Adjuvant and Neoadjuvant Therapy for Melanoma

Surgical Oncology Fall Update

October 5, 2019

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Medical Oncology/Palliative Care

BC Cancer, Vancouver Centre

Objectives

- Understand the mechanism of action of our systemic therapies
- Make aware the adjuvant data following complete resection
- Know the indications for referral for adjuvant therapy
- Understand where we are with regards to neoadjuvant therapy
- Talk about approaches to cases that are not upfront resectable

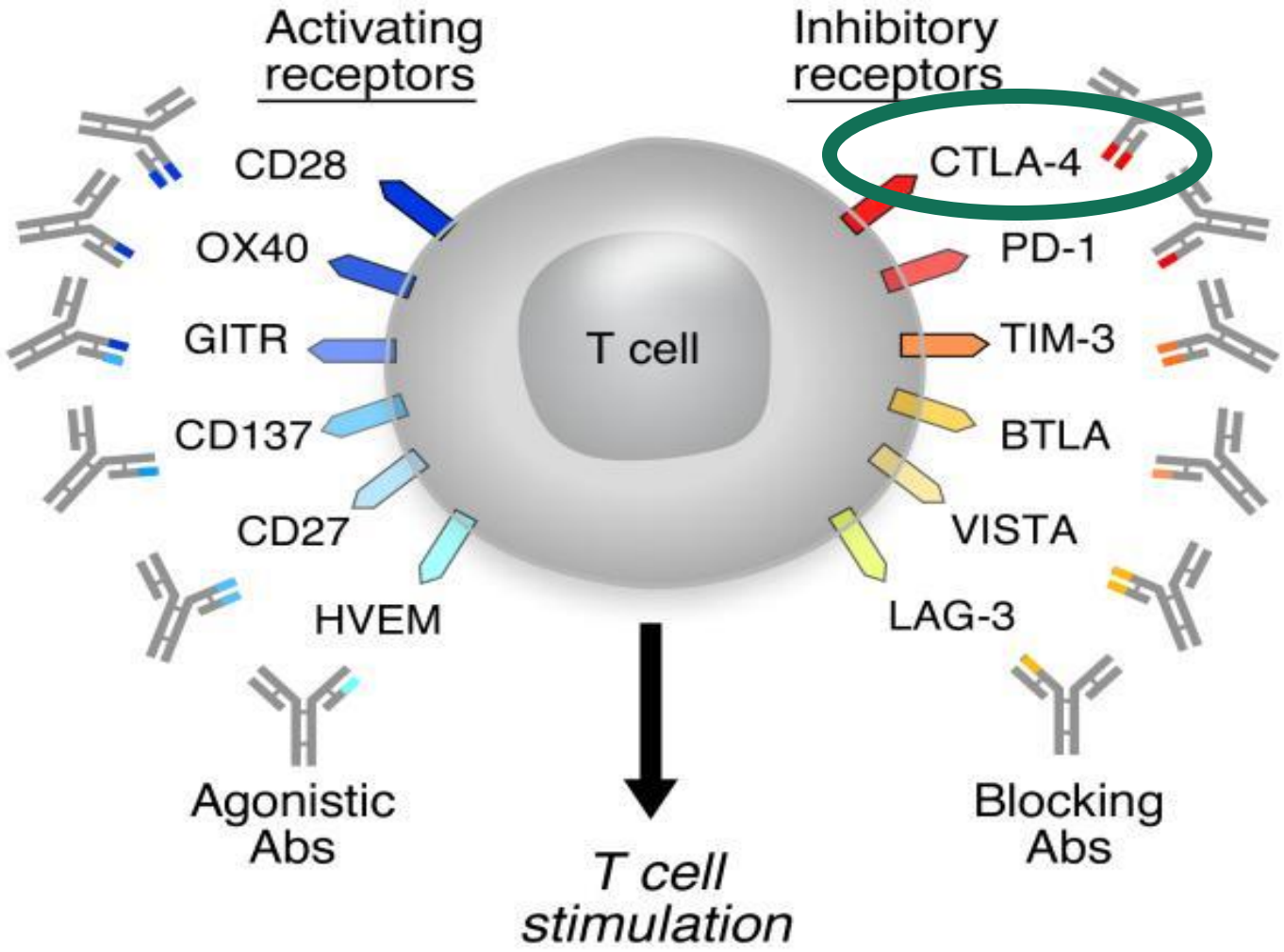
Disclosures

- I have received speaking honoraria from Merck
- I have used slides from Merck, BMS and Novartis with their permission

WHAT IS IMMUNOTHERAPY?

Immuno-Oncology

Checkpoint Inhibitors



Priming Phase
Periphery

T-cell activation
kines, lysis, proliferation,
migration to tumour)

Ipilimumab

CTLA-4 pathway blockade

August, 2010

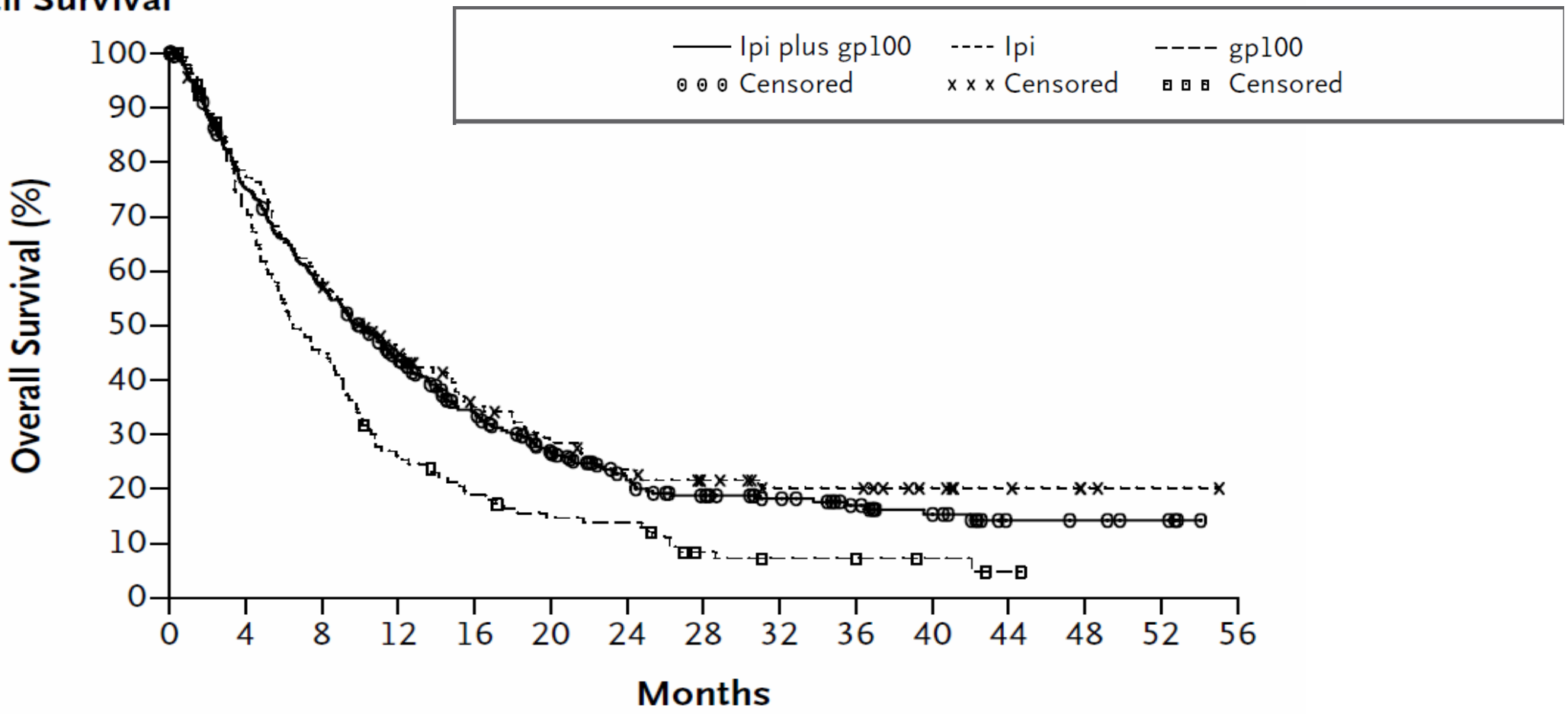
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

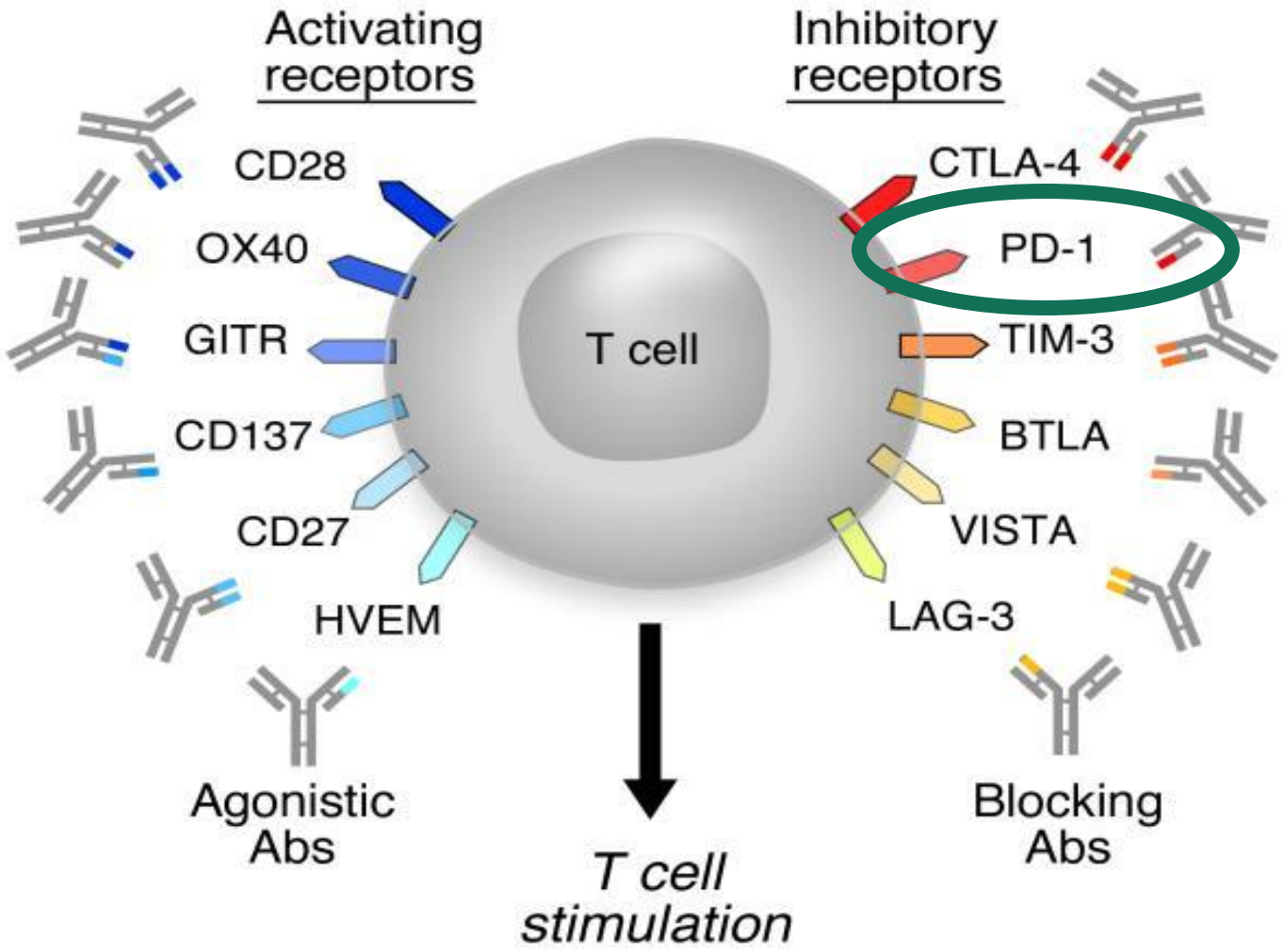
F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., 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 Quirt, 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.

A Overall Survival



No. at Risk

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0


Activating receptors
Inhibitory receptors
CD28
OX40
GITR
CD137
CD27
HVEM
CTLA-4
PD-1
TIM-3
BTLA
VISTA
LAG-3
T cell
Agonistic Abs
Blocking Abs
T cell stimulation

Ef

Tumour

Nivolu

Pembr

PD-1 pathway blockade

September 2017

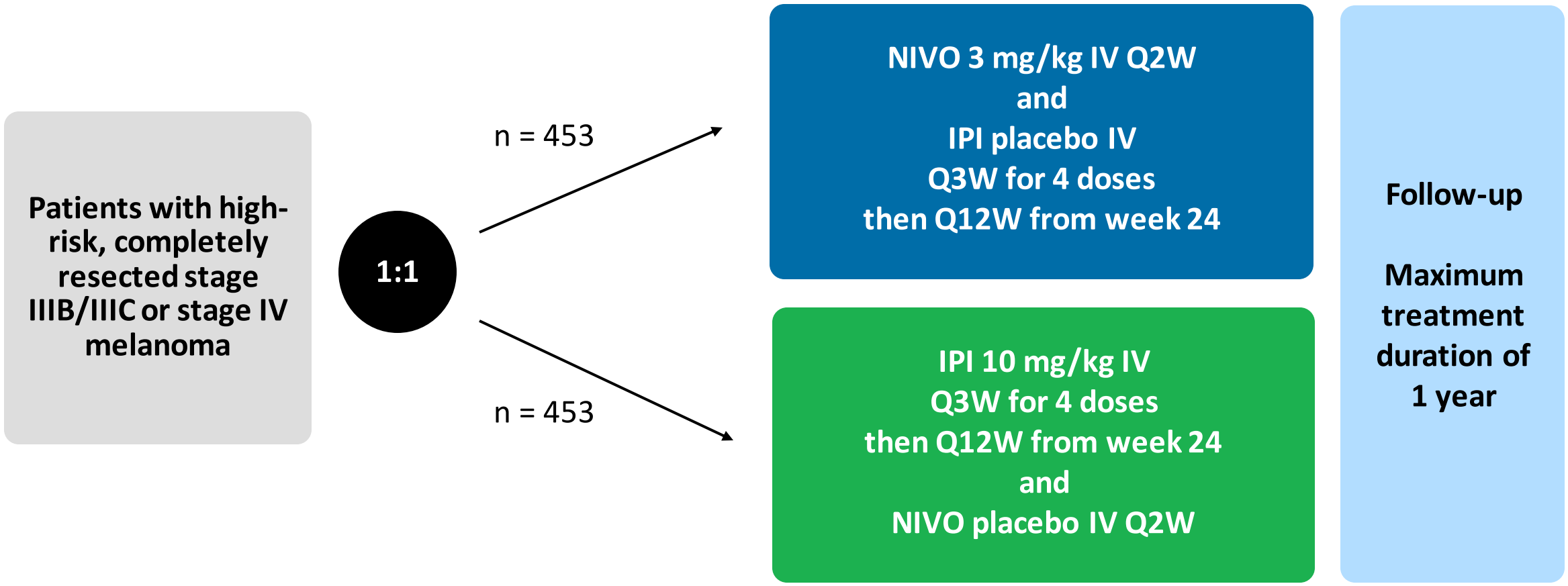
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

CA209-238: Study Design



Enrollment period: March 30, 2015 to November 30, 2015

Weber ESMO 2017

Key Eligibility Criteria

- At least 15 years of age
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Histologically confirmed melanoma metastatic to regional lymph nodes or with distant metastases surgically rendered free of disease
  - Stage IIIB, IIIC, or stage IV melanoma by the American Joint Committee on Cancer 2009 classification, 7th edition
  - Complete regional lymphadenectomy or resection was required within 12 weeks of randomization
- Patients with ocular/uveal melanoma, systemic corticosteroid use >10 mg/day of prednisone or equivalent, or previous systemic therapy for melanoma were excluded
  - Acral and mucosal melanoma were allowed

Study Overview

Primary endpoint

- RFS: time from randomization until first recurrence (local, regional, or distant metastasis), new primary melanoma, or death

Secondary endpoints

- OS
- Safety and tolerability
- RFS by PD-L1 tumor expression
- HRQoL

Current interim analysis

- Primary endpoint (RFS), safety, and HRQoL
  - DMFS (exploratory)
- Duration of follow-up: minimum 18 months; 360 events

DMFS = distant metastasis-free survival; HRQoL = health-related quality of life

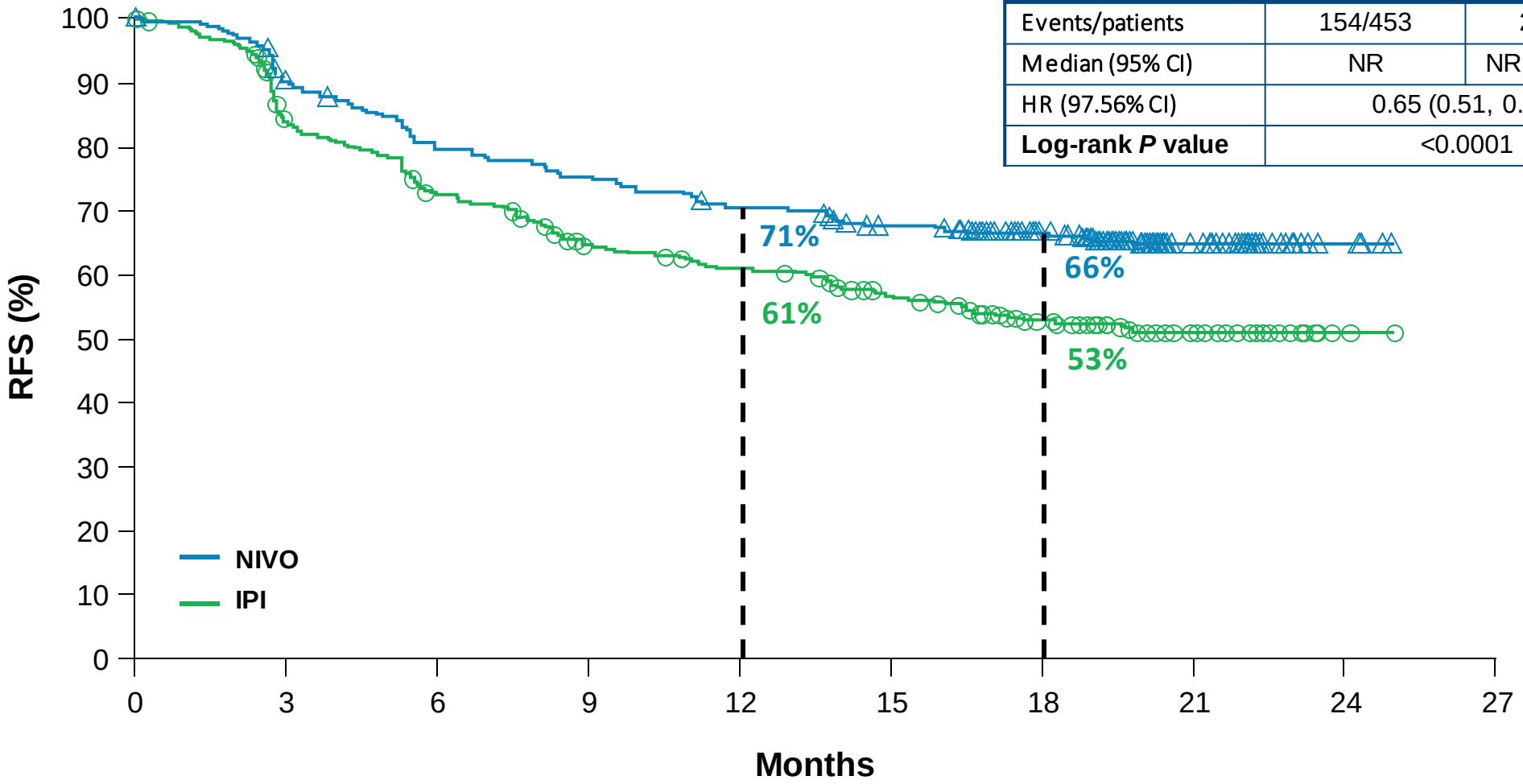
Baseline Patient Characteristics

	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage, **IIIB+IIIC, %**	81	81
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastases (% stage IV)	17	17
PD-L1 expression **≥5%, %**	34	34
BRAF mutation, %	41	43
LDH ≤ ULN, %	91	91

- Most of the patients had cutaneous melanoma (85%), and 4% had acral and 3% had mucosal melanoma
- All 905 patients are off treatment; median doses were 24 (1-26) in the NIVO group and 4 (1-7) in the IPI group
- 397 patients completed 1 year of treatment (61% of the NIVO group and 27% of the IPI group)

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	



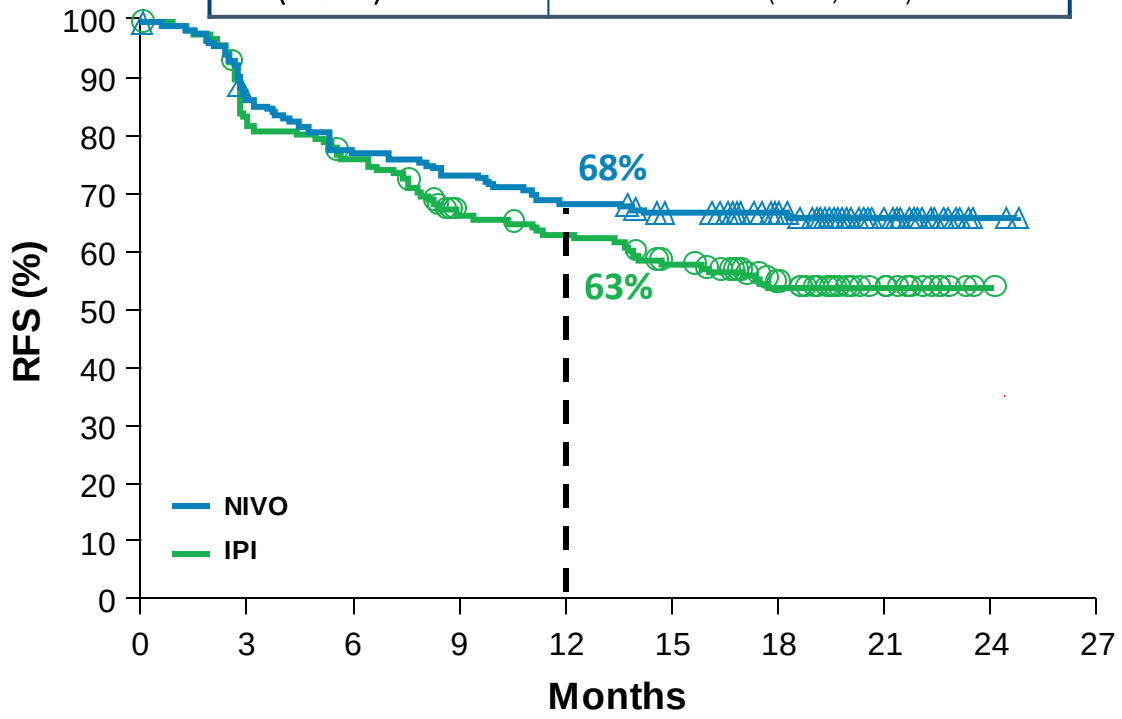
Number of patients at risk

NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

	NIVO	IPI
Events/patients	63/187	84/194
Median (95% CI)	NR	NR (16.1, NR)
HR (95% CI)	0.72 (0.52, 1.00)	

