STADIUM IV MELANOOM: UPDATE

Dr. Sofie Wilgenhof
25 januari 2020

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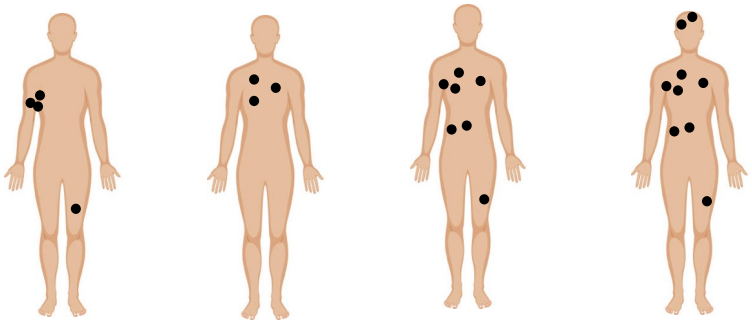
STADIUM IV MELANOOM



IV-M1a
huid, spier en/of kliermetastasen

IV-M1b
longmetastasen

IV-M1c
viscerale metastasen

IV-M1d
hersen-metastasen

Lactaat dehydrogenase: niet verhoogd/verhoogd

In Amin, M.B., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

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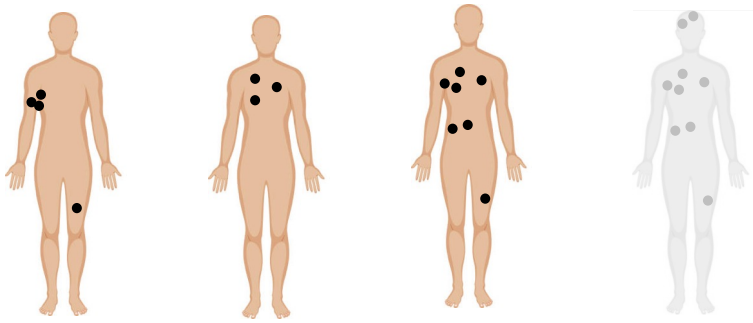
STADIUM IV MELANOOM



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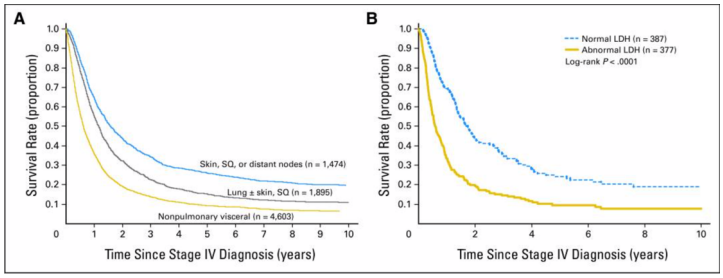
STADIUM IV MELANOOM

Op basis van lokalisatie van de metastasen en lactaat dehydrogenase (LDH):



Balch et al. JCO 2009

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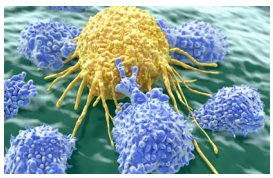
STADIUM IV MELANOOM: BEHANDELING



IMMUNOTHERAPIE (CHECKPOINT REMMERS)

DOELGERICHTE BEHANDELING

(BRAF GEMUTEERD MELANOOM)

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STADIUM IV MELANOOM: BEHANDELING: 2020

IMMUNOTHERAPIE (CHECKPOINT REMMERS)

- Anti-PD-1 antilichaam:
  - Pembrolizumab
  - Nivolumab
- Anti-CTLA-4 antilichaam:
  - Ipilimumab
- Anti-CTLA-4 + anti-PD-1 antlichaam:
  - Ipilimumab + nivolumab

DOELGERICHTE BEHANDELING

- BRAF + MEK inhibitor
  - Vemurafenib + cobimetimib
  - Dabrafenib + trametinib
  - Encorafenib + binimetinib

