UZ GENT

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Snelcursus Melanoom

Prof. dr. Vibeke Kruse

Coördinator Kankercentrum UZ Gent

15 December 2018

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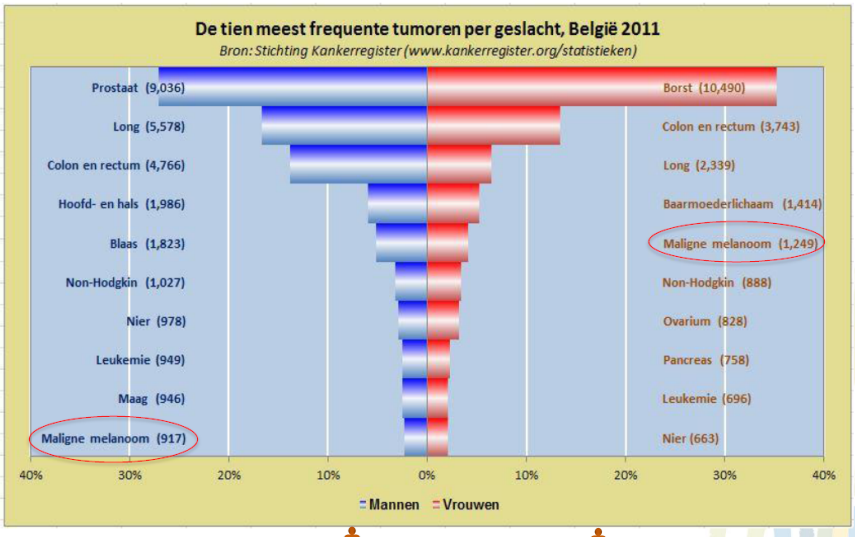


Figure 4: Malignant Melanoma: Age-standardised incidence rates (WSR) by incidence year, sex and region

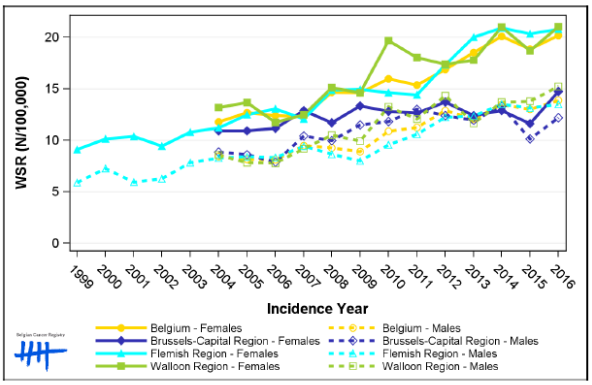
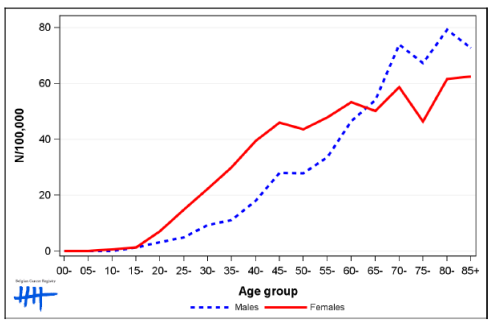


Table 3: Malignant Melanoma: Distribution of combined stage by sex, Belgium 2016

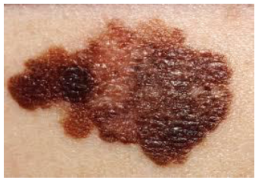
	Stage I	Stage II	Stage III	Stage IV	Stage X	Stage NA	Total
Males							
N	868	210	82	36	42	45	1,283
%	67.7	16.4	6.4	2.8	3.3	3.5	100
Females							
N	1,307	261	111	16	56	35	1,786
%	73.2	14.6	6.2	0.9	3.1	2.0	100

Staging according to the TNM 7th edition (Ref:Sobin LH, Gospodarowicz MK, Wittekind Ch. TNM classification of malignant tumours, UICC 7th edition)
Combined TNM stage : compilation of pathological (pTNM) and clinical (cTNM) stage. pTNM prevails over cTNM, except when cTNM stage is IV
Stage X: diagnoses with an unknown stage
Stage NA: diagnoses with a histological diagnosis where no stage can be evaluated (Not Applicable)

Figure 2: Malignant Melanoma: Age-specific incidence rates by sex, 2016



Malignant melanoma in numbers Belgium, 2011



N = 2166

N=1249
(1/68)

Average age at diagnosis

55,7 year

N=917
(1/88)

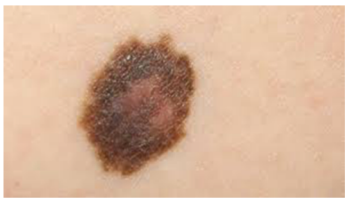
60,4 year

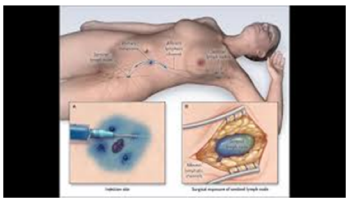
Belgian Cancer Registry

8

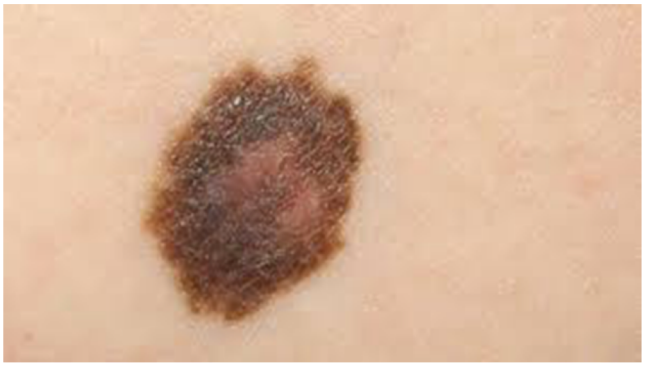
www.kankerregister.org I www.registreducancer.org

Het primaire melanoom (+/- kliermetastasen)





Wat is een melanoom?



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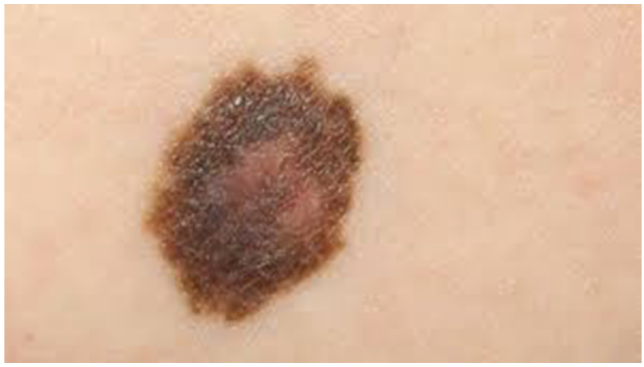
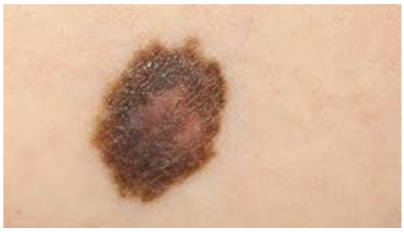


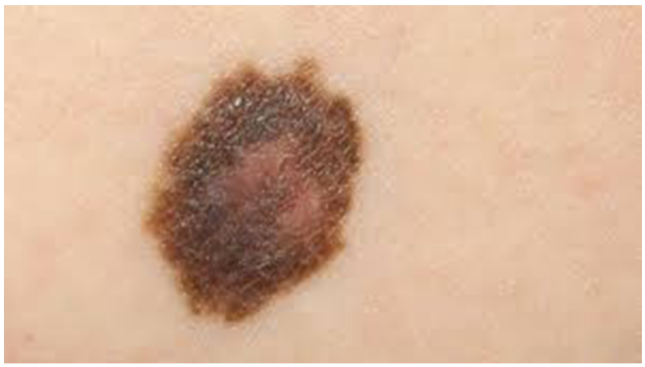
*Melanoom is een vorm van **huidkanker** die uitgaat van **melaninebevattende pigmentcellen of melanocyten**. Een melanoom **kan ontstaan** uit **goedaardige moedervlekken** (naevi naevocellulares), al is de kans hierop per moedervlek erg klein. Verder kan het ontstaan uit **onrustige (dysplastische/atypische) moedervlekken** of **"spontaan" uit normale huid** waar tevoren geen moedervlek was opgemerkt. Ze kunnen in een klein percentage van de patiënten ook elders ontstaan, bijvoorbeeld in de **slijmvliezen, het rectum, de hersenvliezen** of **zelfs in een oog**.*

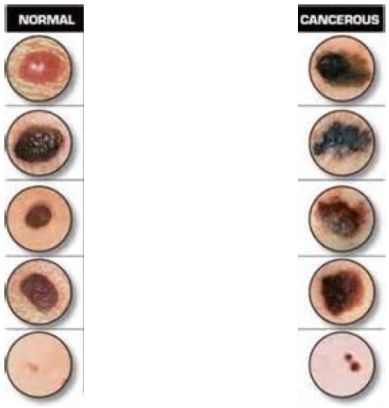
Risicofactoren



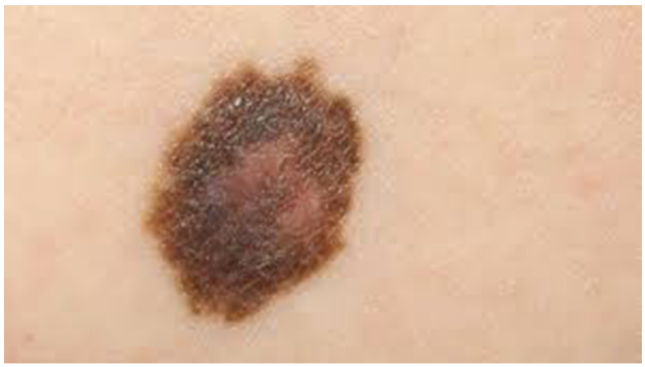
- Erfelijke aanleg
- > 50 gewone moedervlekken of minimaal drie onrustige
- Bleke huid, sproeten of blond/rossig haar
- Zonnebaden / verbranding op jonge leeftijd
- Zonnebankgebruik
- ….

