Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

# Immunotherapy for the Treatment of Skin Cancers

Evan Hall, MD MPhil

Assistant Professor, University of Washington

Assistant Member, Fred Hutchinson Cancer Research Center

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

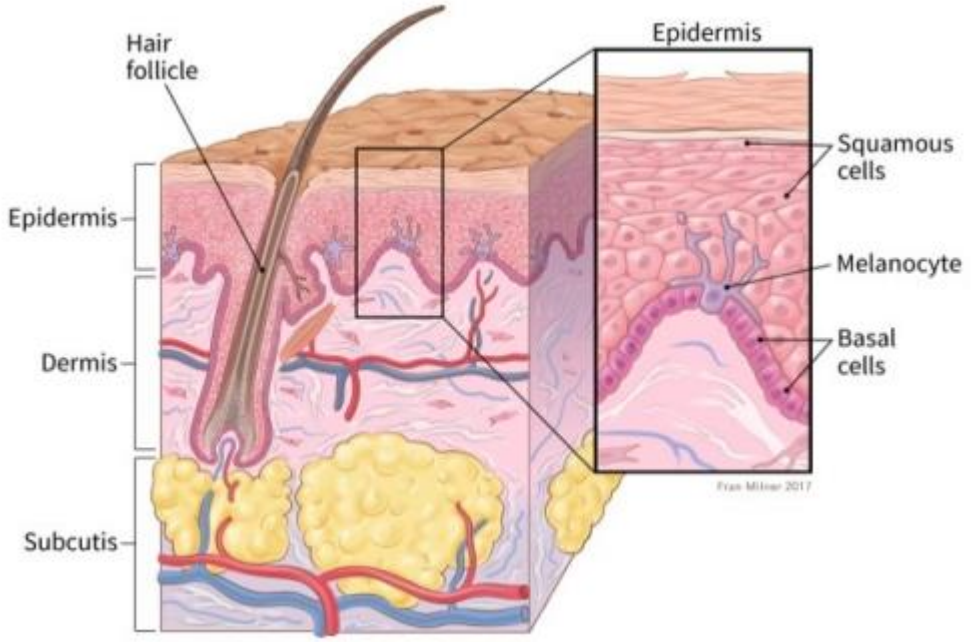
Society for Immunotherapy of Cancer

# Disclosures

- Consulting Fees: Cancer Support Community
- I will be discussing non-FDA approved indications during my presentation.

# Background

- Skin cancer is the most common type of cancer
- Three most common types of skin cancers:
  - Basal cell carcinoma (5.4 million cases in USA in 2020)
  - Squamous cell carcinoma (3.3 million cases in 2020)
  - Melanoma (~100,000 cases in USA in 2020)
- Melanoma was one of the foundational disease states for testing immunotherapies




Cancer.org

# Approved cytokines in melanoma

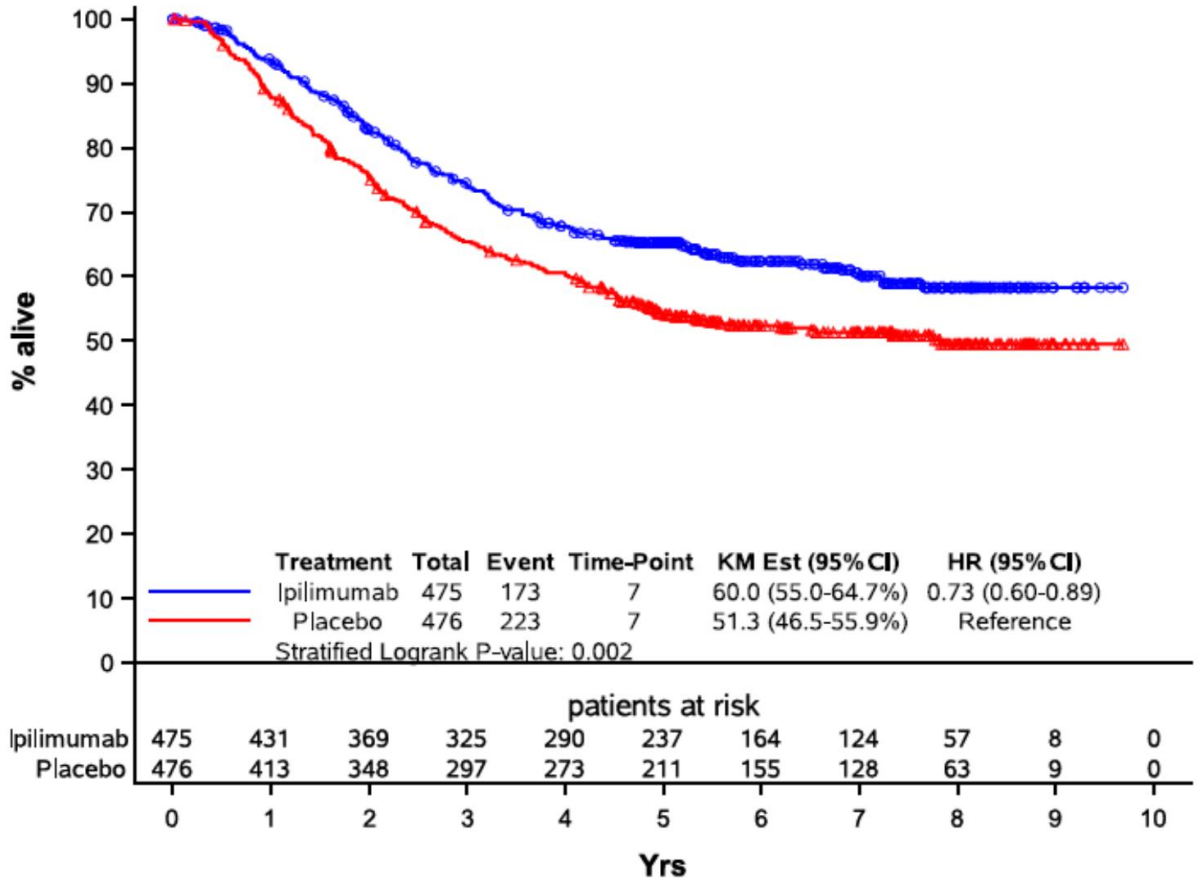
| Drug | Approved | Indication | Dose |
|---|---|---|---|
| High-dose interferon alfa-2b | 1995 | Adjuvant – high risk for systemic recurrence | Induction: 20m IU/$m^2$ IV 5x/wk for 4 wks<br>Maintenance: 10m IU/$m^2$ s.c. 3x/wk for 48 wks |
| Interleukin-2 (Aldesleukin) | 1998 | Stage IV | 600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per course |
| Pegylated Interferon alfa-2b (Sylatron) | 2011 | 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 |

# 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 |

# 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



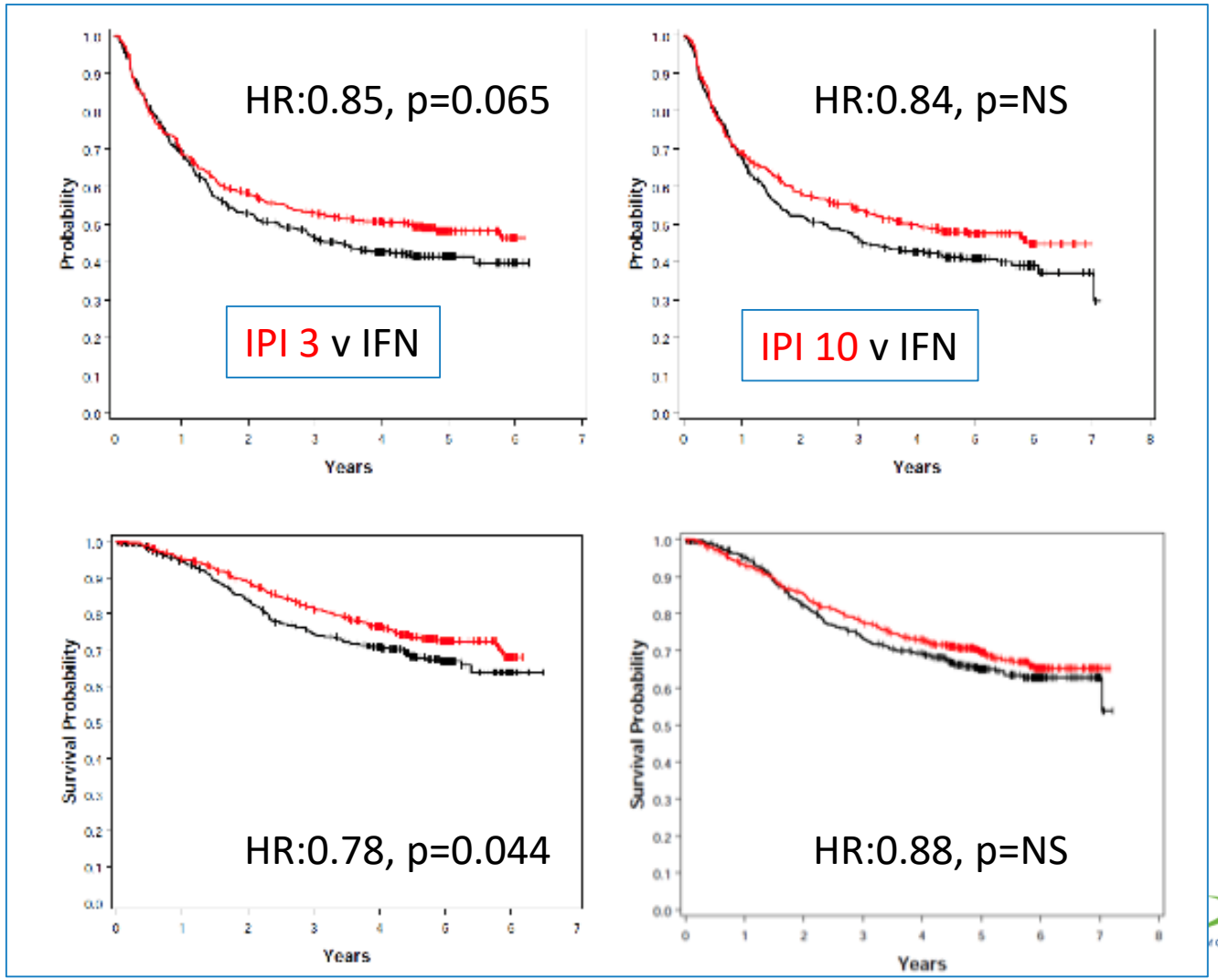

Eggermont, Eur J Can 2019.

# 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”
  - IPI 3 better tolerated than IPI 10

RFS

OS




Tarhini, ASCO Annual Meeting 2019, Tarhini, JC0 2020.

