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

Society for Immunotherapy of Cancer

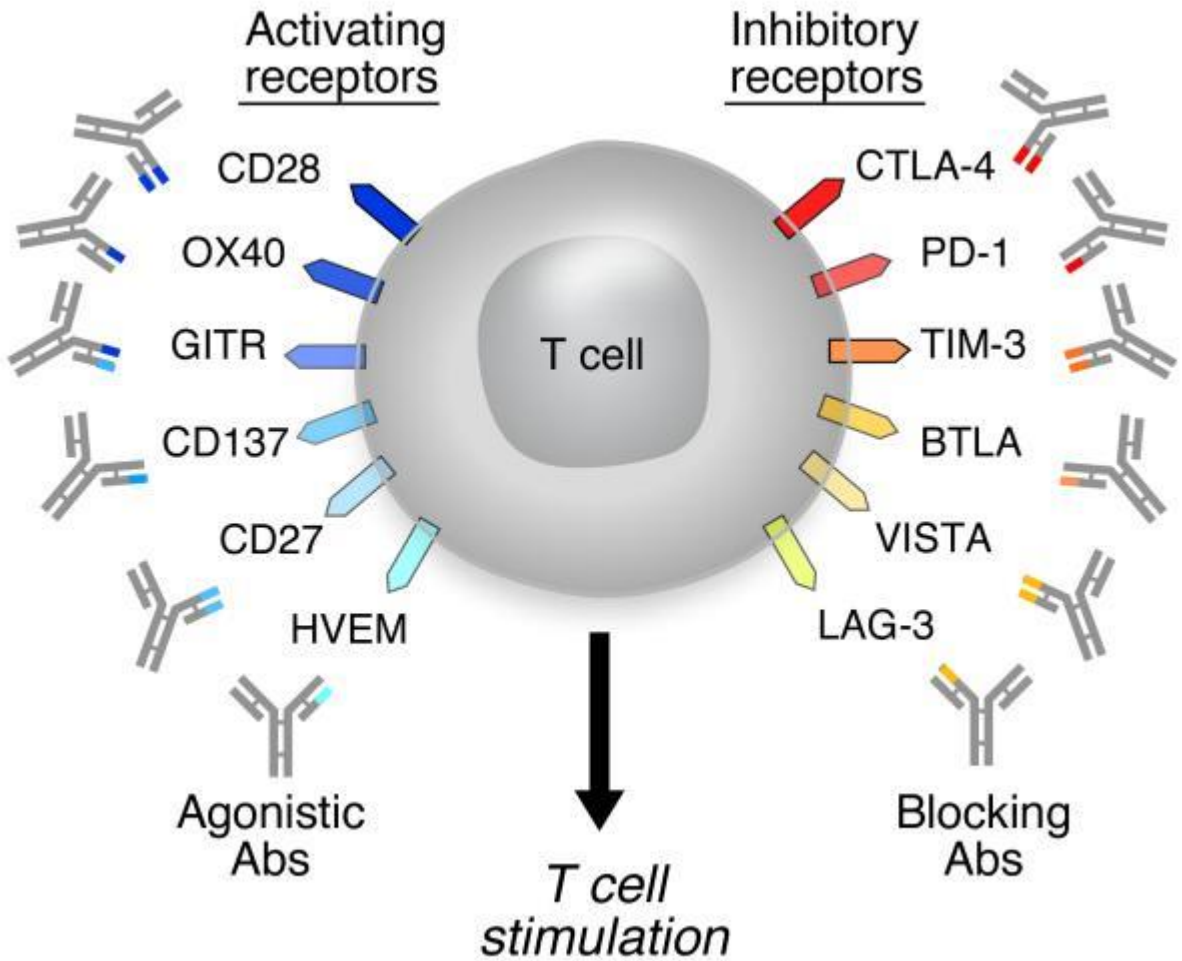
Disclosures

- Nothing to disclose
- I will not be discussing non-FDA approved indications during my presentation.

What is Melanoma?

"Melas"= Black

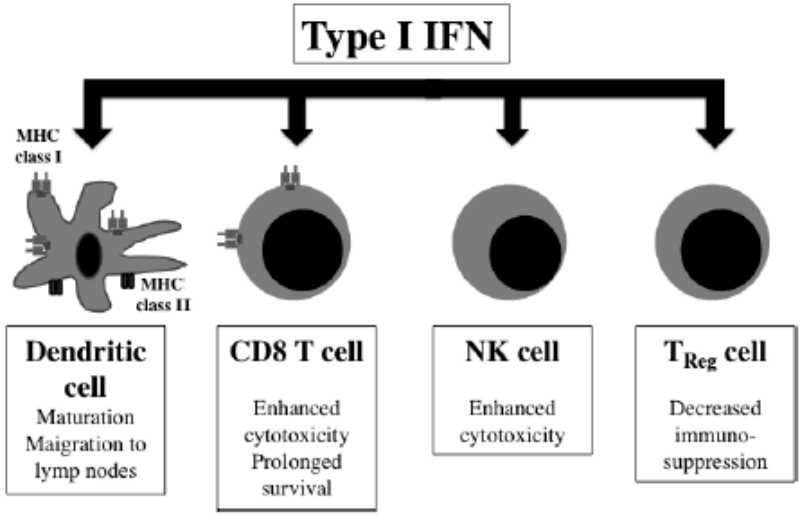
"Oma"= Growth



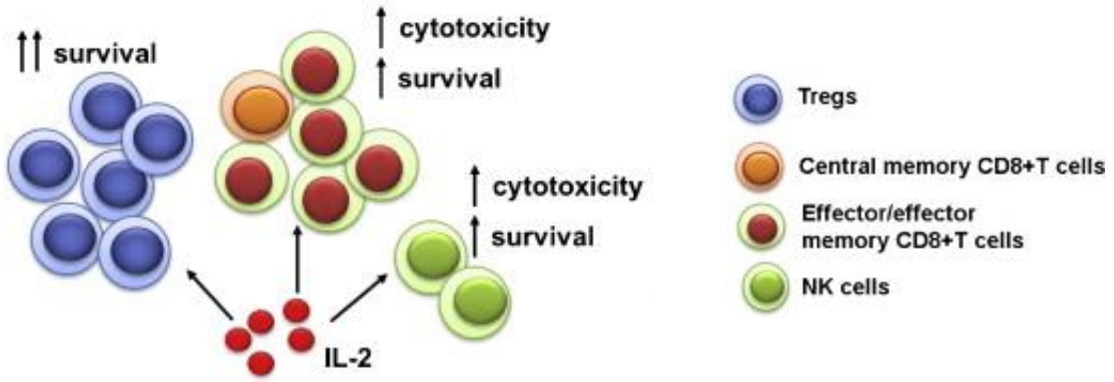
Mellman et al. *Nature* 2011

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.



