Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

April 6, 2019 New Orleans

William Carson, MD

Ohio State University

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

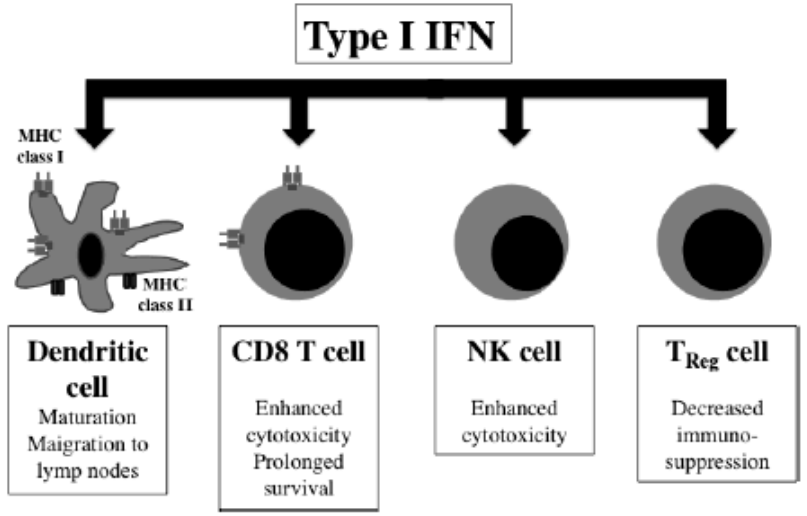
Disclosures

- Dr. Carson has NO DISCLOSURES
- I **will not** be discussing non-FDA approved indications during my presentation.

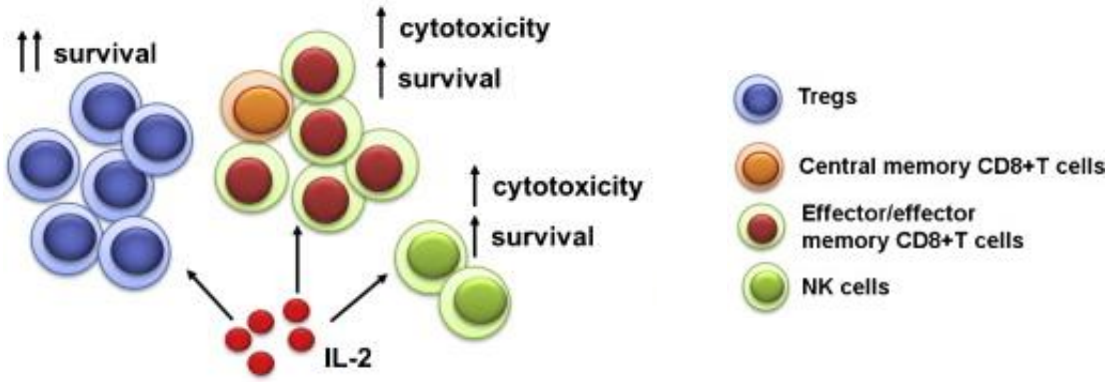
FDA-approved Immunotherapies in Melanoma

Cytokines

- High-dose Interferon
  - Adjuvant therapy
  - High dose I.V., followed by SQ
  - Treatment for up to one year
- Pegylated Interferon
  - Adjuvant therapy
  - SQ only
  - Longer duration than high dose interferon
- Interleukin-2
  - Stage IV
  - I.V., significant toxicities
  - Long term survival



