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

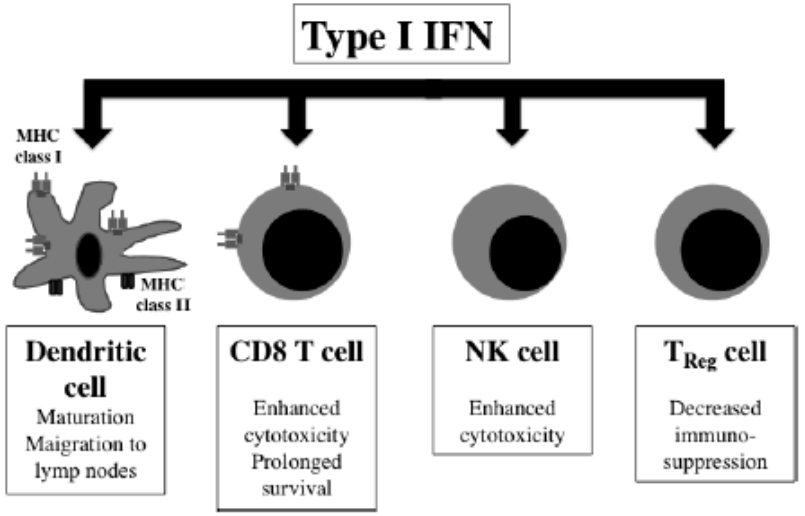
Disclosures

- I will not be discussing non-FDA approved indications during my presentation.

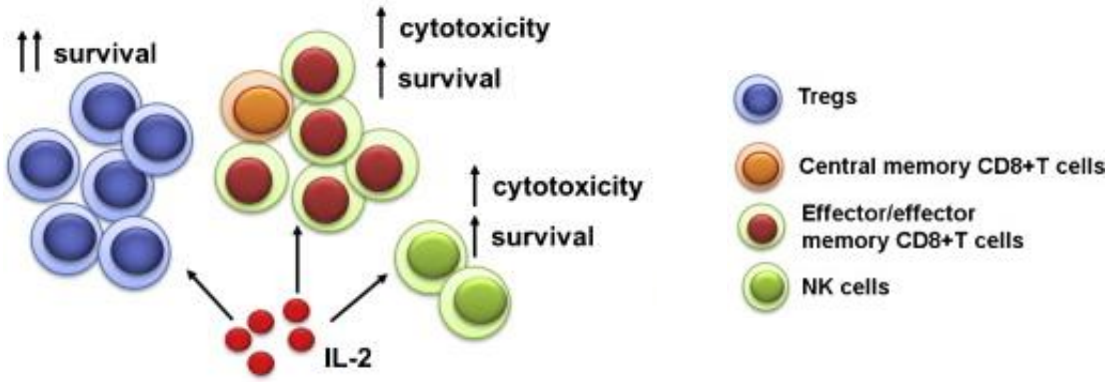
- Consulting: BMS, Array
- Research Funding: Merck, BMS

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.



