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

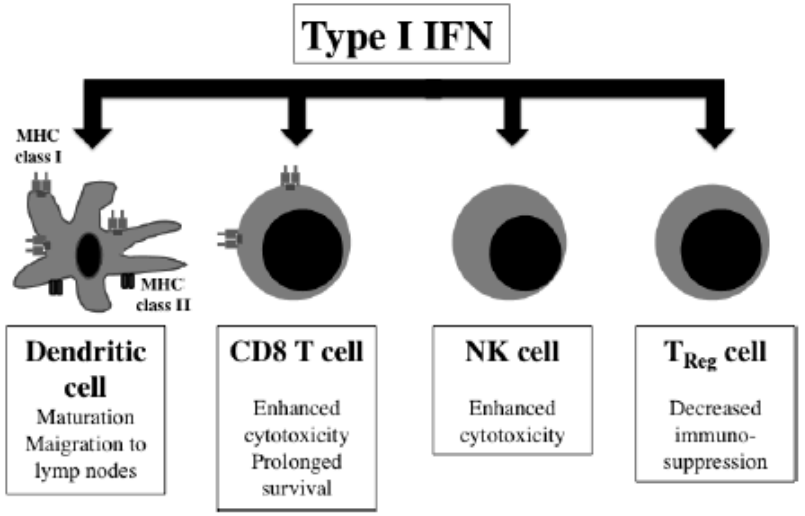
Society for Immunotherapy of Cancer

Disclosures

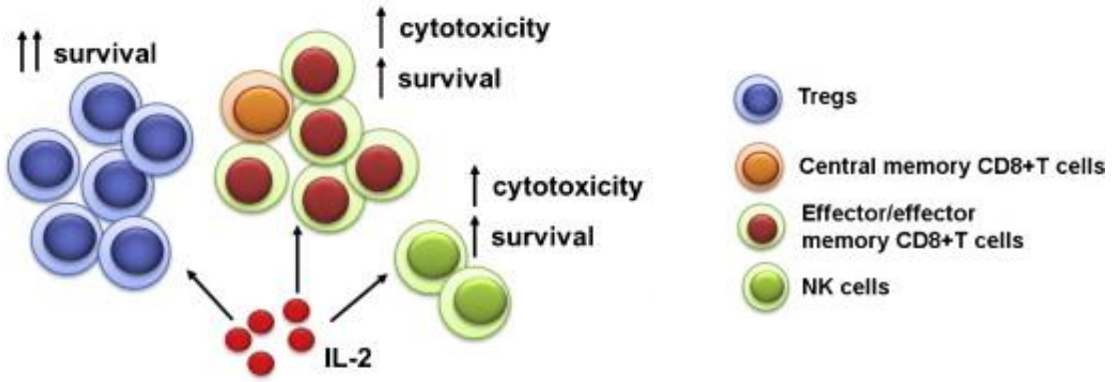
- I am involved in clinical trials funded by Bristol Myers Squibb, Merck, Novartis and Eli Lilly
- I will not be discussing non-FDA approved indications during my presentation.

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.



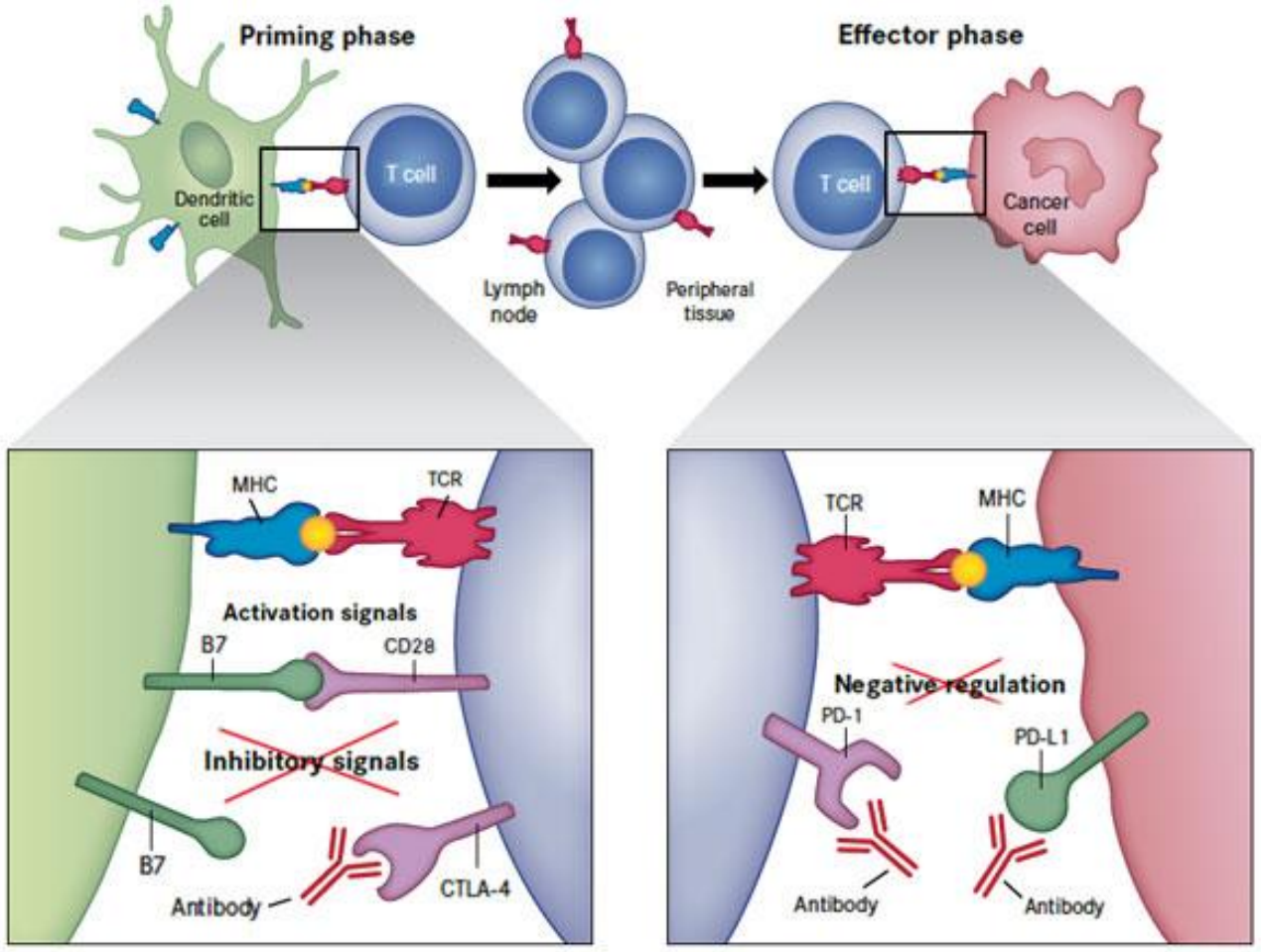
Numasaki et al. Immunotherapy 2016



Sim, Radvanyi Cytogfr 2014

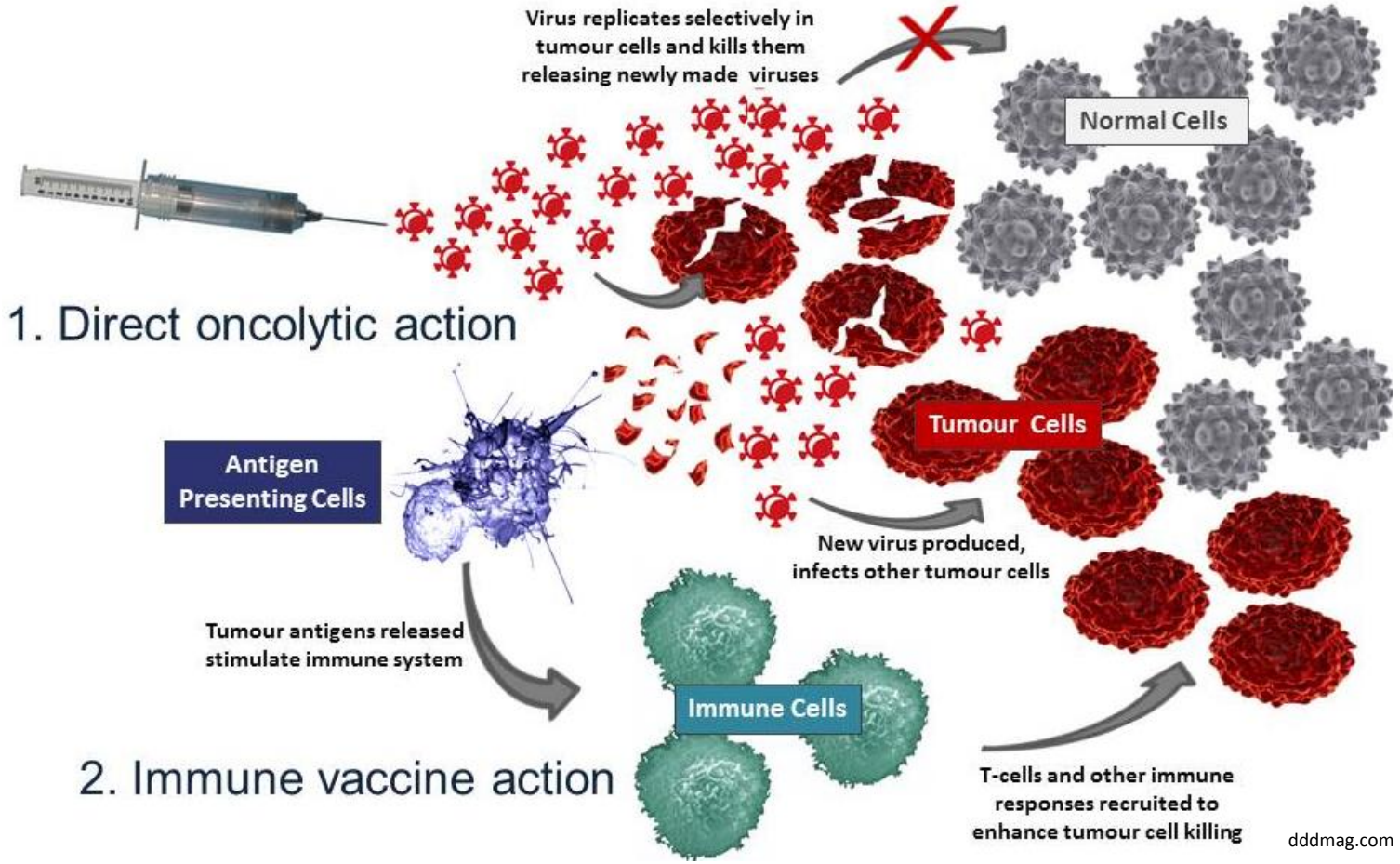
FDA-approved Immunotherapies in Melanoma

