Advanced Melanoma and NMSCs: Current Status and Clinical Trial Update

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CHU de Québec

Disclosure

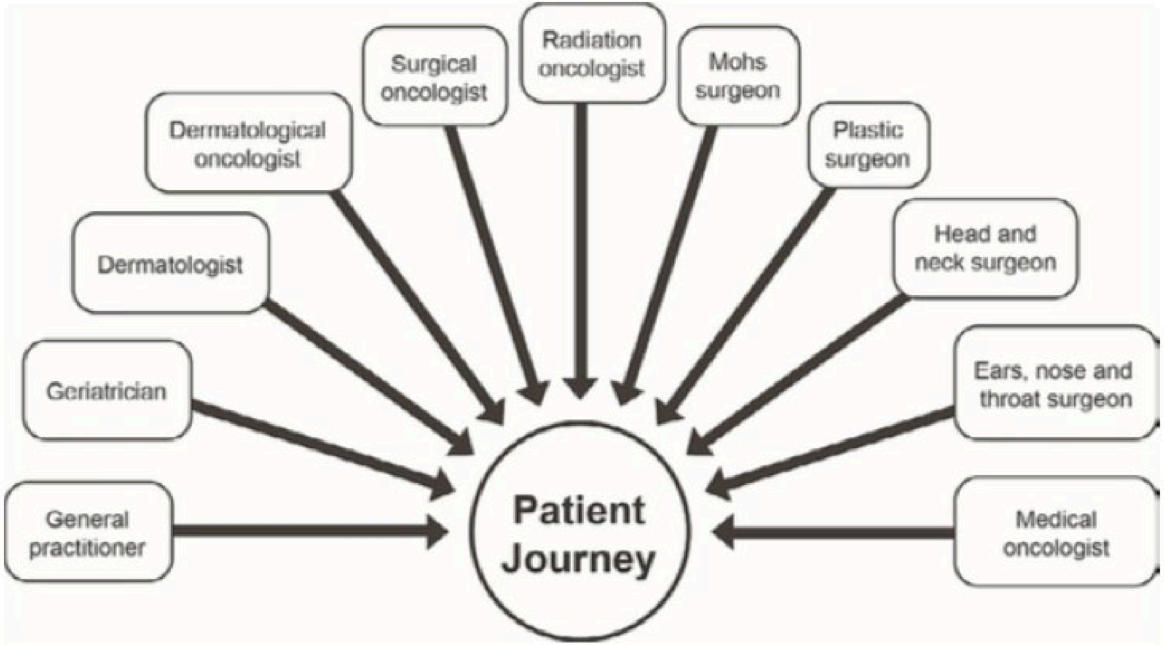
- **Amgen**
- **BMS**
- **EMD-Serono**
- **Merck**
- **Novartis**
- **Pfizer**
- **Roche**
- **Sanofi-Genzyme**

NB possible mentions of *Off-label* drug use

Plan

- Melanoma treatments:
  - Surgical margins
  - Metastatic:
    - Actual treatment options
    - New options
  - Adjuvant therapy:
    - Standard of care stage IIB/IIC or III
    - Clinical Trials
  - Neoadjuvant approach:
    - Pembrolizumab: SWOG 1801
    - Clinical Trials
- Squamous cell carcinoma: Neoadjuvant Cemiplimab
- Basal cell carcinoma: Cemiplimab after Hedgehog inhibitor

Multidisciplinary approach



Surgical treatment of melanoma

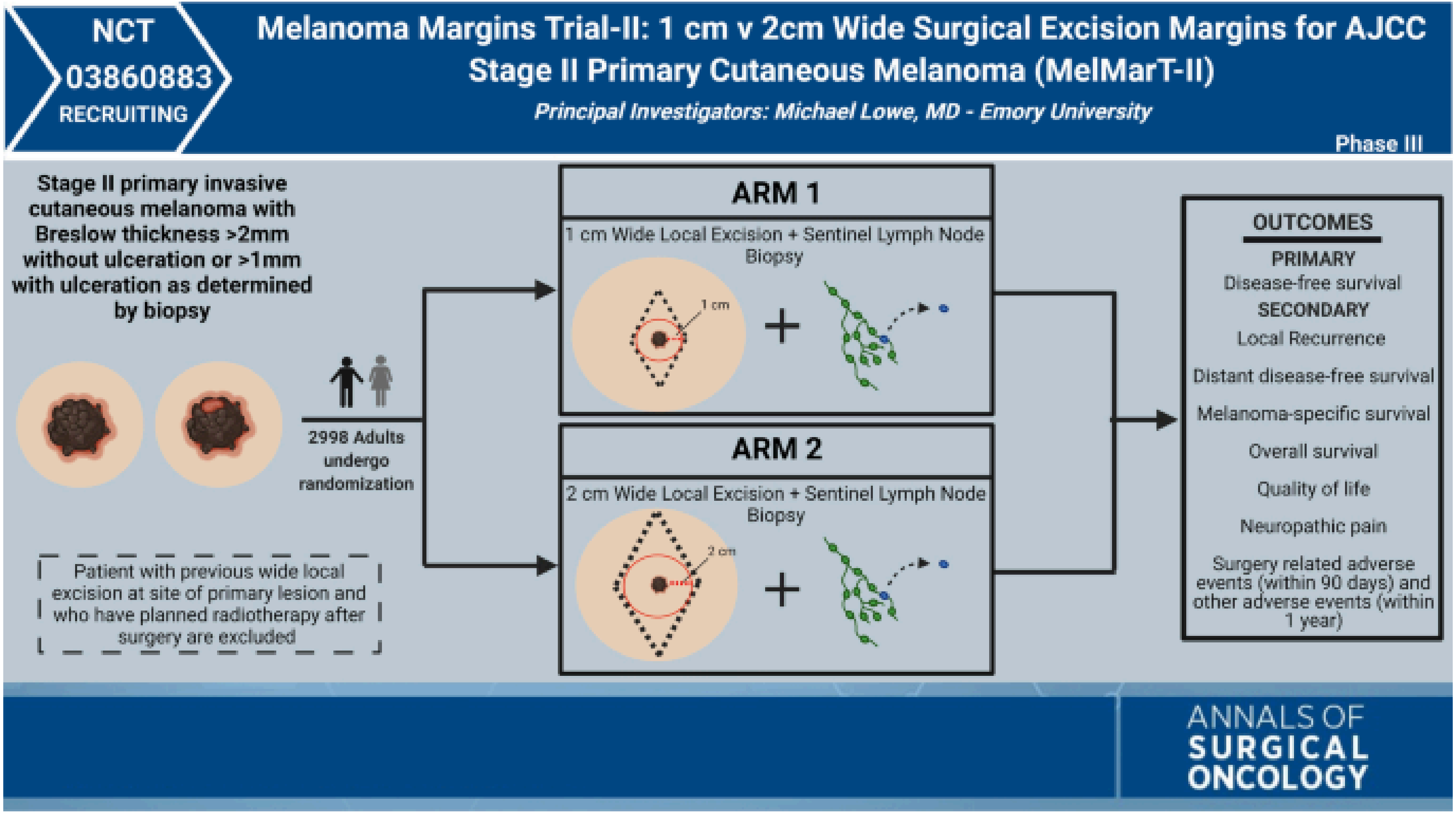
National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Melanoma: Cutaneous

NCCN Guidelines Index
Table of Contents
Discussion

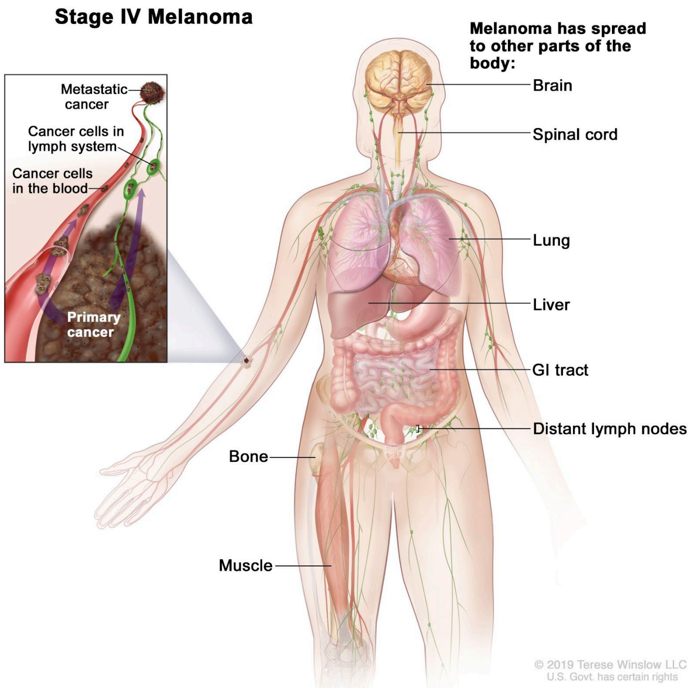
PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Peripheral Surgical Margins[b,1-10]
In situ[a]	0.5–1 cm
≤1.0 mm	1 cm (category 1)
>1.0–2.0 mm	1–2 cm (category 1)
>2.0–4.0 mm	2 cm (category 1)
>4.0 mm	2 cm (category 1)

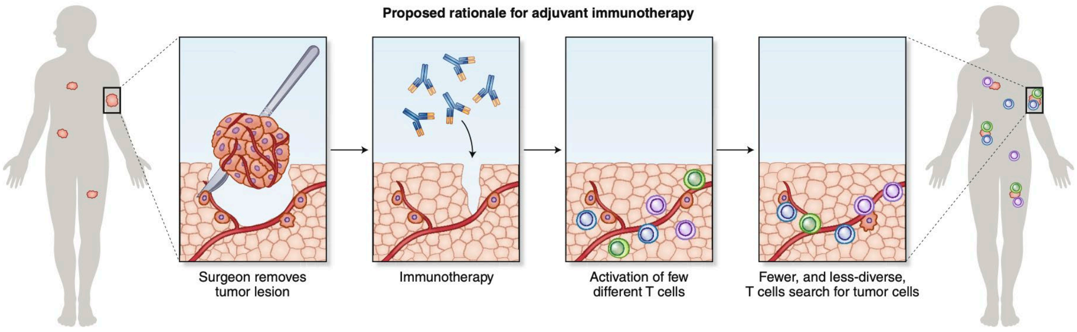

NCT
03860883
RECRUITING
Melanoma Margins Trial-II: 1 cm v 2cm Wide Surgical Excision Margins for AJCC Stage II Primary Cutaneous Melanoma (MelMarT-II)
Principal Investigators: Michael Lowe, MD - Emory University
Phase III
Stage II primary invasive cutaneous melanoma with Breslow thickness >2mm without ulceration or >1mm with ulceration as determined by biopsy
2998 Adults undergo randomization
Patient with previous wide local excision at site of primary lesion and who have planned radiotherapy after surgery are excluded
ARM 1
1 cm Wide Local Excision + Sentinel Lymph Node Biopsy
1 cm
+
ARM 2
2 cm Wide Local Excision + Sentinel Lymph Node Biopsy
2 cm
+
OUTCOMES
PRIMARY
Disease-free survival
SECONDARY
Local Recurrence
Distant disease-free survival
Melanoma-specific survival
Overall survival
Quality of life
Neuropathic pain
Surgery related adverse events (within 90 days) and other adverse events (within 1 year)
ANNALS OF
SURGICAL
ONCOLOGY

Types of Melanoma Treatments

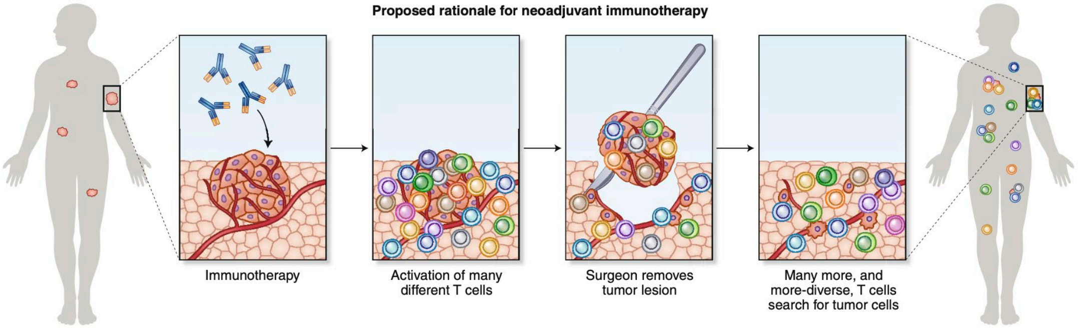
Metastatic



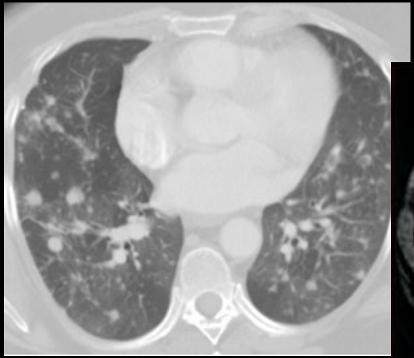
Adjuvant

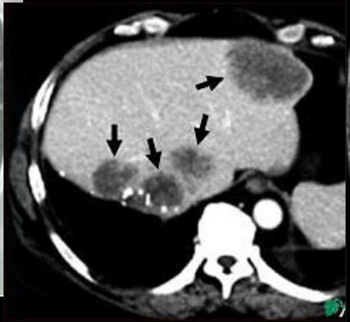


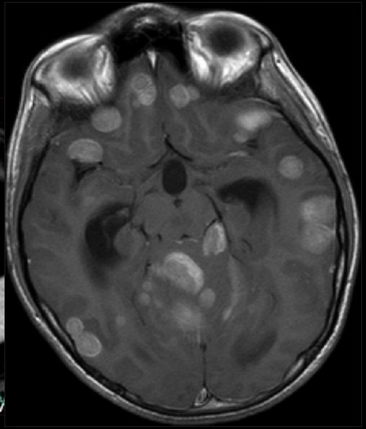
Neoadjuvant



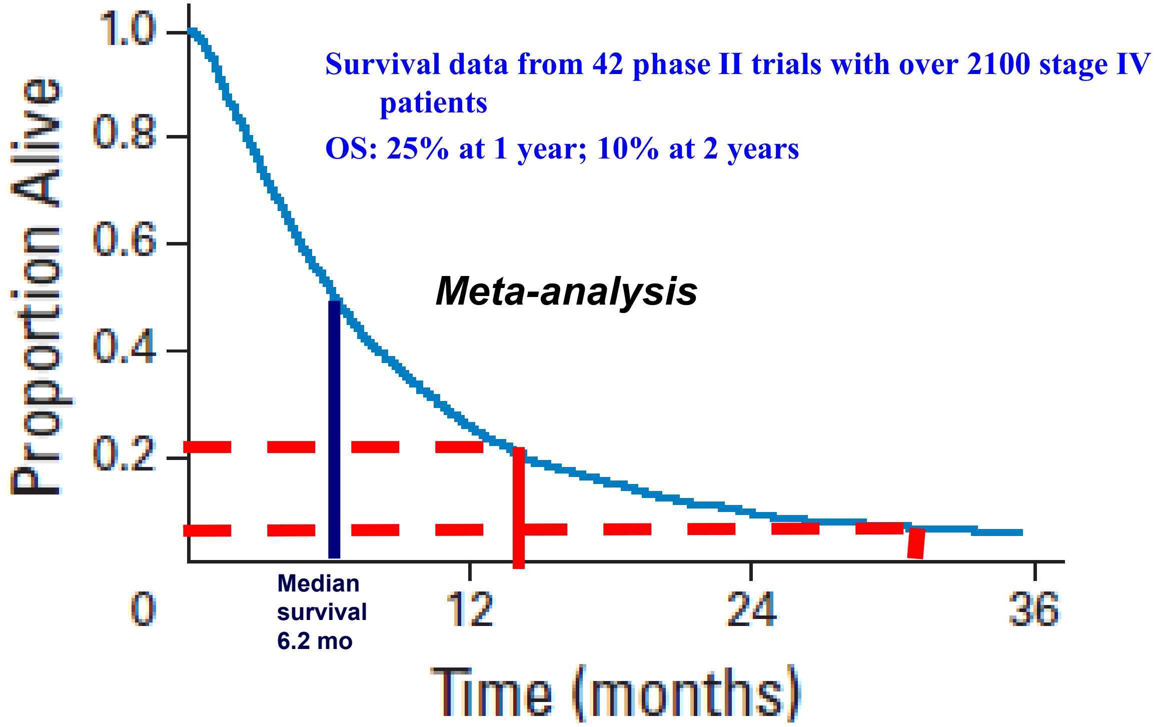
Inoperable or metastastic disease: heterogeneous





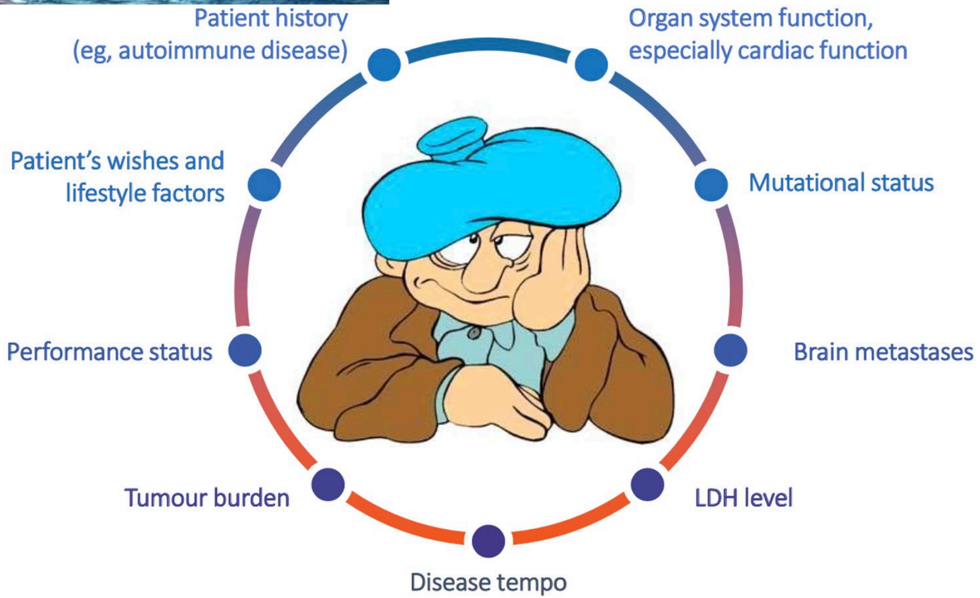


Overall Survival (OS) 15 years ago, stage IV metastatic melanoma



Korn EL, et al. *J Clin Oncol*. 2008;26(4):527-534.