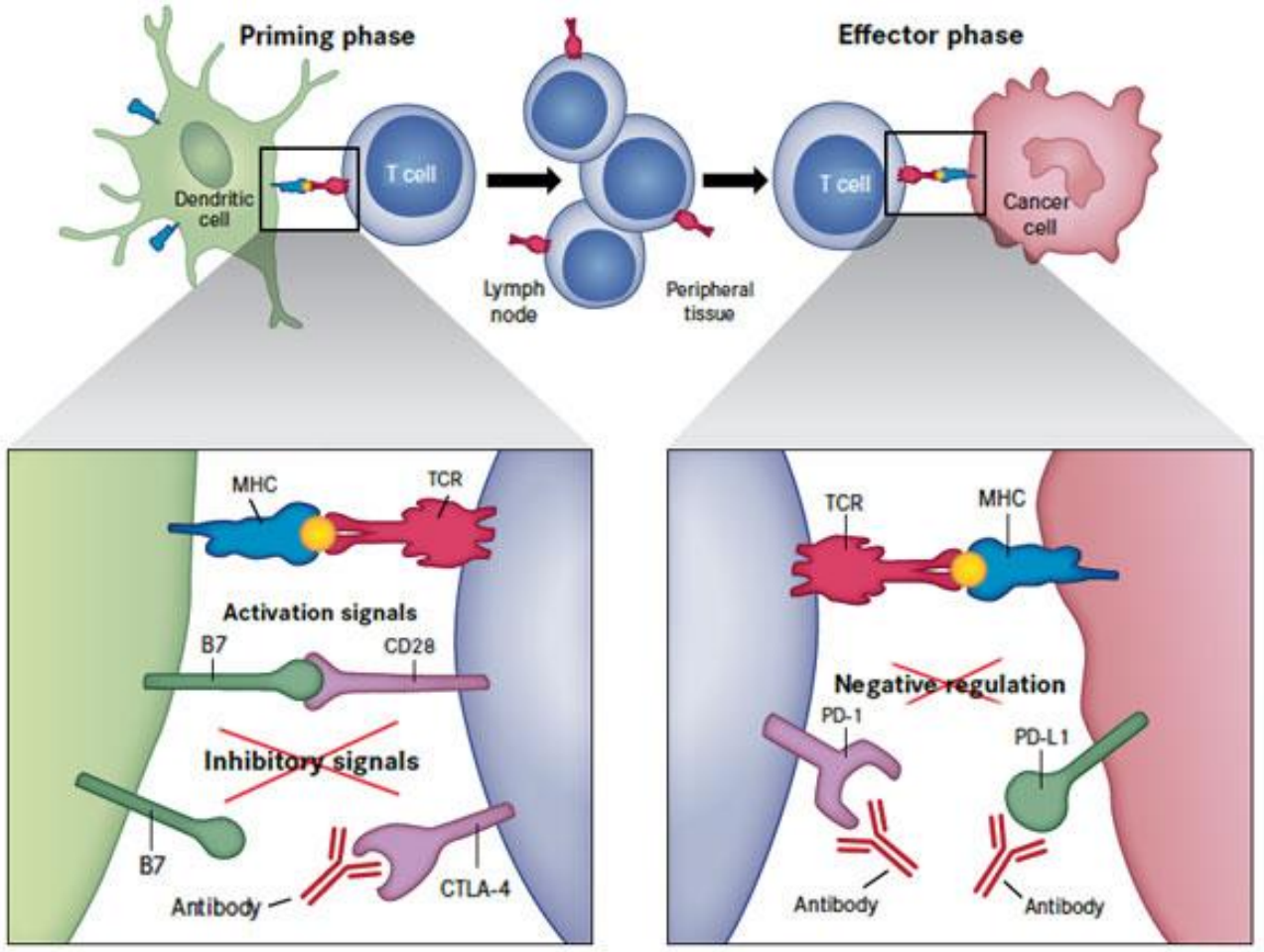
Numasaki et al. Immunotherapy 2016



Sim, Radvanyi Cytogfr 2014

FDA-approved Immunotherapies in Melanoma

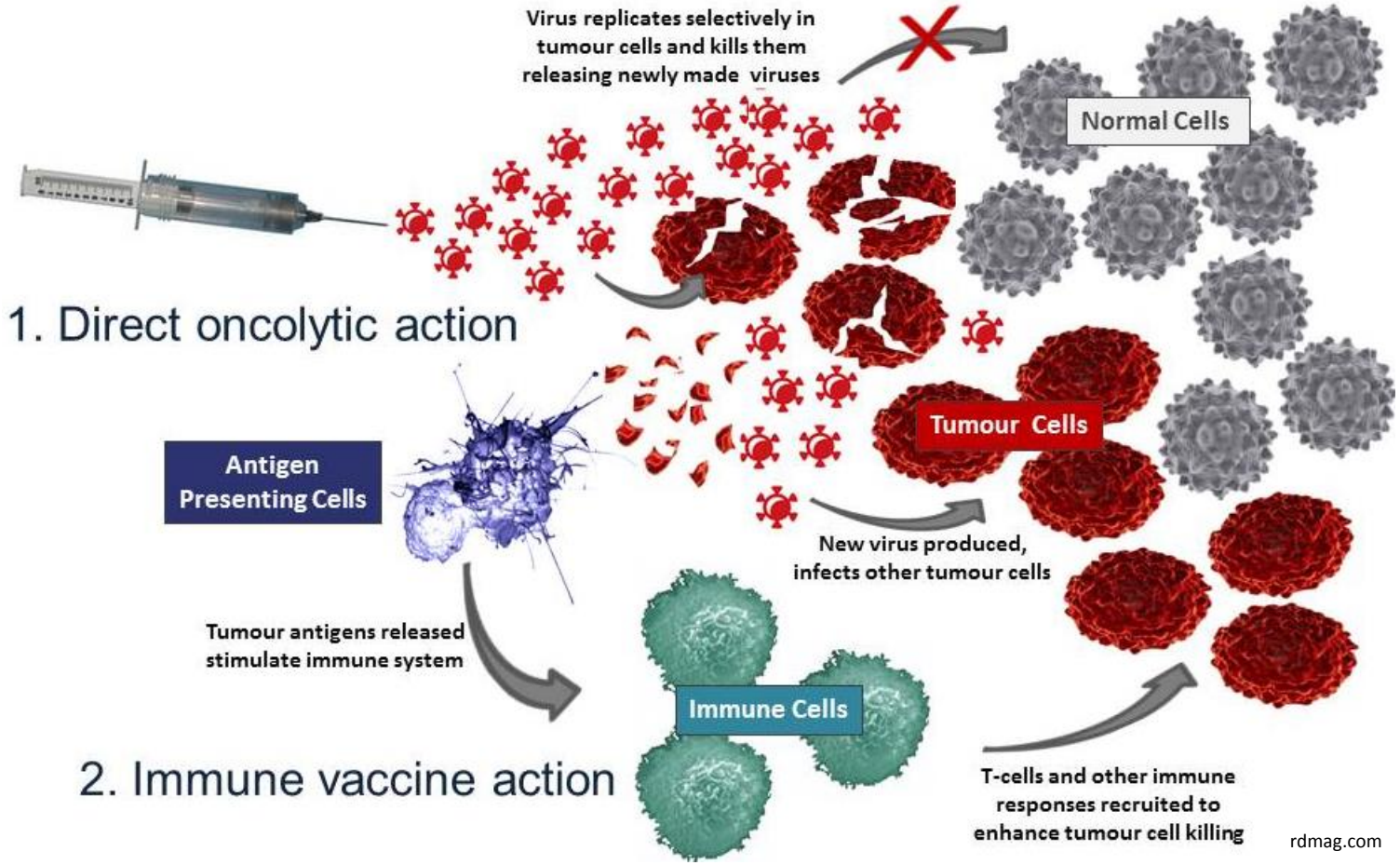
- Checkpoint inhibitors
  - Ipilimumab, adjuvant and nonresectable/Stage IV, I.V.- different dosing for adjuvant and nonresectable/Stage IV
  - Pembrolizumab, nonresectable/Stage IV, I.V.
  - Nivolumab, adjuvant and non resectable/Stage IV, I.V.
  - Ipilimumab in combination with nivolumab, Stage IV



Ribas NEJM 2012
Gordon et al Nature 2017

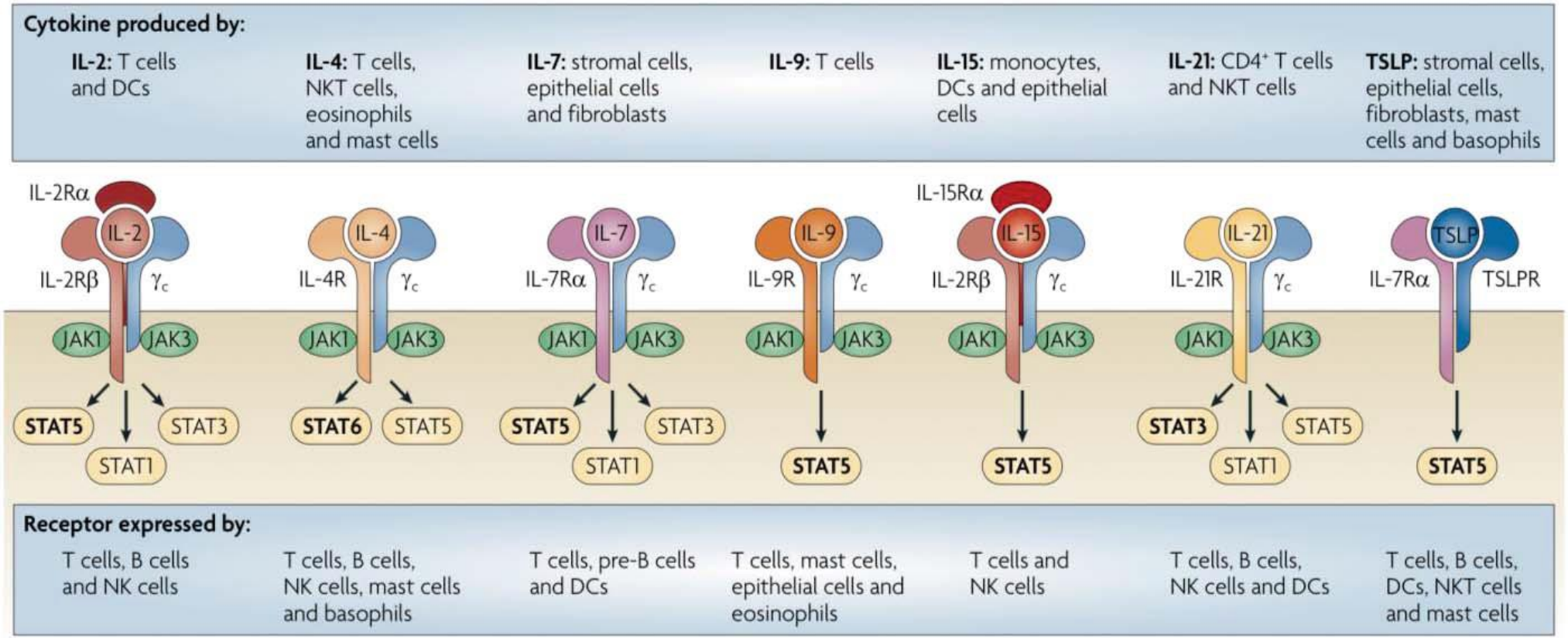
FDA-approved Immunotherapies in Melanoma

