Universitair Ziekenhuis Gent

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UPDATE MELANOOM: NIEUWE BEHANDELINGEN

www.huidkanker-bado.be

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CANCER RESEARCH INSTITUTE GHENT
CRIG

ION immuno-oncology network Ghent

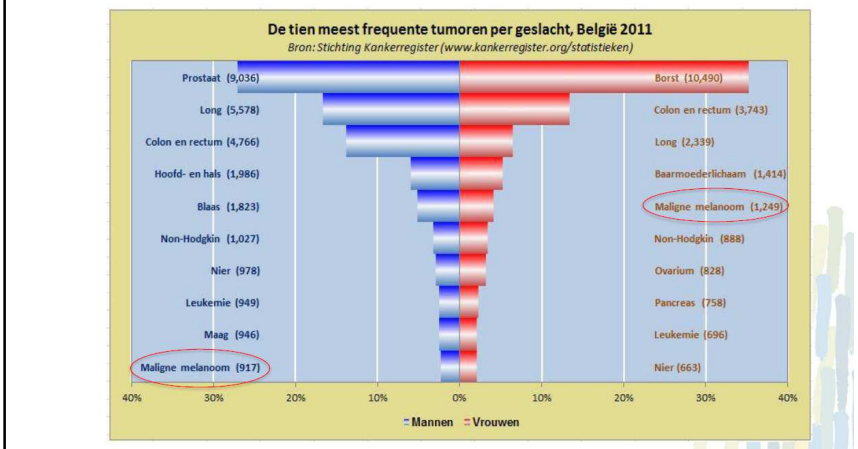

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Table 6 The five most frequently occuring invasive tumours by region, age group and sex, 2004-2005

Boys & Girls (0-14 years)	1	2	3	4	5
Belgium	Leukaemia (30%)	Brain (13%)	Kidney (7%)	Non-Hodgkin lymphoma (7%)	Hodgkin lymphoma (7%)
Brussels Capital Region	Leukaemia (45%)	Adrenal gland (7%)	Brain (6%)	Soft tissue (6%)	Kidney (5%)
Flemish Region	Leukaemia (27%)	Brain (13%)	Kidney (8%)	Hodgkin lymphoma (8%)	Non-Hodgkin lymphoma (7%)
Walloon Region	Leukaemia (27%)	Brain (16%)	Non-Hodgkin lymphoma (8%)	Kidney (7%)	Bone (6%)
Males (15-29 years)	**1**	**2**	**3**	**4**	**5**
Belgium	Testis (26%)	Hodgkin lymphoma (12%)	Non-Hodgkin lymphoma (10%)	Brain (9%)	Melanoma (9%)
Brussels Capital Region	Testis (19%)	Non-Hodgkin lymphoma (17%)	Leukaemia (15%)	Hodgkin lymphoma (11%)	Brain (7%)
Flemish Region	Testis (25%)	Hodgkin lymphoma (13%)	Melanoma (10%)	Brain (9%)	Non-Hodgkin lymphoma (9%)
Walloon Region	Testis (31%)	Hodgkin lymphoma (12%)	Melanoma (10%)	Brain (10%)	Non-Hodgkin lymphoma (7%)
Females (15-29 years)	**1**	**2**	**3**	**4**	**5**
Belgium	Melanoma (20%)	Breast (12%)	Hodgkin lymphoma (11%)	Thyroid gland (11%)	Cervix uteri (5%)
Brussels Capital Region	Melanoma (14%)	Thyroid gland (14%)	Leukaemia (12%)	Breast (11%)	Hodgkin lymphoma (9%)
Flemish Region	Melanoma (19%)	Breast (13%)	Hodgkin lymphoma (12%)	Thyroid gland (10%)	Cervix uteri (6%)
Walloon Region	Melanoma (24%)	Thyroid gland (12%)	Hodgkin lymphoma (11%)	Breast (10%)	Brain (6%)
Males (30-44 years)	**1**	**2**	**3**	**4**	**5**
Belgium	Testis (11%)	Melanoma (11%)	Colorectal (9%)	Head and Neck (8%)	Non Hodgkin lymphoma (8%)
Brussels Capital Region	Melanoma (10%)	Lung (9%)	Head and Neck (9%)	Testis (8%)	Colorectal (8%)
Flemish Region	Melanoma (12%)	Testis (11%)	Colorectal (11%)	Non-Hodgkin lymphoma (8%)	Head and Neck (6%)
Walloon Region	Testis (13%)	Head and Neck (11%)	Lung (9%)	Melanoma (8%)	Colorectal (7%)
Females (30-44 years)	**1**	**2**	**3**	**4**	**5**
Belgium	Breast (47%)	Cervix uteri (9%)	Melanoma (9%)	Thyroid gland (5%)	Colorectal (4%)
Brussels Capital Region	Breast (51%)	Thyroid gland (7%)	Melanoma (7%)	Cervix uteri (6%)	Non-Hodgkin lymphoma (4%)
Flemish Region	Breast (47%)	Cervix uteri (11%)	Melanoma (10%)	Thyroid gland (4%)	Colorectal (4%)
Walloon Region	Breast (47%)	Cervix uteri (9%)	Melanoma (8%)	Thyroid gland (8%)	Colorectal (4%)

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Preventive landscape of skin cancer in Belgium

A clinical and health economical analysis

Isabelle Hoorens

Public Defense

Thesis submitted as fulfilment of the requirements for the degree of Doctor in Health Sciences

Promotor: Lieve Brochez
Department of Dermatology

Co-pomotor: Lieven Annemans
Department of Public Health

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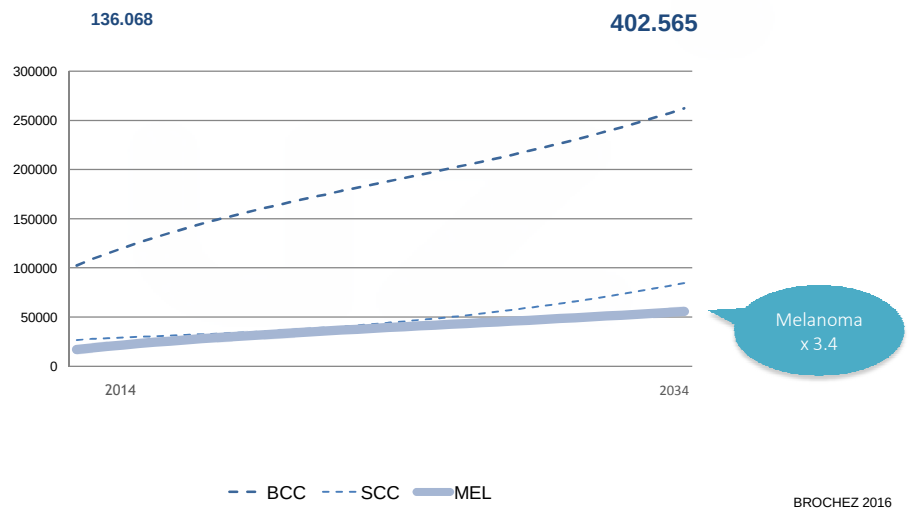
FUTURE PROJECTIONS PREVALENCE IN BELGIUM



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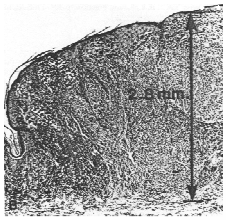
Melanoma TNM Classification

T classification	Thickness	Ulceration Status/Mitoses
Tis	N/A	N/A
T1	≤ 1.0 mm	a: w/o ulceration and mitosis <1/mm²
		b: with ulceration or mitoses ≥ 1/mm²
T2	1.01 - 2.0 mm	a: w/o ulceration
		b: with ulceration
T3	2.01 - 4.0 mm	a: w/o ulceration
		b: with ulceration
T4	> 4.0 mm	a: w/o ulceration
		b: with ulceration
N classification	**# of Metastatic Nodes**	**Nodal Metastatic Mass**
N0	0 nodes	N/A
N1	1 node	a: micrometastasis*
		b: macrometastasis**
N2	2-3 nodes	a: micrometastasis*
		b: macrometastasis**
		c: in-transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in-transit met(s)/satellite(s) with metastatic node(s)	
M classification	**Site**	**Serum LDH**
M0	0 sites	N/A
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table 1a: TNM Criteria for Cutaneous Melanoma (2010)
Adapted from Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010. (Used with permission)



Tumor thickness (Breslow)