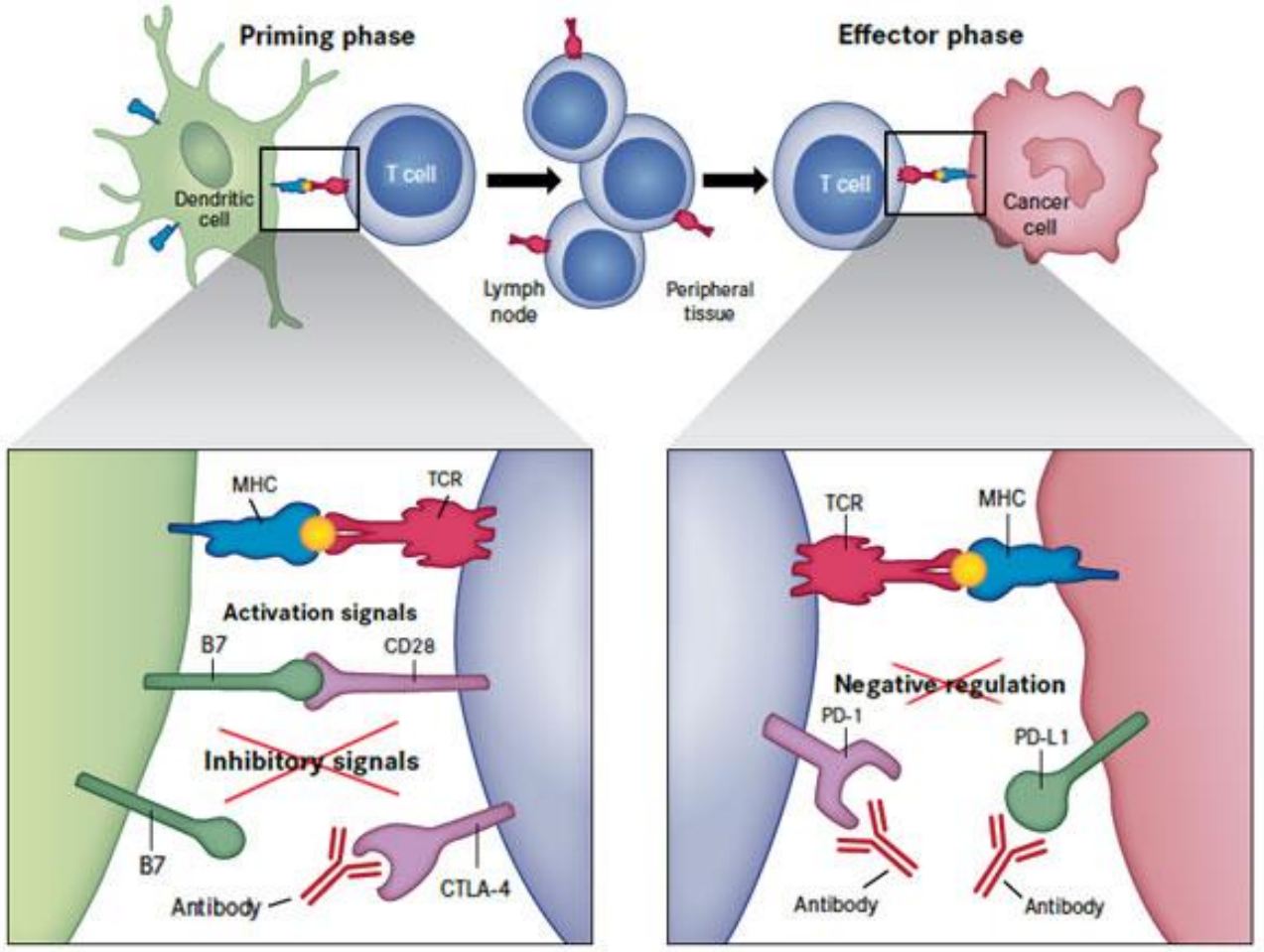
Numasaki et al. Immunotherapy 2016



Sim, Radvanyi Cytogfr 2014

FDA-approved Immunotherapies in Melanoma

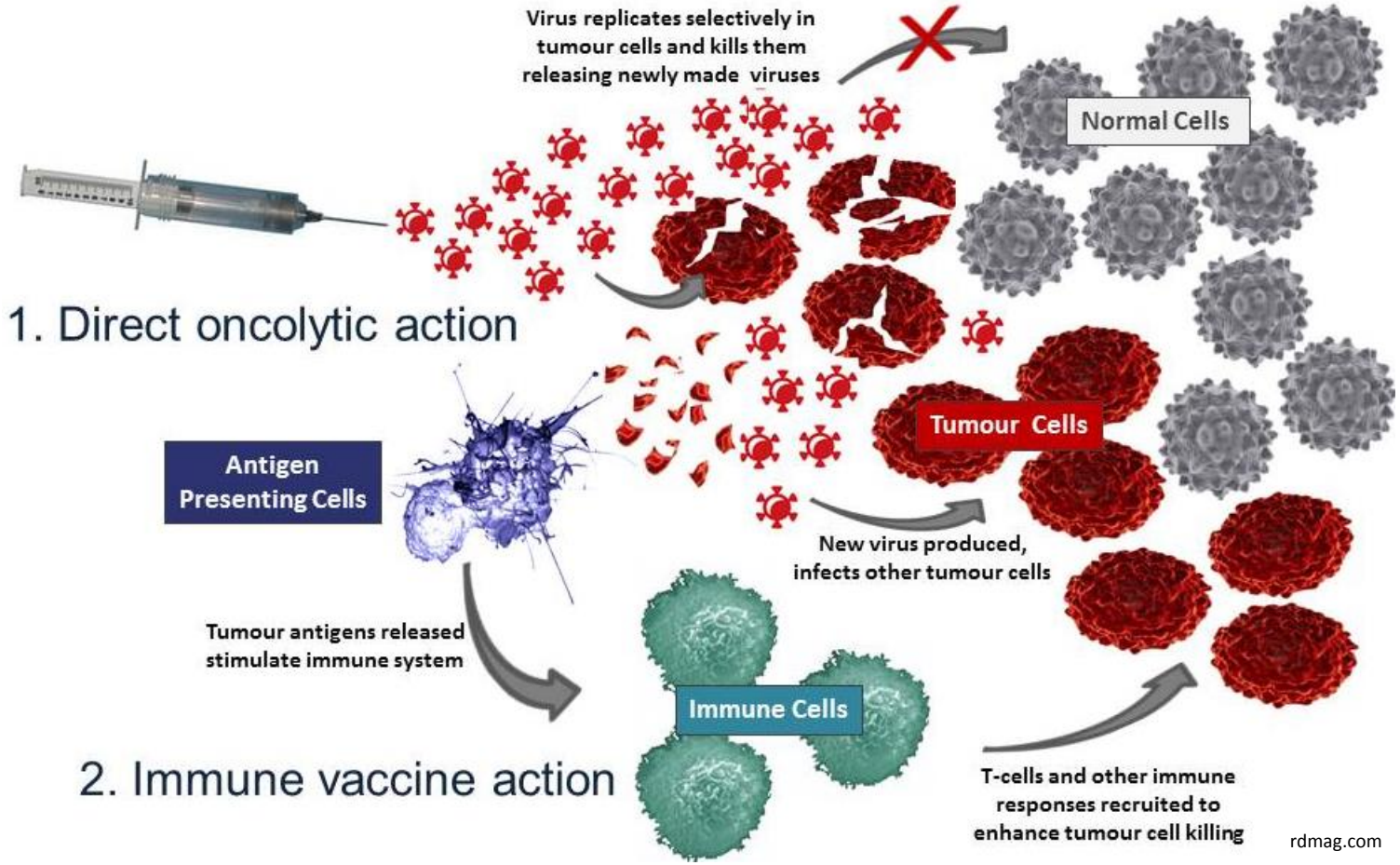
- Checkpoint inhibitors
  - Ipilimumab, adjuvant and nonresectable/Stage IV, I.V.- different dosing for adjuvant and nonresectable/Stage IV
  - Pembrolizumab, nonresectable/Stage IV, I.V.
  - Nivolumab, adjuvant and non resectable/Stage IV, I.V.
  - Ipilimumab in combination with nivolumab, Stage IV



Ribas NEJM 2012
Gordon et al Nature 2017

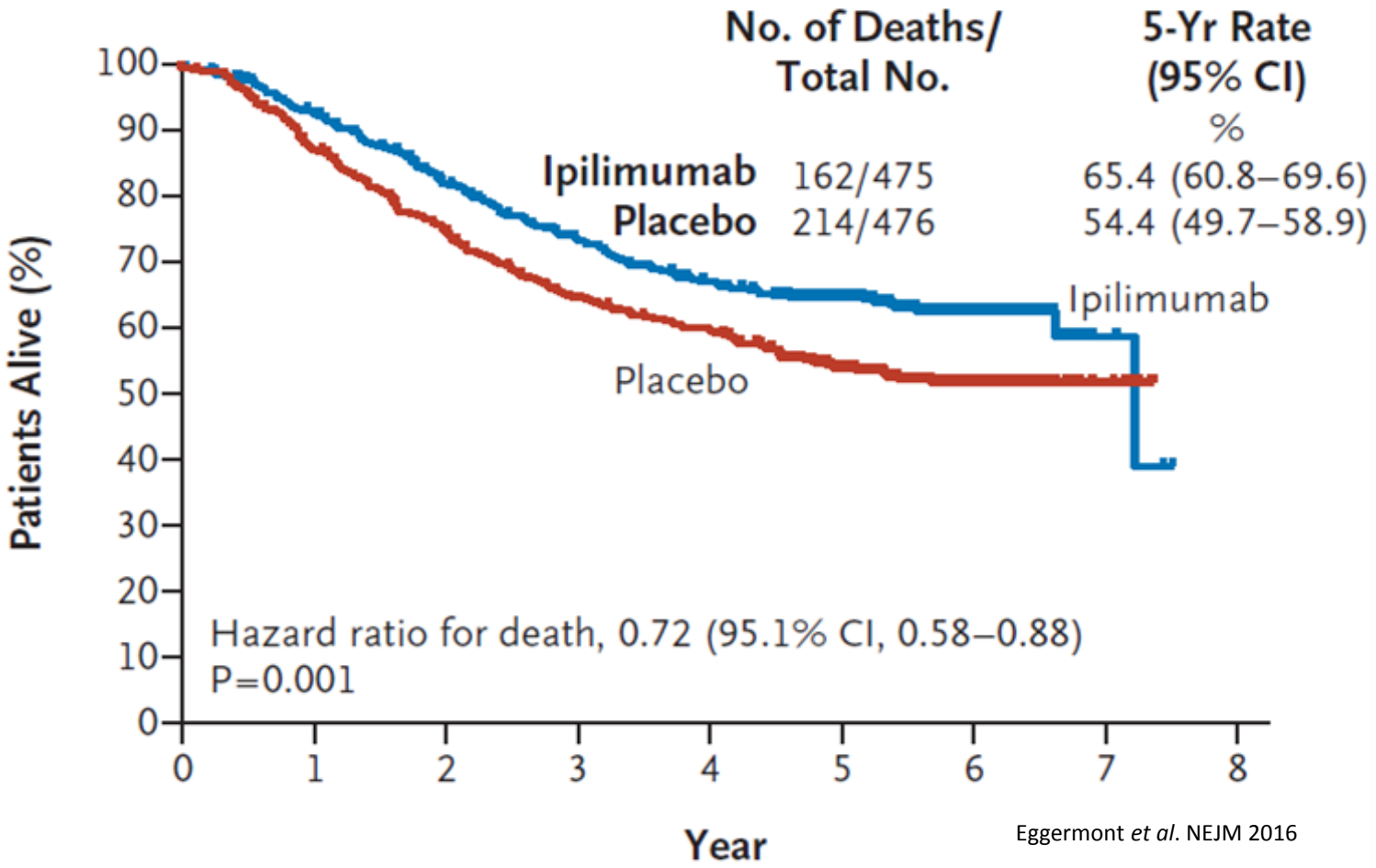
FDA-approved Immunotherapies in Melanoma