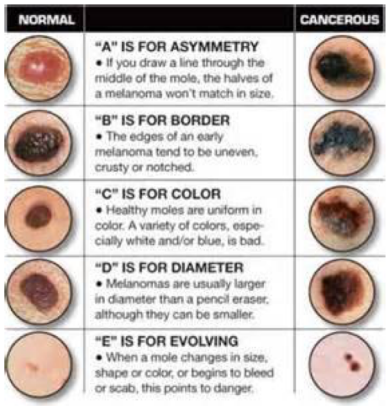
Diagnostiek





Diagnostiek





Diagnostiek

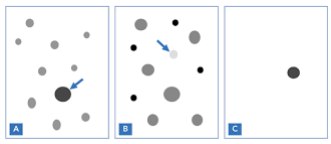
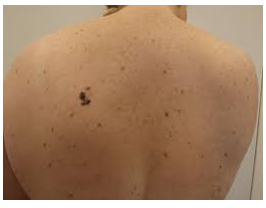
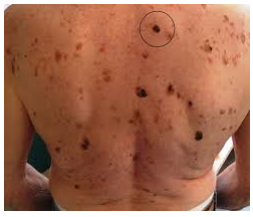
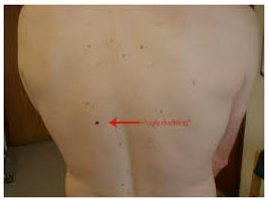


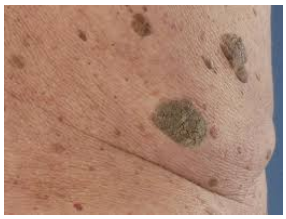
Figure 1. Three Examples of an Ugly Duckling

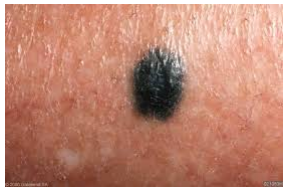
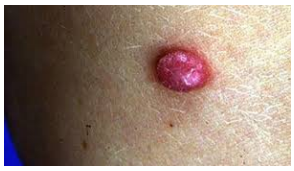
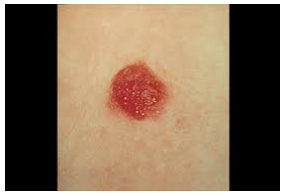
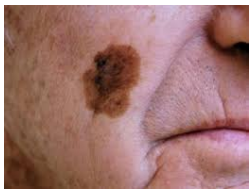




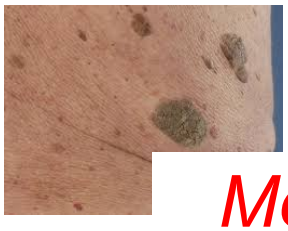


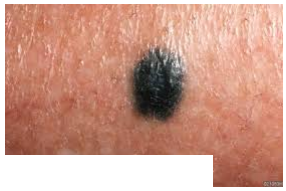
Differentiaaldiagnostiek



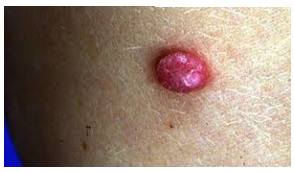
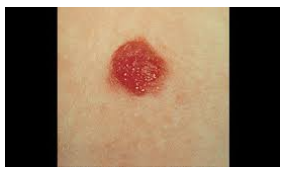





Differentiaaldiagnostiek

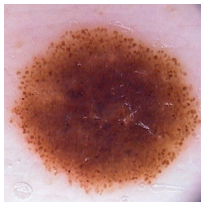


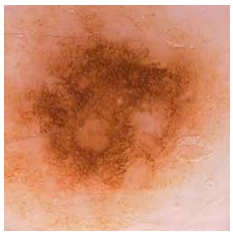


Moeilijke diagnose

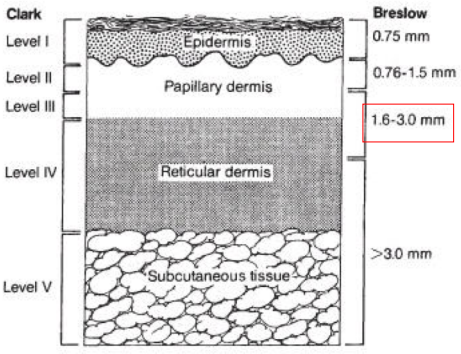

Differentiaaldiagnostiek





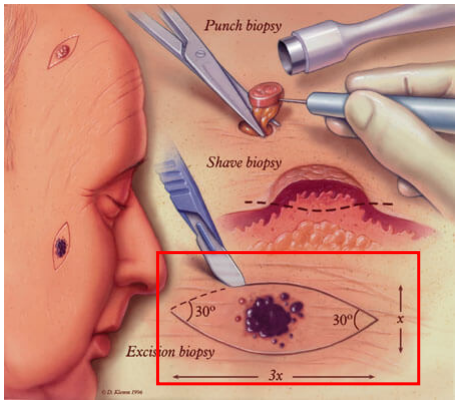
Dermatoscopie → gespecialiseerd onderzoek

APD-verslag



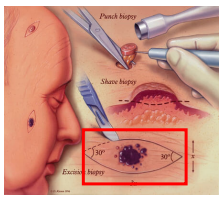
Breslow Thickness	5-year survival
< 1 mm	95-100%
1-2 mm	80-96%
2.1-4 mm	60-75 %
> 4 mm	37-50%

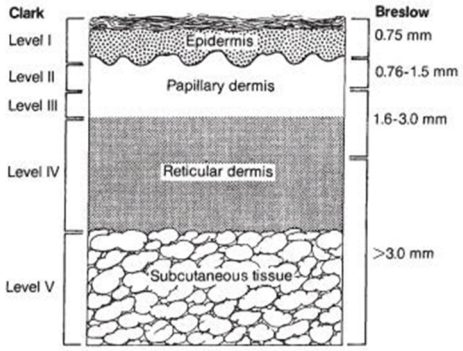
Verdere diagnostiek



https://www.huidarts.com/huidbehandelingen/excisie

Verdere diagnostiek



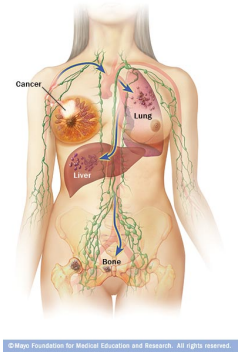


https://www.huidarts.com/huidbehandelingen/excisie

Informatie ivm de tumor

- Primaire tumor
- Lymfeklieren
- Metastasen

TNM classificatie stadium I-IV

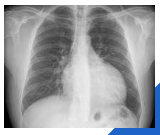


Informatie ivm de patiënt

- Symptomen
- Algemene toestand
- Bloedafname

Performance status

→ RX / echo of CT – PET/CT afhankelijk van Breslow



AJCC Pathological (pTNM) Prognostic Stage Groups[a,1]

When T is ...	And N is ...	And M is ...	Then the pathological stage group is ...
Tis	N0[b]	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b–T2a	N1a or N2a	M0	IIIA
T1a/b–T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a–T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

a. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois.[#]
b. Pathological stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use clinical N information to assign their pathological stage.
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References: 1. Gershenwald JE et al. Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. CA Cancer J Clin 2017;67:472-492. **2.** Gershenwald JE et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563–585.

AJCC = the American Joint Committee on Cancer; TNM = Tumor, Nodes, Metastatis

The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing (modified from: Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563–585)[2].

MSD

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Bruxelles 1200 Brussel

ONCO-1241590-0000 • Date of last revison 01/2018

AJCC Melanoma Staging: 8th Edition (2017)[1]

Definition of Primary Tumor (T)[a,1]

T category	Thickness	Ulceration status
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma in situ)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8–1.0 mm	With ulceration With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

a. Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois.[#] Reprinted with permission from Springer Science + Business Media B.V.

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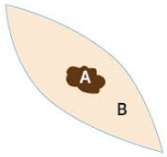
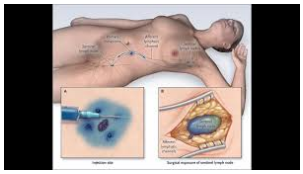
AJCC = the American Joint Committee on Cancer

MSD Oncology

Negatieve staging *(= geen metastasen)*

Brede resectie en sentinel afhankelijk van Breslow





Verdere diagnostiek

Belgian Association of Dermato-Oncology
BADO

update 11/2017

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
preoperatve	/	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 depth level: subcutis	1cm depth level: fascia°	1cm depth level: fascia°	1-2cm depth level: fascia°	1-2cm depth level: fascia°	2cm depth level: fascia°	2cm depth level: fascia°	2cm depth level: fascia°	2cm depth level: fascia°
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; ultrasonography abdomen, chest radiograph
*** ultrasonography draining lymph nodes (strongly advised) AND ultrasonography abdomen/chest radiograph OR CT thorax/CT abdomen/CT brain ; PET-CT only reimbursed from stage IIC (pT4b)
° depth level fascia means that excision involves the whole subcutis and stops at the fascia

> Totale klieruitruiming bij positieve sentinel ?

(= metastasen thv de sentinelklier)

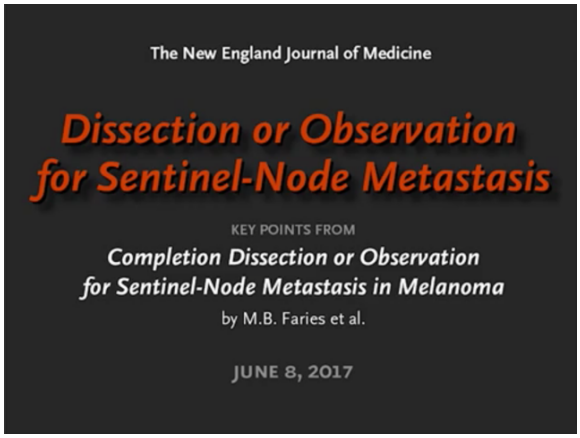
> Nabehandeling ?

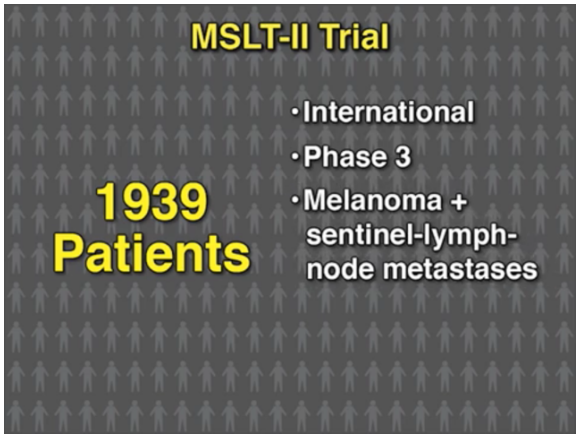
> Totale klieruitruiming bij positieve sentinel ?

(= metastasen thv de sentinelklier)

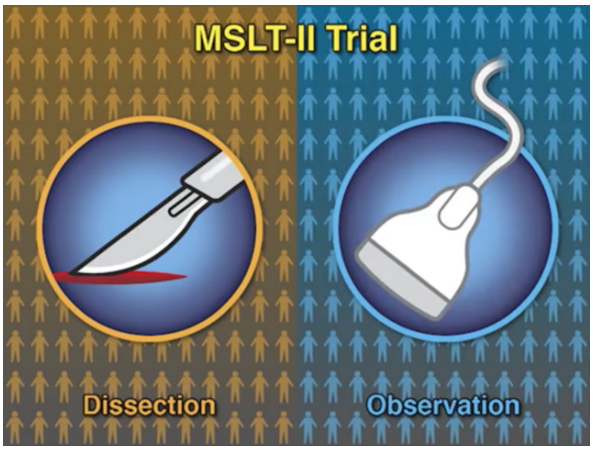
> Nabehandeling ?

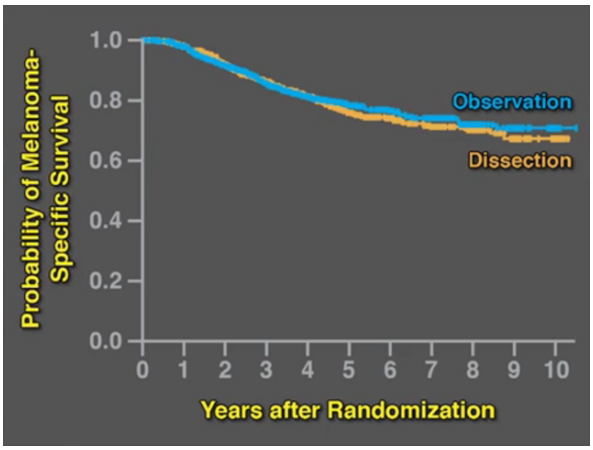
> Totale klieruitruiming bij positieve sentinel ?