Numasaki *Immunotherapy*, 2016

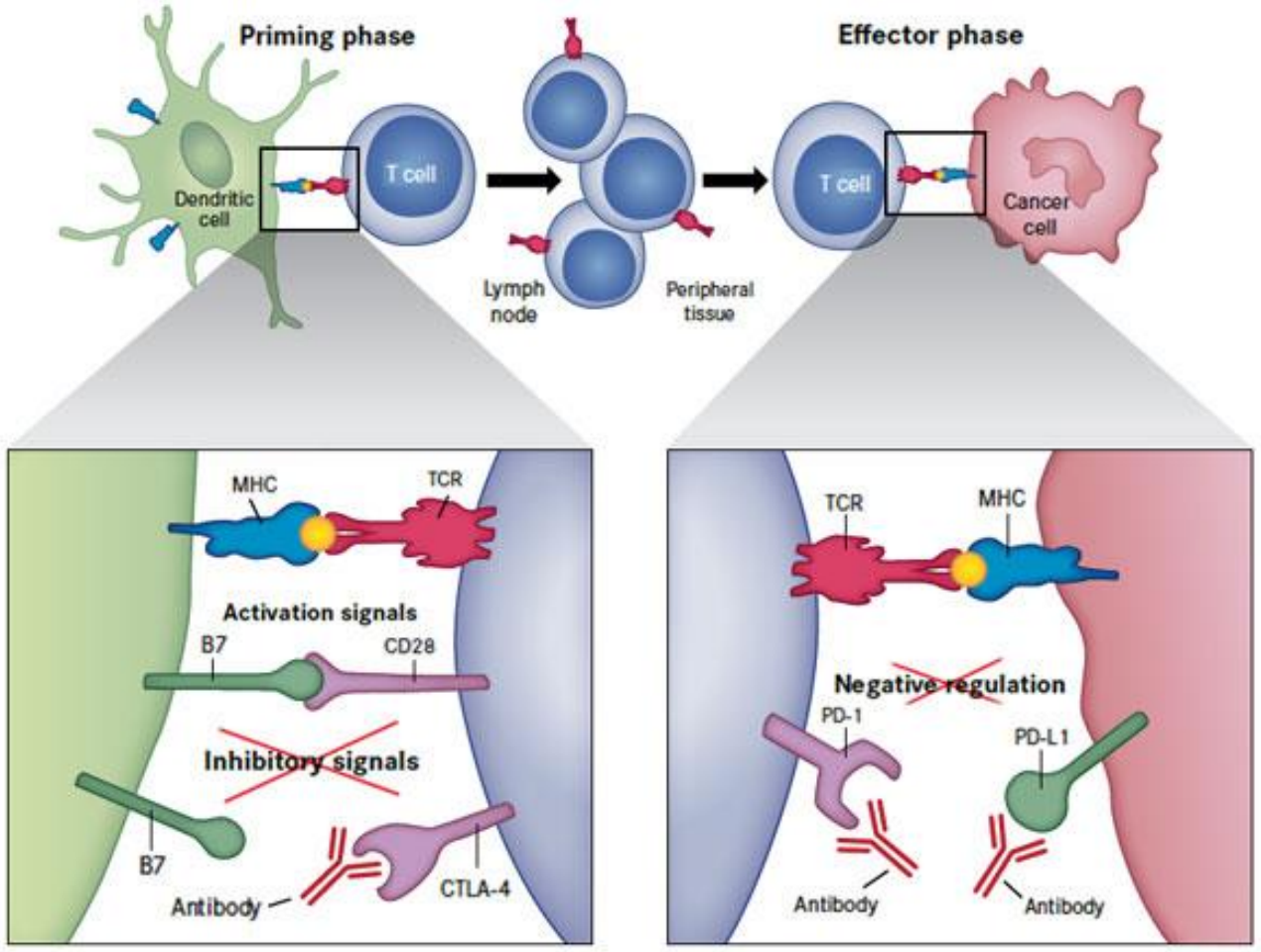


Sim, Radvanyi *Cytokines*, 2014

FDA-approved Immunotherapies in Melanoma

Immune Checkpoint Inhibitors

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

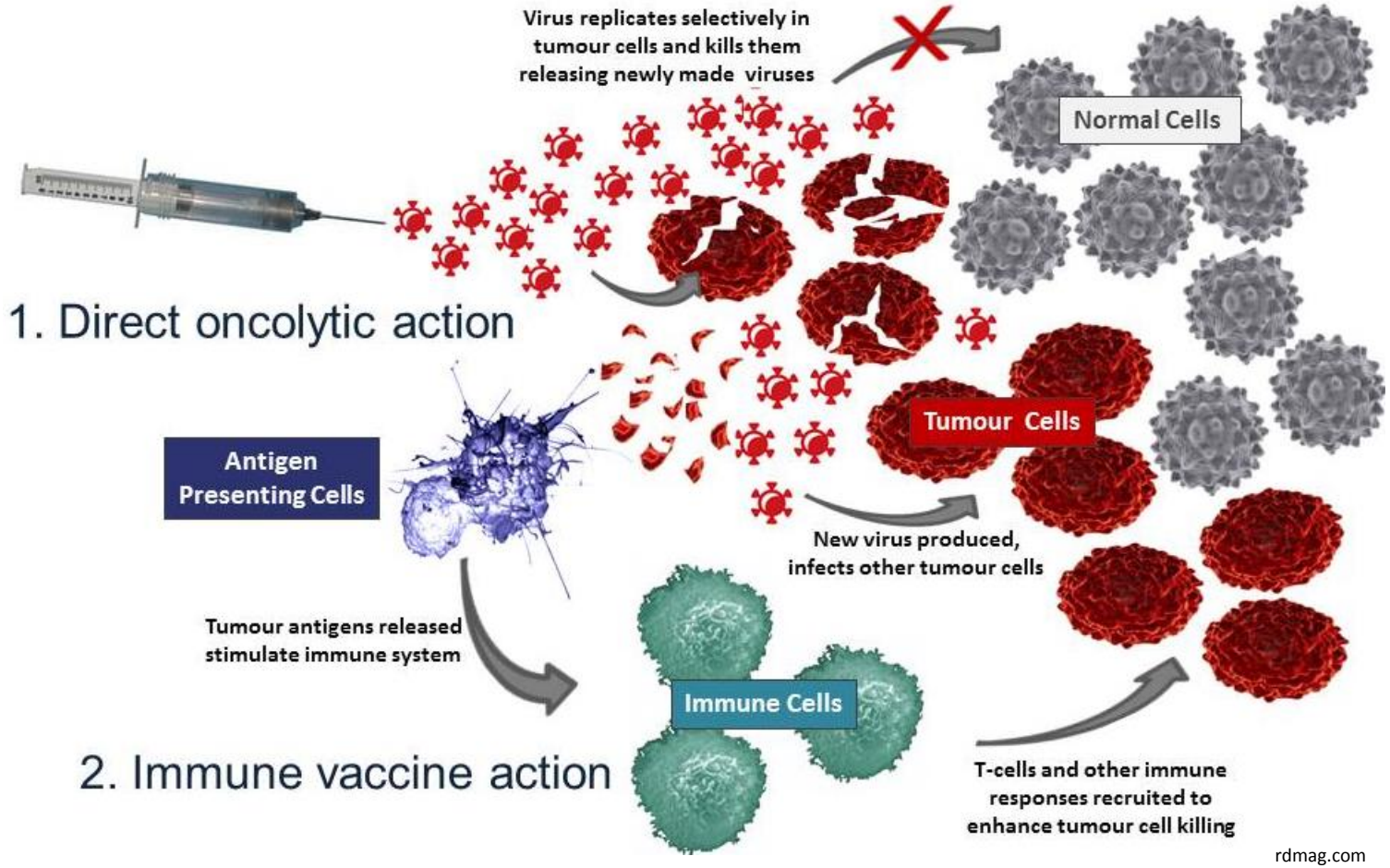


Ribas NEJM 2012
Gordon Nature 2017

FDA-approved Immunotherapies in Melanoma

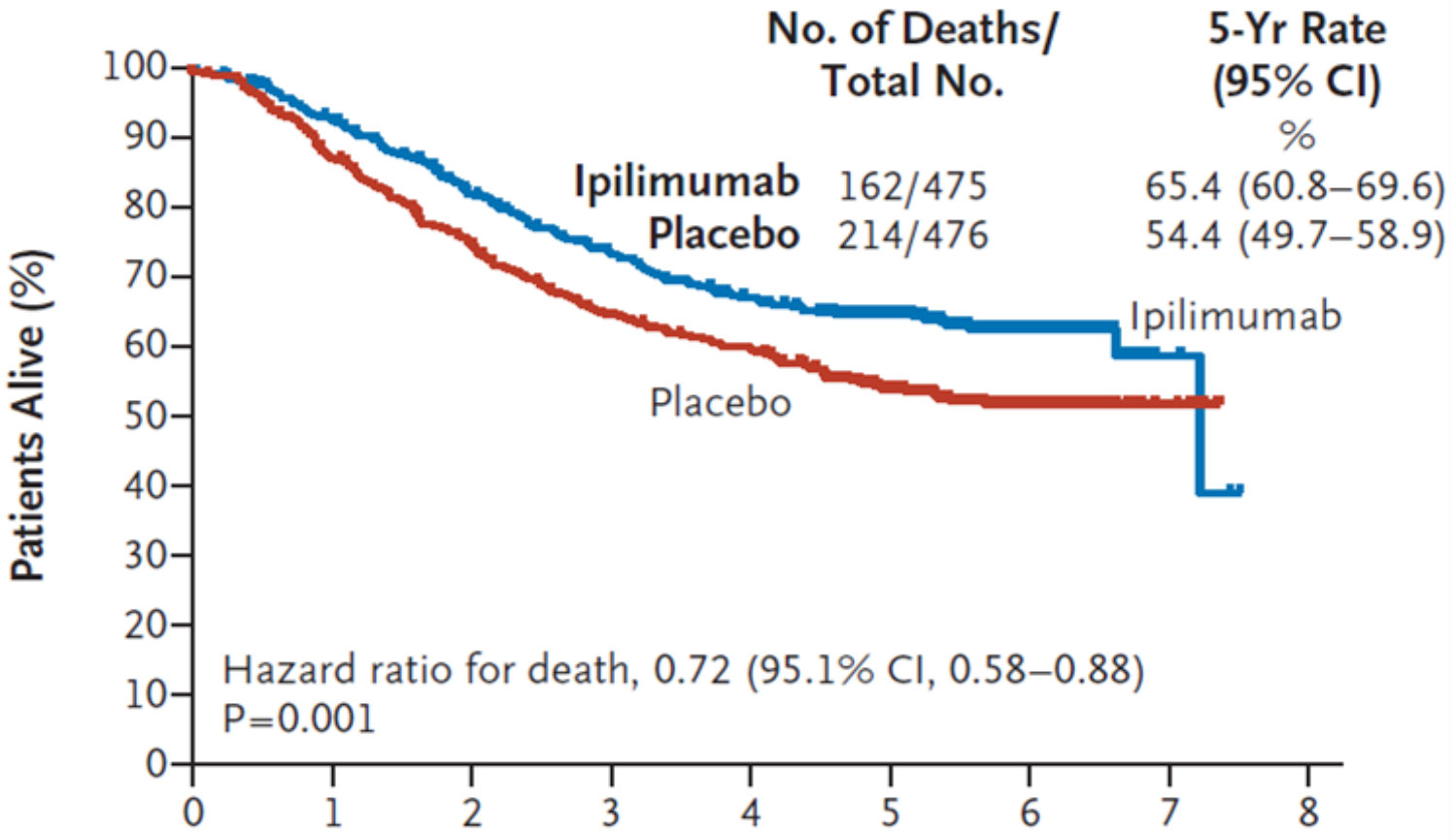
Oncolytic Viruses

- Talimogene Laharparepvec
  - T-VEC
  - Unresectable dz
  - Intratumoral/Intralesional



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)
  - Grade 3/4 AEs 54% vs. 26%



Eggermont *et al*. NEJM 2016

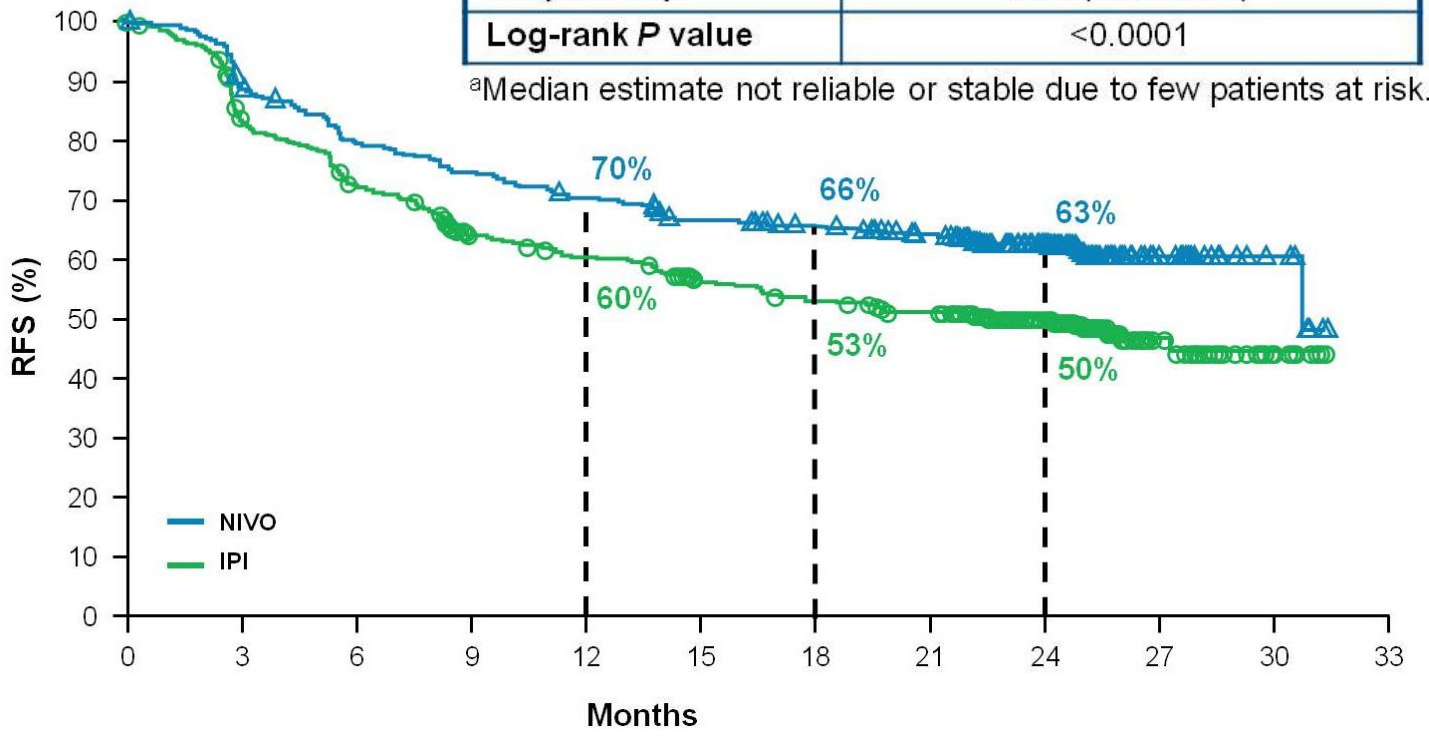
Eggermont *NEJM*, 2016

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)
  - 12 mo RFS 70.5% vs. 60.8%
  - Gr 3/4 AEs 3 x higher with Ipi