- 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



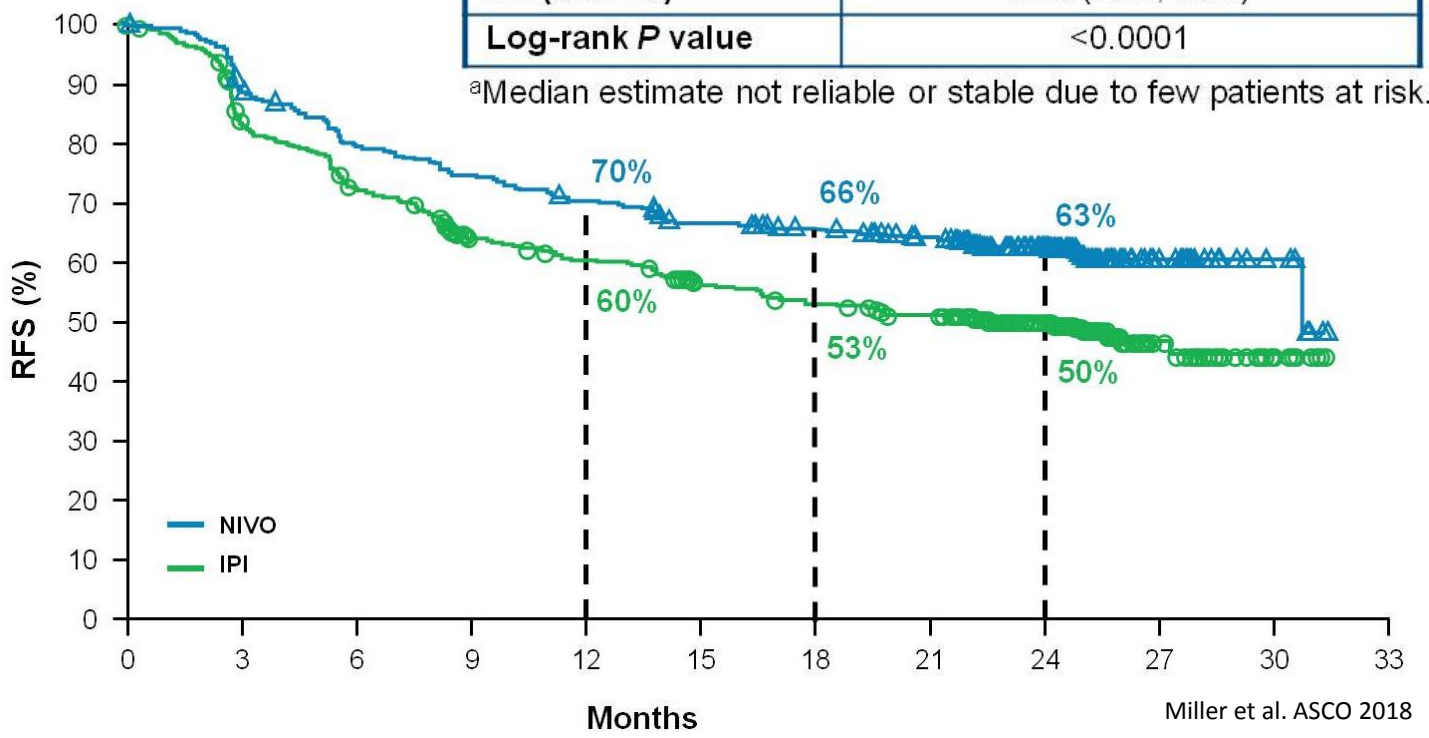
Eggermont *et al*. NEJM 2016

Adjuvant 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	

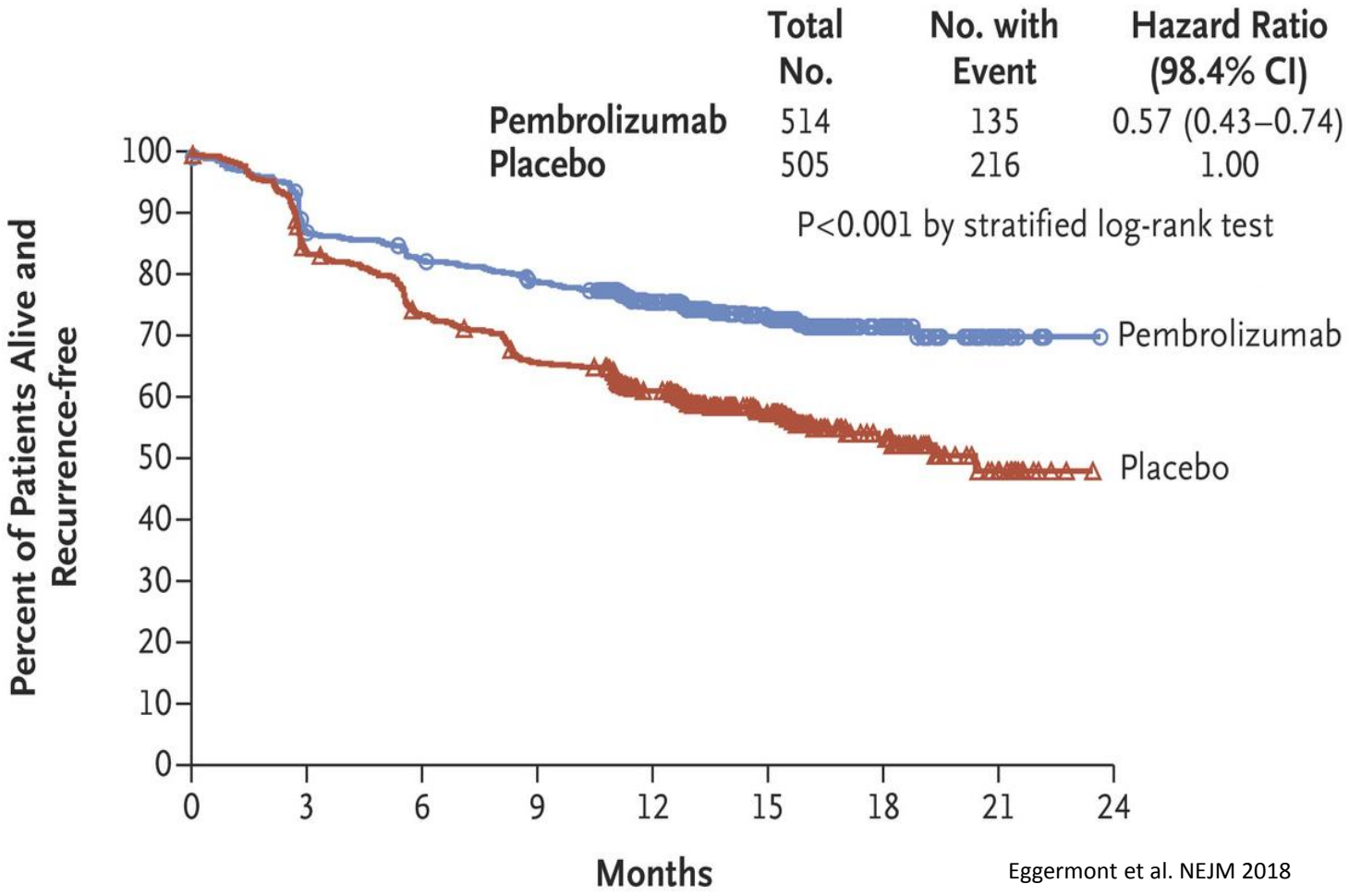
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

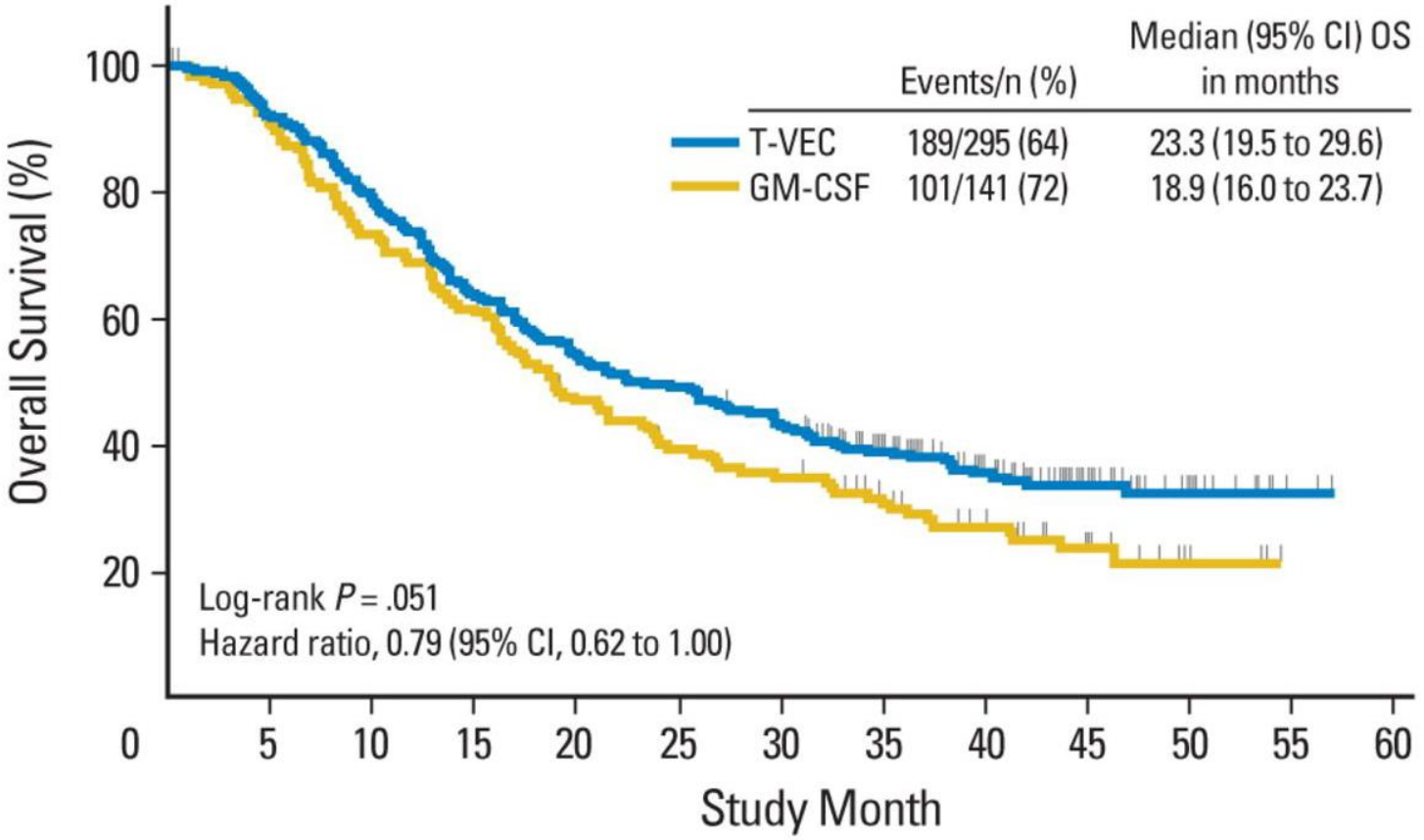
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)