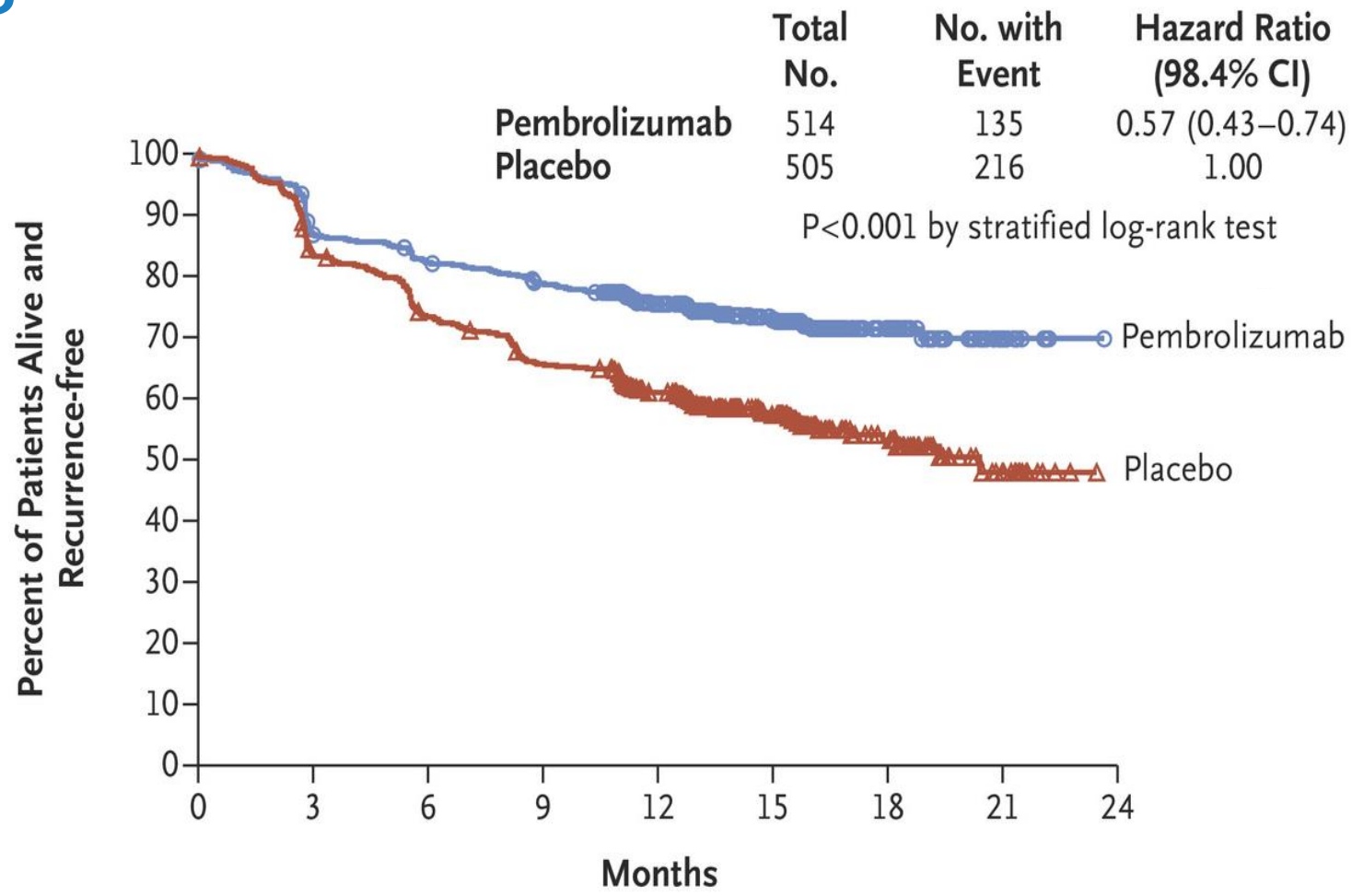
# Approved checkpoint inhibitors in melanoma

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Pembrolizumab | 2014 | Advanced/unresectable melanoma with progression after other therapy | 200 mg Q3W* or 400 mg Q6W |
| | 2015 | 1st line unresectable/metastatic melanoma | 200 mg Q3W* or 400 mg Q6W |
| | 2019 | Adjuvant therapy of melanoma following complete resection | 200 mg Q3W or 400 mg Q6W |

*Original approvals were 2 mg/kg Q3W – updated to flat dosing regimen

# 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)
  - 36 mo update at ASCO 2020 – HR for RFS 0.56

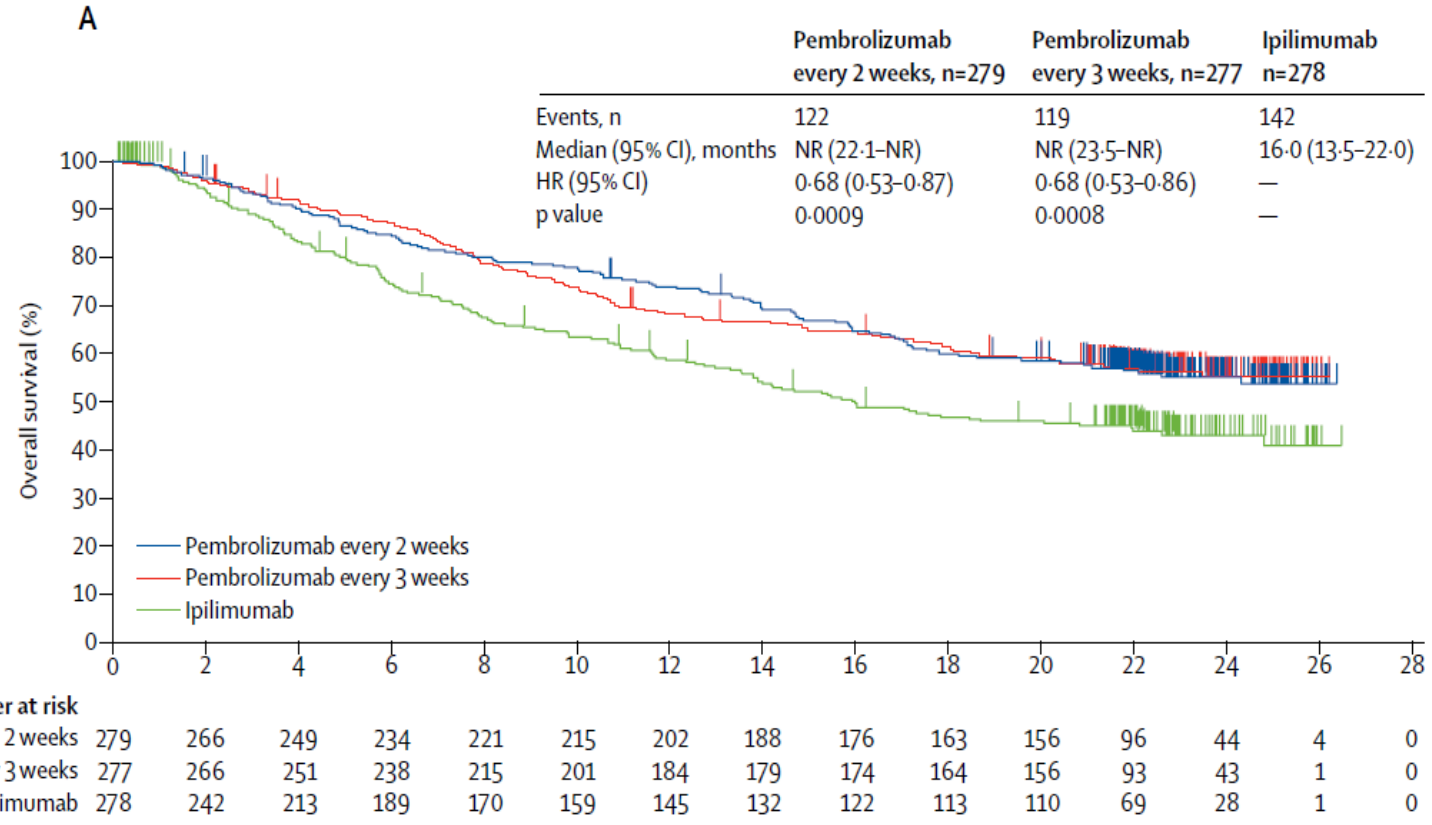



Eggermont, NEJM 2018.

# Pembrolizumab in Unresectable/Metastatic Melanoma

## Phase III KEYNOTE-006 Trial

- KEYNOTE-006 (NCT01866319)
- Pembro (10 mg/kg at 2 dosing intervals) vs ipilimumab 3 mg/kg x 4 doses
- Pembro significantly improved OS and PFS vs Ipi
- Dosing interval for pembro did not appear to impact efficacy



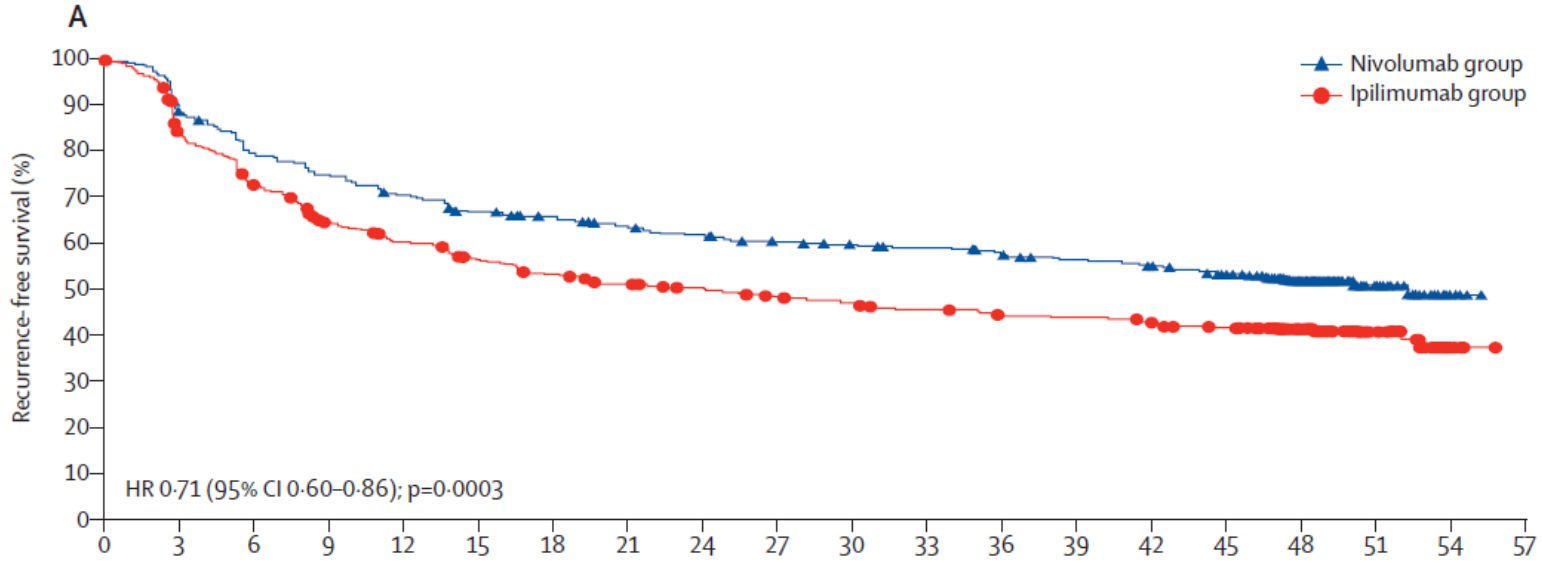

Schachter, Lancet 2017.