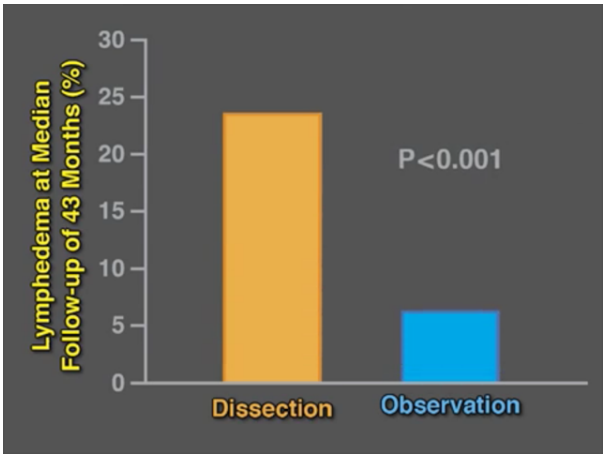


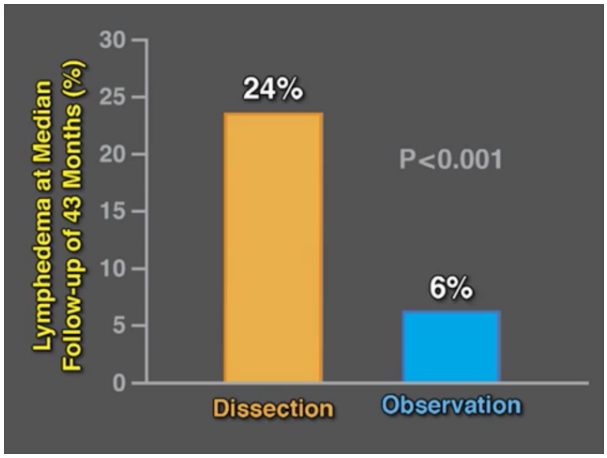
> Totale klieruitruiming bij positieve sentinel ?





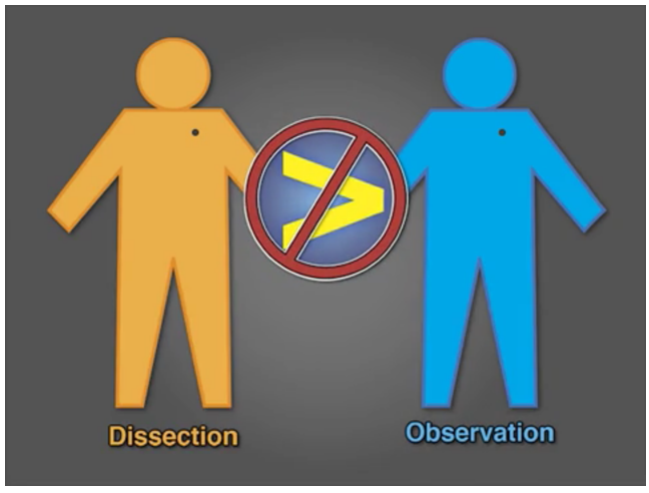
> Totale klieruitruiming bij positieve sentinel ?





> Totale klieruitruiming bij positieve sentinel ?

NEE! *(niet standaard)*

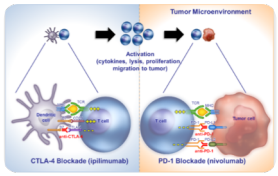


> Totale klieruitruiming bij positieve sentinel ?

(= metastasen thv de sentinelklier)

> Nabehandeling ?

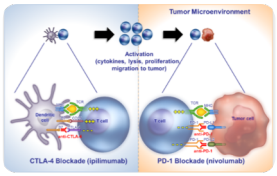
> Nabehandeling ?

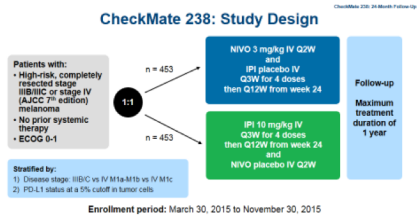


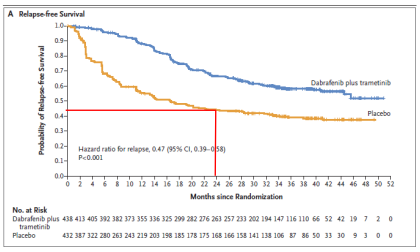
Sinds 1 oktober 2018 is nivolumab terugbetaald voor de behandeling van

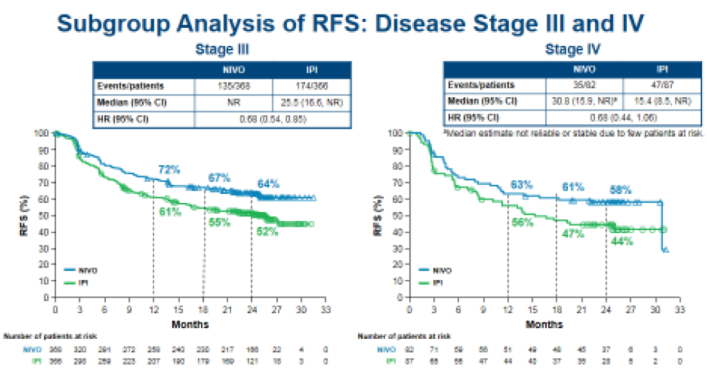
- een melanoom bij volwassene
- waarbij de lymfeklieren betrokken zijn of in geval van gemetastaseerde ziekte, na wegname van alle metastatische letsels.
- De behandeling wordt toegediend om het risico op een recidief te verlagen.
- De behandeling wordt toegediend om de 2 weken gedurende 1 jaar.

Nabehandeling ?





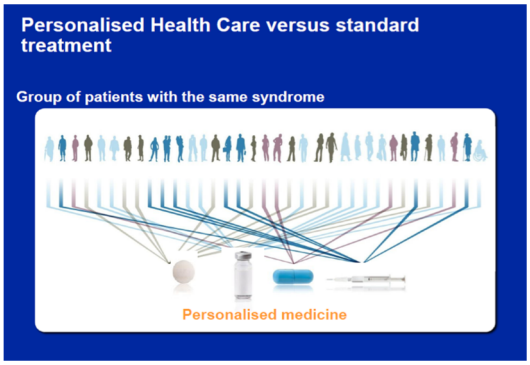




Verlaagt het risico op herval met 15 à 20 %

Long et al. NEJM 2017, Weber et al NEJM 2017

Diagnose van kanker



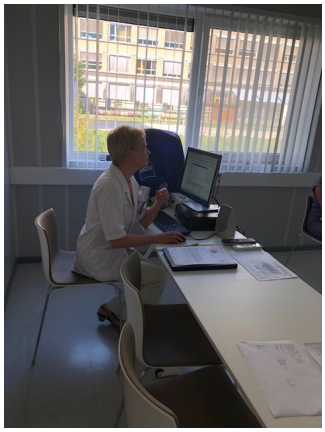
- **Stadium?**
- **Welke therapie?**

MOC

Multidisciplinair Oncologisch Consult

Diagnose van kanker

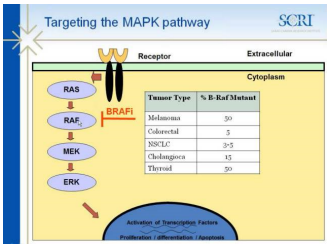
MOC



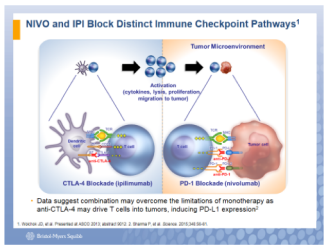
MOC dermato:
- Dermatoloog
- Medisch Oncoloog
- Radiotherapeut

- Hoofd en hals chirurg
- Plastisch chirurg
- (Patholoog)
- (Radioloog)

Bepaling van de verdere therapie



Doelgerichte therapie

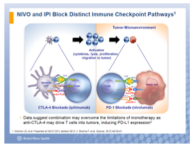


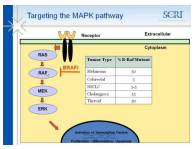
Immunotherapie

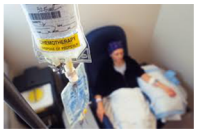
Chemotherapie

Radiotherapie

Heelkunde







Curatieve
of
palliatieve
behandeling

Altijd nood aan follow up !

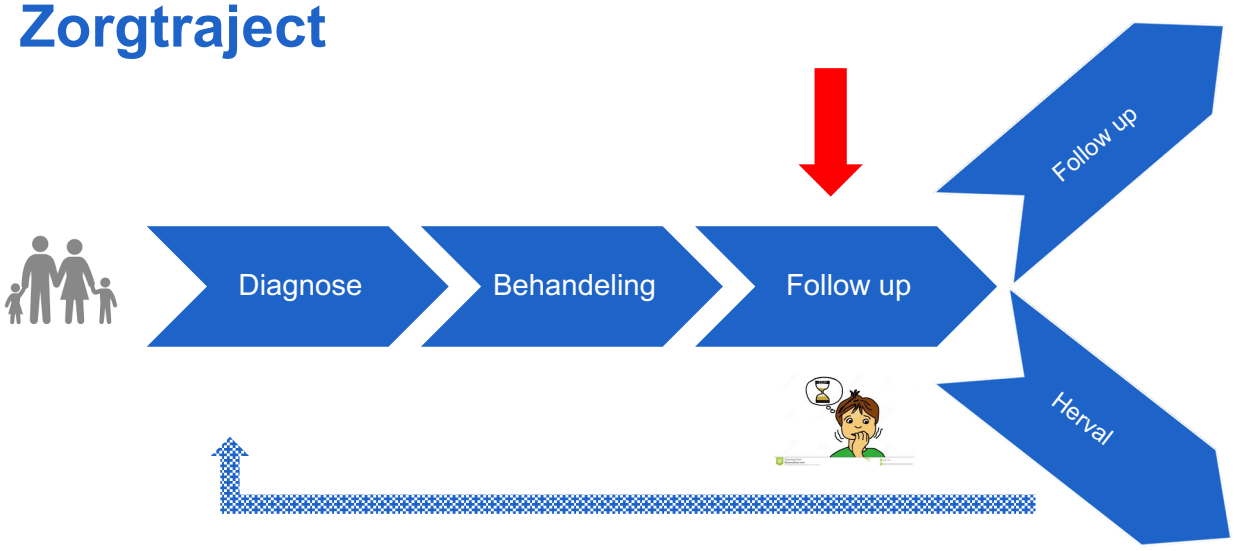
Opvolging

'Herevaluatie' / Controle:

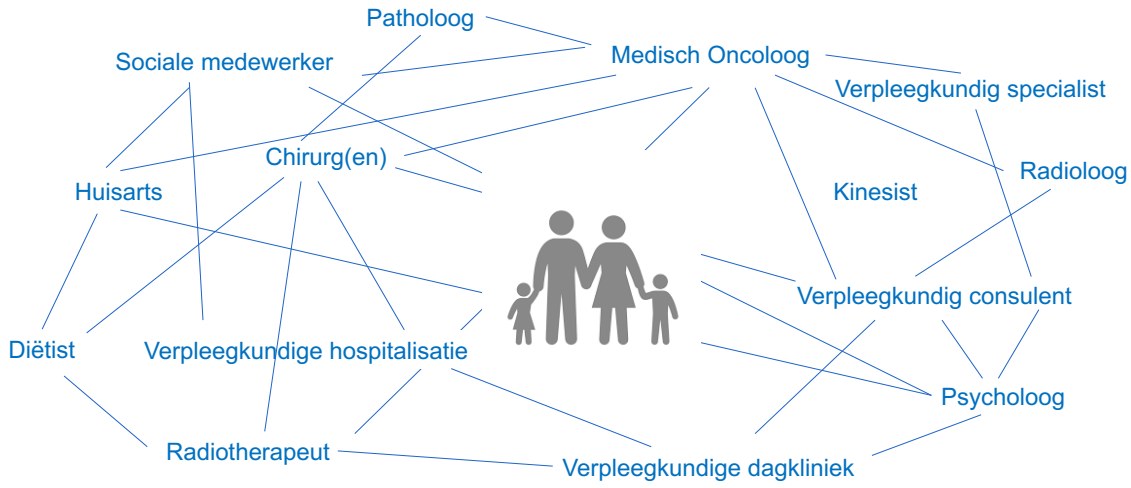
- Klinisch onderzoek
- Beeldvorming
- Bloedafname
- Specifieke onderzoeken per type kanker
- …

36 /

Zorgtraject

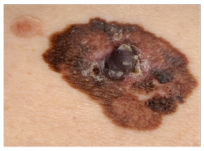


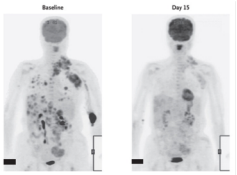
Het team ~ met de patiënt centraal

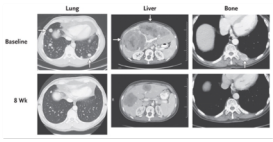


Bij diagnose en tijdens follow up !