Eggermont et al. NEJM 2018

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

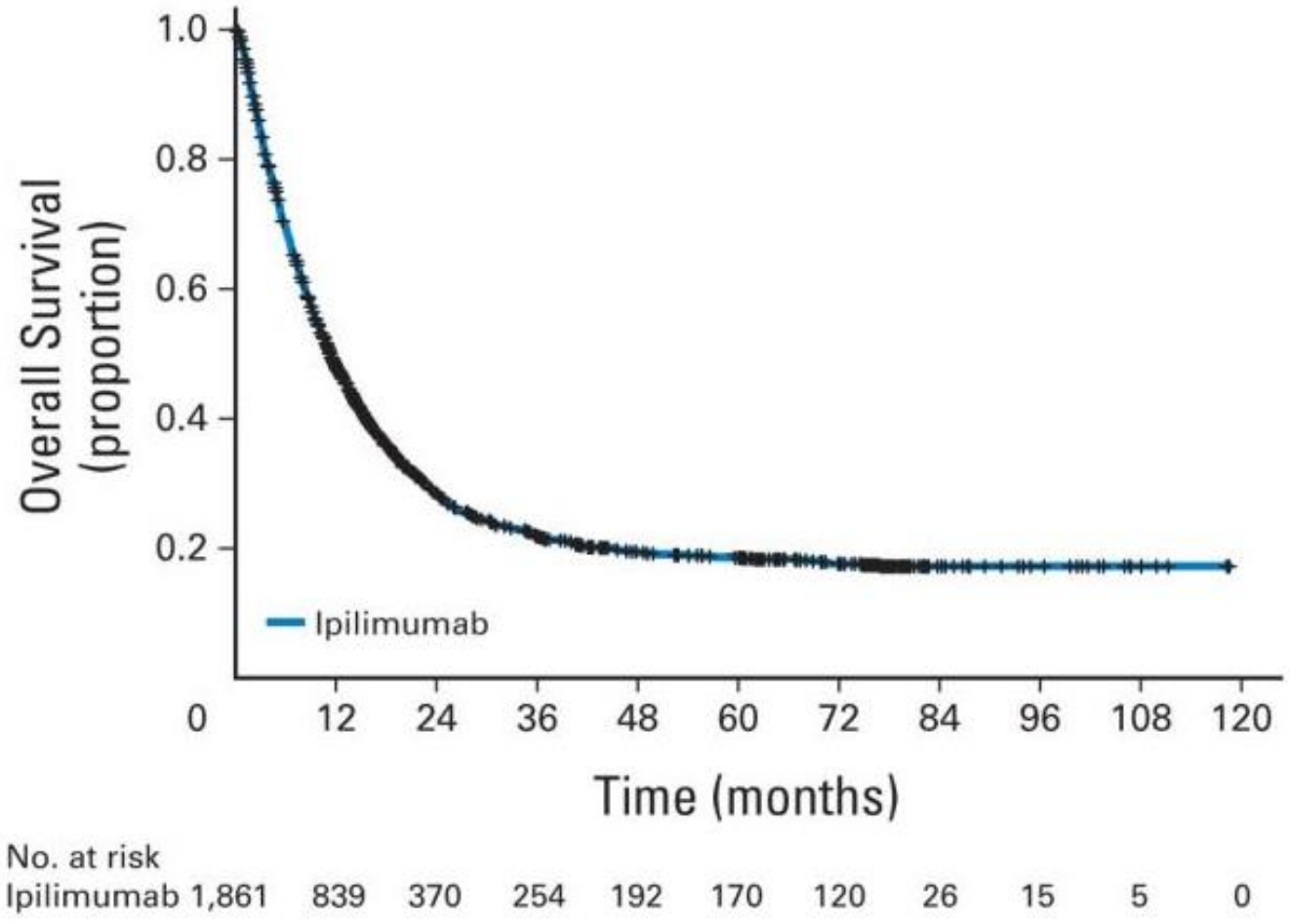
- **Phase III OPTiM Trial**
  - Oncolytic, genetically-engineered herpes virus
  - **Intralesional** T-VEC 10^6 pfu/mL, 10^8 pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF



Andtbacka, Kaufman et al. JCO 2015

Ipilimumab in Stage III/IV Melanoma

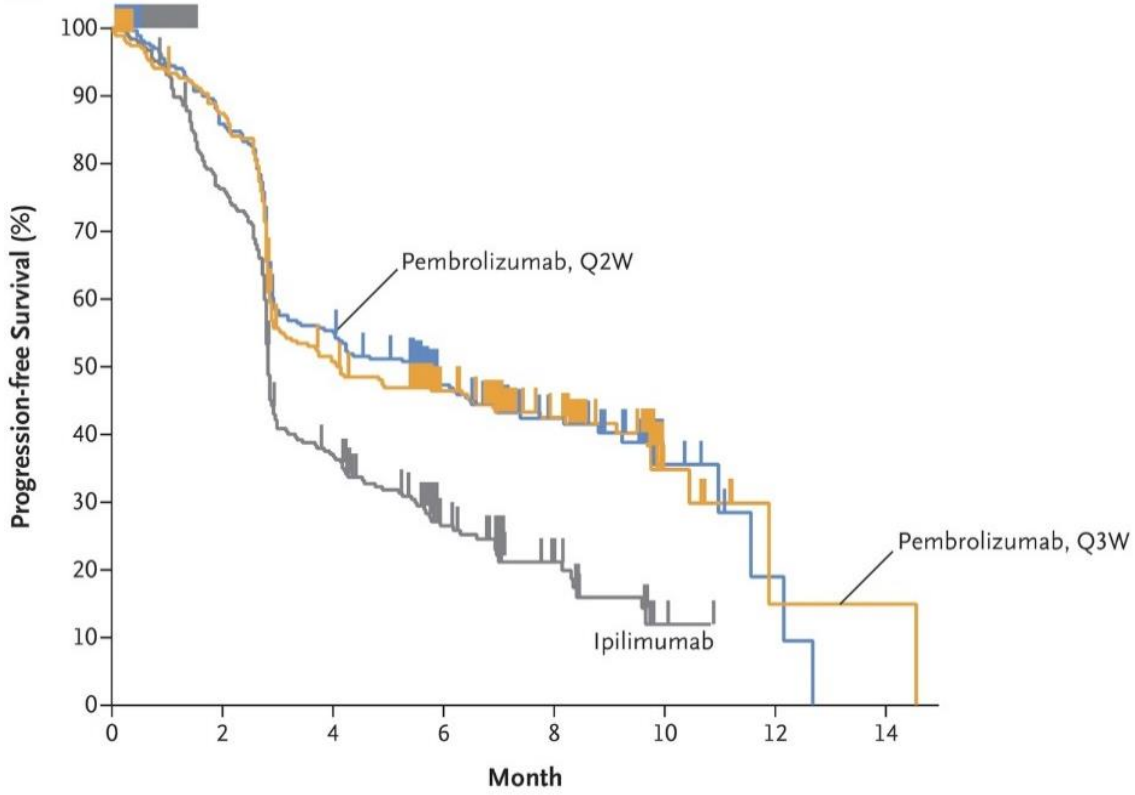
- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)

