LIMBURGS ONCOLOGISCH CENTRUM VZW

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UHASSELT
KNOWLEDGE IN ACTION

De behandeling van het maligne melanoom

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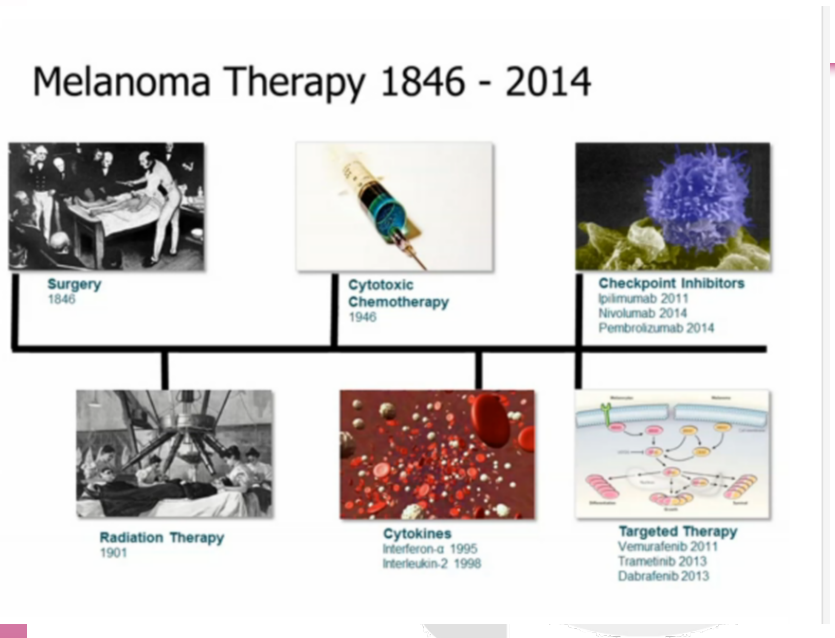
Melanoompunt

Disclosures

- Research funding, advisory boards, travel grants for this topic:
  - MSD, BMS, Pierre Fabre, Roche

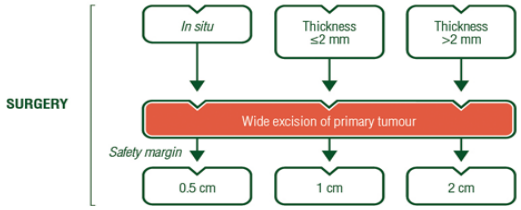
Inhoud voordracht

- Behandeling lokaal beperkt melanoom
- Behandeling gemetastaseerd melanoom
  - Target Therapie
  - Immuuntherapie
  - Andere
- Speciale situaties: Hot news!
  - Adjuvant beleid
  - Hersenuitzaaiingen



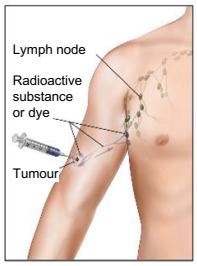
Behandeling gelokaliseerde ziekte

Heelkunde : brede excisie!



Micro-staging of Melanoma[1–4]

- Sentinel lymph node biopsy (SLNB)
  - Number of tumour-positive nodes highly predictive for survival
  - Used to detect micro-metastases
  - Appropriate for patients in whom neither palpation nor lymph node sonography has suggested the presence of lymph node metastases



Radioactive substance and/or dye is injected near the tumour

Injected material detected visually and/or with a probe that detects radioactivity

Sentinel nodes are the first lymph nodes to take up the material and are removed and checked for cancer cells

[1]Garbe C, et al. *Eur J Cancer* 2010;46:270–83
[2]Dummer R. *Ann Oncol* 2010;21(Suppl. 5):v194–7
[3]NCI. *Melanoma Treatment PDQ*. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/Patient/
[4]DeVita VT, et al. In: *Cancer, Principles & Practice of Oncology*. 8th ed: Philadelphia PA, Wolters Kluwer/Lippincott Williams & Wilkins; 2008

Richtlijn sentinel klier ESMO

- Sentinel LN biopsy in melanoma with a tumour thickness of >1 mm and >0.75 mm and additional risk factors such as ulceration or mitotic rate (pT1b) are recommended for precise staging
- Sentinel LN biopsy should be carried out only in experienced centres.

Wat te doen igv + SN

4 studies mbt nut van resectie alle lymfeklieren…

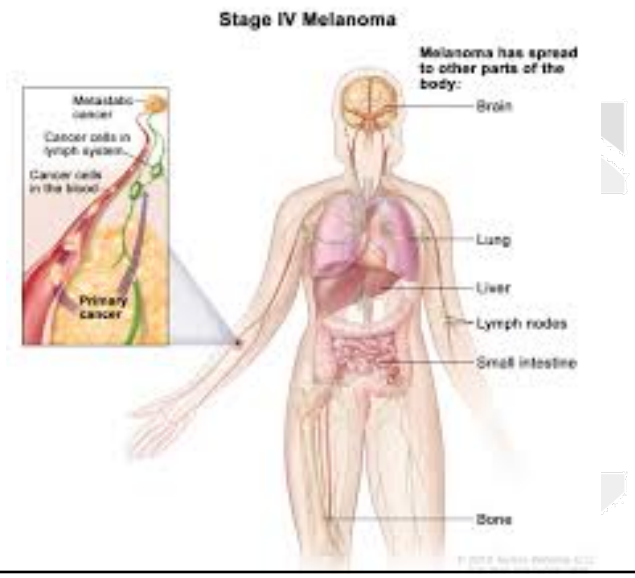
1.Kingham TP, Panageas KS, Ariyan CE, et al: Ann Surg Oncol 17:514-520, 2010.
2. Leiter U, Stadler R, Mauch C, et al: Lancet Oncol 17:757-767, 2016.
3. Faries MB, Thompson JF, Cochran AJ, et al: Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 376:2211-2222, 2017.
4. Balch CM, Soong S, Ross MI, et al: Intergroup Melanoma Surgical Trial. Ann Surg Oncol 7:87-97, 2000.

Conclusie

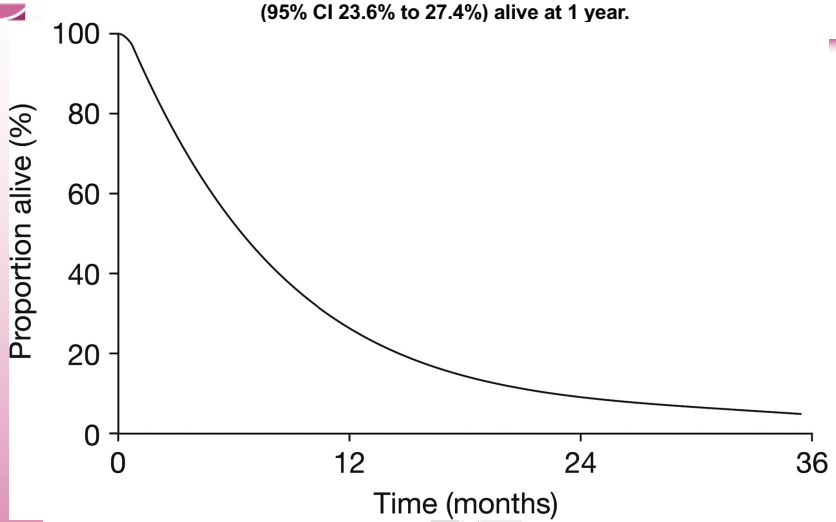
- Geen winst in overleving
- risico op complicaties
- Van belang prognostisch?

Enkel nog voor geselecteerde patiënten

Het gemetastaseerde melanoom (stadium IV)



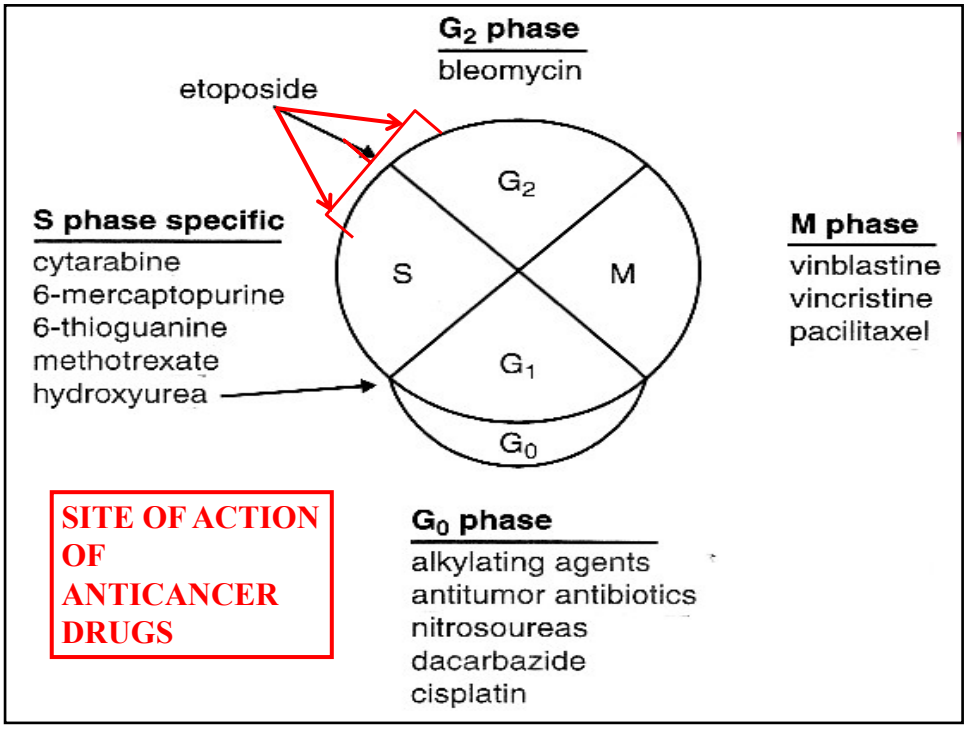
Among 2100 patients with metastatic melanoma enrolled in phase II trials, the median survival time was 6.2 months [95% confidence interval (CI) 5.9–6.5 months], with 25.5% (95% CI 23.6% to 27.4%) alive at 1 year.