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



Developmental Immunotherapeutic Strategies for Melanoma

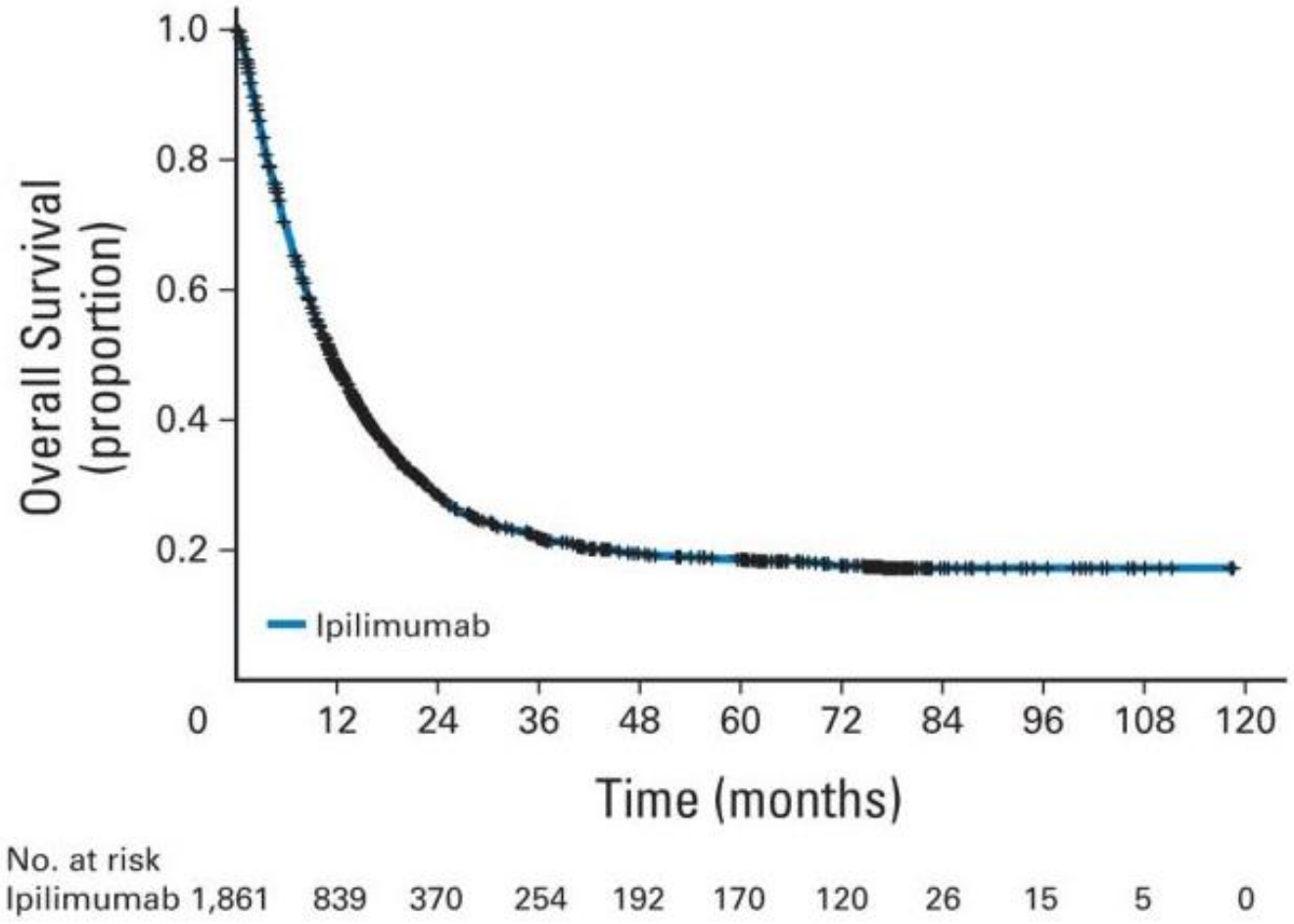
Cytokine-based Strategies



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

Ipilimumab in Stage III/IV Melanoma

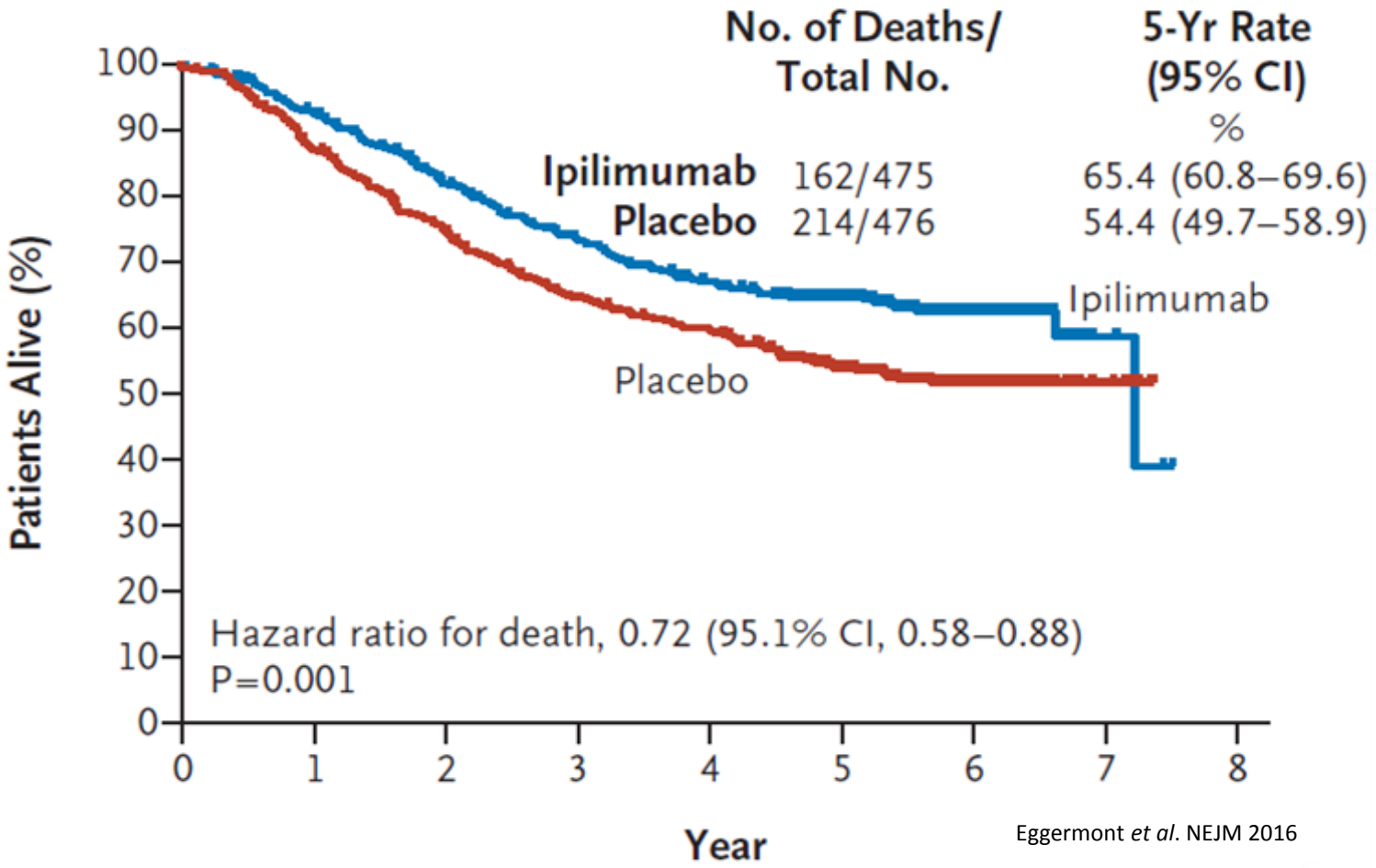
- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)



Schadendorf et al. JCO 2015

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

- Patients with resected stage IIIB, IIIC, IV melanoma (either BRAF mutant or not)
- 1 year of adjuvent nivolumab 3 mg/kg or ipilimumab 10 mg/kg
- Primary endpoint is RFS

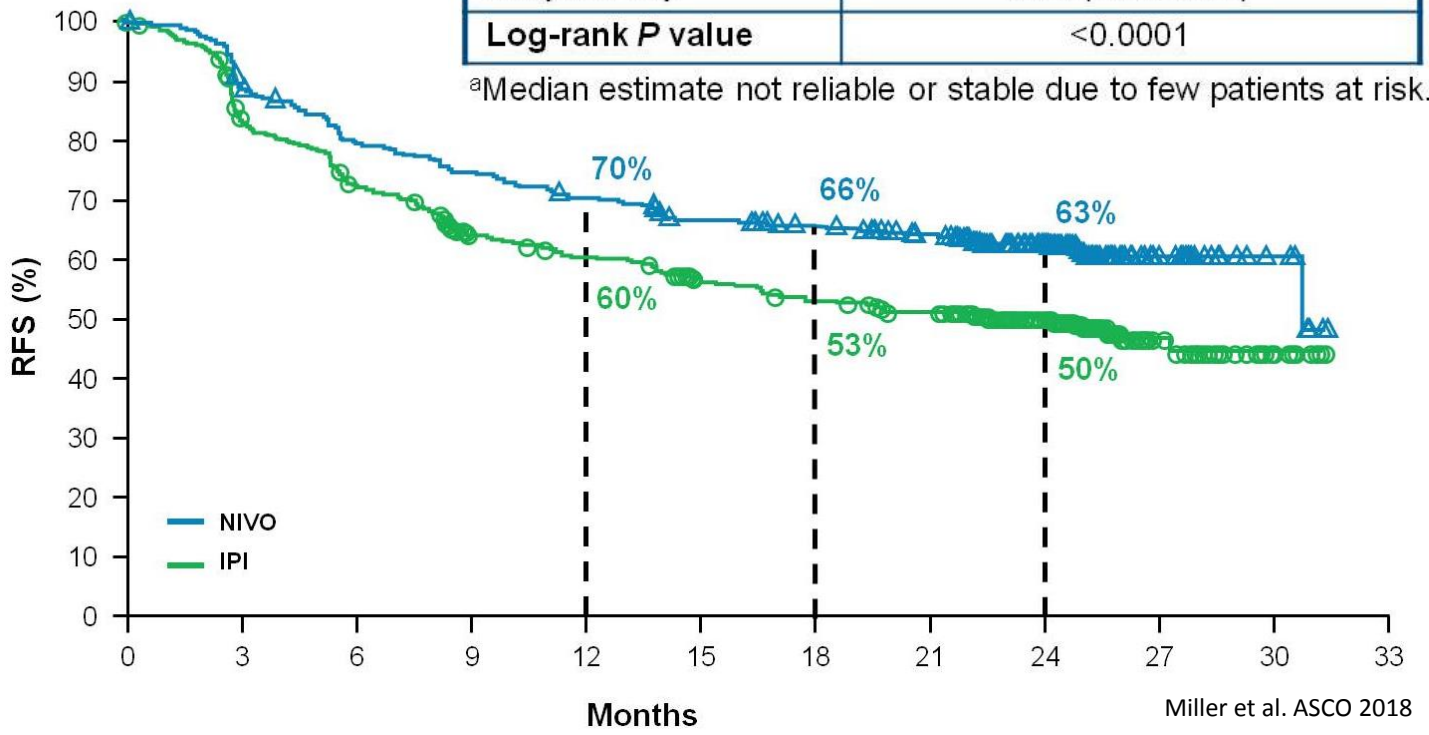
Weber et al. ESMO 2017

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.

