Immunotherapie bij het melanoom: het liefst zo vroeg mogelijk

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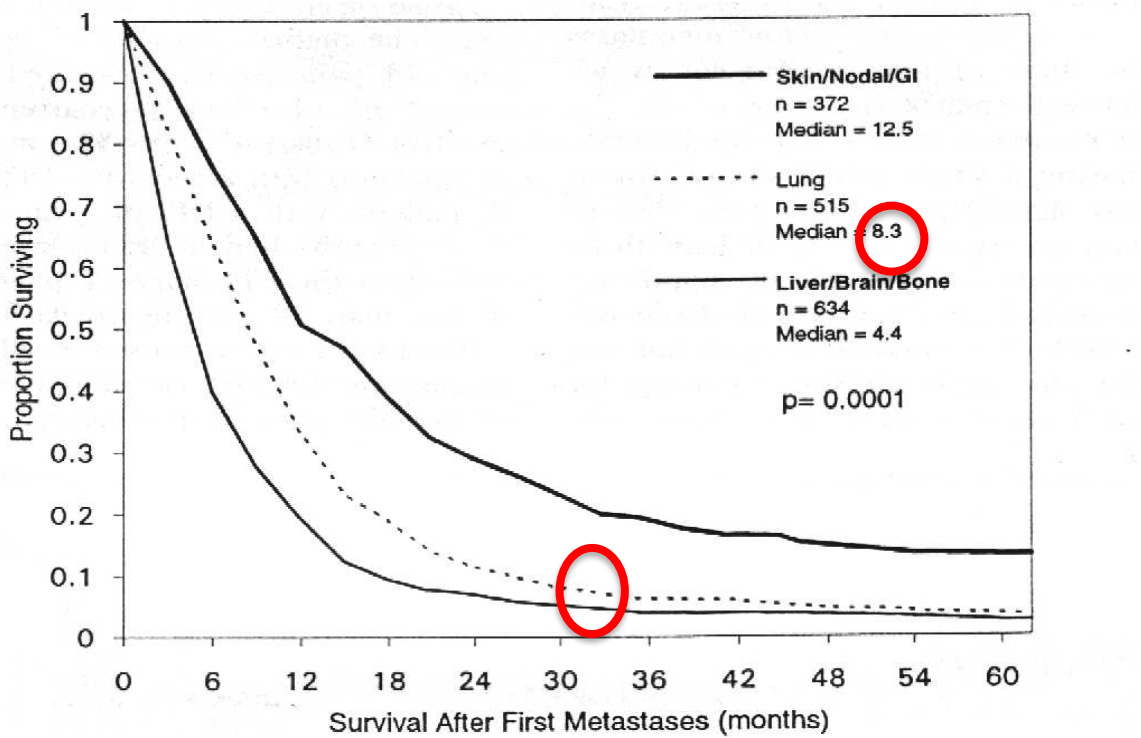
Disclosures Fons van den Eertwegh

Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
•Sponsoring of onderzoeksgeld	BMS en Roche
•Honorarium of andere (financiële) vergoeding adviesraad, congresbezoek, presentaties	BMS, MSD, ROCHE, NOVARTIS, AMGEN, Pierre Fabre
•Aandeelhouder	NVT
•Andere relatie, namelijk …	NVT

Melanoma

- 7000 new patients in the Netherlands and about 800 will get distant metastases
- 10th place of most frequent diagnosed malignancy
- largely confined to whites
- incidence is increasing and varies around the world

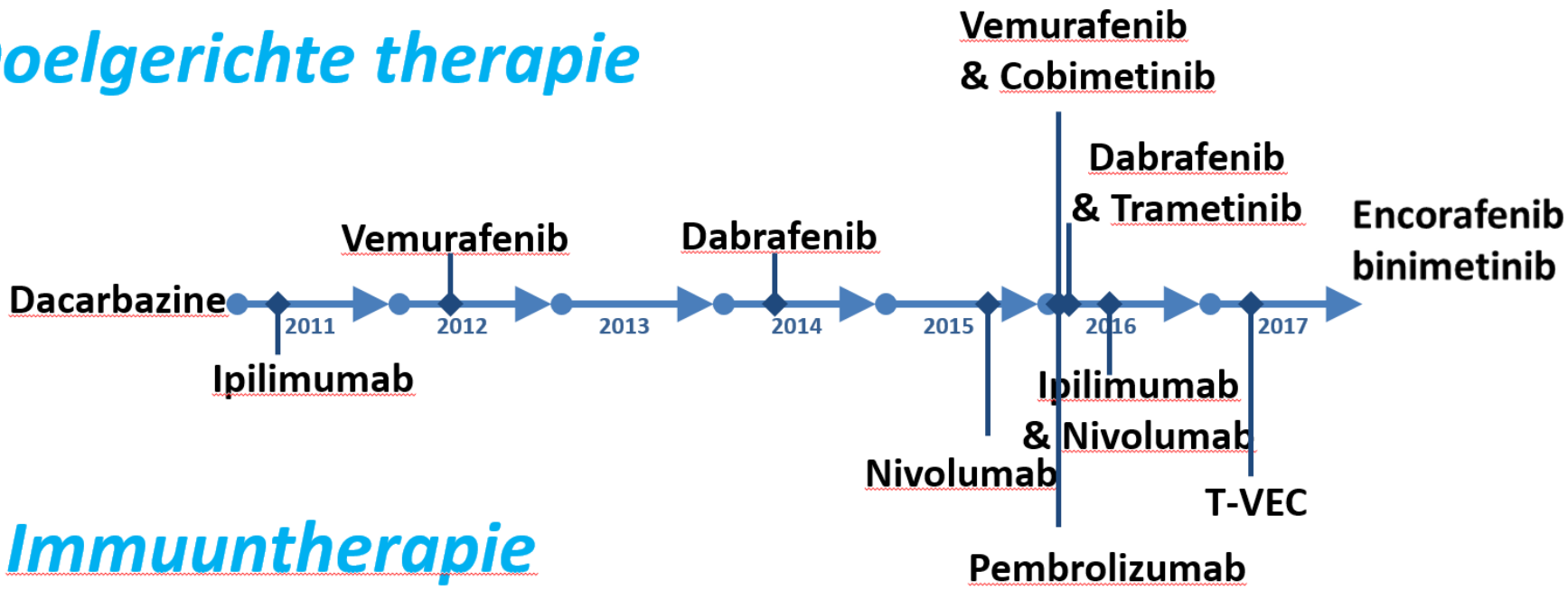
Metastatic Melanoma survival prior to 2010



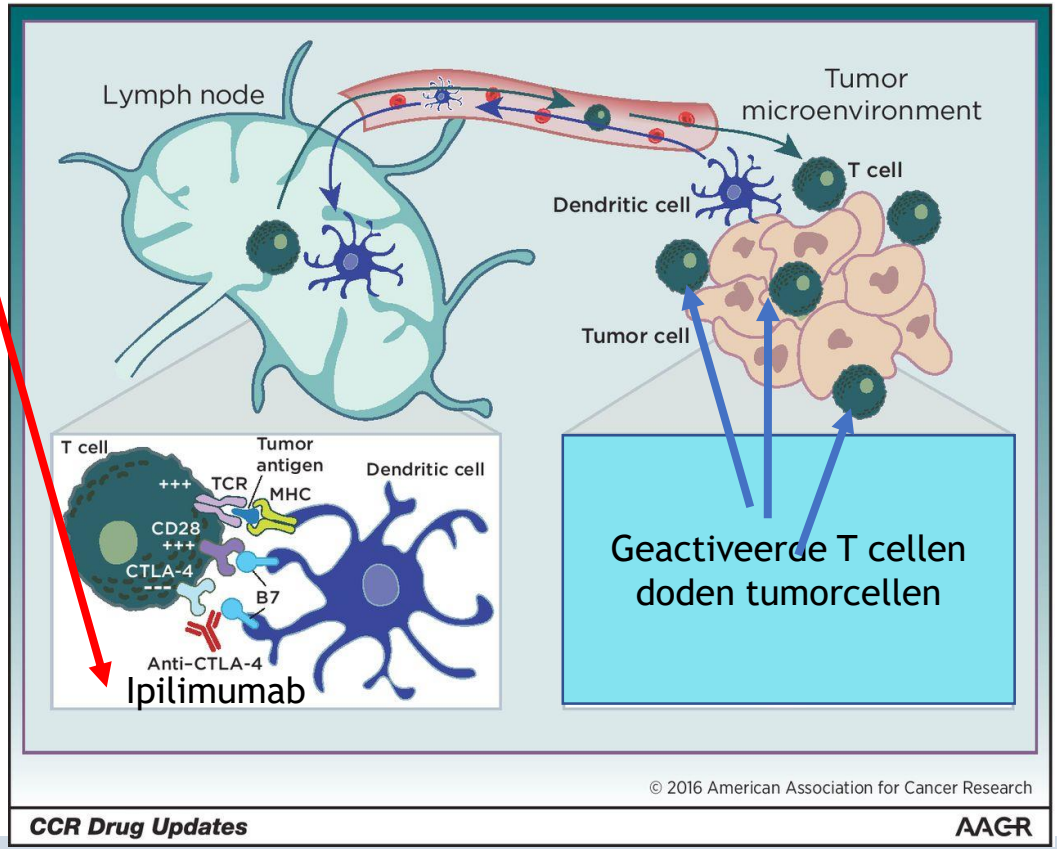
J Am Coll Surg. 181(3):193-201 (1995)