Clinical Staging*				Pathologic Staging+			
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N>N0	M0	IIIA	T1 – 4a	N1a	M0
					T1 – 4a	N2a	M0
				IIIB	T1 – 4b	N1a	M0
					T1 – 4b	N2a	M0
					T1 – 4a	N1b	M0
					T1 – 4a	N2b	M0
					T1 – 4a	N2c	M0
				IIIC	T1 – 4b	N1b	M0
					T1 – 4b	N2b	M0
					T1 – 4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

+ Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Table 1b: Anatomic Stage Groupings for Cutaneous Melanoma
Adapted from Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010. (Used with permission)

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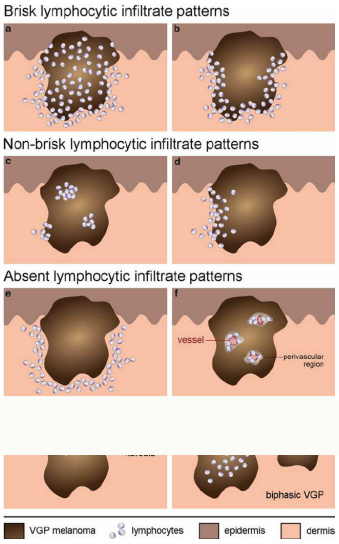
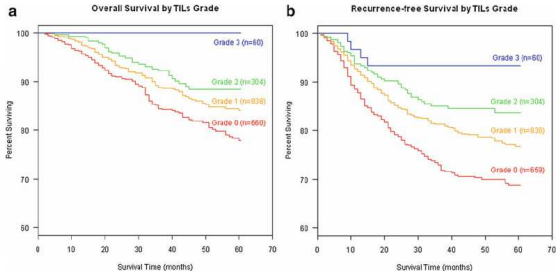
The presence of TILs is an independent positive prognostic factor

Clemente 1996





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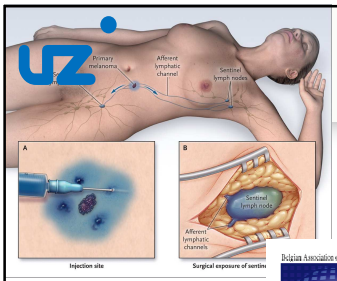
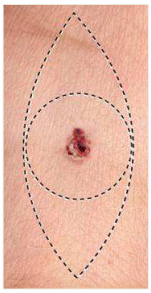
BEHANDELING LOKALE ZIEKTE





Belgian Association of Dermato-Oncology

BADO

RECOMMENDATION MANAGEMENT PRIMARY CUTANEOUS MELANOMA

These recommendations may serve as a guidance but need to be tuned according to the specific situation

	T in situ	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
preoperative	/	none *	medical imaging**	medical imaging**	medical imaging**	medical imaging**	medical imaging**	medical imaging**	medical imaging**
		if staging negative.	if staging negative.	if staging negative.	if staging negative.	if staging negative.	if staging negative.	if staging negative.	if staging negative.
wide excision	0.5cm	1cm	1cm	1-2cm	1-2cm	2cm	2cm	2cm	2cm
sentinel node biopsy	/	/	possible	possible	possible	possible	possible	possible	possible
clinical trial					?	?	?	?	?

* potentially ultrasonography draining lymph nodes, optional ultrasonography abdomen, chest radiograph

** ultrasonography draining lymph nodes (strongly advised) AND ultrasonography abdomen/chest radiograph OR OF CT thorax/CT abdomen/MR brain ; PET-CT only reimbursed from stage IIC (p14b)

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Stimuleert het immuunsysteem om de tumorcel aan te vallen

Grijpt in thv groeimechanisme van de tumorcel

IMMUNOTHERAPY

Anti -CTLA4: ipilimumab (Yervoy®)

Anti-PD1: nivolumab (Opdivo®)
pembrolizumab (Keytruda®)

TARGETED THERAPY

BRAF inhibitors: vemurafenib (Zelboraf®)
dabrafenib (Tafinlar®)

MEK inhibitors: cobimetinib
trametinib (Mekinist®)
selumetinib

c-KIT inhibitors: imatinib (Glivec®)
nilotinib (Tasigna®)
Dasatinib (Sprycel®)

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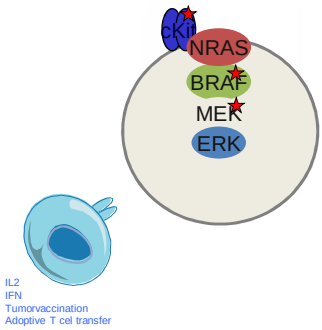
BEHANDELING METASTATISCHE ZIEKTE



latest update 1/2016

RECOMMENDATION MANAGEMENT STAGE IV MELANOMA

These recommendations may serve as a guidance but need to be tuned according to the specific situation, among which the tumor kinetics, the type of clinical trial, ... the most important options are in bold; the options are not necessarily in order of preference

	1° line	2° line	3° line
BRAF negative	> **(anti PD1)#** > **ipilimumab** > (ipilimumab + anti PD1)# > for solitary/few metastases: consider surgery* or gamma knife** > consider clinical trial	> **anti-PD1** > ipilimumab > (ipilimumab + anti PD1)# > chemotherapy > imatinib in case of c kit mutation > consider clinical trial > consider best supportive care	> chemotherapy > imatinib in case of c kit mutation > consider clinical trial > consider best supportive care
BRAF positive	> **BRAF+MEKinhibitor** > as in BRAF negative	> **as in BRAF negative** > **BRAF+MEKinhibitor** in patients not responding to immunotherapy	> as in BRAF negative

( ) # currently not yet available in Belgium
* mostly for one or few metastases of the brain, lung; for some metastases of GI tractus, skin/soft tissue, other
** mostly for one or few metastases of the brain

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latest update 1/2016

RECOMMENDATION MANAGEMENT STAGE IV MELANOMA

These recommendations may serve as a guidance but need to be tuned according to the specific situation, among which the tumor kinetics, the type of clinical trial, ...
The most important options are in bold; the options are not necessarily in order of preference

	1° line	2° line	3° line
BRAF negative	**> (anti-PD1)#** **> ipilimumab** **:- (ipilimumab + anti-PD1)#** > for solitary/few metastases: consider surgery* or gamma knife** > consider clinical trial	**:- anti-PD1** > ipilimumab :- (ipilimumab + anti-PD1)# > chemotherapy > imatinib in case of c-kit mutation > consider clinical trial > consider best supportive care	> chemotherapy :- imatinib in case of c-kit mutation > consider clinical trial :- consider best supportive care
BRAF positive	**> BRAF+MEKinhibitor** **> as in BRAF negative**	**> as in BRAF negative** **:- BRAF+MEKinhibitor** in patients not responding to immunotherapy	:- as in BRAF negative

( ) # currently not yet available in Belgium
* *mostly for one or few metastases of the brain, lung; for some metastases of GI tractus, skin/soft tissue, other*
** *mostly for one or few metastases of the brain*

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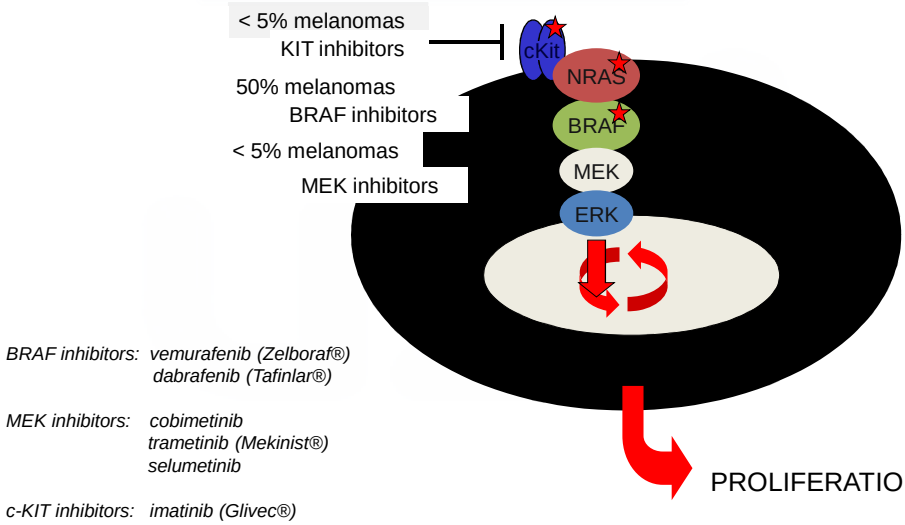
TARGETED THERAPY