Behandeling van het gemetastaseerd melanoom



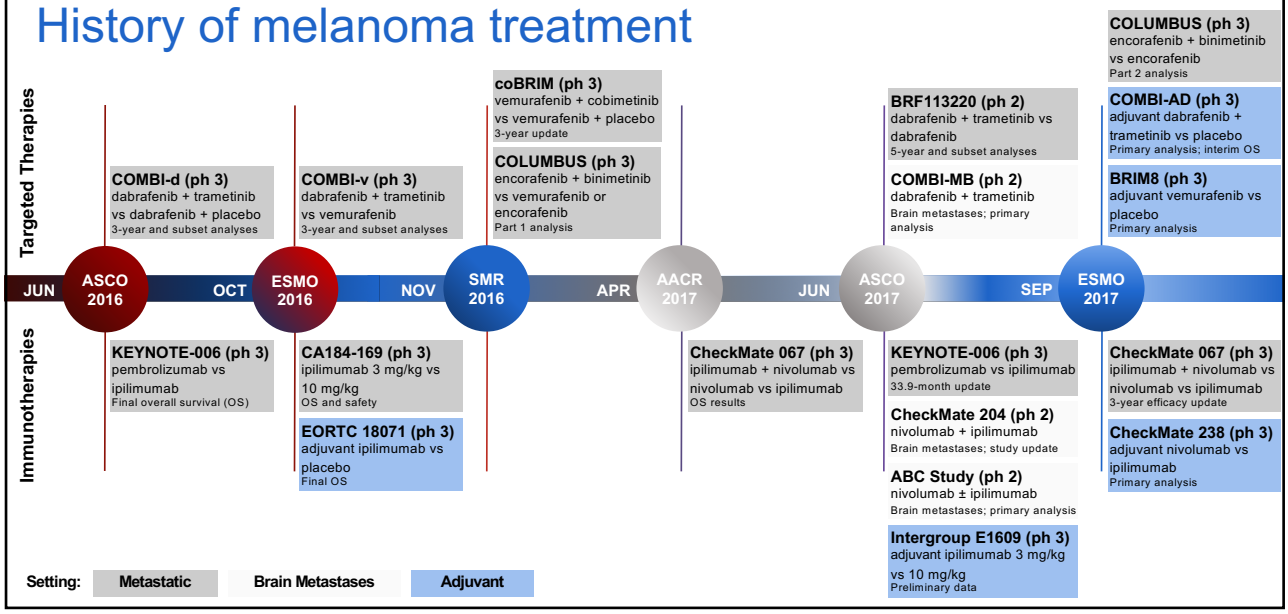




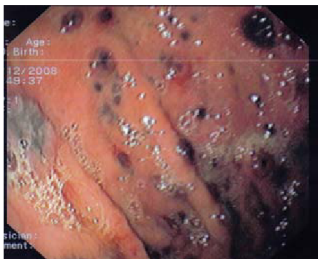
1. **Inleiding**/diagnostiek

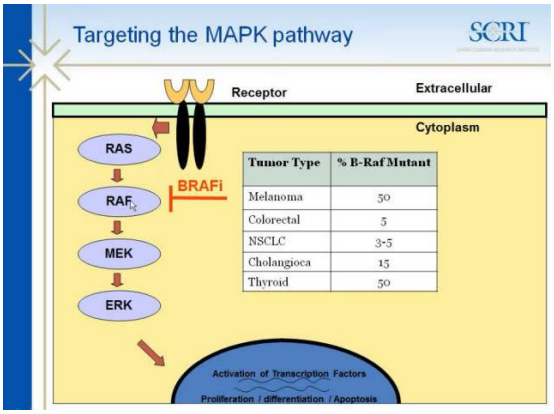
Courtesy of Prof. Dr. B. Neyns, VUB

History of melanoma treatment



1. Inleiding/**diagnostiek**





Bij diagnose van gemetastaseerde ziekte altijd bepaling van de BRAF-status !

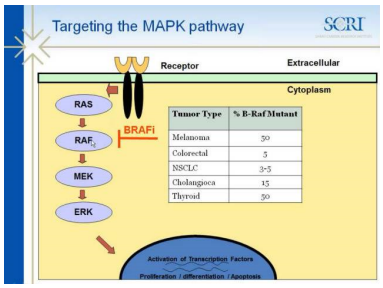
1. Inleiding/**diagnostiek**

- Wat is het stadium van de ziekte?
- Welke therapie ?

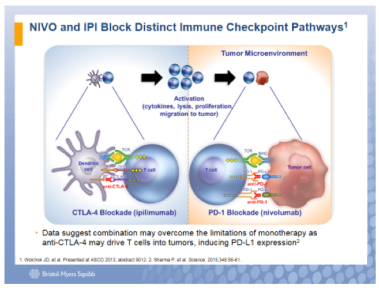
MOC

Multidisciplinair Oncologisch Consult

MOC: Welke therapie?



Targeted therapy (BRAFi/MEKi)

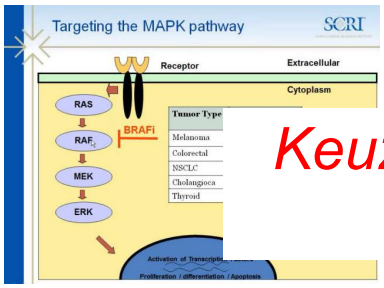


Immunotherapy
(Checkpoint inhibitor)

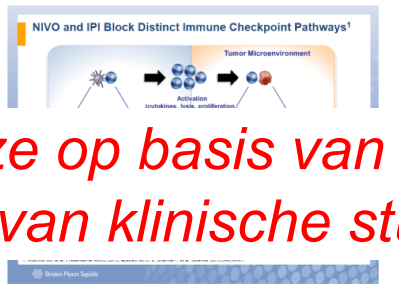
Chirurgie

Radiotherapie

MOC: Welke therapie?



Targeted therapy (BRAFi/MEKi)



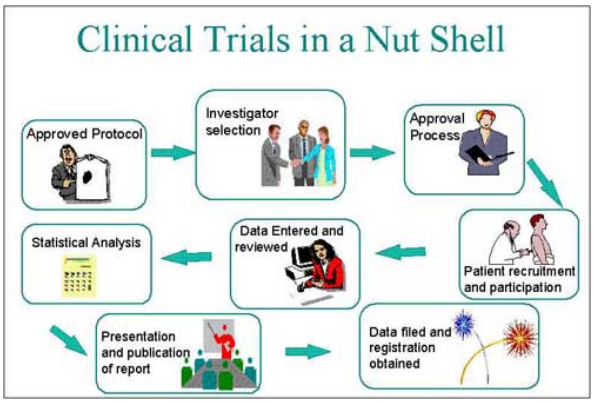
Keuze op basis van gegevens van klinische studies

Immunotherapy
(Checkpoint inhibitor)

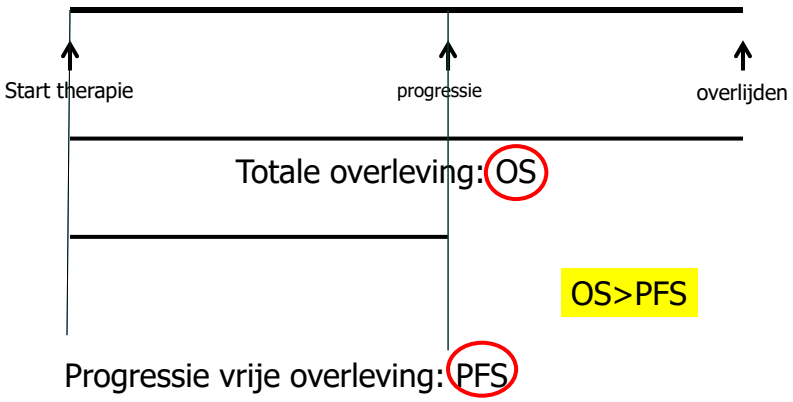
Chirurgie

Radiotherapie

Drug development in oncologie



Definities



Drug development in oncologie

www.cancerinstitute.org.au

CheckMate 066: Phase 3 trial Nivolumab in BRAF wild-type, untreated patients - Study Design [1,2]

Design

Randomized, double-blind, phase 3 study to compare NIVO to DTIC

Populatie	***Randomisatie***	***2 armen***	***Endpoints***
Eligible patients with unresectable stage III or IV MEL **(N = 418)** • *BRAF* wild-type • Treatment-naïve **Stratified by** • PD-L1 status (≥5% expression) • M-stage	**Randomize 1:1**	**NIVO** **3 mg/kg IV Q2W** **+** **Placebo IV Q3W** **N = 210** **(206 treated)** **Placebo IV Q2W** **+** **DTIC** **1000 mg/m² IV Q3W** **N = 208** **(205 treated)**	**Treat until progression[a] or unacceptable toxicity** **Primary endpoint** • OS **Secondary endpoints** • PFS • ORR • PD-L1 correlates

[a]Patients may be treated beyond initial RECIST v1.1-defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug

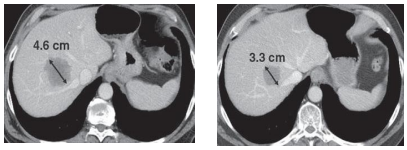
IV = intravenous; Q2W = twice weekly; Q3W = three times a week

1. Atkinson V et al. Presented at SMR 2015. 2. Robert C, et al. *N Engl J Med*. 2015;372:320-323.

Bristol-Myers Squibb

48

Werkt de behandeling ?