- 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 I



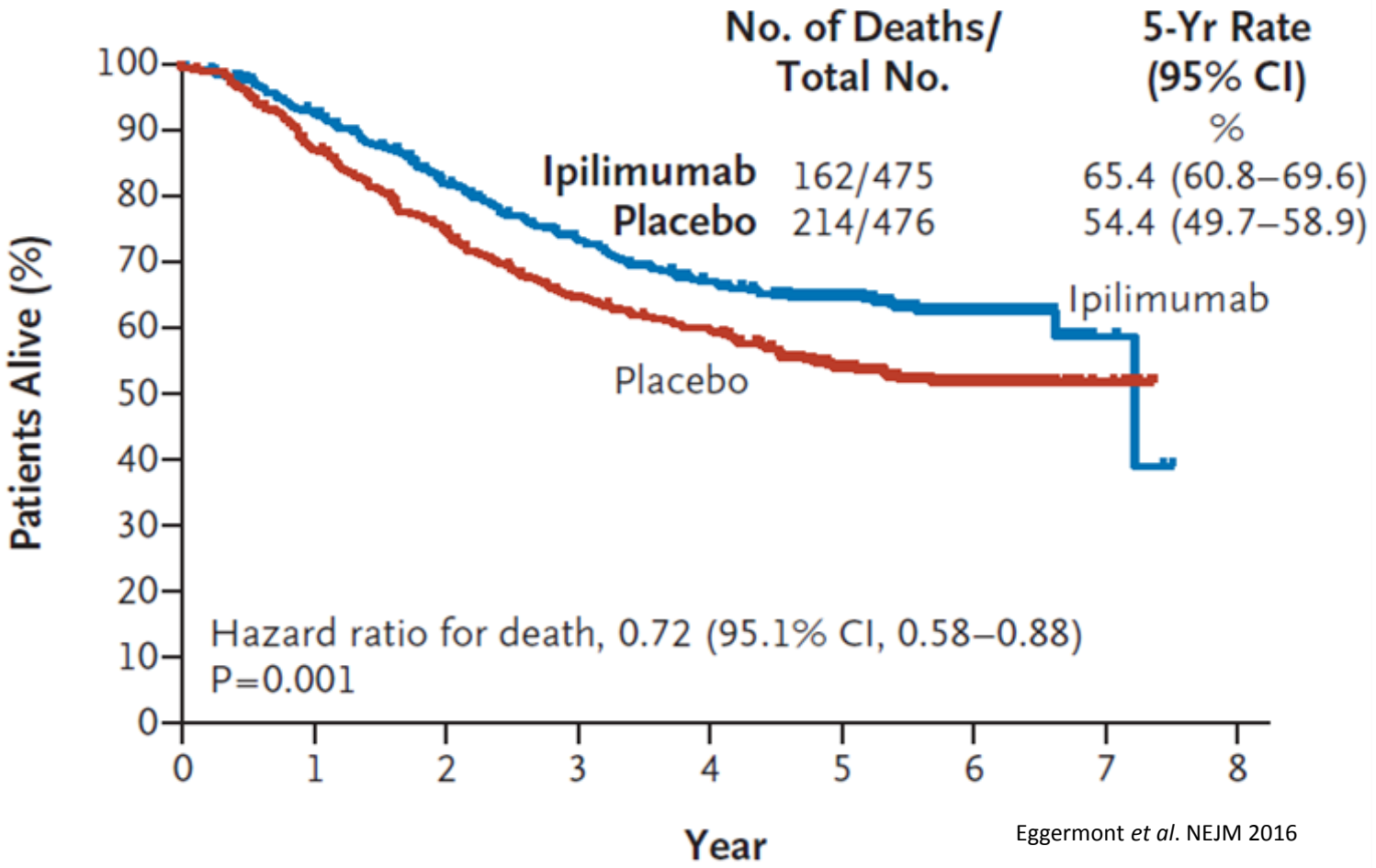
FDA-approved Immunotherapies in Melanoma