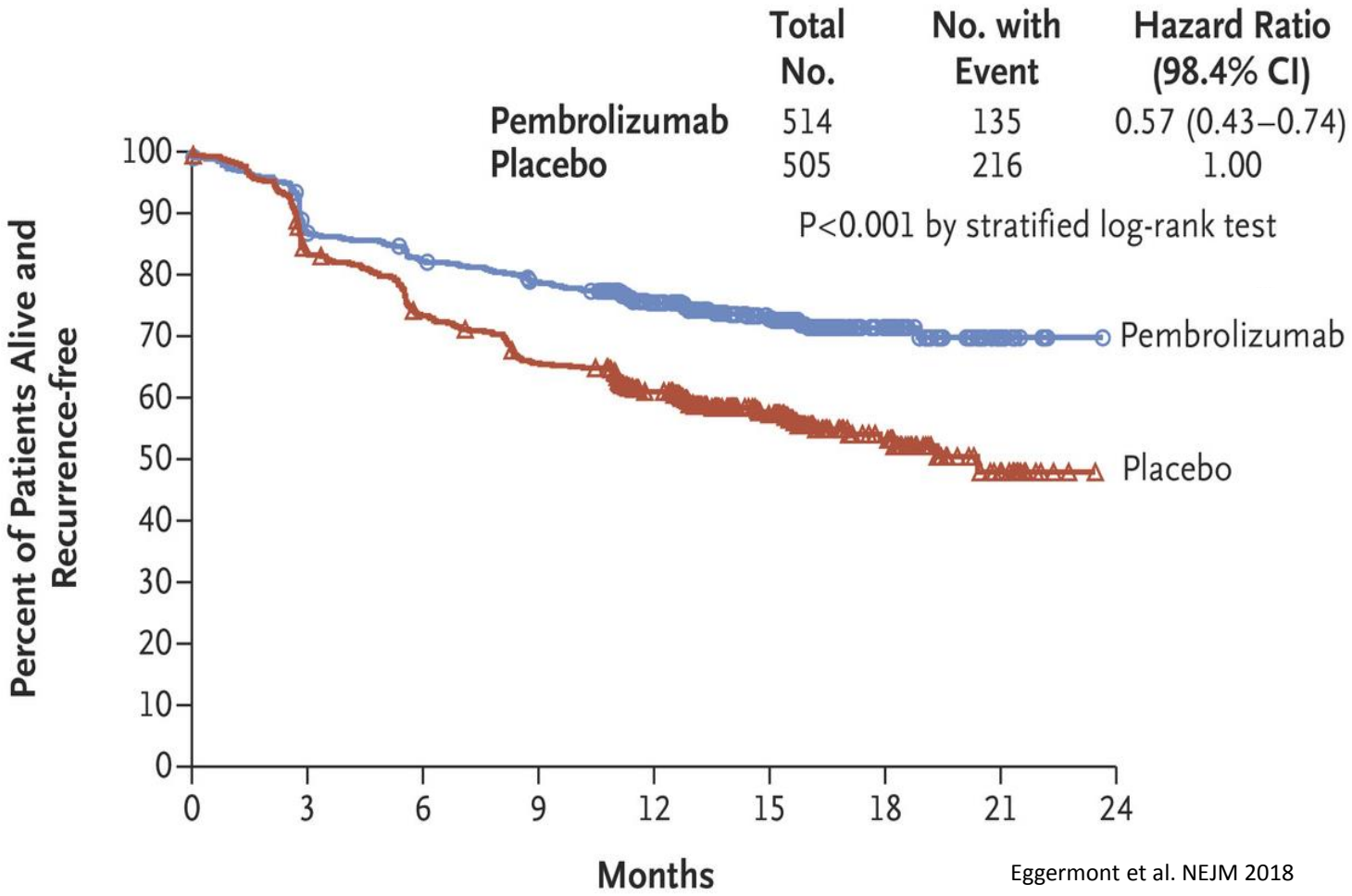


Miller et al. ASCO 2018

Weber et al. ESMO 2017

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)

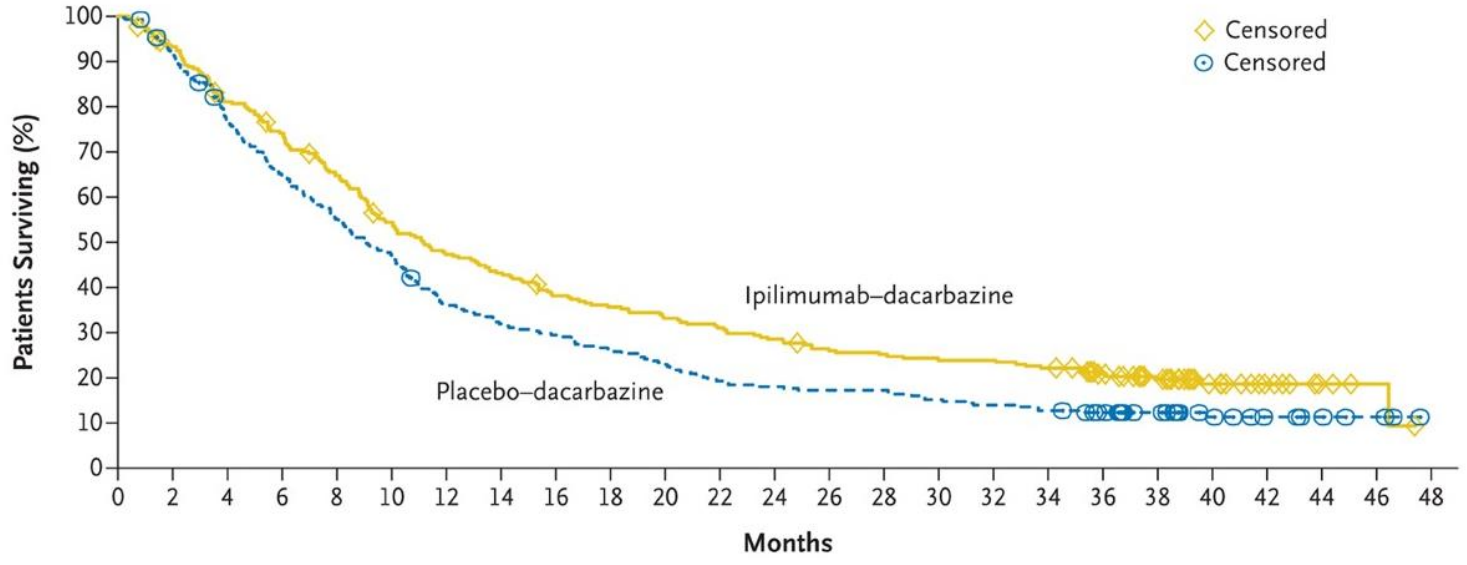


Eggermont et al. NEJM 2018

Treatment of Metastatic Melanoma

- Chemotherapy (not 1st line)
  - Dacarbazine
  - Temozolomide
- Immunotherapy (PD-1 based)
  - Usually 1st line unless giving BRAF+MEK targeted therapy
- Targeted therapy (BRAF+MEK inhibitor combos)

Ipilimumab + dacarbazine vs. dacarbazine



No. at Risk

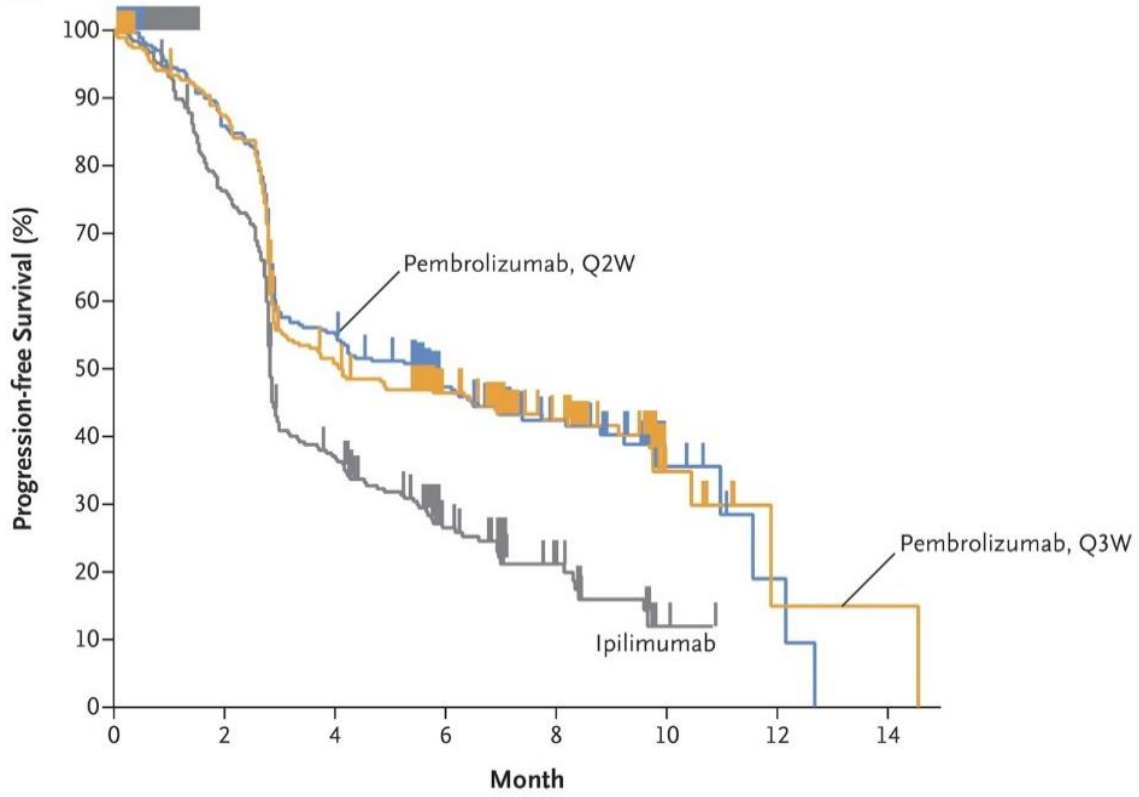
Ipilimumab–dacarbazine	250	230	199	181	157	131	114	104	91	85	79	74	68	61	59	56	56	52	41	31	17	10	4	2	0
Placebo–dacarbazine	252	229	190	160	136	116	89	78	72	64	56	47	44	42	42	37	34	31	26	19	11	7	5	3	0