General approach



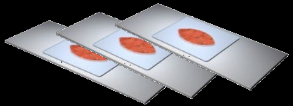
Courtesy of P. Ascierto

BRAF testing done in pathology

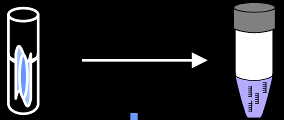
Primary or metastatic melanoma

Tumor Block

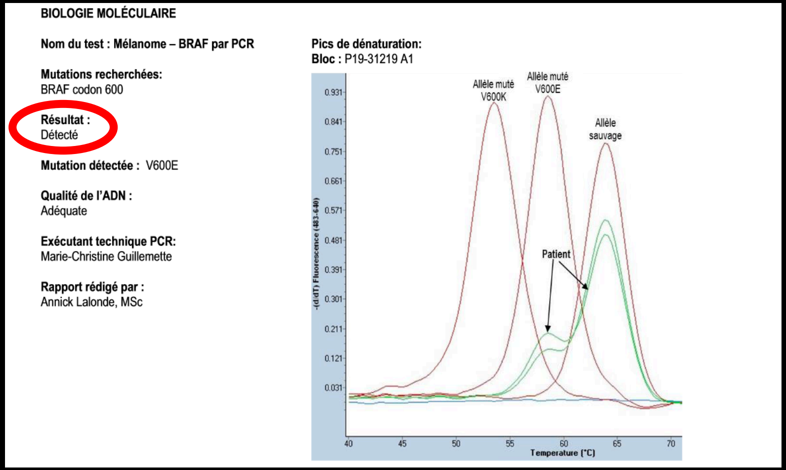
Tissue Preparation



Genomic DNA Extraction



TaqMan Real-time PCR



BIOLOGIE MOLÉCULAIRE

Nom du test : Mélanome – BRAF par PCR

Mutations recherchées:
BRAF codon 600

Résultat :
Détecté

Mutation détectée : V600E

Qualité de l'ADN :
Adéquate

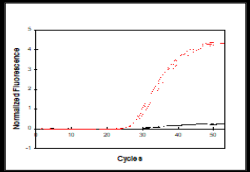
Exécutant technique PCR:
Marie-Christine Guillemette

Rapport rédigé par :
Annick Lalonde, MSc

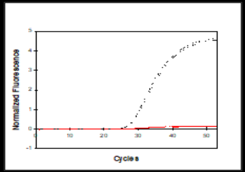
Pics de dénaturation:
Bloc : P19-31219 A1

BRAF+ ~ 40-50%

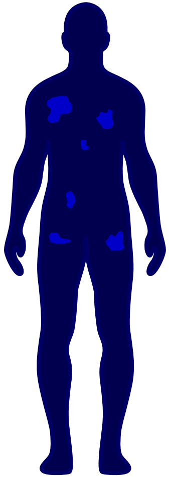
BRAF V600E



BRAF wild type



Current Treatment Options for Patients Metastatic Melanoma



BRAF V600 mutant

- Immunotherapy
  - Nivolumab + ipilimumab
  - Pembrolizumab
  - Nivolumab
- BRAF-targeted therapy
  - Encorafenib + binimetinib
  - Dabrafenib + trametinib
  - Vemurafenib + cobimetinib

BRAF wild type

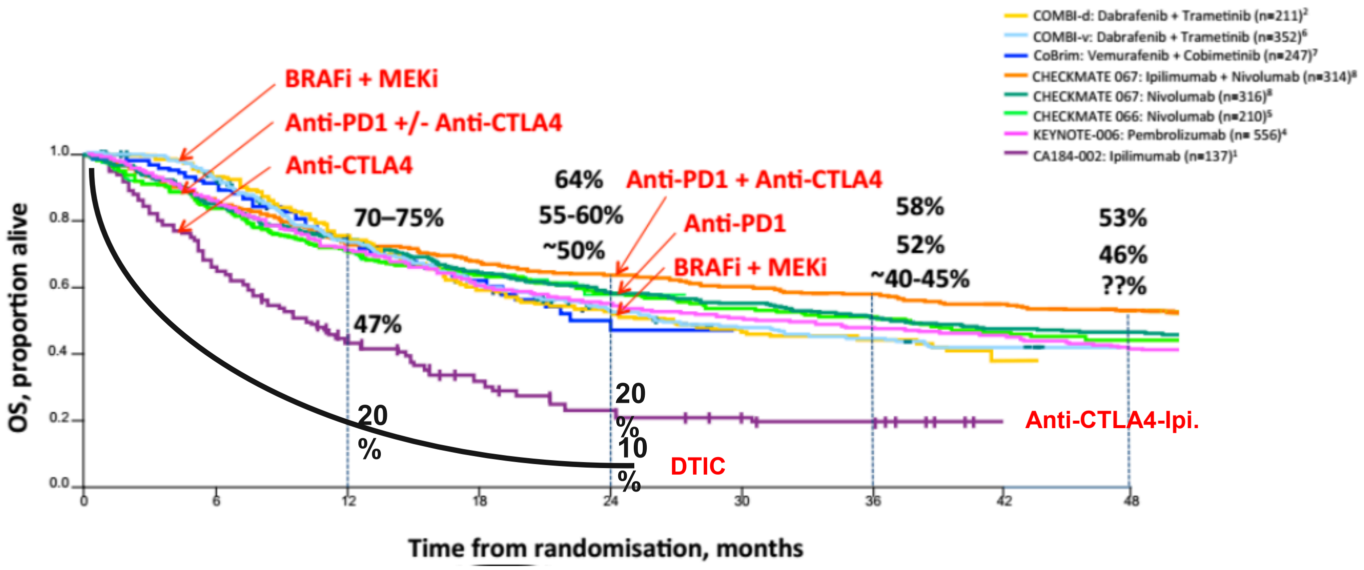
- Immunotherapy
  - Nivolumab + ipilimumab
  - Pembrolizumab
  - Nivolumab

For metastatic melanoma patients with *BRAF* mutation, immunotherapy and targeted therapy can be used either in the first-line or second-line setting.[1-4]

1. Michielin O, et al. *Ann Oncol*. 2019;30:1884-1901.
2. National Comprehensive Cancer Network (NCCN). Cutaneous Melanoma Guidelines Version 4.2020. Date: September 1, 2020.
3. Seth R, et al. *J Clin Oncol*. 2020:Jco2000198.
4. Dankner M, et al. *Clin Cancer Res*. 2018;24:6483-6494.

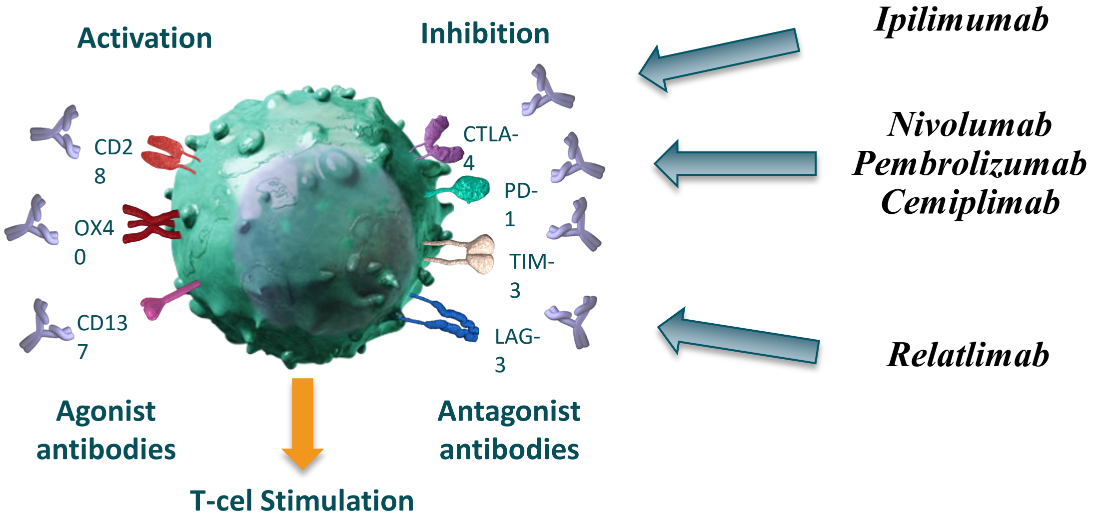
Actual treatments

Overall survival in metastatic melanoma – now we have 5 years data!




Immunotherapy

Checkpoint controls of T lymphocytes



Mellman I *et al. Nature* 2011; 480(7378): 480-9; Pardoll DM. *Nat Rev Cancer* 2012; 12(4): 252-64.

Anti-PD1 alone

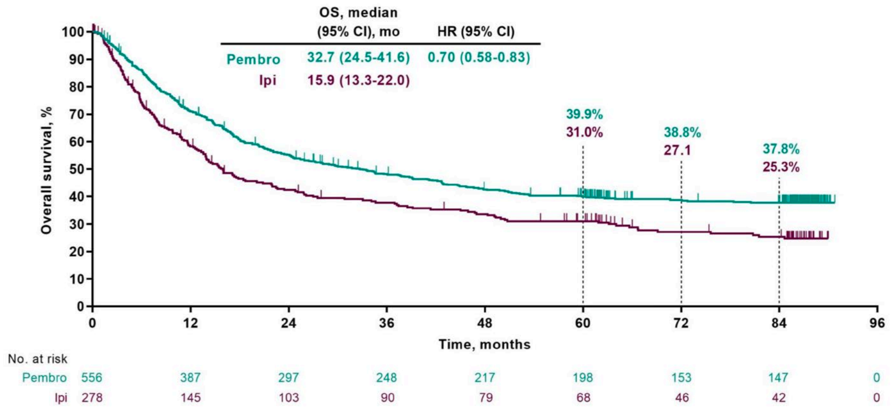
7-Year Follow-Up of KEYNOTE-006: Pembrolizumab Versus Ipilimumab in Advanced Melanoma

C. Robert[1]; M. S. Carlino[2]; C. McNeil[3]; A. Ribas[4]; J. J. Grob[5]; J. Schachter[6]; M. Nyakas[7]; D. Kee[8]; T. M. Petrella[9]; A. Blaustein[10]; M. Lotem[11]; A. Arance Fernandez[12]; A. I. Daud[13]; O. Hamid[14]; J. Larkin[15]; J. Anderson[16]; C. Krepler[16]; D. Grebennik[16]; G. V. Long[17]

[1]Gustave Roussy and Paris-Saclay University, Villejuif, France; [2]Melanoma Institute Australia, The University of Sydney, Westmead and Blacktown Hospitals, Sydney, NSW, Australia; [3]Chris O'Brien Lifehouse Skin and Melanoma Institute Australia, Camperdown, NSW, Australia; [4]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [5]Aix-Marseille University, Hospital of the Timone, Marseille, France; [6]Sheba Medical Center–Tel HaShomer, Ramat Gan, Israel; [7]Oslo University Hospital, Oslo, Norway; [8]Austin Health-Austin Hospital, Heidelberg, VIC, Australia; [9]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [10]Mount Sinai Medical Center Comprehensive Cancer Center, Miami Beach, FL, USA; [11]Sharett Institute of Oncology, Hadassah University Hospital Ein Kerem, Jerusalem, Israel; [12]Hospital Clinic of Barcelona, Barcelona, Spain; [13]University of California San Francisco, San Francisco, CA, USA; [14]The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [15]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

OS by Randomized Treatment

ITT Population



e cut-off: April 19, 2

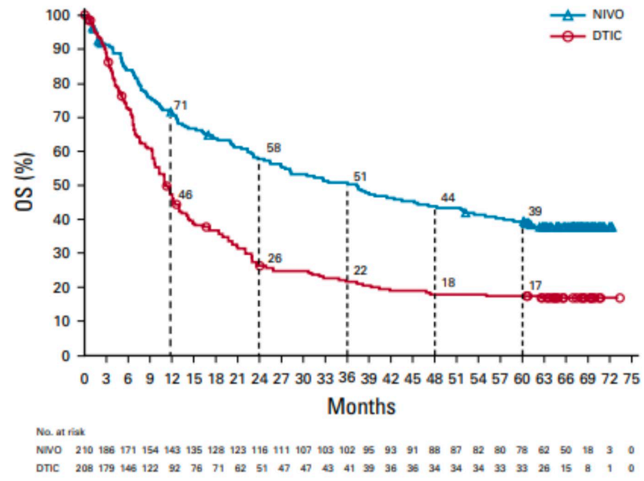
Five-Year Outcomes With Nivolumab in Patients With Wild-Type *BRAF* Advanced Melanoma

Caroline Robert, MD, PhD[1,2]; Georgina V. Long, PhD, MBBS[3]; Benjamin Brady, MD[4]; Caroline Dutriaux, MD, PhD[5]; Anna Maria Di Giacomo, MD, PhD[6]; Laurent Mortier, MD, PhD[7]; Piotr Rutkowski, MD, PhD[8]; Jessica C. Hassel, MD[9]; Catriona M. McNeil, MD[10]; Ewa Anna Kalinka, MD[11]; Céleste Lebbé, MD[12]; Julie Charles, MD, PhD[13]; Micaela M. Hernberg, MD[14]; Kerry J. Savage, MSc, MD[15]; Vanna Chiarion-Sileni, MD[16]; Catalin Mihalcioiu, MD[17]; Cornelia Mauch, MD, PhD[18]; Ana Arance, MD, PhD[19]; Francesco Cognetti, MD[20]; Lars Ny, MD[21]; Henrik Schmidt, MD[22]; Dirk Schadendorf, MD[23,24]; Helen Gogas, MD, PhD[25]; Jesús Zoco, MS[26]; Sandra Re, MD, MBA[27]; Paolo A. Ascierto, MD[28]; and Victoria Atkinson, MD[29]

PURPOSE The CheckMate 066 trial investigated nivolumab monotherapy as first-line treatment for patients with previously untreated *BRAF* wild-type advanced melanoma. Five-year results are presented herein.

PATIENTS AND METHODS In this multicenter, double-blind, phase III study, 418 patients with previously untreated, unresectable, stage III/IV, wild-type *BRAF* melanoma were randomly assigned 1:1 to receive nivolumab 3 mg/kg every 2 weeks or dacarbazine 1,000 mg/m^2 every 3 weeks. The primary end point was overall survival (OS), and secondary end points included progression-free survival (PFS), objective response rate (ORR), and safety.

A



Robert et al, JCO Vol 38 (Issue 33) 2020

Immunotherapy: side effects

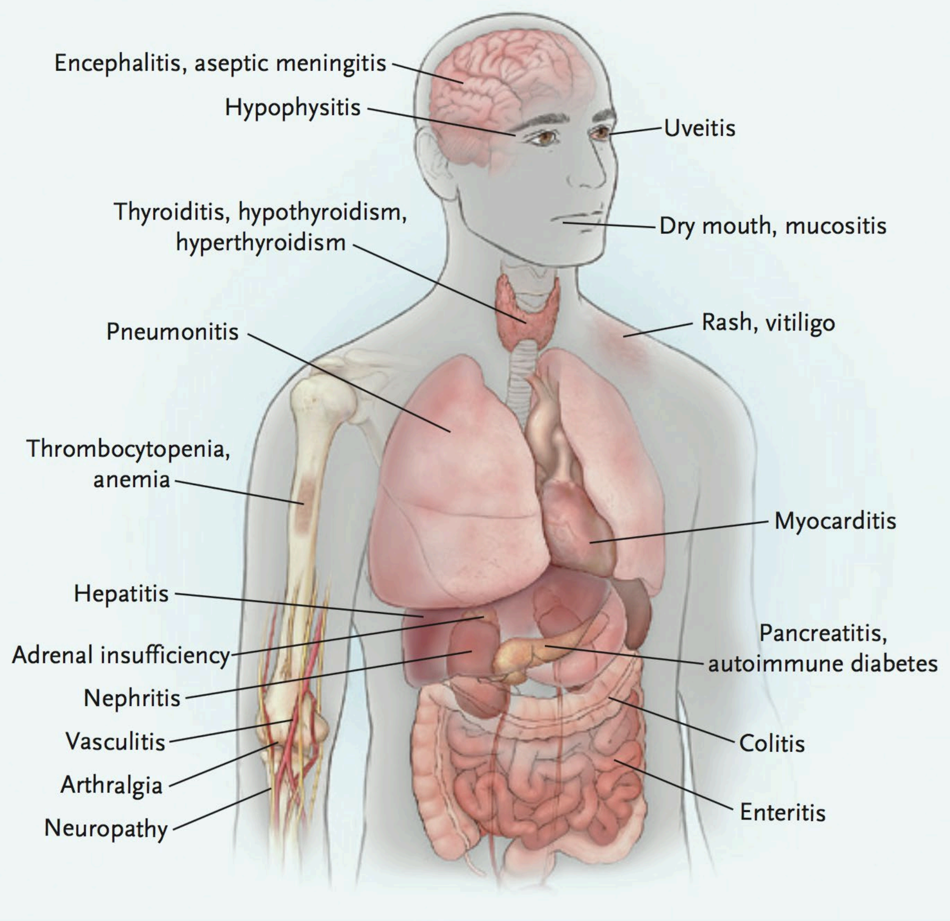


Figure 1. Organs Affected by Immune Checkpoint Blockade. NEJM

Anti-PD1 alone

Side effects: 75% of patients

Grade 3-4: 15-20%

Combo Ipilimumab + Anti-PD1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CheckMate 067

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao, C.L. Cowey, D. Schadendorf, J. Wagstaff, R. Dummer, P.F. Ferrucci, M. Smylie, D. Hogg, A. Hill, I. Márquez-Rodas, J. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, C. Lebbé, G. McArthur, P.A. Ascierto, G.A. Daniels, G.V. Long, L. Bastholt, J.I. Rizzo, A. Balogh, A. Moshyk, F.S. Hodi, and J.D. Wolchok

5-year follow up of a randomized, double-blind, phase 3 study to compare NIVO+IPI or NIVO alone with IPI alone[a]

Unresectable or metastatic melanoma

- **Previously untreated**
- **945 patients**

R 1:1:1

Stratify by:

- ***BRAF* status**
- **AJCC M stage**
- **Tumor PD-L1 expression < 5% versus ≥ 5%**

n = 314 → **NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W**

n = 316 → **NIVO 3 mg/kg Q2W + IPI-matched placebo**

n = 315 → **IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo**

Treat until progression or unacceptable toxicity

Co-primary endpoints[a] were PFS and OS in the NIVO-containing arms versus IPI alone

Database lock: July 2, 2019; minimum follow-up of 60 months for all patients

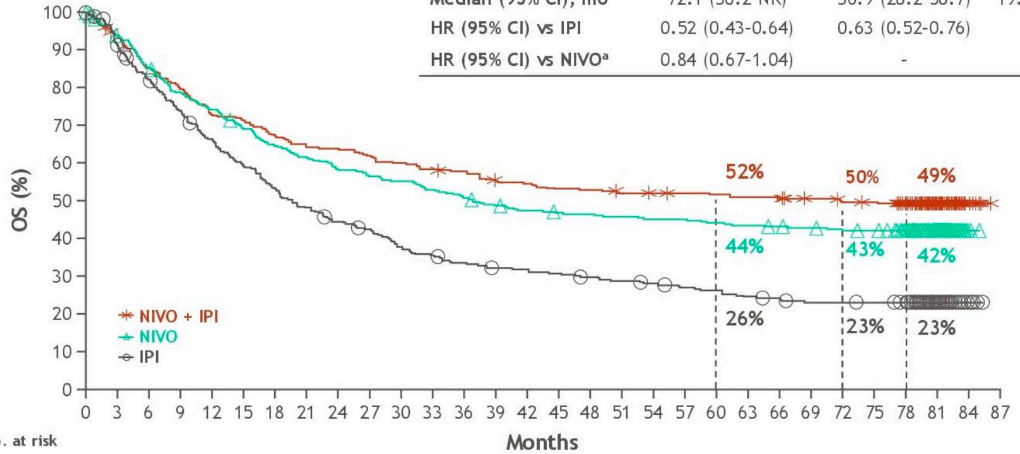
NCT01844505

[a]The study was not powered for a comparison between NIVO+IPI and NIVO.AJCC, American Joint Committee on Cancer.

Nivolumab Plus Ipilimumab: Checkmate 067
6.5 year OS update

Overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-



No. at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87
NIVO + IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

[a]Descriptive analysis.