- 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



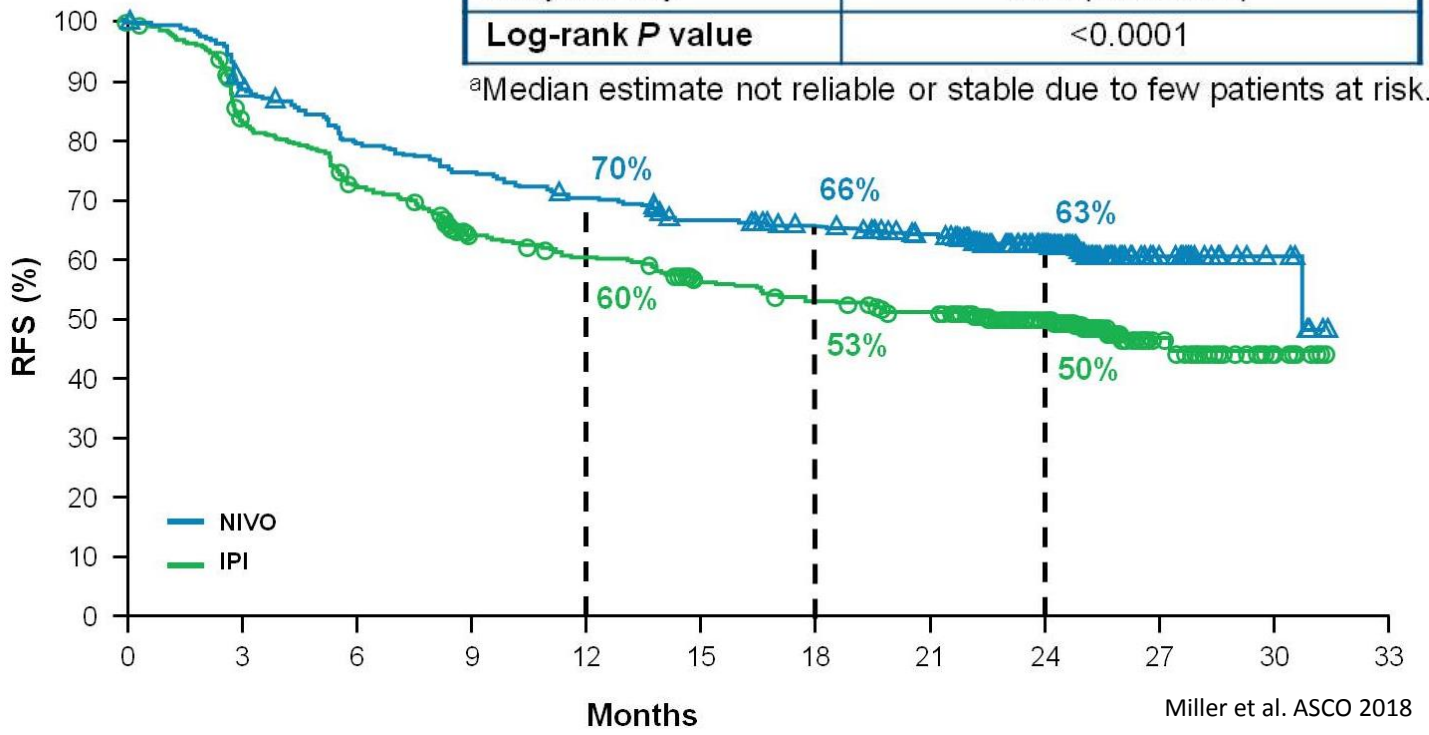
Eggermont *et al*. NEJM 2016

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	

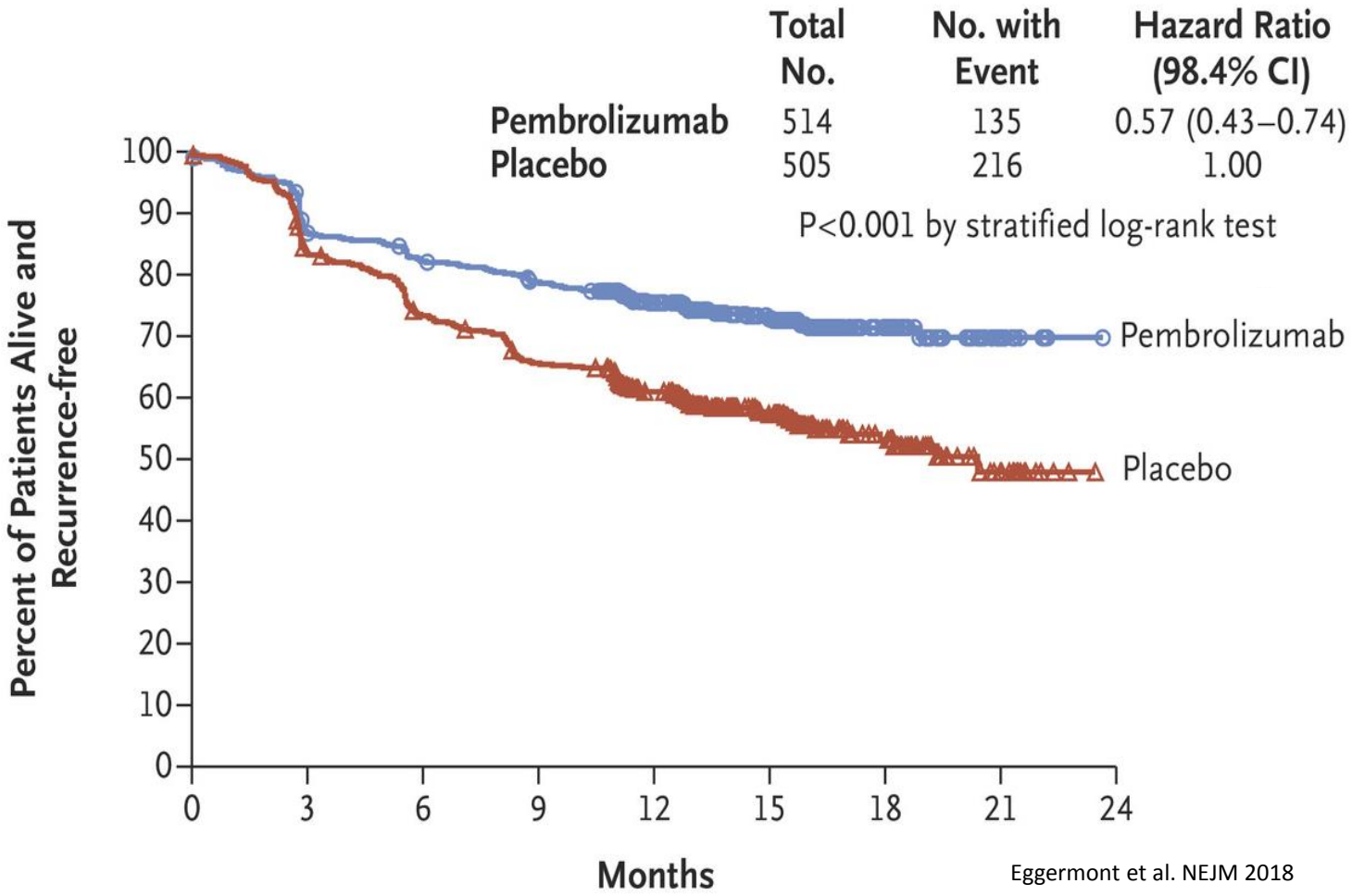
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

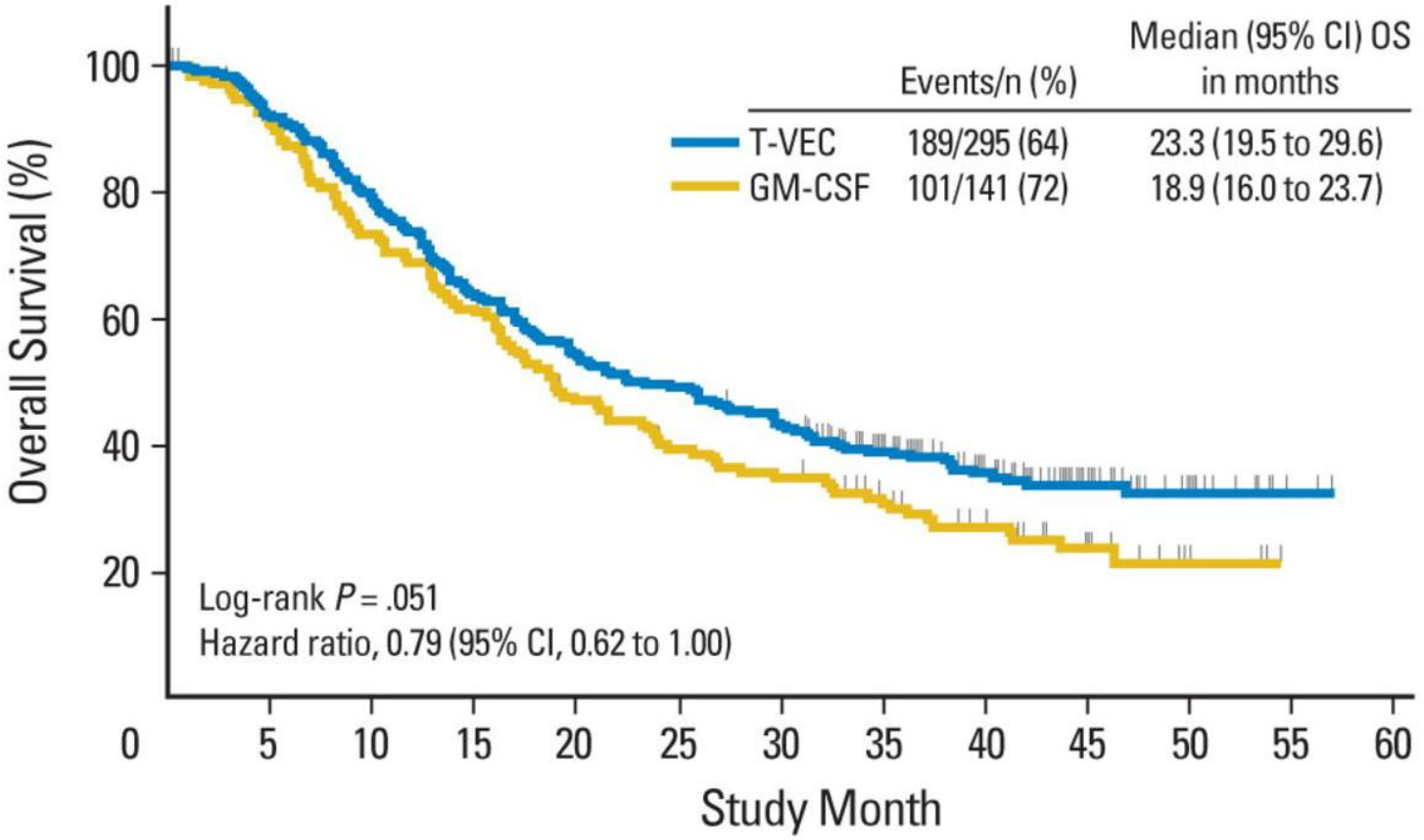
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)



