Melanoom management nu en in de toekomst

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Universiteit Antwerpen

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cutaneous Melanoma

Version 1.2019 — November 1, 2018

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org

https://www.nccn.org/patients/guidelines/melanoma/index.html

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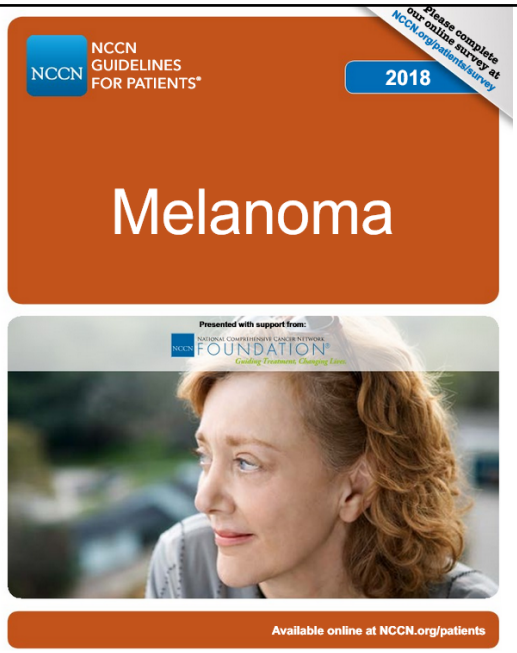
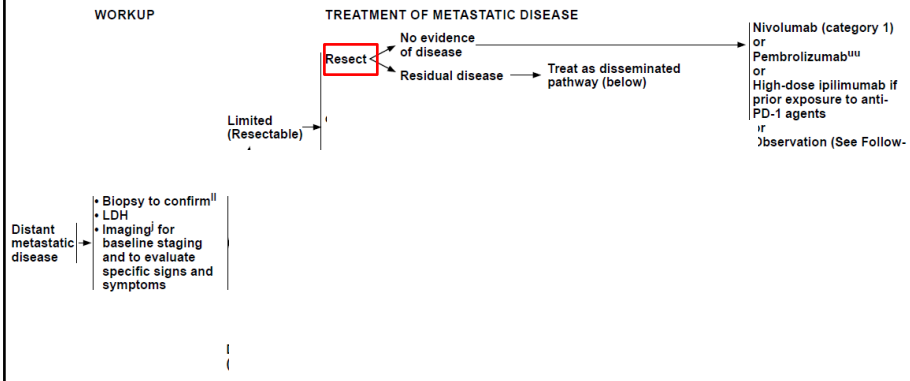


https://www.nccn.org/patients/guidelines/melanoma/index.html

3

Stadium IV

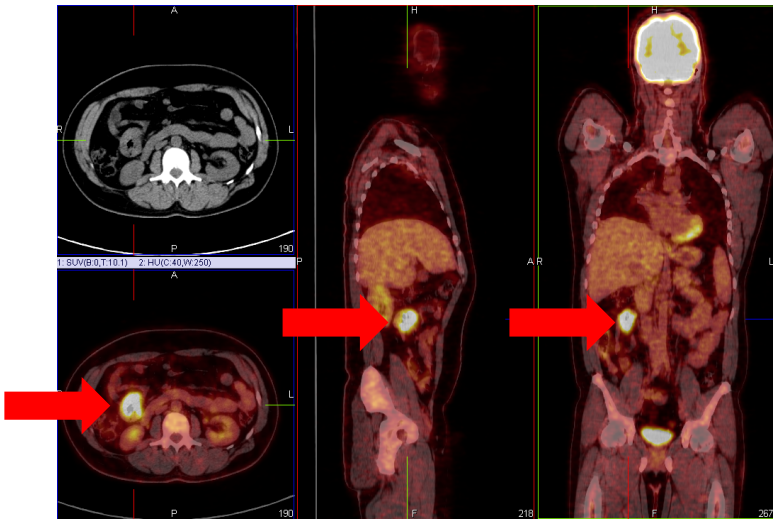


https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

Man 36 jaar

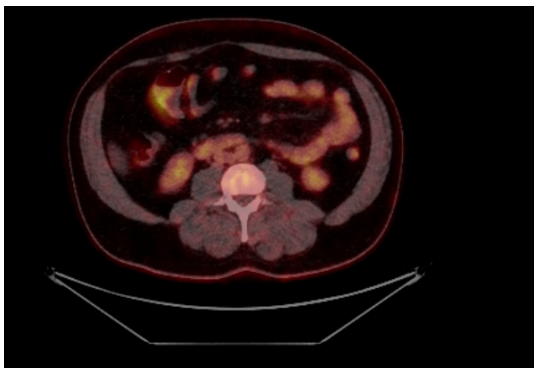
- 11/2006: resectie nodulair melanoom rechterbovenarm Breslow 1.9 mm, Clark 4.
- 06/2008: resectie grote metastatische lymfeklier rechteroksel
- 08/2008: ➟ UZA: verdere okselklieruitruiming rechts (geen tumor meer), resectie 1 metastatische lymfeklier infraclaviculair rechts en resectie lymfeklier rechterlies (reactief) ➟ adjuvante radiotherapie + adjuvante interferon-alfatherapie (4 weken intraveneus, daarna 48 weken subcutaan)

11/2009: einde interferon: PET-scan

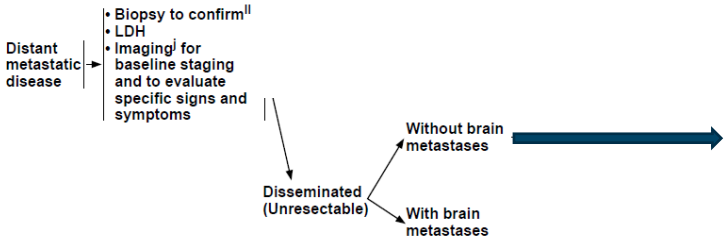


- 17/12/2009: laparoscopie met partiële dundarmresectie, alsook resectie van de rechter musculus sartorius wegens recidief in de musculus sartorius en het terminaal ileum

- 17/12/2009: laparoscopie met partiële dundarmresectie, alsook resectie van de rechter musculus sartorius wegens recidief in de musculus sartorius en het terminaal ileum
- 10/2018



WORKUP



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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]
FIRST-LINE THERAPY[2]

Metastatic or unresectable disease →

- Immunotherapy[3]
  - Anti PD-1 monotherapy[4]
    - ◊ Pembrolizumab (category 1)
    - ◊ Nivolumab (category 1)
  - Nivolumab/ipilimumab (category 1)[4,5]

https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

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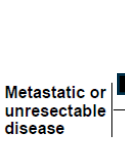
SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]
FIRST-LINE THERAPY[2]



- Immunotherapy[3]
  - Anti PD-1 monotherapy[4]
    - ◊ Pembrolizumab (category 1)
    - ◊ Nivolumab (category 1)
  - Nivolumab/ipilimumab (category 1)[4,5]

https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

MUNICH 2018 ESMO congress

Overall Survival at 4 years of Follow-up in a Phase 3 Trial of Nivolumab Plus Ipilimumab Combination Therapy in Advanced Melanoma (CheckMate 067)

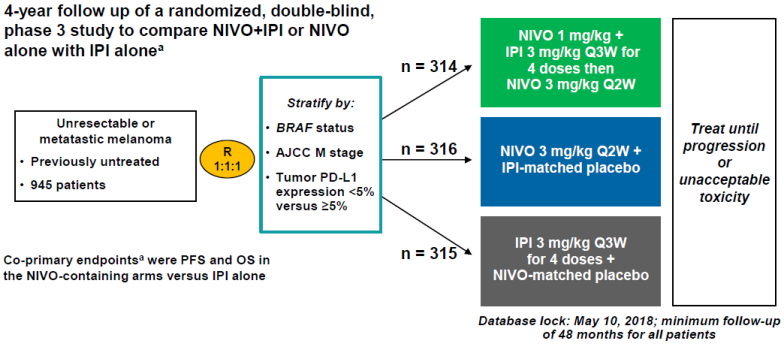
F. Stephen Hodi,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Pier Francesco Ferrucci,[11] Michael Smylie,[12] Andrew G. Hill,[13] David Hogg,[14] Ivan Marquez-Rodas,[15] Joel Jiang,[16] Jasmine Rizzo,[16] James Larkin,[17*] Jedd D. Wolchok[18*]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Denver, CO, USA; [4]Aix-Marseille University, APHM Hospital CHU Timone, Marseille, France; [5]Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [7]University of Michigan, Ann Arbor, MI, USA; [8]University of Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; [9]The College of Medicine, Swansea University, Swansea, UK; [10]Universitäts Spital, Zurich, Switzerland; [11]European Institute of Oncology, Milan, Italy; [12]Cross Cancer Institute, Edmonton, AB, Canada; [13]Tasman Oncology Research, Southport, QLD, Australia; [14]Princess Margaret Cancer Centre, Toronto, ON, Canada; [15]General University Hospital Gregorio Marañón, Madrid, Spain; [16]Bristol-Myers Squibb, Princeton, NJ, USA; [17]The Royal Marsden Hospital NHS Foundation Trust, London, UK; [18]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; *Contributed equally to this study.

Abstract Number LBA44

CheckMate 067: Study Design

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



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

Database lock: May 10, 2018; minimum follow-up of 48 months for all patients

[a]The study was not powered for a comparison between NIVO+IPI and NIVO

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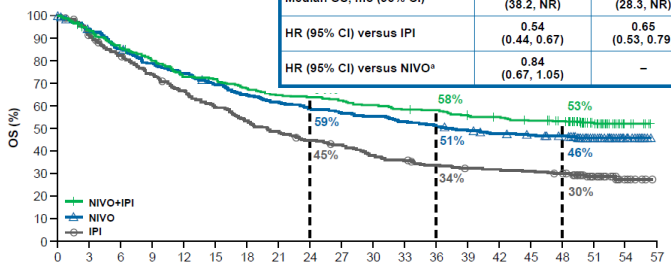
Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

[a]Descriptive analysis

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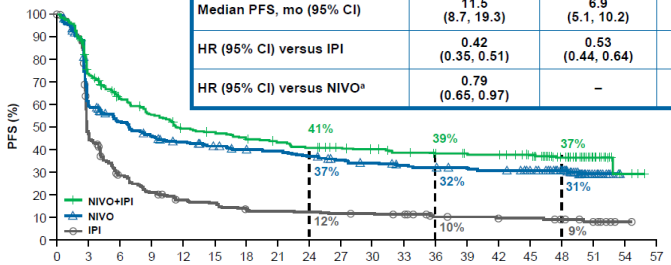
Progression-Free Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	11.5 (8.7, 19.3)	6.9 (5.1, 10.2)	2.9 (2.8, 3.2)
HR (95% CI) versus IPI	0.42 (0.35, 0.51)	0.53 (0.44, 0.64)	–
HR (95% CI) versus NIVO[a]	0.79 (0.65, 0.97)	–	–



Patients at risk:

NIVO+IPI	314	218	175	155	136	131	124	117	110	104	101	95	93	89	88	81	53	19	3	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	79	77	75	72	66	50	18	0	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	19	18	16	16	11	7	1	0

[a]Descriptive analysis

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Response to Treatment

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	58.3 (52.6, 63.8)	44.6 (39.1, 50.3)	19.0 (14.9, 23.8)
Best overall response, %			
Complete response	21.3	17.7	5.1
Partial response	36.9	26.9	14.0
Stable disease	12.1	9.5	21.6
Progressive disease	23.6	38.3	50.5
Unknown	6.1	7.6	8.9
Median duration of response, months (95% CI)	50.1 (44.0, NR)	NR (45.7, NR)	14.4 (8.3, NR)