Wolchok et al ASCO 2021

Safety Summary

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

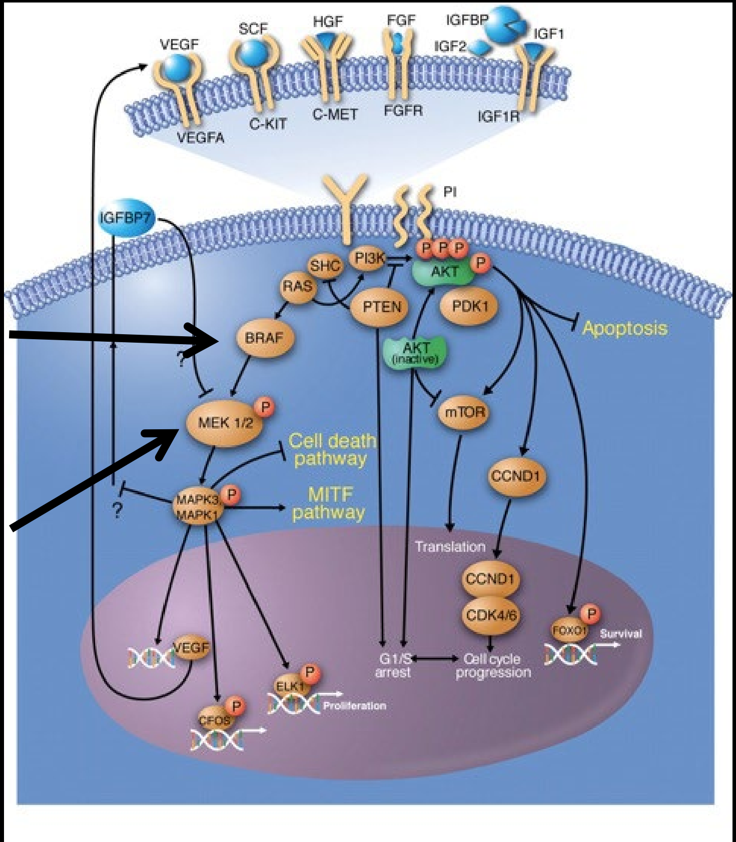
- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

Targeted therapies– MAPK pathway

Anti-BRAF:
Dabrafenib
or Vemurafenib
or Encorafenib

Anti-MEK:
Trametinib
or Cobimetinib
or Binimetinib



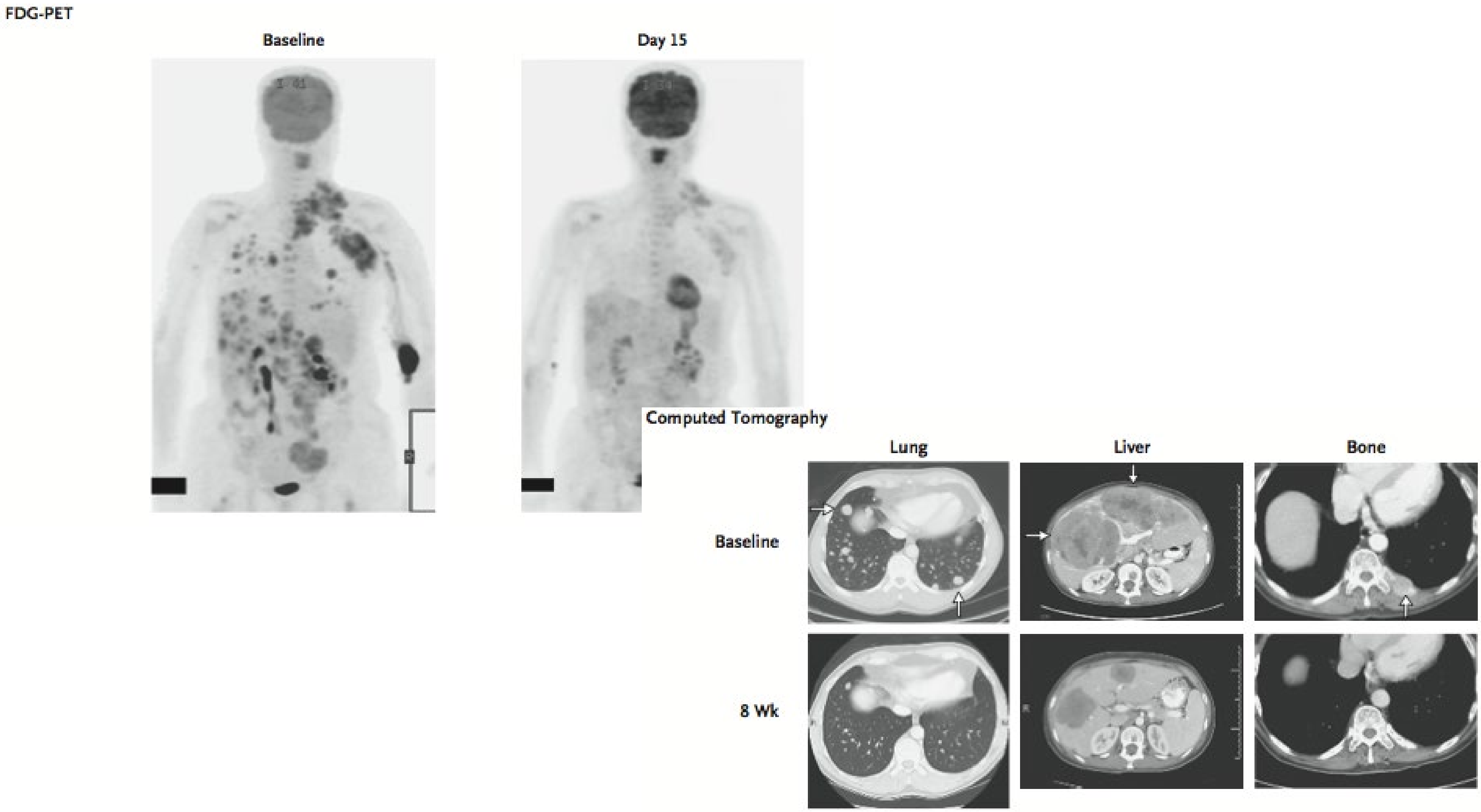
First molecule: Vemurafenib

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.


FDG-PET
Baseline
Day 15
Computed Tomography
Lung
Liver
Bone
Baseline
8 Wk

Actual targeted therapies: combo anti-BRAF/anti-MEK

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma

C. Robert, J.J. Grob, D. Stroyakovskiy, B. Karaszewska, A. Hauschild, E. Levchenko, V. Chiarion Sileni, J. Schachter, C. Garbe, I. Bondarenko, H. Gogas, M. Mandalá, J.B.A.G. Haanen, C. Lebbé, A. Mackiewicz, P. Rutkowski, P.D. Nathan, A. Ribas, M.A. Davies, K.T. Flaherty, P. Burgess, M. Tan, E. Gasal, M. Voi, D. Schadendorf, and G.V. Long

ABSTRACT

BACKGROUND

Patients who have unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation have prolonged progression-free survival and overall survival when receiving treatment with BRAF inhibitors plus MEK inhibitors. However, long-term clinical outcomes in these patients remain undefined. To determine 5-year survival rates and clinical characteristics of the patients with durable benefit, we sought to review long-term data from randomized trials of combination therapy with BRAF and MEK inhibitors.

N ENGL J MED 381;7 NEJM.ORG AUGUST 15, 2019

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

James Larkin, M.D., Ph.D., Paolo A. Ascierto, M.D., Brigitte Dréno, M.D., Ph.D. Victoria Atkinson, M.D., Gabriella Liszkay, M.D., Michele Maio, M.D., Mario Mandalà, M.D., Lev Demidov, M.D., Daniil Stroyakovskiy, M.D., Luc Thomas, M.D., Ph.D., Luis de la Cruz Merino, M.D., Caroline Dutriaux, M.D Claus Garbe, M.D., Mika A. Sovak, M.D., Ph.D., Ilsung Chang, Ph.D., Nicholas Choong, M.D., Stephen P. Hack, M.D., Ph.D., Grant A. McArthur, M.B., B.S., Ph.D., and Antoni Ribas, M.D., Ph.D.

ABSTRACT

BACKGROUND

The combined inhibition of BRAF and MEK is hypothesized to improve clinic outcomes in patients with melanoma by preventing or delaying the onset of resi tance observed with BRAF inhibitors alone. This randomized phase 3 study eval ated the combination of the BRAF inhibitor vemurafenib and the MEK inhibit cobimetinib.

METHODS

We randomly assigned 495 patients with previously untreated unresectable local advanced or metastatic *BRAF* V600 mutation–positive melanoma to receive vem rafenib and cobimetinib (combination group) or vemurafenib and placebo (contr group). The primary end point was investigator-assessed progression-free surviva

original reports

COLUMBUS 5-Year Update: A Randomized, Open-Label, Phase III Trial of Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With *BRAF* V600–Mutant Melanoma

Reinhard Dummer, MD[1]; Keith T. Flaherty, MD[2]; Caroline Robert, MD[3]; Ana Arance, MD[4]; Jan Willem B. de Groot, MD[5]; Claus Garbe, MD[6]; Helen J. Gogas, MD[7]; Ralf Gutzmer, MD[8]; Ivana Krajsová, MD[9]; Gabriella Liszkay, MD[10]; Carmen Loquai, MD[11]; Mario Mandalà, MD[12]; Dirk Schadendorf, MD[13]; Naoya Yamazaki, MD[14]; Alessandra di Pietro, PhD[15]; Jean Cantey-Kiser, PhD[16]; Michelle Edwards, PharmD[17]; and Paolo A. Ascierto, MD[18]

abstract

PURPOSE Combination treatment with BRAF and MEK inhibitors has demonstrated benefits on progression-free survival (PFS) and overall survival (OS) and is a standard of care for the treatment of advanced *BRAF* V600–mutant melanoma. Here, we report the 5-year update from the COLUMBUS trial (ClinicalTrials.gov identifier: NCT01909453).

METHODS Patients with locally advanced unresectable or metastatic *BRAF* V600–mutant melanoma, untreated or progressed after first-line immunotherapy, were randomly assigned 1:1:1 to encorafenib 450 mg once daily plus binimetinib 45 mg twice daily, vemurafenib 960 mg twice daily, or encorafenib 300 mg once daily. An updated analysis was conducted 65 months after the last patient was randomly assigned.

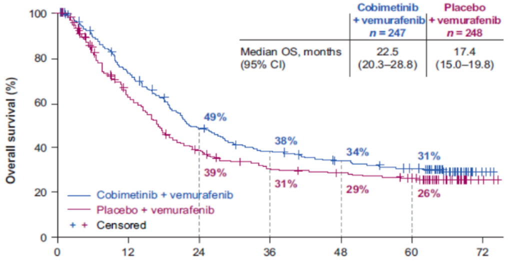
RESULTS Five hundred seventy-seven patients were randomly assigned: 192 to encorafenib plus binimetinib, 191 to vemurafenib, and 194 to encorafenib. The 5-year PFS and OS rates with encorafenib plus binimetinib were 23% and 35% overall and 31% and 45% in those with normal lactate dehydrogenase levels, respectively. In comparison, the 5-year PFS and OS rates with vemurafenib were 10% and 21% overall and 12% and 28% in those with normal lactate dehydrogenase levels, respectively. The median duration of response with encorafenib plus binimetinib was 18.6 months, with disease control achieved in 92.2% of patients. In comparison, the median duration of response with vemurafenib was 12.3 months, with disease control achieved in 81.2% of patients. Long-term follow-up showed no new safety concerns, and results were consistent with the known tolerability profile of encorafenib plus binimetinib. Interactive visualization of the data presented in this article is available at COLUMBUS dashboard.

CONCLUSION In this 5-year update of part 1 of the COLUMBUS trial, encorafenib plus binimetinib treatment demonstrated continued long-term benefits and a consistent safety profile in patients with *BRAF* V600–mutant melanoma.

J Clin Oncol 00. © 2022 by American Society of Clinical Oncology

5 year outcome with targeted anti-BRAF + anti-MEK therapy…

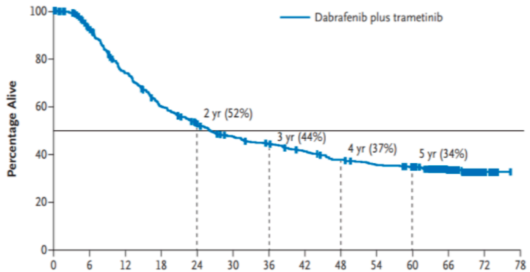
5-year OS: 31%
5-year PFS: 14%



vemurafenib + cobimetinib

Ascierto et al CCR 2021

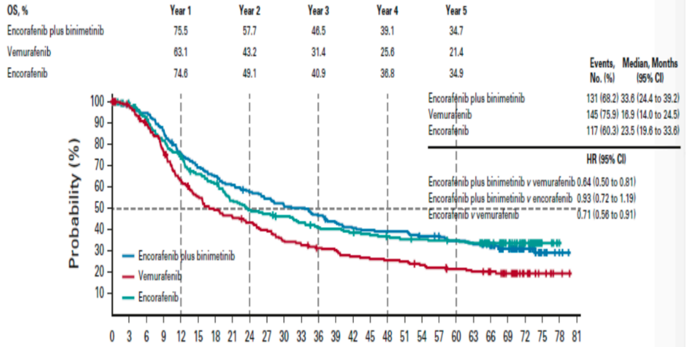
5-year OS: 34%
5-year PFS: 19%



dabrafenib + trametinib

Robert et al NEJM 2019

5-year OS: 34.7%
5-year PFS: 22.9%



encorafenib + binimetinib

Dummer et al JCO 2022

Presenter Caroline Robert


What are the side effects of targeted therapy for melanoma?
Chills
Fever
Feeling tired
Itching
Rash
Joint pain
Precancerous skin lesions
Sun sensitivity
© Mechanisms in Medicine Inc.
www.YouAndMelanoma.com

Multiples in transit metastases

cancers

Intralesional therapy

MDPI

Review

Talimogene Laherparepvec (T-VEC): An Intralesional Cancer Immunotherapy for Advanced Melanoma

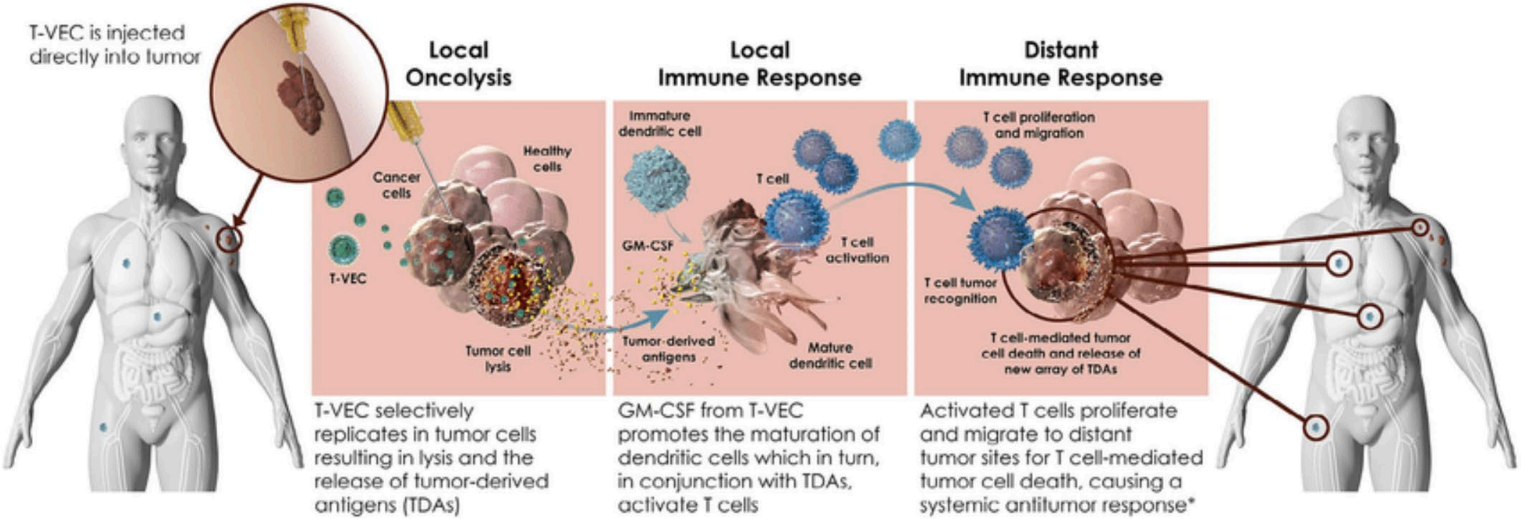
Pier Francesco Ferrucci [1,*], Laura Pala [2], Fabio Conforti [2] and Emilia Cocorocchio [3]

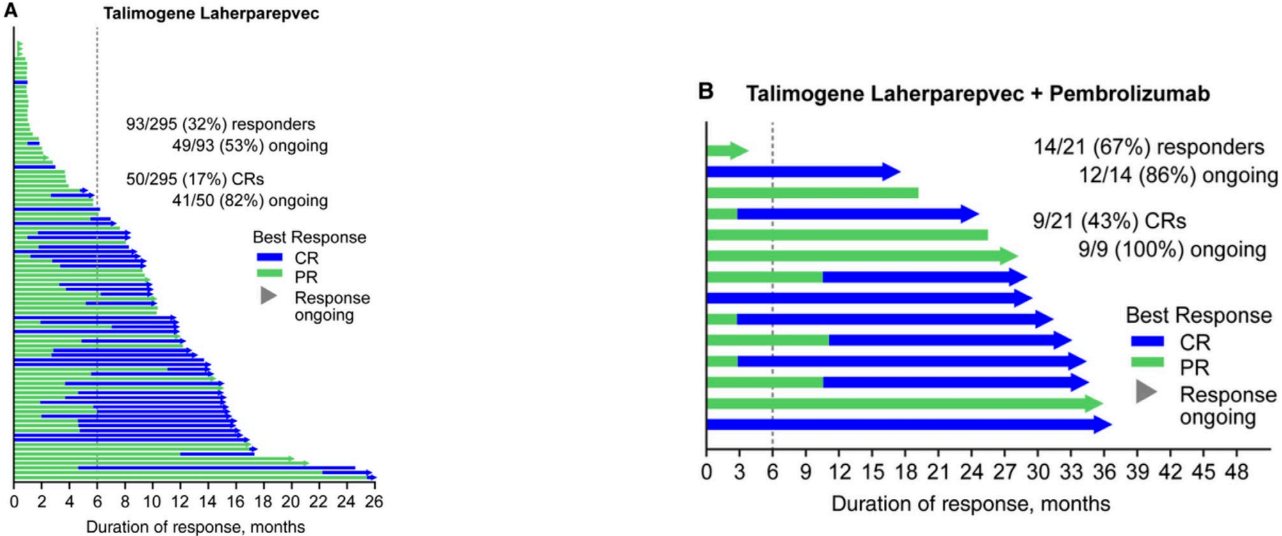
1 Tumor Biotherapy Unit, Department of Experimental Oncology, European Institute of Oncology, IRCCS, 20141 Milan, Italy
2 Division of Melanoma, Sarcoma and Rare Tumors, European Institute of Oncology, IRCCS, 20141 Milan, Italy; laura.pala@ieo.it (L.P.); fabio.conforti@ieo.it (F.C.)
3 Hemato-Oncology Division, European Institute of Oncology, IRCCS, 20141 Milan, Italy; emilia.cocorocchio@ieo.it
* Correspondence: pier.ferrucci@ieo.it; Tel.: +39-0294371094

Simple Summary: Talimogene laherparepvec (T-VEC; IMLYGIC®, Amgen Inc.) is the first oncolytic viral immunotherapy to be approved for the local treatment of unresectable metastatic stage IIIB/C–IVM1a melanoma. Its direct intratumoral injection aim to trigger local and systemic immunologic responses leading to tumor cell lysis, followed by release of tumor-derived antigens and subsequent activation of tumor-specific effector T-cells. Its approval has fueled the interest to study its possible sinergy with other immunotherapeutics in preclinical models as well as in clinical contextes. In fact, it has been shown that intratumoral administration of this immunostimulatory agent successfully synergizes with immune checkpoint inhibitors. The objectives of this review are to resume the current state of the art of T-VEC treatment when used in monotherapy or in combination with immune checkpoint inhibitors, describing the strong rationale of its development, the adverse events of interest and the clinical outcome in selected patient's populations.

check for updates

Citation: Ferrucci, P.F.; Pala, L.; Conforti, F.; Cocorocchio, E.


