CHECKPOINT INHIBITORS IN DE KLINISCHE PRAKTIJK ENDOCRINOLOGISCHE BIJWERKINGEN

Sofie Wilgenhof, internist-oncoloog Antoni van Leeuwenhoek ziekenhuis

8 December 2021

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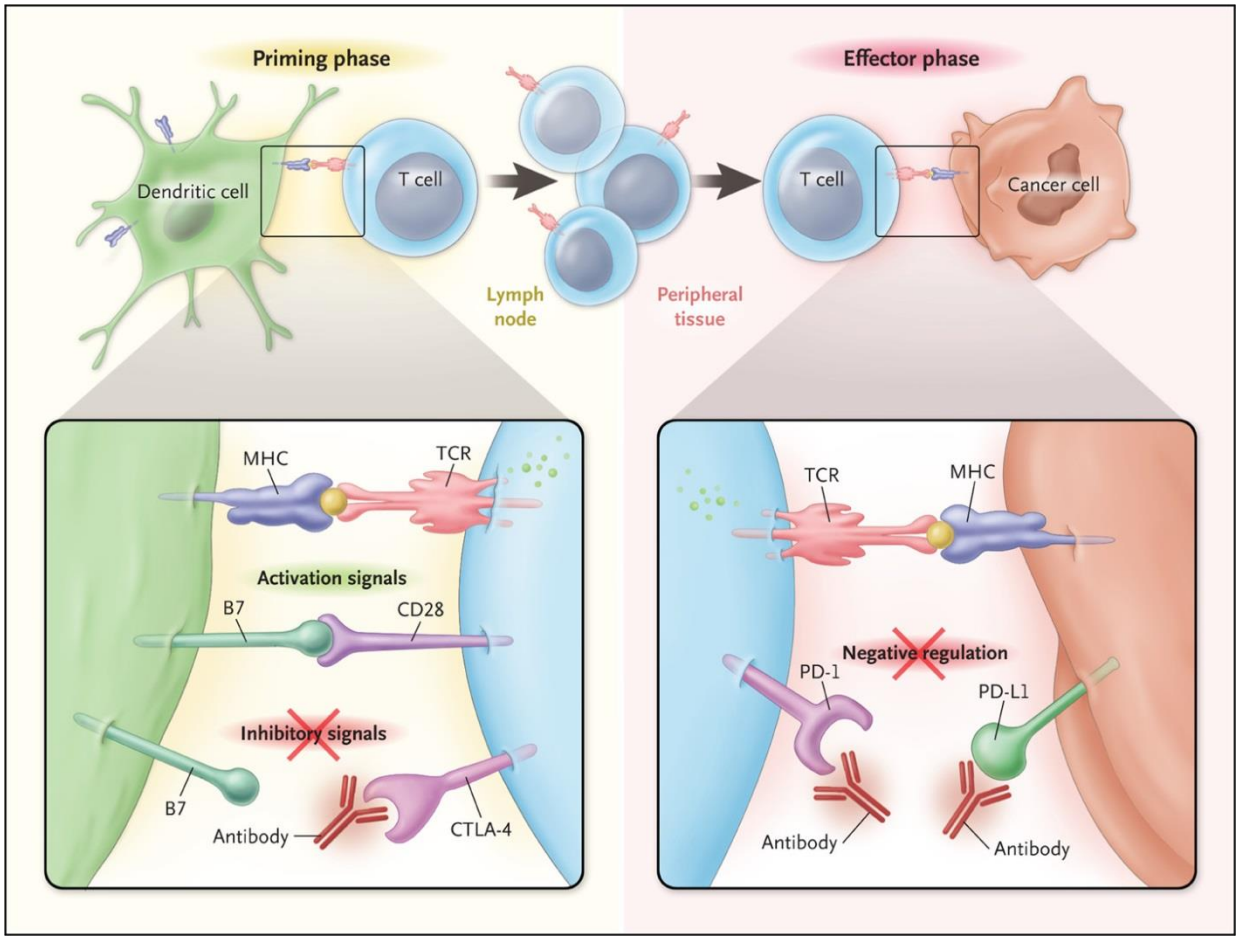
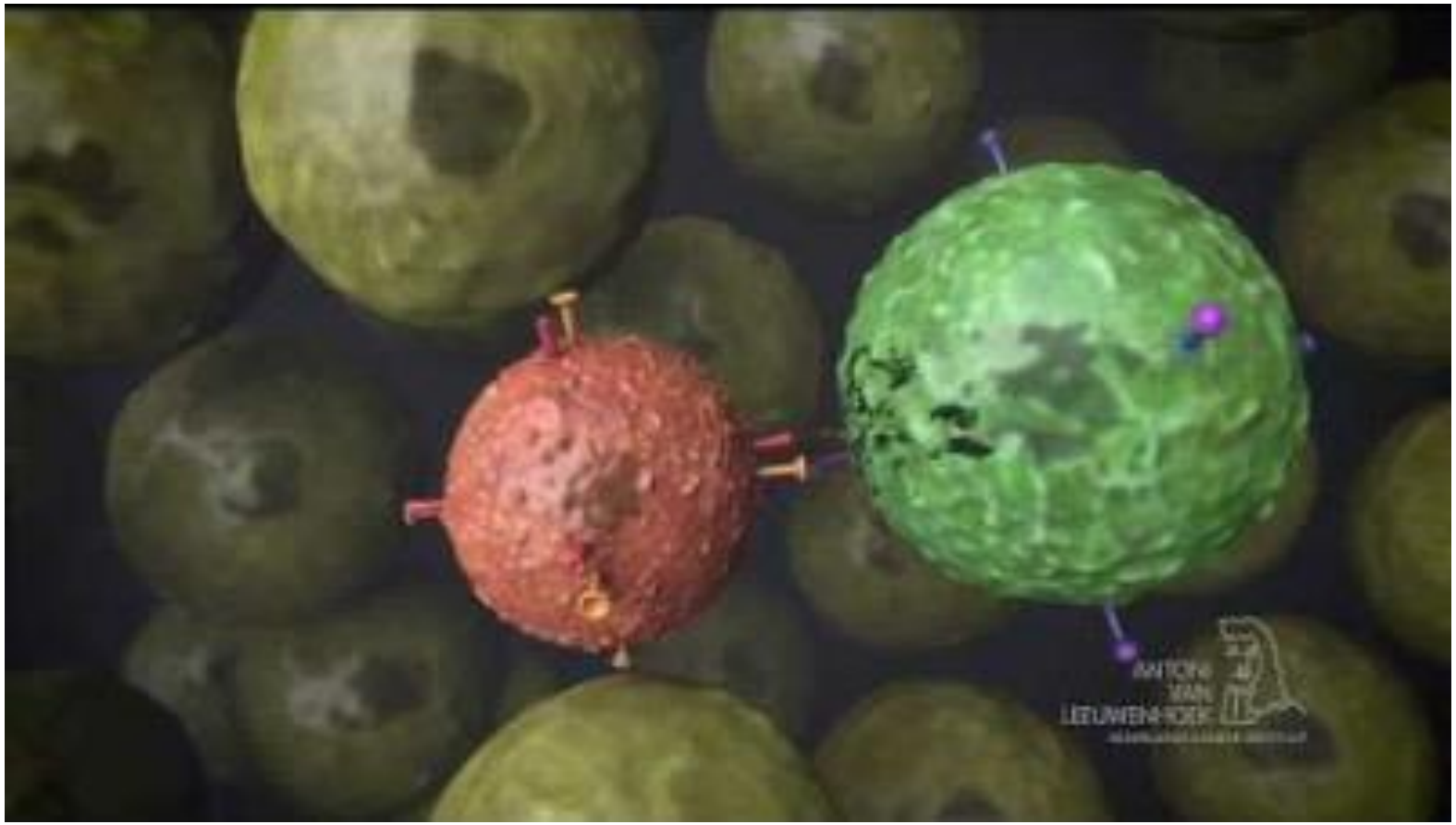
ANTI-CTLA-4 EN ANTI-PD-1/L1 ANTILICHAMEN



