When to stop or resume immunotherapy data from melanoma

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DISCLOSURES

- Personal financial compensation from Novartis, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, and Pierre-Fabre for public speaking, and participation in advisory board meetings
- My institution (UZ Brussel) received research funding related to research projects conducted by my department (medical oncology) from Pfizer, Novartis, Roche, and Merck-Serono

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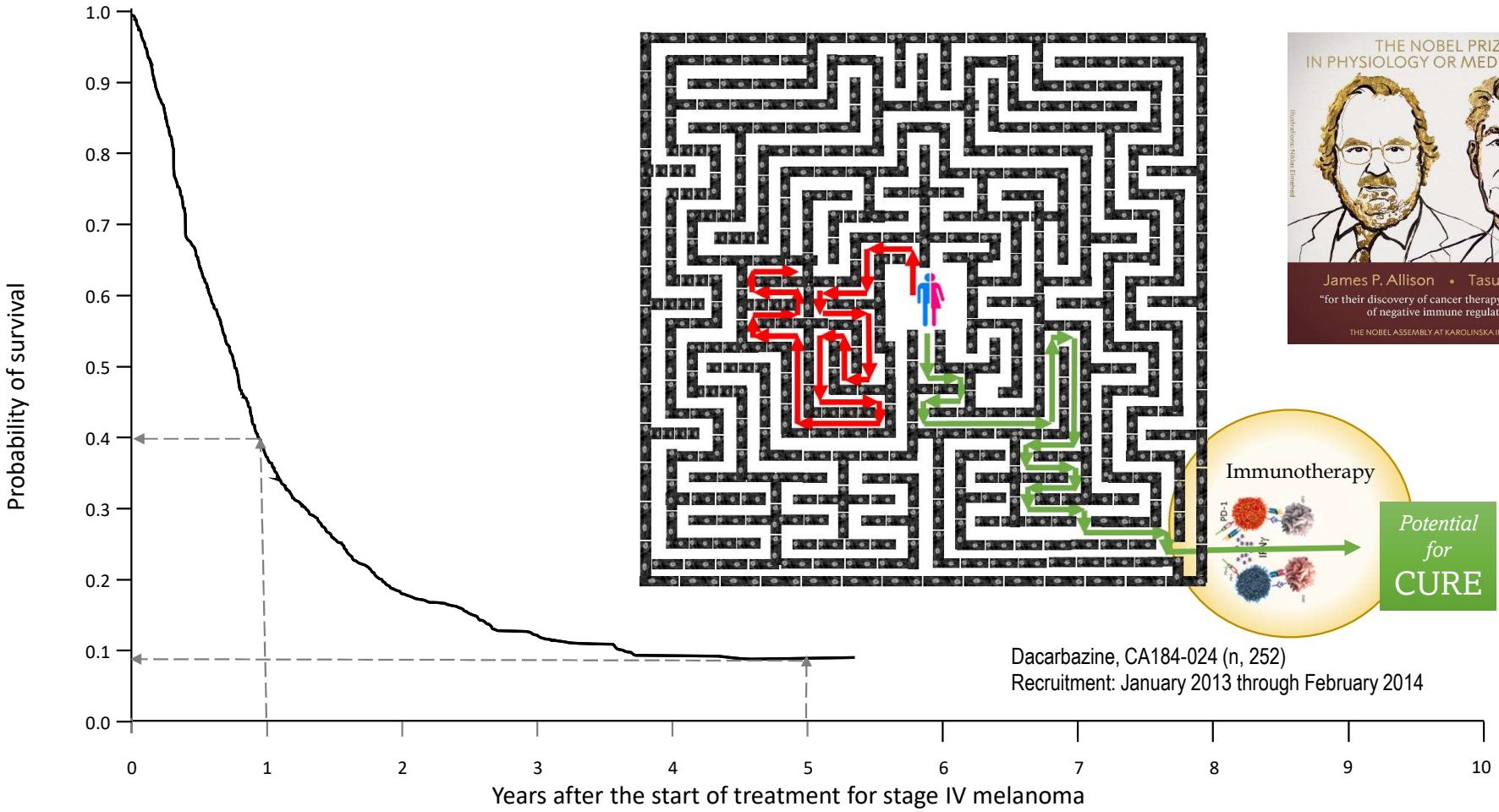
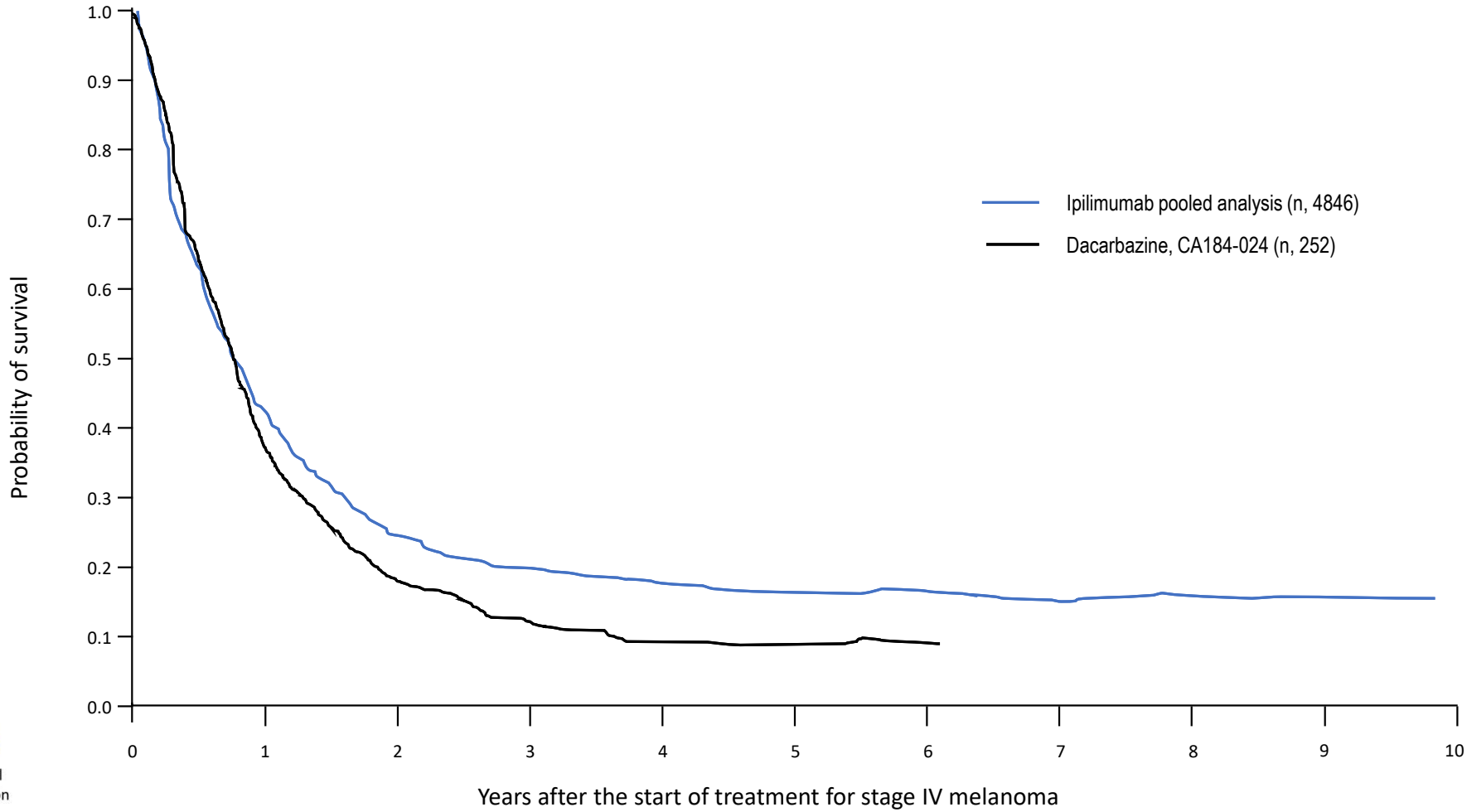
OVERALL SURVIVAL OF ADVANCED MELANOMA PATIENTS ACCORDING TO FIRST-LINE THERAPY



Adapted from A. Rogiers et al. Journal of Oncology, 2019:5269062.

Overall Survival of Advanced Melanoma Patients According to First-Line Therapy



Cross-trial comparison

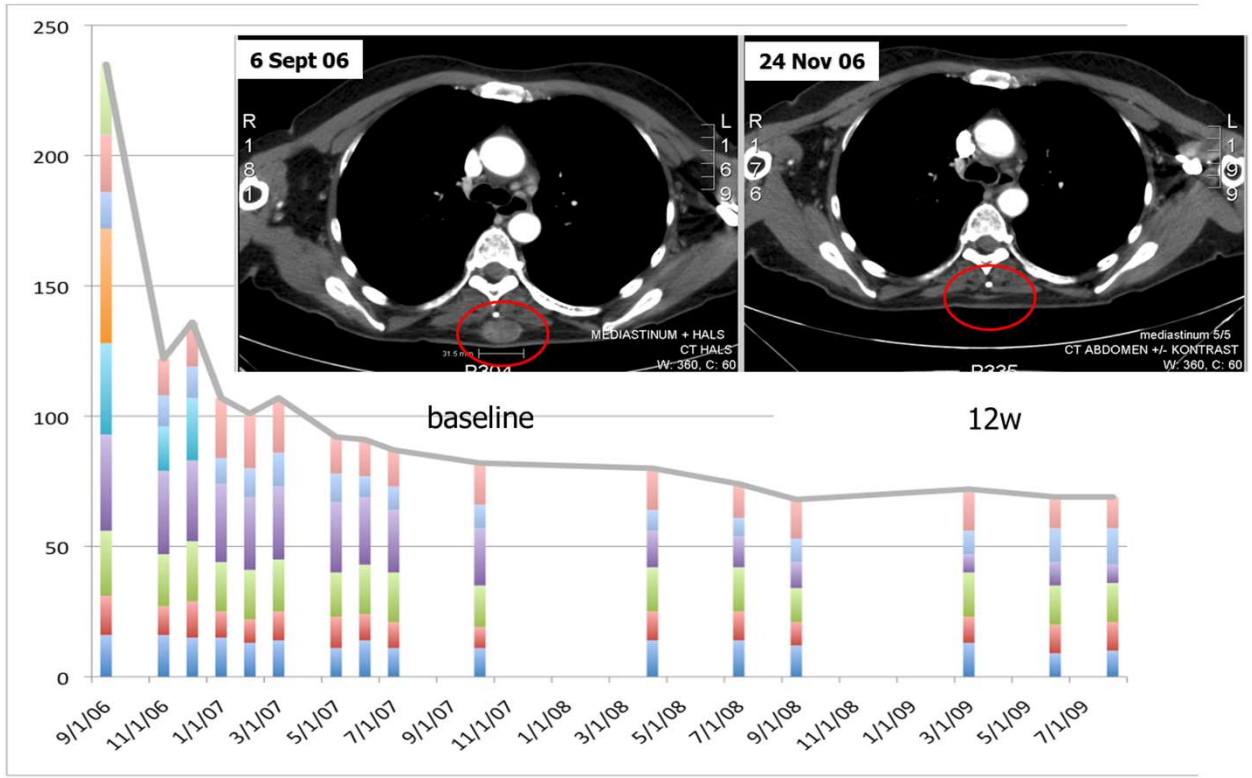
Cross trial comparisons cannot be inferred.