T-VEC is injected directly into tumor
Local Oncolysis
Local Immune Response
Distant Immune Response
Healthy cells
Cancer cells
T-VEC
Tumor cell lysis
Immature dendritic cell
T cell
GM-CSF
T cell activation
Tumor-derived antigens
Mature dendritic cell
T cell proliferation and migration
T cell tumor recognition
T cell-mediated tumor cell death and release of new array of TDAs
T-VEC selectively replicates in tumor cells resulting in lysis and the release of tumor-derived antigens (TDAs)
GM-CSF from T-VEC promotes the maturation of dendritic cells which in turn, in conjunction with TDAs, activate T cells
Activated T cells proliferate and migrate to distant tumor sites for T cell-mediated tumor cell death, causing a systemic antitumor response*


A
Talimogene Laherparepvec
93/295 (32%) responders
49/93 (53%) ongoing
50/295 (17%) CRs
41/50 (82%) ongoing
Best Response
CR
PR
Response ongoing
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Duration of response, months
B
Talimogene Laherparepvec + Pembrolizumab
14/21 (67%) responders
12/14 (86%) ongoing
9/21 (43%) CRs
9/9 (100%) ongoing
Best Response
CR
PR
Response ongoing
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Duration of response, months

A: at diagnosis B: after 6 months C: after 12 months

Brain metastasis

Long-term Outcomes from the Randomized Ph 2 Study of Nivolumab or Nivolumab + Ipilimumab in Patients With Melanoma Brain Metastases: Anti-PD1 Brain Collaboration (The ABC Trial)

Georgina V. Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Michael P. Brown, Maria Gonzalez, Alexander Guminski, Richard A. Scolyer, Louise Emmett, Alexander M. Menzies, Grant A. McArthur

Study Design

Total 76 Patients Recruited

- Melanoma Brain Metastases
  ≥ 5mm & < 40mm
- No previous
  Anti-CTLA-4
  Anti-PD-1 or -PD-L1 agents
- Previous BRAFi+MEKi allowed
- ECOG PS 0-2
- No serious autoimmune disease
- No corticosteroids
  (Cohort C > 10mg prednisone allowed)

R 1:1
up to n=51

A
No prior local brain Rx & asymptomatic
n=35
Nivolumab + Ipilimumab

B
No prior local brain Rx & asymptomatic
n=25
Nivolumab

C
Previously treated or symptomatic or leptomeningeal, with MRI progression
n=16
Nivolumab

Primary Endpoint: **Intracranial Response Rate ≥ wk 12**
Secondary Endpoints: Extracranial Response Rate
Overall Response Rate
PFS (Intracranial, Extracranial, Overall)
Overall Survival

BARCELONA 2019 ESMO congress

Presented by Georgina V Long @ProfGLongMIA

Best Intracranial RECIST Response

Melanoma Institute Australia

	A: Nivo+Ipi N=35	B: Nivo N=25	C: Nivo† N=16
Intracranial Response, n (%)	**18 (51%)**	**5 (20%)**	**1 (6%)**
CR	9 (26%)	4 (16%)	0 (0%)
PR	9 (26%)	1 (4%)	1 (6%)
SD	2 (6%)	0 (0%)	2 (13%)
PD	14 (40%)	19 (76%)	13 (81%)
NE*	1 (3%)	1 (4%)	0 (0%)

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable
*Pts who deceased prior to wk 12 = PD
† Leptomeningeal, previous local treatment or symptoms

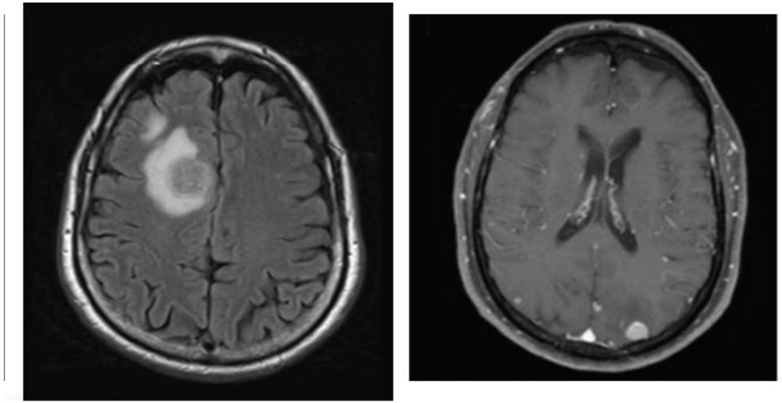
BARCELONA 2019 ESMO congress

Presented by Georgina V Long @ProfGLongMIA

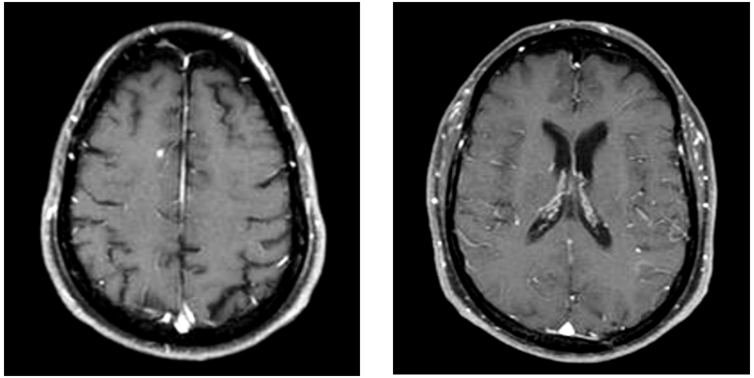
Patient Case

71 year old male with *BRAF* V600E-mutated MEL,
~7 brain mets, no steroids or SRT

Baseline



1 year



New: Nivolumab (anti-PD1)-Relatlimab (anti-LAG3)

2023 ASCO ANNUAL MEETING

Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

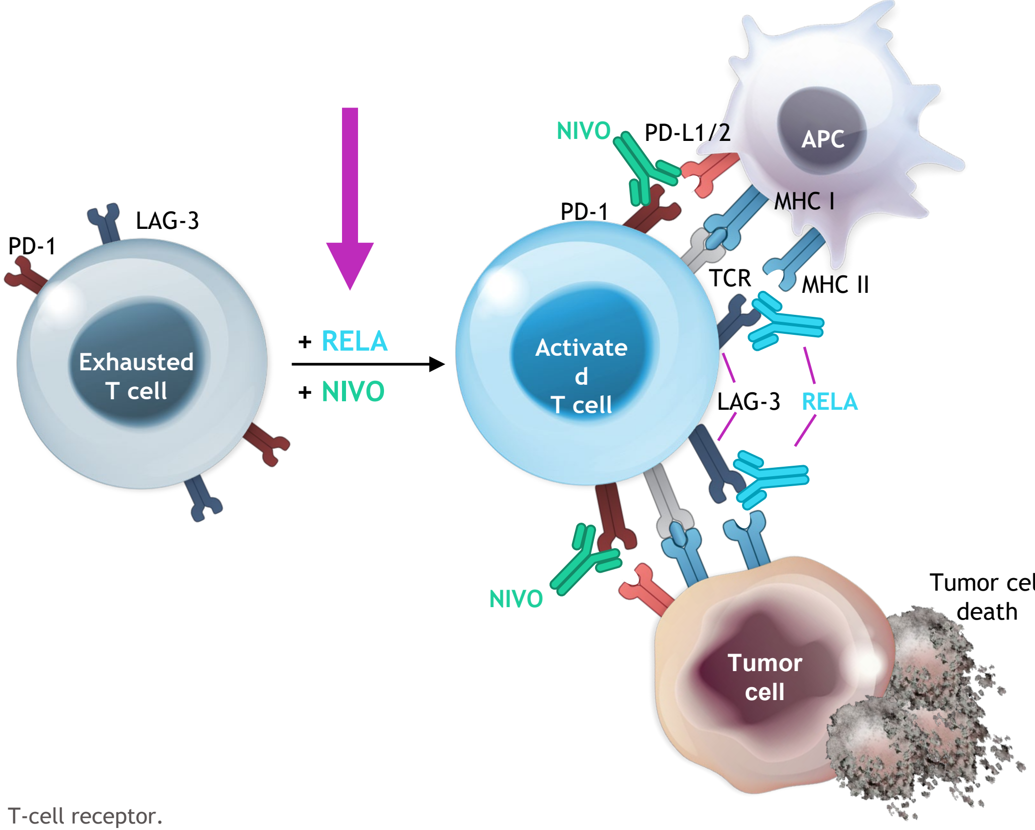
Hussein A. Tawbi,[1] F. Stephen Hodi,[2] Evan J. Lipson,[3] Dirk Schadendorf,[4] Paolo Antonio Ascierto,[5] Luis Matamala,[6] Erika Castillo Gutiérrez,[7] Piotr Rutkowski,[8] Helen Gogas,[9] Christopher D. Lao,[10] Juliana Janoski De Menezes,[11] Stéphane Dalle,[12] Ana Maria Arance,[13] Jean-Jacques Grob,[14] Barbara Ratto,[15] Saima Rodriguez,[15] Yuanfang Xu,[15] Peter Wang,[15] Sonia Dolfi,[15] Georgina V. Long[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [4]University of Essen and the German Cancer Consortium, Essen, Germany; [5]Istituto Nazionale dei Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; [6]Instituto Oncológico Fundación Arturo López Pérez and Department of Oncology, Instituto Nacional del Cáncer, Santiago, Chile; [7]FAICIC Clinical Research, Veracruz, Mexico; [8]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]National and Kapodistrian University of Athens, Athens, Greece; [10]Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI; [11]Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; [12]Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; [13]Hospital Clinic Barcelona and IDIBAPS, Barcelona, Spain; [14]Aix-Marseille University, CHU Timone, Marseille, France; [15]Bristol Myers Squibb, Princeton, NJ; [16]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Abstract number 9502

Rationale for RELA + NIVO

- LAG-3 and PD-1 are distinct immune checkpoints, often co-expressed on TIL and contribute to tumor-mediated T-cell exhaustion[1,2]
- Synergistic antitumor activity[1]
- RELA + NIVO demonstrated clinically meaningful antitumor activity including durable objective responses and was well tolerated in patients that was relapsed/refractory to anti–PD-1 therapy[3,4]

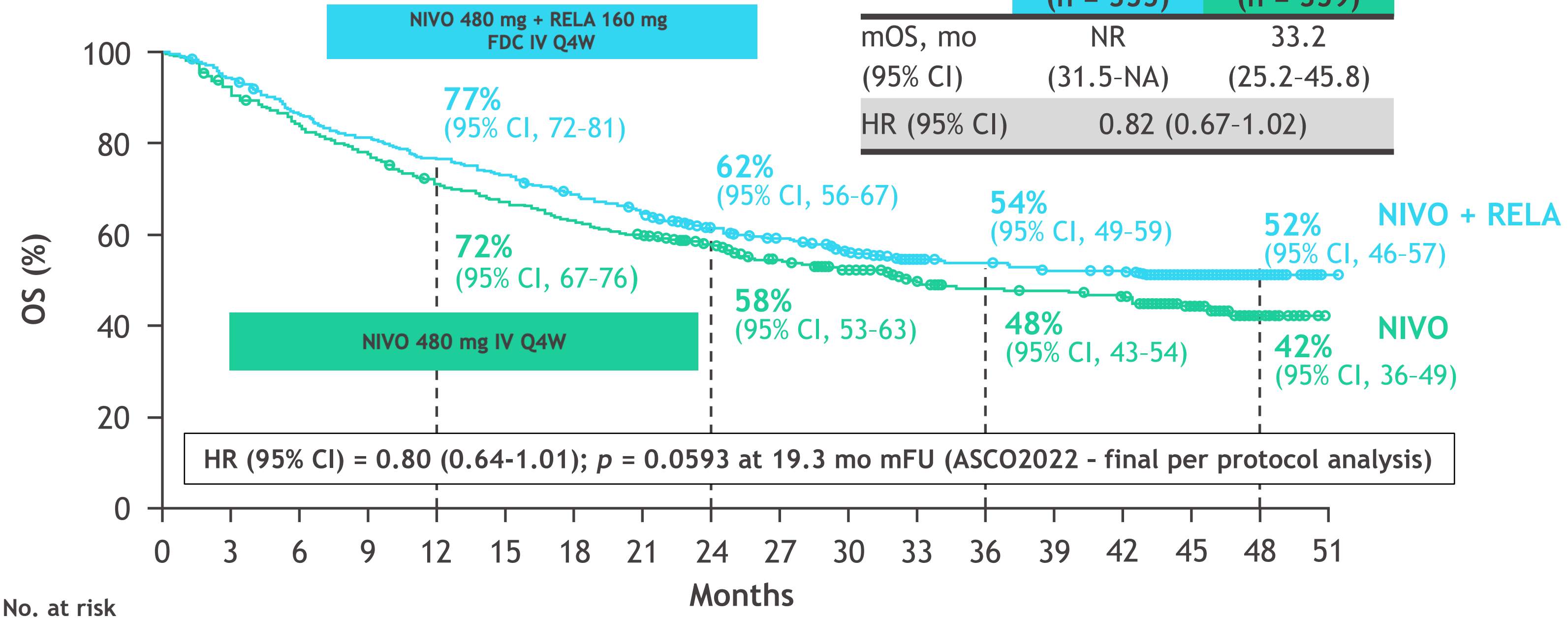


APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Woo S-R, et al. *Cancer Res* 2012;72:917–927; 2. Anderson AC, et al. *Immunity* 2016;44:989–1004; 3. Ascierto PA, et al. Oral presentation at ASCO Annual Meeting; June 2-6, 2017; Chicago, IL. Abstract 9520; 4. Ascierto PA, et al. Oral presentation at ESMO Congress; September 8-12, 2017; Madrid, Spain. Abstract LBA18.

OS

Updated secondary endpoint



	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo	NR	33.2
(95% CI)	(31.5-NA)	(25.2-45.8)
HR (95% CI)	0.82 (0.67-1.02)	

No. at risk																		
NIVO + RELA	355	334	305	287	270	258	241	226	197	179	160	136	128	122	120	78	26	2
NIVO	359	329	301	278	253	238	224	211	185	162	144	118	106	104	100	64	17	0

RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

Hussein A. Tawbi et al. Oral presentation at ASCO 2023

Safety summary

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99)	161 (45)	344 (96)	139 (39)
TRAE	301 (85)	78 (22)	262 (73)	43 (12)
Leading to discontinuation	61 (17)	34 (10)	31 (9)	14 (4)
Treatment-related deaths[a]	4 (1)		2 (1)	

Sequencing

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): A phase III trial—ECOG-ACRIN EA6134

@pawel_sobczuk

#ASCOPlenarySeries

AIM: to compare the efficacy and toxicity of the sequence of nivolumab/ipilimumab followed by dabrafenib/trametinib to the converse sequence

PATINETS: treatment-naive BRAFV600-mutant advanced melanoma, ECOG 0-1

265 pts

1:1

Nivolumab + Ipilimumab
N=133

ORR 46%

G3+ toxicity: 60%

PD

Dabrafenib + Trametinib
N=24

ORR 48%

Dabrafenib + Trametinib
N=132

ORR 43%

G3+ toxicity: 52%

PD

Nivolumab + Ipilimumab
N=46

ORR 30%

**Median follow-up:
27.7 months**

2-year OS

72%

vs

52%

p=0.0095

CONCLUSION:

- **the treatment sequence beginning with Nivolumab+Ipilimumab resulted in superior OS**
- **The difference became evident at 10 months**

2021 ESMO congress

SECOMBIT: The best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma: A phase II randomized study

Population:
- metastatic BRAFV600-mutated melanoma
- treatment naïve
- ECOG PS 0 or 1

Primary endpoint:
- overall survival

209 pts, randomized 1:1:1

Arm	Treatment	mOS	2-year OS	3-year OS
A	E+B → N+I (n=69)	NR	65%	54%
B	B N+I→E+B (n=71)	NR	73%	62%
C	E+B (8 weeks) → N+I →E+B (n=69)	NR	69%	60%

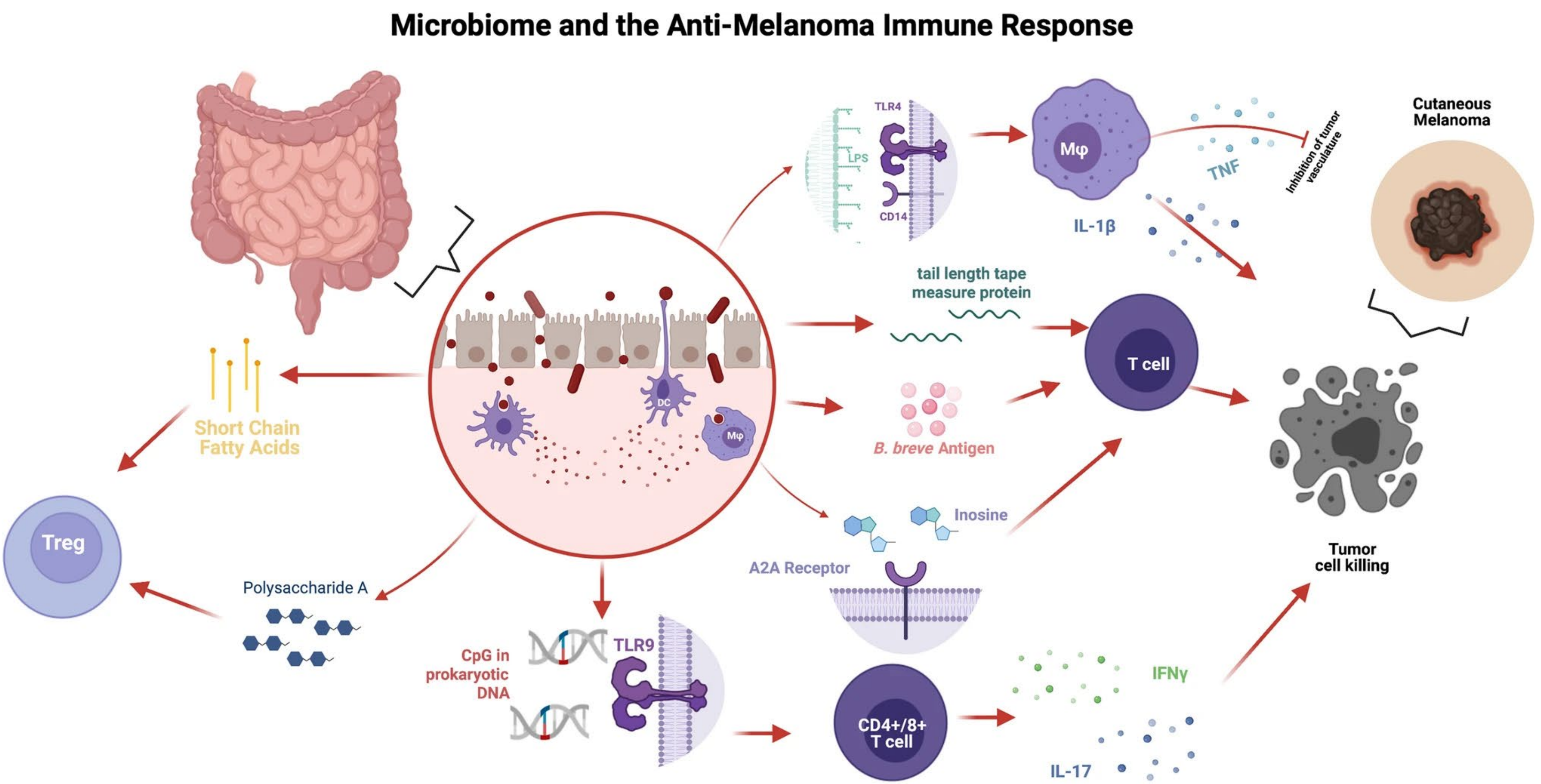
Median follow-up: 32.2 months

Exploratory HR: A vs B (0.73, 95%CI 0.42-1.26), A vs C (0.81, 95%CI 0.48-1.37),

No statistical differences for overall survival depending on the sequence of therapy in BRAF-muated patients.