BRAF inhibitors: *vemurafenib (Zelboraf®)*
dabrafenib (Tafinlar®)

MEK inhibitors: *cobimetinib*
trametinib (Mekinist®)
selumetinib

c-KIT inhibitors: *imatinib (Glivec®)*
nilotinib (Tasigna®)
Dasatinib (Sprycel®)

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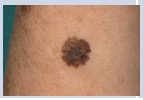
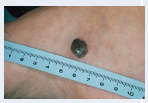
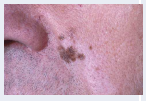
Subtype	Frequentie	Lokalisatie	Kenmerken	Microscopie	Moleculair
Superficieel spreidend 	70%	M: romp V: OL	Intermittente zonexpositie	RGP (pagetoid) 1-5jaar	> BRAF < NRAS
Nodulair 	10-25%	M: romp V: OL	Intermittente zonexpositie	RGP kort (0.5-1.5j)	> BRAF < NRAS
Acraal lentigineus 		HP/VZ/nagels	Merendeel vd melanomen bij fototypes 5 en 6	Lentigineus patroon	> c-kit
Lentigo maligna 		Hoofd/hals	Chronische zonexpositie	Lentigineus patroon	> c-kit

Modified from Chudnovsky J. Clin. Invest. 115(4): 813-824

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De moleculaire onderverdeling van melanoom heeft geleid tot nieuwe behandelingen

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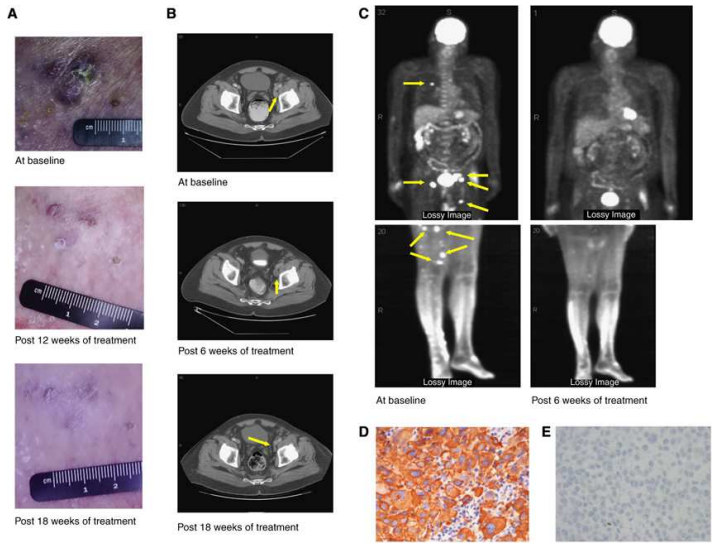
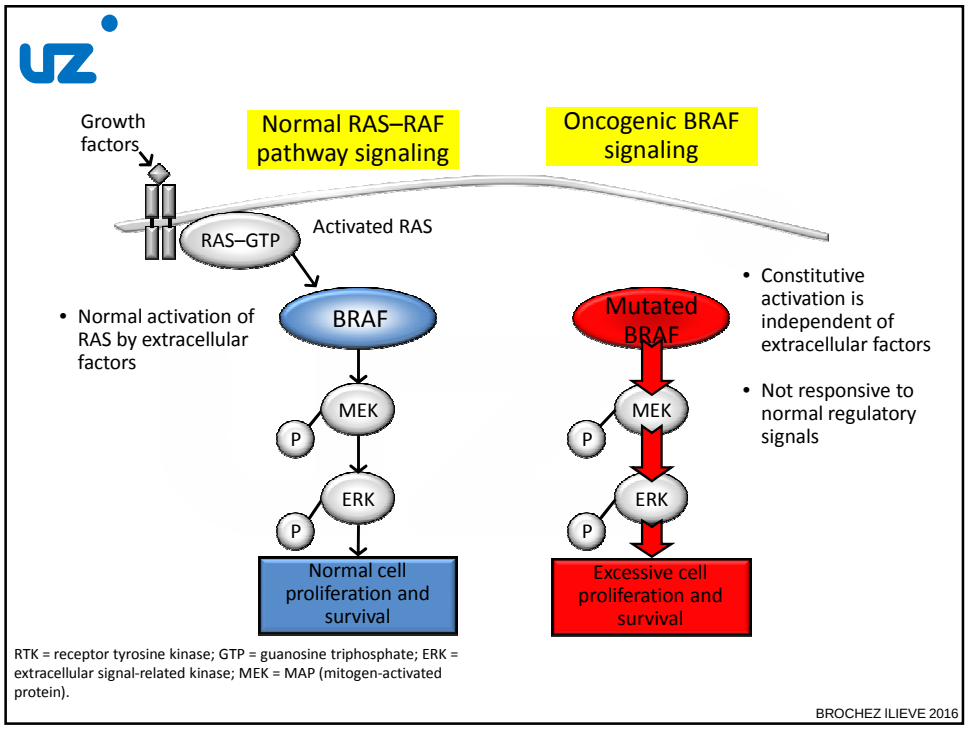
- Phase II trial of imatinib mesylate in patients with metastatic melanoma



Clinical and radiological studies of a partial response to imatinib. All metastatic lesions shrank.
(A) Response of in-transit metastases on right thigh.
(B) Computed tomographic scan showing response of left external iliac lymph node (arrow).
(C) Positron emission tomographic scans showing decrease in fluorodeoxyglucose uptake in all lesions (arrows).
(D) Photomicrograph of the strong c-kit expression in the tumour of the responder.
(E) Photomicrograph of a case of negative c-kit expression.

BJC 2008; 99: 734


Growth factors
Normal RAS–RAF pathway signaling
Oncogenic BRAF signaling
RAS–GTP
Activated RAS
BRAF
Mutated BRAF
MEK
ERK
P
Normal cell proliferation and survival
Excessive cell proliferation and survival
• Normal activation of RAS by extracellular factors
• Constitutive activation is independent of extracellular factors
• Not responsive to normal regulatory signals
RTK = receptor tyrosine kinase; GTP = guanosine triphosphate; ERK = extracellular signal-related kinase; MEK = MAP (mitogen-activated protein).
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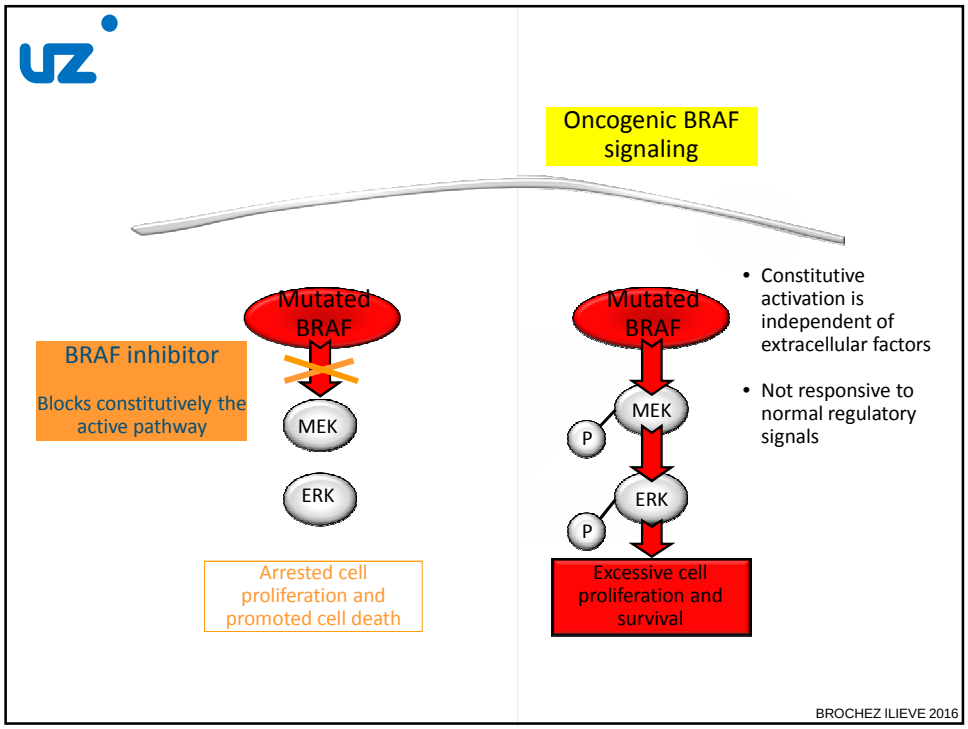
Oncogenic BRAF signaling
Mutated BRAF
BRAF inhibitor
Blocks constitutively the active pathway
MEK
ERK
P
Arrested cell proliferation and promoted cell death
Excessive cell proliferation and survival
• Constitutive activation is independent of extracellular factors
• Not responsive to normal regulatory signals
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2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., [illegible], John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