NR = not reached

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Safety Summary

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

LBA47 **Initial results from a phase IIIb/IV study evaluating two dosing regimens of nivolumab (NIVO) in combination with ipilimumab (IPI) in patients with advanced melanoma (CheckMate 511)**

C. Lebbé[1], N. M
A.M. Menzies[7],
R. Gonzalez[13],

Table: LBA47

	NIVO3+IPI1 (N = 180)	NIVO1+IPI3 (N = 178)
Safety		
Treatment-related grade 3-5 AEs, % (95% CI)	33.9 (27.0–41.3)	48.3 (40.8–55.9)
P value	0.0059	
Efficacy		
Investigator-assessed ORR, % (95% CI)	45.6 (38.1–53.1)	50.6 (43.0–58.1)
Difference in ORR, % (95% CI)	-4.9 (-15.2–5.3)	
P value	0.3451	
Median PFS, months (95% CI)	9.9 (6.0–20.0)	8.9 (6.0–NR)
Hazard ratio (95% CI)	1.06 (0.79–1.42)	
12-month PFS rate, %	47.2	46.4
Median OS, months	NR	NR
Hazard ratio (95% CI)	1.09 (0.73–1.62)	
12-month OS rate, %	79.7	81.0

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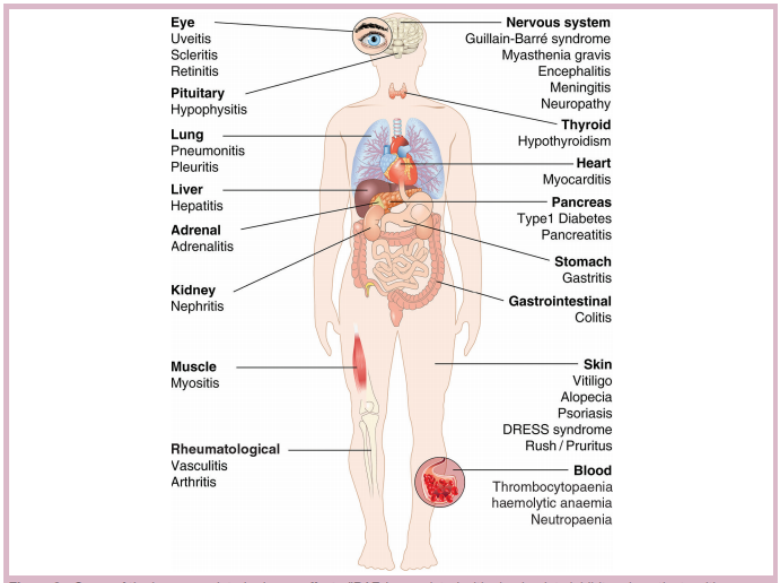

Figure 3 Some of the immune-related adverse effects (IRAEs) associated with checkpoints inhibitors in patients with cancer. DRESS, drug rash with eosinophilia and systemic symptoms.

Varricchi G et al. ESMO Open 2017;2:e000247. doi:10.1136/ esmoopen-2017-000247

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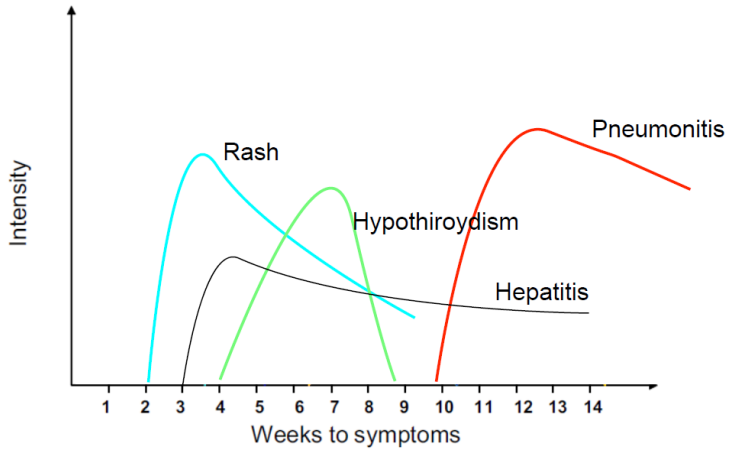
Toxicity Patterns - Anti-PD-1 Mab



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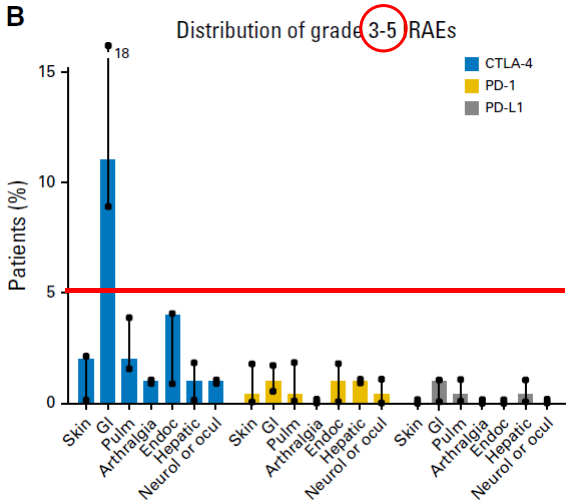

http://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385

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

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

http://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy

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Hoe lang?

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ESMO 2018 Lecture
Checkpoint Inhibition: What is the optimal duration of therapy?

Jeffrey S Weber MD PhD
Deputy Director, Laura and Isaac Perlmutter Cancer Center
NYU Langone Health

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Why would you want to stop checkpoint inhibitors?

- Patient choice
  - Inconvenience
  - Risk of toxicity
  - Ongoing low grade toxicity
  - 'I want to get on with life'
- Resources
  - Health economic
  - Limited clinic/day ward space

Thanks to Matt Carlino MD, MIA

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

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

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

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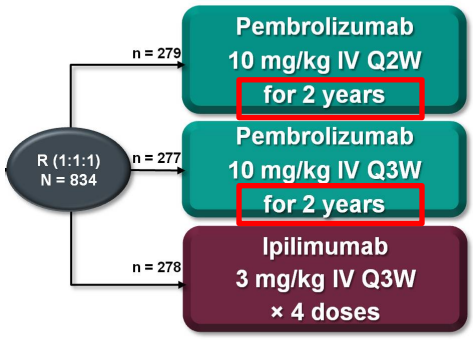
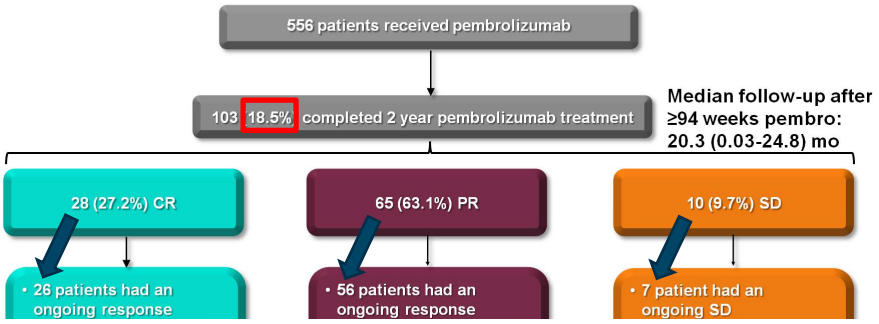
KEYNOTE-006 Study Design (NCT01866319)



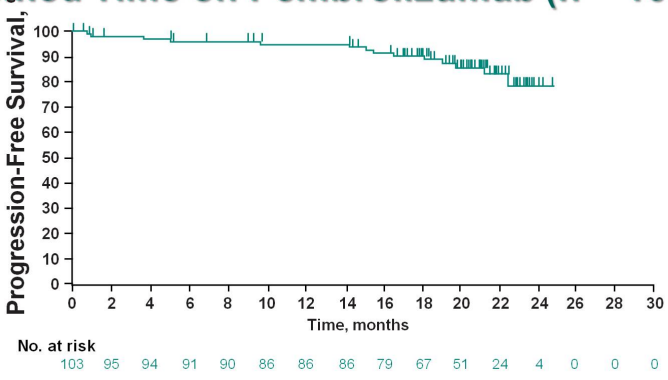
Presented By Georgina Long at 2018 ASCO Annual Meeting

Disposition of Patients Completing ≥94 Weeks of Pembrolizumab Treatment



Presented By Georgina Long at 2018 ASCO Annual Meeting

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



[a]Per immune-related response criteria by investigator review; time is measured from last dose of pembrolizumab. Data cutoff: Dec 4, 2017.

Presented By Georgina Long at 2018 ASCO Annual Meeting

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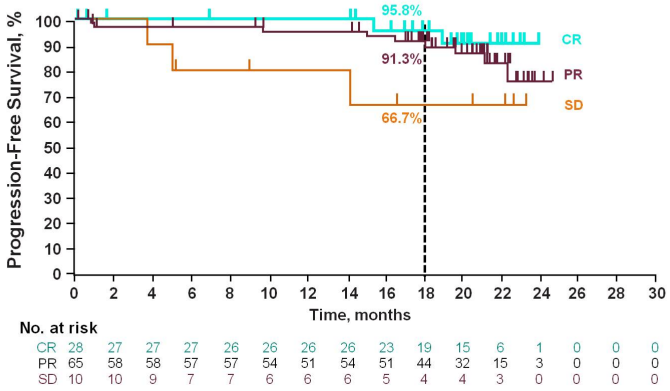
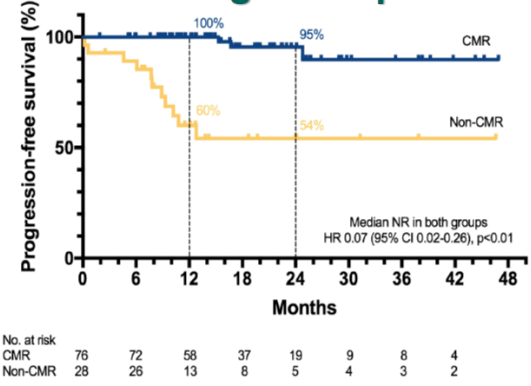


[a]Per immune-related response criteria by investigator review; time is measured from last dose of pembrolizumab. Data cutoff: Dec 4, 2017.

Presented By Georgina Long at 2018 ASCO Annual Meeting

Relapse by PET response in melanoma patients receiving checkpoint inhibition



Tan et.al……Menzies Annals of Onc 2018 (in press); thanks to Matt Carlino, MD, MIA

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Have any trials prospectively evaluated duration of CPI therapy?