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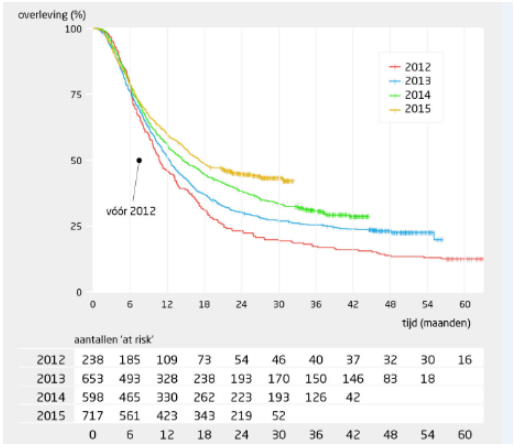
VERBETERING VAN OVERLEVING: NEDERLAND



Van Zeijl et al. NTvG 2018

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STADIUM IV MELANOOM: BEHANDELING: RECENTE GEGEVENS

4. Combinatie immunotherapie + BRAFi + MEKi

IMMUNOTHERAPIE (CHECKPOINT REMMERS)

- Anti-PD-1 antilichaam:
  - Pembrolizumab
  - Nivolumab

2. update

- Anti-CTLA-4 antilichaam:
  - Ipilimumab
- Anti-CTLA-4 + anti-PD-1 antlichaam:
  - Ipilimumab + nivolumab

3. update

DOELGERICHTE BEHANDELING

- BRAF + MEK inhibitor
  - Vemurafenib + cobimetimib
  - Dabrafenib + trametinib
  - Encorafenib + binimetinib

1. update

5. nieuw/verwacht?

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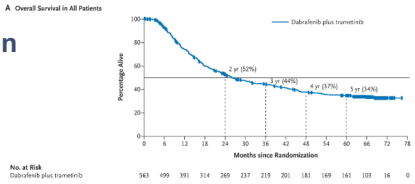
1. DABRAFENIB + TRAMETINIB: UPDATE

- **Hoge** responskans: **70%**
- Mediane tijd tot progressie: **11 maanden**
- Na **5 jaar**: nog **34%** van de patiënten in leven



- Patiënten met **normaal LDH**, **weinig uitzaaiingen**, **goede conditie**: betere uitkomst
- **Bijwerkingen**: koorts, vermoeidheid, misselijkheid, diarree, gewrichts-en spierpijn

Robert C. et al. NEJM 2019

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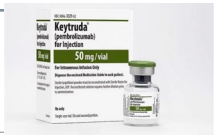
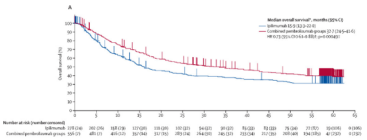
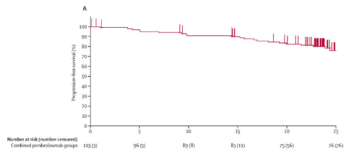
2. PEMBROLIZUMAB: UPDATE



- **Anti-PD-1 antilichaam** is beter dan een anti-CTLA-4 antlichaam
- Responskans: **45%**
- Na **5 jaar**: nog **38%** van de patiënten in leven



- Patiënten met respons op de behandeling, hebben een erg goede uitkomst na stoppen van behandeling (2 jaar)
- De optimale duur van behandeling is onbekend



- Ernstige immunotherapie-gerelateerde bijwerkingen: **15%**

Robert C. et al. Lancet Oncol. 2019

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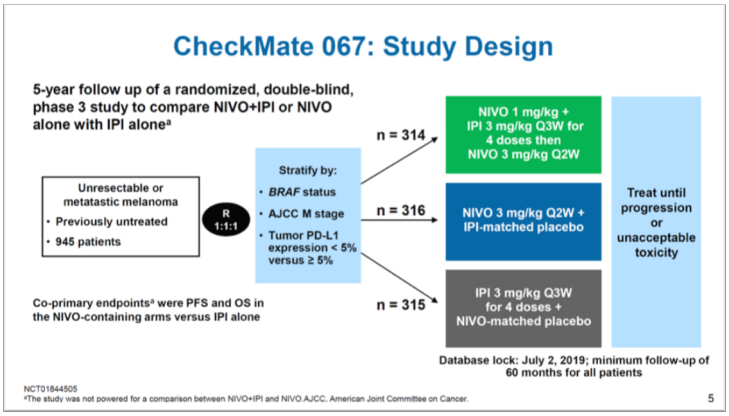
3. IPILIMUMAB + NIVOLUMAB: UPDATE