Maio M Ann Oncol 2012;23:viii10-viii14

Systeem therapieën bij het MM

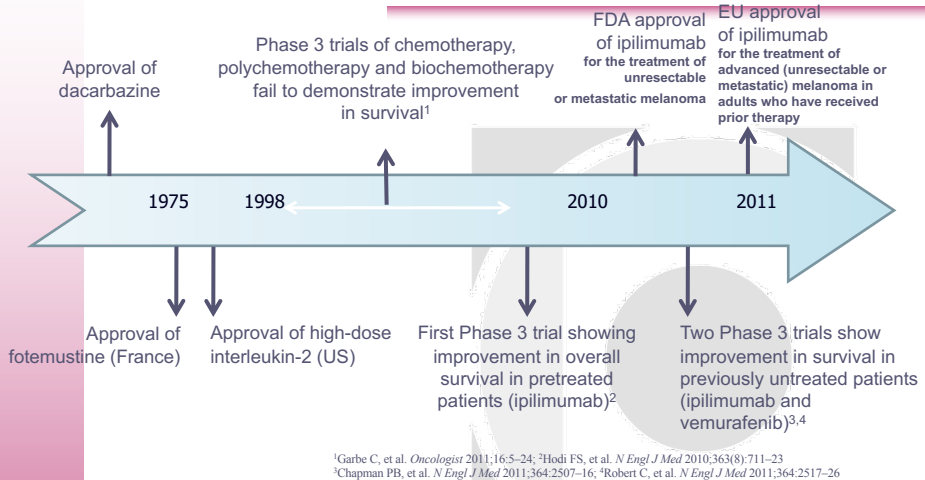
- BRAF en MEK inhibitoren
  - Tafinlar/Mekinist
  - Zelboraf/Cotellic
- Immuuntherapie
  - Yervoy (ipilimumab)
  - Opdivo (Nivolumab)
  - Keytruda (Pembrolizumab)
  - Combinaties
- Chemotherapie
  - DTIC, CDDP, Taxol, …



Welk effect heeft chemotherapie?

TABLE 4: Selected chemotherapy agents – Results from phase II and phase III trials in melanoma

Chemotherapy	Patients (N)	Objective response rate
Alkylating agents		
Dacarbazine	2,470	18%
Temozolomide	350	15%
Nitrosoureas		
Lomustine	270	13%
Fotemustine	153	24%
Platinum analog		
Cisplatin	188	23%
Carboplatin	43	16%
Microtubule stabilizing/destabilizing		
Paclitaxel	85	13%
Docetaxel	105	11%
Vincristine	52	12%
Vinblastine	62	13%
Vindesine	273	14%

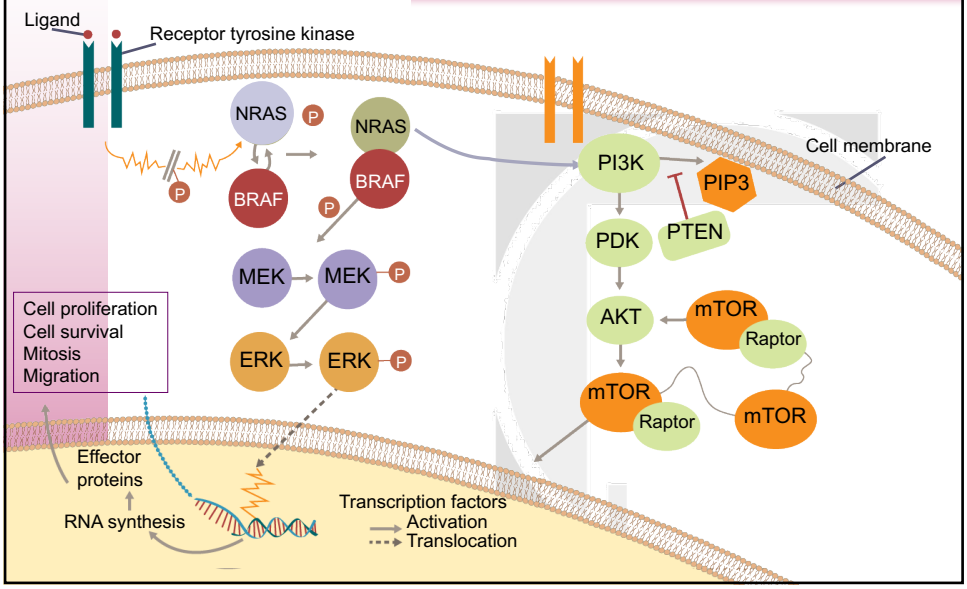


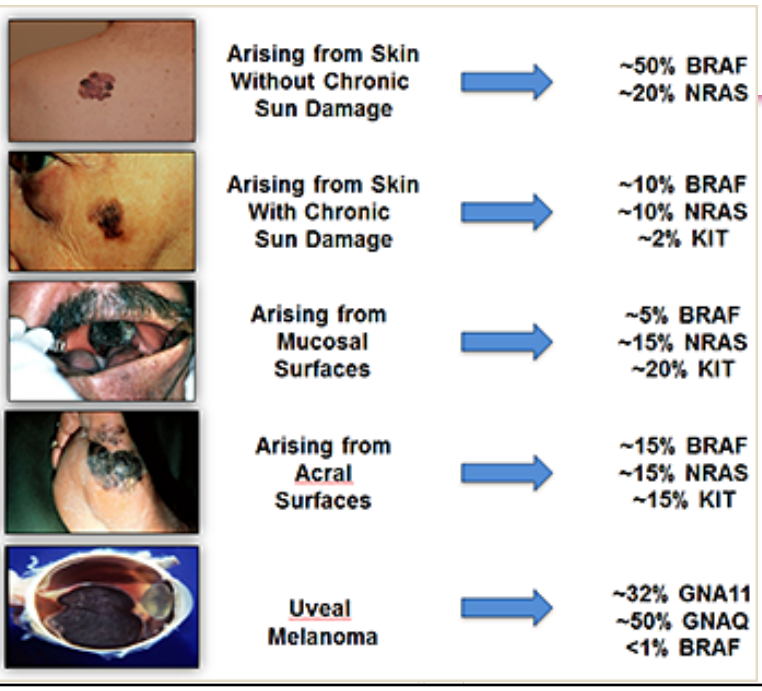
[1]Garbe C, et al. *Oncologist* 2011;16:5–24; [2]Hodi FS, et al. *N Engl J Med* 2010;363(8):711–23
[3]Chapman PB, et al. *N Engl J Med* 2011;364:2507–16; [4]Robert C, et al. *N Engl J Med* 2011;364:2517–26

BRAF en MEK-inhibitoren

- = doelgerichte therapie!

Melanoma cell-signalling pathways
The MAPK and PI3K pathways



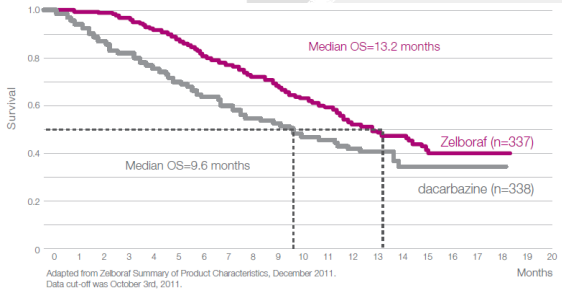


Welk effect hebben BRAF inhibitoren?

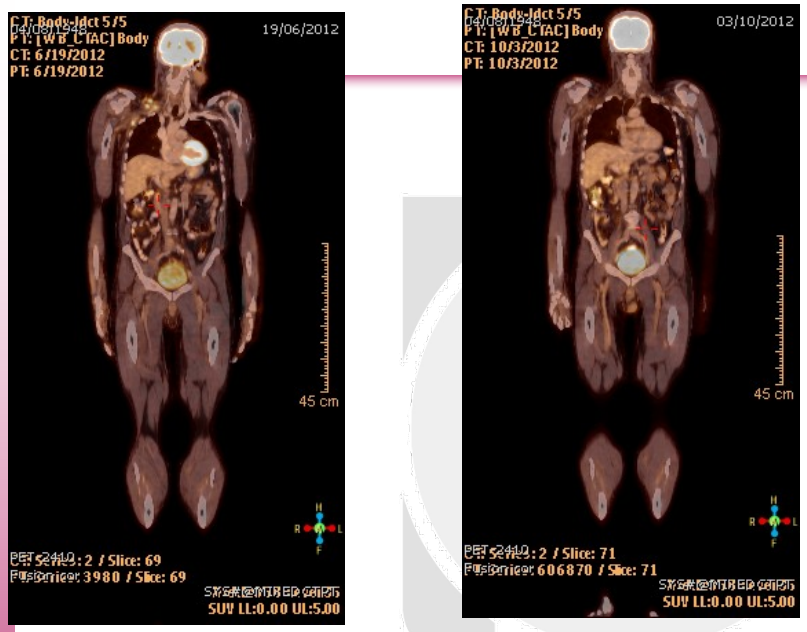
Vemurafenib efficacy in previously untreated patients

BRIM3

- Overall Survival in 1L stage IIIC and IV melanoma: Zelboraf vs DTIC



- Median Progression-free survival **tripled** in Zelboraf arm (5.6 mo) vs. DTIC (1.6 mo)
- Overall Response Rate **9x** higher in Zelboraf arm (48%) vs DTIC (5.5%)

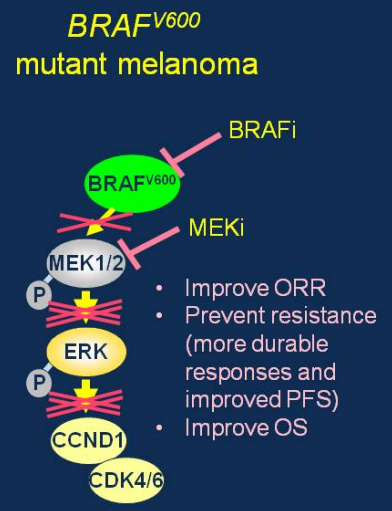


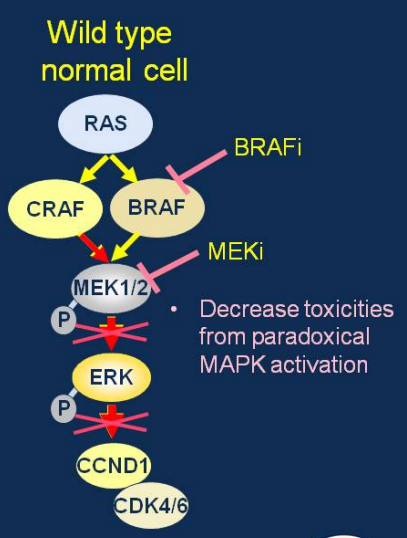
Nevenwerkingen

Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100
	Folliculitis	
CuSCC , seborrheic keratosis, skin papilloma	Basal cell carcinoma	
Decreased appetite		
Headache, dysgeusia	7th nerve paralysis	Neuropathy peripheral
	Uveitis	Retinal vein occlusion
		Vasculitis
Cough		
Diarrhoea, vomiting, nausea, constipation		
Photosensitivity reaction, actinic keratosis, rash, pruritus, hyperkeratosis, erythema, alopecia, dry skin, sunburn	Palmar-plantar erythrodysaesthesia syndrome,erythema nodosum, keratosis pilaris	Toxic epidermal necrolysis, Stevens-Johnson syndrome
Arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain	Arthritis	
Fatigue, pyrexia, oedema peripheral, asthenia		
GGT increase	ALT, alkaline phosphatase & bilirubin increase weight decreased	AST increase