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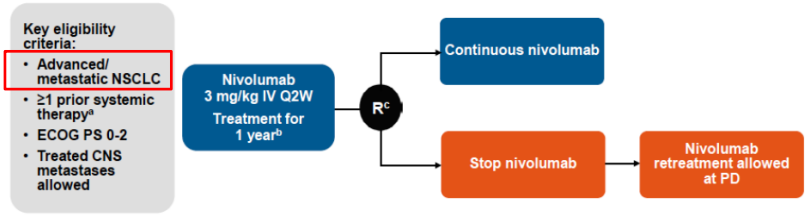
Checkmate-153: Study Design



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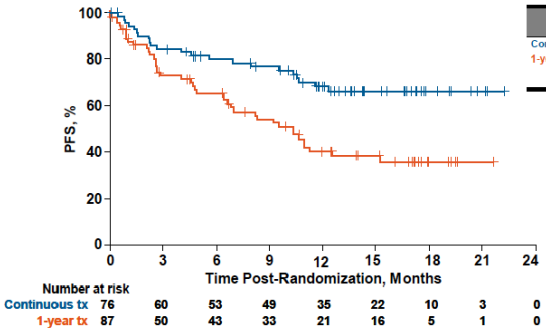
PFS From Randomization[a]



	Median, Months (95% CI)	PFS Rate, % 6-Month	1-Year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)

[a]Patients who did not have PD at randomization. minimum/median follow-up time post-randomization, 10.0/14.9 months. [b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

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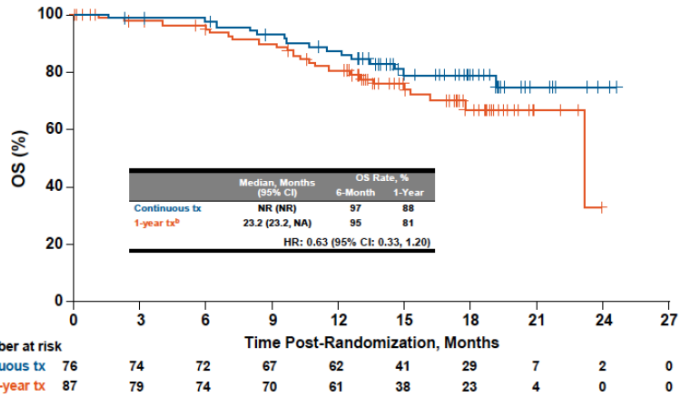
OS From Randomization[a]



	Median, Months (95% CI)	OS Rate, % 6-Month	1-Year
Continuous tx	NR (NR)	97	88
1-year tx[b]	23.2 (23.2, NA)	95	81

HR: 0.63 (95% CI: 0.33, 1.20)

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months. [b]With optional retreatment allowed at PD

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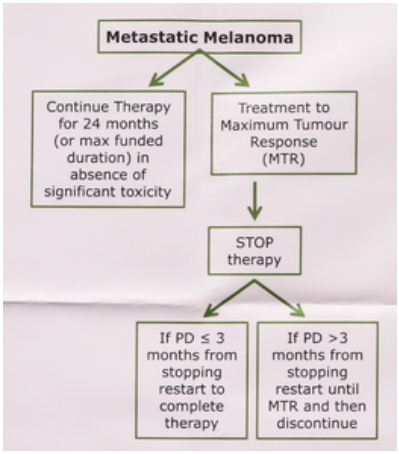
A RANDOMIZED PHASE III STUDY OF DURATION OF ANTI-PD-1 THERAPY IN METASTATIC MELANOMA (STOP-GAP): CANADIAN CLINICAL TRIALS GROUP STUDY (CCTG) ME.13

Trial in Progress

Tara D. Baetz, Xinni Song, D. Scott Ernst, Elaine McWhirter, Teresa M. Petrella, Kerry J. Savage, Michael Smylie, Ralph Wong, Christopher W Lee, Nicole Look Hong, Diane Logan, Muhammed Saleem Raza, Tahir Abbas, Dora Nomikos, Roger Leung, Bingshu E. Chen, Janet Dancey



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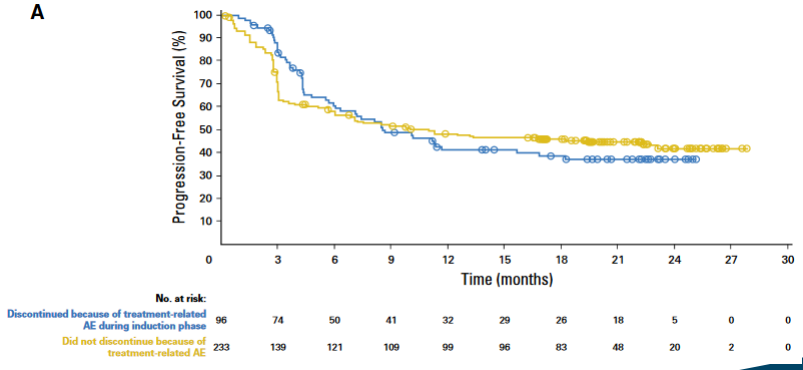
Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials

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



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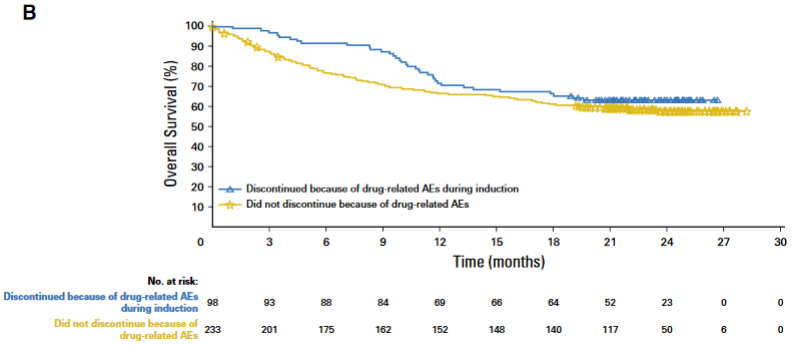
Dirk Schadendorf, Jedd D. Wolchok, F. Stephen Hodi, Vanna Chiarion-Sileni, Rene Gonzalez, Piotr Rutkowski, Jean-Jacques Grob, C. Lance Cowey, Christopher D. Lao, Jason Chesney, Caroline Robert, Kenneth Grossmann, David McDermott, Dana Walker, Rafia Bhore, James Larkin, and Michael A. Postow

B



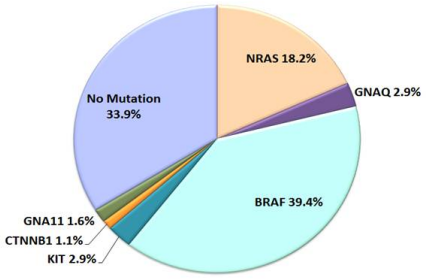
No. at risk:

Discontinued because of drug-related AEs during induction	98	93	88	84	69	66	64	52	23	0	0
Did not discontinue because of drug-related AEs	233	201	175	162	152	148	140	117	50	6	0

39

Melanoma Molecular Profiling

60% BRAF WT



Mutation Distribution

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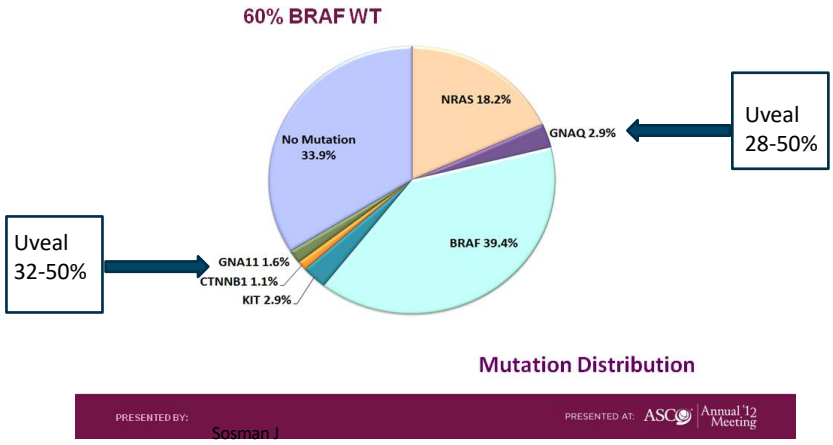
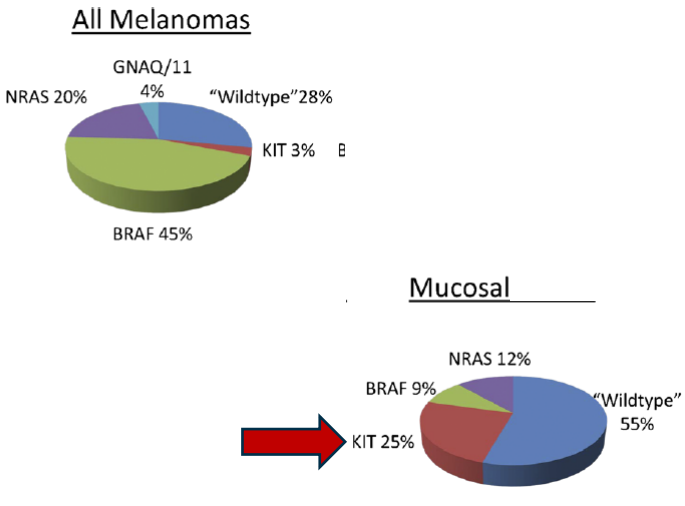
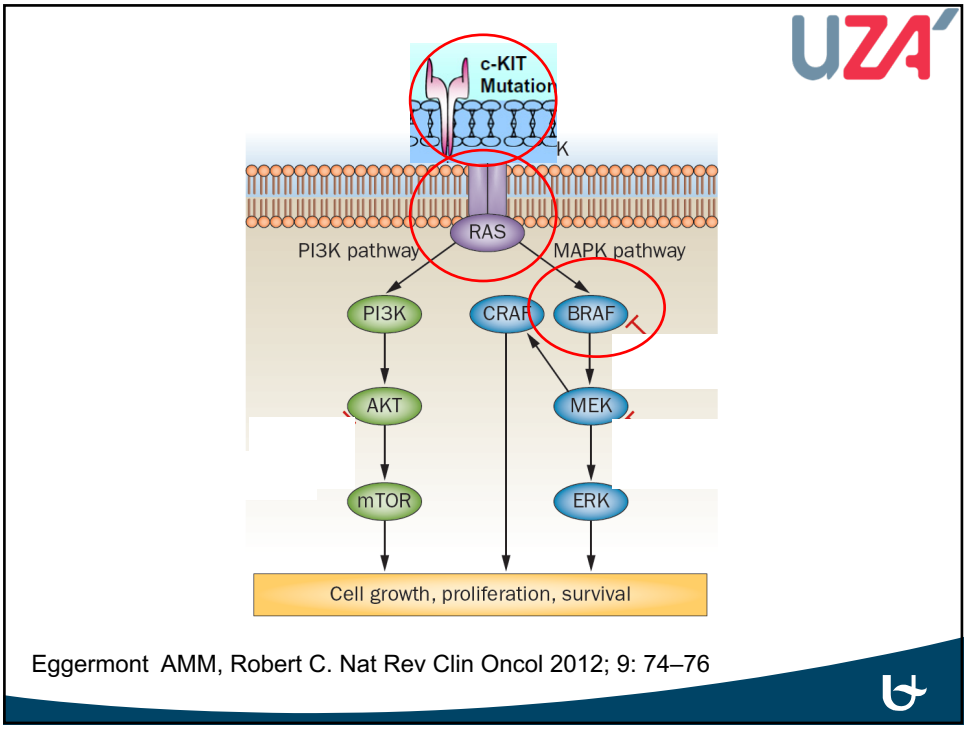
Melanoma Molecular Profiling