#ESMO21

Clinical trials


Microbiome and the Anti-Melanoma Immune Response
TLR4
LPS
CD14
Mφ
TNF
Inhibition of tumor vasculature
IL-1β
Cutaneous Melanoma
tail length tape measure protein
T cell
DC
Mφ
B. breve Antigen
Short Chain Fatty Acids
Inosine
A2A Receptor
Tumor cell killing
Treg
Polysaccharide A
CpG in prokaryotic DNA
TLR9
CD4+/8+ T cell
IFNγ
IL-17

Dermatol Ther (Heidelb) (2022) 12:2489–2497
https://doi.org/10.1007/s13555-022-00810-1

REVIEW

Modulation of the Gut Microbiome to Enhance Immunotherapy Response in Metastatic Melanoma Patients: A Clinical Review

Maleka Najmi · Tiffaney Tran · Russell G. Witt · Kelly C. Nelson

There has been ongoing research evaluating interventions (e.g., fecal microbiota transplantation, probiotics, dietary modifications) to alter the gut microbiota in order to optimize immunotherapy response rates in patients.

Microbiota enhancing ICI therapy

- Bacteroides fragilis
- Bifidobacterium species
- Faecalibacterium species
- Akkermansia muciniphila
- Enterococcus faecium
- Collinsella aerofaciens
- Clostridiales family
- Barnesiella intestinihominis

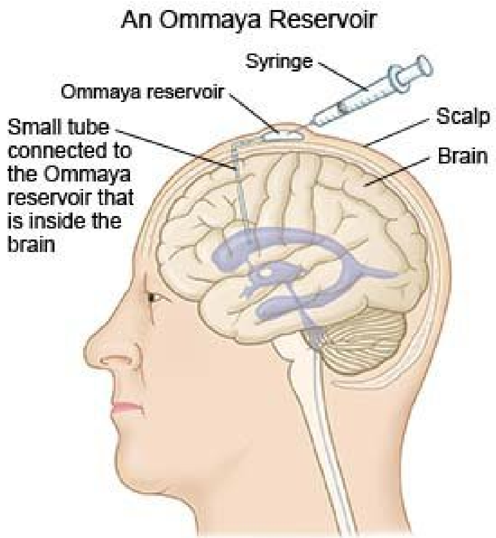
MADRID 2023 ESMO congress

Concurrent Intrathecal (IT) and Intravenous (IV) Nivolumab (N) for Melanoma (MM) Patients (pts) with Leptomeningeal Disease (LMD)

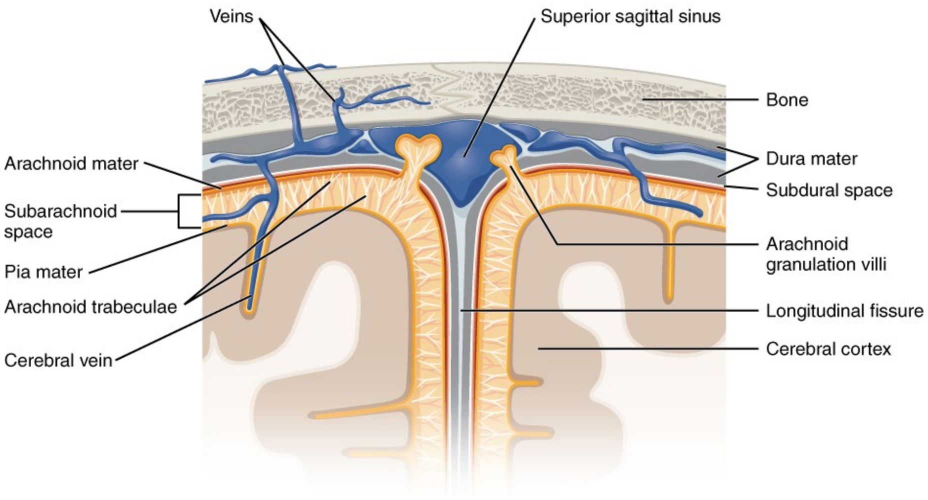
Final Analysis

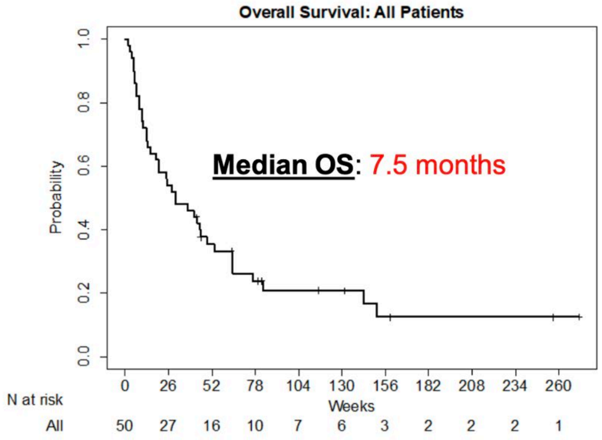
Isabella C. Glitza Oliva, MD, PhD, MS
University of Texas MD Anderson Cancer Center
Houston, Texas

Madrid, October 23rd 2023

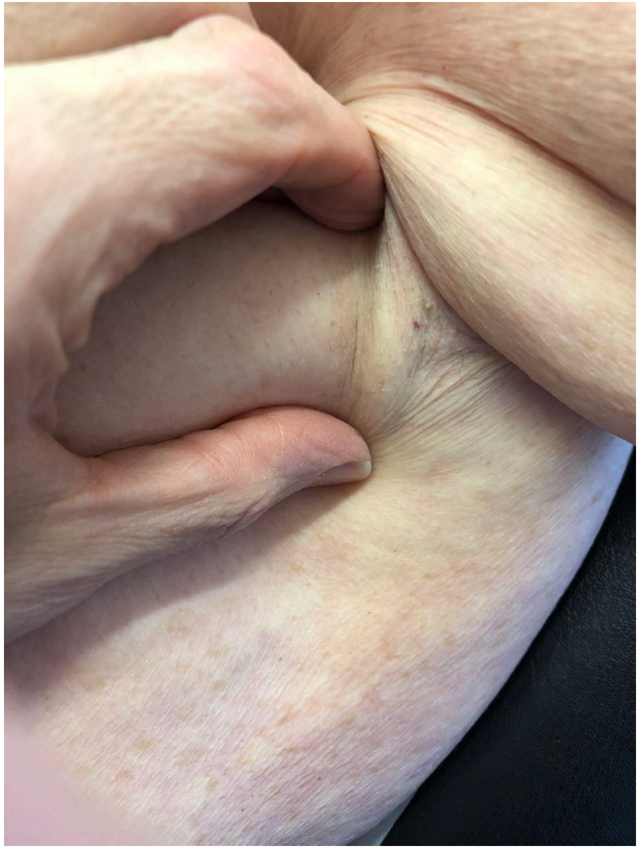


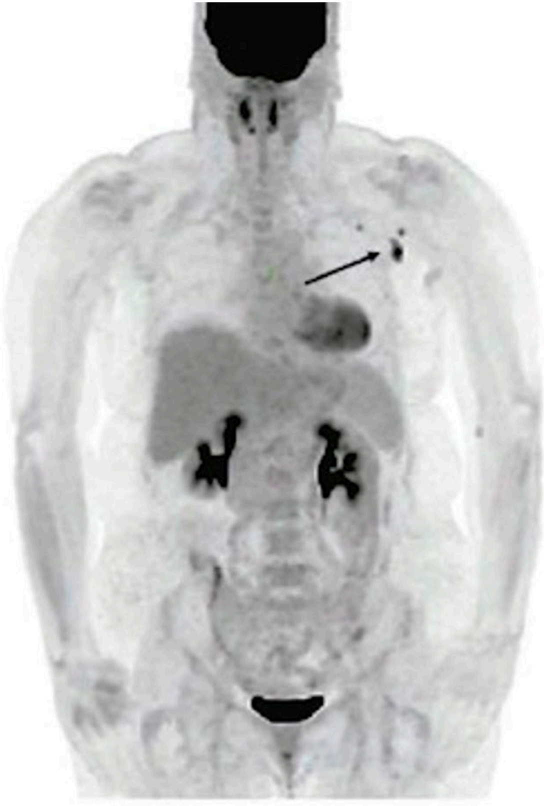
Treatment	Baseline	Cycle 1				Cycle 2					Cycle 3			Cycle 4		Cycle 5 and beyond	
		D1	D1 + 4 hrs	D2	D8	D1	D1 + 4 hrs	D2	D3	D8	D1	D2	D8	D1	D2	D1	D2
IT Nivo (4 Levels: 5, 10, 20, **50 mg**)																	
IV Nivo (240 mg)																	



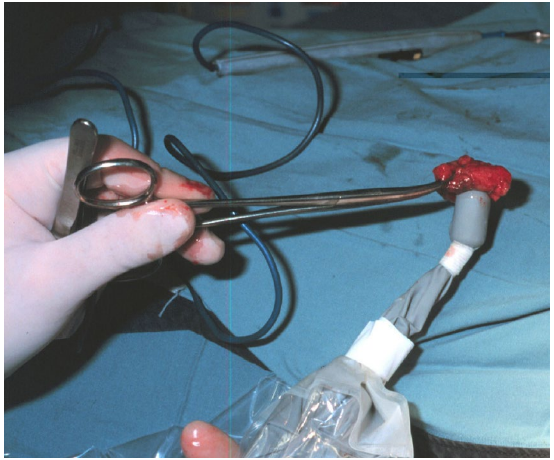


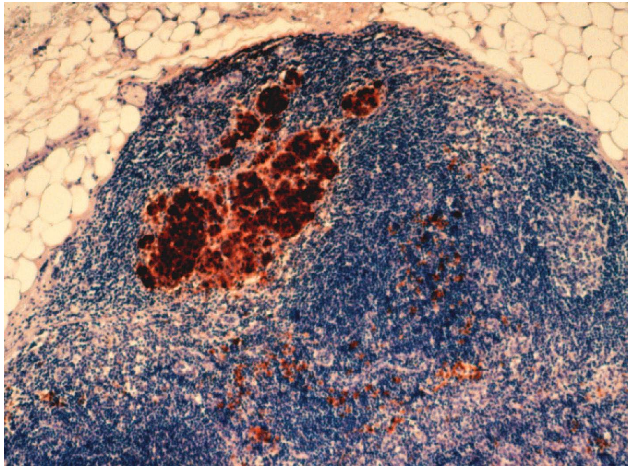
Stage III melanoma: nodal disease





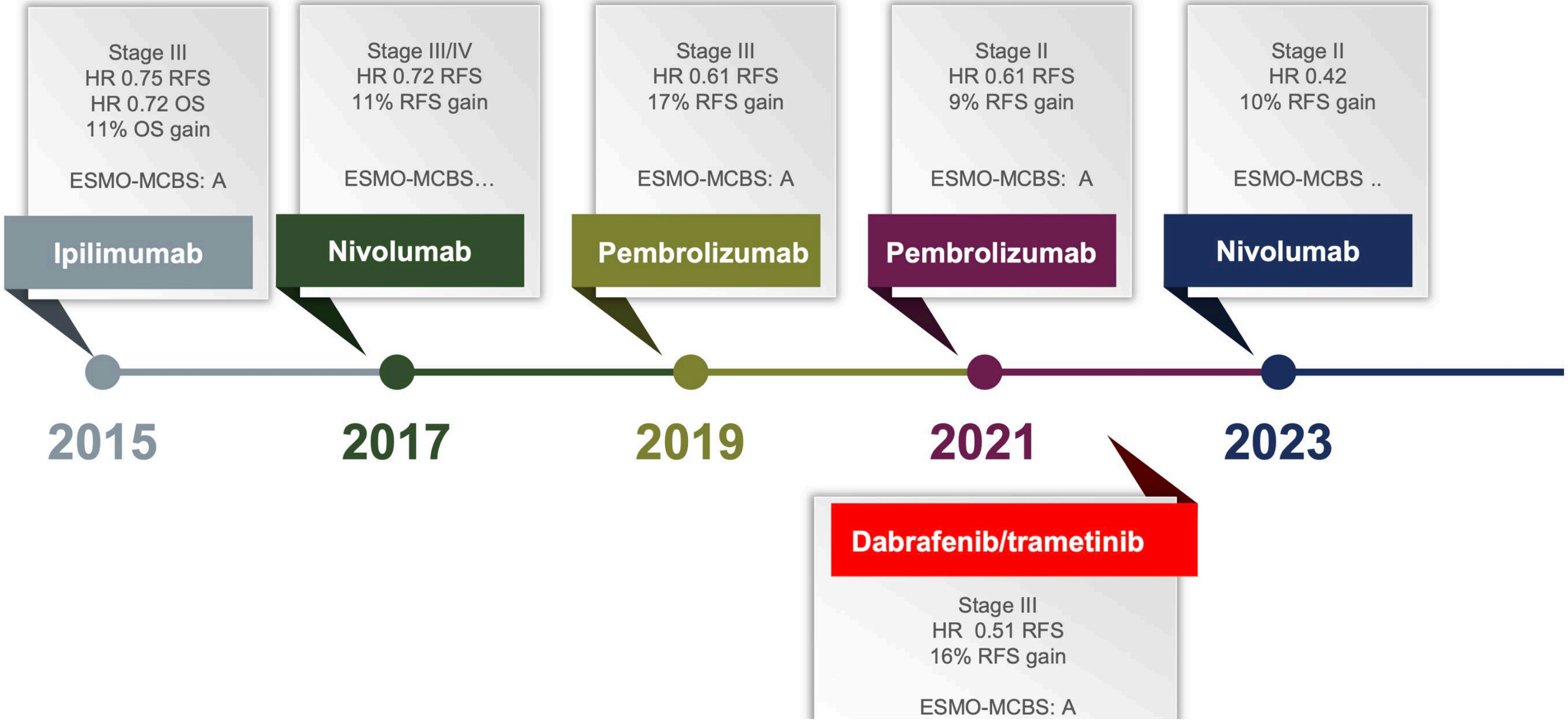
FDG PET





Adjuvant therapy

Adjuvant therapy for resectable melanoma



Eggermont et al NEJM 2016, Larkin CCR 2023, Eggermont et al. NEJM Evidence 2022, Luke et al Lancet 2022, Dummer et al NEJM 2022, Kirkwood Nature Medicine 2023

Adjuvant therapy for stage III melanoma

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

ABSTRACT

BACKGROUND

Combination therapy with the BRAF inhibitor dabrafenib plus the MEK inhibito trametinib improved survival in patients with advanced melanoma with *BRAF* V600 mutations. We sought to determine whether adjuvant dabrafenib plus trametinib would improve outcomes in patients with resected, stage III melanoma with *BRAF* V600 mutations.

METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 870 patients with completely resected, stage III melanoma with *BRAF* V600E or V600K mutations to receive oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily (combination therapy, 438 patients) or two matched placebo tablets (432 patients) for 12 months. The primary end point was relapse-free survival. Secondary end points included overall survival, distant metastasis–free survival, freedom from relapse, and safety.

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*

ABSTRACT

BACKGROUND

Nivolumab and ipilimumab are immune checkpoint inhibitors that have been approved for the treatment of advanced melanoma. In the United States, ipilimumab has also been approved as adjuvant therapy for melanoma on the basis of recurrence-free and overall survival rates that were higher than those with placebo in a phase 3 trial. We wanted to determine the efficacy of nivolumab versus ipilimumab for adjuvant therapy in patients with resected advanced melanoma.

METHODS

In this randomized, double-blind, phase 3 trial, we randomly assigned 906 patients (≥15 years of age) who were undergoing complete resection of stage IIIB, IIIC, or IV melanoma to receive an intravenous infusion of either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks (453 patients) or ipilimumab at a dose of 10 mg per kilogram every 3 weeks for four doses and then every 12 weeks (453 patients). The patients were treated for a period of up to 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The primary end point was recurrence-free survival in the intention-to-treat population.

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.

ABSTRACT

BACKGROUND

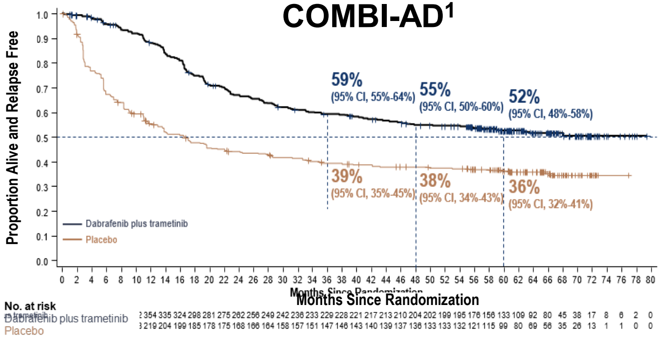
The programmed death 1 (PD-1) inhibitor pembrolizumab has been found to prolong progression-free and overall survival among patients with advanced melanoma. We conducted a phase 3 double-blind trial to evaluate pembrolizumab as adjuvant therapy in patients with resected, high-risk stage III melanoma.

METHODS

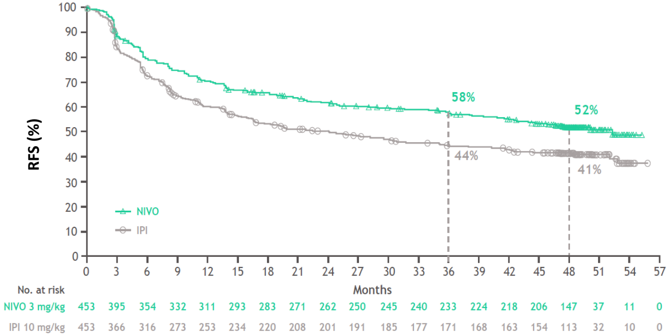
Patients with completely resected stage III melanoma were randomly assigned (with stratification according to cancer stage and geographic region) to receive 200 mg of pembrolizumab (514 patients) or placebo (505 patients) intravenously every 3 weeks for a total of 18 doses (approximately 1 year) or until disease recurrence or unacceptable toxic effects occurred. Recurrence-free survival in the overall intention-to-treat population and in the subgroup of patients with cancer that was positive for the PD-1 ligand (PD-L1) were the primary end points. Safety was also evaluated.

Key RFS data from pivotal adjuvant melanoma trials

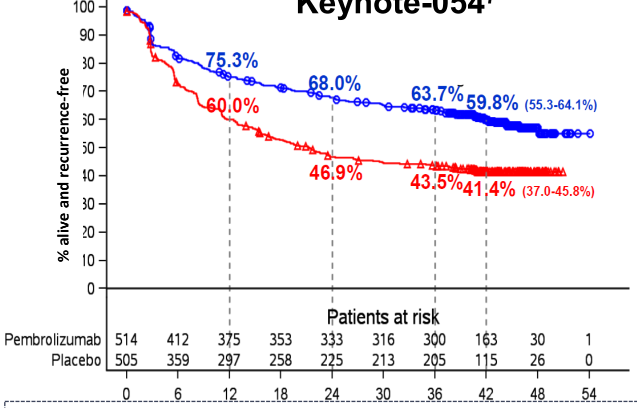
COMBI-AD[1]



Checkmate-238[8]



Keynote-054[7]



RFS	COMBI-AD [1,2]		KN-054 [3,4]		CM-238 [5,6,8]	
	DT	PCB	Pembro	PCB	Nivo	Ipi
1-yr	88%	56%	75%	60%	70%	61%
2-yr	67%	44%	68%	47%	62%	51%
3-yr	59%	39%	64%	44%	58%	44%
4-yr	55%	38%	-	-	52%	41%
5-yr	52%	36%	-	-	-	-
HR (95%CI)	0.51 (0.42-0.61)		0.56 (0.47-0.68)		0.71 (0.60-0.86)*	

*In an indirect comparison of Nivo vs Placebo, the HR value was determined to be 0.53 (HemstockM et al., EurJ Cancer 2020)

Note: Cross trial comparisons should not be made, curves from articles shown for illustrative purposes of discussion only

1. Hauschild A et al. Long-term benefit of adjuvant dabrafenib + trametinib (D+T) in patients (pts) with resected stage III BRAF V600-mutant melanoma: five year analysis of COMBI-AD. Presented at ASCO 2020. 2. Hauschild A et al. Journal of Clinical Oncology 2018. 36 (35): 3441-3449. 3. Eggermont AM et al. Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: new recurrence-free survival results from the EORTC 1325-MG/Keynote 054 double-blinded phase III trial at three-year median follow up. Presented at ASCO 2020. 4. Eggermont A, et al. N Engl J Med. 2018 378(19):1789-1801. 5. ESMO 2019: 3-Year Results From CheckMate 238: Adjuvant Nivolumab vs Ipilimumab in Advanced Melanoma. https://www.ascopost.com/news/october-2019/3-year-results-from-checkmate-238-adjuvant-nivolumab-vs-ipilimumab-in-advanced-melanoma/. 6. Weber J *et al. N Engl J Med*. 2017; 377(19):1824-1835. 7. Eggermont et al. Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: final results regarding distant metastasis-free survival results from the EORCT 1325-MG/Keynote-054 double-blinded phase 3 trial. Presented at ESMO 2020. 8. Weber J et al. Adjuvant nivolumab vs ipilimumab in resected stage III/IV melanoma: 4-year recurrence-free and overall survival results from CheckMate 238. Presented at ESMO 2020. Presentation 10760.