RECIST

- Target lesions*

Evaluation	RECIST guideline
CR	Dissapearance of all
PR	≥ 30% decrease from baseline
PD	≥ 20% increase from baseline
SD	Neither PR or PD

- Non-target lesions

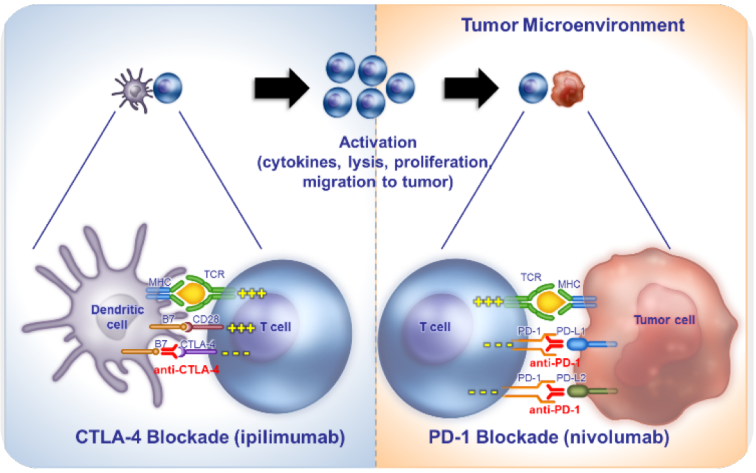
Evaluation	RECIST guideline
CR	Dissapearance of all
PD	Appearance of 1 new lesion or PD of existing lesion
SD	Persistence ≥1 lesion

*All measurable lesions (≥ 10mm); max 2 per organ; 5 in total

1. **Immunotherapie**
2. **Doelgerichte therapie**
3. **Keuze van therapie**

UZ GENT UNIVERSITEIT GENT

NIVO and IPI Block Distinct Immune Checkpoint Pathways[1]



- Data suggest combination may overcome the limitations of monotherapy as anti-CTLA-4 may drive T cells into tumors, inducing PD-L1 expression[2]

1. Wolchok JD, et al. Presented at ASCO 2013; abstract 9012. 2. Sharma P, et al. *Science*. 2015;348:56-61.

Bristol-Myers Squibb

2. **Immunotherapie bij Melanoom** (terugbetaald)

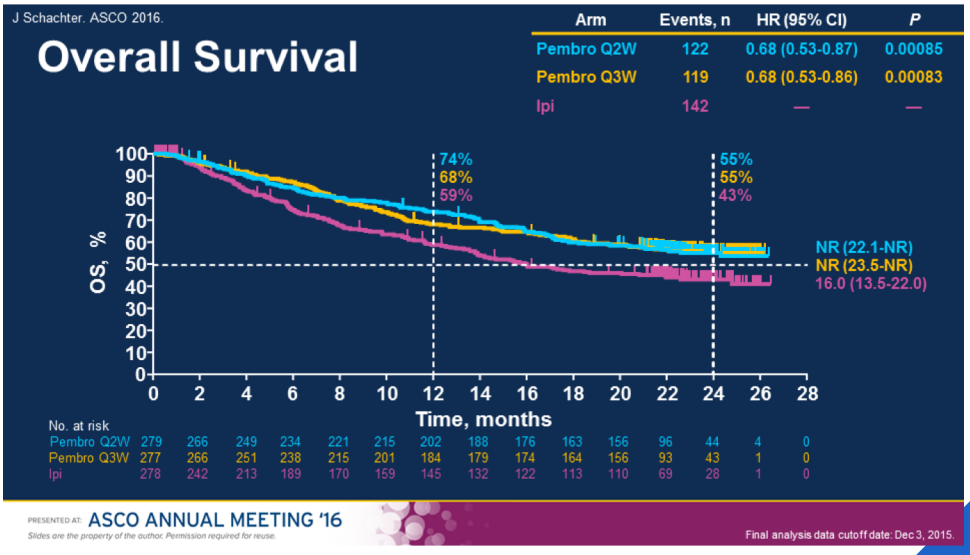
Anti-CTLA4

Anti-PD1

2. **Immunotherapie bij Melanoom** (terugbetaald)

Anti-CTLA4

Anti-PD1



J Schachter. ASCO 2016.

Tumor Response[a]

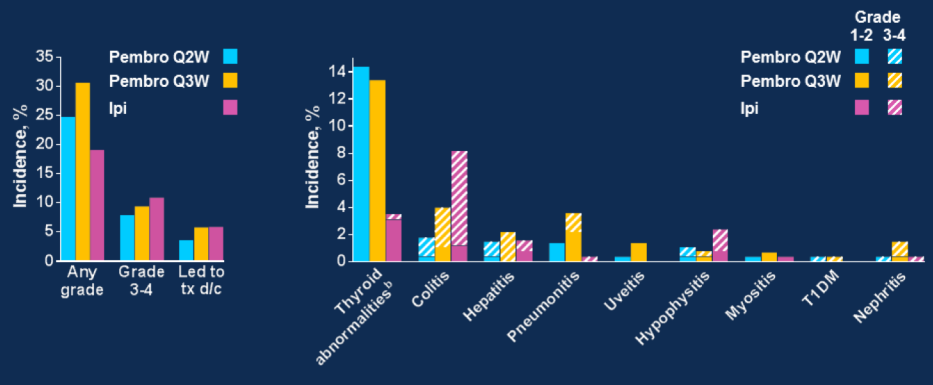
Characteristic	Pembro Q2W N = 279	Pembro Q3W N = 277	Ipilimumab N = 278
ORR, % (95% CI)	37% (30%-42%)	36% (30%-42%)	13% (10%-18%)
Best overall response			
Complete response (CR)	33 (12%)	36 (13%)	14 (5%)
Partial response	70 (25%)	64 (23%)	23 (8%)
Stable disease	30 (11%)	30 (11%)	43 (15%)
NonCR/NonPD[b]	12 (4%)	14 (5%)	9 (3%)
Progressive disease (PD)	107 (38%)	115 (42%)	137 (49%)
Not evaluable[c]	19 (7%)	15 (5%)	50 (18%)
No assessment[d]	8 (3%)	3 (1%)	2 (<1%)

PRESENTED AT: ASCO ANNUAL MEETING '16

[a]Assessed per RECIST v1.1 by independent central review. [b]Patients without measurable disease per central review at baseline who did not experience CR or disease progression. [c]Target lesion not captured by postbaseline scan or for who a target lesion was surgically removed. [d]No postbaseline scan performed or scans not able to be evaluated. Final analysis data cutoff date: Dec 3, 2015.

J Schachter. ASCO 2016.

Incidence of Immune-Mediated AEs[a]



PRESENTED AT: ASCO ANNUAL MEETING '16

[a]Not adjusted for exposure. Immune-mediated AEs are based on a list of terms specified by the sponsor and were considered regardless of attribution by the investigator. Includes hyper- and hypothyroidism and thyroiditis. Final analysis data cutoff date: Dec 3, 2015.

2. Immunotherapie bij Melanoom (terugbetaald)

Anti-CTLA4

Anti-PD1

CA209-067

Vergelijking tussen nivolumab + ipilimumab en ipilimumab monotherapie

STUDIES

TOPIC

CA209-067: Study Design[1-3]

Randomized, double-blind, phase 3 study to compare NIVO + IPI or NIVO alone with IPI alone

Unresectable or Metastatic Melanoma
- **Previously untreated**
- **945 patients**

R 1:1:1

Stratify by:
- **PD-L1 expression[a]**
- ***BRAF* status**
- **AJCC M stage**

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

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

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

Treat until progression[b] or unacceptable toxicity

[a]Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.
[b]Patients could have been treated beyond progression under protocol-defined circumstances.
AJCC, American Joint Committee on Cancer; IPI, ipilimumab; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomize.

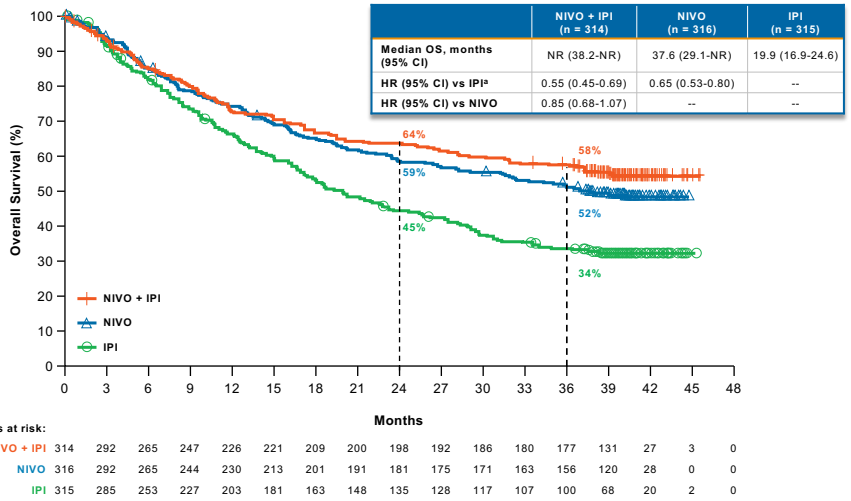
1. Adapted from Wolchok JD, et al. Presented at ASCO 2015, abstract LBA1.
2. Larkin J, et al. *N Engl J Med* 2015;373:23-34.
3. Wolchok JD, et al. *N Engl J Med* 2017;377:1345-1356.

CA209-067

STUDIES

TOPIC

Overall Survival (Intent-to-Treat)



	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, months (95% CI)	NR (38.2-NR)	37.6 (29.1-NR)	19.9 (16.9-24.6)
HR (95% CI) vs IPI[a]	0.55 (0.45-0.69)	0.65 (0.53-0.80)	--
HR (95% CI) vs NIVO	0.85 (0.68-1.07)	--	--

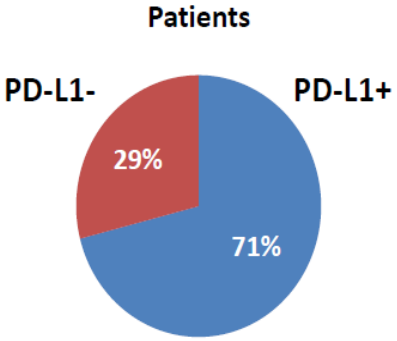
Patients at risk:

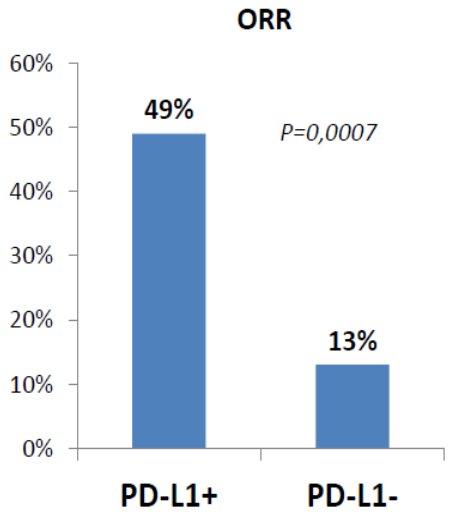
NIVO + IPI	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
NIVO	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
IPI	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

[a]P < 0.001.
Database lock May 24, 2017; minimum follow up of 36 months.
CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival.

Adapted from Wolchok JD, et al. *N Engl J Med* 2017;377:1345-1356.

PD1 and PDL1-status: predictive value?



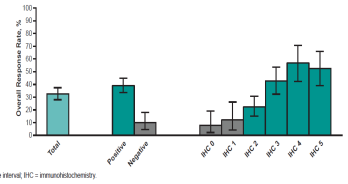


Kefford R, et al. Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475. Abstract Number: 3005. 2014 ASCO Annual Meeting.

PD1 and PDL1-status: predictive value?

- Abstract at SMR 2015 by Daud A et al: 491 pts treated with pembrolizumab in different cohorts of Keynote-001: 497 pts, 76,3% PD-L1 pos.

Figure 2. Response assessed per RECIST v1.1 by central review. Error bars represent the 95% CI.