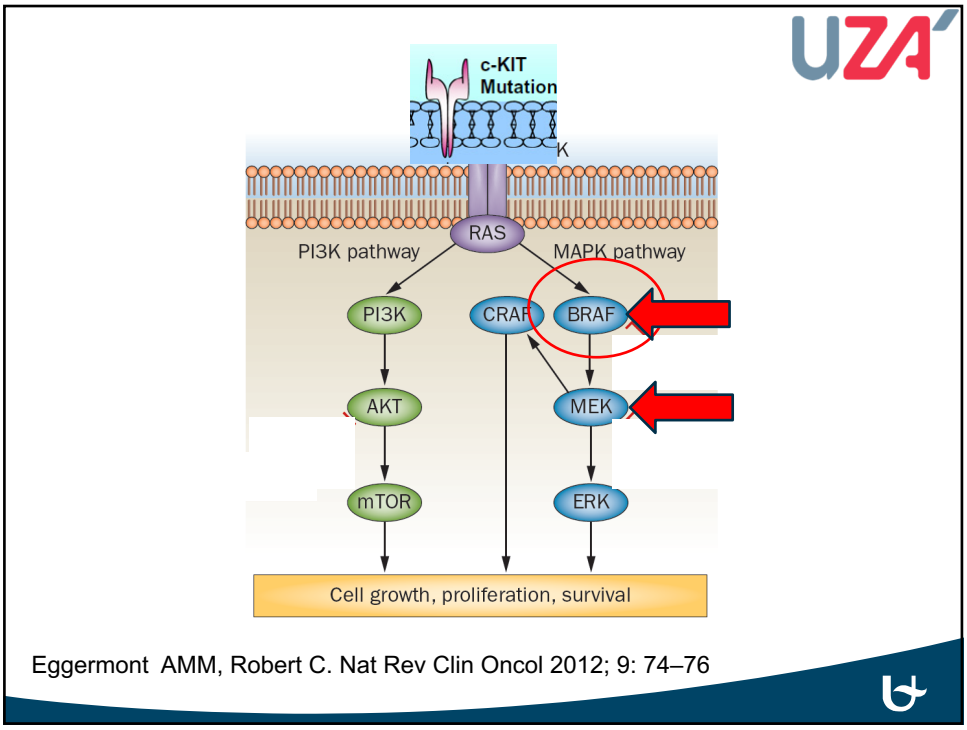
Driver mutations in melanoma



Postow MA, D. Carvajal RD. Cancer J 2012; 18: 137-141

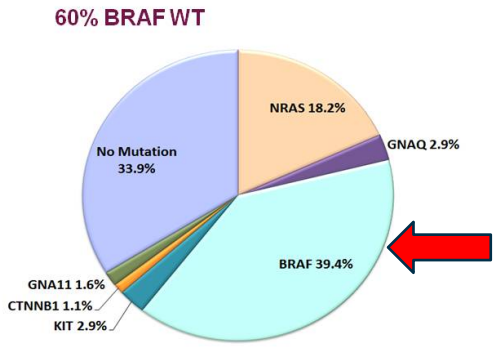


Eggermont AMM, Robert C. Nat Rev Clin Oncol 2012; 9: 74–76



Eggermont AMM, Robert C. Nat Rev Clin Oncol 2012; 9: 74–76

Melanoma Molecular Profiling



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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]

FIRST-LINE THERAPY[2]

Metastatic or unresectable disease →

- Immunotherapy[3]
  - Anti PD-1 monotherapy[4]
    - Pembrolizumab (category 1)
    - Nivolumab (category 1)
  - Nivolumab/ipilimumab (category 1)[4,5]
- Targeted therapy if BRAF V600 activating mutation:[6] preferred if clinically needed for early response[7]
  - Combination therapy[8,9,10]
    - Dabrafenib/trametinib (category 1)
    - Vemurafenib/cobimetinib (category 1)
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https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

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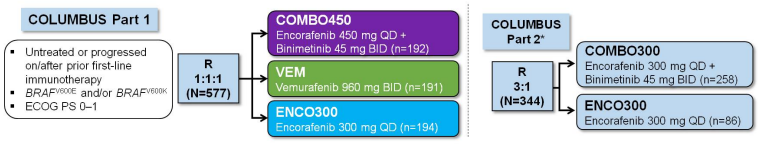
Overall Survival in COLUMBUS: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) vs Vemurafenib (VEM) or ENCO in *BRAF*-Mutant Melanoma

Reinhard Dummer, Paolo A. Ascierto, Helen J. Gogas, Ana Arance, Mario Mandala, Gabriella Liszkay, Claus Garbe, Dirk Schadendorf, Ivana Krajsova, Ralf Gutzmer, Vanna Chiarion-Sileni, Caroline Dutriaux, Jan Willem B. de Groot, Naoya Yamazaki, Carmen Loquai, Laure A. Moutouh-de Parseval, Michael D. Pickard, Victor Sandor, Caroline Robert, Keith T. Flaherty

Study Design and Objectives



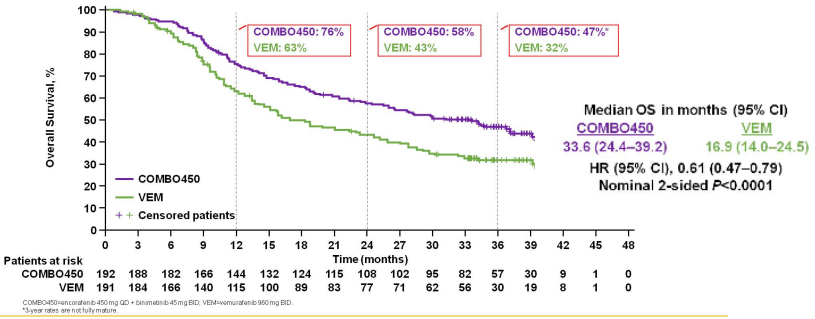
Efficacy update with additional follow-up of 18 months:

OS:
- Secondary endpoint†
- Planned after 232 events in the COMBO450 and VEM groups combined
- Median duration of follow-up‡: 36.8 months

PFS:
- Primary endpoint
- Median duration of follow-up‡: 32.1 months

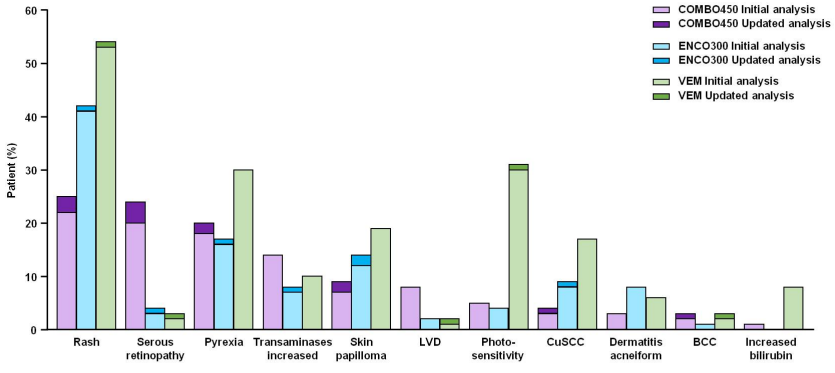
COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PFS=progression-free survival; R=randomization; VEM=vemurafenib 960 mg BID.
*Arm-3 met requested by FDA.
†Included in hierarchical testing approach.
‡Median follow-up of patients assessed using reverse Kaplan-Meier approach (i.e. median potential follow-up).

Overall Survival Landmark Data: COMBO450 vs VEM



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; VEM=vemurafenib 960 mg BID.
*3-year rates are not fully mature.

Groupings of AEs Associated With BRAFi and MEKi



Terms represent groupings of similar or related adverse events.

BCC=basal cell carcinoma; BRAFi=BRAF inhibitor; COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; CuSCC=cutaneous squamous cell carcinoma; ENCO300=encorafenib 300 mg QD; LVD=left ventricular dysfunction; MEKi=MEK inhibitor; VEM=vemurafenib 960 mg BID.

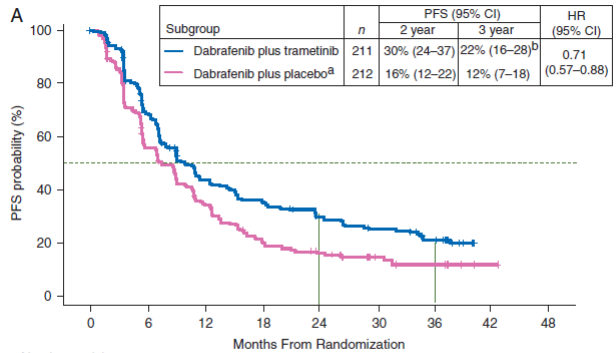
Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic *BRAF* V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study

G. V. Long[1*], K. T. Flaherty[2], D. Stroyakovskiy[3], H. Gogas[4], E. Levchenko[5], F. de Braud[6], J. Larkin[7], C. Garbe[8], T. Jouary[9], A. Hauschild[10], V. Chiarion-Sileni[11], C. Lebbe[12], M. Mandalà[13], M. Millward[14], A. Arance[15], I. Bondarenko[16], J. B. A. G. Haanen[17], J. Hansson[18], J. Utikal[19], V. Ferraresi[20], P. Mohr[21], V. Probachai[22], D. Schadendorf[23,24], P. Nathan[25], C. Robert[26], A. Ribas[27], M. A. Davies[28], S. R. Lane[29], J. J. Legos[29], B. Mookerjee[29] & J.-J. Grob[30]

Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic *BRAF* V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study

A

Subgroup	*n*	PFS (95% CI) 2 year	PFS (95% CI) 3 year	HR (95% CI)
Dabrafenib plus trametinib	211	30% (24–37)	22% (16–28)[b]	0.71 (0.57–0.88)
Dabrafenib plus placebo[a]	212	16% (12–22)	12% (7–18)	



Number at risk

D + T	211	137	84	69	54	45	31	0
D + Pbo	212	110	67	41	29	11	7	1	0

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]
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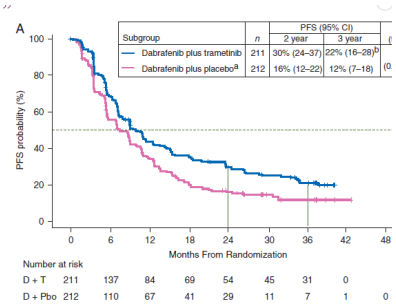
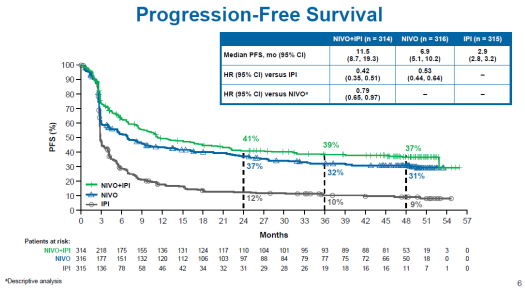
→ Disease progression or Maximum clinical benefit from BRAF targeted therapy

https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf





6

56

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]

FIRST-LINE THERAPY[2]

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    - ◊ Dabrafenib/trametinib (category 1)
    - ◊ Vemurafenib/cobimetinib (category 1)
    - ◊ Encorafenib/binimetinib (category 1)

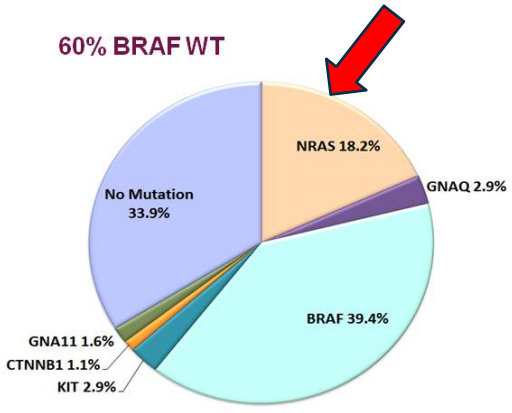
→ Disease progression or Maximum clinical benefit from BRAF targeted therapy →

SECOND-LINE OR SUBSEQUENT THERAPY[11]

- Anti PD-1 monotherapy[3,4]
  - Pembrolizumab
  - Nivolumab
- Nivolumab/ipilimumab[3,4,5]
- Targeted therapy if BRAF V600 activating mutation
  - Combination therapy[8,9,10]
    - ◊ Dabrafenib/trametinib
    - ◊ Vemurafenib/cobimetinib
    - ◊ Encorafenib/binimetinib
- Ipilimumab[3]
- Ipilimumab[3]/intralesional injection with T-VEC (category 2B)
- High-dose IL-2[12]
- Cytotoxic agents[13]
- Imatinib for tumors with activating mutations of KIT
- Consider best supportive care for poor performance status

https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

Melanoma Molecular Profiling



Sosman J

Mutation Distribution

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Binimetinib versus dacarbazine in patients with advanced *NRAS*-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial