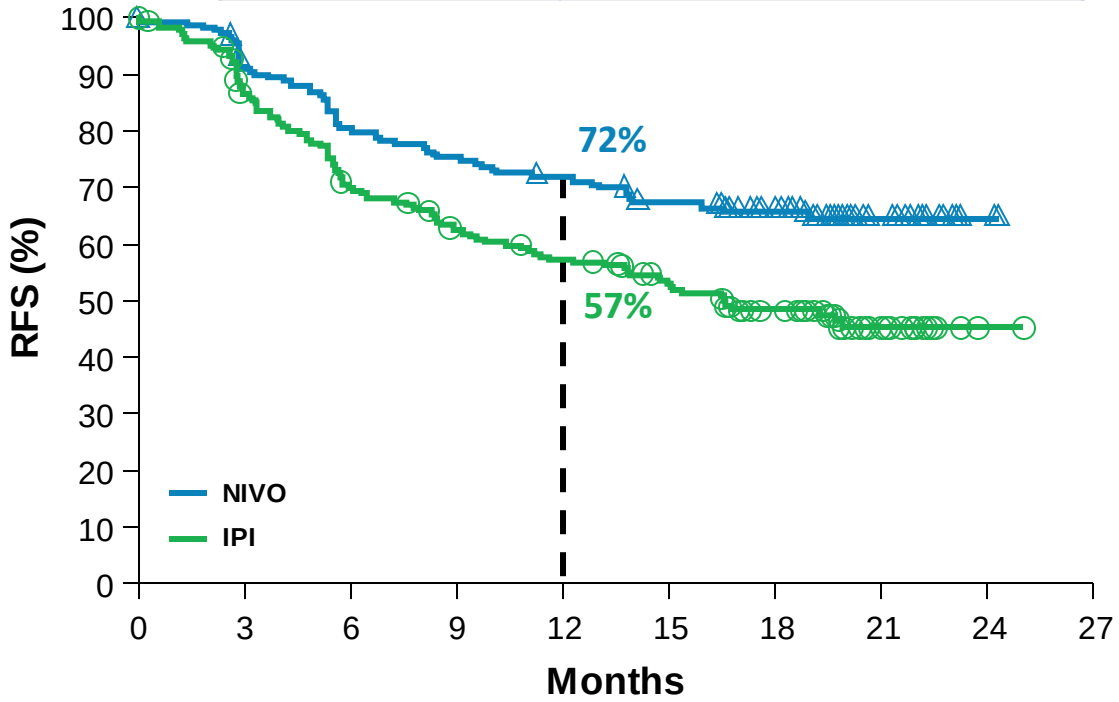


Number of patients at risk

NIVO	187	159	142	135	126	118	102	32	2	0
IPI	194	155	142	118	112	100	78	26	1	0

BRAF Wild type

	NIVO	IPI
Events/patients	67/197	105/214
Median (95% CI)	NR	16.6 (12.3, NR)
HR (95% CI)	0.58 (0.43, 0.79)	



Number of patients at risk

NIVO	197	175	154	145	137	127	108	26	2	0
IPI	214	174	140	122	111	96	80	22	1	0

Safety Summary

AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Treatment-Related Select Adverse Events

AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin	201 (44.5)	5 (1.1)	271 (59.8)	27 (6.0)
Gastrointestinal	114 (25.2)	9 (2.0)	219 (48.3)	76 (16.8)
Hepatic	41 (9.1)	8 (1.8)	96 (21.2)	49 (10.8)
Pulmonary	6 (1.3)	0	11 (2.4)	4 (0.9)
Renal	6 (1.3)	0	7 (1.5)	0
Hypersensitivity/infusion reaction	11 (2.4)	1 (0.2)	9 (2.0)	0
Endocrine				
Adrenal disorder	6 (1.3)	2 (0.4)	13 (2.9)	4 (0.9)
Diabetes	2 (0.4)	1 (0.2)	1 (0.2)	0
Pituitary disorder	8 (1.8)	2 (0.4)	56 (12.4)	13 (2.9)
Thyroid disorder	92 (20.4)	3 (0.7)	57 (12.6)	4 (0.9)

- Median time to onset of treatment-related select AEs was generally shorter for patients receiving IPI (range 2.6-10 weeks) than for those receiving NIVO (range 3.3-14.2 weeks)

May, 2018

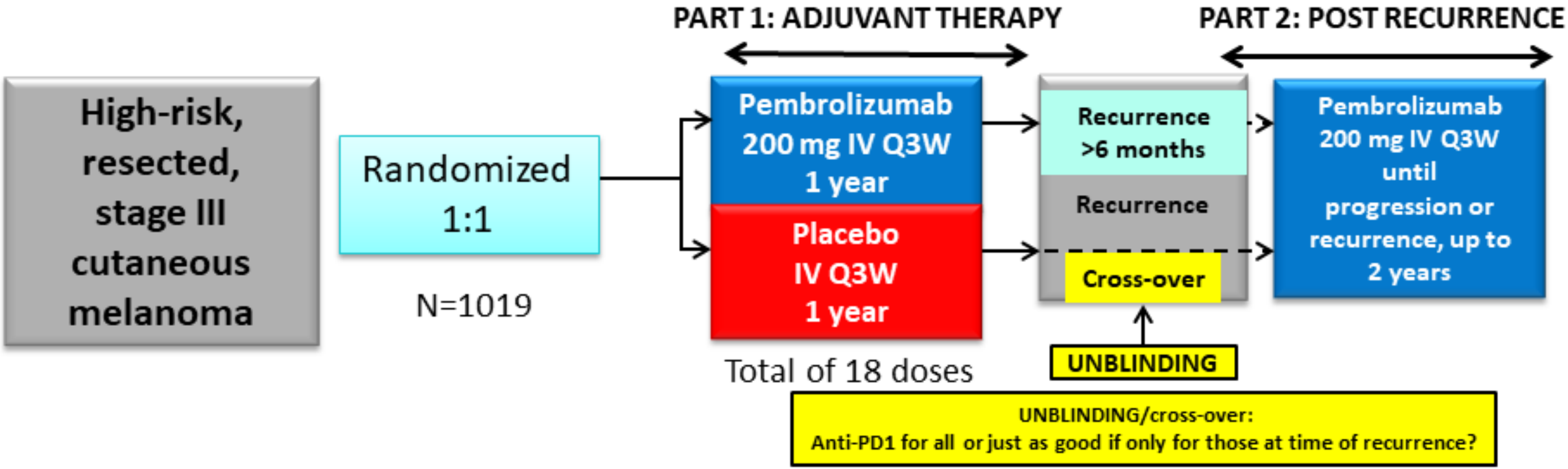
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Mario Mandala, M.D., Georgina V. Long, M.D., Ph.D., Victoria Atkinson, M.D., Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D., Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D., James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D., Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D., Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D., Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D., Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D., Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D., and Caroline Robert, M.D., Ph.D.

EORTC 1325/KEYNOTE-54: Study Design



Stratification factors:

✓ **AJCC-7 Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes

✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

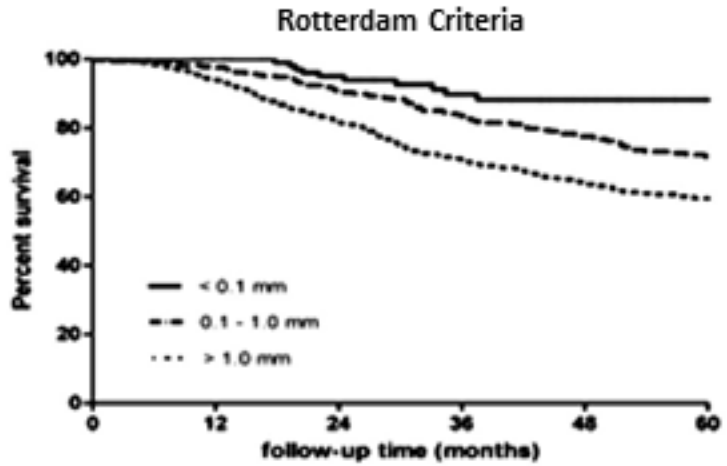
- **RFS (per investigator) in overall population,** and **RFS in patients with PD-L1-positive tumors**

Secondary Endpoints:

- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

Key Eligibility Criteria

- At least 18 years of age
- Complete and adequate resection of stage III melanoma
- Histologically confirmed melanoma metastatic to lymph node
- Stage **IIIA (if N1a, at least 1 metastasis >1 mm);** stage **IIIB** or **IIIC** (no in transit meta)
- No prior systemic therapy for melanoma
- No autoimmune disease
- Documented NED following surgery
- Randomization within 12 weeks of surgery



Van der Ploeg, et al. *Eur J Cancer* 2014;50:111-20.

Baseline Patient Characteristics

	Pembrolizumab (N=514)	Placebo (N=505)
Median age, (years)	54	54
Male, (%)	63	60
PD-L1 status, (%)		
Positive (MEL 2, 3, 4 or 5)	83	84
Negative (MEL 0 or 1)	11	11
Inevaluable	5	5
Ulceration of primary, (%)	41	39
1 vs. 2-3 vs. ≥4 positive LN, (%)	44 vs. 34 vs. 21	47 vs. 33 vs. 20
Lymph-node involvement, (%)		
Microscopic	36	32
Macroscopic	64	68

L. Eggermont AACR 2018

Baseline Patient Characteristics

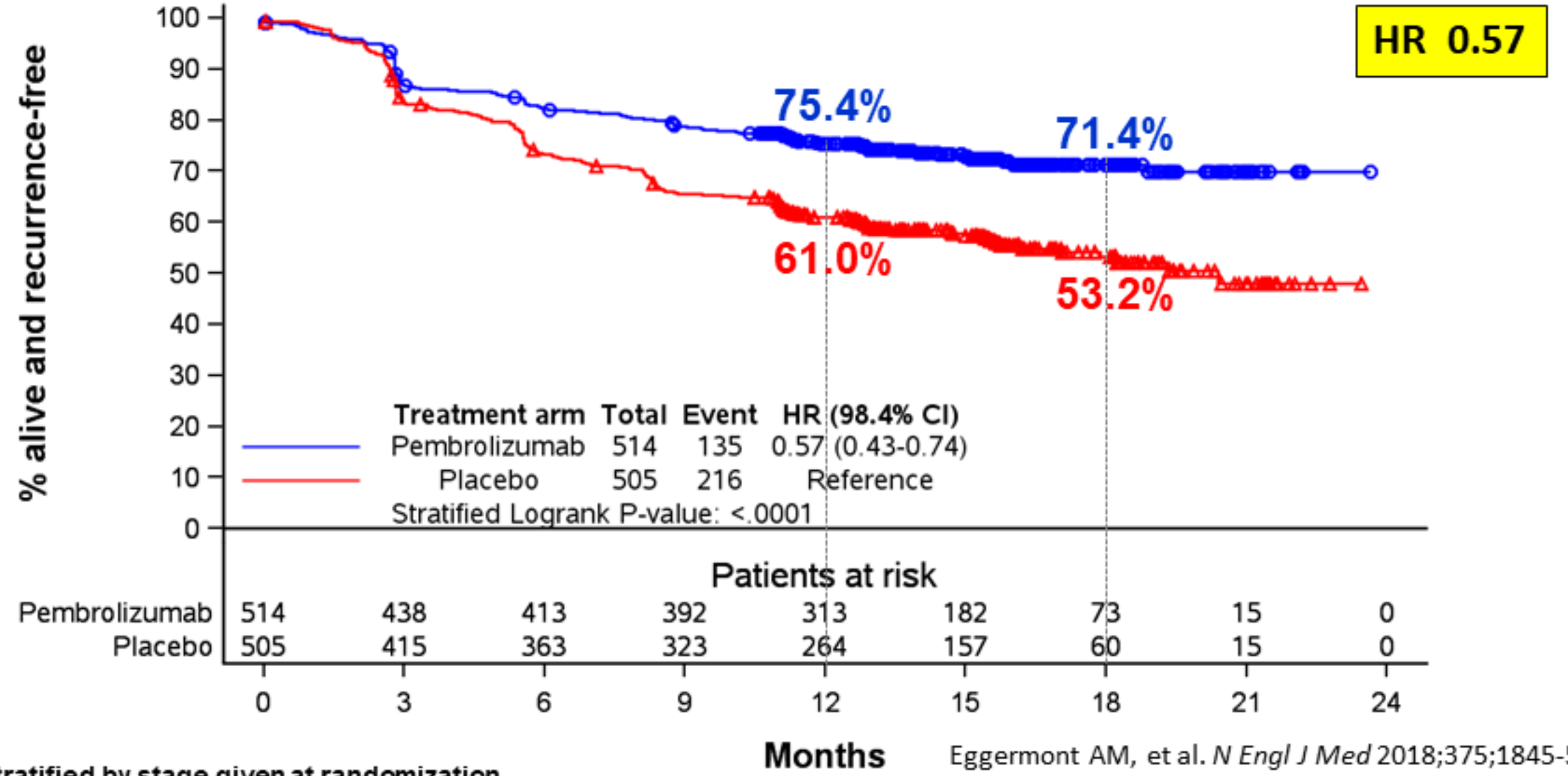
	Pembrolizumab (N=514)	Placebo (N=505)
PD-L1 status (%)		
Positive (MEL 2, 3, 4 or 5)	83	84
Negative (MEL 0 or 1)	11	11
Inevaluable	5	5
BRAF-mutation status (%)		
Wild type	45	42
V600E/K mutated	41	46
Other mutation	7	6
Not assessable	7	6

EORTC

The future of cancer therapy

Recurrence-Free Survival in the ITT Population

Primary endpoint



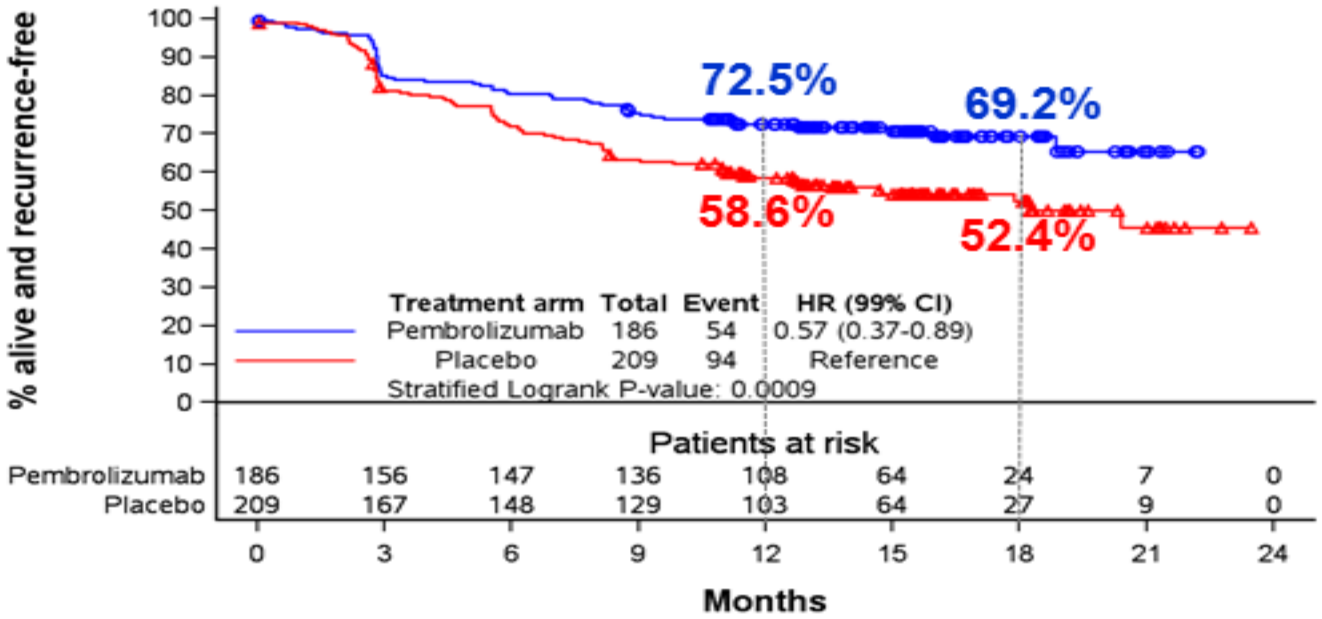
*Stratified by stage given at randomization

Eggermont AM, et al. *N Engl J Med* 2018;375;1845-55

Recurrence-Free Survival

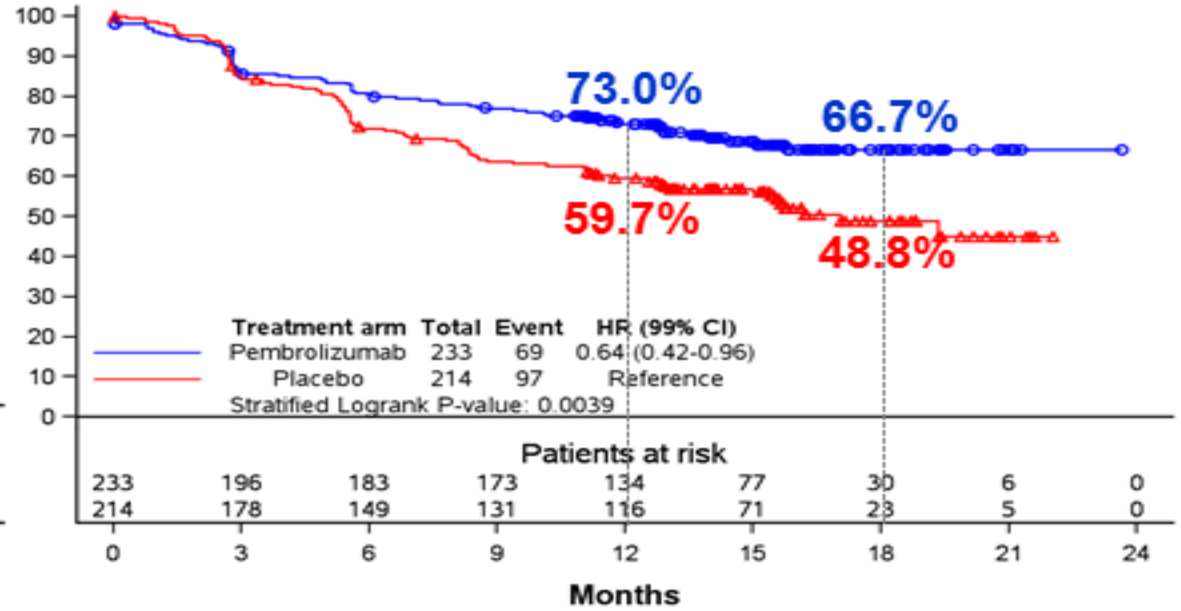
BRAF V600E/K

HR 0.57



BRAF WT

HR 0.64



*Stratified by stage given at randomization

EORTC

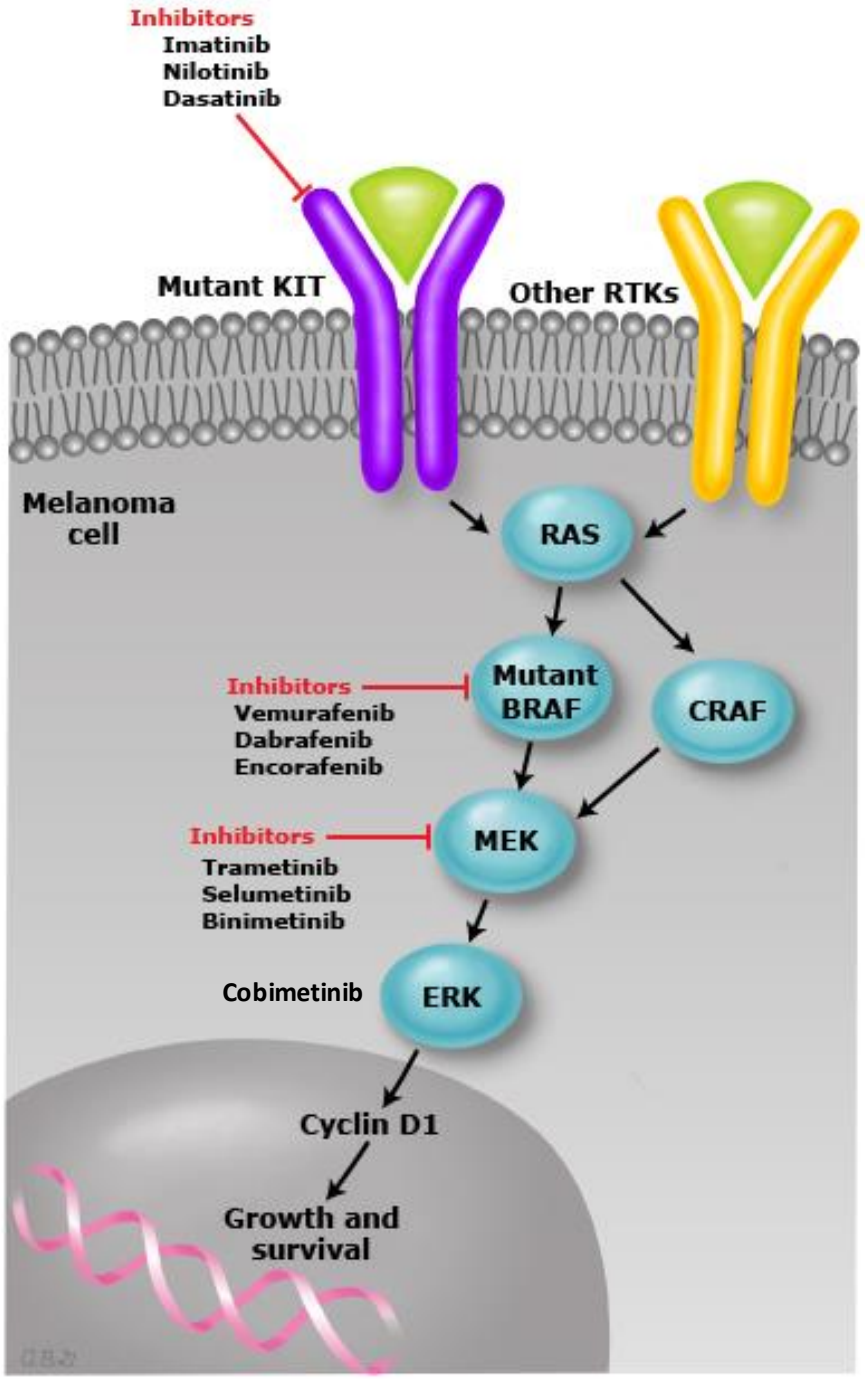
The future of cancer therapy

L. Eggermont AACR 2018

General Adverse Events

	Pembrolizumab (N=509)		Placebo (N=502)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Any adverse events (AE)	93.3	31.6	90.2	18.5
Any treatment-related AE	77.8	14.7	66.1	3.4
Fatigue/asthenia	37.1	0.8	33.3	0.4
Skin reactions	28.3	0.2	18.3	0
Rash	16.1	0.2	10.8	0
Pruritus	17.7	0	10.2	0
Diarrhea	19.1	0.8	16.7	0.6
Arthralgia	12.0	0.6	11.0	0
Nausea	11.4	0	8.6	0


Targeted Therapy



MAPK Pathway

- Multiple oncogenes in melanoma
- Tested for in BC using next generation sequencing “Oncopanel”
- BRAF mutation in ~ 50% of Canadians