- RR: 15.2%
- Median OS: 11.2 mos
- 28.5% alive at 2 years

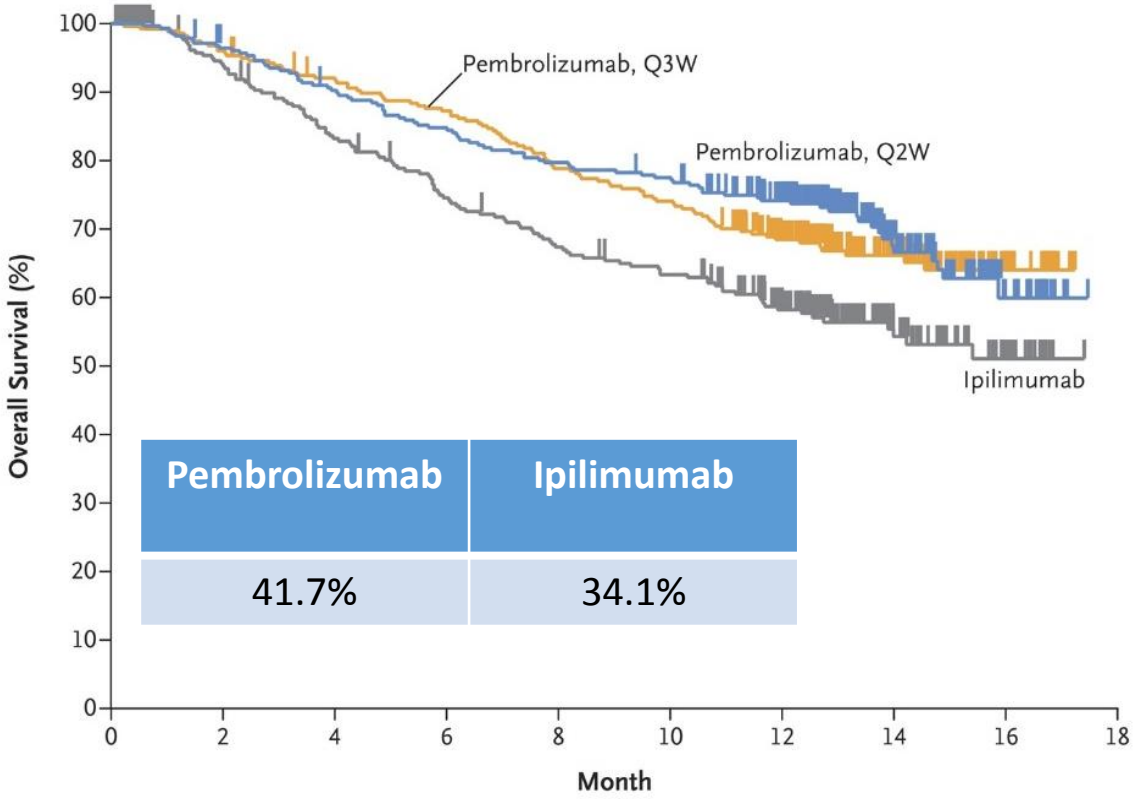
Robert et al. *NEJM* 2011

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial



Q2W Pembrolizumab	Q3W Pembrolizumab	Ipilimumab
31%	28%	14%



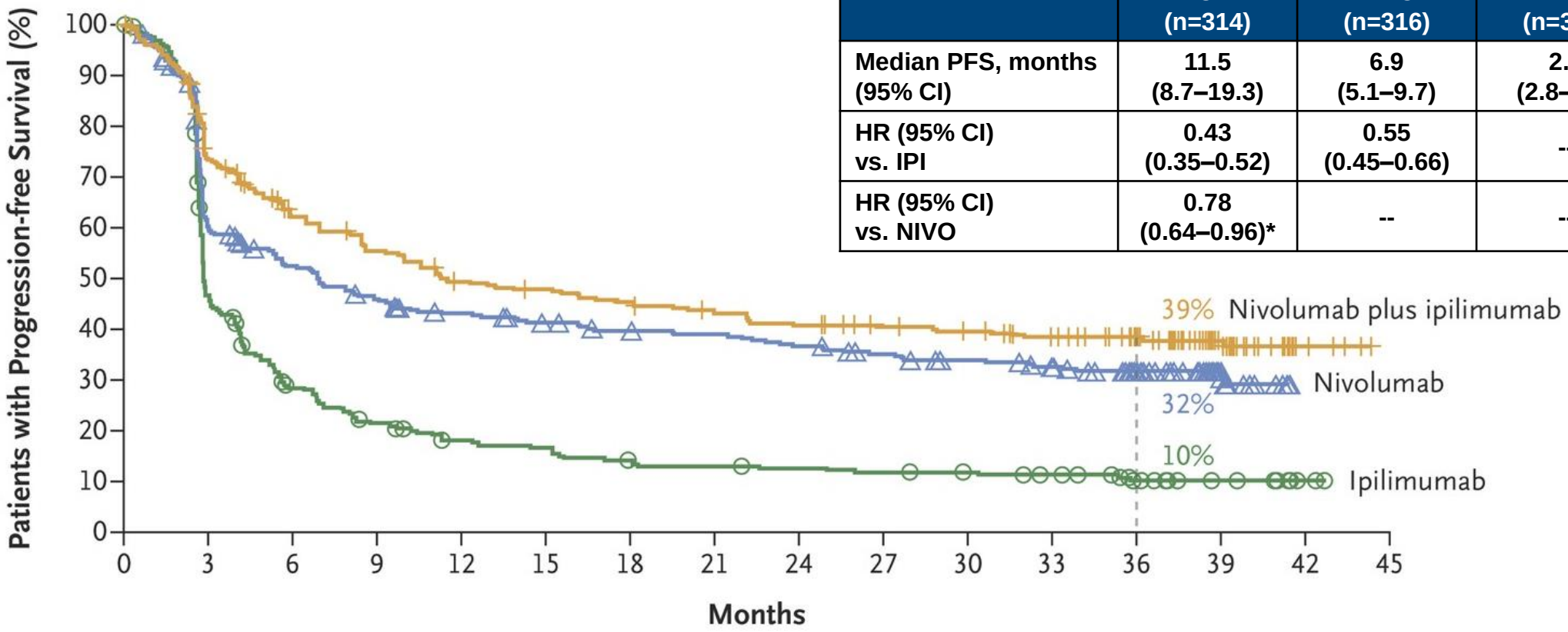
Pembrolizumab	Ipilimumab
41.7%	34.1%

