

Immunotherapy for the Treatment of Melanoma

Theodore F. Logan, MD

Associate Professor

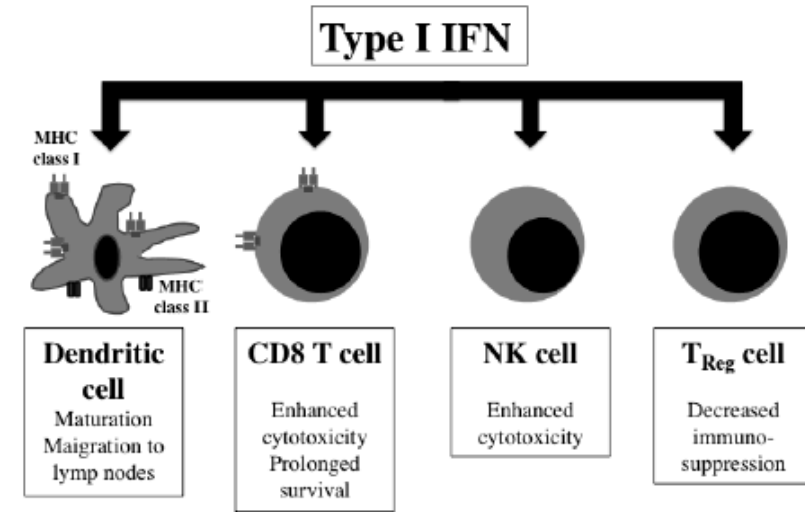
Indiana University Simon Cancer Center

Disclosures

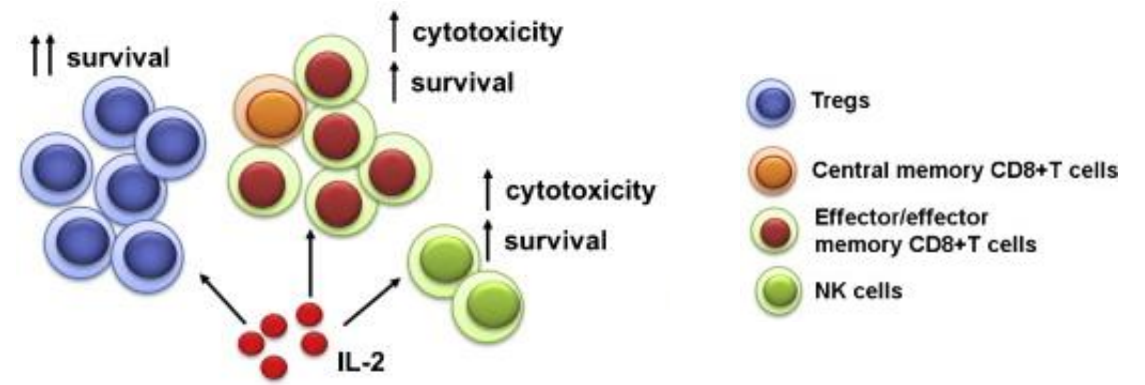
- Contracted Research:
 - Abbott Laboratories, Abraxis BioScience, Acceleron Pharma, Amgen, Argos Therapeutics, AstraZeneca, AVEO, BioVex, BMS, Eisai, Lilly, GlaxoSmithKline, Roche, Immatics, Merck, Novartis, Pfizer, Roche, Synta, Threshold Pharmaceuticals, Millennium, TRACON Pharma, Cerulean Pharma, EMD Serono, Prometheus Laboratories, MacroGenics, Peloton Therapeutics, Iovance Biotherapeutics, MedImmune, Dynavax
- I will not be discussing non-FDA approved indications during my presentation.

FDA-approved Immunotherapies in Melanoma

- Cytokines
 - Interferon- α 2b- 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