CI = confidence interval; IHC = immunohistochemistry.

Figure 3. Duration of response assessed per RECIST v1.1 by central review.

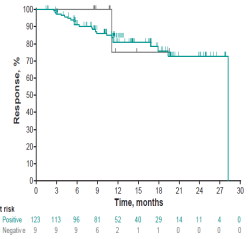
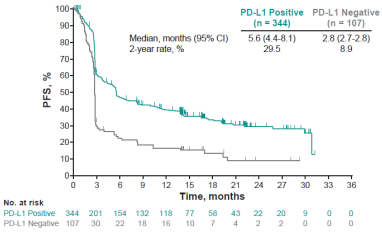
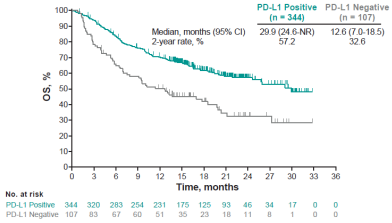


Figure 4. Kaplan-Meier estimates of PFS (RECIST v1.1, central review).



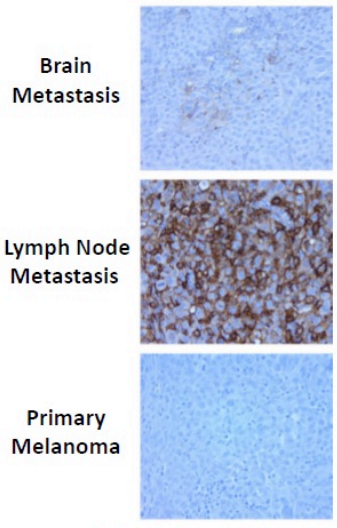
CI = confidence interval; IHC = immunohistochemistry; PD-L1 = programmed death ligand 1; PFS = progression-free survival.

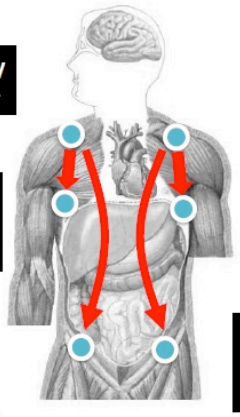
Figure 5. Kaplan-Meier estimates of OS.



CI = confidence interval; IHC = immunohistochemistry; OS = overall survival; PD-L1 = programmed death ligand 1.

Intrapatient PD-L1 Discordance





Primary PD-L1+

Primary PD-L1-

18% PD-L1- Loco-Regionale Metastases

36% PD-L1+ Loco-Regionale Metastases

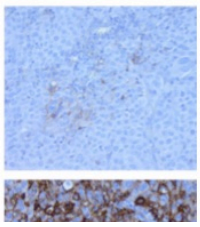
42% PD-L1- Distant Metastases

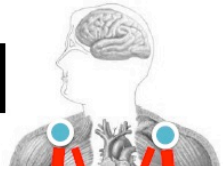
55% PD-L1+ Distant Metastases

anti-PD-L1, Merck 22C3 IHC clone, 40x

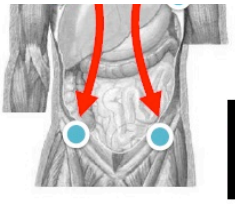
Adapted from Madore J, et al. Pigment Cell Melanoma Res 2015

Intrapatient PD-L1 Discordance





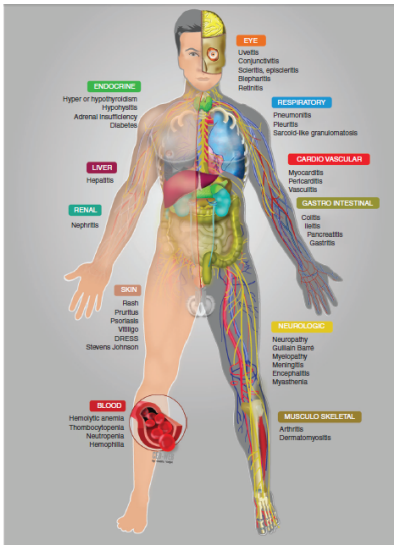
Bij melanoom wordt de PD-L1 score enkel bepaald in studieverband



anti-PD-L1, Merck 22C3 IHC clone, 40x

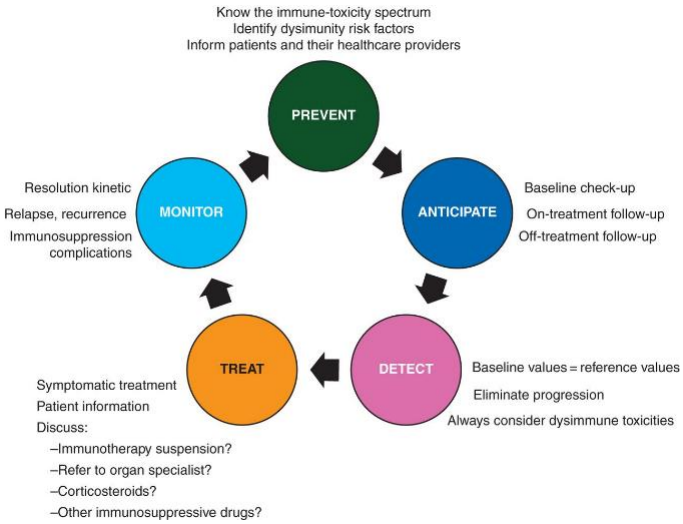
Adapted from Madore J, et al. Pigment Cell Melanoma Res 2015

Spectrum van immuungerelateerde bijwerkingen



Champiat *et al. Annals of Oncology*, 2016;27:559-74.

The five pillars of immunotherapy toxicity management:



S. Champiat et al. Ann Oncol 2016;annonc.mdv623

Specialist + Huisarts + Verpleegkundige

Vibeke Kruse 2017

Introduction BSMO ImmunoManager

BSMO

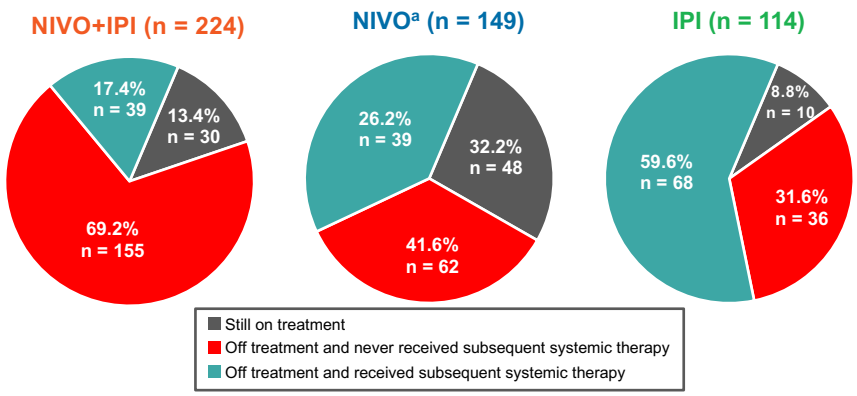
Immune related adverse events (irAE)

- Arthralgia →
- Colitis →
- Skin toxicity →
- Hepatitis →
- Nephritis →
- Neurologic →
- Pneumonitis →
- Endocrine →

➢ **Ipilimumab + Nivolumab**

- **Wat gebeurt er na stop therapie** *(ongeacht reden)* **?**

Patients Alive at 3 Years – On and Off Treatment



- In the NIVO+IPI arm, median duration of response was not reached with 69% of patients alive and remaining treatment free

[a]NIVO arm was from CheckMate 067 study only

68

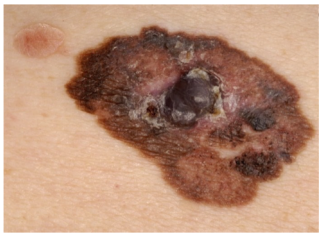
sitc
Society for Immunotherapy of Cancer

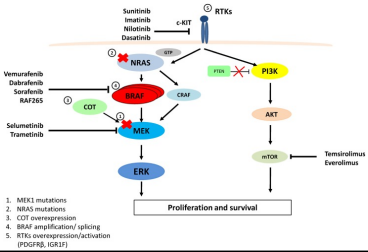
1. Immunotherapie
2. Doelgerichte therapie
3. Keuze van therapie

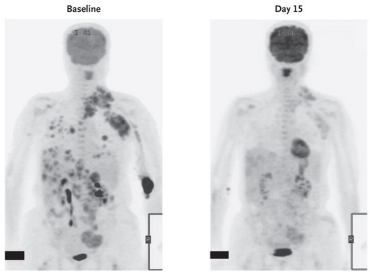
UZ GENT UNIVERSITEIT GENT

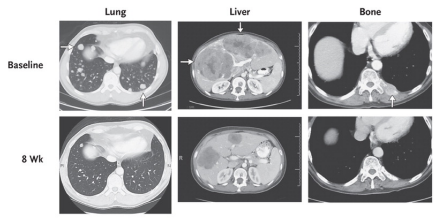
3. Doelgerichte therapie

BRAF gemuteerd melanoom





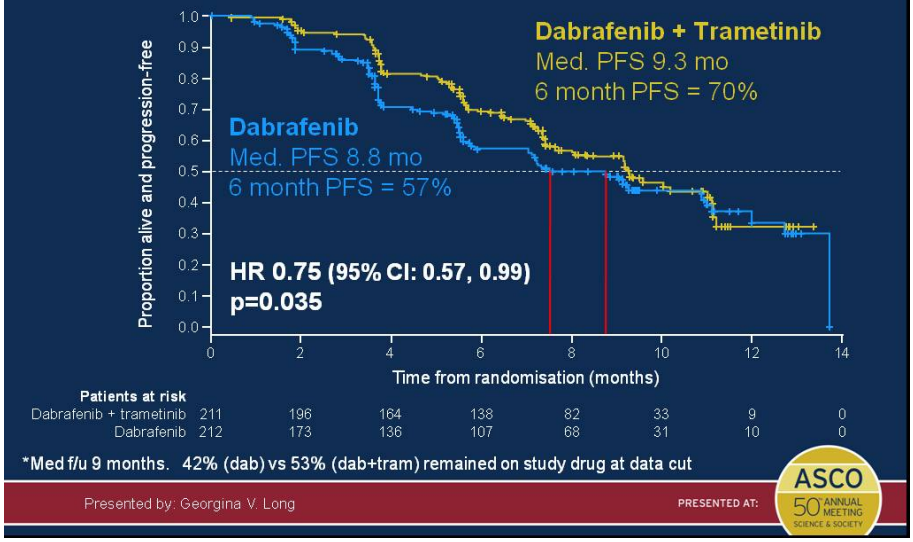




Vibeke Kruse 2017

COMBI-d: Investigator-Assessed PFS

Data cut August 2013*



*Med f/u 9 months. 42% (dab) vs 53% (dab+tram) remained on study drug at data cut

Presented by: Georgina V. Long

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Georgina Long at 2014 ASCO Annual Meeting

COMBI-d: Best Confirmed Response

	Dabrafenib + Placebo (N=210[a]) n (%)	Dabrafenib + Trametinib (N=210[a]) n (%)
Best response		
CR	18 (9)	22 (10)
PR	90 (43)	118 (56)
SD	69 (33)	54 (26)
PD	19 (9)	13 (6)
NE	14 (7)	3 (1)
Response rate		
CR+PR	**108 (51)**	**140 (67)**
95% CI	(44.5, 58.4)	(59.9, 73.0)
		P-value[b] 0.0015

