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# Immunotherapy for the treatment of Melanoma

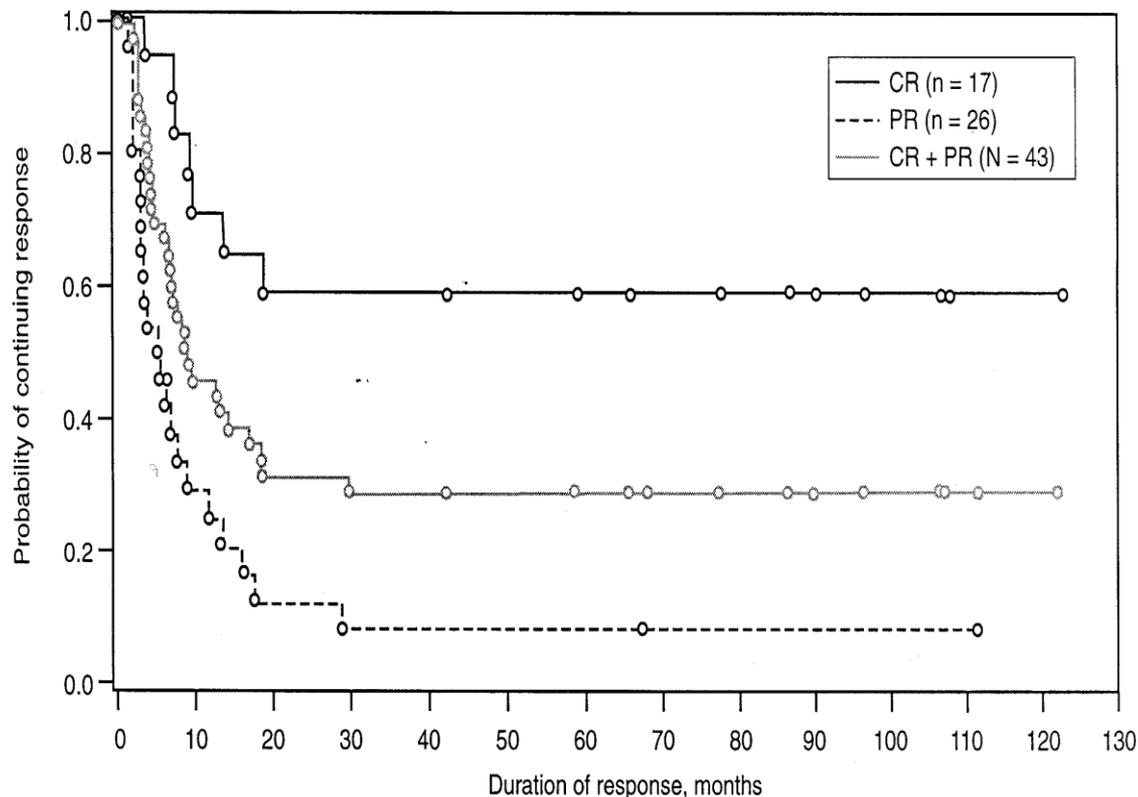
Elizabeth Buchbinder, MD  
Physician, Melanoma Disease Center  
Dana-Farber Cancer Institute  
Instructor, Harvard Medical School

# Disclosures

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- DFCI receives clinical trial support from Merck and Bristol Myers Squibb
- Dr. Buchbinder has received consulting fees from Biodesix and Karyopharm
- Non-FDA approved treatments will not be discussed

# High Dose IL-2 Therapy

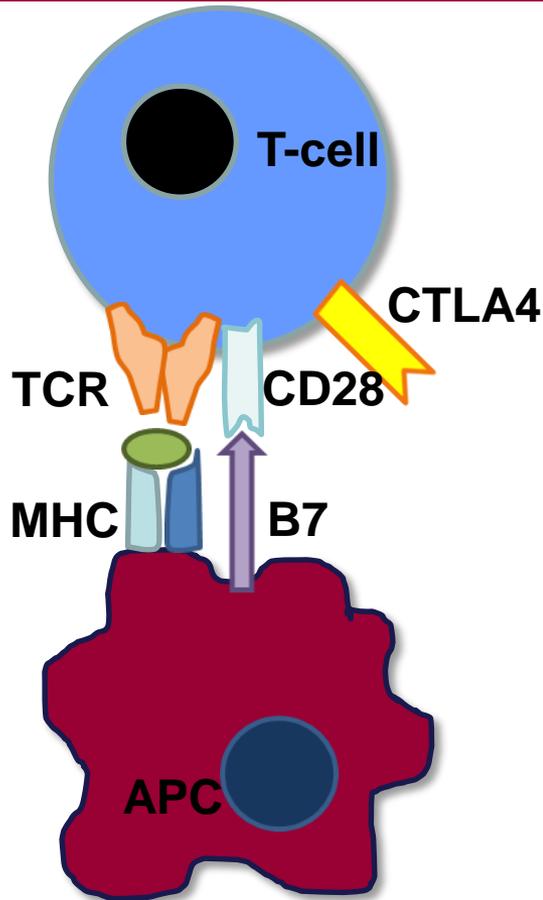


- RR: 16% (43 / 270)
  - Some large volume and visceral
  - Most soft tissue and lung
- Durable responses
  - Median 8.9 mos
  - CR: not reached
- Survival
  - Median 12 mos
  - 11% >@ 5yrs

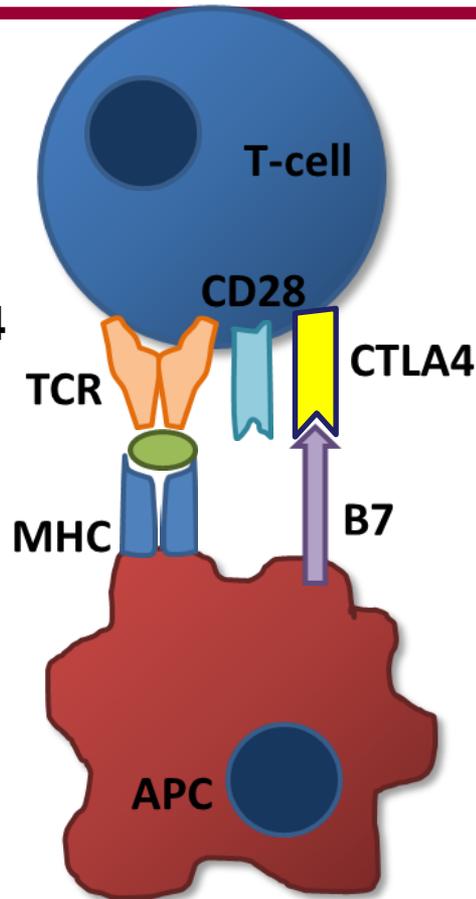
Atkins et al JCO, 1999 (N=270)

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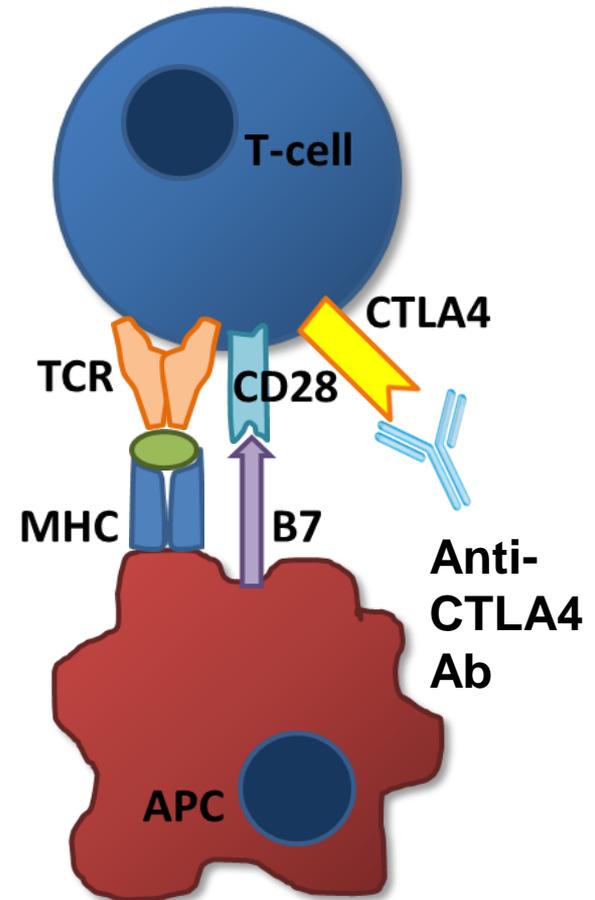
T-cell  
Activation



