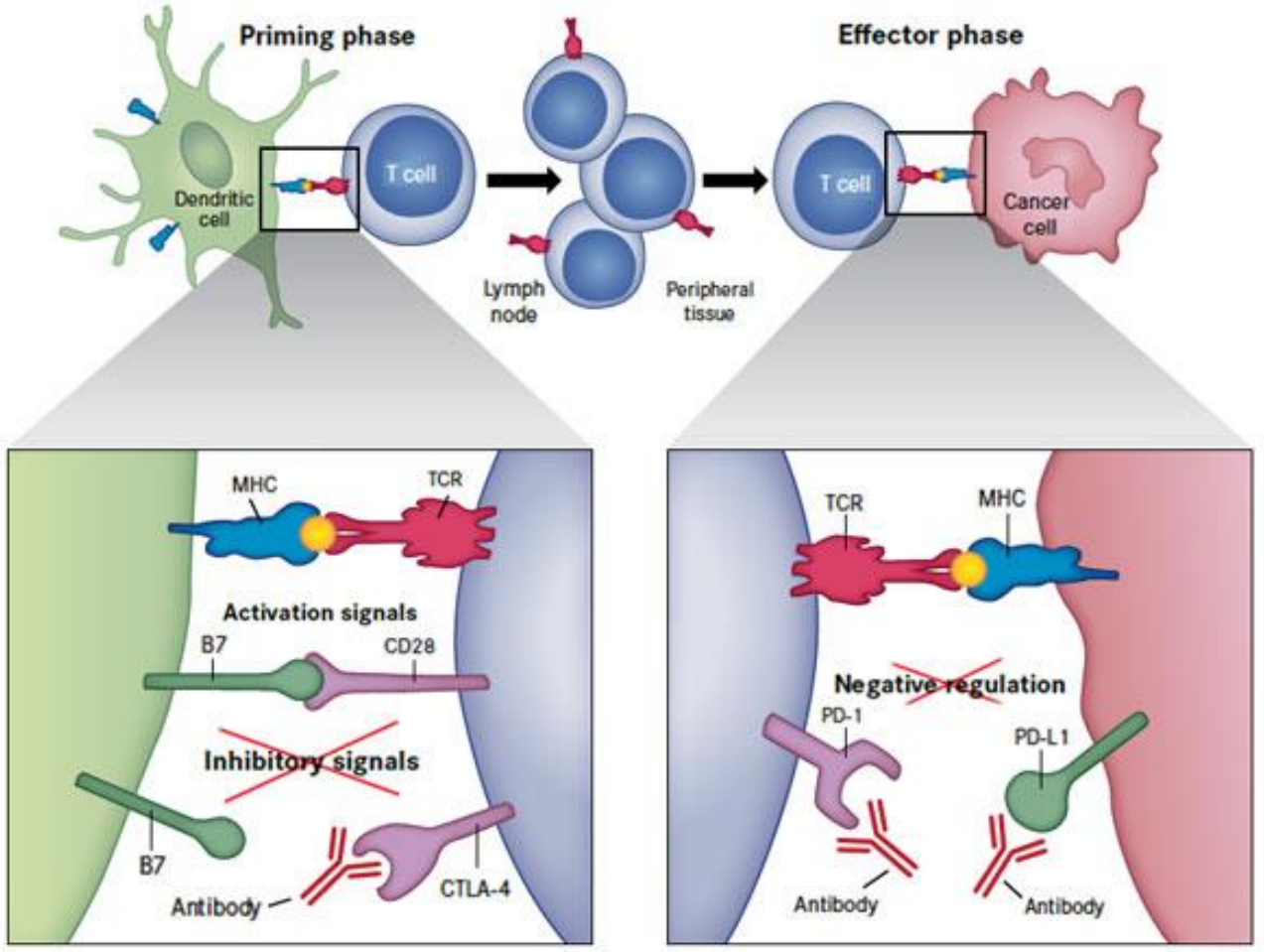
Numasaki et al. Immunotherapy 2016



Sim, Radvanyi Cytogfr 2014

FDA-approved Immunotherapies in Melanoma

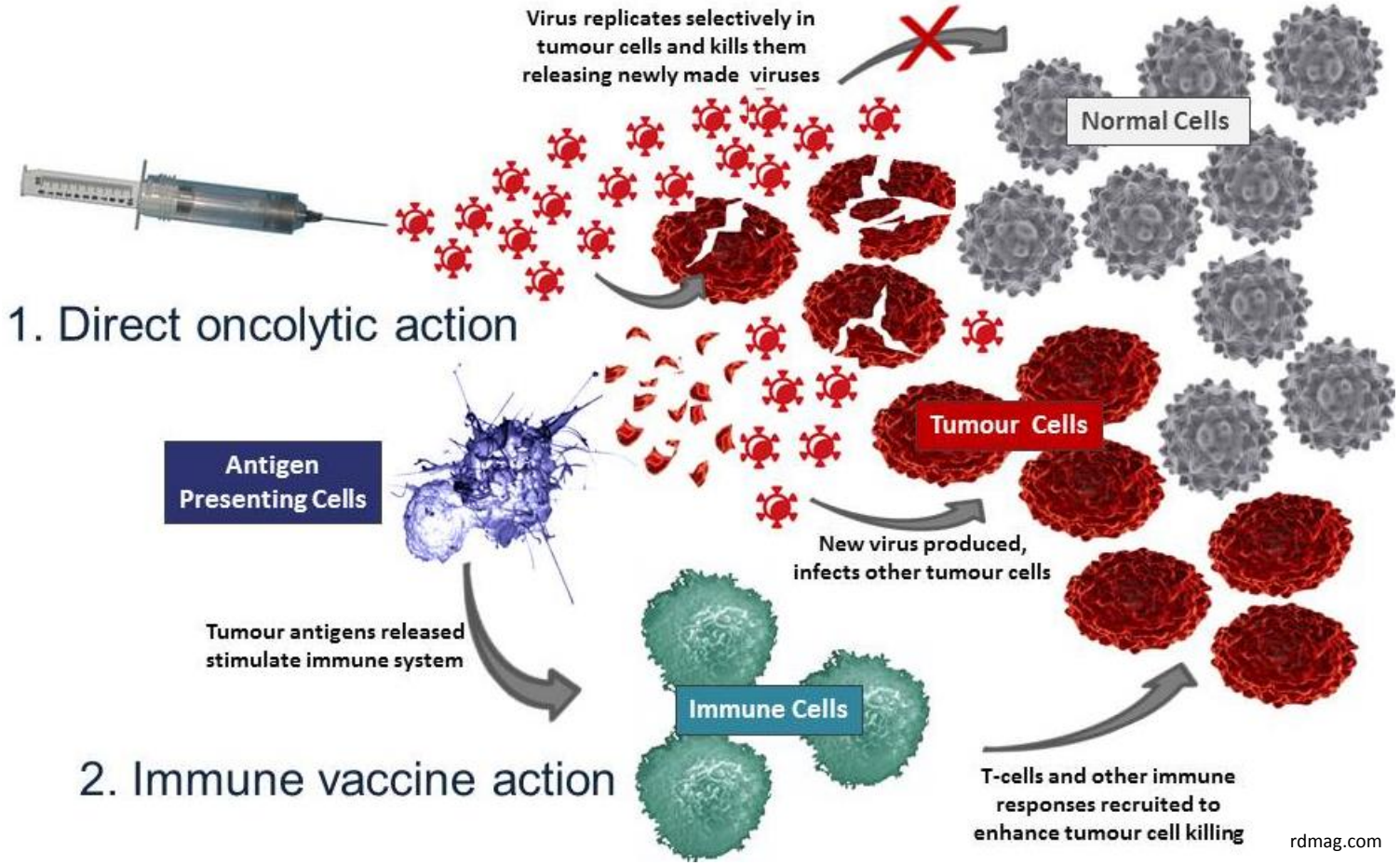
- Checkpoint inhibitors
  - Ipilimumab, adjuvant and nonresectable/Stage IV, I.V.- different dosing for adjuvant and nonresectable/Stage IV
  - Pembrolizumab, nonresectable/Stage IV, I.V.
  - Nivolumab, adjuvant and non resectable/Stage IV, I.V.
  - Ipilimumab in combination with nivolumab, Stage IV