BRAF inhibitors

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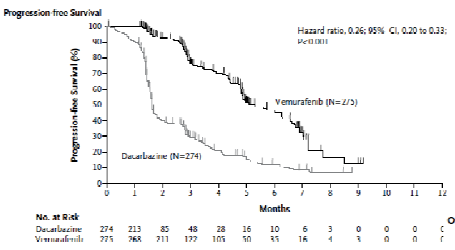
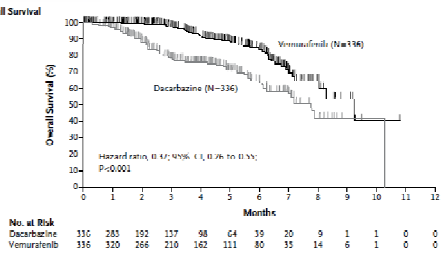
CONCLUSIONS

Vemurafenib produced improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation. (Funded by Hoffmann–La Roche; BRIM-3 ClinicalTrials.gov number, NCT01006980.)



Estimated PFS 5.3 months vs 1.7 months



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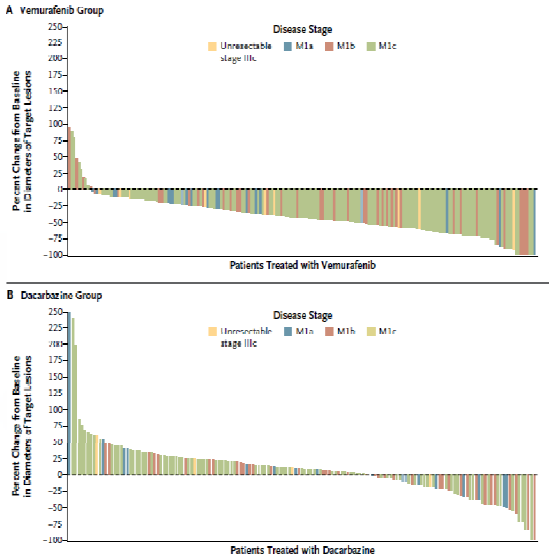
Hoge respons



Chapman PB et al. *N Eng J Med* 2011;364(26):2507-16.

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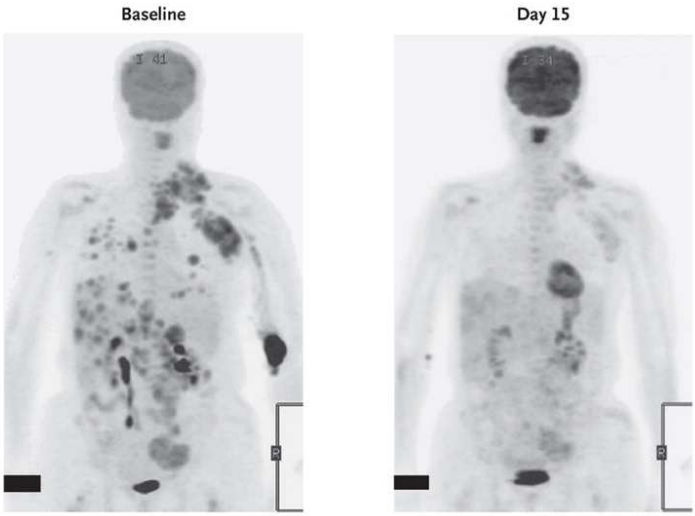
Snelle respons



FDG = F-18-fluorodeoxyglucose; PET = positron emission tomography.

Flaherty KT, *et al. N Engl J Med* 2010;363:809–19.

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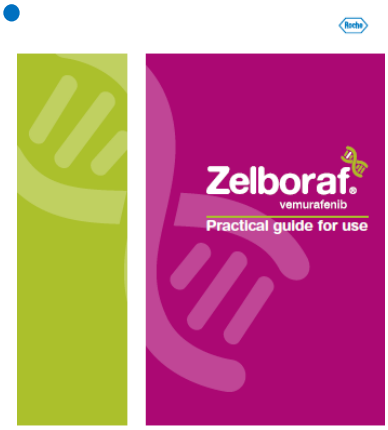

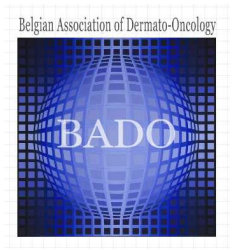

Zelboraf
vemurafenib

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Meest frequente bijwerkingen op Zelboraf

Arthralgia
Fatigue
Rash
Photosensitivity
Nausea
Alopecia
Pruritus

da Rocha Dias S. et al., The European Medicines Agency review of vemurafenib (Zelboraf) for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma: Summary of the scientific assessment of the Committee for Medicinal Products for Human Use, Eur J Cancer (2013), http://dx.doi.org/10.1016/j.ejca.2013.01.015

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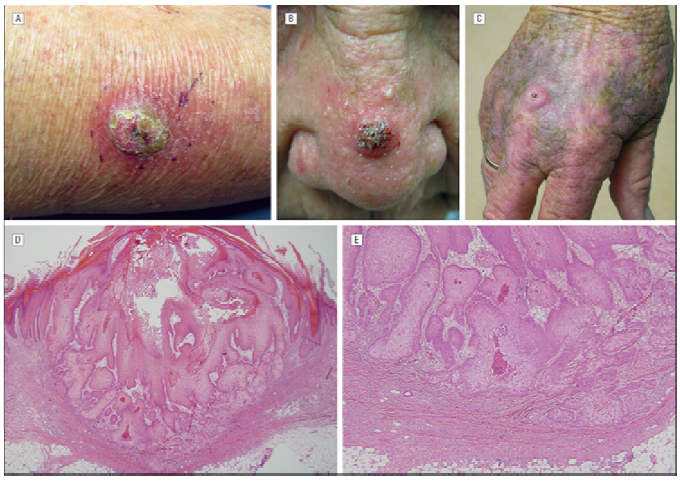

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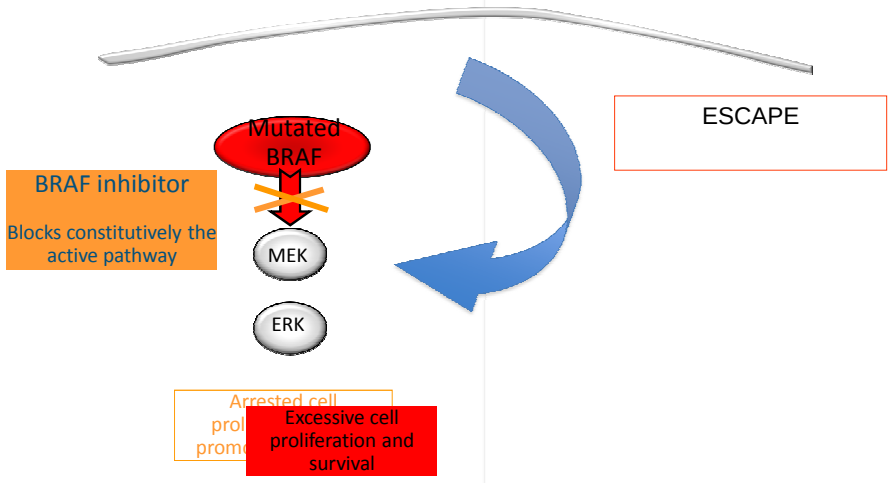
Respons beperkt in de tijd



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2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffrey R. Infante, M.D., Adil Daud, M.D.,
Rene Gonzalez, M.D., Richard S. Kefford, M.D., Jeffrey Sosman, M.D.,
Omid Hamid, M.D., Lynn Schuchter, M.D., Matthew Cebon, M.D., Ph.D.,
Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris III, M.D.,
Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D.,
Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I.,
Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H.,
Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D.,
Tara Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