Ribas. NEJM. 2012

CHECKPOINTREMMERS



https://www.youtube.com/watch?v=zNvcG_1ffok

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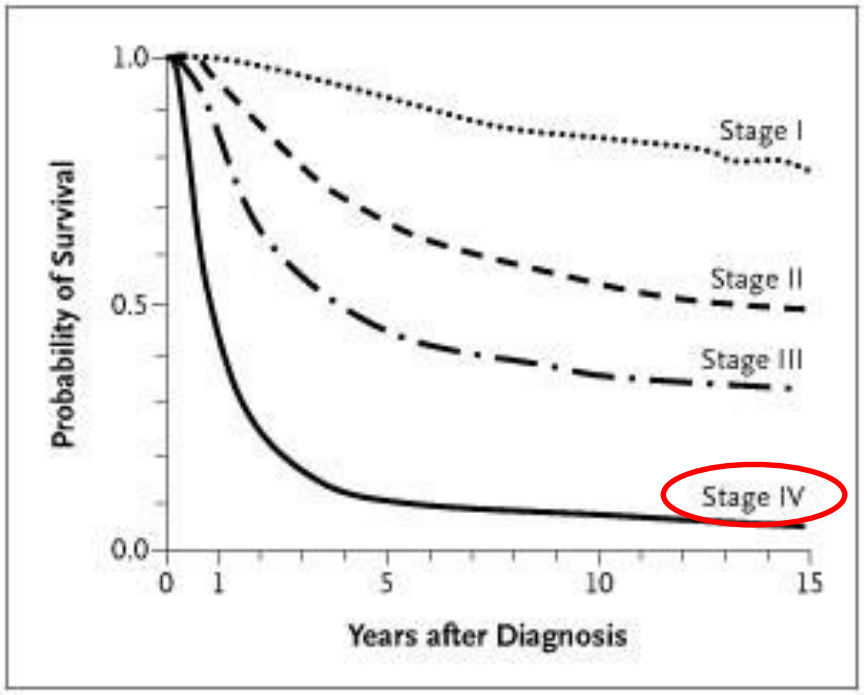
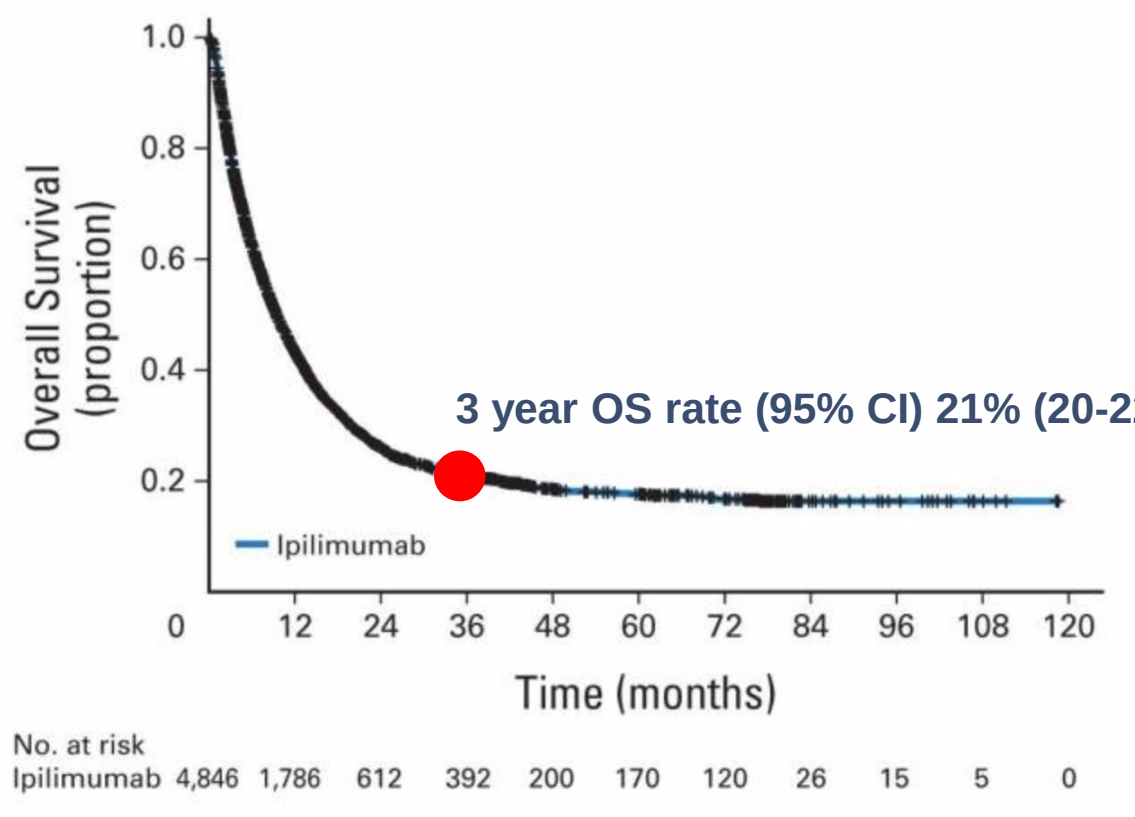
TOT 2010: STADIUM IV MELANOOM