Impact van BRAF en MEK inhibitie

Double oncogenic pathway inhibition to treat melanoma





Presented by: Antoni Ribas

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Antoni Ribas at 2014 ASCO Annual Meeting

Summary of responses and PFS of single agent BRAFi and BRAFi+MEKi combined therapy

	Chapman et al. 2011	Hauschild et al. 2012	Flaherty et al. 2013		Long et al. 2014	
Phase	III	III	II		III	
Agent	vemurafenib	dabrafenib	dabrafenib	dabrafenib + trametinib	dabrafenib	dabrafenib + trametinib
ORR	48%	50%	54%	76%	51%	67%
PFS	5.3 months	5.1 months	5.8 months	9.4 months	8.8 months	9.3 months

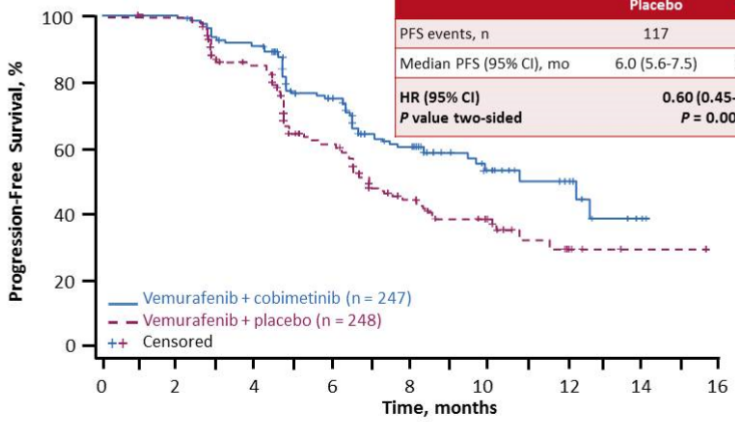
Presented by: Antoni Ribas

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

MADRID 2014 ESMO congress

PFS by Independent Review Facility

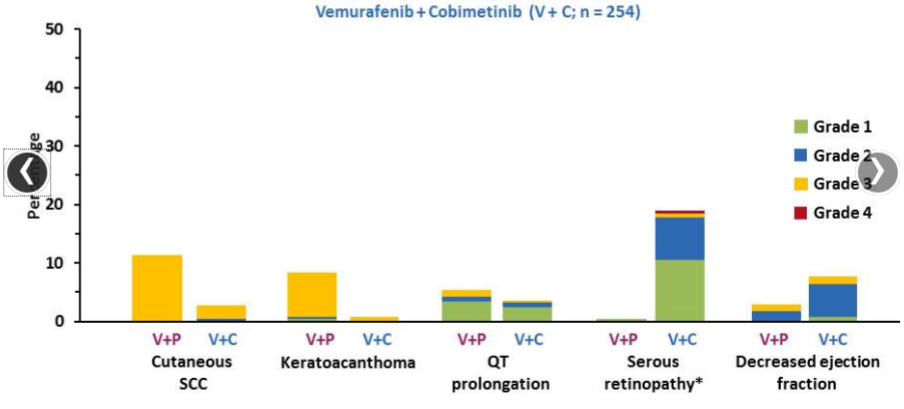
	Vemurafenib + Placebo	Vemurafenib + Cobimetinib
PFS events, n	117	82
Median PFS (95% CI), mo	6.0 (5.6-7.5)	11.3 (8.5-NE)
HR (95% CI)	**0.60 (0.45-0.79)**	
***P* value two-sided**	***P* = 0.0003**	



MADRID 2014 ESMO congress

coBRIM: Summary of Selected AEs

Vemurafenib + Placebo (V + P; n = 239)
Vemurafenib + Cobimetinib (V + C; n = 254)

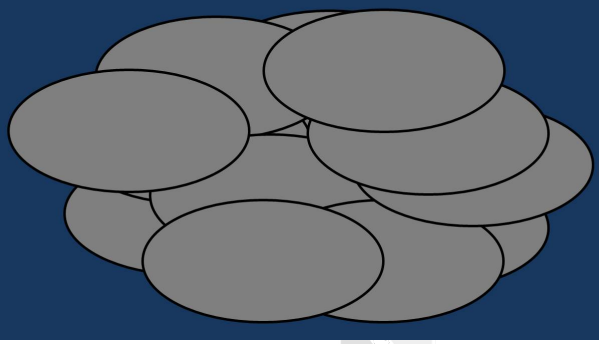


Immuuntherapie

Immunotherapy = T cell kills a tumor

Presented By Michael Postow at 2017 ASCO Annual Meeting

Tumor



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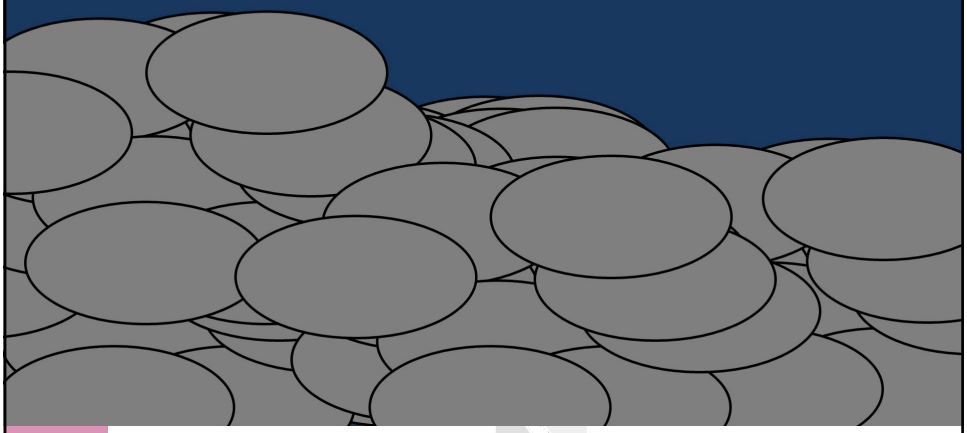
Tumors can be hard to see



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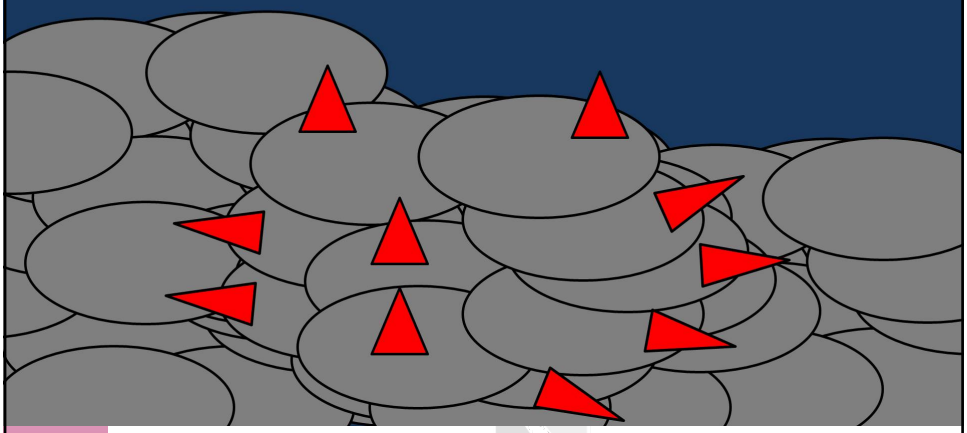
Tumors expressing antigens



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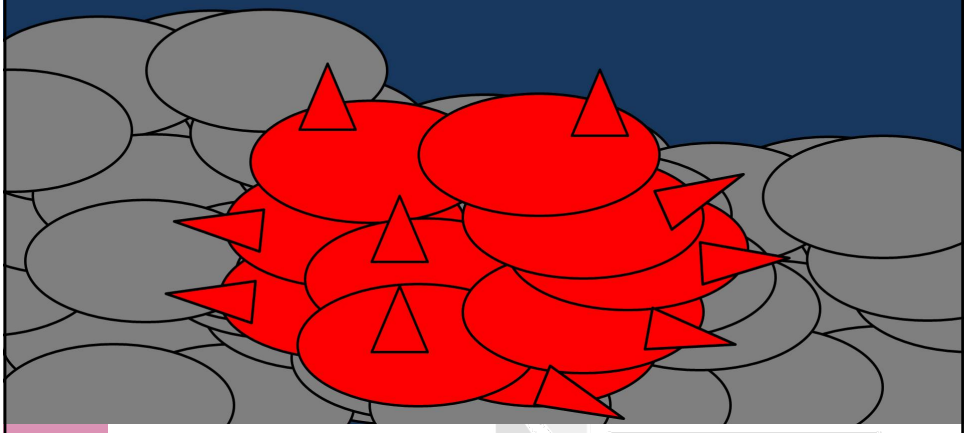
Tumor recognized as foreign



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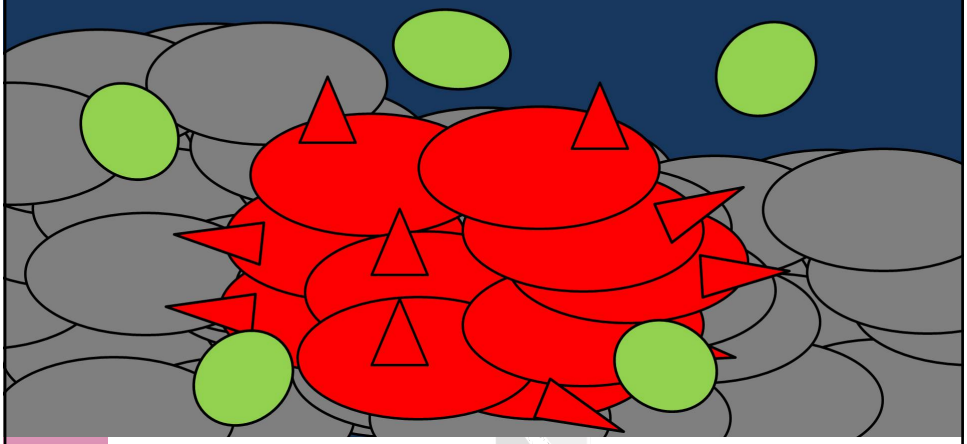
T cells in tumor microenvironment