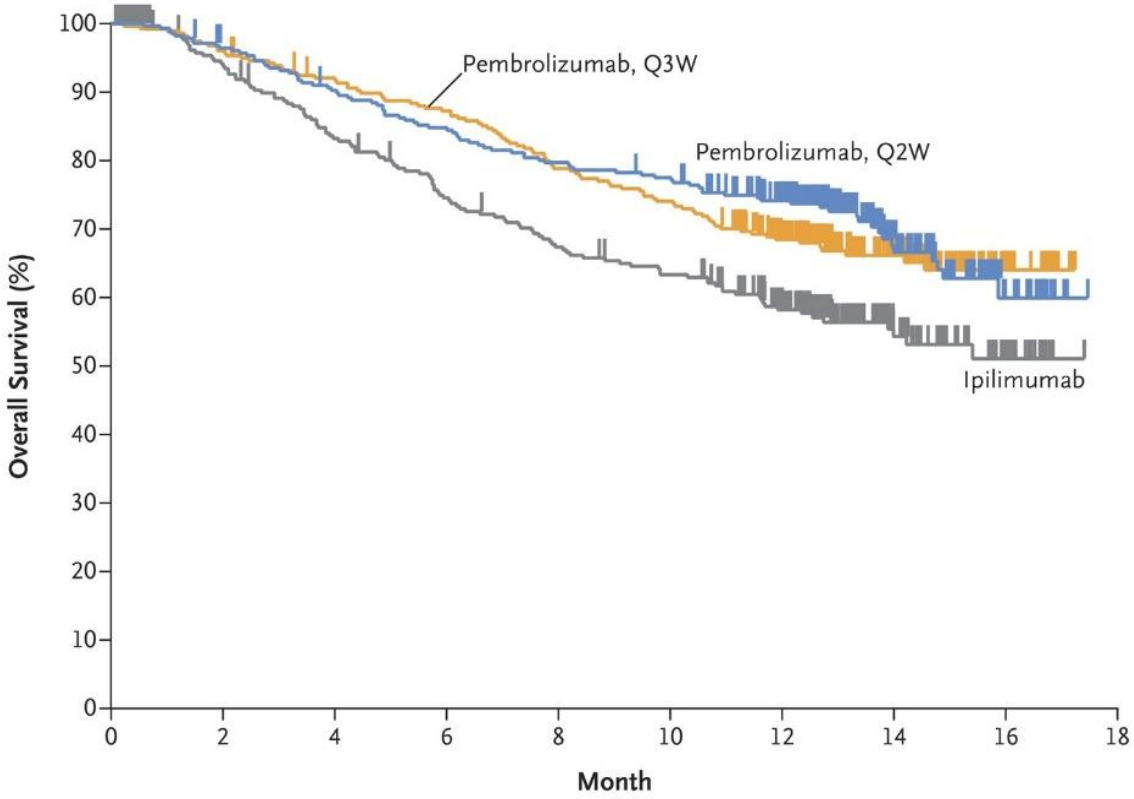


Schadendorf et al. JCO 2015

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial



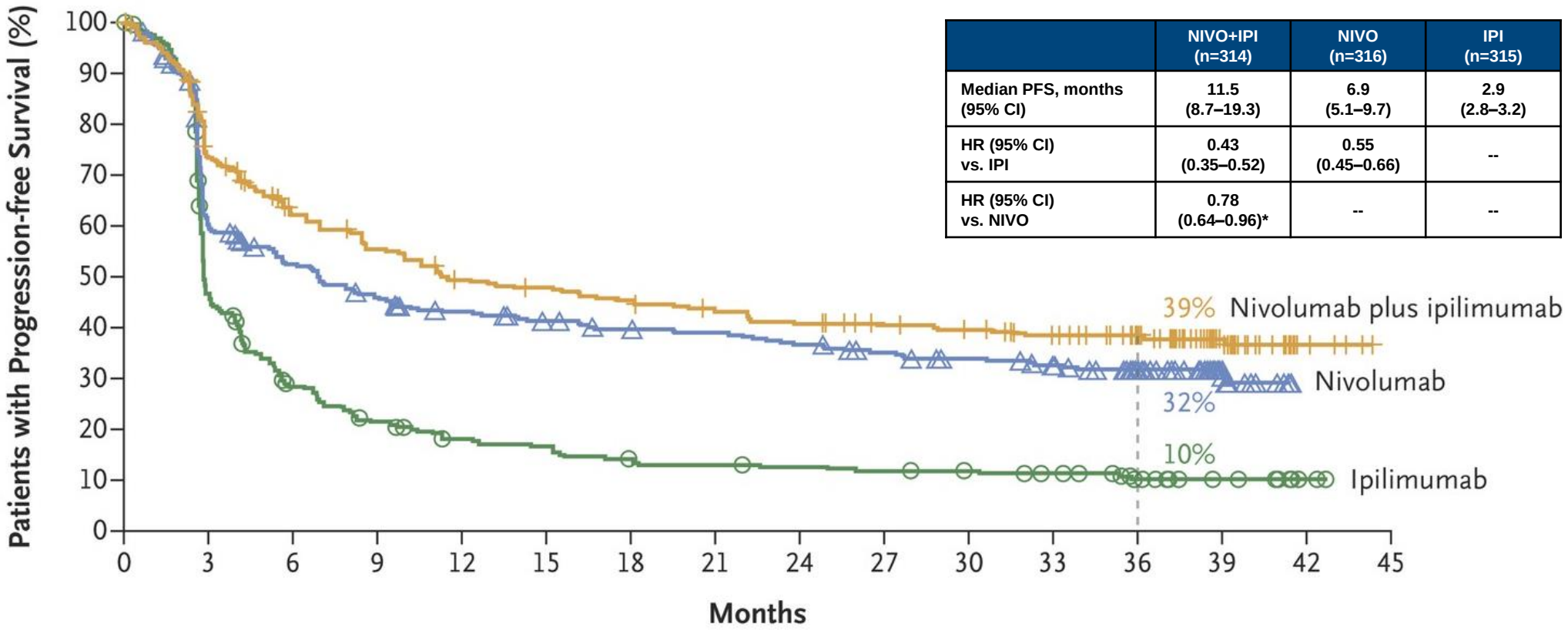


Robert et al. NEJM 2015

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)*	--	--



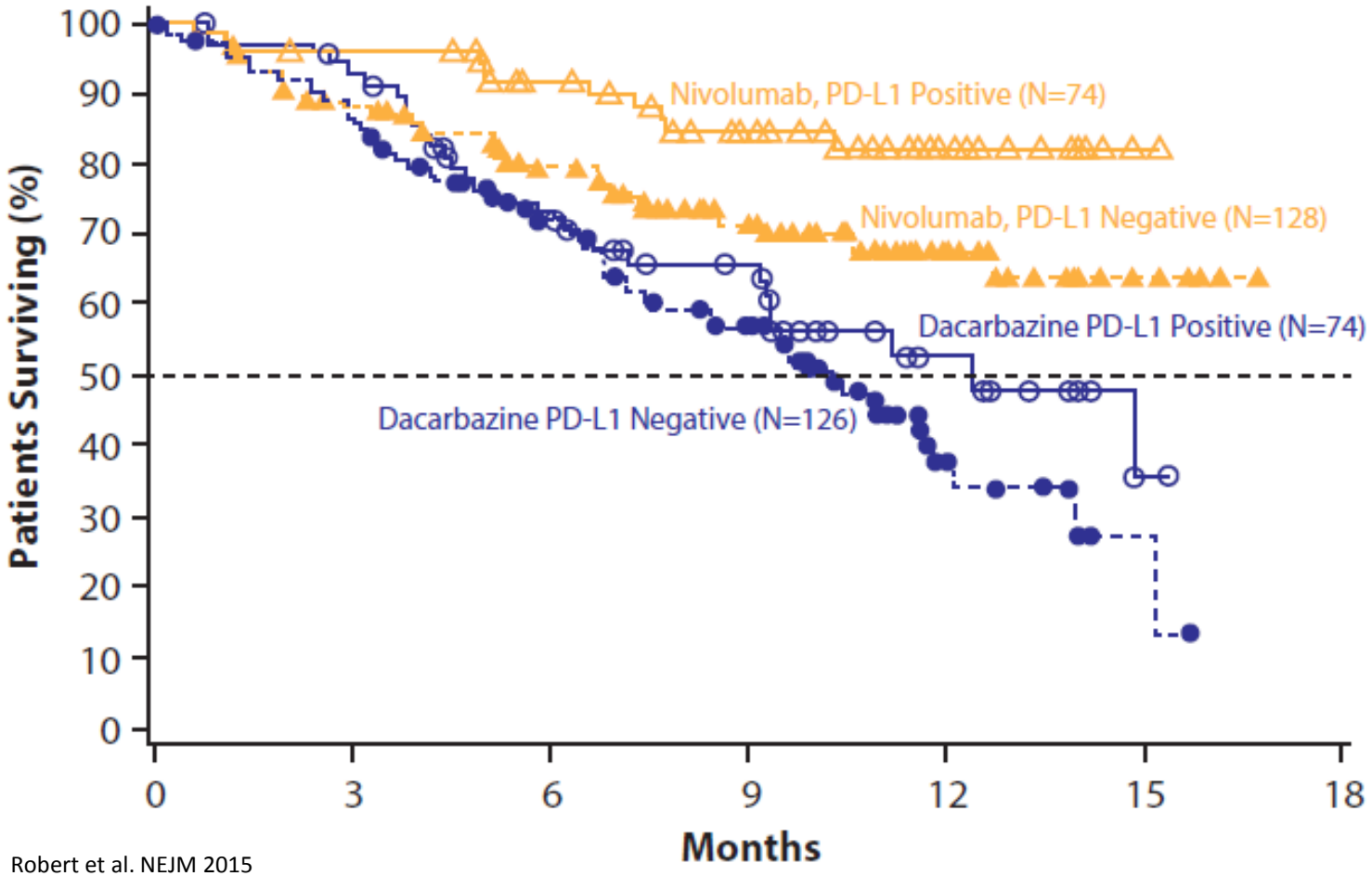