	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	

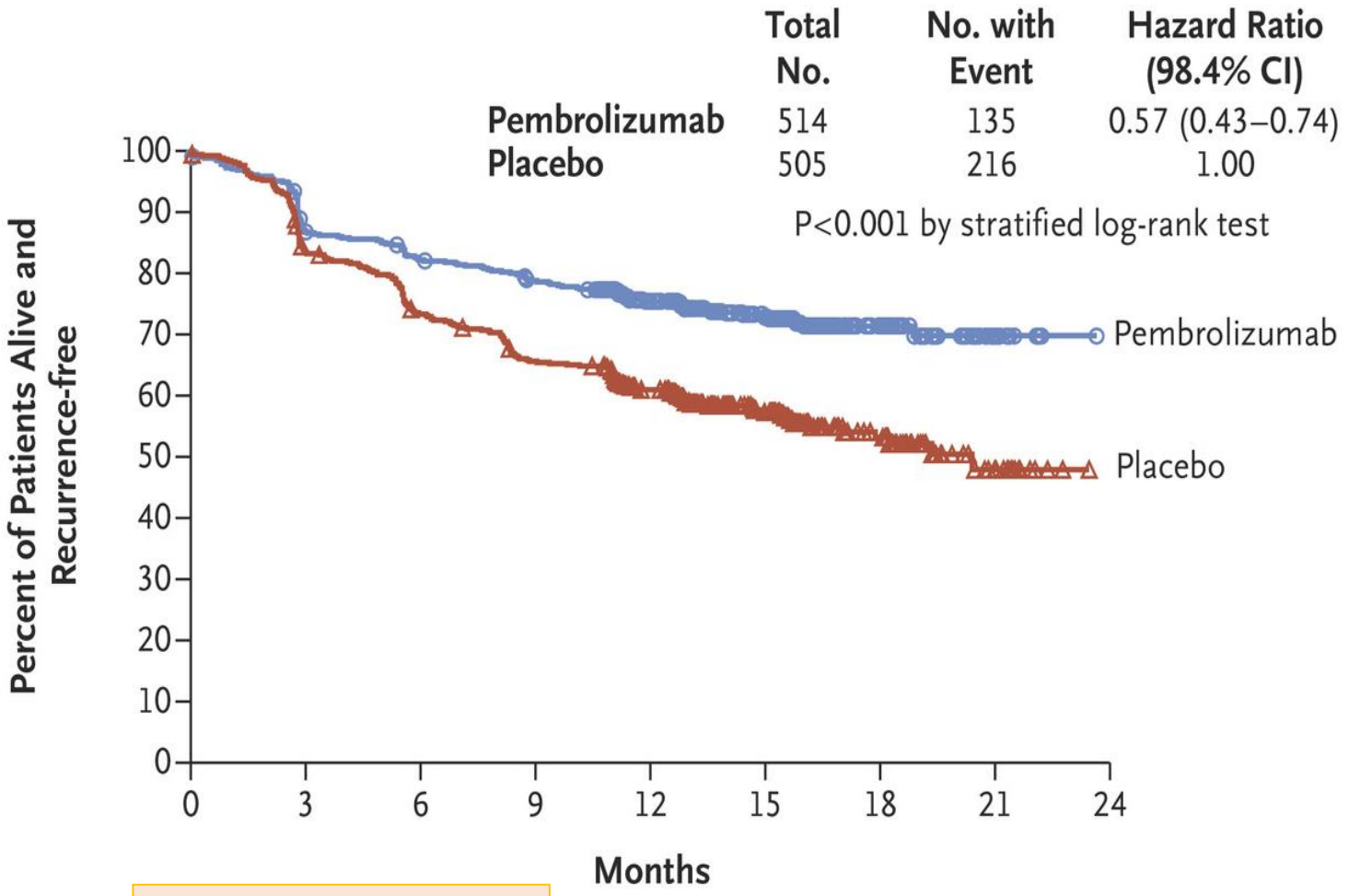
[a]Median estimate not reliable or stable due to few patients at risk.



Weber *NEJM*, 2017

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

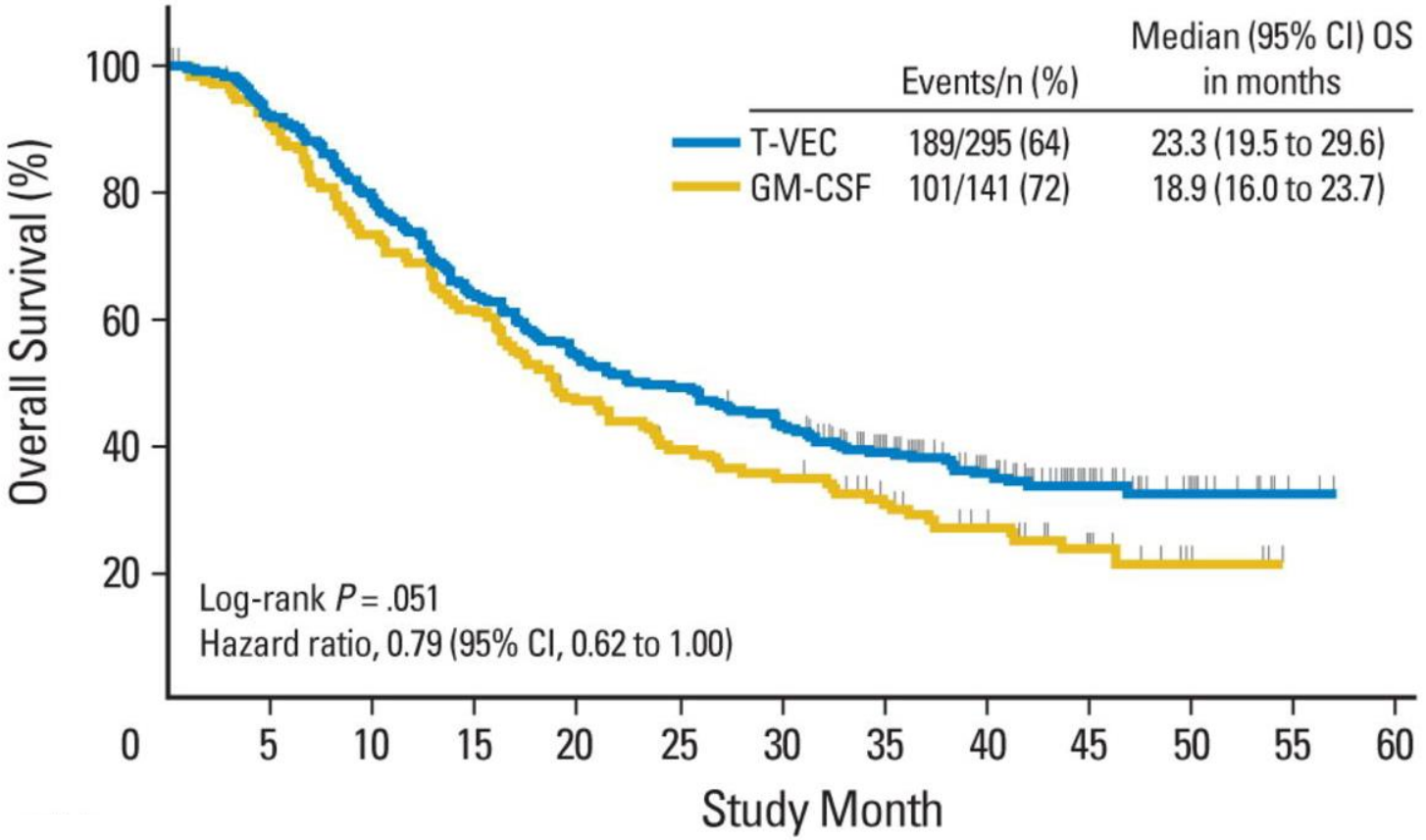
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs. placebo
  - Pembrolizumab 200 mg Q3W for up to 1 year (~18 total doses)
  - RFS @ 15 mos 75.4% for Pembro (vs. 62.6% placebo)



Eggermont *NEJM*, 2018

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

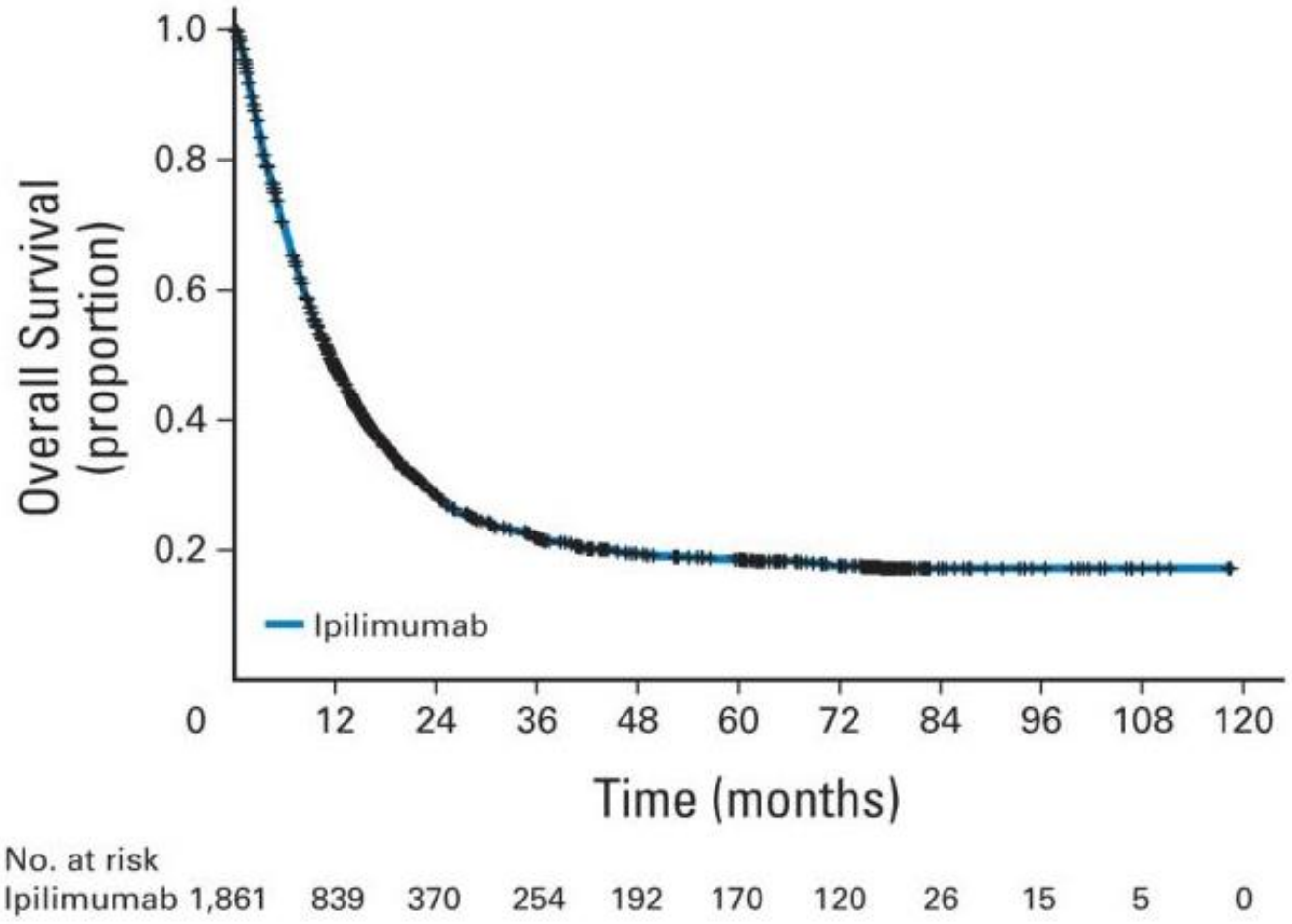
- **Phase III OPTiM Trial**
  - Oncolytic, genetically-engineered herpes virus
  - **Intralesional** T-VEC 10^6 pfu/mL, 10^8 pfu/mL 3 weeks after initial dose, then Q2W
  - vs. s.c. GM-CSF
  - Durable RR 16.3% vs. 2.1%
  - T-VEC → Fatigue, fever, chills



