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

- Advisory boards and honoraria: Merck, Novartis, InCyte, BMS, Sanofi Genzyme.
- Research Grants: Roche, Novartis
- I will be discussing non-HC approved indications during my presentation.

Era of Hope

- In 2011 Ipilimumab was approved
- We now have 7 drugs that have shown an improvement in OS in metastatic melanoma
  - VEMURAFENIB –BRAF positive melanoma
  - COBIMETINIB - BRAF positive melanoma
  - DABRAFENIB - BRAF positive melanoma
  - TRAMETINIB - BRAF positive melanoma
  - IPILIMUMAB – immunotherapy
  - PEMBROLIZUMAB – immunotherapy
  - NIVOLUMAB - immunotherapy

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- We now have 7 drugs that have shown an improvement in OS in metasta
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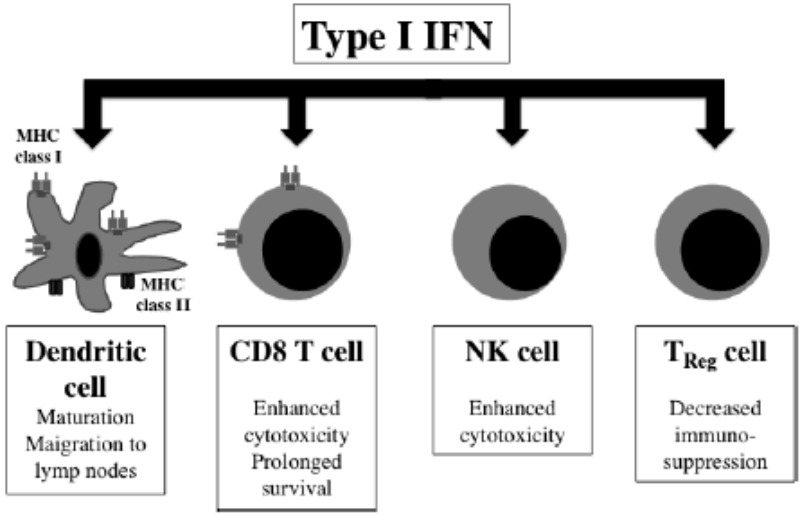
  - COBI
  - DABR
  - TRAM
  - IPILIMUMAB – immunotherapy
  - PEMBROLIZUMAB – immunotherapy
  - NIVOLUMAB - immunotherapy

Benefit in Adjuvant therapy

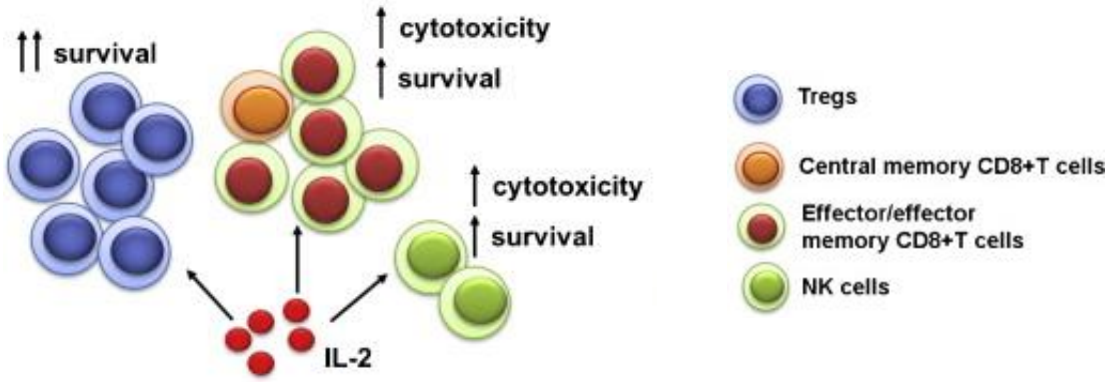
HC-approved Immunotherapies in Melanoma

Cytokines

- High-dose Interferon
  - Adjuvant therapy
  - High dose I.V., followed by SQ
  - Treatment for up to one year
- Interleukin-2
  - Stage IIIc
  - Intralesional for intransit metastases



Numasaki et al. Immunotherapy 2016

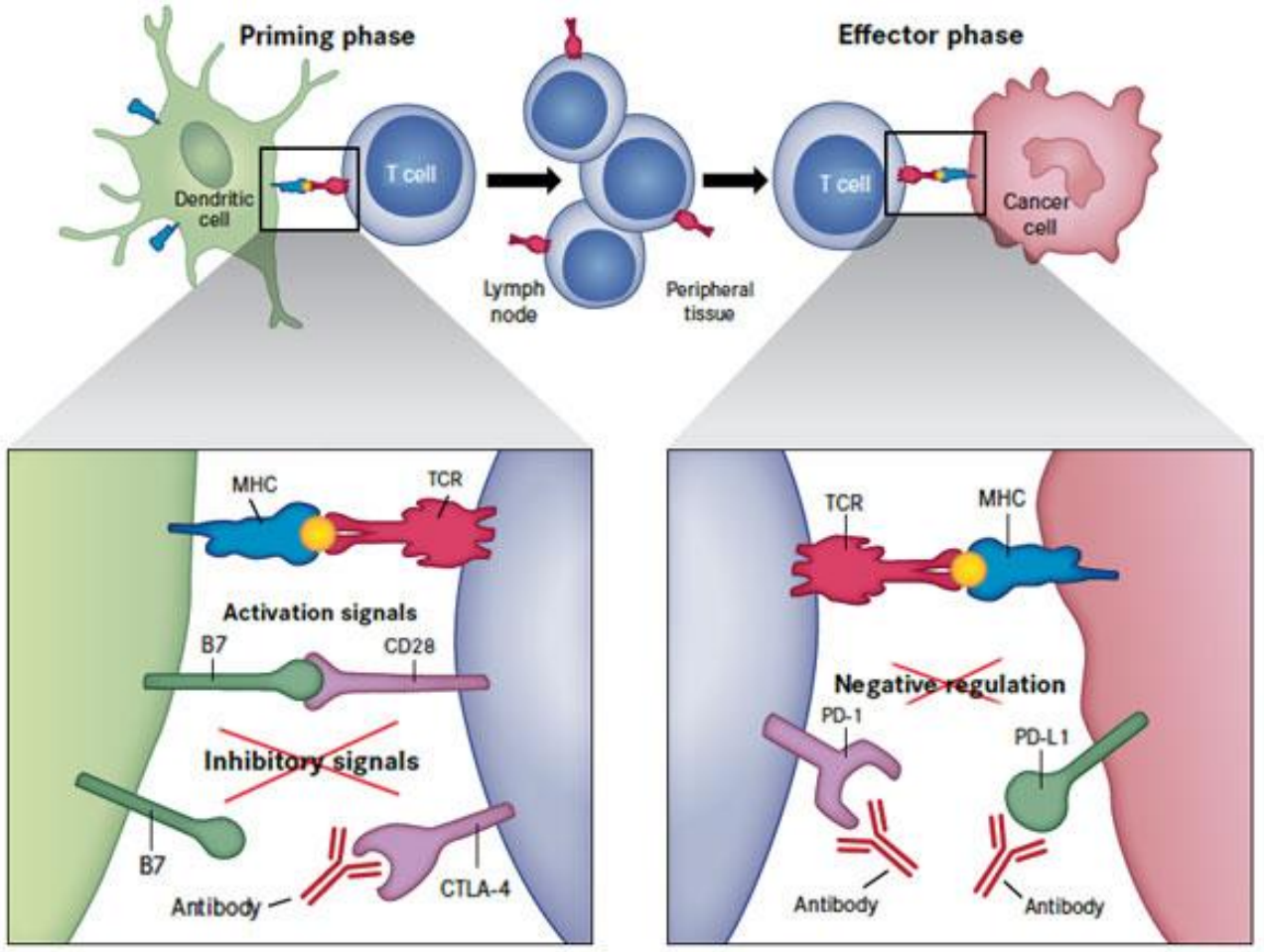


Sim, Radvanyi Cytogfr 2014

HC-approved Immunotherapies in Melanoma

Immune Checkpoint Inhibitors

- Ipilimumab: nonresectable/Stage IV, I.V.- 3mg/kg
- 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