T-cell  
Inhibition



T-cell remains  
activated



# CTLA-4 inhibition

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*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

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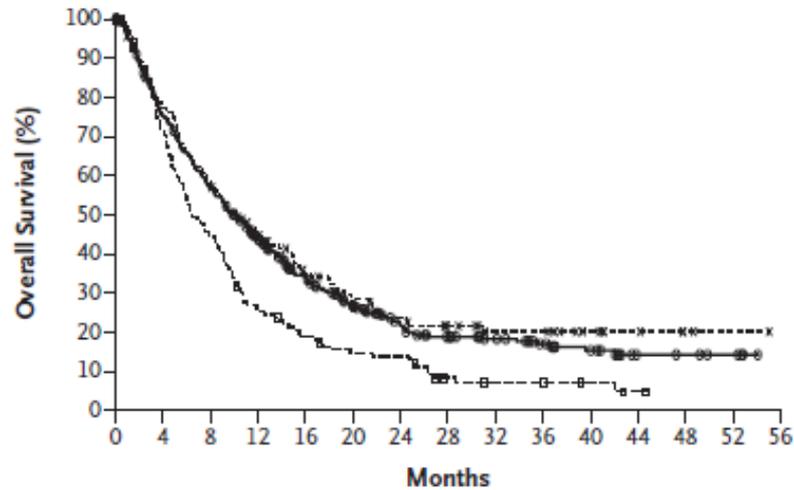
Improved Survival with Ipilimumab in Patients  
with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Qirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

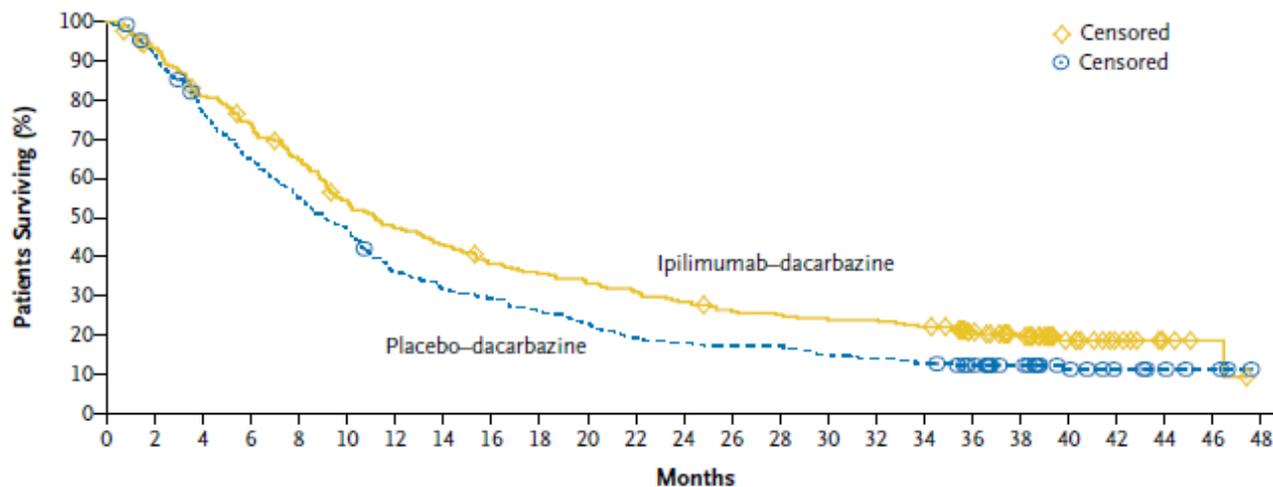
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# Ipilimumab

Overall Survival

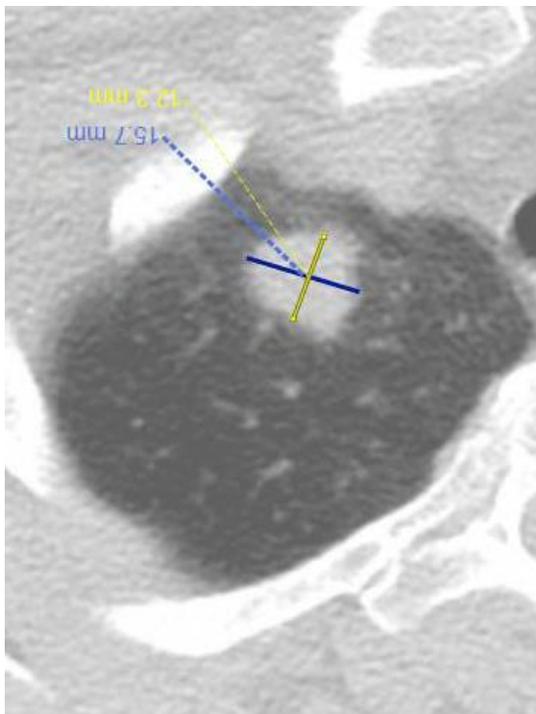


Hodi *et al*, NEJM 2010

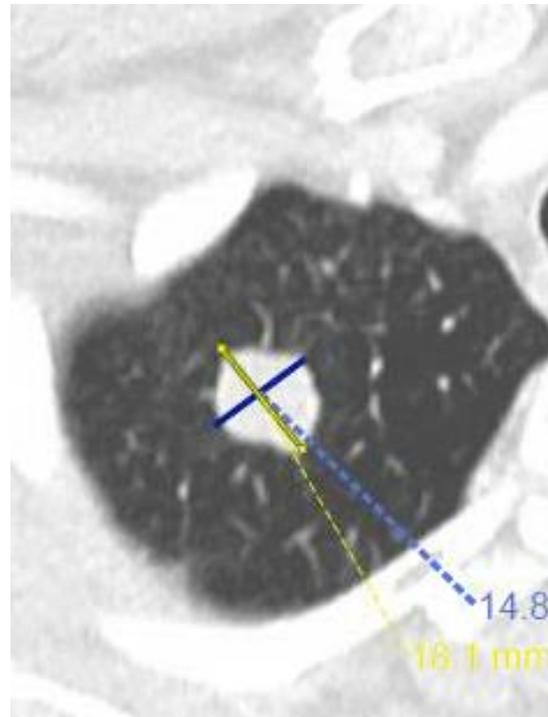


Robert *et al*,  
NEJM  
2011

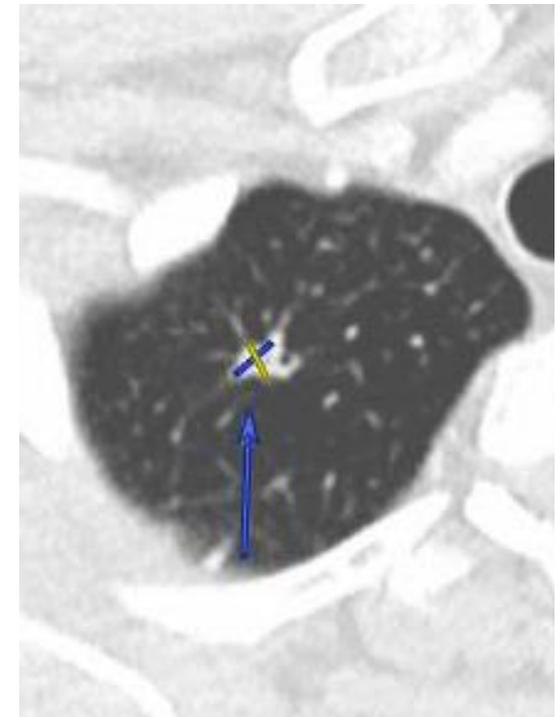
## CTLA4 Ab Treatment: Immune response criteria