Stage IIB & IIC (T3b-T4)

Stage IIB & IIC

Stage IIB (T3b)
(Breslow 2,5 mm, ulcerated)

Stage IIB (T4a)
(Breslow 4,5 mm, non-ulcerated)

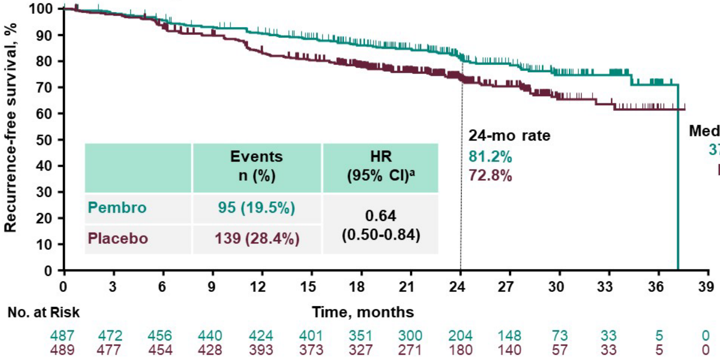
Stage IIC (T4b)
(Breslow 6 mm, ulcerated)

Keynote 716

Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial

Georgina V Long, Jason J Luke*, Muhammad A Khattak, Luis de la Cruz Merino, Michele Del Vecchio, Piotr Rutkowski, Francesco Spagnolo, Jacek Mackiewicz, Vanna Chiarion-Sileni, John M Kirkwood, Caroline Robert, Jean-Jacques Grob, Federica de Galitiis, Dirk Schadendorf, Matteo S Carlino, Peter Mohr, Reinhard Dummer, Jeffrey E Gershenwald, Charles H Yoon, Xi Lawrence Wu, Mizuho Fukunaga-Kalabis, Clemens Krepler, Alexander M M Eggermont, Paolo A Ascierto, on behalf of the KEYNOTE-716 Investigators†*

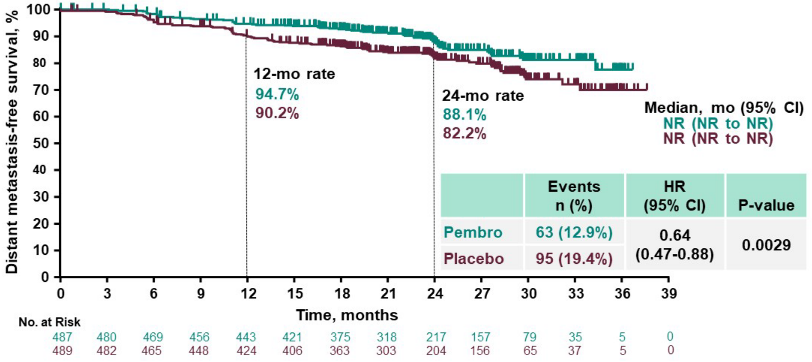
RFS With Longer Follow-up at IA3[1]



	Events n (%)	HR (95% CI)[a]
Pembro	95 (19.5%)	0.64 (0.50-0.84)
Placebo	139 (28.4%)	

Median follow-up of 27.4 months (range, 14.0-39.4) at IA3. Database cutoff: January 4, 2022.
[a]HR for RFS with pembrolizumab versus placebo was 0.65 (95% CI, 0.46-0.92; P = 0.0066) at IA1 and 0.61 (95% CI, 0.45-0.82) at IA2.[2]
1. Long GV et al. Distant Metastasis-free Survival With Pembrolizumab Versus Placebo as Adjuvant Therapy in Stage IIB or IIC Melanoma: The Phase 3 KEYNOTE-716 Study. 2022 American Society of Clinical Oncology Annual Meeting. Abstract LBA9500. Presented June 5, 2022. 2. Luke JJ et al. *Lancet.* 2022;399:1718-1729.

DMFS: Secondary End point[1]



	Events n (%)	HR (95% CI)	P-value
Pembro	63 (12.9%)	0.64 (0.47-0.88)	0.0029
Placebo	95 (19.4%)		

Median follow-up of 27.4 months (range, 14.0-39.4). Database cutoff: January 4, 2022.
1. Long GV et al. Distant Metastasis-free Survival With Pembrolizumab Versus Placebo as Adjuvant Therapy in Stage IIB or IIC Melanoma: The Phase 3 KEYNOTE-716 Study. 2022 American Society of Clinical Oncology Annual Meeting. Abstract LBA9500. Presented June 5, 2022.

Clinical Trial: mRNA vaccine + pembrolizumab

MADRID 2023 ESMO congress

mRNA-4157 (V940) individualized neoantigen therapy + pembrolizumab versus pembrolizumab in high-risk resected melanoma: clinical efficacy and correlates of response

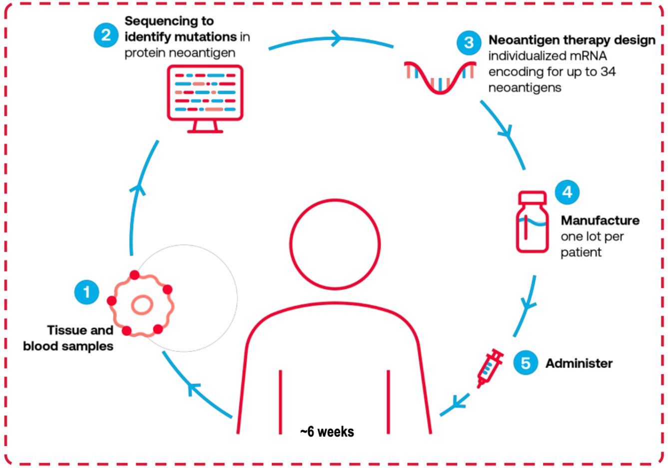
Jeffrey S. Weber,[1] Adnan Khattak,[2] Matteo S. Carlino,[3] Ryan J. Sullivan,[4] Jason J. Luke,[5] Tarek Meniawy,[6] Matthew H. Taylor,[7] George Ansstas,[8] Kevin B. Kim,[9] Meredith McKean,[10] Mark B. Faries,[11] Thuy Tran,[12] C. Lance Cowey,[13] Andrew L. Pecora,[14] Theresa M. Medina,[15] Victoria Atkinson,[16] Geoffrey T. Gibney,[17] Elizabeth I. Buchbinder,[18] Robert S. Meehan,[19] Moderna Author Group,[19] Georgina V. Long[20]

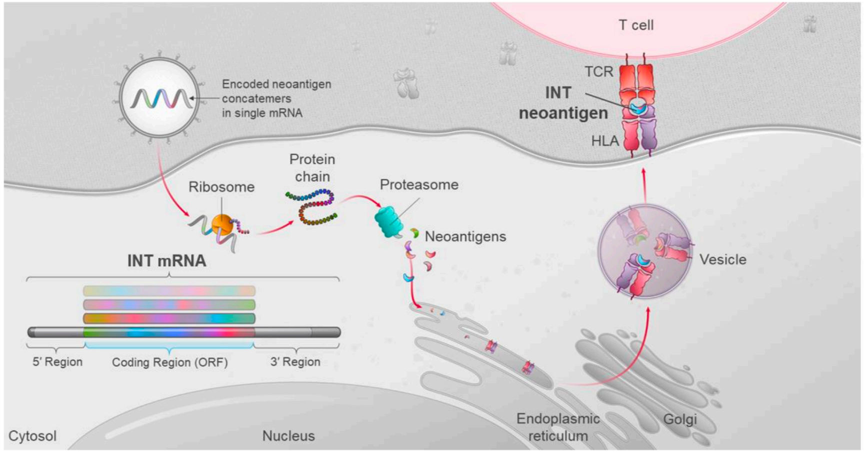
[1]Department of Medicine, Perlmutter Cancer Center, Laura and Isaac Perlmutter Cancer Center, New York, NY, USA; [2]Medical Oncology, Hollywood Private Hospital & Edith Cowan University, Perth, WA, Australia; [3]Medical Oncology Department, Crown Princess Mary Cancer Centre Westmead, Westmead, NSW, Australia; [4]Cancer Center, Massachusetts General Hospital, Boston, MA, USA; [5]Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA; [6]Oncology, Saint John of God Subiaco Hospital, Subiaco, WA, Australia; [7]Medical Oncology, Providence Cancer Institute, Portland, OR, USA; [8]Oncology, Siteman Cancer Center, Washington University School of Medicine in St. Louis, St. Louis, MO, USA; [9]Oncology, California Pacific Medical Center Research Institute, San Francisco, CA, USA; [10]Drug Development Unit, Sarah Cannon Research Institute, Nashville, TN, USA; [11]Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [12]Oncology, Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA; [13]Oncology, Texas Oncology – Baylor Sammons Cancer Center, Dallas, TX, USA; [14]Oncology, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [15]Cutaneous Oncology Department, University of Colorado Cancer Center Anschutz Cancer Pavilion, Aurora, CO, USA; [16]Division of Cancer Services, Princess Alexandra Hospital – Metro South Health, Woolloongabba, QLD, Australia; [17]Medical Oncology, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; [18]Medical Oncology Department, Dana-Farber Cancer Institute, Boston, MA, USA; [19]Oncology, Moderna, Inc. Global Headquarters, Cambridge, MA, USA; [20]Medical Oncology, Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

The Moderna Author Group: Manju Morrissey MD, Sr. Director, Global Safety Physician, Oncology; Vasudha Sehgal PhD, Associate Director, Biostatistics; Peijie Hou PhD, Associate Director, Biostatistics; Lili Zhu PhD, Director, Biostatistics; Praveen Aanur MD, VP, Therapeutic Area Head – Oncology; Michelle Brown MD PhD, VP, Portfolio Leadership, INT; Igor Feldman PhD, Executive Director, Translational Bioinformatics

mRNA-4157 (V940): An individualized neoantigen therapy (INT) mechanism of action

- mRNA-4157 (V940) is a **customizable,** individualized neoantigen therapy encoding up to 34 neoantigens[1,2]
- Therapies targeting neoantigens can increase endogenous **neoantigen T-cell responses and induce epitope spreading** to novel antigens with the ability **to drive antitumor responses** and **maintain memory** with cytolytic properties, potentially **producing long-term disease control** for patients[3-7]





HLA, human leukocyte antigen; INT, individualized neoantigen therapy; mRNA, messenger RNA; ORF, open-reading frame; TCR, T-cell receptor.

1. Burris HA, et al. *J Clin Oncol* 2019;37(suppl 15). Abstract 2523. 2. Zhong S, et al. *Cancer Res* 80(suppl 16). Abstract 6539. 3. Wirth TC, Kühnel F. *Front Immunol* 2017;8:1848. 4. Ott PA, et al. *Nature* 2017;547:217–221. 5. Hu Z, et al. *Nat Med* 2021;27:515–525. 6. Ott PA, et al. *Cell* 2020;183:347-362. 7. Palmer CD, et al. *Nat Med* 2022;28:1619–1629.
Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14–19, 2023; Orlando, FL, USA. Oral presentation CT001. Khattak A, et al. Presented at the American Society of Clinical Oncology® (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA. LBA9503.

mRNA-4157-P201/KEYNOTE-942 (NCT03897881) study design

Randomized, phase 2, open-label study in adjuvant resected melanoma patients at high risk of recurrence

Key eligibility criteria

- Resected stage IIIB,[a] IIIC, IIID, or IV cutaneous melanoma
- Complete surgical resection within 13 weeks prior to first pembrolizumab dose
- Disease free at study entry
- ECOG PS score 0–1
- Tissue available for NGS

2:1 randomization

Stratified by disease stage[b]

Combination treatment arm: mRNA-4157 (V940) + pembrolizumab
Up to 1 year of pembrolizumab treatment
mRNA-4157 (V940) 1 mg IM Q3W for up to 9 doses +
pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 107)

Control treatment arm: pembrolizumab monotherapy
Up to 1 year of pembrolizumab treatment
pembrolizumab 200 mg IV Q3W for up to 18 cycles
(n = 50)

Primary endpoint: RFS[c,d]

Secondary endpoints:
DMFS,[e]
safety, tolerability

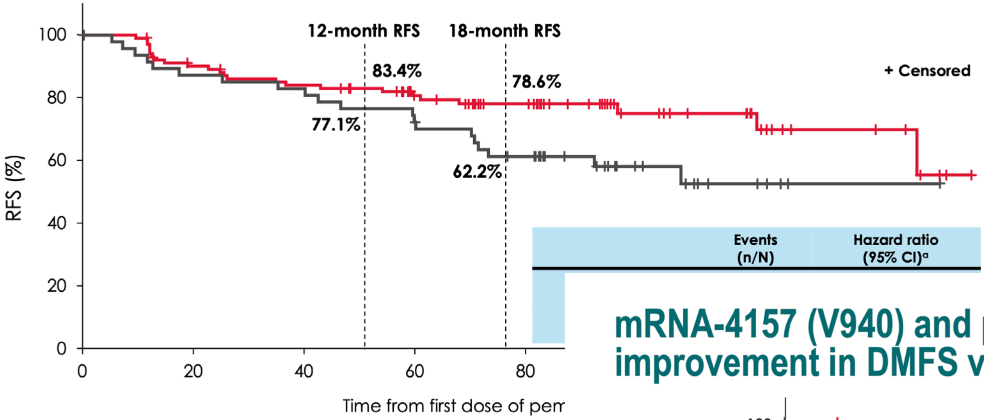
Exploratory endpoints:
Potential predictive biomarkers
(ctDNA, BRAF)

Follow-up:
up to 3 years following the first dose of pembrolizumab

Designed with 80% power to detect a HR of 0.5 with ≥40 RFS events (with a 1-sided alpha of 0.1)
DMFS analysis was prespecified for testing following positive RFS in the ITT population[f]
Median follow-up[g]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

[a]Patients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent. [b]According to the 8th edition of the American Joint Committee on Cancer Staging Manual. [c]The primary endpoint was investigator-assessed RFS (defined as the time from first dose of pembrolizumab until the date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the intent-to-treat population. [d]The primary analysis for RFS was specified to occur after all patients completed ≥12 months on study and ≥40 RFS events were observed. Descriptive analysis was specified to occur when ≥51 RFS events were observed. [e]Investigator-assessed DMFS was defined as the time from first dose of pembrolizumab until the date of first distant recurrence or death from any cause. [f]The stratified log-rank test was used for comparison. [g]Time of database cutoff was November 14, 2022.
BRAF, B-Raf proto-oncogene; ctDNA, circulating tumor DNA; DMFS, distant metastasis-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IM, intramuscular; ITT, intent to treat; IV, intravenous; mRNA, messenger RNA; NGS, next generation sequencing; Q3W, every 3 weeks; RFS, recurrence-free survival. Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14–19, 2023; Orlando, FL, USA. Oral presentation CT001. Khattak A, et al. Presented at the American Society of Clinical Oncology® (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA. LBA9503.

mRNA-4157 (V940) and pembrolizumab demonstrated an improvement in RFS versus pembrolizumab monotherapy



	Events (n/N)	Hazard ratio (95% CI)[a]

Number at risk					
mRNA-4157 + pembrolizumab	107	92	85	73	49
pembrolizumab	50	42	40	37	28

ITT population.
[a]The HR and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox
for randomization. The p-value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or
CI, confidence interval; ITT, intent to treat; mRNA, messenger RNA; RFS, recurrence-free survival.
Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14–1

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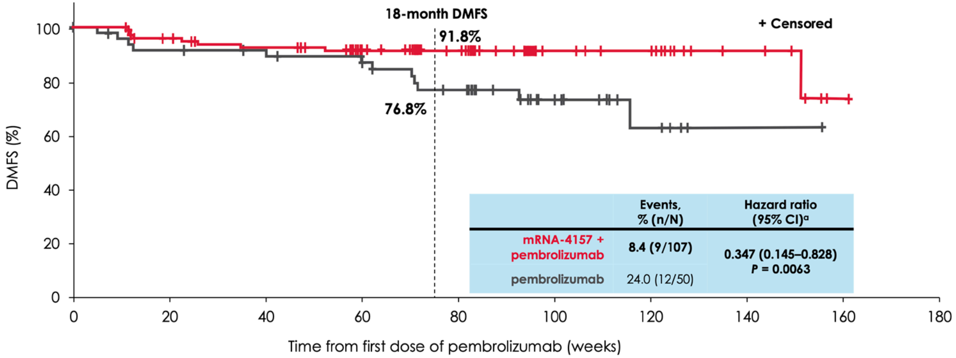
mRNA-4157 (V940) and pembrolizumab demonstrated an improvement in DMFS versus pembrolizumab monotherapy



	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 + pembrolizumab	8.4 (9/107)	0.347 (0.145–0.828) P = 0.0063
pembrolizumab	24.0 (12/50)	

Number at risk									
mRNA-4157 + pembrolizumab	107	94	86	73	49	23	20	8	1
pembrolizumab	50	43	41	39	29	14	6	1	0

ITT population.
[a]The HR and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID versus stage IV) used for randomization. The p-value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID versus stage IV) used for randomization.
CI, confidence interval; DMFS, distant metastasis-free survival; ITT, intent to treat; mRNA, messenger RNA.
Khattak A, et al. Presented at the American Society of Clinical Oncology® (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA. LBA9503.