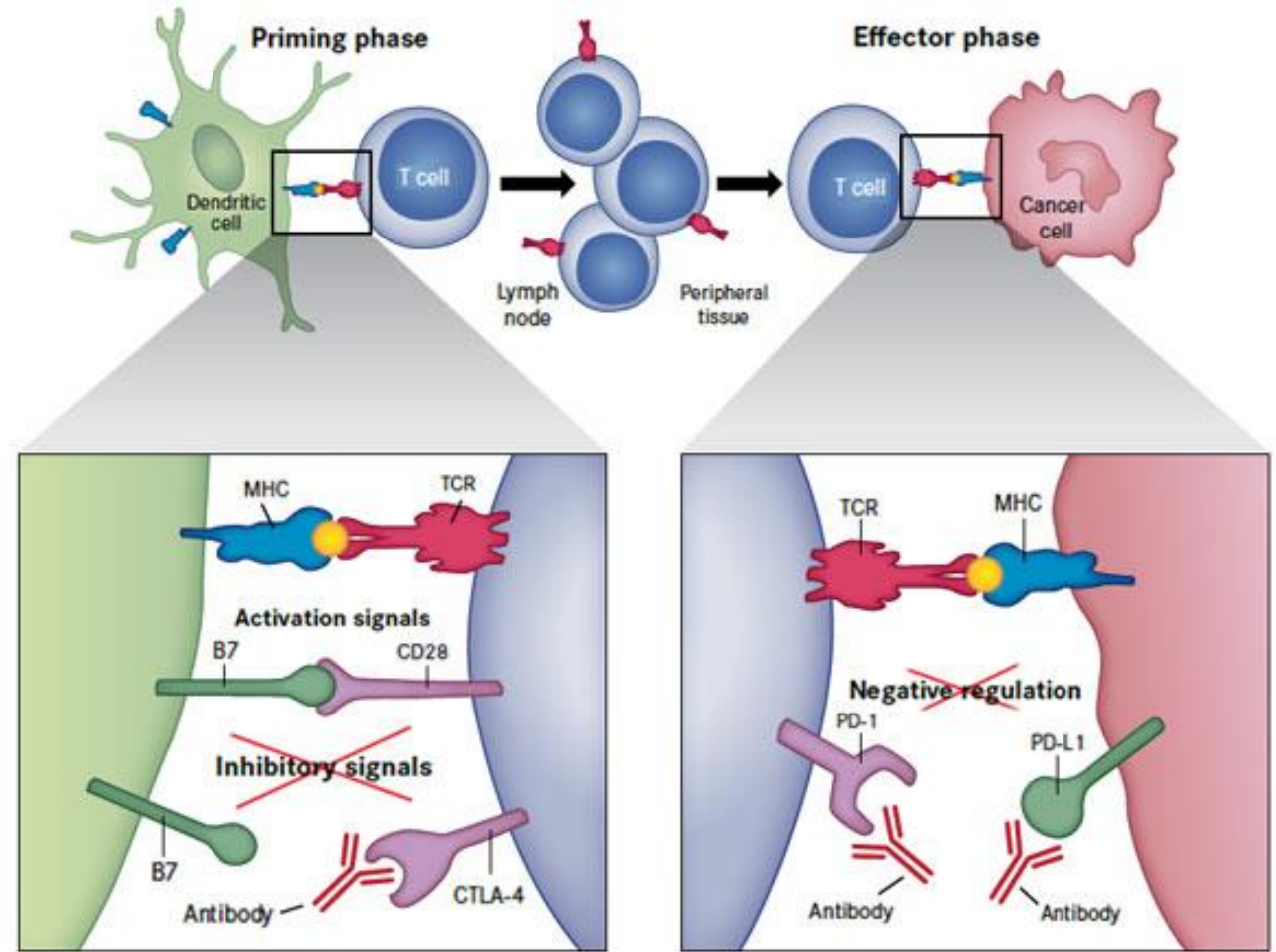


Sim, Radvanyi Cytogfr 2014

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

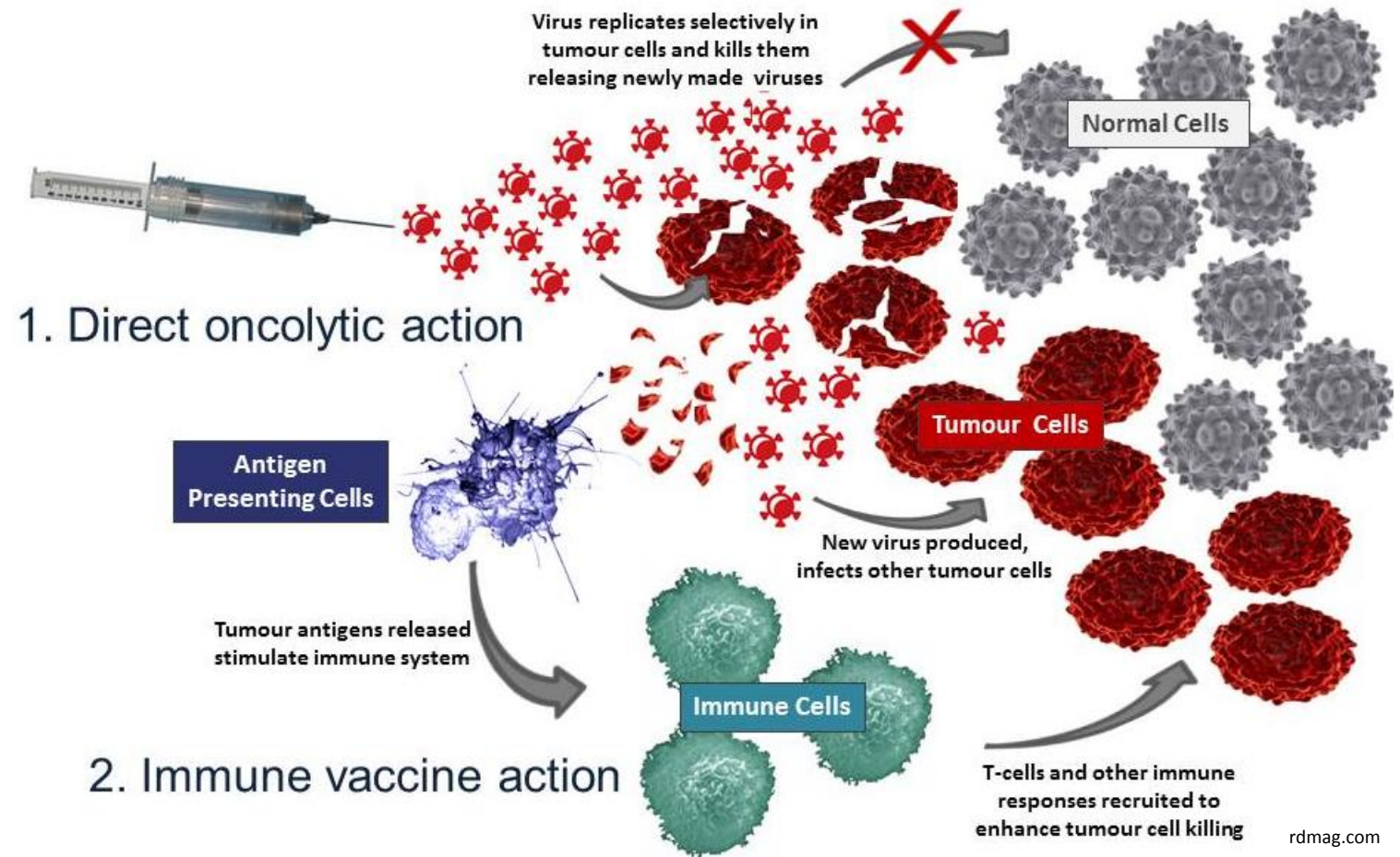


Ribas NEJM 2012
Gordon et al Nature 2017

FDA-approved Immunotherapies in Melanoma

- Oncolytic Viruses

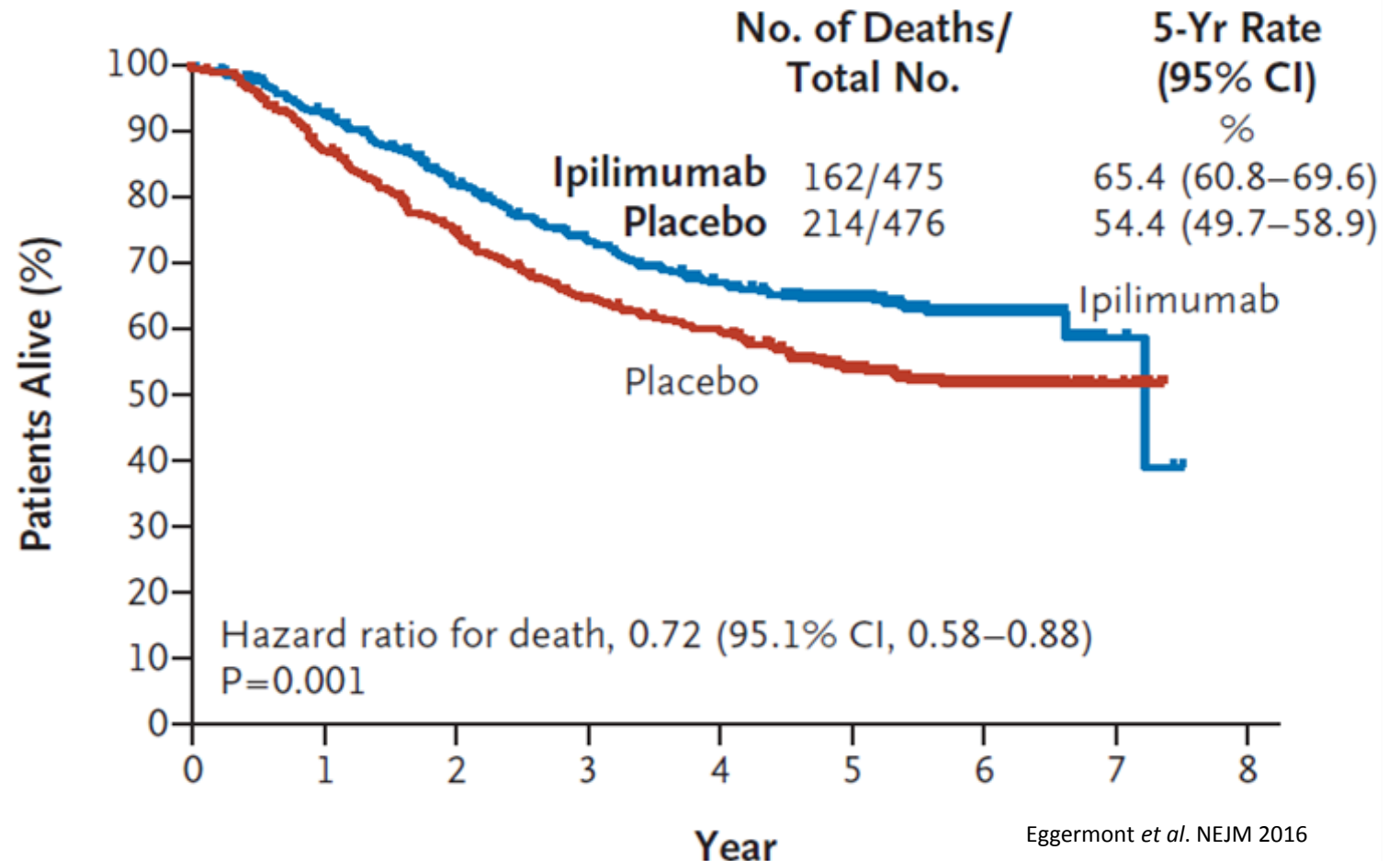
- Talimogene Laharparepvec; TVEC - non resectable, intratumoral



rdmag.com

Adjuvant Ipilimumab in High-Risk Stage III Melanoma

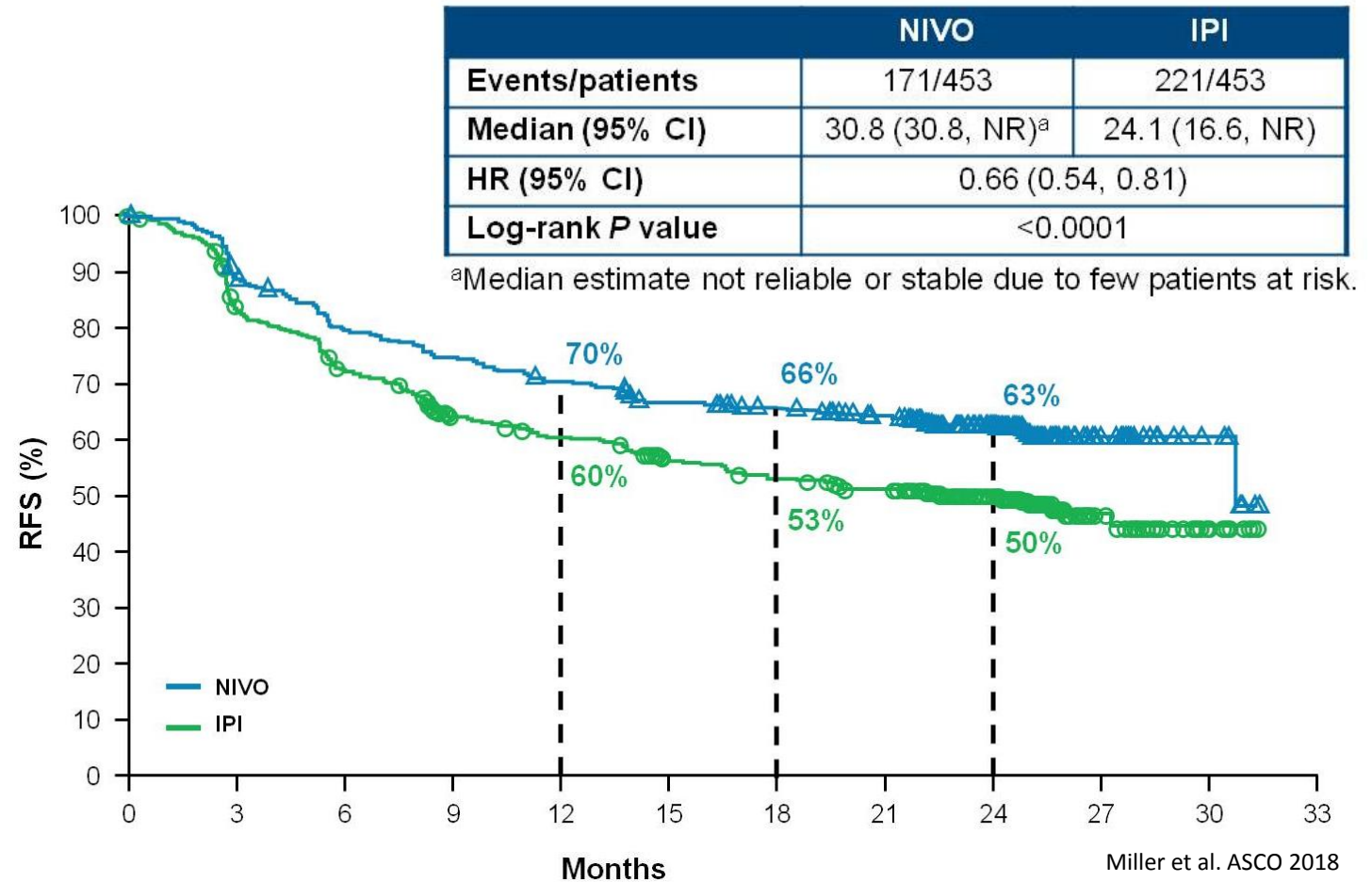
- EORTC 18071 phase III trial
 - NCT00636168
 - Adjuvant ipilimumab vs placebo
 - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 3 years



Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

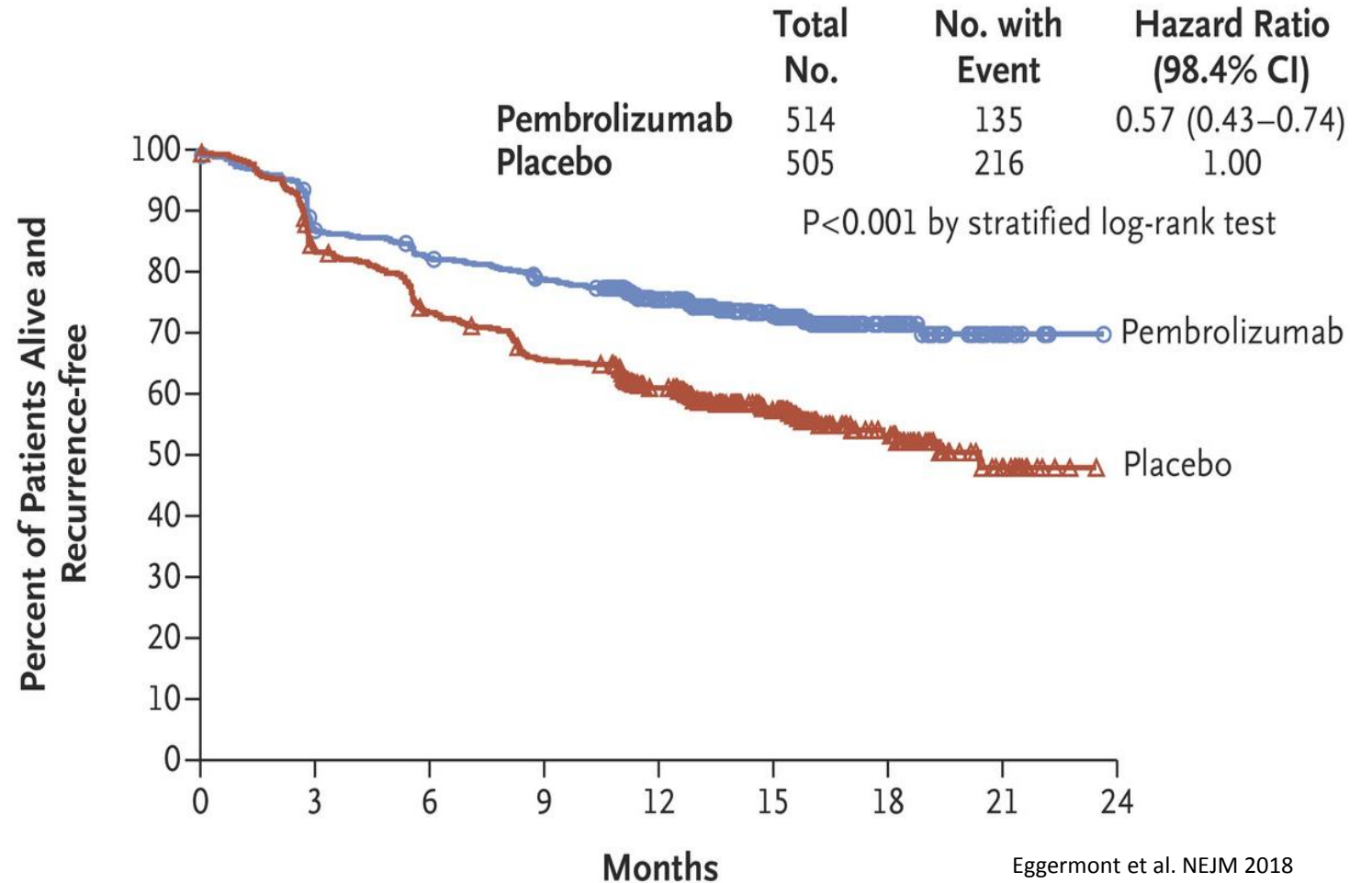
- CheckMate 238 phase III trial

- 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



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)

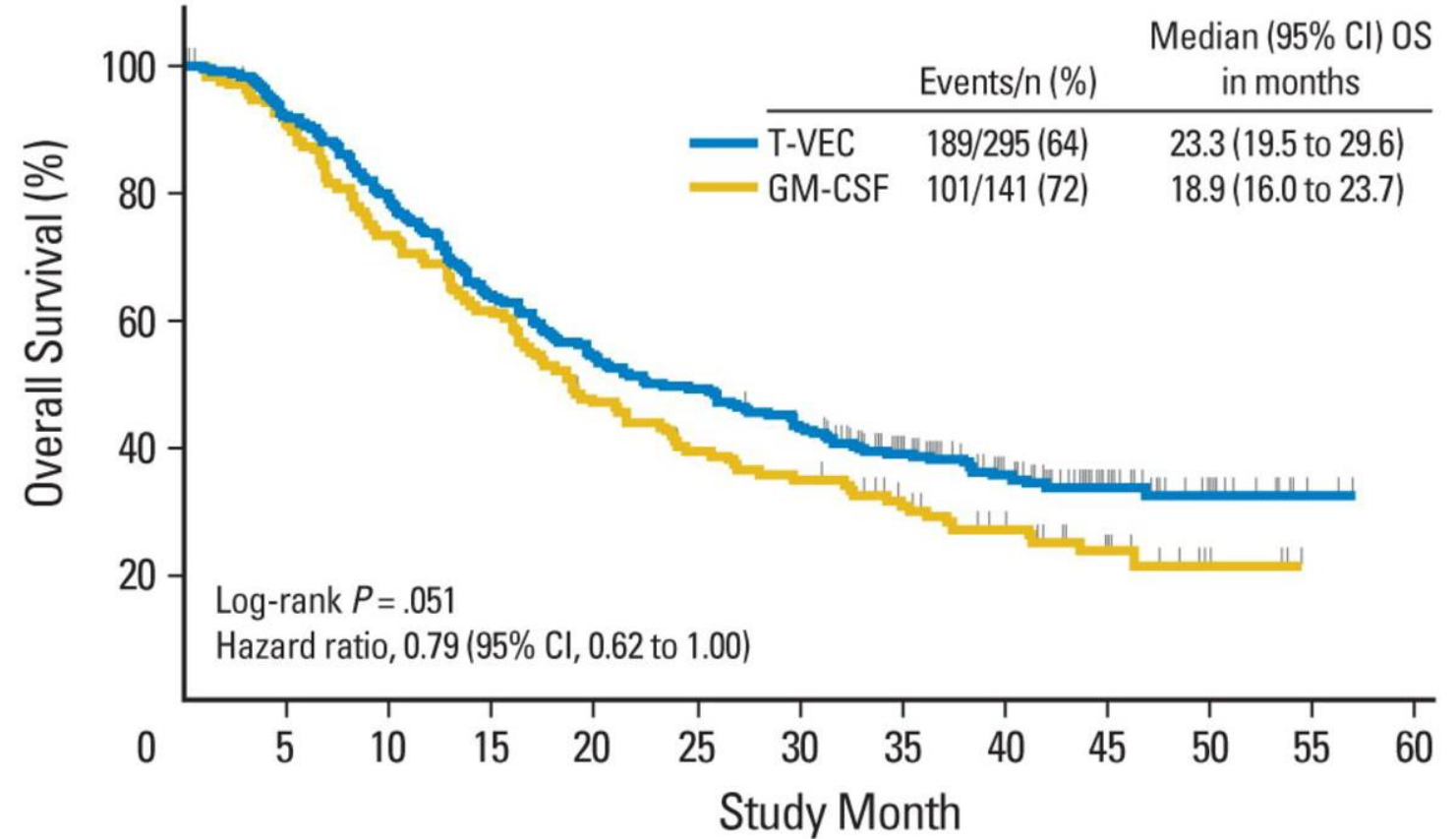


Eggermont et al. NEJM 2018

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

- **Phase III OPTiM Trial**

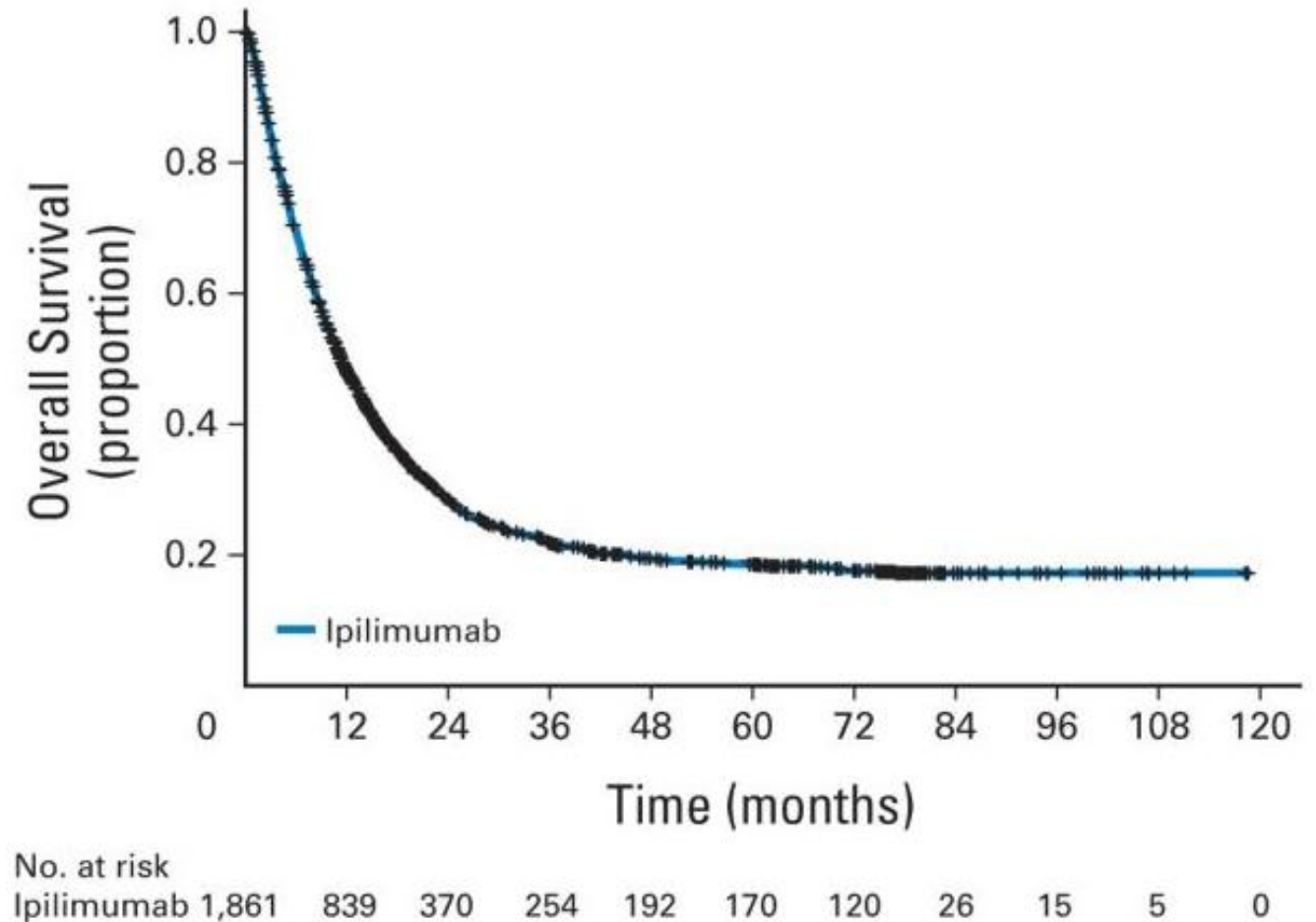
- Oncolytic, genetically-engineered herpes virus
- **Intralesional T-VEC**
10⁶ pfu/mL, 10⁸ pfu/mL 3 weeks after initial dose, then Q2W
- Subcutaneous GM-CSF