Andtbacka *JCO*, 2015

Ipilimumab in Stage III/IV Melanoma

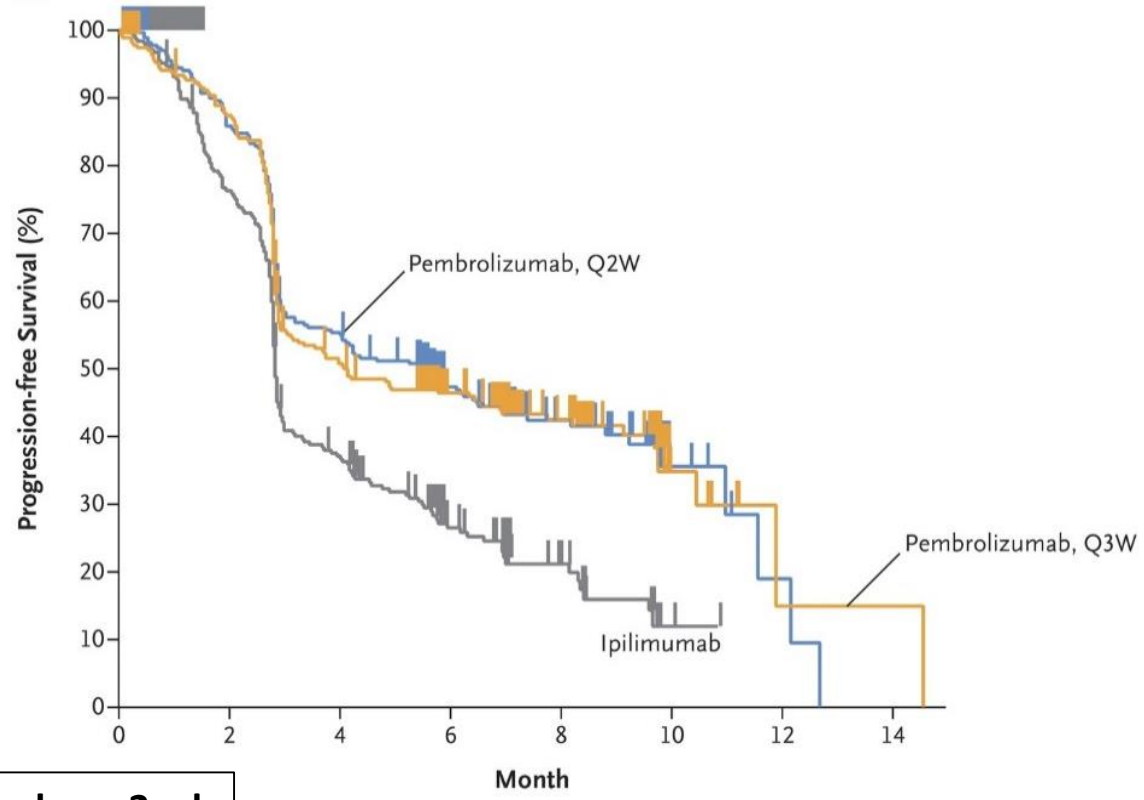
- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) *or* Treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) *or* 10 mg/kg (n = 706)