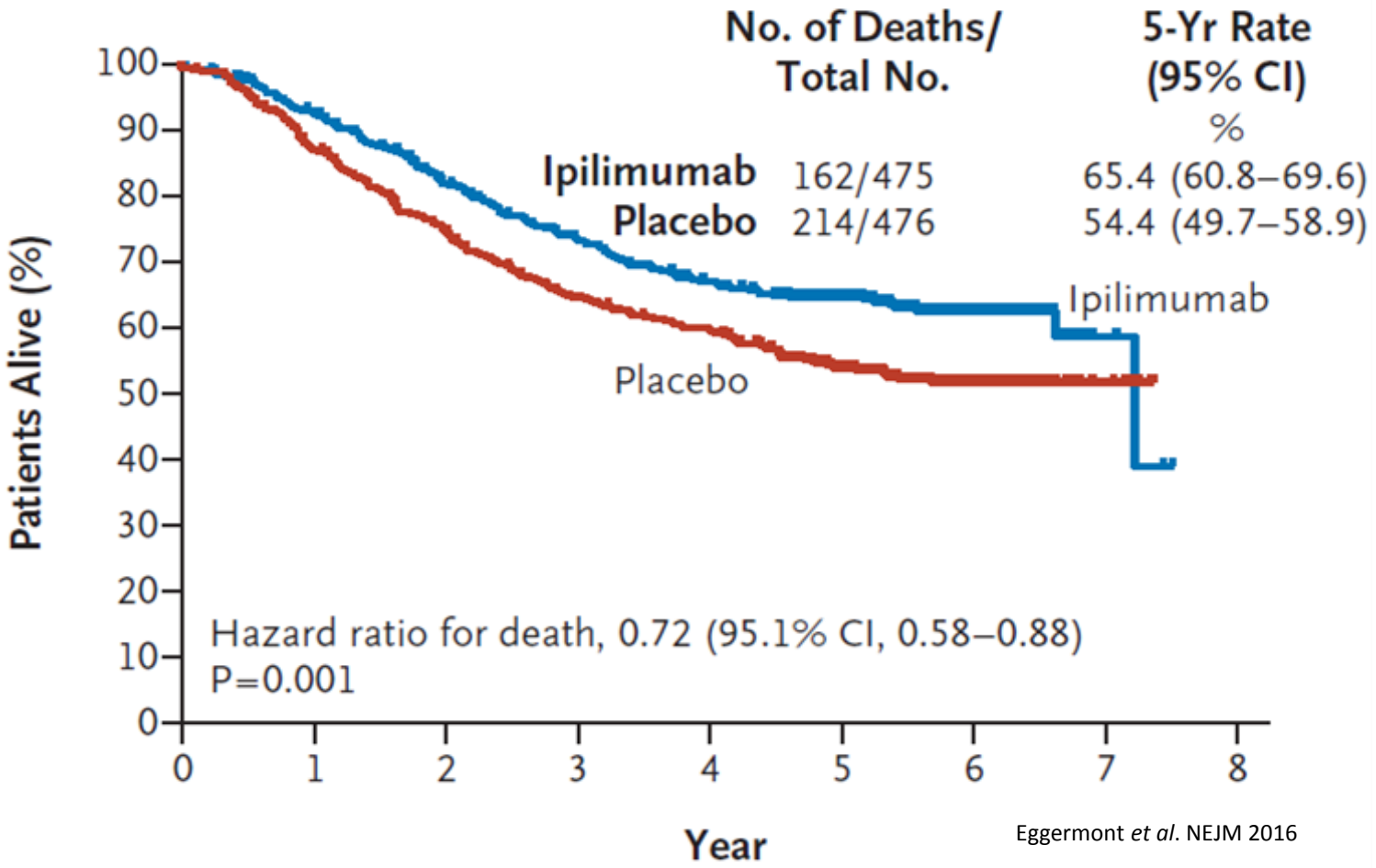
Adjuvant Melanoma Data

Adjuvant Trials:

EORTC 18071-Ipilimumab Vs Placebo
CheckMate 238- Nivolumab Vs Ipilimumab
EORTC 1325 - Pembrolizumab Vs Placebo

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



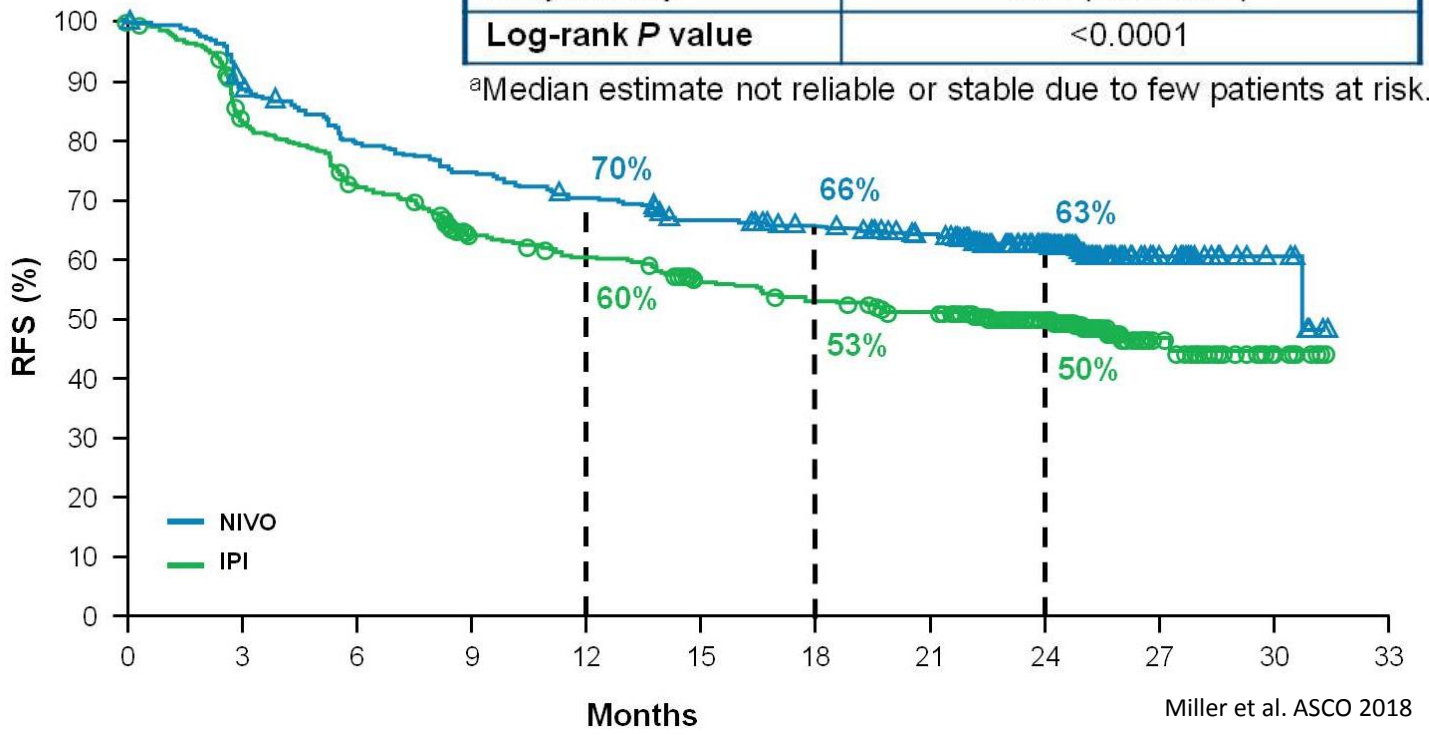
Eggermont *et al*. NEJM 2016

Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

- CheckMate 238 phase III trial
  - Stage IIIB, C, or resected Stage IV
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 1 year
  - Nivolumab 3mg/kg Q2W 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	

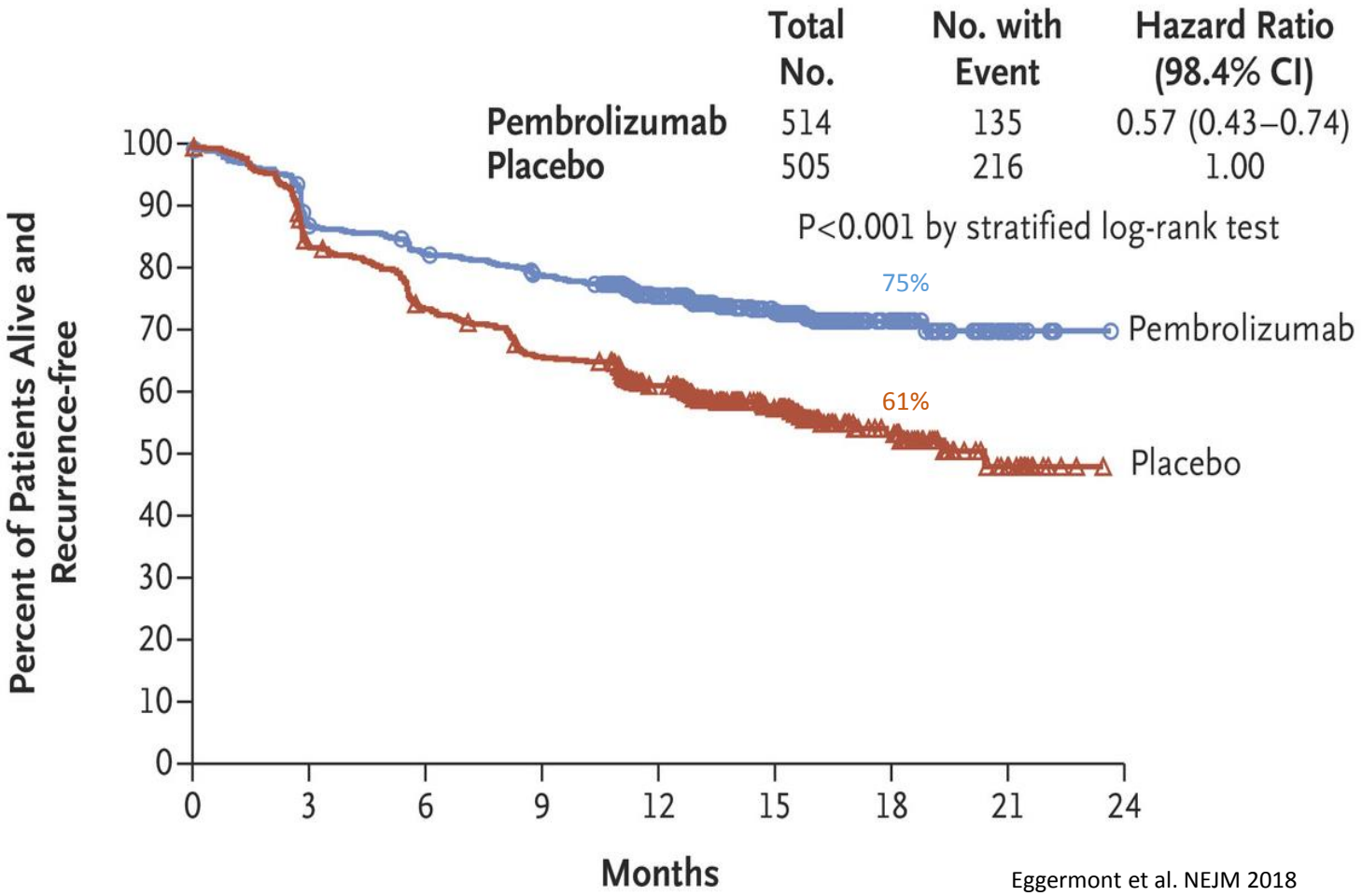
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