Eggermont et al. NEJM 2018

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

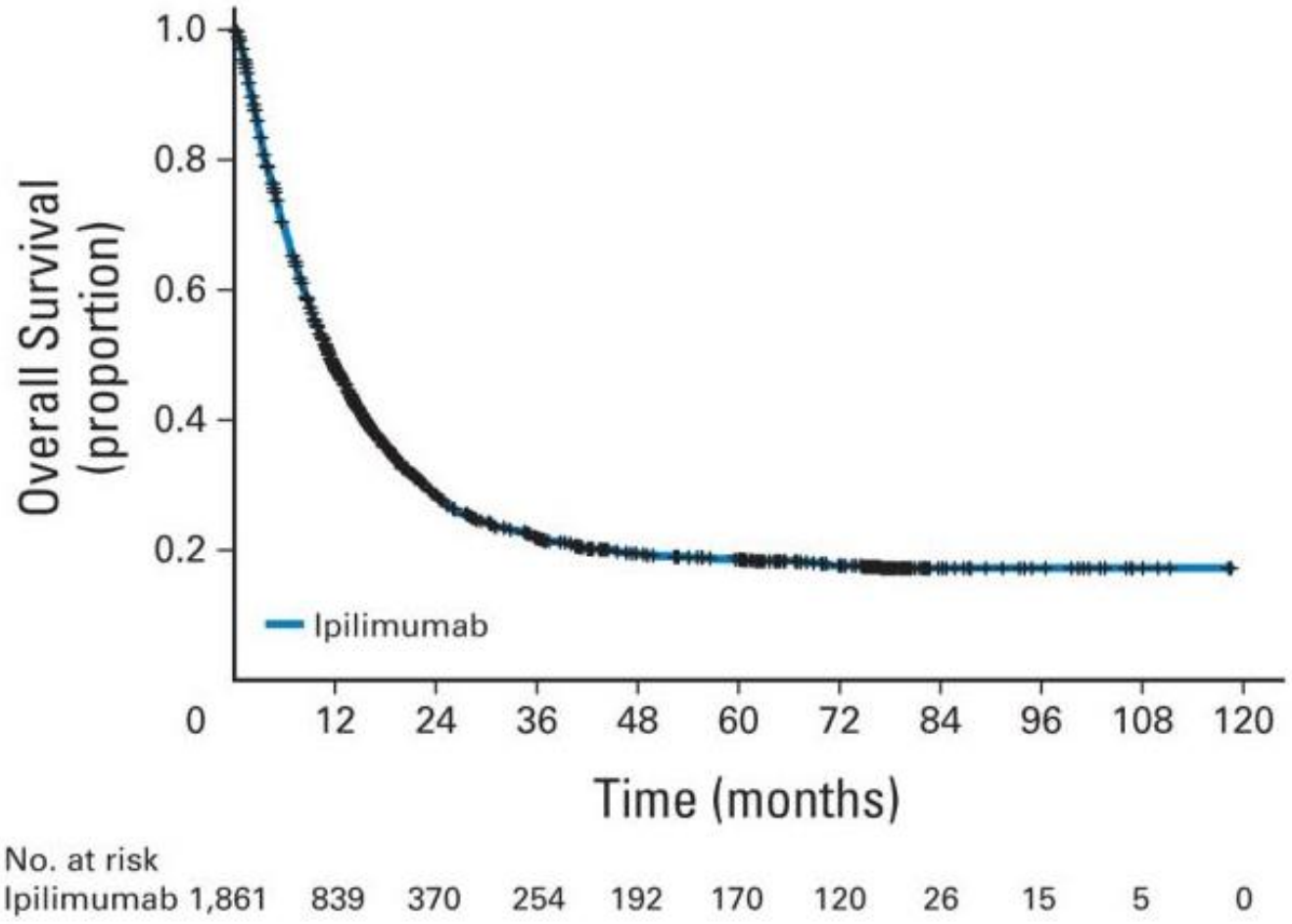
- Phase III Trial
  - NCT00769704
  - **Intralesional** T-VEC vs subcutaneous GM-CSF
  - T-VEC 10^6 pfu/mL, 10^8 pfu/mL 3 weeks after initial dose, then Q2W



Andtbacka, Kaufman et al. JCO 2015

Ipilimumab in Stage III/IV Melanoma

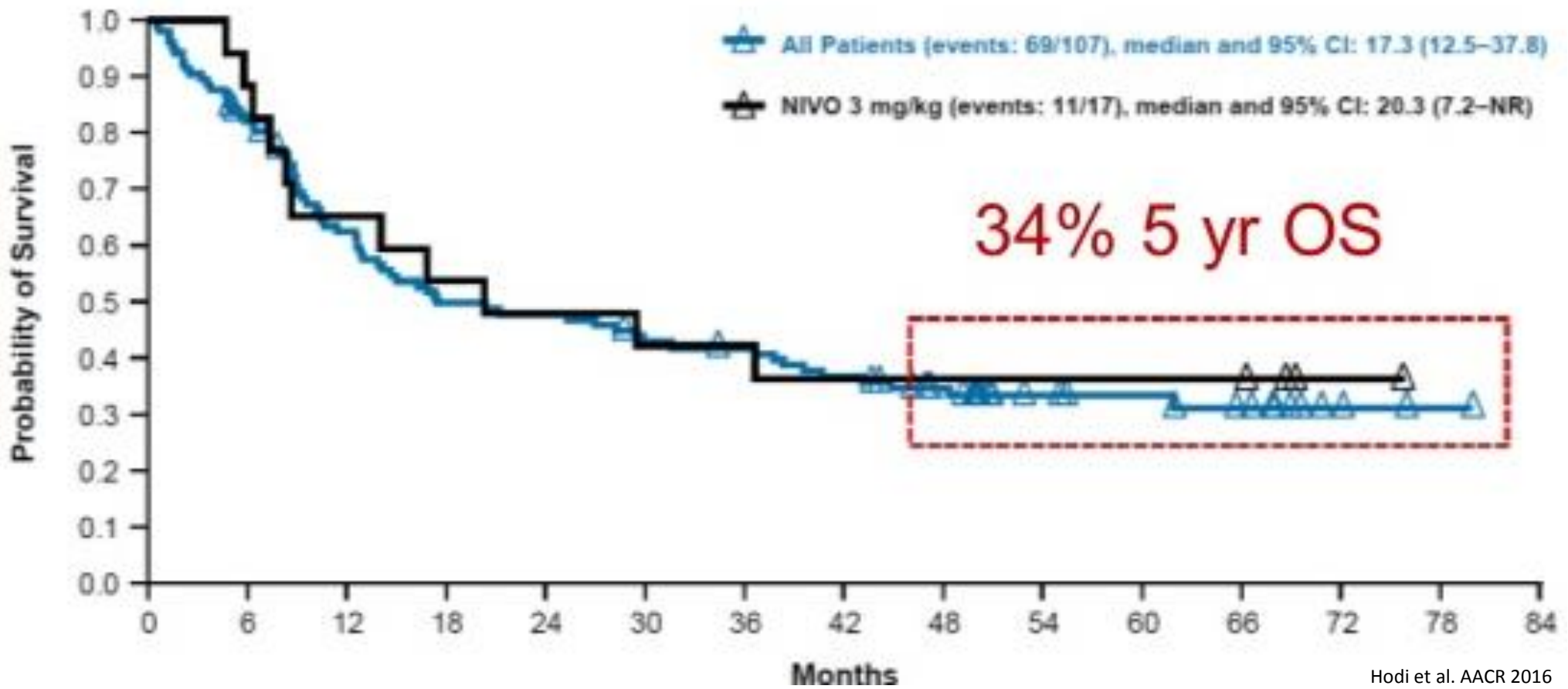
- Pooled OS data from 10 phase II/III trials
  - NCT01024231
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)



Schadendorf et al. JCO 2015

Nivolumab in Stage III/IV Melanoma

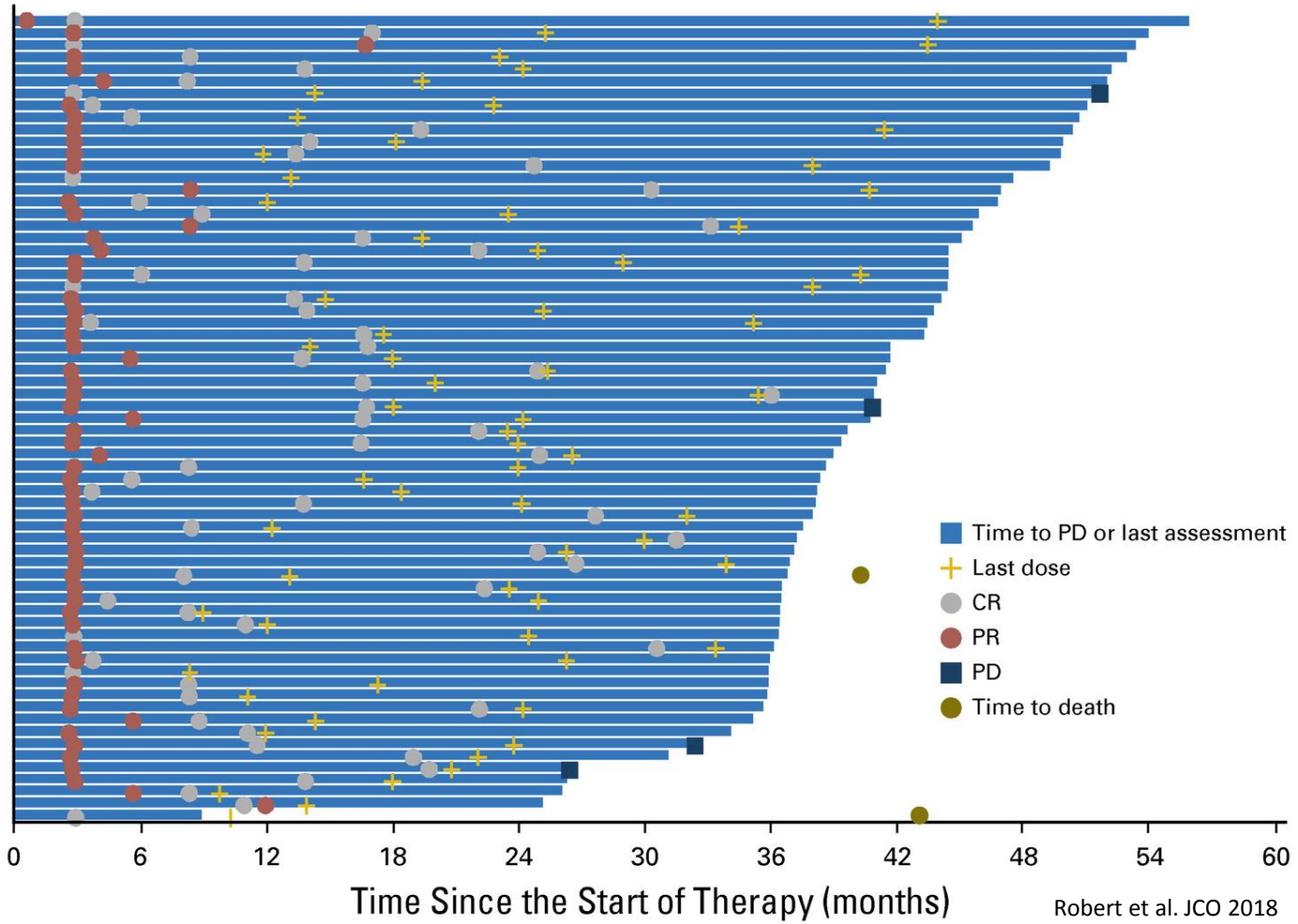
Extended Analysis from CA209-003 Phase I Trial



