ADJUVANTE BEHANDELING BIJ MELANOOM

Sofie Wilgenhof, Medisch oncoloog
29 Januari 2022

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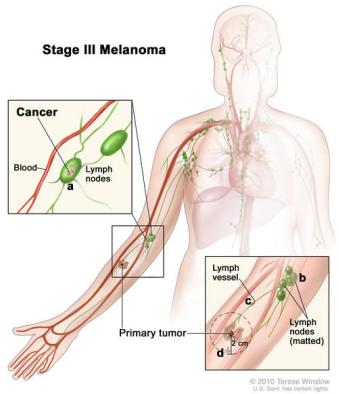
ADJUVANTE BEHANDELING BIJ HOOG RISICO PATIENTEN



Clinically apparent macro-metastases

Clinically occult micro-metastases

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AJCC STAGING (8TH EDITION)

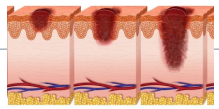
Definitions		
Primary Tumor (T)	**Thickness (mm)**	**Ulceration**
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Melanoma in situ	
T1	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤1.0 mm w/ ulceration
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	
T4	>4.0	
Regional Lymph Nodes (N)	**Number of regional nodes**	**Microsatellite instability (MSI)* status, clinically detectable**
NX	Nodes cannot be assessed	
N0	No regional metastases detected	
N1	0-1 node	a: no MSI, clinically occult b: no MSI, clinically detected c: MSI present, 0 nodes
N2	2-3 nodes	a: no MSI, clinically occult b: no MSI, clinically detected
	1 node	c: MSI present, detectable or occult
N3	>3 nodes	a: no MSI, all occult b: no MSI, ≥ 1 detected or matted
	>1 node	c: MSI present, detectable or occult
Distant Metastasis (M)	**Site of metastases**	**Serum LDH**
M0	No distant metastases detected	
M1a-d	(a) Skin/subcutaneous/distant node, (b) lung, (c) other visceral sites, (d) brain	Not assessed
M1a-d (0)		Normal
M1a-d (1)		Elevated

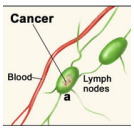
*MSI refers to any satellite, locally recurrent, or in transit lesions.

Quick tips for melanoma staging:

- 8th Ed omits mitosis status and T1a is <0.8 mm rather than <1.0mm
- Clinical and pathologic staging (TNM) is the same except for stage 3
- Nodal involvement → at least stage 3
- Distant metastases → stage 4

www.aad.org/DIR





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STAGING EN PROGNOSIS

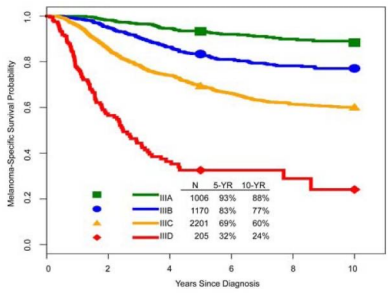
AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details.[4]

Legend	
A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID



Gershenwald et al. CA Cancer J Clin. 2017

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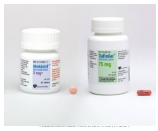
ADJUVANTE BEHANDELING

1. Immuuntherapie:

- Anti-CTLA-A4: ipilimumab
- Anti-PD-1: pembrolizumab / nivolumab
- Combinatiebehandeling: ipilimumab + nivolumab