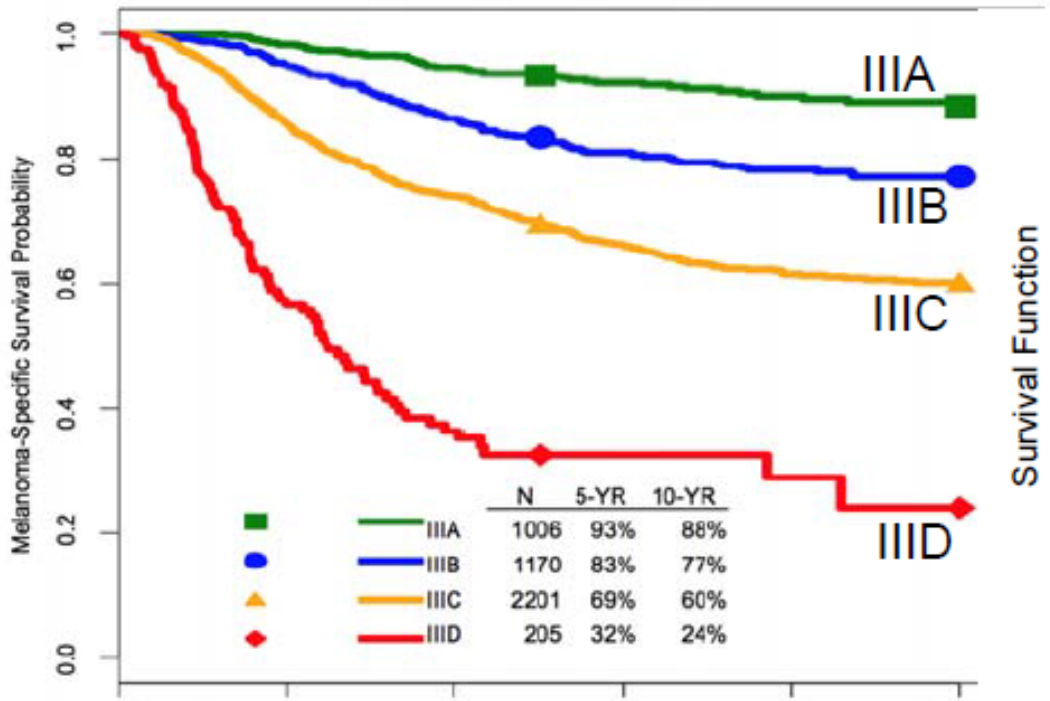
- EORTC 1325/KEYNOTE-054 phase III trial
  - Stage III (IIIA >1mm)
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)



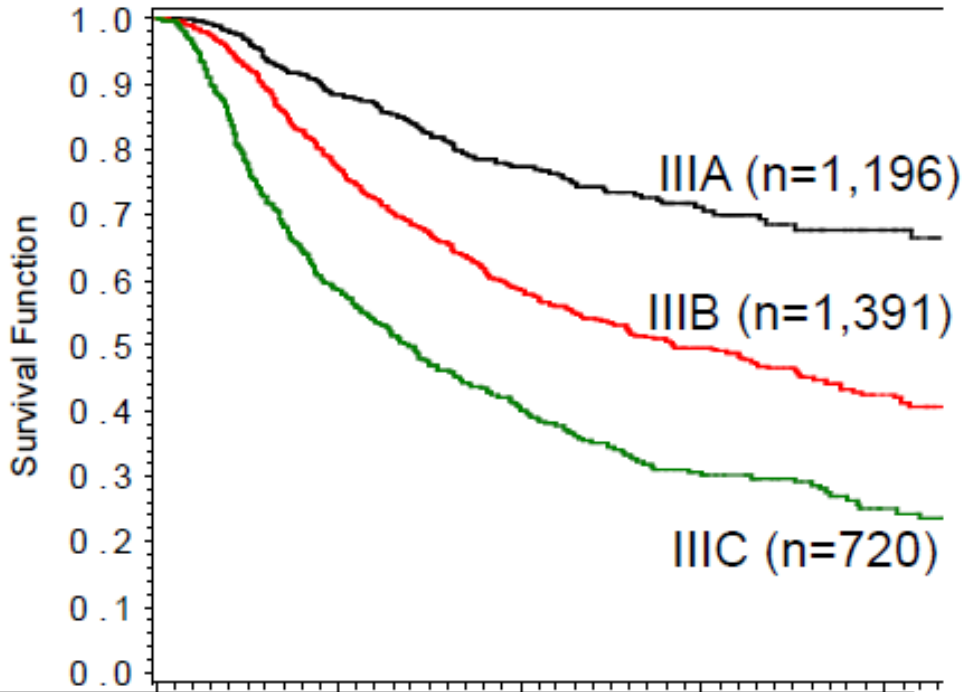
Eggermont et al. NEJM 2018

MSS according to AJCC Stage III Group

AJCC 8th Edition



AJCC 7th Edition

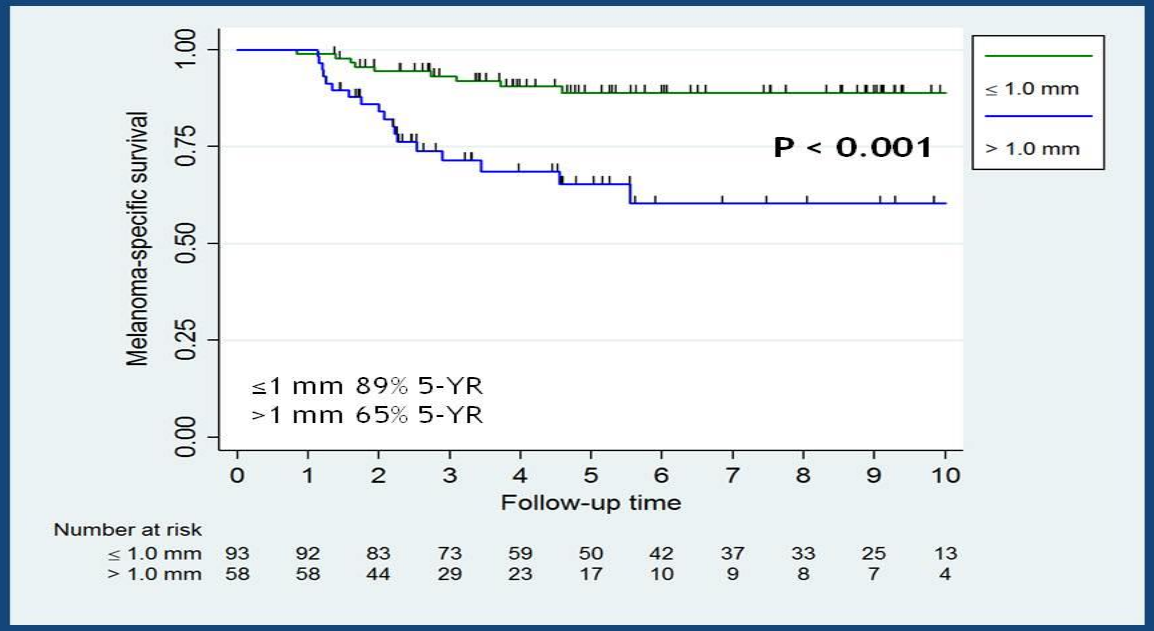


Implications for Patient Counseling, Management & Contemporary Adjuvant Clinical Trial Design