Reinhard Dummer, Dirk Schadendorf, Paolo A Ascierto, Ana Arance, Caroline Dutriaux, Anna Maria Di Giacomo, Piotr Rutkowski, Michele Del Vecchio, Ralf Gutzmer, Mario Mandala, Luc Thomas, Lev Demidov, Claus Garbe, David Hogg, Gabriella Liszkay, Paola Queirolo, Ernesto Wasserman, James Ford, Marine Weill, L Andres Sirulnik, Valentine Jehl, Viviana Bozón, Georgina V Long, Keith Flaherty

Binimetinib versus dacarbazine in patients with advanced *NRAS*-mutant melanoma (NEMO): a multicentre, open-label,

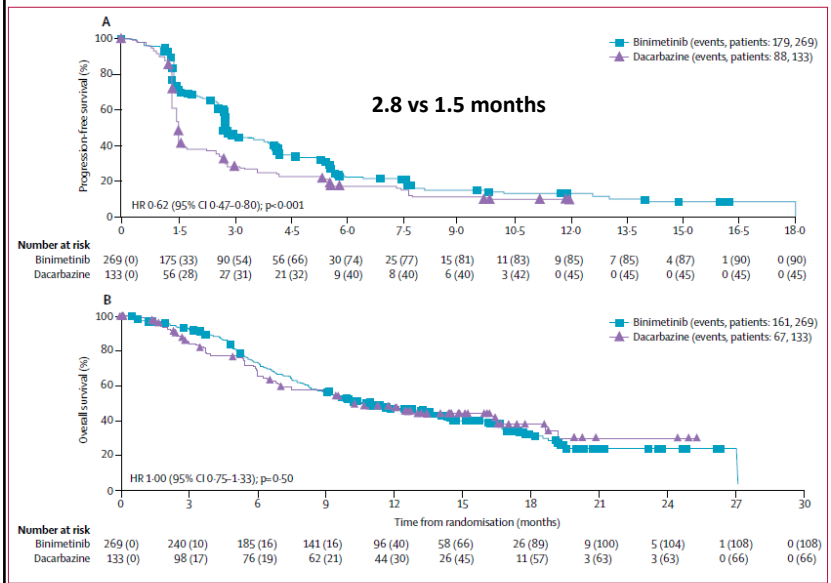
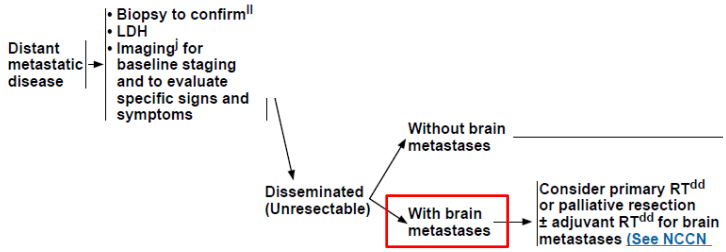


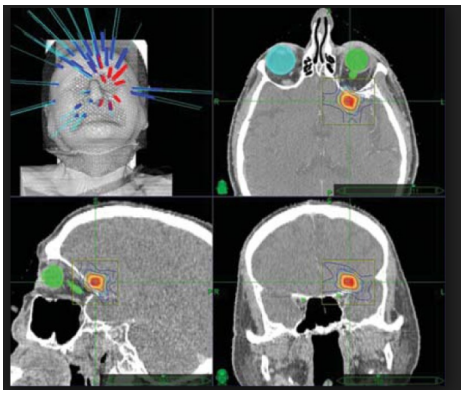
Figure 2: **Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)**

WORKUP



- Stereotactic radiosurgery (SRS) and fractionated stereotactic radiation therapy (SRT) are techniques for delivering a high dose of radiation to a specific target while delivering a minimal dose to surrounding tissues, generally in the brain and spine and in 1 to 5 sessions. IGRT should be used to improve accuracy of radiotherapy delivery, where clinically appropriate.
- SRS or SRT as primary treatment
  - Smaller tumors may be treated with maximal doses of 15–24 Gy in 1 fraction according to volume guidelines based on maximum tolerated dose results from the RTOG 90-05 dose escalation study (shown below).[23] Caution is recommended for lesions >3 cm, and single fraction radiosurgery is not typically recommended for lesions >4 cm.
    - Lesions with maximum diameter ≤20 mm receive up to 24 Gy
    - Lesions with maximum diameter 21–30 mm receive up to 18 Gy
    - Lesions with maximum diameter 31–40 mm receive up to 15 Gy
  - Larger tumors, however, may be treated with fractionated SRT. Potential regimens include, but are not limited to:[24,25]
    - 24–27 Gy in 3 fractions
    - 25–35 Gy in 5 fractions

- Whole brain radiation therapy (WBRT) as primary treatment (See ME-15)
  - Upfront WBRT is generally not recommended for metastatic melanoma, and SRS/SRT is the preferred strategy when feasible.
  - WBRT can be considered for selected patients with too many lesions for SRS and/or are symptomatic from intracranial tumor burden.

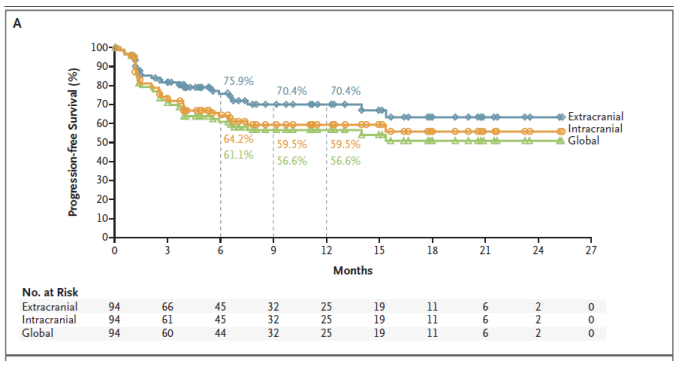


ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., David A. Reardon, M.D., Igor Puzanov, M.D., Ragini R. Kudchadkar, M.D., Reena P. Thomas, M.D., Ph.D., Ahmad Tarhini, M.D., Ph.D., Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Alexandre Avila, M.D., Ph.D., Sheena Demelo, M.D., and Kim Margolin, M.D.

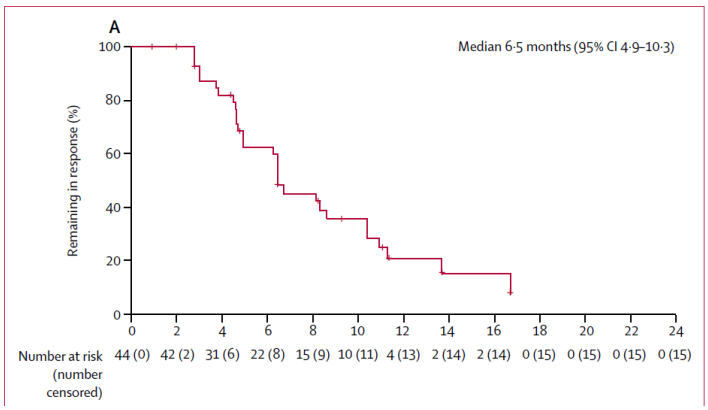
Among 94 patients with a median follow-up of 14.0 months, the rate of intracranial clinical benefit was 57% (95% confidence interval [CI], 47 to 68); the rate of



Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Michael A Davies, Philippe Saiag*, Caroline Robert, Jean-Jacques Grob, Keith T Flaherty, Ana Arance, Vanna Chiarion-Sileni, Luc Thomas, Thierry Lesimple, Laurent Mortier, Stergios J Moschos, David Hogg, Iván Márquez-Rodas, Michele Del Vecchio, Céleste Lebbé, Nicolas Meyer, Ying Zhang, Yingjie Huang, Bijoyesh Mookerjee, Georgina V Long*

median follow-up of 8·5 months (IQR 5·5–14·0), 44 (58%; 95% CI 46–69) of 76 patients in cohort A achieved an intracranial response. Intracranial response by investigator assessment was also achieved in nine (56%; 95% CI 30–



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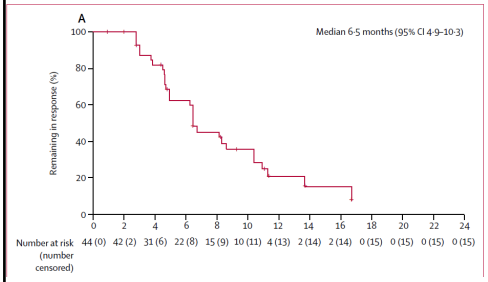

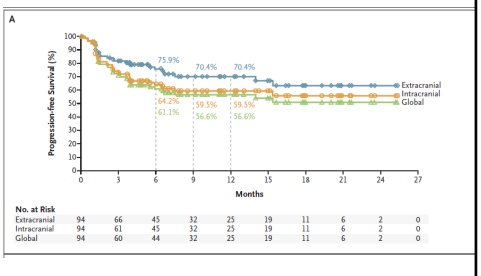

Optimale sequens bij BRAF-gemuteerde patiënten

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Brussel 1200 Bruxelles
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EORTC protocol 1612-MG

Combination of targeted therapy (encorafenib and binimetinib) followed by combination of immunotherapy (ipilimumab and nivolumab) vs immediate combination of immunotherapy in patients with unresectable or metastatic melanoma with BRAF V600 mutation : an EORTC randomized phase II study (EBIN)

(EudraCT 2017-002887-42)
(NCT 03235245)

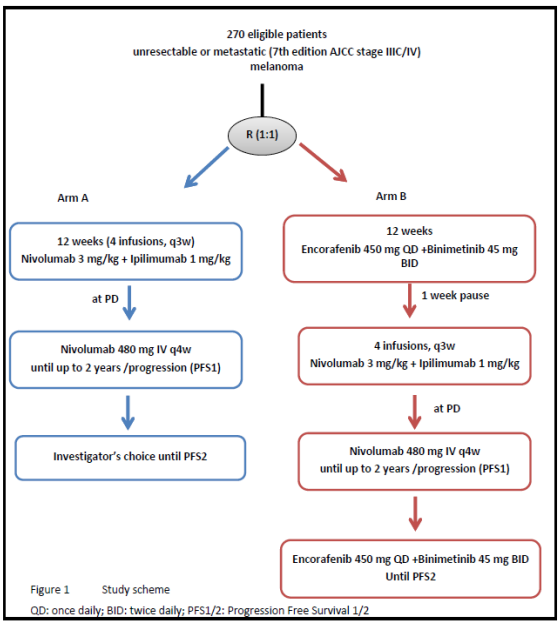

Figure 1 Study scheme

QD: once daily; BID: twice daily; PFS1/2: Progression Free Survival 1/2

SEquential COMBo Immuno and Target therapy (SECOMBIT) Study

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivoluma b) followed by combo target therapy (encorafenib/ binimetinib) and vice-versa
- Patients affected by metastatic melanoma BRAF V600 mutated
- Sample size 230 pts

ARM A Combo T encorafenib 450 mg binimetinib 162 45 mg → PD → Combo I until PD

ARM B Combo I Ipilimumab 3 mg/Kg Nivolumab 1mg /Kg → PD → Combo T until PD

ARM C Sandwich encorafenib 450 mg binimetinib 45 mg for 8 weeks → Combo I until PD → Combo T until PD

This study is designed as a phase II randomized trial with no formal comparative test.
Endpoints:
Primary – OS
Secondary – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR;
Duration of Response, Toxicity, Biomarkers study