2. Doelgerichte behandeling (indien BRAF mut):

BRAF + MEK inhibitie: dabrafenib + trametinib



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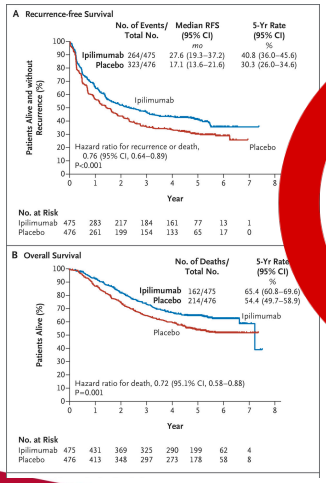
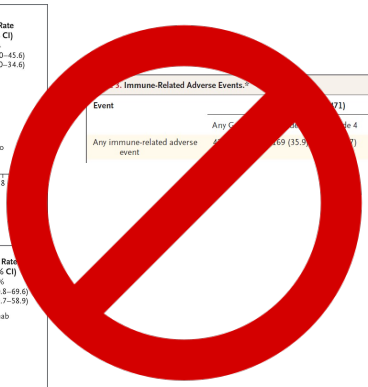
ADJUVANT IPILIMUMAB





Eggermont AM et al. N Engl J Med 2016;375:1845-1855.

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ADJUVANT ANTI-PD-1 ANTILICHAAM BIJ MELANOOM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

Alexander M.M. Eggermont, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Mario Mandala, M.D., Georgina V. Long, M.D., P.D., Victoria Atkinson, M.D., Stéphane Dalle, M.D., Andrew Haydon, M.D., Mikhail Lichinitser, M.D., Adnan Khattak, M.D., Matteo S. Carlino, M.D., Ph.D., Shahneen Sandhu, M.D., James Larkin, M.D., Susana Puig, M.D., Ph.D., Paolo A. Ascierto, M.D., Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D., Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D., Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D., Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D., Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D., and Caroline Robert, M.D., Ph.D.

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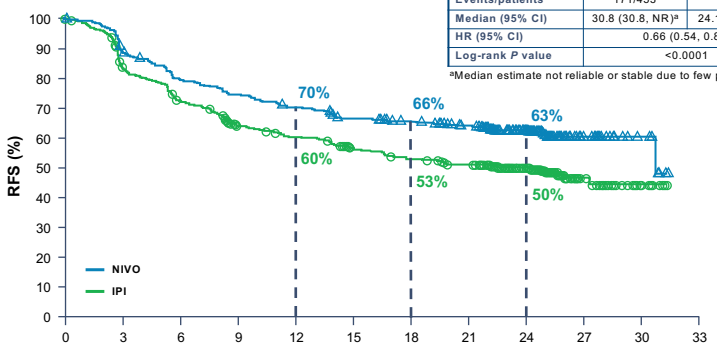
NIVOLUMAB VERSUS IPILIMUMAB

Primary Endpoint: RFS in All Patients

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

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



Number of patients at risk

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

Checkmate-238 24m follow-up

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TERUGKEER VAN ZIEKTE

	NIVO (n = 453)	IPI (n = 453)
Events, n (%)	171 (38)	221 (49)
Recurrence	171 (38)	216 (48)
Disease at baseline	1 (<1)	2 (<1)
Local recurrence	31 (7)	46 (10)
Regional recurrence	35 (8)	36 (8)
Distant metastasis	97 (21)	128 (28)
New primary melanoma	7 (2)	4 (1)
Death	0	5 (1)

Checkmate-238 24m follow-up

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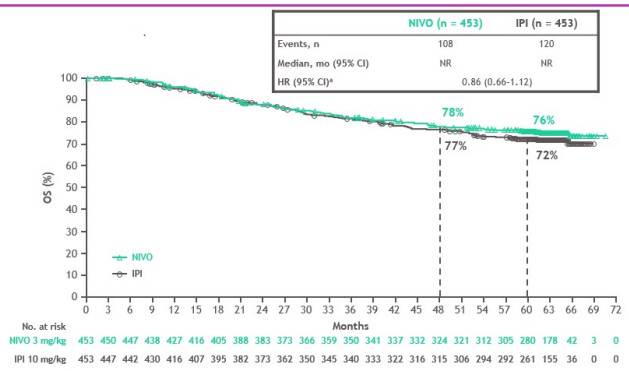
GLOBALE OVERLEVING

CheckMate 238

Secondary endpoint: 60-month OS update in all patients



- 228 of 302 anticipated events (75%); 17 new deaths since 4-year database lock (8 NIVO and 9 IPI), mainly attributed to disease

aStratified. NR, not reached.

