Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

# Immunotherapy for the Treatment of Skin Cancers

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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# Disclosures

- I will be discussing non-FDA approved indications during my presentation.

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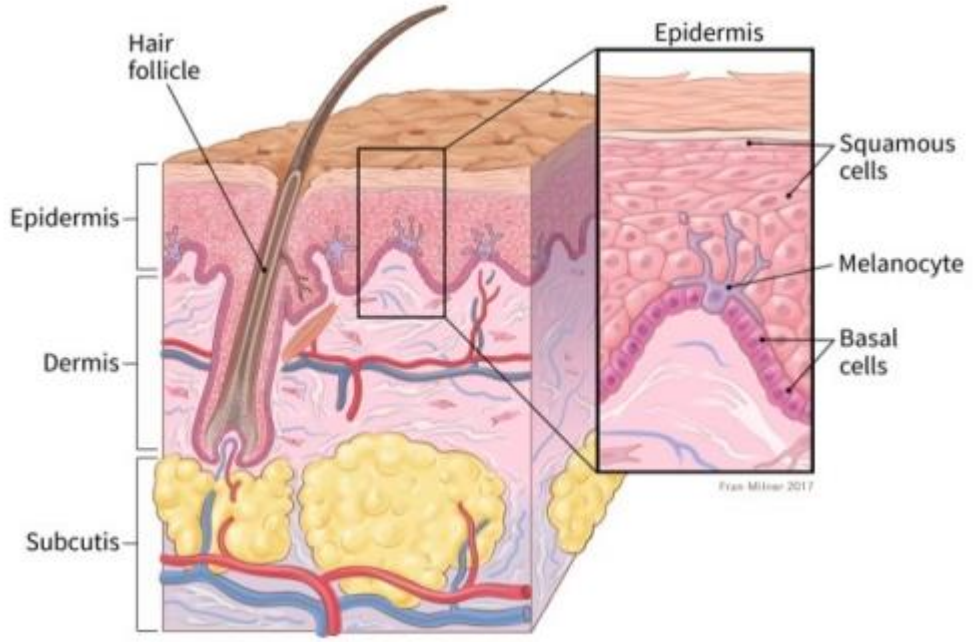
# Background

- Skin cancer is the most common type of cancer
- Three most common types of skin cancers:
  - Basal cell carcinoma
  - Squamous cell carcinoma
  - Melanoma
- Melanoma was one of the foundational disease states for testing immunotherapies




Cancer.org

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# Approved cytokines in melanoma

| Drug | Indication | Dose |
|---|---|---|
| High-dose interferon alfa-2b | Adjuvant – high risk for systemic recurrence | Induction: 20m IU/$m^2$ IV 5x/wk for 4 wks<br>Maintenance: 10m IU/$m^2$ s.c. 3x/wk for 48 wks |
| Interleukin-2 (Aldesleukin) | Stage IV | 600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per course |
| Pegylated Interferon alfa-2b (Sylatron) | Adjuvant – microscopic or gross nodal involvement | 6 mcg/kg/wk s.c. for 8 doses, then 3 mcg/kg/wk s.c. for up to 5 years |

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# Approved checkpoint inhibitors in melanoma

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Ipilimumab | 2011 | Unresectable/Metastatic melanoma: newly diagnosed or after progression | 3 mg/kg Q3W for 4 doses |
| | 2015 | Adjuvant therapy in stage III melanoma after complete resection | 10 mg/kg Q3W for 4 doses, then 10 mg/kg Q12W for 3 years |
| | 2017 | Unresectable/Metastatic melanoma: newly diagnosed or after progression, all patients ≥ 12 yr | 3 mg/kg Q3W for 4 doses |

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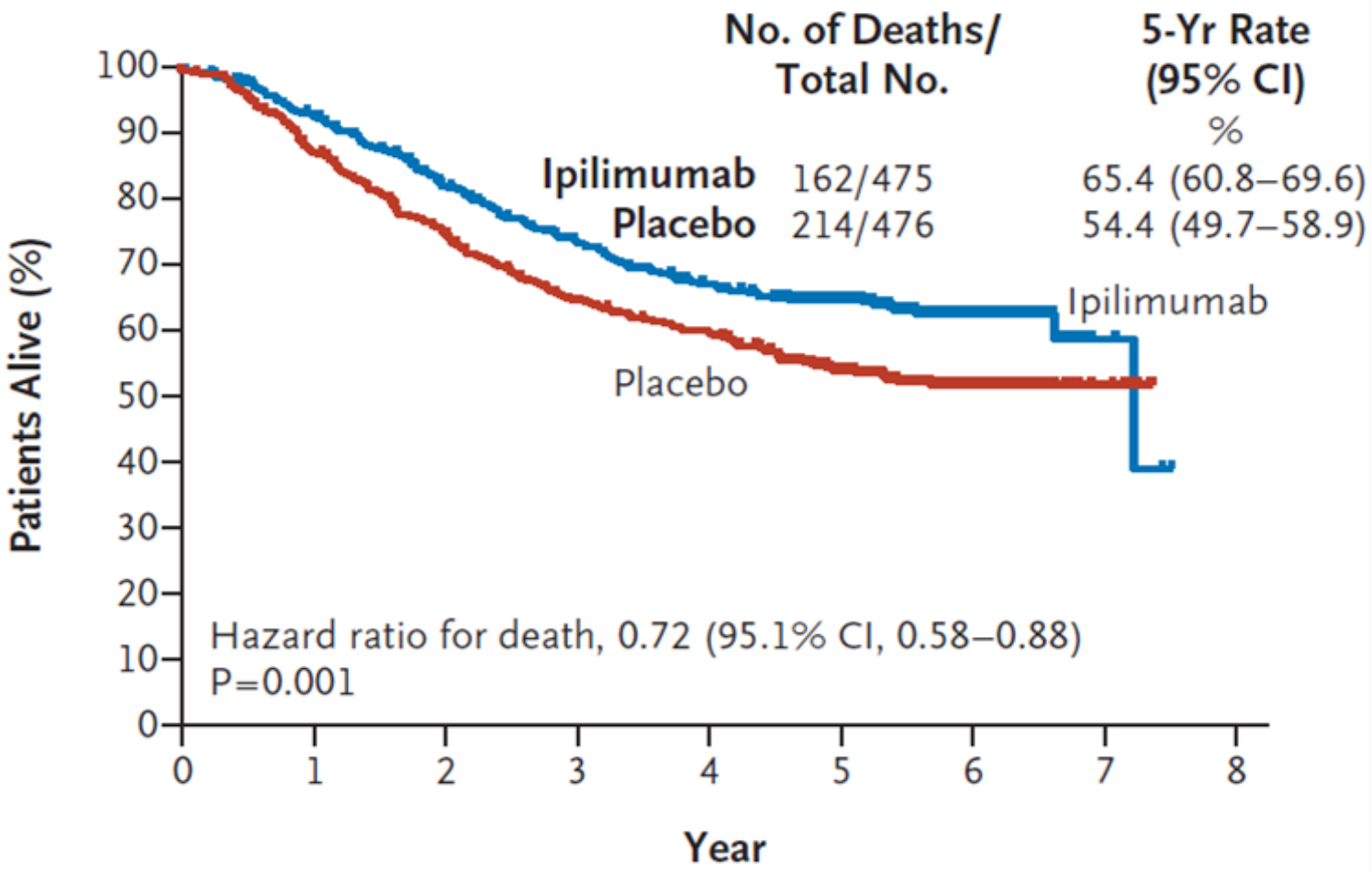
# Adjuvant Ipilimumab in High-Risk Stage III Melanoma

- EORTC 18071 phase III trial
  - NCT00636168
  - Adjuvant ipilimumab vs placebo
  - Ipilimumab 10mg/kg Q3W for four doses, then every 12 weeks for up to 3 years




Eggermont, NEJM 2016.

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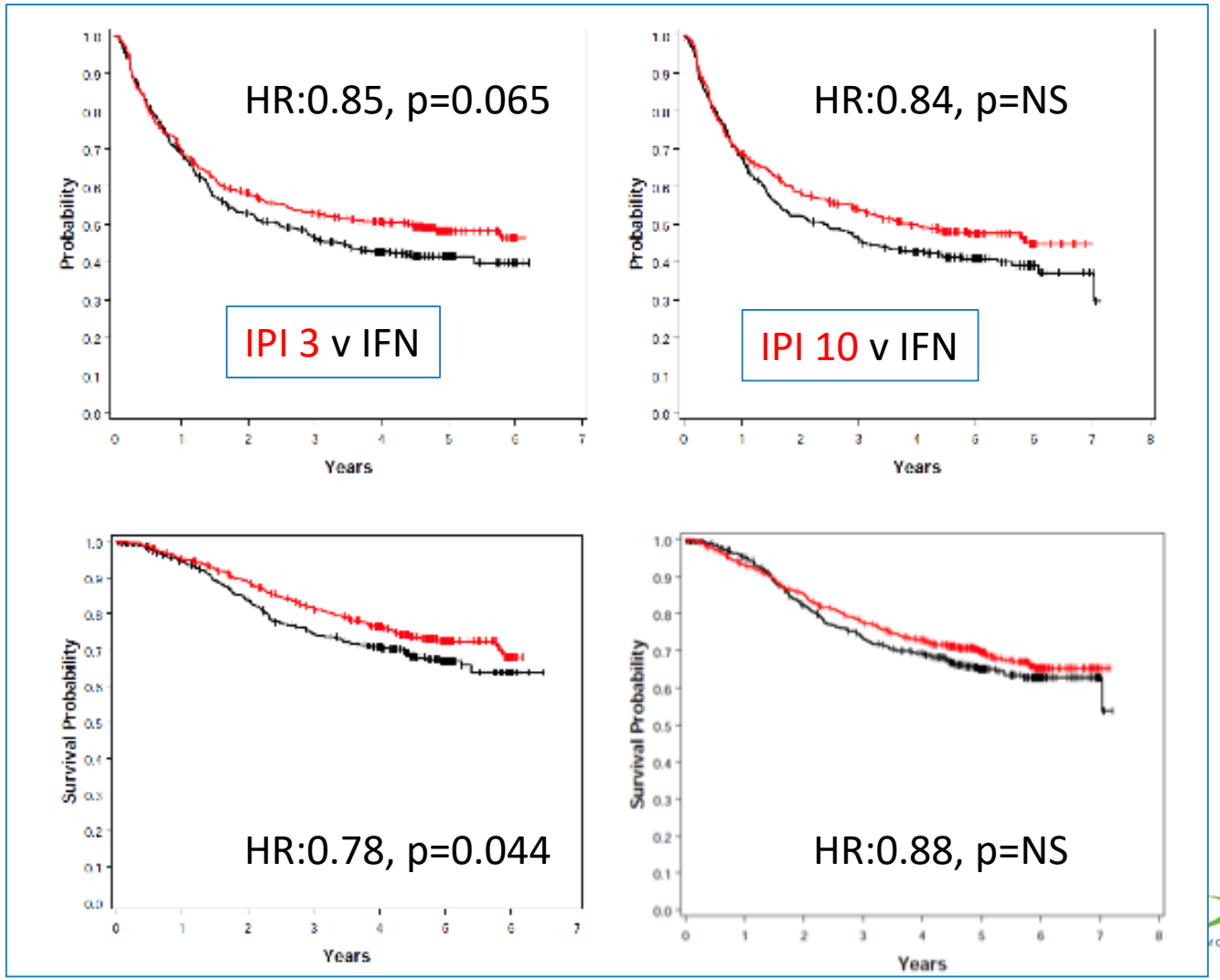
# Adjuvant Ipilimumab in High-Risk Stage III Melanoma