Baseline

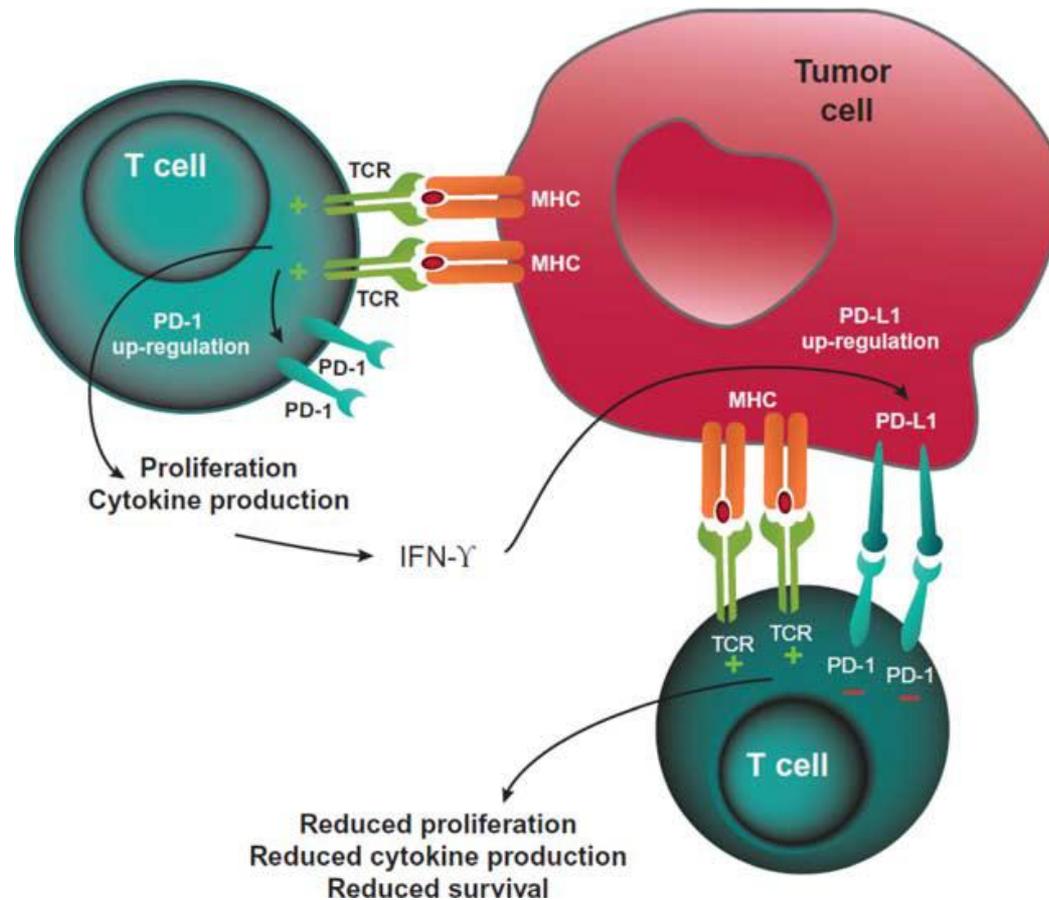


3 months



4 months

# PD-1 mediated inhibition of T cells





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# Nivolumab

VOLUME 32 · NUMBER 10 · APRIL 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Survival, Durable Tumor Remission, and Long-Term Safety  
in Patients With Advanced Melanoma Receiving Nivolumab

*The* NEW ENGLAND JOURNAL of MEDICINE

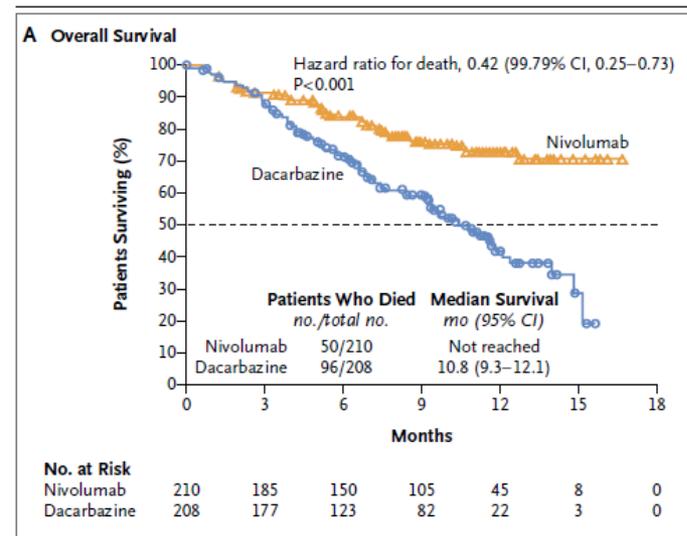
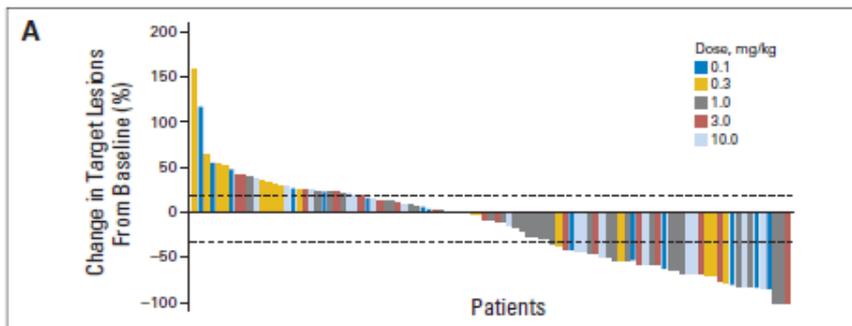
ORIGINAL ARTICLE

Nivolumab in Previously Untreated  
Melanoma without BRAF Mutation

# Nivolumab

Overall Response Rate  
after Ipilimumab: 31%

Overall Response Rate  
Front line therapy: 40%



Topalian et al. JCO 2013  
Robert et al. NEJM 2015

# Pembrolizumab

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Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial

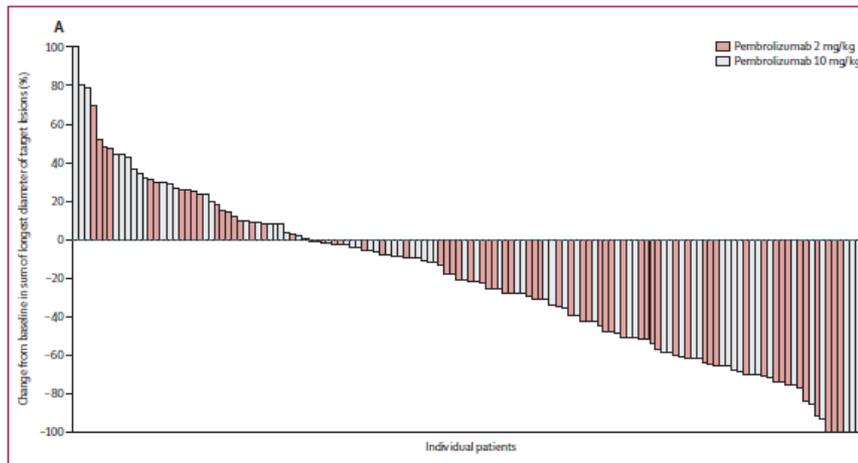
*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