Hodi et al. AACR 2016

Pembrolizumab in Stage III/IV Melanoma

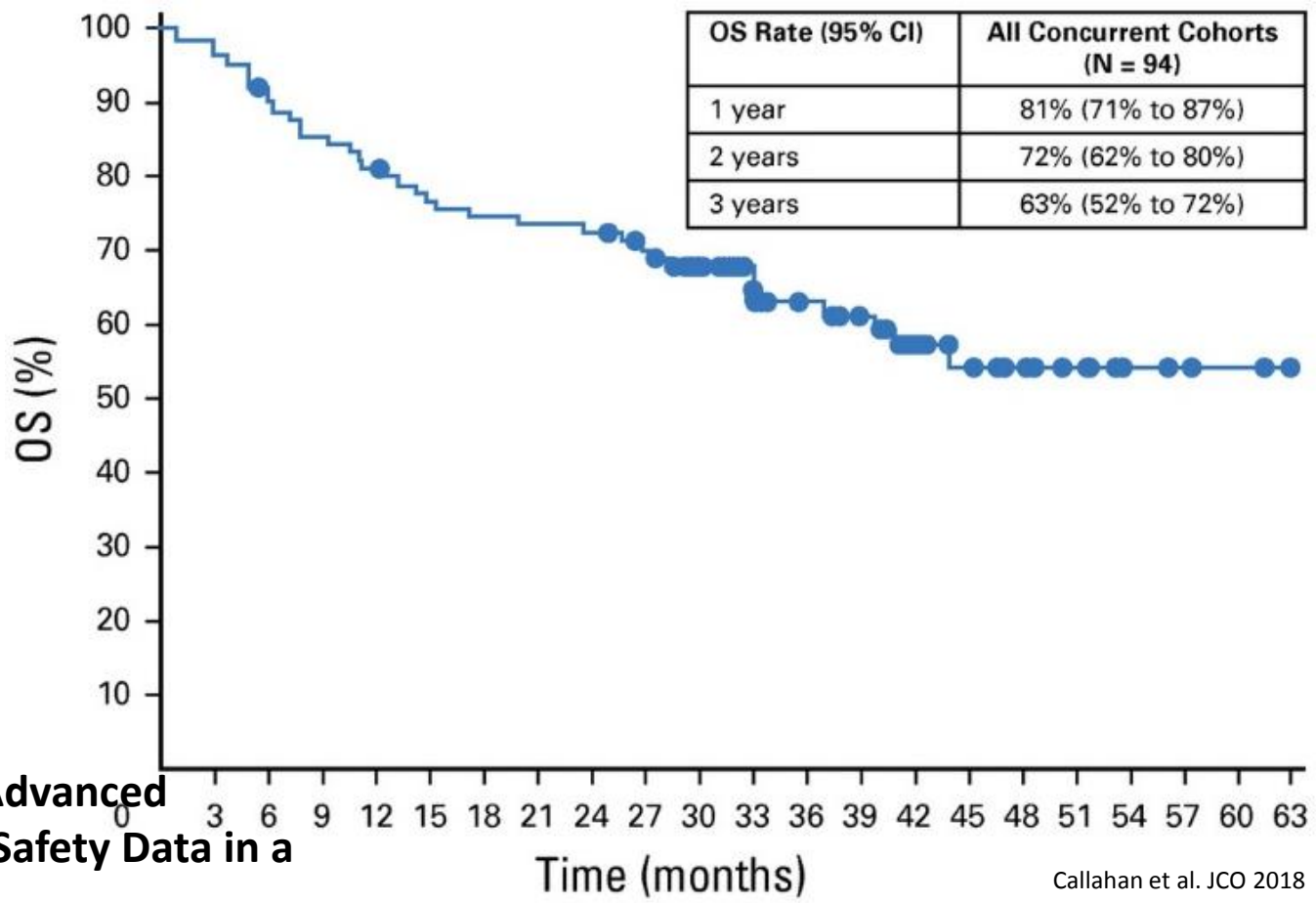
- Phase 1 KEYNOTE-001 Trial
  - NCT01295827
  - Pembrolizumab 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W
  - Durable responses in complete responders patients who discontinued pembrolizumab



Robert et al. JCO 2018

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

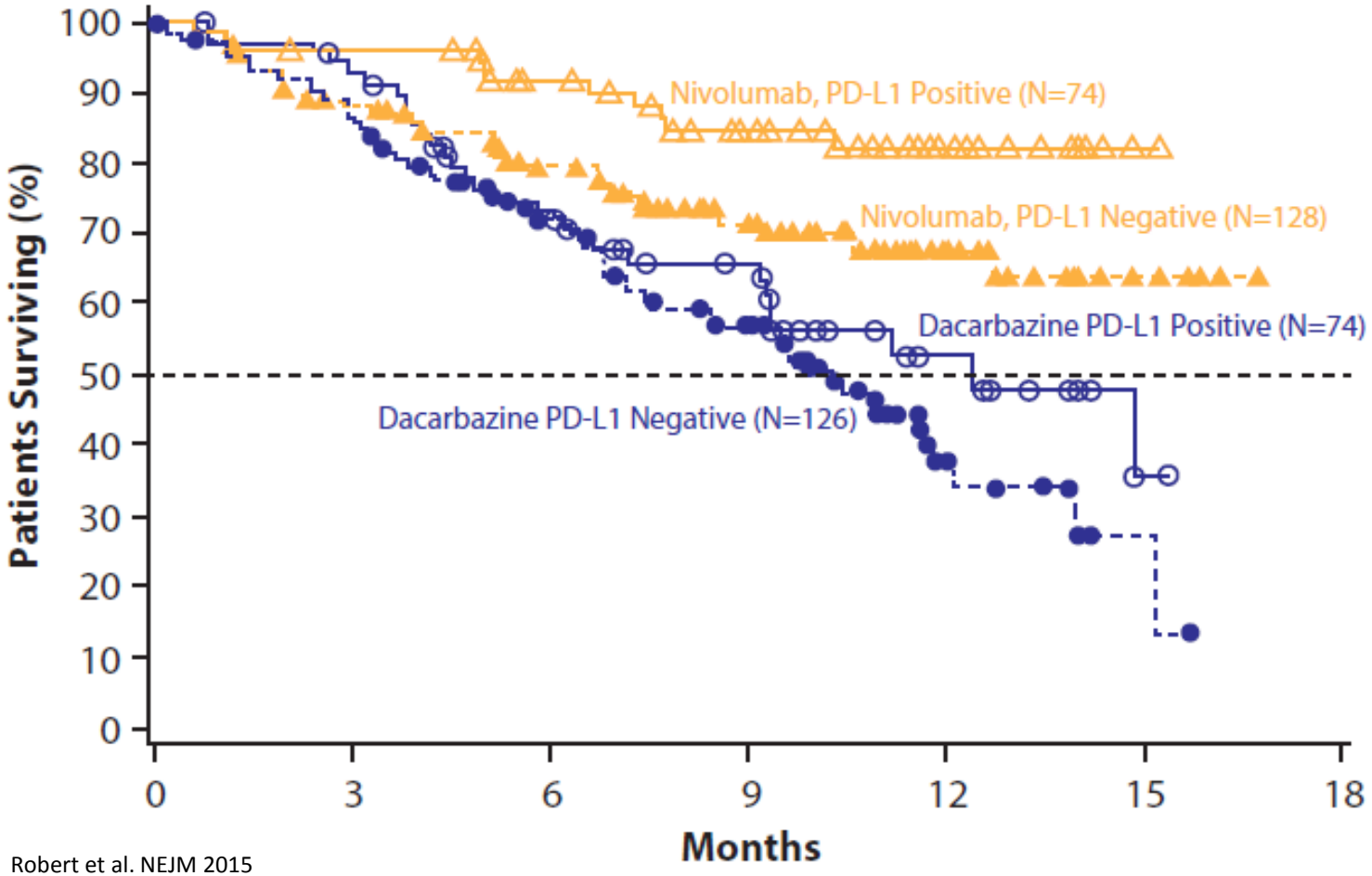
- Phase 1b CA209-004 Trial
  - NCT01024231
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)



Nivolumab Plus Ipilimumab in Patients With Advanced Melanoma: Updated Survival, Response, and Safety Data in a Phase I Dose-Escalation Study.