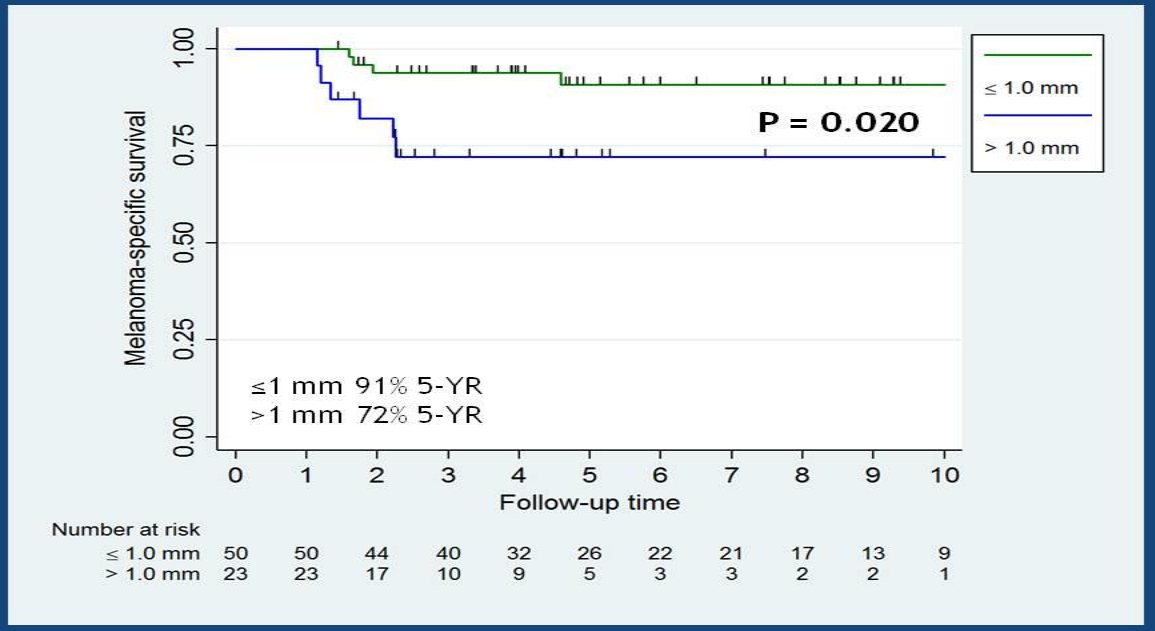
Stage IIIA Remains a Heterogeneous Group

Survival differentiation in stage IIIA

7th edition



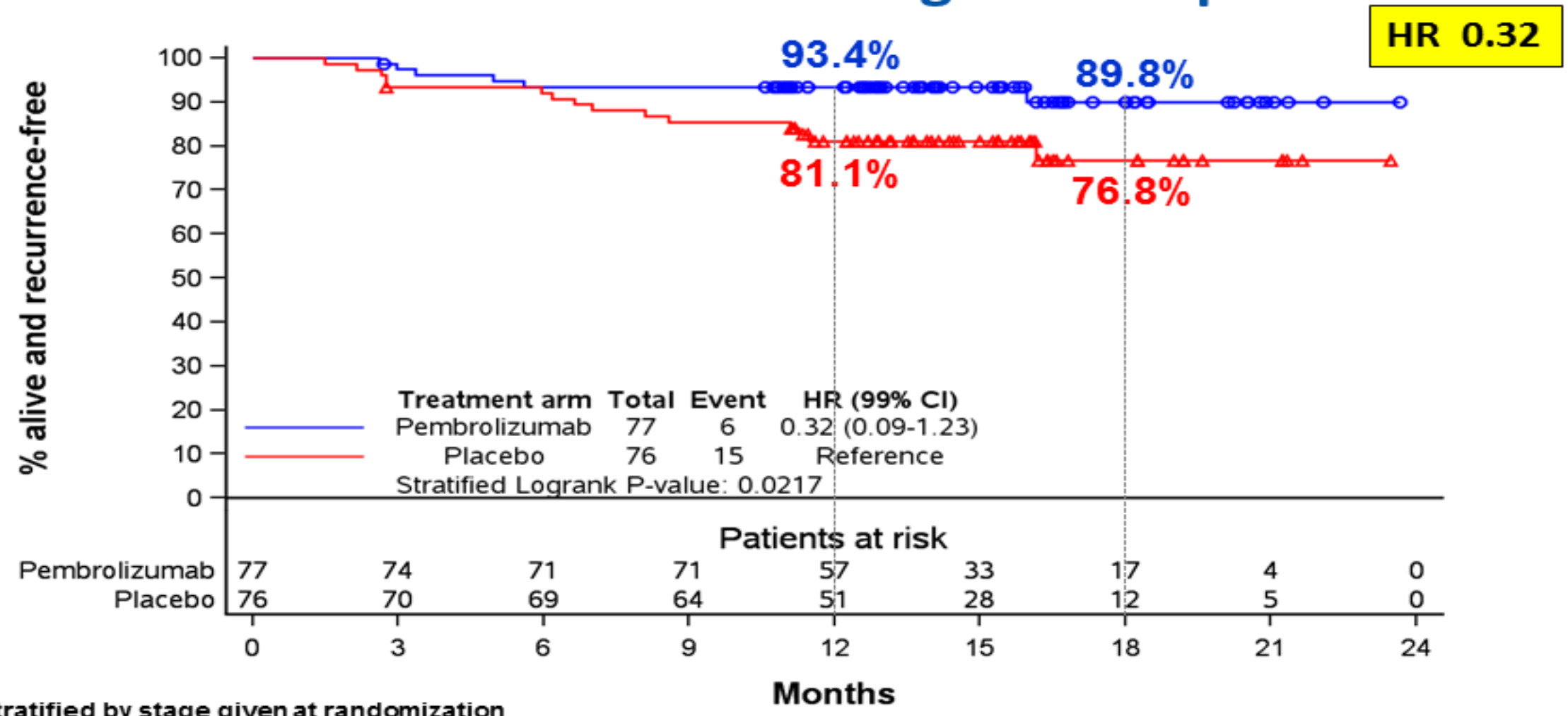
8th edition



Presented By Max Madu at 2018 ASCO Annual Meeting

L. Eggermont AACR 2018

Recurrence-Free Survival in Stage IIIA Population



*Stratified by stage given at randomization

EORTC

The future of cancer therapy

AAEM American Academy of Emergency Medicine

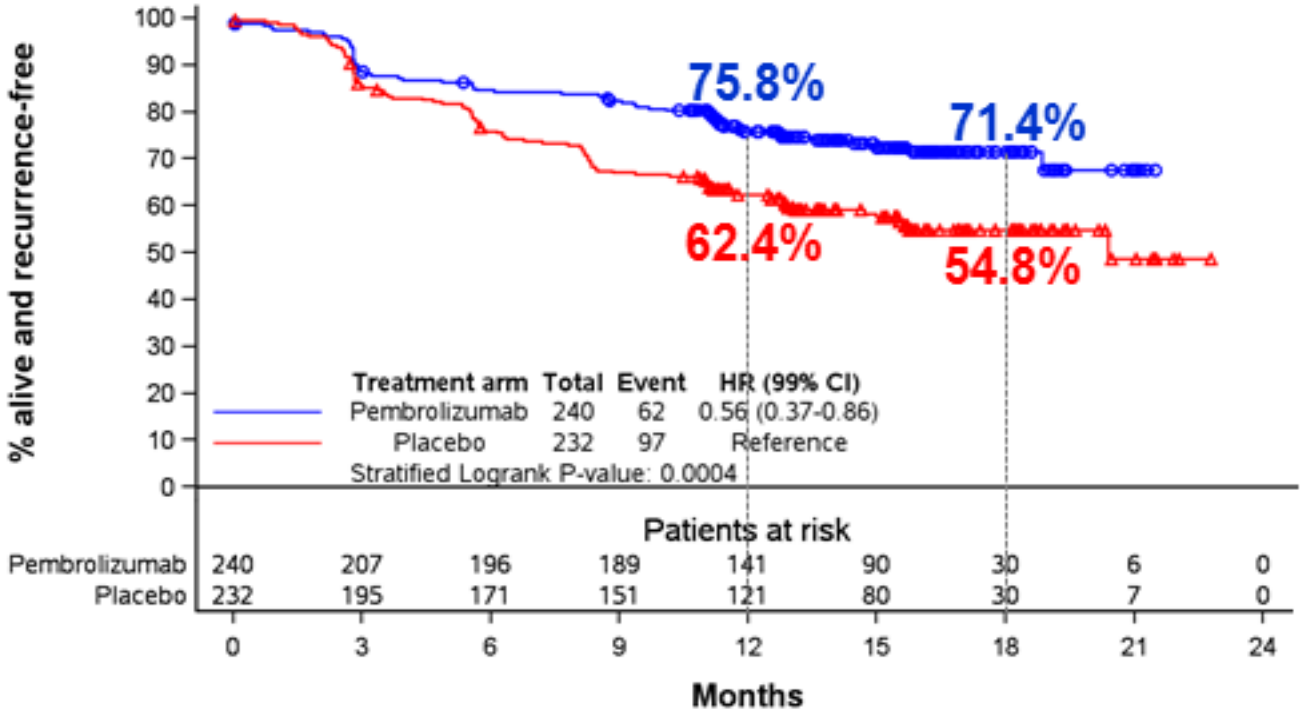
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Recurrence-Free Survival