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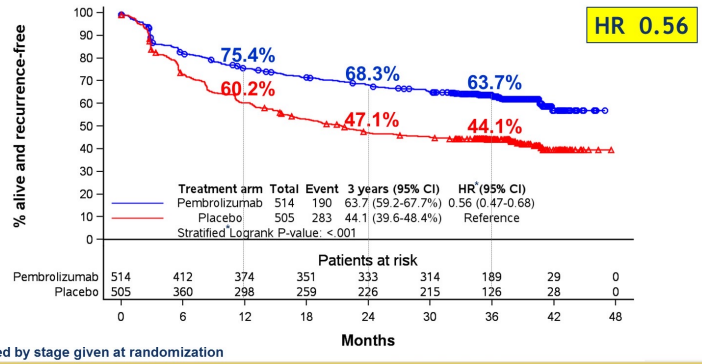
PEMBROLIZUMAB

EORTC 1325/KEYNOTE-54: New RFS analysis (ASCO 2020)

- ***Cut-off date*** (30-Sep-2019); duration of follow-up: median **3** years; **473** RFS events



*Stratified by stage given at randomization

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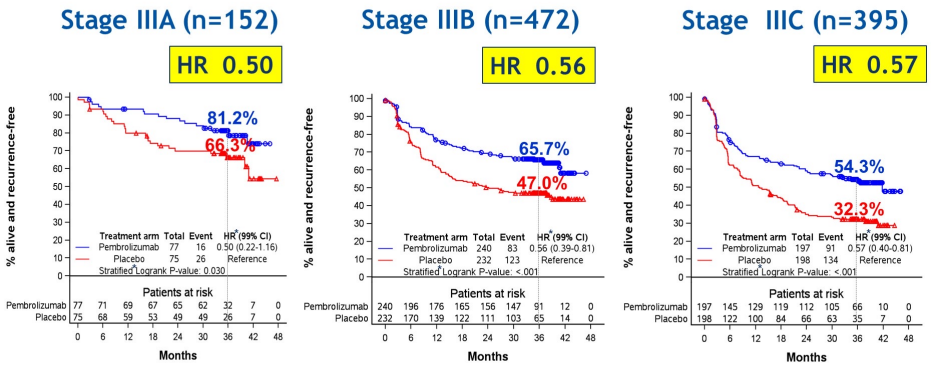
Recurrence-free survival according to AJCC-7 staging



*Stratified by stage given at randomization

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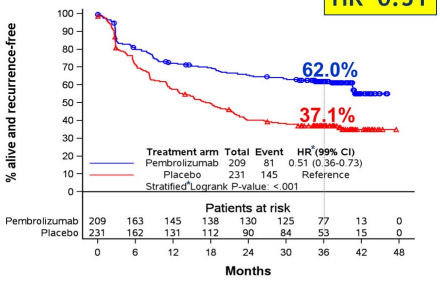
RFS according to BRAF-V600 E-K mutation status

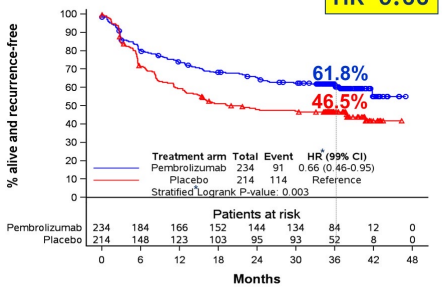
BRAF-mutated (n=440)

HR 0.51



BRAF-WT (n=448)