Andtbacka, Kaufman et al. JCO 2015

Ipilimumab in Stage III/IV Melanoma

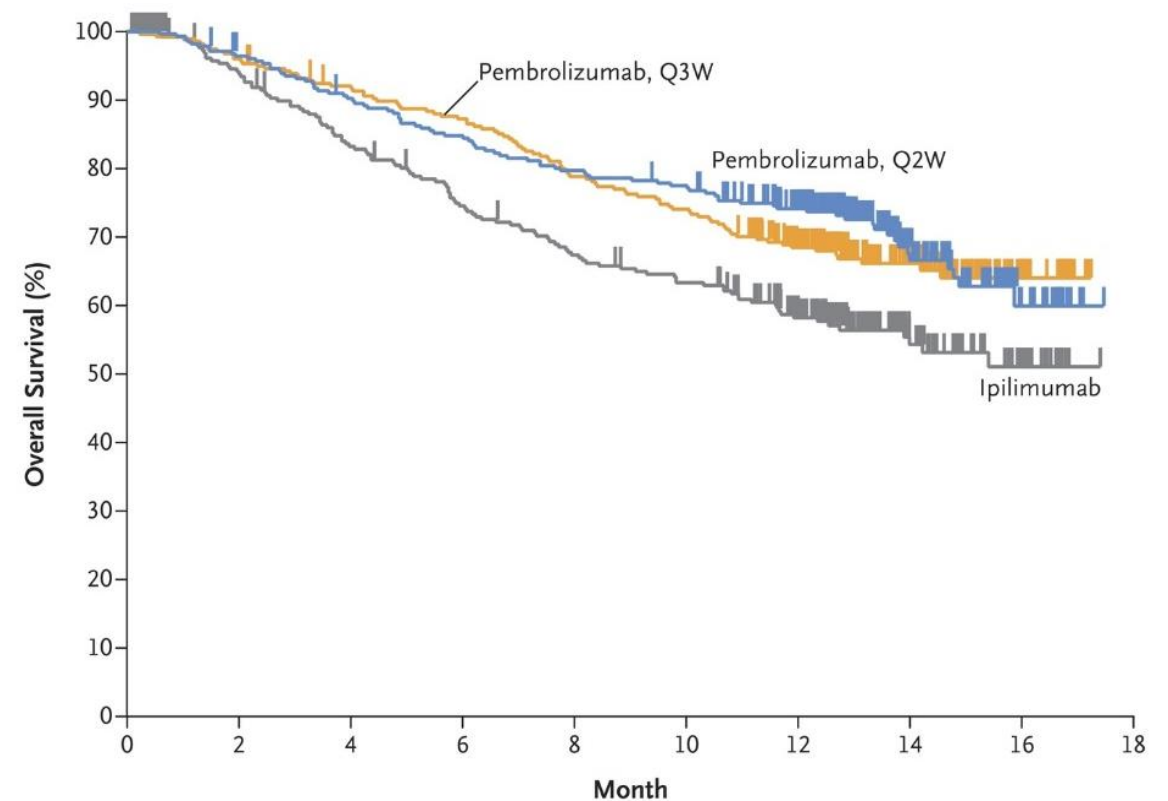
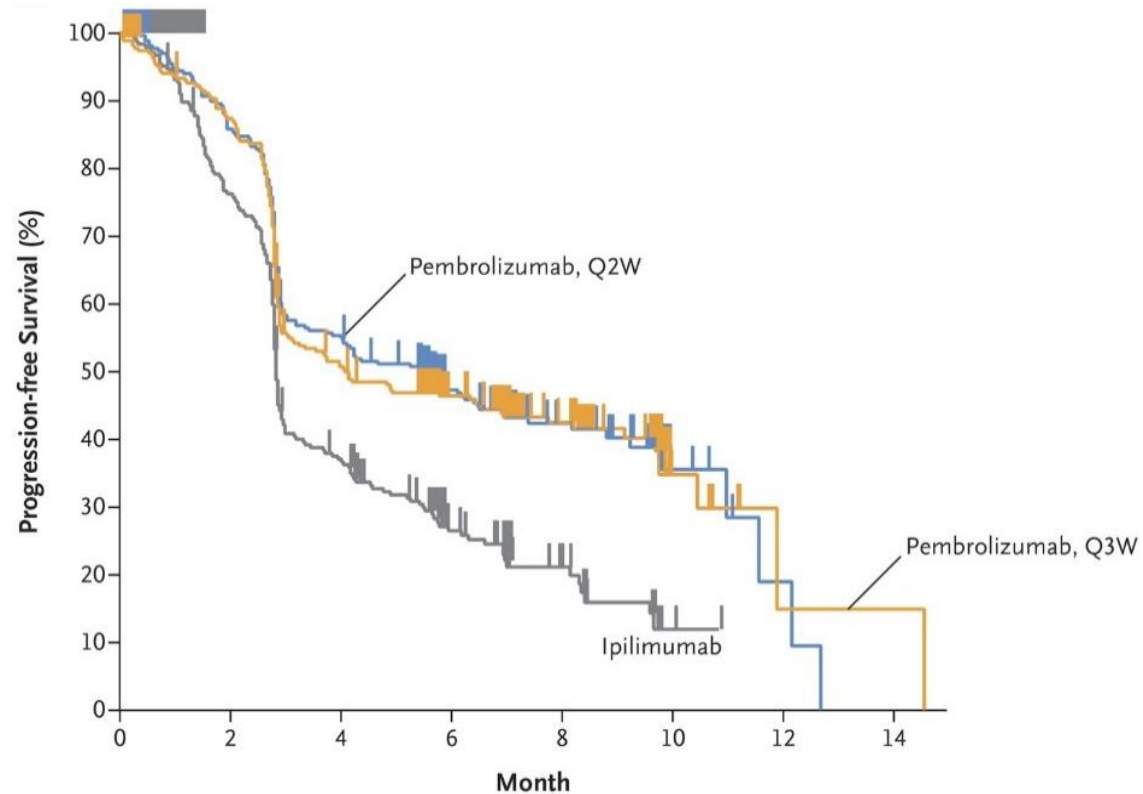
- Pooled OS data from 10 phase II/III trials
 - Previously treated (n = 1,257) or treatment-naïve (n = 604)
 - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)