Larkin et al. NEJM 2019

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Response to Treatment

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR, % (95% CI)	**58 (53–64)**	**45 (39–50)**	**19 (15–24)**
Best overall response, %			
Complete response	22	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
ITT median duration of response, months (95% CI)	**NR[a]**	**NR (50.4–NR)**	**14.4 (8.3–53.6)**
Continued response, n/N (%)	113/183 (62)	86/141 (61)	24/60 (40)

- While ORR has remained stable, rates of CR have increased over the 3-, 4-, and 5-year analyses[1,2]
  - 19%, 21%, and 22% for NIVO+IPI
  - 16%, 18%, and 19% for NIVO
  - 5%, 5%, and 6% for IPI

[a]Although a median was reported at the previous analysis, that estimate was immature and greater than the minimum study follow-up. ITT, intention to treat.
1. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

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Larkin et al. NEJM 2019

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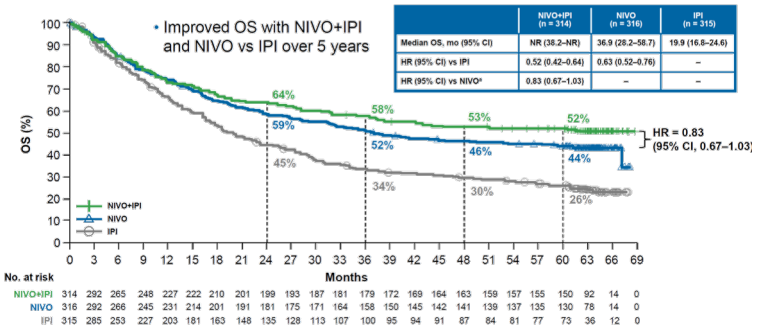
Overall Survival



	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

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Larkin et al. NEJM 2019

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Safety Summary

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

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Larkin et al. NEJM 2019

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3. IPILIMUMAB + NIVOLUMAB: UPDATE SAMENGEVAT

- Combinatiebehandeling (ipi + nivo) heeft een **hoge responskans: 60%**
  (ipilimumab behoudt een repsonskans van 15% na anti-PD-1)
- Er is **geen significant overlevingsvoordeel** aangetoond van combinatiehandeling (ipi+nivo) in vergelijking met nivolumab monotherapie.
- Na **5 jaar**: nog **52%** van de patiënten in leven
- Combinatiebehandeling (ipi+nivo) gaat vaak gepaard met **ernstige** immunotherapie-gerelateerde **bijwerkingen**: **60%**

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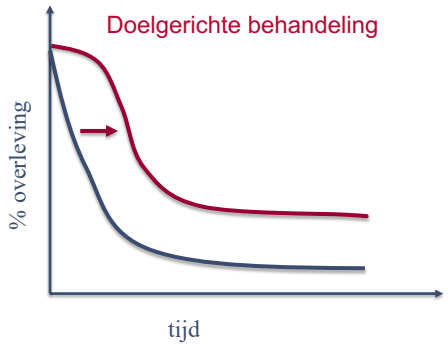
4. COMBINATIE IMMUNOTHERAPIE + DOELGERICHTE BEHANDELING



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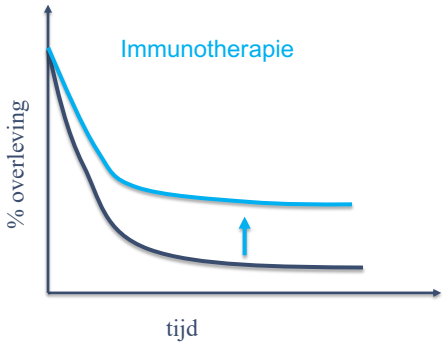