HR 0.66



*Stratified by stage given at randomization

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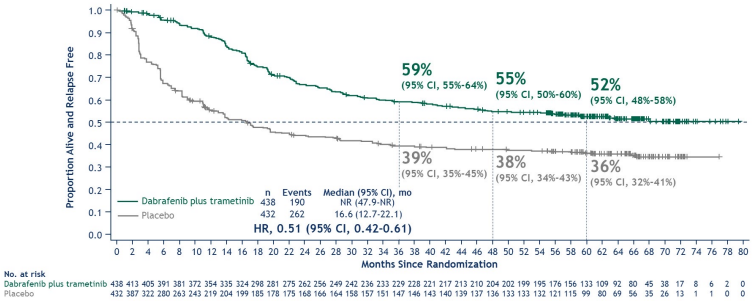
ADJUVANT DABRAFENIB + TRAMETINIB

Relapse-Free Survival



HR, hazard ratio; NR, not reached.

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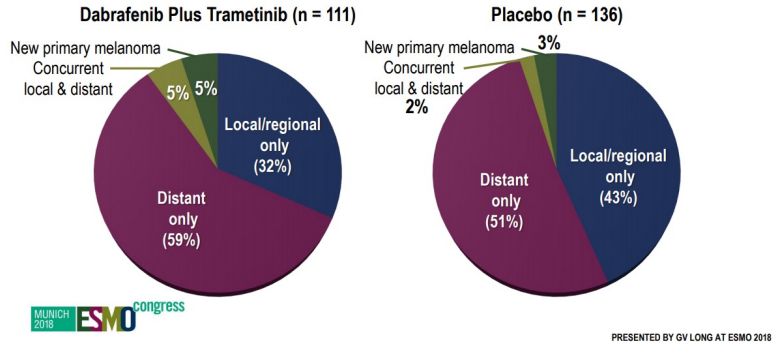
LOKALISATIE VAN ZIEKTE BIJ HERVAL



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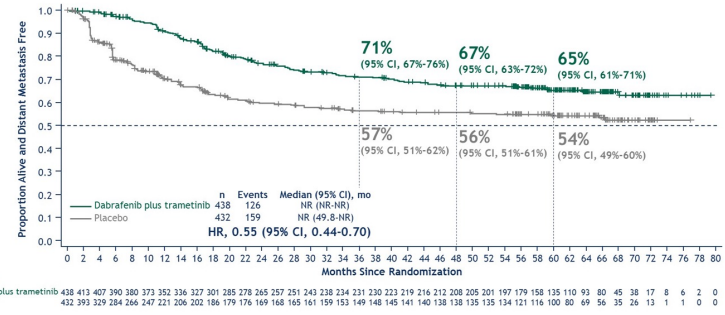
Distant Metastasis-Free Survival

Distant Metastasis as First Relapse Only[a]



[a] Due to informative censoring, patients who had a local or regional first recurrence may not be represented in this analysis. Per protocol, patients with a first relapse at a locoregional site were not required to continue follow-up for distant metastases and were censored at the time of locoregional recurrence if follow-up was not complete.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Axel Hauschild 17

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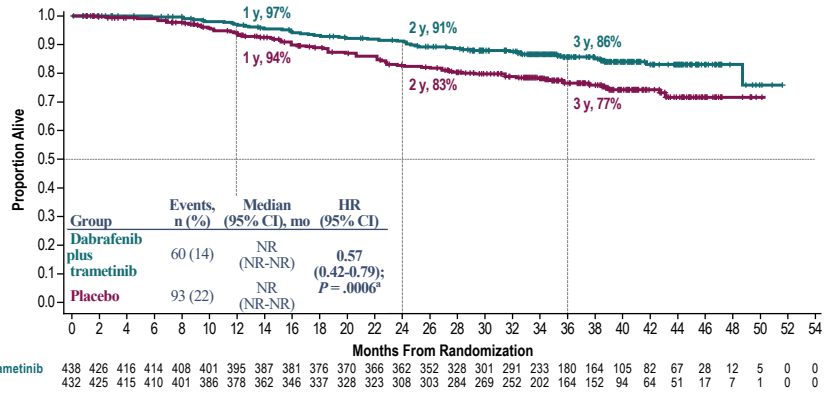
MADRID 2017 ESMO congress