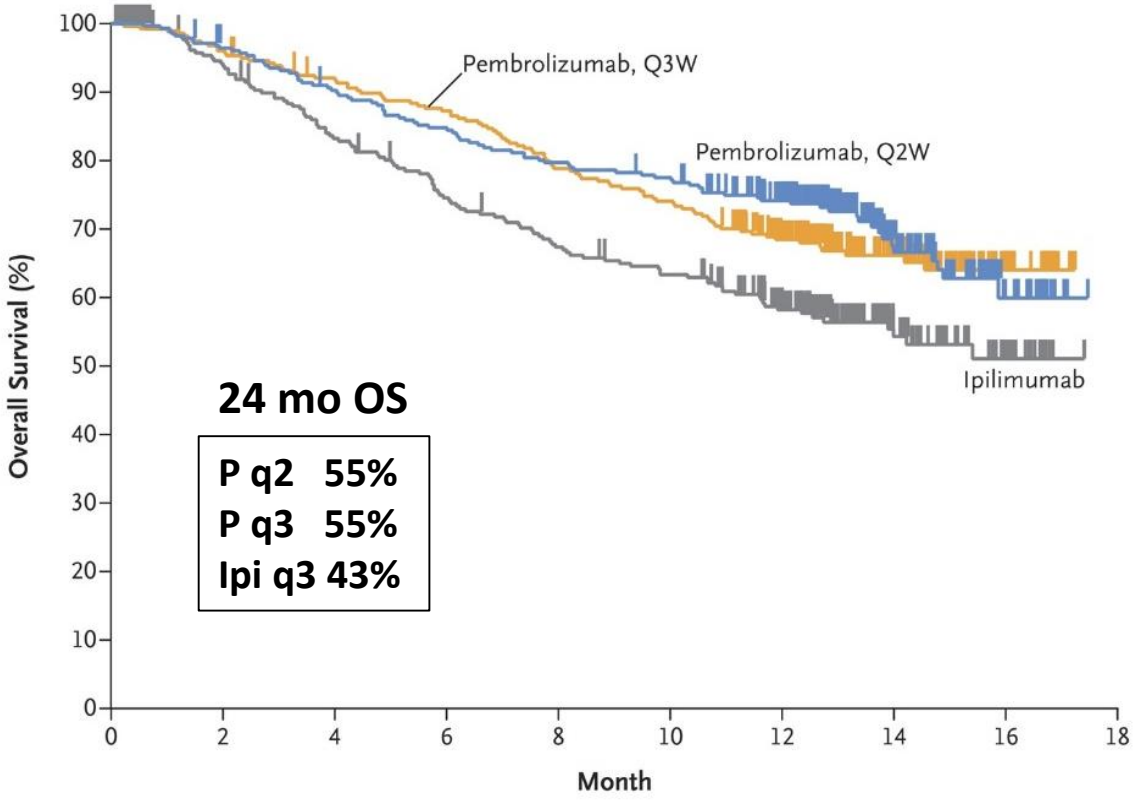
Schadendorf JCO 2015

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial - from 87 Institutions



Pembro q2 wk
Pembro q3 wk
Ipi q3 wk



24 mo OS

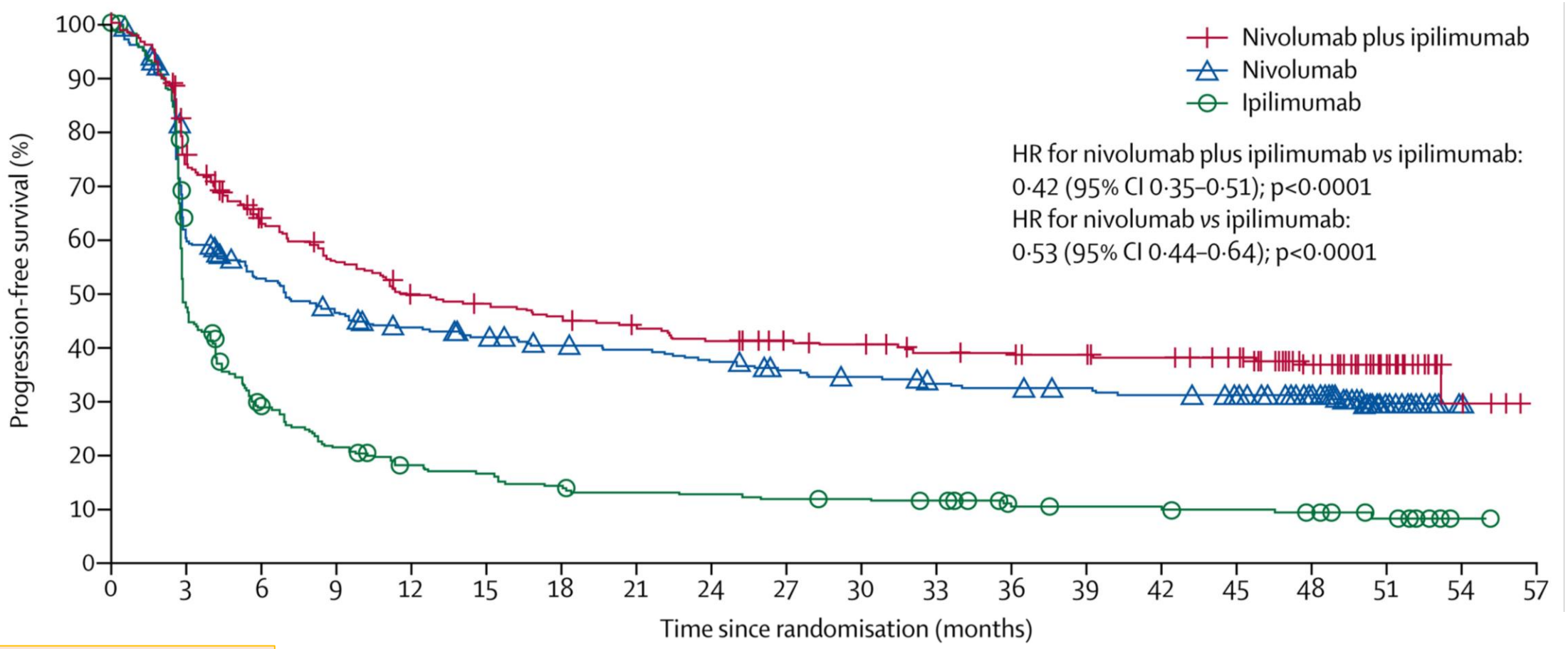
P q2 55%
P q3 55%
Ipi q3 43%

Robert et al. NEJM 2015

Schacter *Lancet*, 2017

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

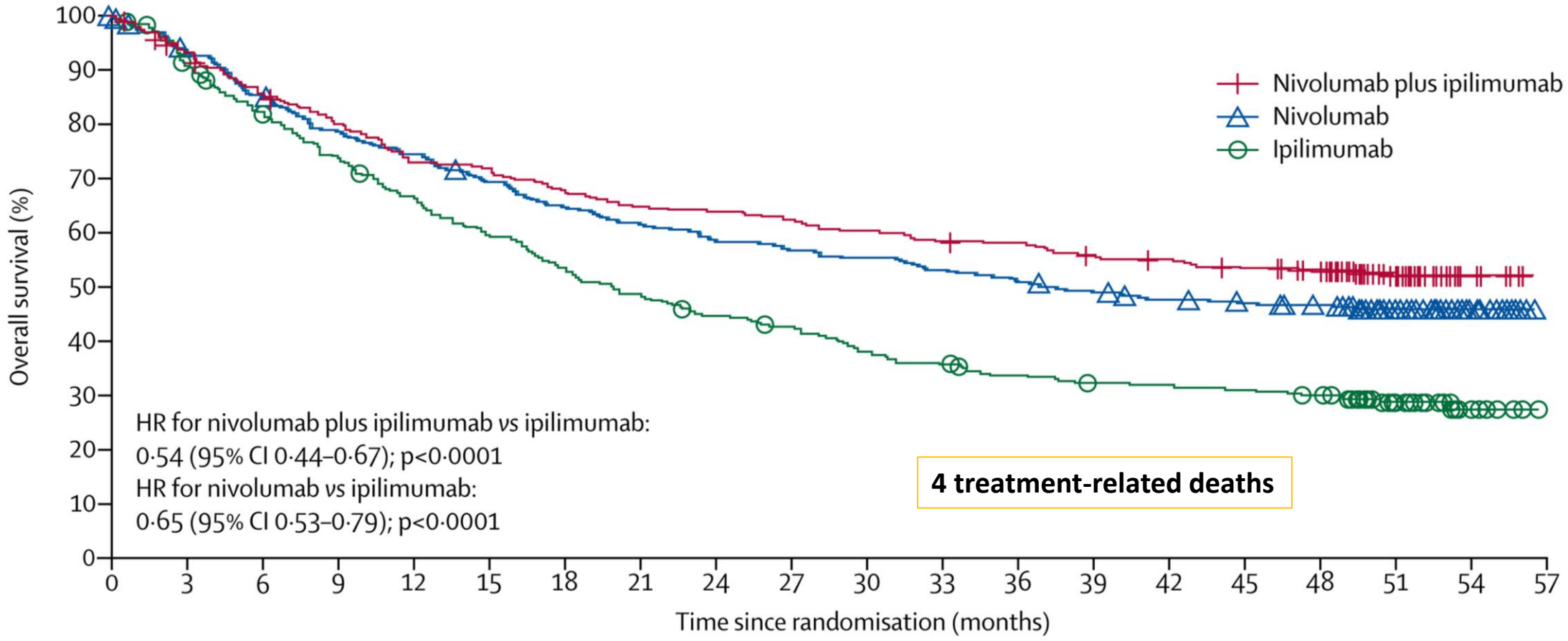
Phase III CheckMate 067 Trial



Hodi *Lancet Oncol*, 2018

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

Phase III CheckMate 067 Trial



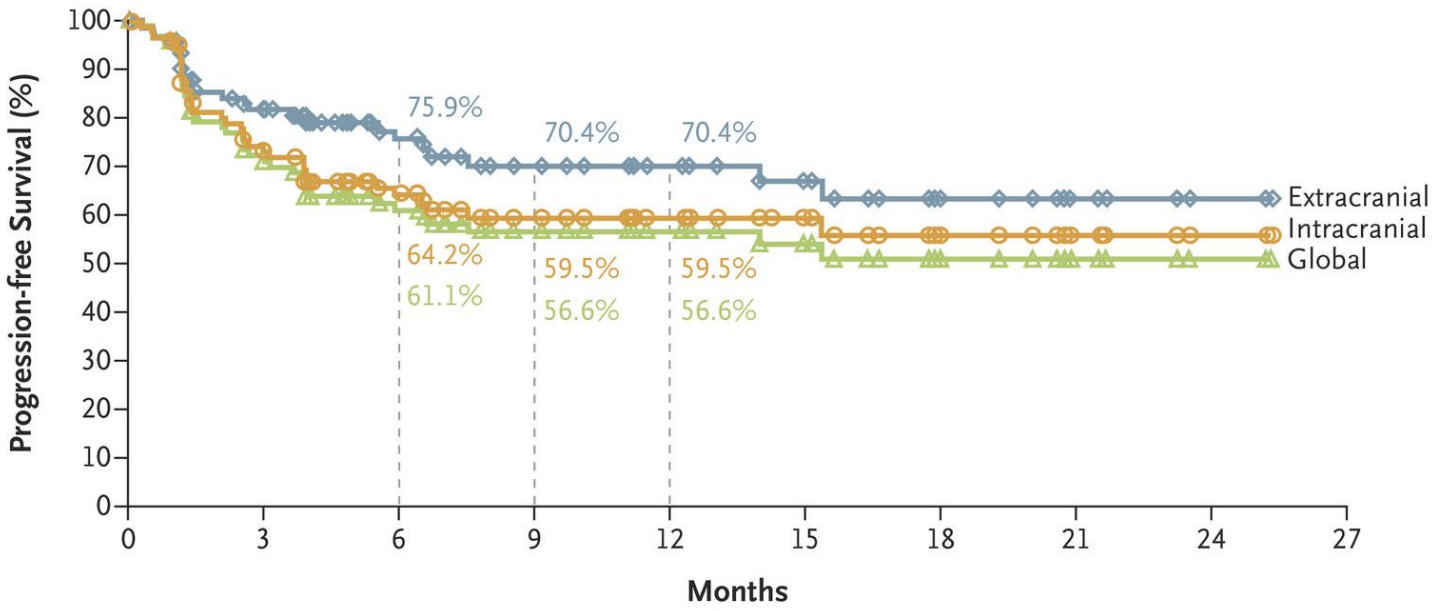
4 treatment-related deaths

Hodi *Lancet Oncol*, 2018

Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

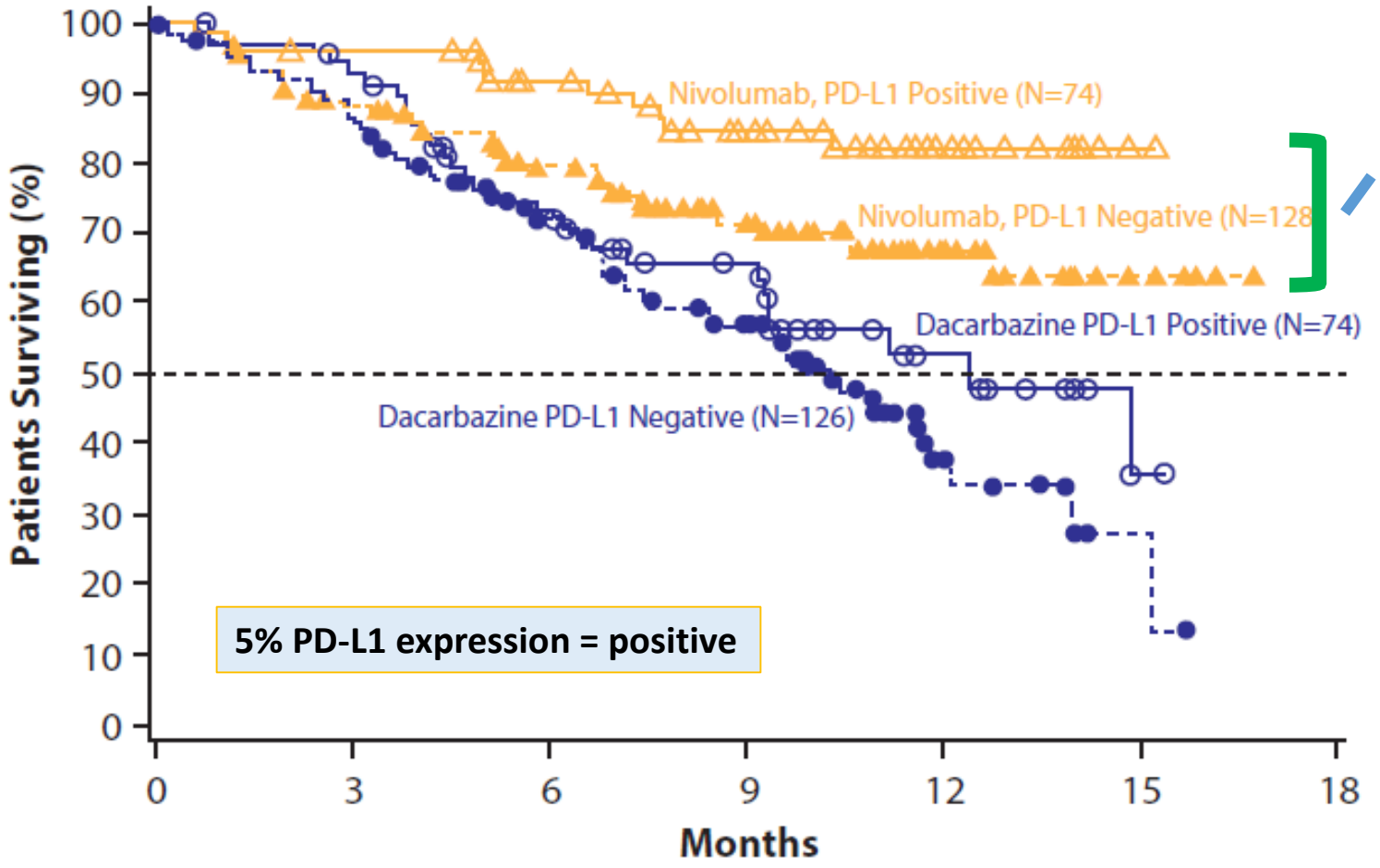
94 pts accrued

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)