Callahan et al. JCO 2018

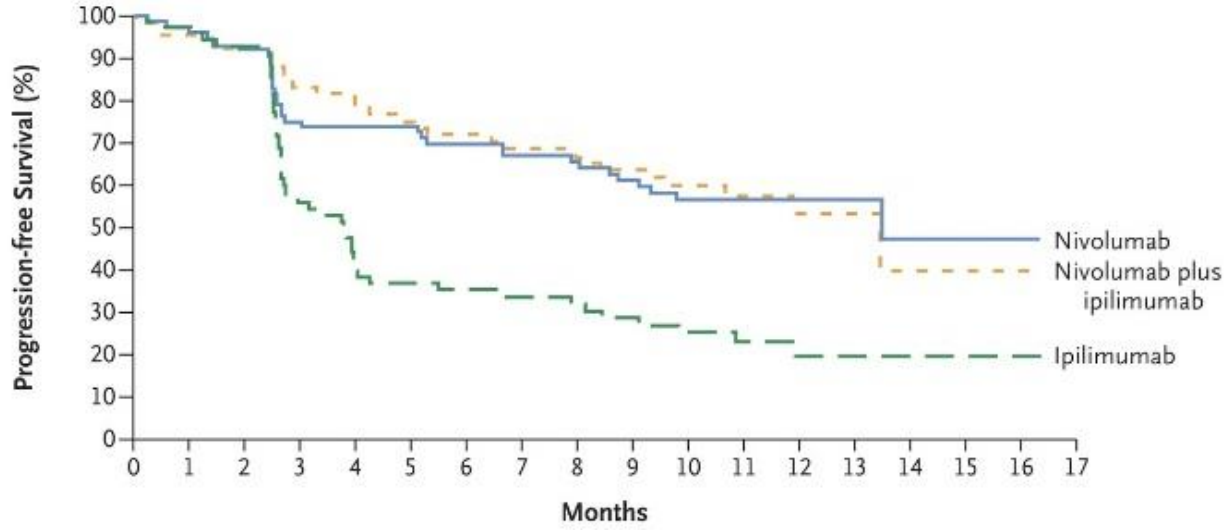
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



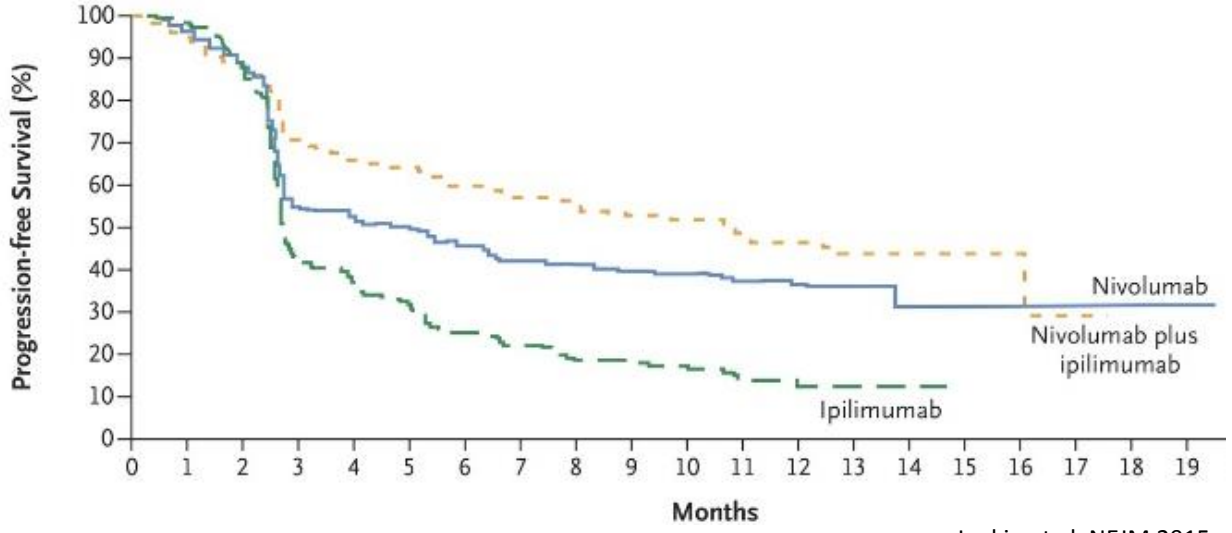
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