Ribas NEJM 2012
Gordon et al Nature 2017

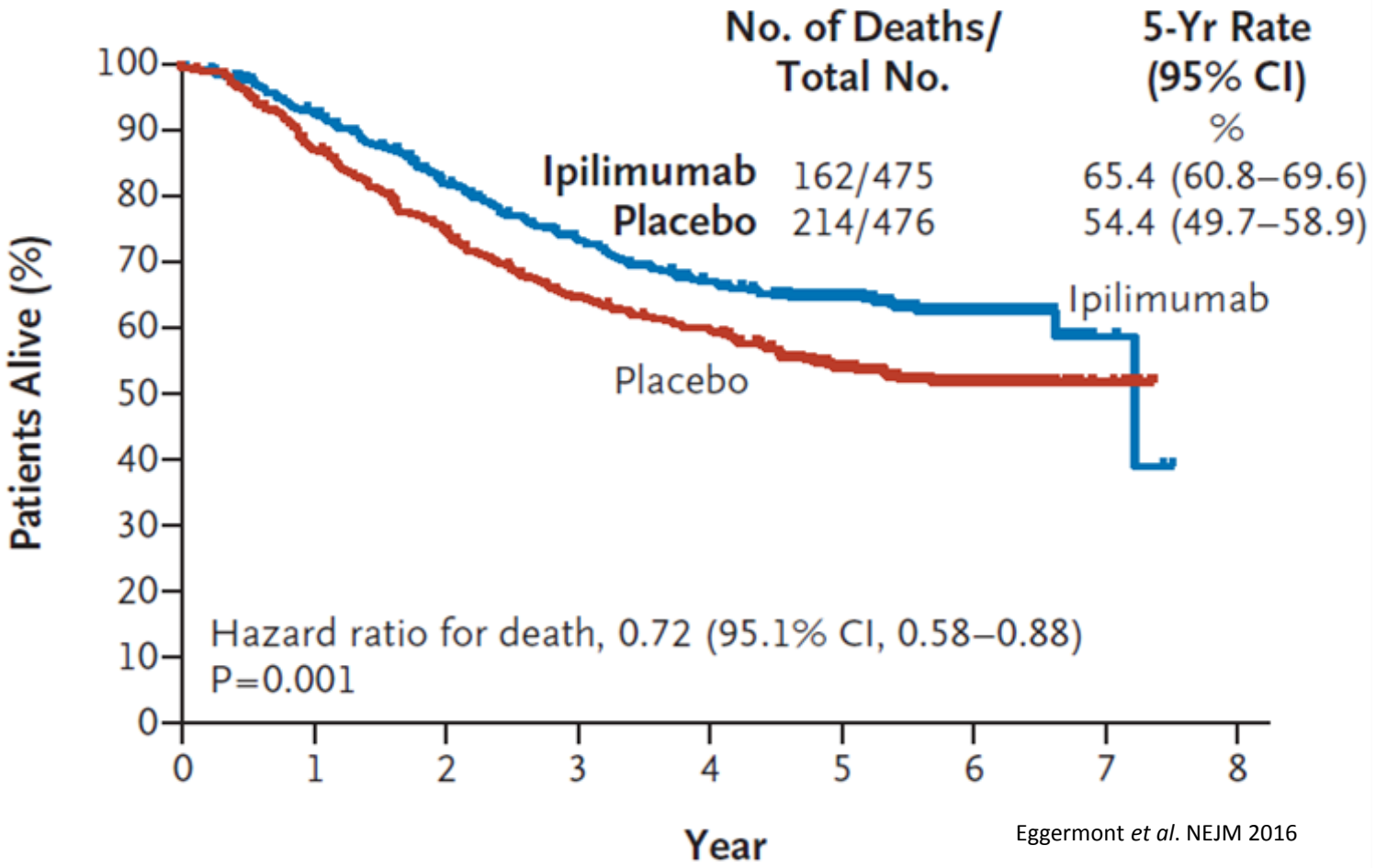
FDA-approved Immunotherapies in Melanoma

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



Adjuvant Ipilimumab in High-Risk Stage III Melanoma

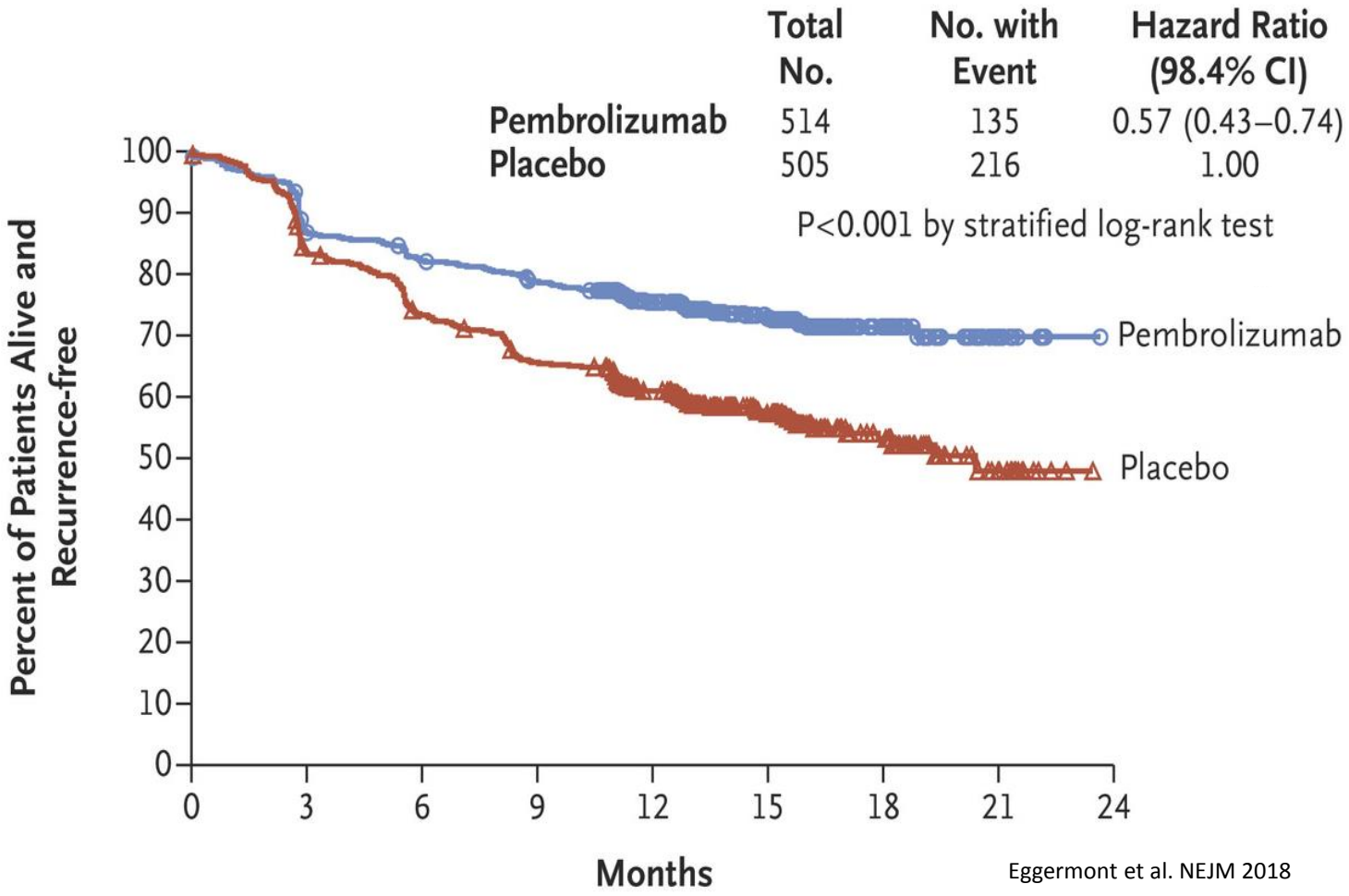
- EORTC 18071 phase III trial
  - NCT00636168
  - Adjuvant ipilimumab vs placebo
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 3 years



Eggermont *et al*. NEJM 2016

Adjuvant 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)