# 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 | | | |

# 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




Ascierto, Lancet Oncol 2020

# Approved checkpoint inhibitors in melanoma

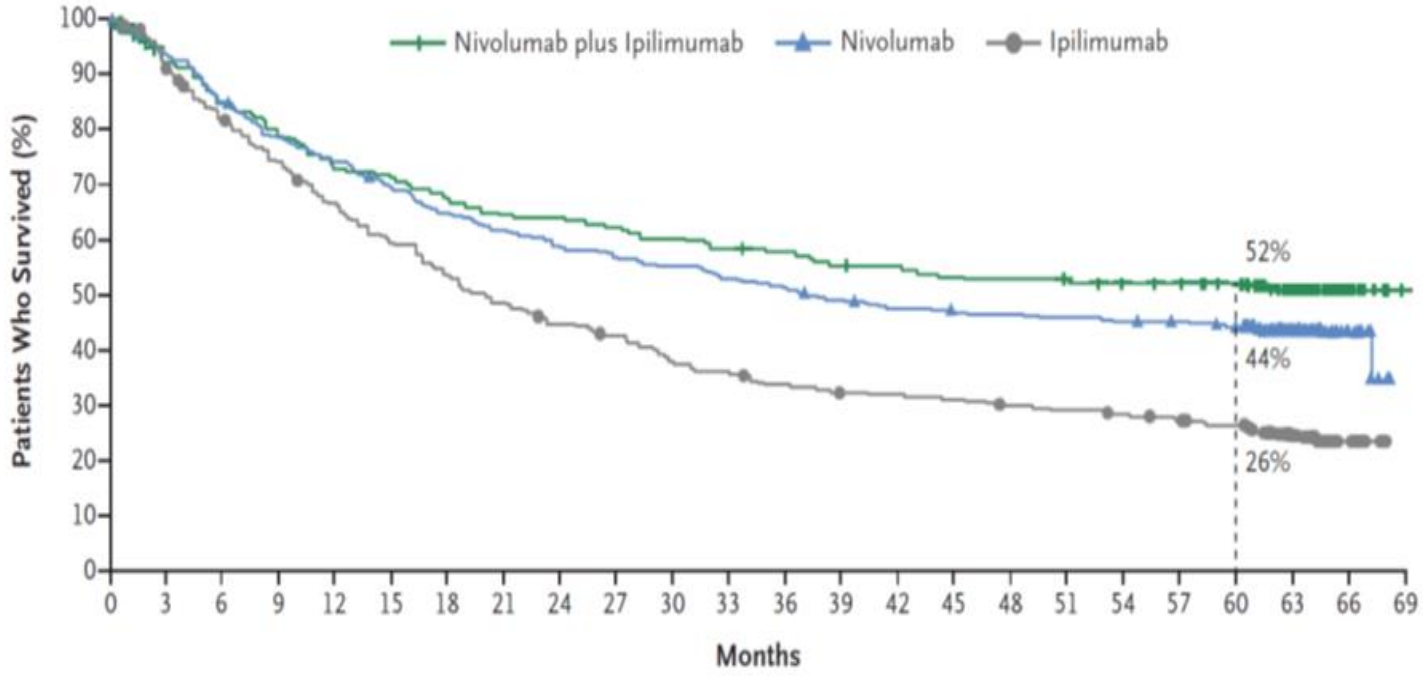
| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Nivolumab + Ipilimumab | 2015 | BRAF V600 WT unresectable/metastatic melanoma | 1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W |
| | 2016 | BRAF V600 WT or mutant unresectable/metastatic melanoma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

# Ipilimumab + Nivolumab in Stage III/IV Melanoma

CHECKMATE-067 (NCT01844505)

Nivo 1 mg/kg + Ipi 3 mg/kg x 4 doses --> nivolumab 3 mg/kg q2wks
vs.
Nivo 3mg/kg q2wks
vs
Ipi 3 mg/kg q3wks x 4 doses

Both Nivo + Ipi and Nivo were superior to Ipi for OS.

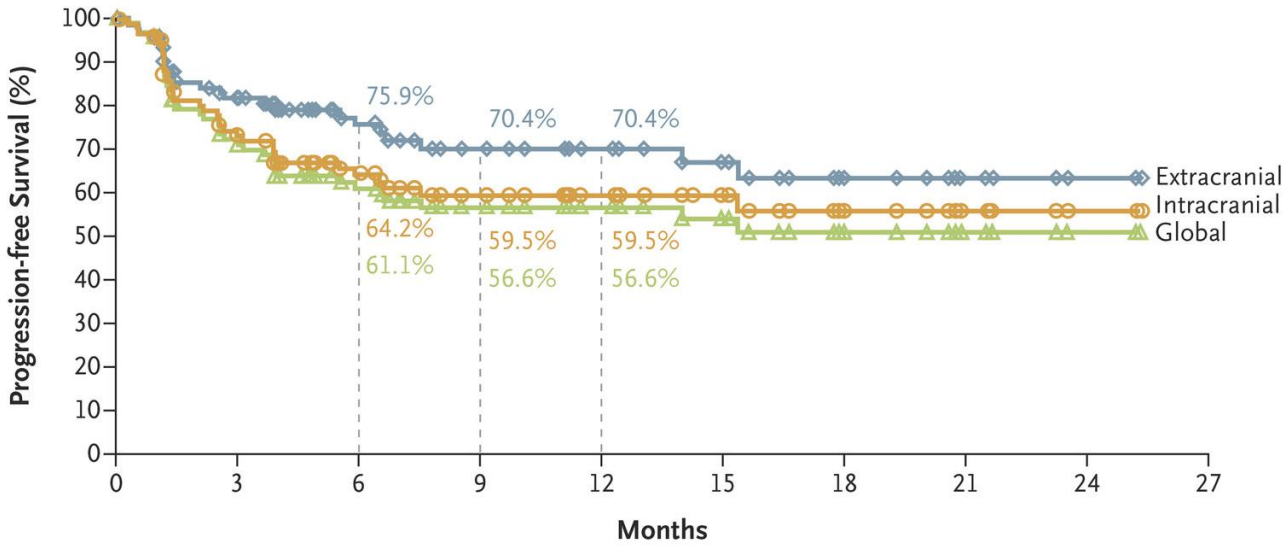



| No. at Risk | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab plus ipilimumab | 314 | 292 | 265 | 248 | 227 | 222 | 210 | 201 | 199 | 193 | 187 | 181 | 179 | 172 | 169 | 164 | 163 | 159 | 157 | 155 | 150 | 92 | 14 | 0 |
| Nivolumab | 316 | 292 | 266 | 245 | 231 | 214 | 201 | 191 | 181 | 175 | 171 | 164 | 158 | 150 | 145 | 142 | 141 | 139 | 137 | 135 | 130 | 78 | 14 | 0 |
| Ipilimumab | 315 | 285 | 253 | 227 | 203 | 181 | 163 | 148 | 135 | 128 | 113 | 107 | 100 | 95 | 94 | 91 | 87 | 84 | 81 | 77 | 73 | 36 | 12 | 0 |

Larkin, NEJM 2019.

# 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.

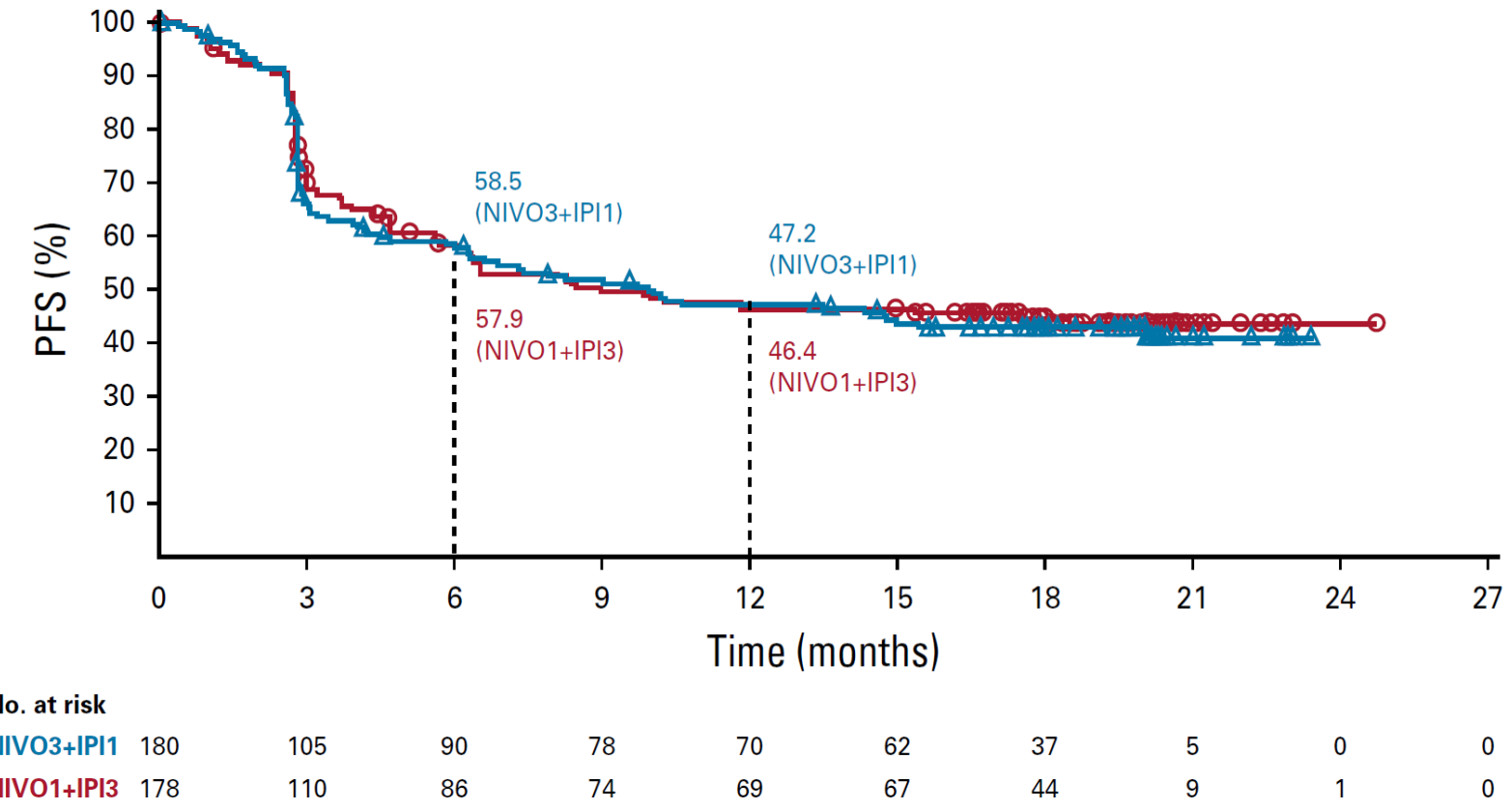
# Nivolumab + Ipilimumab in Metastatic Melanoma: Alternate Dosing

CHECKMATE-511 (NCT02714218)

Standard melanoma dosing:
Nivo 1 mg/kg + Ipi 3 mg/kg
vs
Alternate melanoma dosing:
Nivo 3 mg/kg + Ipi 1 mg/kg

1° outcome: Rate of G3+ AEs

G3+ AEs significantly lower in alternate dosing (34% vs 48%)