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Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02224781

Recruitment Status : Recruiting
First Posted : August 25, 2014
Last Update Posted : December 5, 2018

See Contacts and Locations

Sponsor:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
National Cancer Institute (NCI)

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Universiteit Antwerpen

UZA

A Belgian prospective study assessing PD-L1 expression in BRAFV600 mutated metastatic melanoma patients at low risk of early progression, before the initiation of first line therapy

Combinaties

75

KEYNOTE-022 Part 3: Phase 2 Randomized Study of First-Line Dabrafenib and Trametinib Plus Pembrolizumab or Placebo for *BRAF*-Mutant Advanced Melanoma

P. A. Ascierto,[1,a] P. F. Ferrucci,[2,a] R. Fisher,[3] M. Del Vecchio,[4] V. Atkinson,[5] H. Schmidt,[6] J. Schachter,[7] P. Queirolo,[8] G. V. Long,[9] A. M. Di Giacomo,[10] I.M. Svane,[11] M. Lotem,[12] G. Bar-Sela,[13] F. Couture,[14] B. Mookerjee,[15] R. Ghori,[16] N. Ibrahim,[16] B. Homet Moreno,[16] A. Ribas[17]

[a]Both authors contributed equally

[1]Istituto Nazionale Tumori Fondazione G. Pascale, Napoli, Italy; [2]European Institute of Oncology, IRCCS, Milan, Italy; [3]Auckland City Hospital, Auckland, New Zealand; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Brisbane, QLD, Australia; [6]Aarhus University Hospital, Aarhus, Denmark; [7]Ella Lemelbaum Institute for Melanoma, The Chaim Sheba Medical Center at Tel HaShomer, Cancer Center (Oncology Institute), Ramat Gan, Israel; [8]IRCCS San Martino-IST, Genova, Italy; [9]Melanoma Institute Australia and the University of Sydney, Sydney, NSW, Australia; [10]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [11]Herlev Hospital, University of Copenhagen, Herlev, Denmark; [12]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [13]Rambam Health Care Campus, Haifa, Israel; [14]Centre Hospitalier Universitaire de Québec Research Center, Laval University, Québec, QC, Canada; [15]Novartis, East Hanover, NJ, USA; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA

KEYNOTE-022 Part 3 Study Design (NCT02130466)

Patients
- Histologically confirmed unresectable or metastatic stage IV *BRAF*$^{V600E/K}$-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

Stratification factors[a]
- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

R (1:1)
N = 120

N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

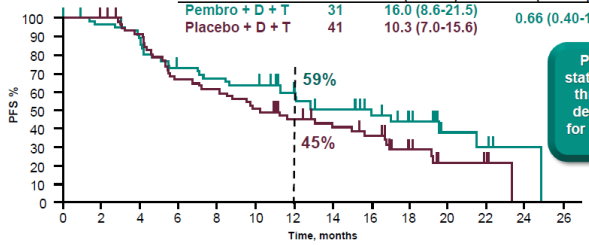
N = 60 → Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		



PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, *P* ≤ 0.025)

No. at risk

Pembro + D + T	60	55	49	39	36	34	27	21	17	12	5	4	1	0
Placebo + D + T	60	59	52	38	35	29	23	20	16	9	4	3	0	0

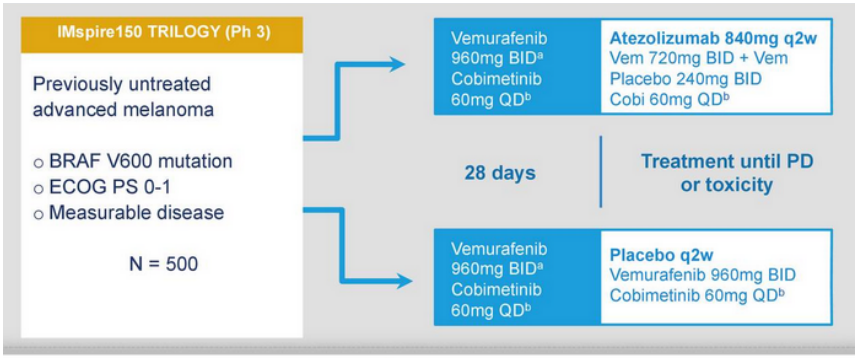
[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

Summary of Adverse Events

	Pembro + D + T n (%) N = 60	Placebo + D + T n (%) N = 60
Any-grade AE	59 (98)	58 (97)
Grade 3-4	40 (67)	27 (45)
Led to death[a]	2 (3)	0 (0)
Led to discontinuation	25 (42)	13 (22)
Led to discontinuation of all 3 study drugs	15 (25)	9 (15)
Treatment-related AE	57 (95)	56 (93)
Grade 3-4	34 (57)	16 (27)
Led to death	1 (2)	0 (0)
Led to discontinuation of ≥1 study drug	24 (40)	12 (20)

[a]One patient died due to treatment-related pneumonitis and one died of unknown cause. Data cutoff: Feb 15, 2018.

Median follow-up: 9.6 months (range, 2.7-23.4 months)



Key Study Objectives

- **Primary:** Investigator-assessed PFS
- **Secondary:** PFS (IRF-assessed), OS, ORR, DOR, Safety, PK

First patient enrolled in January 2017

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Nieuwe middelen

Epacadostat Plus Pembrolizumab Versus Pembrolizumab Alone in Patients With Unresectable or Metastatic Melanoma: Results of the Phase 3 ECHO-301/KEYNOTE-252 Study

Georgina V. Long,[1] Reinhard Dummer,[2] Omid Hamid,[3] Thomas Gajewski,[4] Christian Caglevic,[5] Stephane Dalle,[6] Ana Arance,[7] Matteo S. Carlino,[8] Jean-Jacques Grob,[9] Tae Min Kim,[10] Lev Demidov,[11] Caroline Robert,[12] James Larkin,[13] James R. Anderson,[14] Janet Maleski,[15] Mark Jones,[15] Scott J. Diede,[14] Tara C. Mitchell[16]

[1]Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; [2]University Hospital Zürich, Zurich, Switzerland; [3]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [4]University of Chicago Medical Center, Chicago, IL, USA; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Hospices Civils De Lyon, Cancer Research Center of Lyon, Claude Bernard University Lyon, Pierre Benite, France; [7]Hospital Clinic de Barcelona, Barcelona, Spain; [8]Westmead and Blacktown Hospitals, Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [9]Aix-Marseille University, Marseille, France; [10]Seoul National University Hospital, Seoul, South Korea; [11]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [12]Gustave Roussy Comprehensive Cancer Center, Villejuif, France; [13]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Incyte Corporation, Wilmington, DE, USA; [16]Abramson Cancer Center of the University of Philadelphia, Philadelphia, PA, USA.

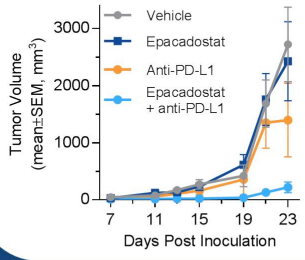
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Georgina V. Long

Background: Rationale for Combination and Dosing

Preclinical Model[1,2]

- Marked synergy with anti-PD-L1 mAbs



BID, twice daily; IDO1, indoleamine 2,3 dioxygenase 1; Kyn, kynurenine; mAb; monoclonal antibody; PD-L1, programmed death ligand-1.
1. WIPO #WO/2014/066834 https://patentscope.wipo.int/ Accessed August 2, 2017. 2. Spranger S, et al. *J Immunother Cancer.* 2014;2:3. 3. Beatty GL, et al. *Clin Cancer Res.* 2017;23:3269-3276, with permission from AACR.

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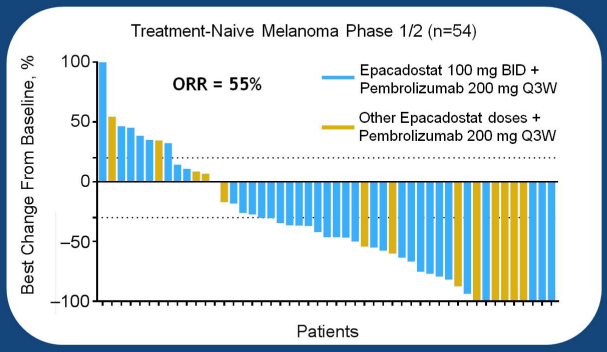
Background: Rationale for Combination and Dosing



ECHO-202 / KEYNOTE-037

- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
- Phase 1/2 efficacy in treatment-naive melanoma:
  - ORR = 55%
  - Median PFS = 22.8 mo (12.4 mo all melanoma)

BID, twice daily; MTD, maximally tolerated dose; PD-L1, programmed death ligand-1; Q3W, every 3 weeks.
Hamid O, et al. *Ann Oncol.* 2017;28(suppl 5):1214O.

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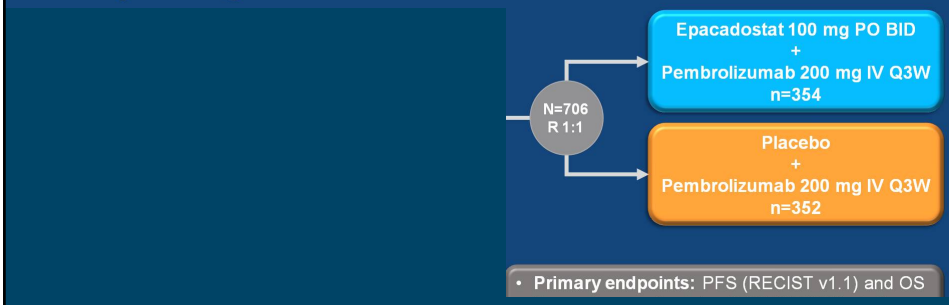
Study Design: Phase III Randomized Controlled Trial



- **Primary endpoints:** PFS (RECIST v1.1) and OS

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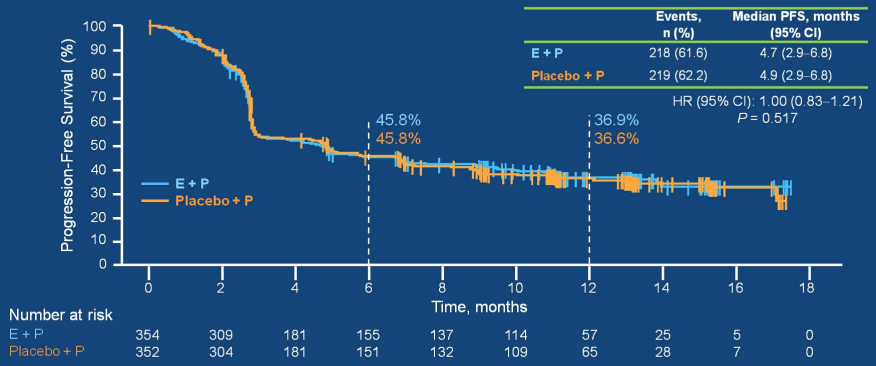
Progression-Free Survival (RECIST v1.1, BICR)



	Events, n (%)	Median PFS, months (95% CI)
E + P	218 (61.6)	4.7 (2.9–6.8)
Placebo + P	219 (62.2)	4.9 (2.9–6.8)

HR (95% CI): 1.00 (0.83–1.21)
P = 0.517

Number at risk

E + P	354	309	181	155	137	114	57	25	5	0
Placebo + P	352	304	181	151	132	109	65	28	7	0

BICR, blinded independent central review; CI, confidence interval; E, epacadostat; HR, hazard ratio; P, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors. PFS defined as time from randomization to disease progression or death, whichever occurred first.