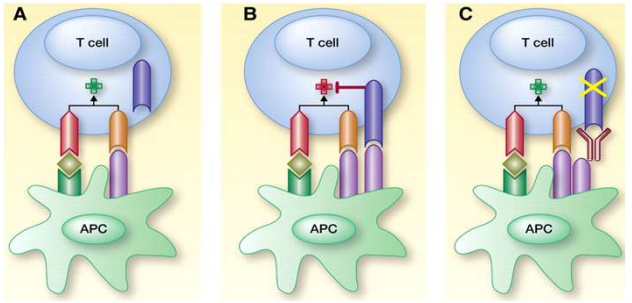
Adapted from A. Rogiers et al. Journal of Oncology, 2019:5269062.

Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study

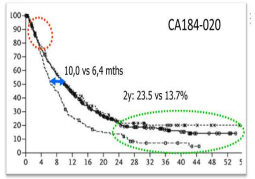
Jedd D Wolchok, Bart Neyns, Gerald Linette, Sylvie Negrier, Jose Lutzky, Luc Thomas, William Waterfield, Dirk Schadendorf, Michael Smylie, Troy Guthrie Jr, Jean-Jacques Grob, Jason Chesney, Kevin Chin, Kun Chen, Axel Hoos, Steven J O'Day, Celeste Lebbé

Lancet Oncol 2010; 11: 155–64

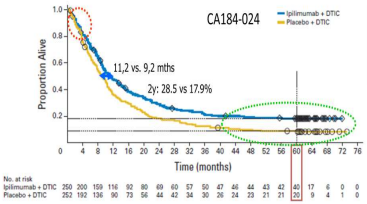




Overall survival following treatment with ipilimumab in Phase III Clinical Trials



- Ipilimumab, 3 mg/kg Q3w x4
- Patients without PD or TLT @w24 were offered additional courses of therapy (re-induction) if they had PD
- BORR = 6/31 (19.3%) re-induction-eligible patients; DCR 70%



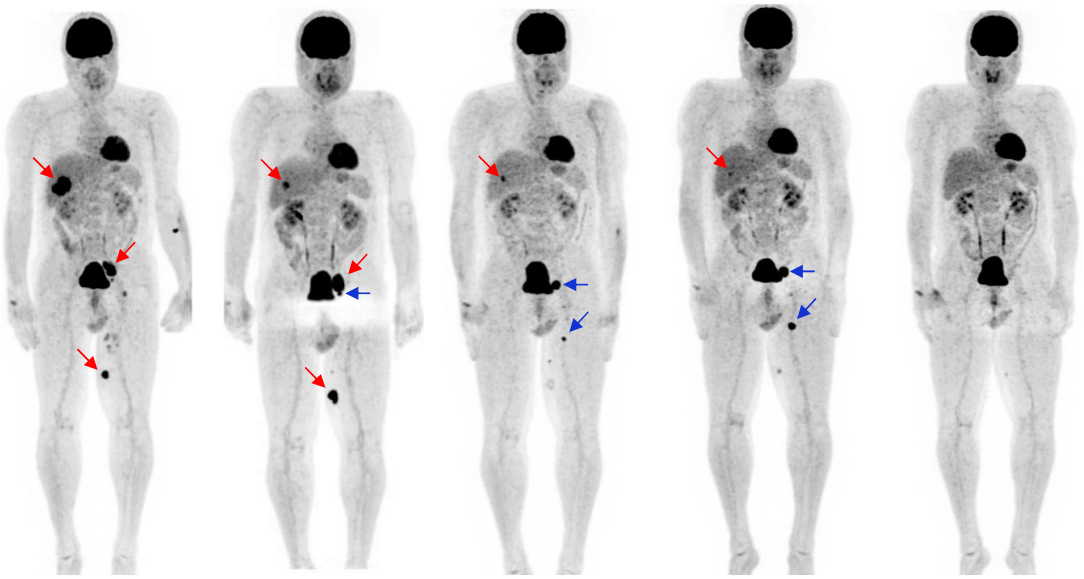
- DTIC + placebo or ipilimumab (10 mg/kg, Q3w x4)
- Patients without PD or LT @6mths could receive ipilimumab or placebo maintenance therapy (Q12w beginning @w24)

Hodi et al. NEJM, 2010; Robert et al. CCR 2013; Maio et al. JCO 2015

Wolchok JD, et al. Lancet Oncol. 2010;11:155-64.

Case illustration – durable complete response after CTLA-4 blockade

61y M acral ulcerated cKIT-wt melanoma on the third toe of his left foot in Jan 2009 (pT4bN1Mx)
April 2010: stage IV-M1c disease with liver, lymph node and subcutaneous metastases
PD following 2x DTIC

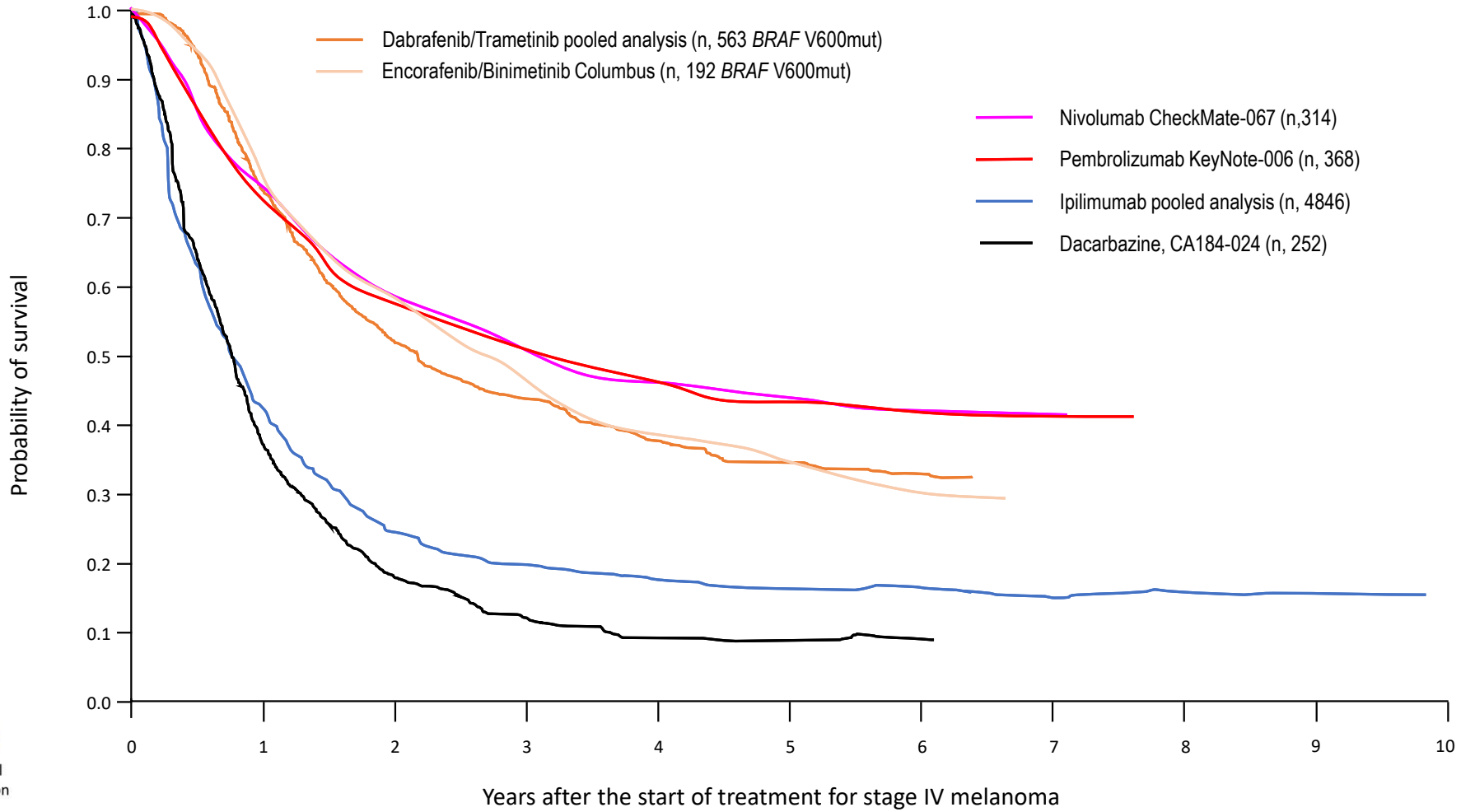


Baseline	12 weeks	24 weeks	43 weeks (pre re-induction)	56 weeks (post re-induction)
20/08/2010	17/11/2010	15/02/2011	28/06/2011	27/09//2011

CTLA-4, cytotoxic T-lymphocyte associated protein 4; DTIC, dacarbazine; M, male; PD, progressive disease; wt, wildtype; y, year.

Wilgenhof S. et al. Cancer Invest. 2012; 30(10): 712–20.

Overall Survival of Advanced Melanoma Patients According to First-Line Therapy

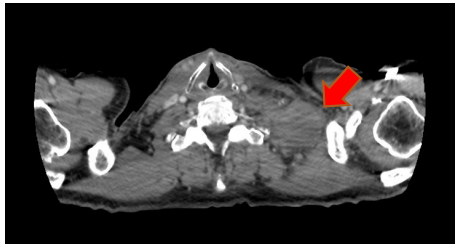


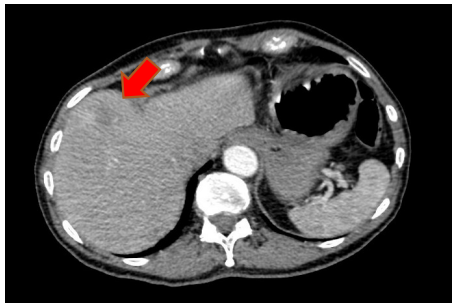
Cross-trial comparison

Cross trial comparisons cannot be inferred.

Adapted from A. Rogiers et al. Journal of Oncology, 2019:5269062.