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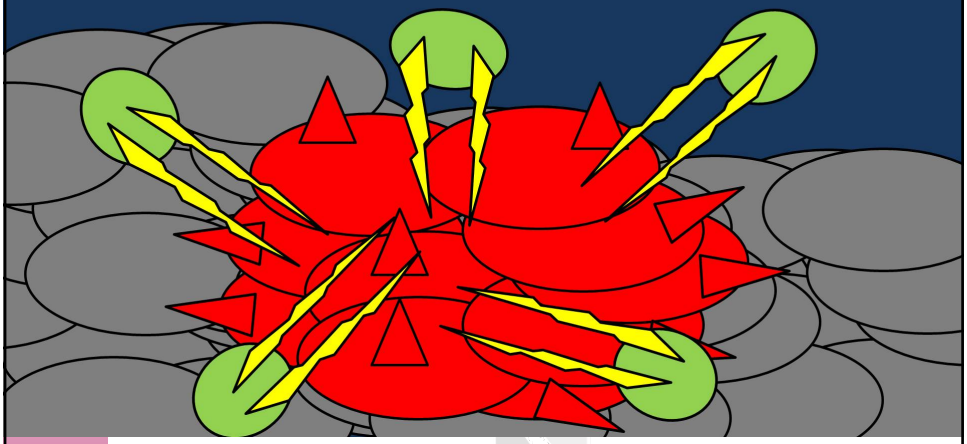
T cell attack



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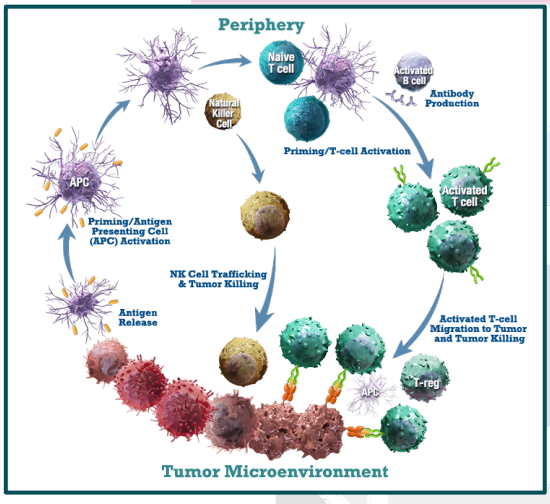
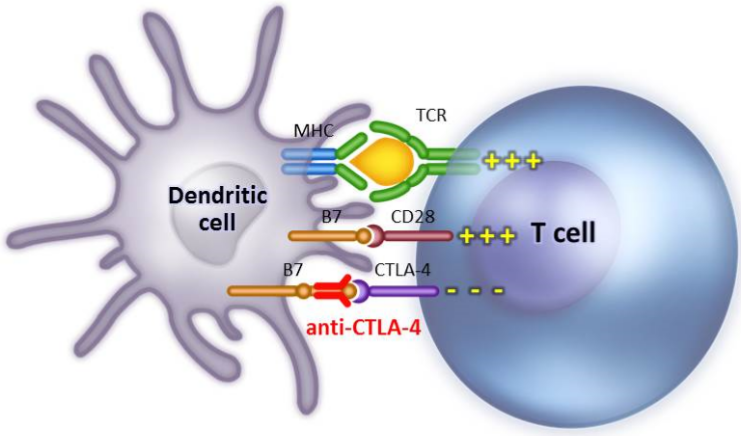
The Immune System Recognizes and Eliminates Cancer via Multiple, Complex Mechanisms



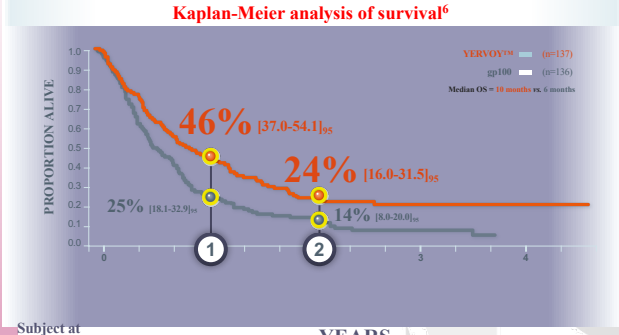
Immune Checkpoint Inhibitor Ipilimumab



Ipi: fully human, monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) to augment antitumor immunity[1]

- YERVOY™ monotherapy **increased median overall survival by 4 months**
over the control arm (10 months *vs.* 6 months, HR=0.66; $[0.51\text{-}0.87]_{95}$; p=0.0026)

Kaplan-Meier analysis of survival[6]



Adapted from Hodi *et al.* 2010

Subject at risk	YEARS													
YERVOY™	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

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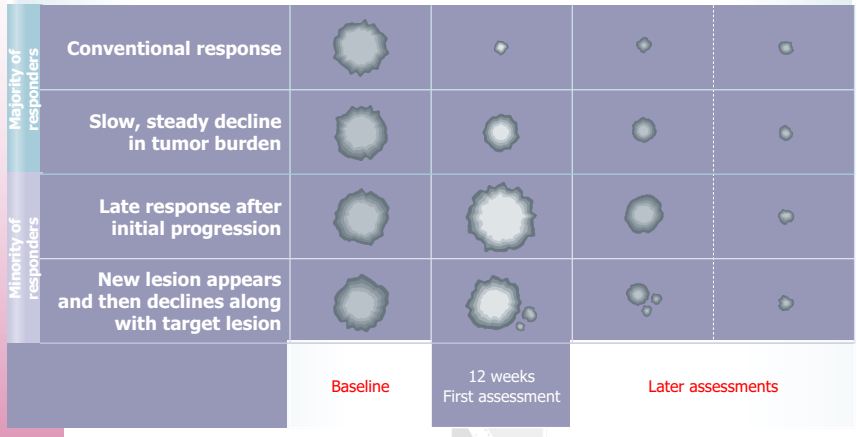
Potential changes in tumour burden with YERVOY™ [8]



Adapted from Wolchok *et al.* 2009

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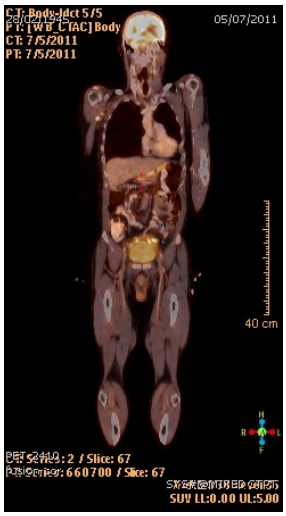
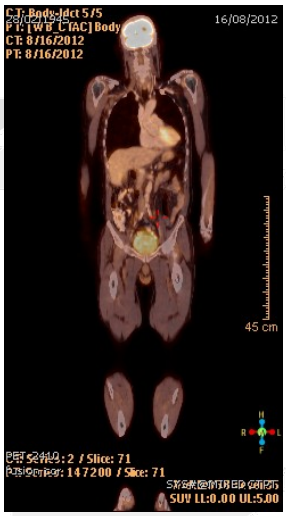
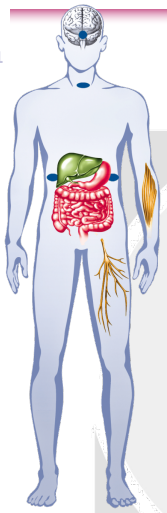
Ptn voorbeeld





- GASTROINTESTINAL[1]
  - **Signs and symptoms such as:**
    - Diarrhoea
    - Abdominal pain
    - Blood or mucus in stool
    - Bowel perforation
    - Peritoneal signs
    - Ileus
- **SKIN[1]**
  - **Symptoms such as:**
    - Pruritus
    - Rash
- **NEUROLOGIC[1]**
  - **Symptoms such as:**
    - Unilateral or bilateral weakness
    - Sensory alterations
    - Paraesthesia



- **ENDOCRINE[1]**
  - **Signs and symptoms such as:**
    - Fatigue
    - Headache
    - Mental status changes
    - Abdominal pain
    - Unusual bowel habits
    - Hypotension
    - Abnormal thyroid function tests and/or serum chemistries
- **LIVER[1]**
  - **Signs such as:**
    - Abnormal liver function
    - tests (e.g. elevated AST, ALT
    - or total bilirubin)
- **OTHER ADVERSE REACTIONS[1]**
  - **Including ocular manifestations**

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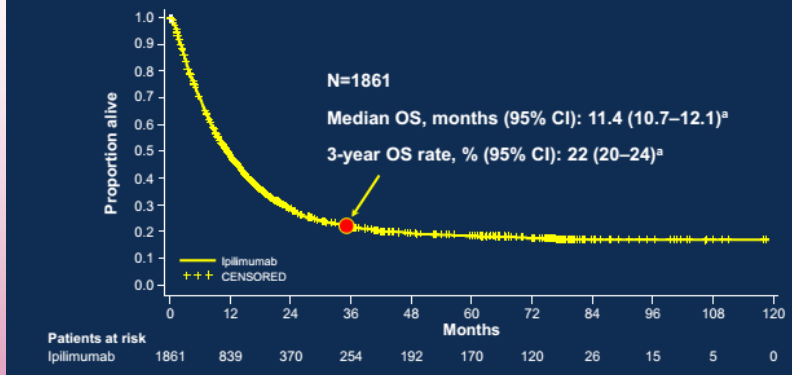
CTLA-4 Immune Checkpoint Pathway Inhibition Using Ipilimumab: Pooled OS Data From Melanoma Patients

- In a pooled analysis of 12 studies, an OS plateau starts at approximately 3 years with follow-up of up to 10 years in some patients



Patients at risk											
Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

[a]Ipilimumab was given at different doses and lines of therapy, and using different schedules across the 12 studies
Schadendorf D, et al. ECC Congress. 2013 Abs 124LBA

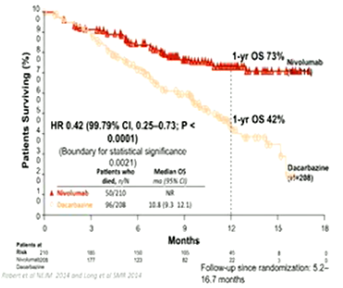
Presented by: F. Stephen Hodi, MD

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

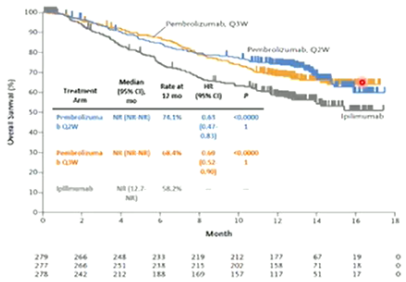
Anti PD1

Winst van Anti PD1 versus ipilimumab

Phase III
Nivolumab vs chemotherapy



Phase III
pembrolizumab vs ipilimumab



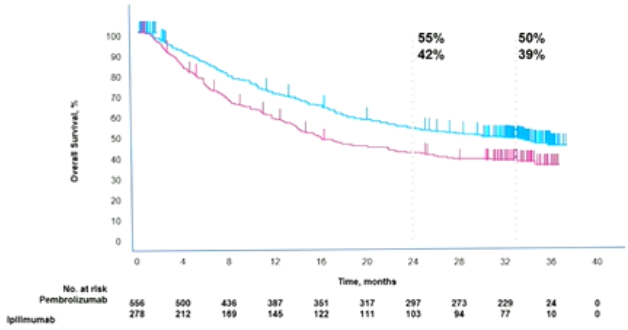
ORR 35-42%
Grade3/4 AE 15-17%
Anti-PD1 are superior to chemotherapy and to ipilimumab