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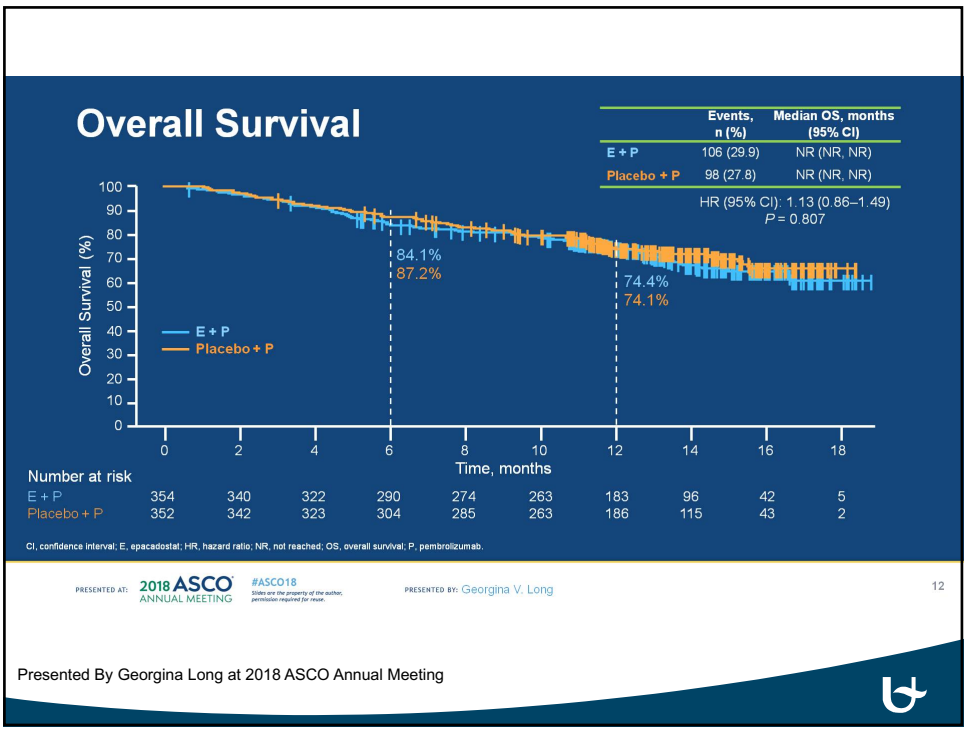

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NewLink GENETICS

PROTOCOL NUMBER: NLG2107

TITLE: A Phase 2/3 (Adaptive Design) Study of the Concomitant Administration of Indoximod or Placebo plus Pembrolizumab or Nivolumab in Adult Patients with Unresectable Stage III or Stage IV Malignant Melanoma

NCT03301636

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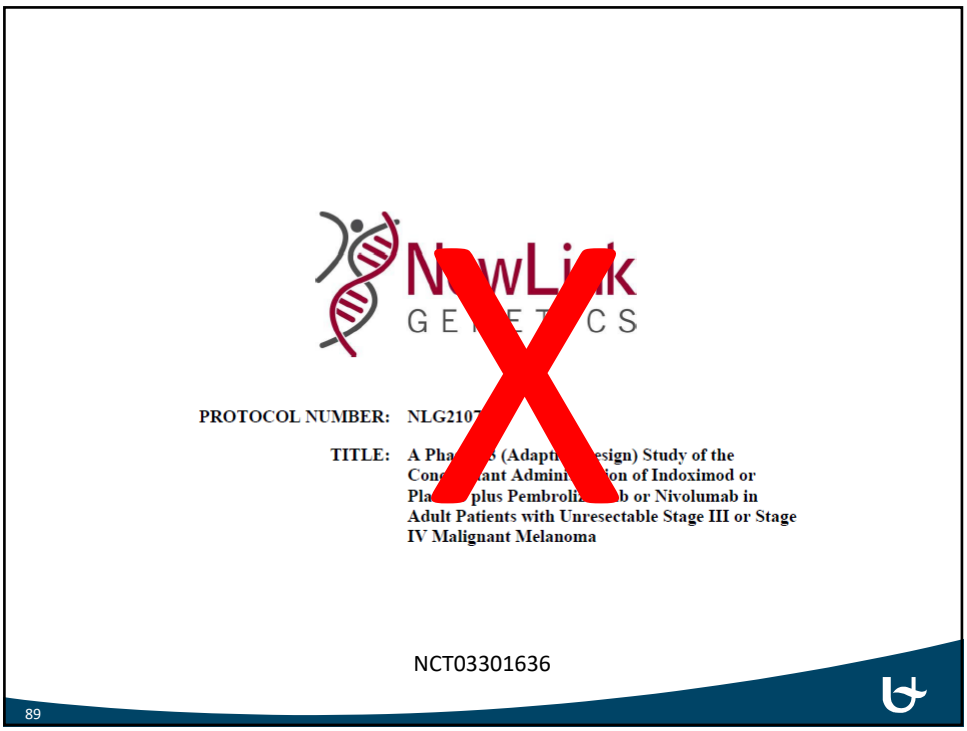
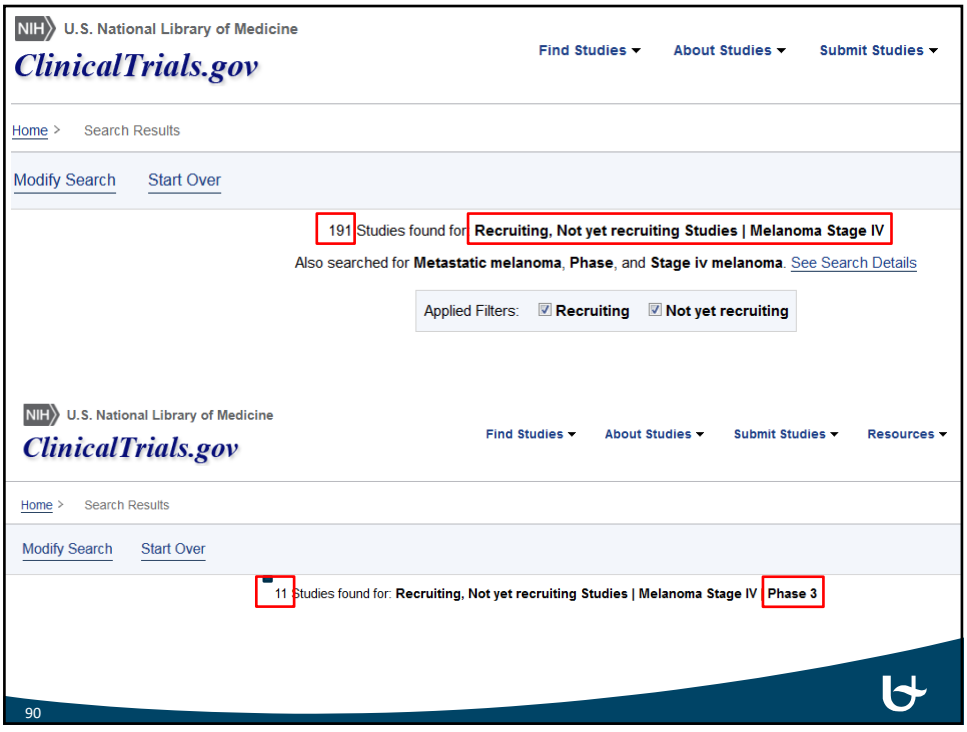

PROTOCOL NUMBER: NLG2107
TITLE: A Pha (Adapti esign) Study of the
Con ant Admini ion of Indoximod or
Pla plus Pembroli b or Nivolumab in
Adult Patients with Unresectable Stage III or Stage
IV Malignant Melanoma
NCT03301636
89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Start Over
191 Studies found for Recruiting, Not yet recruiting Studies | Melanoma Stage IV
Also searched for Metastatic melanoma, Phase, and Stage iv melanoma. See Search Details
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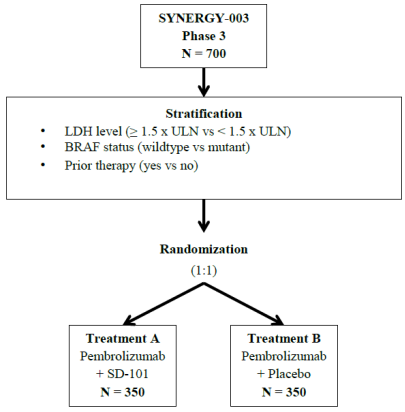
11 Studies found for: Recruiting, Not yet recruiting Studies | Melanoma Stage IV Phase 3
90

Protocol Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Pembrolizumab in Combination With SD-101 or Placebo in Cancer-Immunotherapy Naïve Subjects With Unresectable or Metastatic Melanoma

Protocol No.: SYNERGY-003

Study Design Schema



TLR9 agonist

91

A Study of NKTR-214 Combined With Nivolumab vs Nivolumab Alone in Participants With Previously Untreated Inoperable or Metastatic Melanoma

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03635983

Recruitment Status : Recruiting
First Posted : August 17, 2018
Last Update Posted : December 4, 2018

See Contacts and Locations

Sponsor:
Bristol-Myers Squibb

Collaborator:
Nektar Therapeutics

Information provided by (Responsible Party):
Bristol-Myers Squibb

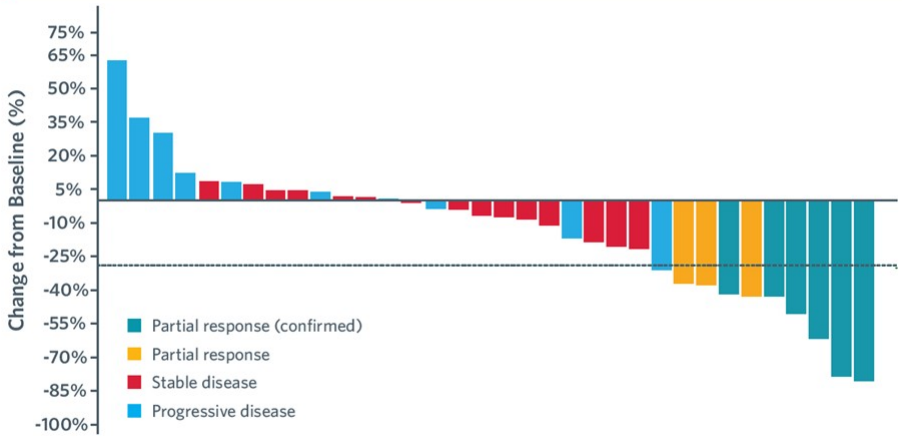
prodrug of conjugated IL2

92

Efficacy and safety of entinostat (ENT) and pembrolizumab (PEMBRO) in patients with melanoma progressing on or after a PD-1/L1 blocking antibody.

Sanjiv S. Agarwala[1], Stergios J. Moschos[2], Melissa Lynne Johnson[3], Mateusz Opyrchal[4], Dmitry Gabrilovich[5], Patrick Danaher[6], Fang Wang[6], Susan Brouwer[6], Peter Ordentlich[6], Serap Sankoh[6], Emmett V. Schmidt[7], Michael L. Meyers[8], Ryan J. Sullivan[9]
[1]St. Luke's Hospital, Easton, PA; [2]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; [3]Sarah Cannon Research Institute, Nashville, TN; [4]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [5]The Wistar Institute, Philadelphia, PA; [6]NanoString Technologies, Inc., Seattle, WA; [7]Syndax Pharmaceuticals, Inc., Waltham, MA; [8]Merck & Co., Inc., Kenilworth, NJ; [9]Syndax Pharmaceuticals, Inc., New York, NY; [9]Massachusetts General Hospital, Boston, MA. For inquiries regarding this poster, please email: ssagarwala0501@gmail.com

Figure 2. **Percentage Change in Tumor Size from Baseline (Sum of Diameters of Target Lesions).** Nine partial responses have been observed to date.