September, 2017

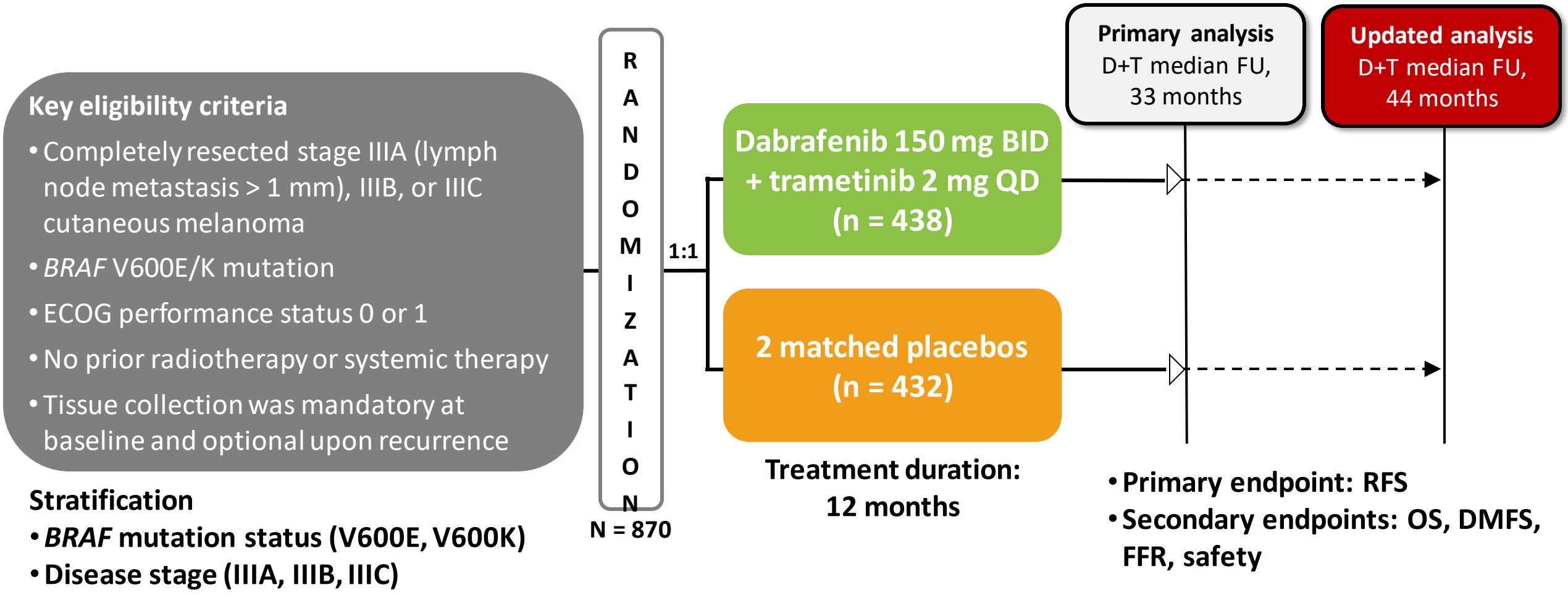
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood

COMBI-AD: STUDY DESIGN—EXTENDED FOLLOW-UP ANALYSIS



BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

Baseline Characteristics

Table 1. Characteristics of the Patients at Baseline.*

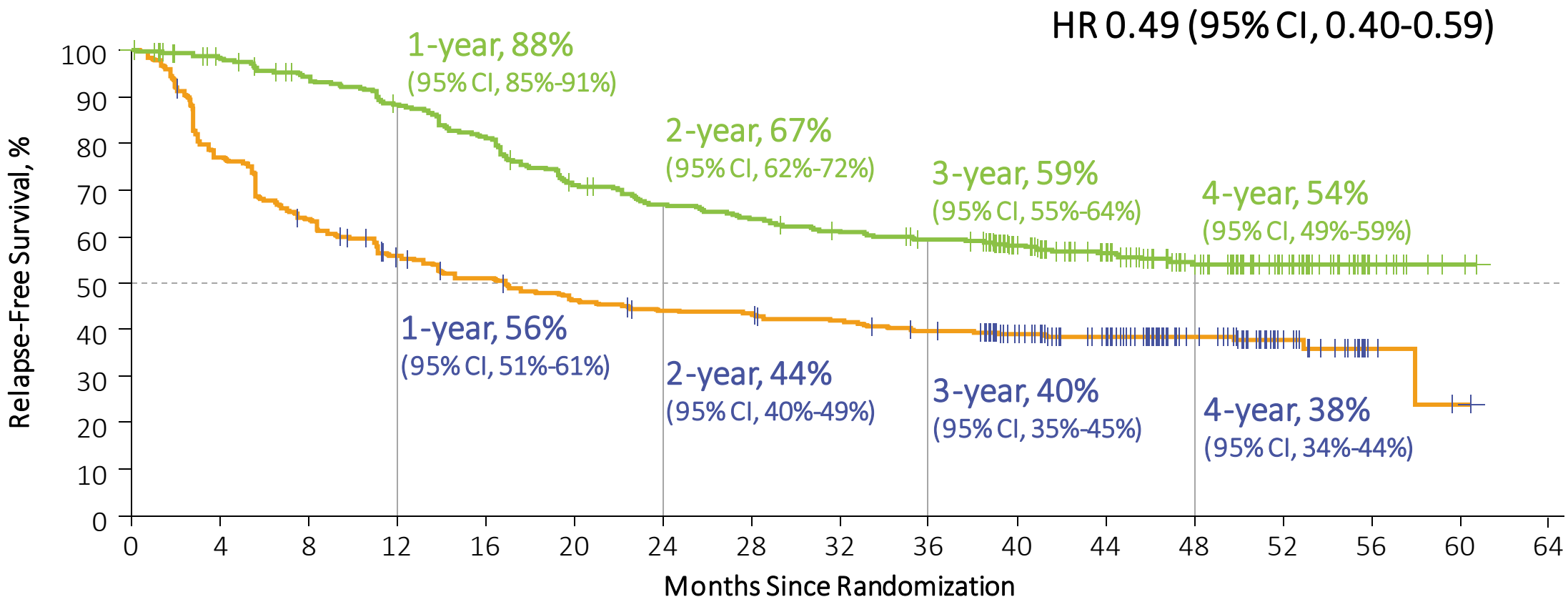
Characteristic	Dabrafenib plus Trametinib (N = 438)	Placebo (N = 432)
Median age (range) — yr	50 (18–89)	51 (20–85)
Disease stage — no. (%)		
IIIA	83 (19)	71 (16)
IIIB	169 (39)	187 (43)
IIIC	181 (41)	166 (38)
III unspecified	5 (1)	8 (2)
No. of positive lymph nodes — no. (%)		
1	177 (40)	183 (42)
2 or 3	158 (36)	150 (35)
≥4	73 (17)	72 (17)
Unknown	30 (7)	27 (6)
Type of lymph-node involvement — no. (%)		
Microscopic	152 (35)	157 (36)
Macroscopic	158 (36)	161 (37)
Unknown	128 (29)	114 (26)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dabrafenib plus Trametinib (N = 438)	Placebo (N = 432)
Primary-tumor ulceration — no. (%)		
Yes	179 (41)	177 (41)
No	253 (58)	249 (58)
Unknown	6 (1)	6 (1)
In-transit metastases — no. (%)‡		
Yes	51 (12)	36 (8)
No	387 (88)	395 (91)
Unknown	0	1 (<1)

Long et al, NEJM, 2017

RELAPSE-FREE SURVIVAL



No. at risk

Dabrafenib + trametinib	438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
Placebo	432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0

RESULTS

- The most common AE reported in patients who received dabrafenib plus trametinib was pyrexia (63%; **Table 1**)
  - Of patients with pyrexia, 28% had one occurrence, 20% had 2 occurrences, and 52% had 3 or more occurrences

Table 1. Common AEs (≥ 15% of patients)[6]

AEs, n (%)	Dabrafenib + Trametinib n = 435		Placebo n = 432	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE[a]	**422 (97)**	**180 (41)**	**380 (88)**	**61 (14)**
Pyrexia	273 (63)	23 (5)	47 (11)	2 (< 1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (< 1)
Nausea	172 (40)	4 (1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhea	144 (33)	4 (1)	65 (15)	1 (< 1)
Vomiting	122 (28)	4 (1)	43 (10)	0
Arthralgia	120 (28)	4 (1)	61 (14)	0

AE, adverse event.

[a] **All cause.**

RESULTS (cont)

Table 1. Common AEs (≥ 15% of patients)[6] (cont)

AEs, n (%)	Dabrafenib + Trametinib n = 435		Placebo n = 432	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Rash	106 (24)	0	47 (11)	1 (< 1)
Cough	73 (17)	0	33 (8)	0
Myalgia	70 (16)	1 (< 1)	40 (9)	0
ALT increase	67 (15)	16 (4)	6 (1)	1 (< 1)
Influenza-like illness	67 (15)	2 (< 1)	29 (7)	0

[a] All causes. AE, adverse event; ALT, alanine aminotransferase.

Summary

- Checkmate 209-238
  - Stage IIIB-IV NED
  - Ipilimumab – 12m RFS 71% v 61%, 18m RFS 66% v 53% (HR 0.65)
- Keynote-54
  - Stage IIIa (>1mm)-IIIC
    - NO in transit
  - Placebo 12m RFS – 75.4% v 61%, 18m RFS 71.4% v 53.2% (HR0.57)
- COMBI-AD
  - Stage IIIA (>1mm)-IIIC
  - Placebo 12m RFS – 88% v 56%; 3yr RFS 59% v 40% (HR 0.49)

Current Landscape in BC

- Proposals in for all 3 treatments
  - Resected stage III-IV NED, including in transit
- Access programs for Nivolumab and Pembrolizumab
  - Within 3m of surgery
  - Based on their enrollment criteria
    - They are overlapping though!
- BRAF mutated access closed for now
- Private pay always an option

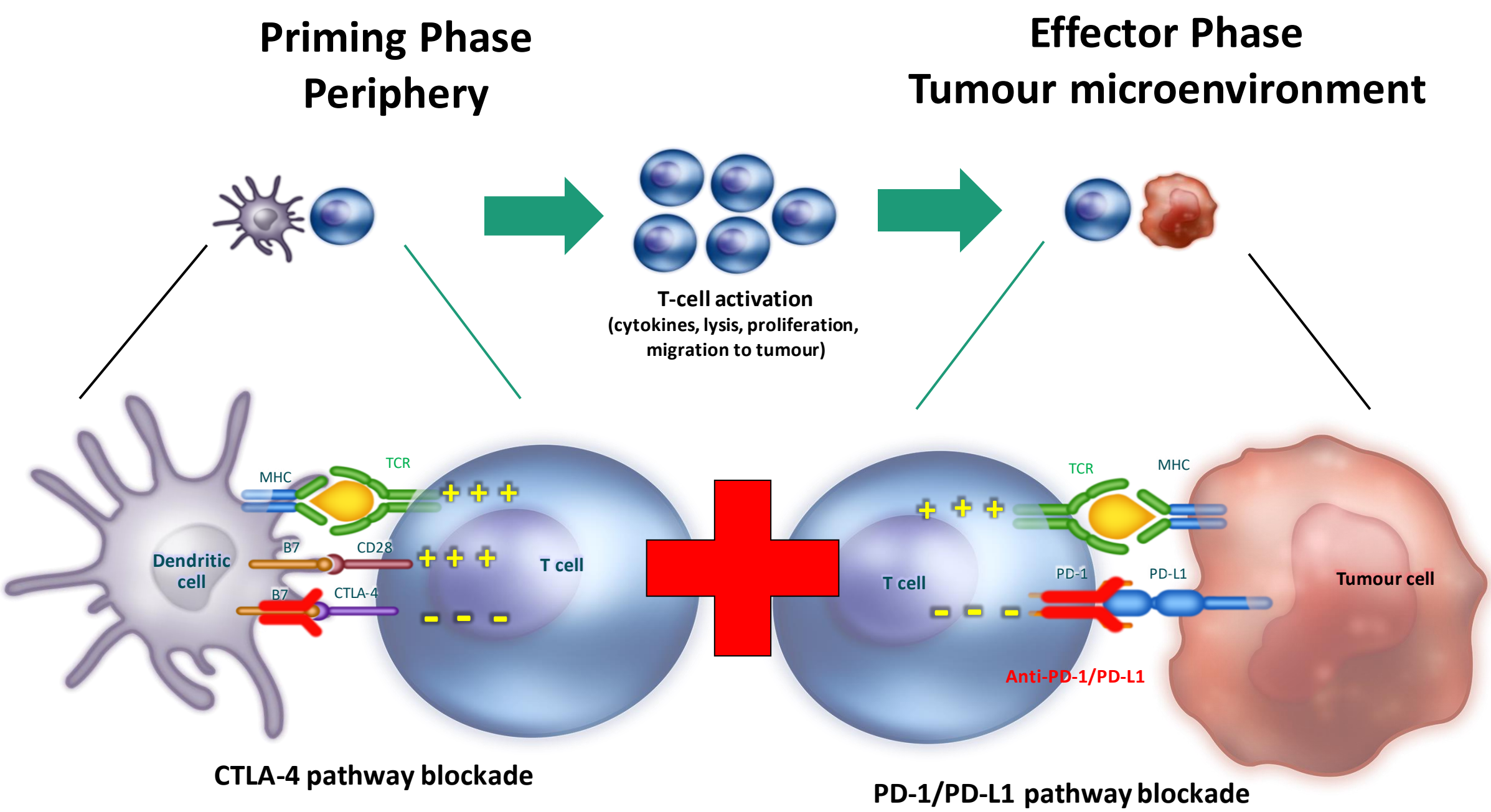

Neoadjuvant therapy

Basic Tenets of Chemotherapeutics

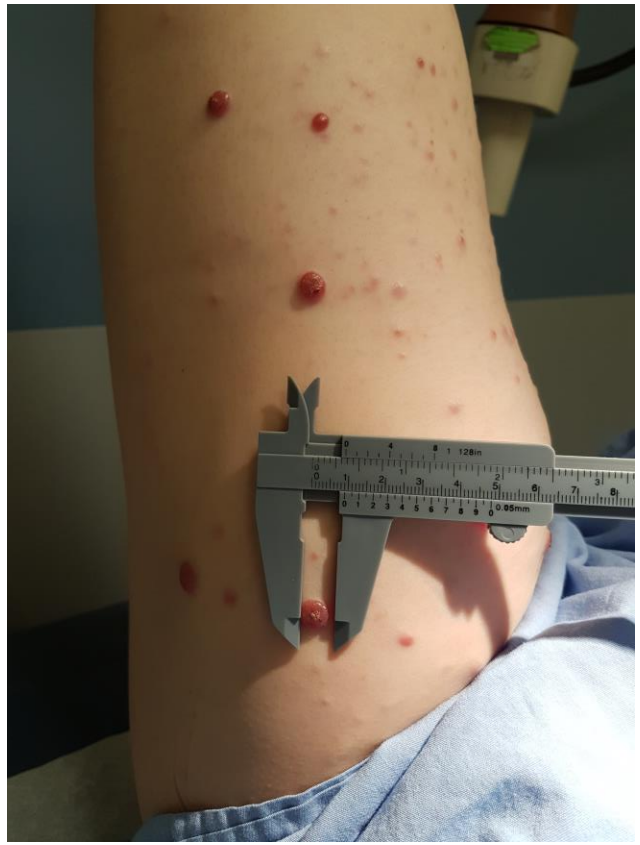
Try it first in the incurable setting

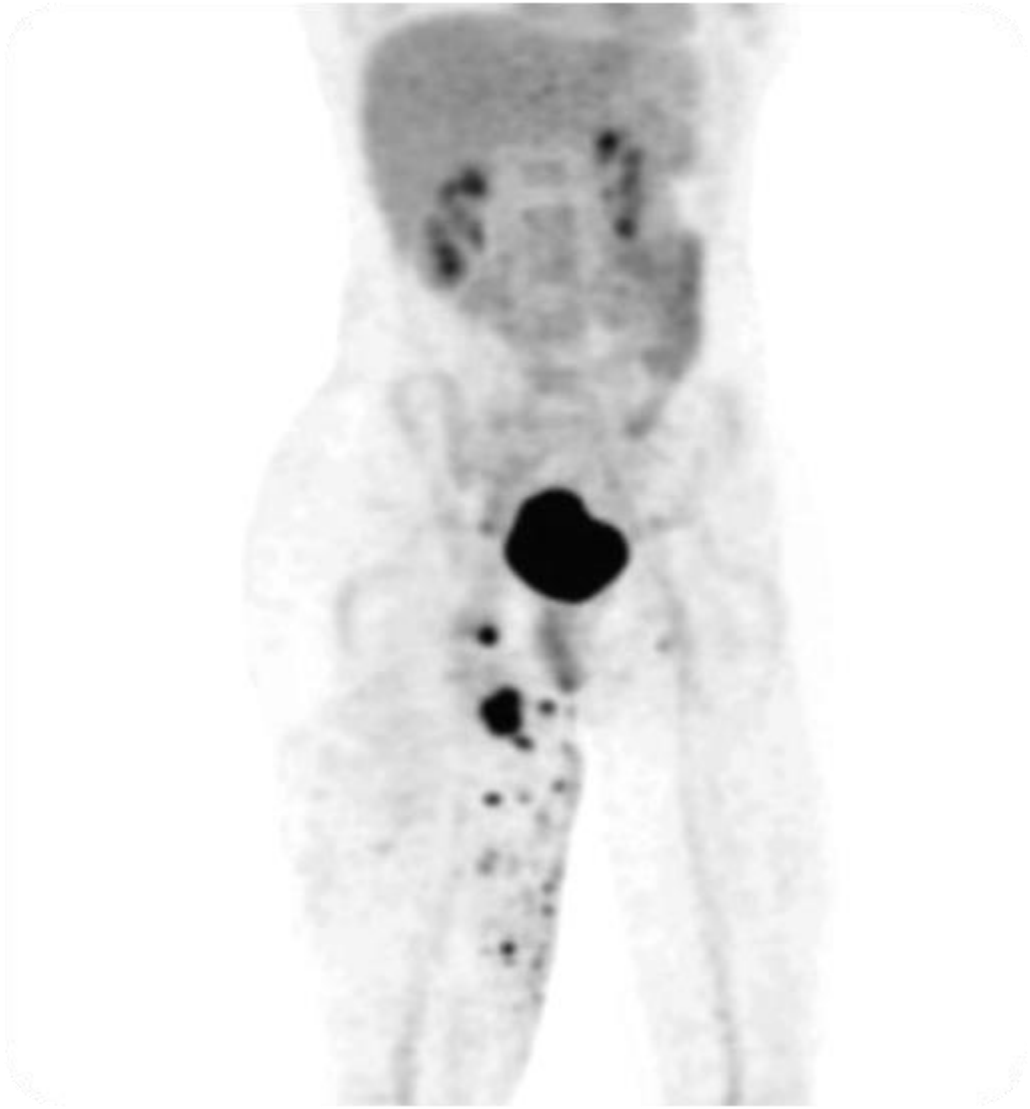
If it works for the incurable, try it on the curable

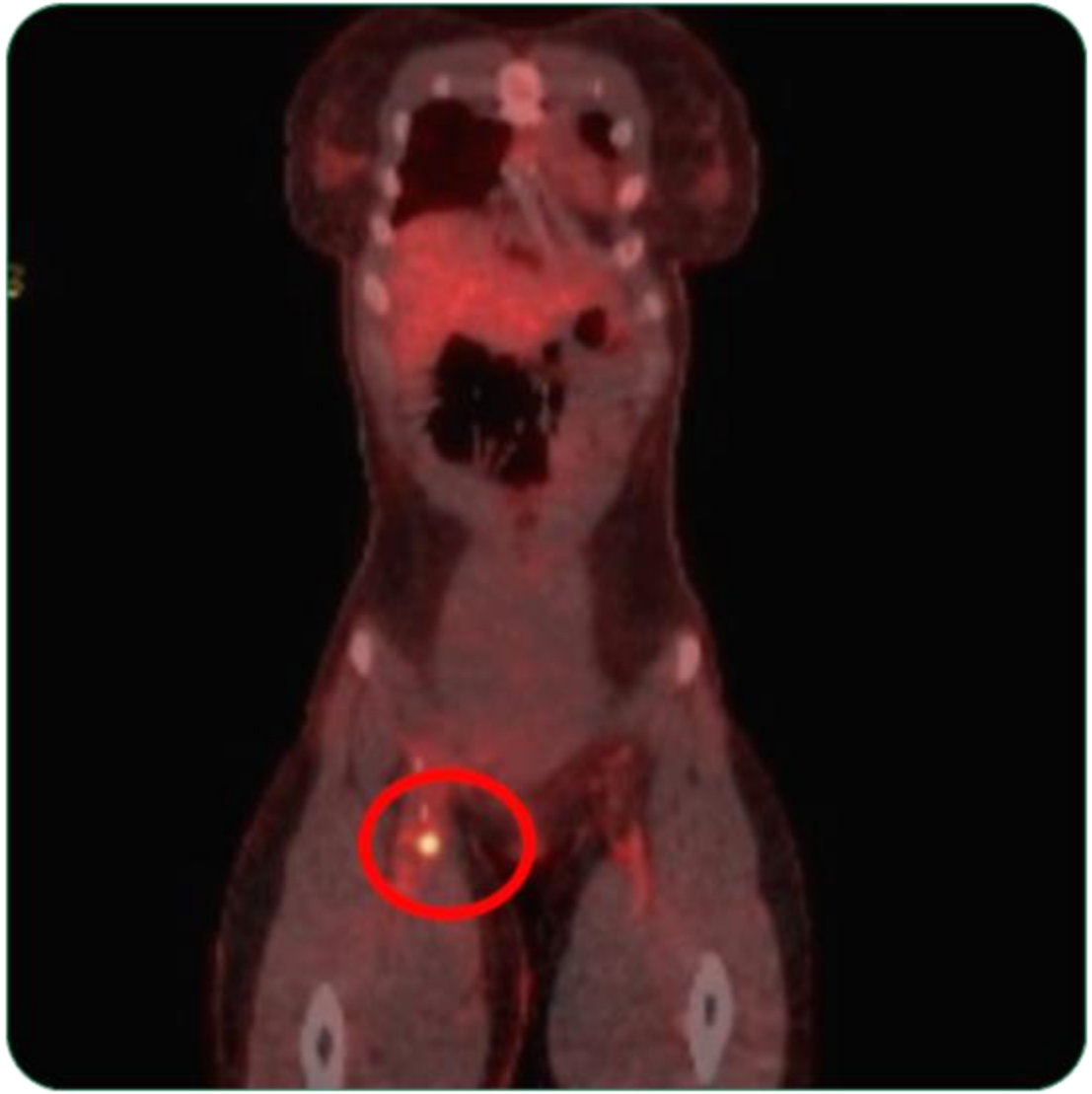
If two different drugs seem to improve survival, then why not put them together?