Robert et al NEJM 2015

Robert et al NEJM 2015

Long term effect of pembrolizumab
Keynote 006 OS (Median Follow-Up, 33.9 mo)

Arm	Events, n	HR (95% CI)	Median, mo (95% CI)
Pembrolizumab	278	0.70 (0.58-0.86)	32.3 (24.5-NR)
Ipilimumab	155	—	15.9 (13.3-22.0)



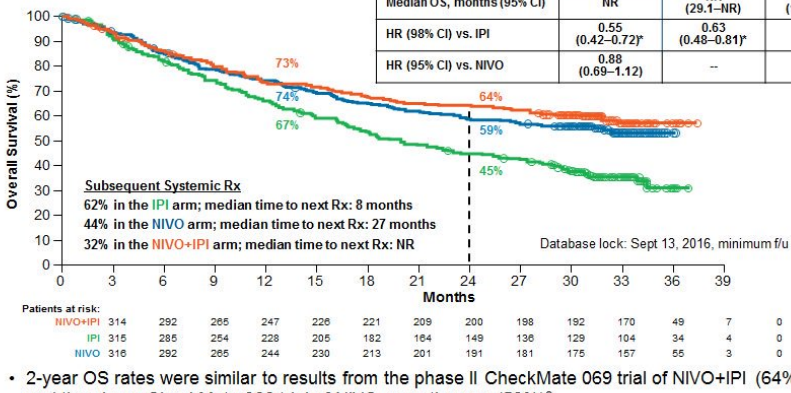
Robert et al ASCO 2017

Wat bij combinatie van immuuntherapie?

Overall Survival (Co-Primary Endpoint)

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, months (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Subsequent Systemic Rx
62% in the IPI arm; median time to next Rx: 8 months
44% in the NIVO arm; median time to next Rx: 27 months
32% in the NIVO+IPI arm; median time to next Rx: NR

Database lock: Sept 13, 2016, minimum f/u of 28 months

- 2-year OS rates were similar to results from the phase II CheckMate 069 trial of NIVO+IPI (64%)[1] and the phase CheckMate 066 trial of NIVO monotherapy (58%)[2]

1. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress; 2. Hodi FS, et al. *Lancet Oncol* 2016;17:1558–68.

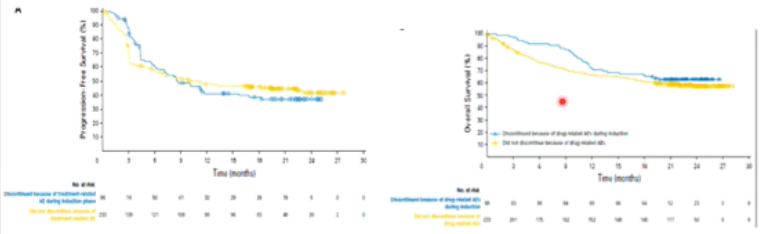
But : high toxicity of the combination

	Grade 3/5 AE %	discontinuation for AE %
Ipilimumab 3mg/kg	19	16
Nivolumab	13	6
Pembrolizumab	13	5
Ipilimumab + nivolumab	57	39

Ascierto et al ESMO 2016, Ascierto et al NEJM 2017; Ribas et al JAMA 2016; Atkinson et al SMR 2015; Wolchok et al NEJM 2017

Ipilimumab + nivolumab : pooled data from Checkmate 067 and 069

- PFS and OS not significantly different between the patients who discontinued for AE during the induction period and those who did not discontinue

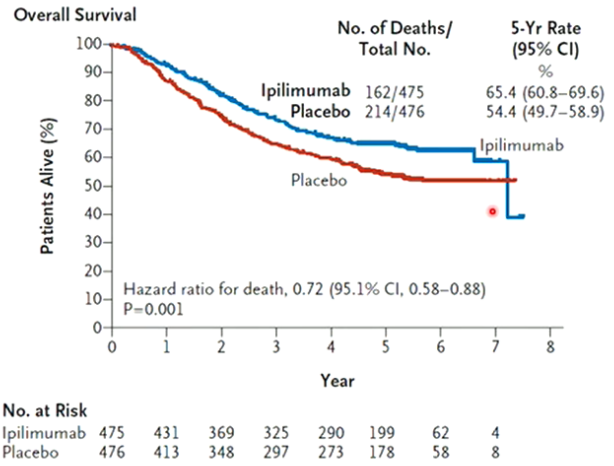


Schadendorf et al J Clin Oncol 2017

Hot news!

- Adjuvante behandelingen
- Hersenuitzaaiingen

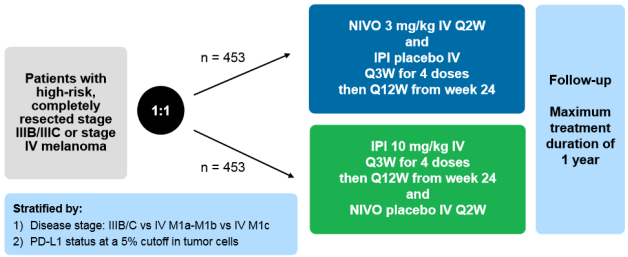
Adjuvant treatment with ipilimumab



Eggermont et al NEJM 2016

Adjuvante behandeling

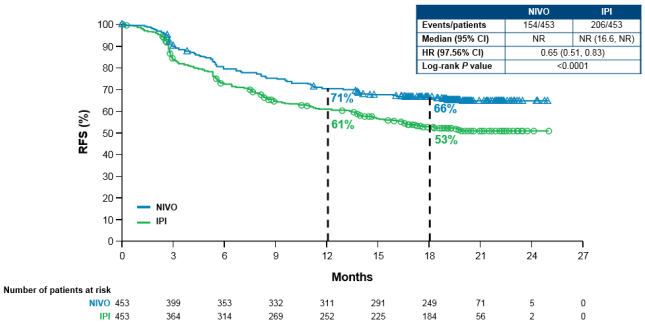
CA209-238: Study Design



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

4

Primary Endpoint: RFS



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

Number of patients at risk

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

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Safety Summary

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

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

Hersenuitzaaiingen

Studies report fantastic results….

Intracranial disease control rates

50%	60%	75%
ABC	CheckMate 204	COMBI MB

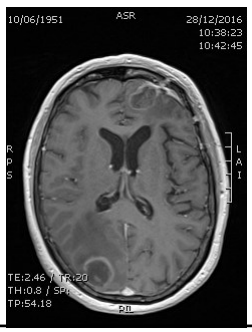
Presented By Lynn Schuchter at 2017 ASCO Annual Meeting

09/2016 progression frontal left metastasis with edema and dysarthria, with right occipital progressive disease

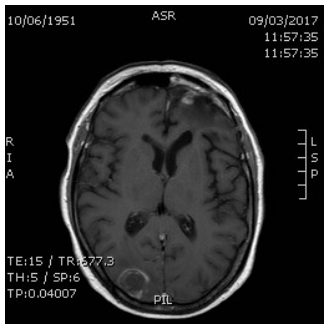
- Resection frontal metastasis: pathology metastatic melanoma, NRAS mutation

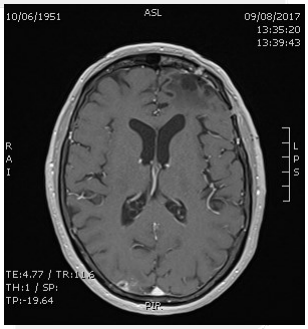
10/2016: stable disease

- Partial adrenal insufficiency: start Medrol, intolerance hydrocortisone



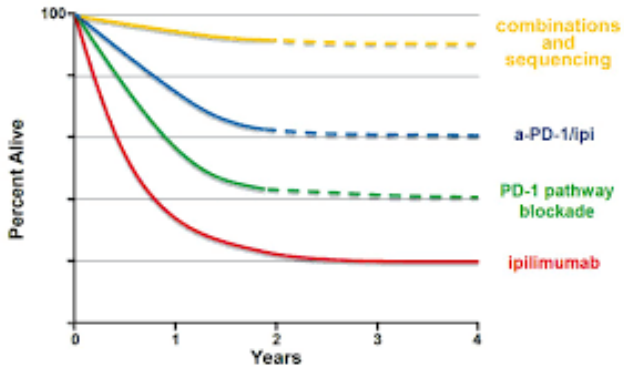
12/2016: relapse in operation zone with dural thickening and progression of metastasis right occiput





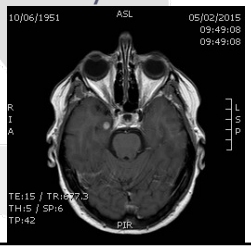
Conclusie

- Belangrijke vooruitgang in behandeling
- Genezing van ST IV????



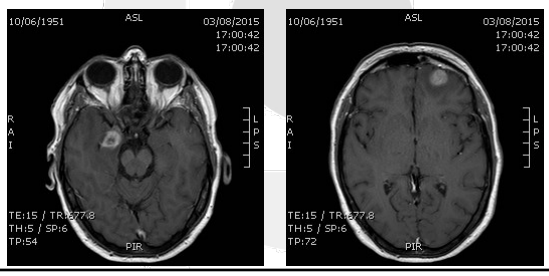
- Dank voor uw aandacht!