OVERALL SURVIVAL (FIRST INTERIM ANALYSIS)

ESMO Congress



Group	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Dabrafenib plus trametinib	60 (14)	NR (NR-NR)	0.57 (0.42-0.79); $P = .0006$[a]
Placebo	93 (22)	NR (NR-NR)	

No. at Risk																										
Dabrafenib plus trametinib	438	426	416	414	408	401	395	387	381	376	370	366	362	352	328	301	291	233	180	164	105	82	67	28	12	5	0	0
Placebo	432	425	415	410	401	386	378	362	346	337	328	323	308	303	284	269	252	202	164	152	94	64	51	17	7	1	0	0

[a] Prespecified significance boundary ($P = .000019$).

Long et al. N Engl J 2017 Adjuvant Dabrafenib plus Trametinib in Stage III 377: 1813-23

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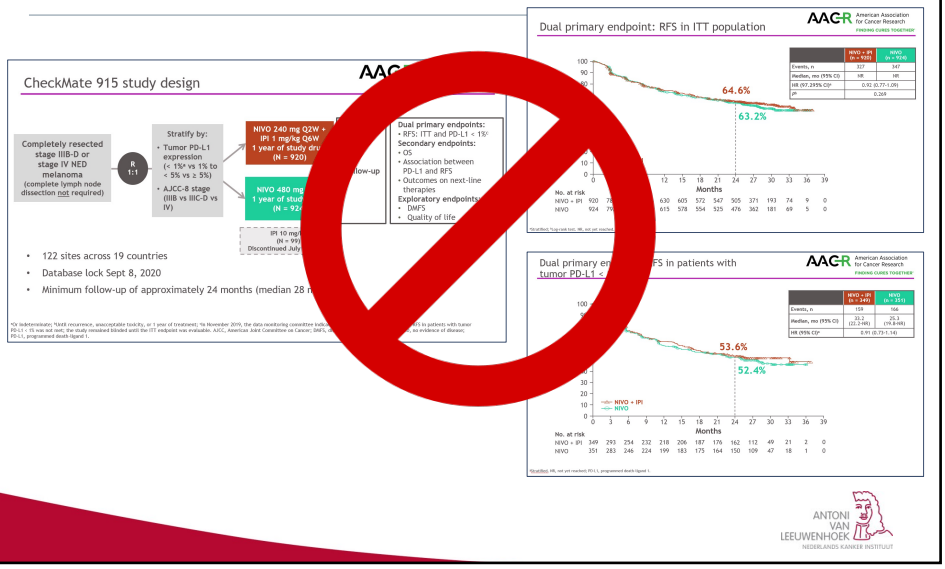
ADJUVANT IPILIMUMAB + NIVOLUMAB



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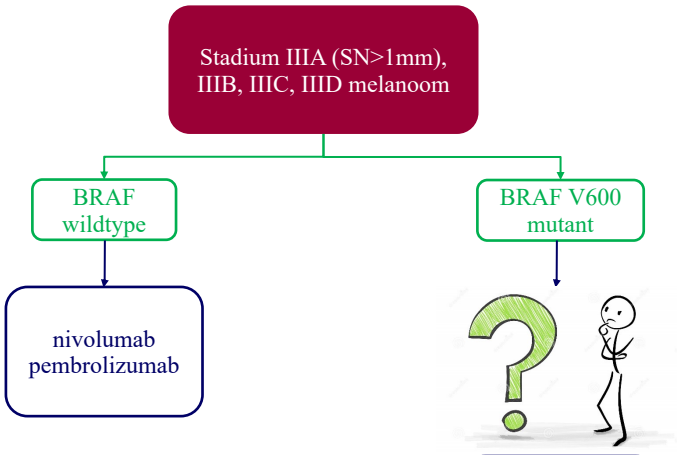
SAMENGEVAT



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ADJUVANTE BEHANDELING BRAF-GEMUTEERD MELANOOM

	Anti-PD-1	BRAF +MEK
MEDICIJN	infuus	pillen
BEHANDELDUUR	12 maanden	12 maanden
RISICOREDUCTIE (TERUGKEER VAN ZIEKTE)	~50%	~50%
OVERLEVINGSVOORDEEL	?	?