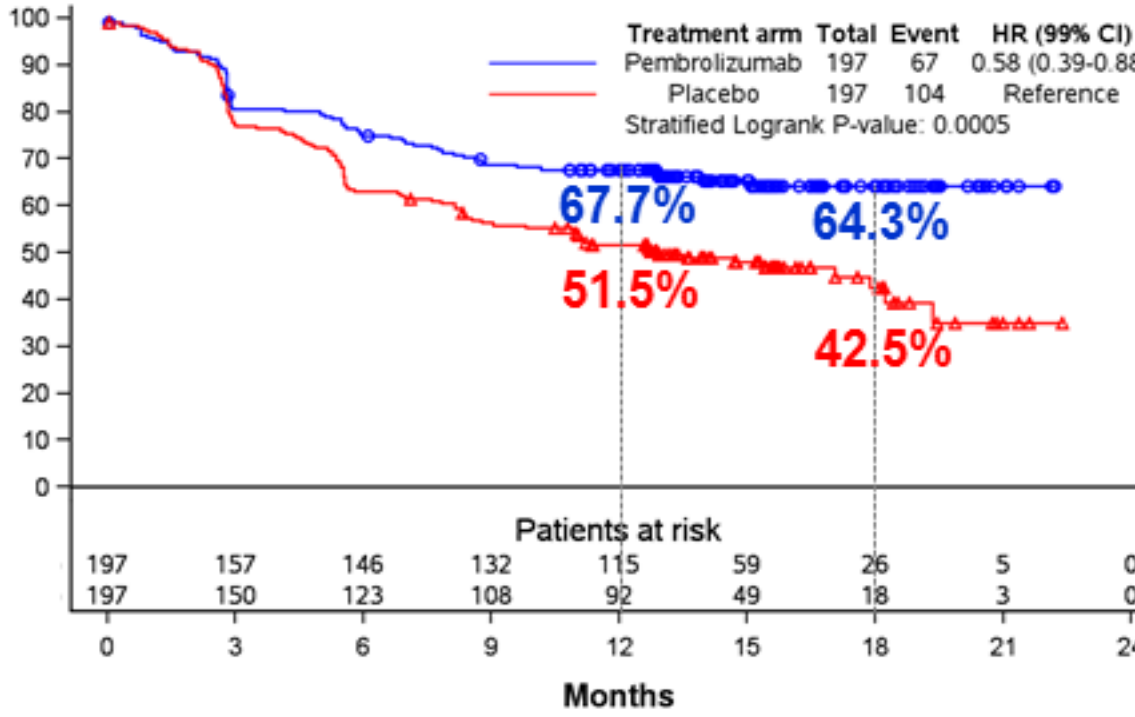
Stage IIIB

HR 0.56



Stage IIIC

HR 0.58



*Stratified by stage given at randomization

EORTC

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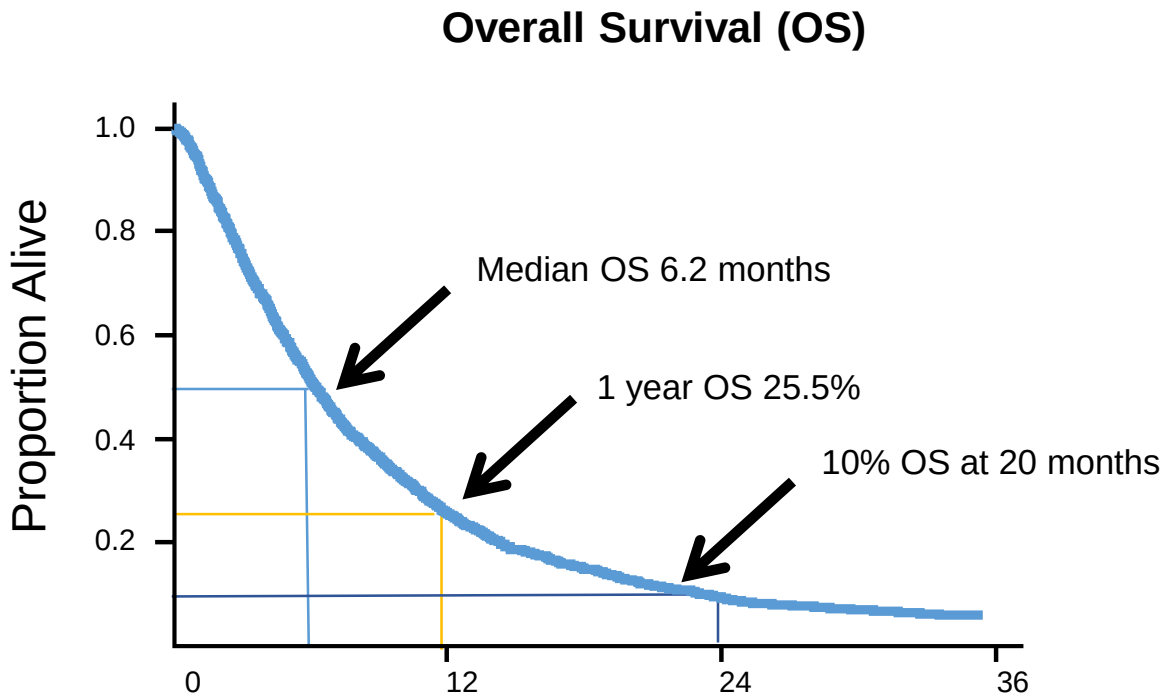
Metastatic Melanoma

Benchmark Metastatic Melanoma Survival



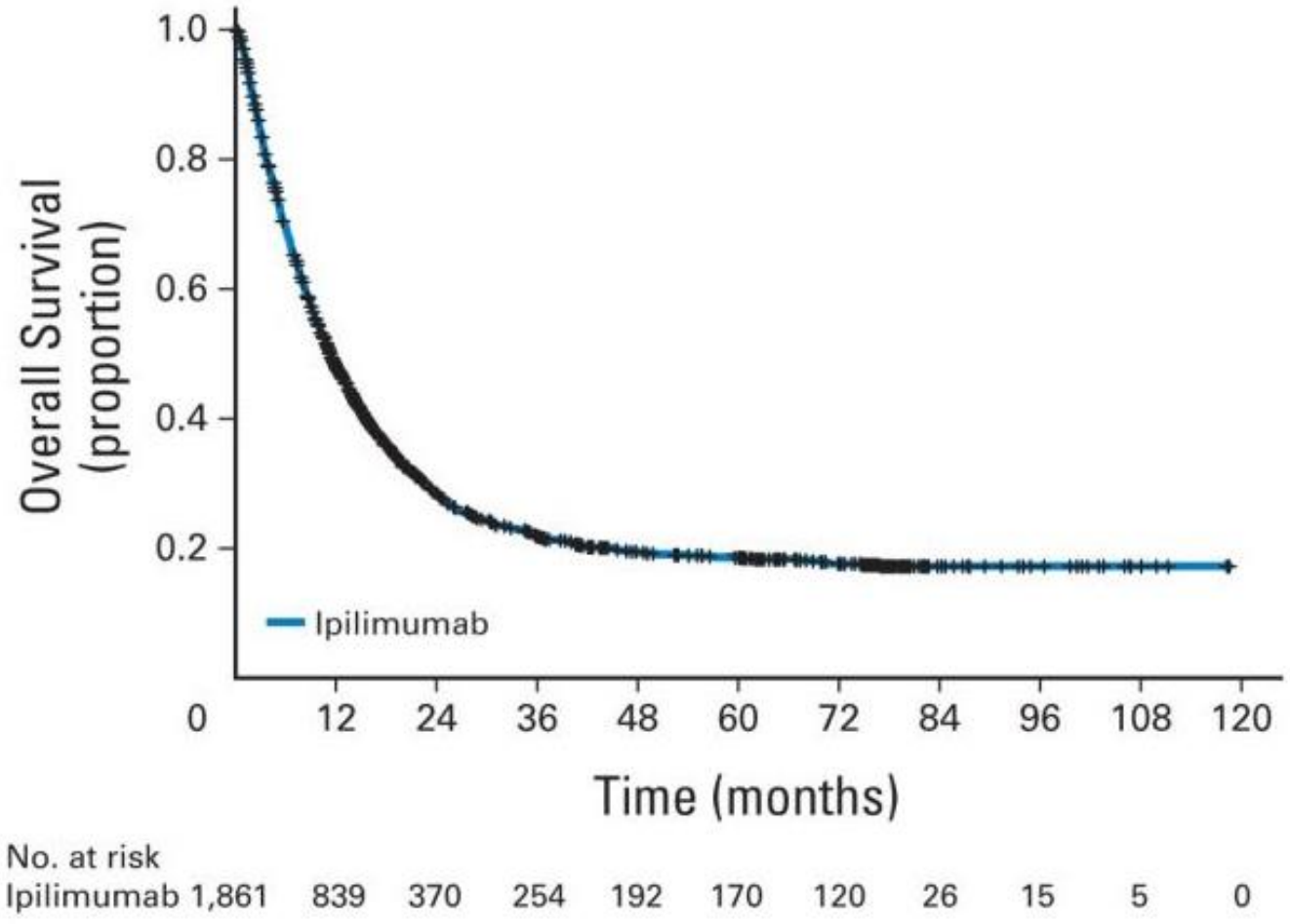
OS (months) based on historical data 1975-2005 - Prior to Introduction of Immunotherapy

Survival of Patients with Metastatic Melanoma Has Changed

Korn EL et al. *J Clin Oncol* 2008;26:527-34

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

4-Year Survival and Outcomes After Cessation of Pembrolizumab After 2 Years in Patients With Ipilimumab-Naive Advanced Melanoma in KEYNOTE-006

Georgina V. Long[1]; Jacob Schachter[2]; Antoni Ribas[3]; Ana Arance[4]; Jean-Jacques Grob[5]; Laurent Mortier[6]; Adil Daud[7]; Matteo S. Carlino[8]; Catriona McNeil[9]; Michal Lotem[10]; James Larkin[11]; Paul Lorigan[12]; Bart Neyns[13]; Christian Blank[14]; Teresa M. Petrella[15]; Omid Hamid[16]; James R. Anderson[17]; Clemens Krepler[17]; Nageatte Ibrahim[17]; Caroline Robert[18]