Priming Phase
Periphery
Effector Phase
Tumour microenvironment
T-cell activation
(cytokines, lysis, proliferation,
migration to tumour)
Dendritic cell
MHC
TCR
B7
CD28
B7
CTLA-4
T cell
T cell
TCR
MHC
PD-1
PD-L1
Tumour cell
Anti-PD-1/PD-L1
CTLA-4 pathway blockade
PD-1/PD-L1 pathway blockade

LuLu Lemon



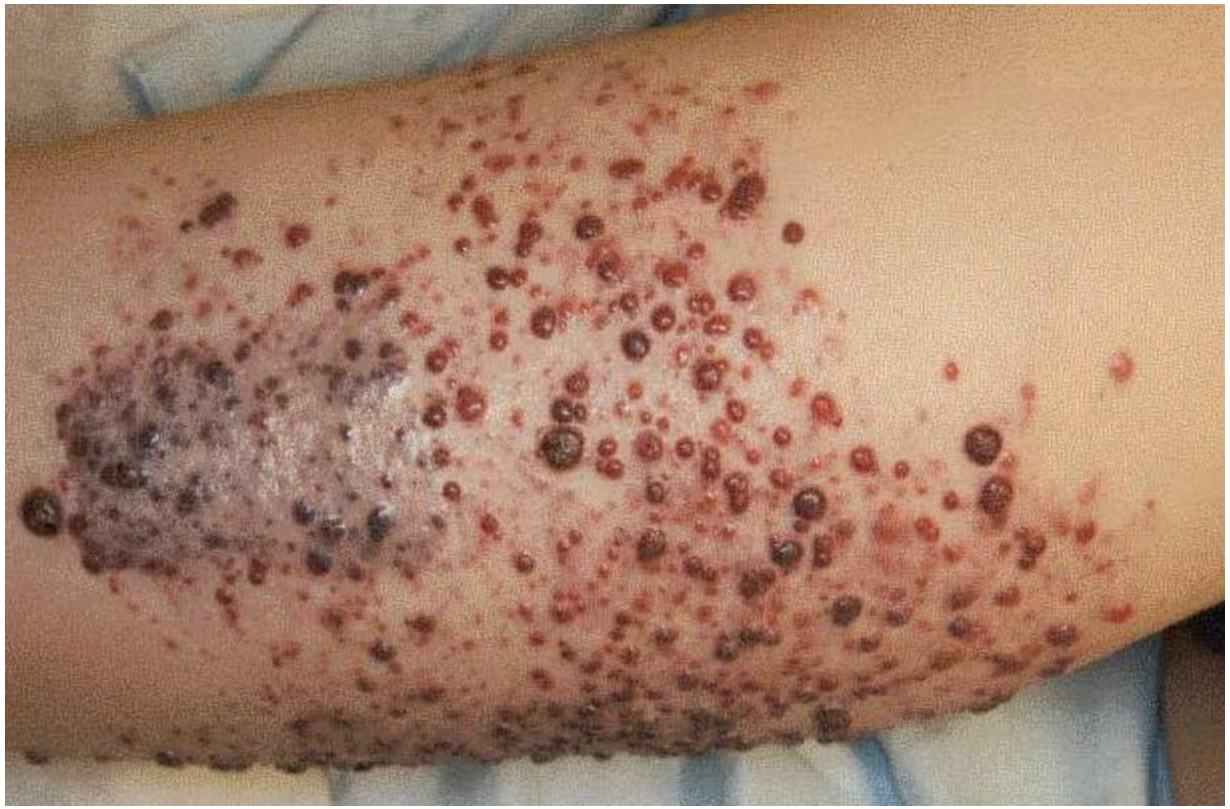


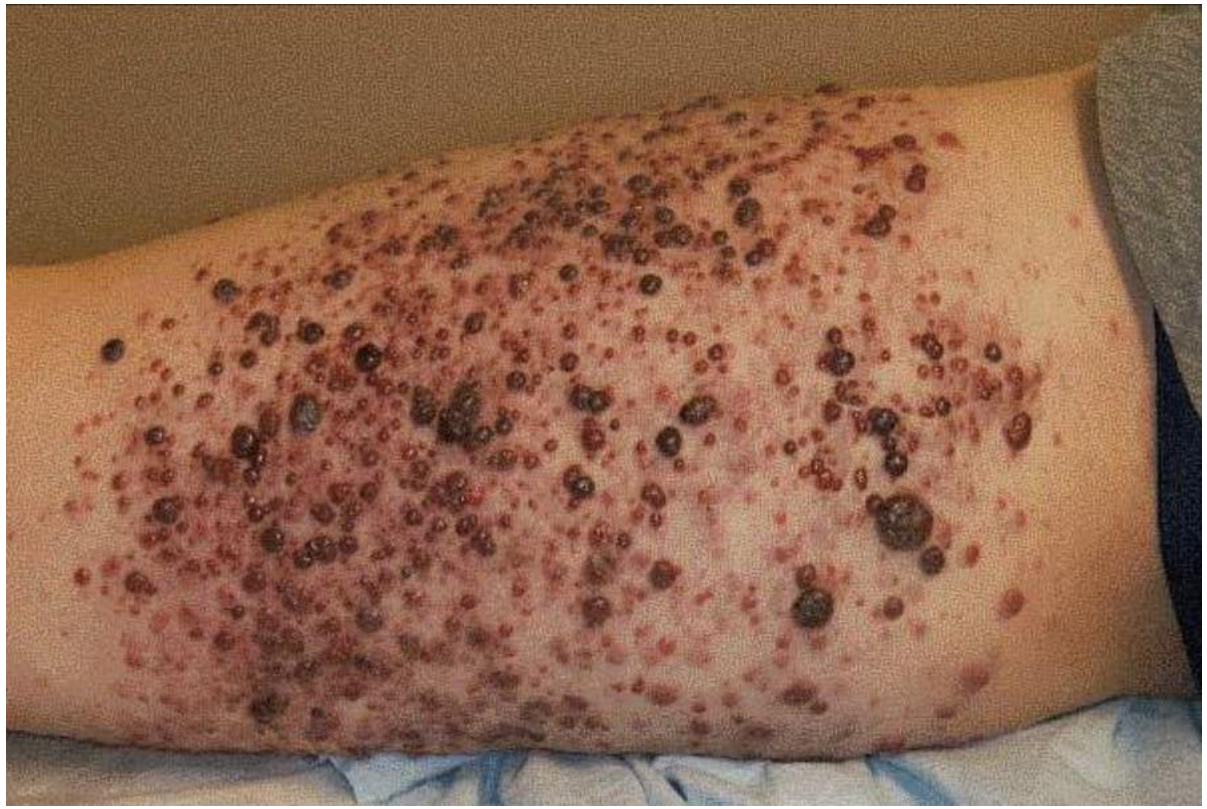


PET Scan

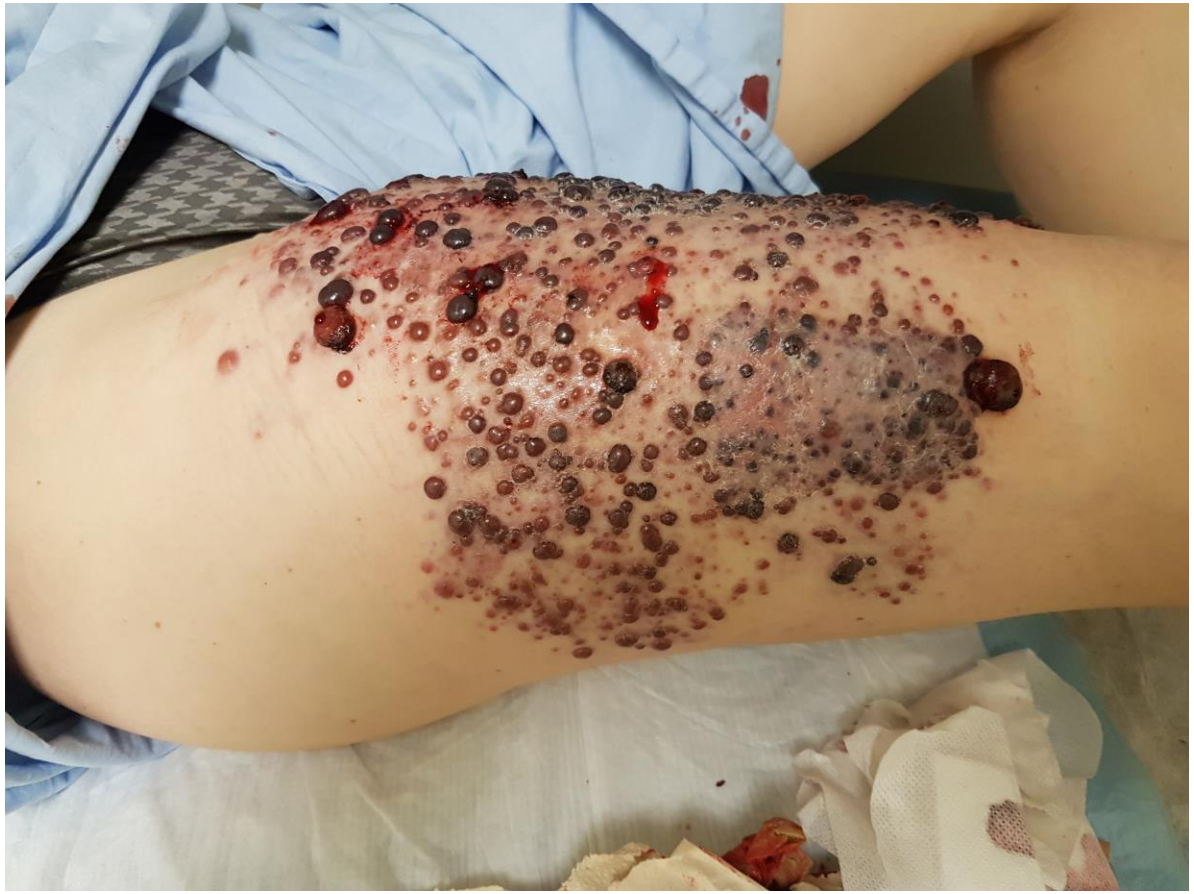
Ipi/nivo started Aug 11, 2016

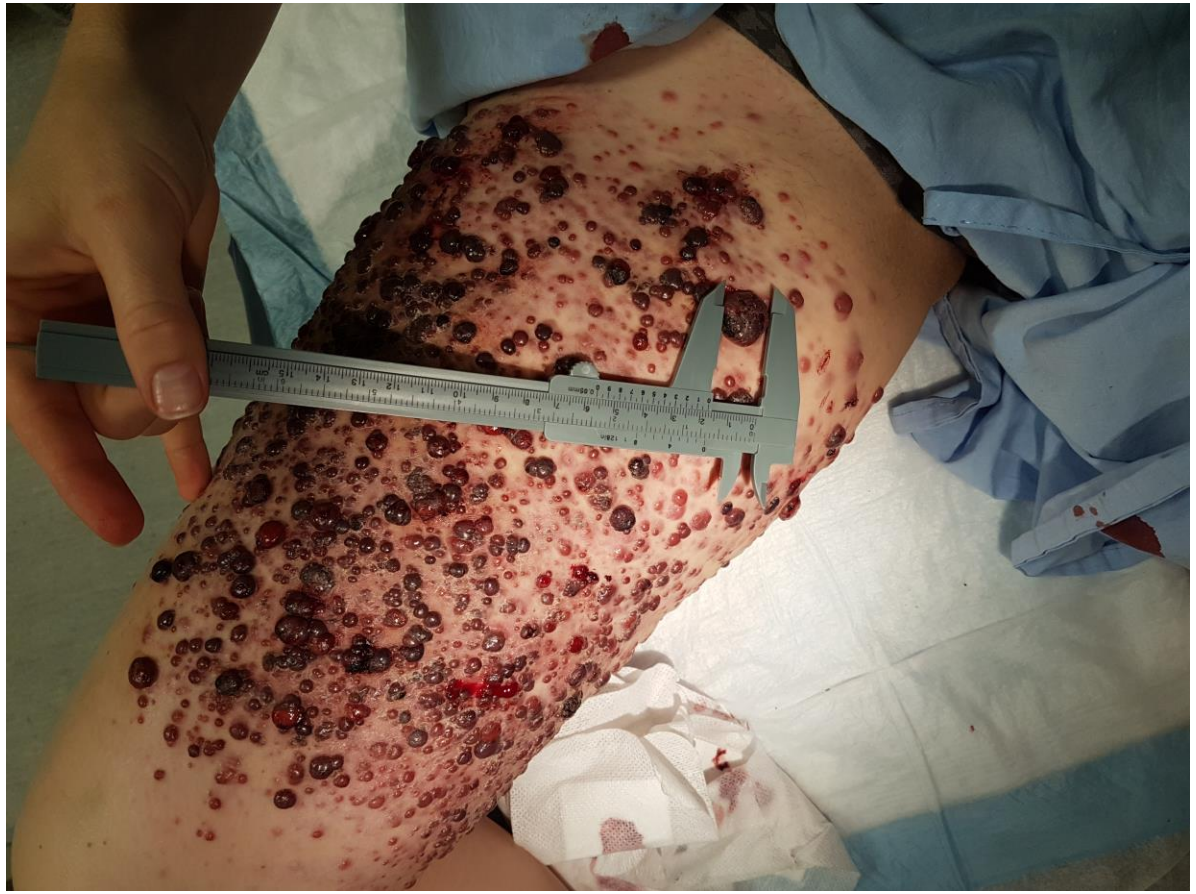
- initiation of treatment assessment



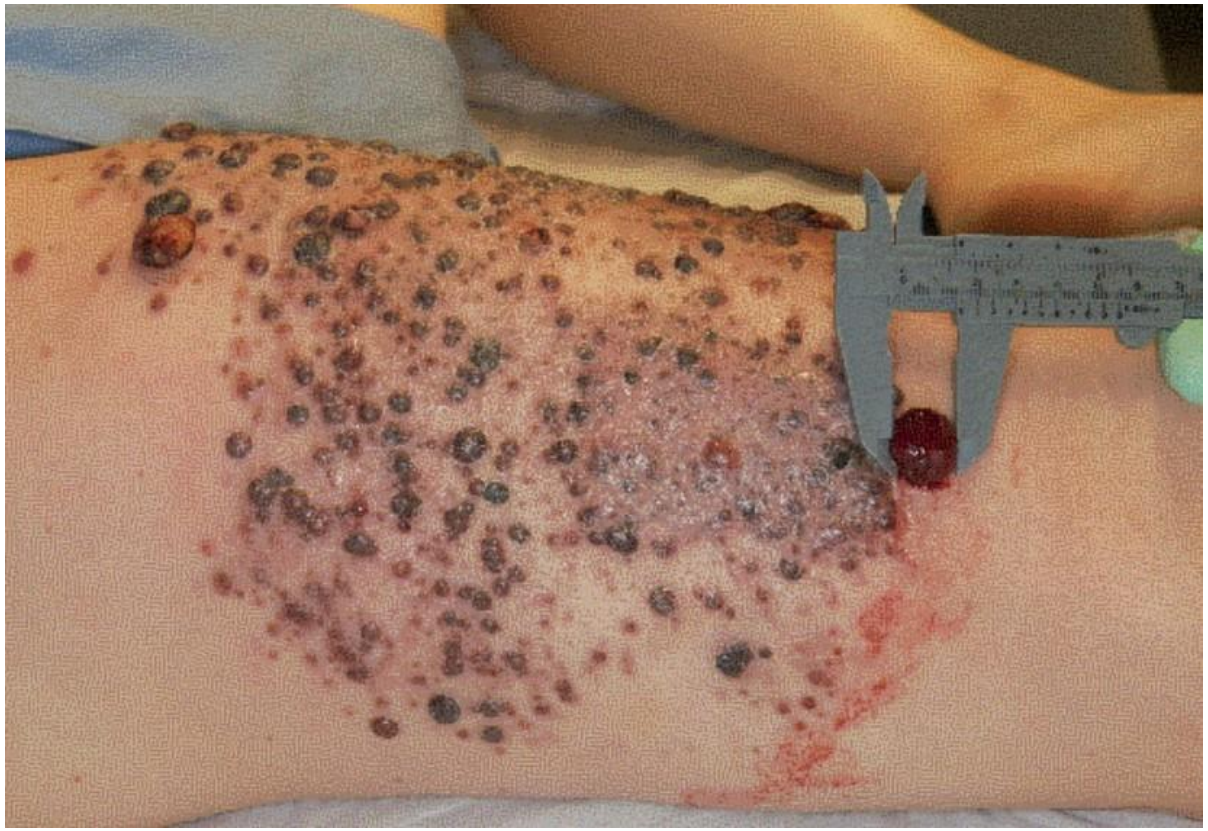


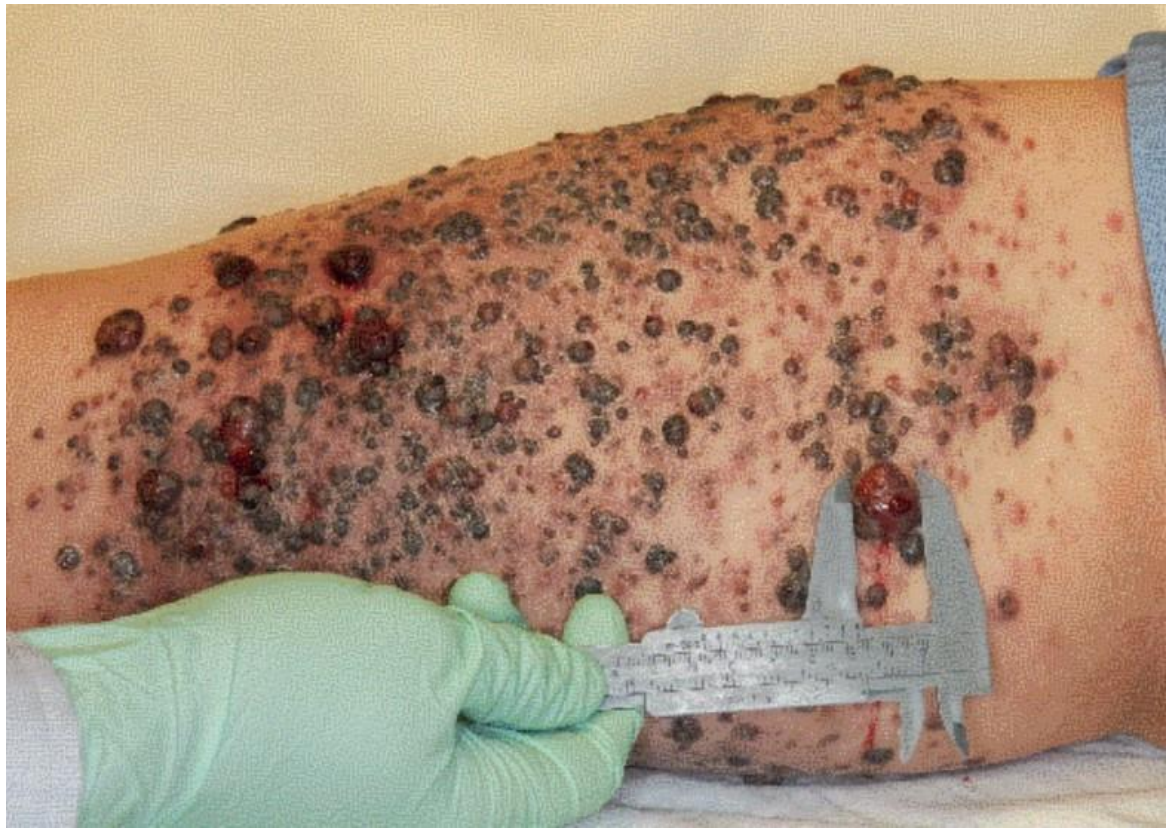
Assessment prior to cycle 2
3 weeks after starting





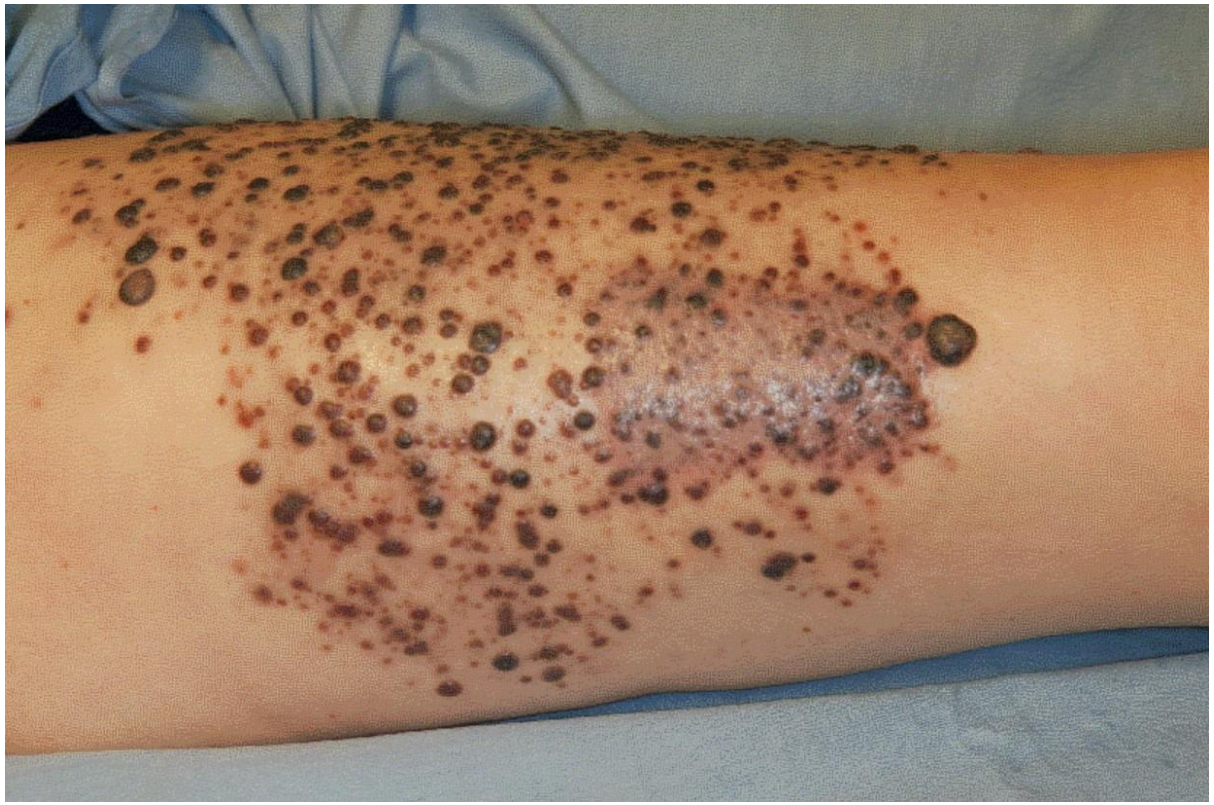
Assessment prior to cycle 3
6 weeks after starting