- ECOG 1609
  - NCT01274338
  - Adjuvant interferon (IFN) vs ipilimumab 3 mg/kg (IPI 3) vs ipilimumab 10 mg/kg (IPI 10)
  - Ipilimumab Q3W for four doses, then every 12 weeks for up to 3 years
  - IPI 3 “better than IFN”, IPI 10 “not better than IFN”
  - IPI3 better tolerated than IPI 10

RFS

OS




Tarhini, ASCO Annual Meeting 2019.

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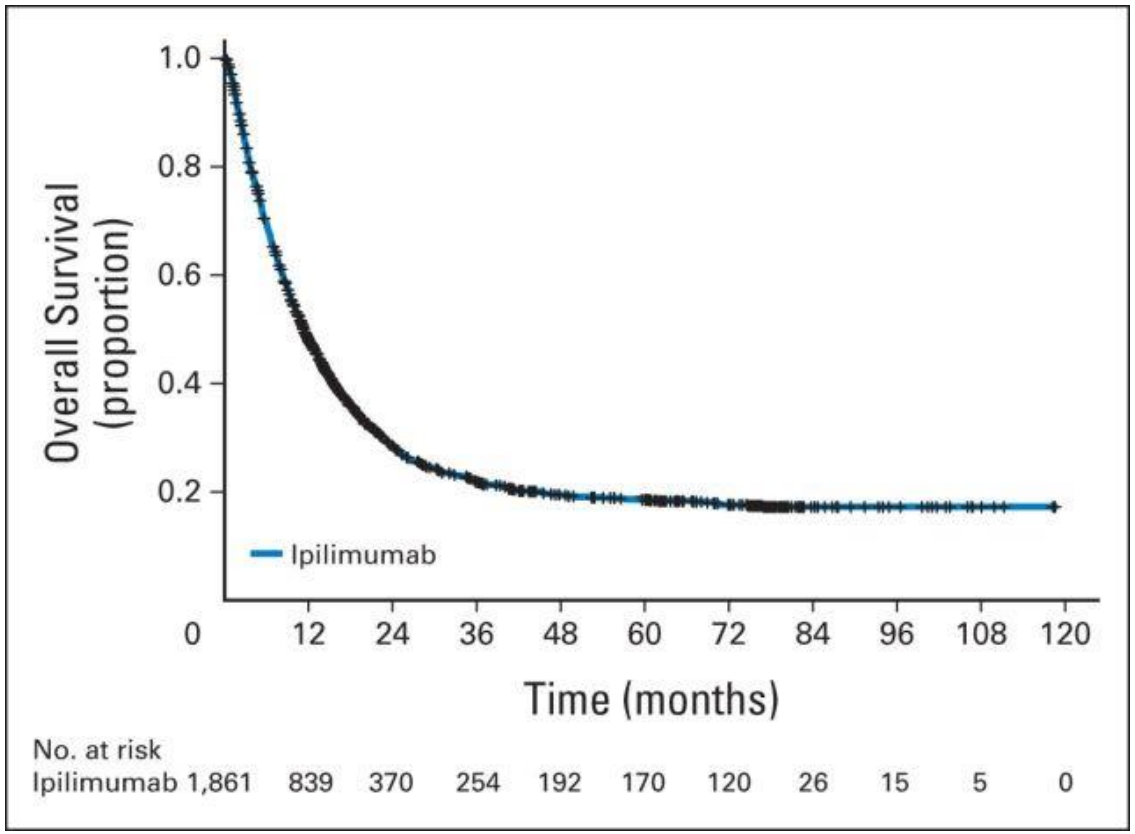
# Ipilimumab in Stage III/IV Melanoma

- 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.

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# Approved checkpoint inhibitors in melanoma

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Pembrolizumab | 2014 | Advanced/unresectable melanoma with progression after other therapy | 200 mg Q3W* |
| | 2015 | 1st line unresectable/metastatic melanoma | 200 mg Q3W* |
| | 2019 | Adjuvant therapy of melanoma following complete resection | 200 mg Q3W |
| *Original approvals were 2 mg/kg Q3W – updated to flat dosing regimen | | | |

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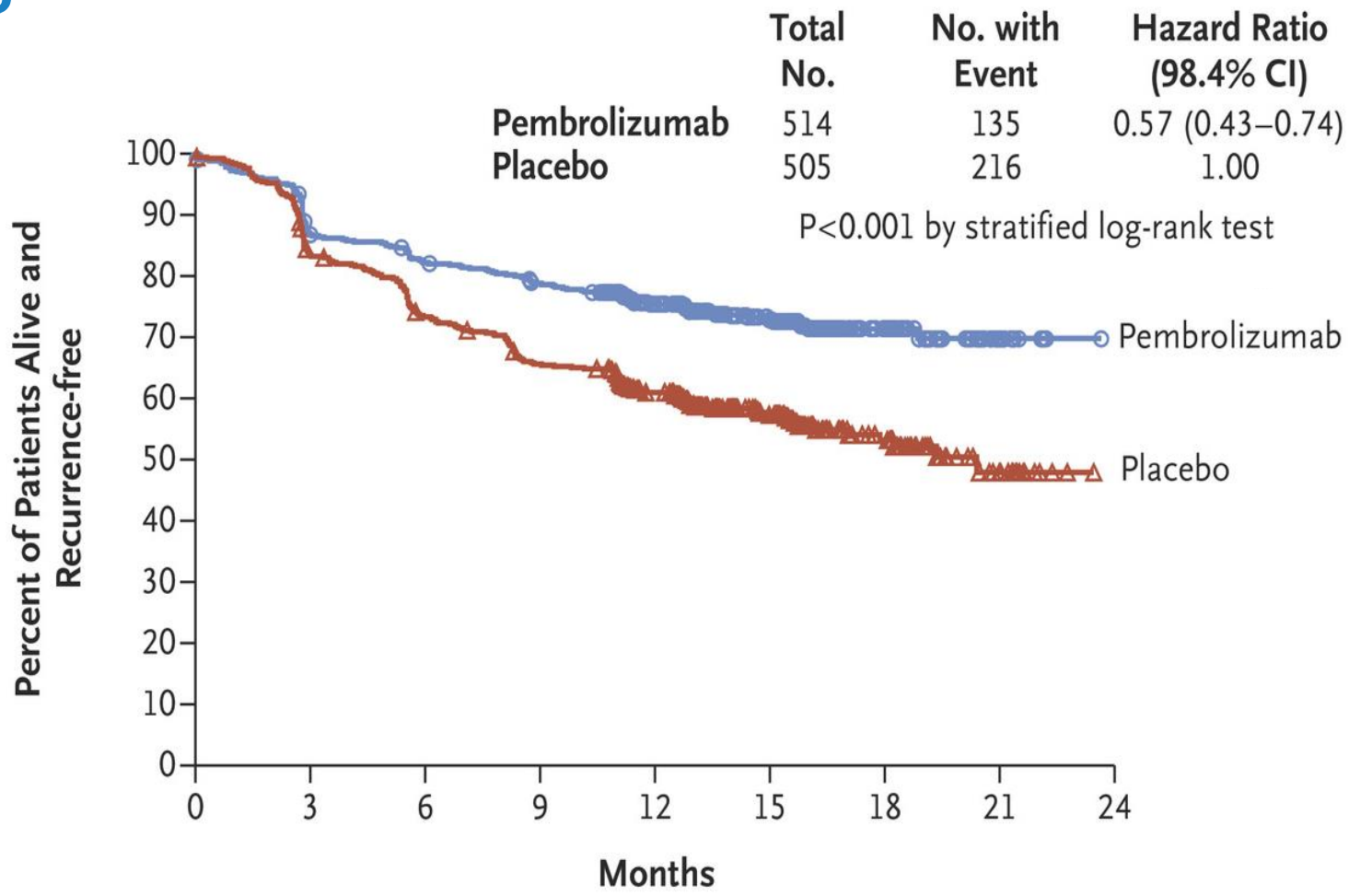
# Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

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




Eggermont, NEJM 2018.