Veranderd therapeutisch landschap

gemetastaseerd melanoom

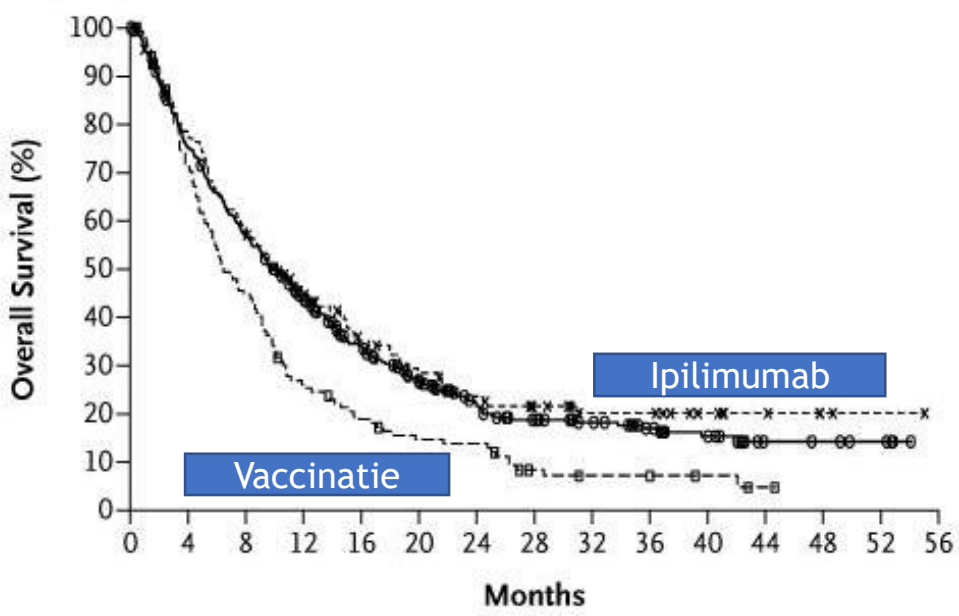


Ipilimumab blokkeert de remming van de geactiveerde T cel door binding aan CTLA-4 (checkpoint)



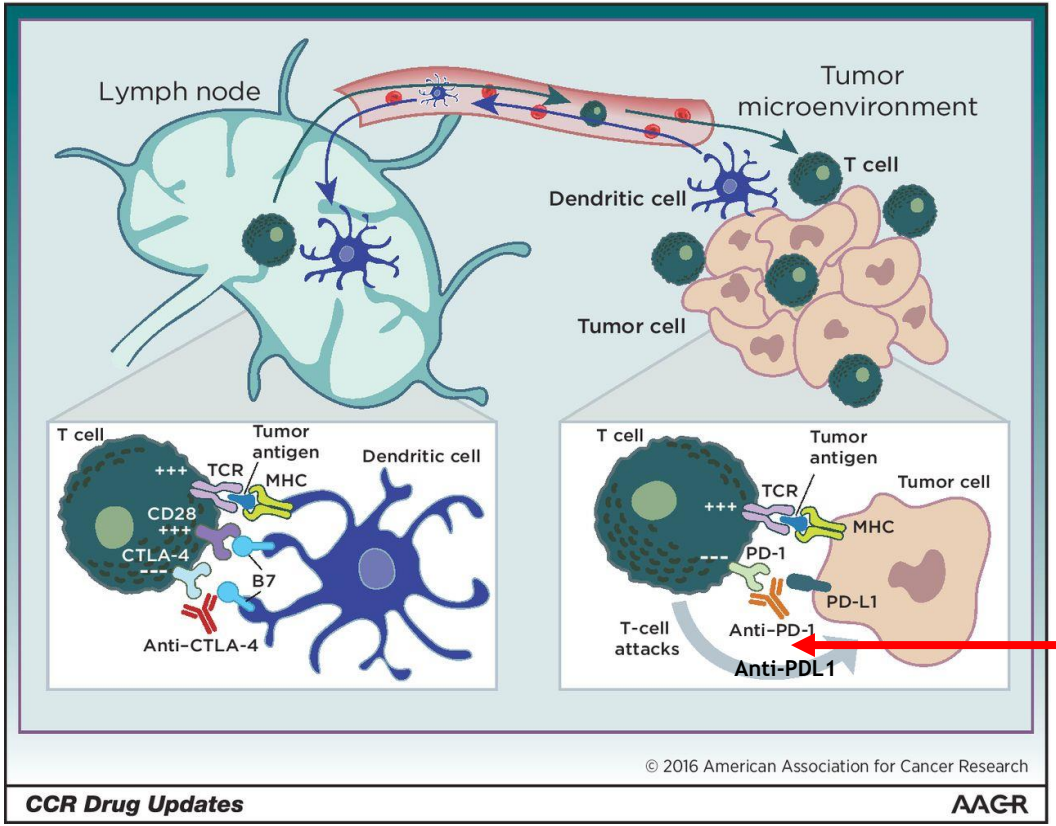
Adapted from Matteo S. Carlino, and Georgina V. Long Clin Cancer Res 2016;22:3992-3998

Ipilimumab verbetert de overleving van gemetastaseerde melanoompatiënten



N Engl J Med. 2010 Aug 19; 363(8): 711–723.

Anti-PD1 of anti-PDL1 antistoffen blokkeren de PDL1-PD1 interactie in de tumor zodat T cel niet uitgeschakeld kan worden in het micro-milieu van de tumor

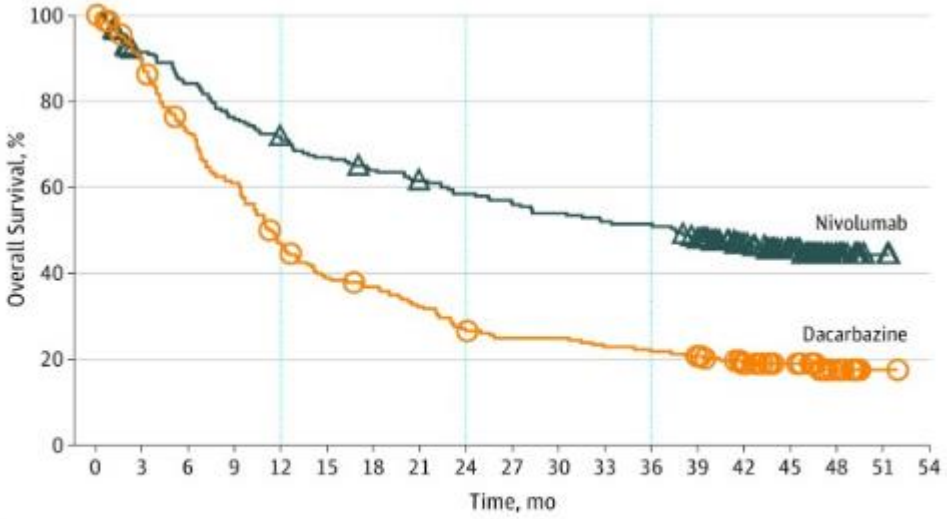


Anti-PD1
- nivolumab
- pembrolizumab

Anti-PDL1
- atezolizumab
- avelumab
- durvalumab

Adapted from Matteo S. Carlino, and Georgina V. Long Clin Cancer Res 2016;22:3992-3998

Nivolumab improves survival in BRAF-wild type Metastatic Melanoma

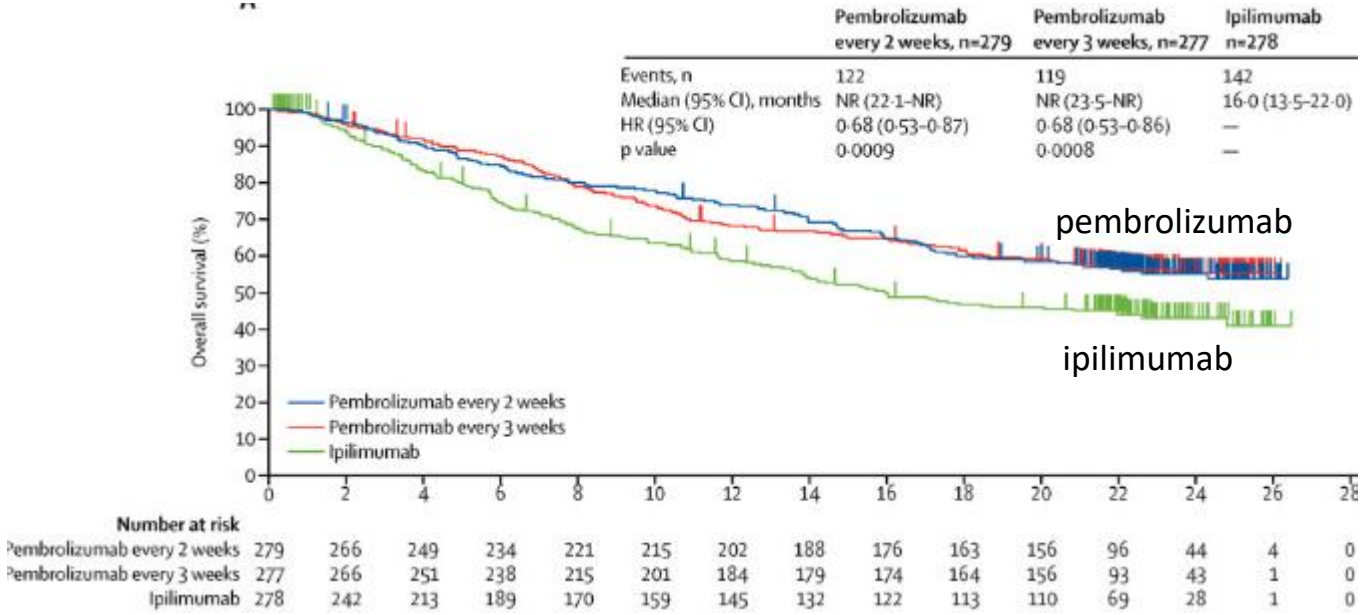


No. at risk

Nivolumab	210	186	171	154	143	135	128	122	116	111	107	103	102	92	72	53	16	2	0
Dacarbazine	208	179	146	122	92	76	71	62	51	47	47	43	41	38	26	19	7	1	0

Update in JAMA Oncol. 2019 Feb; 5(2): 187–194.