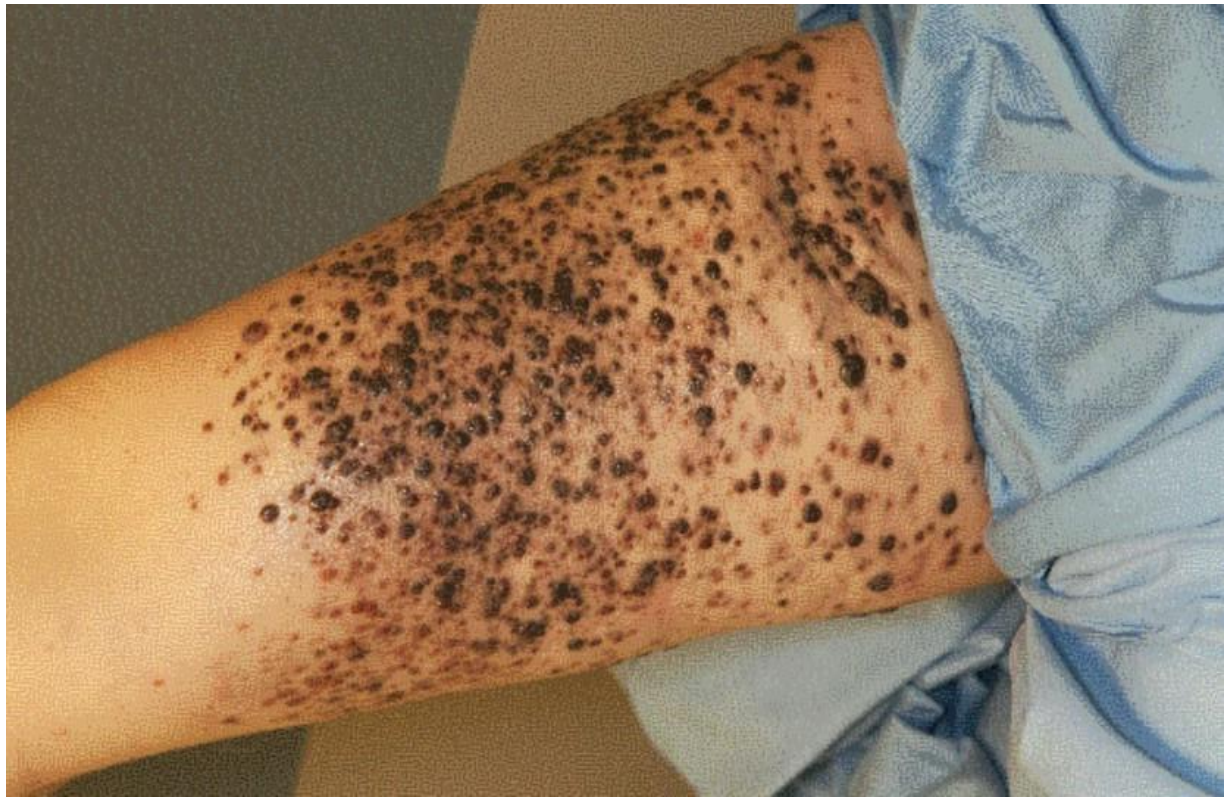




Assessment prior to cycle 4

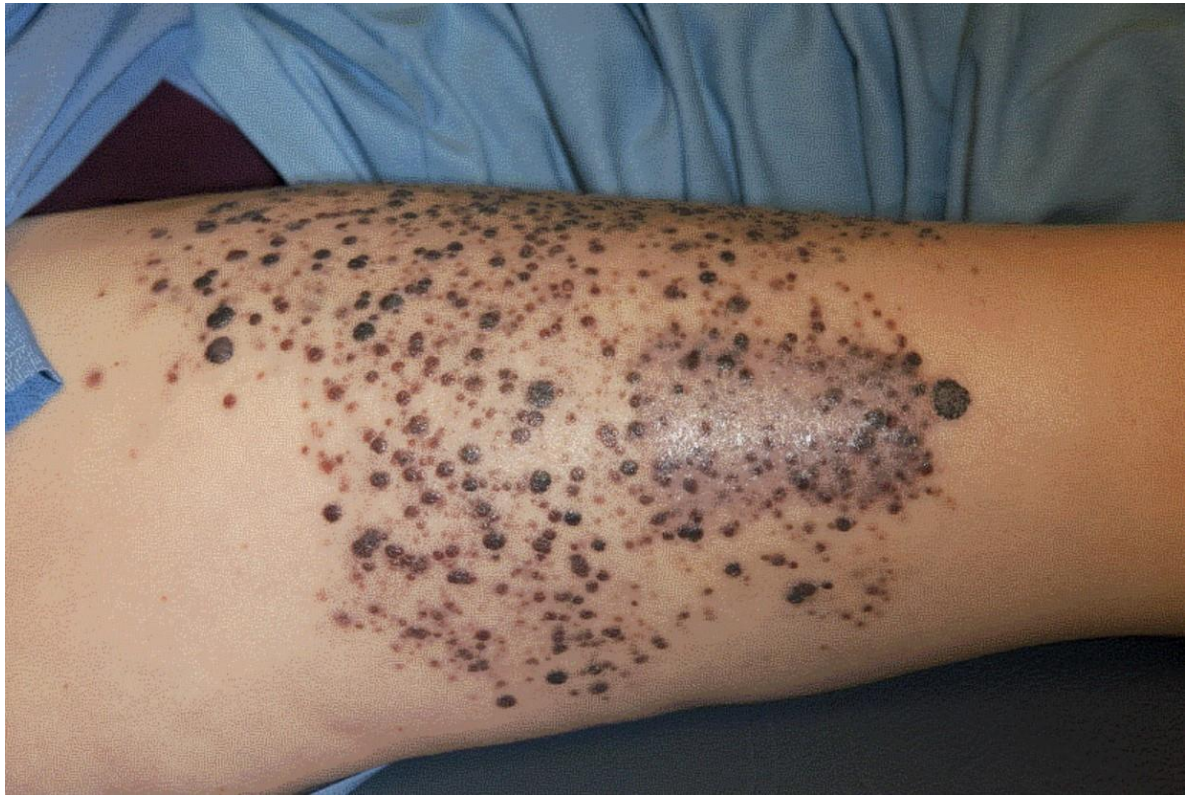
9 weeks after starting

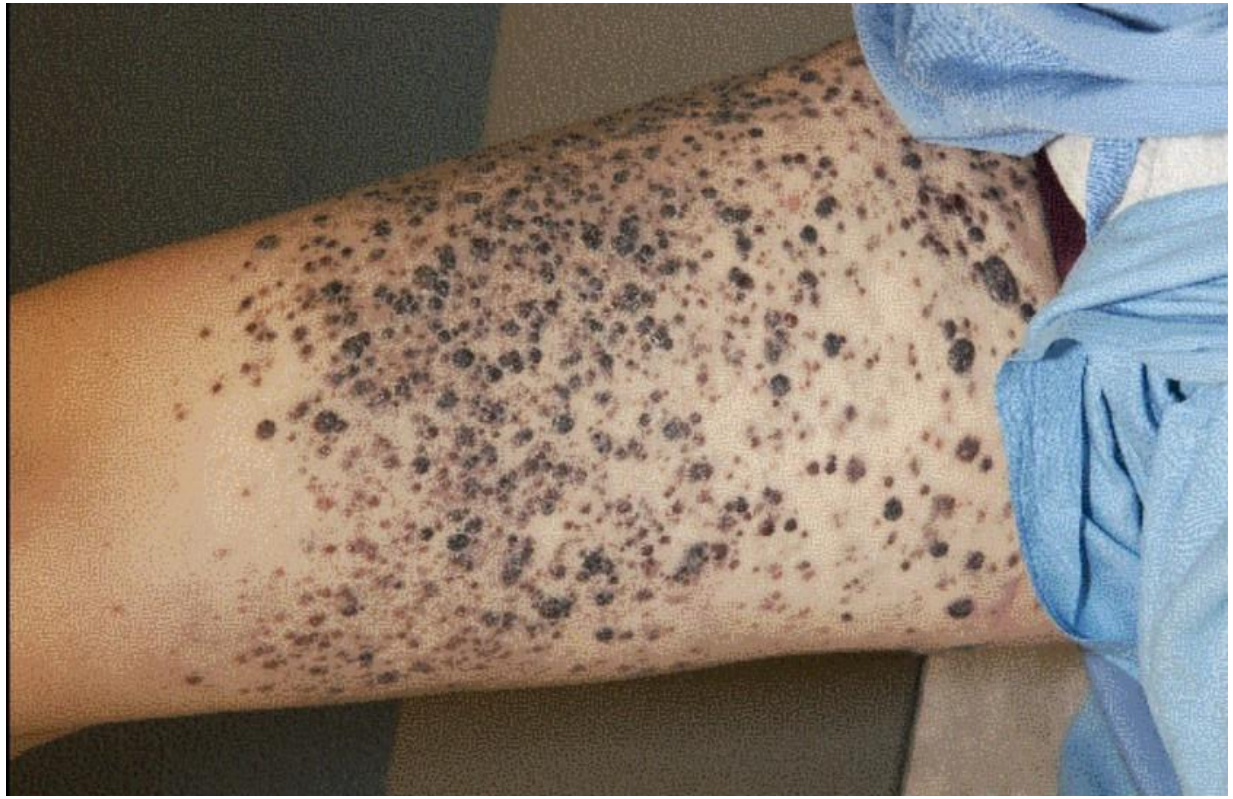


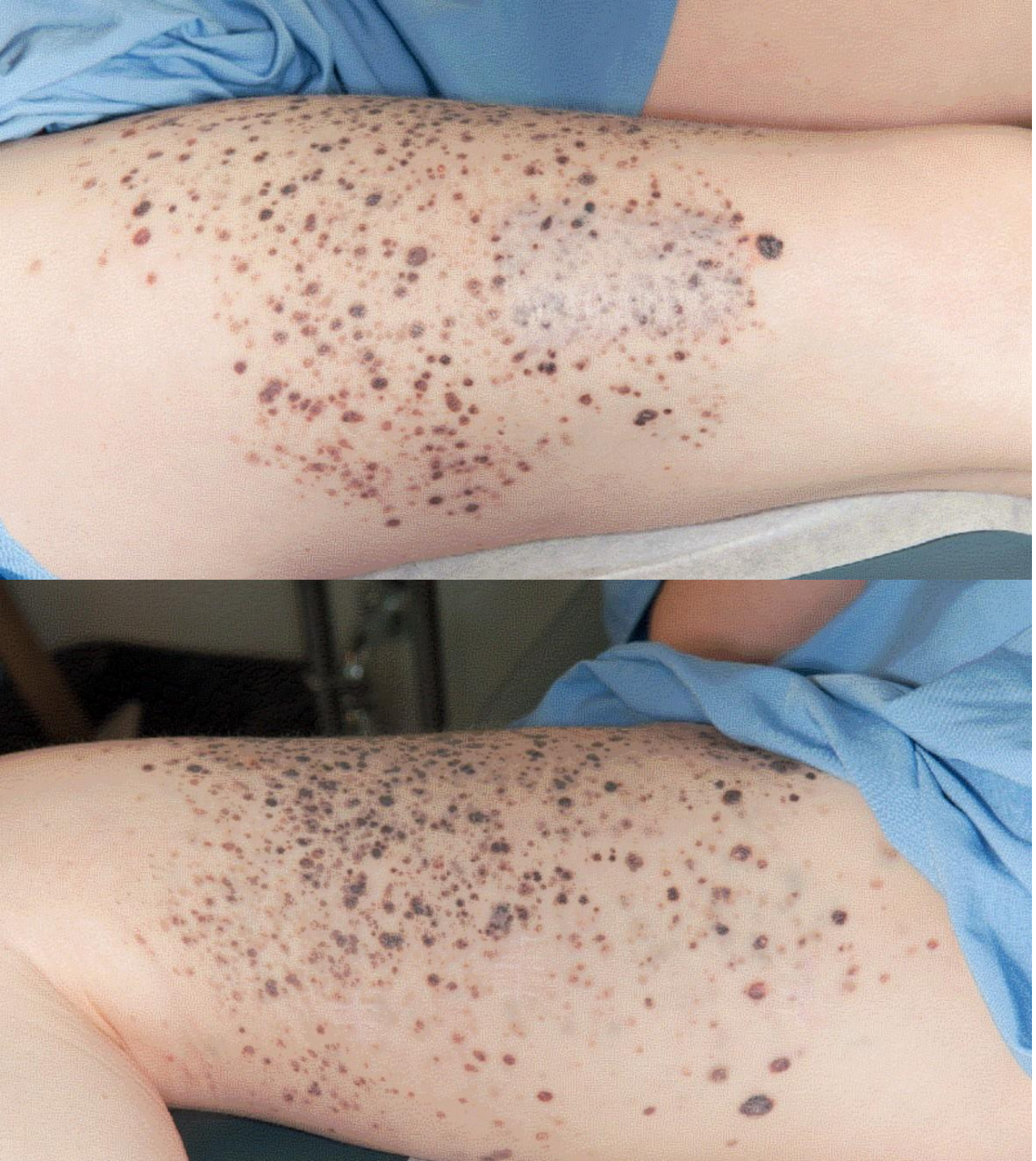


Assessment prior to maintenance

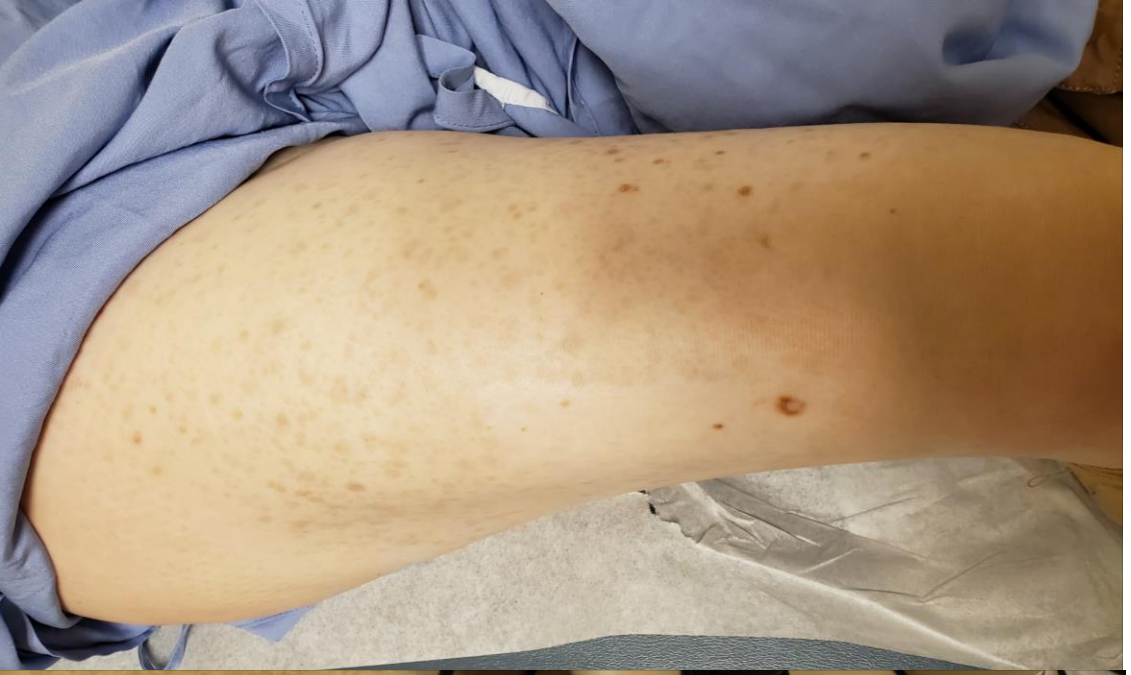
12 weeks after starting

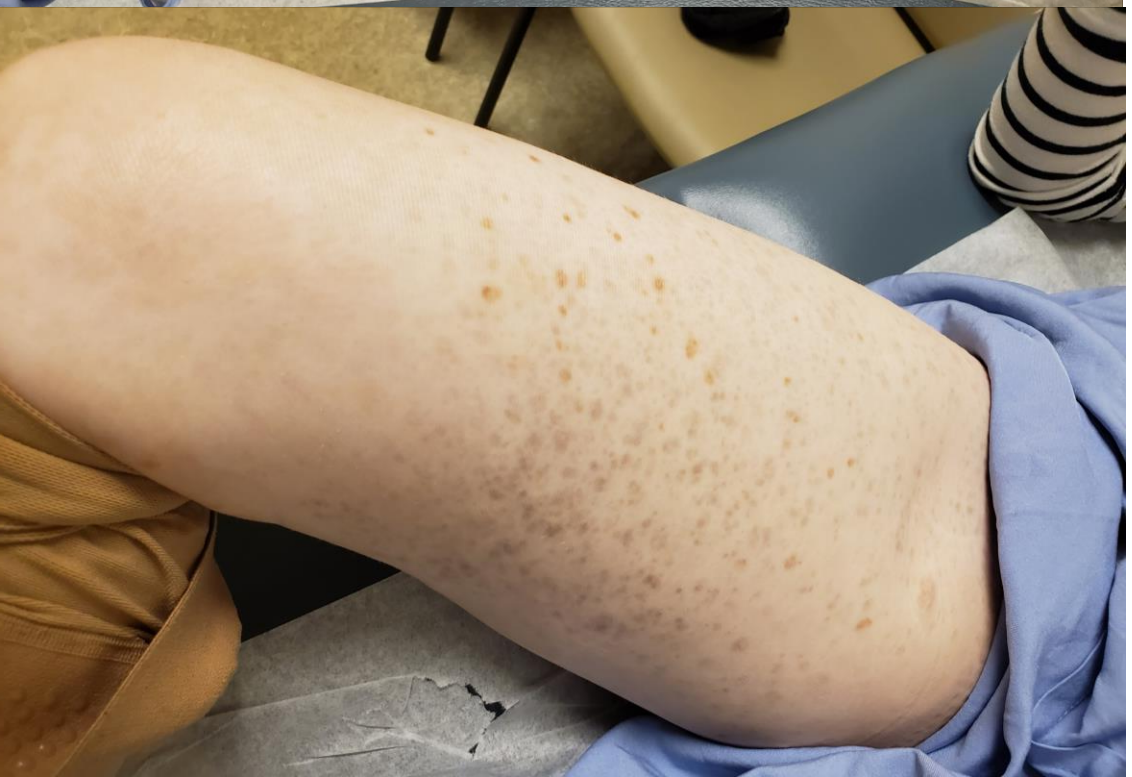






March 6, 2017
Complete response





Oct 2, 2019

Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial

Elisa A Rozeman, Alexander M Menzies, Alexander C J van Akkooi, Chandra Adhikari, Carolien Bierman, Bart A van de Wiel, Richard A Scolyer, Oscar Krijgsman, Karolina Sikorska, Hanna Eriksson, Annegien Broeks, Johannes V van Thienen, Alexander D Guminski, Alex Torres Acosta, Sylvia ter Meulen, Anne Miek Koenen, Linda J W Bosch, Kerwin Shannon, Loes M Pronk, Maria Gonzalez, Sydney Ch'ng, Lindsay G Grijpink-Ongering, Jonathan Stretch, Stijn Heijmink, Harm van Tinteren, John B A G Haanen, Omgo E Nieweg, Willem M C Klop, Charlotte L Zuur, Robyn P M Saw, Winan J van Houdt, Daniel S Peeper, Andrew J Spillane, Johan Hansson, Ton N Schumacher, Georgina V Long, Christian U Blank

Lancet Oncol 2019; 20: 948–60

Summary

Background The outcome of patients with macroscopic stage III melanoma is poor. Neoadjuvant treatment with

- Prior study (Blank et al 2018)
  - Pathologic response predictive of RFS
  - Gr. 3 toxicity 90% for ipi/nivo
- Current study to find optimal dosing scheme
  - Grp A: Ipi 3mg/kg + Nivo 1mg/kg q3w x 2 -> surgery
  - Grp B: Ipi 1mg/kg + Nivo 3mg/kg q3w x 2 -> surgery
  - Grp C: Ipi 3mg/kg q3w x2 -> nivo 3mg/kg q2w x2 (start on day of last ipi) -> surgery

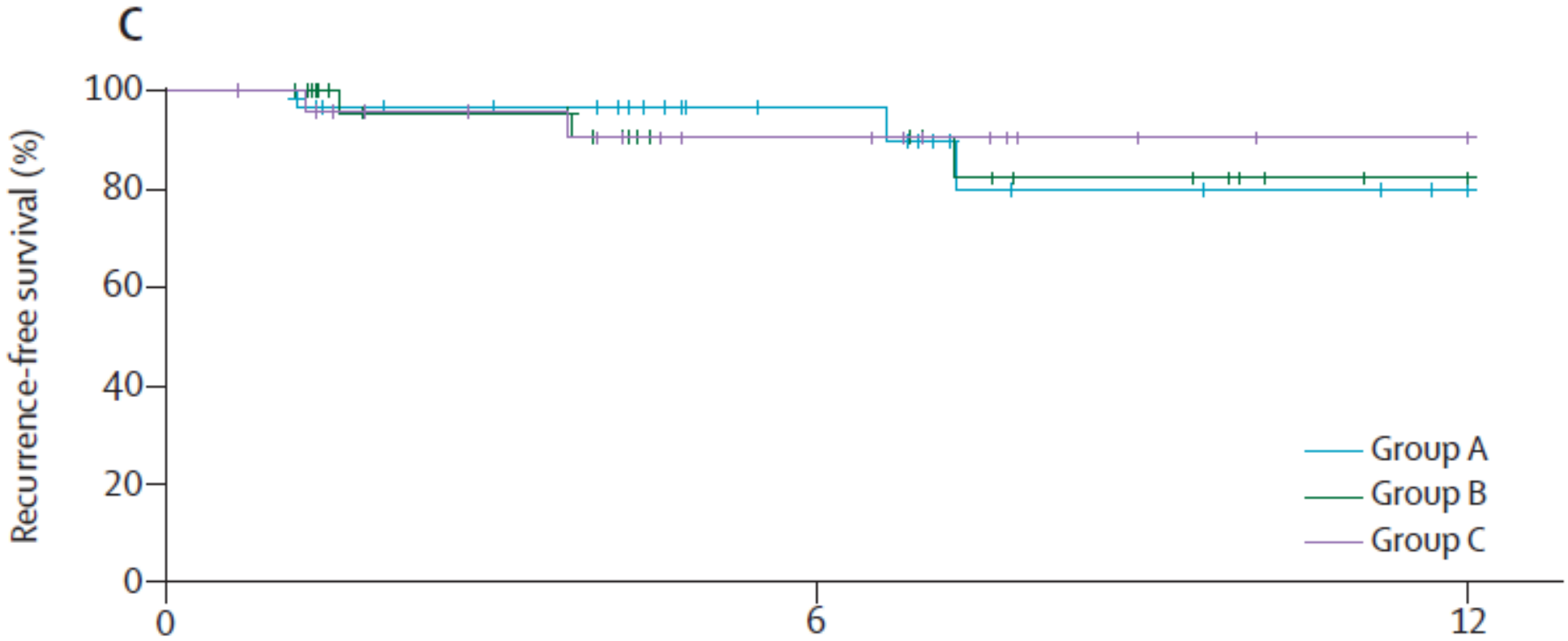
- Median follow up 8.3m
- None achieving pathologic response have relapsed
- 9/21 without pathologic response have relapsed

Radiological response			
Complete repsonse	2 (7%)	3 (10%)	1 (4%)
Partial response	17 (57%)	14 (47%)	8 (31%)
Stable disease	9 (30%)	10 (33%)	12 (46%)
Progressive disease	2 (7%)	2 (7%)	5 (19%)
Local progressive disease	2 (7%)	1 (3%)	4 (16%)
Distant metastasis	0	1 (3%)	1 (4%)
Not evaluable	0	1 (3%)*	0
Patients who achieved an objective response	19 (63% [44–80])	17 (57% [37–75])	9 (35% [17–56])
Pathological response			
Pathological complete response	14 (47%)	17 (57%)	6 (23%)
Near pathological complete response	7 (23%)	2 (7%)	6 (23%)
Pathological partial response	3 (10%)	4 (13%)	5 (19%)
Pathological non-response	6 (20%)	7 (23%)†	8 (38%)
Not evaluable	0	0	1 (4%)‡
Patients who achieved a pathological responses	24 (80% [61–92])	23 (77% [58–90])	17 (65% [44–83])

Data are n (%) or n (% [95% CI]). *For one patient the target lesion was not pictured on the CT images and could not be evaluated for response. †One patient had only palliative resection of largest lymph node. ‡Surgery was not done because of toxicity (severe polyradiculitis with peripheral motor neuropathy); this patient had a radiological complete response.