Case illustration: long-term outcome following early discontinuation of pembrolizumab because of an irAE in a 81y old stage IV-M1c BRAFwt melanoma patient





LDH 2690 U/L (ULN 618)
CRP 34,1 mg/l (ULN <5)

13/1/2014

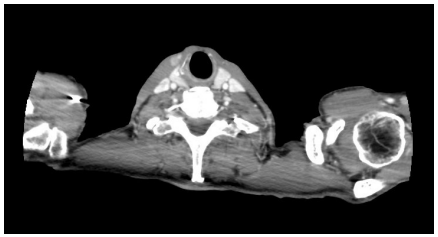
3 months

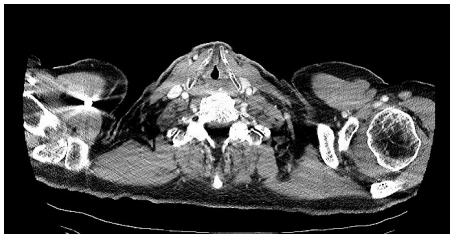
KN006

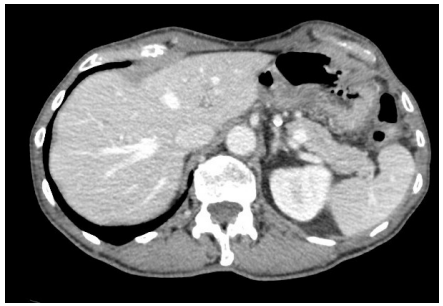
24/1/2014
14/2/2014

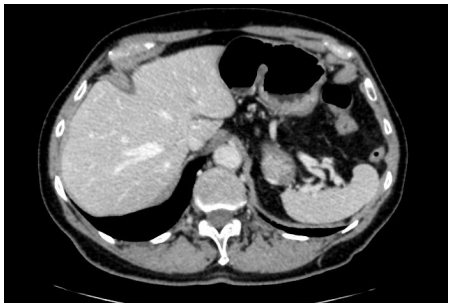
28/3/2014
PNP grade 2

STOP PEMBRO









LDH 364 U/L
CRP <0,5 mg/l

18/4/2014

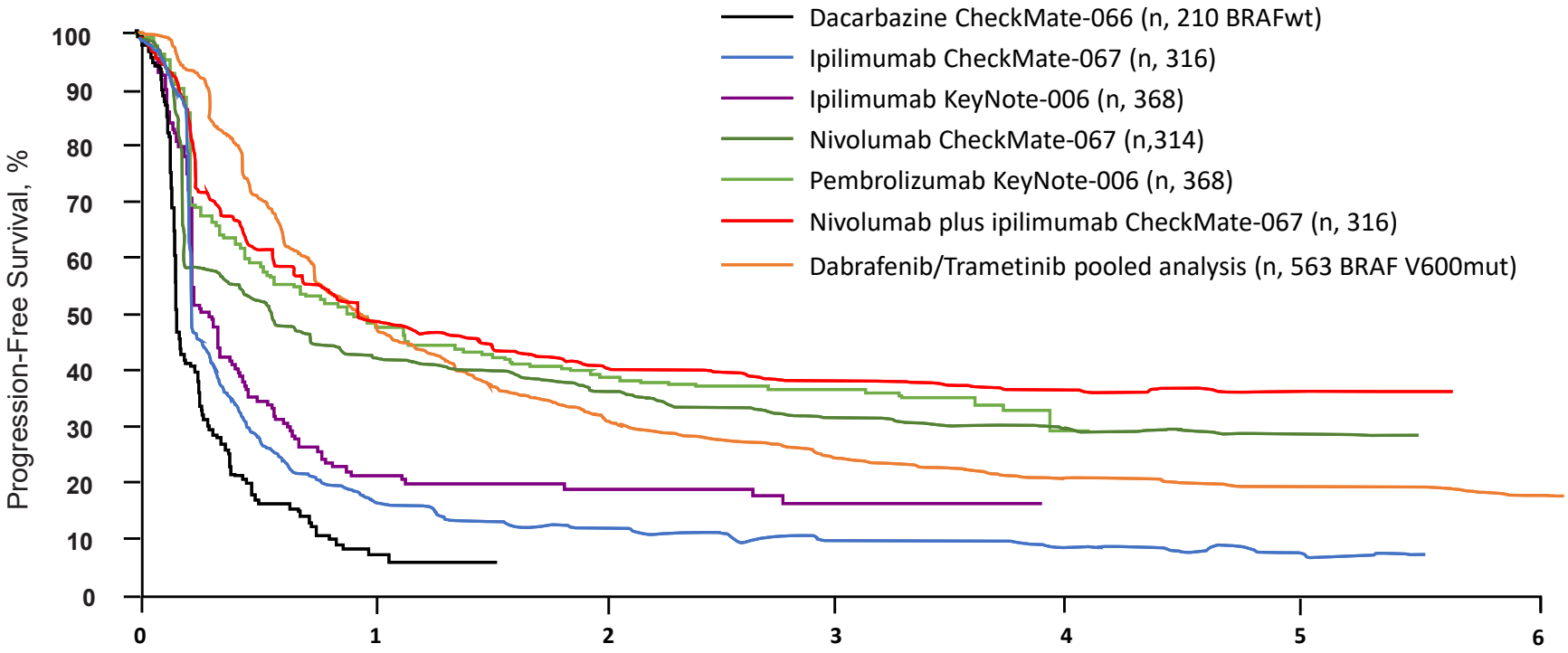
4,5 years

14/06/2018

CRP, c-reactive protein; irAE, immune-related adverse event; KN, KeyNote; LDH, lactate dihydrogenase; pembro, pembrolizumab; PNP, polyneuropathy; ULN, upper limit of normal; wt, wildtype; y, year.

Case courtesy of Prof. Neyns.

Progression-Free Survival of Advanced Melanoma Patients on First Line Therapy

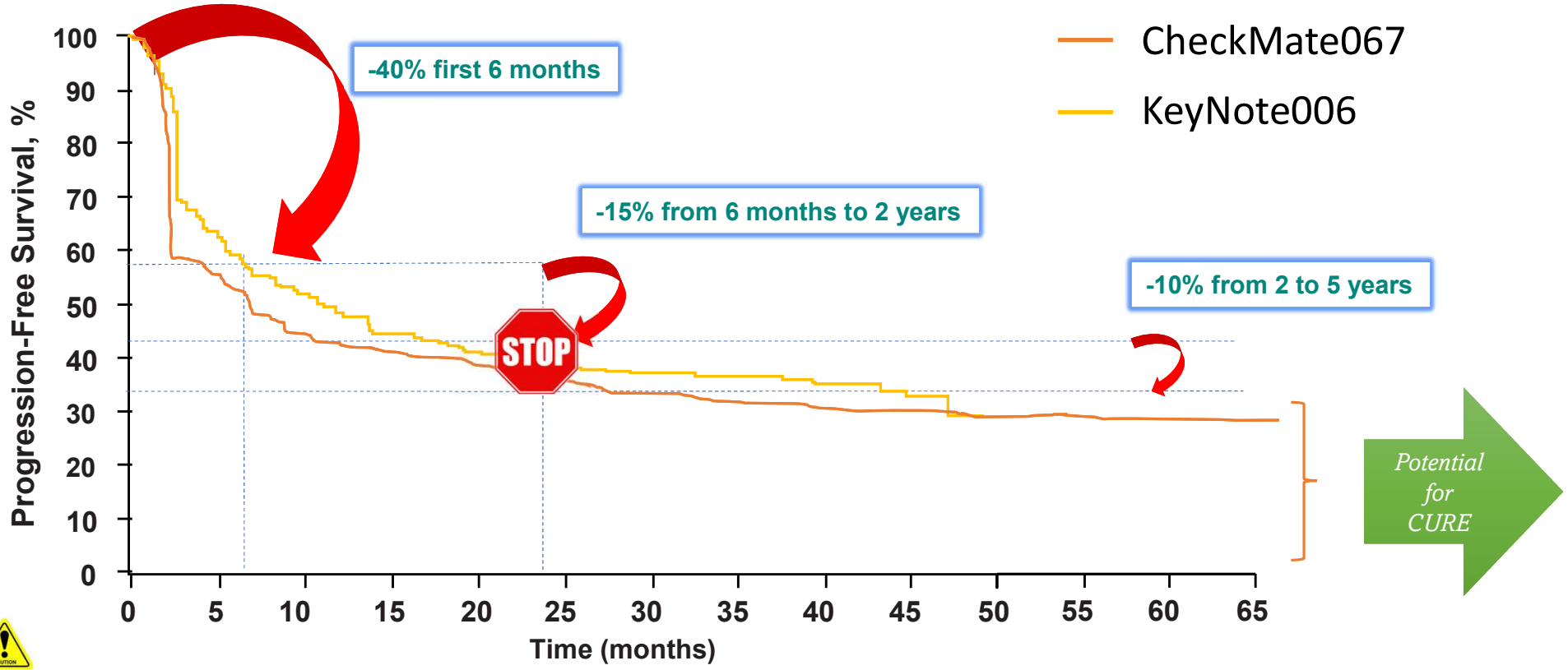


Cross-trial comparison

Cross trial comparisons cannot be inferred.

Adapted from A. Rogiers et al. Journal of Oncology, 2019:5269062.

Overlay of Progression-Free Survival Estimates of First-Line Treatment with Pembrolizumab (KeyNote-006) or Nivolumab (CheckMate-067)



Cross-trial comparison

Adapted from Larkin J. et al. NEJM 2019;381(16):1535-46.

Adapted from Robert C et al. Lancet Oncology 2019;20(9):1239-51.

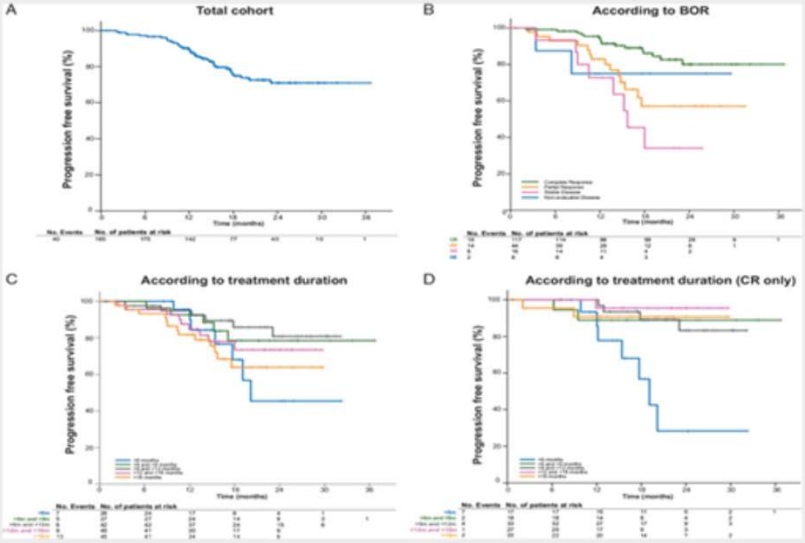
Cross trial comparisons cannot be inferred.

Annals of Oncology 30: 1154–1161, 2019
doi:10.1093/annonc/mdz110
Published online 28 March 2019

ORIGINAL ARTICLE

Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma

Y. J. L. Jansen[1*†], E. A. Rozeman[2†], R. Mason[3,4], S. M. Goldinger[5,6], M. H. Geukes Foppen[2], L. Hoejberg[7], H. Schmidt[8], J. V. van Thienen[2], J. B. A. G. Haanen[2], L. Tiainen[9], I. M. Svane[10], S. Mäkelä[11], T. Seremet[1], A. Arance[12], R. Dummer[6], L. Bastholt[7], M. Nyakas[13], O. Straume[14], A. M. Menzies[5,15,16], G. V. Long[5,15,16], V. Atkinson[4,3], C. U. Blank[2‡] & B. Neyns[1‡]



Kaplan–Meier probability curves for progression-free survival from discontinuation of anti-PD-1. Progression free survival from discontinuation of anti-PD-1 for the total cohort that discontinued in the absence of PD or TLT (A); according to best overall (B) and according to time on anti-PD-1 therapy for the whole cohort (C) and only for patients with a CR (D). The h marks designate patients who were censored at that time point. Abbreviations: PD-1, programmed cell death protein 1; BOR, best overall response; PD, progressive disease; eatment limiting toxicity.