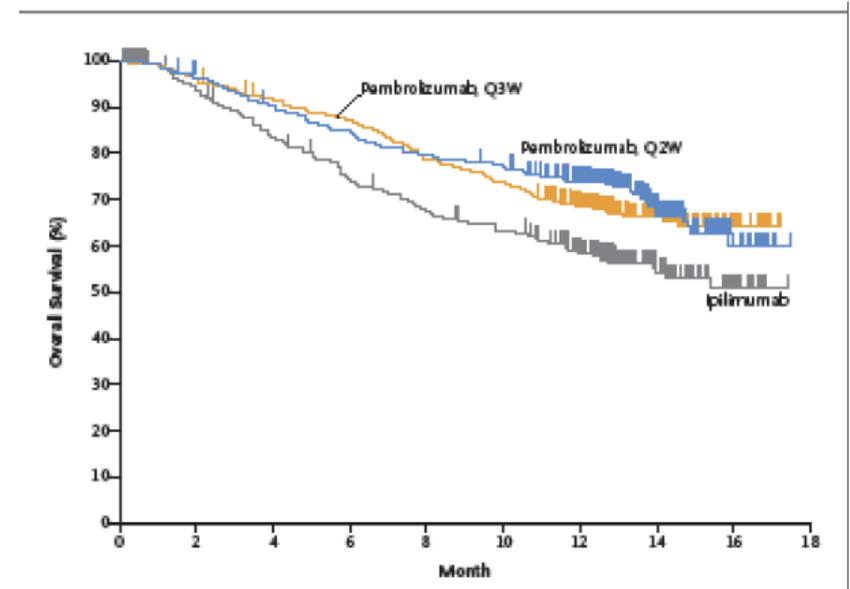
Pembrolizumab versus Ipilimumab  
in Advanced Melanoma

# Pembrolizumab

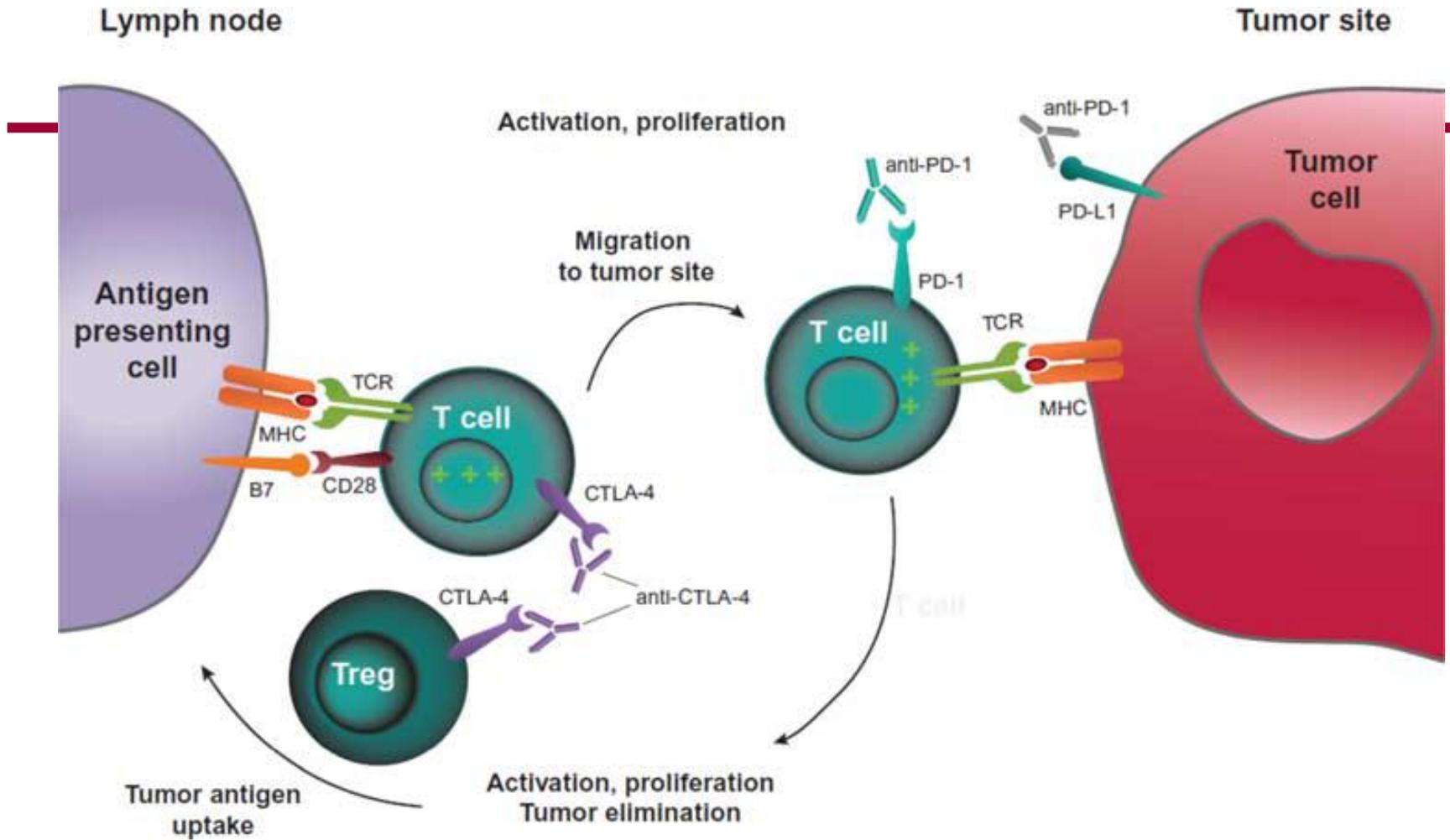
Overall Response Rate  
after Ipilimumab: 26%



Overall Response Rate  
Front line therapy: 34%



Robert et al. The Lancet 2014  
Robert et al. NEJM 2015



ORIGINAL ARTICLE

## Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao,  
D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill,  
J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas,  
G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow,  
K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak,  
F.S. Hodi, and J.D. Wolchok