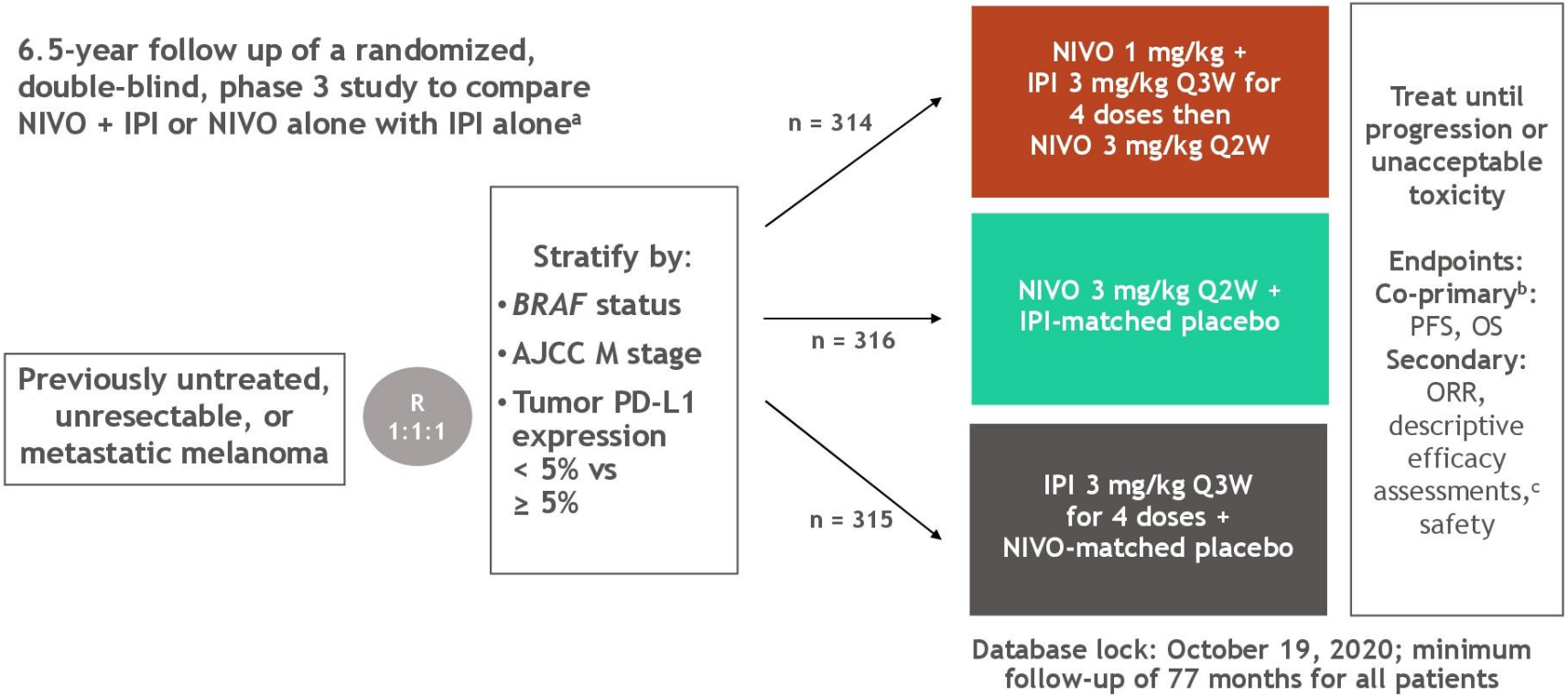
Pembrolizumab improves survival in Metastatic Melanoma



Update in Lancet . 2017 21;390(10105):1853-1862.

CheckMate 067: study design

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



Database lock: October 19, 2020; minimum follow-up of 77 months for all patients

[a]The study was not powered for a comparison between NIVO+IPI and NIVO. [b]NIVO + IPI or NIVO vs IPI alone. [c]NIVO + IPI vs NIVO alone. AJCC, American Joint Committee on Cancer; M stage, metastasis stage; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks.

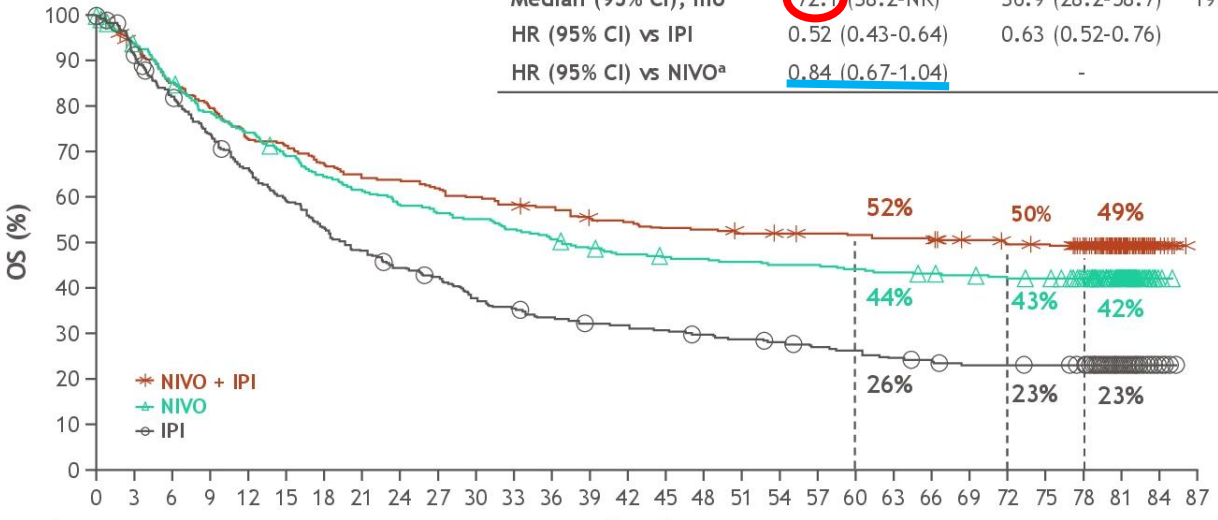
Response to treatment at 6.5 years

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR (95% CI), %	58 (53-64)	45 (39-51)	19 (15-24)
Best overall response, %			
Complete response	23	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
Median duration of response (95% CI), months	NR (61.9-NR)	NR (45.7-NR)	19.2 (8.8-47.4)

CI, confidence interval; NR, not yet reached.

Overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-



No. at risk

NIVO + IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

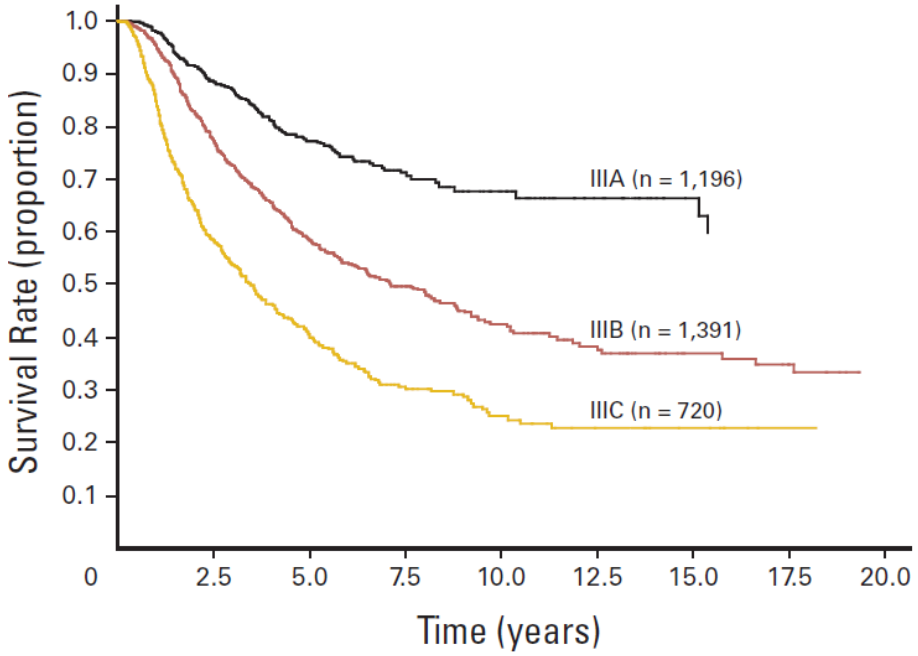
[a]Descriptive analysis.