Lebbe, JCO 2019

# Combination immunotherapy + BRAF/MEKi in metastatic melanoma

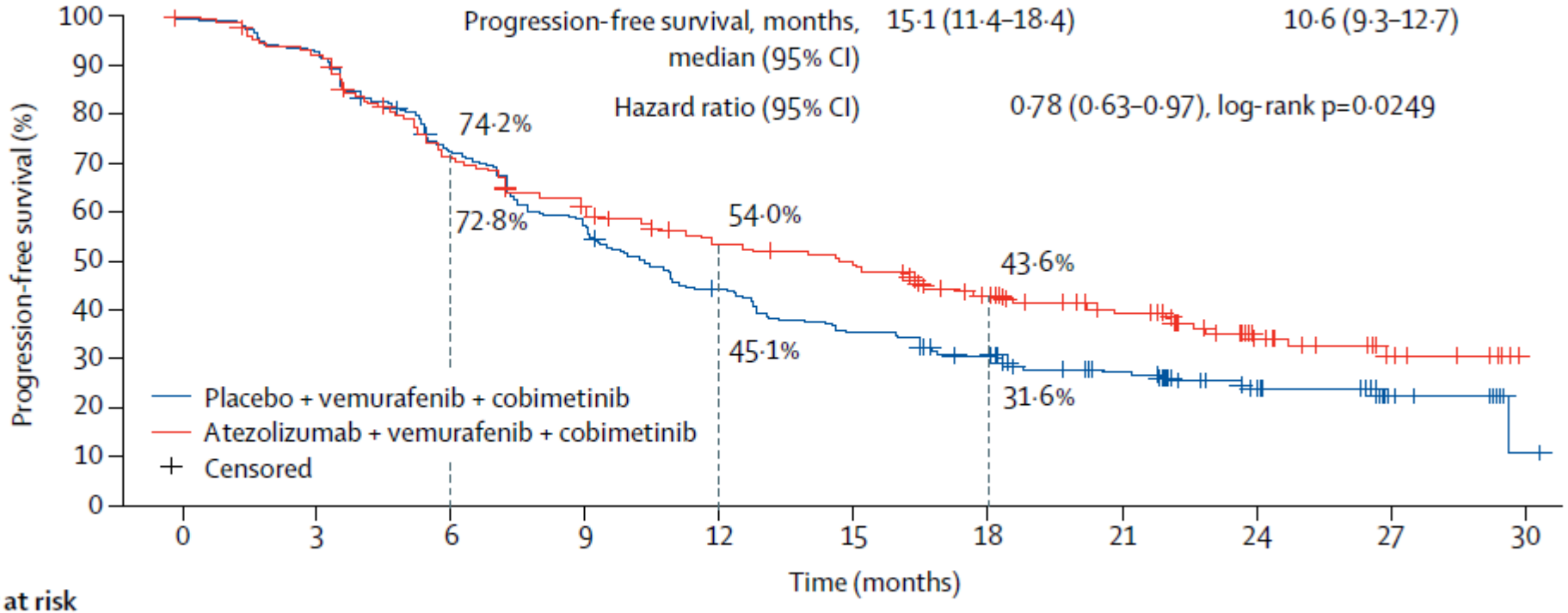
- IMSPIRE150 (NCT02908672)
  - Atezolizumab + cobimetinib + vemurafenib vs placebo + cobimetinib + vemurafenib
  - Both arms had 28 day treatment with cobimetinib + vemurafenib only, then began atezolizumab or placebo.
  - Improvement in PFS shown for the Atezo + Vem + Cobi arm
  - OS data is not mature

- FDA approval given to this triplet regimen on July 30, 2020 for firstline metastatic/unresectable melanoma

Gutzmer, Lancet 2020

# IMSPIRE150: Atezolizumab + Vemurafenib + Cobimetinib

| | Atezolizumab + vemurafenib + cobimetinib | Placebo + vemurafenib + cobimetinib |
|---|---|---|
| Progression-free survival, months, median (95% CI) | 15·1 (11·4–18·4) | 10·6 (9·3–12·7) |
| Hazard ratio (95% CI) | 0·78 (0·63–0·97), log-rank p=0·0249 | |




| Number at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo + vemurafenib + cobimetinib | 258 | 230 | 179 | 143 | 107 | 86 | 71 | 51 | 27 | 11 | 1 |
| Atezolizumab + vemurafenib + cobimetinib | 256 | 229 | 174 | 149 | 123 | 114 | 90 | 66 | 34 | 11 | |

Gutzmer, Lancet 2020

# Immunotherapy + BRAF/MEK inhibitor combination therapy

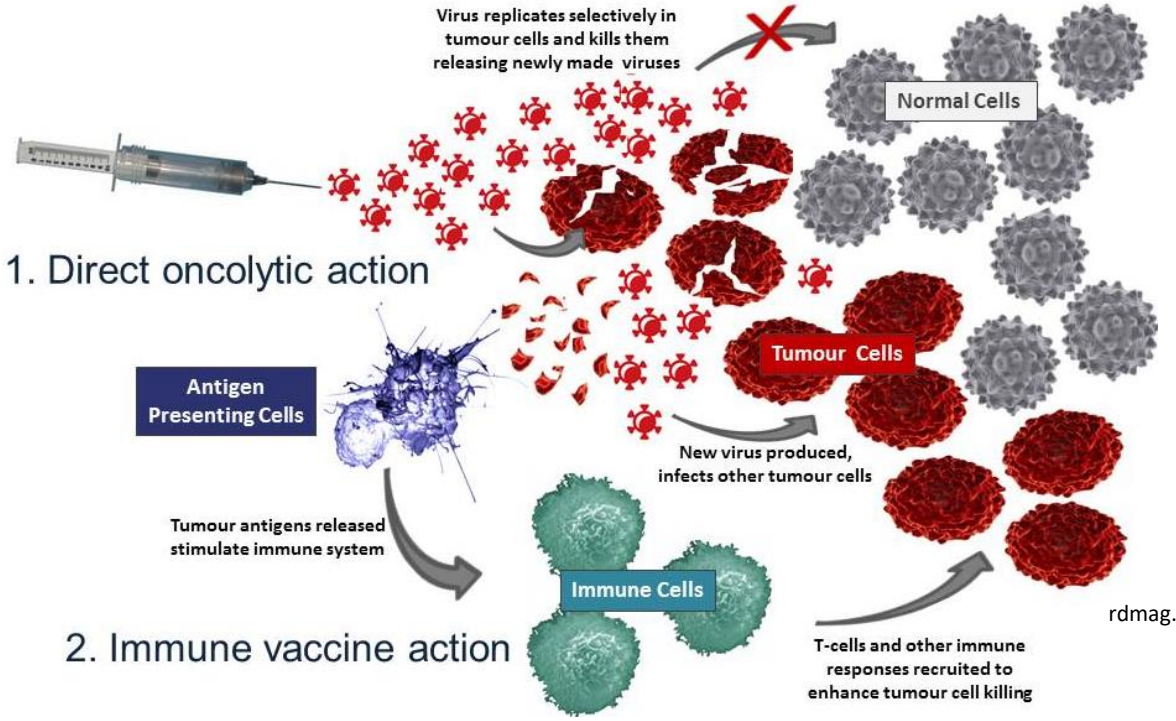
- Selected ongoing BRAF/MEK/PD-1 combination trials
  - COMBI-i: Dabrafenib/trametinib/spartalizumab (investigational PD-1 Ab) vs dabrafenib/trametinib (NCT02967692)
  - KEYNOTE-022: Dabrafenib/trametinib/pembrolizumab vs dabrafenib/trametinib (NCT02130466)

# **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.

# Approved oncolytic virus in melanoma

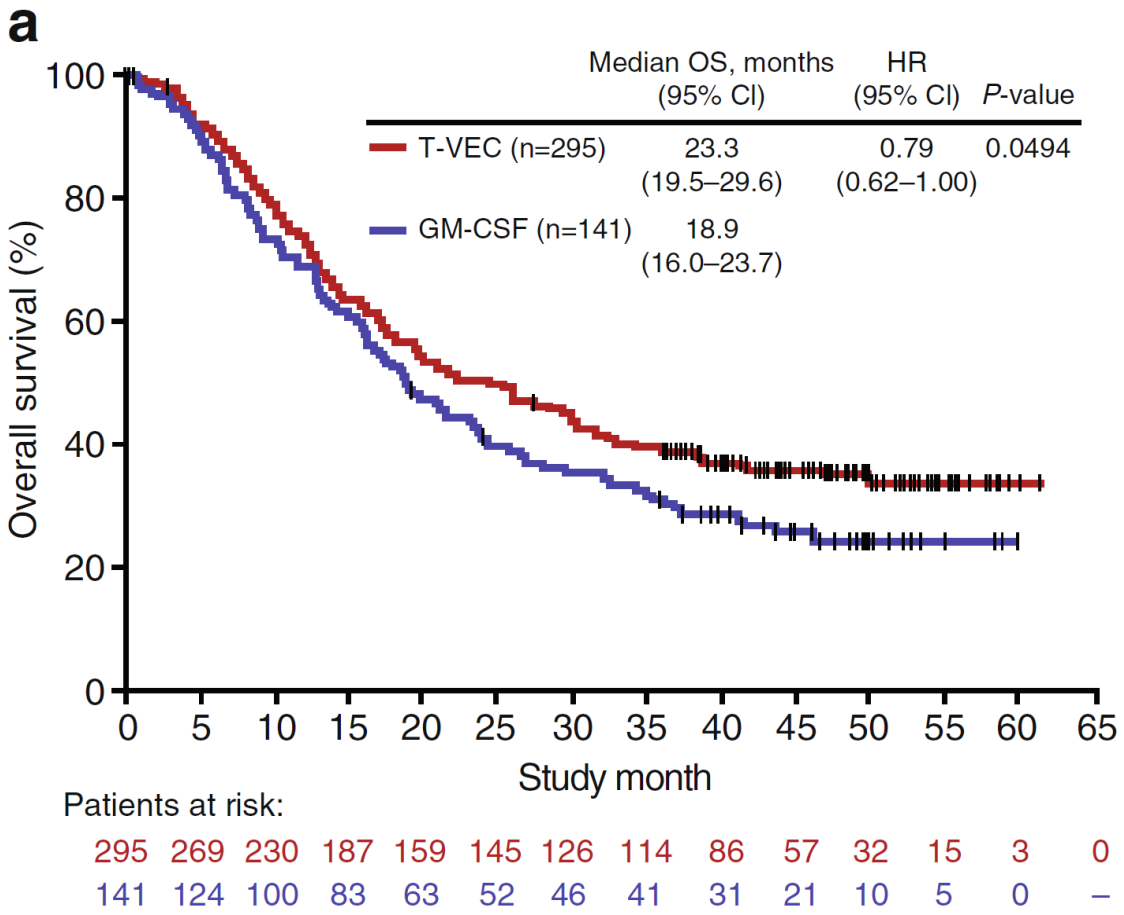



rdmag.com

| 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 |

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

- Phase III OPTiM Trial
  - NCT00769704
  - Oncolytic, genetically-engineered herpes virus
  - Intralesional T-VEC 106 pfu/mL, 108 pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF
  - Enrolled 2009-2011*
  - Durable response rate: 19.0% vs 1.4%