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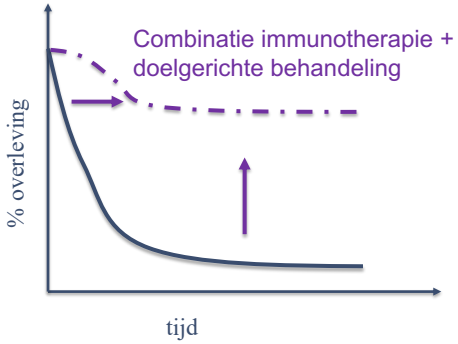

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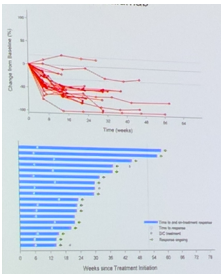
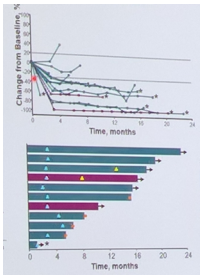
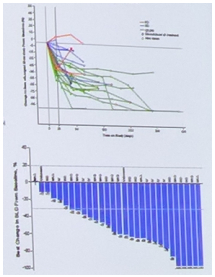
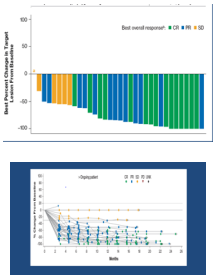
4. COMBINATIE IT (PD-1/-L1 mAb) + BRAF/MEKi fase 1 studies

Dabrafenib/Trametinib Durvalumab	Dabrafenib/Trametinib Pembrolizumab	Vemurafenib/Cobimetinib Atezolizumab	Dabrafenib/Trametinib Spartalizumab
			
Ribas*et al.* ASCO AM 2015	Ribas *et al.* ESMO 2017	Hwu et al. ESMO 2016	Dummer R. et al. SMR 2019

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PEMBROLIZUMAB + DABRAFENIB + TRAMETINIB

KEYNOTE-022 Part 3 Study Design (NCT02130466)

Patients
- Histologically confirmed unresectable or metastatic stage IV *BRAF*$^{V600E/K}$-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

Stratification factors[a]
- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

R (1:1) N = 120

N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

N = 60 → Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.

Ascierto et al. ESMO Meeting 2018

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Summary of Adverse Events

	Pembro + D + T n (%) N = 60	Placebo + D + T n (%) N = 60
Any-grade AE	59 (98)	58 (97)
Grade 3-4	40 (67)	27 (45)
Led to death[a]	2 (3)	0 (0)
Led to discontinuation	25 (42)	13 (22)
Led to discontinuation of all 3 study drugs	15 (25)	9 (15)
Treatment-related AE	57 (95)	56 (93)
Grade 3-4	34 (57)	16 (27)
Led to death	1 (2)	0 (0)
Led to discontinuation of ≥1 study drug	24 (40)	12 (20)

[a]One patient died due to treatment-related pneumonitis and one died of unknown cause. Data cutoff: Feb 15, 2018.

Ascierto PA, et al. *Ann Oncol.* 2018;29(Suppl 8): Abstract 1244O.

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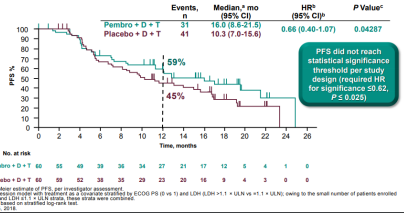
Progression-Free Survival

	Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	31	16.0 (6.6-21.5)	0.66 (0.40-1.07)	0.04287
Placebo + D + T	41	10.3 (7.0-15.6)		

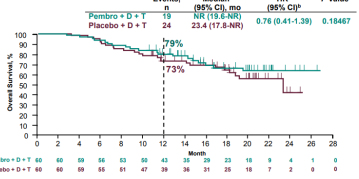


PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, $P \leq 0.025$)

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[c]*P* values are provided for descriptive purposes only, no multiplicity adjustment is made. One-sided *P* value based on stratified log-rank test.
Data cutoff: Feb 15, 2018.