Prognostische factoren

- performance
- LDH
- M3A beter dan M3c
- aantal organen met metastasen
- totale hoeveelheid tumor
- mutational load

Hoe lager de tumorload
des te beter de
immunotherapie werkt

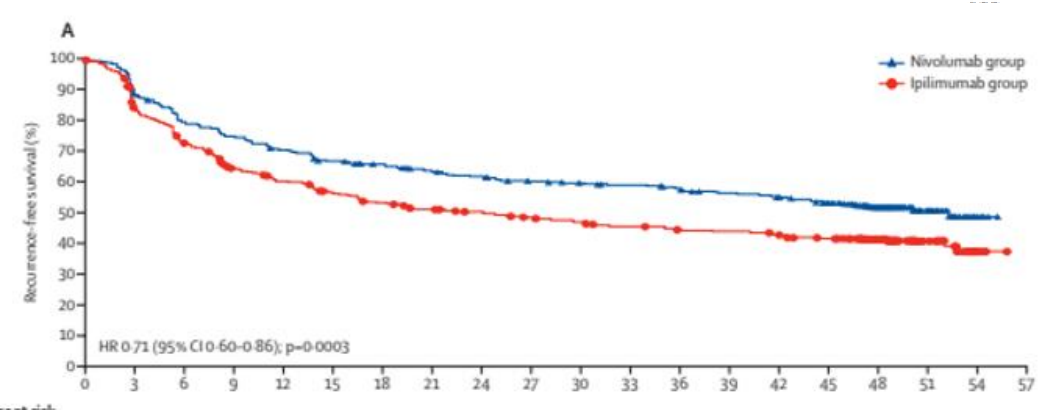
Stadium 3 melanoom zonder (neo-)adjuvant overleving



Balch et al. J Clin Oncol 2009

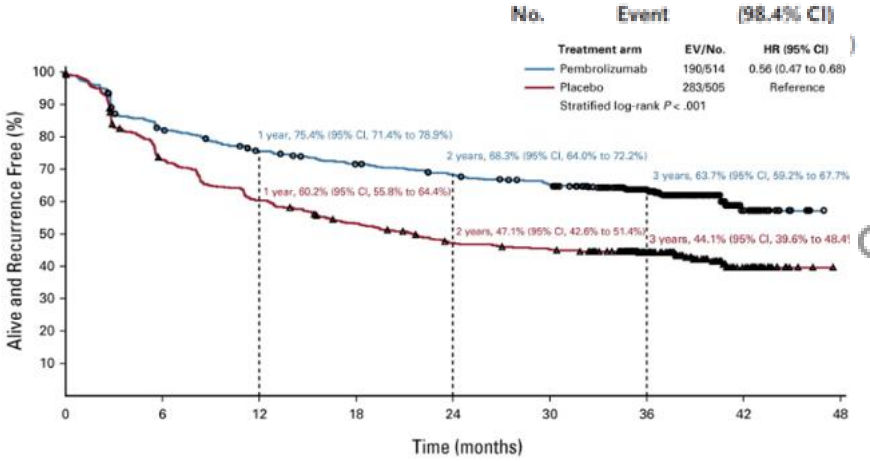
Anti-PD1 behandeling bij hoogrisico stadium 3 melanoom: betere recidiefvrije overleving

Nivolumab vs ipilimumab



Weber et al, Lancet Oncology 2020

Pembrolizumab vs placebo

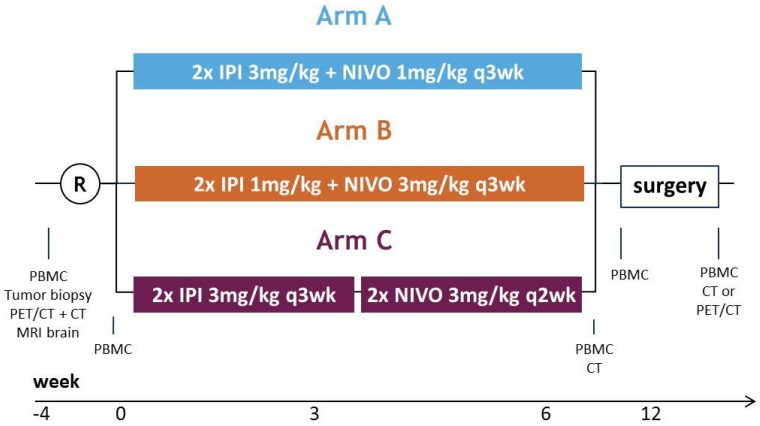


Eggermont, JCO 2020

Rationale neoadjuvante immunotherapie stadium 3 melanoom

- geeft inzicht of behandeling aanslaat
- aanwijzingen dat er een sterkere en bredere T cel respons wordt geinduceerd (Blank et al. Nat. Med. 2018)
- biedt potentieel de mogelijkheid om af te zien van een lymfekliertoilet
- biedt potentieel de mogelijkheid om duur en type adjuvante behandeling aan te passen

The OpACIN-neo study identified neoadjuvant IPI 1 mg/kg + NIVO 3 mg/kg as the optimal treatment scheme



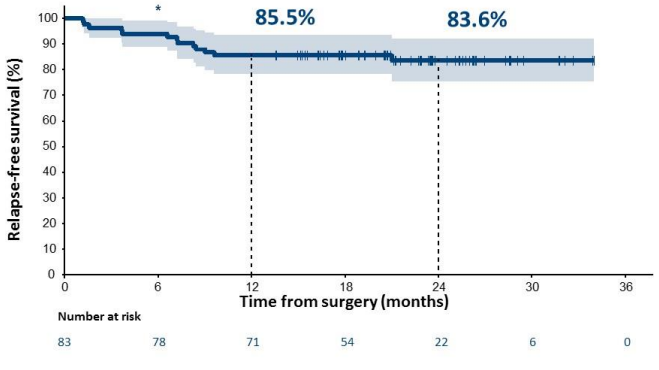
	Grade 3-4 toxicity	Pathologic Response
Arm A	40%	80%
Arm B	20%	77%
Arm C	50%	65%

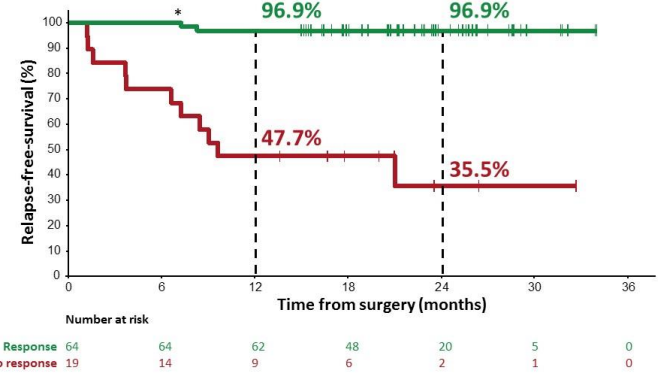
Rozeman et al., Lancet Oncology, 2019

Dosing in Arm A, B, and C based on data from Blank, et al. Nat Med 2018, Long, et al. Lancet Oncol 2017, Meerveld-Eggink et al. Ann Oncol 2017

Promising RFS after 2 years follow-up and pathologic response predicts outcome

- **OpACIN-neo:** After a median follow-up of 24.6 months, only 1/64 (2%) patients with pathologic response has relapsed



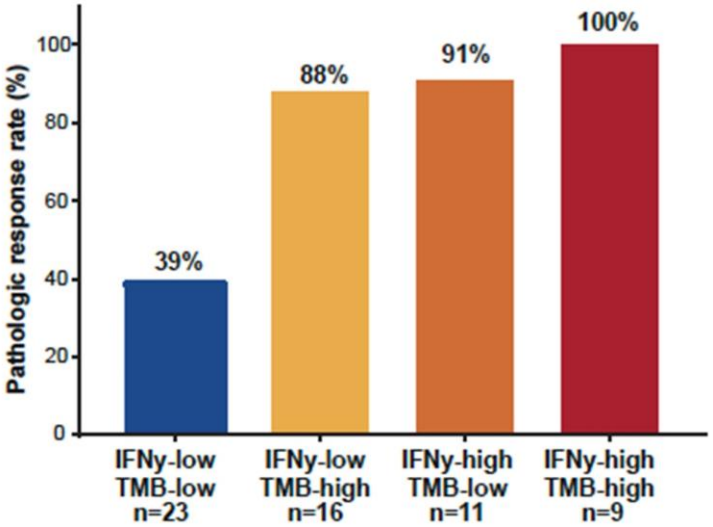


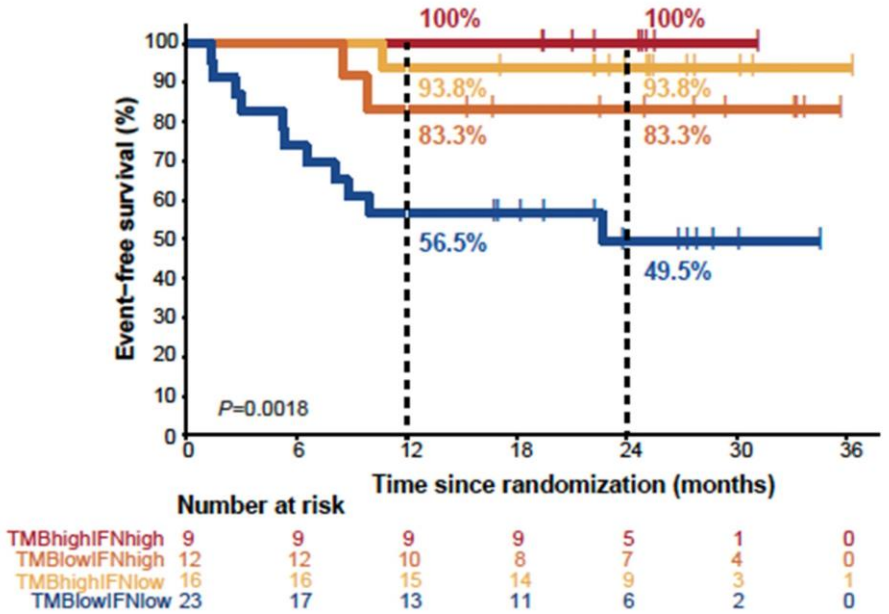
(near-)pCR = (near) pathologic complete response, pPR = pathologic partial response, pNR = pathologic non-response

Rozeman et al., abstract 10015, ASCO 2020

* patient died due to toxicity without signs of melanoma relapse

Can we identify baseline response marker for response upon neo-adjuvant IPI+NIVO? –OpACIN-neo