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)*	--	--



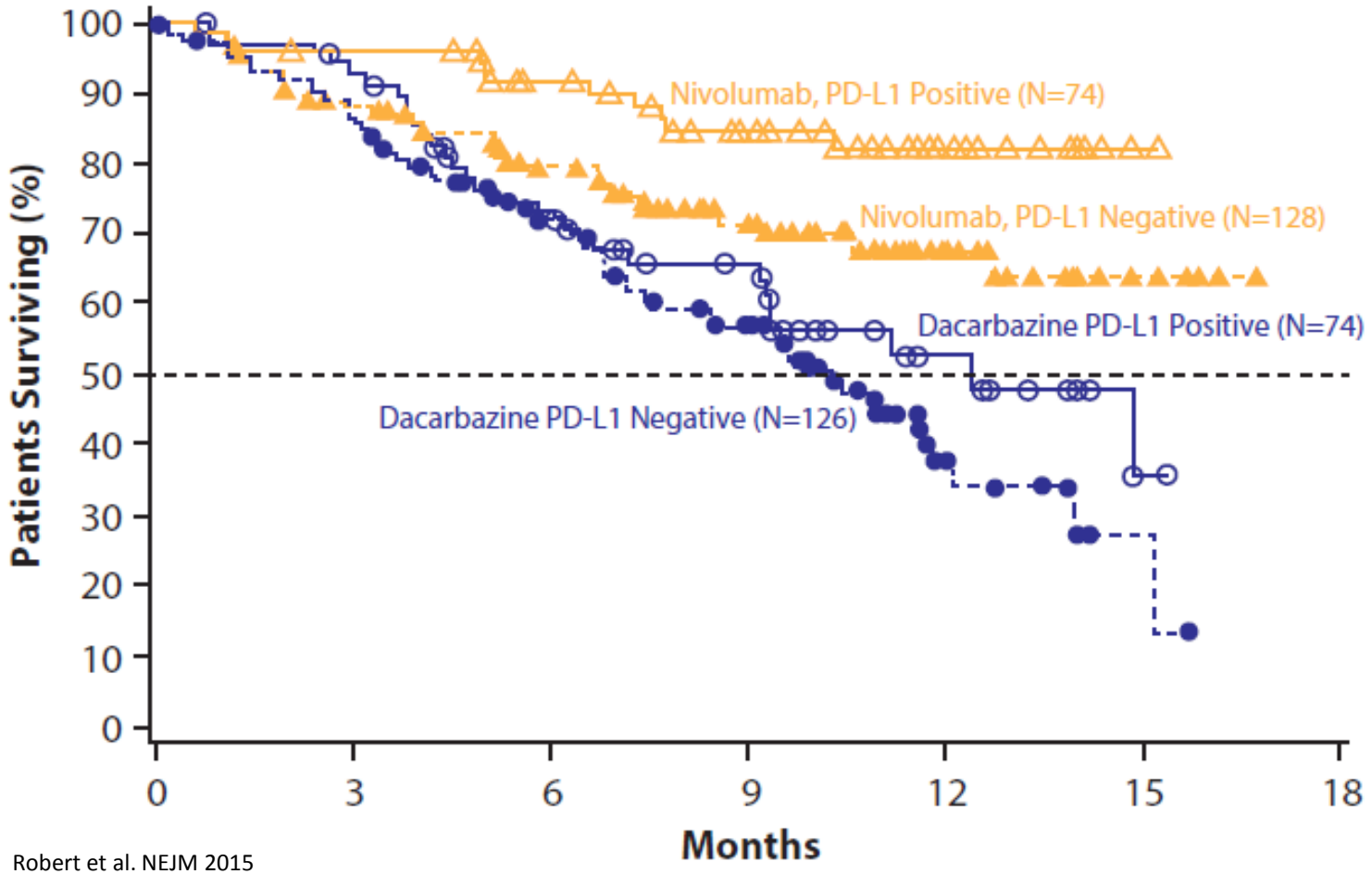
Wolchok et al. *NEJM* 2017

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

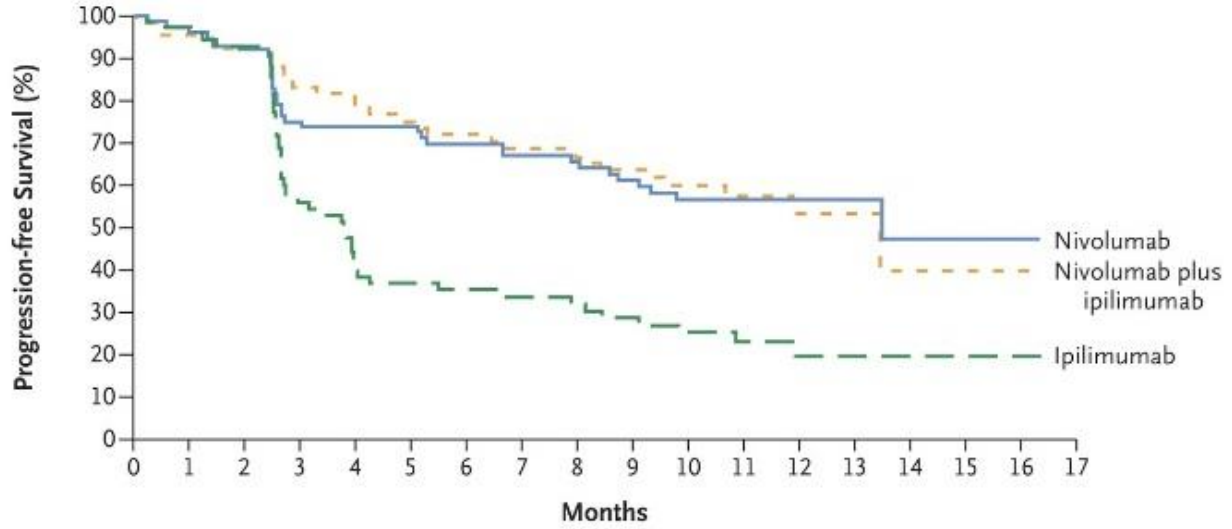
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



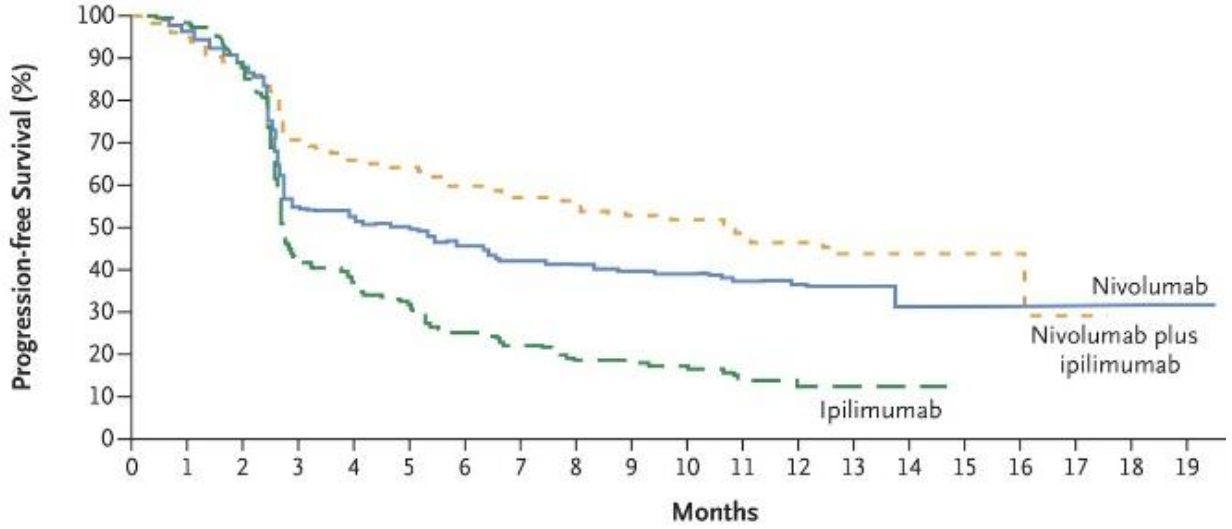
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