93

A Phase I/II Study of the PI3Kβ inhibitor GSK2636771 in combination with Pembrolizumab (P) in Patients (pts) with PD-1 refractory metastatic melanoma (MM) and PTEN Loss

Hussein A. Tawbi, Weiyi Peng, Denái R. Milton, Rodabe N. Amaria, Adi Diab, Isabella C. Glitza, Wen-Jen Hwu, Sapna P. Patel, Michael K. K. Wong, Scott Woodman, Cassian Yee, Jennifer McQuade, Michael Tetzlaff, Alexander Lazar, Suzanne Cain, Elizabeth M. Burton, Patrick Hwu, Michael A. Davies
The University of Texas MD Anderson Cancer Center, Houston, Texas

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- SX-682: can block cancers from attracting myeloid-derived suppressor cells (MDSCs)
- ADU-1604: anti-CTLA-4 monoclonal antibody
- Autologous dendritic cells loaded with autologous tumor antigens (ATA)
- JS001: monoclonal antibody against programmed cell death protein 1 (PDCD-1)
- Relatlimab: anti-lymphocyte activation gene-3 (anti-LAG-3)
- BGB324: inhibitor of Axl
- …….

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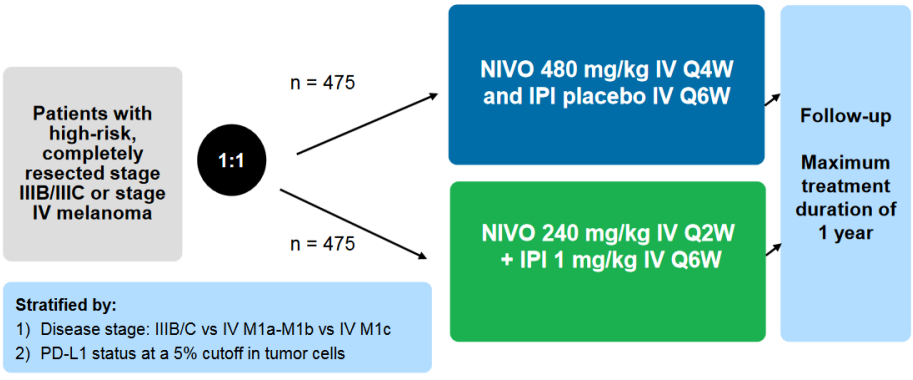
Adjuvante behandeling

	KEYNOTE-054		CheckMate 238		Combi-AD	
	Pembrolizumab	Placebo	Nivolumab	Ipilimumab	D/T	placebo
Median FU	14.7	15.4	19.5		44	42
Relapse-free survival						
HR	**0.57**		**0.65**		**0.49**	
95 % CI	**0.43-0.74**		**0.51-0.83*** **		**0.40-0.59**	
p	**<0.001**		**<0.001**		**<0.001**	
V600E mutation						
HR	**0.59**		**0.72**			
95 % CI	**0.38-0.92[§]**		**0.52-1.00**			
Any adverse event	93.3%	90.2%	96.9%	98.5%	97%	88%
Grade 3-4 adverse events	**31.6%**	**18.5%**	**25.4%**	**55.2%**	**41%**	**14%**
Study treatment related grade 3-4 AEs	**14.7%**	**3.4%**	**14.4%**	**45.9%**	**41%**	**14%**
discontinuation	**13.8%**	2.2%	**9.7%**	42.6%	**26%**	3%

97

CA209-915: Study Design



Stratified by:
1) Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c
2) PD-L1 status at a 5% cutoff in tumor cells

Anticipated enrollment period: September 30, 2017 to November 30, 2018

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UPDATED RELAPSE-FREE SURVIVAL AND BIOMARKER ANALYSIS IN THE COMBI-AD TRIAL OF ADJUVANT DABRAFENIB + TRAMETINIB IN PATIENTS WITH RESECTED *BRAF* V600–MUTANT STAGE III MELANOMA

Georgina V. Long, Axel Hauschild, Mario Santinami, Victoria Atkinson, Mario Mandalà, Vanna Chiarion-Sileni, James Larkin, Caroline Robert, Dirk Schadendorf, Kohinoor Dasgupta, Mark Shilkrut, James Garrett, Jan C. Brase, Richard Kefford, John M. Kirkwood, Reinhard Dummer

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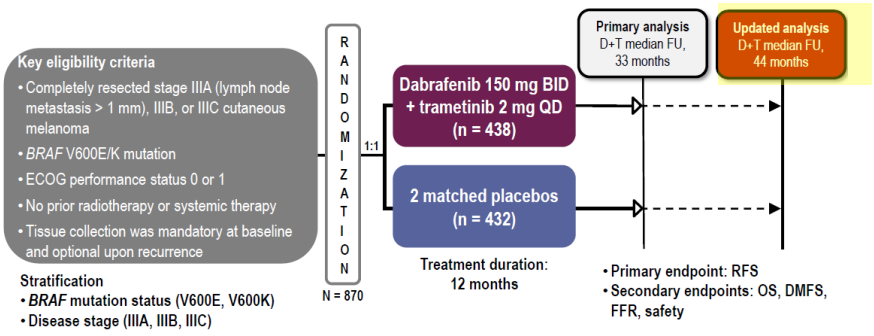
COMBI-AD: STUDY DESIGN—EXTENDED FOLLOW-UP ANALYSIS



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

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

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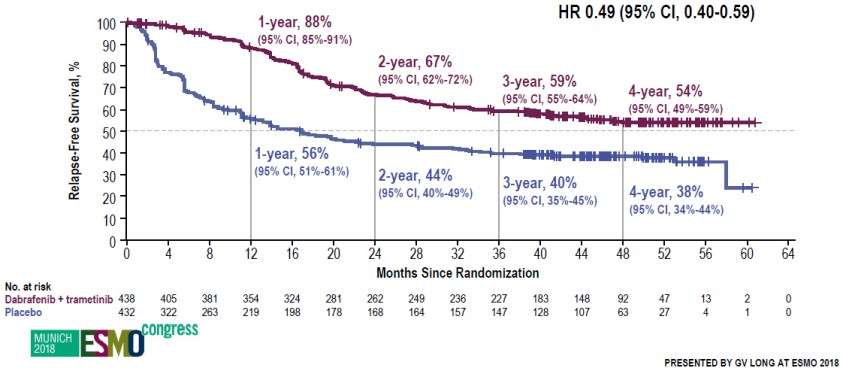
RELAPSE-FREE SURVIVAL



MUNICH 2018 ESMO congress

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2018 ASCO ANNUAL MEETING

Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: Updated Results from a Phase 3 Trial (CheckMate 238)

Jeffrey Weber,[1] Mario Mandala,[2] Michele Del Vecchio,[3] Helen Gogas,[4] Ana M. Arance,[5] C. Lance Cowey,[6] Stéphane Dalle,[7] Michael Schenker,[8] Vanna Chiarion-Sileni,[9] Ivan Marquez-Rodas,[10] Jean-Jacques Grob,[11] Marcus Butler,[12] Mark R. Middleton,[13] Michele Maio,[14] Victoria Atkinson,[15] Reinhard Dummer,[16] Veerle de Pril,[17] Anila Qureshi,[17] Abdel Saci,[17] James Larkin,[18*] Paolo A. Ascierto[19*]

[1]NYU Perlmutter Cancer Center, New York, New York, USA; [2]Papa Giovanni XIII Hospital, Bergamo, Italy; [3]Medical Oncology, National Cancer Institute, Milan, Italy; [4]University of Athens, Athens, Greece; [5]Hospital Clinic de Barcelona, Barcelona, Spain; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, Texas, USA; [7]Hospices Civils de Lyon, Pierre Bénite, France; [8]Oncology Center Sf Nectarie Ltd., Craiova, Romania; [9]Oncology Institute of Veneto IRCCS, Padua, Italy; [10]General University Hospital Gregorio Marañón, Madrid, Spain; [11]Hôpital de la Timone, Marseille, France; [12]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [13]Churchill Hospital, Oxford, United Kingdom; [14]Center for Immuno-Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [15]Gallipoli Medical Research Foundation and University of Queensland, Brisbane, Australia; [16]University Hospital Zurich, Switzerland; [17]Bristol-Myers Squibb, Princeton, New Jersey, USA; [18]Royal Marsden NHS Foundation Trust, London, UK; [19]Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; *Contributed equally to this study.

Abstract Number 9502

CheckMate 238: 24-Month Follow-Up

CheckMate 238: Study Design

Patients with:
- High-risk, completely resected stage IIIB/IIIC or stage IV (AJCC 7th edition) melanoma
- No prior systemic therapy
- ECOG 0-1

1:1

n = 453 → NIVO 3 mg/kg IV Q2W and IPI placebo IV Q3W for 4 doses then Q12W from week 24

n = 453 → IPI 10 mg/kg IV Q3W for 4 doses then Q12W from week 24 and NIVO placebo IV Q2W

Follow-up

Maximum treatment duration of 1 year

Stratified by:
1) Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c
2) PD-L1 status at a 5% cutoff in tumor cells

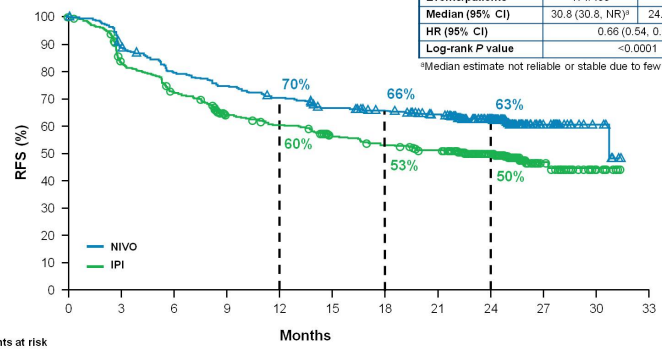
Enrollment period: March 30, 2015 to November 30, 2015

CheckMate 238: 24-Month Follow-Up

Primary Endpoint: RFS in All Patients

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

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



Number of patients at risk

NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

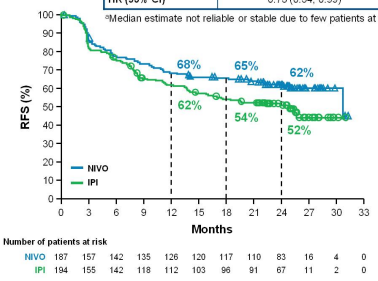
CheckMate 238: 24-Month Follow-Up

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

	NIVO	IPI
Events/patients	73/187	95/194
Median (95% CI)	30.8 (30.8, NR)[a]	24.6 (14.8, NR)
HR (95% CI)	0.73 (0.54, 0.99)	

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

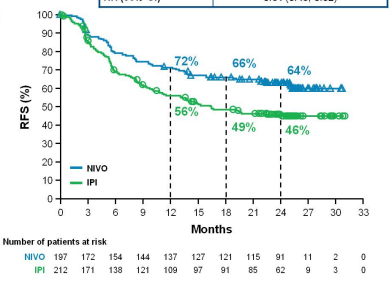


Number of patients at risk

NIVO	187	157	142	135	126	120	117	110	83	16	4	0
IPI	194	155	142	118	112	103	96	91	67	11	2	0

BRAF Wild type

	NIVO	IPI
Events/patients	73/197	107/212
Median (95% CI)	NR	16.6 (11.4, NR)
HR (95% CI)	0.61 (0.45, 0.82)	



Number of patients at risk

NIVO	197	172	154	144	137	127	121	115	91	11	2	0
IPI	212	171	138	121	109	97	91	85	62	9	3	0

Dank U

Vragen?

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