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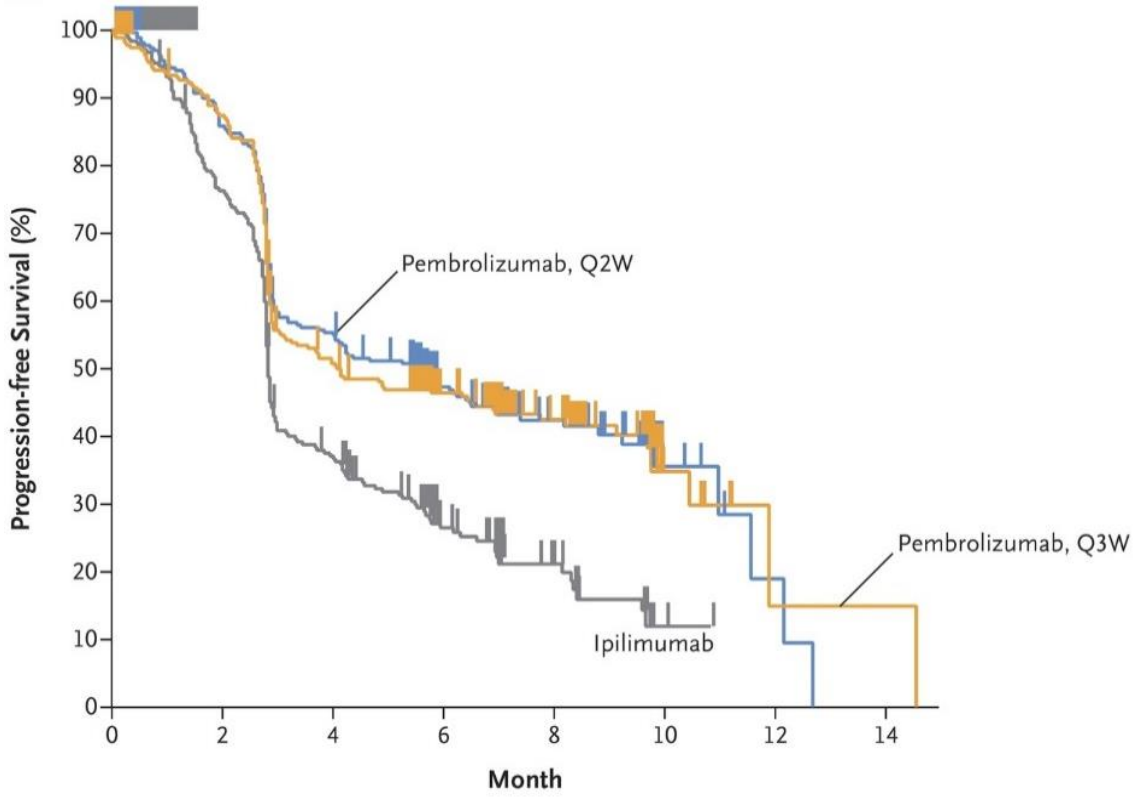
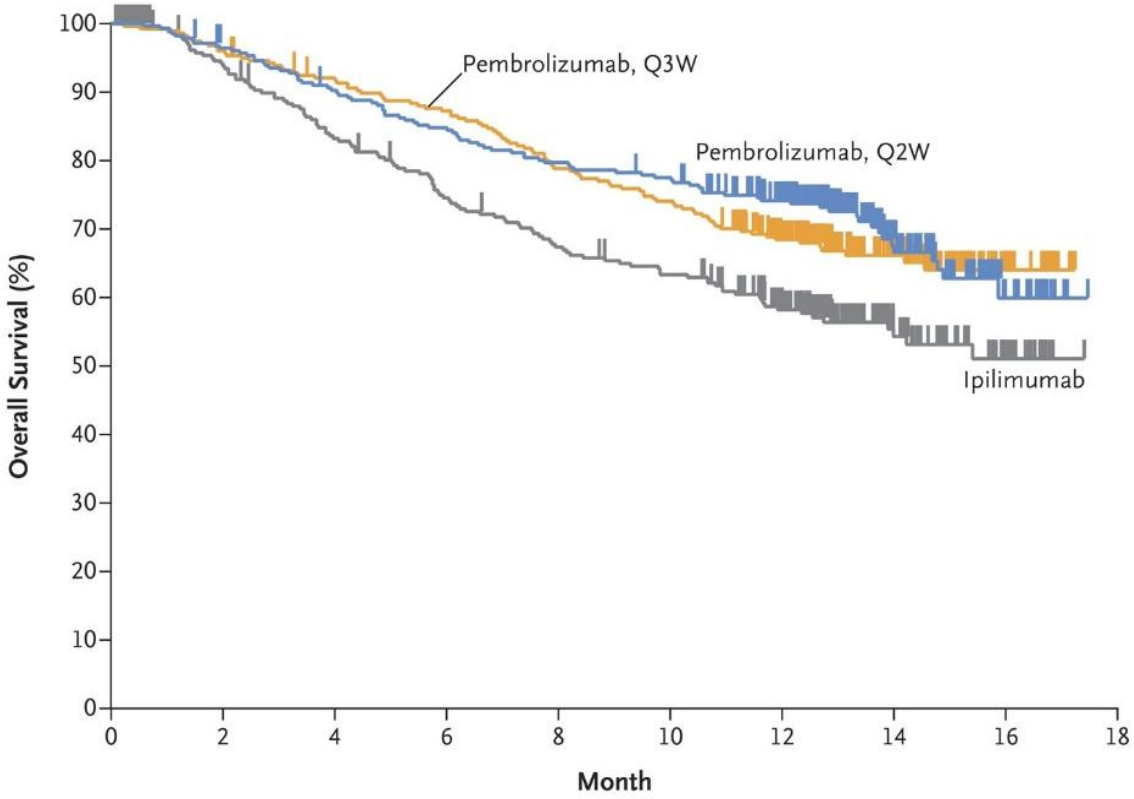
# Pembrolizumab in Stage III/IV Melanoma

## Phase III KEYNOTE-006 Trial




Robert, NEJM 2015.

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# Approved checkpoint inhibitors in melanoma

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Nivolumab | 2014 | Unresectable/metastatic melanoma with progression after other therapy | 240 mg Q2W or 480 mg Q4W* |
| | 2017 | Adjuvant treatment of melanoma after complete resection | 240 mg Q2W or 480 mg Q4W |
| *Original approval was 3 mg/kg Q2W, updated to flat dosing regimen | | | |

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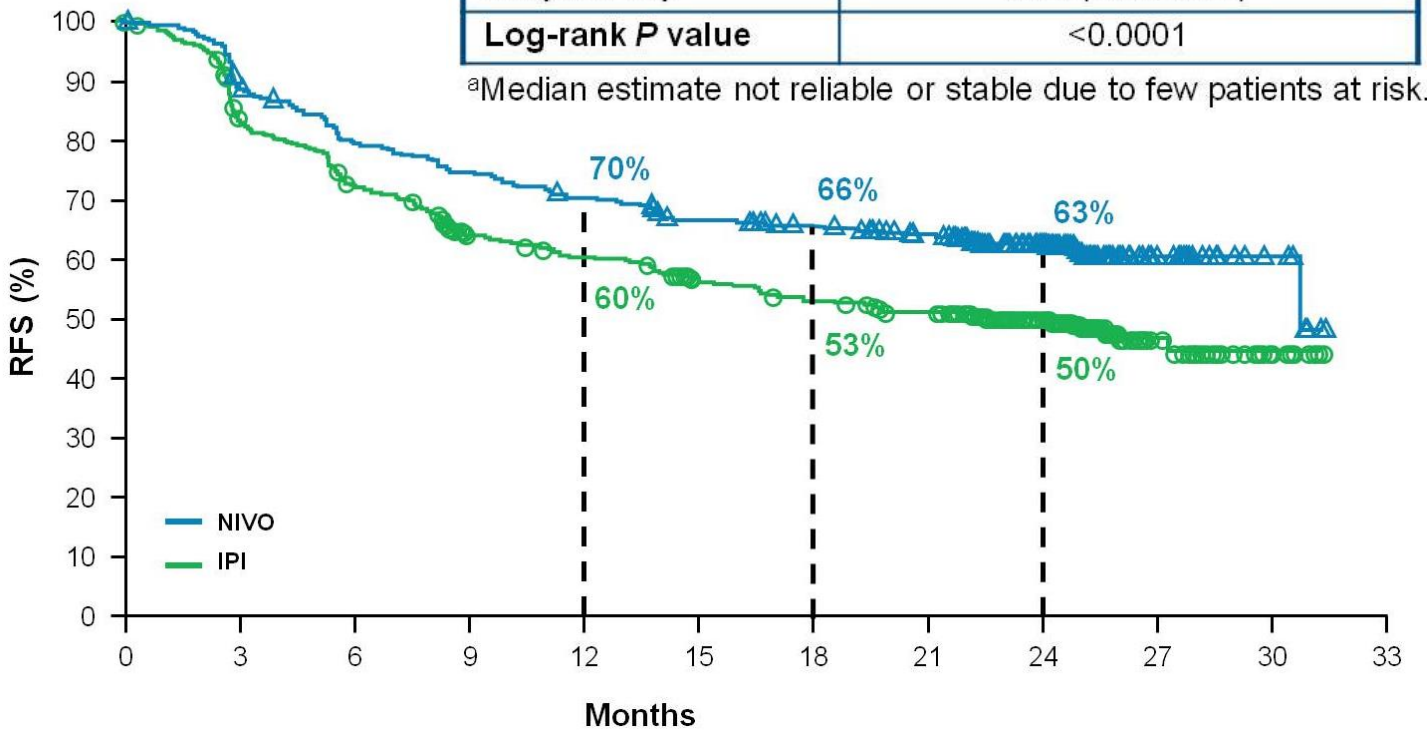
# Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

- 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, ASCO 2018.