Wolchok et al. NEJM 2017

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

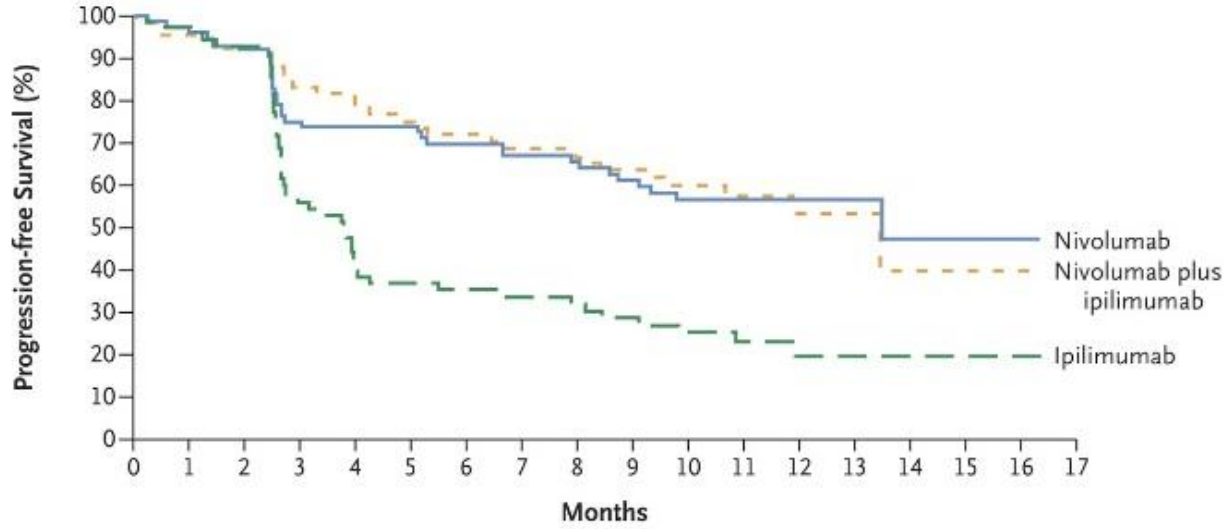
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



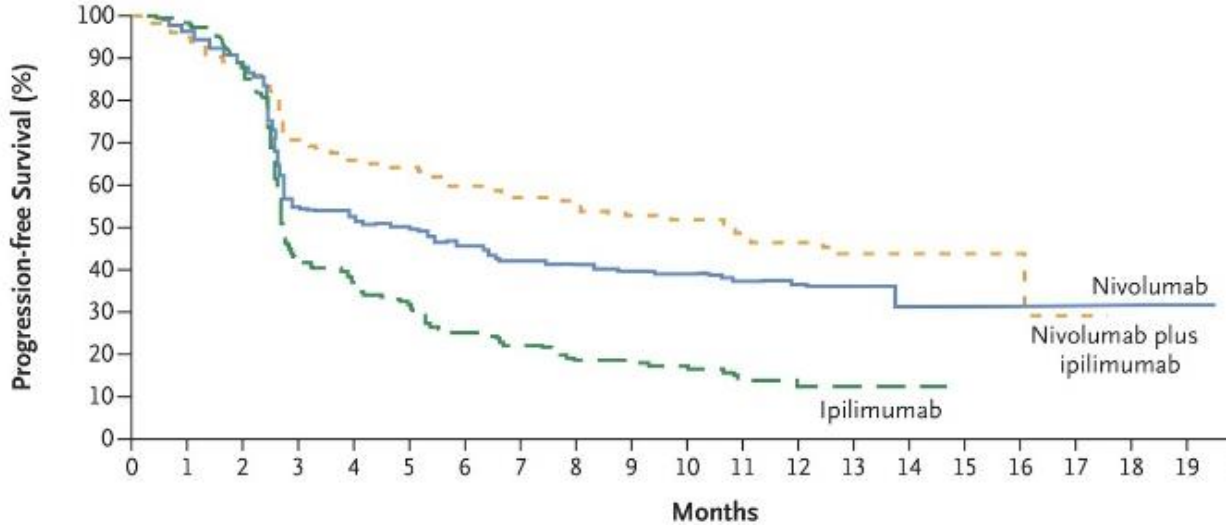
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