- Mediane overleving 6 tot 10 maanden
- 5j OS < 5%

Tsao et al. NEJM 2004

LANGE TERMIJN OVERLEVING BIJ 4846 PATIENTEN BEHANDELD MET IPILIMUMAB



Schadendorf et al. J Clin Oncol. 2015

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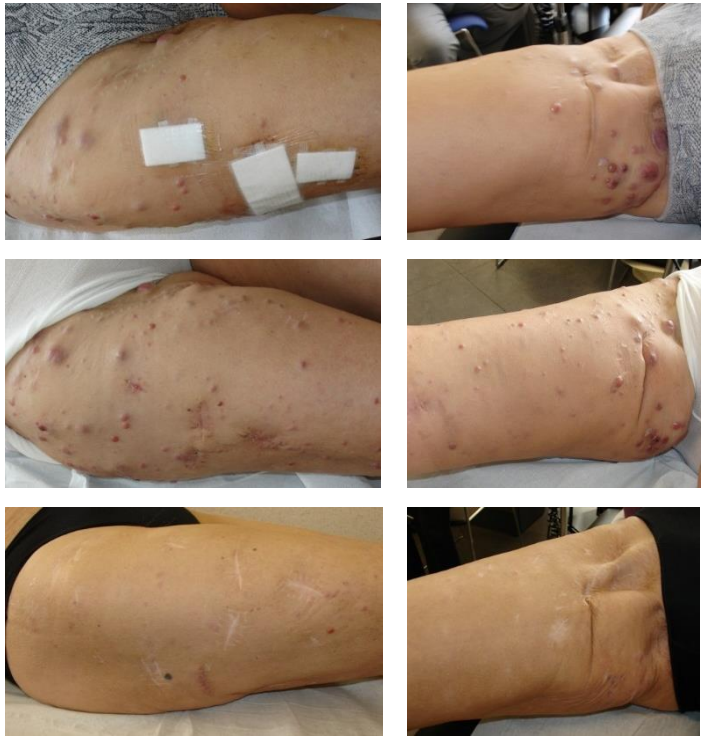
ATYPISCHE TUMORRESPONSEN

Pre-treatment

During treatment
(3 weeks)

1 year
Post-treatment



Toename van metastasen

Afname van metastasen

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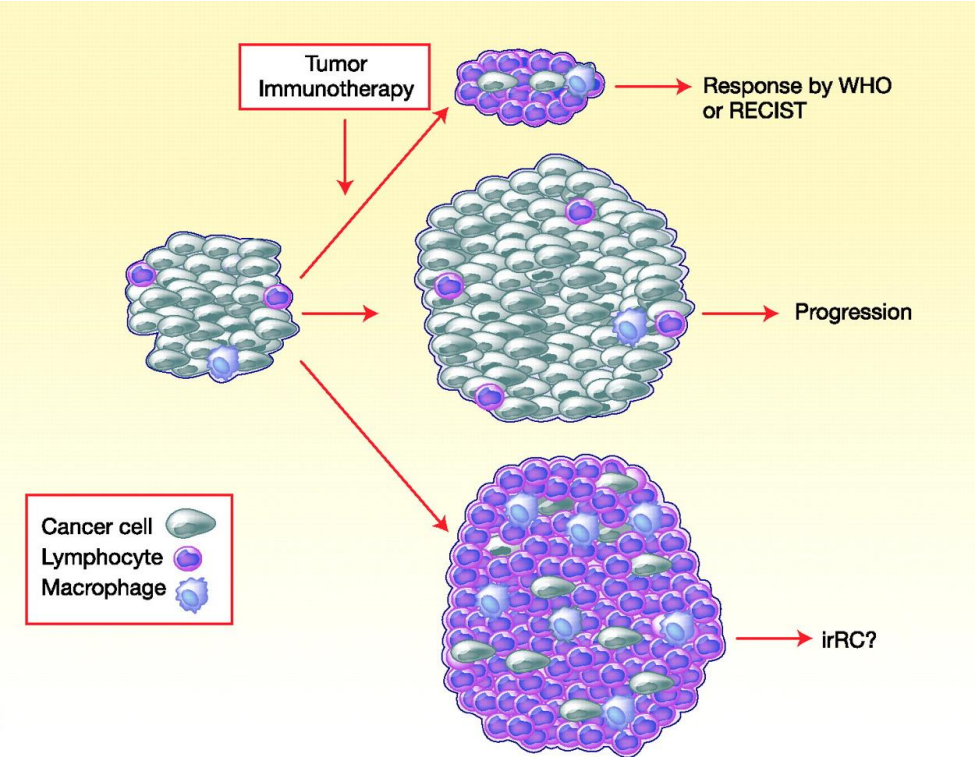
PSEUDOPROGRESSIE