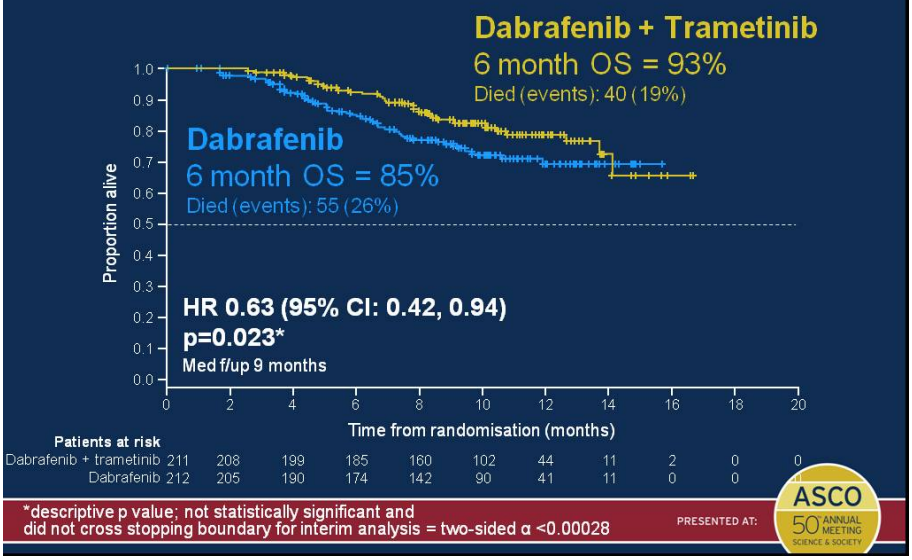
[a] Number of patients with measurable disease at baseline
[b] Chi-square test was used to calculate the p-value for difference between response rates.

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Georgina Long at 2014 ASCO Annual Meeting

COMBI-d: Overall Survival

Data cut August 2013



*descriptive p value; not statistically significant and did not cross stopping boundary for interim analysis = two-sided α <0.00028

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Georgina Long at 2014 ASCO Annual Meeting

COMBI-d: Adverse Events (≥20%) of Patients

Preferred Term	Dabrafenib + Placebo N=211 n (%)			Dabrafenib + Trametinib* N=209 n (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
All Events	203 (96)	72 (34)	7 (3)	199 (95)	66 (32)	7 (3)
Pyrexia	59 (28)	4 (2)	0	107 (51)	12 (6)	0
Fatigue	74 (35)	2 (<1)	0	74 (35)	4 (2)	0
Headache	62 (29)	3 (1)	0	63 (30)	1 (<1)	0
Nausea	54 (26)	3 (1)	0	63 (30)	0	0
Chills	33 (16)	0	0	62 (30)	0	0
Arthralgia	58 (27)	0	0	51 (24)	1 (<1)	0
Diarrhoea	30 (14)	2 (<1)	0	51 (24)	2 (<1)	0
Rash	46 (22)	2 (<1)	0	48 (23)	0	0
Hypertension	29 (14)	10 (5)	0	46 (22)	8 (4)	0
Vomiting	29 (14)	1 (<1)	0	42 (20)	2 (<1)	0
Alopecia	55 (26)	0	0	15 (7)	0	0
Hyperkeratosis	68 (32)	1 (<1)	0	7 (3)	0	0
Skin papilloma	45 (21)	0	0	3 (1)	0	0

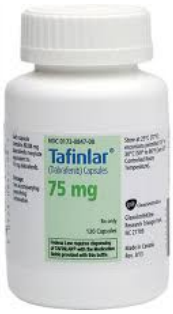
*4 fatal SAEs, not treatment related: 3 intracranial hemorrhage, 1 pneumonia

Presented by: Georgina V. Long

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Georgina Long at 2014 ASCO Annual Meeting

Combinatietherapie met BRAFinhibitor + MEKinhibitor geniet de voorkeur



BRAFi

MEKi

Dosering

BRAFi

MEKi

Dosering

1. Immunotherapie
2. Doelgerichte therapie
3. **Keuze van therapie**

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Phase 3 data in 1st Line advanced melanoma*

First-Line advanced melanoma	Immune checkpoint blockade				BRAF/MEK inhibition	
	Anti-CTLA-4	Anti-PD-1		Anti-PD-1 + Anti-CTLA-4	DABRA/TRAME [4,5]	VEMU/COBI [6]
	IPI [1,2]	PEMBRO [2] 10mg/kg q2w or q3w **	NIVO [1,3]	NIVO+IPI [1]		
ORR (%)	13-19	36-37	43-44	58	66-69	70
mPFS (months)	2.8-2.9	4.1-5.6	5.4-6.9	11.5	11.0-12.6	12.3
mOS (months)	16	Not yet reached	Not yet reached	Not yet reached	25.1-25.6	22.3
OS 1y (%)	58	68-74	71	(73) [c,9 phase2]	73-74	75
OS 2y (%)	43	55	58	(64) [c,9 phase2]	51-52	48
OS 3y (%)	34[10]	(40-45)[a,7]	52[10]	58[10]	44	-
mDOR (months)	14.4	Not yet reached	22.3	Not yet reached	10.6-13.8	13.0
G3-4 AEs (%)	19-27	17	13-19.8	56.5	41-52	60

* **For summary purposes only. Cross-trial comparisons cannot be made.**

** 2mg/kg q3w is the approved dose for pembrolizumab
a Pooled pembrolizumab doses of 2 mg/kg q3w, 10 mg/kg q3w, or 10 mg/kg q2w from phase 1 KN-001 including IPI naïve and IPI pre-treated patients
c 3y-OS data from phase 1 CM-003 in previously treated patients
c 2y-OS data from phase 2 CM-069

1. Wolchok et al. Updated Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naive Patients With Advanced Melanoma (CheckMate 067). Presented at ASCO 2016. Abstract #9505. 2. Schachter et al. Pembrolizumab Versus Ipilimumab for Advanced Melanoma: Final Overall Survival Analysis of KEYNOTE-006. Presented at ASCO 2016. Abstract #9504. 3. Atkinson et al. Two-Year Survival and Safety Update in Patients With Treatment-Naive Advanced Melanoma Receiving Nivolumab or Dacarbazine in CheckMate 066. Presented at SMR 2015. 4.Flaherty et al. Update of Combi-d: A Phase 3 Study of Dabrafenib + Trametinib vs Dabrafenib Monotherapy in Patients With Unresectable or Metastatic BRAF V600E/K-mutant Cutaneous Melanoma. Presented at ASCO 2016. Abstract #9502 5. Long et al. Presented at ASCO 2015. Abstract #102 6. Ascierto et al. Lancet Oncol. 2016 Sep;17(9):1248–1260. 7. Robert et al. Presented at ASCO 2016. Abstract #9503 8. Hodi et al. Presented at AACR 2016. 9. Hodi et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trialLancet Oncol. 2016 Nov;17(11):1558-1568. 10. J.D. Wolchok et al. NEJM sep 11, 2017.

4. Keuze van therapie

update 11/2017

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 + anti-PD1 > for solitary/few metastases: consider surgery* or gamma knife** > consider clinical trial	> **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	> **rechallenge with BRAF/MEK inhibitor**** > 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*
**** *rechallenge after progression on BRAF/MEK inhibitor in first line and immunotherapy in second line (preferably min 12 weeks)*

4. Keuze van therapie

- ***BRAF mutatie***
- ***Ziekteload***
- ***Lokalisatie metastasen***
- ***Hersenmetastasen***
- ***Verhoogd LDH***
- ***Symptomatisch vs niet symptomatisch***
- ***Voorgeschiedenis (vooral autoimmuniteit?)***
- ***Leeftijd en comorbiditeit***
- ***Voorkeur van de patiënt***
- ***….***

Toekomstperspectieven

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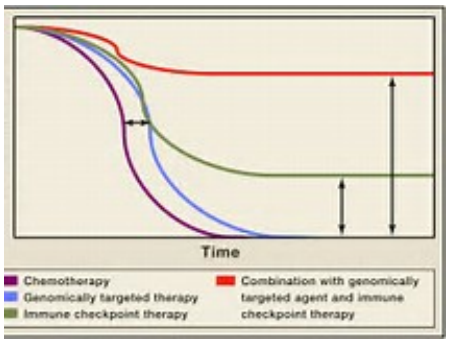
Inleiding / strategieën om respons te verbeteren



KANS OP RESPONS

Tijd

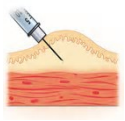
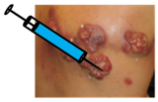
Doel: efficiënte langdurige respons ⇨ ⇨ ⇨ GENEZING

Strategieën om respons te verbeteren

- **Nieuwe geneesmiddelen ontwikkelen:**

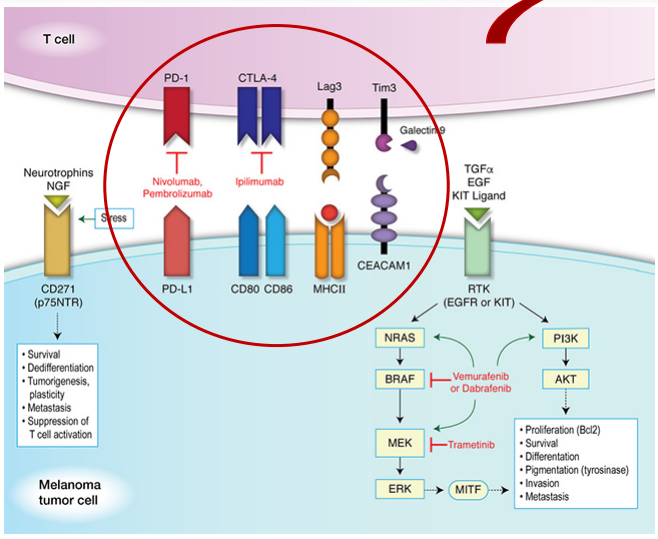
Peroraal (PO) Intraveneus (IV) SC (subcutaan) Intralesionaal

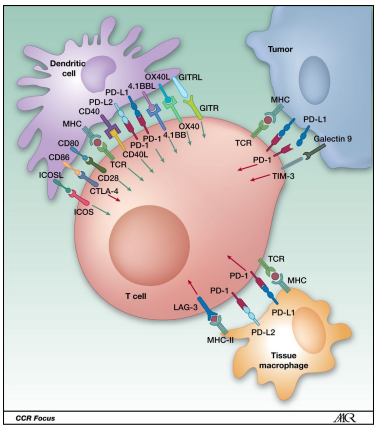


- **Combinatie van ≥ 2 geneesmiddelen**
- **Oude geneesmiddelen gebruiken in een nieuwe context**
- **Combinatie van ≥ 1 geneesmiddel + Radiotherapie**
- **Optimale volgorde van behandelingen definiëren**
- **Betere selectie van patiënten (biomarkers)**

Immunotherapie – aangrijpingspunten?

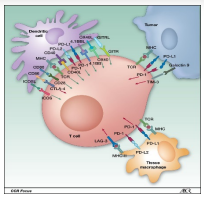




Keller et al. Oncotarget 2017.