ABSTRACT

# Ipilimumab plus Nivolumab

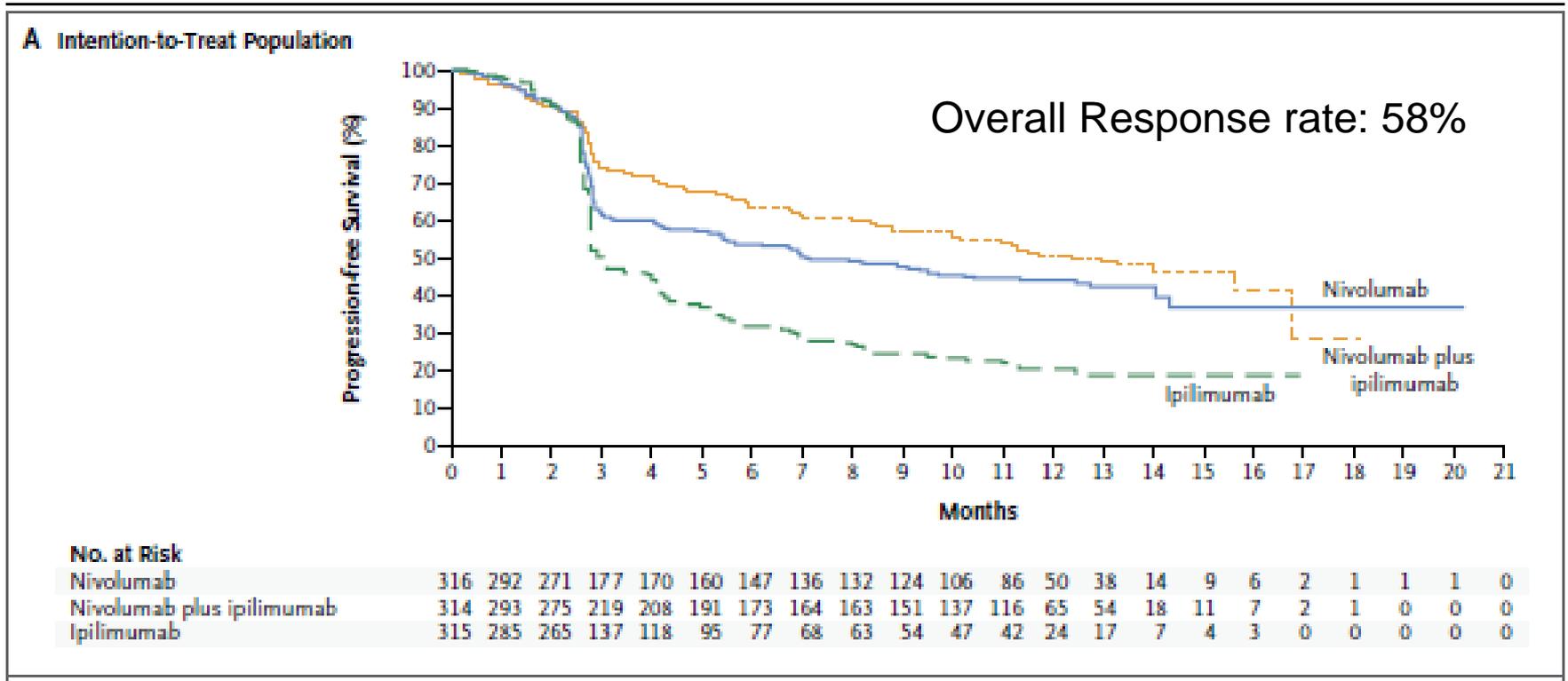


Table 3. Adverse Events.\*

Event	Nivolumab (N= 313)		Nivolumab plus Ipilimumab (N= 313)		Ipilimumab (N= 311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	<i>number of patients with event (percent)</i>					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino- transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino- transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

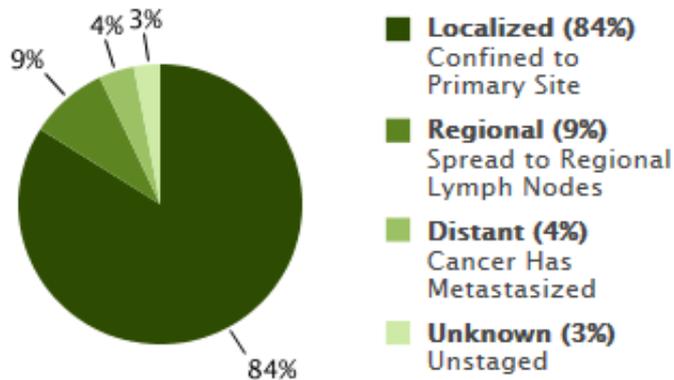
\* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

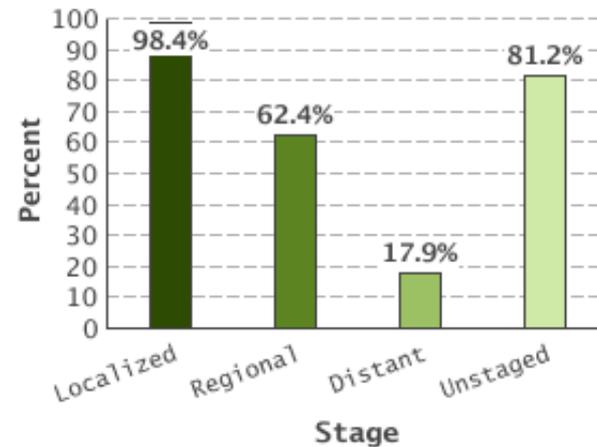
# Stage at Diagnosis

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Melanoma of the Skin

Percent of Cases by Stage



5-Year Relative Survival

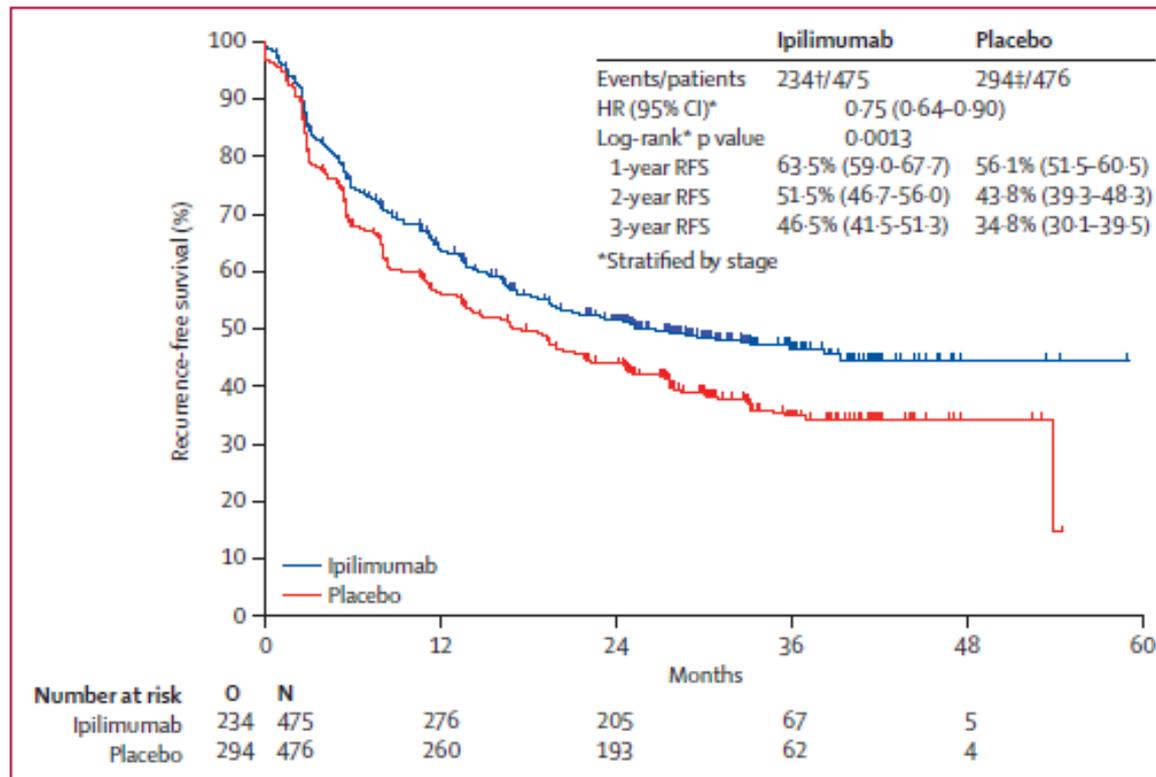


## In Australia initial stage of presentation in patients who died from melanoma

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- <1 mm melanoma – 23% of deaths
- 1-2 mm melanoma – 21% of deaths
- 2-4 mm melanoma – 20% of deaths
- >4 mm melanoma – 14% of deaths
- Metastatic at presentation – 16% of deaths

# EORTC 18071



Eggermont et al. The Lancet Oncology 2015

# ECOG 1609

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High dose Interferon  
Induction: 20 MU/m<sup>2</sup>/d IV 5 days/week for 4 weeks  
Maintenance: 10 MU/m<sup>2</sup>/d SC 3Xweek for 48 weeks