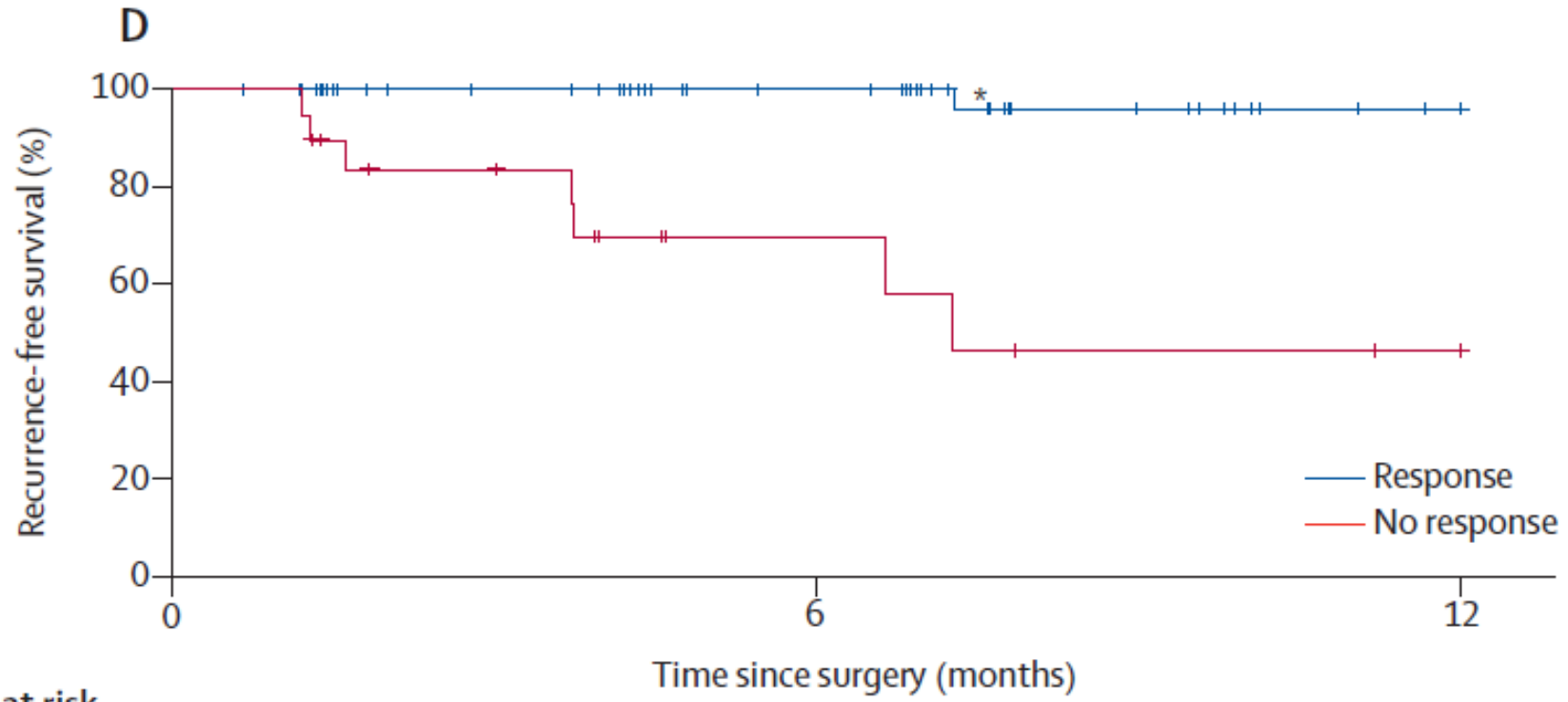
***Table 3*: Response to treatment**

RFS



Number at risk (number censored)			
Group A	30 (0)	14 (15)	4 (23)
Group B	29 (0)	13 (14)	3 (23)
Group C	24 (0)	13 (9)	5 (17)

RFS Based on Pathologic Response



Number at risk (number censored)			
Response	64 (0)	34 (30)	10 (53)
No response	19 (0)	6 (8)	2 (10)

Toxicity

NB: One patient in group A died without relapse from late ir encephalitis

	Group A (n=30)			Group B (n=30)			Group C (n=26)		
	Grade 1–2	Grade 3	Grade 4*	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Immune-related adverse events									
Total number of patients with at least one immune-related adverse event†	17 (57%)	11 (37%)	1 (3%)	23 (77%)	5 (17%)	1 (3%)	13 (50%)	11 (42%)	2 (8%)

November 2018

nature medicine

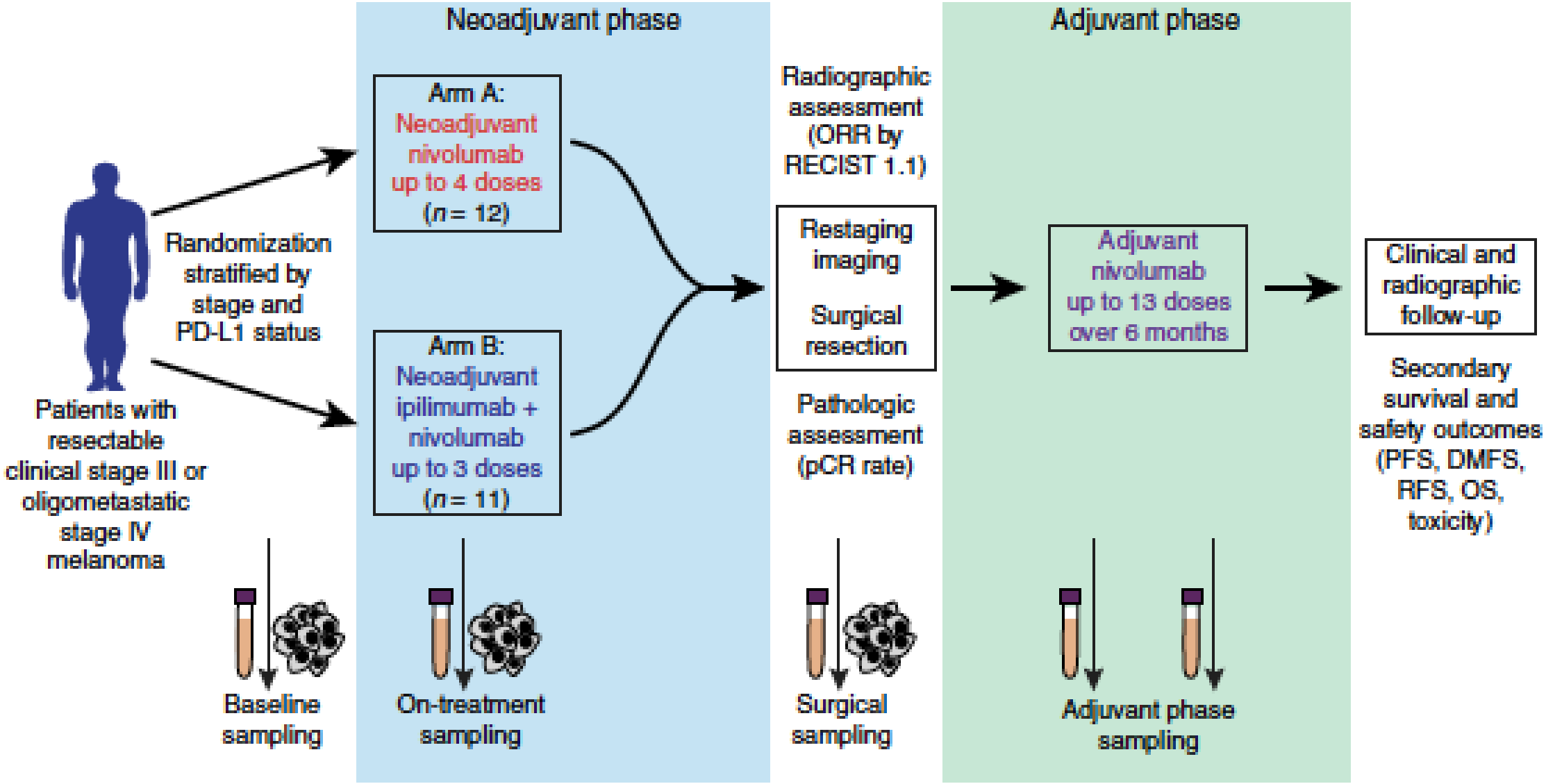
LETTERS

https://doi.org/10.1038/s41591-018-0197-1

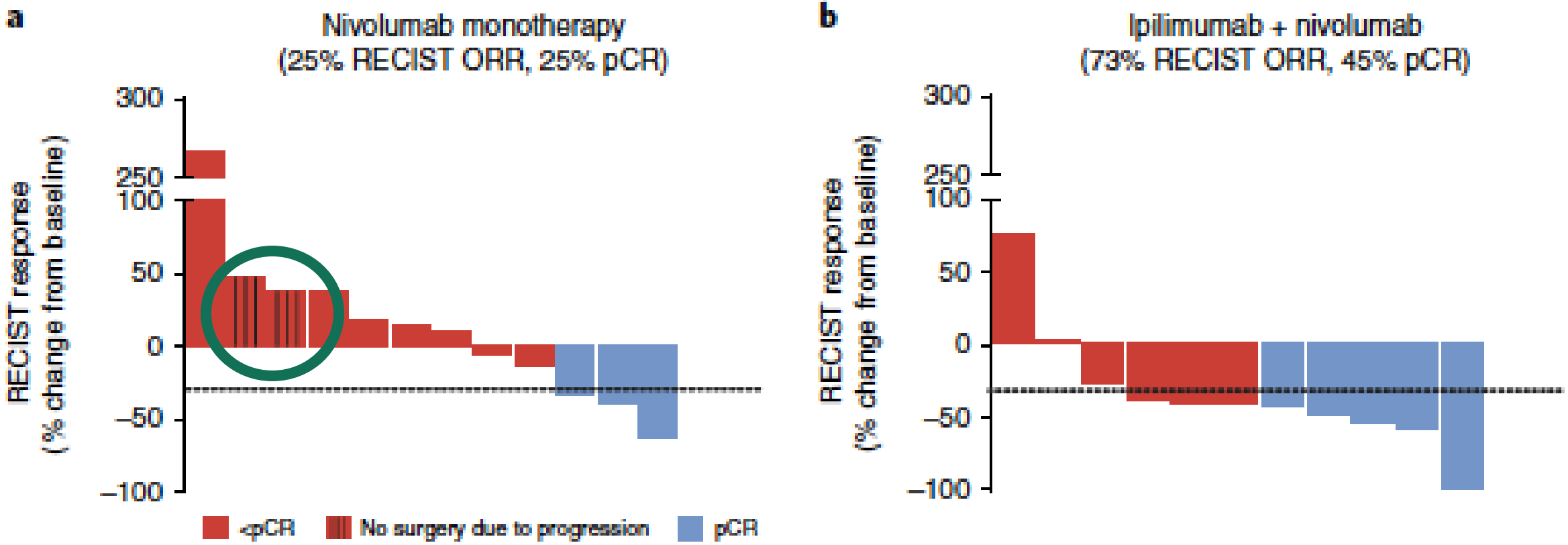
Corrected: Author Correction; Publisher Correction

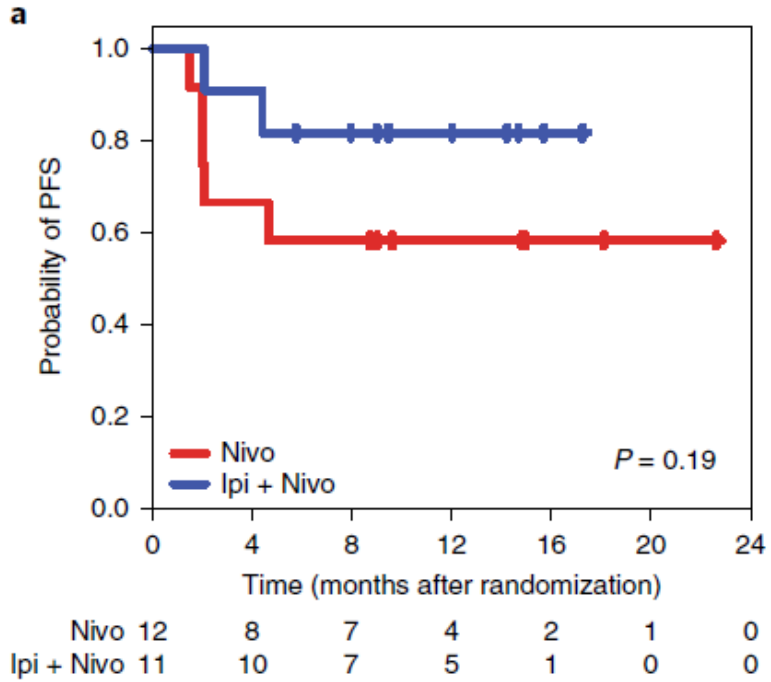
Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma

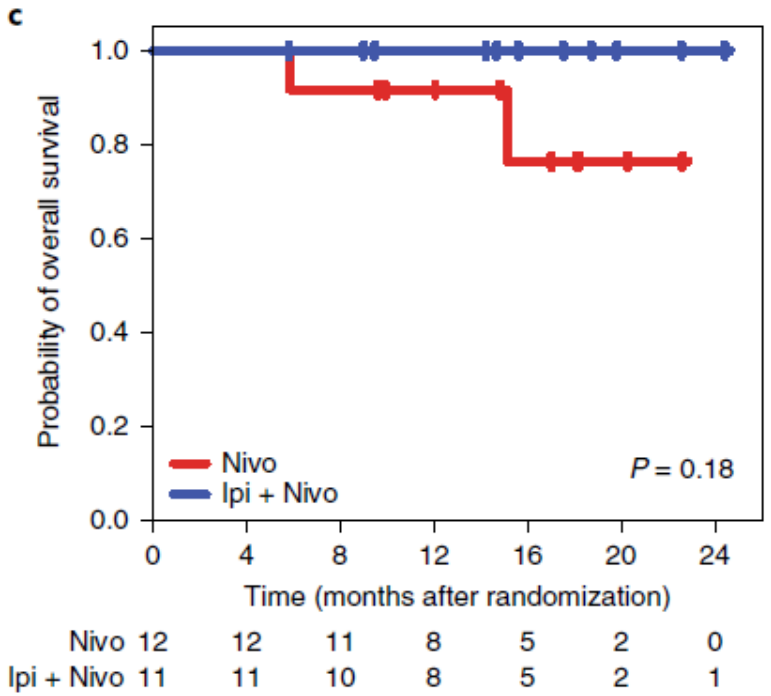
Rodabe N. Amaria[1,12], Sangeetha M. Reddy[2,12], Hussein A. Tawbi[1], Michael A. Davies[1], Merrick I. Ross[3], Isabella C. Glitza[1], Janice N. Cormier[3], Carol Lewis[4], Wen-Jen Hwu[1], Ehab Hanna[4], Adi Diab[1], Michael K. Wong[1], Richard Royal[3], Neil Gross[4], Randal Weber[4], Stephen Y. Lai[4], Richard Ehlers[3], Jorge Blando[5], Denái R. Milton[6], Scott Woodman[1], Robin Kageyama[7], Daniel K. Wells[7], Patrick Hwu[1], Sapna P. Patel[1], Anthony Lucci[3], Amy Hessel[4], Jeffrey E. Lee[3], Jeffrey Gershenwald[3], Lauren Simpson[1], Elizabeth M. Burton[3], Liberty Posada[1], Lauren Haydu[3], Linghua Wang[8], Shaojun Zhang[8], Alexander J. Lazar[9], Courtney W. Hudgens[9], Vancheswaran Gopalakrishnan[3], Alexandre Reuben[3], Miles C. Andrews[3], Christine N. Spencer[8], Victor Prieto[9], Padmanee Sharma[5,10], James Allison[5], Michael T. Tetzlaff[9,11,13] and Jennifer A. Wargo[3,8,13]*


Neoadjuvant phase
Adjuvant phase
Arm A:
Neoadjuvant
nivolumab
up to 4 doses
(n = 12)
Arm B:
Neoadjuvant
ipilimumab +
nivolumab
up to 3 doses
(n = 11)
Randomization
stratified by
stage and
PD-L1 status
Patients with
resectable
clinical stage III or
oligometastatic
stage IV
melanoma
Radiographic
assessment
(ORR by
RECIST 1.1)
Restaging
imaging
Surgical
resection
Pathologic
assessment
(pCR rate)
Adjuvant
nivolumab
up to 13 doses
over 6 months
Clinical and
radiographic
follow-up
Secondary
survival and
safety outcomes
(PFS, DMFS,
RFS, OS,
toxicity)
Baseline
sampling
On-treatment
sampling
Surgical
sampling
Adjuvant phase
sampling

Responses


a
Nivolumab monotherapy
(25% RECIST ORR, 25% pCR)
RECIST response
(% change from baseline)
300
250
100
50
0
–50
–100
<pCR
No surgery due to progression
pCR
b
Ipilimumab + nivolumab
(73% RECIST ORR, 45% pCR)
RECIST response
(% change from baseline)
300
250
100
50
0
–50
–100





- Median follow up of 15.9m
- Stopped early
  - Progression preventing sugery in nivo arm
  - Gr 3 toxicity in Ipi/Nivo arm 73% (8% for Nivo)

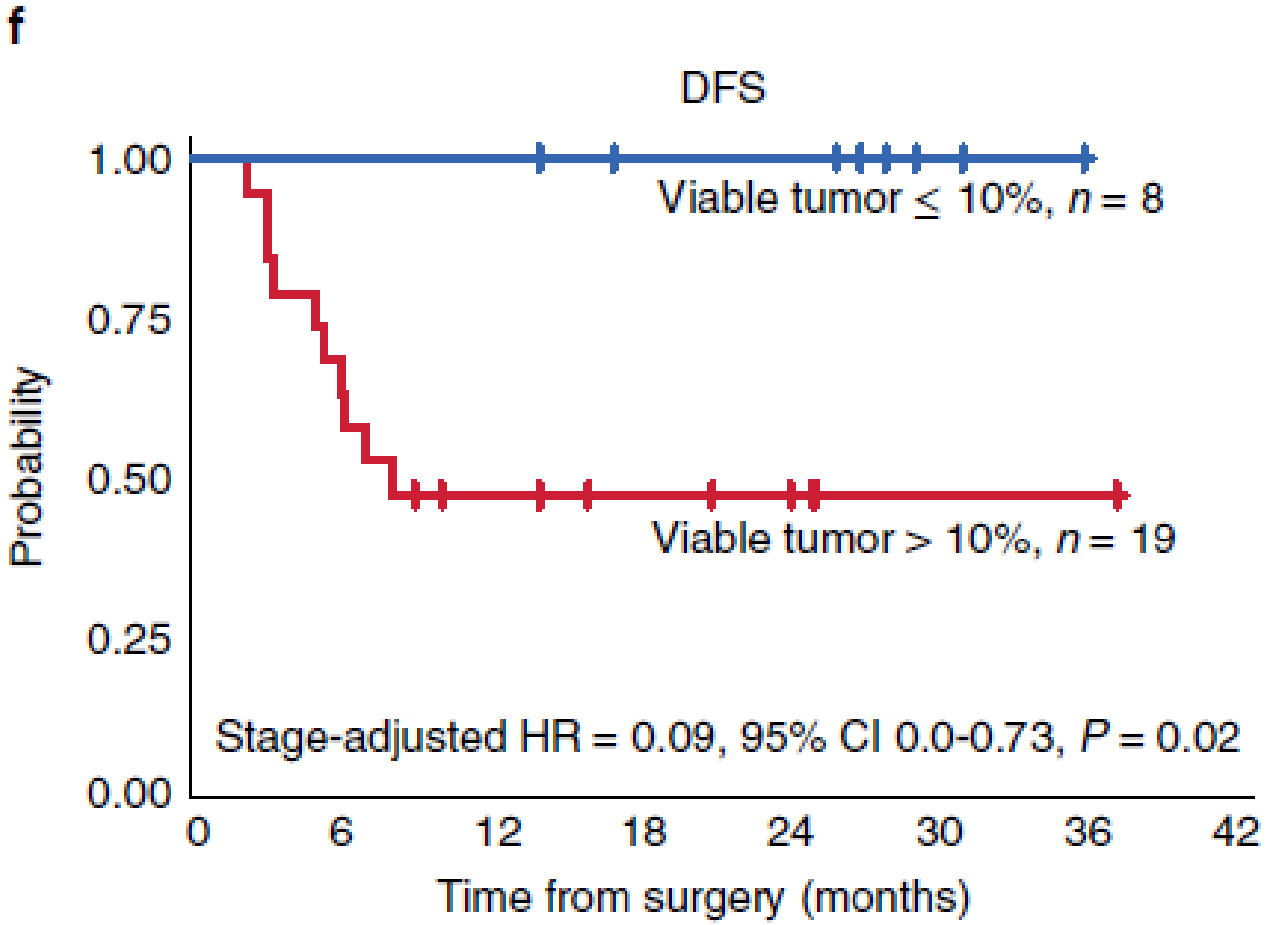
March 2019

LETTERS | FOCUS
https://doi.org/10.1038/s41591-019-0357-y
nature medicine

A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma

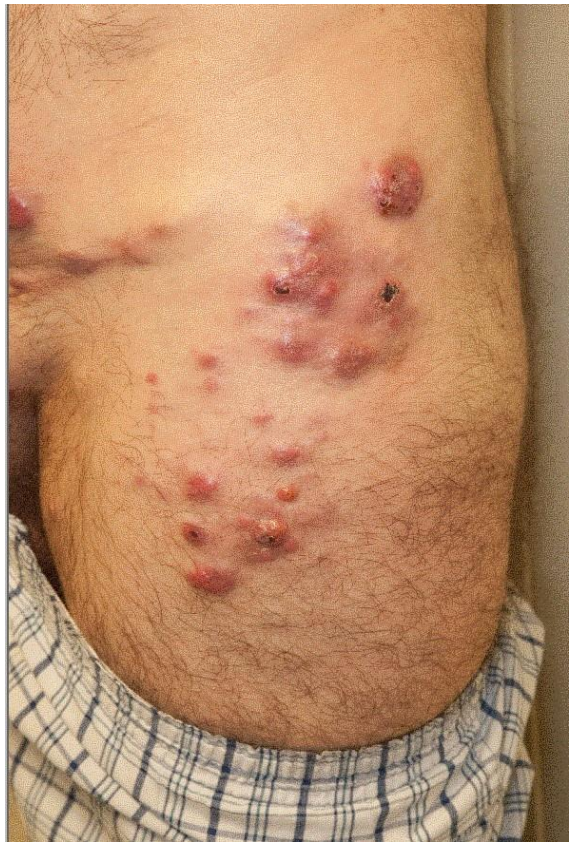
Alexander C. Huang[1,2,3,4,16*], Robert J. Orlowski[1,11,16], Xiaowei Xu[4,5], Rosemarie Mick[3,4,6], Sangeeth M. George[7,12], Patrick K. Yan[2,7], Sasikanth Manne[2,7], Adam A. Kraya[1,4], Bradley Wubbenhorst[1,4], Liza Dorfman[1,4], Kurt D'Andrea[1,4], Brandon M. Wenz[1,4], Shujing Liu[4,5], Lakshmi Chilukuri[2,7], Andrew Kozlov[4,8], Mary Carberry[1,4], Lydia Giles[1,4], Melanie W. Kier[1], Felix Quagliarello[2,13], Suzanne McGettigan[1,4], Kristin Kreider[1,4], Lakshmanan Annamalai[9], Qing Zhao[9], Robin Mogg[9,14], Wei Xu[1,4], Wendy M. Blumenschein[9], Jennifer H. Yearley[9], Gerald P. Linette[1,2,3,4], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Ramin S. Herati[1,2], Bertram Bengsch[2,15], Katherine L. Nathanson[1,3,4], Michael D. Farwell[4,8,17], Giorgos C. Karakousis[4,10,17], E. John Wherry[2,3,4,7,17*] and Tara C. Mitchell[1,4,17*]

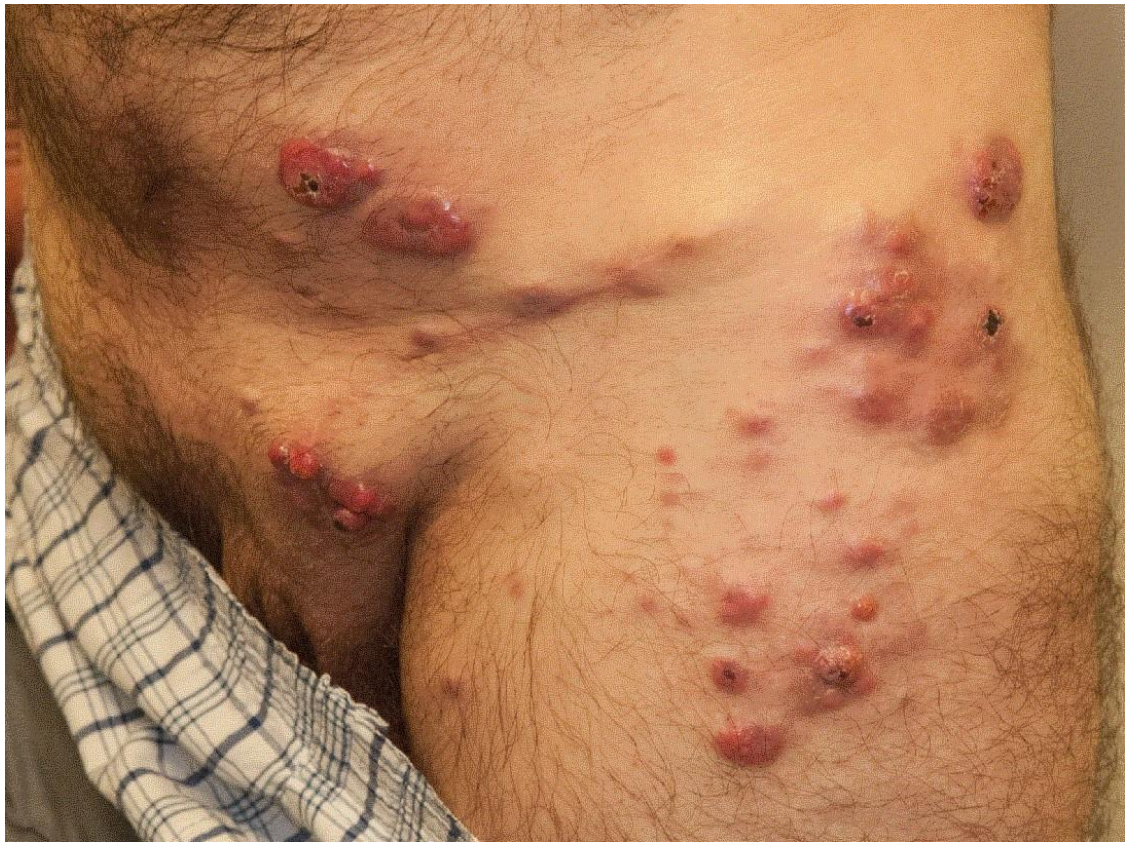
- 27 patients St IIIB/C/IV melanoma
- 1 dose 200mg pembrolizumab -> 3weeks -> surgery
- 8/27 (30%) had complete or major (<10% viable tumor) response at resection
- Response correlated with DFS again (8/8 have not relapsed)
  - Median fu 25m