Schadendorf et al. JCO 2015

Pembrolizumab in Stage III/IV Melanoma

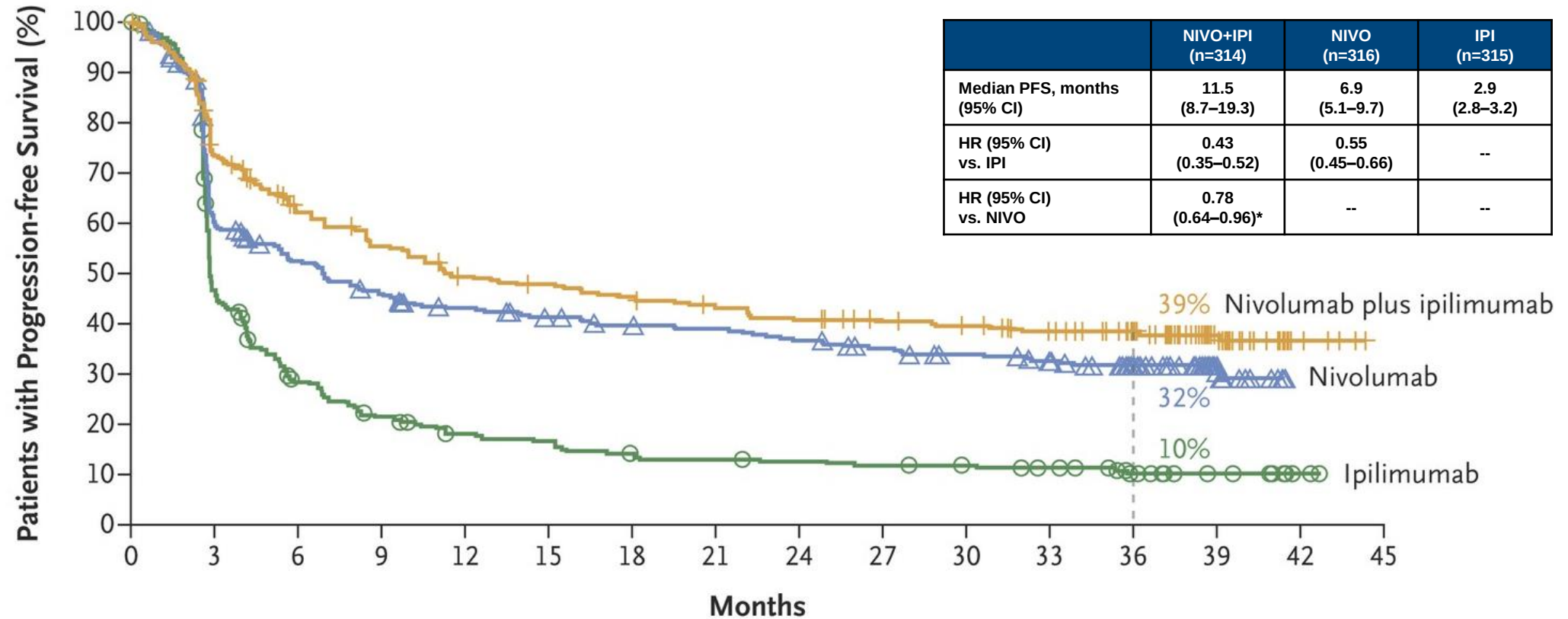
Phase III KEYNOTE-006 Trial



Robert et al. NEJM 2015

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

Phase III CheckMate 067 Trial



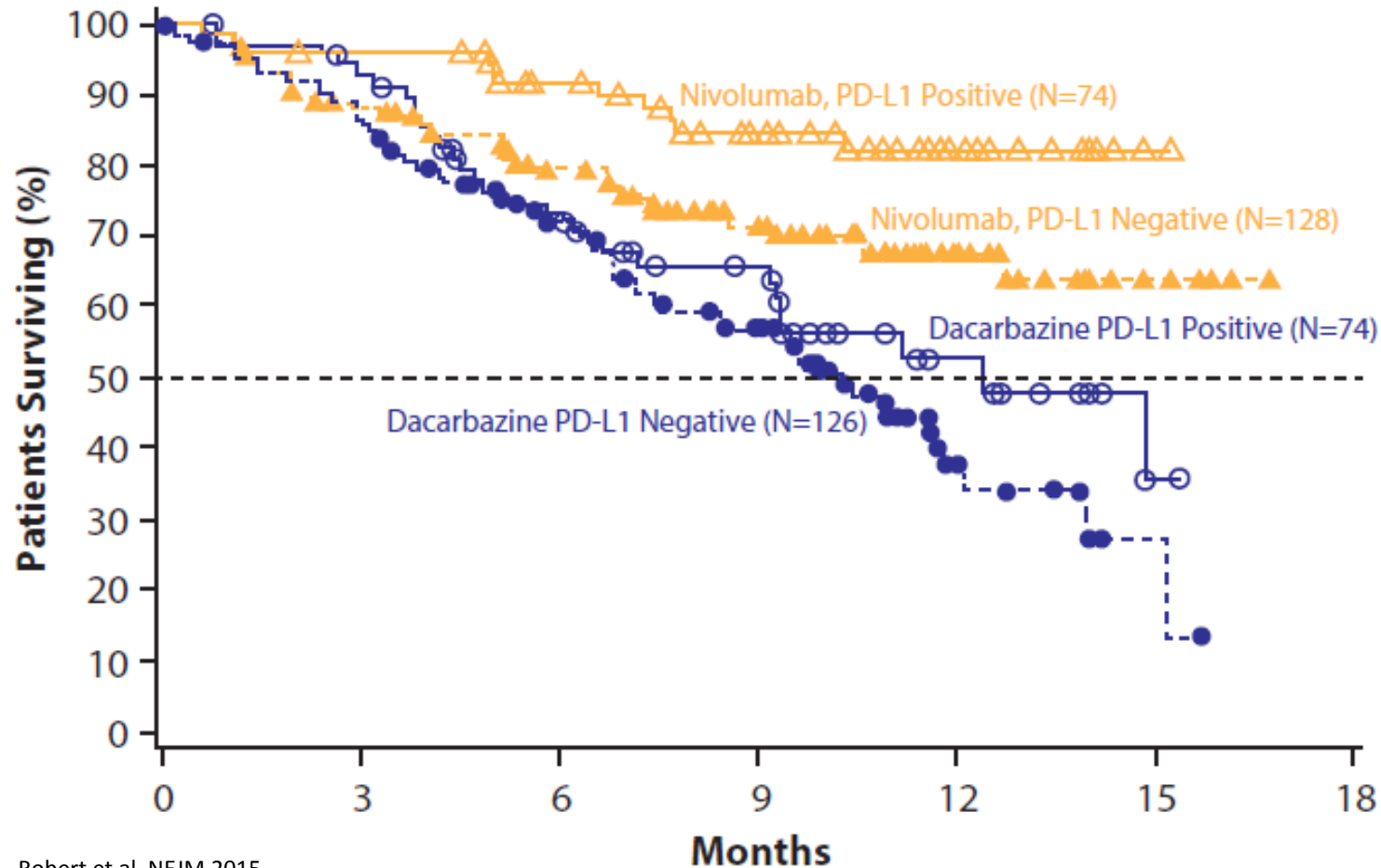
Wolchok et al. NEJM 2017

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

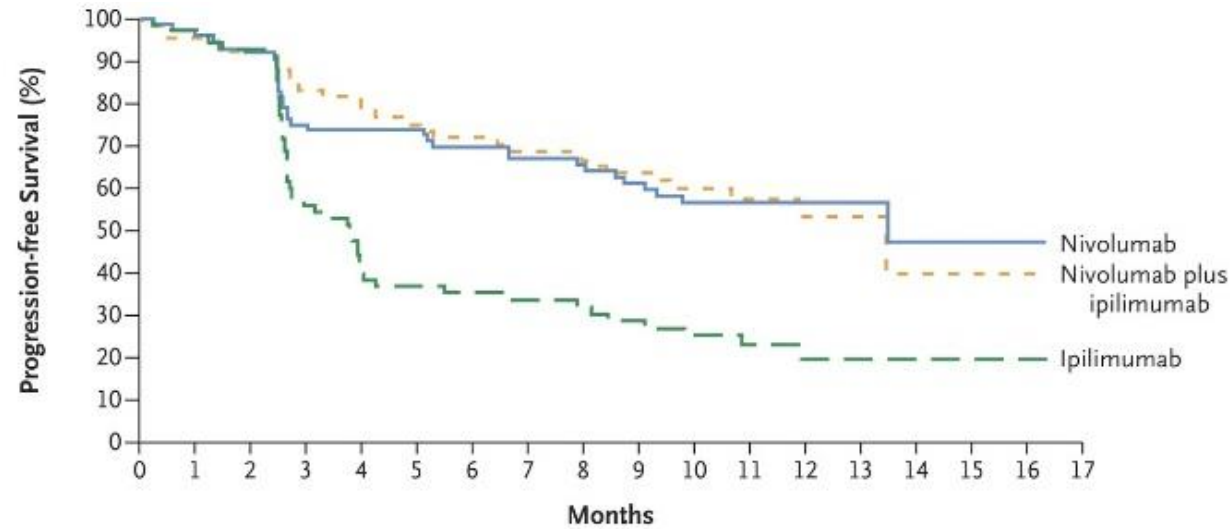
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



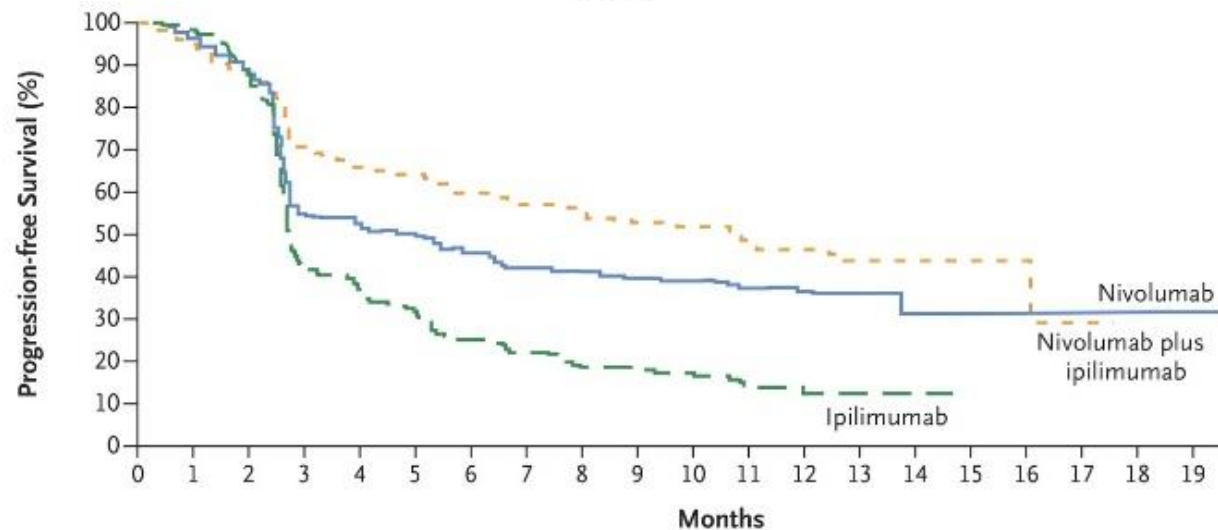
	Patients Who Died n/N	Median Survival mo (95% CI)
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