ANNALS OF ONCOLOGY
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SPECIAL ARTICLE

ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee

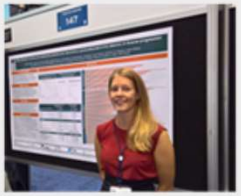
U. Keilholz[1*], P. A. Ascierto[2], R. Dummer[3], C. Robert[4,5], P. Lorigan[6], A. van Akkooi[7], A. Arance[8], C. U. Blank[9], V. Chiarion Sileni[10], M. Donia[11,12], M. B. Faries[13], C. Gaudy-Marqueste[14], H. Gogas[15], J. J. Grob[14], M. Guckenberger[16], J. Haanen[9], A. J. Hayes[17], C. Hoeller[18], C. Lebbé[19,20], I. Lugowska[21], M. Mandalà[22], I. Márquez-Rodas[23], P. Nathan[24], B. Neyns[25], R. Olofsson Bagge[26,27,28], S. Puig[29,30,31], P. Rutkowski[32], B. Schilling[33], V. K. Sondak[34], H. Tawbi[35], A. Testori[36] & O. Michielin[37]

Recommendation 6.1. Patients with a CR that persists at the following radiological evaluation (at least 4 weeks after), and who have received at least 6 months of anti-PD-1 treatment, can be considered for stopping therapy.

Recommendation 6.2. Stopping treatment with anti-PD-1 therapy should be considered after 2 years of treatment in the case of PR.

Recommendation 6.3. Stopping treatment with anti-PD-1 therapy can be considered after 2 years of treatment in the case of SD.

ESMO consensus conference recommendations



Jansen Y et al. Ann Oncol. 2019;30(7):1154-1161
Keilholz U. et al Ann Oncol 2020 31(11): 1435-1448

Current Oncology Reports
https://doi.org/10.1007/s11912-022-01264-6

MELANOMA (DB JOHNSON, SECTION EDITOR)

Anti-PD-1: When to Stop Treatment

Y. Jansen[1] · A. A. M. van der Veldt[2] · G. Awada[3] · B. Neyns[3]

Accepted: 28 January 2022

Future: Prospective Data

- The Dutch Safe stop trial (Trial NL7293) will evaluate the rate of ongoing response in the patients with advanced melanoma who discontinue first-line monotherapy with nivolumab or pembrolizumab upon achieving CR or PR according to RECIST. The patients are required to obtain a confirmed PR/CR before treatment discontinuation.
- The Canadian STOP-GAP study (NCT02821013) is designed to randomize patients between standard of care (treatment to 2 years) and discontinuation after confirmed maximum tumor response. The results are expected in 2029.
- The Dante trial is a multicenter, randomized, phase III, non-inferiority trial. Patients will be randomized at 12 months to continue anti-PD-1 for 2 years or discontinue independent of response at randomization.

PD-1, programmed death-1.

Table 1 Overview of trials evaluating outcome after treatment discontinuation of anti-PD-1 in patients with metastatic melanoma

Reference	Trial design	Studied therapy	Reason for discontinuation	BOR	Number of patients	Median FU (months) after discontinuation	Median treatment duration (months)	Number of relapses	TT PD after discontinuation (months)
Keynote (001)[§]	Prospective clinical trial exploratory analysis	Single agent anti-PD-1	Elective discontinuation	CR 67 PR 5	72	22	24	6 1	18
Keynote (006)	Prospective clinical trial exploratory analysis	Single agent anti-PD-1	Elective discontinuation*	CR 21 PR 69 SD 13	103	N.A	N.A	5 16 6	33
Jansen (2019)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR SD NE	185 117 44 16 8	18 20 16 16 17	12 11 15 14 17	40 16 14 8 2	N.A
Van Zeijl (2021)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR SD	180 67 98 15	18	12 12 13 11	87	N.A
Valentin (2021)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR/SD	37 25 12	15.7	14.1 16.8 21.2	5 3 2	9.3 11.9
Schvartsman (2018)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL (CR 56%)	41	16	19.5	3	
Pokorny (2020)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	ALL CR PR SD	52 13 28 11	20.5	11.1	13	3.9
Gibney (2021)	Retrospective analysis	Single-agent anti-PD-1 ($n=10$) Anti-PD-1 + anti-CTLA-4 ($n=14$)	Elective discontinuation	CR***	24	N.A	12.1	2	N.A
Ladwa (2016)	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation	CR	29	8	12.5/24/9[§§]	3	N.A
Makela (2020)	Prospective trial	Single agent anti-PD-1	Per protocol 6 months**	ALL CR PR SD PD	17 4 7 4 2	N.A	6	14	N.A
Warner (2019)*	Retrospective analysis	Single agent anti-PD-1	Elective discontinuation ($n=72$) TLT ($n=24$)	CR	102	21.1	9.4	23	
Asher (2021)	Retrospective analysis	Single-agent anti–PD-1 ($n=86$) Anti-PD-1 + anti-CTLA-4 ($n=20$)	Elective discontinuation (CR: $n=32$, PR: $n=14$) TLT ($n=60$)	ALL CR PR SD	106 80 22 4	20.8	15.2	34	8.5
Schank (2021)	Retrospective analysis	Single agent anti-PD-1 ($n=31$) Single agent ipilimumab ($n=4$) Anti-PD-1 + anti-CTLA-4 ($n=10$)	Elective discontinuation ($n=27$) TLT ($n=16$)	All CMR Non-CMR	45 32 13	34	21	9 3 6	N.A
Swami (2021)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL	16	30.3	4.7	9	15,3
Van Zeijl (2021)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL CR PR SD	89 7 61 21	N.A	6.9 7.2 3.5	N.A	N.A
Valentin (2021)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL CR PR/SD	28 25 24	N.A	7.2	7 0 7	7.1
Schvartsman (2018)	Retrospective analysis	Single agent anti-PD-1	TLT	ALL (CR 56%)	34	N.A	6.5	5	N.A
Gibney (2021)	Retrospective analysis	Single-agent anti–PD-1 ($n=7$) Anti-PD-1 + anti-CTLA-4 ($n=21$)	TLT	All CR PR SD	28 5 22 1	N.A	3.7	2	N.A

Table 2 Response after treatment rechallenge in patients with metastatic melanoma

Reference	Trial design	Reason for discontinuation	Time on treatment months	BOR at first course (n)	Number second course	Time to relapse (months)	Type of immunotherapy on second course	BOR on reintroduction
Keynote (001)	Prospective clinical trial	Elective discontinuation	23	ALL 72 CR 67 PR 5	4	18	Single-agent anti-PD-1	CR 1, SD/PR 1*
Keynote (006)	Prospective clinical trial	Elective discontinuation	24	ALL 103 CR 21 PR 69 SD 13	13 5 + 1 6 1	N.A	Single-agent anti-PD-1	CR 3, PR 4, SD 3 CR 3, PR 1, SD 1 PR 3, SD 1 SD 1
Jansen (2019)	Retrospective analysis	Elective discontinuation	12 11 15 14 7	185 CR 117 PR 44 SD 1 Ne 8	19 9 6 4	12	Single-agent anti-PD-1	CR 2, PR 4, SD 5 CR 2, PR 3, SD 1 PR 1, SD 2 SD 2
Pokorny (2020)	Retrospective analysis	Elective discontinuation	11.1	ALL 41 CR 10 PR 18 SD 13	7	3.9	Single-agent anti-PD-1 ± resection	4
Warner (2019)	Retrospective analysis	Elective discontinuation (n = 72), TLT toxicity ($n=24$), **other ($n=5$)	9.4 36.1	ALL 78 CR 10, PR 18, SD 13, PD 37	78	6.3	Single agent anti-PD-1 34 Anti-PD-1 + anti-CTLA-4 44	OR in 5 -CR 2 OR 11- CR 3
Asher (2021)	Retrospective analysis	Elective discontinuation (CR: n = 32, PR: n = 14) TLT ($n=60$)	15.2	ALL 106 CR 80, PR 22, SD 4	21	8.5	Single-agent anti-PD-1 19 Anti-PD-1 + anti-CTLA-4 1 Single agent anti-CTLA-4 1	CR 5, PR 4, SD 4 CR 3, PR 2 PR 2, CR 3
Valentin (2021)	Retrospective analysis	Elective discontinuation	14.1	ALL 65 CR 25 PR/SD 12 AE 28	12 3 2 4	ALL 9 CR 9.3 PR 11.9 AE	Single-agent anti-PD-1	CR 4, SD 1 CR 1, SD 1 CR 1 CR 2
Makela (2020)	Prospective trial	Per protocol defined at 6 months	6	ALL 17 CR 4, PR 7, SD 4, PD 2	6		Single-agent anti-PD-1	RR 50%
Van Zeijl (2021)	Retrospective analysis	TLT ($n=53$) or elective discontinuation ($n=67$)	11 12 7	87 CR PR SD	27	N.A	Single-agent anti-PD-1	CR 2, PR 6, SD 9
Schwartsman (2018)	Retrospective analysis	Elective discontinuation ($n=41$) TLT ($n=34$)	19.5 6.5	CR 56%, PR 35%, SD 9%	2 1	N.A	Single-agent anti-PD-1 1 Single agent anti-CTLA-4 2	CR 1, PR 3

N.A. data not available in published manuscript, *n* number, *m* months, *pts* patients, *NR* not reached, *CR* complete response, *PR* partial response, *SD* stable disease, *OR* objective response

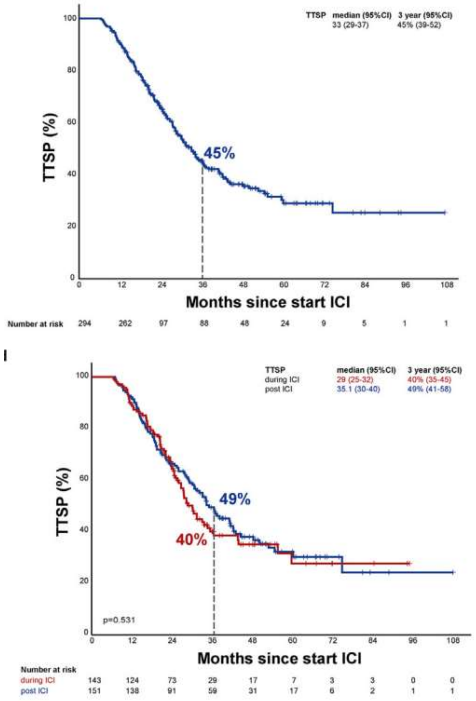
*Patient had SD at date cut-off and had PR two weeks later; **other = progression (3), per protocol (1) or other (2). Warner evaluated all the patients who discontinued due to all the reasons

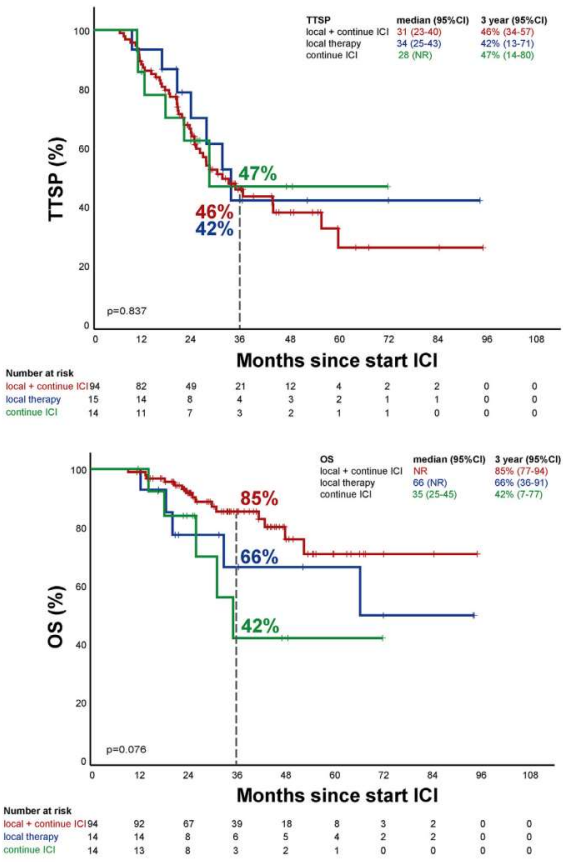
Jansen Y, et al. Curr Oncol Rep. 2022;24(7):905-915.