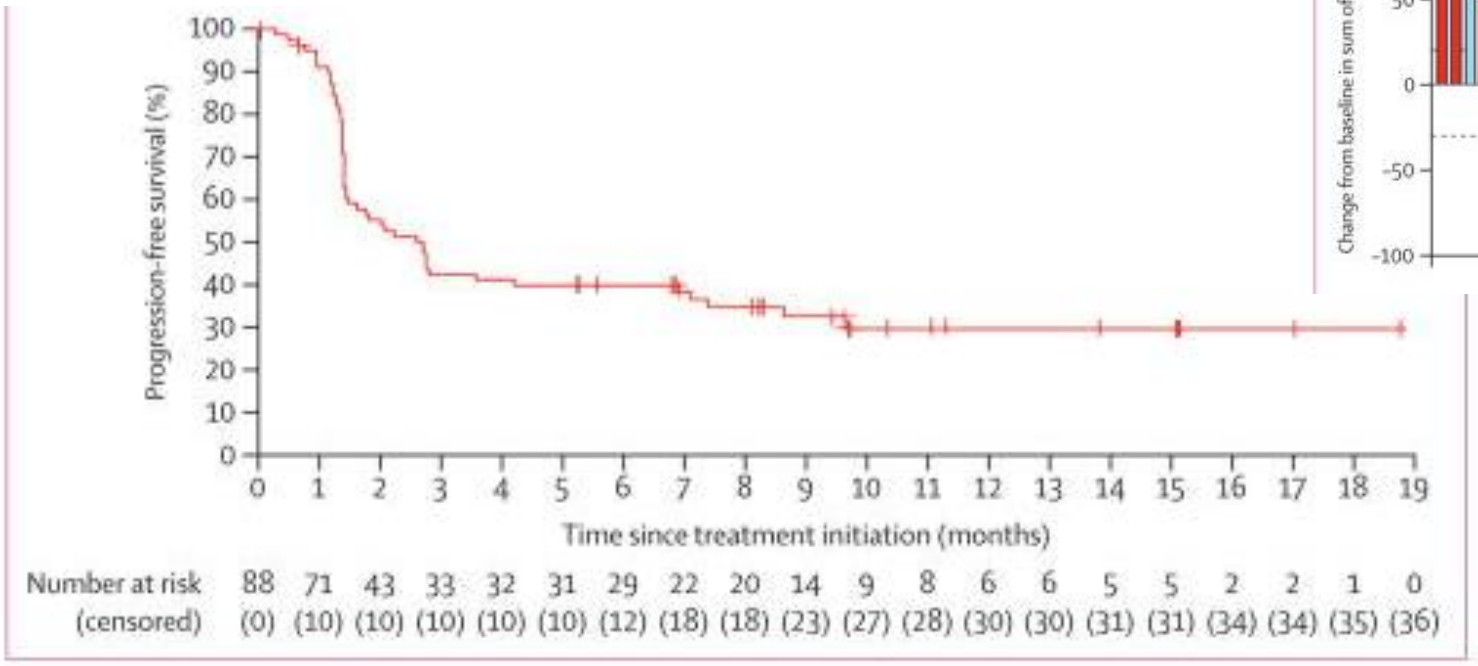

Andtbacka, JITC 2019.

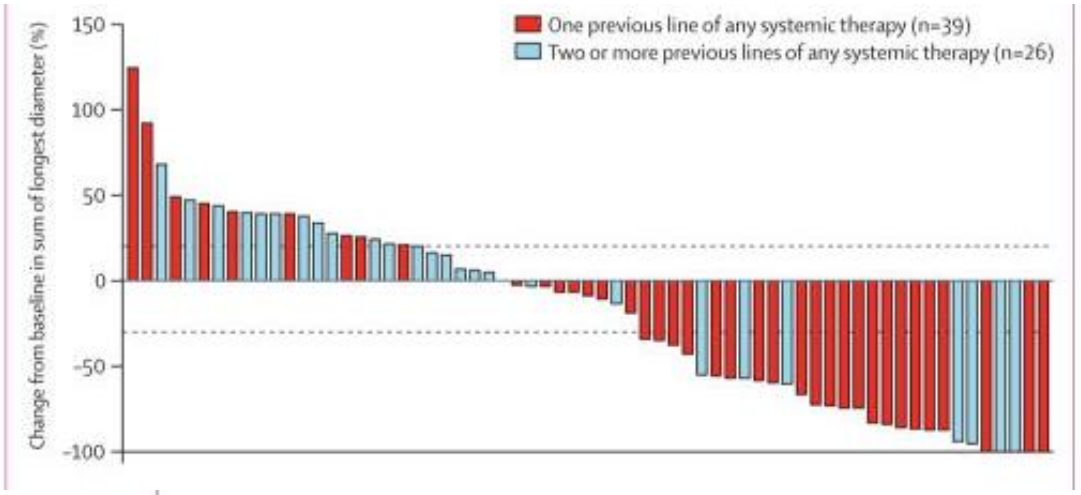
# Approved checkpoint inhibitors in other skin cancers

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| Avelumab | 2017 | Metastatic **Merkel cell carcinoma** | 800 mg Q2W + premedication (first 4 cycles) |
| Pembrolizumab | 2018 | Advanced/metastatic **Merkel cell carcinoma** | 200 mg Q3W or 400 mg Q6W |
| | 2020 | Metastatic **cutaneous squamous cell carcinoma**, not candidate for curative therapies | |
| Cemiplimab-rwlc | 2018 | Metastatic **cutaneous squamous cell carcinoma**, not candidate for curative therapies | 350 mg Q3W |

# 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%

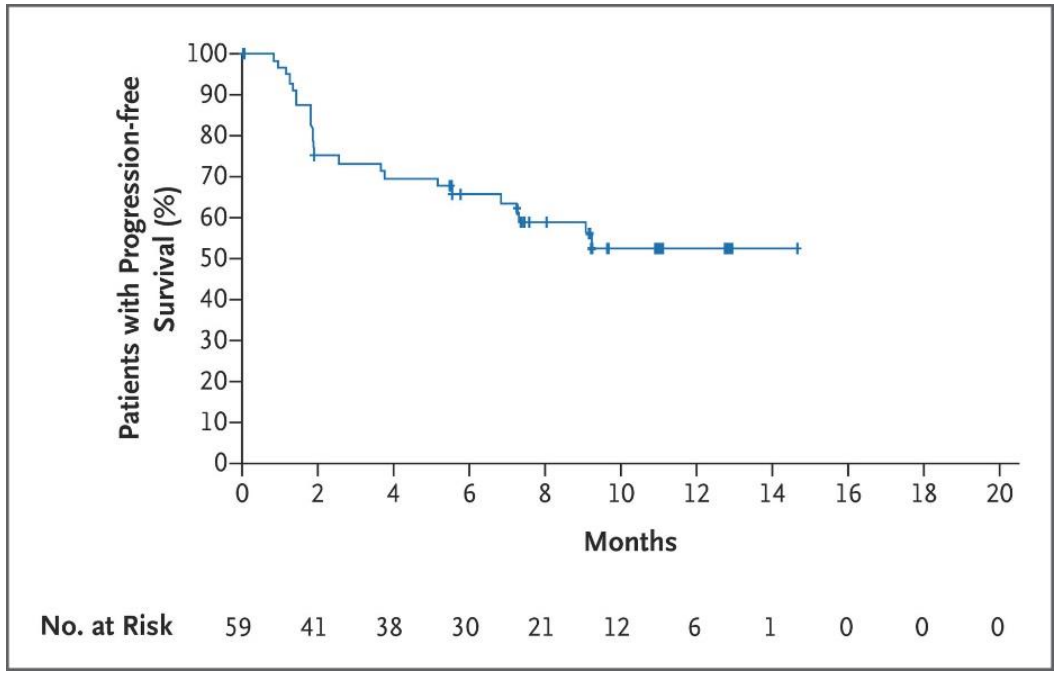


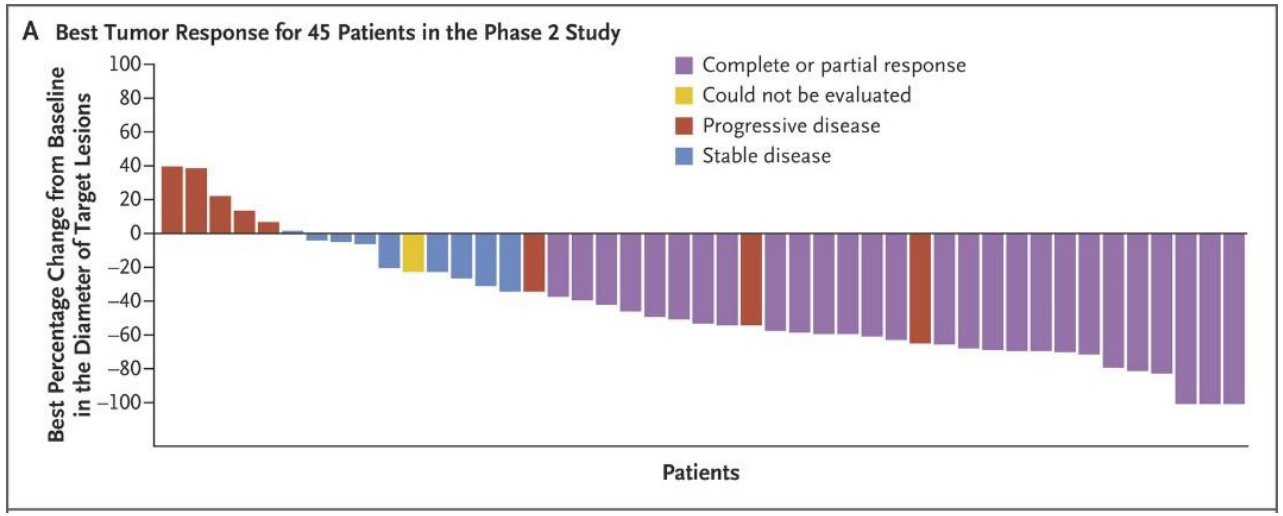




Kaufman, Lancet Oncol 2016.

# 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

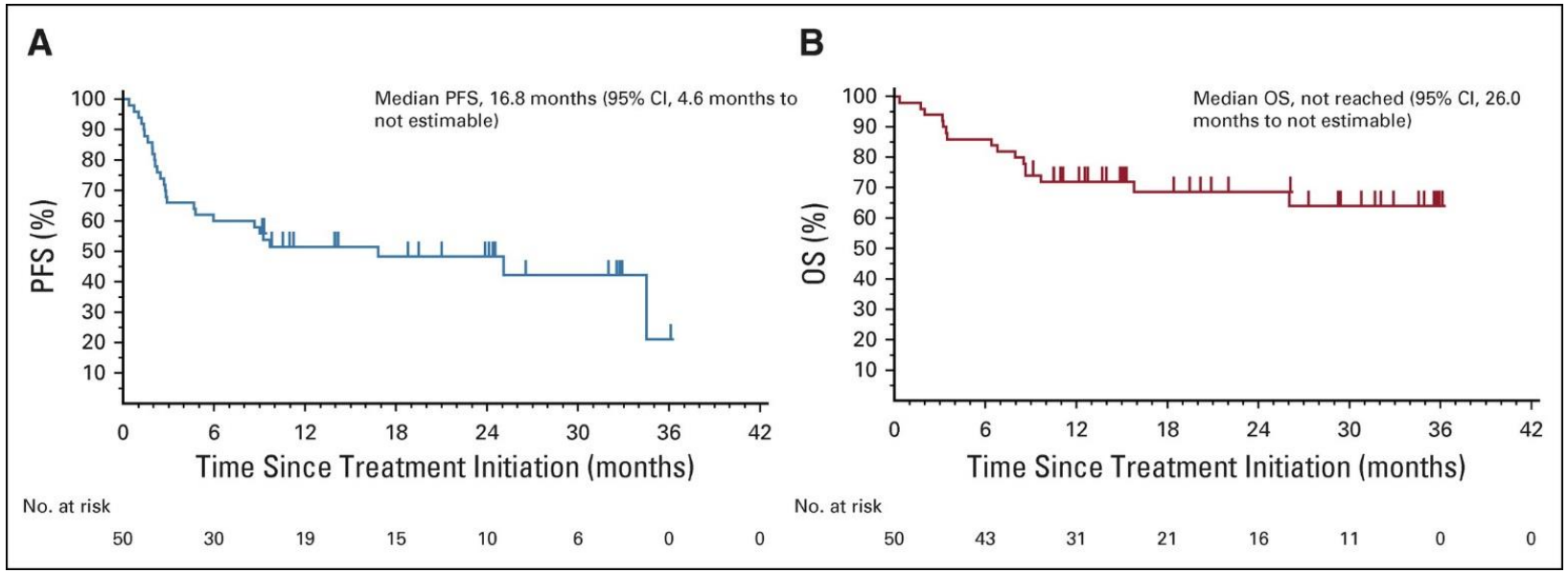



Migden, NEJM 2018.