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



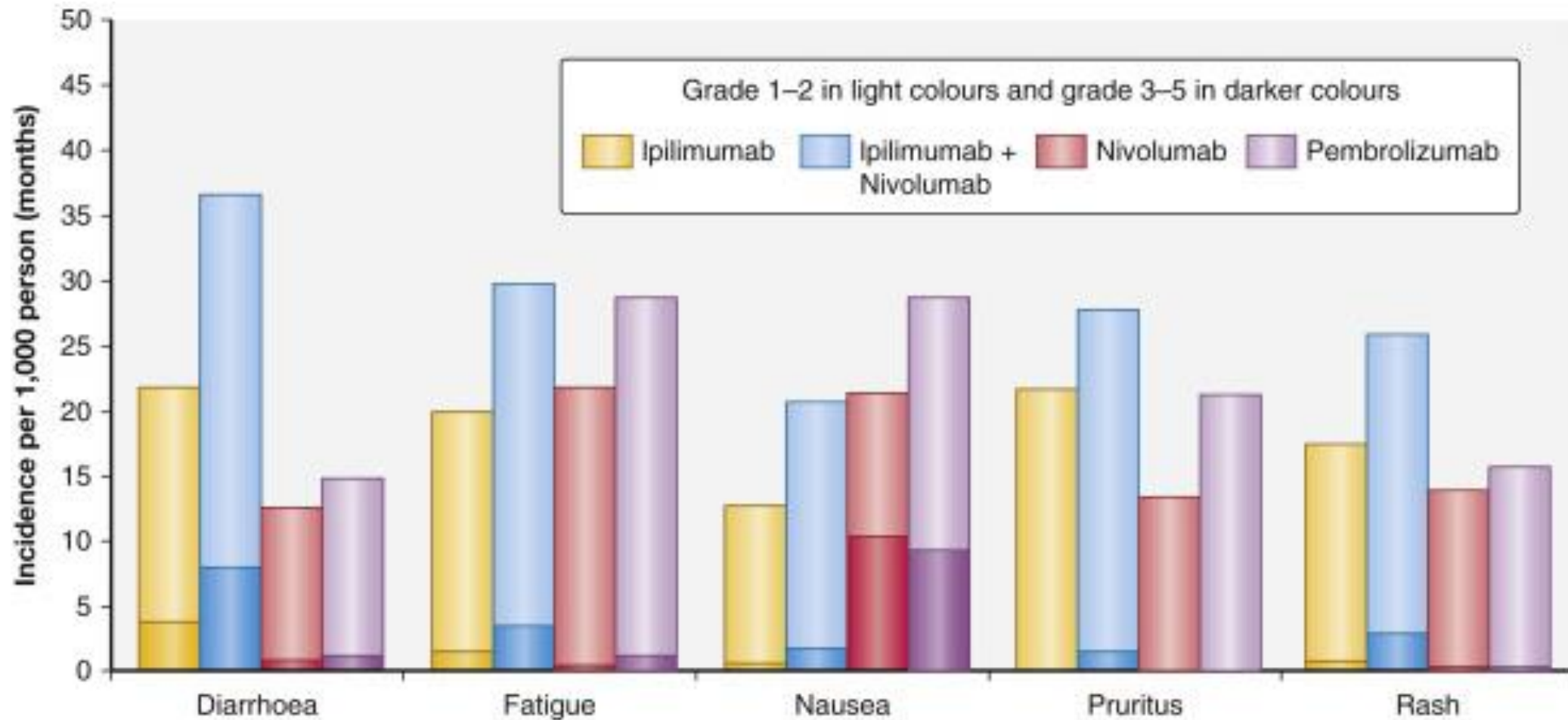
Tumor PD-L1 Positive Patients



Tumor PD-L1 Negative Patients

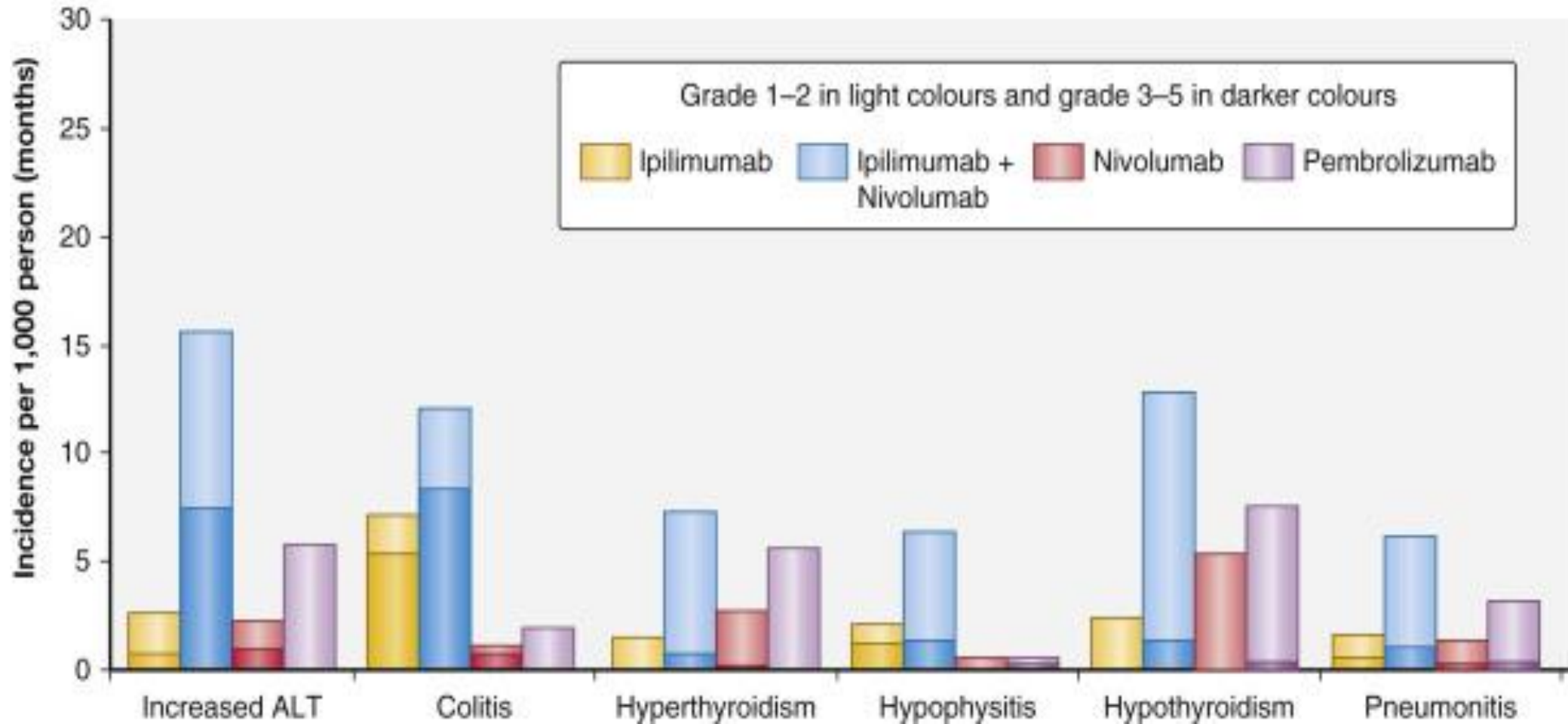
Larkin et al. NEJM 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