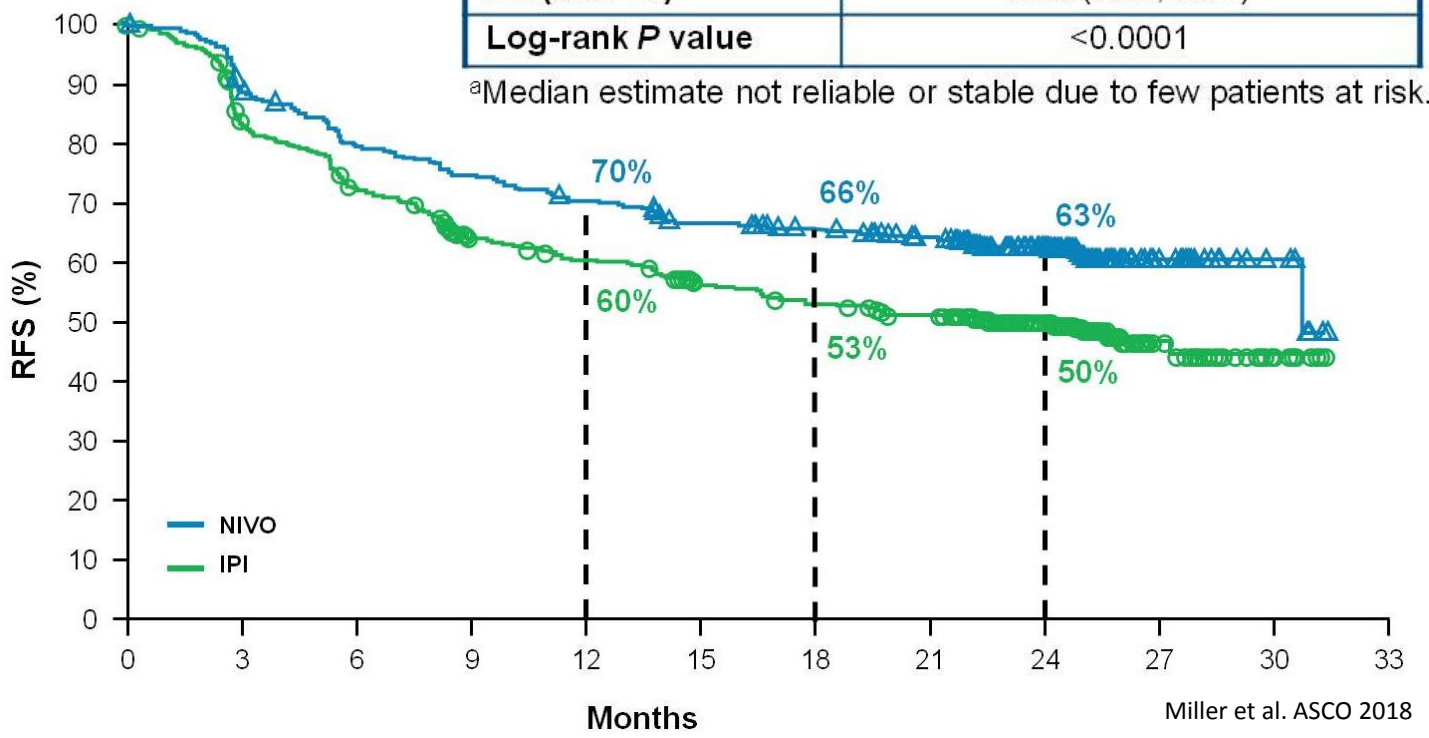
Eggermont et al. NEJM 2018

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	

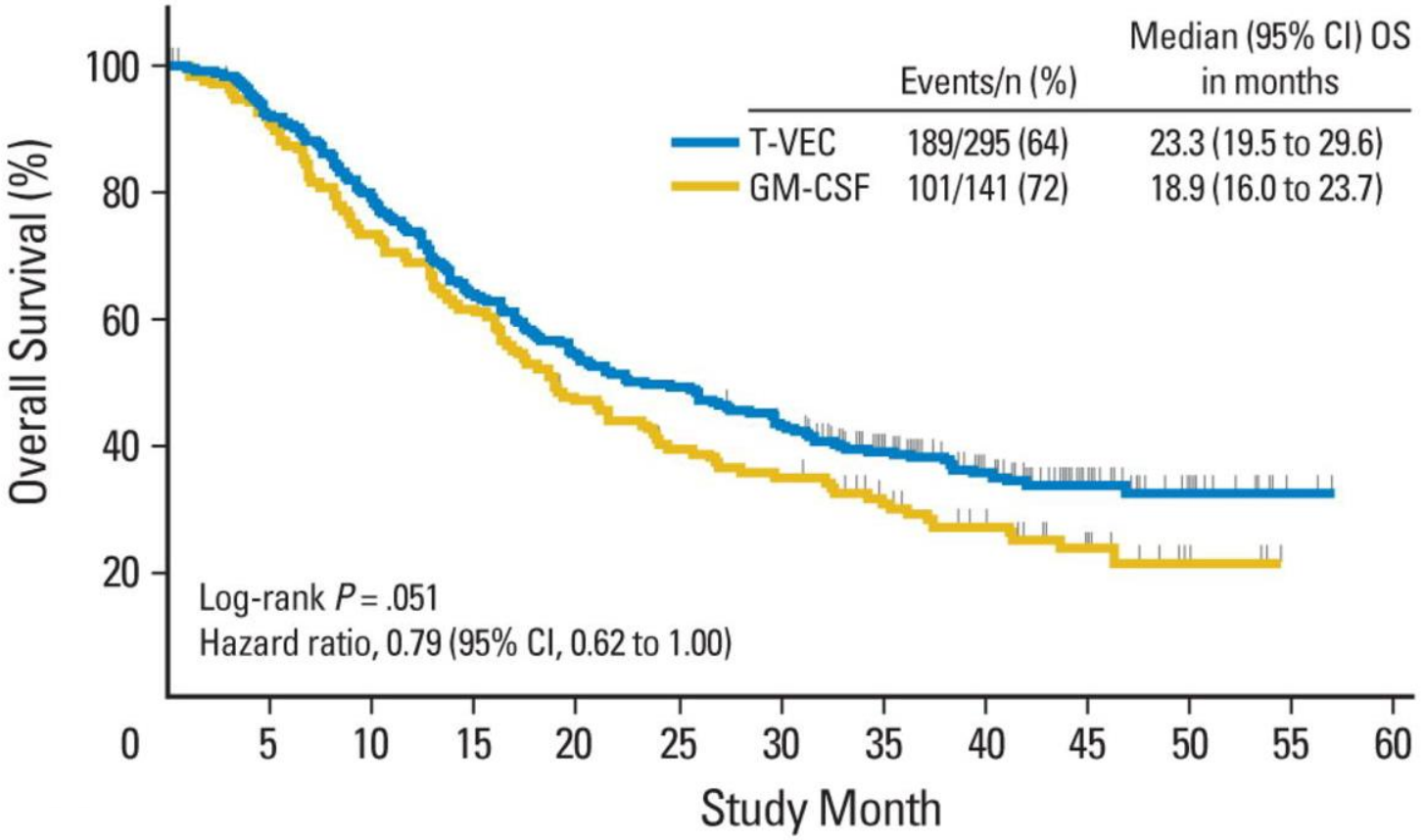
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

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

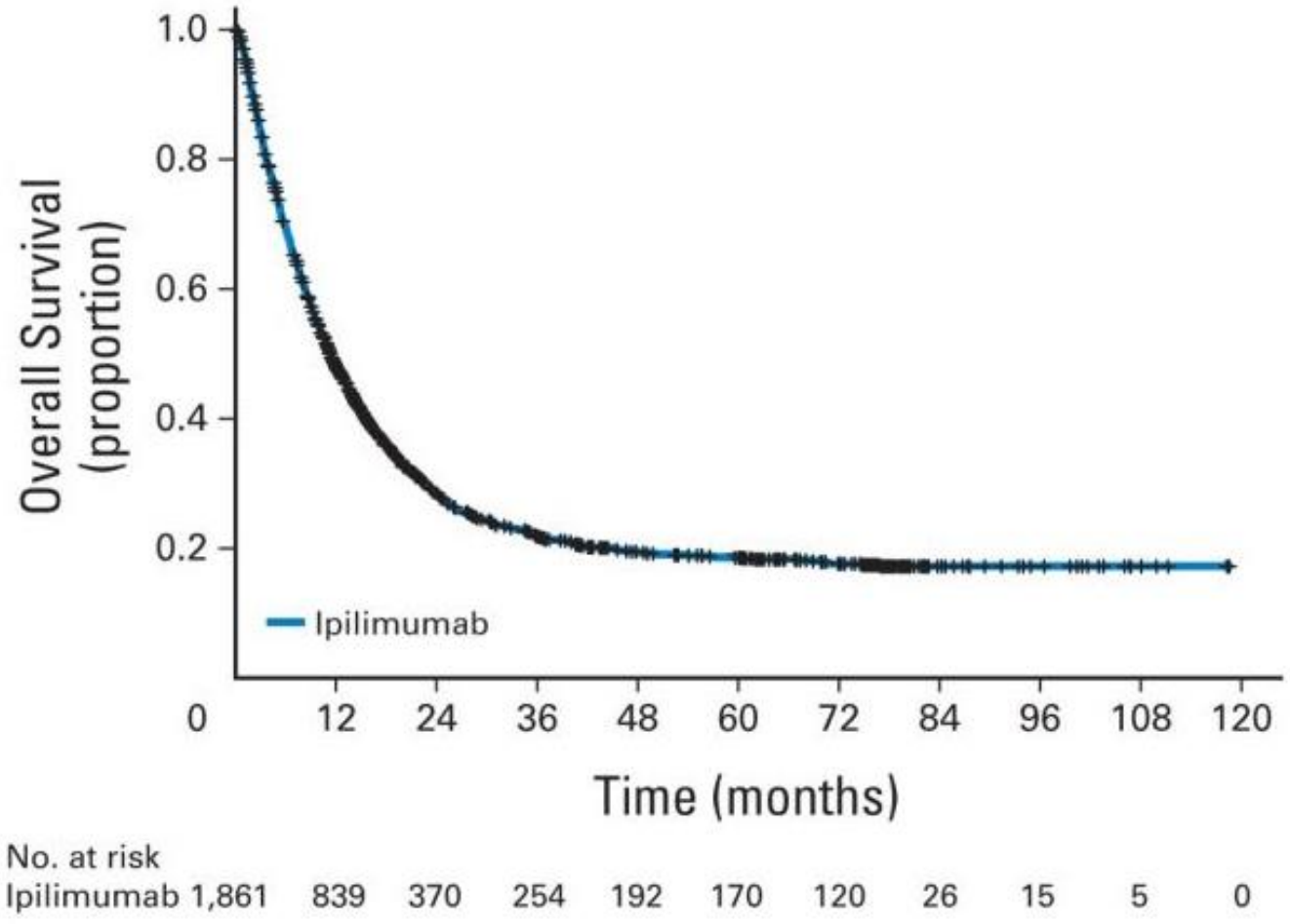
- **Phase III OPTiM Trial**
  - Oncolytic, genetically-engineered herpes virus
  - **Intralesional** T-VEC 10^6 pfu/mL, 10^8 pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF



Andtbacka, Kaufman et al. JCO 2015

Ipilimumab in Stage III/IV Melanoma

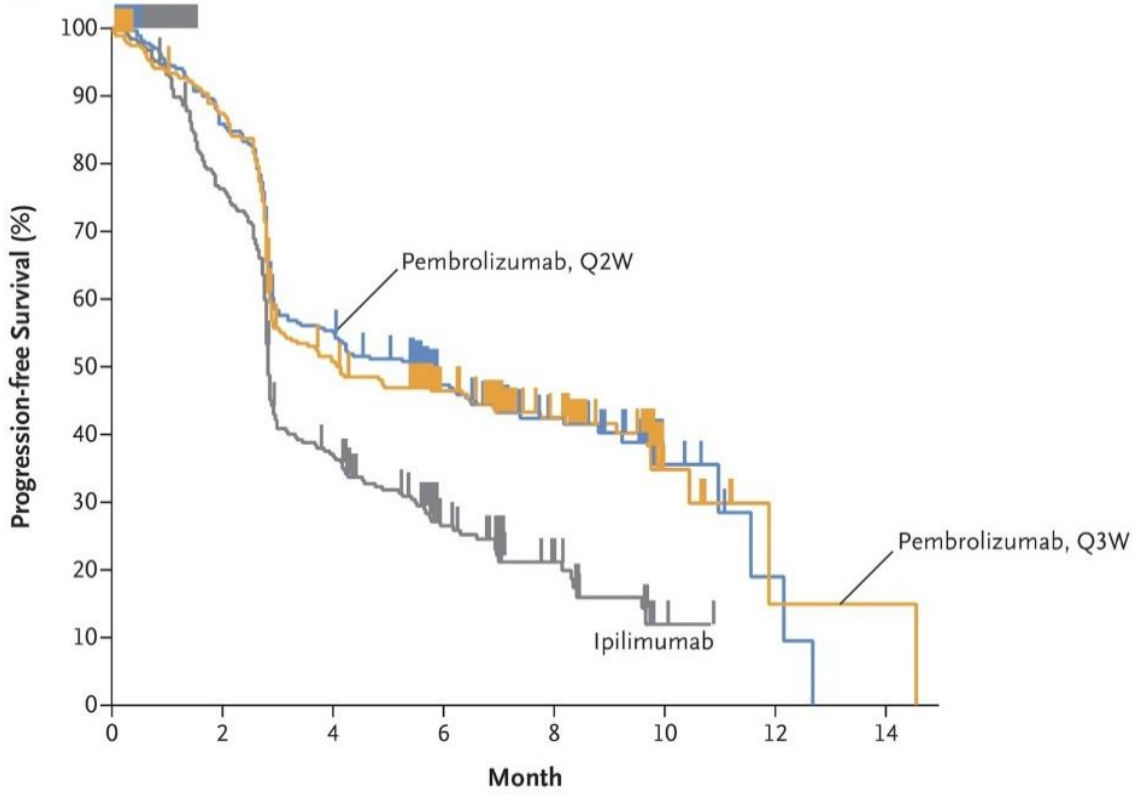
- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)