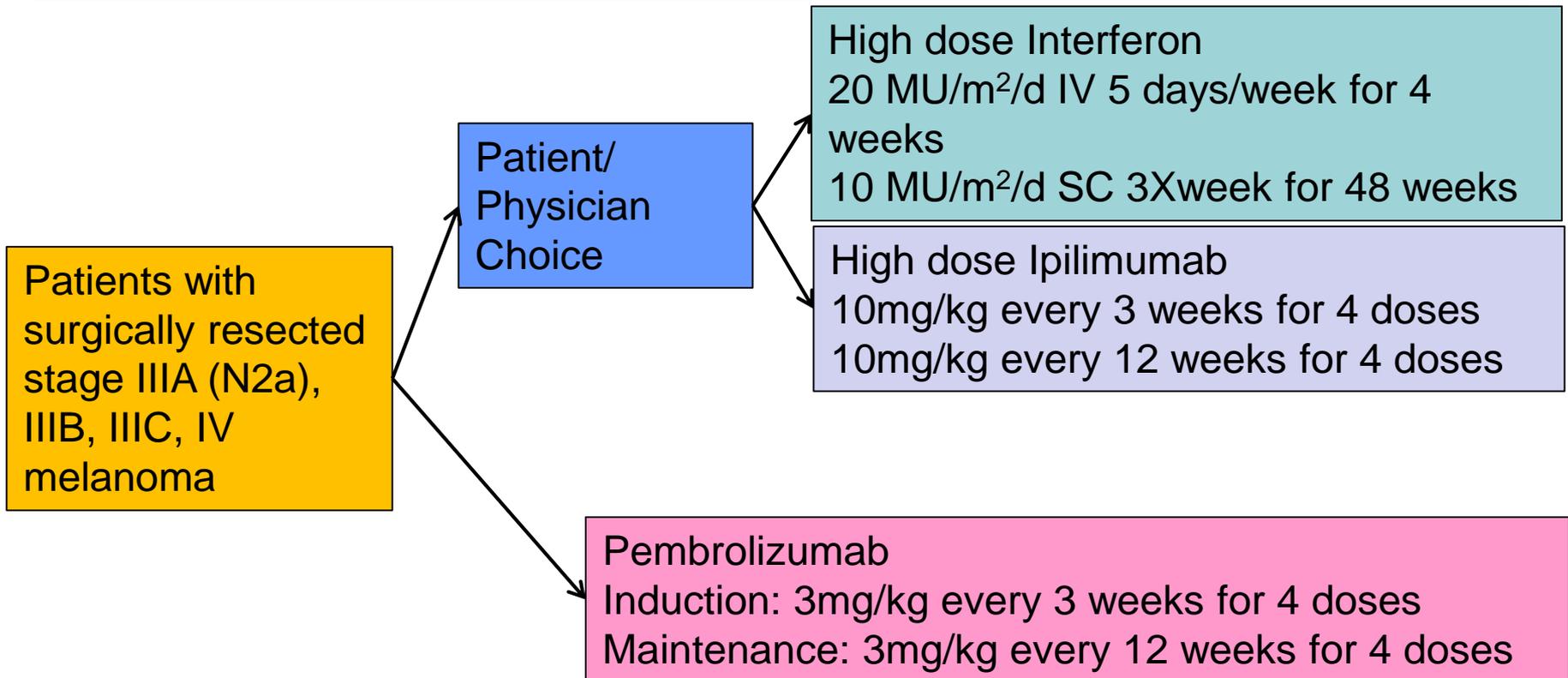
High dose Ipilimumab  
Induction: 10mg/kg every 3 weeks for 4 doses  
Maintenance: 10mg/kg every 12 weeks for 4 doses

Low dose Ipilimumab  
Induction: 3mg/kg every 3 weeks for 4 doses  
Maintenance: 3mg/kg every 12 weeks for 4 doses

Patients with  
surgically resected  
stage IIIB, IIIC,  
M1a, M1b  
melanoma

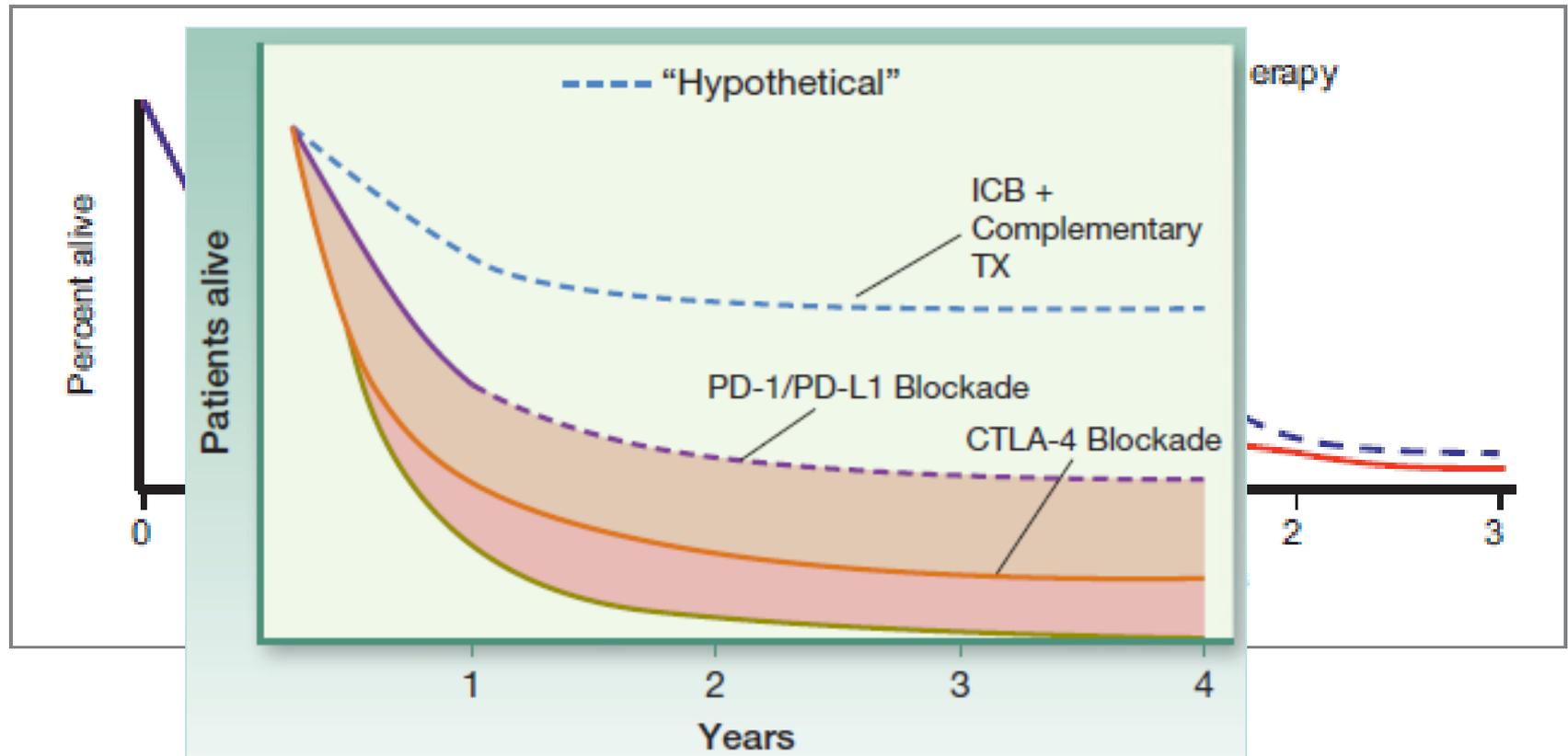
NCT01274338

# SWOG 1404



NCT01274338

## Combination therapy: “lifting the overall survival curve”



# Immunotherapy is rapidly changing clinical care

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- Timing of immunotherapy
- Sequencing of immunotherapy
- Changing paradigms