- 10/2013 Relapse locally in skin transplant
  - Broad excision 7.5 cm x 4,8 cm x 1 cm
  - NGS: BRAF wild type, NRAS mutation
- 07/2014 Metastatic lymph node left groin
  - groin complete lymph node extirpation
  - 3/13 lymph nodes metastatic involvement
- 02/2015 vomiting and headache: Solitary brain metastasis parasellair right



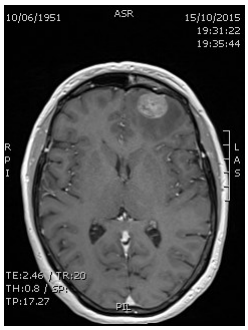
- Stereotactic radiosurgery 18 Gray

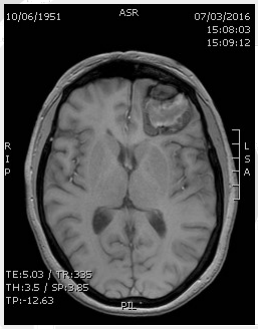
08/2015 new brain met left frontal: refusal of surgery or RT



11/2015 brain metastasis frontal left progressive and more symptoms

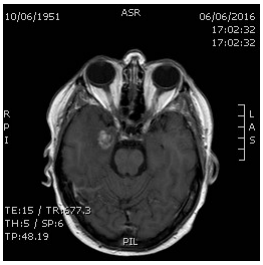
Refusal surgery, Stereotactic radiosurgery 16 Gray

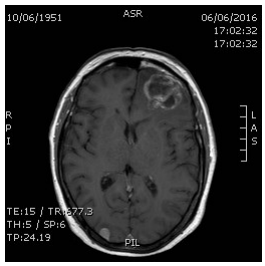




03/2016: bleeding in meta left frontal: start Medrol

06/2016 new asymptomatic metastatic brain lesion right occiput: SRS 20 Gray





09/2016 progression frontal left metastasis with edema and dysarthria, with right occipital progressive disease

- Resection frontal metastasis: pathology metastatic melanoma, NRAS mutation

10/2016: stable disease

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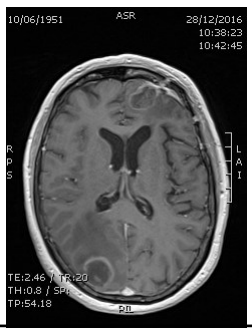


12/2016: relapse in operation zone with dural thickening and progression of metastasis right occiput

Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients with Melanoma Metastatic to the Brain: Results of the Phase II Study CheckMate 204

Hussein Tawbi,[1] Peter Forsyth,[2] Alain Algazi,[3] Omid Hamid,[4] F. Stephen Hodi,[5] Stergios Moschos,[6] Nikhil Khushalani,[2] Rene Gonzalez,[7] Christopher Lao,[8] Michael Postow,[9] Michael B. Atkins,[10] Marc Ernstoff,[11] Igor Puzanov,[11] Ragini Kudchadkar,[12] Reena Thomas,[13] Ahmad Tarhini,[14] Joel Jiang,[15] Alexandre Avila,[15] Sheena Demelo,[15] Kim Margolin[16]

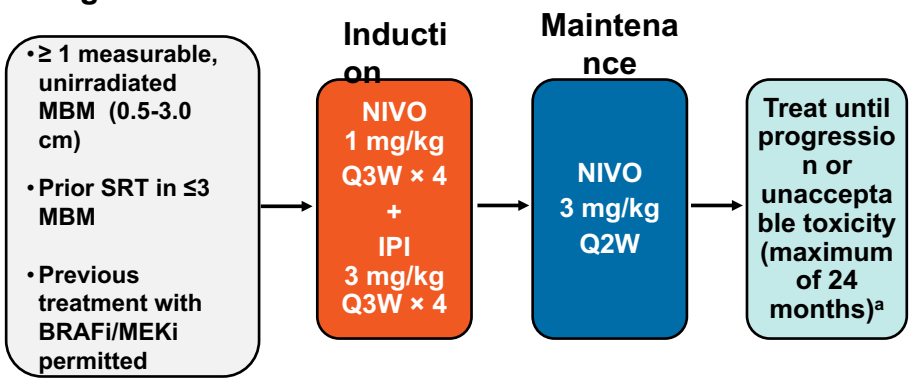
[1]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [2]Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [3]University of California-San Francisco, San Francisco, CA, USA; [4]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [7]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [8]University of Michigan, Ann Arbor, MI, USA; [9]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [10]Georgetown-Lombardi Comprehensive Cancer Center, Washington DC, USA; [11]Roswell Park Cancer Institute, Buffalo, NY, USA; [12]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [13]Stanford University Hospital, Palo Alto, CA, USA; [14]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [15]Bristol-Myers Squibb, Princeton, NJ, USA; [16]Department of Medical Oncology, City of Hope, Duarte, CA, USA

PRESENTED AT: ASCO ANNUAL MEETING | #ASCO17 Abstract Number 9507

Trial Design

Key eligibilities

- ≥ 1 measurable, unirradiated MBM (0.5-3.0 cm)
- Prior SRT in ≤3 MBM
- Previous treatment with BRAFi/MEKi permitted



- Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease
- Original planned enrollment of 110 asymptomatic patients

Q2W = every 2 weeks; Q3W = every 3 weeks

[a]Patients with grade 3-4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved; all patients who discontinued proceeded to follow-up

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Demographic and Patient Characteristics

	All patients (N = 75)
Male, n (%)	53 (71)
Median age, years (range)	59 (22–79)
***BRAF* mutation, n (%)**	41 (55)
***NRAS* mutation, n (%)**	5 (7)
LDH > ULN, n (%)	31 (41)
LDH > 2x ULN, n (%)	11 (15)
Prior systemic cancer therapy, n (%)	12 (16)
Dabrafenib/Trametinib	6 (8)
Vemurafenib	2 (3)
Prior SRT, n (%)	7 (9)
Median of median target lesion diameters, mm (IQR)	9.0 (6.5–14.0)
Target lesions, n (%)	
1-2 lesions	59 (79)
>3 lesions	16 (21)

IQR = interquartile range

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Response to Treatment – All Patients (N = 75)

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)

[a]Confirmed and unconfirmed progressive disease
[b]Includes unconfirmed responses
[c]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months

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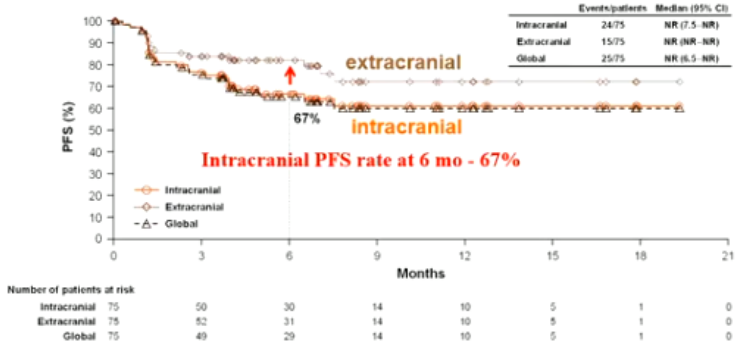
PFS



Intracranial PFS rate at 6 mo - 67%

Number of patients at risk

Intracranial	75	50	30	14	10	5	1	0
Extracranial	75	52	31	14	10	5	1	0
Global	75	49	29	14	10	5	1	0

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Treatment-related Adverse Events

Events reported in at least 5% of patients, n (%)*	All patients (N = 75) Any grade	Grade 3–4
Patients with an event	72 (96)	38 (52)
Skin	57 (76)	6 (8)
General disorders	45 (60)	5 (7)
Gastrointestinal	44 (59)	10 (13)
Endocrine	29 (39)	8 (11)
Nervous system	28 (37)	6 (8)
Musculoskeletal	25 (33)	1 (1)
Metabolism	18 (24)	4 (5)
Respiratory	13 (17)	2 (3)
Eye	11 (15)	1 (1)
Blood	6 (8)	0
Hepatobiliary	4 (5)	2 (3)
Psychiatric	4 (5)	0
Patients who discontinued due to an AE	29 (39)	19 (25)

*One death reported: treatment-related grade 5 myocarditis

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Treatment-related Nervous System AEs

n (%)	All treated patients (N = 75)	
	Any grade	Grade 3–4
Patients with an event	28 (37)	6 (8)
Headache	19 (25)	3 (4)
Paresthesia	3 (4)	0
Aphasia	2 (3)	0
Dysgeusia	2 (3)	0
Peripheral sensory neuropathy	2 (3)	0
Seizure	2 (3)	0
Brain edema	1 (1)	1 (1)
Carpal tunnel syndrome	1 (1)	0
Dizziness	1 (1)	0
Intracranial hemorrhage	1 (1)	1 (1)
Peripheral motor neuropathy	1 (1)	1 (1)
Polyneuropathy	1 (1)	0
Syncope	1 (1)	1 (1)
Tremor	1 (1)	0
Visual field defect	1 (1)	0

- Median time to onset of grade 3–4 nervous system AEs was 33 days (n=6)
- Median time to resolution of grade 3–4 nervous system AEs was 4 days (3/3)

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Summary/Conclusions

- In patients with advanced MEL and untreated brain metastases, NIVO+IPI demonstrates clinically meaningful efficacy, and can become a new treatment option
- With over 9 months of follow-up, NIVO+IPI resulted in an intracranial ORR of 55%, with 21% of patients achieving a complete response
  - Median PFS is not reached; 6-month PFS rate > 60%
- The safety profile was consistent with earlier experience in patients without MBM[1,2]
- Further investigations of systemic therapy should consider
  - Patients who are symptomatic/requiring steroids: cohort of 20 is actively enrolling
  - Approaches to incorporate and sequence radiation therapy
  - Earlier inclusion of this MBM population into randomized studies of novel combinations to accelerate drug development for MBM