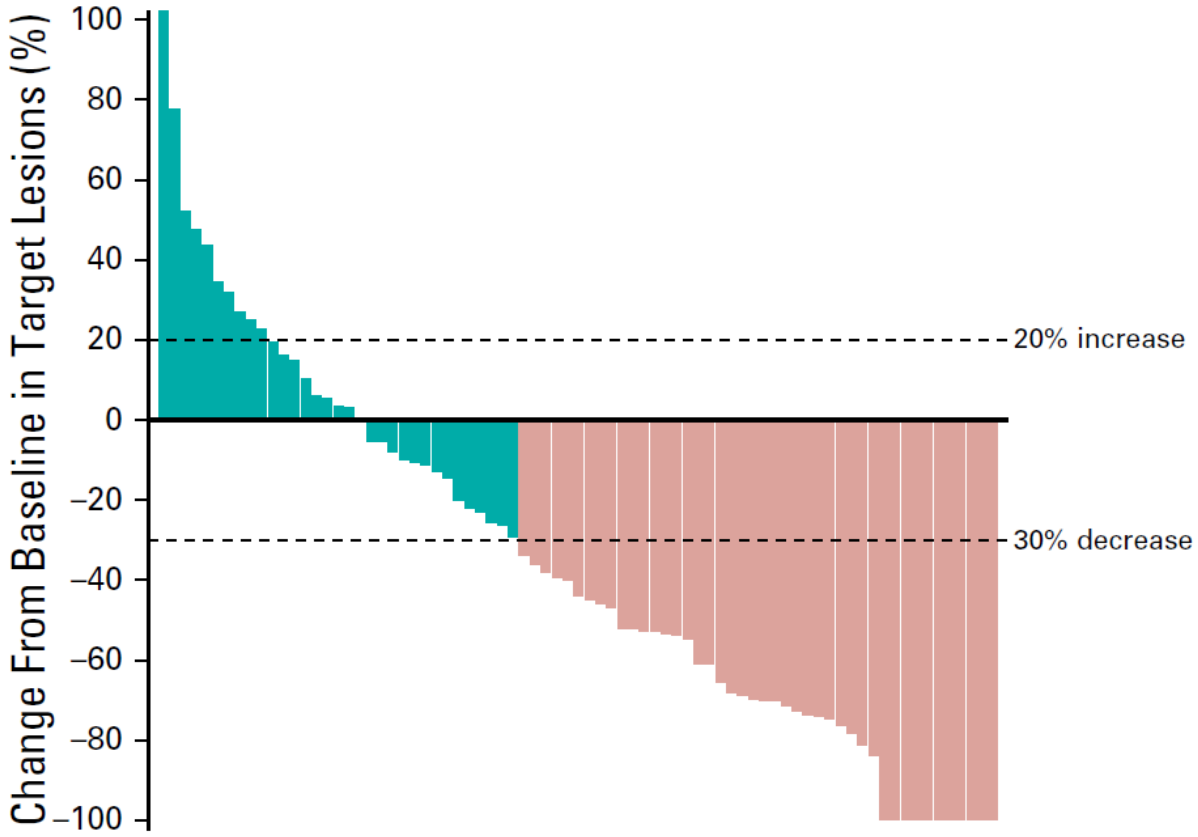
# Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

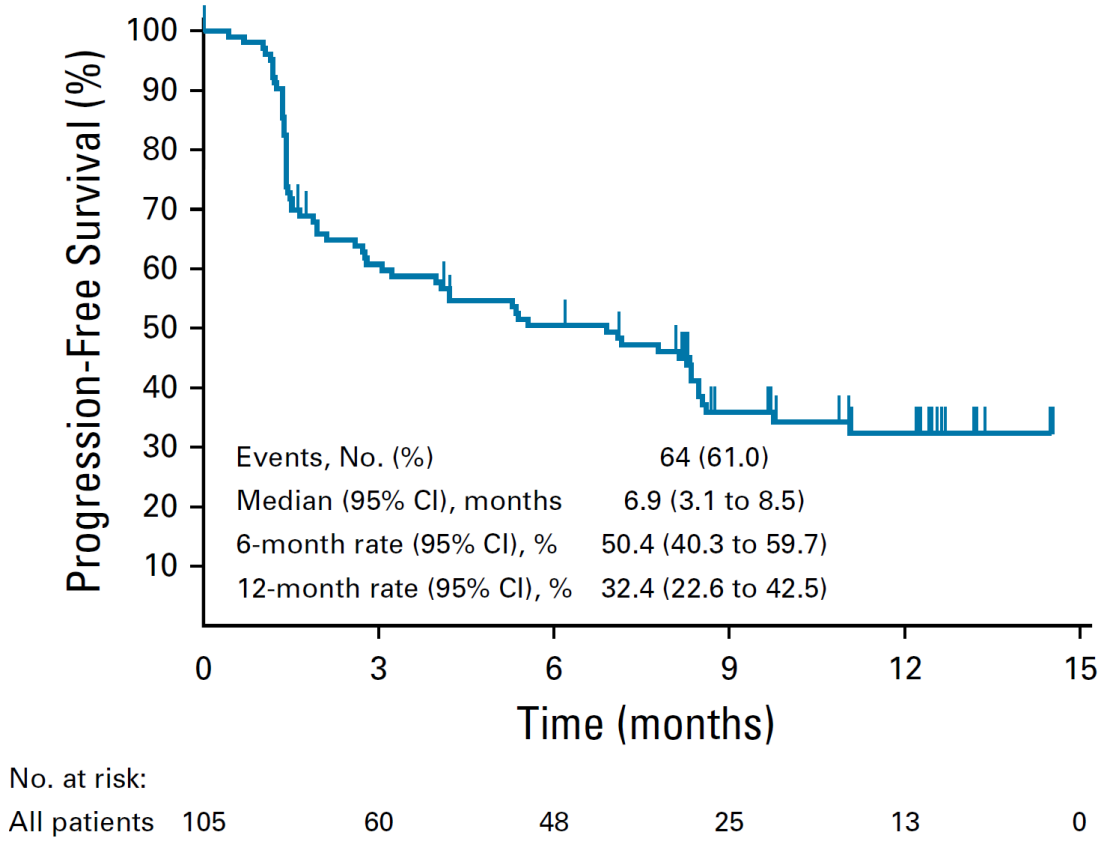
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%




Nghiem, J Clin Oncol 2019.

# Pembrolizumab in advanced/metastatic cutaneous squamous cell carcinoma:KEYNOTE-629 (NCT03284424)



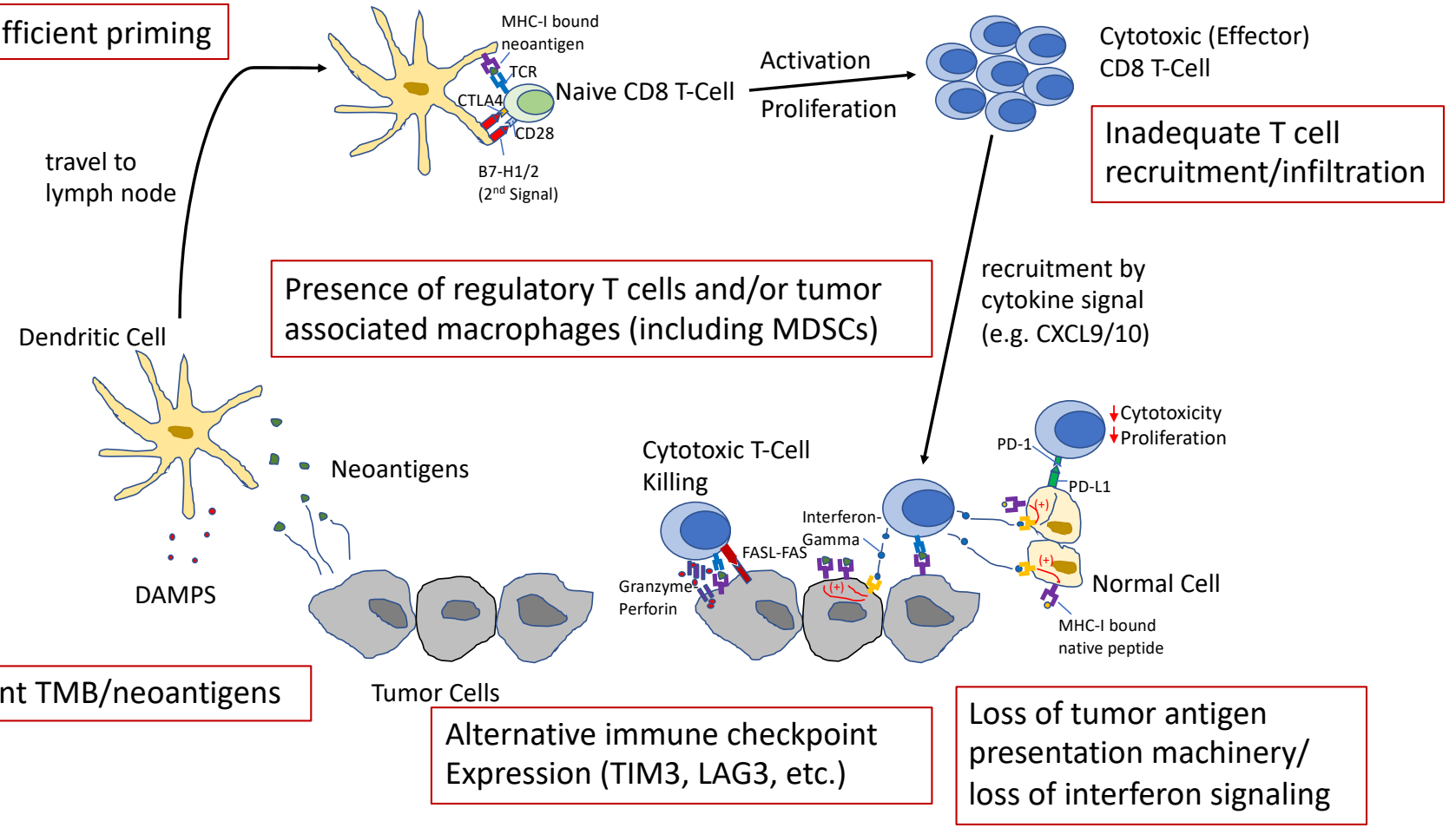

No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| All patients | 105 | 60 | 48 | 25 | 13 | 0 |

Grob, JCO 2020

# Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?