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



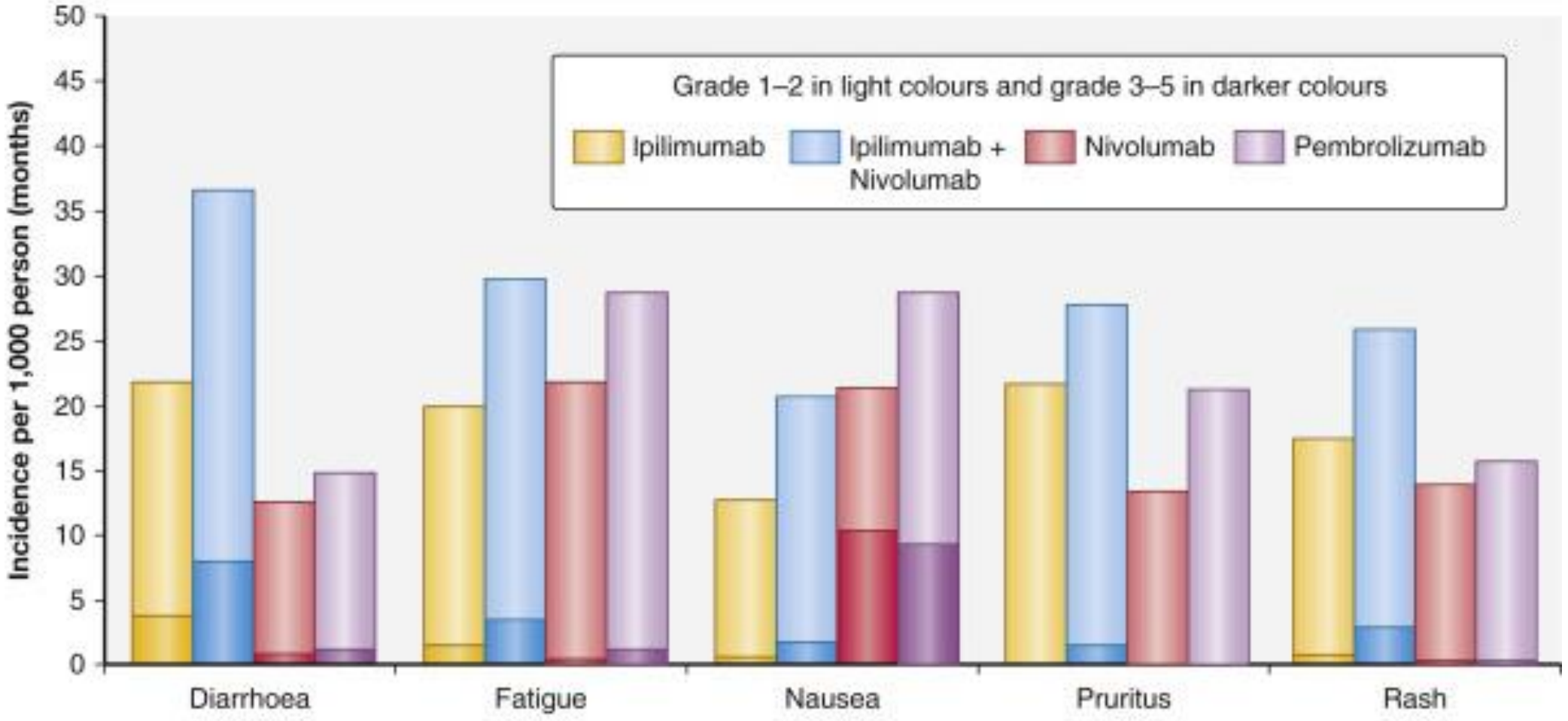
Tumor PD-L1 Negative Patients



Tumor PD-L1 Positive Patients

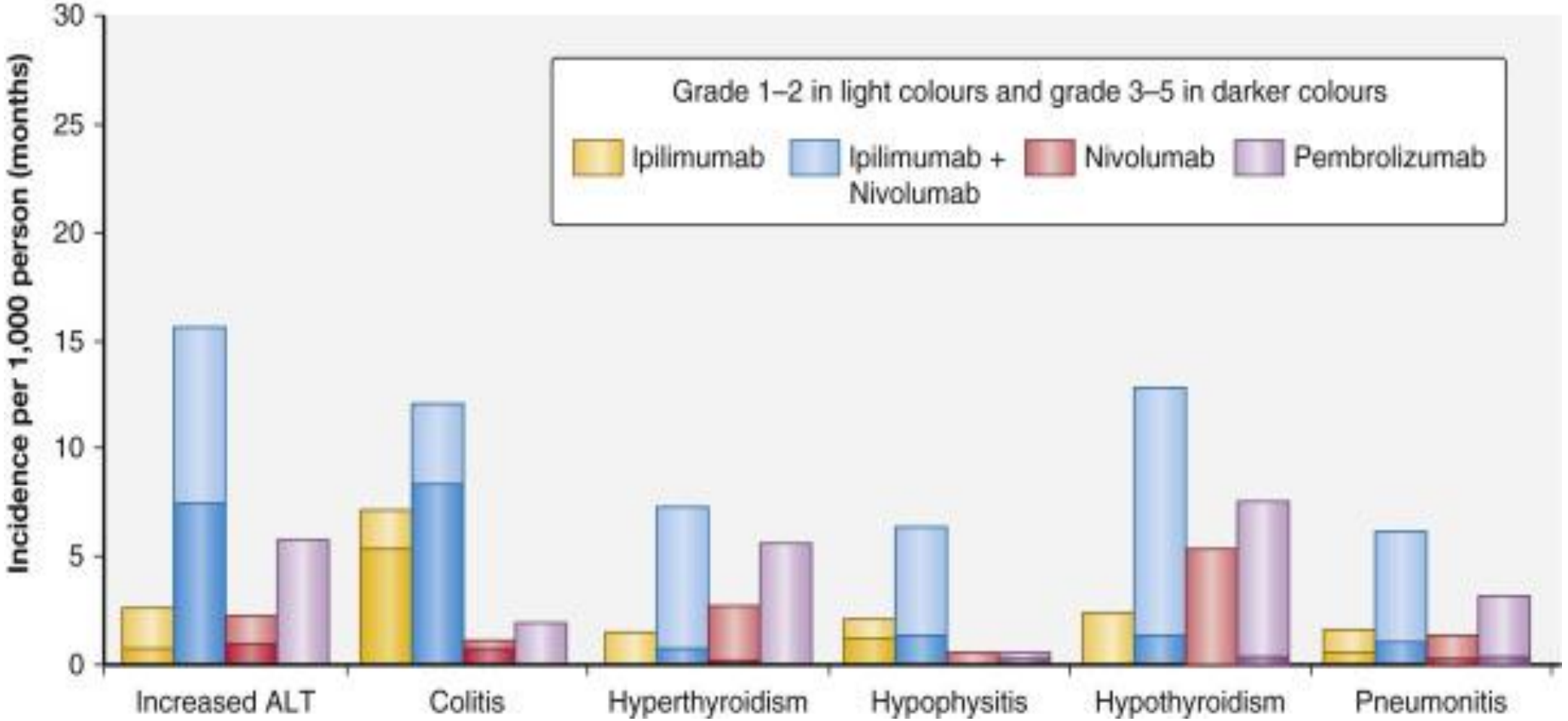
Larkin et al. NEJM 2015

Adverse Events with Immunotherapies



Emens et al. Eur J Cancer 2017

Adverse Events with Immunotherapies



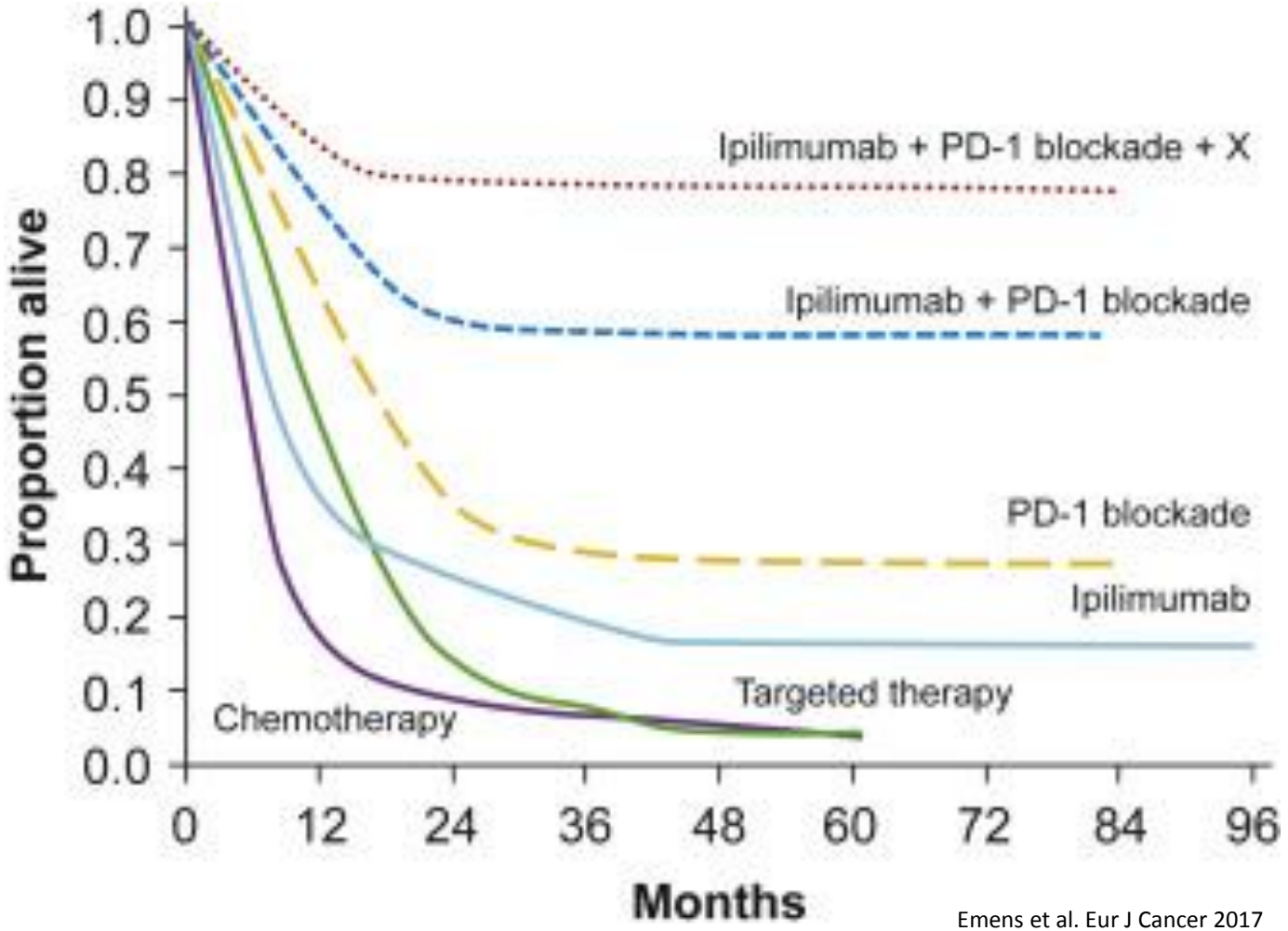
Emens et al. Eur J Cancer 2017

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

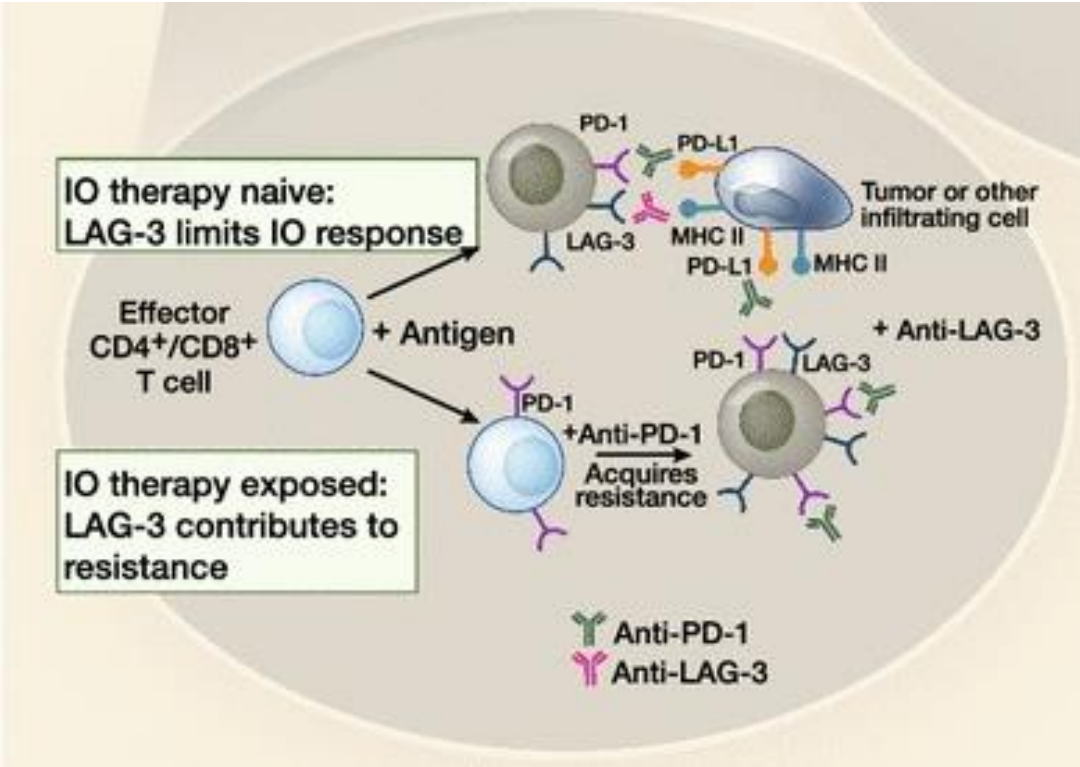
Developmental Immunotherapeutic Strategies for Melanoma