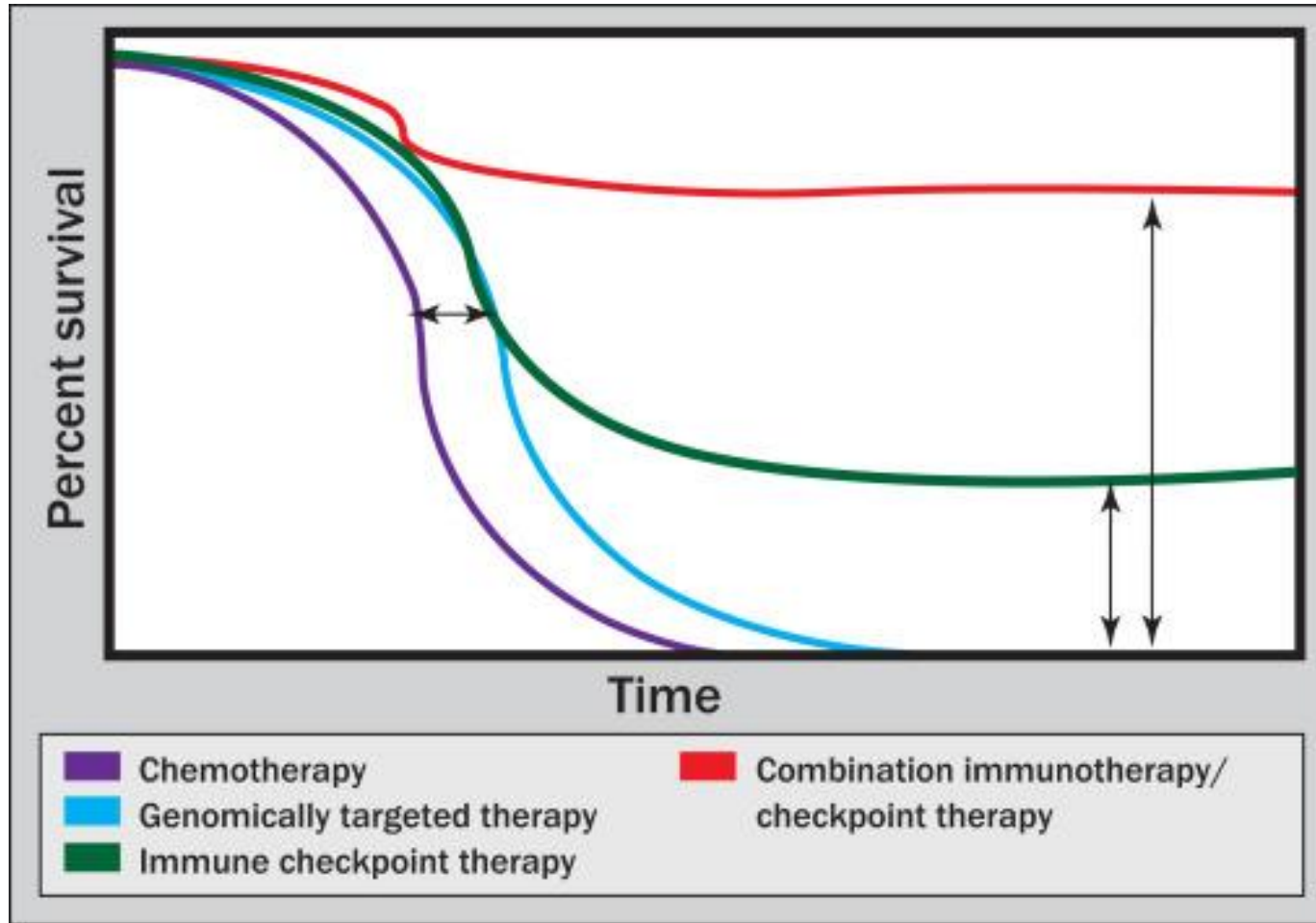
Emens et al. Eur J Cancer 2017

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

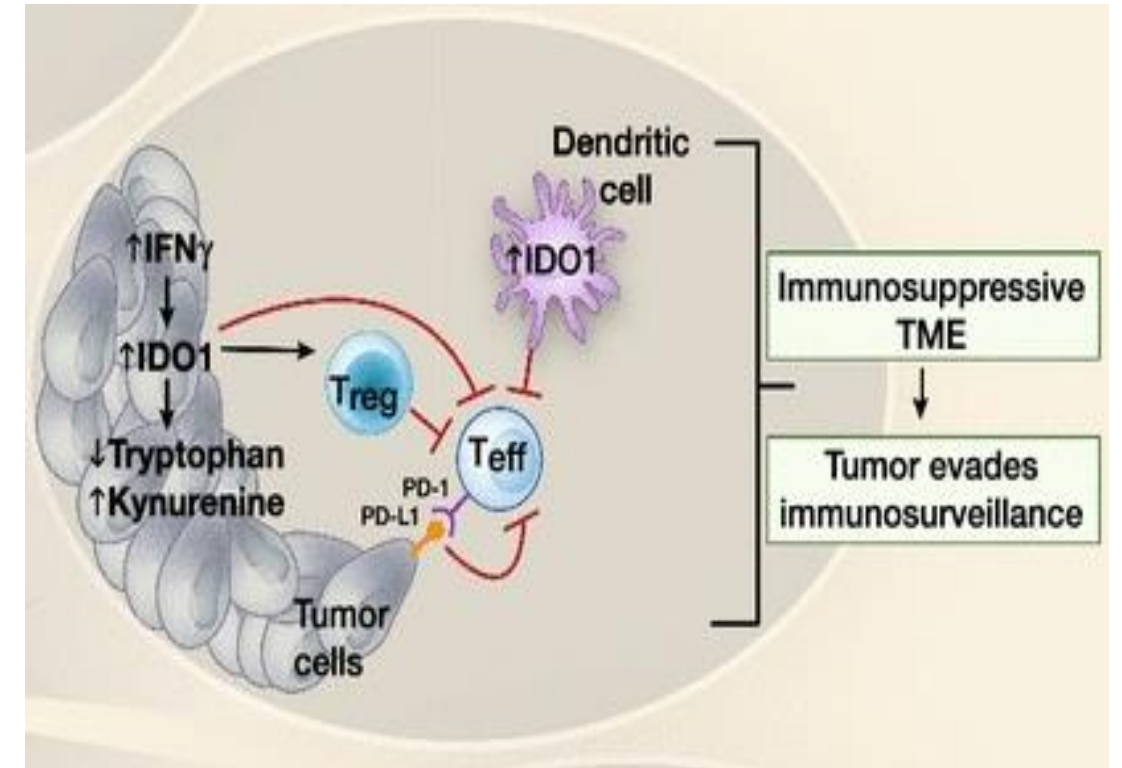
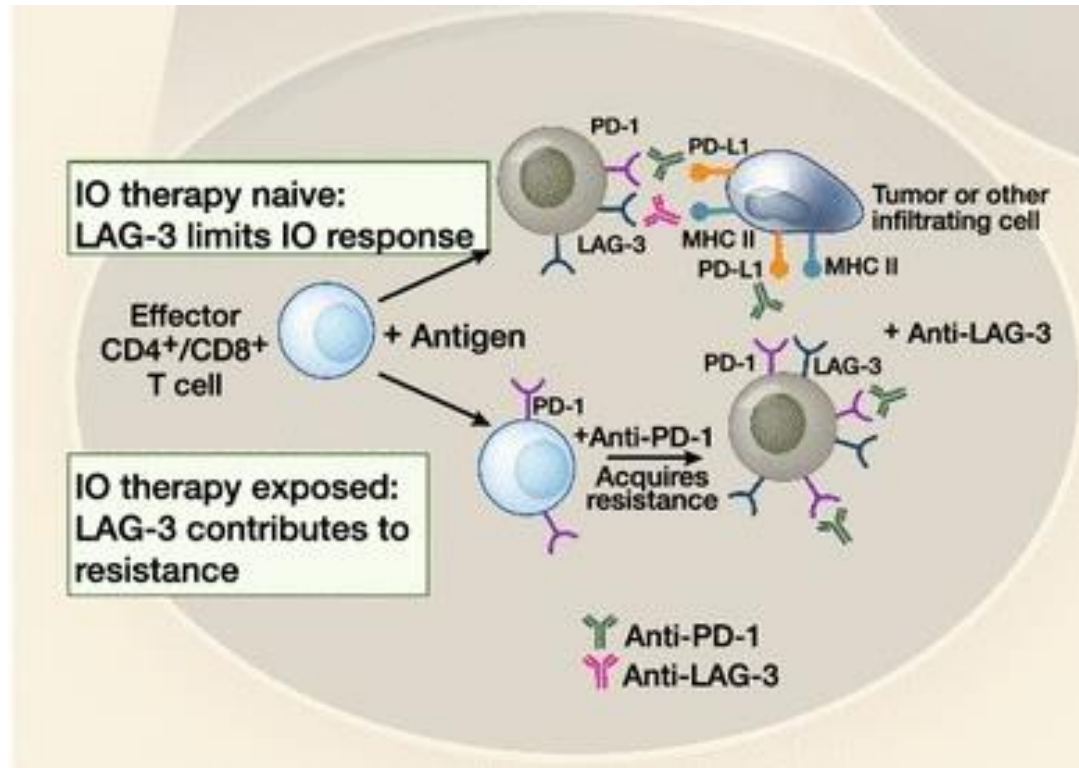
Developmental Immunotherapeutic Strategies for Melanoma



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

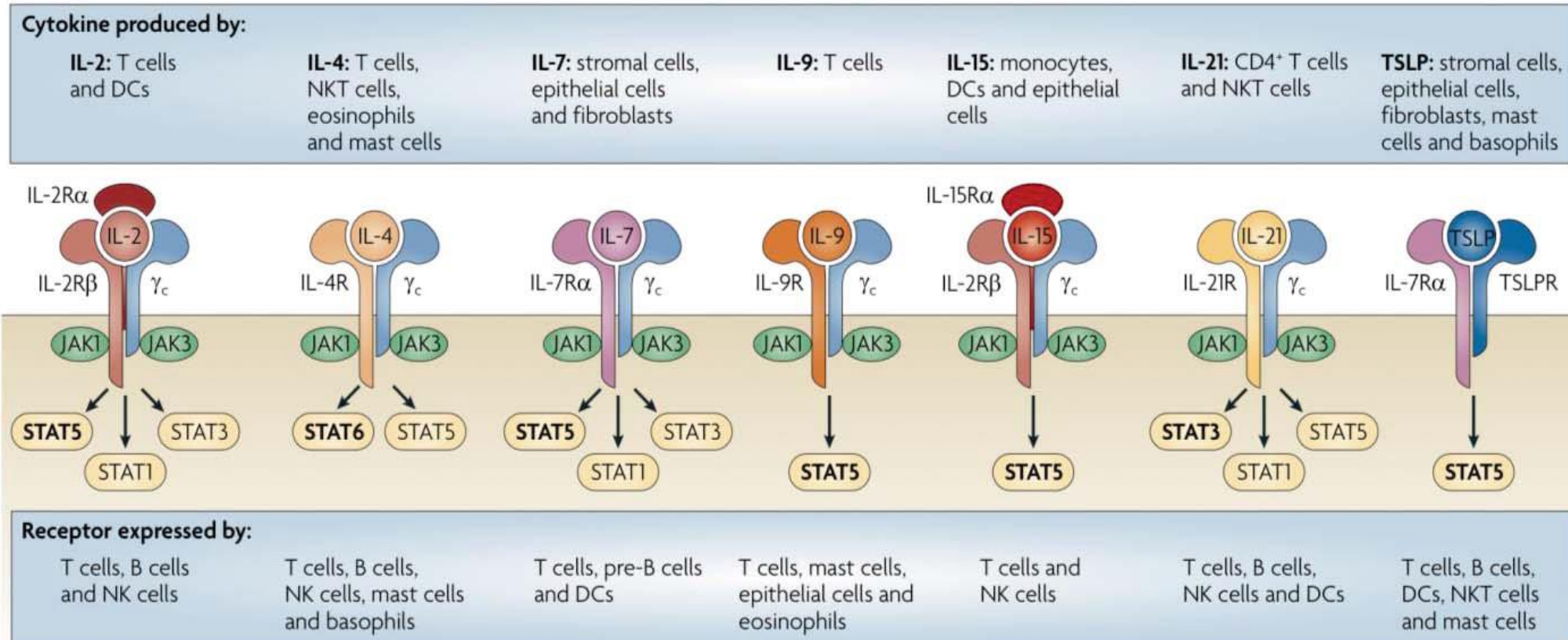
Laboratory Co-Chair: Jacqueline A. Hand, Ph.D

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

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

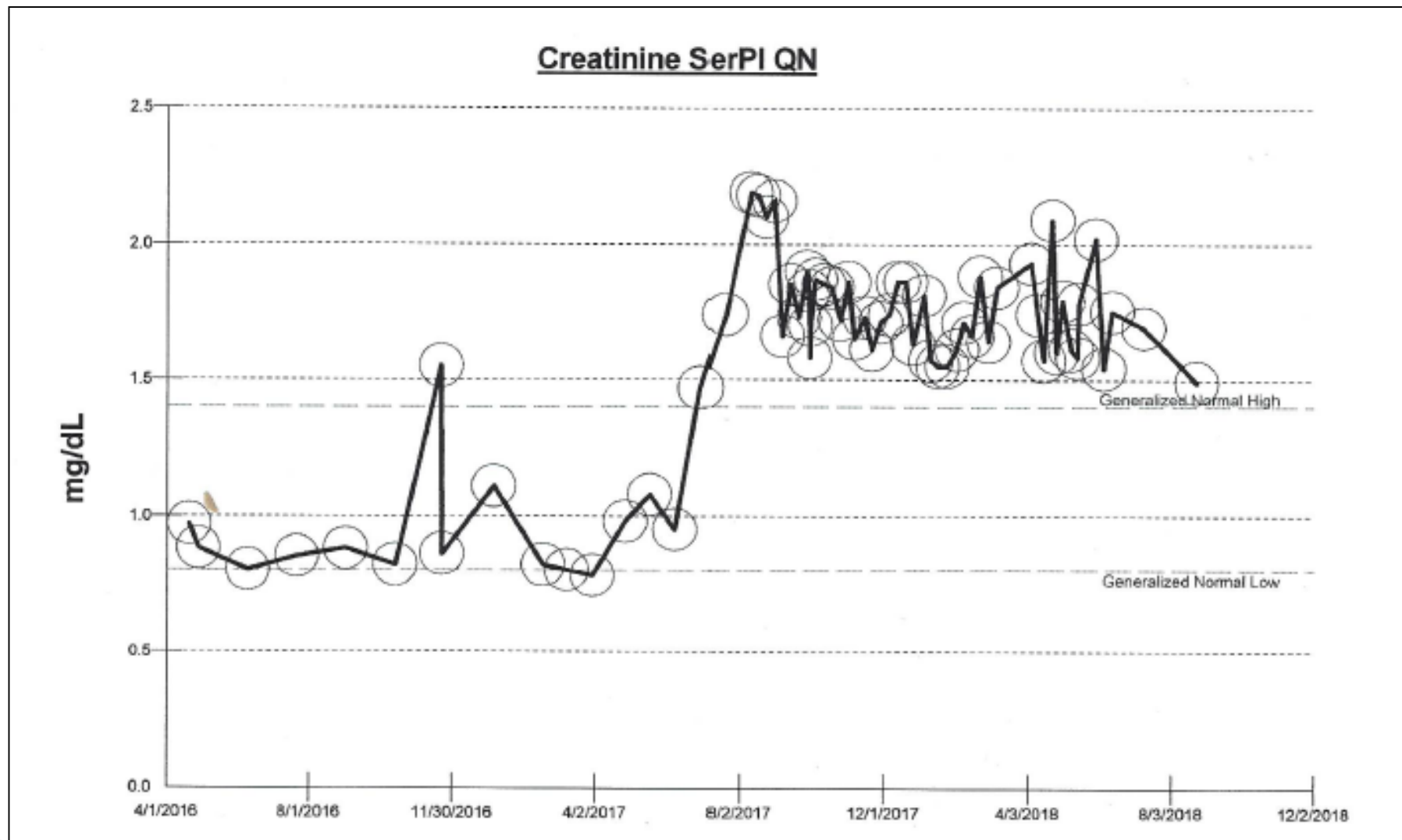
Ryan J. Sullivan¹, Michael B. Atkins², John M. Kirkwood³, Sanjiv S. Agarwala⁴, Joseph I. Clark⁵, Marc S. Ernstoff⁶, Leslie Fecher⁷, Thomas F. Gajewski⁸, Brian Gastman⁹, David H. Lawson¹⁰, Jose Lutzky¹¹, David F. McDermott¹², Kim A. Margolin¹³, Janice M. Mehnert¹⁴, Anna C. Pavlick¹⁵, Jon M. Richards¹⁶, Krista M. Rubin¹, William Sharfman¹⁷, Steven Silverstein¹⁸, Craig L. Slingluff Jr¹⁹, Vernon K. Sondak²⁰, Ahmad A. Tashiri²¹, John A. Thompson²², Walter J. Urbani²³, Richard L. White²⁴, Eric D. Whitman²⁵, F. Stephen Hodi²⁶ and Howard L. Kaufman^{1*}

Case Study 1

- 53 yowm s/p resection T4b, N2a L arm melanoma. S/p adjuvant IFN, 2014.
- 2015, L arm recurrence, 3 pulmonary nodules on PET/CT. Bx-melanoma, BRAF V600E+.
- EA 6134, randomized Dabrafenib/Trametinib.
- Treated 1 yr initial response then progression.
- Crossed over Ipi/Nivo, rec'd 4 doses.
- Creatinine rose baseline- 2.19. grade 2.