Original Research

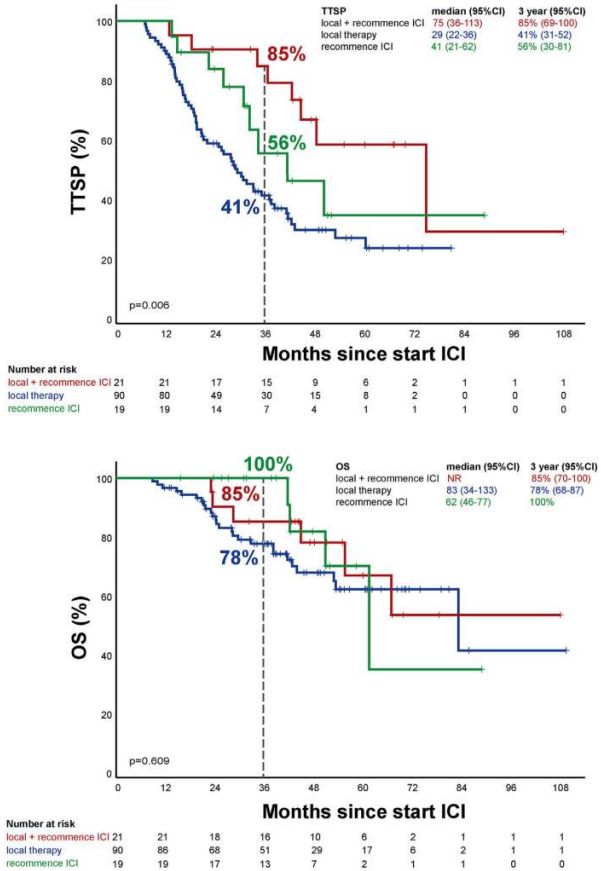
The role of local therapy in the treatment of solitary melanoma progression on immune checkpoint inhibition: A multicentre retrospective analysis

Judith M. Versluis [a,1], Anne M. Hendriks [b,1], Alison M. Weppler [c], Lauren J. Brown [d], Karlijn de Joode [e], Karijn P.M. Suijkerbuijk [f], Lisa Zimmer [g], Ellen W. Kapiteijn [h], Clara Allayous [i], Douglas B. Johnson [j], Adriana Hepner [k,l], Joanna Mangana [m], Prachi Bhave [n], Yanina J.L. Jansen [o], Claudia Trojaniello [p], Victoria Atkinson [q], Lucy Storey [r], Paul Lorigan [r], Paolo A. Ascierto [p], Bart Neyns [o], Andrew Haydon [n], Alexander M. Menzies [k,s,t], Georgina V. Long [k,s,t], Celeste Lebbe [i], Astrid A.M. van der Veldt [e,u], Matteo S. Carlino [d,k,s], Shahneen Sandhu [c], Harm van Tinteren [v], Elisabeth G.E. de Vries [b], Christian U. Blank [a,w,x,1], Mathilde Jalving [b,*,1]





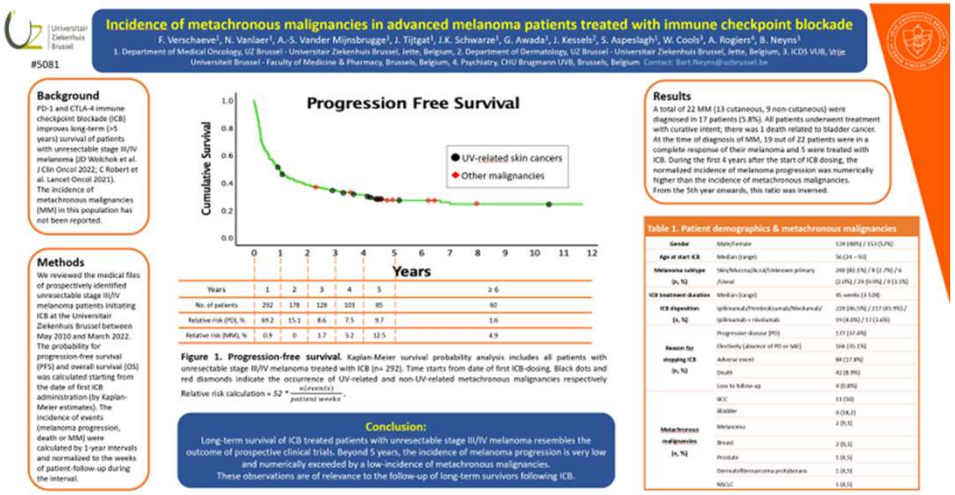
Time to subsequent progression after treatment of the solitary progressive lesion (TTSP) and overall survival (OS) for patients with solitary progression **during** immune checkpoint inhibition



Time to subsequent progression after treatment of the solitary progressive lesion (TTSP) and overall survival (OS) for patients with solitary progression **post** immune checkpoint inhibition

Versluis JM, et al. Eur J Cancer. 2021;151:72-83.

Long-term Follow-up (>5y)



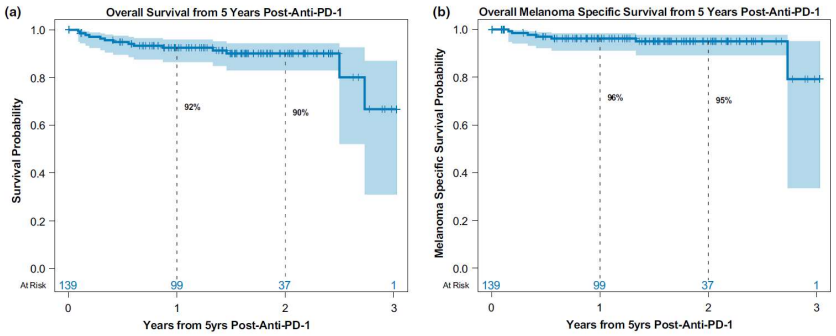
Received: 22 October 2022 | Revised: 31 January 2023 | Accepted: 12 March 2023
DOI: 10.1111/pcmr.13083

SHORT COMMUNICATION

WILEY

Beyond the 5-year milestone: Long-term survivorship of melanoma patients treated off-trial with anti-PD-1

Kimberly Loo[1,2] | Hannah L. Kalvin[3] | Katherine S. Panageas[3] | Margaret K. Callahan[1,4] | Paul B. Chapman[1,4] | Parisa Momtaz[1,4] | Alexander N. Shoushtari[1,4] | Jedd D. Wolchok[1,4] | Michael A. Postow[1,4] | Allison Betof Warner[1,4]



Patients treated with anti-PD-1 regimens off clinical trials who survive at least 5 years from initial anti-PD-1 treatment can be reassured of their excellent long-term prognosis, particularly if they did not require additional melanoma treatment during the first 5 years.

PD-1, programmed death-1; y, year.

Verschaeve F, et al. Poster presentation at ESMO 2022; 839P. Loo K, et al. Pigment Cell Melanoma Res. 2023;36(3-4):314-20.

cancers

MDPI

Article

A Comprehensive Analysis of Baseline Clinical Characteristics and Biomarkers Associated with Outcome in Advanced Melanoma Patients Treated with Pembrolizumab

Gil Awada [1], Yanina Jansen [2], Julia Katharina Schwarze [1], Jens Tijtgat [1], Lennert Hellinckx [1], Odrade Gondry [3], Sim Vermeulen [3], Sarah Warren [4], Kelly Schats [5], Pieter-Jan van Dam [5], Mark Kockx [5], Marleen Keyaerts [3], Hendrik Everaert [3], Teofila Seremet [1], Anne Rogiers [6] and Bart Neyns [1,*]

2021, *13*, 168. https://doi.org/10.3390/cancers13020168

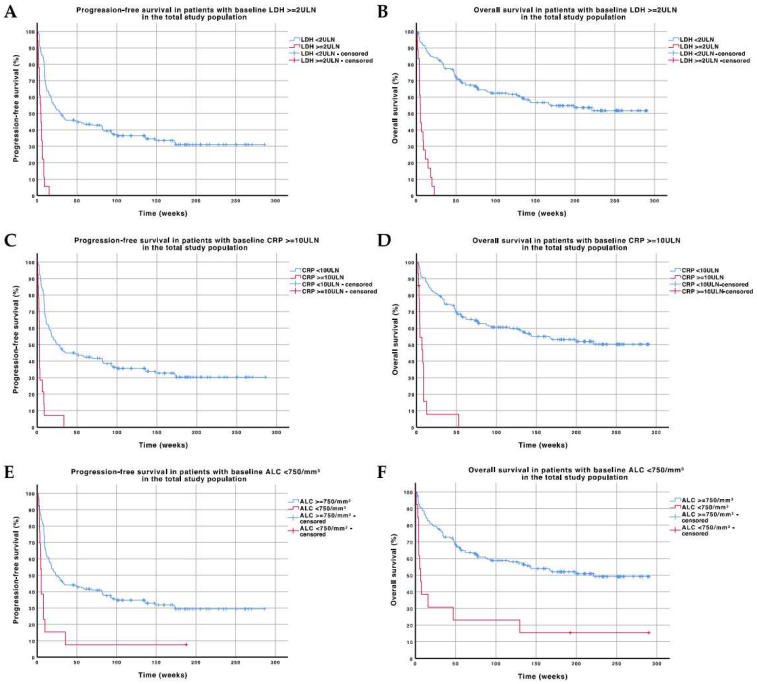
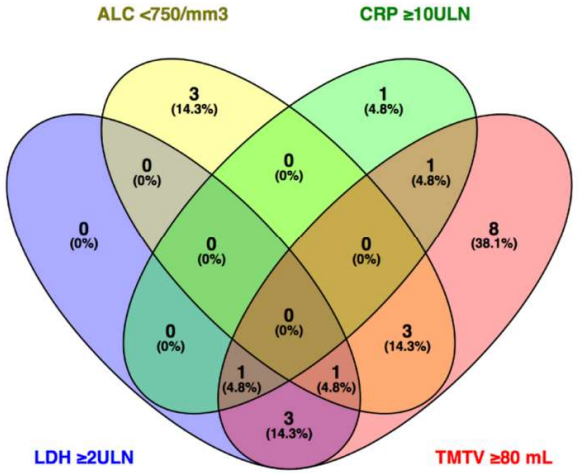


Figure 1. Progression-free and overall survival in subgroups of patients with LDH ≥ 2ULN (panels **A**,**B**), CRP ≥ 10ULN (panels **C**,**D**), and ALC < 750/mm^3 (panels **E**,**F**) in the total study population. Abbreviations: ALC—absolute lymphocyte count; CRP—C-reactive protein; LDH—lactate dehydrogenase; ULN—upper limit of normal.