Wolchock et al. CCR. 2009

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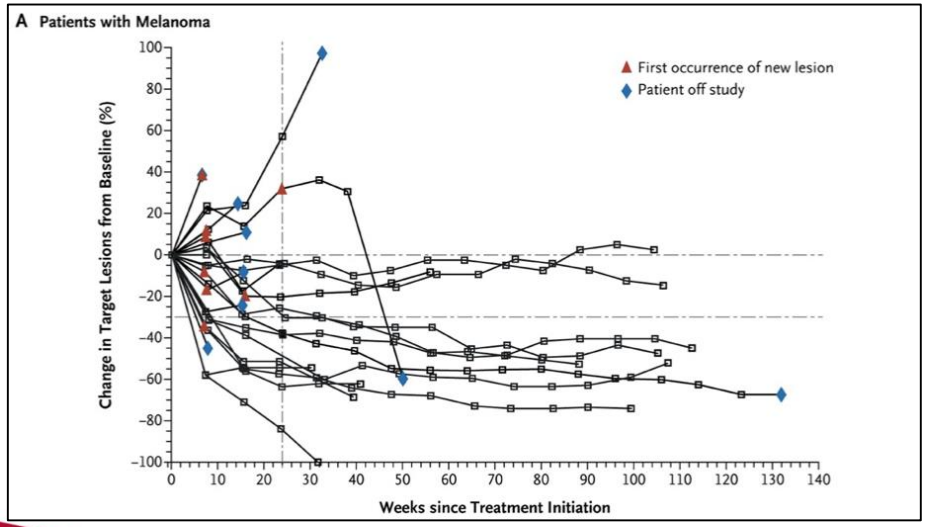
ANTI-PD-1 ANTILICHAAM

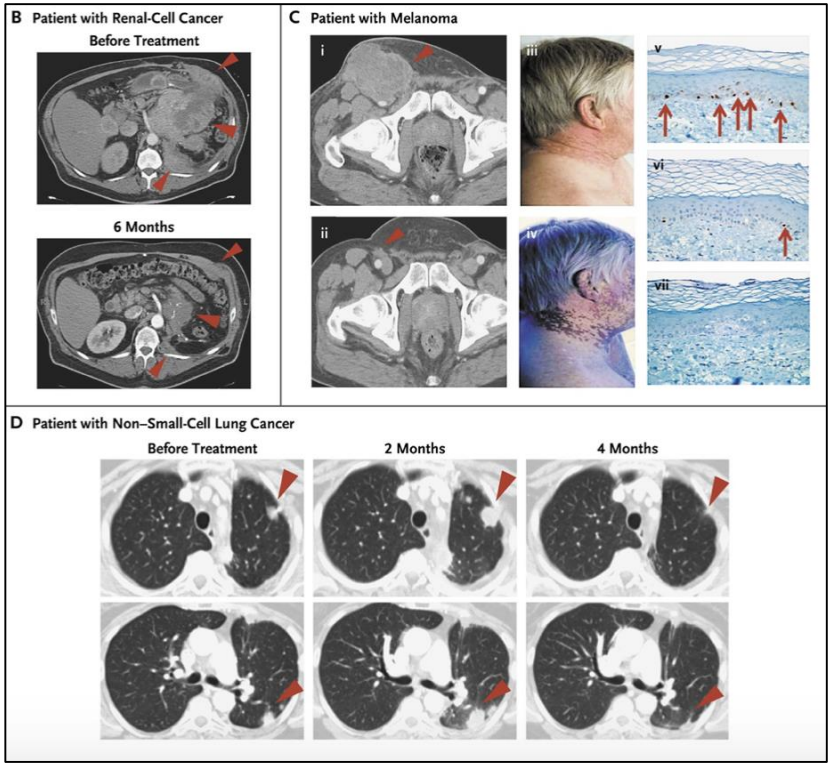
The NEW ENGLAND JOURNAL of MEDICINE

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

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

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.





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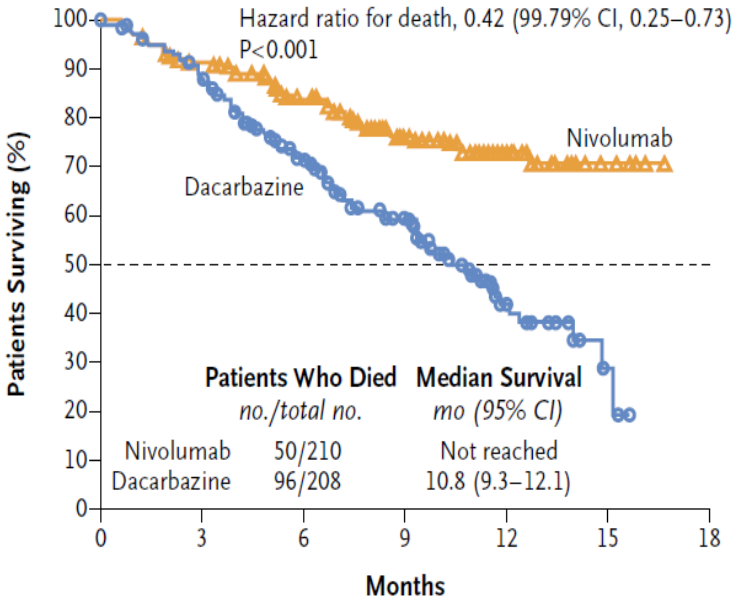
ANTI-PD-1 ANTILICHAAM: MELANOOM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

A Overall Survival



No. at Risk

Nivolumab	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

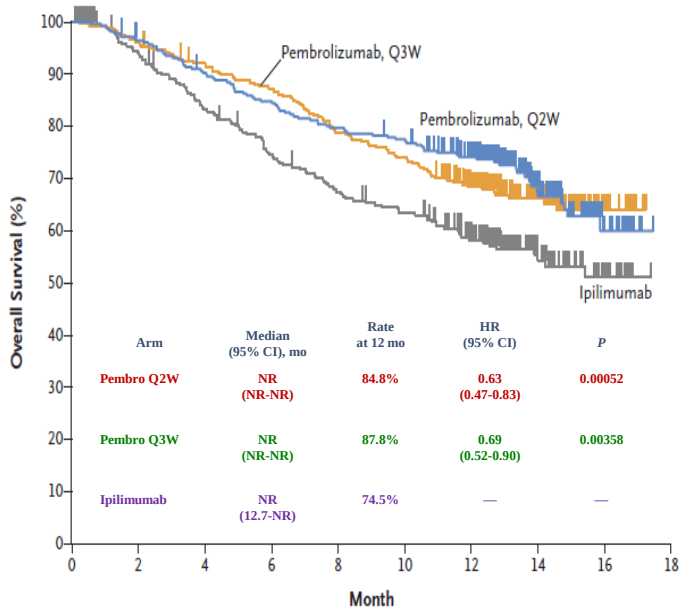
This article was published on November 16, 2014, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