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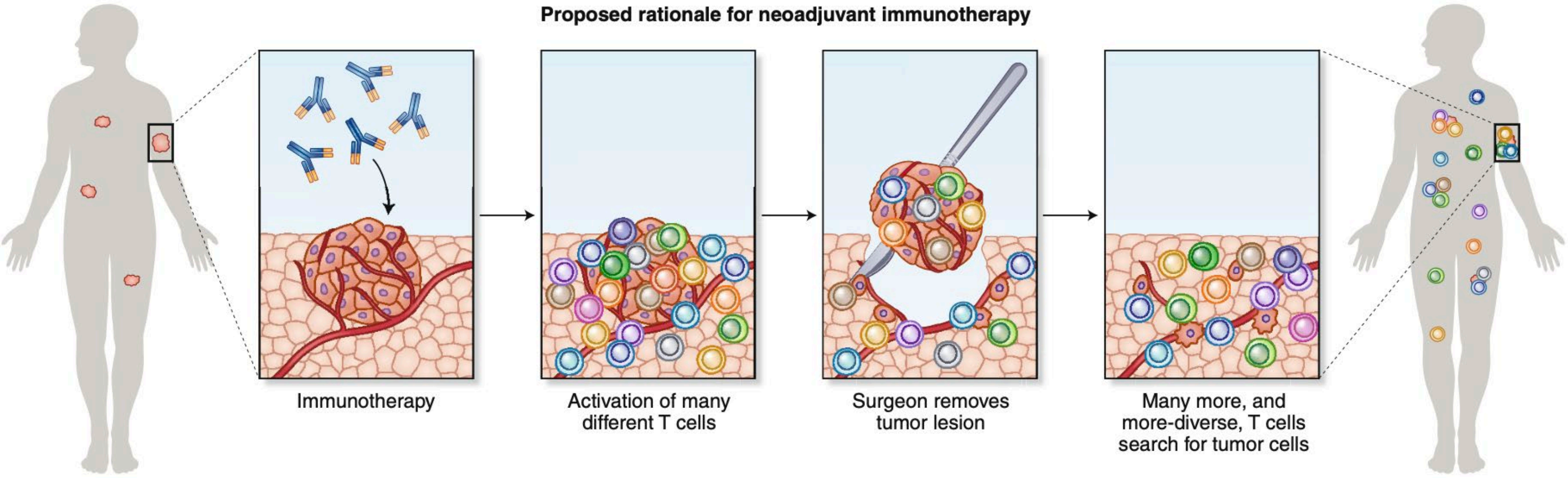
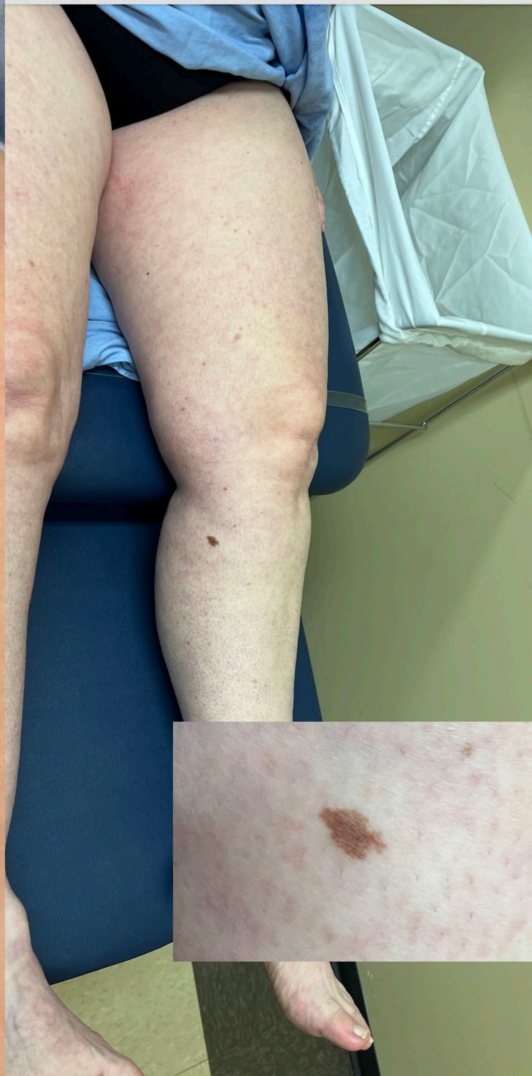
Neoadjuvant: the Future is Now…



Breakthrough of the Year

ORIGINAL ARTICLE

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

S.P. Patel, M. Othus, Y. Chen, G.P. Wright, Jr., K.J. Yost, J.R. Hyngstrom, S. Hu-Lieskovan, C.D. Lao, L.A. Fecher, T.-G. Truong, J.L. Eisenstein, S. Chandra, J.A. Sosman, K.L. Kendra, R.C. Wu, C.E. Devoe, G.B. Deutsch, A. Hegde, M. Khalil, A. Mangla, A.M. Reese, M.I. Ross, A.S. Poklepovic, G.Q. Phan, A.A. Onitilo, D.G. Yasar, B.C. Powers, G.C. Doolittle, G.K. In, N. Kokot, G.T. Gibney, M.B. Atkins, M. Shaheen, J.A. Warneke, A. Ikeguchi, J.E. Najera, B. Chmielowski, J.G. Crompton, J.D. Floyd, E. Hsueh, K.A. Margolin, W.A. Chow, K.F. Grossmann, E. Dietrich, V.G. Prieto, M.C. Lowe, E.I. Buchbinder, J.M. Kirkwood, L. Korde, J. Moon, E. Sharon, V.K. Sondak, and A. Ribas

ABSTRACT

BACKGROUND

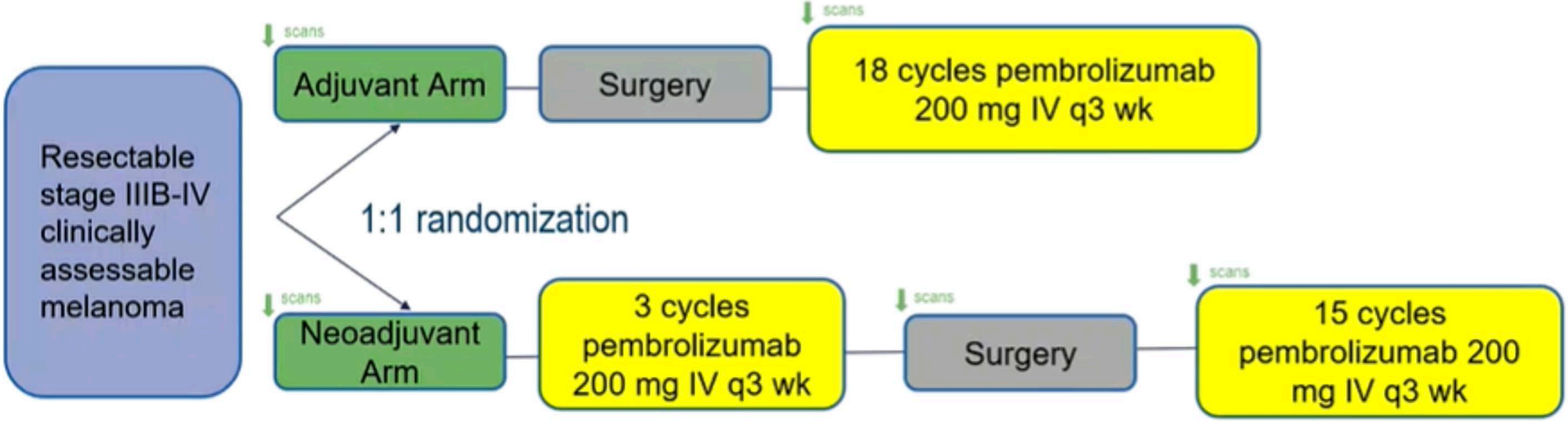
Whether pembrolizumab given both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy), as compared with pembrolizumab given as adjuvant therapy alone, would increase event-free survival among patients with resectable stage III or IV melanoma is unknown.

METHODS

In a phase 2 trial, we randomly assigned patients with clinically detectable, measurable stage IIIB to IVC melanoma that was amenable to surgical resection to three doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (neoadjuvant–adjuvant group) or to surgery followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year or until disease recurred or unacceptable toxic effects developed (adjuvant-only group). The primary end point was event-free survival in the inten-

S1801 Study Schema

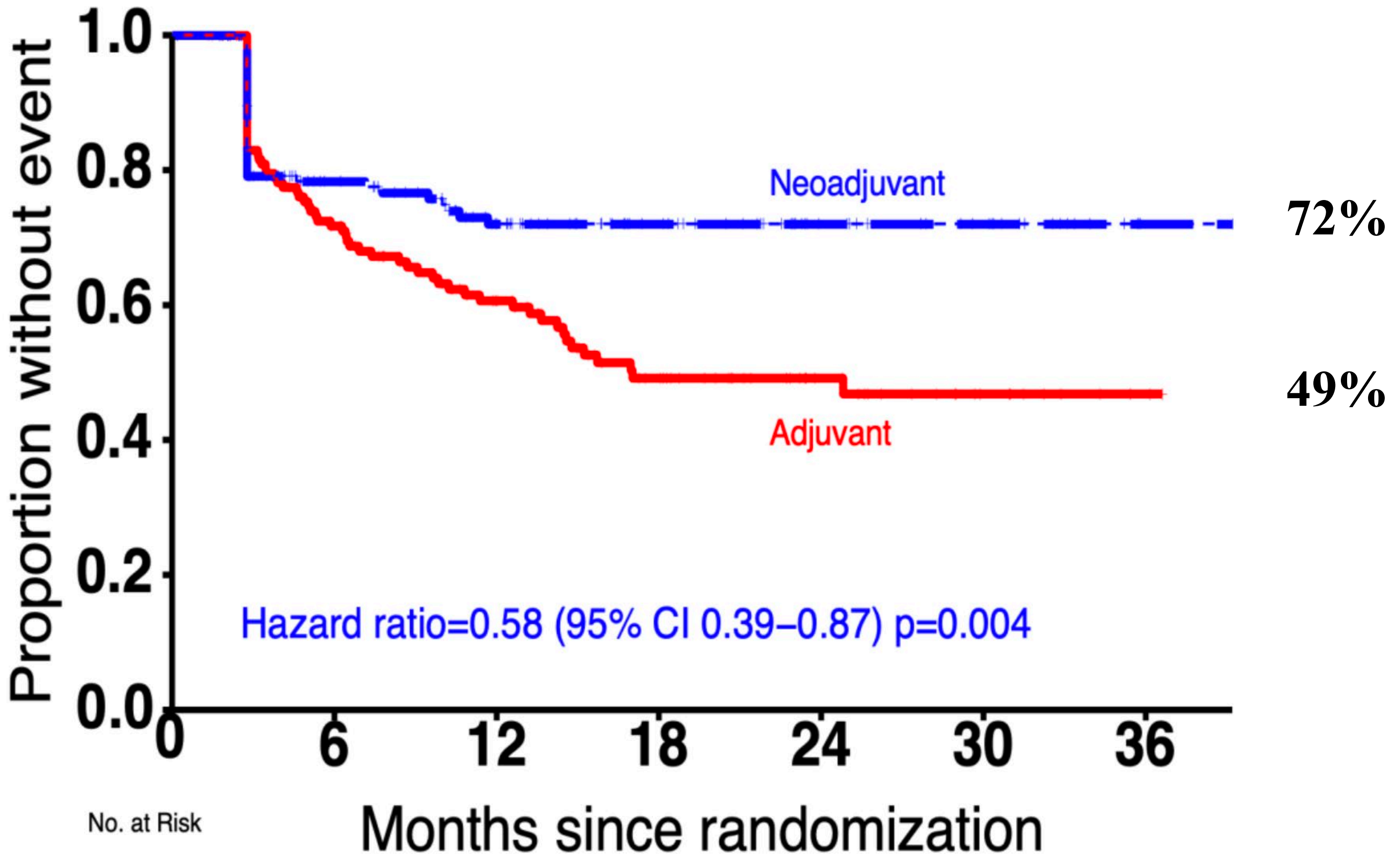
Primary endpoint: Event-free survival



⬇ radiographic assessment (scans)

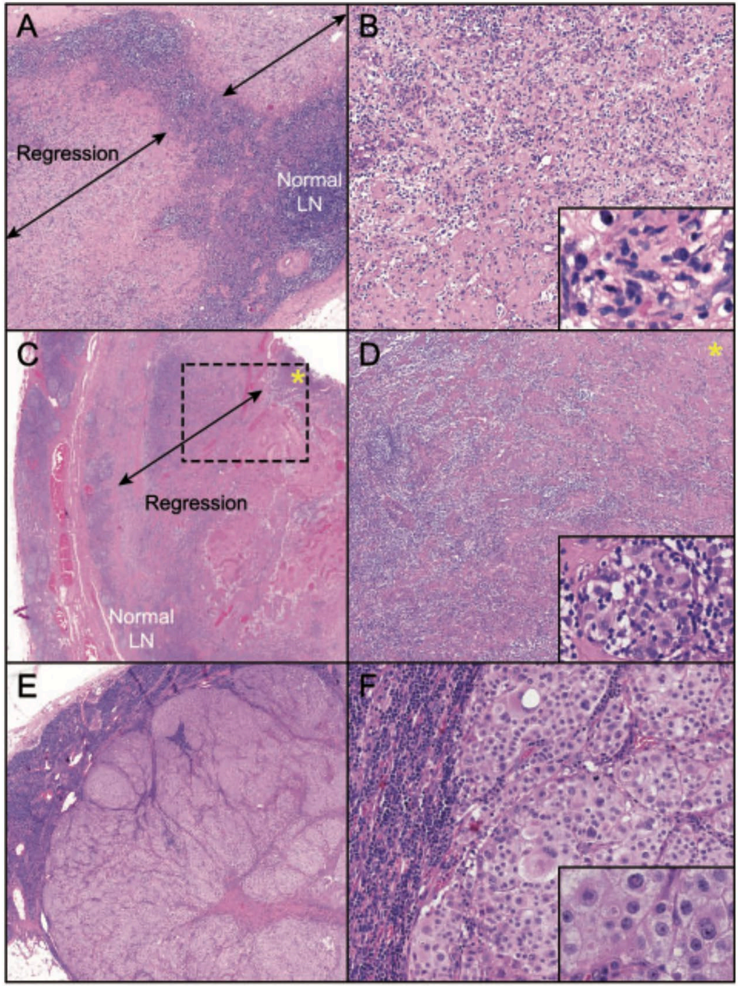
Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy



No. at Risk

159	98	67	40	22	10	2	Adjuvant
154	96	69	46	25	17	1	Neoadjuvant



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 1861–1868, 2018
doi:10.1093/annonc/mdy226
Published online 25 June 2018

ORIGINAL ARTICLE

Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

- **Complete response**

- **Partial response**

- **No response**

		Viable cells
Complete response	pCR	0%
Near complete response	near-pCR	1 - 10%
Partial response	pPR	11 - 50%
No response	pNR	> 50%

MPR

S1801 Pathologic Response and Recurrence-Free Survival (RFS)

Pathologic response by blinded independent central review in submitted specimens

	n (%)	12-month RFS (95% CI)	24-month RFS (95% CI)
pCR	40 (38%)	92% (84-100)	89% (80-100)
pnCR	16 (15%)	87% (71-100)	87% (71-100)
pPR	27 (26%)	93% (83-100)	88% (77-100)
pNR	22 (21%)	76% (60-97)	70% (53-94)
MPR	56 (53%)	91% (83-99)	88% (80-98)
No MPR	49 (47%)	85% (75-96)	80% (70-93)

Pathological response and Survival

nature medicine

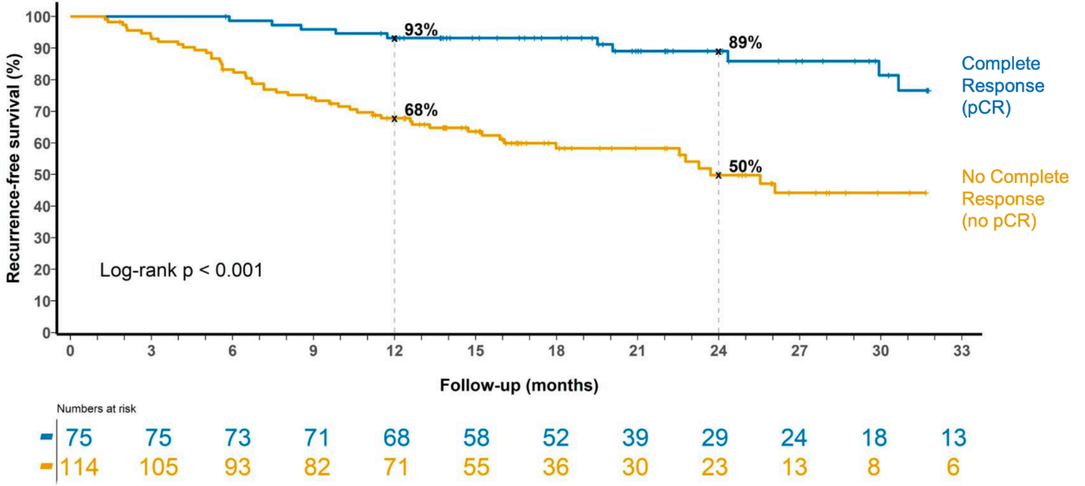
ARTICLES

https://doi.org/10.1038/s41591-020-01188-

Check for upda

Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC)

Alexander M. Menzies[1,2,3,12], Rodabe N. Amaria[4,12], Elisa A. Rozeman[5,12], Alexander C. Huang[6,7,12], Michael T. Tetzlaff[4,12], Bart A. van de Wiel[5,12], Serigne Lo[1,2,12], Ahmad A. Tarhini[8], Elizabeth M. Burto, Thomas E. Pennington[1,2,9], Robyn P. M. Saw[1,2,9], Xiaowei Xu[6], Giorgos C. Karakousis[6], Paolo A. Ascierto[10], Andrew J. Spillane[1,2,3], Alexander C. J. van Akkooi[5], Michael A. Davies[4,13], Tara C. Mitchell[6,13], Hussein A. Tawbi[4,13], Richard A. Scolyer[1,2,11,13], Jennifer A. Wargo[4,13], Christian U. Blank[5,13] and Georgina V. Long[1,2,3,13]



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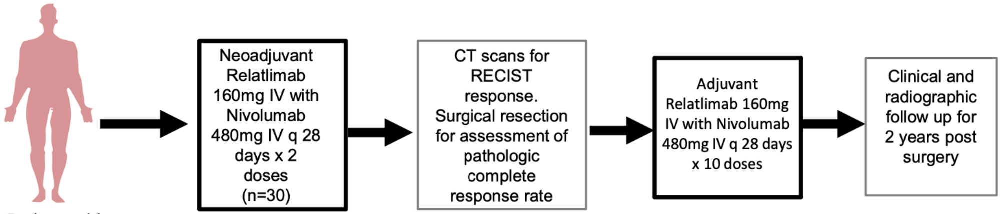
Alexander Menzies

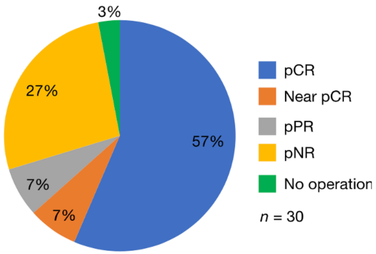
Menzies Nat Med 2021

Clinical Trials: neoadjuvant with double immunotherapy

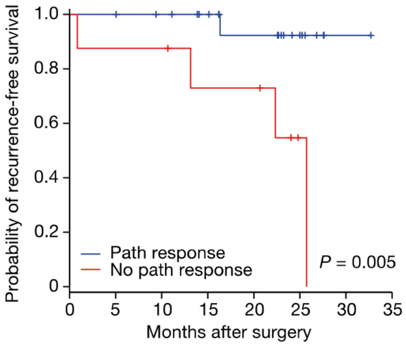
PD1 + LAG3



Patients with resectable stage IIIB/IIIC melanoma, oligometastatic stage IV



pRR 77%, pCR 59%

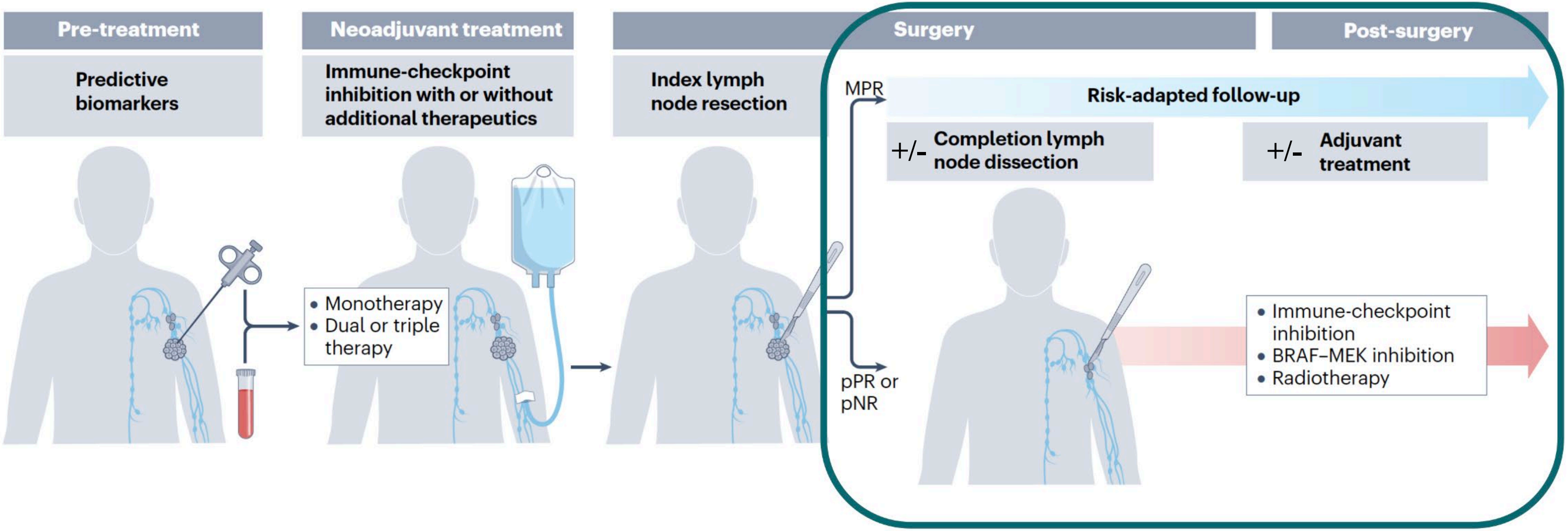


little toxicity

Amaria Nature 2022

Clinical Trials: neoadjuvant with less surgery

Personalization of neoadjuvant immunotherapy



Lukas et et al., Nat Rev Clin Oncol 2023

Advanced cSCC: Cemiplimab Neoadjuvant

MADRID 2023 ESMO congress

FPN 1088MO

A Phase 2 Study of Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous Cell Carcinoma (CSCC): One-Year Follow-up