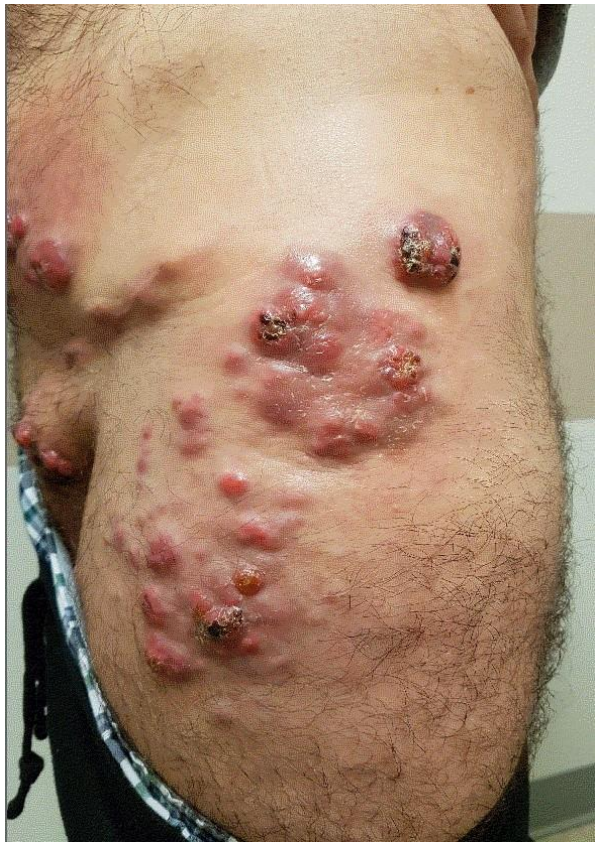
Nyetta Biggdyele

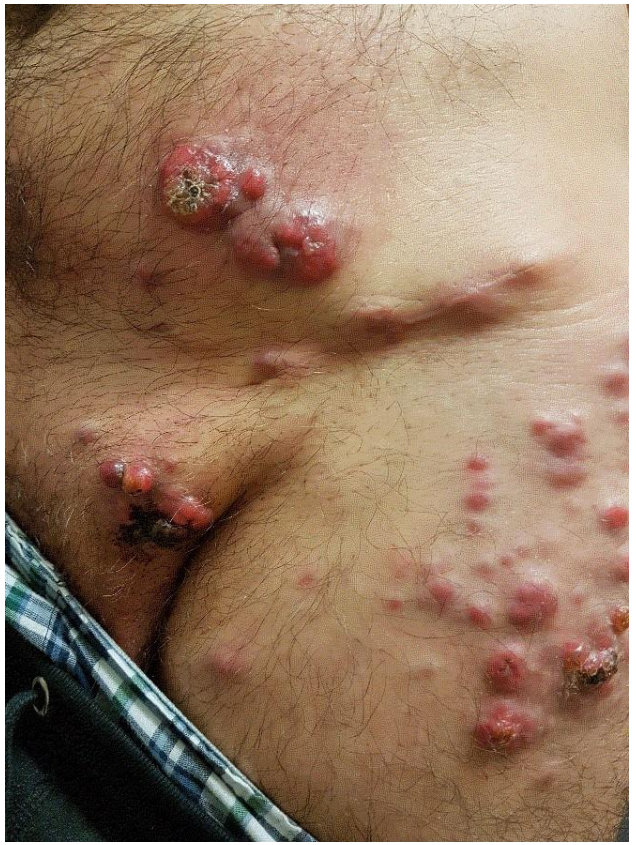
April 12 – Ipi/Nivo Dose 2



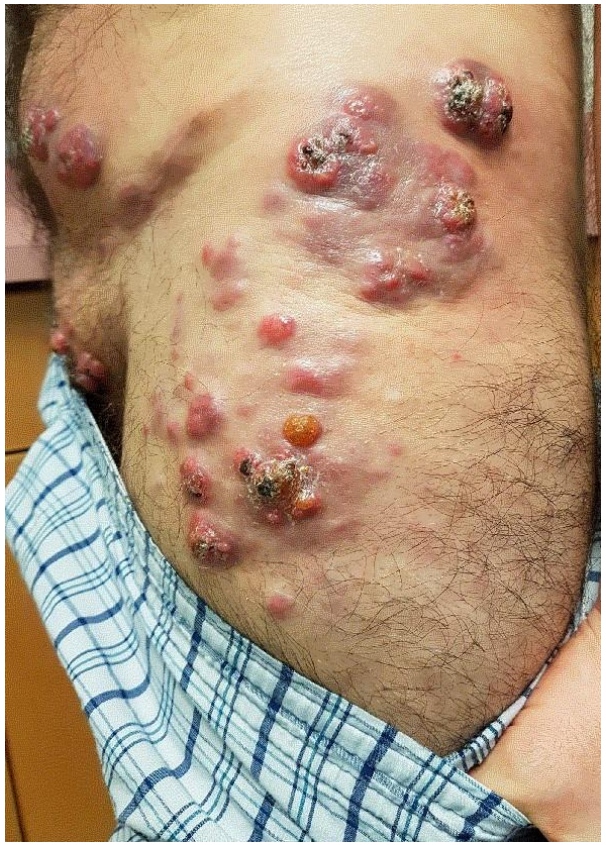


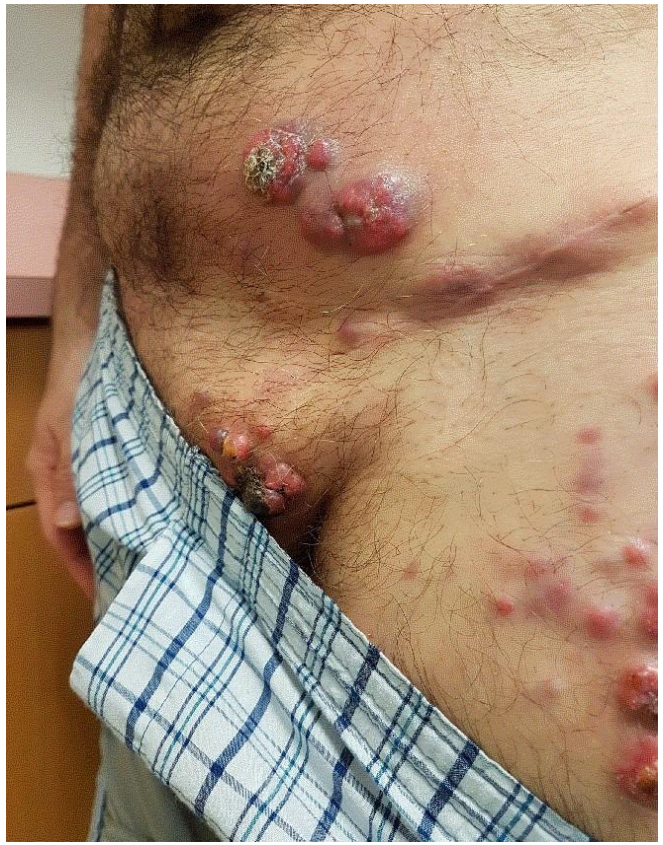
April 25 – Ipi/Nivo Dose 3



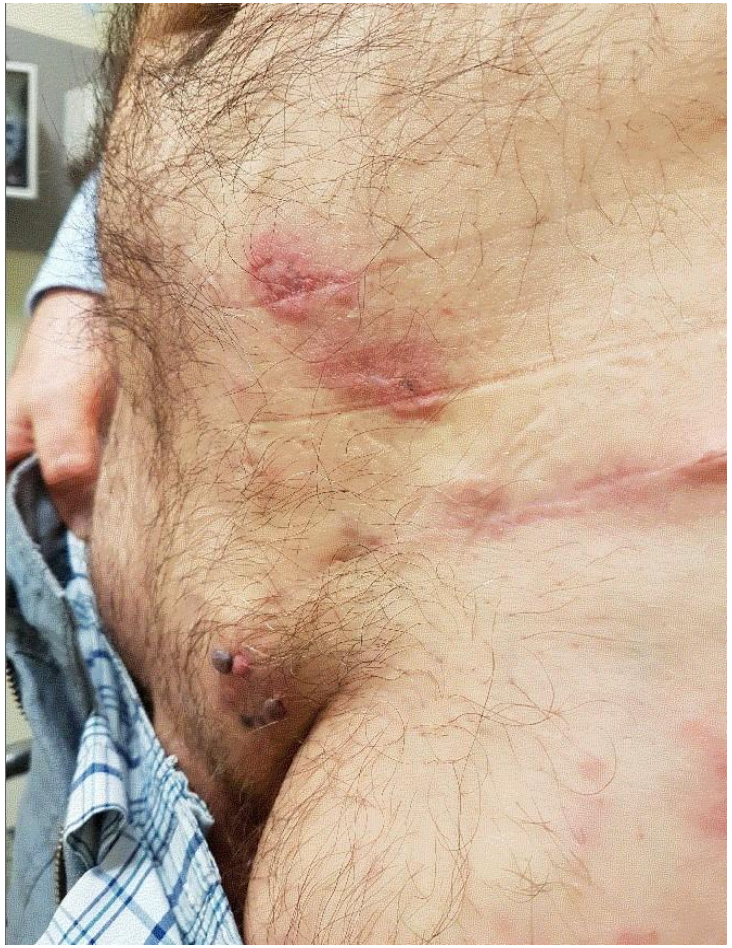


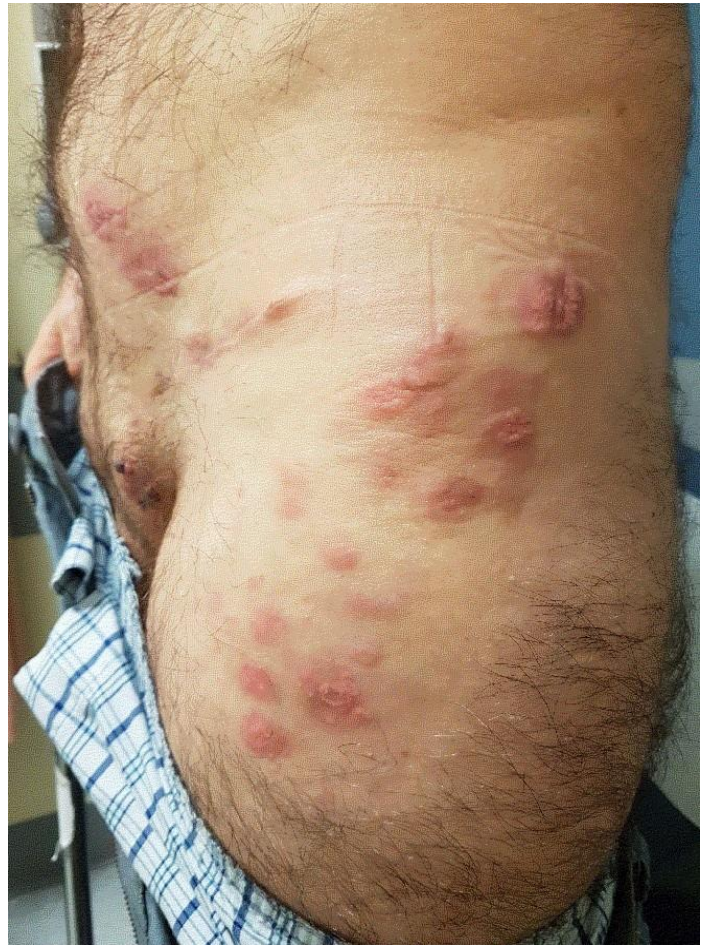
May 4 – Start of Dab/Tram
Ipi/Nivo stopped





June 2





Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial

Rodabe N Amaria, Peter A Prieto*, Michael T Tetzlaff, Alexandre Reuben, Miles C Andrews, Merrick I Ross, Isabella C Glitza, Janice Cormier, Wen-Jen Hwu, Hussein A Tawbi, Sapna P Patel, Jeffrey E Lee, Jeffrey E Gershenwald, Christine N Spencer, Vancheswaran Gopalakrishnan, Roland Bassett, Lauren Simpson, Rosalind Mouton, Courtney W Hudgens, Li Zhao, Haifeng Zhu, Zachary A Cooper, Khalida Wani, Alexander Lazar, Patrick Hwu, Adi Diab, Michael K Wong, Jennifer L McQuade, Richard Royal, Anthony Lucci, Elizabeth M Burton, Sangeetha Reddy, Padmanee Sharma, James Allison, Phillip A Futreal, Scott E Woodman, Michael A Davies†, Jennifer A Wargo†*

Summary

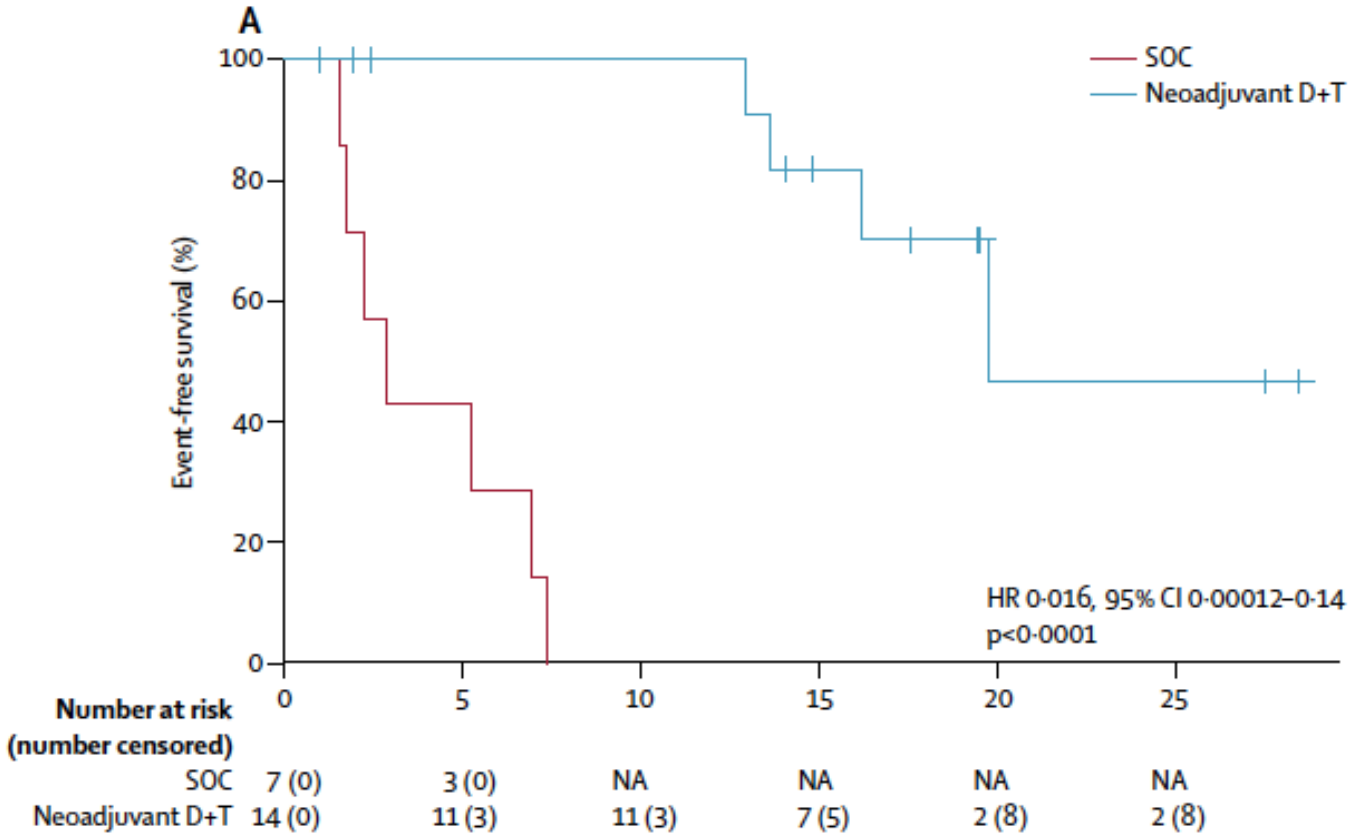
Background Dual BRAF and MEK inhibition produces a response in a large number of patients with stage

Lancet Oncol 2018; 19: 181–93

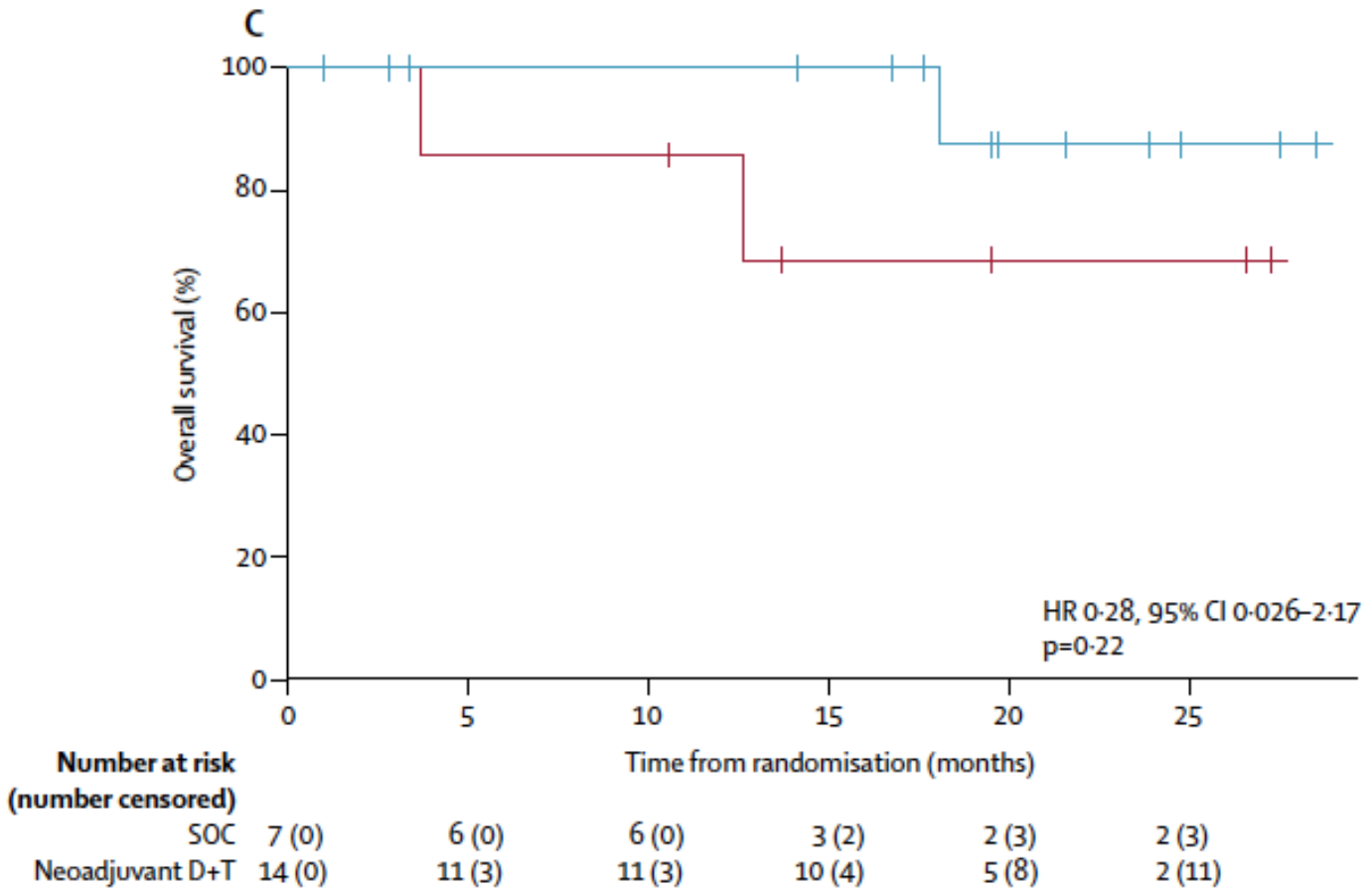
- 21 patients randomized 2:1 (planned to enroll 84)
- Stage III or IV resectable melanoma
- 14 set to receive dab/tram x 8w -> surgery
  - 13 received drug, 12 patients underwent surgery
- 7 patients surgery followed by treatment of choice
  - Chemo, interferon, observation (no set standard)
- Trial stopped early due to marked difference between arms

	Standard of care (n=7)	Neoadjuvant plus adjuvant dabrafenib and trametinib (n=14)
Clinical stage†		
IIIB	3 (43%)	2 (14%)
IIIC	3 (43%)	10 (71%)
IV	1 (14%)	2 (14%)
Primary tumour ulceration status		
Ulcerated	3 (43%)	7 (50%)
Not ulcerated	2 (29%)	1 (7%)
Unknown	1 (14%)	2 (14%)
NA (unknown primary)	1 (14%)	4 (29%)
Lactate dehydrogenase status		
Raised	1 (14%)	1 (7%)
Not raised	6 (86%)	13 (93%)