Table 1. Baseline parameters investigated in this analysis.

Clinical Factors	Blood Values	Plasma ctDNA	Imaging	Tissue
- Age • - Sex • - World Health Organization Performance Status • - Tumor stage • - Presence of inactive/active brain metastases • - Number of affected organs • - Number of prior therapies • - Corticosteroid use •	- Albumin • (35–50 g/L) - Lactate dehydrogenase • (313–618 U/L) - C-reactive protein • (<5 mg/L) - Absolute lymphocyte count • (1200–3500/mm^3) - Absolute neutrophil count • (1200–7500/mm^3) - Neutrophil-to-lymphocyte ratio •	- Detection of $BRAF^{V600}$ or $NRAS^{Q61/G12/G13}$ mutant ctDNA •*	- TMTV •*	- $BRAF^{V600}$ mutation status • - NanoString IO360 gene expression profiling scores •

Tumor stage was determined by the American Joint Committee on Cancer TNM 8th edition. Active brain metastases are defined as symptomatic brain metastases or brain metastases requiring corticosteroids for symptom control. Corticosteroid use was defined as the use of ≥8 mg of methylprednisolone (or equivalent). Normal institutional laboratory values are shown in the table. • analyzed as a categorical variable; * analyzed as a continuous variable. Abbreviations: ctDNA—circulating tumor DNA; TMTV—total metabolic tumor volume; U/L—units/liter.



Awada G, et al. Cancers. 2021;13:168.

cancers

MDPI

Article

A Comprehensive Analysis of Baseline Clinical Characteristics and Biomarkers Associated with Outcome in Advanced Melanoma Patients Treated with Pembrolizumab

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2021, *13*, 168. https://doi.org/10.3390/cancers1302...

Gil Awada MD PhD

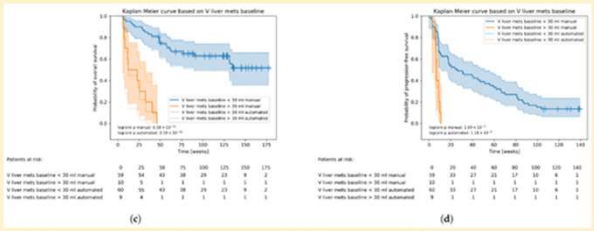
Ine Dirks Ir.

Prof Jef Vandemeulebroucke

Open Access Article

Development and Validation of a Predictive Model for Metastatic Melanoma Patients Treated with Pembrolizumab Based on Automated Analysis of Whole-Body [18F]FDG PET/CT Imaging and Clinical Features

by Ine Dirks [1,2,*], Marleen Keyaerts [3], Iris Dirven [4], Bart Neyns [4] and Jef Vandemeulebroucke [1,2,5]



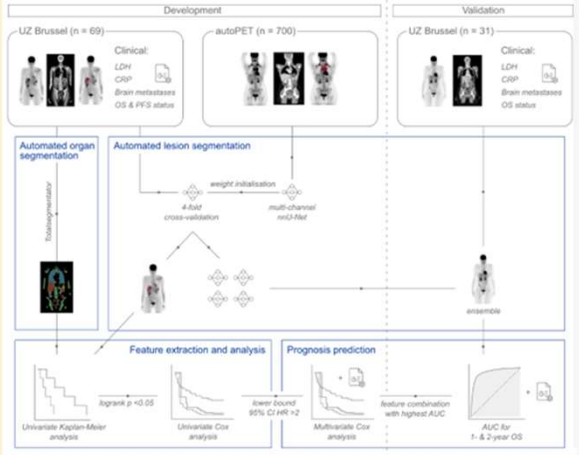
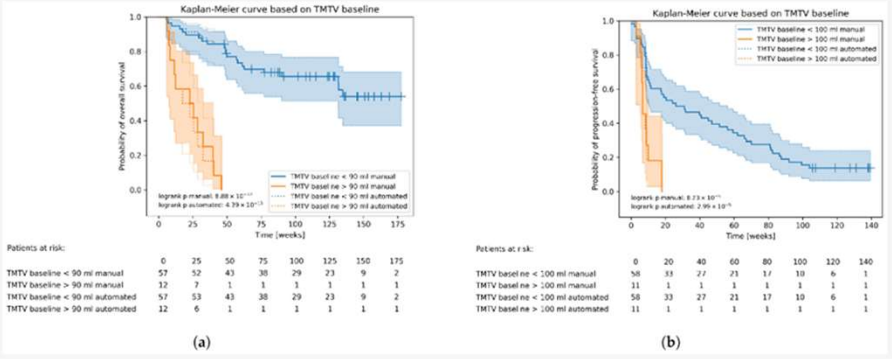
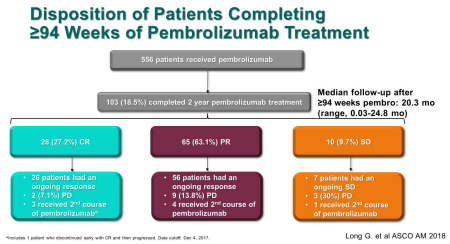


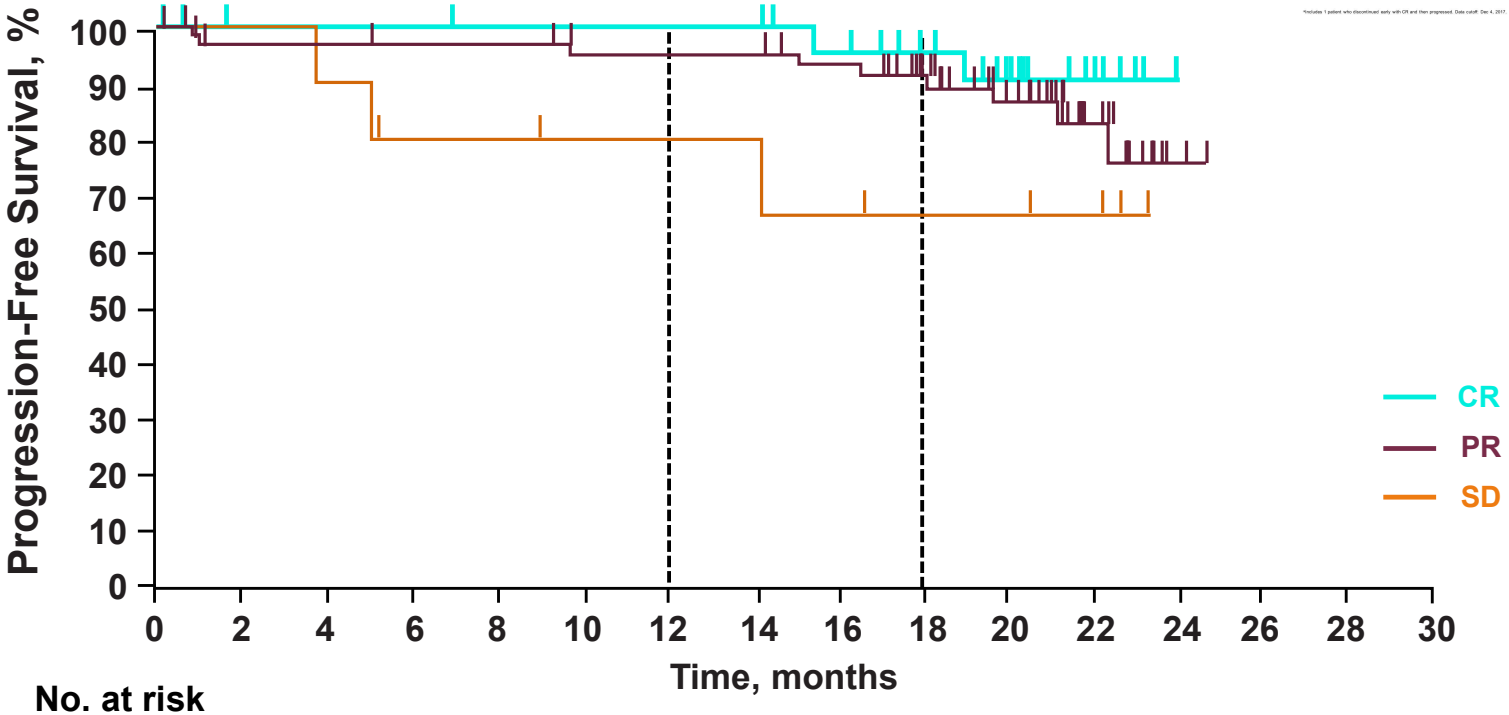
Figure 2. Kaplan–Meier curves and life tables based on a TMTV at baseline below or above 90 mL for OS (**a**) and below or above 100 mL for PFS (**b**).



Awada G, et al. Cancers. 2021;13:168. Dirks I, et al. Cancers (Basel). 2023;15(16):4083.

PFS[a] in Patients Who Completed Protocol-Specified Time on Pembrolizumab (n = 103)





No. at risk

CR	28	27	27	27	26	26	26	26	23	19	15	6	1	0	0	0
PR	65	58	58	57	57	54	51	54	51	44	32	15	3	0	0	0
SD	10	10	9	7	7	6	6	6	5	4	4	3	0	0	0	0

[a]Per immune-related response criteria by investigator review. Data cutoff: Dec 4, 2017.
CR, complete response; PFS, progression-free survival; PR, partial response; SD, stable disease.

Long GV. et al. ASCO Annual Meeting 2018; 9503.

Utility of 1-year FDG-PET (PET) to determine outcomes from anti-PD-1 (PD1) based therapy in patients (pts) with metastatic melanoma (MM)

Aaron C. Tan[1,2], Louise Emmett[1,3,4], Serigne Lo[1], Victor Liu[3], Alexander D. Guminski[1,2,5], Georgina V. Long[1,2,5], Alexander M. Menzies[1,2,5]
[1]Melanoma Institute Australia and The University of Sydney; [2]Royal North Shore Hospital; [3]St Vincent's Hospital; [4]The University of New South Wales; [5]Mater Hospital

Table 2. Correlation of CT and PET response at 1 year

		No. of pts (%)			
		CT response at 1 year			
		CR	PR	SD	Total
PET response at 1 year	CMR	27 (26)	47 (45)	2 (2)	76 (73)
	PMR	2 (2)	15 (14)	2 (2)	19 (18)
	SMD	0 (0)	1 (1)	0 (0)	1 (1)
	PMD	0 (0)	6 (6)	2 (2)	8 (8)
	Total	29 (28)	69 (66)	6 (6)	

104 patients were evaluated with median follow-up 30.1 months and 98% remain alive