Combination
BRAFi + MEKi

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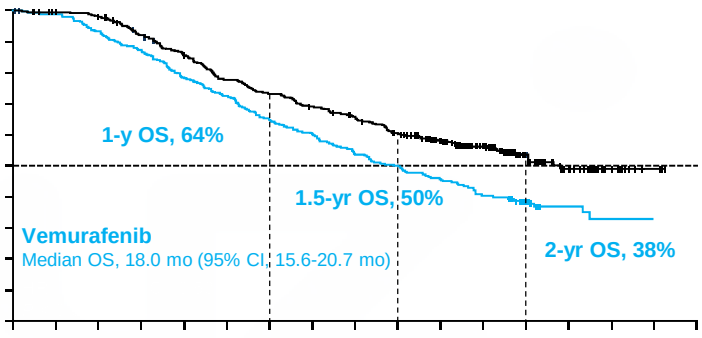
COMBI-v: Overall Survival



Patients at risk[a]																	
Dabrafenib + trametinib	352	342	336	311	286	260	245	230	217	198	173	128	68	38	16	5	0
Vemurafenib	352	341	315	286	252	231	201	187	166	152	129	88	46	28	7	0	0

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COMBI-v: Summary of AEs (≥ 20% of patients)

AE, n (%)	Dabrafenib + Trametinib (n = 350)	Vemurafenib (n = 349)
Any AE	**345 (99)**	**345 (99)**
Pyrexia	193 (55)	74 (21)
Nausea	126 (36)	130 (37)
Diarrhea	120 (34)	136 (39)
Chills	116 (33)	28 (8)
Headache	112 (32)	84 (24)
Fatigue	110 (31)	117 (34)
Vomiting	107 (31)	55 (16)
Hypertension	103 (29)	82 (23)
Arthralgia	93 (27)	182 (52)
Rash	84 (24)	150 (43)
Cough	77 (22)	40 (11)
Decreased appetite	44 (13)	70 (20)
Pruritis	36 (10)	78 (22)
Alopecia	23 (7)	136 (39)
Hyperkeratosis	18 (5)	89 (26)
Photosensitivity reaction	15 (4)	81 (23)
Skin papilloma	8 (2)	82 (23)

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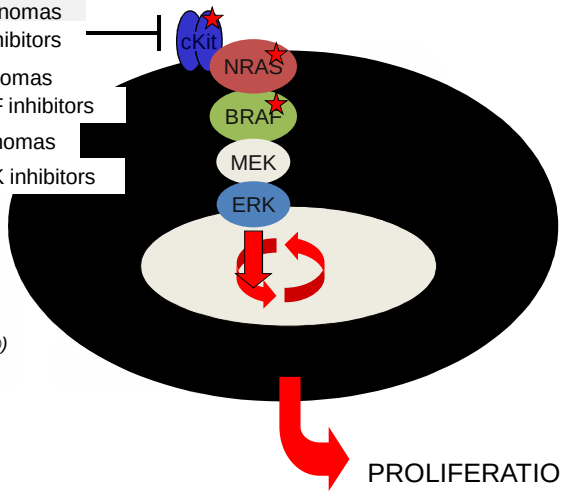
TARGETED THERAPY

< 5% melanomas
KIT inhibitors

50% melanomas
BRAF inhibitors

< 5% melanomas
MEK inhibitors



BRAF inhibitors: *vemurafenib (Zelboraf®)*
dabrafenib (Tafinlar®)

MEK inhibitors: *cobimetinib*
trametinib (Mekinist®)
selumetinib

c-KIT inhibitors: *imatinib (Glivec®)*
nilotinib (Tasigna®)
Dasatinib (Sprycel®)

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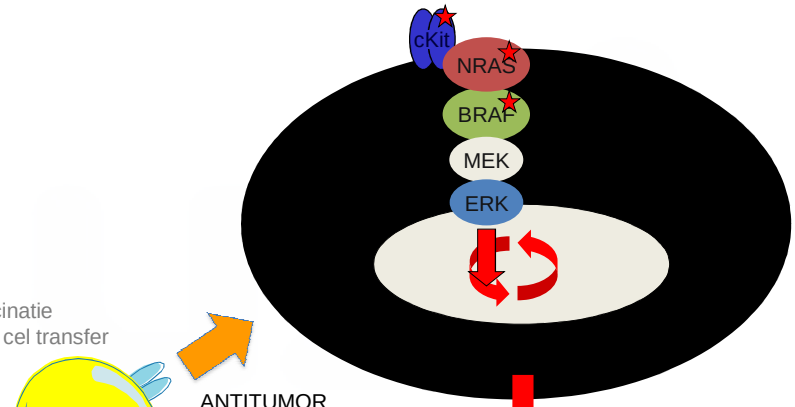
IMMUNOTHERAPY



IL2
IFN
Tumorvaccinatie
Adoptive T cel transfer

ANTITUMOR IMMUNE RESPONSE

PROLIFERATION

Anti -CTLA4: ipilimumab (Yervoy®)

Anti-PD1: nivolumab (Opdivo®)
pembrolizumab (Keytruda®)

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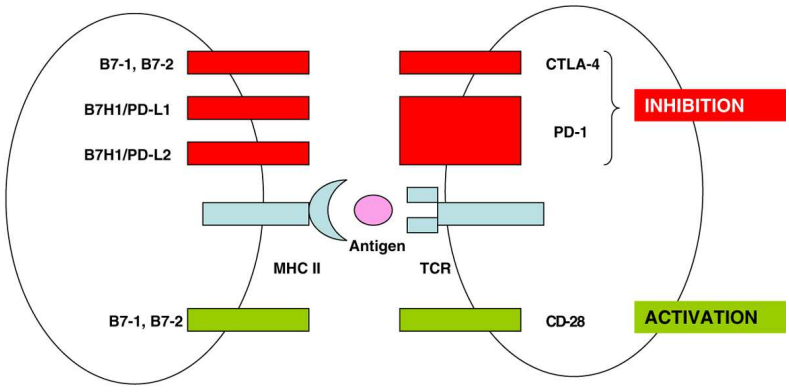