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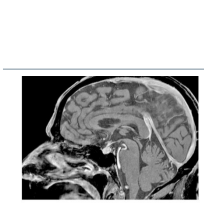
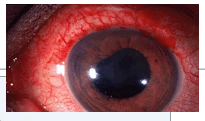
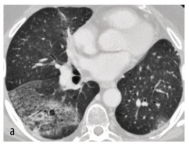
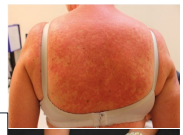
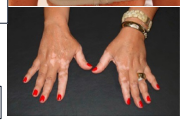
BIJWERKINGEN IMMUNOTHERAPIE

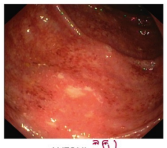












Postow et al. NEJM. 2018; Steebruggen et al. NTvG 2016

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BIJWERKINGEN NIVOLUMAB/PEMBROLIZUMAB

Event	Nivolumab (N=452)	
	Any Grade	Grade 3 or 4
		number of patients wi
Any adverse event	438 (96.9)	115 (25.4)
Treatment-related adverse event†	385 (85.2)	65 (14.4)
Fatigue	156 (34.5)	2 (0.4)
Diarrhea	110 (24.3)	7 (1.5)
Pruritus	105 (23.2)	0
Rash	90 (19.9)	5 (1.1)
Nausea	68 (15.0)	1 (0.2)
Arthralgia	57 (12.6)	1 (0.2)
Asthenia	57 (12.6)	1 (0.2)
Hypothyroidism	49 (10.8)	1 (0.2)
Headache	44 (9.7)	1 (0.2)
Abdominal pain	29 (6.4)	0
Increase in ALT level	28 (6.2)	5 (1.1)
Increase in AST level	25 (5.5)	2 (0.4)
Maculopapular rash	24 (5.3)	0
Hypophysitis	7 (1.5)	2 (0.4)
Pyrexia	7 (1.5)	0

Event	Pembrolizumab (N=509)	
	Any Grade	Grade ≥3
Immune-related adverse events, regardless of investigator attribution		
Any	190 (37.3)	36 (7.1)
Endocrine disorders	119 (23.4)	9 (1.8)
Hypothyroidism	73 (14.3)	0
Hyperthyroidism	52 (10.2)	1 (0.2)
Thyroiditis	16 (3.1)	0
Hypophysitis, including hypopituitarism	11 (2.2)	3 (0.6)
Type 1 diabetes mellitus	5 (1.0)	5 (1.0)
Adrenal insufficiency	5 (1.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	24 (4.7)	4 (0.8)
Pneumonitis or interstitial lung disease	17 (3.3)	4 (0.8)
Sarcoidosis	7 (1.4)	0
Vitiligo or severe skin reactions	27 (5.3)	3 (0.6)
Vitiligo	24 (4.7)	0
Severe skin reactions	3 (0.6)	3 (0.6)
Gastrointestinal conditions	20 (3.9)	10 (2.0)
Colitis	19 (3.7)	10 (2.0)
Pancreatitis	2 (0.4)	1 (0.2)
Hepatobiliary disorders	9 (1.8)	7 (1.4)
Hepatitis	9 (1.8)	7 (1.4)
Other immune-related adverse events	15 (2.9)	5 (1.0)
Nephritis	2 (0.4)	2 (0.4)
Uveitis	2 (0.4)	0
Myositis	1 (0.2)	1 (0.2)
Myocarditis	1 (0.2)	1 (0.2)