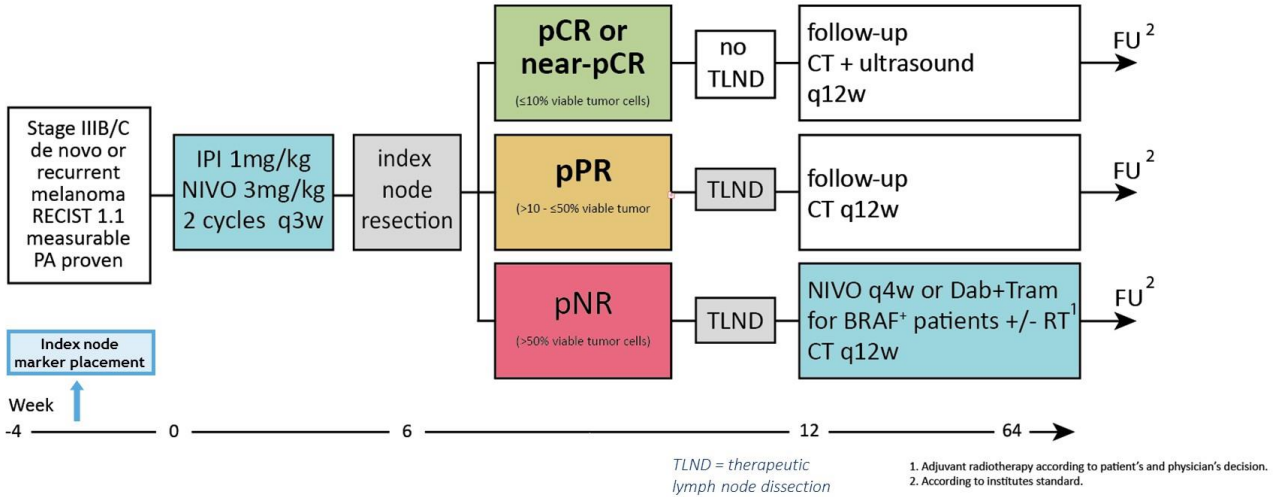


Rozeman et al. Nat Med 2021

Rozeman et al. Nat Med 2020, accepted

PRADO: study design

Personalized **R**esponse-driven **Ad**juvant therapy after C**o**mbination of Ipilimumab and Nivolumab in stage IIIB/C melanoma

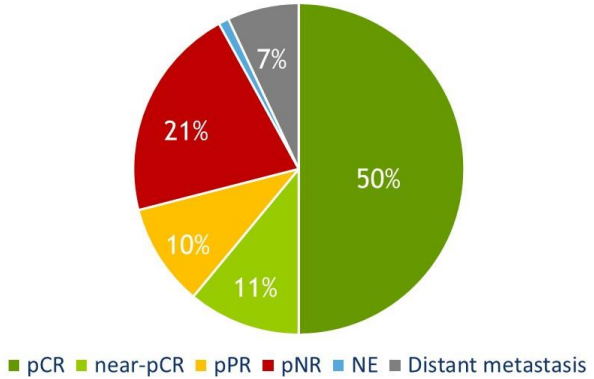


Presented By Christian Blank at TBD

Pathologic response

PRADO	Total cohort (n=99) [1]
pRR	70 (71%)
pCR	49 (50%)
Near-pCR	11 (11%)
pPR	10 (10%)
pNR	21 (21%)
Not evaluable [2]	1 (1%)
Distant metastases	7 (7%)

1. In two patients the pathologic response was based on the TLND.
2. One patient did not undergo surgery due to toxicity. This patient had a radiologic response.



MPR 61%

Immune-related AEs within the first 12 weeks

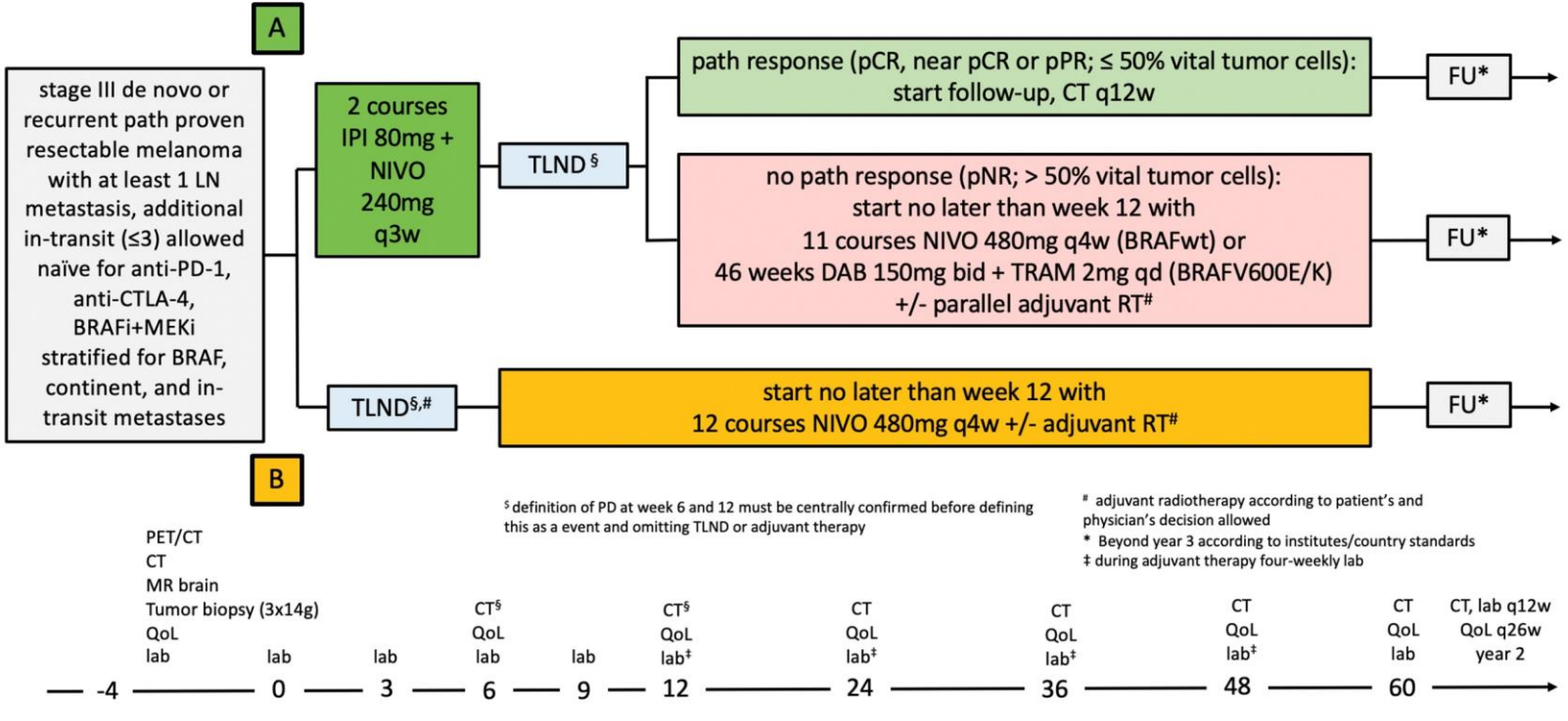
Adverse event	All grade (%)	Grade 3-4 (%)	Adverse event	All grade (%)	Grade 3-4 (%)
Any adverse event	**96 (97)**	**22 (22)**	Serum lipase increased	8 (8)	3 (3)
Fatigue	54 (55)	–	Dry skin	7 (7)	–
Rash	47 (47)	3 (3)	Fever	7 (7)	–
Pruritus	27 (27)	–	Colitis	6 (6)	4 (4)
Alanine aminotransferase increased	22 (22)	7 (7)	Creatine kinase increased	6 (6)	1 (1)
Hyperthyreoidism	22 (22)	–	Dry eye	6 (6)	–
Diarrhea	21 (21)	5 (5)	Dyspnea	5 (5)	–
Aspartate aminotransferase increased	20 (20)	5 (5)	Serum amylase increased	4 (4)	1 (1)
Nausea	18 (18)	1 (1)	Myocarditis	2 (2)	2 (2)
Dry mouth	16 (16)	–	Ggt increased	2 (2)	1 (1)
Hypothyreoidism	16 (16)	–	Cholangitis	1 (1)	1 (1)
Arthralgia	15 (15)	–	Confusion	1 (1)	1 (1)
Headache	13 (13)	1 (1)	Myelitis transversa-like syndrome	1 (1)	1 (1)
Myalgia	10 (10)	–			
Infusion related reaction	8 (8)	–			

Adverse events that occurred in ≥ 5 patients or were grade 3-4 are displayed in the table