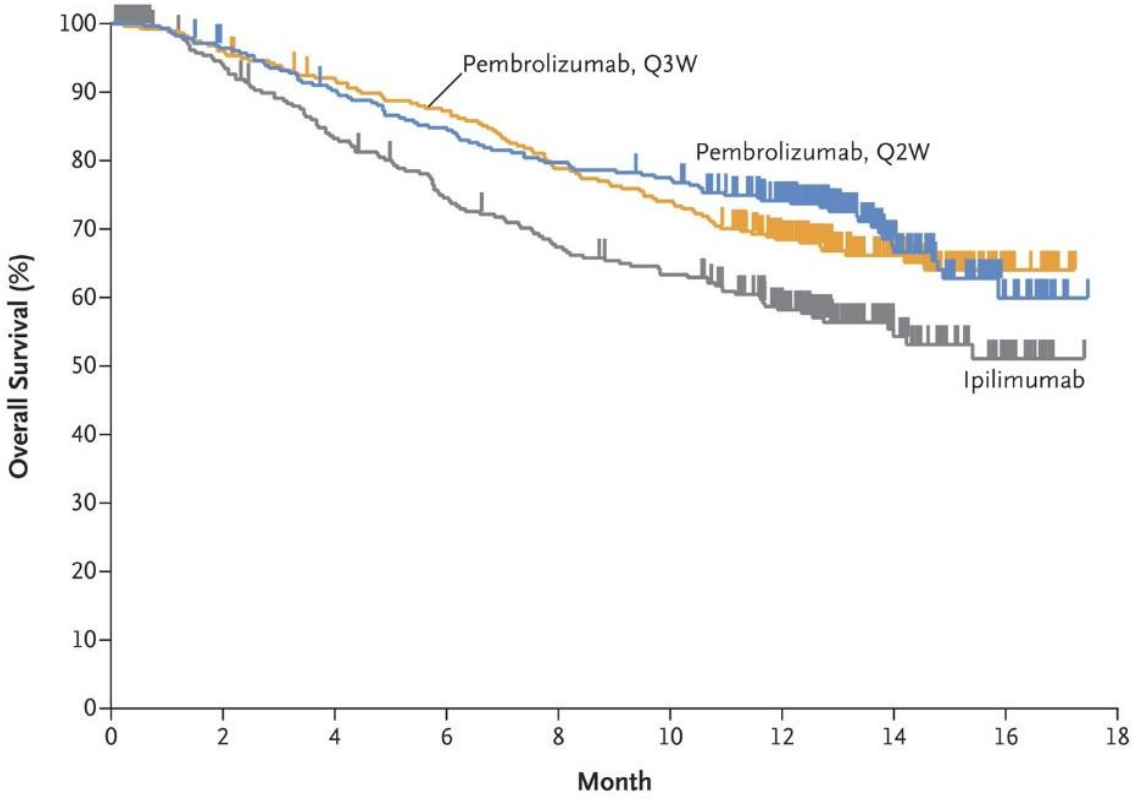


Schadendorf et al. JCO 2015

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial



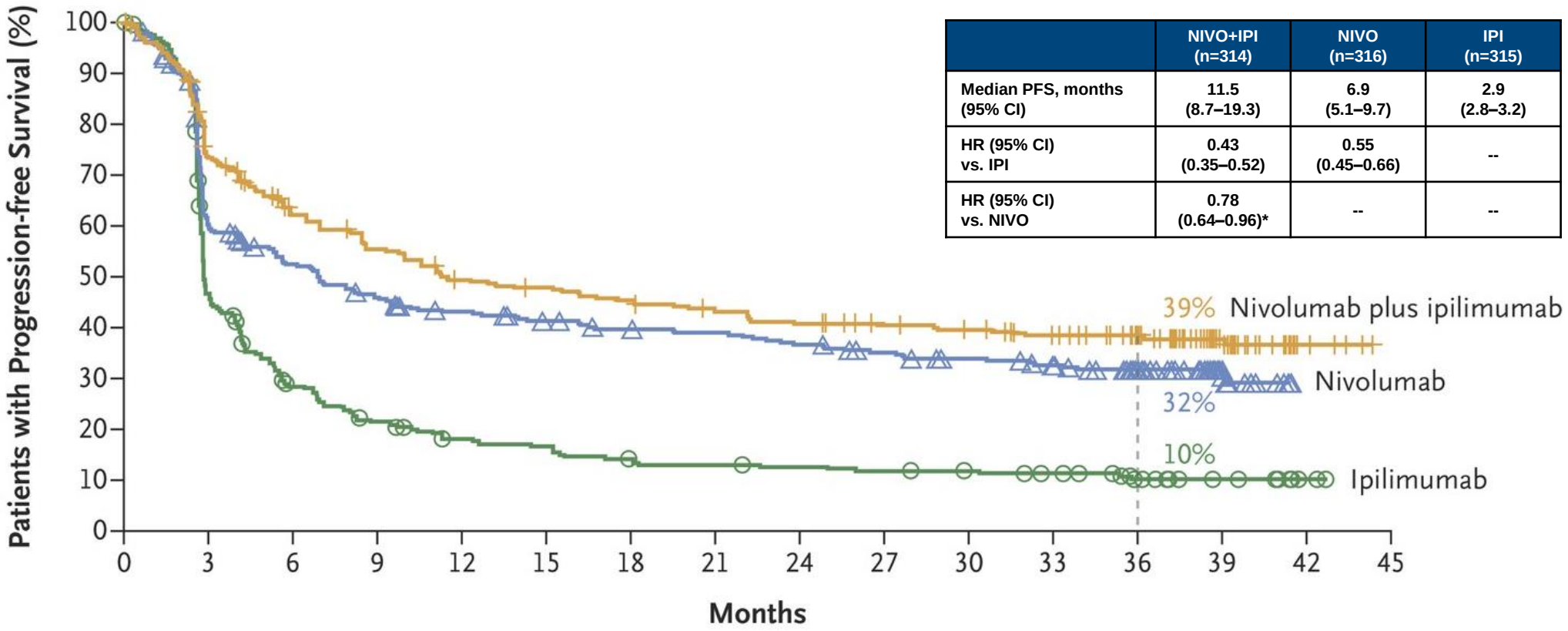


Robert et al. NEJM 2015

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)*	--	--



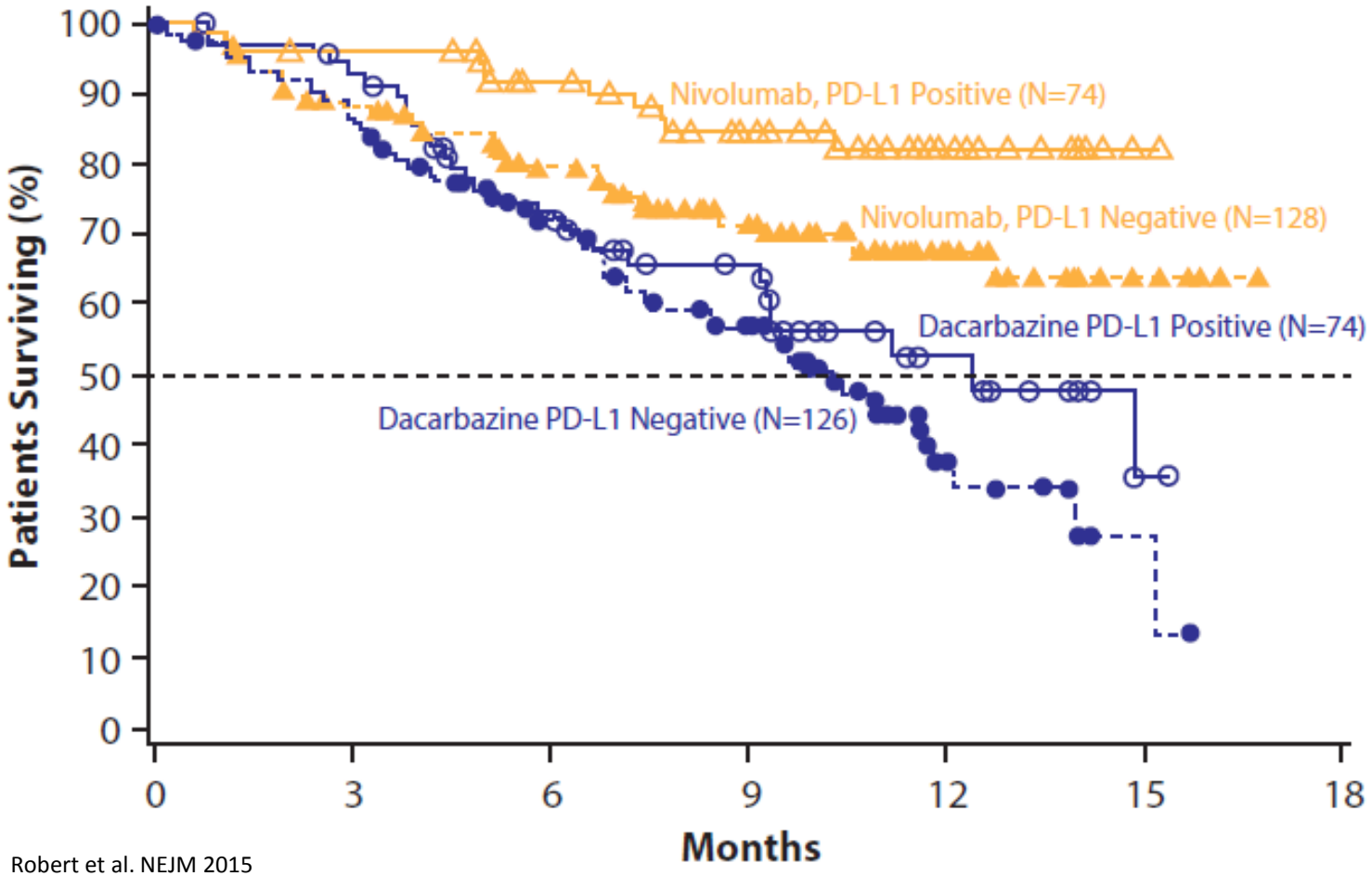
Wolchok et al. NEJM 2017

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

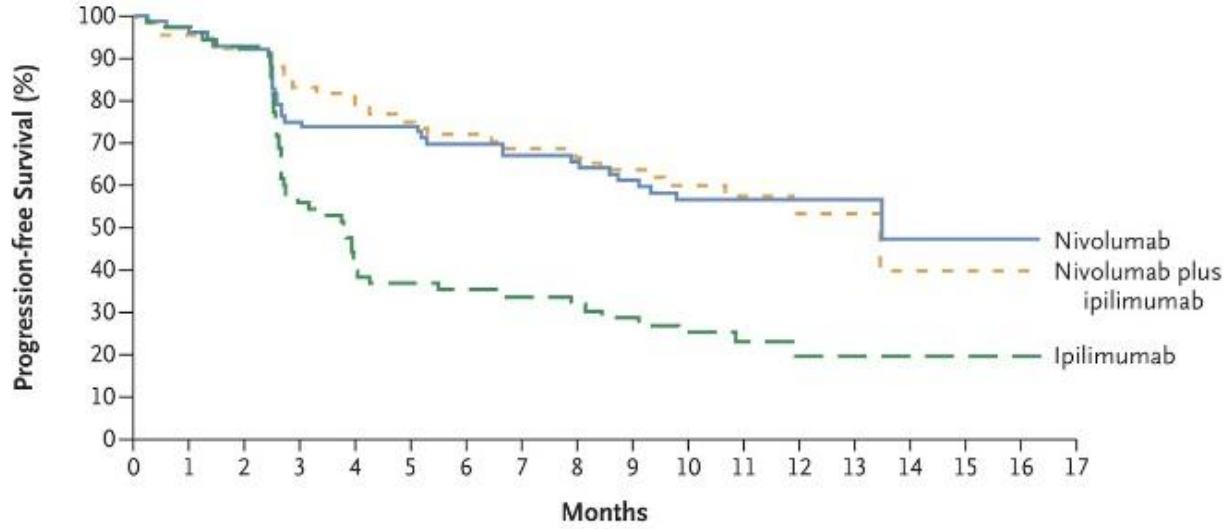
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



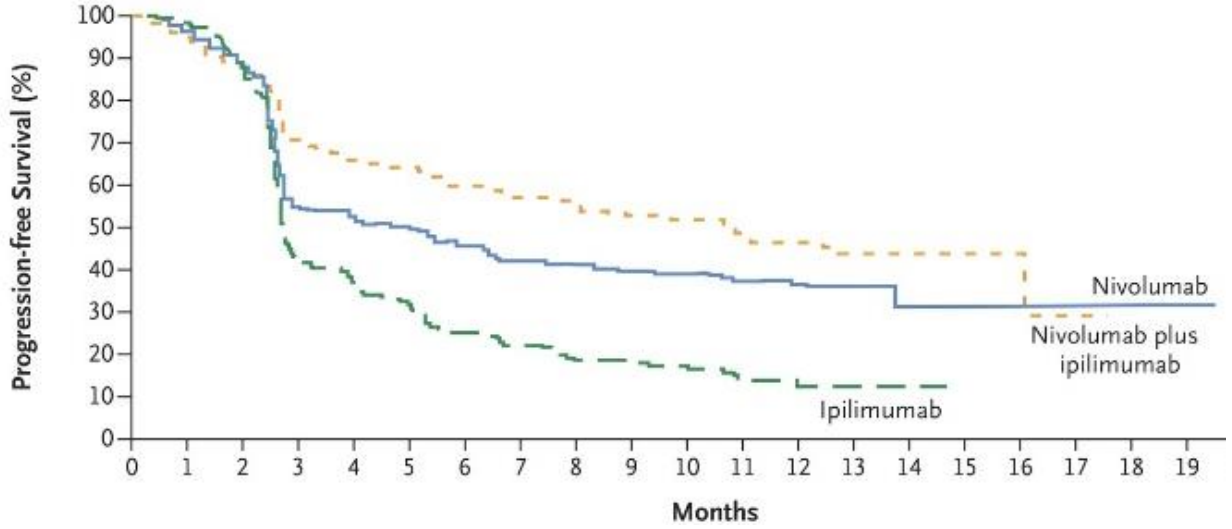
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