Weber et al., NEJM 2017; Eggermont et al., NEJM 2018

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BIJWERKINGEN ADJUVANT DABRAFENIB EN TRAMETINIB

	Dabrafenib Plus Trametinib (n = 435)	
AEs, n (%)	All Grades	Grade 3/4
Any AE (> 20% with dabrafenib plus trametinib)[a]	422 (97)	180 (41)
Pyrexia	273 (63)	23 (5)
Fatigue	204 (47)	19 (4)
Nausea	172 (40)	4 (1)
Headache	170 (39)	6 (1)
Chills	161 (37)	6 (1)
Diarrhoea	144 (33)	4 (1)
Vomiting	122 (28)	4 (1)
Arthralgia	120 (28)	4 (1)
Rash	106 (24)	0

Long et al. N Engl J Med 2017

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ADJUVANTE BEHANDELING BRAF-GEMUTEERD MELANOOM

	Anti-PD-1	BRAF +MEK
MEDICIJN	infuus	pillen
BEHANDELDUUR	12 maanden	12 maanden
RISICOREDUCTIE (TERUGKEER VAN ZIEKTE)	~50%	~50%
OVERLEVINGSVOORDEEL	?	?
ERNSTIGE BIJWERKINGEN	15%	40%
BLIJVENDE BIJWEKRINGEN	Ja (15% endocriene bijwerkingen)	Neen

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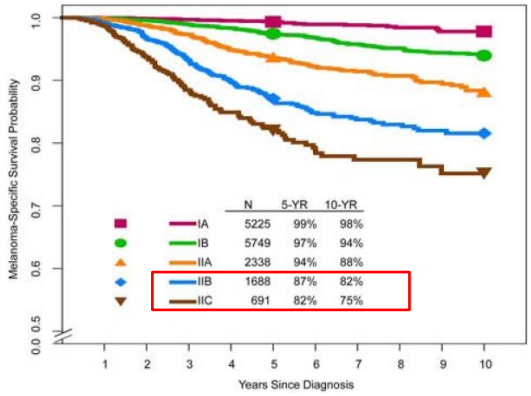
STADIUM II MELANOOM?



Gershenwald et al. CA Cancer J Clin. 2017

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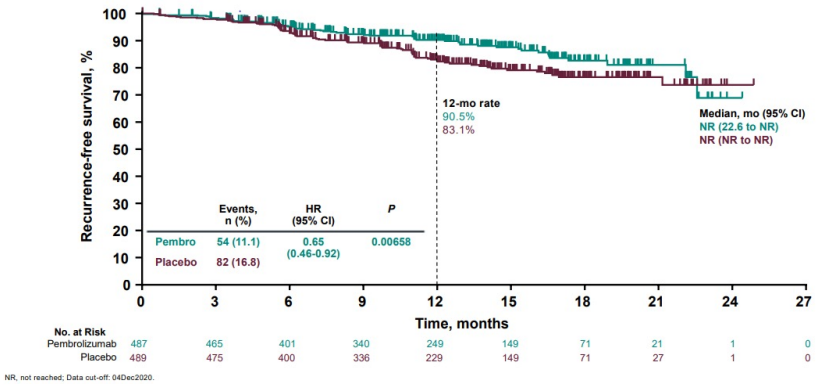
ADJUVANT PEMBROLIZUMAB IN STADIUM IIB-C MELANOOM

Recurrence-Free Survival (Primary Endpoint)



NR, not reached; Data cut-off: 04Dec2020.

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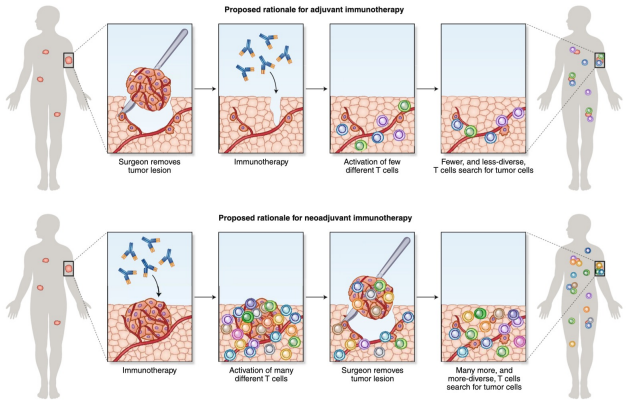
NEO-ADJUVANTE BEHANDELING