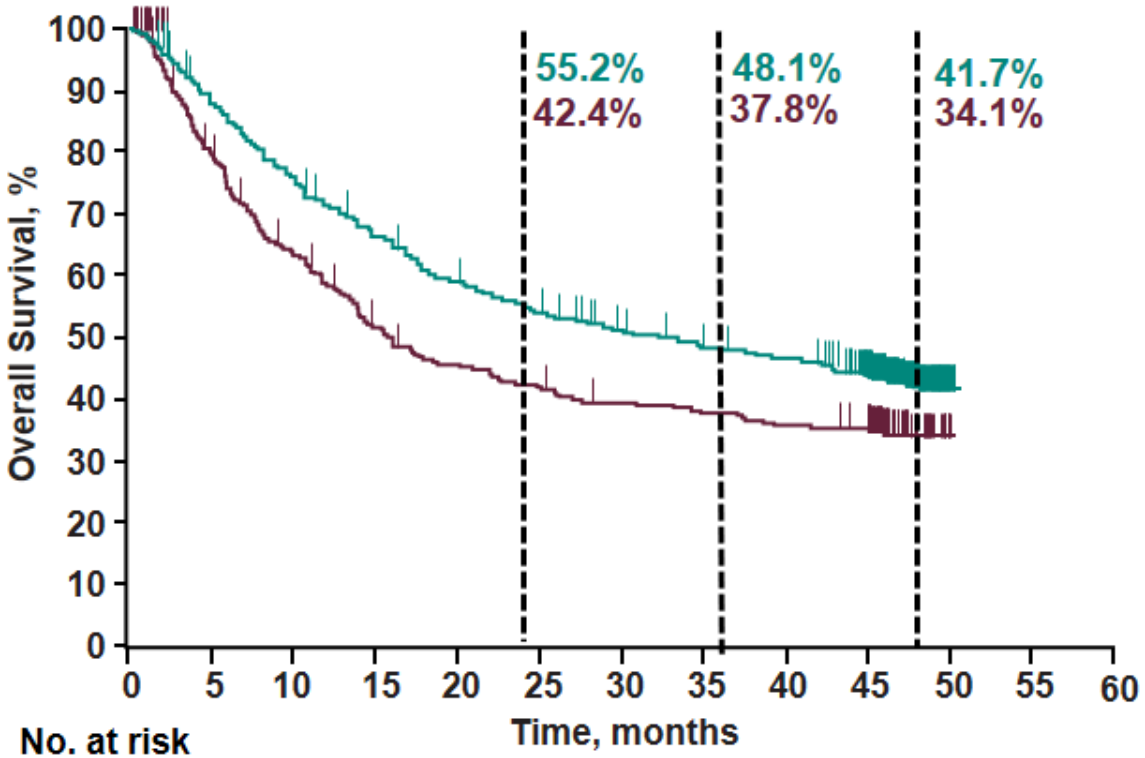
[1]Melanoma Institute Australia, The University of Sydney, Mater Hospital, and Royal North Shore Hospital, Sydney, NSW, Australia; [2]Sheba Medical Center at Tel Hashomer, Ramat Gan, Israel; [3]University of California, Los Angeles, Los Angeles, CA, USA; [4]Hospital Clinic de Barcelona, Barcelona, Spain; [5]Aix Marseille University, Hôpital de la Timone, Marseille, France; [6]Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France; [7]University of California, San Francisco, San Francisco, CA, USA; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, and The University of Sydney, Sydney, NSW, Australia; [9]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [10]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [11]The Royal Marsden Hospital, London, UK; [12]University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; [13]Universitair Ziekenhuis Brussel, Brussels, Belgium; [14]Netherlands Cancer Institute, Amsterdam, Netherlands; [15]Sunnybrook Health Sciences Center, Toronto, ON, Canada; [16]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [17]Merck & Co, Inc., Kenilworth, NJ, USA; [18]Gustave Roussy, Villejuif, France

Overall Survival

Median Follow-Up 45.9 (0.3-50.0) Months

All Patients

	Events, n	HR[a] (95% CI)	Median,[b] mo (95% CI)
Pembro	309	0.73 (0.61-0.89)	32.7 (24.5-41.6)
Ipi	164	-	15.9 (13.3-22.0)

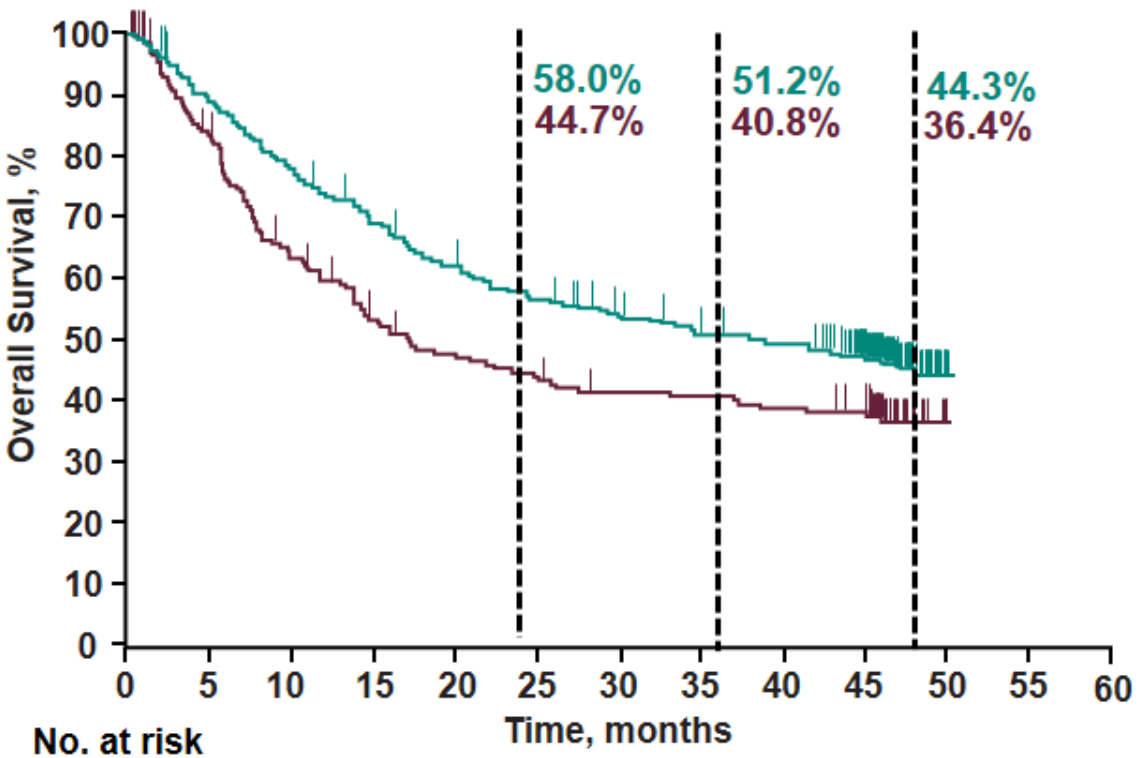


No. at risk

556	481	416	357	317	289	266	250	239	181	0	0	0
278	202	158	127	111	102	94	90	85	76	0	0	0

Treatment-Naive Patients

	Events, n	HR[a] (95% CI)	Median,[b] mo (95% CI)
Pembro	193	0.73 (0.57-0.93)	38.7 (27.3-NR)
Ipi	104	-	17.1 (13.8-26.2)



No. at risk

368	324	284	248	221	201	186	174	167	124	0	0	0
181	140	105	86	76	70	64	63	60	51	0	0	0

[a]Based on Cox regression model with treatment as covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative), and ECOG (0 vs 1); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum was excluded from treatment comparison. [b]Derived by the product-limit (Kaplan-Meier) method for censored data. Data cutoff: Dec 4, 2017.

Combination Immunotherapy

Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

Frank Stephen Hodi, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Charles Lance Cowey, Christopher D Lao, Dirk Schadendorf, John Wagstaff, Reinhard Dummer, Pier Francesco Ferrucci, Michael Smylie, Andrew Hill, David Hogg, Ivan Marquez-Rodas, Joel Jiang, Jasmine Rizzo, James Larkin, Jedd D Wolchok**