Tawbi *NEJM*, 2018

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

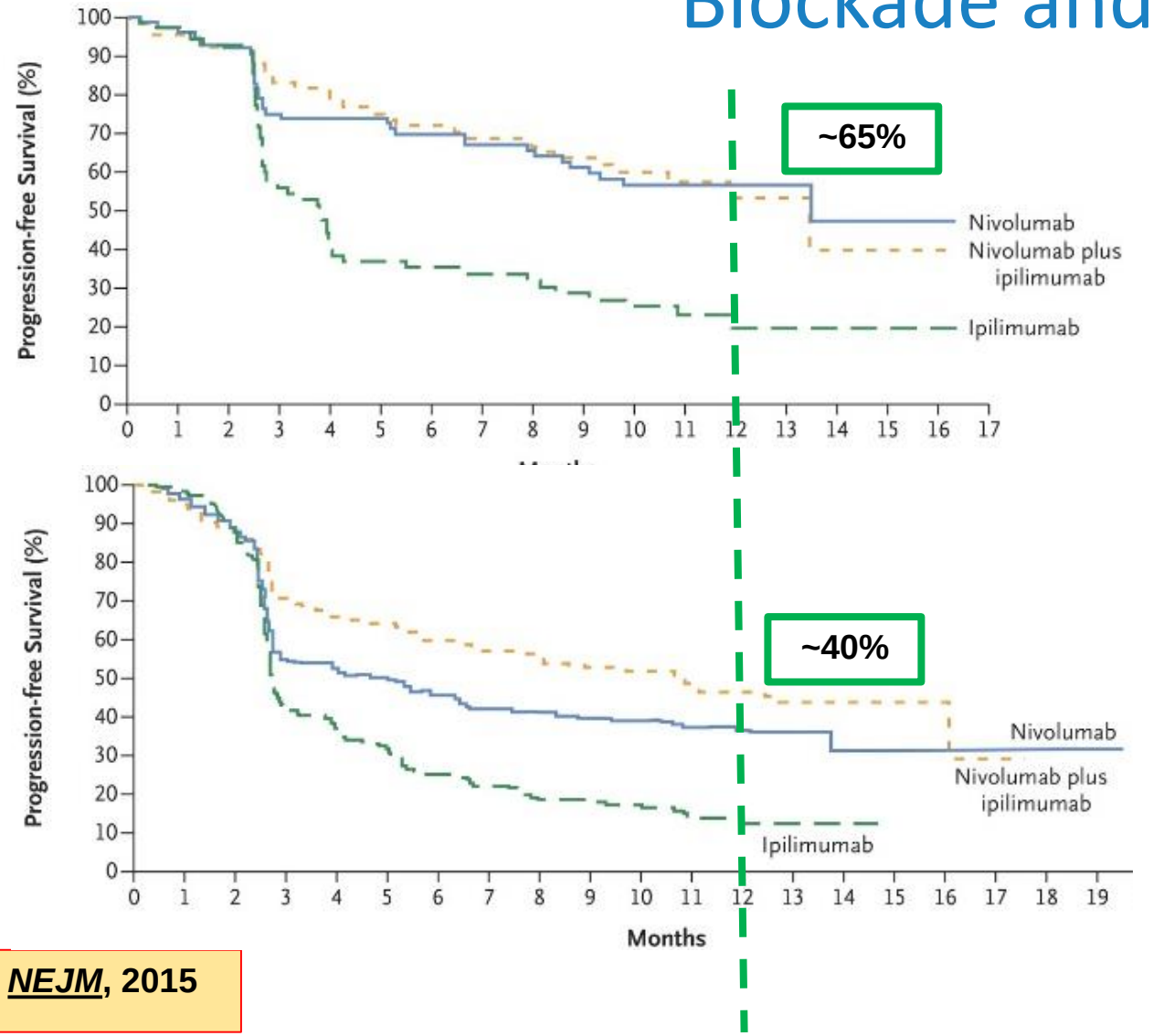


~20% difference in OS

	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 *NEJM*, 2015

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

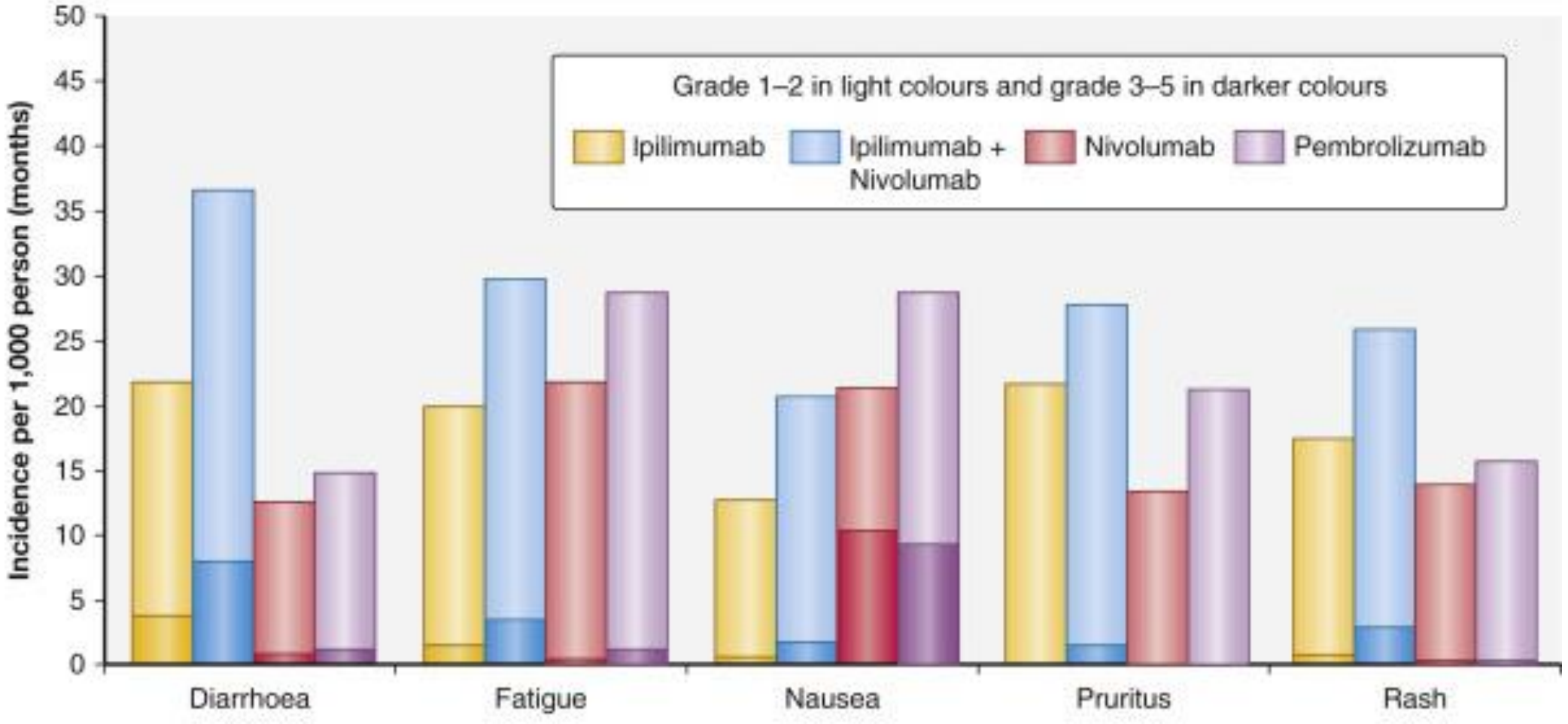


Tumor PD-L1 Positive Patients

Tumor PD-L1 Negative Patients

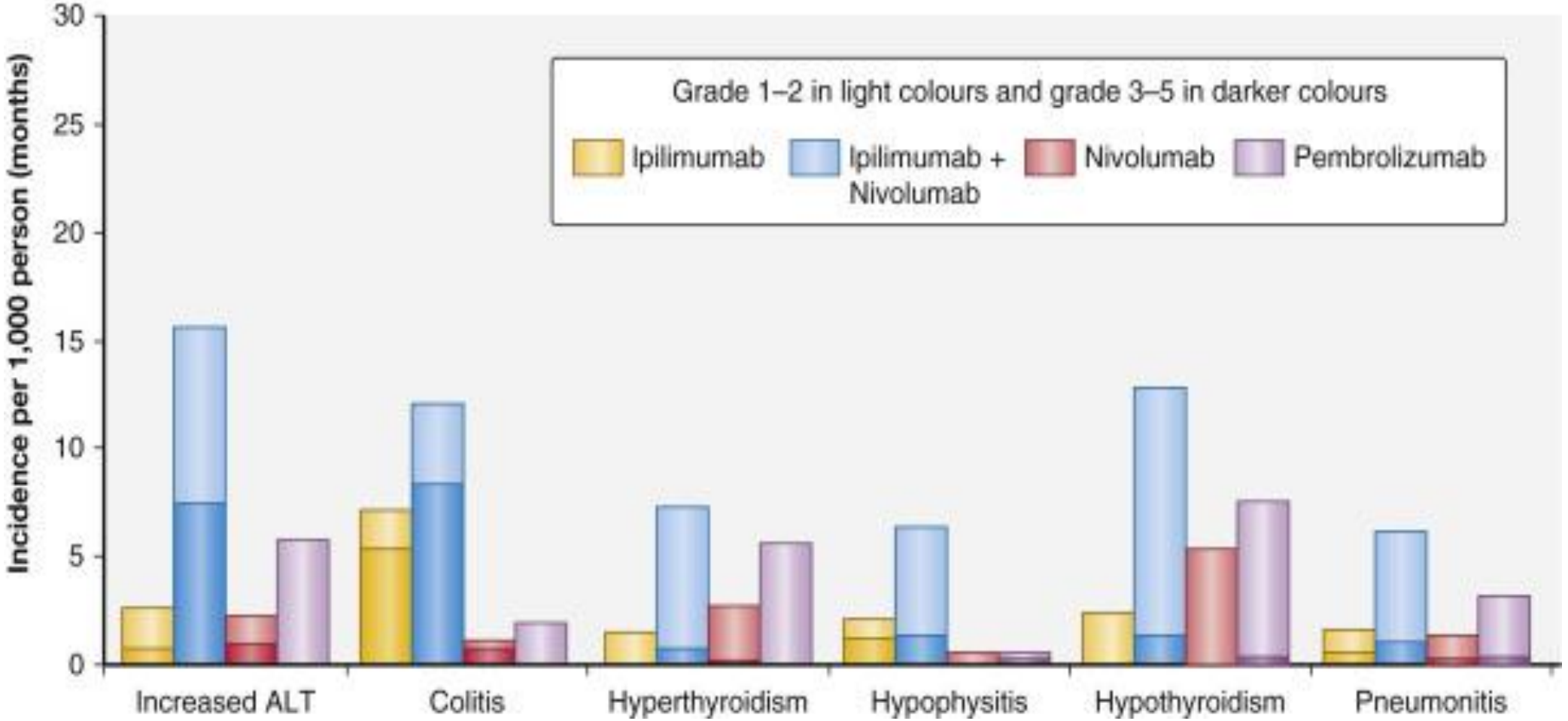
Larkin *NEJM*, 2015

Adverse Events with Immunotherapies

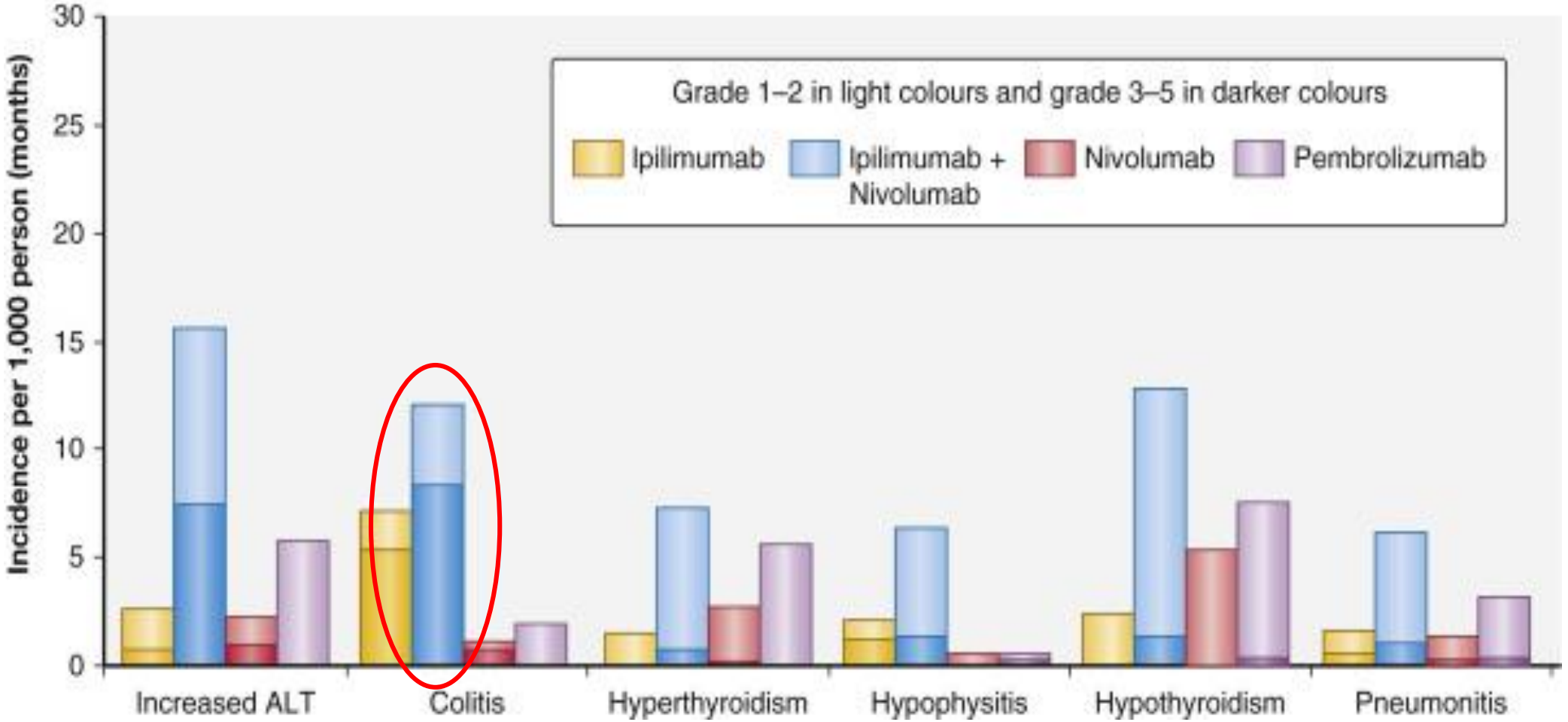


Emens *Eur J Cancer*, 2017

Adverse Events with Immunotherapies



Adverse Events with Immunotherapies

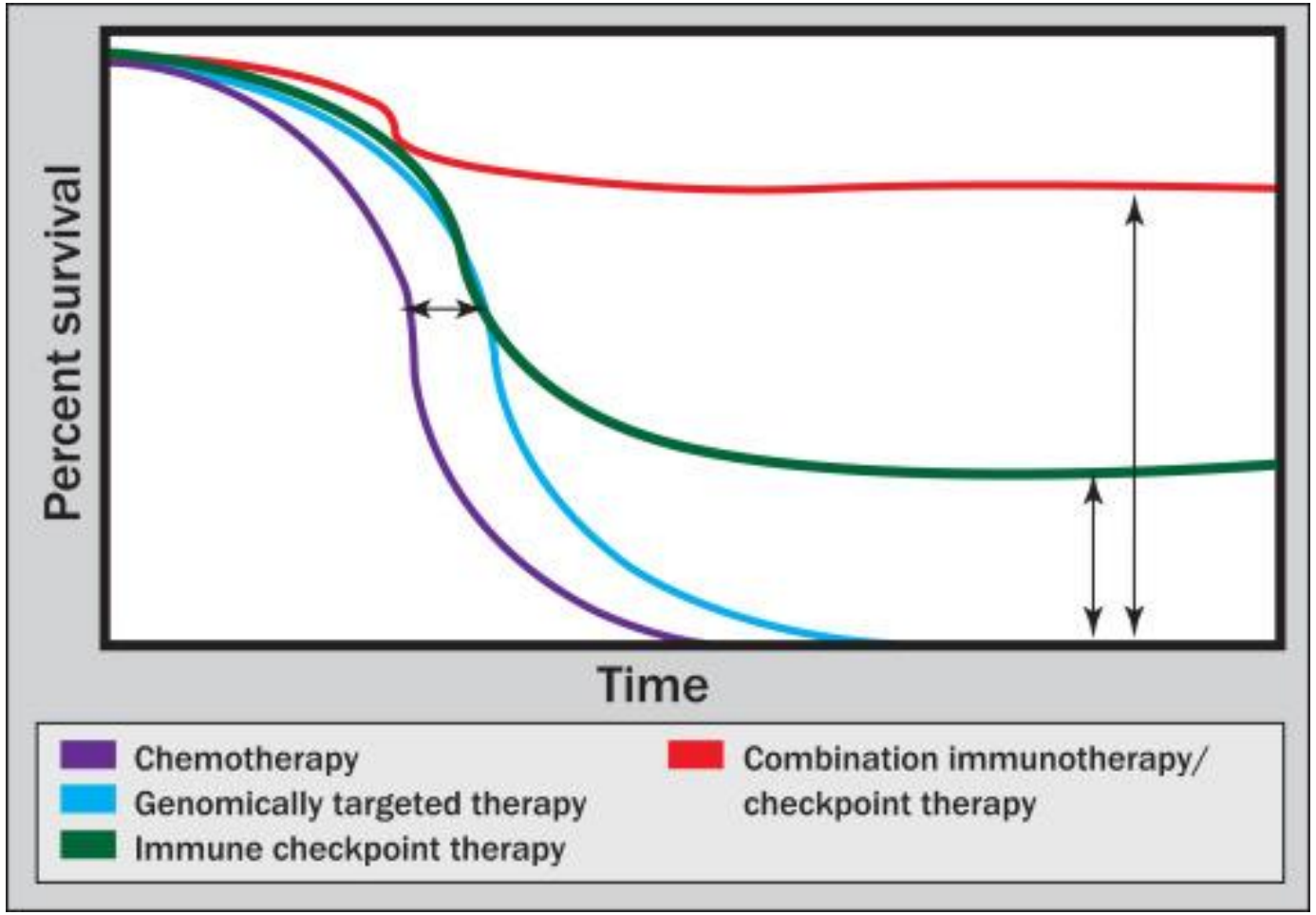


Treatment of Immune-Related AEs

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

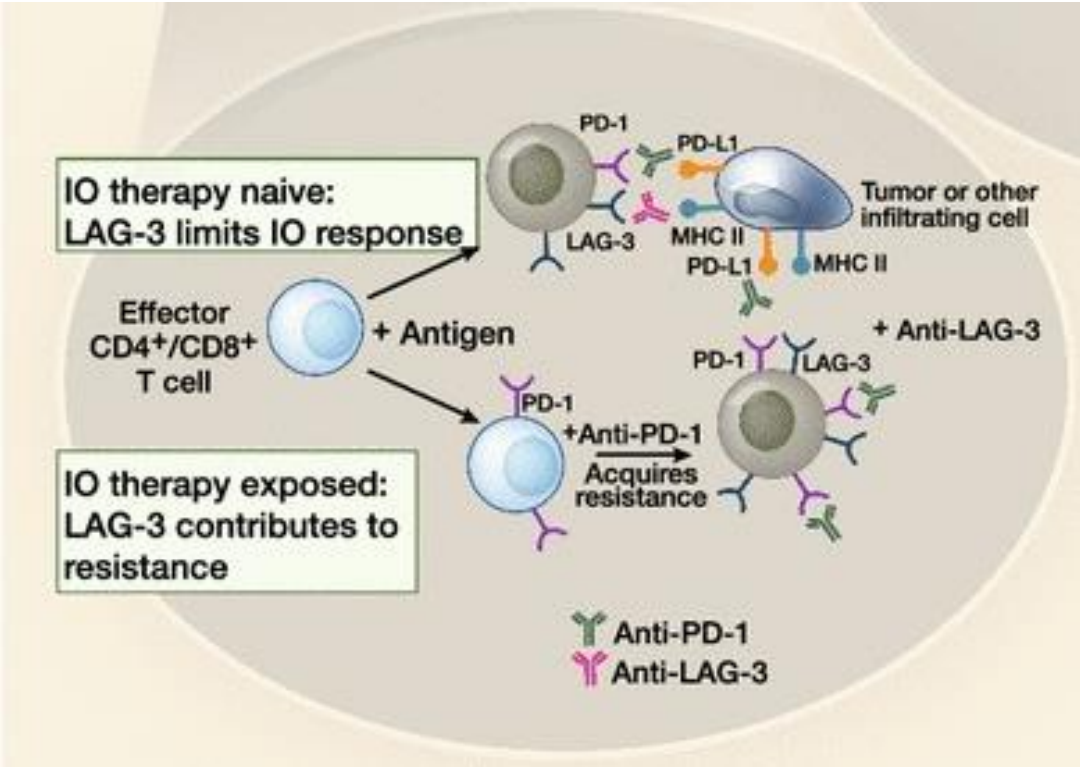
Developmental Immunotherapeutic Strategies for Melanoma

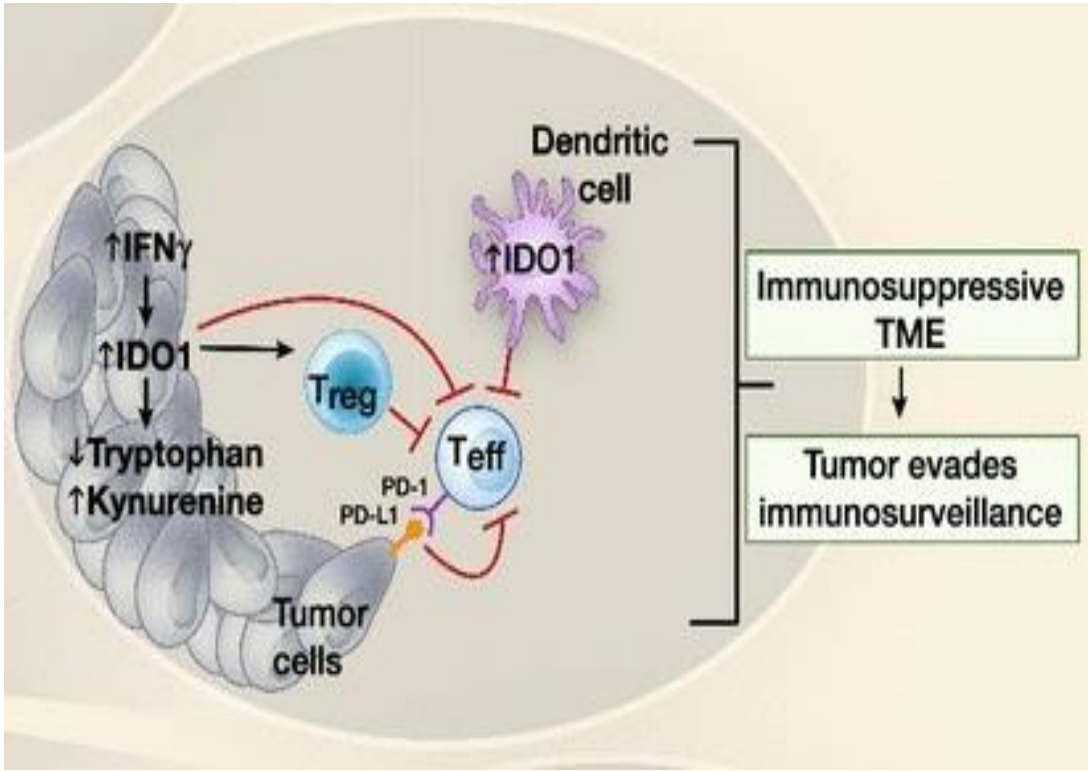


Atkins, Semi. Oncology 2015

Developmental Immunotherapeutic Strategies for Melanoma

Targeting New Immune Checkpoints





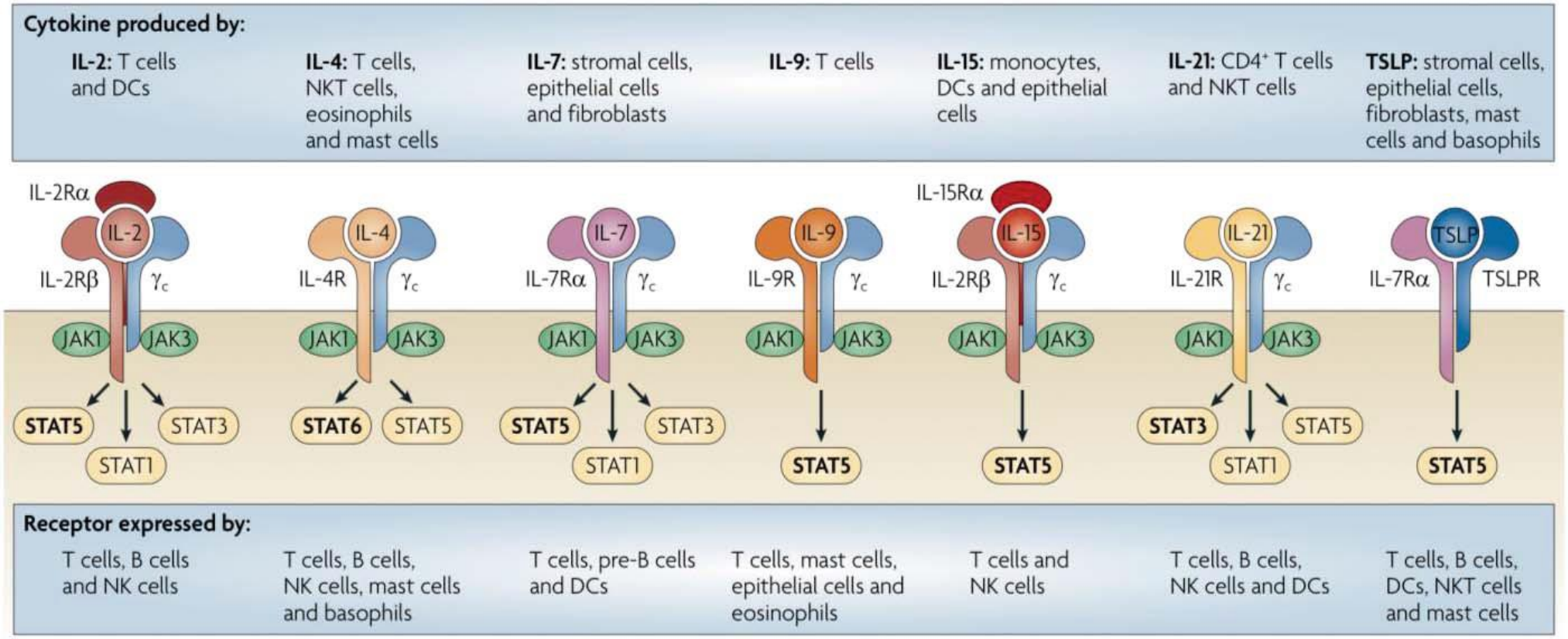
Ascierto, McArthur J Transl Med 2017

Clinical study concepts in development

- **Checkpoint inhibitor (CPI) + mAb therapy (trastuzumab, cetuximab)**