## Case 1

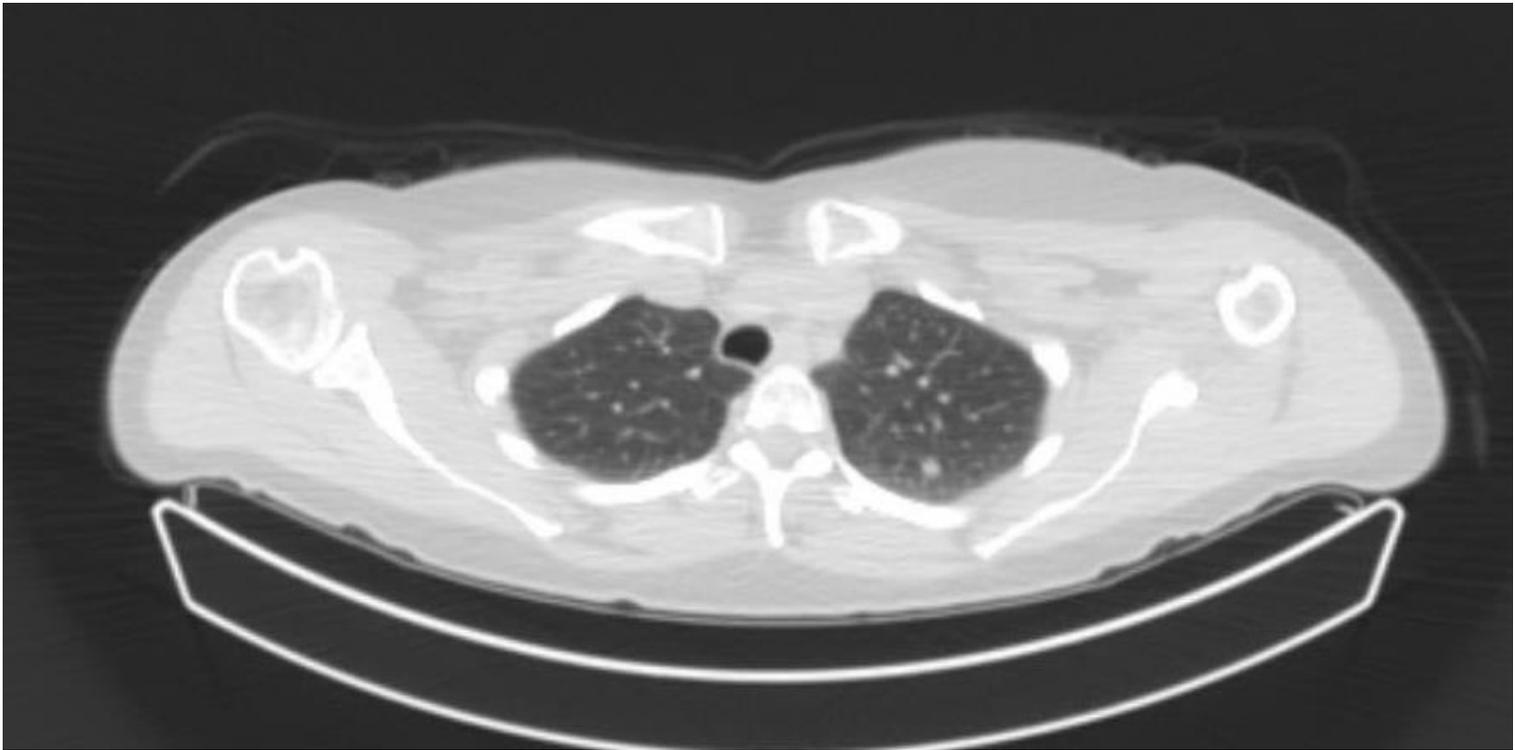
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- 56 year old female with T4bN0/IIC melanoma in June 2015
- On routine follow up imaging in September 2015 she had a new FDG-avid 5mm lung nodule.
- Biopsy performed which came back positive for melanoma.

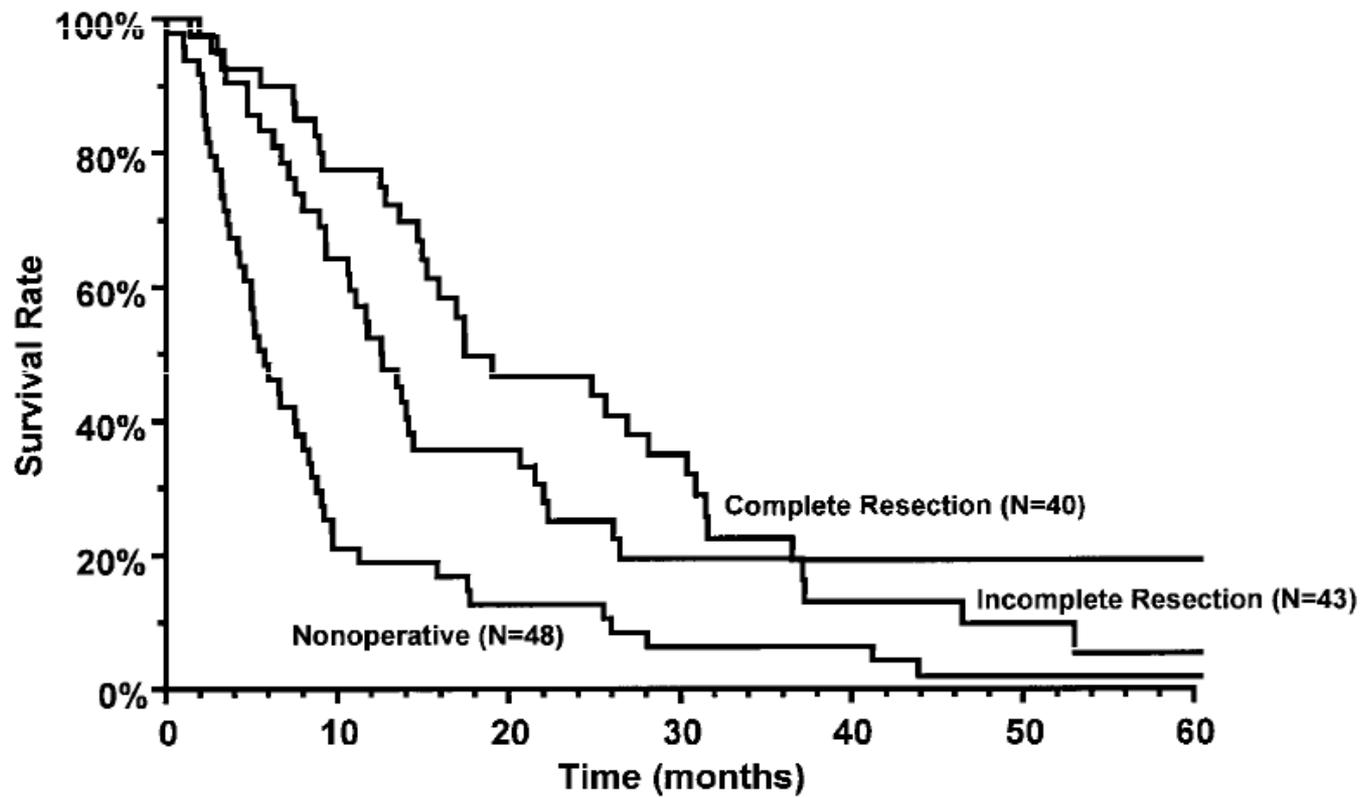
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# Imaging