1. Larkin J et al. *N Engl J Med.* 2015;373:23-34. 2. Hodi FS et al. *Lancet Oncol.* 2016;17:1558-1568.

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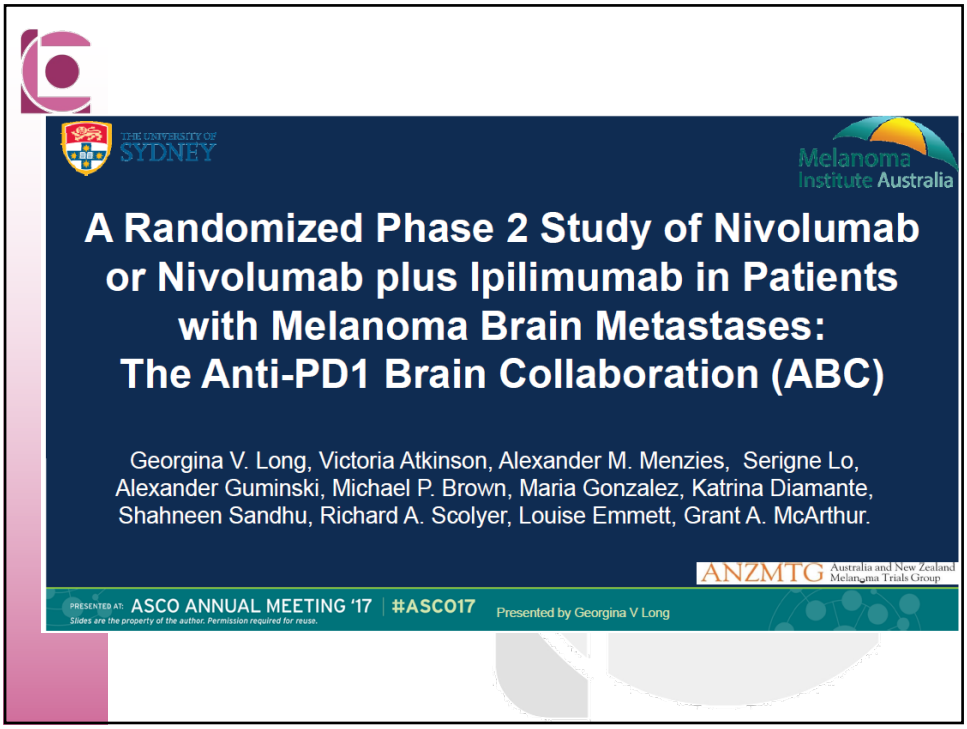
THE UNIVERSITY OF SYDNEY
Melanoma Institute Australia
A Randomized Phase 2 Study of Nivolumab or Nivolumab plus Ipilimumab in Patients with Melanoma Brain Metastases: The Anti-PD1 Brain Collaboration (ABC)
Georgina V. Long, Victoria Atkinson, Alexander M. Menzies, Serigne Lo, Alexander Guminski, Michael P. Brown, Maria Gonzalez, Katrina Diamante, Shahneen Sandhu, Richard A. Scolyer, Louise Emmett, Grant A. McArthur.
ANZMTG Australia and New Zealand Melanoma Trials Group
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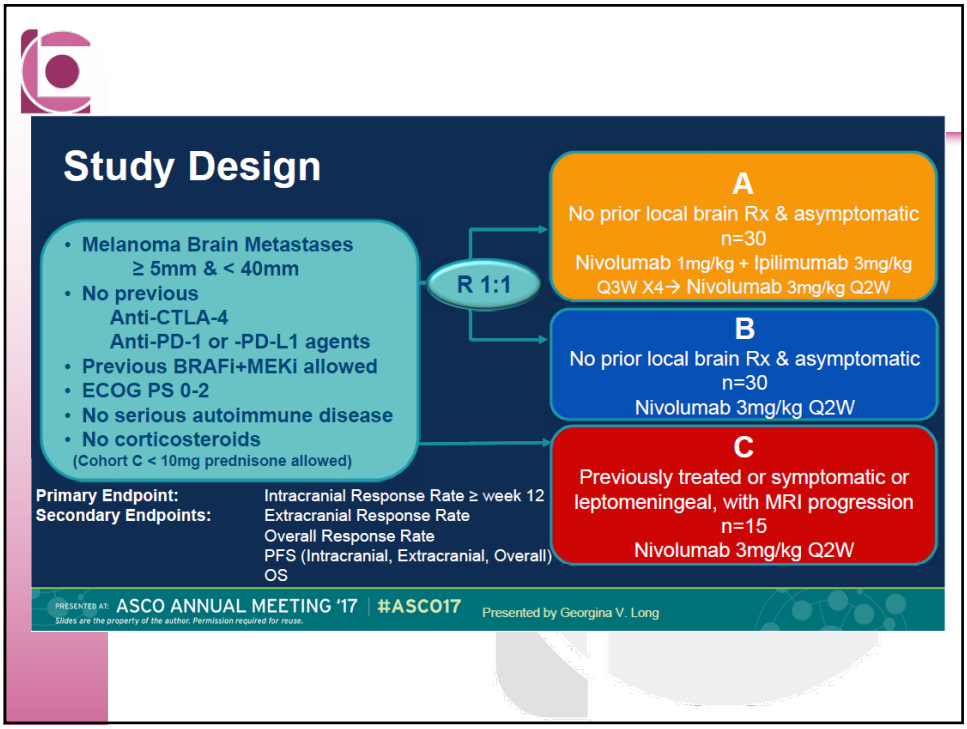
Study Design
• Melanoma Brain Metastases ≥ 5mm & < 40mm
• No previous Anti-CTLA-4 Anti-PD-1 or -PD-L1 agents
• Previous BRAFi+MEKi allowed
• ECOG PS 0-2
• No serious autoimmune disease
• No corticosteroids
(Cohort C < 10mg prednisone allowed)
R 1:1
A
No prior local brain Rx & asymptomatic
n=30
Nivolumab 1mg/kg + Ipilimumab 3mg/kg Q3W X4→ Nivolumab 3mg/kg Q2W
B
No prior local brain Rx & asymptomatic
n=30
Nivolumab 3mg/kg Q2W
C
Previously treated or symptomatic or leptomeningeal, with MRI progression
n=15
Nivolumab 3mg/kg Q2W
Primary Endpoint: Intracranial Response Rate ≥ week 12
Secondary Endpoints: Extracranial Response Rate
Overall Response Rate
PFS (Intracranial, Extracranial, Overall)
OS
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Patient Characteristics

	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Age, median (range)	61 (29-76)	62 (31-86)	54 (28-73)
Sex, male n (%)	22 (85%)	19 (76%)	11 (69%)
ECOG performance status, n (%)			
1	6 (23%)	9 (36%)	7 (44%)
2	1 (4%)	0	1 (6%)
LDH > ULN, n (%)	11 (42%)	14 (58%)	6 (38%)
V600 BRAF mutation-positive, n (%)	12 (46%)	14 (56%)	13 (81%)
Target brain metastases, n (%)			
1	5 (19%)	5 (20%)	1 (6%)
2-4	9 (35%)	15 (60%)	7 (44%)
>4	12 (46%)	5 (20%)	8 (50%)
Extracranial metastases, n(%)	21 (81%)	20 (80%)	12 (75%)
Prior BRAFi+MEKi	6 (23%)	6 (24%)	12 (75%)
Prior local brain therapy	0	0	16 (100%)

† Leptomeningeal, previous local treatment or symptoms

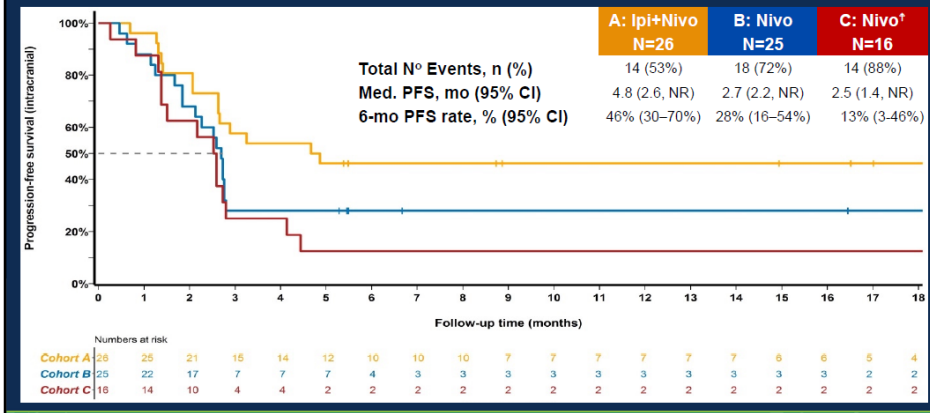
Best Intracranial RECIST Response

	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Intracranial Response, n (%)	**11 (42%)**	**5 (20%)**	**1 (6%)**
CR	4 (15%)	3 (12%)	0
PR	7 (27%)	2 (8%)	1 (6%)
SD	2 (8%)	1 (4%)	4 (25%)
PD	12 (46%)	18 (72%)	11 (69%)
NE*	1 (4%)	1 (4%)	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

Intracranial Progression Free Survival



	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Total N° Events, n (%)	14 (53%)	18 (72%)	14 (88%)
Med. PFS, mo (95% CI)	4.8 (2.6, NR)	2.7 (2.2, NR)	2.5 (1.4, NR)
6-mo PFS rate, % (95% CI)	46% (30–70%)	28% (16–54%)	13% (3-46%)

Numbers at risk

Cohort A	26	25	21	15	14	12	10	10	10	7	7	7	7	7	7	6	6	5	4
Cohort B	25	22	17	7	7	7	4	3	3	3	3	3	3	3	3	3	3	2	2
Cohort C	16	14	10	4	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Summary

- Nivolumab combined with ipilimumab or nivolumab alone have activity in active, asymptomatic melanoma brain metastases, without prior local therapy
  - Nivo+Ipi Intracranial: Response Rate = 42%; 6-month PFS 46%
  - Nivo alone Intracranial: Response Rate = 20%; 6-month PFS 29%
- Activity is **high** when nivo+ipi given upfront
  - Nivo+Ipi: Intracranial Response Rate = 50%
- Intracranial and extracranial responses were mostly concordant

Abstract 9506

COMBI-MB

A Phase 2 Study of Combination Dabrafenib and Trametinib in Patients With *BRAF* V600–Mutant Melanoma Brain Metastases

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

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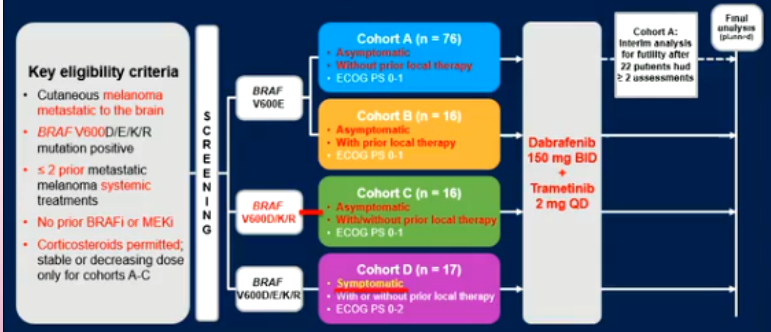
COMBI-MB: Study Design (phase 2)



- **Primary endpoint:** intracranial response (IR) rate in cohort A[a]
- **Secondary endpoints:** IR rate in cohorts B, C, and D; extracranial response (ER) and overall response (OR) rates; intracranial, extracranial, and overall DCRs; duration of IR, ER, and OR; PFS; OS; and safety

Median follow up = 9 mo

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; QD, once daily.
[a] Null hypothesis: IR rate of ≤ 35% in cohort A (based on activity of dabrafenib monotherapy in the BREAK-MB trial, Long GV, et al. *Lancet Oncol.* 2012;13:1087-1095). Investigator-assessed efficacy was confirmed by a blinded independent review committee (BIRC). Data cutoff date: November 28, 2016.