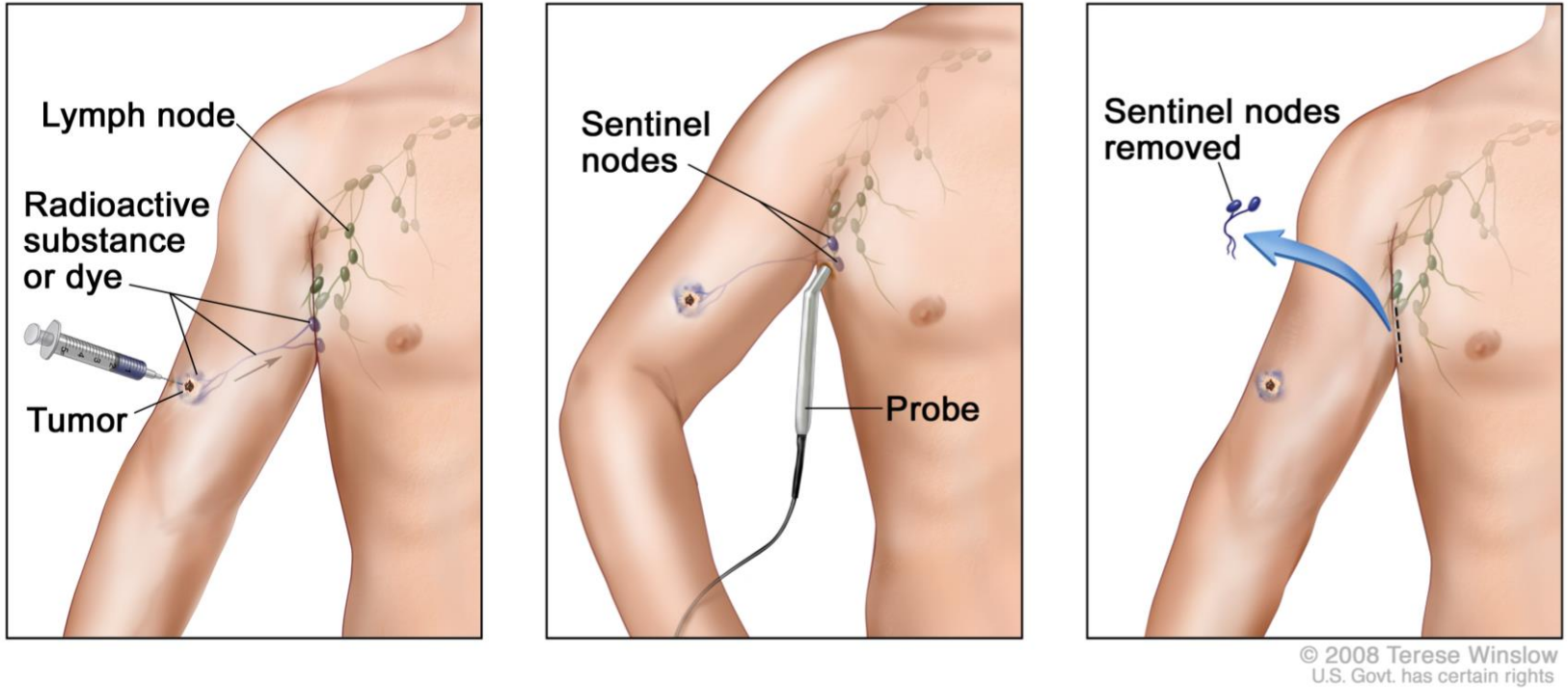
Presented By Christian Blank at TBD

Phase 3 trial comparing response driven neo-adjuvant combination of ipilimumab + nivolumab versus adjuvant nivolumab (NADINA 2021)

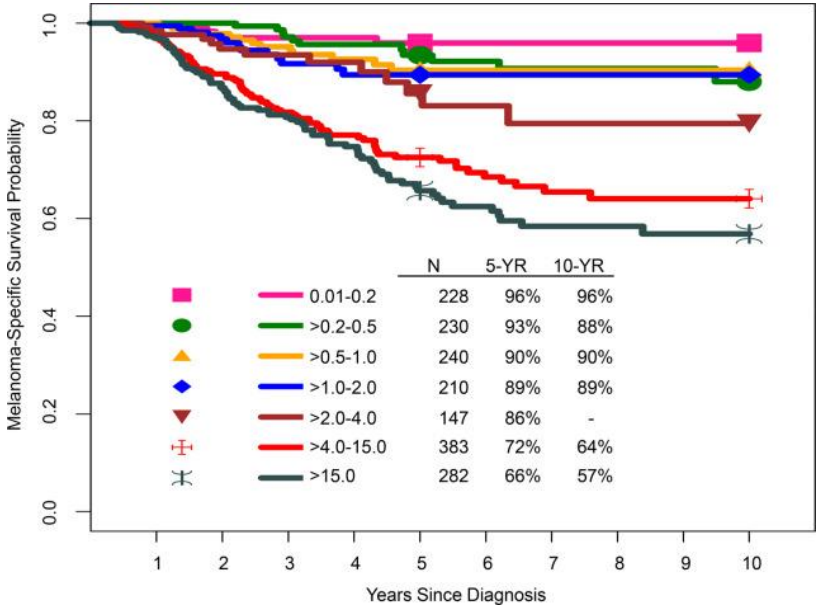
(420 pts, EFS at 24 months 60%->75%, alpha two-sided 0.05, power 90%, cure model statistics)



Sentinel node biopsy/schildwachtklierprocedure bij melanoom geeft inzicht in prognose



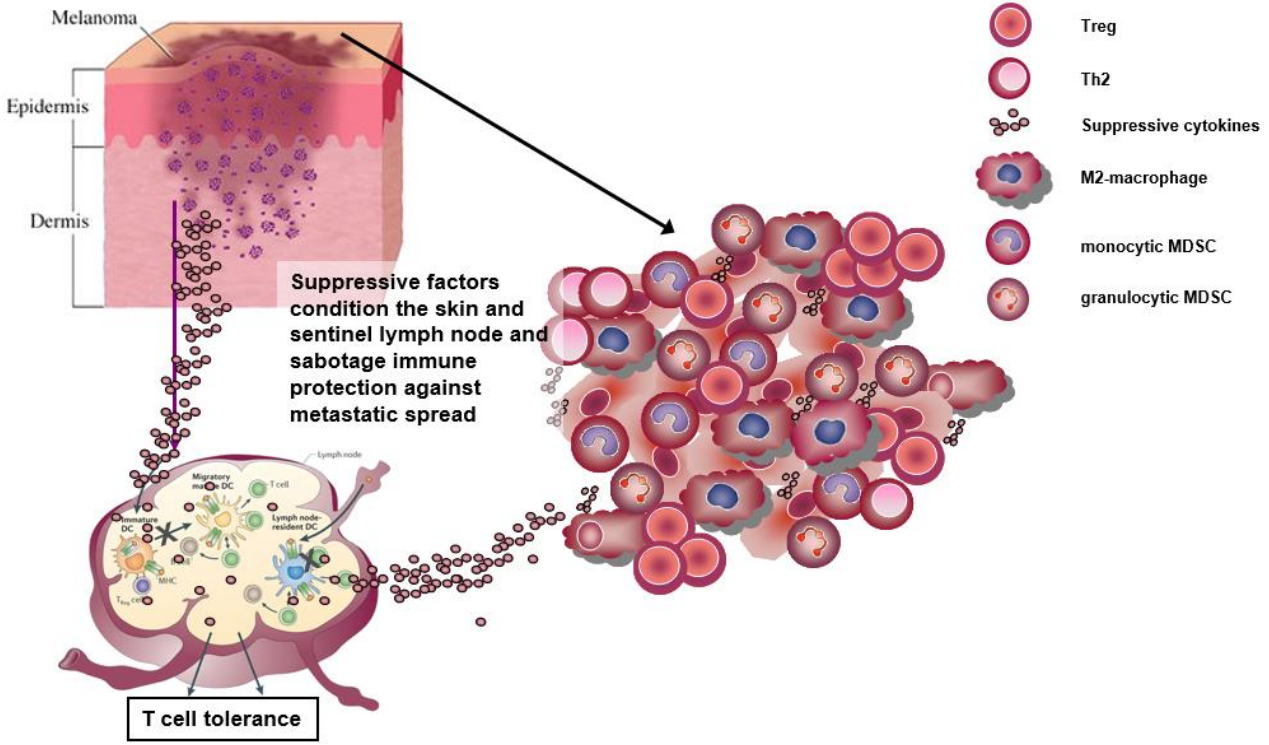
Grootte metastase in schildwachtklier prognose



CA: A Cancer Journal for Clinicians, Volume: 67, Issue: 6, Pages: 472-492, First published: 13 October 2017, DOI: (10.3322/caac.21409)