Neil D Gross,[1] David M Miller,[2] Nikhil I Khushalani,[3] Vasu Divi,[4] Emily S Ruiz,[5] Evan J Lipson,[6] Friedegund Meier,[7] Yungpo Bernard Su,[8] Paul L Swiecicki,[9] Jennifer Atlas,[10] Jessica L Geiger,[11] Axel Hauschild,[12] Jennifer H Choe,[13]* Brett GM Hughes,[14] Dirk Schadendorf,[15] Vishal A Patel,[16] Jade Homsi,[17] Janis M Taube,[18] Annette M Lim,[19] Renata Ferrarotto,[1] Suk-Young Yoo,[20] Melissa Mathias,[20] Hyunsil Han,[20] Frank Seebach,[20] Israel Lowy,[20] Matthew G Fury,[20] Danny Rischin[19]

[1]University of Texas MD Anderson Cancer Centre, Houston, TX, USA; [2]Massachusetts General Hospital, Boston, MA, USA; [3]Moffitt Cancer Centre, Tampa, FL, USA; [4]Stanford University School of Medicine, Stanford, CA, USA; [5]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [6]Bloomberg-Kimmel Institute for Cancer Immunotherapy and Sidney Kimmel Comprehensive Cancer Centre at Johns Hopkins, Baltimore, MD, USA; [7]University Hospital Carl Gustav Carus, Technische Universität Dresden and Skin Cancer Center at the University Cancer Centre Dresden and National Center for Tumor Diseases, Dresden, Germany; [8]Head and Neck Medical Oncology, Nebraska Cancer Specialists, Omaha, NE, USA; [9]Rogel Comprehensive Cancer Centre, University of Michigan, Ann Arbor, MI, USA; [10]Levine Cancer Institute, Carolinas HealthCare System/Atrium Health, Charlotte, NC, USA; [11]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [12]Schleswig-Holstein University Hospital, Kiel, Germany; [13]Duke Cancer Institute, Durham, NC, USA; [14]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, Queensland, Australia; [15]University Hospital of Essen and German Cancer Consortium, Partner Site Essen, Essen, Germany; [16]George Washington University School of Medicine and Health Sciences, Washington, DC, USA; [17]Harold C Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA; [18]Johns Hopkins Hospital, Baltimore, MD, USA; [19]Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Victoria, Australia; [20]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

**Currently affiliated with Vanderbilt-Ingram Cancer Center, Nashville, TN, USA.*

Neil D. Gross, M.D., F.A.C.S.

NCT04154943

Background

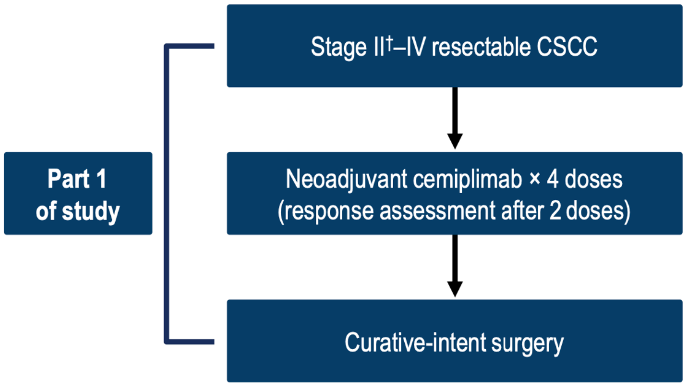
Phase II, non-randomised, multicentre trial

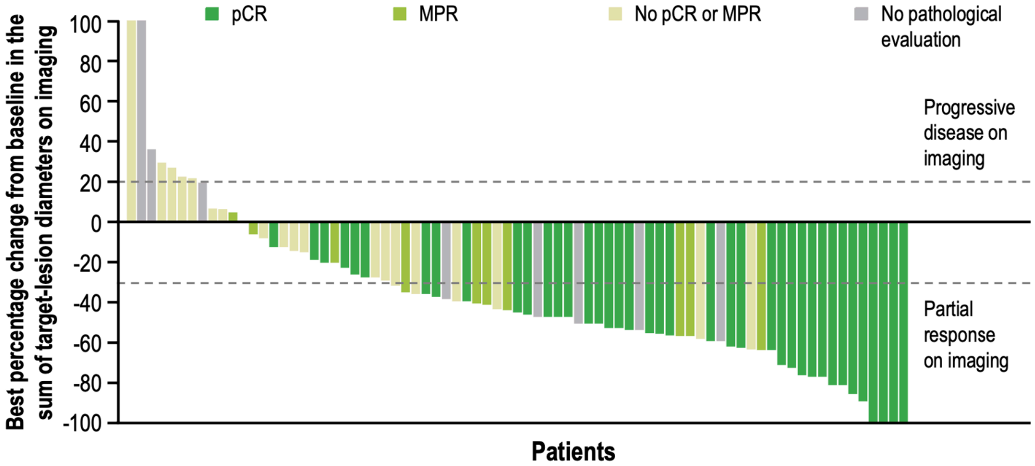
Primary endpoint

- **Pathologic complete response** (pCR, 0% residual viable tumour) rate per central review = **51%**[1]

Secondary endpoint

- **Major pathologic response** (MPR, >0% and ≤ 10% residual viable tumour) rate per central review = **13%**[1]





[1]Gross ND, et al. *N Engl J Med*. 2022;387:1557-1568

†Stage II required to have primary tumour ≥3 cm at the longest diameter.
CSCC, cutaneous squamous cell carcinoma.

NCT04154943

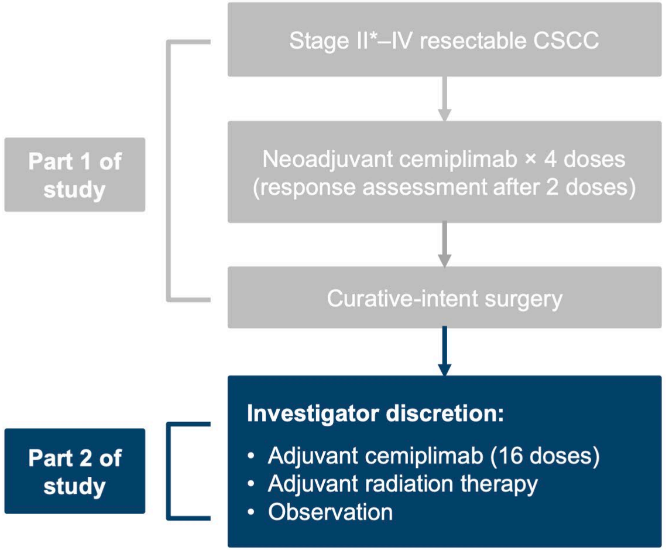
Methods

Phase II, non-randomised, multicentre trial

<u>**Secondary endpoints (new)**</u>
- **Event-free survival**
- **Disease-free survival**
- **Overall survival**

<u>**Post-hoc analysis (new)**</u>

Pathologic partial response
(pPR, >10 and ≤50% residual viable tumour)



Data cut-off: 1 December 2022.
[†]Stage II required to have primary tumour ≥3 cm at the longest diameter.
CSCC, cutaneous squamous cell carcinoma.

Post-surgical management

Adjuvant treatment,[†] n (%)	Total patients enrolled (N=79)			
	Pathologic response by central pathology review (n=70 patients had surgery)			
	pCR (n=40)	MPR (n=10)	pPR (n=7)	Non-responder (n=13)
Cemiplimab	12 (30)	1 (10)	2 (29)	1 (8)
Radiotherapy	1 (2)	5 (50)	3 (43)	8 (62)
Observation only	24 (60)	3 (30)	2 (29)	3 (23)
Not reported	3[‡] (8)	1[§] (10)	0	1[‖] (8)

[†]Investigators decided post-surgical management for individual patients based on local pathology review.

[‡]Lost to follow-up (n=1), death to to COVID pneumonia (n=1), death due to multiple post-surgical adverse events (n=1).
[§]Withdrawal of consent (n=1).
[‖]Lost to follow-up (n=1).

MPR, major pathologic response (>0 and ≤ 10% RVT); pCR, pathologic complete response (0% RVT); pPR, pathologic partial response (>10 and ≤ 50% RVT); RVT, residual viable tumour.

Results

	All patients (N=79)	pCR (n=40)	MPR (n=10)	pPR (n=7)	No surgery or non-responder† (n=22)
Median EFS (95% CI)	NR (NE–NE)	NR (NE–NE)	NR (8.3–NE)	NR (NE–NE)	25.1 (8.1–NE)
Estimated 12-month EFS (95% CI)	**89.0 (79.1−94.3)**	**94.9 (81.0−98.7)**	**88.9 (43.3−98.4)**	**100.0 (NE–NE)**	**72.0 (43.8−87.7)**
Events, n (%)	11 (13.9)	3 (7.5)	1 (10.0)	0	7 (31.8)
Progressive disease that precludes surgery	2 (2.5)	0	0	0	2 (9.1)
Disease recurrence	3 (3.8)	0	1 (10.0)	0	2 (9.1)
Death	6 (7.6)	3 (7.5)‡	0	0	3 (13.6)

12-month OS (all patients) = 92% (95% CI: 83–96%)

†9 patients did not have surgery and 13 surgical patients were non-responders.
‡One death due to COVID-19, one death due to complications of cardiac valve repair surgery in year 2, and one death approximately 3 months after surgery in a patient who had multiple post-operative adverse events including myocardial infarction.
EFS, event-free survival; MPR, major pathologic response (>0 and ≤10% RVT); NE, not estimable; NR, not reached; OS, overall survival; pCR, pathologic complete response (0% RVT); pPR, pathologic partial response (>10 and ≤50% RVT); RVT, residual viable tumour.

Advanced BCC after hedgehog inhibitor: Cemiplimab

Enormous BCC treated with Vismodegib

Courtesy of Dr Marie-Michèle Blouin

Resistance to Vismodegib

Courtesy of Dr Marie-Michèle Blouin

Phase 2 study of cemiplimab in patients with locally advanced basal cell carcinoma after hedgehog inhibitor therapy: Longer-term follow-up

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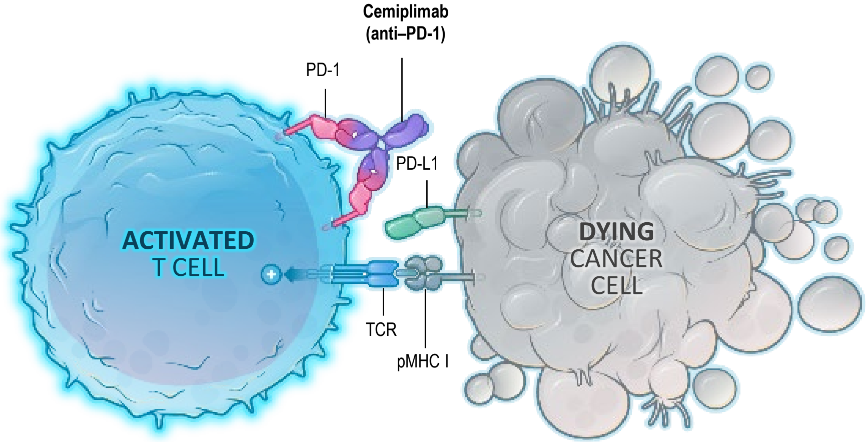
Presented at the 18th European Association of Dermato-Oncology (EADO) Congress 2022, April 21–23, 2022.

Cemiplimab and locally advanced BCC



Primary analysis outcome (17 Feb 2020)[2]	laBCC (N=84)
Best overall response	
Objective response rate, % (95% CI)	31 (21–42)
Complete response, n (%)	5 (6)
Partial response, n (%)	21 (25)
Disease control rate, % (95% CI)	80 (70–88)
Durable disease control rate, % (95% CI)	60 (48–70)
Median duration of response (range), months	4.3 (4.2–7.2)

- High-affinity, human, hinge-stabilised IgG4 monoclonal antibody to the PD-1 receptor[1]
- In the primary analysis of the Phase 2 study, cemiplimab demonstrated clinically meaningful activity and an acceptable safety profile in patients with locally advanced BCC (NCT03132636)[2]
- Data from the longer-term follow-up at ~40 months are presented here

CI, confidence interval; Fc, fragment crystallisable; Ig, immunoglobin; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; pMHC I, peptide-bound major histocompatibility complex I; TCR, T-cell receptor.

1. Burova E et al. *Mol Cancer Ther*. 2017;16:861–870. 2. Stratigos AJ et al. *Lancet Oncol*. 2021;22:848–857.

The data cut-off date was 20 May, 2021.

Study design

Group 1
Adult patients with **metastatic** (nodal and distant) BCC

Group 2
Adult patients with laBCC

Primary endpoint: ORR by ICR

Secondary endpoints: ORR by IA, DOR, CR rate, PFS, OS, and safety and tolerability

Cemiplimab 350 mg IV Q3W for up to 93 weeks (or until disease progression, unacceptable toxicity or withdrawal of consent)

Tumor assessments 1–5 Q9W, 6–9 Q12W

Tumor response assessment by ICR (RECIST 1.1 for visceral lesions or modified WHO criteria for skin lesions)†

Inclusion criteria
- Histologically confirmed diagnosis of BCC
- Prior progression or intolerance to HHI therapy or no better than stable disease after 9 months on HHI therapy
- At least one measurable baseline lesion
- ECOG performance status of 0 or 1

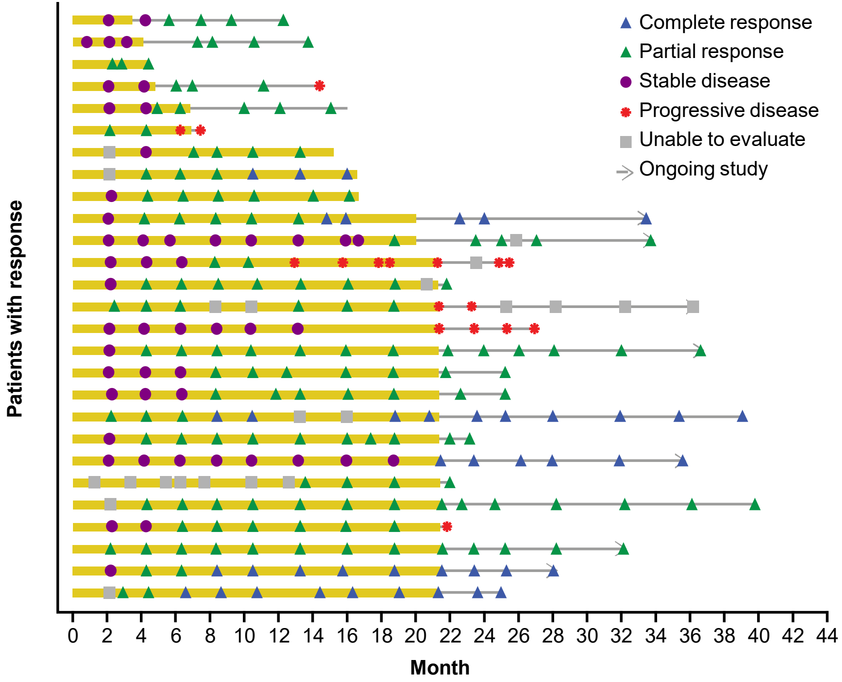
Exclusion criteria
- Ongoing or recent (≤5 years) autoimmune disease requiring systemic immunosuppression
- Prior anti–PD-1 or anti–PD-L1 therapy
- Concurrent malignancy other than BCC and/or history of malignancy other than BCC within 3 years of date of first planned dose of cemiplimab, except for tumours with negligible risk of metastasis or death

†Or by composite response criteria for patient with both visceral and skin lesions, including ICR review of digital medical photography, radiology and pathology reports from on-treatment biopsies (if any).
BCC, basal cell carcinoma; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HHI, hedgehog inhibitor; ICR, independent composite review; IA, investigator assessment; IV, intravenous; laBCC, locally advanced BCC; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; WHO, World Health Organization.

The data cut-off date was 20 May, 2021.

Tumour response per ICR

Outcome	laBCC (N=84)
Duration of follow-up, median (range), months	15.9 (0.5–39.7)
Best overall response per ICR	
ORR, % (95% CI)	32.1 (22.4–43.2)†
CR, n (%)	6 (7.1)
PR, n (%)	21 (25.0)
Stable disease, n (%)	40 (47.6)
Non-CR/non-progressive disease, n (%)	0
PD, n (%)	9 (10.7)
Not evaluable, n (%)‡	8 (9.5)
Observed DOR at 6 months, n (%)#	23 (85.2%)
Disease control rate, % (95% CI)§	79.8 (69.6–87.7)
Durable disease control rate, % (95% CI)¶	59.5 (48.3–70.1)
Time to response, median (range), months#	4.3 (2.1–21.4)
Kaplan–Meier estimation of DOR, median (95% CI), months #	NR (15.5–NE)
6 months	88.5 (68.4–96.1)
12 months	83.8 (62.2–93.6)
24 months	56.6 (29.6–76.6)



Each horizontal bar represents one patient. All patients completed treatment. Patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments. †ORR per investigator was 36.9% (95% CI, 26.6–48.1). ‡Not evaluable response includes the missing and unknown tumour response. §Defined as the proportion of patients with CR, PR, stable disease or non-PR/non-PD. ¶Defined as the proportion of patients with CR, PR, stable disease or non-PR/non-PD for ≥182 days without PD. #Data shown are for patients with response.
CI, confidence interval; CR, complete response; DOR, duration of response; ICR, independent central review, laBCC, locally advanced basal cell carcinoma; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response.

The data cut-off date was 20 May, 2021.

Conclusions

- Melanoma treatments:
  - Surgical margins: trial 1 cm vs 2 cm
  - Metastatic:
    - Actual treatment options: double immunotx vs simple vs TT
    - New: new combo, sequencing, microbiome, intrathecal
  - Adjuvant therapy:
    - Standard of care stage IIB/IIC or III: anti-PD1 or TT
    - Clinical Trials: mRNA vaccine + Pembrolizumab
  - Neoadjuvant approach:
    - Pembrolizumab: SWOG 1801
    - Clinical Trials: combo immunotx and less surgery
- Squamous cell carcinoma: Neoadjuvant Cemiplimab
- Basal cell carcinoma: Cemiplimab after Hedgehog inhibition

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Melanoma and Skin Cancer Clinic Quebec city

Merci!