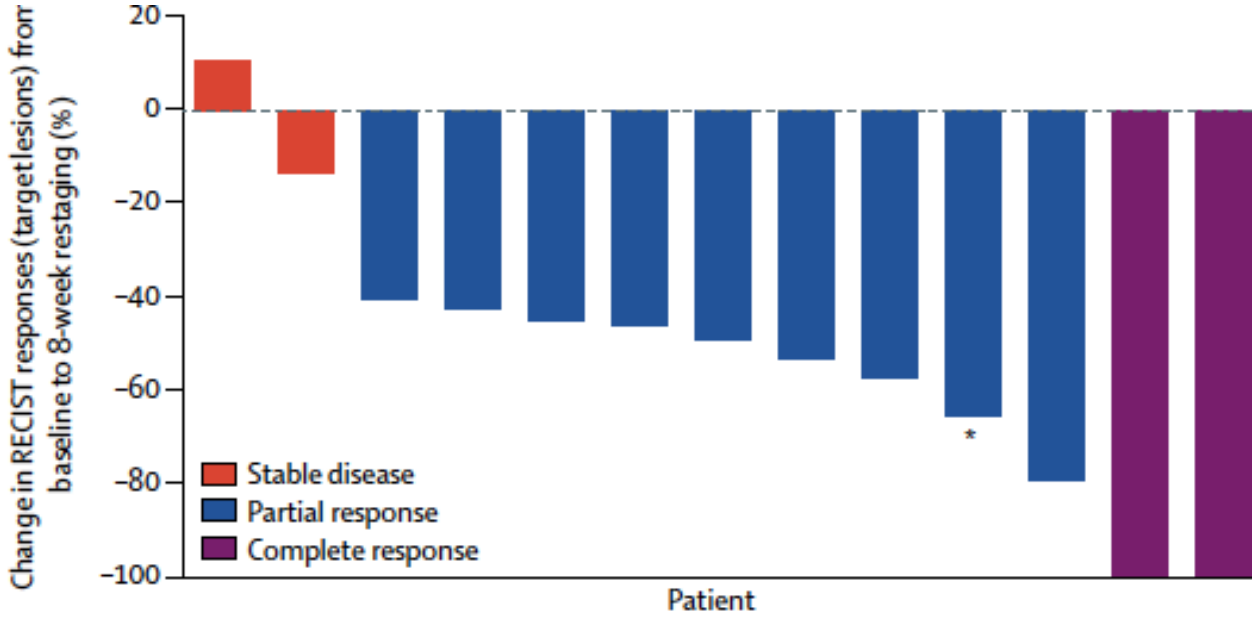
Event Free Survival

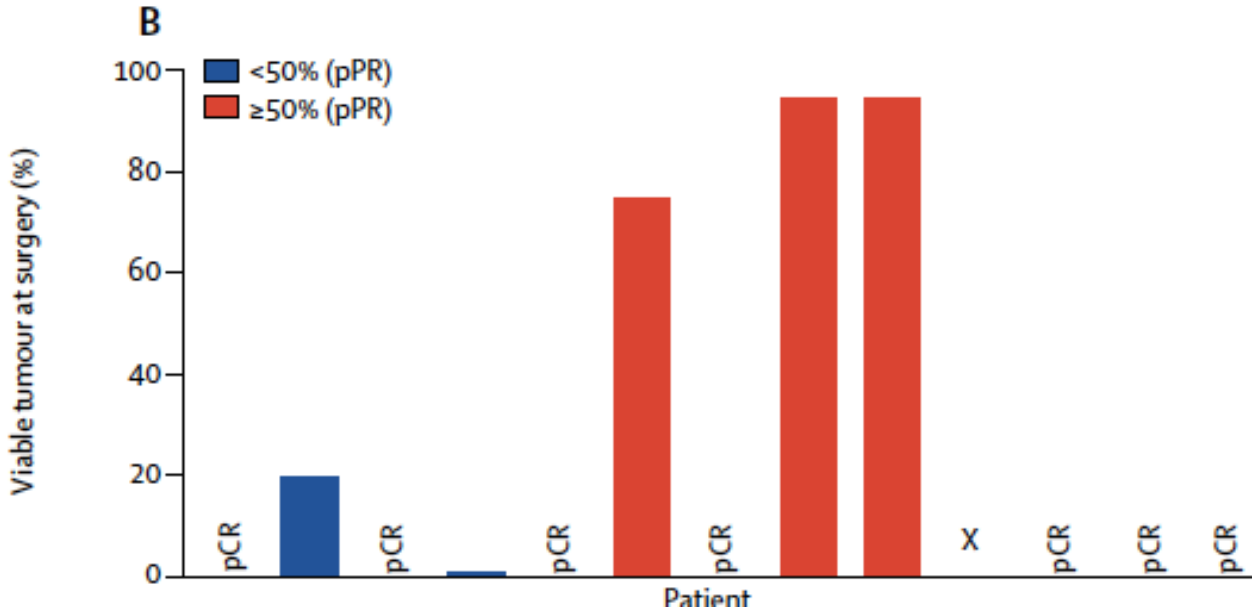


Overall Survival

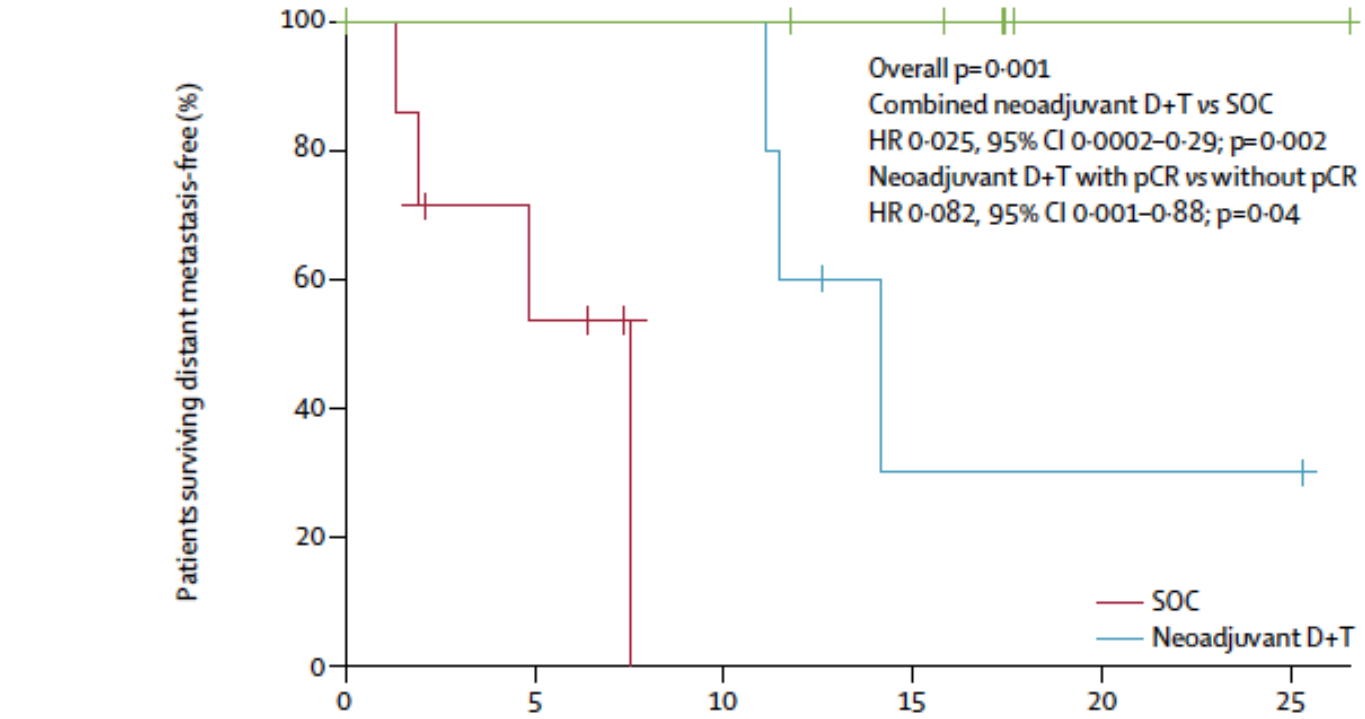


Radiologic vs Pathologic Responses





DMFS Based on Pathologic Response



Number at risk (number censored)						
SOC	7 (0)	3 (1)	NA	NA	NA	NA
Neoadjuvant D+T/no pCR	5 (0)	5 (0)	5 (0)	1 (1)	1 (1)	1 (1)
Neoadjuvant D+T/pCR	6 (1)	6 (1)	6 (1)	5 (2)	1 (6)	1 (6)

Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB–C, *BRAF*^{V600} mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial

Georgina V Long, Robyn P M Saw, Serigne Lo, Omgo E Nieweg, Kerwin F Shannon, Maria Gonzalez, Alexander Guminski, Jenny H Lee, Hansol Lee, Peter M Ferguson, Robert V Rawson, James S Wilmott, John F Thompson, Richard F Kefford, Sydney Ch'ng, Jonathan R Stretch, Louise Emmett, Rony Kapoor, Helen Rizos, Andrew J Spillane, Richard A Scolyer, Alexander M Menzies

Summary

Background Adjuvant dabrafenib plus trametinib therapy improves relapse-free survival in patients with resected

Lancet Oncol 2019; 20: 961–71

- Single arm phase II trial
- 35 patients, resectable IIIB-IIIC
- Dab/Tram for 8 weeks -> resection -> complete 1 year Dab/Tram
- 60% concordance in responses

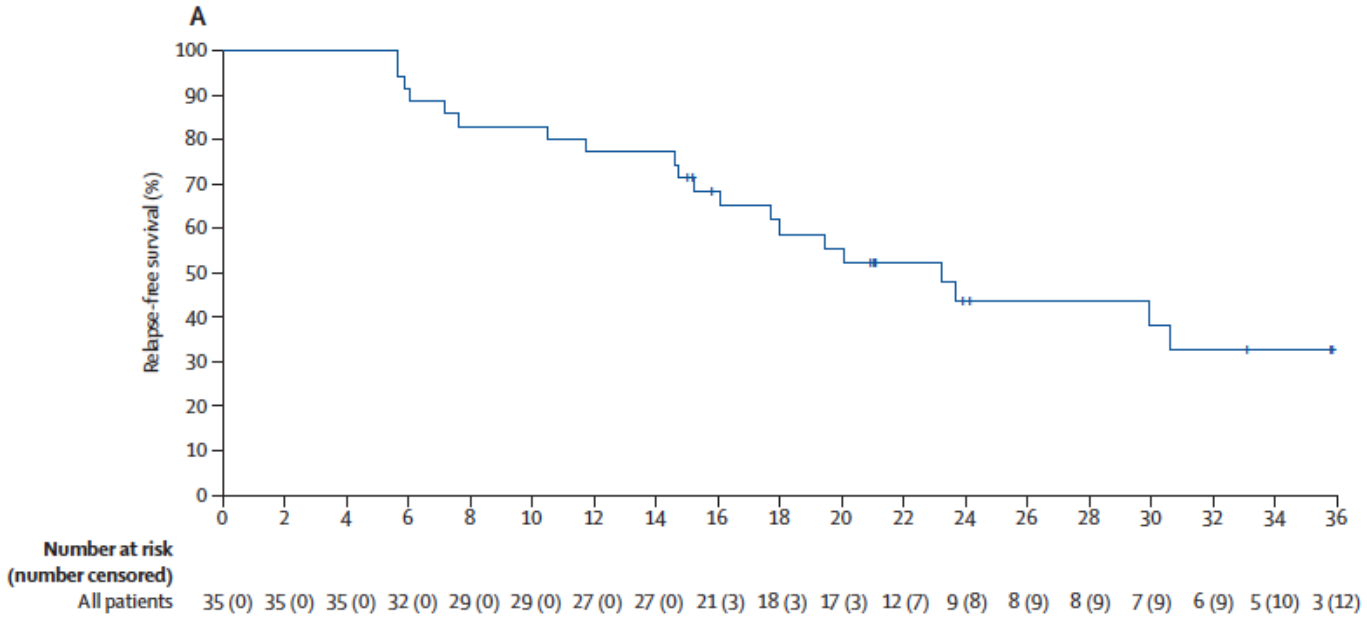
	Study population (n=35)
Pathological response	
Complete	17 (49%; 95% CI 31–66)
Non-complete	18 (51%; 95% CI 34–69)
RECIST response	
Complete response	16 (46%; 95% CI 29–63)
Partial response	14 (40%; 95% CI 24–58)
Stable disease	5 (14%; 95% CI 5–30)
Metabolic response	
Complete	18 (51%; 95% CI 34–69)
Non-complete	17 (49% 95% CI 31–61)

Data are n (%; 95% CI). RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2: **Patients with pathological, RECIST, and metabolic responses at 12 weeks**

Relapse Free Survival

- **57% of patients recurred (20 patients)**
- **4 patients recurred on treatment**
- **16 patients recurred following 1 year of D+T**



	Total population (n=35)	Patients with a complete pathological response (n=17)	Patients with a non-complete pathological response (n=18)
Number of events	20	8	12
Median, months (95% CI)	23·3 (17·7 to not reached)	30·6 (20·1 to not reached)	18·0 (14·6 to not reached)
1-year relapse-free survival (95% CI)	77·1% (64·4 to 92·4)	82·4% (66·1 to 100)	72·2% (54·2 to 96·2)
2-year relapse-free survival (95% CI)	43·4% (28·6 to 65·7)	63·3% (43·7 to 91·7)	24·4% (9·7 to 61·8)

Table 3: **Relapse-free survival from start of dabrafenib plus trametinib treatment**

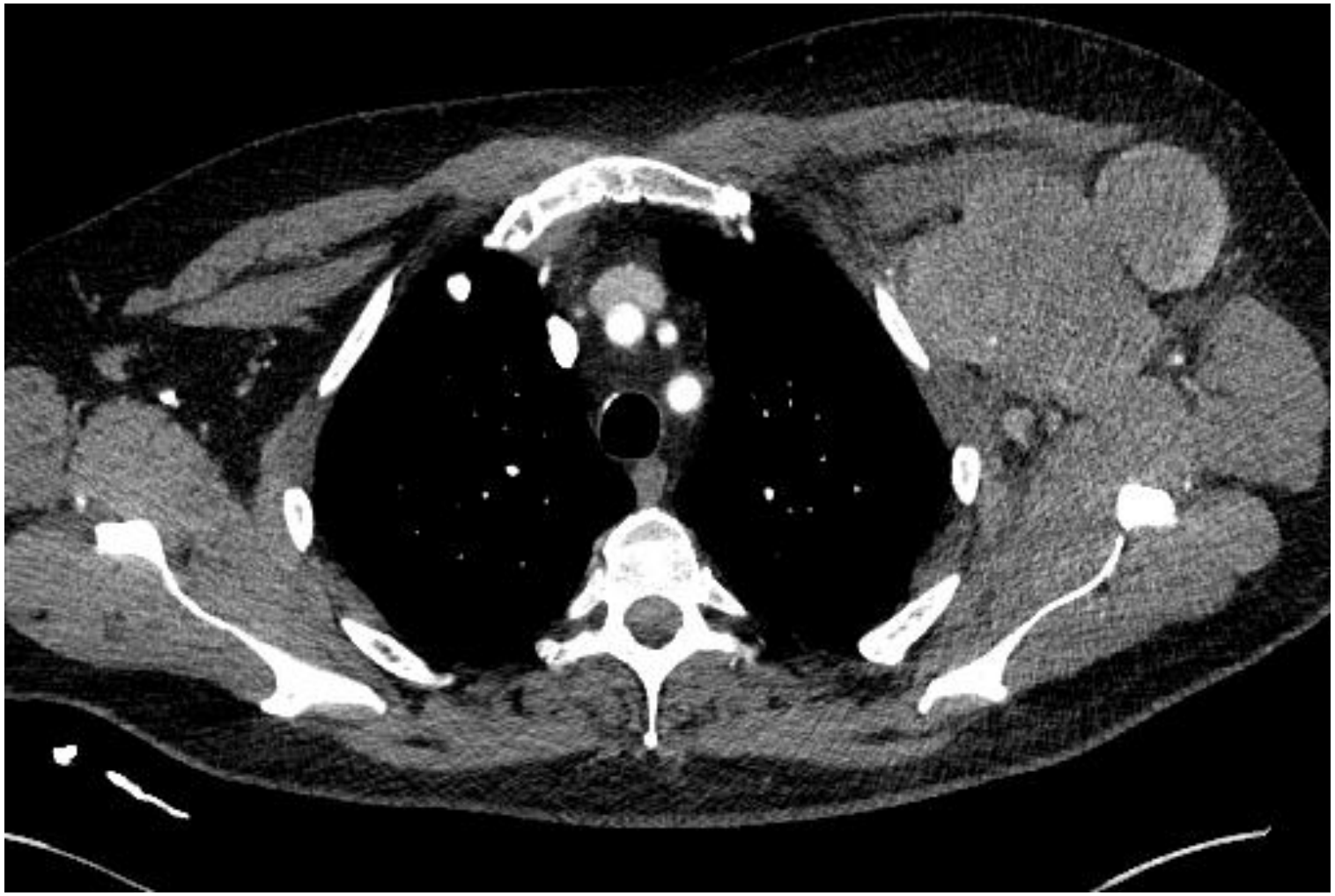
RFS Based on Pathologic Response

NB

COMBI AD Stage IIIC 1yr RFS 86% vs 77%; 2yr RFS 61% vs 43%

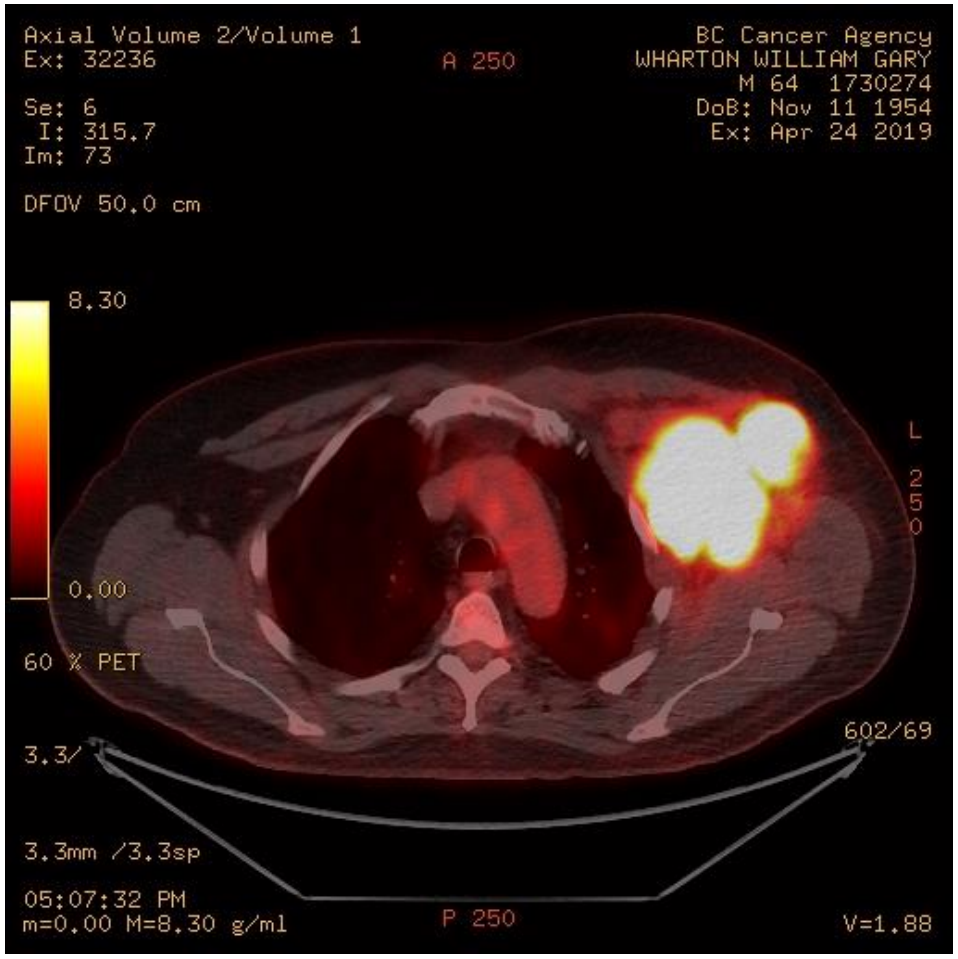
Unresectable Disease

Mr. Wu Tang



April 2019

May 2019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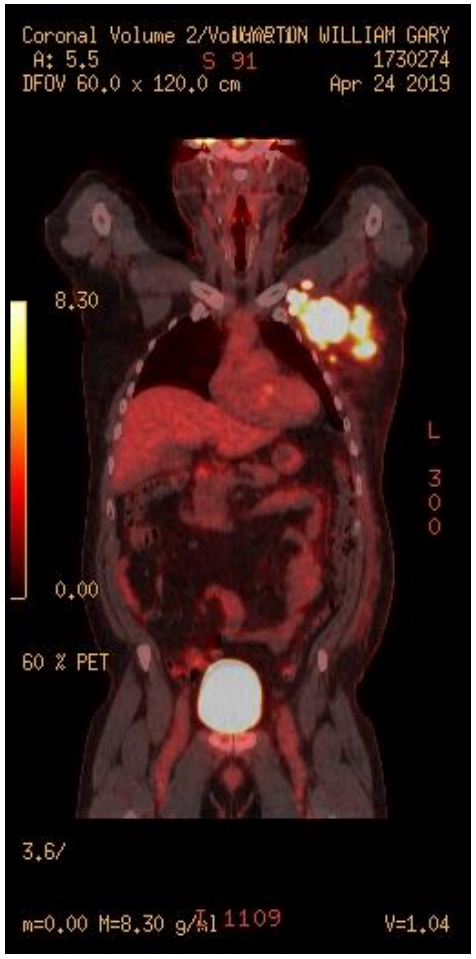
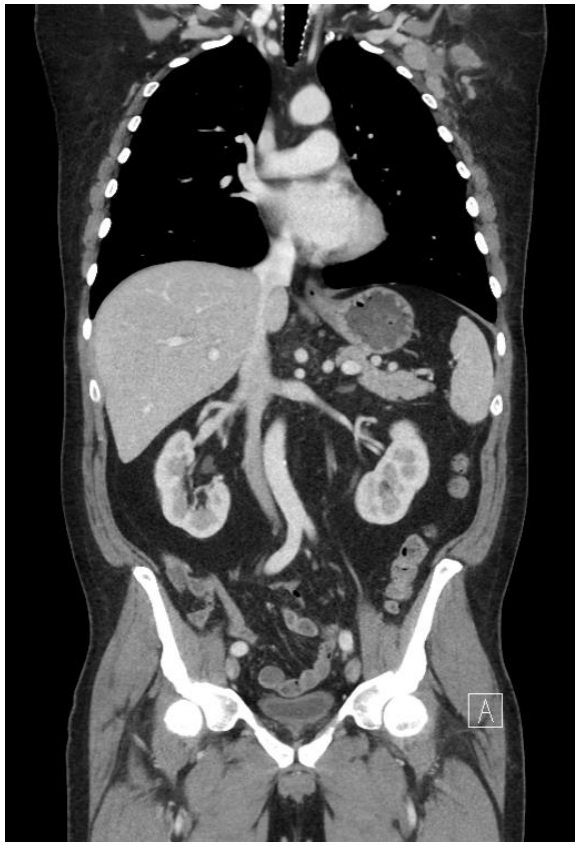
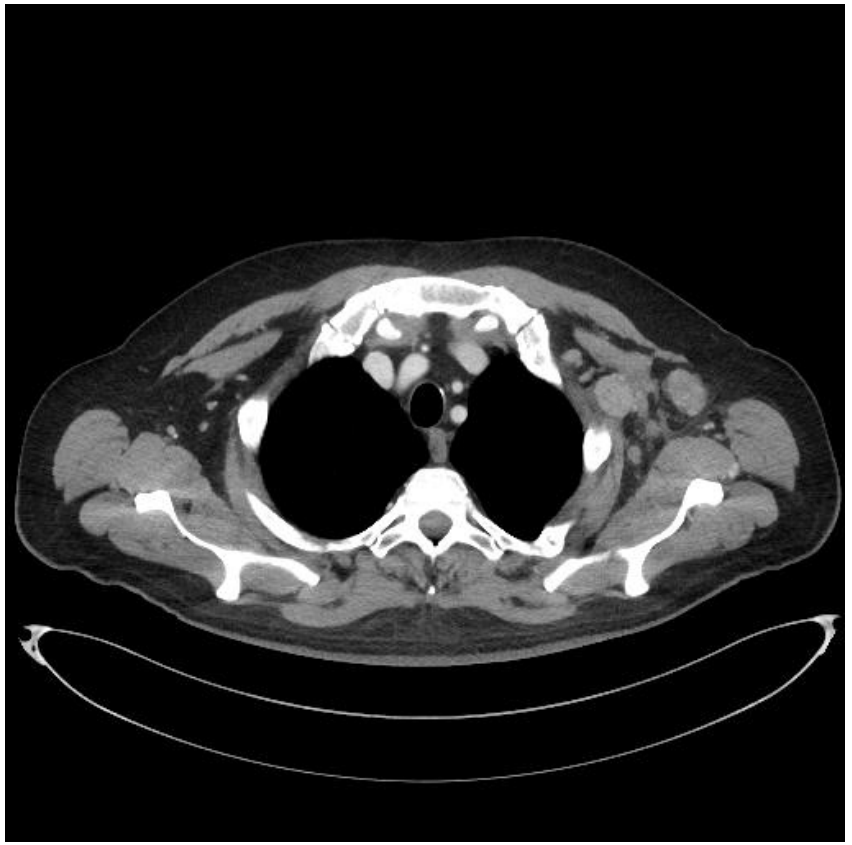
Ex: 32236
A 250
BC Cancer Agency
WHARTON WILLIAM GARY
M 64 1730274
DoB: Nov 11 1954
Ex: Apr 24 2019
Se: 6
I: 315.7
Im: 73
DFOV 50.0 cm
8.30
0.00
60 % PET
L 250
602/69
3.3/
3.3mm /3.3sp
05:07:32 PM
m=0.00 M=8.30 g/ml
P 250
V=1.88


Coronal Volume 2/Volume 1
WHARTON WILLIAM GARY
A: 5.5
S 91
1730274
DFOV 60.0 x 120.0 cm
Apr 24 2019
8.30
0.00
60 % PET
L 300
3.6/
m=0.00 M=8.30 g/ml
1109
V=1.04

July 2019 – 3 doses of Ipi/Nivo





4/19 nodes positive for melanoma

Largest deposit 2mm

Complete loss of pituitary function

Conclusions

- Adjuvant therapy now available for all fully resected stage III/IV NED melanoma
  - Consider sentinel node biopsy as it may qualify someone for adjuvant
  - Full lymph node dissection not required for microscopic disease
- Neoadjuvant for resectable disease is not proven or funded at present
- UNRESECTABLE disease can be considered for neoadjuvant approach
  - Appropriate for multidisciplinary discussion