B Overall Survival



Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	P
Pembro Q2W	NR (NR-NR)	84.8%	0.63 (0.47-0.83)	0.00052
Pembro Q3W	NR (NR-NR)	87.8%	0.69 (0.52-0.90)	0.00358
Ipilimumab	NR (12.7-NR)	74.5%	—	—

No. at Risk

Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

This article was published on April 19, 2015, at NEJM.org.

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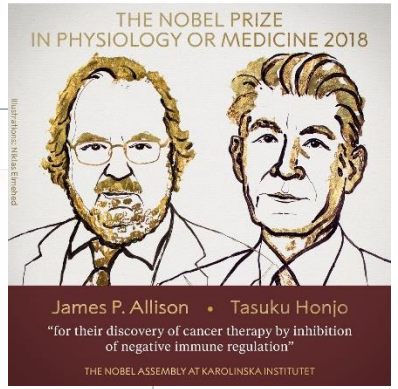
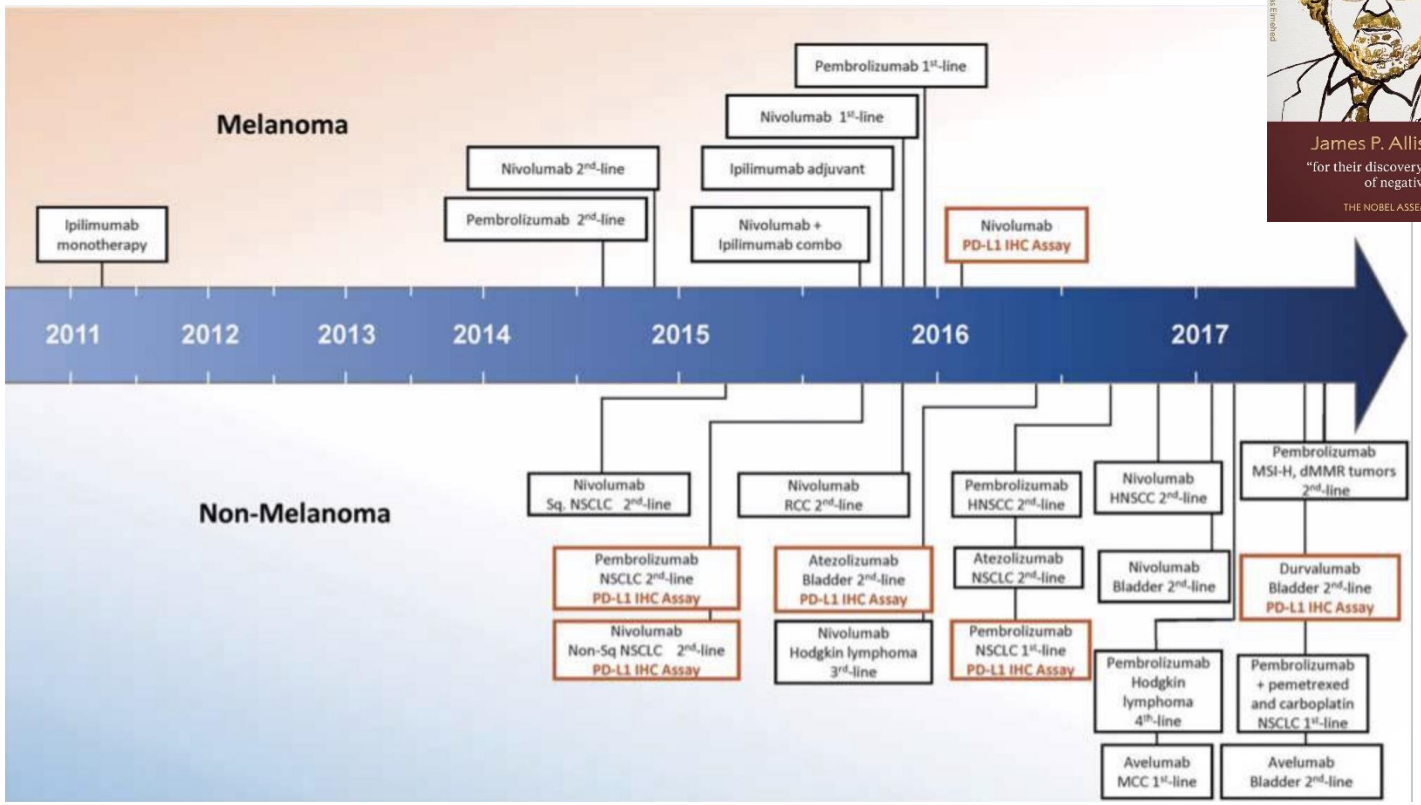
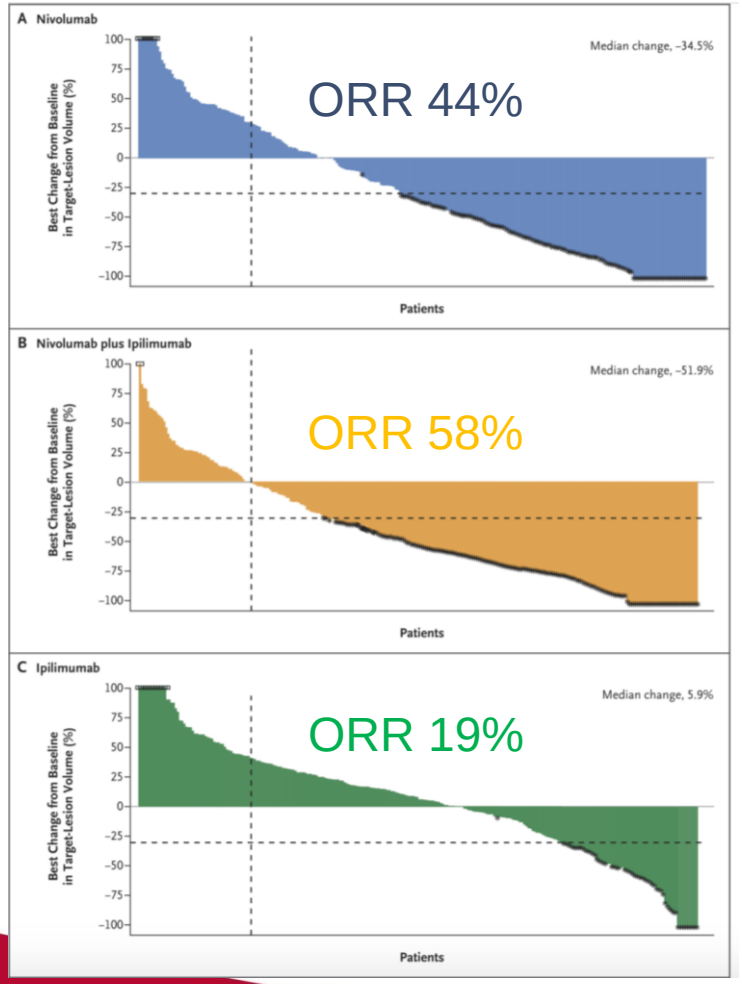
FDA GOEDKEURINGEN CHECKPOINT INHIBITOREN