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

# Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

**Combination therapy**

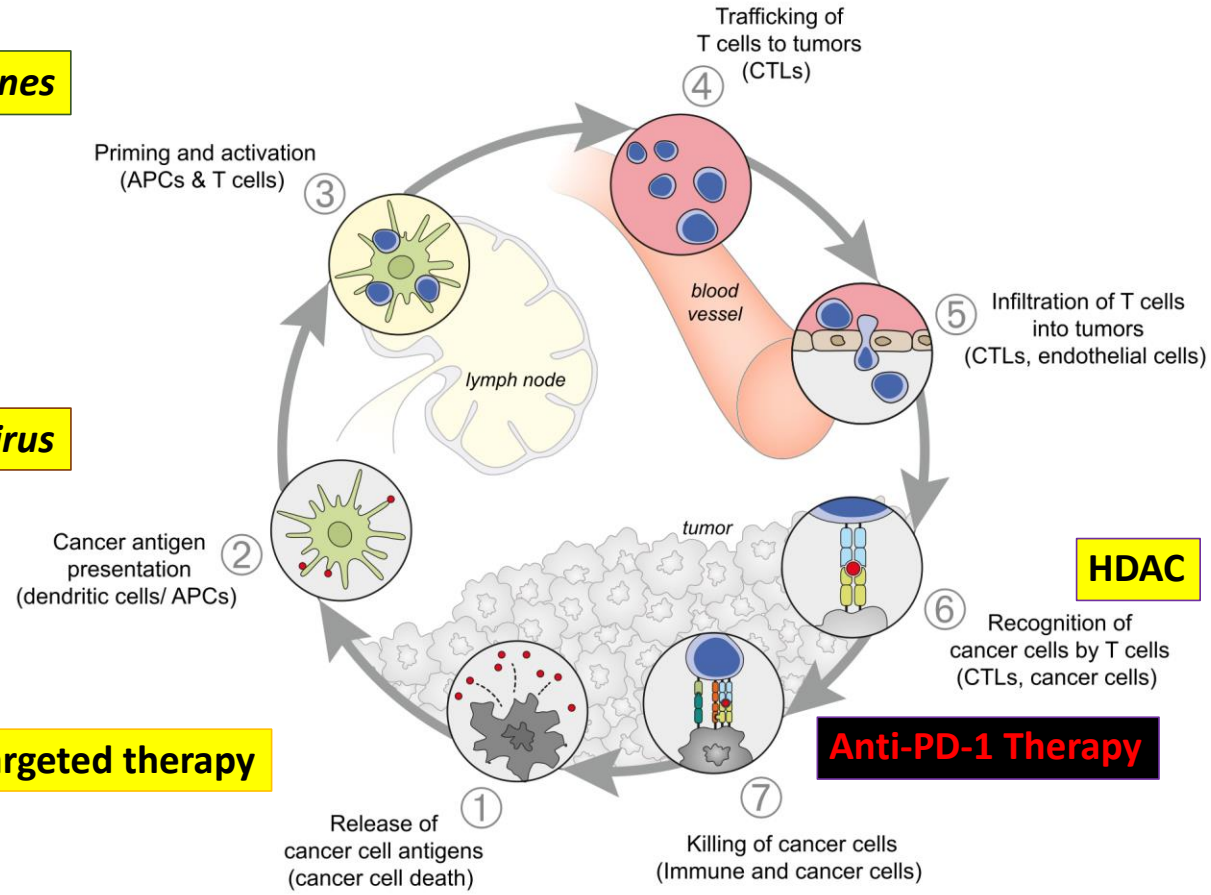
***Cytokines***

***Oncolytic virus***

**Targeted therapy**

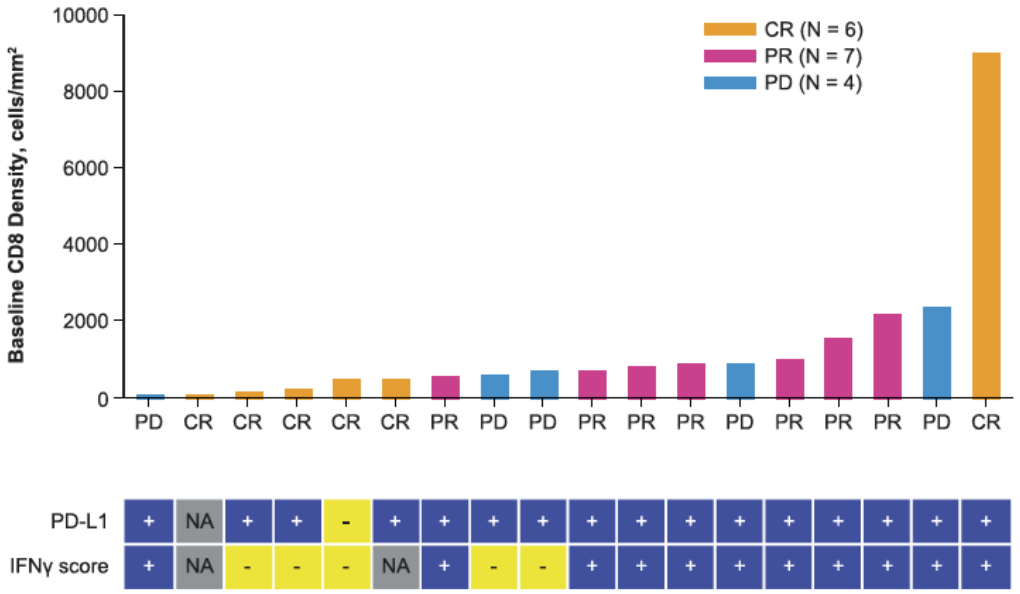
**HDAC**

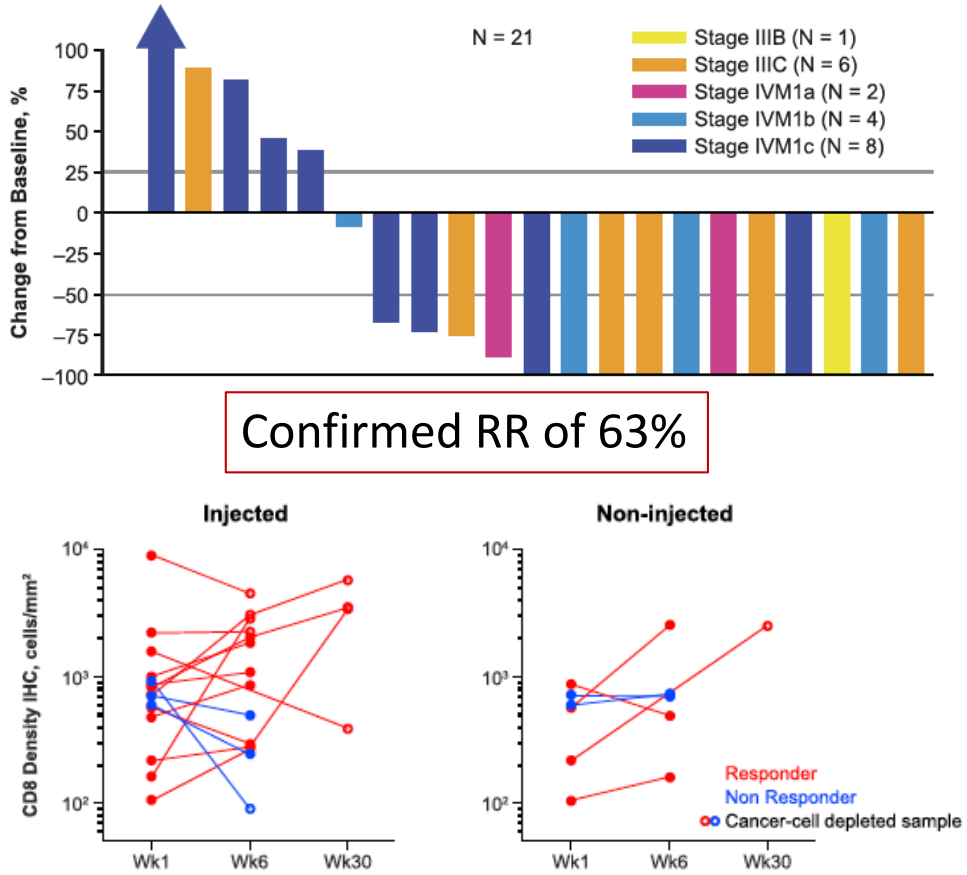
**Anti-PD-1 Therapy**




Modified from Chen and Melman. Immunity 2015.