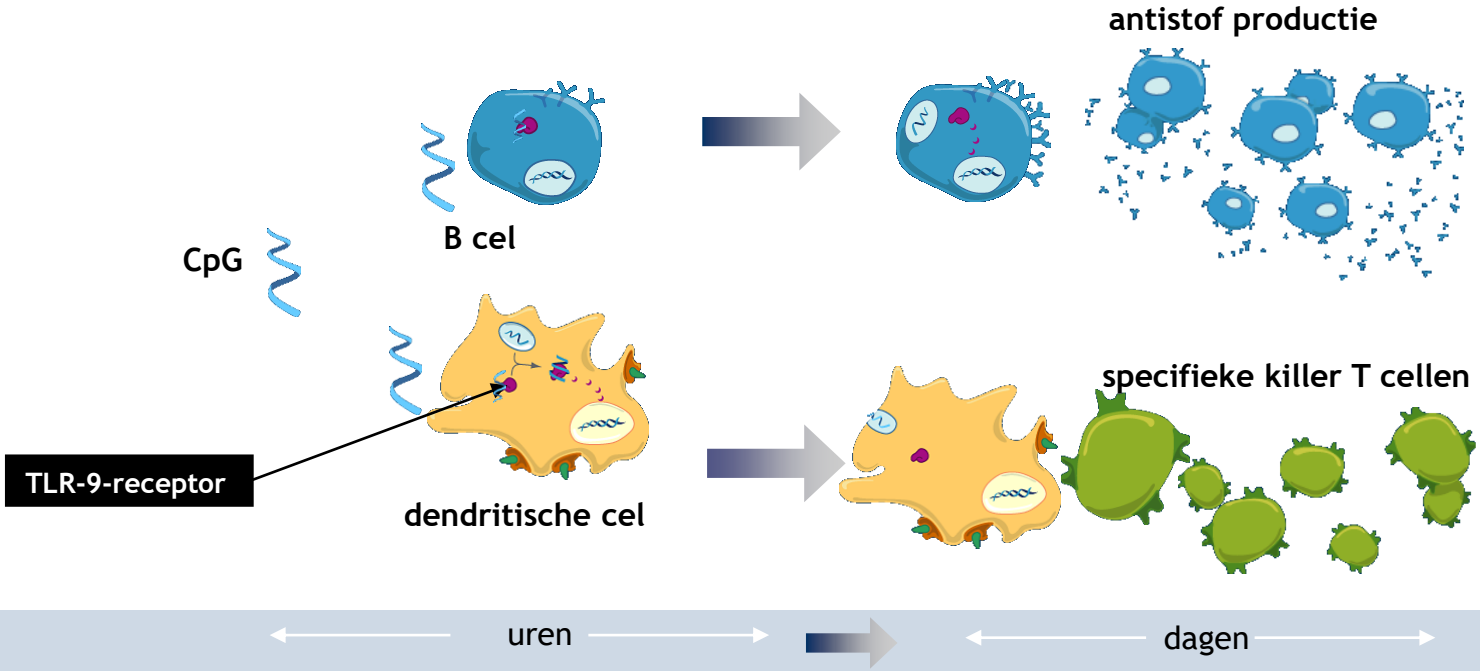
Melanoom

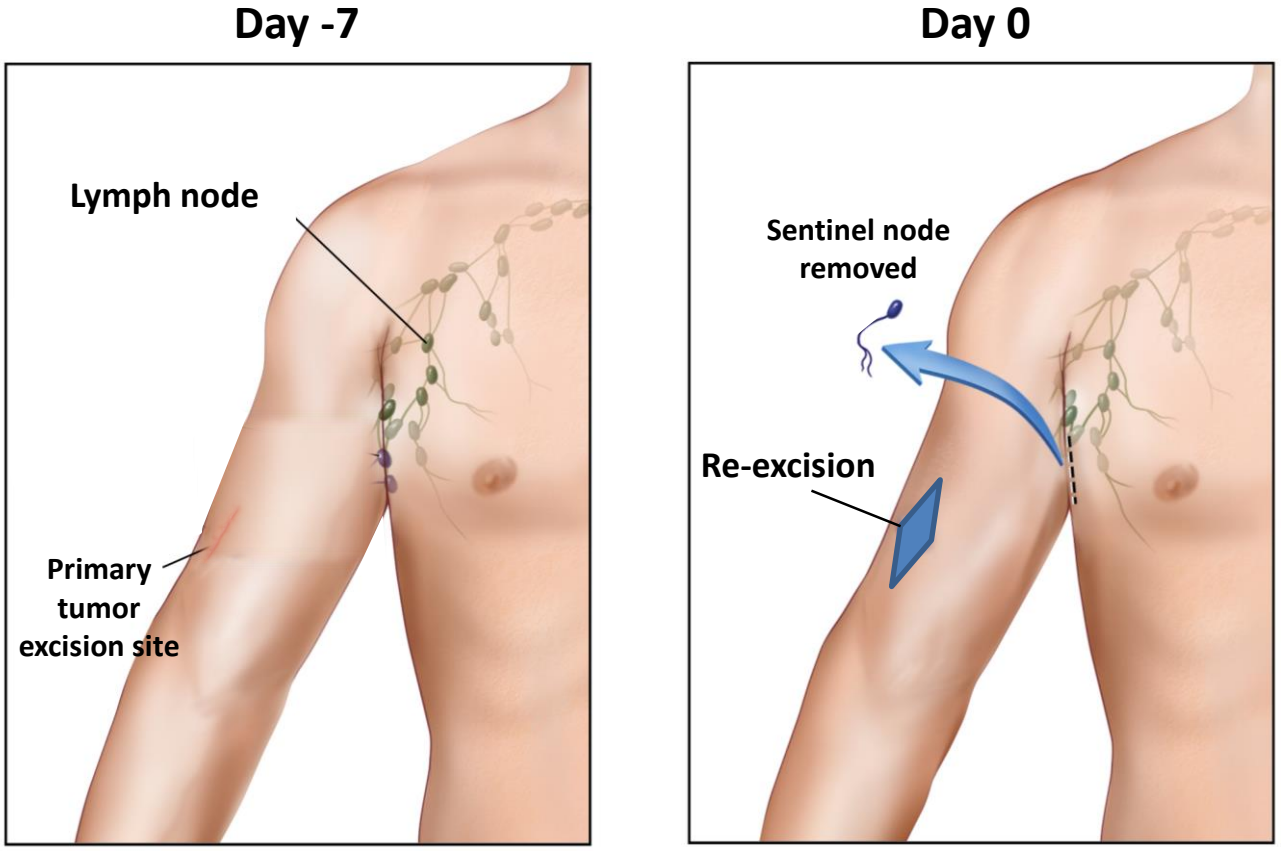
zorgt voor immuunsuppressief milieu in lymfeklier



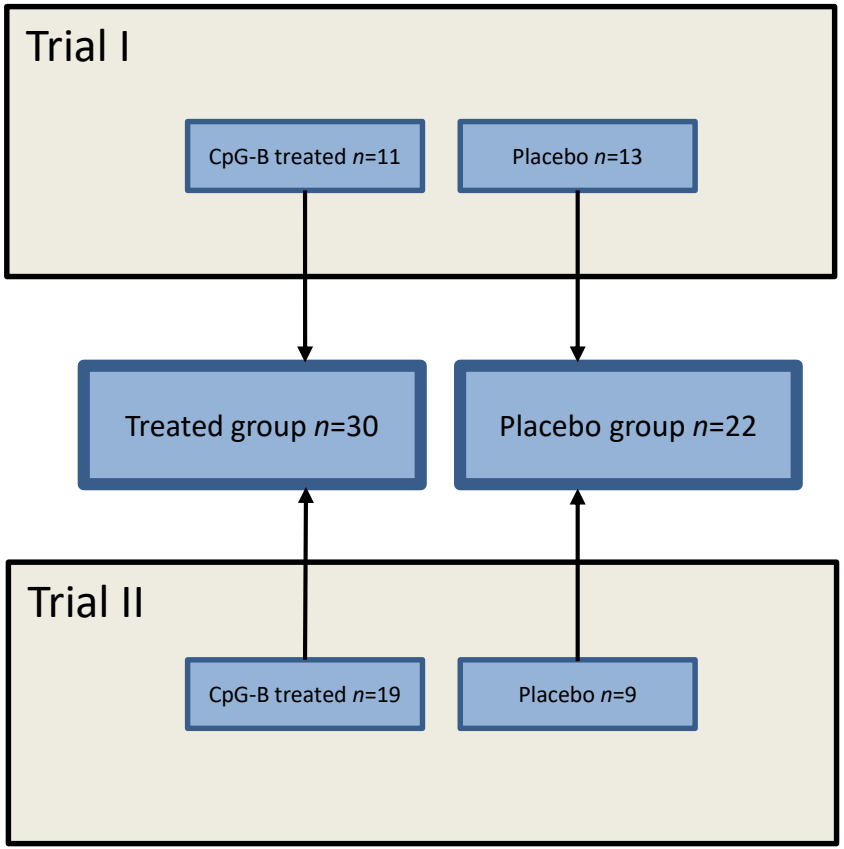
CpG

stimuleert dendritische cellen, T cellen en antistofproductie





Adapted from cancer.org



Clin Cancer Res 2007

Intradermal CpG-B Activates Both Plasmacytoid and Myeloid Dendritic Cells in the Sentinel Lymph Node of Melanoma Patients

Barbara G. Molenkamp,[1] Paul A.M. van Leeuwen,[1] Sybren Meijer,[1] Berbel J.R. Sluijter,[1] Pepijn G.J.T.B. Wijnands,[2] Arnold Baars,[3] Alfons J.M. van den Eertwegh,[3] Rik J. Scheper,[2] and Tanja D. de Gruijl[3]

Clin Cancer Res 2008

Local Administration of PF-3512676 CpG-B Instigates Tumor-Specific CD8$^+$ T-Cell Reactivity in Melanoma Patients

Barbara G. Molenkamp,[1] Berbel J.R. Sluijter,[1] Paul A.M. van Leeuwen,[1] Saskia J.A.M. Santegoets,[2] Sybren Meijer,[1] Pepijn G.J.T.B. Wijnands,[3] John B.A.G. Haanen,[4] Alfons J.M. van den Eertwegh,[2] Rik J. Scheper,[3] and Tanja D. de Gruijl[2]

Research Article

Cancer Immunology Research 2015

Arming the Melanoma Sentinel Lymph Node through Local Administration of CpG-B and GM-CSF: Recruitment and Activation of BDCA3/CD141$^+$ Dendritic Cells and Enhanced Cross-Presentation

Berbel J.R. Sluijter[1], Mari F.C.M. van den Hout[2], Bas D. Koster[3], Paul A.M. van Leeuwen[1], Famke L. Schneiders[3], Rieneke van de Ven[3], Barbara G. Molenkamp[1], Saskia Vosslamber[2], Cornelis L. Verweij[2], M. Petrousjka van den Tol[1], Alfons J.M. van den Eertwegh[3], Rik J. Scheper[2], and Tanja D. de Gruijl[3]

Significant difference in tumor positive SLN after 7 days

***Table 1*: Patient and tumor characteristics**

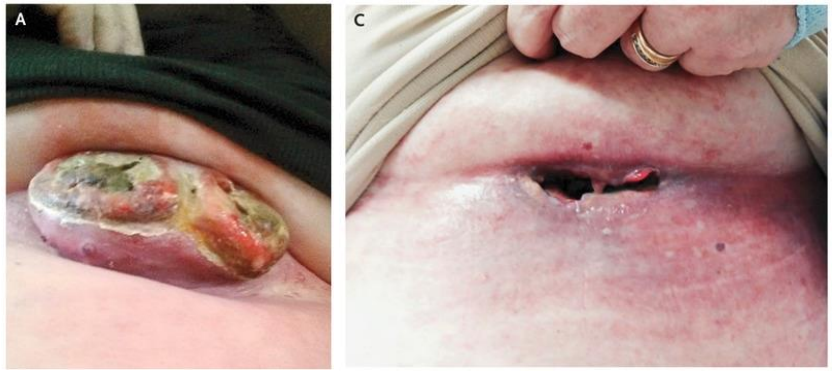
1a. At study enrolment

	Treated group (n = 30)	Saline group (n = 22)	Overall (n=52)
Age, in years			
Mean (SD)	54.1 (12.6)	50.9 (13.4)	52.7 (12.9)
Gender			
Male	16 (53.3)	13 (59.1)	29 (55.8)
Female	14 (46.7)	9 (40.9)	23 (44.2)
Location			
Head neck and trunk	20 (66.7)	12 (54.5)	32 (61.5)
Extremeties	10 (33.3)	10 (45.5)	20 (38.5)
Histological subtype			
SSM	23 (76.7)	17 (77.3)	40 (76.9)
Nodular	4 (13.3)	4 (18.2)	8 (15.4)
Other or unknown	3 (10.0)	1 (4.5)	4 (7.7)
Breslow, in mm			
Mean (SD)	1.77 (0.98)	1.86 (1.24)	1.81 (1.09)
Ulceration			
Yes	5 (16.7)	4 (18.2)	9 (17.3)
No	25 (83.3)	18 (81.8)	43 (82.7)