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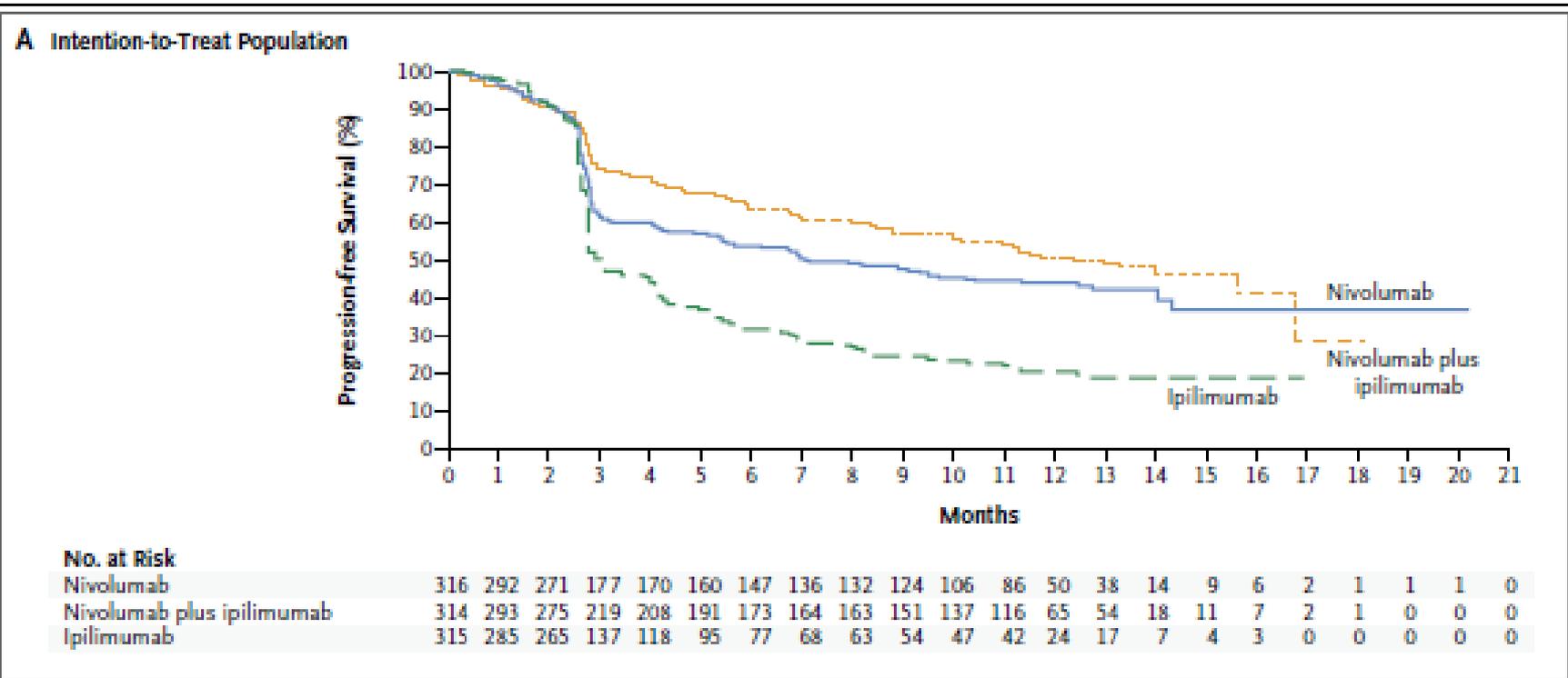


# Metastatectomy in melanoma



Ollilia et al. J Surg Onc 1999

# Systemic therapy



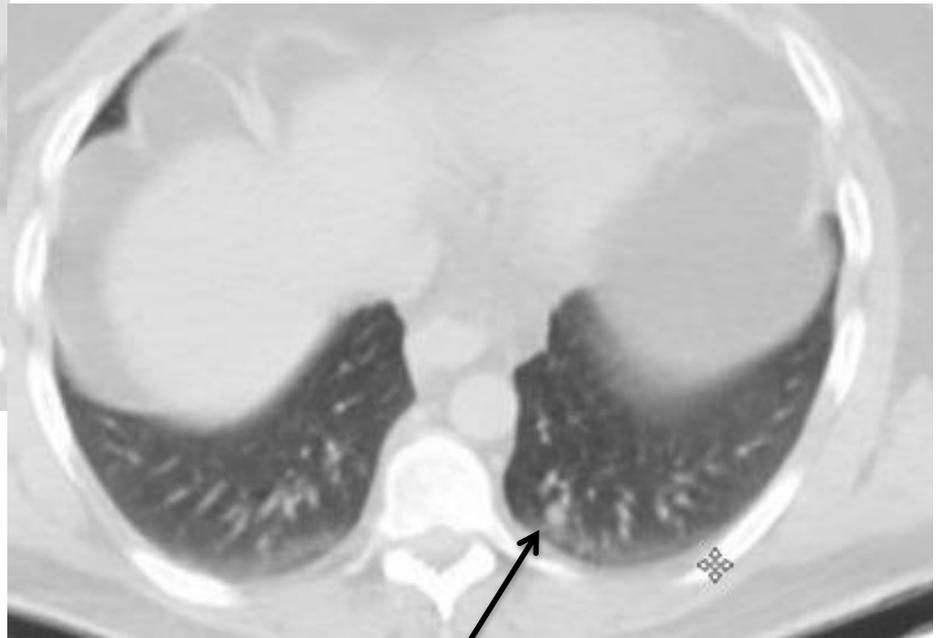
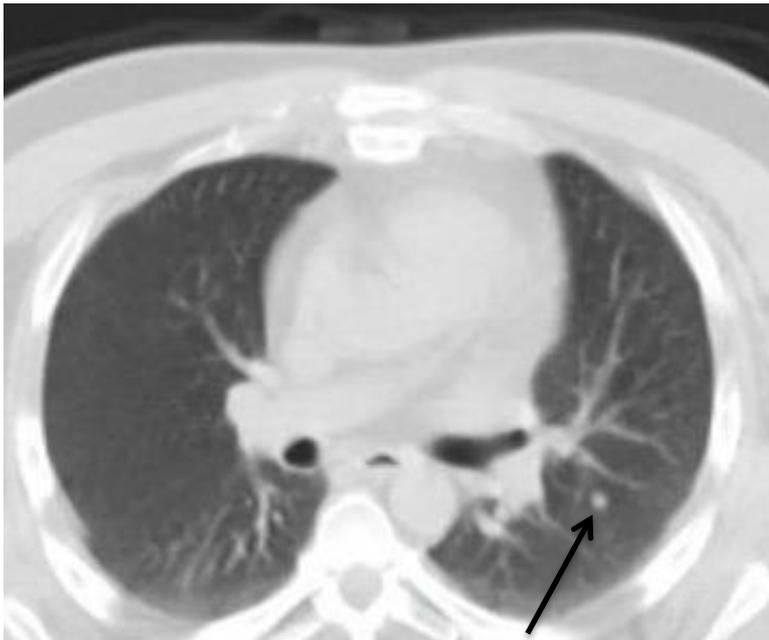
## Case 2

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- 39 year old male diagnosed with a thick primary melanoma (stage IIC) in 2011
- Treated with surgery and adjuvant interferon
- Had numerous local recurrences in 2015 treated with surgical excision
- Presents in March of 2016 with numerous pulmonary nodules.

## Numerous small pulmonary nodules

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## Biopsy proven metastatic melanoma

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- Mutation testing reveals BRAF V600E mutation
- What treatment do you start with?
- If the patient chooses immunotherapy do you use single agent PD1 or combination ipilimumab and nivolumab?