Fisher *et al. EPMA Journal 2012 3:1*

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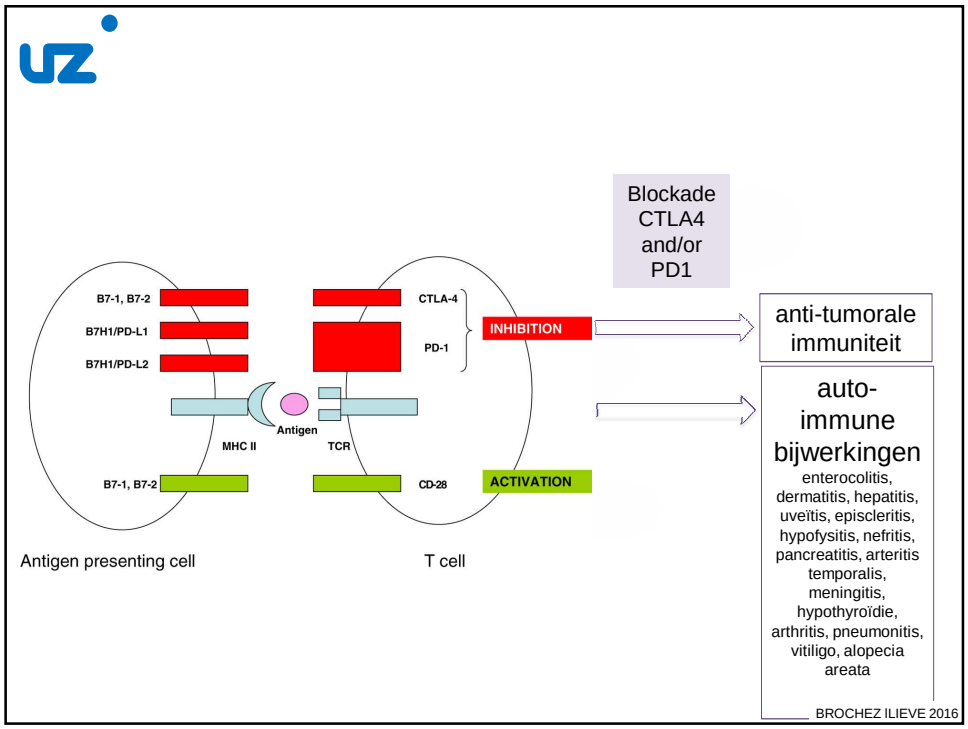
Blockade CTLA4 and/or PD1
B7-1, B7-2
B7H1/PD-L1
B7H1/PD-L2
CTLA-4
PD-1
INHIBITION
anti-tumorale immuniteit
Antigen
MHC II
TCR
B7-1, B7-2
CD-28
ACTIVATION
auto-immune bijwerkingen
enterocolitis, dermatitis, hepatitis, uveïtis, episcleritis, hypofysitis, nefritis, pancreatitis, arteritis temporalis, meningitis, hypothyroïdie, arthritis, pneumonitis, vitiligo, alopecia areata
Antigen presenting cell
T cell
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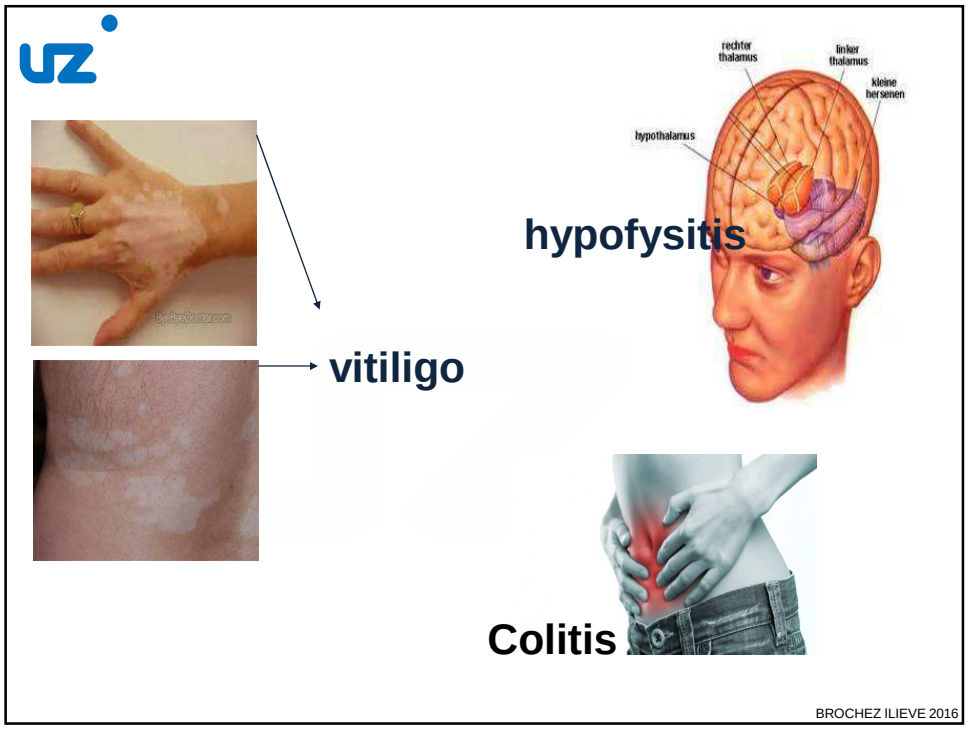
rechter thalamus
linker thalamus
kleine hersenen
hypothalamus
hypofysitis
vitiligo
Colitis
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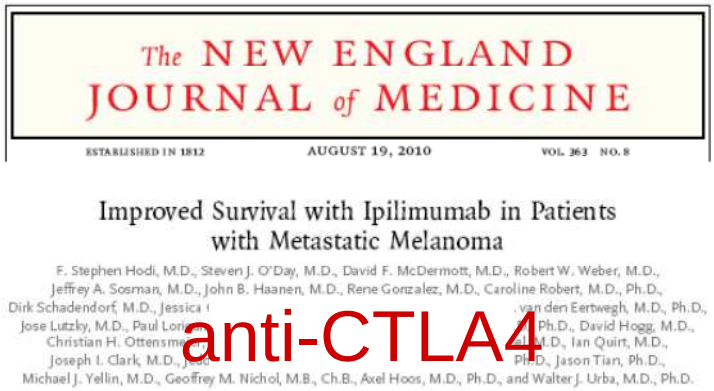
2010



The NEW ENGLAND JOURNAL of MEDICINE

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

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica . van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lori Ph.D., David Hogg, M.D., Christian H. Ottensm M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

anti-CTLA4

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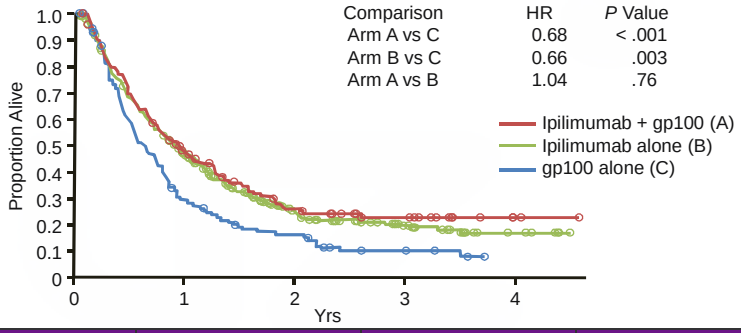
Lage respons maar evt langdurig



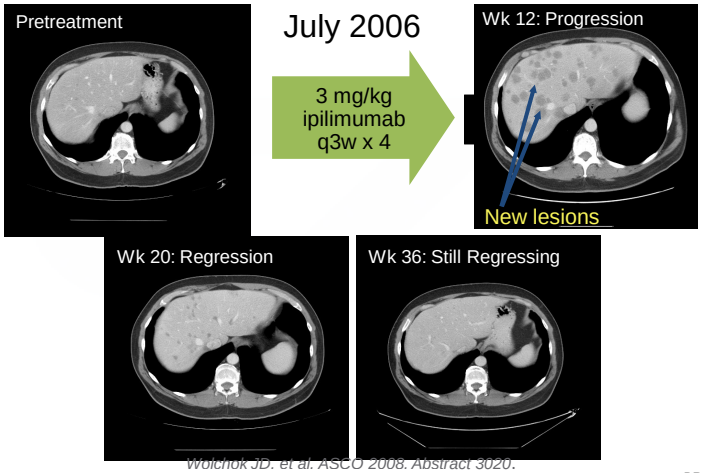
OS	Ipilimumab + gp100	Ipilimumab Alone	gp100 Alone
1 yr, %	44	46	25
2 yr, %	22	24	14
Median, mos	10.0	10.1	6.4

Hodi FS, et al. N Engl J Med. 2010;363:711-723.

BROCHEZ ILIEVE 2016

Trage respons (specifiek patroon)

- Responses after appearance and subsequent disappearance of new lesions



Wolchok JD. et al. ASCO 2008. Abstract 3020.

BROCHEZ ILIEVE 2016

2012

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., , David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., I Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., Wi Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiyin el, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

anti-PD1

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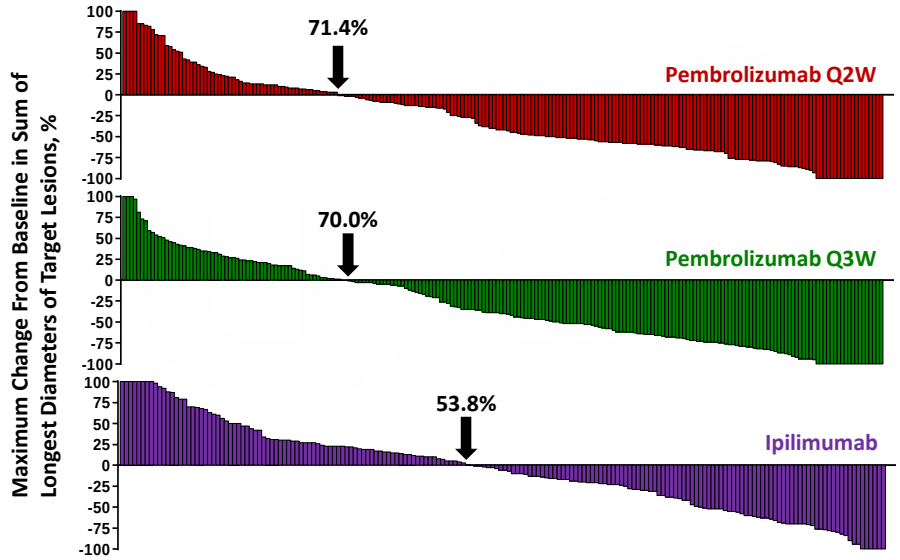
Best Percentage Change From Baseline in Target Lesions at IA1 (RECIST v1.1, Central Review)

PN006



Analysis cut-off date: September 3, 2014.