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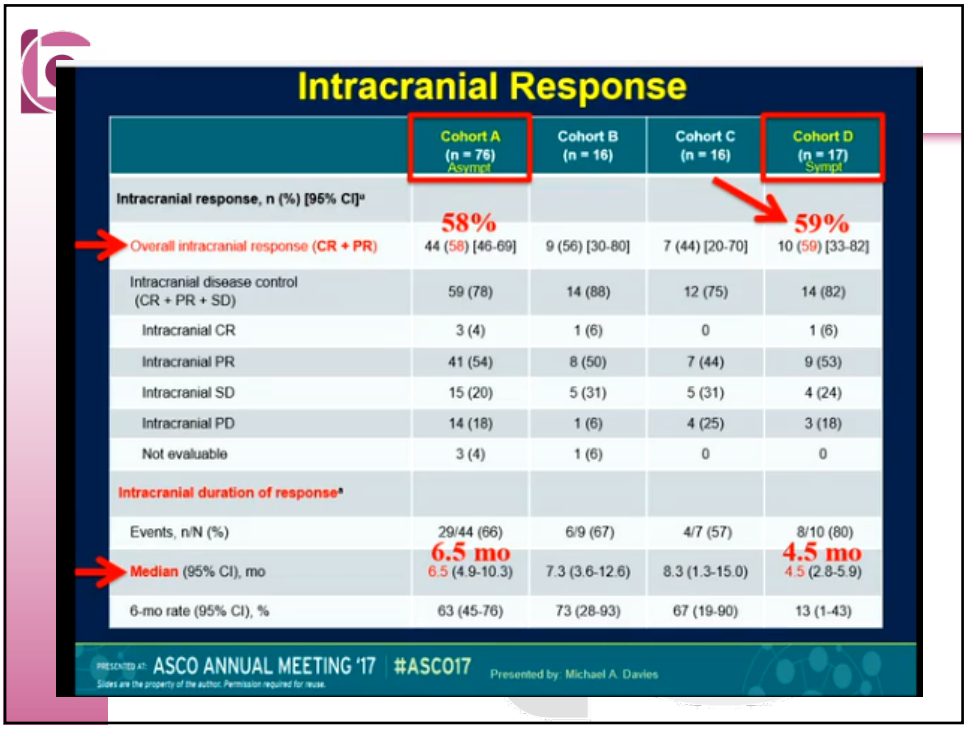
Presented by: Michael A. Davies


Intracranial Response
Cohort A (n = 76) Asympt
Cohort B (n = 16)
Cohort C (n = 16)
Cohort D (n = 17) Sympt
Intracranial response, n (%) [95% CI]a
58%
59%
Overall intracranial response (CR + PR)
44 (58) [46-69]
9 (56) [30-80]
7 (44) [20-70]
10 (59) [33-82]
Intracranial disease control (CR + PR + SD)
59 (78)
14 (88)
12 (75)
14 (82)
Intracranial CR
3 (4)
1 (6)
0
1 (6)
Intracranial PR
41 (54)
8 (50)
7 (44)
9 (53)
Intracranial SD
15 (20)
5 (31)
5 (31)
4 (24)
Intracranial PD
14 (18)
1 (6)
4 (25)
3 (18)
Not evaluable
3 (4)
1 (6)
0
0
Intracranial duration of responsea
Events, n/N (%)
29/44 (66)
6/9 (67)
4/7 (57)
8/10 (80)
6.5 mo
4.5 mo
Median (95% CI), mo
6.5 (4.9-10.3)
7.3 (3.6-12.6)
8.3 (1.3-15.0)
4.5 (2.8-5.9)
6-mo rate (95% CI), %
63 (45-76)
73 (28-93)
67 (19-90)
13 (1-43)
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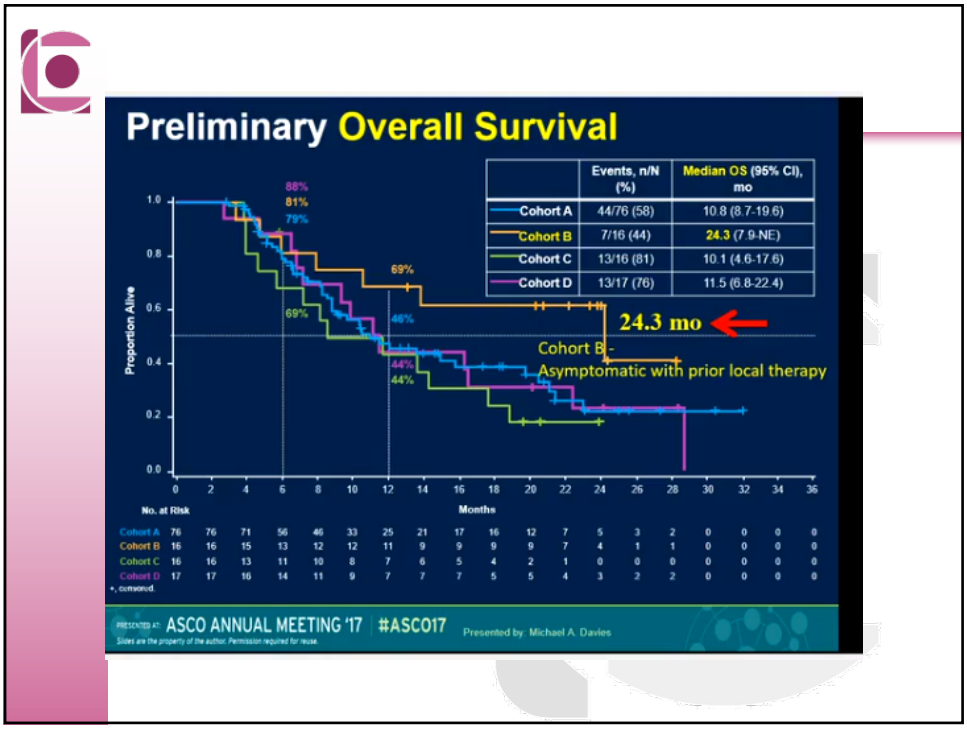
Preliminary Overall Survival
Events, n/N (%)
Median OS (95% CI), mo
Cohort A 44/76 (58) 10.8 (8.7-19.6)
Cohort B 7/16 (44) 24.3 (7.9-NE)
Cohort C 13/16 (81) 10.1 (4.6-17.6)
Cohort D 13/17 (76) 11.5 (6.8-22.4)
24.3 mo
Cohort B - Asymptomatic with prior local therapy
Proportion Alive
Months
No. at Risk
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Conclusions

- First report of a phase 2 trial evaluating BRAFi + MEKi in patients with melanoma brain metastases
- Clinical benefit and tolerability were achievable with dabrafenib + trametinib in some patients with *BRAF* V600–mutant melanoma metastasized to the brain
  - IR rate of 58% (95% CI, 46%-69%) in cohort A patients; primary endpoint was met
  - Median duration of OR (eg, 6.5 months in cohort A) was generally shorter than that observed in patients without melanoma brain metastases (12-14 months)[1-3]
  - No unexpected safety issues were observed with the combination
- These results support:
  - Use of dabrafenib + trametinib as a treatment option for patients with brain metastases
  - Need for continued research to improve outcomes in this advanced melanoma population

1. Long GV, et al. *Lancet*. 2015;386:444-451; 2. Long GV, et al. *Ann Oncol*. 2017 May 5. [Epub ahead of print]; 3. Robert C, et al. *Ann Oncol*. 2016;27(suppl 6) [abstract LBA48].

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- Symptomatic brain mets: start Nivolumab/ipilimumab in 1/2017

Patient developed 3 months after initiation of treatment

- vomiting, confusion, fever and anorexia
- Brain imaging : response of brain mets
- Hyponatremia
- Adrenal insuffiency
  - Start Hydrocortison
  - Solucortef once IV
- Asymptomatic hyperthyroidie

Evaluation 5/2017: central response, no new lesions on pet

Evaluation 8/2017: stable disease

Conclusion

Progression central metastasis

No local therapy possible

Durable response with symptomatic brain mets and corticosteroids

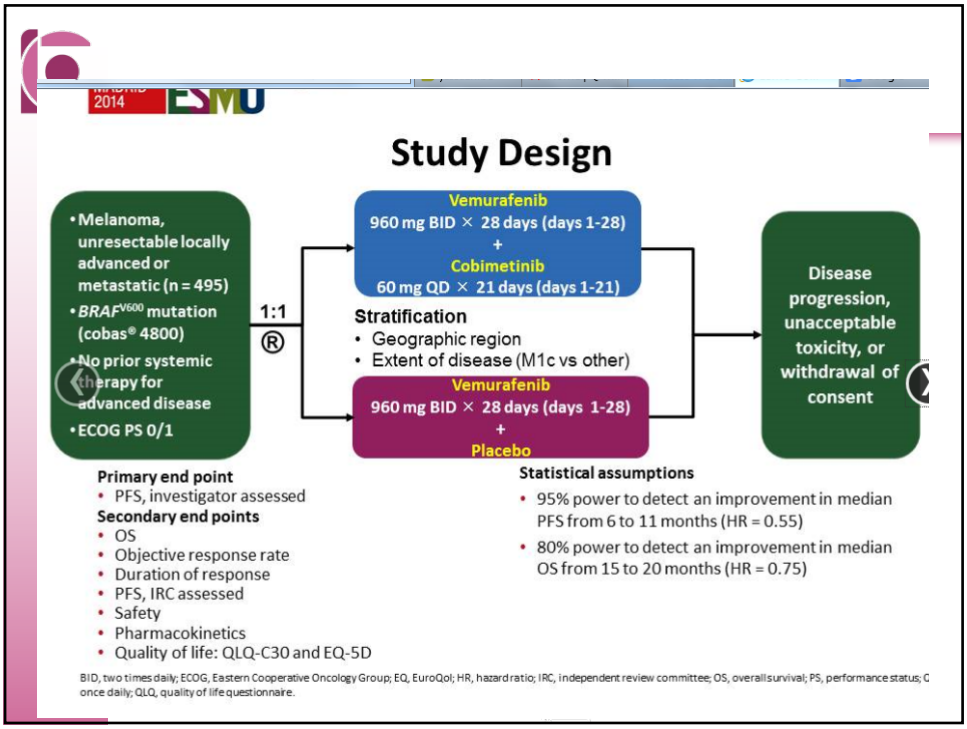

Table 2.
Treatment modalities for melanoma metastases.

Number and localization of the metastases	Treatment modalities (i) First choice (ii) Second choice (iii) Third choice	Grade of recommendation
In-transit metastases (few) (pTXN2cM0)	(i) Surgical removal	C
	(ii) Radiotherapy	C
In-transit metastases (multiple, >5) (pTXN2cM0)	(i) Perfusion of the extremity[a]	C
	(ii) Radiotherapy	C
	(iii) Systemic therapy[a]	C
Locoregional lymph nodes (pTxN1a,2a)	(i) Resection and trial participation	B
	(ii) Additional IFN-α treatment[a]	B
Locoregional lymph nodes (pTxN2b,2c,3)	(i) Radical lymphadenectomy, in case of incomplete resection: irradiation	C
	(ii) Consider trial participation	C
Solitary central nervous system metastases (pTxNxM3)	(i) Neurosurgical removal	C
	(ii) Stereotactic irradiation[a] (according to localization this could also be the first choice)	C
	(iii) Consider clinical trial participation	
Solitary lung metastases (pTxNxM1)	(i) Surgical removal	C
	(ii) Consider clinical trial participation	
	(iii) Systemic therapy[a]	C
Multiple metastases (pTxNxM1a-1c)	(i) Consider clinical trial participation	
	(ii) Systemic therapy[a]	B
Painful bone metastases (pTxNxM1a-1c)	(i) Consider clinical trial participation	
	(ii) Radiotherapy	C

[a]These therapies should be preferentially carried out at specialized centers.