Figure 2. PFS post 1-year imaging by CT response

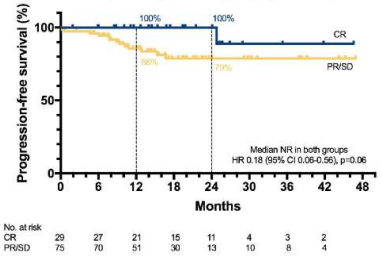


Figure 3. PFS post 1-year imaging by PET response

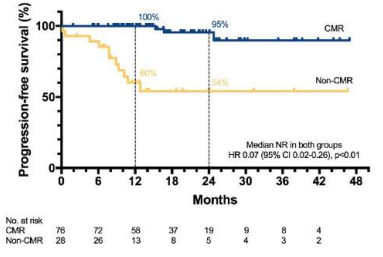
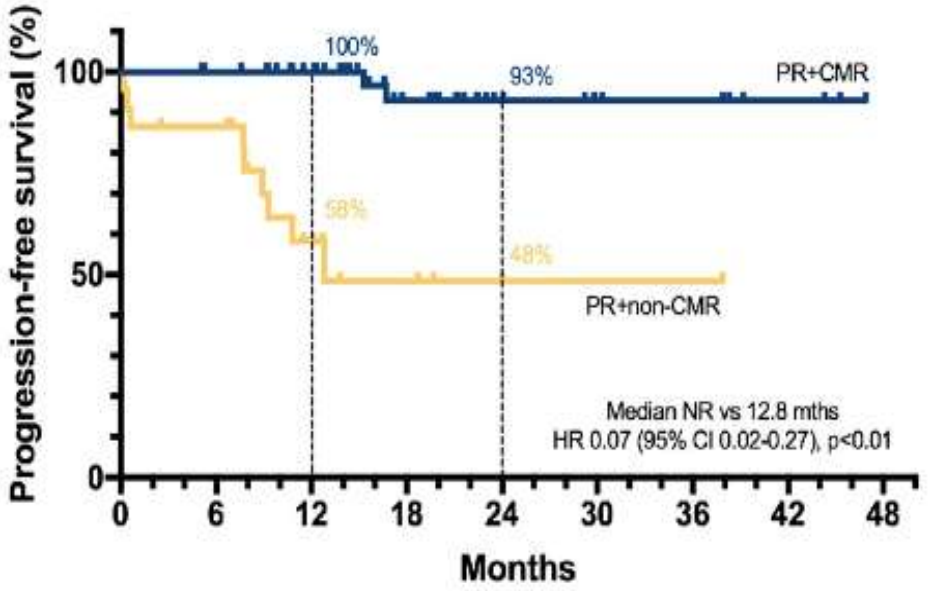


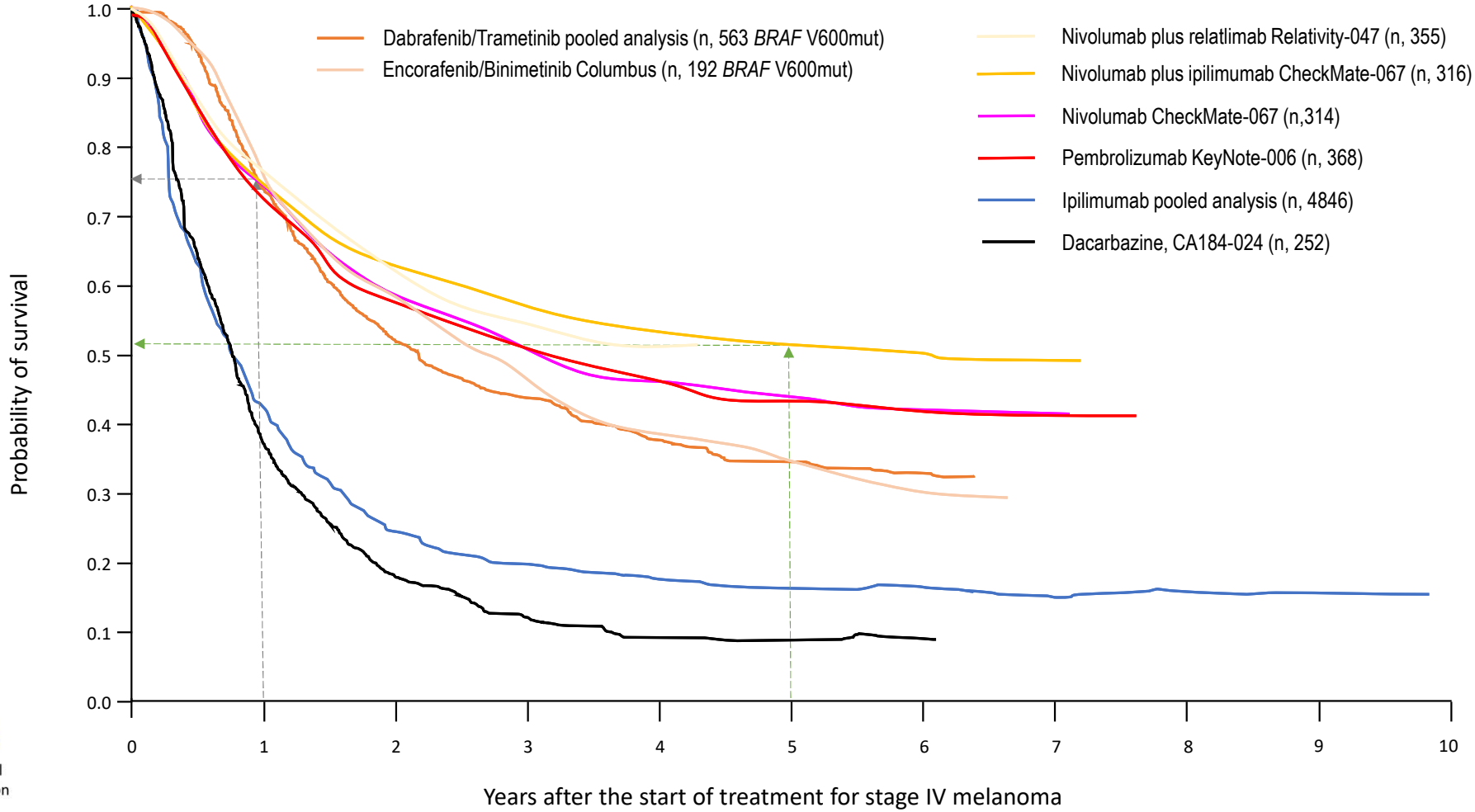
Figure 4. PFS post 1-year imaging in pts with PR on CT



CMR/CR, complete response; CT, computed tomography; FDG, fluorodeoxyglucose; PD-1, programmed death-1; PET, positron emission tomography; PFS, progression-free survival; PMD, progressive disease; PMR/PR, partial response; SD/SMD, stable disease.

Tan AC, et al. ASCO Annual Meeting 2018; 9517.
Tan et al. *Annals of Oncology 2018*;29(10):2115-2120.

Overall Survival of Advanced Melanoma Patients According to First-Line Therapy



Cross-trial comparison

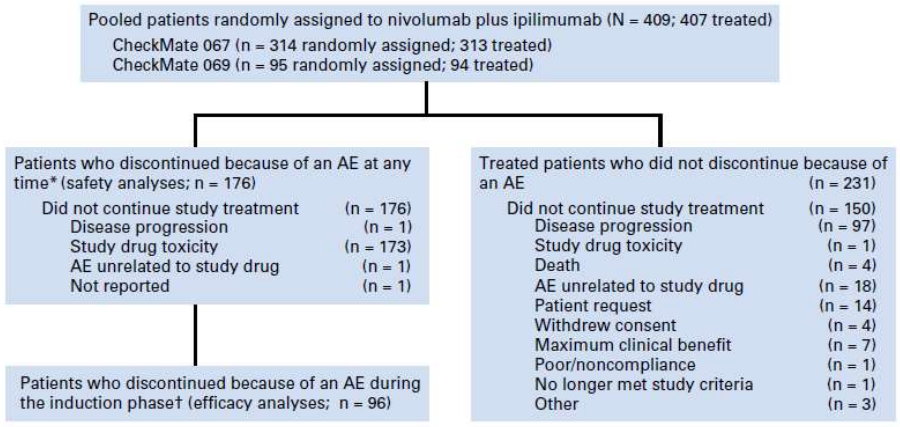
Cross trial comparisons cannot be inferred.

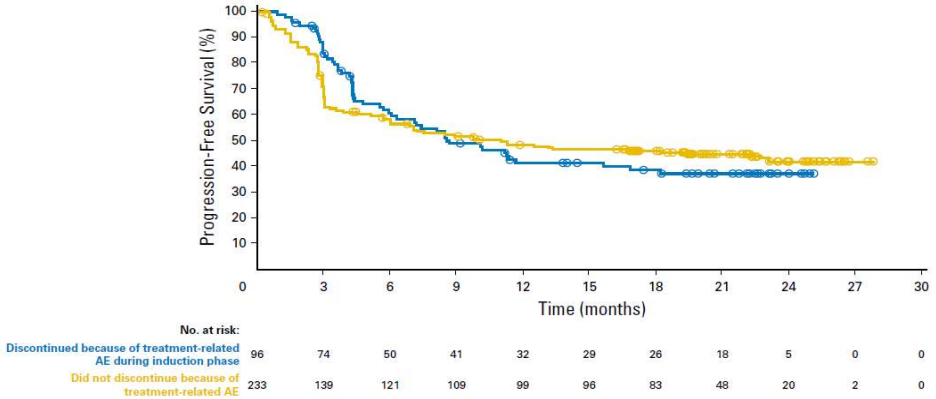
Adapted from A. Rogiers et al. Journal of Oncology, 2019:5269062.

Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials

Dirk Schadendorf, Jedd D. Wolchok, F. Stephen Hodi, Vanna Chiarion-Sileni, Rene Gonzalez, Piotr Rutkowski, Jean-Jacques Grob, C. Lance Cowey, Christopher D. Lao, Jason Chesney, Caroline Robert, Kenneth Grossmann, David McDermott, Dana Walker, Rafia Bhore, James Larkin, and Michael A. Postow

- Approximately 40% of patients with advanced melanoma who received nivolumab + ipilimumab in clinical trials discontinued treatment because of AEs
- Patients who discontinued treatment at any time because of an AE were less likely to have an elevated LDH level (27% v 39%) or M1c disease (49% v 61%) compared with the patients who did not discontinue.
- Data were pooled from phase II and III trials of patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, Q3w x4, followed by nivolumab monotherapy 3 mg/kg Q2w (N = 409)
- Efficacy was assessed in all randomly assigned patients who discontinued because of AEs during the induction phase (n = 96) and in those who did not discontinue because of AEs (n = 233)
- The objective response rate was 58.3% for patients who discontinued because of AEs during the induction phase and 50.2% for patients who did not discontinue
- 64% of patients who ceased treatment during induction for AEs had an ongoing response compared with 80% of those who did not cease therapy for an AE
- At > 18 mths of follow-up, median PFS was 8.4 months for pts who discontinued treatment because of AEs during the induction phase and 10.8 mths for pts who did not discontinue because of AEs (P = .97)
- Median overall survival had not been reached in either group (P = .23).