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# Approved checkpoint inhibitors in melanoma

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Nivolumab + Ipilimumab | 2015 | BRAF V600 WT unresectable/metastatic melanoma | 1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W |
| | 2016 | BRAF V600 WT or mutant unresectable/metastatic melanoma | 1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W |

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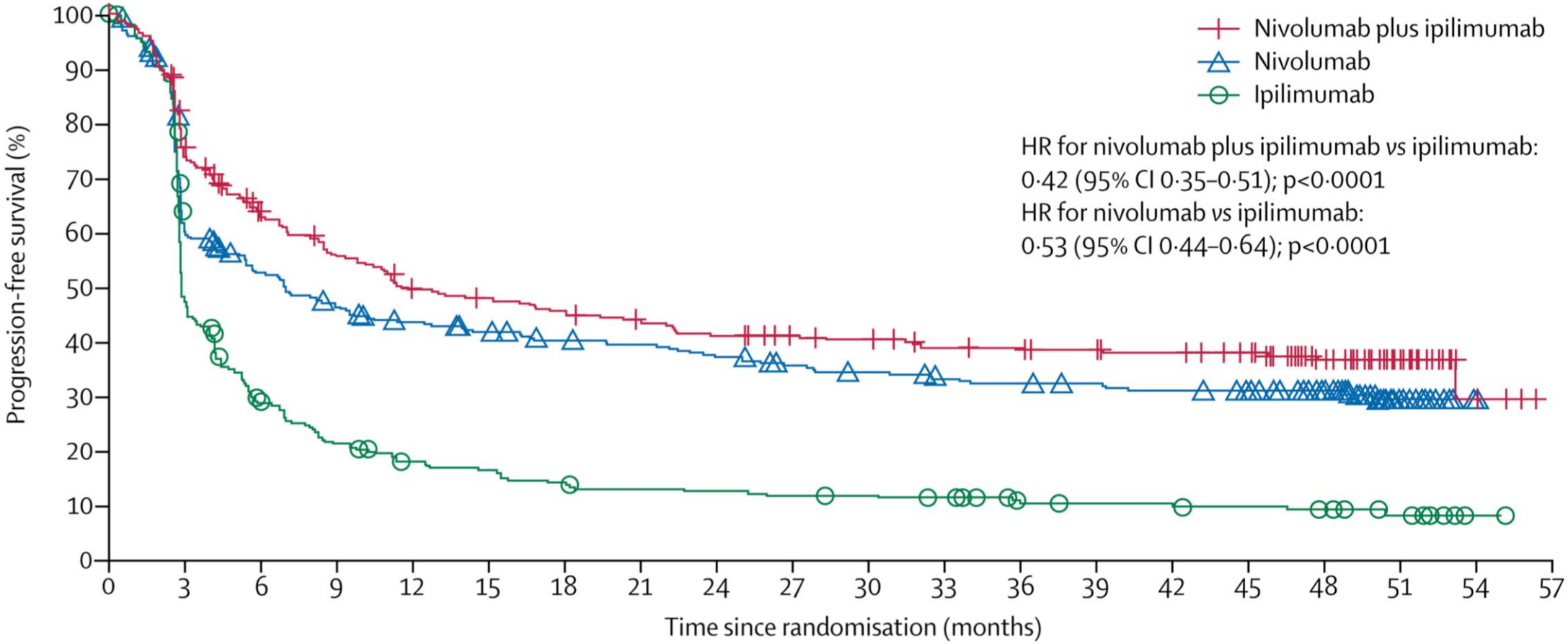
# Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

## Phase III CheckMate 067 Trial




Hodi, Lancet Oncol 2018.

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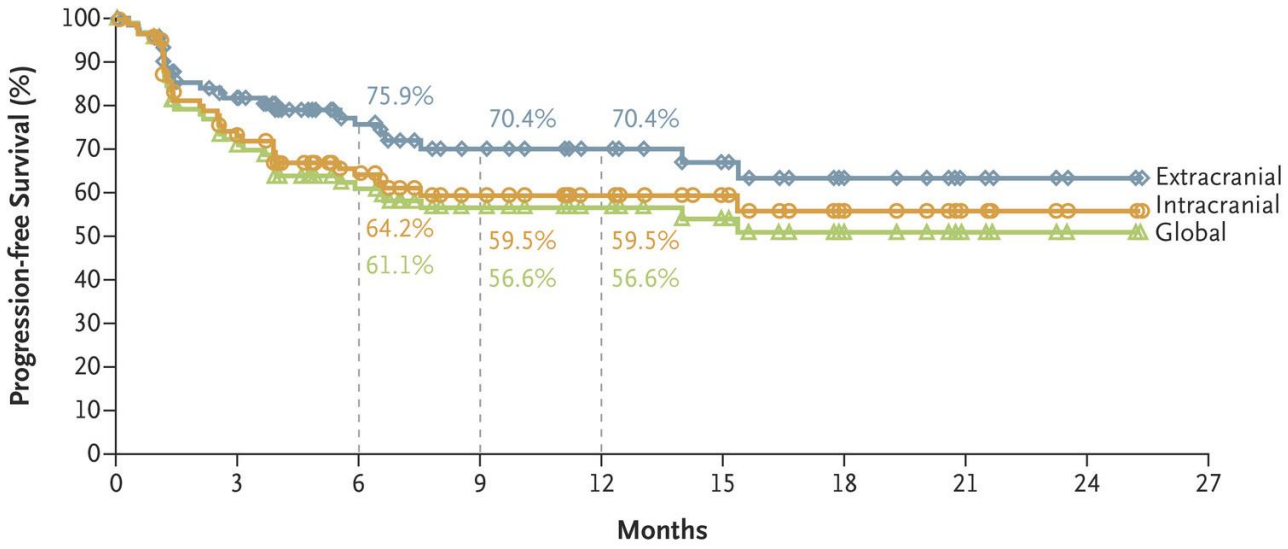
# Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

| 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.

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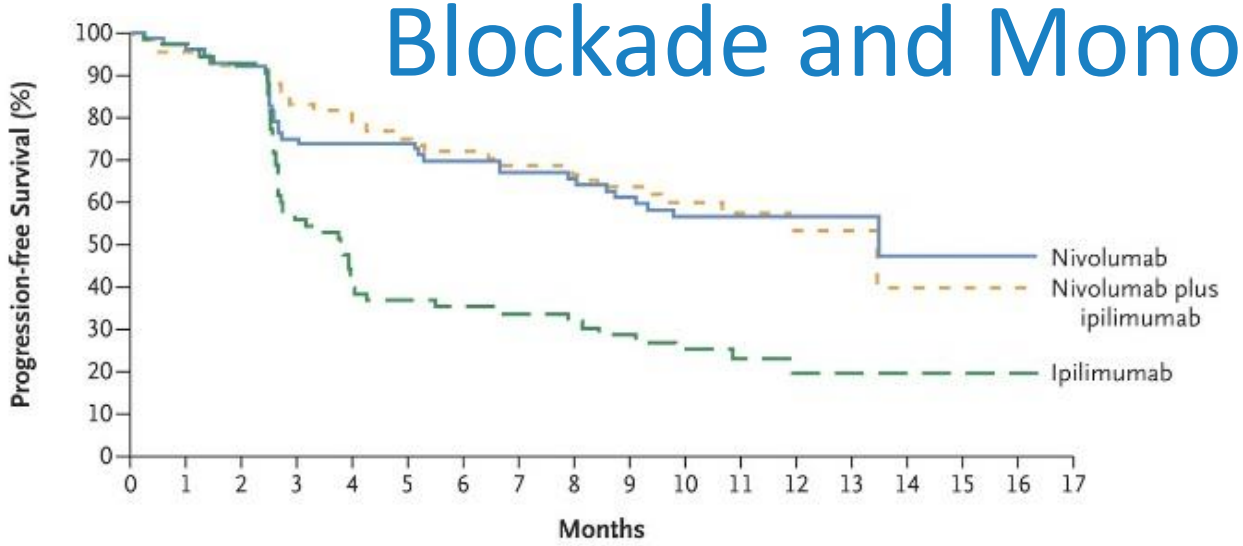
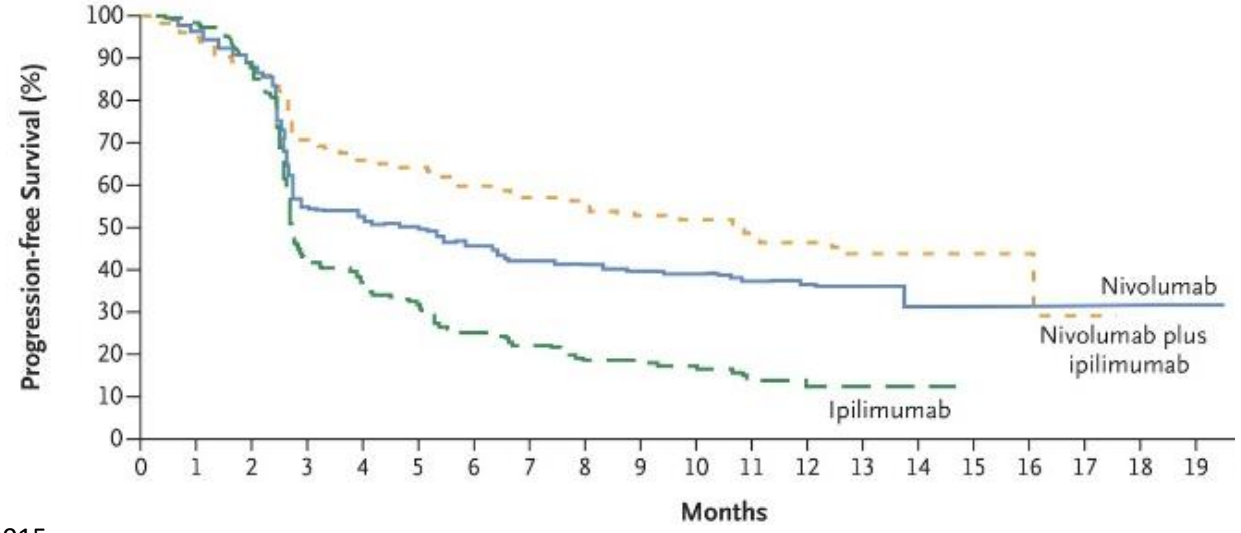
# Importance of Tumor PD-L1 Status between Combination Checkpoint Blockade and Monotherapy




Tumor PD-L1 Positive Patients




Tumor PD-L1 Negative Patients

Larkin, NEJM 2015.