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



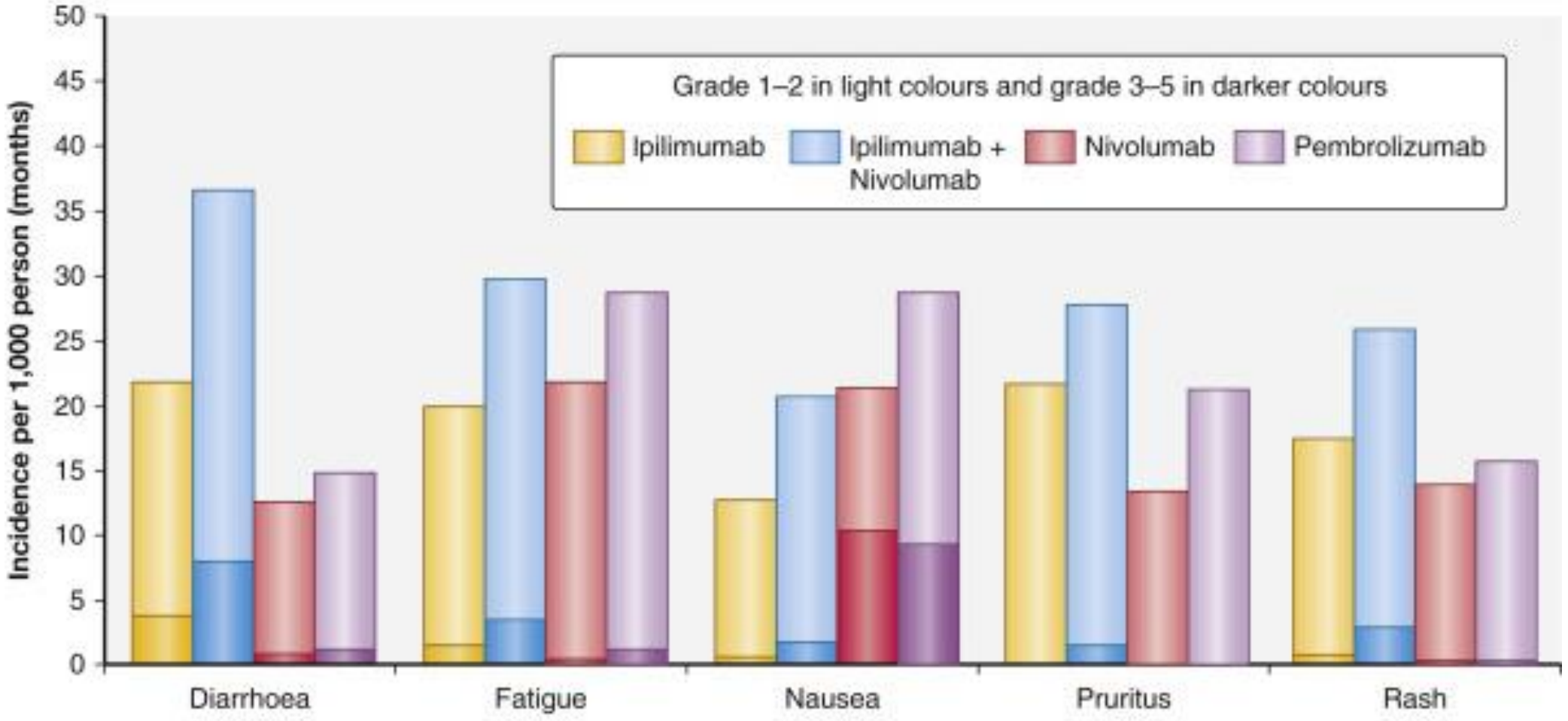
Tumor PD-L1 Positive Patients



Tumor PD-L1 Negative Patients

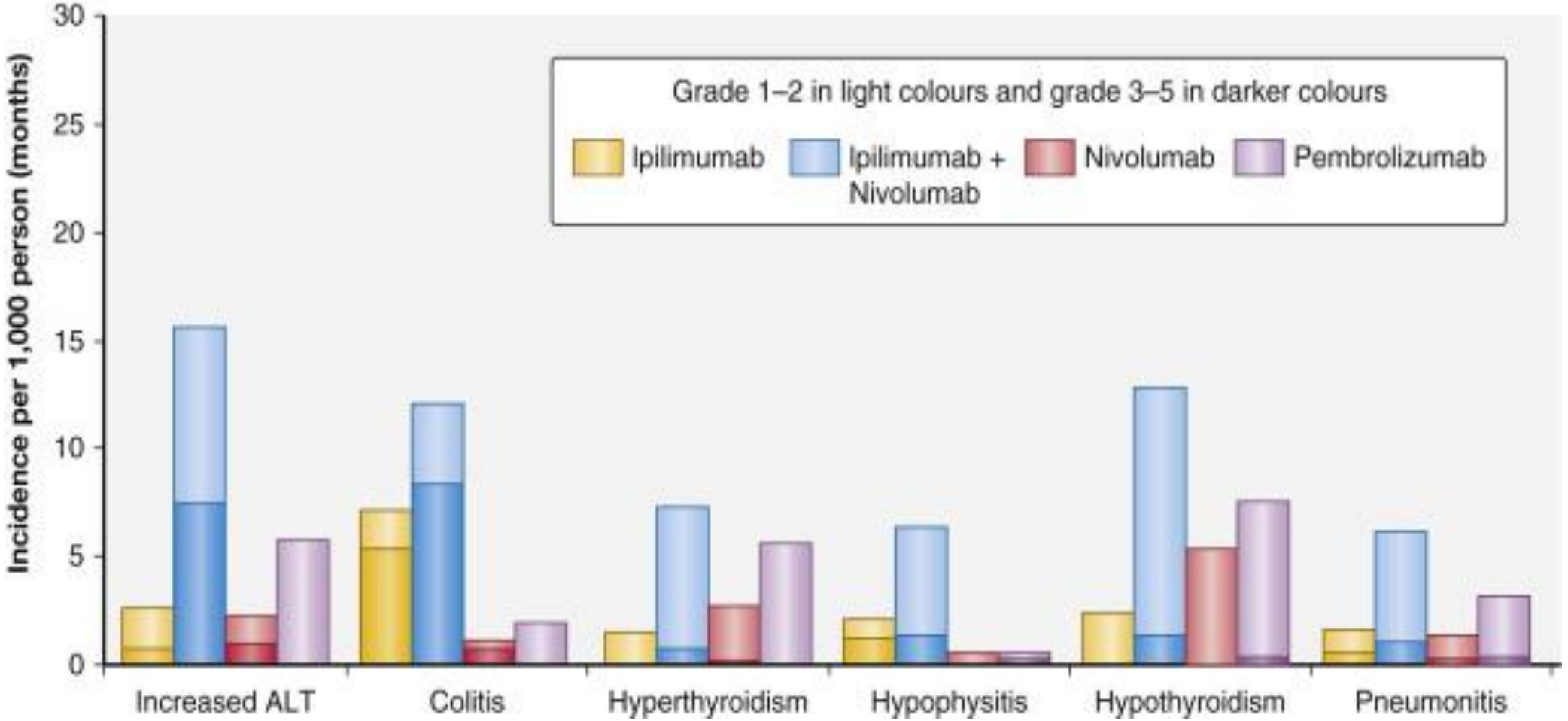
Larkin et al. NEJM 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