Overall Survival

	Events, n	Median[a] (95% CI), mo	HR[b] (95% CI)[b]	*P* Value[c]
Pembro + D + T	19	NR (19.6-NR)	0.76 (0.41-1.39)	0.18467
Placebo + D + T	24	23.4 (17.8-NR)		



[a]Based on Kaplan-Meier estimate of overall survival.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
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Data cutoff: Feb 15, 2018.

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5. VERWACHT…

COMBINATIE BEHANDELING

- **Immunotherapie + immunotherapie**
  - Pembrolizumab + T-VEC versus pembrolizumab
  - Nivolumab + anti-LAG-3 versus nivolumab
  - Nivolumab + NKTR-214 versus nivolumab
- **Immunotherapie + doelgerichte behandeling**
  - Atezolizumab + vemurafenib + cobimetinib versus placebo + vemurafenib + cobimetinib
  - PDR001 (anti-PD-1) + dabrafenib + trametinib versus placebo + dabrafenib + trametinib

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CELTHERAPIE

- 2e lijnsbehandeling: TIL (tumor infiltrerende lymfocyten) versus ipilimumab (AVL-Amsterdam)

SWITCHEN?

- Tijdelijke doelgerichte behandeling gevolgd door switchen naar immunotherapie versus onmiddellijk immunotherapie

WANNEER IMMUNOTHERAPIE STOPPEN?

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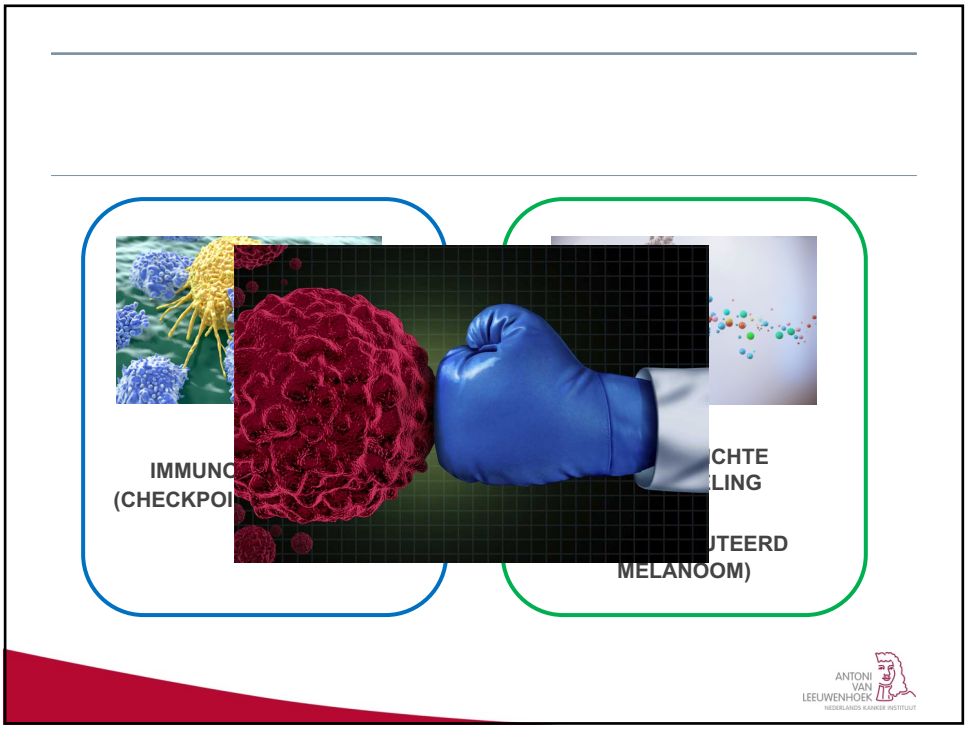
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(CHECKPOI
CHTE
LING
UTEERD
MELANOOM)
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