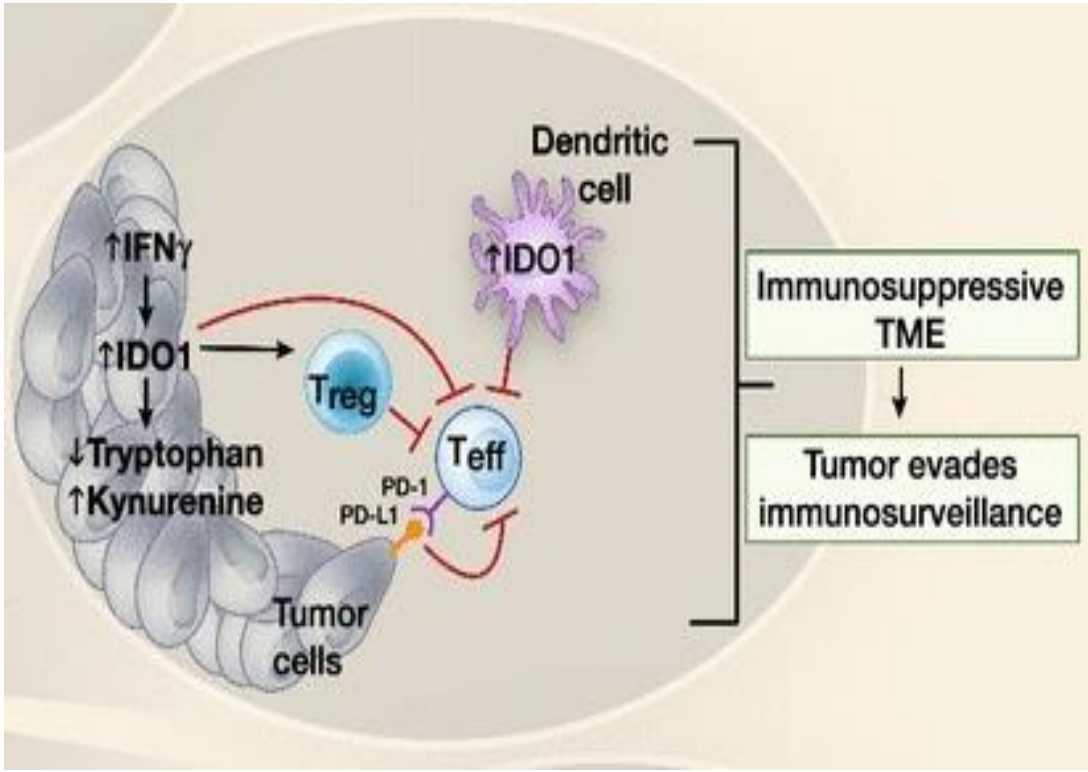


Emens et al. Eur J Cancer 2017

Developmental Immunotherapeutic Strategies for Melanoma

Targeting New Immune Checkpoints

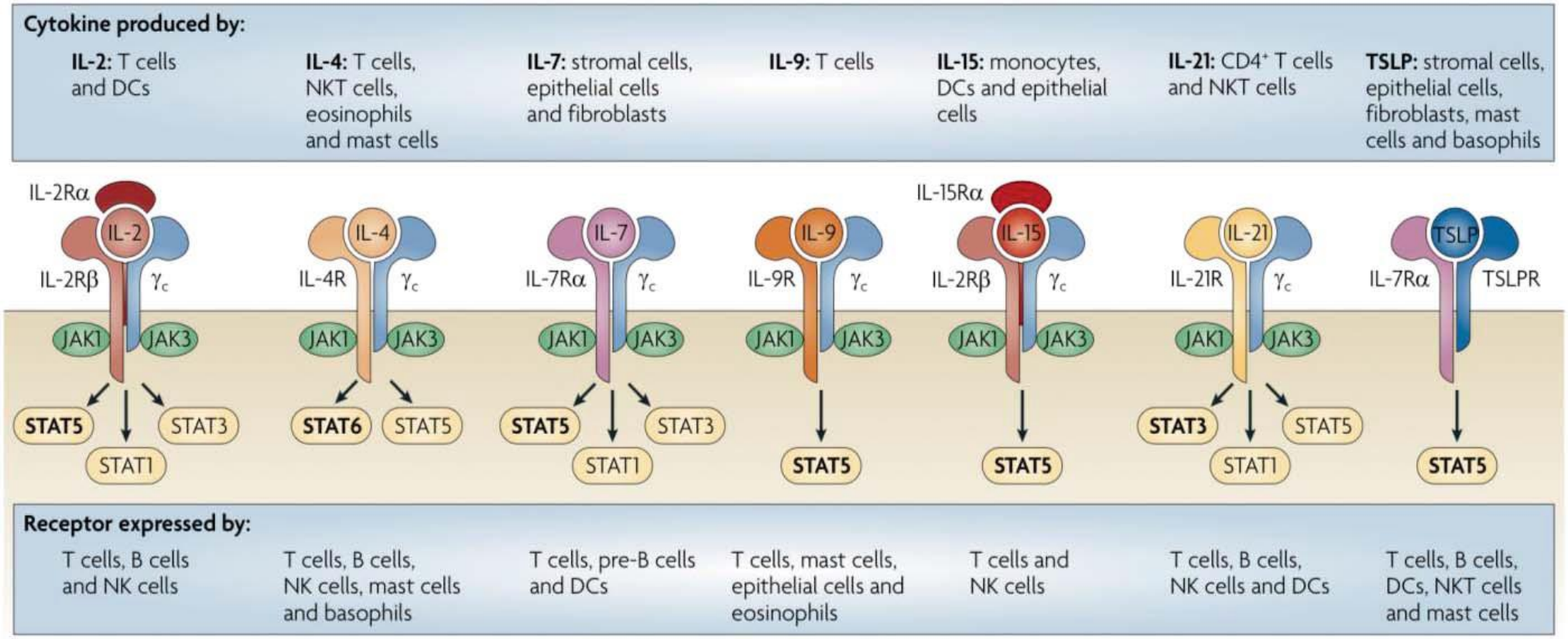




Ascierto, McArthur J Transl Med 2017

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 #1: Stage IV

JS, male patient in 60s

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer, thoracic surgeon feels this is unresectable
- Biopsy performed and reveals malignant melanoma, BRAF wt

Case #1: Stage IV BRAF wt

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - Targeted Rx based on next-generation sequencing
  - Clinical trial

Case #1: Stage IV BRAF wt

- Systemic therapy
  - **Nivolumab**
  - **Pembrolizumab**
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  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - Targeted Rx based on next-generation sequencing
  - Clinical trial

Case #2: Stage IV

JS, male patient in 60s – SAME PATIENT

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer
- Biopsy performed and reveals malignant melanoma, BRAF MUTATED

Case #2: Stage IV BRAF mutant

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Case #2: Stage IV BRAF mutant

- Systemic therapy
  - **Nivolumab**
  - **Pembrolizumab**
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Case #3: Stage IV

JS, male patient in 60s – SAME PATIENT

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer
- Biopsy performed and reveals malignant melanoma, BRAF MUTATED
- Patient having hip pain and found to have right acetabular bony lesion

Case #3: Stage IV BRAF mutant

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Radiation to hip lesion

Case #3: Stage IV BRAF mutant

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - **Nivolumab plus ipilimumab**
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Radiation to hip lesion

Case #3: What if the patient is found to have a brain metastasis?

Sullivan et al. Journal for ImmunoTherapy of Cancer (2018) 6:44
https://doi.org/10.1186/s40425-018-0362-6

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Case #3: What if the patient is found to have a brain metastasis?

- Systemic therapy
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  - Nivolumab plus ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Radiation to brain lesion?

Case #3: What if the patient is found to have a brain metastasis?

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - **Nivolumab plus ipilimumab**
  - High-dose IL-2
  - BRAF/MEK targeted therapy

Radiation to brain lesion?