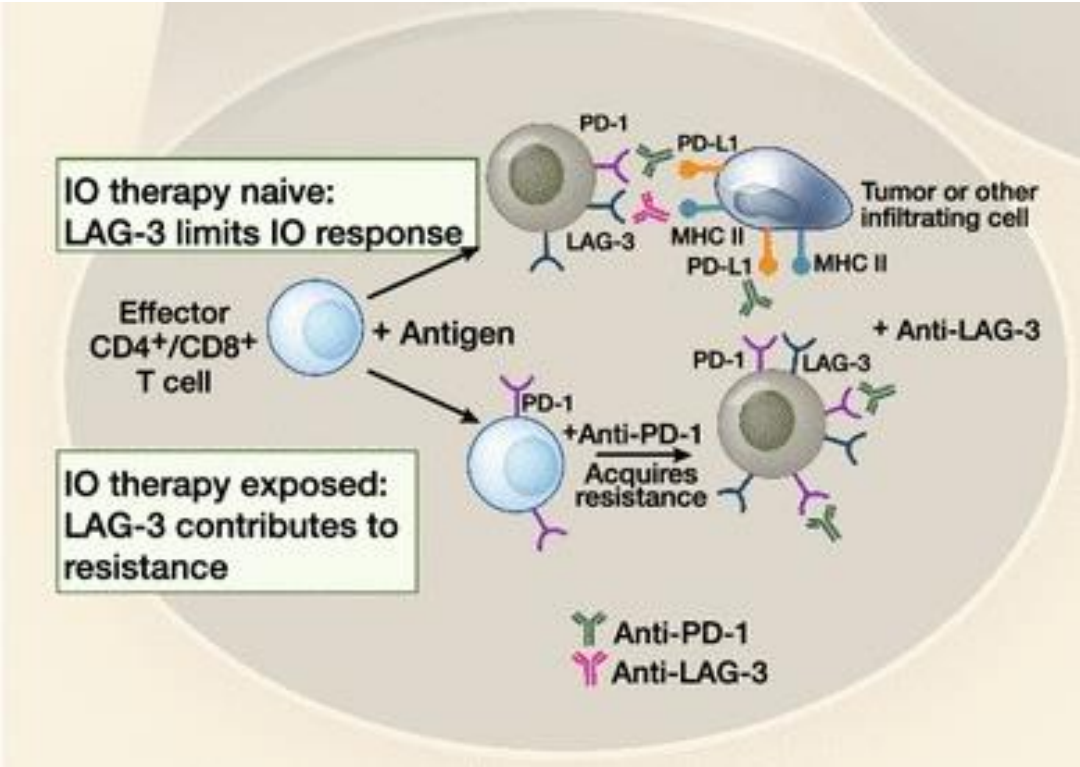
Treatment of Immune-Related AEs

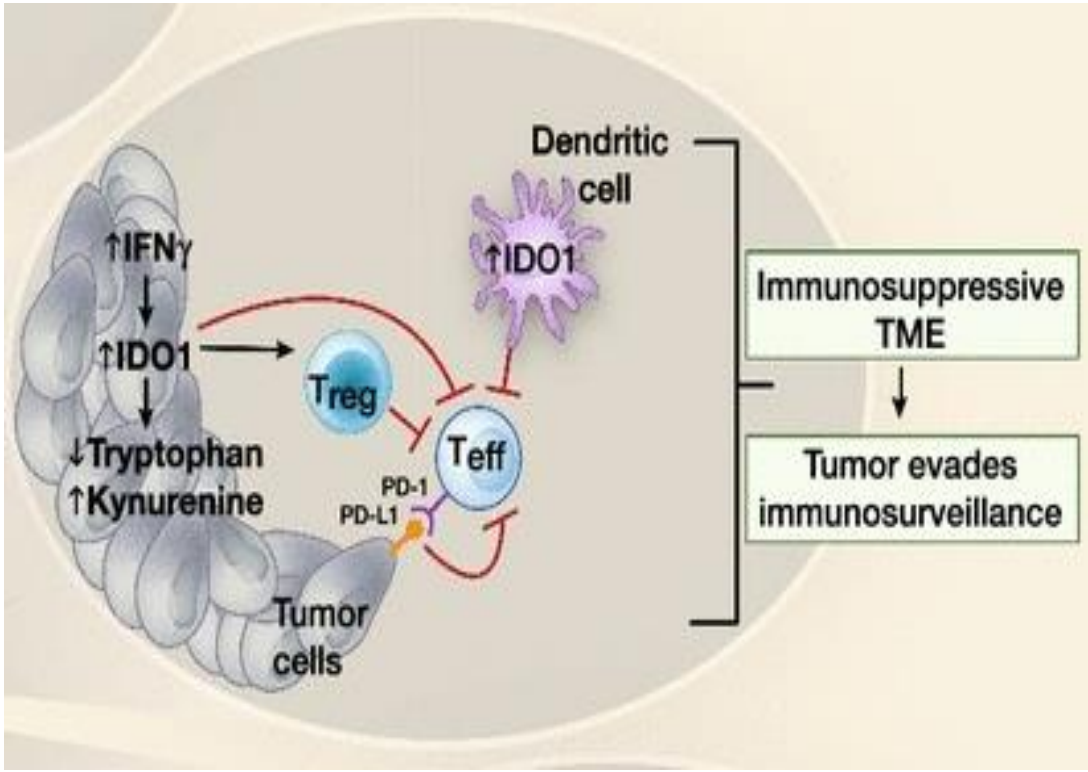
Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day 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

Targeting New Immune Checkpoints





Ascierto, McArthur J Transl Med 2017

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

- Background:

  A 77 year old female has received 9 cycles of nivolumab with overall good tolerance, and only accompanied with a mild grade 1 hepatitis and hypothyroidism, requiring levothyroxine. She has been a lifelong smoker, however has cut down in recent years. During today's visit she appears short of breath and admits to dyspnea, which started fairly rapid, and has worsened over the last few hours. Pulse oximetry at rest shows 88% saturation, however when walking, the saturation drops down to 83%. Physical exam reveals decreased breath sounds with some wheezing, left mildly worse than right. She also is febrile at 101.6.

- Lab Results:

  Slightly elevated WBC, hemoglobin 10.8 g/l

Case Study 1

What is the most important differential diagnosis for the patient's symptoms?

A. Pneumonitis - Pneumonitis is a well described side effect of anti-PD1 therapy. The median time at onset is typically after 8 weeks of treatment initiation; however it can occur at any time during treatment.

B. COPD exacerbation – less likely, and can be treated al per guidelines.

C. Pulmonary embolus- cancer patients have a high risk of developing thromboembolic event. While pulmonary embolus is possible, CT scan evaluation of the patient will be able to exclude this, and will show

D. Pneumonia- This is a possible differential diagnosis, and has some overlap with pneumonitis. In both pneumonia and pneumonitis the WBC and temperature can be elevated, however, if pneumonitis is considered, rapid initiation of high dose corticosteroids can be lifesaving.

E. Tumor progression – while tumor progression is certainly possible, it typically does not present with sudden onset shortness of breath.

Case Study 1

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E. Tumor progression – while tumor progression is certainly possible, it typically does not present with sudden onset shortness of breath.

Case Study 1 - Conclusion

- Pneumonitis represents a potential life threatening emergency, and clinicians should actively rule out pneumonitis in a patient with new onset shortness of breath while on immunotherapy.

Case Study 2

- Background:

  A 37 year old male is being diagnosed with metastatic melanoma, with sites of disease including his brain (3 small brain metastases), lungs, liver and bones. The mutation analysis performed on a liver biopsy shows that his tumor is no BRAF V600 mutant. He has read extensively about systemic treatment options and is here to discuss his next treatment options.

- Lab Results:

  His hemoglobin is 9.8 g/L, and his LDH is 2 times upper normal institutional limit. All other labs are within normal limit.

Case Study 2

Which regimen could be considered and has shown to most improve outcomes in melanoma patients with CNS metastases?

A. Pembrolizumab – the reported intracranial response rate for 18 melanoma patients with brain metastases was 22% in a phase II trial (Goldberg et al., Lancet Onc 2016)

B. Ipilimumab – While Ipilimumab has shown some efficacy in patients with melanoma brain metastases, both single pembrolizumab and the combination of ipilimumab and nivolumab have led to higher intracranial response rates as well as progression free survival, making Ipilimumab not a first line choice.

C. Ipilimumab and Nivolumab- At a median follow-up of 9.2 months in the CheckMate-204 study (*N* = 75), the intracranial ORR was 55% and the complete response rate was 21%, with intracranial and extracranial responses largely concordant. Importantly, duration of response was not reached at time of report, suggesting that, similar to extracranial responses, intracranial responses to immunotherapy can be profound and durable.

D. Temozolomide- In the era of immunotherapy, chemotherapy is rarely ever used in the frontline setting. As a single agent, temozolomide only shows a very modest therapeutic effect.

E. Dabrafenib and Trametinib- While the COMBI-MB trial (dabrafenib plus trametinib in patients with MBM and *BRAF* mutation) reported an intracranial response of 58% in patients without (44/76) and 56% in patients with (9/16) previous local brain therapy (median follow-up, 8.5 and 20.0 months, respectively), the key point is that patient must have a BRAF V600 mutation in order to be eligible for this regimen.

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Case Study 2 - Conclusion

- For immunotherapy, there is now increasing evidence that checkpoint inhibitors may also be effective in patients with melanoma brain metastases with a high rate of durable intracranial responses observed with combination therapy

Case Study 3

- Background:

  A 27 year old male has started therapy with the combination of ipilimumab and nivolumab for her stage IV melanoma, with metastases in his axillary and hilar lymphnodes as well as metastasis in the liver, measuring 2 and 3 cm in diameter. He returns to clinic for cycle 4 of the combination immunotherapy, but reports fatigue, increased in bowel movements, with diarrhea starting 5 days ago (3-4 bowel movements/day).

- Lab Results:

  On laboratory exam his ALT is 310 and his AST is 320. Bilirubin is only minimally elevated.

Case Study 2

Which of the following is the most appropriate next management step?

A. Hold ipilimumab but continue with nivolumab, as the CTLA-4 agent is more likely to cause the diarrhea and the liver enzyme elevation

B. Hold both the ipilimumab and nivolumab and start infliximab and high dose steroids.

C. Hold both ipilimumab and nivolumab, and repeat labs weekly until normalized- combination therapy should be resumed at this point.

D. Hold both the ipilimumab and nivolumab and start high dose corticosteroids

E. Hold nivolumab, but continue with ipilimumab, as the PD-1 agent is more likely to cause the diarrhea and the liver enzyme elevation

Case Study 2

Which of the following is the most appropriate next management step?

A. Hold ipilimumab but continue with nivolumab, as the CTLA-4 agent is more likely to cause the diarrhea and the liver enzyme elevation

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D. Hold both the ipilimumab and nivolumab and start high dose corticosteroids

E. Hold nivolumab, but continue with ipilimumab, as the PD-1 agent is more likely to cause the diarrhea and the liver enzyme elevation

Case Study 3 - Conclusion

- This patient has grade 3 liver toxicity, with the AST and ALT being 3x above the upper normal limit. In this case the immunotherapy should be held, and high dose corticosteroids should be initiated, with a preferred dose if 1-2 mg/kg/day of methylprednisolone.