Case Study 1

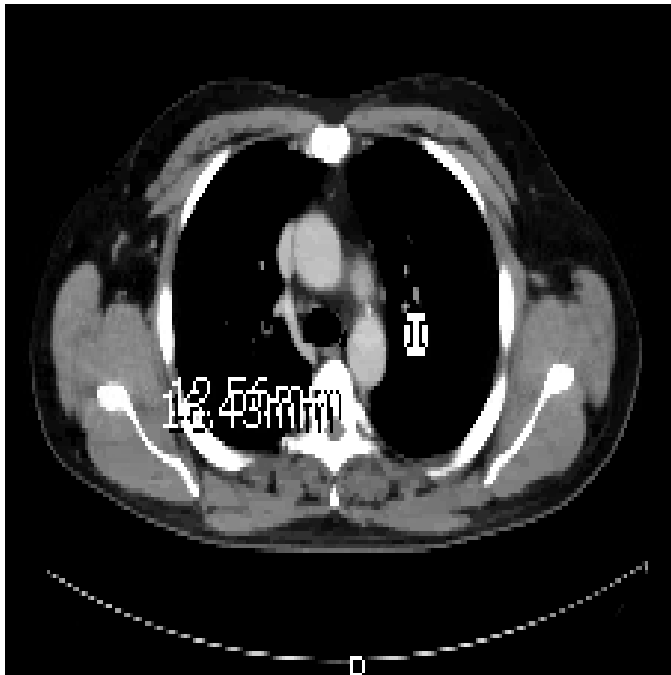
Flowsheet Graph



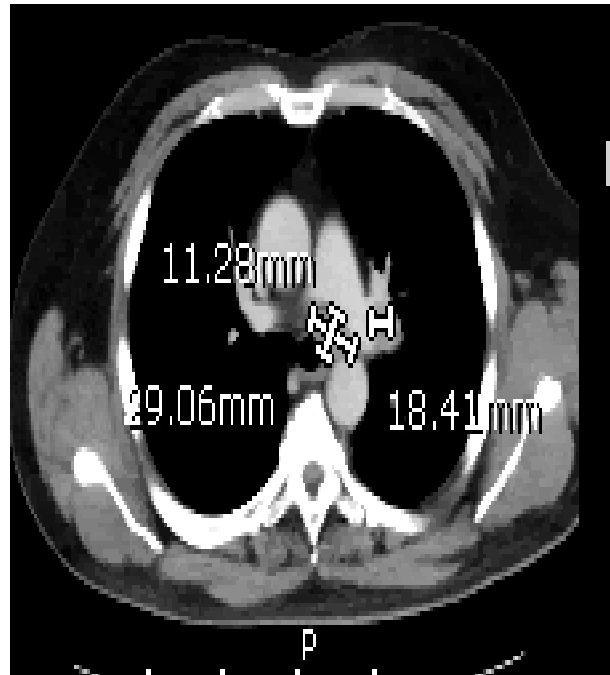
Case Study 1

CT Scans

Pre Rx



During Rx



PostRx



Case Study 1

Prednisone 60 mg/kg

- Renal Bx- lymphocytic infiltration. Not able to taper off prednisone.
- Mycophenolate mofetil -CellCept started. Prednisone and CellCept weaned off.
- Chest – new nodule, solitary , removed.
- Path:



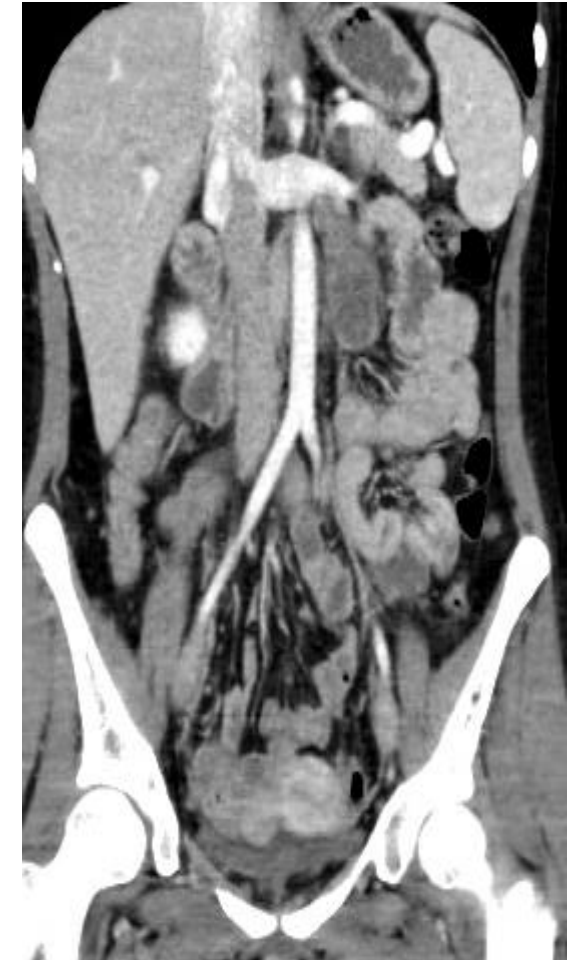
Case study 2

- 23 yo wf student with multiple new SQ nodules Bx + for metastatic melanoma, BRAF -
- w/u- widely metastatic, brain (12), SQ , LNs, lung, pleura, GB, adrenals, spleen, RP LNs.
- Treated SRS brain, Ipi /Nivo-got 3 cycles.
- Developed diarrhea > 5 stools over normal
- Colonoscopy inflamed, Bx- “-itis”
- Steroids X1 month, diarrhea continues. Next?

Case Study 2

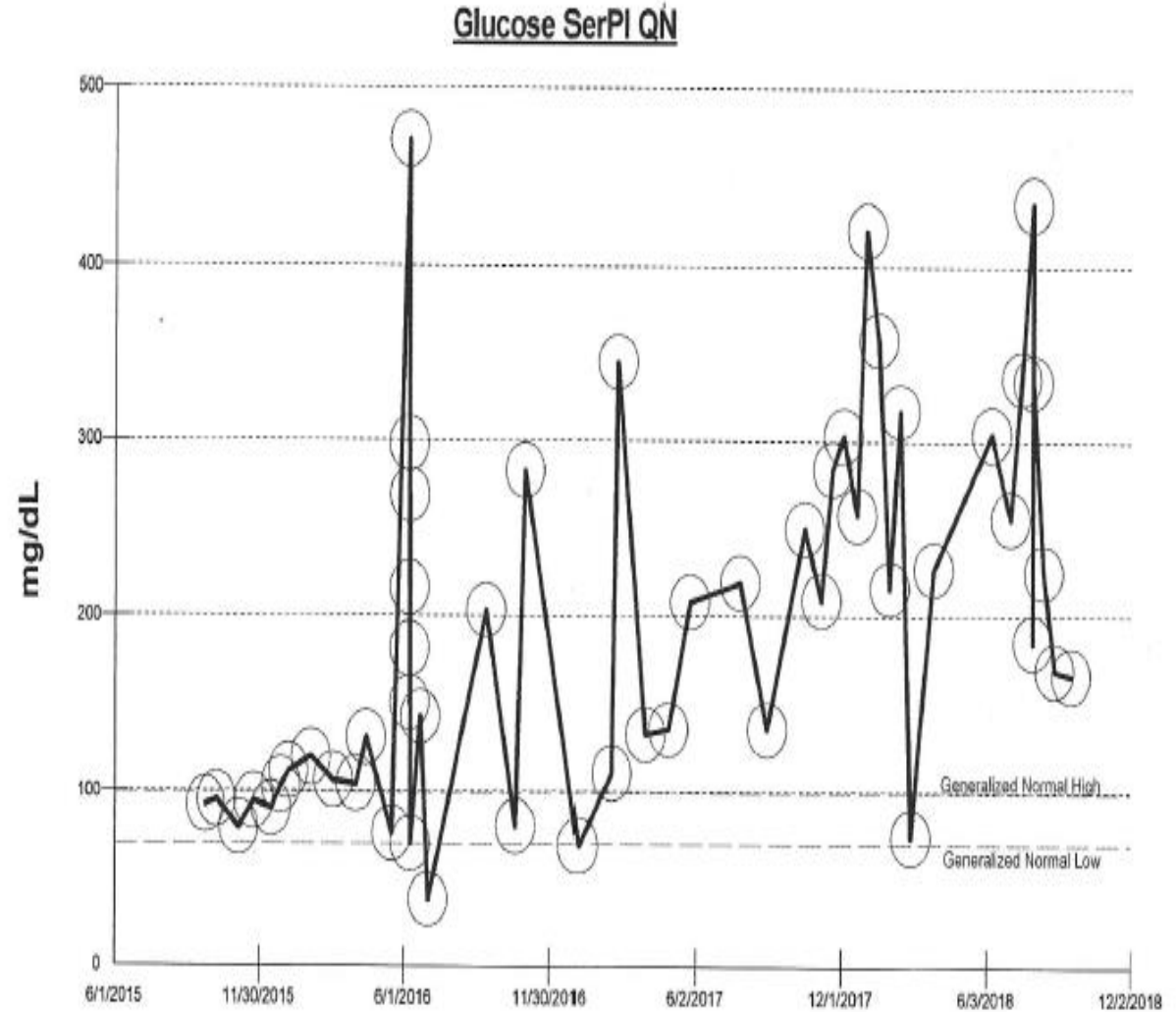
March 2015 and September 2015 CTs

- Colitis resolved
 - Restart nivo alone
- Elevated lipase 727
 - What now?
- Visual blurring -can't read Jan 2016
- What's next?



Case study 2

**Holding Nivo, June
 2016 ER visit “Feeling
 ill”**



Case study 2

Complains of hair “turning white”

?

Nov 2017 1st progression on CTs

Nivo restarted.