Summary

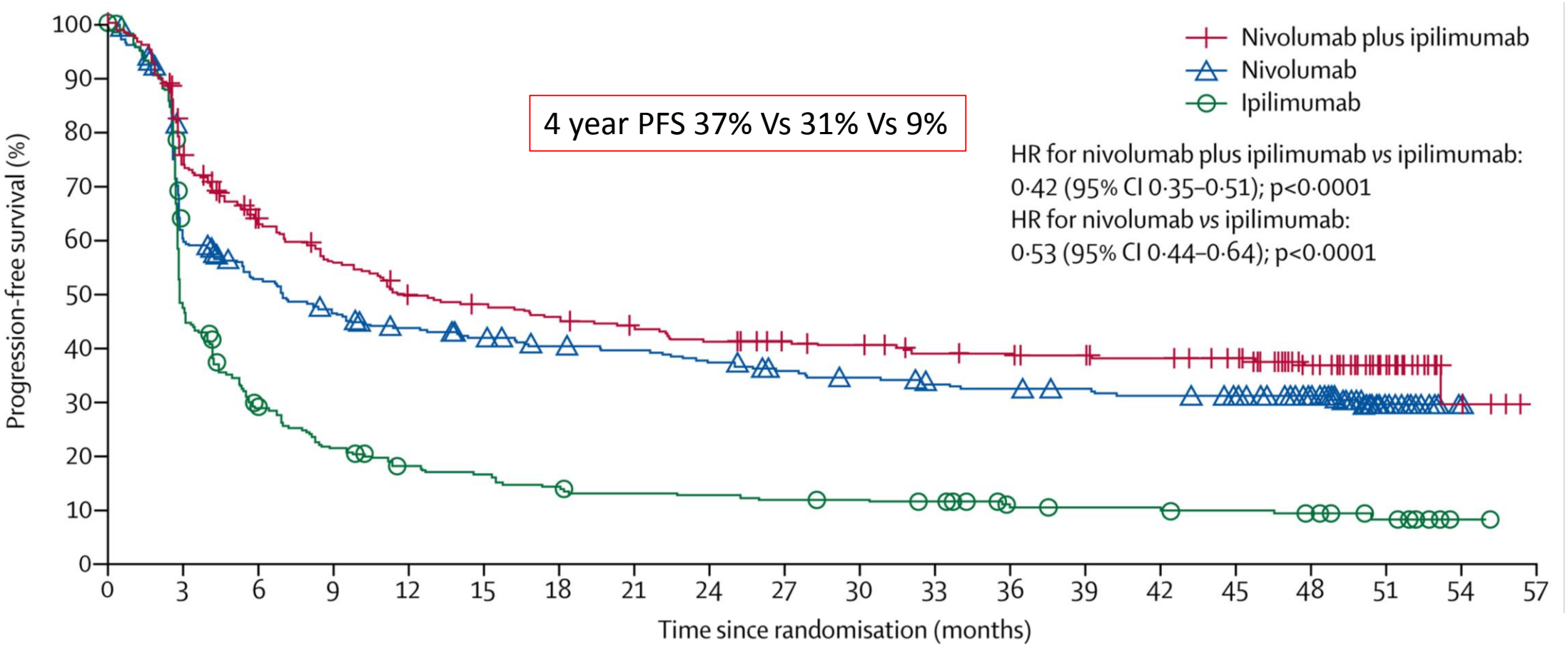
Background Previously reported results from the phase 3 CheckMate 067 trial showed a significant improvement in objective responses, progression-free survival, and overall survival with nivolumab plus ipilimumab or nivolumab alone compared with ipilimumab alone in patients with advanced melanoma. The aim of this report is to provide 4-year updated efficacy and safety data from this study.

Lancet Oncol 2018

Published Online
October 22, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30700-9

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

Phase III CheckMate 067 Trial

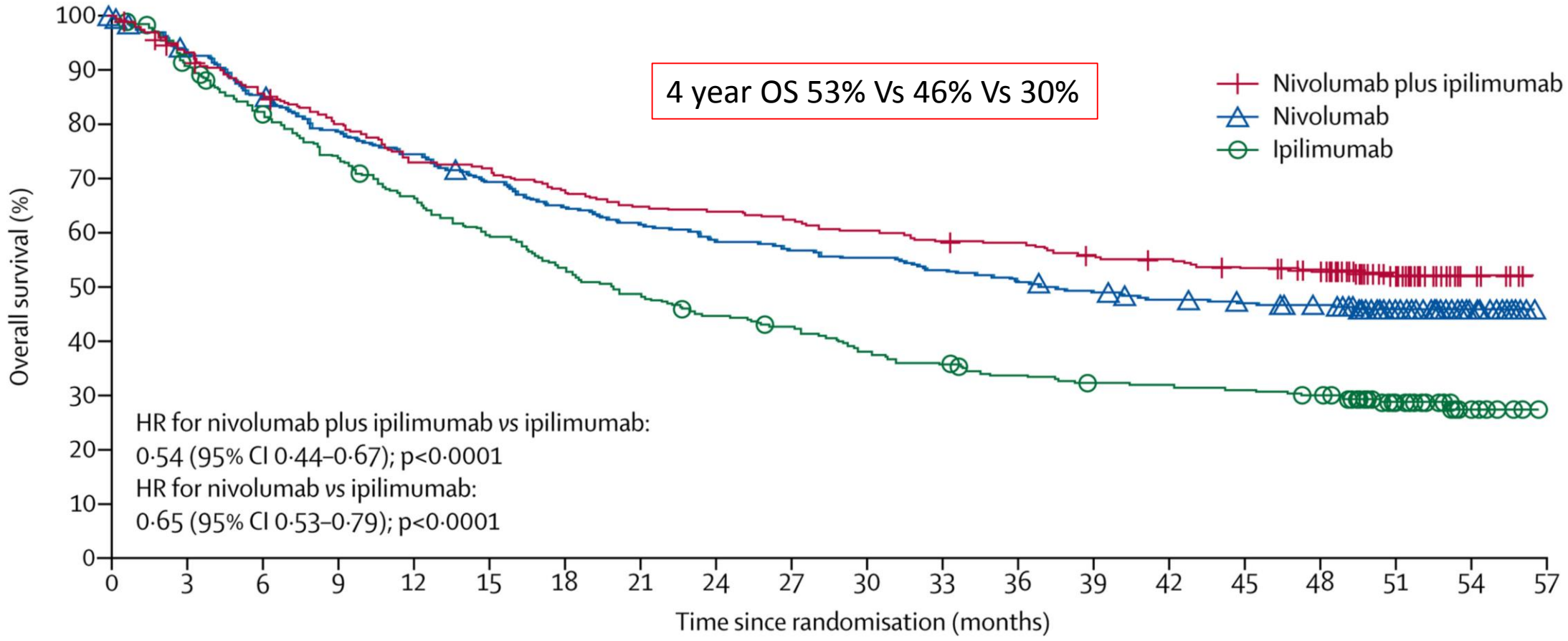


4 year PFS 37% Vs 31% Vs 9%

Hodi et. al. Lancet Oncol 2018

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

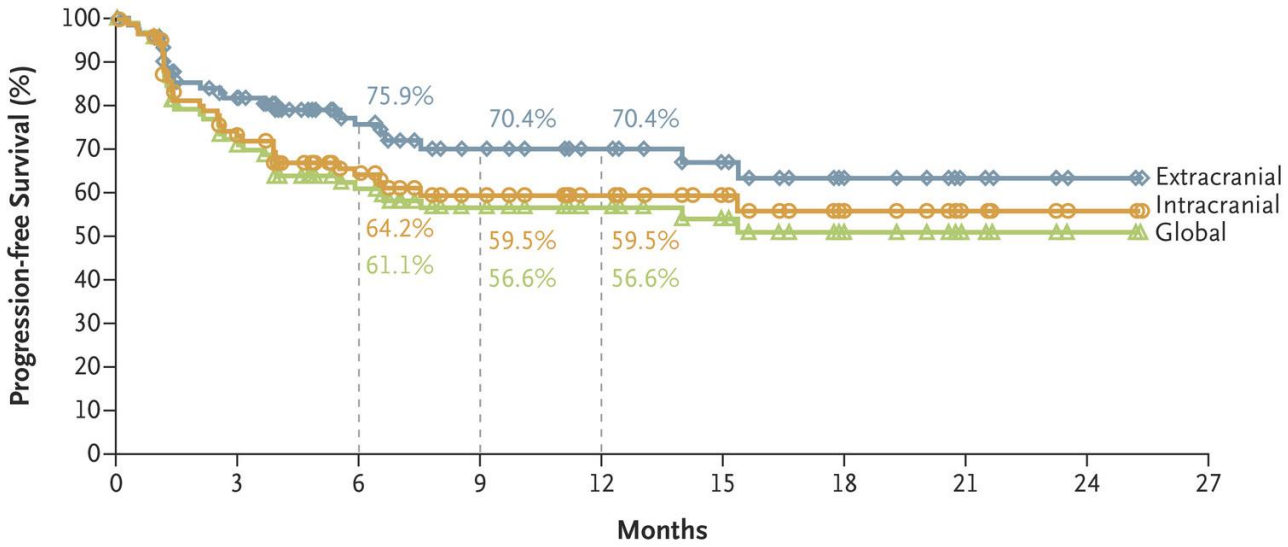
Phase III CheckMate 067 Trial



Hodi et. al. Lancet Oncol 2018

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)