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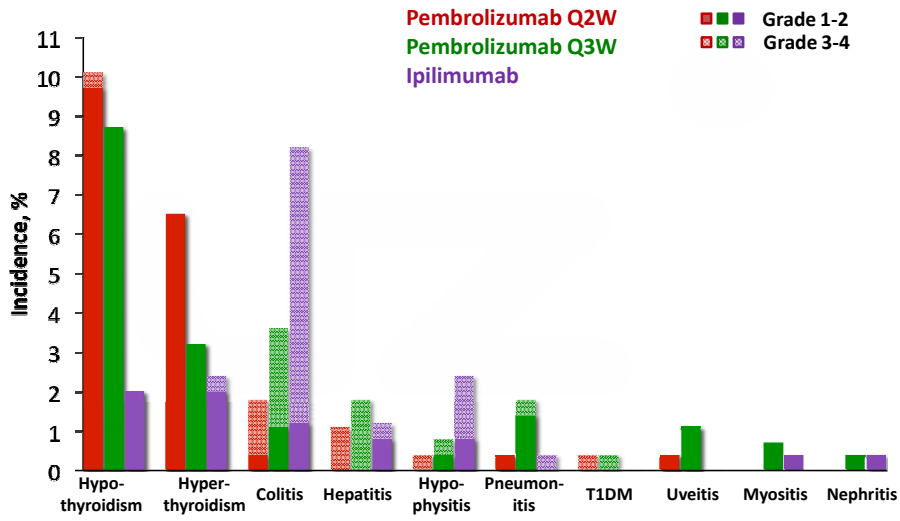
AEs of Special Interest at IA1

PN006



[a]Incidence not adjusted for duration of exposure.
Analysis cut-off date: September 3, 2014.

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ION GENT

Immuno-Oncologisch Netwerk Gent

IMMUNOTHERAPIE

- Routine gebruik bij kanker:
  Melanoom, long Kanker, nierkanker, hemato,…

- Komende indicaties:
  darmkanker, blaaskanker, borstkanker (subtype), cervix kankers, hersentumoren, hoofd-en halstumoren

  => Nood uitwisselen ervaringen
  => Innovatie

- Klinisch
- Onderzoek

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ION GENT

irAE task force:
multidisciplinaire opvang van bijwerkingen op immunotherapie


Prof Dr Lieve BROCHEZ
Dermatologist


Prof Dr. Piet OST
Radiation-Oncologist


Prof Dr Tessa KERRE
Hematologist


Prof Dr Karim VERMAELEN
Pneumologist


Dr Vibeke KRUSE
Medical Oncologist


Dr Katrien De Wolf
Radiation-Oncologist In training


Dr Ines Chevolet
Dermatologist In training


Prof Dr Bruno LAPAUW
Endocrinologist


Prof Dr Dimitri HEMELSOET
Neurologist


Dr Marijn SPEECKAERT
Nephrologist


Dr Xavier VERHELST
Gastro-enterologist


Dr Ruth WITTOEK
Rheumatologist


Dr Julie DE ZAEYTIJD
Ophthalmologist


Dr Fiona TROMP
Cardiologist

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Colitis

6. Behandeling

Graad	Behandeling	Follow-up
Graad 1: < 4 ontlastingen per dag	Immunotherapie verder Strikte follow up	Geen
Graad 2: 4-6 ontlastingen per dag	Linker coloscopie plannen via gastroenteroloog van wacht Immunotherapie op wacht Symptomatische behandeling	- Bij resolutie tot gr1, herstart immunotherapie. - Bij persisterende klachten voor > 5-7d, start methyl-prednisolone 0,5-1mg/kg/d. - Bij resolutie tot gr 1, afbouw corticoiden over 1m, ev herstart immunotherapie. - Bij progressieve klachten, te behandelen als graad 3-4
Graad 3-4: ≥7 ontlastingen per dag, levensbedreigend, risico op perforatie	Linker coloscopie plannen via gastroenteroloog van wacht; Stop immunotherapie. Start methylprednisolone 1 à 2 mg/kg/d PO of IV.	- Indien persisterende klachten voor > 3-5d, start Infliximab 5mg/kg (zo geen contra-indicatise; off label use, na overleg met gastro-enteroloog).

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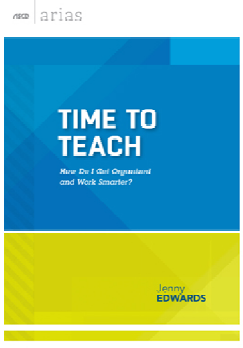
ION GENT

irAE task force

- **OPLEIDINGEN**



- ***Huisartsen***
- ***Specialisten***
- ***Verpleegkundigen***
- ***Studenten geneeskunde***
- ***Workshops***
- ***…***

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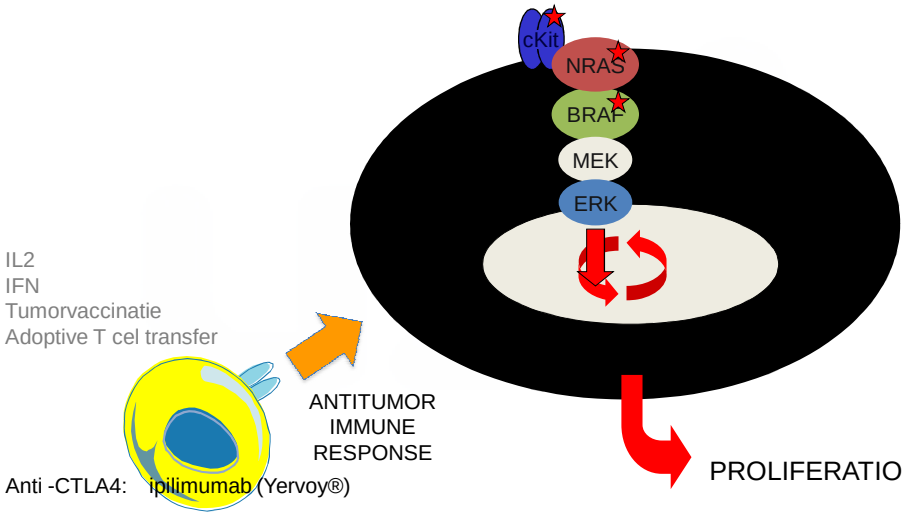
IMMUNOTHERAPY



Anti -CTLA4: ipilimumab (Yervoy®)

Anti-PD1: nivolumab (Opdivo®)
pembrolizumab (Keytruda®)

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Stimuleert het immuunsysteem om de tumorcel aan te vallen

IMMUNOTHERAPY

Anti -CTLA4: ipilimumab (Yervoy®)

Anti-PD1: nivolumab (Opdivo®)
pembrolizumab (Keytruda®)

Grijpt in thv groeimechanisme van de tumorcel

TARGETED THERAPY

BRAF inhibitors: vemurafenib (Zelboraf®)
dabrafenib (Tafinlar®)

MEK inhibitors: cobimetinib
trametinib (Mekinist®)
selumetinib

c-KIT inhibitors: imatinib (Glivec®)
nilotinib (Tasigna®)
Dasatinib (Sprycel®)

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latest update 1/2016

RECOMMENDATION MANAGEMENT STAGE IV MELANOMA

These recommendations may serve as a guidance but need to be tuned according to the specific situation, among which the tumor kinetics, the type of clinical trial, ...
The most important options are in bold; the options are not necessarily in order of preference

	1° line	2° line	3° line
BRAF negative	> **(anti-PD1)#** > **ipilimumab** > (ipilimumab + anti-PD1)# > for solitary/few metastases: consider surgery* or gamma knife** > consider clinical trial	> **anti-PD1** > ipilimumab > (ipilimumab + anti-PD1)# > chemotherapy > imatinib in case of c-kit mutation > consider clinical trial > consider best supportive care	> chemotherapy > imatinib in case of c-kit mutation > consider clinical trial > consider best supportive care
BRAF positive	> **BRAF+MEKinhibitor** > **as in BRAF negative**	> **as in BRAF negative** > **BRAF+MEKinhibitor** in patients not responding to immunotherapy	> as in BRAF negative

( ) # currently not yet available in Belgium
* *mostly for one or few metastases of the brain, resp. for some melanomas of GI location, skin/soft tissue, ulcer*
** *mostly for one or few metastases of the brain*