- **CPI plus vaccine**
- **CPI plus cytokine (e.g., IL-12)**

Developmental Immunotherapeutic Strategies for Melanoma

Cytokine-based Strategies



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 created by Isabella C. Glitza, MD, PhD

Case Study 1

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

A. Pneumonitis

B. COPD exacerbation

C. Pulmonary embolus

D. Pneumonia

E. Tumor progression

Case study created by Isabella C. Glitza, MD, PhD

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 as 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 created by Isabella C. Glitza, MD, PhD

Case Study 1

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

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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 created by Isabella C. Glitza, MD, PhD

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 created by Isabella C. Glitza, MD, PhD

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 not 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 created by Isabella C. Glitza, MD, PhD

Case Study 2

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

A. Pembrolizumab
B. Ipilimumab
C. Ipilimumab and Nivolumab
D. Temozolomide
E. Dabrafenib and Trametinib

Case study created by Isabella C. Glitza, MD, PhD

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.

Case study created by Isabella C. Glitza, MD, PhD

Case Study 2

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Case study created by Isabella C. Glitza, MD, PhD

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 created by Isabella C. Glitza, MD, PhD

Case Study 2.1

What if our patient were indeed BRAF mutant but without brain mets?

What comes first? (*hint*: no one knows)

- **EA6134 Dabrafenib + Trametinib followed by Ipilimumab + Nivolumab vs. Ipilimumab + Nivolumab followed by Dabrafenib + Trametinib**

This randomized phase III trial studies how well initial treatment with ipilimumab and nivolumab followed by dabrafenib and trametinib works and compares it to initial treatment with dabrafenib and trametinib followed by ipilimumab and nivolumab in treating patients with stage III-IV melanoma that contains a mutation known as BRAFV600 and cannot be removed by surgery

Case study created by Isabella C. Glitza, MD, PhD

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Thank You!

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