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



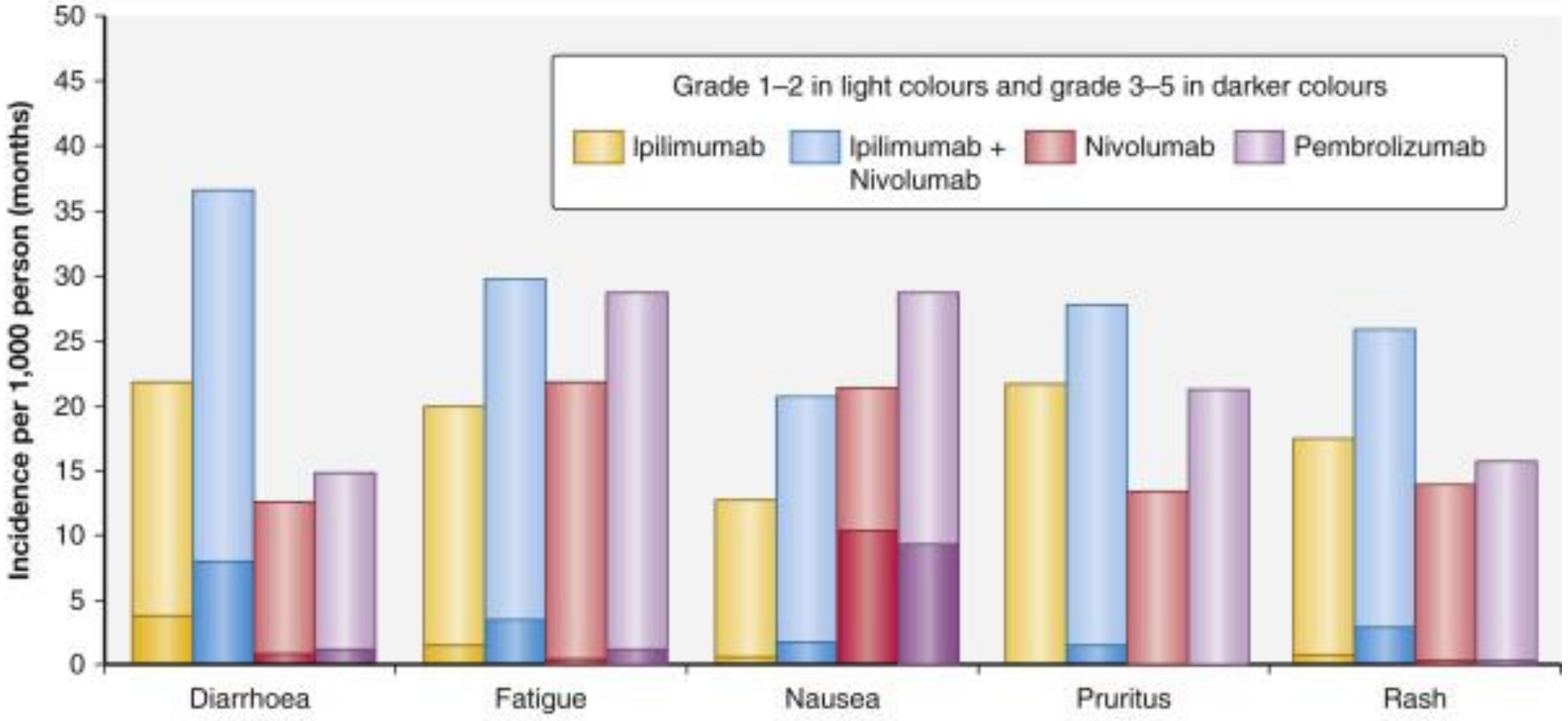
Tumor PD-L1 Positive Patients



Tumor PD-L1 Negative Patients

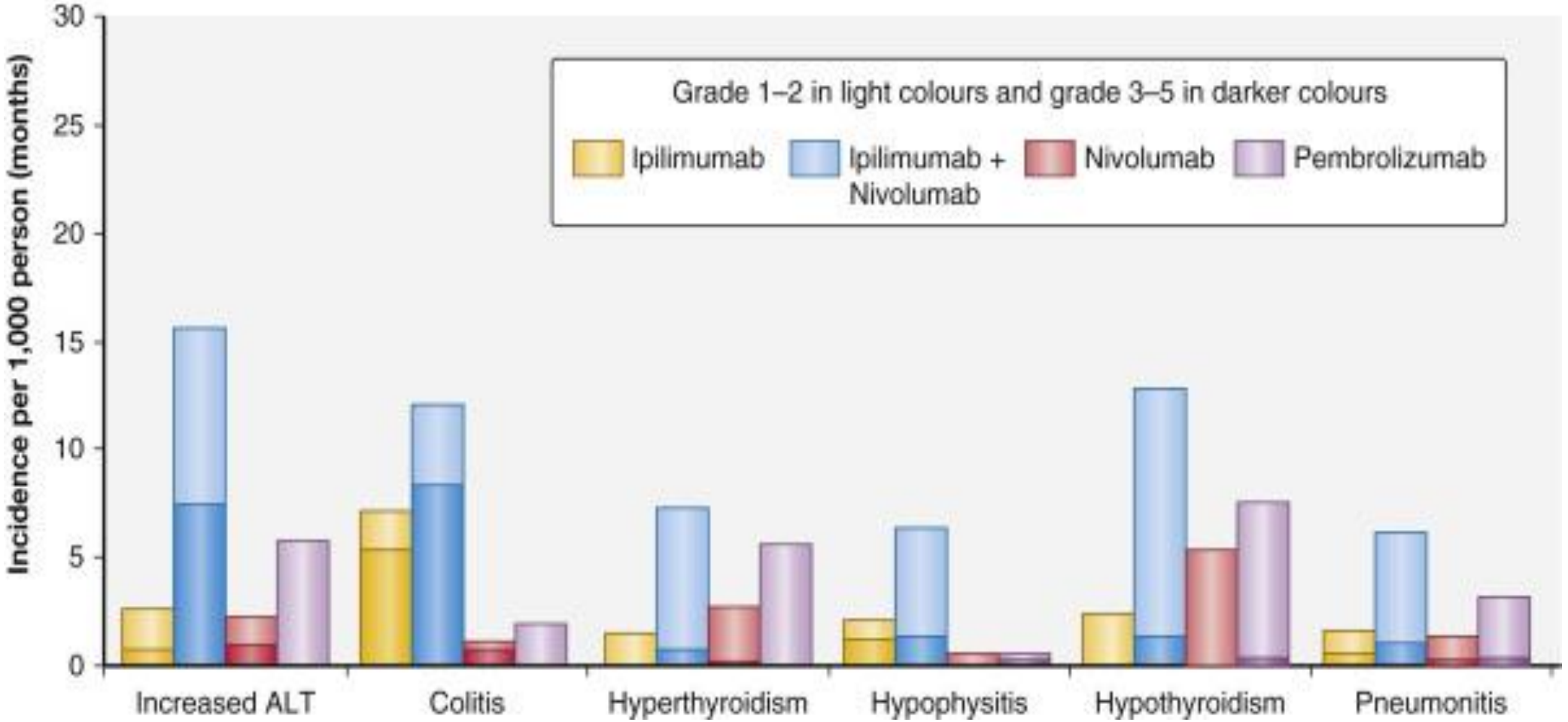
Larkin et al. NEJM 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



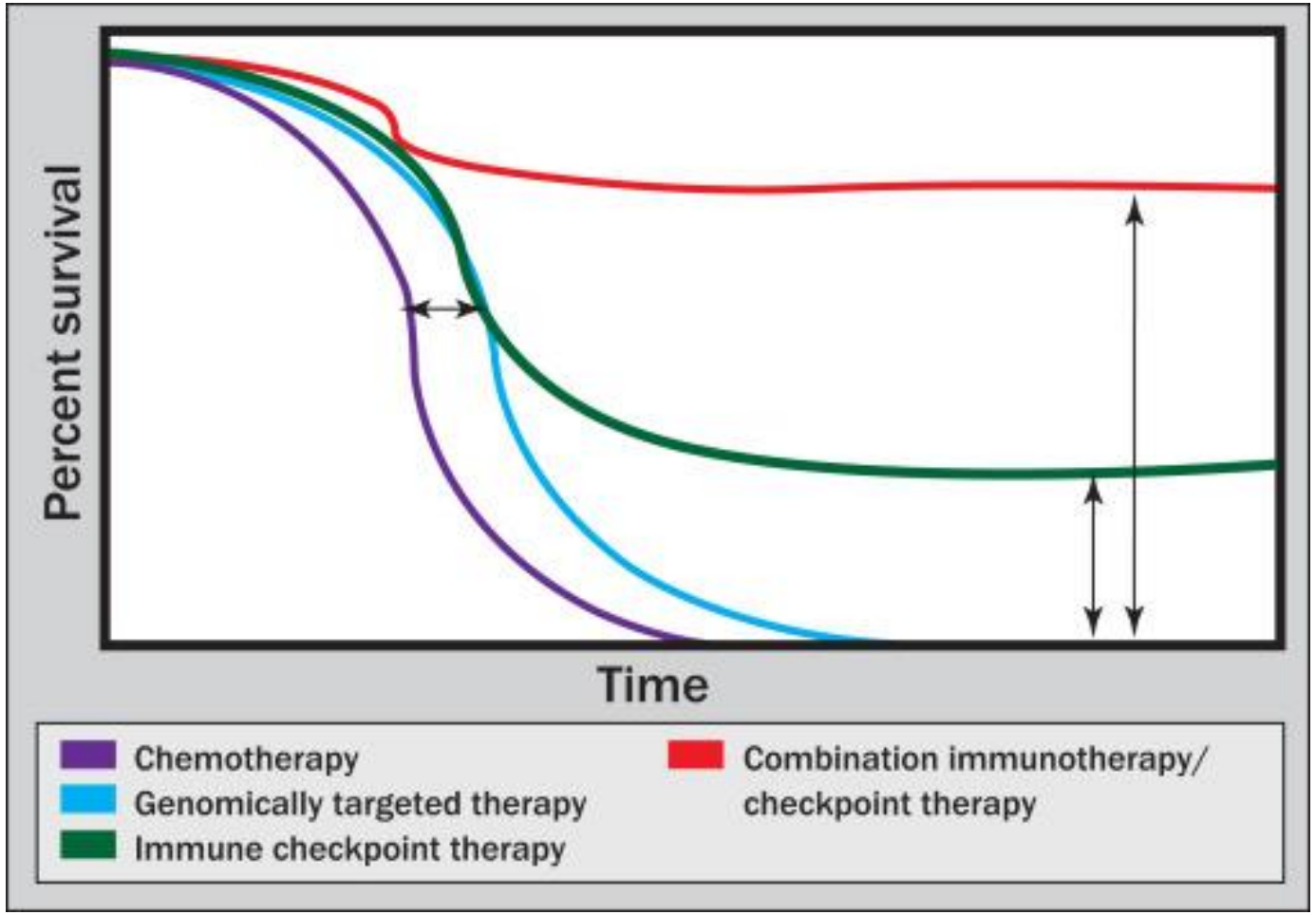
Emens et al. Eur J Cancer 2017

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

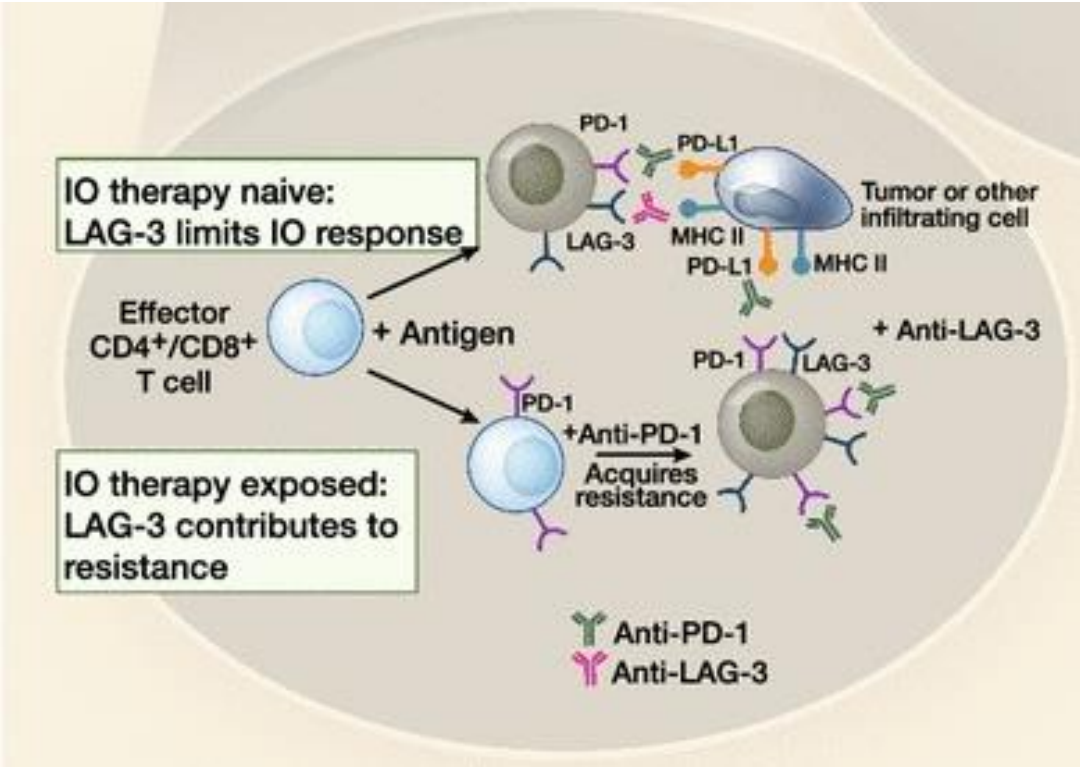
Developmental Immunotherapeutic Strategies for Melanoma