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TOEKOMST

Combinatiebehandelingen

Onderzoek naar markers voor respons en naar escape mechanismen

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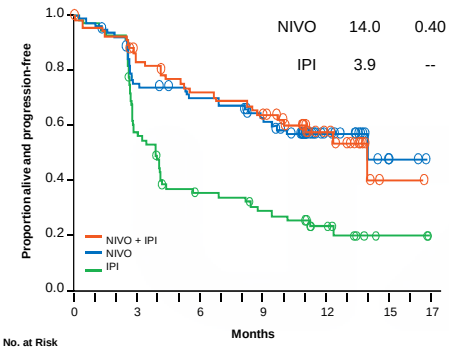
PD-L1

PFS by PD-L1 Expression Level (5%)

PD-L1 ≥5%*

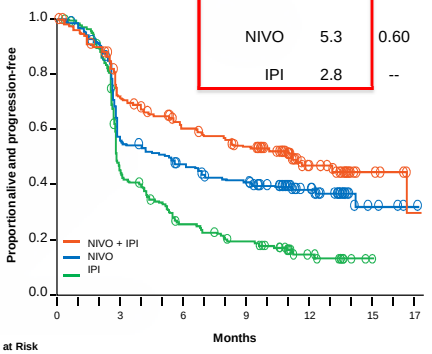
	mPFS	HR
NIVO + IPI	14.0	0.40
NIVO	14.0	0.40
IPI	3.9	--



No. at Risk							
NIVO + IPI	68	53	44	39	16	1	0
NIVO	80	57	51	43	16	4	0
IPI	75	40	22	17	9	2	0

PD-L1 <5%*

	mPFS	HR
NIVO + IPI	11.2	0.42
NIVO	5.3	0.60
IPI	2.8	--



No. at Risk							
NIVO + IPI	210	142	112	96	42	9	2
NIVO	208	108	88	74	31	5	2
IPI	202	82	44	31	12	1	–

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

50

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Oncologisch Centrum

Deze richtlijnen zijn slechts een aanbeveling en dienen telkens afgestemd te worden op de specifieke situatie

BELEID STADIUM IV MELANOOM - versie 3/2016

Multidisciplinaire tumorwerkgroep melanoom en non-melanoom huidkankers UZ Gent

Auteur: Prof Dr Lieve Brochez, Dermatologie UZ Gent

	1e line	2e line	3e line
BRAF negative	> anti PD1 > ipilimumab > for solitary/few metastases: consider surgery* or gamma knife** > clinical trial immunotherapy combined with radiotherapy	> anti-PD1 > ipilimumab > chemotherapy > imatinib in case of c-kit mutation > consider best supportive care*** > consider clinical trial	> chemotherapy > imatinib in case of c kit mutation > consider clinical trial > consider best supportive care***
BRAF positive	> BRAF+MEKinhibitor > as in BRAF negative	> as in BRAF negative > BRAF+MEKinhibitor in patients not responding to immunotherapy	> as in BRAF negative

* *mostly for one or few metastases of the brain, lung; for some metastases of GI tractus, skin/soft tissue, other*

** *mostly for one or few metastases of the brain*

*** *may also include surgery / radiotherapy*

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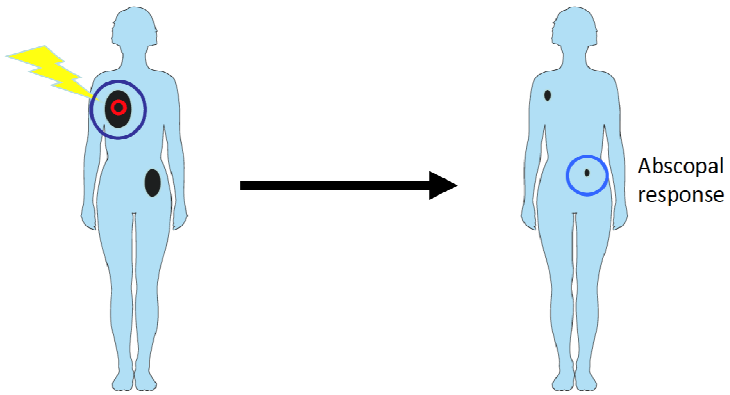
Abscopal effect

Latin *ab* (position away from) and *scopus* (mark or target)

Mole RJ. Whole body irradiation - radiology or medicine? *Br J Radiol* 1953; 26:234

RELEVANCE TO METASTATIC CANCER



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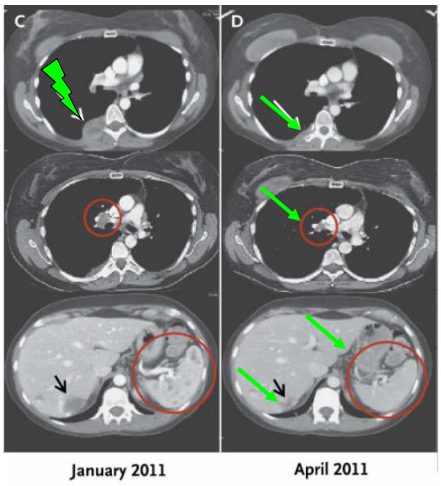
Abscopal effect



Progression under ipilimumab treatment for metastatic melanoma

↓

Antalgic radiotherapy to the painful paraspinal mass

↓

Regression of the irradiated lesion AND of other distant metastases outside the radiation field

N Engl J Med. Mar 8, 2012; 366(10): 925–931.

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UNIVERSITEIT GENT

Ghent University

Faculty of Medicine and Health Sciences

Department of Dermatology

A translational exploration of melanoma immunology focused on indoleamine 2,3-dioxygenase

-

Lessons for immunoprofiling and immunotherapy

Inès Chevolet

This thesis is submitted as fulfilment of the requirements

for the degree of

DOCTOR IN HEALTH SCIENCES

2014

Promotor: Prof. Dr. Lieve Brochez Copromotor: Dr. Mireille Van Gele

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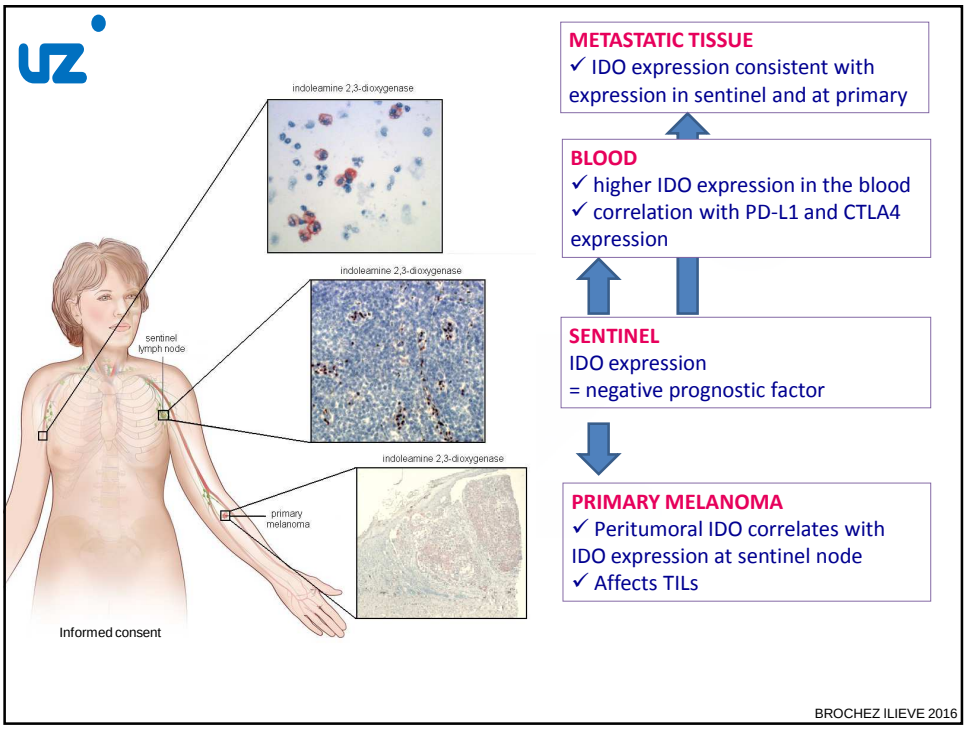

Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

UPDATE MELANOOM
NIEUWE BEHANDELINGEN

Belgian Association of Dermato-Oncology
BADO
www.huidkanker-bado.be

Prof Dr Lieve Brochez

Lieve.Brochez@ugent.be

CANCER RESEARCH INSTITUTE GHENT
CRIG

ION
immuno-oncology network Ghent