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



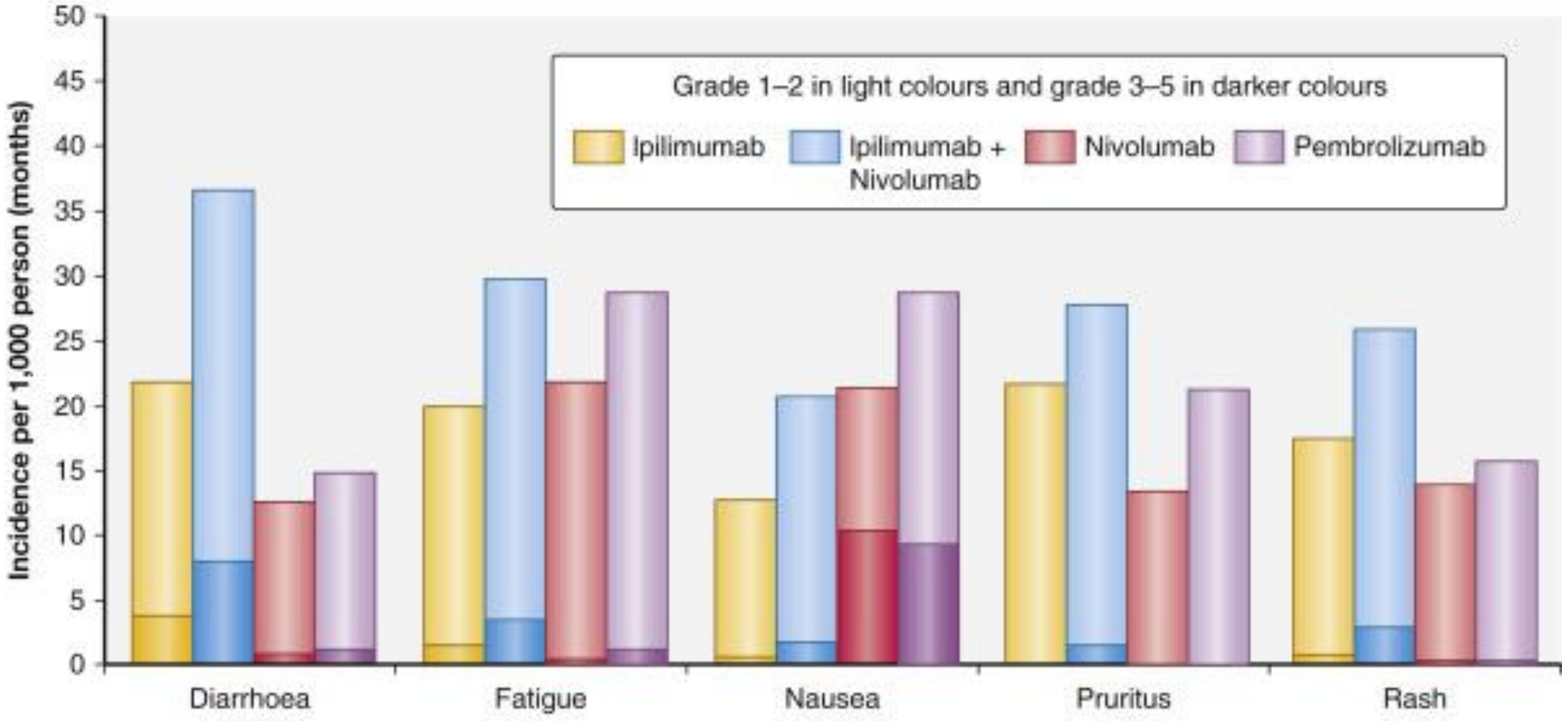
Tumor PD-L1 Positive Patients



Tumor PD-L1 Negative Patients

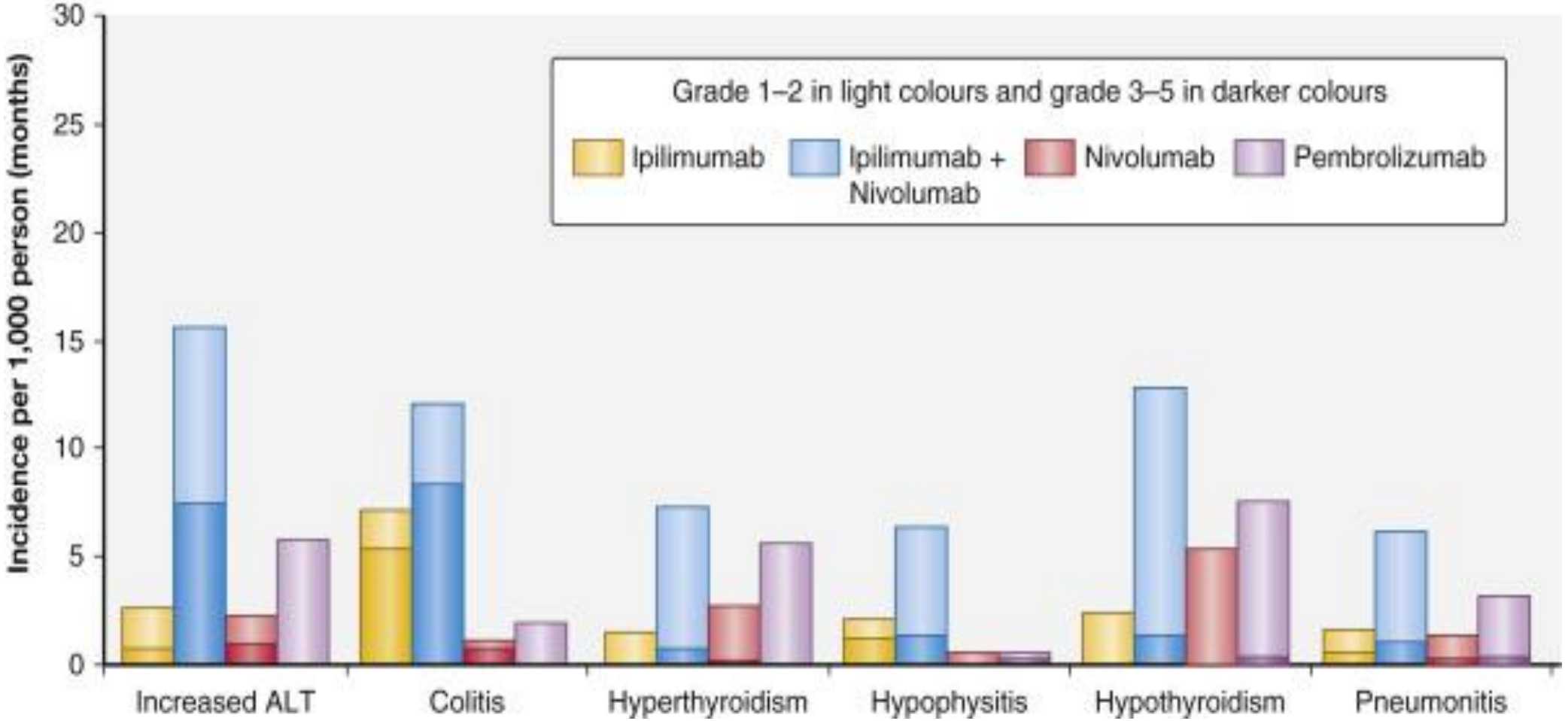
Larkin et al. NEJM 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