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# The use of PD-L1 status to predict overall survival is poor with single-agent PD-1 or combined ipi/nivo…

| PDL-1 (%) | ≥ 1 | < 1 | ≥ 5 | < 5 | ➢ 10 | < 10 |
|---|---|---|---|---|---|---|
| Ipilimumab | 19% | 18% | 21% | 17% | 20% | 18% |
| Nivolumab | 54% | 35% | 58% | 42% | 58% | 44% |
| Ipi/Nivo | 65% | 54% | 72% | 56% | 85% | 55% |

## …but, PD-L1 status predicts higher response rate with combo at every PD-L1 expression cut-off

Wolchok, NEJM 2017.

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# Approved combination therapy in melanoma

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Atezolizumab + cobimetinib + vemurafenib | 2020 | BRAF V600 mutation-positive unresectable or metastatic melanoma | 28-day cycle of vem/cobi, then atezo 840 mg Q2W + cobi 60 mg Q1D (21 D on, 7 D off) + vem 720 mg twice daily |

**IMspire150 – BRAFV600-positive melanoma**

Atezolizumab + cobimetinib + vemurafenib vs Placebo + cobimetinib + vemurafenib

Median PFS: 15.1 vs 10.6 months

AEs leading to discontinuation: 13% vs 16%

Gutzmer, Lancet 2020

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# **In development:** Neoadjuvant immunotherapy in advanced melanoma

| Trial | Regimen | N | pCR (%) | med RFS (mo) | med FU (mo) |
|---|---|---|---|---|---|
| Amaria Lancet Oncol 2018 | *Dab/Tram* | 21 | 58 | 19.7 | 18.6 |
| Long Lancet Oncol 2019 | *Dab/Tram* | 35 | 49 | 23.0 | 27.0 |
| Blank Nat Med 2018 | Ipi+nivo | 10 | 33 | NR | 32 |
| Amaria Nat Med 2018 | Nivo<br>Ipi+nivo | 12<br>11 | 25<br>45 | NR<br>NR | 20 |
| Huang Nat Med 2019 | Pembro | 30 | 19 | NR | 18 |
| Rozeman Lancet Oncol 2019 | Ipi+nivo | 86 | 57 | NR | 8.3 |

Menzies ASCO Annual Meeting 2019.

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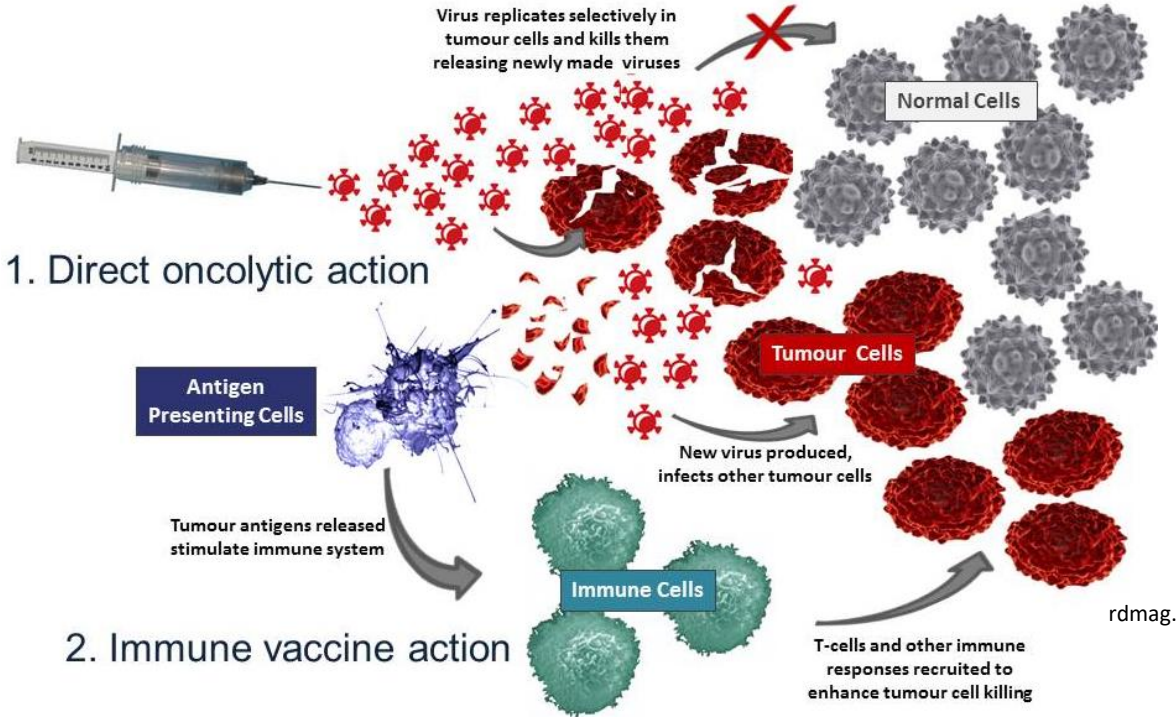
# Approved oncolytic virus in melanoma




rdmag.com

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Talimogene laherparepvec (T-Vec) | 2015 | Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in recurrent melanoma after surgery | Intralesional injection: ≤4 mL at $10^6$ PFU/mL starting; $10^8$ PFU/mL subsequent |

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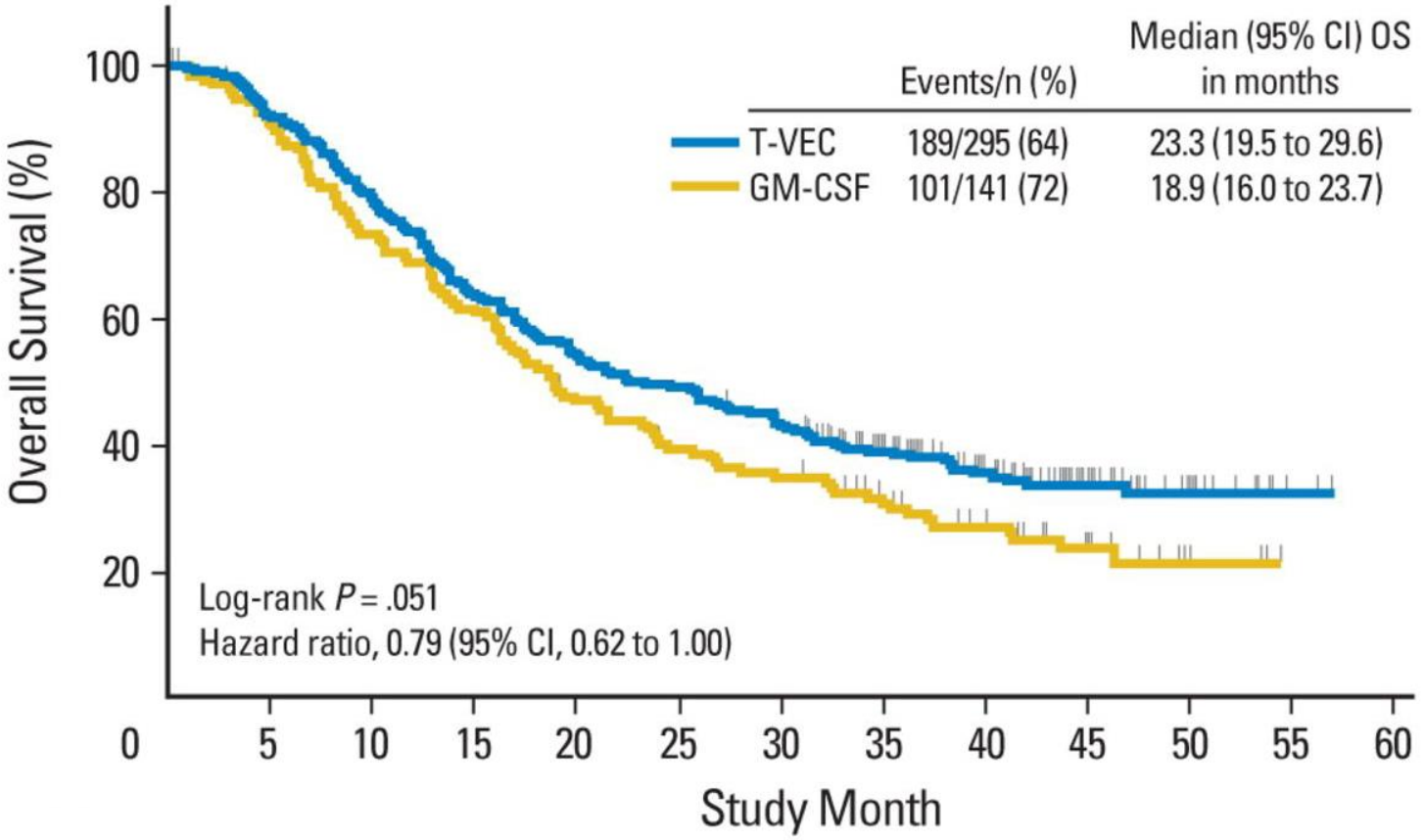
# Talimogene laherparepvec (T-VEC) in Stage III/IV Melanoma

- 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, JCO 2015.