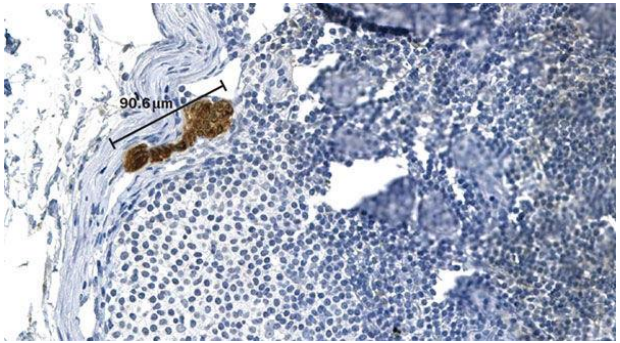
1b. After the Sentinel Lymph Node (SLN) procedure

Disease stage			
Stage I	16 (53.3)	8 (36.4)	24 (46.2)
Stage II	11 (36.7)	6 (27.3)	17 (32.7)
Stage III*	3 (10.0%)	8 (36.4)	11 (21.2)
Follow-up RFS, months			
Median (range)	81.2 (5-129)	97.3 (5-133)	88.8 (5-133)

Koster et al., *Clin Cancer Res*, 2017

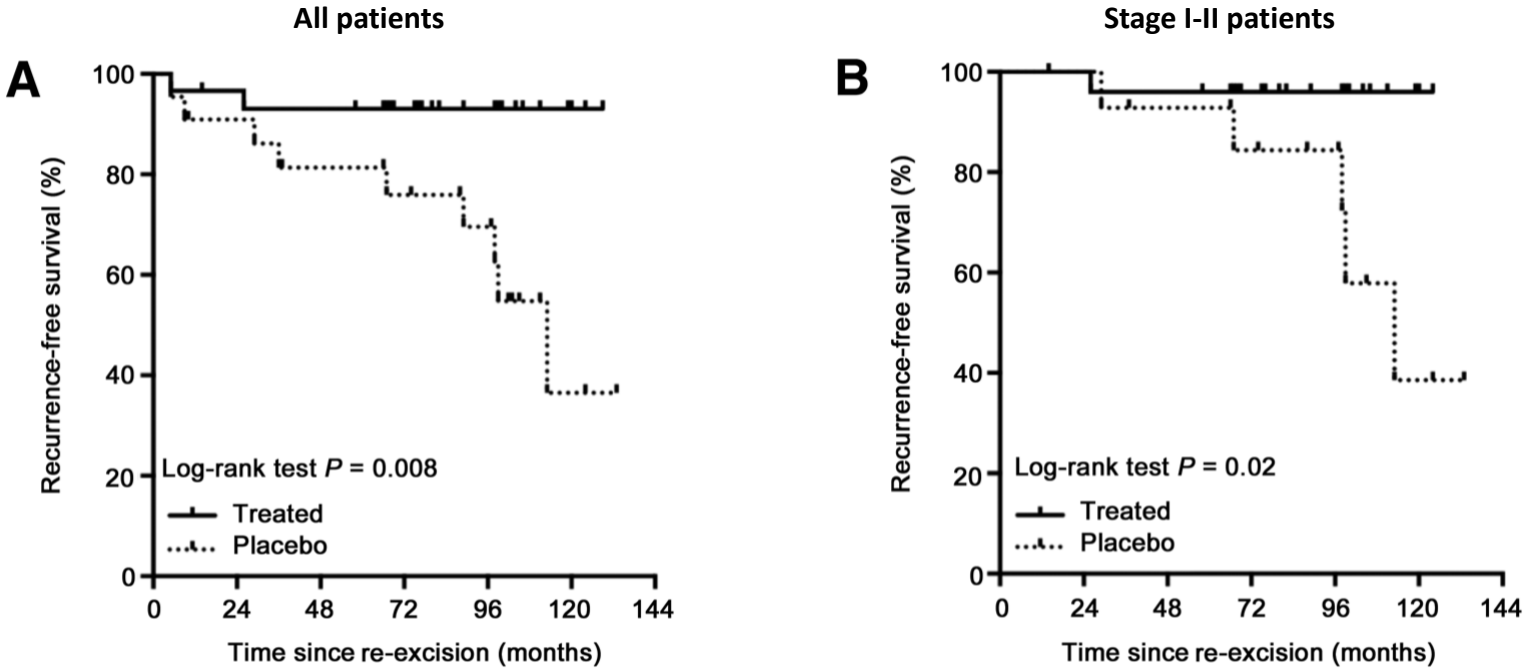


Chapman et al., *N Engl J Med*, 2015



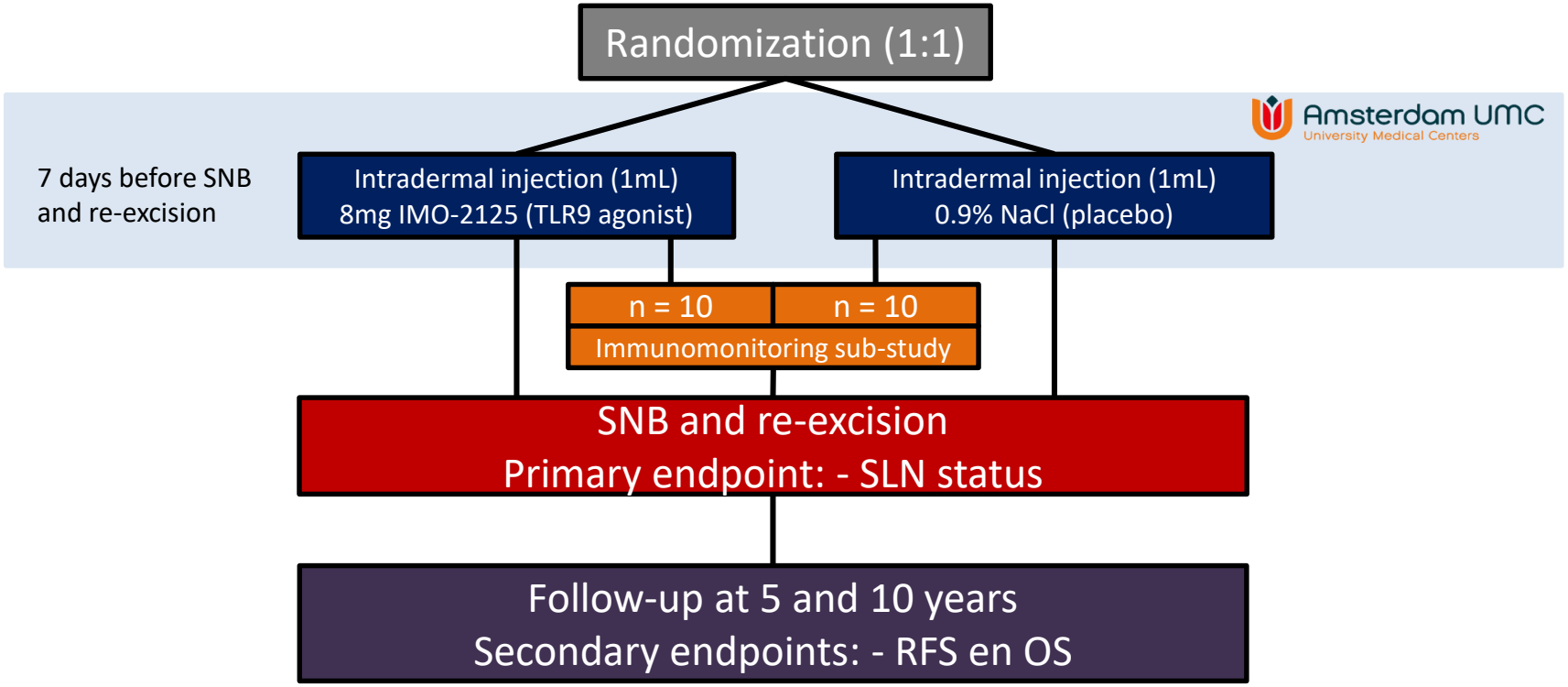
van Akkooi et al., *Nat Rev Clin Oncol*, 2010

Verbeterde recidiefvrije overleving na behandeling met CPG



Koster et al., *Clin Cancer Res*, 2017

INTRIM 1 trial design (n = 214)
cT3-4N0M0 melanoma



Immunotherapie in melanoom
hoe eerder, hoe beter

- lagere tumorload en dus minder immuunsuppressief
- minder vaak een recidief (adjuvant)
- inzicht of behandeling aanslaat en minder snel een recidief (neo-adjuvant)
- IFN-γ–signature voorspelt mogelijk de effectiviteit van neo-adjuvante immunotherapie
- goedkoper, minder bijwerkingen en misschien wel minder vaak een recidief (INTRIM-studie / CPG)

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