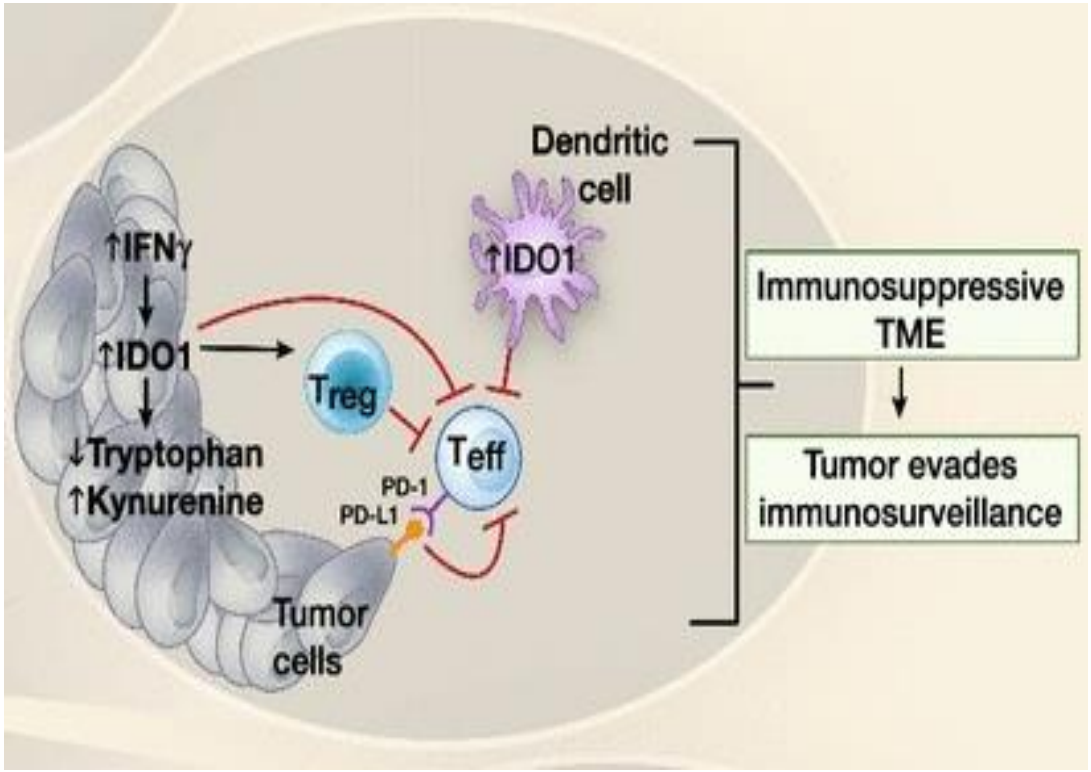


Atkins, Semi. Oncology 2015

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

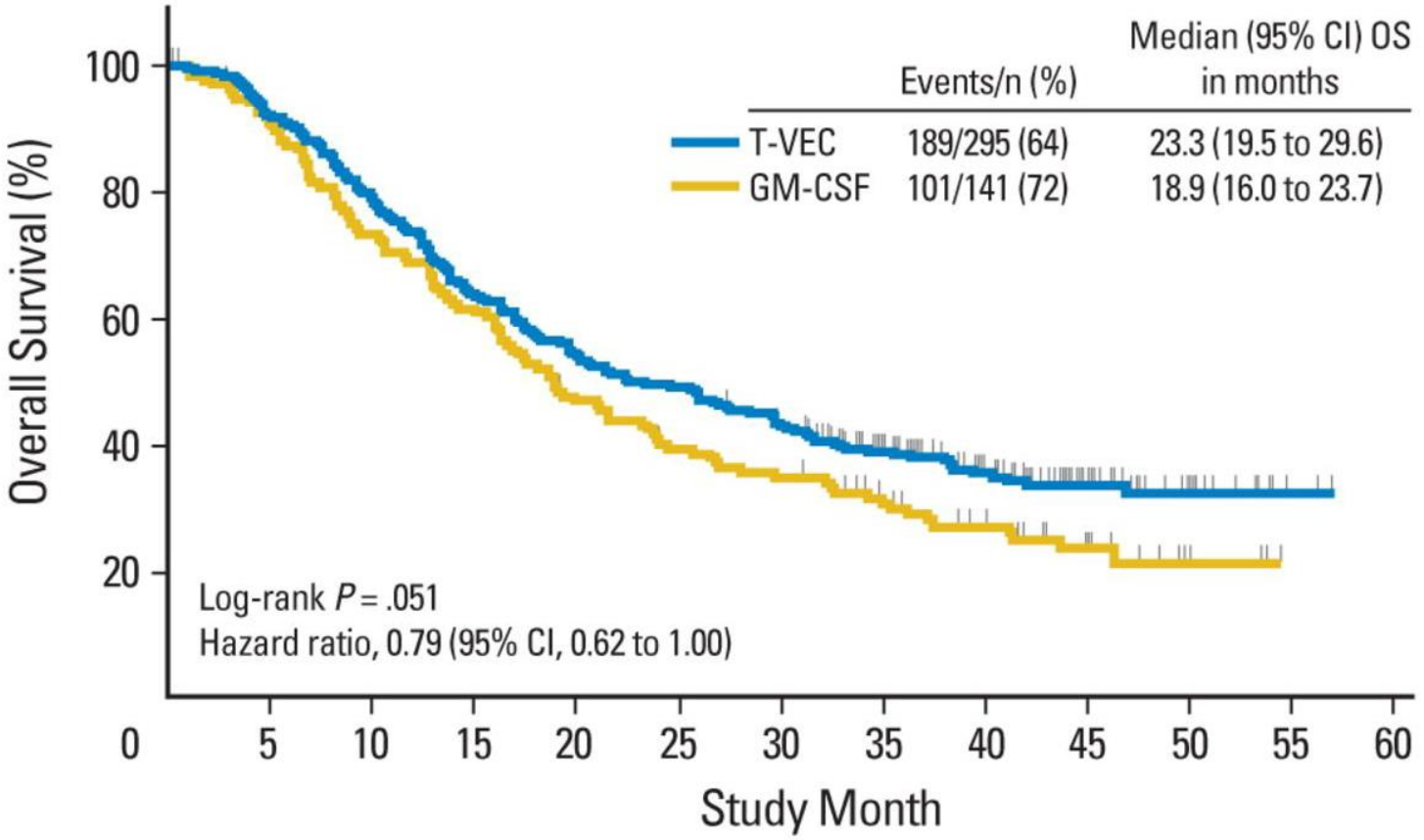
A UWCCC Clinical Trial (IND being prepared) with collaboration from Apeiron, NMS and NCI

- 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.

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

Case Study 1

- A 65 year old man undergoes biopsy of an enlarging pigmented mole on the left shoulder. Pathologic review identifies a malignant melanoma, 2.4 mm deep, with ulceration. Margins are positive for in situ disease.
- Patient received wide excision
- Options for Adjuvant Therapy for Melanoma?

Case Study 1

- Options for Adjuvant Therapy for Melanoma?
  - Observation
  - Interferon
  - Ipimumab
  - Nivolumab
  - Dabrafenib+Trametinib if BRAF V600 mutated

Kirkwood et al. *J Clin Oncol* 1996
Eggermont *JCO* 2012
Eggermont *NEJM* 2016

Case Study 1

- High dose interferon
  - Improvements in RFS
  - Unclear whether it improves OS
  - Side effects (myalgias, hematologic, liver, thyroid, fatigue)
- Pegylated interferon
  - No OS benefit
  - Weekly injection
- Ipilimumab 10 mg/kg
  - OS benefit vs. placebo
  - Toxicity (1% death rate)

Kirkwood et al. *J Clin Oncol* 1996
Eggermont *JCO* 2012
Eggermont *NEJM* 2016

Case Study 1

- Adjuvent vemurafenib vs. placebo (BRIM-8)
  - Negative study
- Adjuvent dabrafenib +trametinib vs. placebo (COMBI-AD)
  - Improve RFS
- Adjuvent nivolumab vs. ipilimumab (Checkmate-238)

Long et al. *NEJM* 2017
Weber et al. ESMO 2017
Eggermont *NEJM* 2016

Case study 2

- A 67 year old women with stage IV melanoma involving liver, skin and bone
- No other comorbitidies
- Disease progression after 2 doses of ipilimumab

Case study 2

After the third pembrolizumab infusion, the patient develops new dyspnea and hypoxia. Which of the following us a nivolumab-related adverse effect that should be considered in the differential diagnosis?

A. Pulmonary embolus
B. Pneumonitis
C. Pleural effusion
D. Fungal pneumonia
E. Congestive heart failure

Case study 2

- After 4 cycles of pembrolizumab patient reported a severe new headache behind her eyes. On physical exam, she has no abnormal findings. Which of the following is the most appropraite initial management?
- A. Order a brain MRI
- B. Start high-dose prednisone
- C. Check labs
- D. Discontinue pembrolizumab