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# Approved checkpoint inhibitors in other skin cancers

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Avelumab | 2017 | Patients >12 yr with metastatic **Merkel cell carcinoma** | 800 mg Q2W + premedication (first 4 cycles) |
| Pembrolizumab | 2018 | Adult/pediatric with recurrent advanced/metastatic **Merkel cell carcinoma** | Adults: 200 mg Q3W<br>Pediatric: 2 mg/kg (up to 200 mg) Q3W |
| Cemiplimab-rwlc | 2018 | Metastatic **cutaneous squamous cell carcinoma**, not candidate for curative therapies | 350 mg Q3W |
| Pembrolizumab | 2020 | Metastatic cutaneous squamous cell carcinoma | 200 mg Q3W or 400 mg Q6W |

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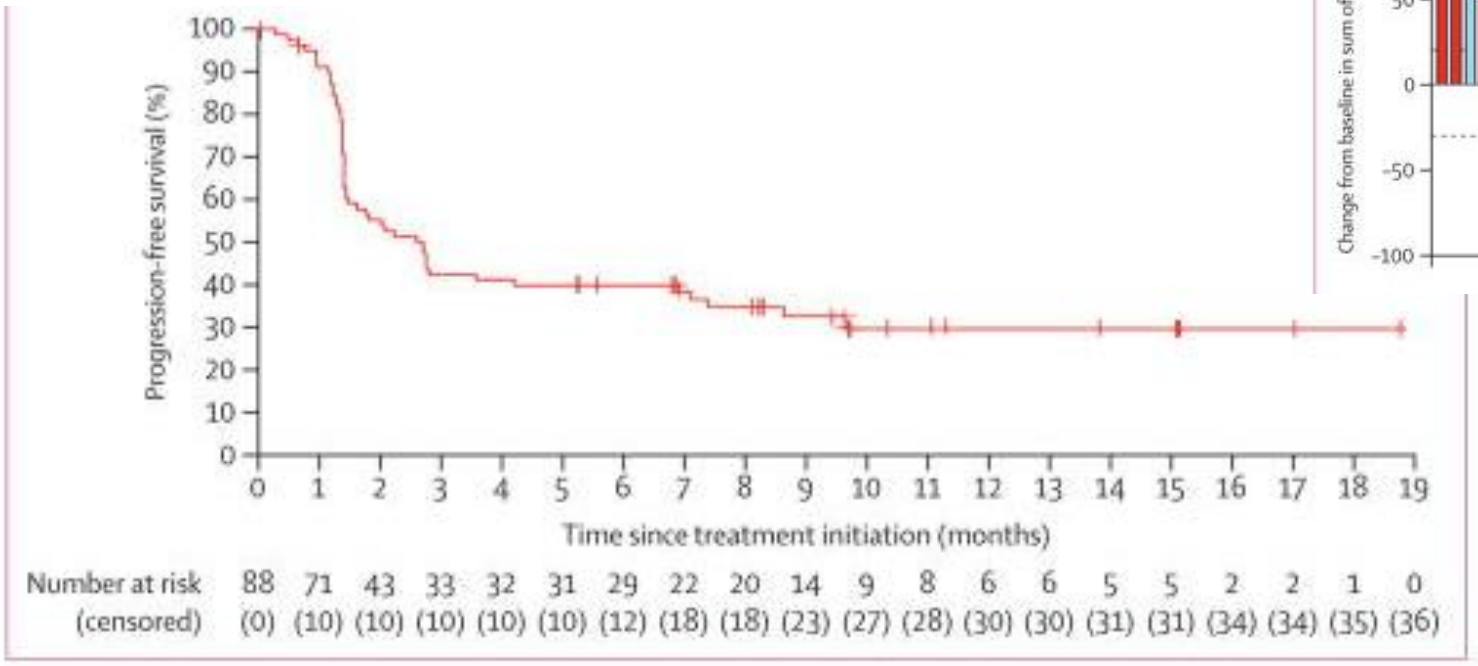
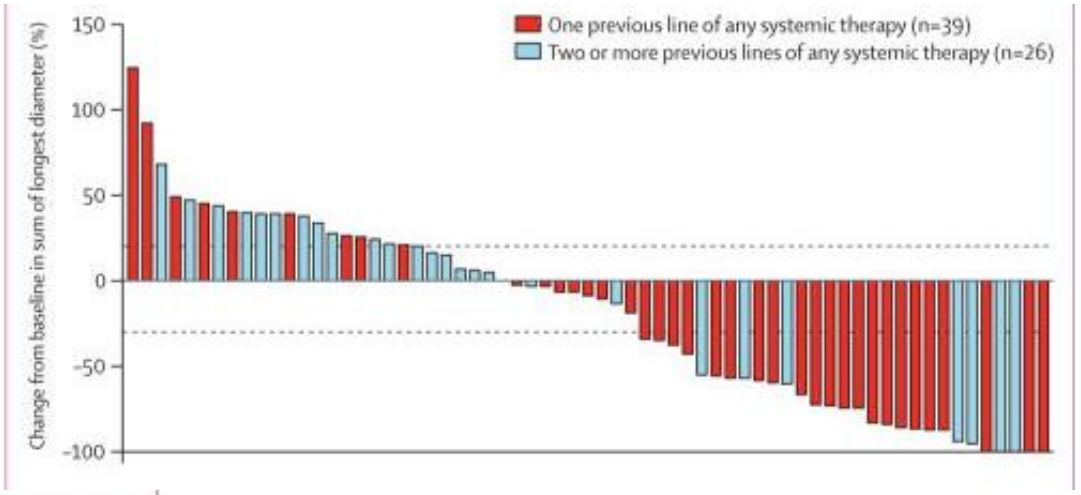
# Avelumab in 2nd-line metastatic Merkel Cell carcinoma

- 1st FDA-approved treatment for this status
- Avelumab 10 mg/kg Q2W
- ORR: 32%, CR: 9%; PR: 23%




Kaufman, Lancet Oncol 2016.

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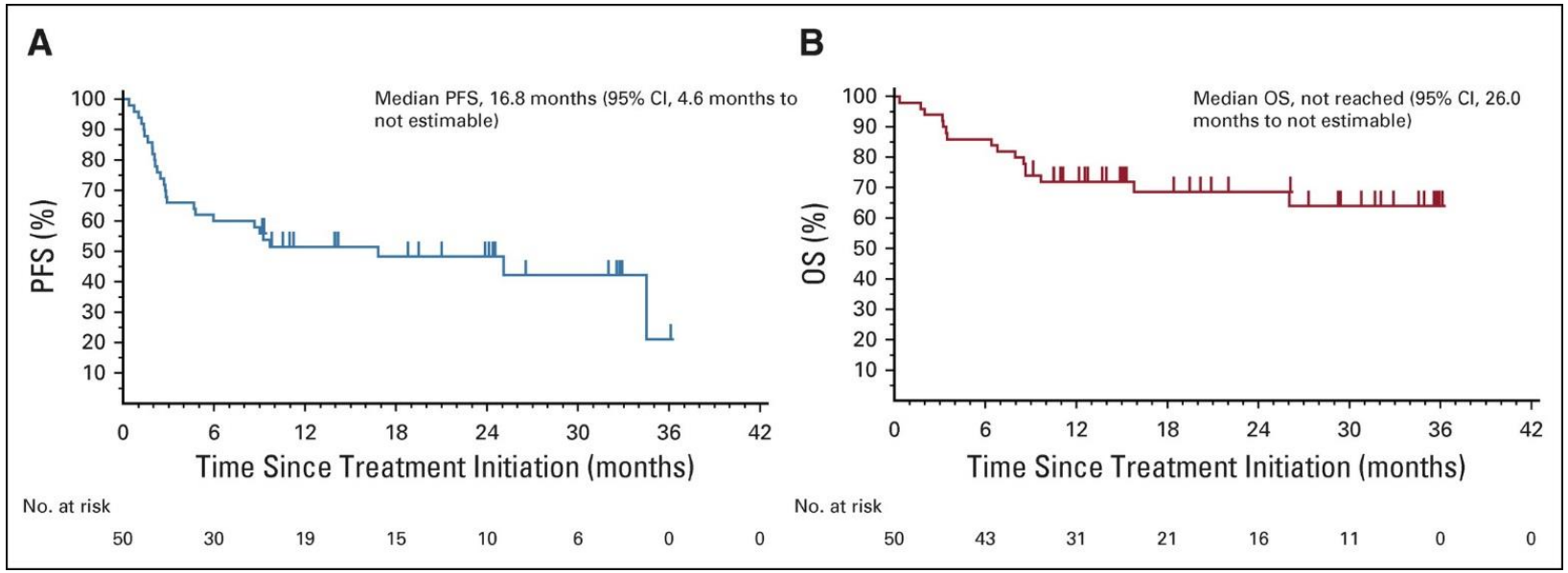
# Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%




Nghiem, J Clin Oncol 2019.