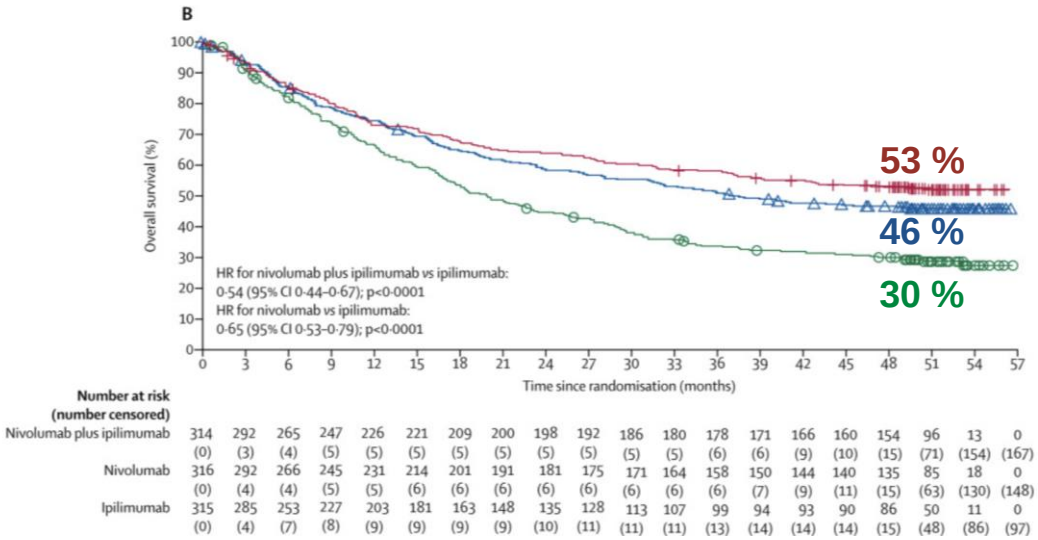




Taube et al. Mod Pathol. 2018

COMBINATIE IMMUNOTHERAPIE BIJ MELANOOM: IPILIMUMAB + NIVOLUMAB





Larkin et al. NEJM. 2015; Hodi et al. Lancet Oncol. 2018

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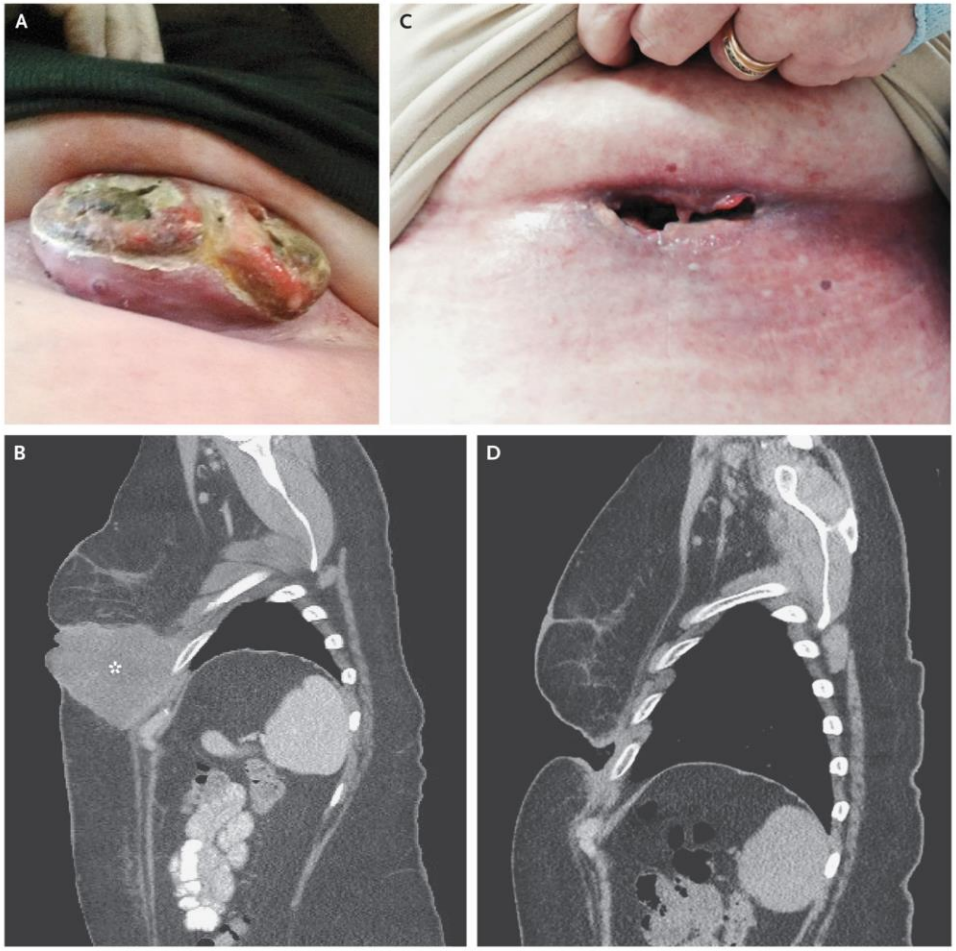
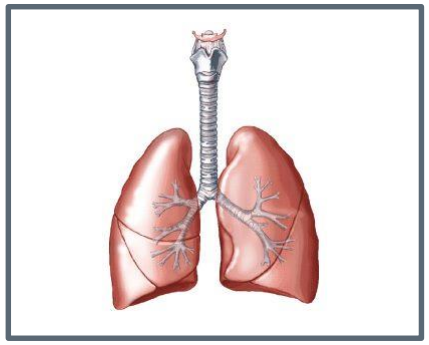
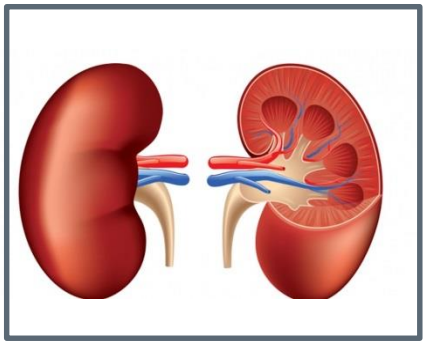
SNELLE TUMORRESPONS NA SLECHTS 1 TOEDIENING IPILIMUMAB + NIVOLUMAB:

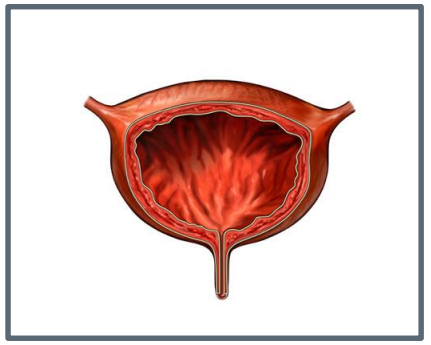


Chapman et al. NEJM. 2015

BIJ WELKE KANKERS WORDEN CHECKPOINTREMMERS VANDAAG GEBRUIKT?







BIJ WELKE KANKERS WORDEN CHECKPOINTREMMERS GEBRUIKT?

Melanoma
45%
[58% bij combi]

Niet-kleincellig longkanker
20%
[hoge (>50%) PD-L1 expressie (25%): 45%]

Nierkanker
25%
[42% bij combi]

Blaaskanker
15%

Merkel cel carcinoom
30-50%

Hodgkin lymfoom
65-85%

Hoofd-en hals tumoren
15%

Plaveiselcelcarcinoom van de huid
50%

Darmkanker
[MSI-H (5%): 50%]

Slokdarm/maagkanker
60% (icm chemotherapie)

Leverkanker
30%

Borstkanker
(PD-L1+ TNBC)
53% (icm chemotherapie)

Mesothelioom
40% (combi)

Kleincellig longkanker
60% (icm chemotherapie)

KLINISCHE STUDIES

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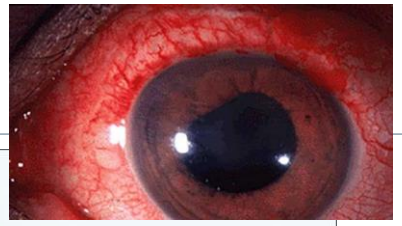
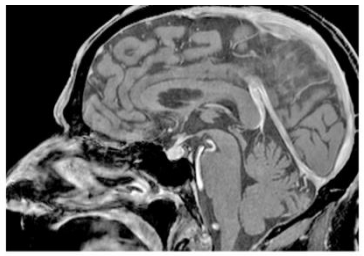
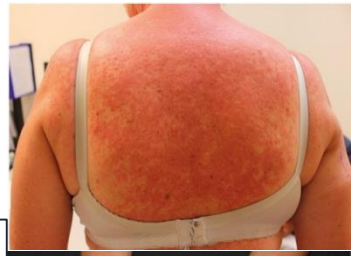
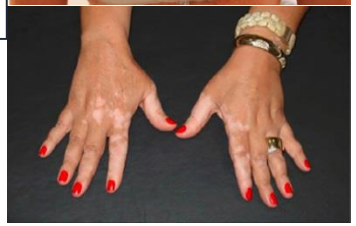
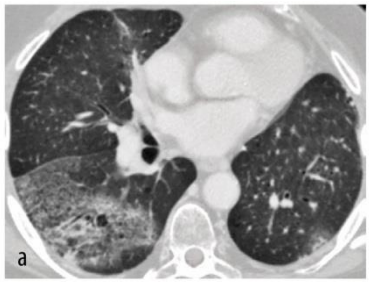
BIJWERKINGEN