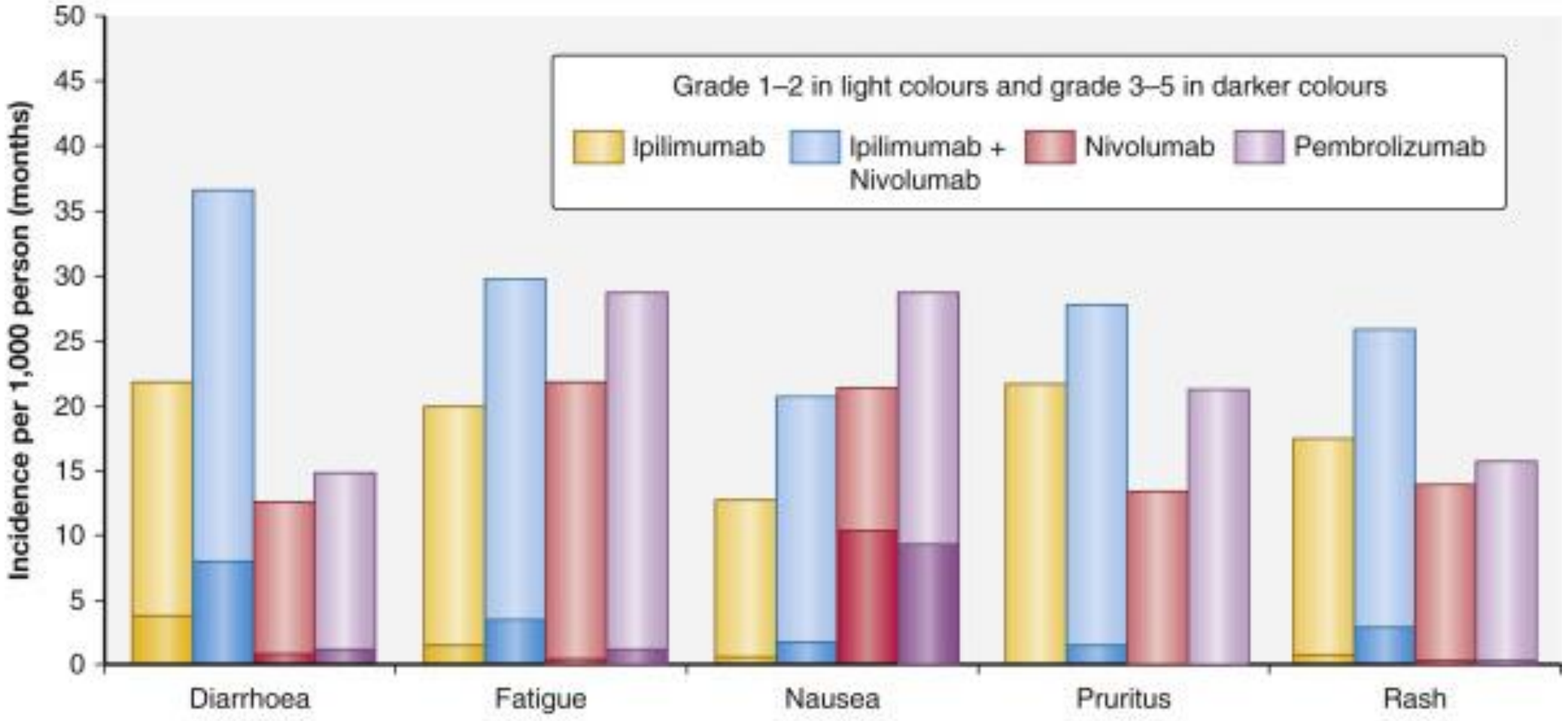
Tawbi et al. NEJM 2018

Safety Summary

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	95.8	59.1	86.3	22.4	86.2	27.7
Treatment-related AE leading to discontinuation, %	40.3	30.4	12.5	8.0	15.1	13.5
Treatment-related death, n (%)	2 (0.6)		1 (0.3)		1 (0.3)	

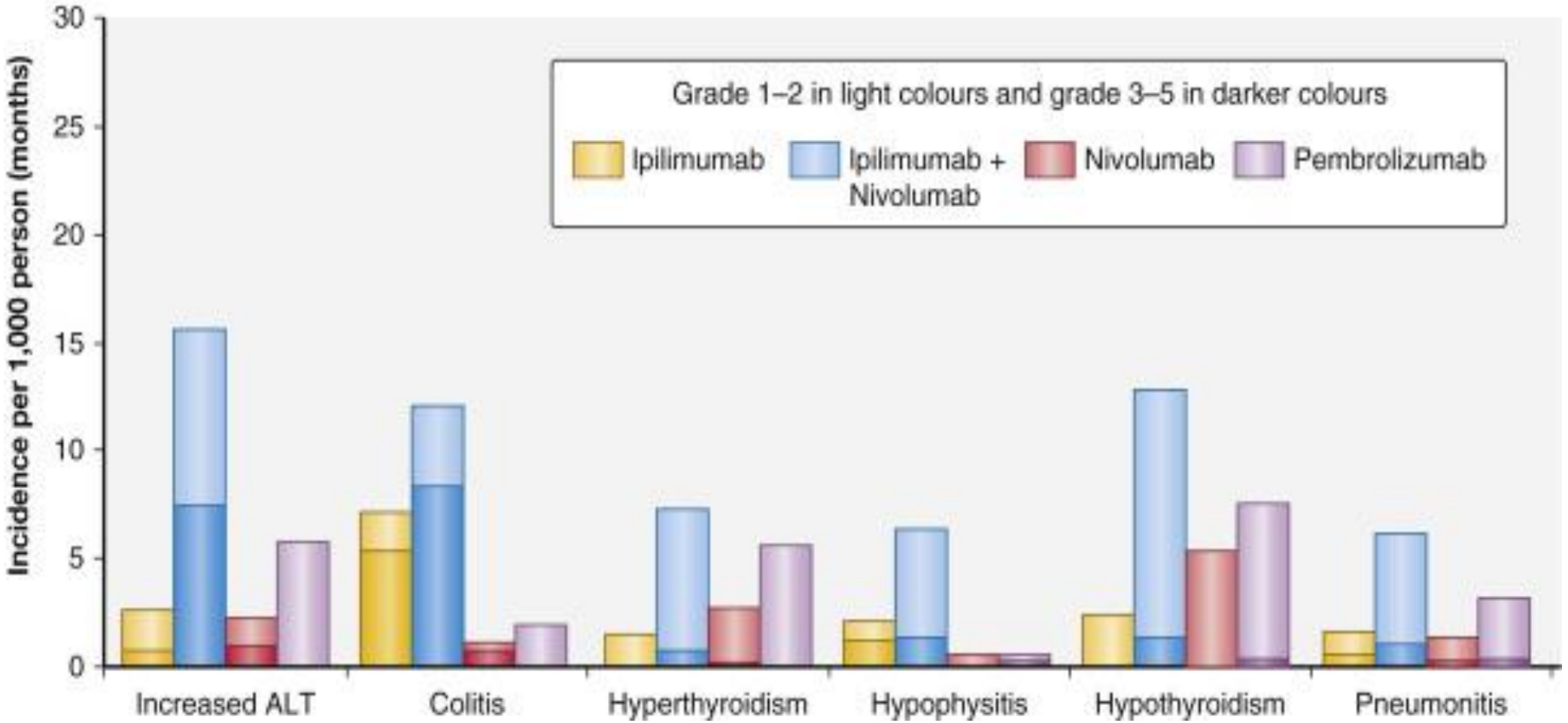
- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis
  - Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each and both occurred >100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1)
- Patients who discontinued NIVO+IPI during induction due to a treatment-related AE had similar 4-year PFS (35%) and OS (54%) to patients in the overall population (37% and 53%, respectively)

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

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

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

- 68 yo woman diagnosed with a back melanoma in 1996
- Had a subsequent axillary recurrence in 2000 and underwent resection and 3 years of levamisole
- In 2012 developed Brain met in frontal lobe and underwent resection
- In 2013 developed bowel metastases and an obstruction and required surgery
- She also had lung, adrenal, spleen and nodal metastases

Case Study 1

- Went on to receive 2 cycles of DTIC and progressed
- She was referred to us for clinical trial in Nov 2013 with new metastatic melanoma to brain, and progression in lungs, adrenals, spleen and nodes
- She received SRS for her 5 brain lesions in Nov 2013
- She went on participate in the Keynote 006 trial and was randomized to Q2 weekly pembrolizumab starting Feb 4, 2014
- After 3 doses she developed uveitis in her Rt eye and treatment was held

Case Study 1

- Was seen by Ophthalmology and started on prednisone drops
- Uveitis resolved and resumed treatment
- She was held several times due to worsening bilateral uveitis with decreased ocular pressure and stopped her treatment due to the uveitis after 17 treatments In Oct 2014
- She also developed striking vitiligo affecting her skin, eye lashes, eye brows and hair
- Was last seen Jan 2019 and MRI shows stable small brain lesions and CTscans show stable lesions with some continuing to decrease

Case study 2

- 66 yo woman diagnosed with vaginal melanoma in March 2018
  - Excision and SLNB: 5mm ulcerated with 1/6 nodes positive with a 10 mm focus
- June 2018: Vaginal recurrence and pelvic nodes as well as bone metastases
- Started Pembrolizumab July 13, 2018
- 5 days later admitted to community hospital with fever and feeling unwell
  - No focus of infection found, fever never resolved
  - discharged after 8 days

Case Study 2

- Seen in clinic after discharge:
  - Looked very unwell, very fatigued couldn't get out of bed
  - Had been having ongoing fevers 38 – 40C, malaise, edema
  - Imaging at previous hospital showed splenomegaly and no focus of infection
- What would you do next?
  - Admit to hospital
  - Bloodwork, cultures
- Admitted and bloodwork shows:
  - HB 106, WBC 2.0, Neuts 1.2, Plts 120
  - Alt 68 ALK 133

Case Study 2

- What's the diagnosis?
  - Cytokine release syndrome Vs hemophagocytic lymphohistiocytotis (HLH)
- What do you do next?
  - Started IV solumedrol, hematology consult
- Next day was sitting up, fever gone and felt a lot of better, looked like a different person
- Hematology consult:
  - Her Hscore is 198 which correlates with a 86.8% of having HLH
  - Switched to dexamethasone

Case Study 2

- She improved and was discharged home a few days later
- 1 week later presented back to ER with watery diarrhea 8-10 BM/day
- Was on tapering doses of dexamethasone 8mg/day
- What do you do now?
  - Admit and treat as colitis – IV steroids
- Improved with steroids and discharged home on taper
- CTscans showed that her disease had responded until 1month ago
- Now progressing
- Would you retreat with pembrolizumab?