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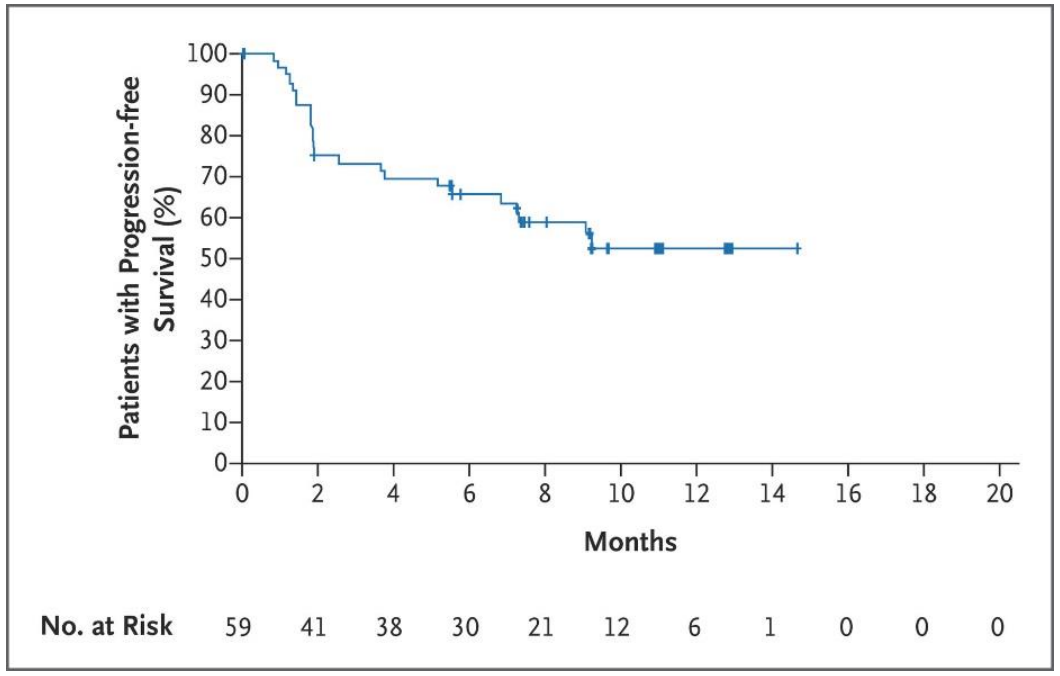
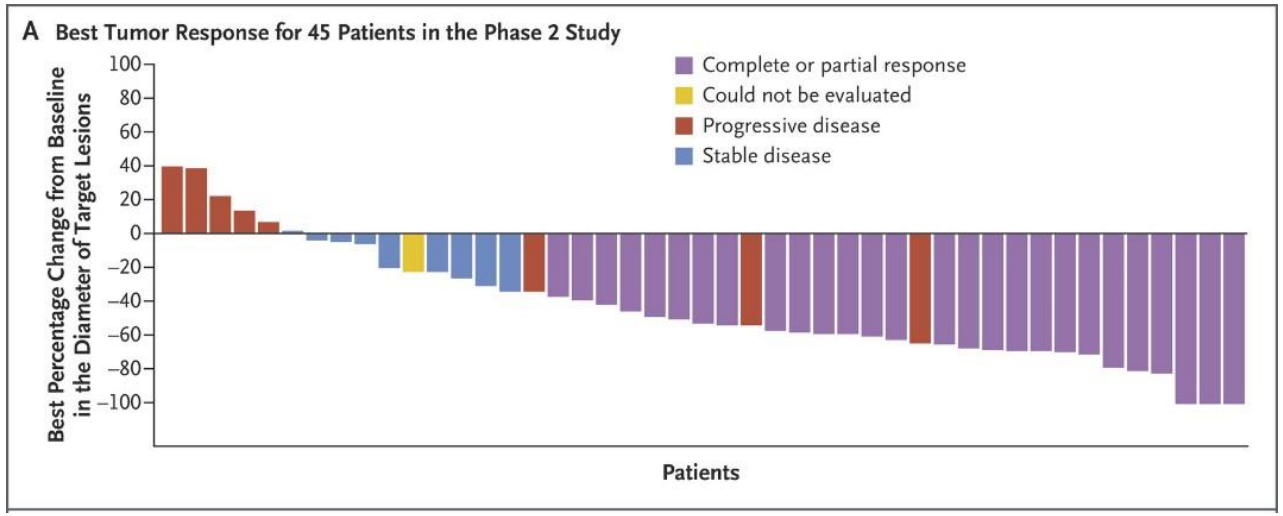
# Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

- Cemiplimab 3mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response




Migden, NEJM 2018.

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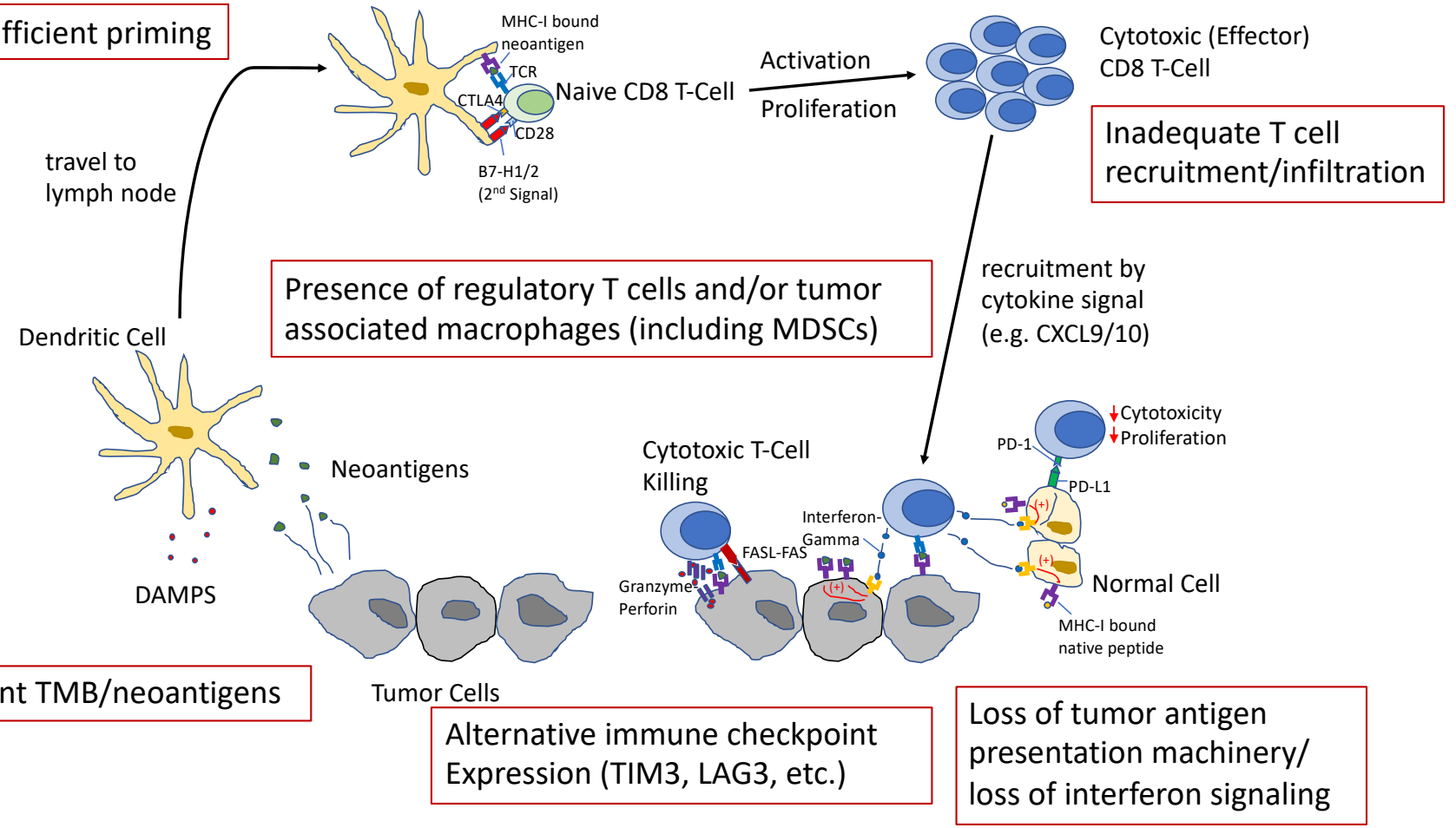
# Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?




Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

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# Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

**Combination therapy**

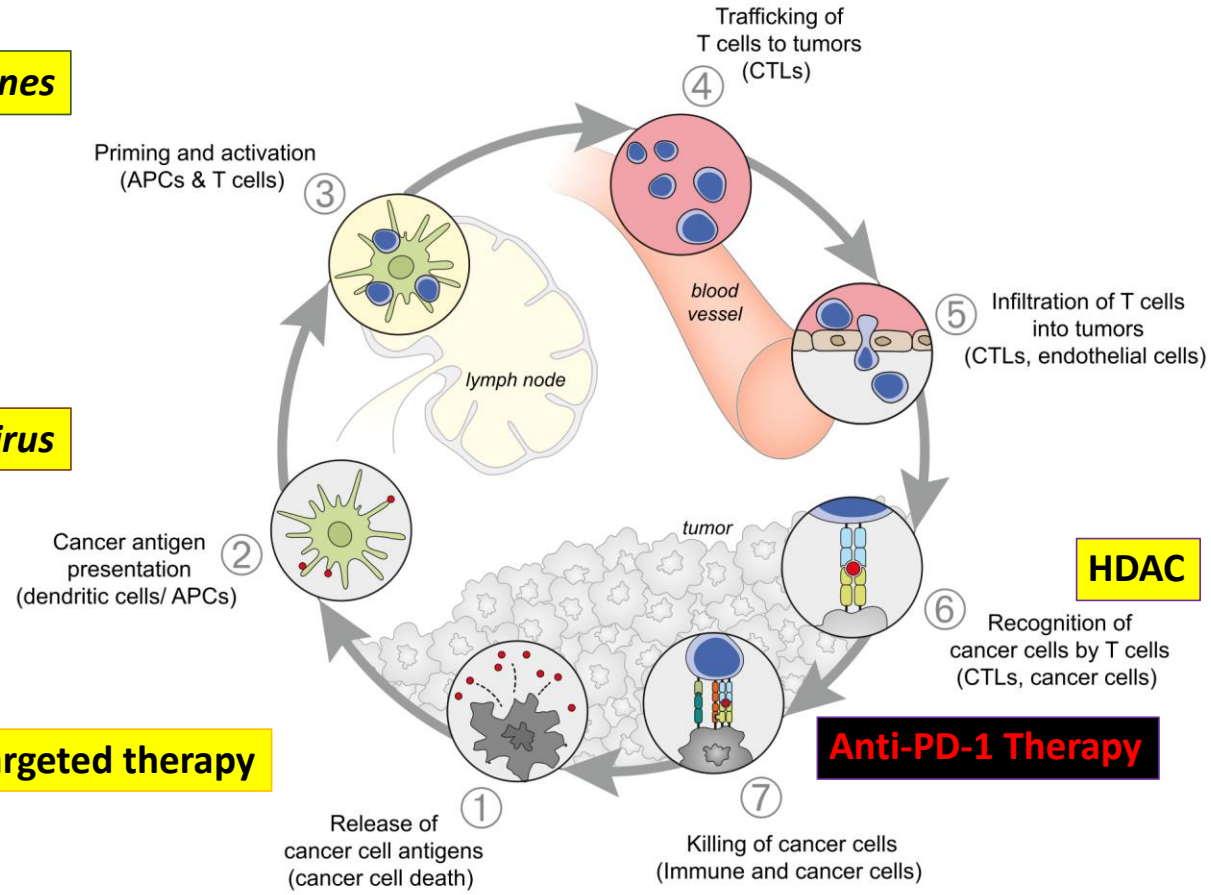
***Cytokines***

***Oncolytic virus***

**Targeted therapy**

**HDAC**

**Anti-PD-1 Therapy**




Modified from Chen and Melman. Immunity 2015.