Vibeke Kruse 2017

Combinatie immunotherapie en radiotherapie



+

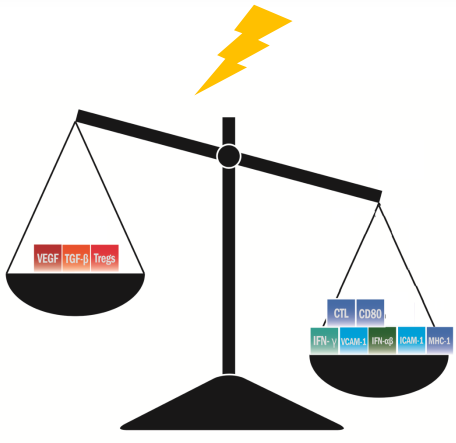
De Wolf et al. J Transl Med (2017) 15:21
DOI 10.1186/s12967-017-1123-x

Journal of
Translational Medicine

PROTOCOL Open Access

A phase II trial of stereotactic body radiotherapy with concurrent anti-PD1 treatment in metastatic melanoma: evaluation of clinical and immunologic response

Katrien De Wolf[1*], Vibeke Kruse[2], Nora Sundahl[1], Mireille van Gele[3], Ines Chevolet[3], Reinhart Speeckaert[3], Lieve Brochez[3] and Piet Ost[1]

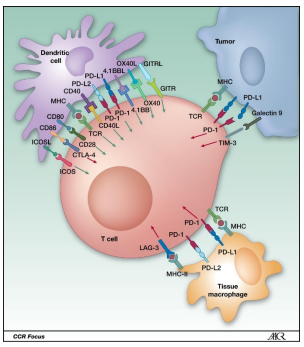


ANTI-IMMUNOGENIC PRO-IMMUNOGENIC

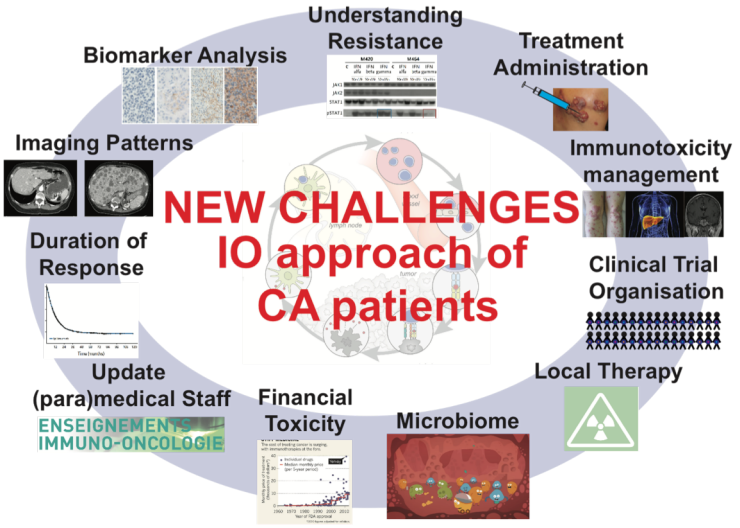
OncoImmunology 4:10 2015, De Wolf et al.

Vibeke Kruse 2017

Uitdagingen bij de verdere ontwikkeling van immunotherapie…



Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309



Courtesy of Dr. S. Aspeslagh, Jules Bordet Instituut

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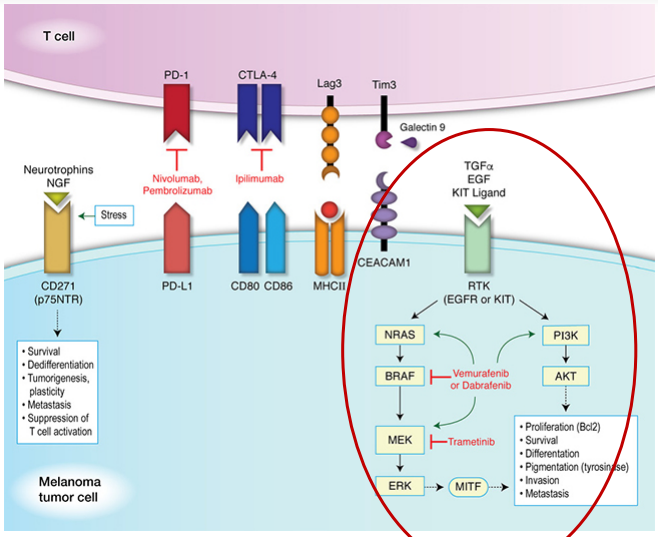
Doelgerichte therapie



RECHALLENGE

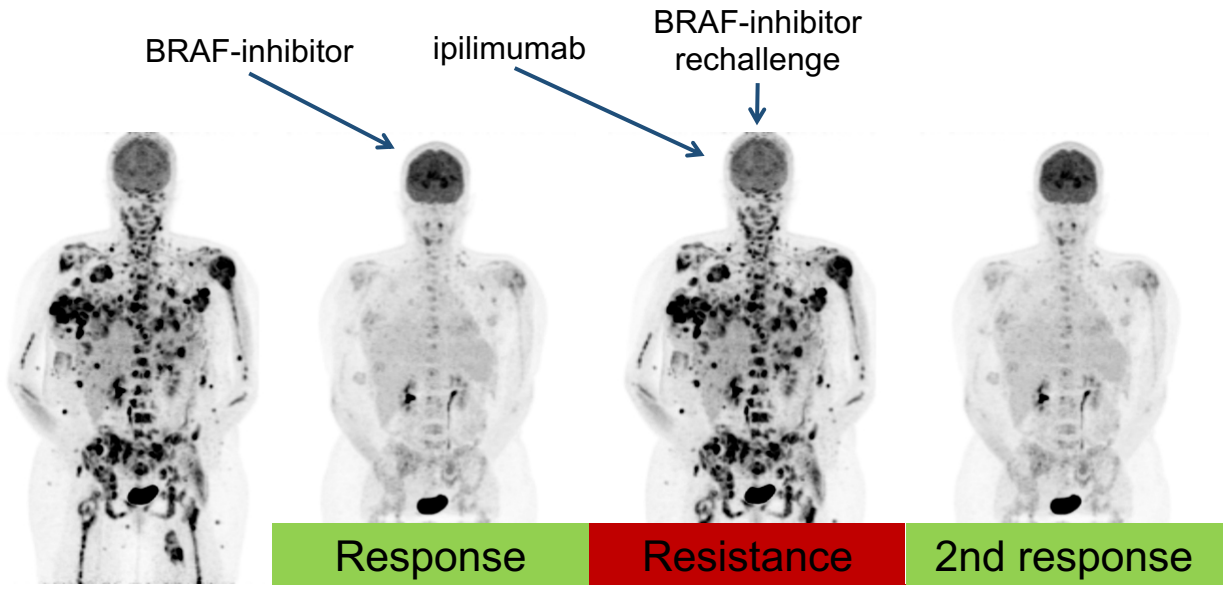
met BRAFi/MEKi

Keller et al. Oncotarget 2017.

Vibeke Kruse 2017

Rechallenge

Courtesy of dr. M. Schreuer



Besluit

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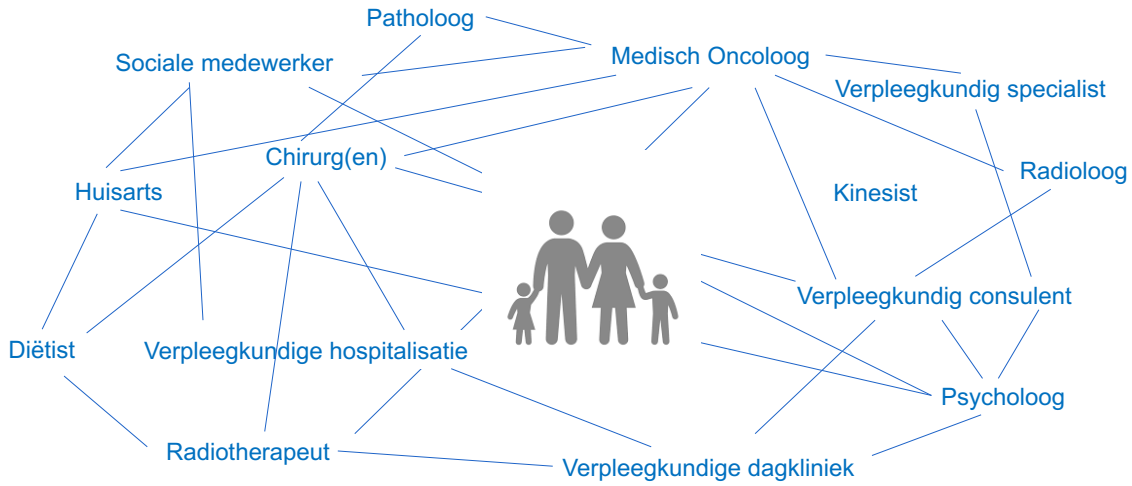
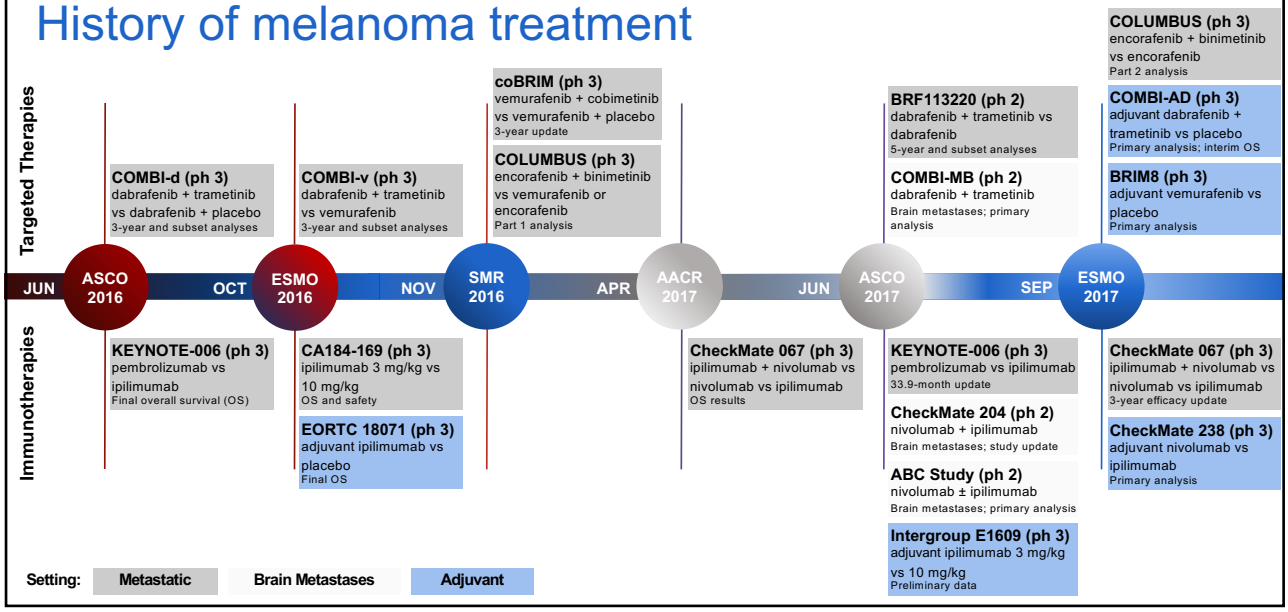
Het team ~ met de patiënt centraal



Bij diagnose en tijdens follow up !

History of melanoma treatment



update 11/2017

RECOMMENDATION MANAGEMENT STAGE IV MELANOMA

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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 + anti-PD1 > for solitary/few metastases: consider surgery* or gamma knife** > consider clinical trial	> **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	> **rechallenge with BRAF/MEK inhibitor**** > 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*
**** *rechallenge after progression on BRAF/MEK inhibitor in first line and immunotherapy in second line (preferably min 12 weeks)*

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