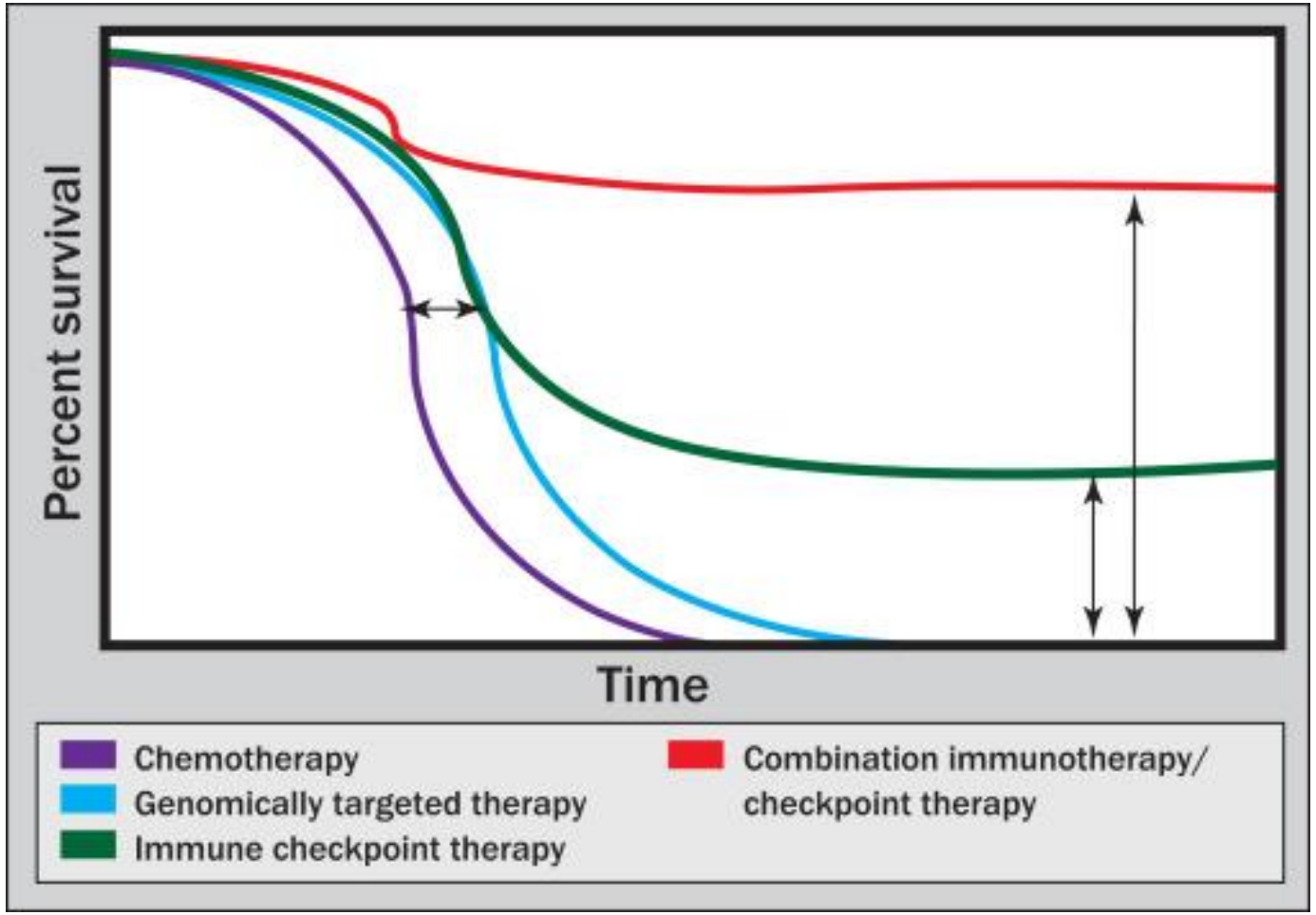
Emens et al. Eur J Cancer 2017

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

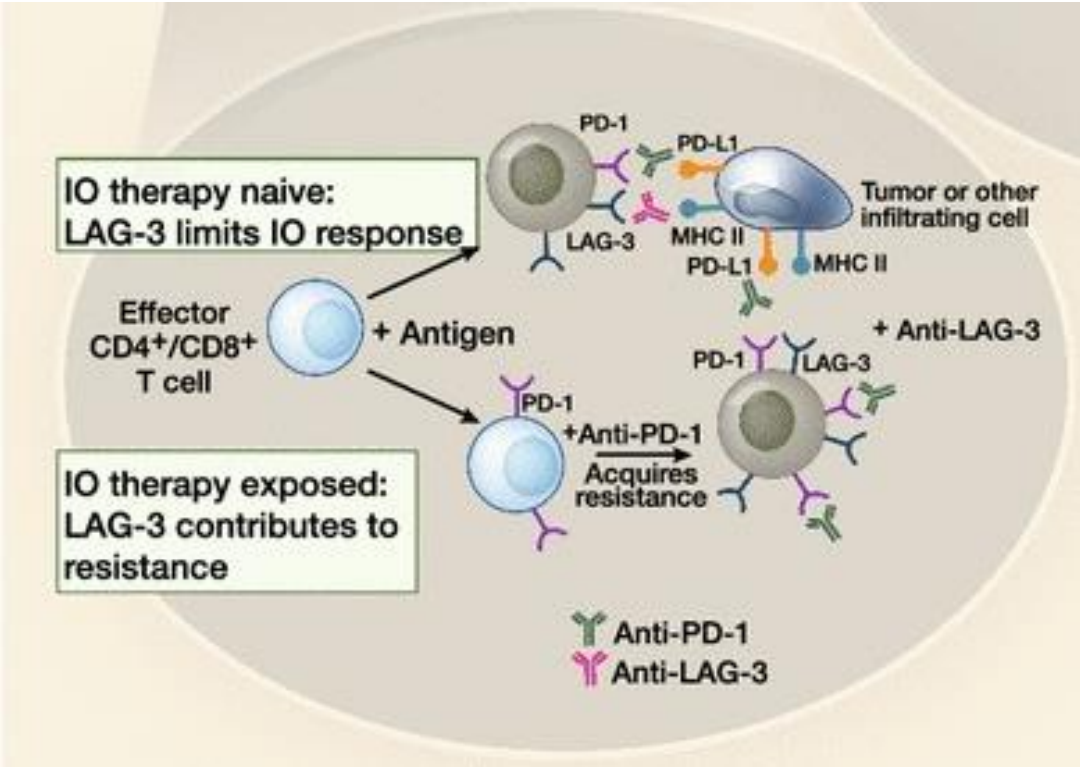
Developmental Immunotherapeutic Strategies for Melanoma

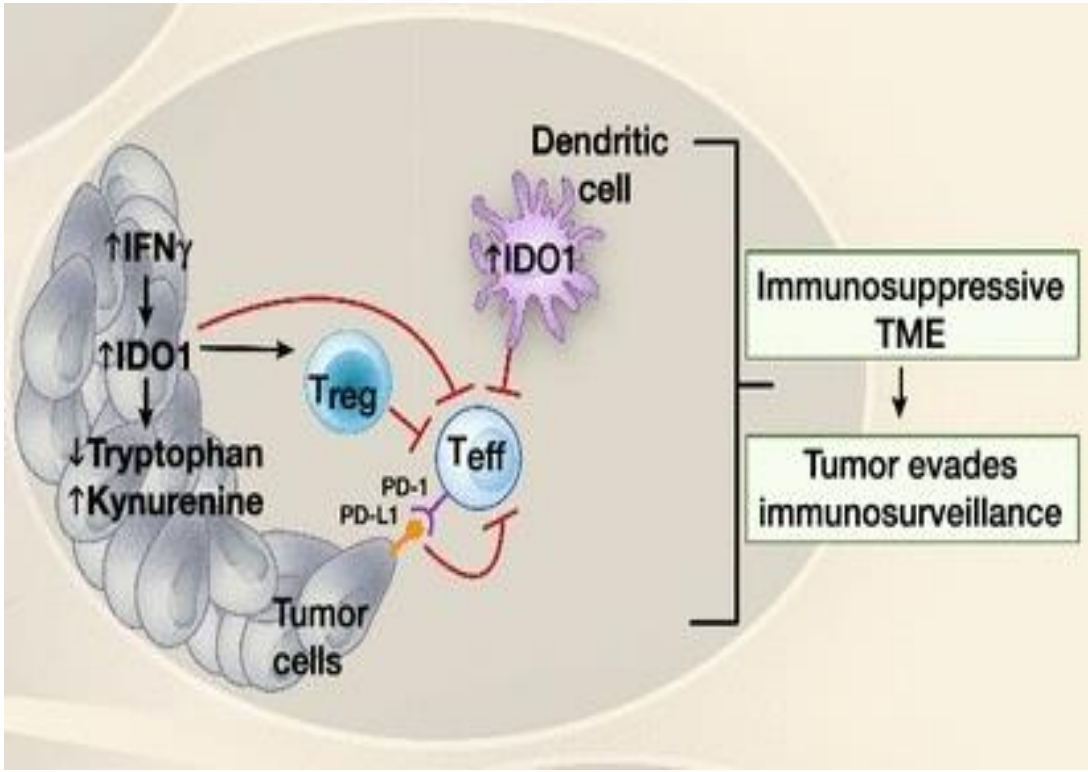


Atkins, Semi. Oncology 2015

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

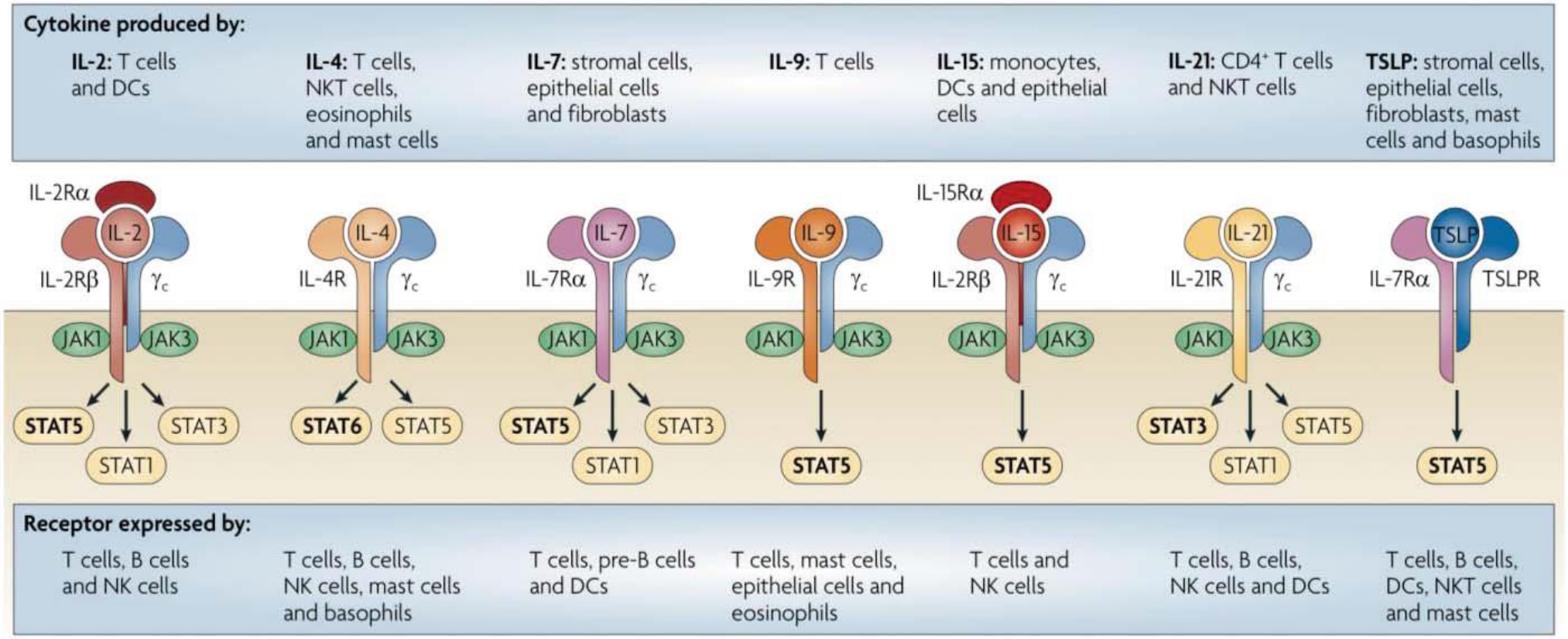
A UWCCC Clinical Trial (IND being prepared) with collaboration from Apeiron, NMS and NCI