# **In development:** Combined IO with Oncolytic Virus



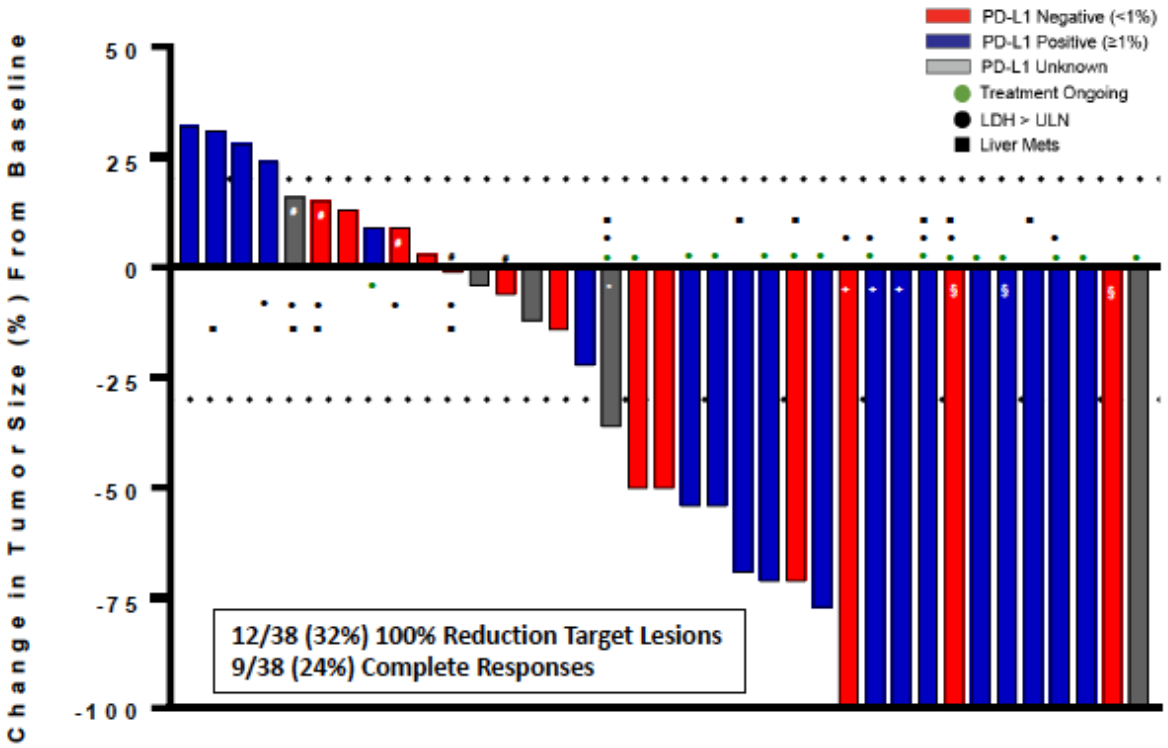

Phase I: Pembrolizumab + TVEC

Multiple ongoing studies in PD-1 naïve and post-PD-1 therapy

Ribas et al Cell 2017

# **In development:** Combined IO with IL-2 (NKTR-214)

## Stage IV IO-Naïve 1L Melanoma Cohort at RP2D Best Overall Response by Independent Radiology



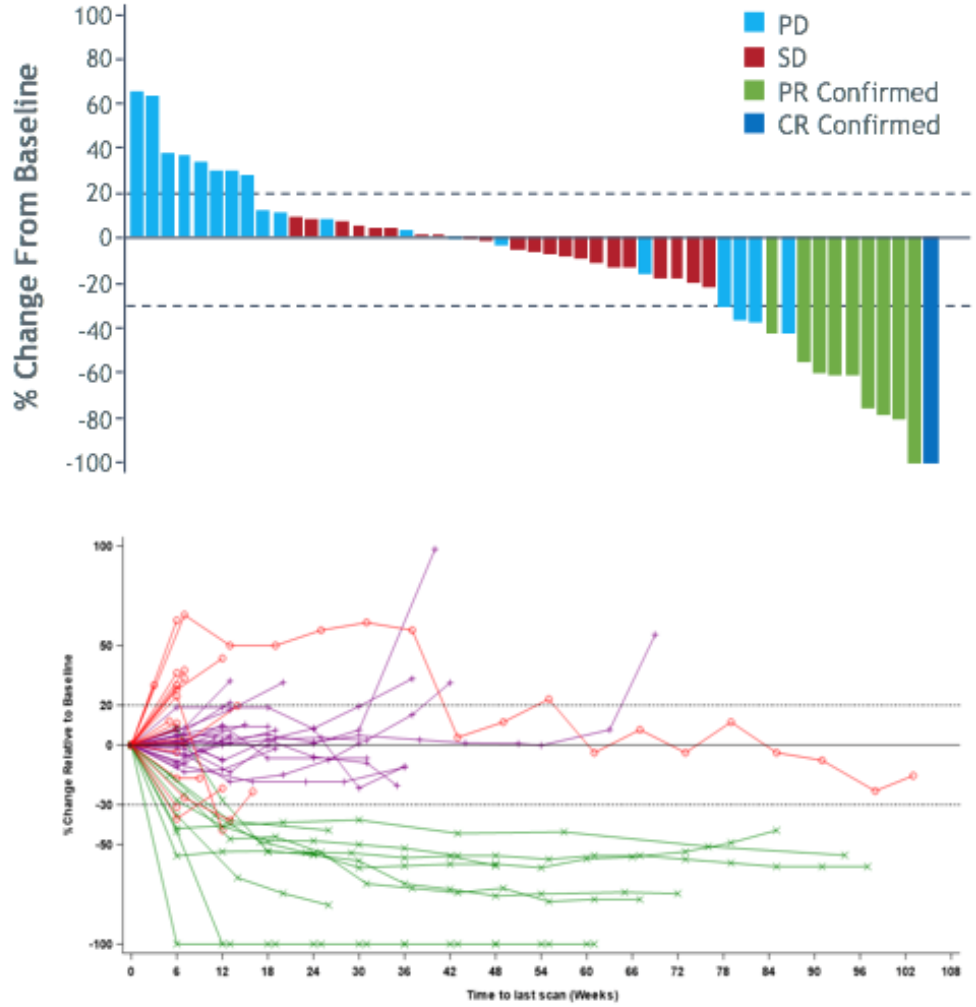

| 1L Melanoma (n=38 Efficacy Evaluable) | Overall Response Rate |
|---|---|
| Confirmed ORR (CR+PR) | 20 (53%) |
| CR | 9 (24%) |
| DCR (CR+PR+SD) | 29 (76%) |
| PD-L1 negative (n=14) | 6 (43%) |
| PD-L1 positive (n=19) | 13 (68%) |
| PD-L1 unknown (n=5) | 1 (20%) |
| LDH > ULN (n=11) | 5 (45%) |
| Liver metastases (n=10) | 5 (50%) |

**High level of concordance in ORR between independent central radiology (53%) and investigator-assessed 19/38 (50%).**

Diab et al, ASCO 2018.
Diab et al, SITC 2018.

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

- Entinostat + pembrolizumab in patients with prior PD-1 exposure
- 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.

# In development: IO strategies in non-melanoma skin cancers

| Disease | Immunotherapy Strategy | Clinical Trial |
|---|---|---|
| **Merkel cell carcinoma** | Activated NK cells + IL-15 agonist | NCT03853317 |
| | Gene-modified autologous T-cell therapy | NCT03747484 |
| | Combination CTLA-4/PD-1 blockade ± radiotherapy | NCT03071406 |
| | Intralesional TLR agonist + PD-1 antibody | NCT03684785 |
| | Radiation therapy + PD-1 antibody | NCT03988647, NCT03304639 |
| **CSCC** | Avelumab + cetuximab | NCT03944941 |
| | PD-L1 + long-acting IL-7 compound | NCT03901573 |
| | Intralesional autologous cancer cell/Streptococcal antigen vaccine (IFx-Hu2.0) | NCT04160065 |
| | Intralesional Talimogene laherparepvec | NCT03714828 |
| | Intralesional glatiramer acetate | NCT03982212 |
| **BCC** | Cemiplimab | NCT03132636 |
| | CTLA-4 + PD-1 combination immunotherapy | NCT03521830 |

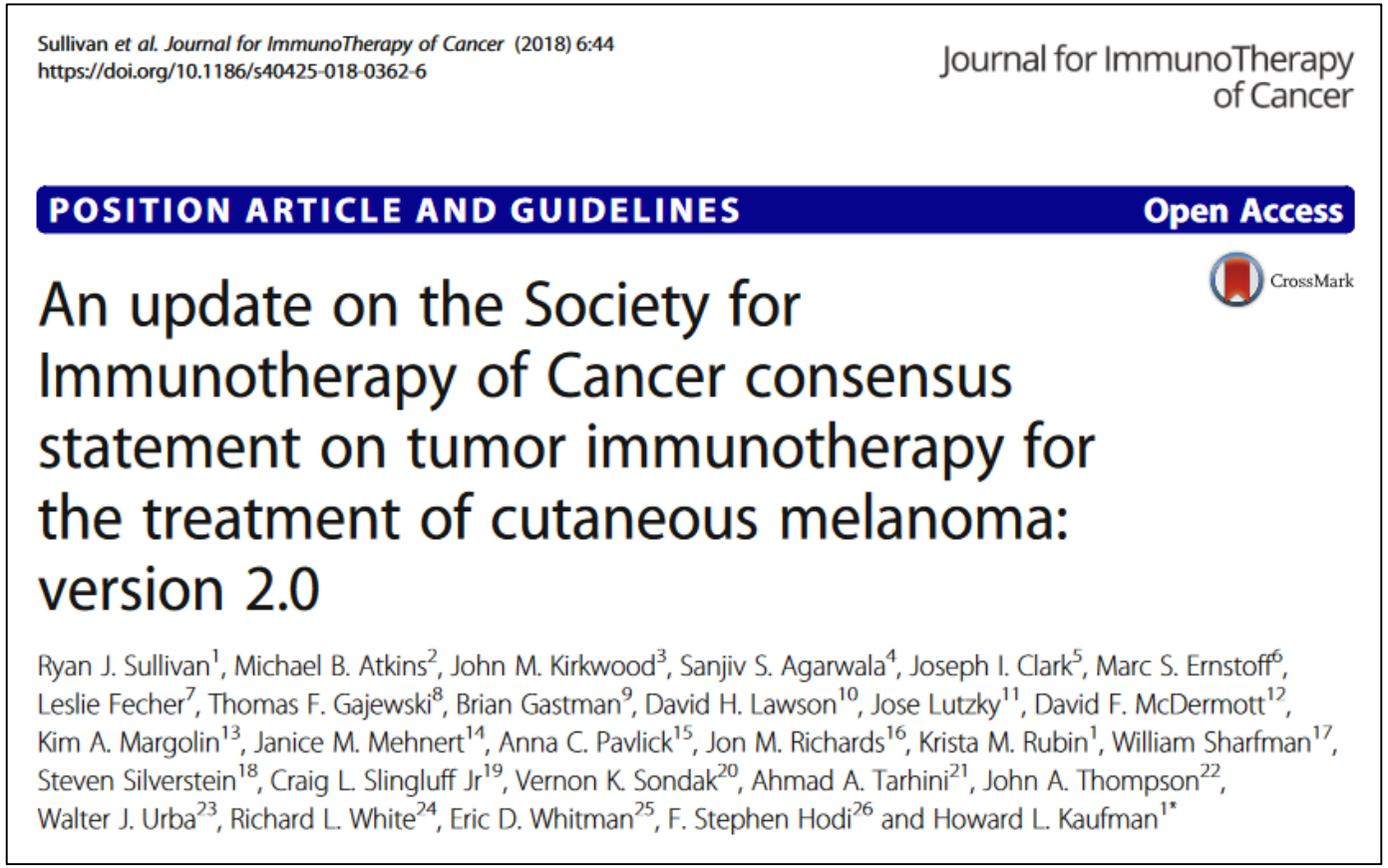
Abbreviations: NK, natural killer; IL, interleukin; TLR, Toll-like receptor; CSCC, cutaneous squamous cell carcinoma; BCC, basal cell carcinoma.

Hall, ASCO Ed Book 2020

# 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

# 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

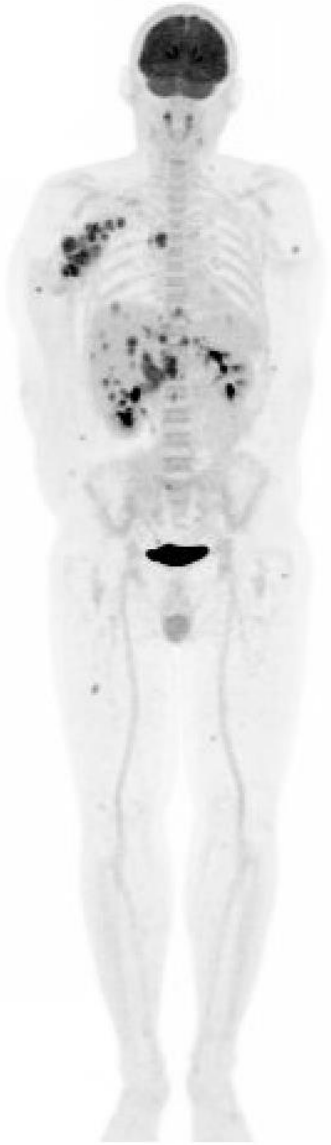
POSITION ARTICLE AND GUIDELINES Open Access

## 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*]

# Case Studies

# Case Study 1



38 year old male with widely metastatic BRAF V600E mutant melanoma including lung, liver, bone and a small, asymptomatic brain metastasis. LDH >2x ULN. He has significant pain related to the tumor but no headaches or associated neurologic symptoms. His goal is to optimize his chances for long-term survival.

What would you recommend as first-line treatment?

A. Pembrolizumab
B. Ipilimumab + nivolumab
C. BRAF/MEK inhibitor therapy
D. Vemurafenib/cobimetinib/atezolizumab
E. Stereotactic radiosurgery to brain metastasis first, then subsequent systemic therapy

# Case Study 2

75 yo F with history of coronary artery disease s/p PCI, COPD on home oxygen, who presents with large (6-7cm) primary, BRAF wildtype melanoma of the periorbital region after being referred from a plastic surgeon who feels that she is too high-risk for surgical resection. There is no known metastatic disease. She does not have symptoms from the mass. She wants to minimize potential side effects from medications.

What therapy do you recommend?

A. Radiation therapy

B. Talimogene laherparepvec (T-Vec)

C. PD-1 monotherapy with nivolumab or pembrolizumab

D. Nivolumab + ipilimumab

E. Observation

# Case Study 2

She proceeds to therapy with T-Vec and completes several treatments, but has clear local disease progression. There begins to be bleeding and increasing pain associated with the lesion. Restaging imaging shows no evidence of distant disease.

What would you recommend as a second-line therapy?

A. PD-1 monotherapy (nivolumab or pembrolizumab)
B. Nivolumab + ipilimumab
C. Radiation therapy