C. Blank



Versluis JM, Long GV, Blank CU. Nat Med. 2020

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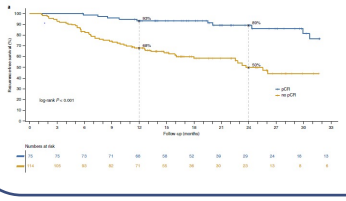
NEO-ADJUVANTE BEHANDELING

Table 4. Neoadjuvant Therapies According to Clinical Trial.[a]

Variable	Amaria et al.[49]	Amaria et al.[47]	OpACIN	NeoCombi	Huang et al.[50]	OpACIN-Neo
Eligible clinical stages	Stage III or IV (BRAF-mutated)	Stage III or IV	Stage III	Stage III (BRAF-mutated)	Stage III or IV	Stage III
Preoperative therapy (no. of patients)	Dab+tram for 8 wk (14) vs. none (7)	Nivo 3 mg/kg (12) vs. ipi 3 mg/kg+nivo 1 mg/kg (11) for 12 wk	Ipi 3 mg/kg+nivo 1 mg/kg for 6 wk (20) vs. none (10)	Dab+tram for 12 wk (35) (single group)	Single-dose pembro, resection at 3 wk (30)	2 courses ipi 3 mg/kg+nivo 1 mg/kg (30) vs. 2 courses (ipi 1 mg/kg+nivo 3 mg/kg (30) vs. 2 courses ipi 3 mg/kg followed by 2 courses nivo 3 mg/kg (30)[†]
Postoperative therapy	Dab+tram vs. observation until recurrence	Nivo 3 mg/kg vs. ipi 3 mg/kg+nivo 1 mg/kg for 24 wk	Ipi 3 mg/kg+nivo 1 mg/kg for 6 wk vs. for 12 wk	Dab+tram for 40 wk	Pembro for 1 yr	None
RFS	Median, 19.7 mo vs. 2.9 mo	Ipi+nivo, 90% at 14.9 mo	No relapse in neoadjuvant group at 25.8 mo	Median, 23 mo	100% among patients with pCR or near pCR (90% of patients)	Not mature (no deaths from melanoma in patients with pathological response)
Other findings	Toxic effects did not delay planned surgery	Patients with a response had increased TIL with higher clonality; 73% of patients had grade ≥3 toxic effects	Neoadjuvant therapy increased T-cell clones; 90% of patients had grade ≥3 toxic effects	49% pCR	Potential mechanisms of resistance examined	Pathological response in 80% vs. 77% vs. 65%; group 3 closed early because of toxicity

[a] The abbreviation pCR denotes pathological complete response, and TIL tumor-infiltrating lymphocytes.
[†] Two courses of therapy (one course every 3 wk) were administered for each treatment group.

Patients who had a complete pathologic response (pCR) with neoadjuvant therapy have superior RFS than those who did not achieve a pCR



Curti BD, Faries MB. N Engl J Med 2021
Versluis JM, Long GV, Blank CU. Nat Med. 2020
Menzies AM, Blank CU, et al. Nat Med. 2021

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CONCLUSIE

- Adjuvante behandeling met immuuntherapie (anti-PD-1: **nivolumab** of **pembrolizumab**) of **dabrafenib en trametinib** (bij BRAF-gemuteerd melanoom) gedurende 1 jaar verkleint significant de kans op terugkeer van de ziekte.
- De toediening en het bijwerkingsprofiel van beide behandelingen zijn verschillend
- Behandelbeslissing wordt genomen na uitgebreide informatie en op basis van stadium ziekte, onderliggende aandoeningen patiënt, bijwerkingen en behandelwens.

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VRAGEN?

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