- 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

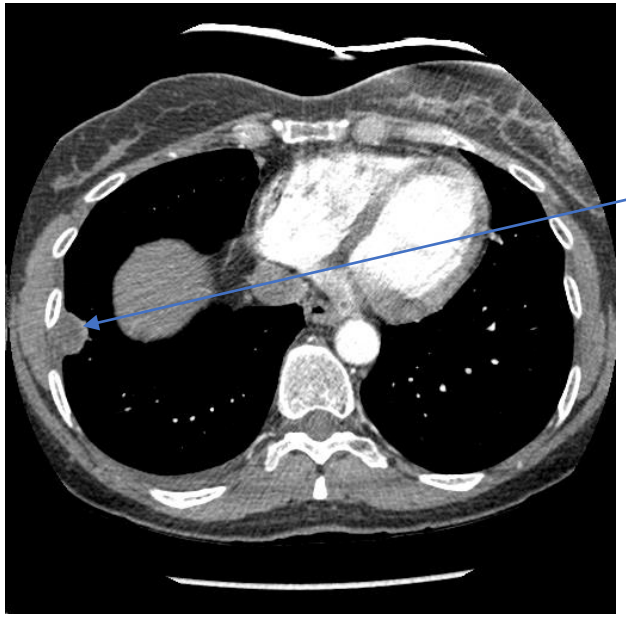
POSITION ARTICLE AND GUIDELINES Open Access

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

- 50 year old woman who presented with a changing pigmented lesion of the left temple in 2013. Biopsy showed a 0.91 mm melanoma without ulceration and < 1 mitosis/mm^2. SLN was negative. The initial pathological stage was pT1apN0M0 (Stage 1A).
- She developed RUQ pain in May 2017. She reported to the ER and CT showed:



There were multiple pulmonary, lymph node and soft tissue nodules. Biopsy confirmed melanoma and a BRAF V600E mutation was present. There was no PD-L1 expression detected.

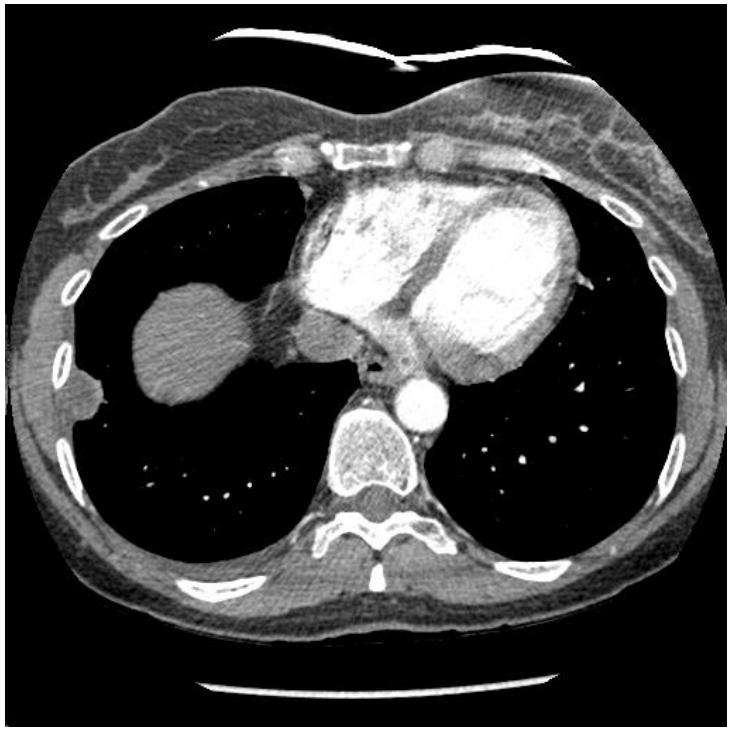
What are her treatment options?

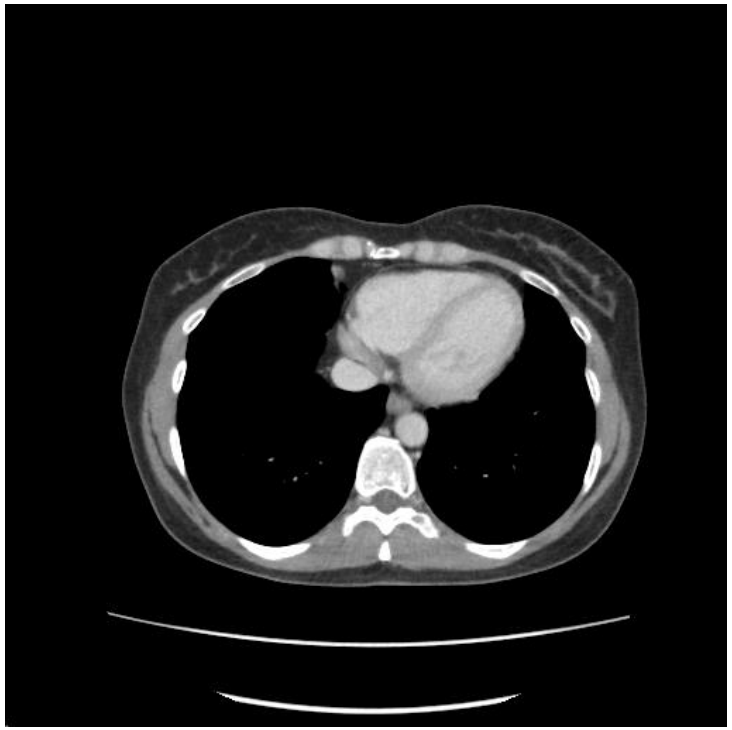
Case Study 1 continued:

- The patient volunteered for the E6134 study (DREAMseq:Doublet, Randomized Evaluation in Advanced Melanoma Sequencing). A Phase III Study BRAF and MEK inhibition or ipilimumab/nivolumab. She was randomized to ipi/nivo
- Ipilimumab + Nivolumab was administered x 3 cycles only
- Immune-mediated adverse events included:
  - Grade 3 diarrhea
  - Grade 3 transaminitis (ALT max ~300)
  - Grade 3 hypothyroidism (TSH ~80)
- High-dose (2 mg/kg) oral steroids with a slow taper and levothyroxine (ongoing) have addressed the irAEs.

Case Study 1 continued:

- Restaging imaging showed:





Complete response of all target lesions, now 20+ months after diagnosis.

Case Study 1 continued:

- How would management of this patient change if her ongoing medical problems including rheumatoid arthritis requiring immunosuppressive medications?
- What treatment would you consider if she has a recurrence?

Case study 2

- 25 year old man who presented with a changing pigmented lesion on the mid-back in May 2014. Biopsy revealed a 10mm ulcerated melanoma. SLN mapping showed drainage to both axillae and 4 LNs (2 from each side) were negative (pT4bpN0M0 stage IIC).
- He did well until December 2017 when he developed fatigue, SQ nodules and right abdominal pain.
  - Initial Evaluation?

Case study 2 continued:

- CT showed multiple pulmonary, subcutaneous and intra-abdominal nodules including a large mesenteric mass. The hemoglobin was 6 g/dL.
- Transfusion relieved the fatigue, but he had rapid onset of jejunal intussusception. Surgical resection ameliorated the SBO and confirmed a BRAF V600E+ metastatic melanoma.
  - Any other evaluation?
  - What treatments would you discuss with this patient?

Case 2 continued:

- The patient volunteered for the E6134 trial.
- Brain MRI is required for initial staging on this trial and showed a 2.6 cm right frontal lesion. He was treated by gamma knife radiosurgery and started on dabrafenib + trametinib in February 2018.
- There was a mixed response of pulmonary and intra-abdominal nodules (stable by RECIST), and 3 new small brain metastases. The brain lesions were treated with another gamma knife radiosurgery.
  - Would you continue BRAF targeted therapy or switch to immunotherapy?

Case study 2 continued:

- He was switched to ipilimumab + nivolumab on 8/28/2018.
- He was admitted to PPMC on 8/30/2018 with new onset seizure. Brain MRI showed rapid progression of a right parietal metastatic deposit. He had resection of the brain metastasis (pathology confirmed melanoma) and resumption of ipi/nivo.
- After 2 more cycles, he developed grade 3 diarrhea, not responsive to steroids. The diarrhea resolved with 1 dose of infliximab.
- Interval imaging showed regression of melanoma.
- Maintenance nivolumab ongoing without recurrence of diarrhea or other irAEs.
- Patient currently with a complete response of pulmonary and abdominal metastases.