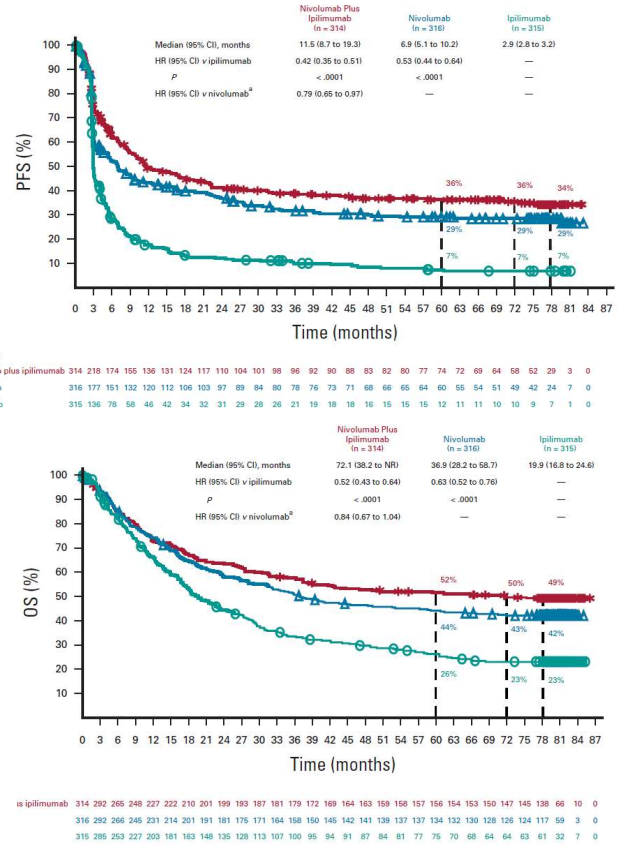


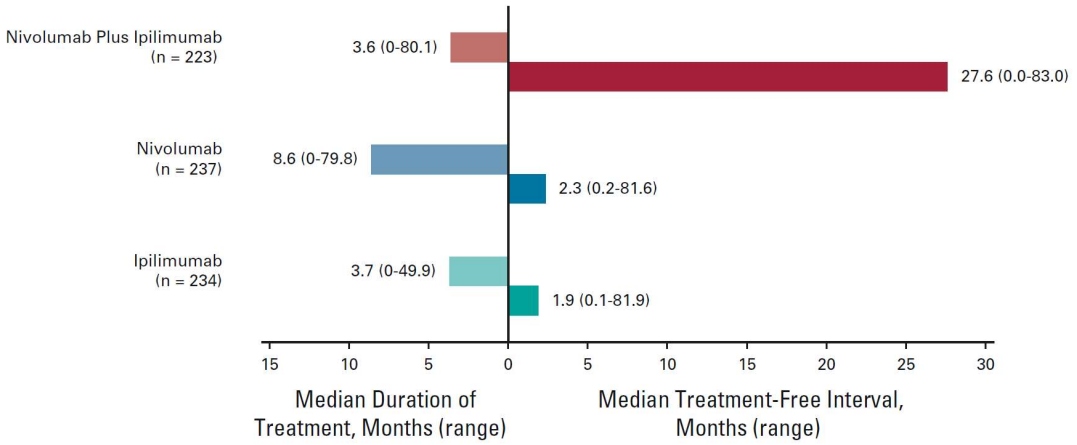
Schadendorf D, et al. J Clin Oncol. 2017;35(34):3807-14.

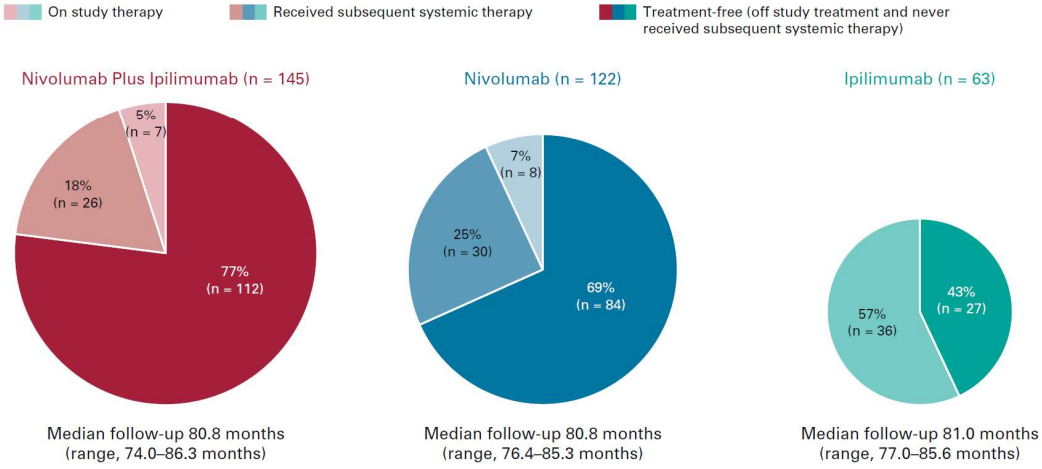
Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma

Jedd D. Wolchok, MD, PhD[1]; Vanna Chiarion-Sileni, MD[2]; Rene Gonzalez, MD[3]; Jean-Jacques Grob, MD[4]; Piotr Rutkowski, MD[5]; Christopher D. Lao, MD[6]; C. Lance Cowey, MD[7]; Dirk Schadendorf, MD[8]; John Wagstaff, MB, ChB[9]; Reinhard Dummer, MD[10]; Pier Francesco Ferrucci, MD[11]; Michael Smylie, MB, ChB[12]; Marcus O. Butler, MD[13]; Andrew Hill, BHB, MBChB[14]; Ivan Márquez-Rodas, MD, PhD[15]; John B. A. G. Haanen, MD, PhD[16]; Massimo Guidoboni, MD[17]; Michele Maio, MD[18]; Patrick Schöffski, MD, MPH[19]; Matteo S. Carlino, BMedSc, MBBS, PhD[20]; Céleste Lebbé, MD, PhD[21]; Grant McArthur, MD, PhD[22]; Paolo A. Ascierto, MD[23]; Gregory A. Daniels, MD, PhD[24]; Georgina V. Long, BSc, PhD, MBBS[25]; Tuba Bas, PhD[26]; Corey Ritchings, PharmD[26]; James Larkin, MD, PhD[27]; and F. Stephen Hodi, MD[28]

Published at ascopubs.org/journal/jco on November 24, 2021

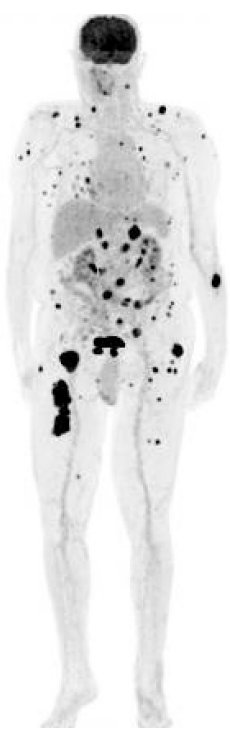




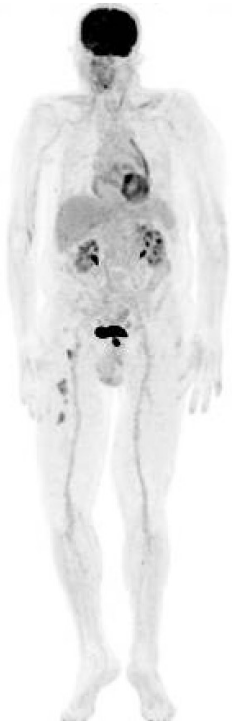


Wolchok JD, et al. J Clin Oncol. 2022;40(2):127-37.

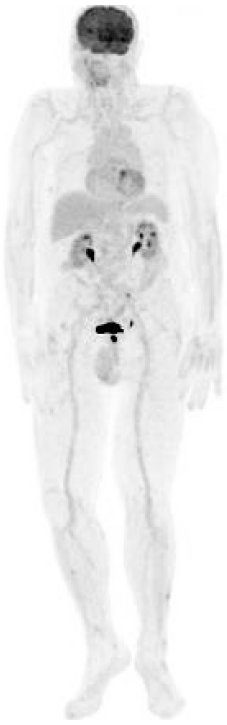
Case illustration: 85y old M, 2017: SSM pT1a (Breslow 0.55 mm), Nov 2021: NRAS Q61mut melanoma AJCC stage IV-M1d



8 Nov 2021



10 Feb 2022



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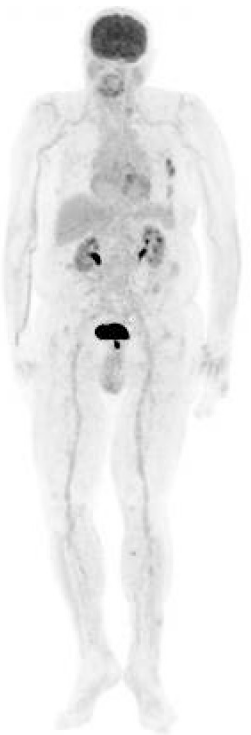
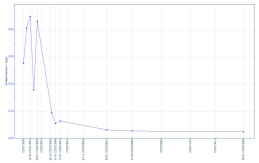


30 NOV2023

25 Nov ’21: ipilimumab 3mg/kg + nivolumab 1mg/kg
16 Dec ’21: ipilimumab 3mg/kg + nivolumab 1mg/kg

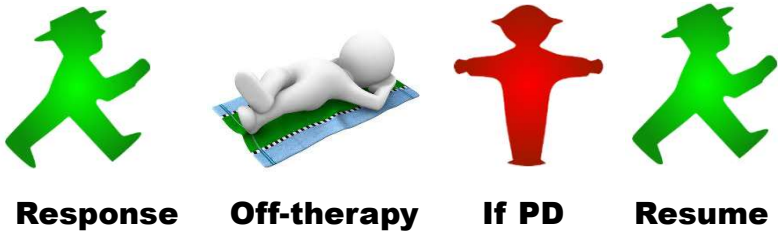
G2 Cardiomyositis, corticotherapy



AJCC, American Joint Committee on Cancer; G, grade; M, male; mut, mutation; NRAS, neuroblastoma RAS; SSM, superficial spreading melanoma; y, year.

Case courtesy of Prof. Neyns.

Melanoma: when to stop immuno-therapy?



- Anti-PD-1 immunotherapy can be stopped in advanced melanoma patients who benefit from therapy and do not experience treatment limiting toxicities with an acceptable low risk for progression
- The optimal duration of aPD-1 mono-therapy has not been established prospectively and may vary between individual patients
  - Largest body of evidence relates to an arbitrary treatment duration of 2y (KN006)
  - Real-world data support shorter duration of therapy (ESMO guideline)
  - CR on CT can be used as a main driver in decision making
  - CMR on [18F] FDG-PET response seems most useful to aid decision making
- Retreatment at the time of PD following elective treatment discontinuation has demonstrated activity in small case series and can be considered @PD following elective discontinuation

aPD-1, anti-programmed death-1; CMR/CR, complete response; CT, computed tomography; ESMO, European Society for Medical Oncology; FDG, fluorodeoxyglucose; KN, KeyNote;; PET, positron emission tomography; PD, progressive disease; y, year.

Acknowledgements

ACKNOWLEDGMENTS

Patients, their families & caregivers

All collaborators (co-investigators, data managers, study nurses)

The non-for-profit entities who financed this clinical trial

Kom op tegen Kanker

Stichting tegen Kanker

"I offered to help my consulting physician to raise funds, not for myself, but for others like me."

VUB-UZB PAUL DE KNOP FUND

Shortly after the end of his mandate as rector of Vrije Universiteit Brussel prof. Paul De Knop was diagnosed with (metastised) melanoma; still today one of the most aggressive forms of cancer. During his treatment at UZ Brussel he came in contact with Prof. Bart Neyns and his research team. His experimental treatment, i.e. immunotherapy, has shown promising results but requires additional research to help more people, in a quicker and more affordable way out of their penile situation.

fwo

#LIVE FOR BETTER DAYS VZW

Thank you for your attention!