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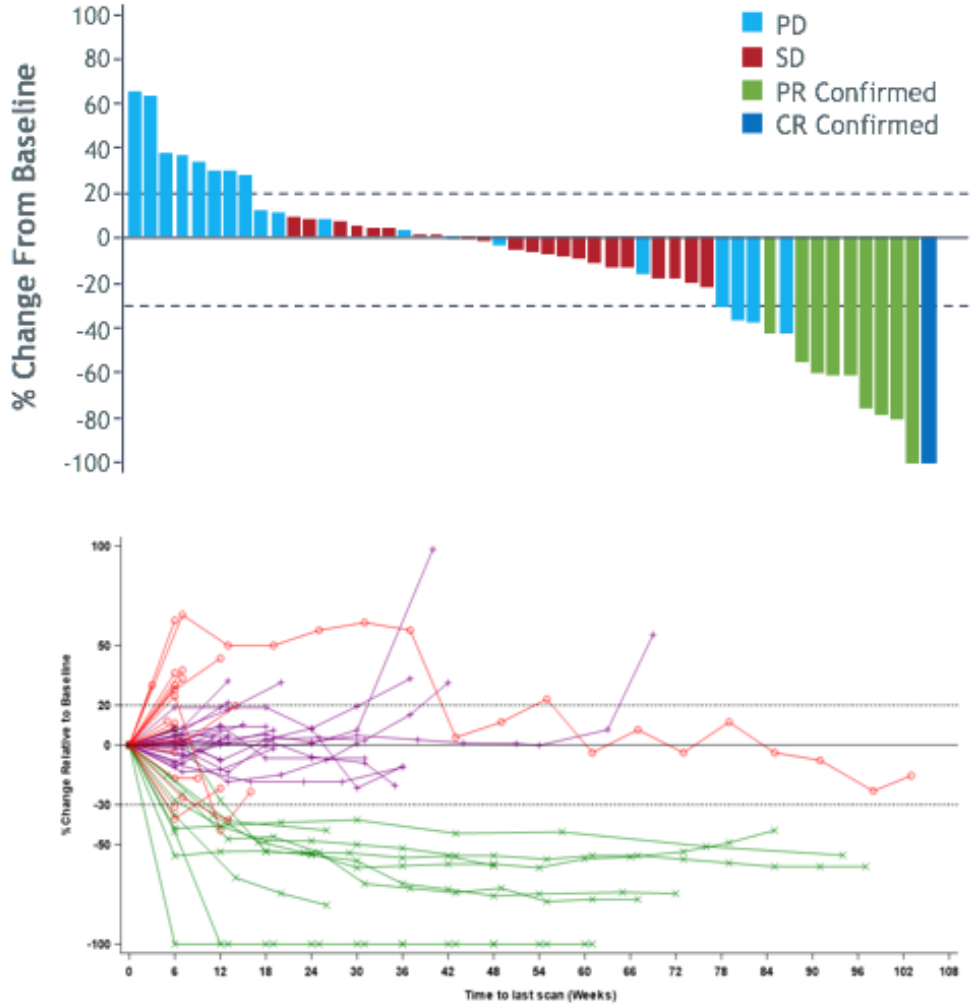
# **In development:** Combined IO with HDAC inhibitor

- Entinostat + pembrolizumab
- 19% ORR (1 CR, 9 PR)
- Median duration of response: 13 mo
- 9 additional patients with SD for >6 mo




Sullivan et al, AACR 2019.

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# Conclusions

- Melanoma was one of the foundational disease states for testing immunotherapies
- Avelumab and pembrolizumab are now approved for Merkel cell carcinoma, and cemiplimab is approved for cutaneous squamous cell carcinoma
- Combination immunotherapies may lead to higher response rates and more durable responses

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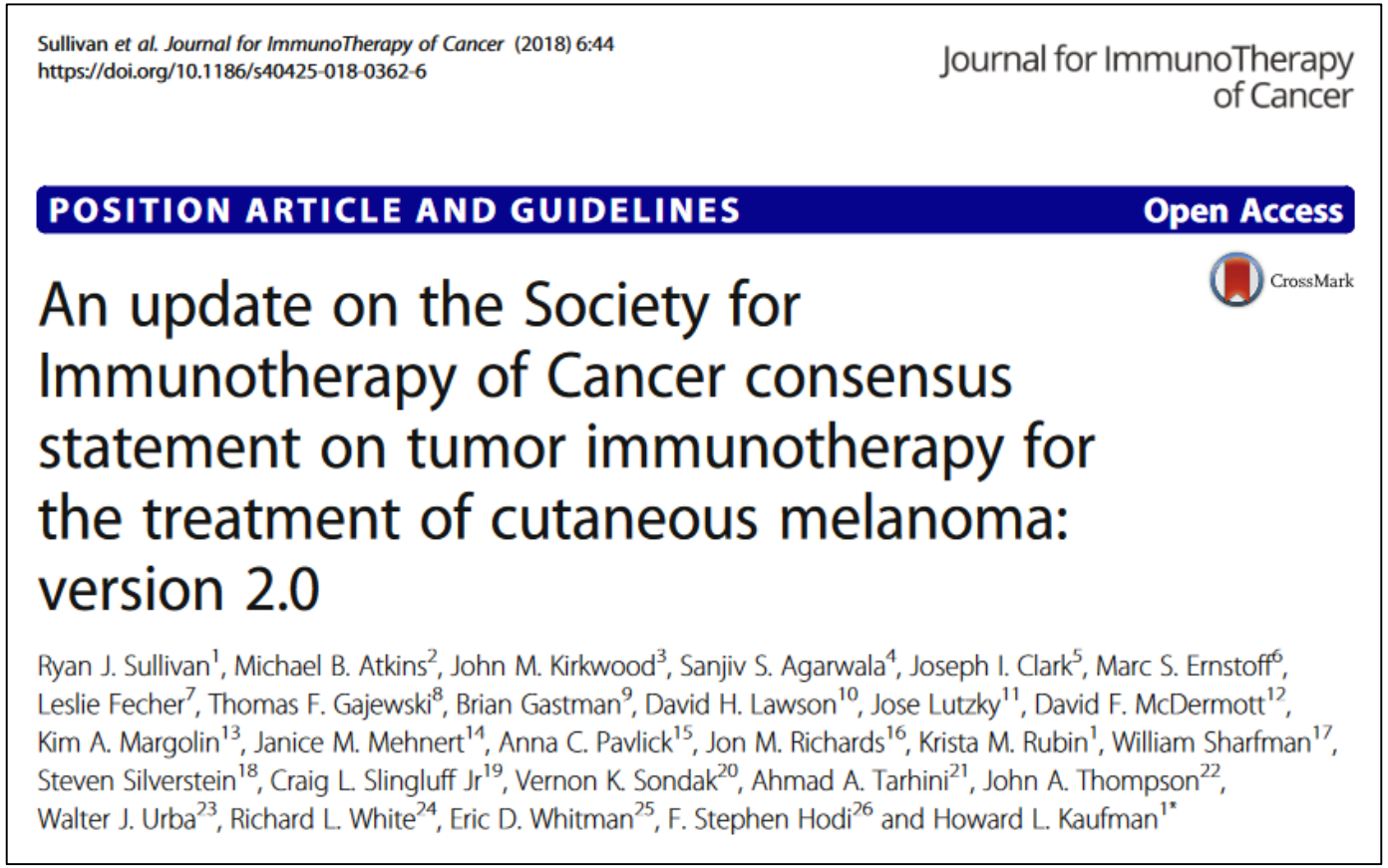
# Additional Resources



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*]

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# Case Studies

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# Case Study 1

- 75 y-o male, with history of Stage IIC melanoma of abd wall diagnosed a year earlier, presents with pathologic fracture of LUE.
- PET scan reveals multiple met foci in lungs ( 1-4 cms), and a couple of bone mets in upper and lower Exts.
- ORIF of LUE fracture reveals met melanoma
- ROS is otherwise normal.
- What other investigations, if any, are needed?

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# Case Study 1

- MRI brain reveals a single met focus, in occipital lobe.
- Molecular profile reveals WT B-RAF

What would you do next?

- 1- referral to neurosurgeon for resection
- 2-referral to radiation oncologist for brain radiosurgery
- 3-referral to radiation oncologist for Bone XRT
- 4-single agent PD1 ab
- 5-combination of PD1 and CTLA ab

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# Case Study 1

- He receives ipilimumab 3 mg/kg and nivolumab 1 mg/kg and after 2 doses MRI brain reveals shrinkage of the single brain lesion.
- He is seen by radiation oncologist and receives palliative XRT dose to the LUE for pain control.
- After 3 doses of ipi/ nivo he develops grade 4 diarrhea. What would you do?
- 1-immodium and hydration.
- 2-prednisone I mg/kg po.
- 3-IV steroids such as solumedrol.
- 4- infliximab IV

And after he recovers would you continue therapy or not?

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# Case Study 2

- 70 y-o male presents with met neoplasm to R orbit ( ptosis) , and multiple subcutaneous , peritoneal cavity and soft tissue lesions.
- Bx reveals met melanoma of unknown primary.
- Molecular analysis uncovers B-RAF V600E mutation.
- MRI brain reveals a single 7 mm asymptomatic lesion.
- He is referred to radiation oncology and receives brain radiosurgery in a single dose.
- What would you do next?

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# Case Study 2

- 1- B-RAF inhibitor as single agent
- 2-PD1 ab as a single agent
- 3- combination of B-raf and Mek inh
- 4- combination of ipilimumab and nivolumab

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# Case Study 2

- He receives dabrafenib and trametinib and achieves a complete response,
- After 16 months he slowly progresses in one soft tissue location in lower back area.
- The rest of lesions continue to be in remission.
- What are the mechanisms of resistance to B-RAF inh?
- He undergoes XRT to that location and and starts ipilimumab and nivolumab for 4 doses following by maintenance nivolumab.
- He develops hematuria and is diagnosed with superficial bladder ca while on maintenance nivolumab.
- Pd1 ab is placed on hold and he receives BCG.
- Pd1 maintenance is subsequently resumed and he continues for a year with no progression.

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