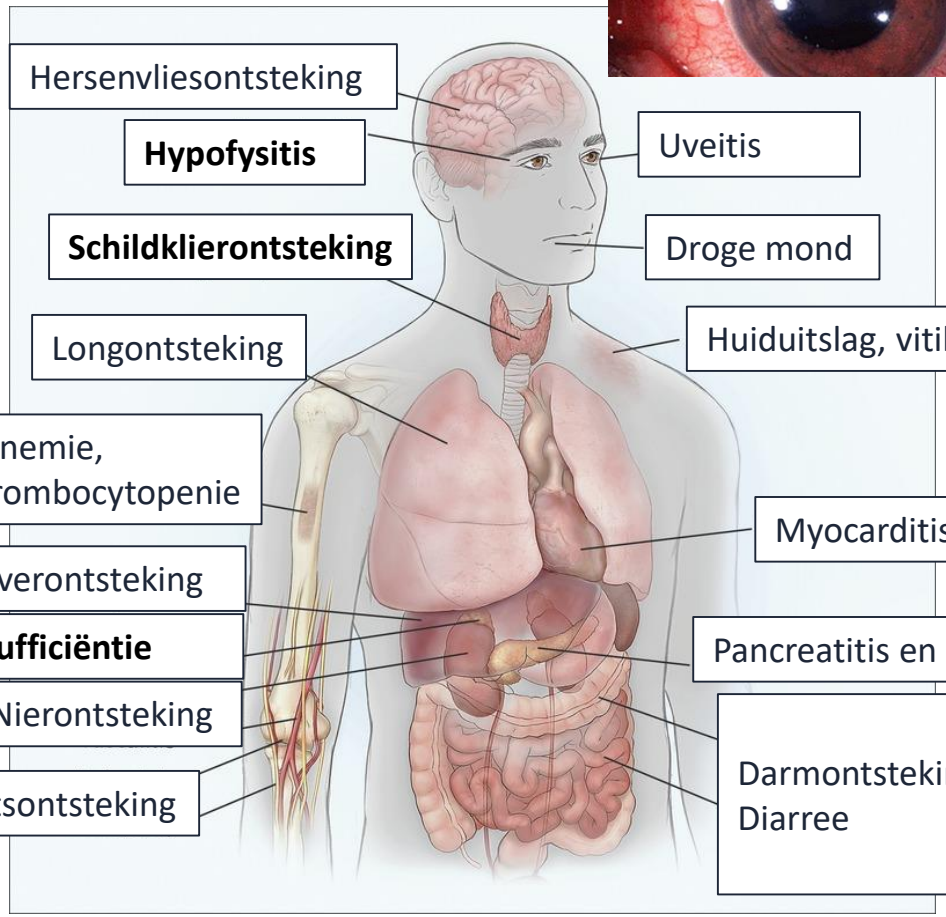












Hersenvliesontsteking

Hypofysitis

Schildklierontsteking

Longontsteking

Anemie, trombocytopenie

Leverontsteking

Bijnierschorsinsufficiëntie

Nierontsteking

Gewrichtsontsteking

Uveitis

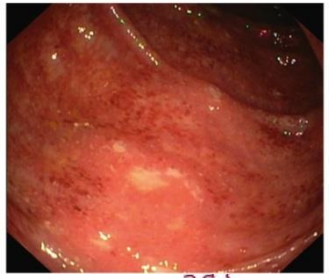
Droge mond

Huiduitslag, vitiligo

Myocarditis

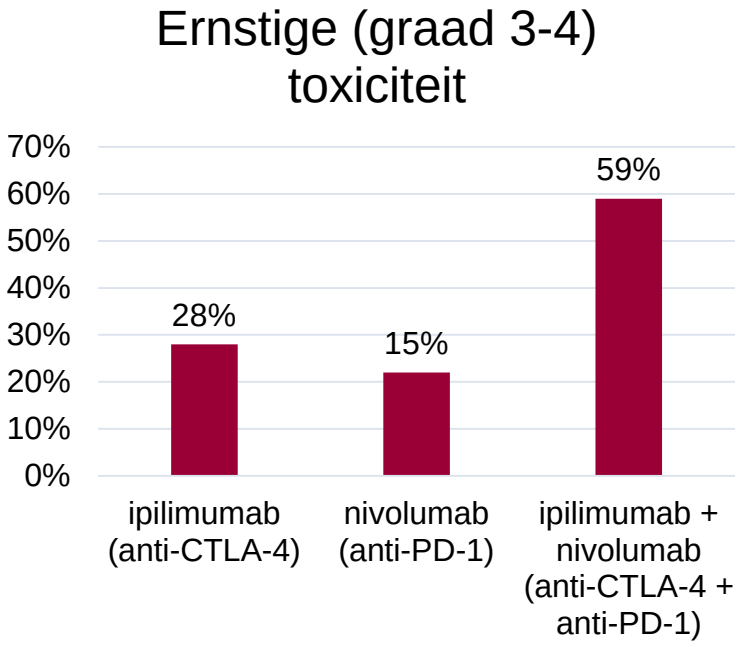
Pancreatitis en **diabetes mellitus**

Darmontsteking
Diarree

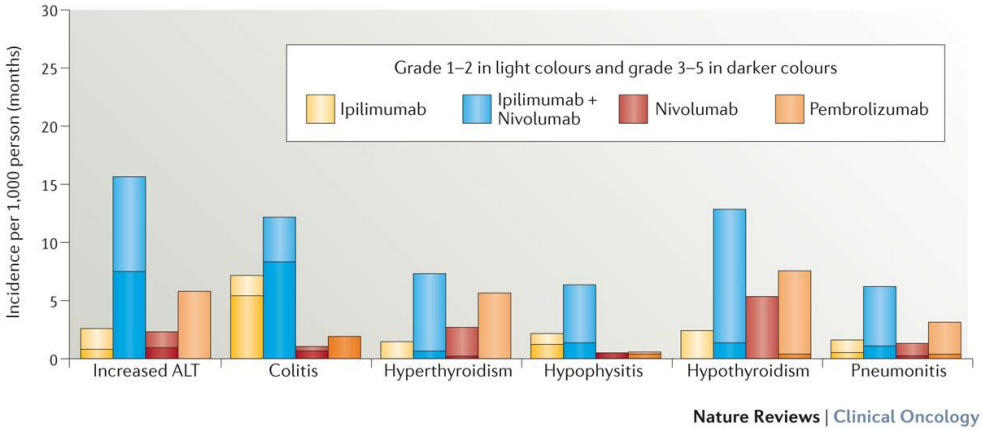


Postow et al. NEJM. 2018; Steebruggen et al. NTvG 2016

ERNSTIGE BIJWERKINGEN



Hodi et al. Lancet Oncol. 2018



Boutros, C. et al. Nat. Rev. Clin. Oncol. 2016

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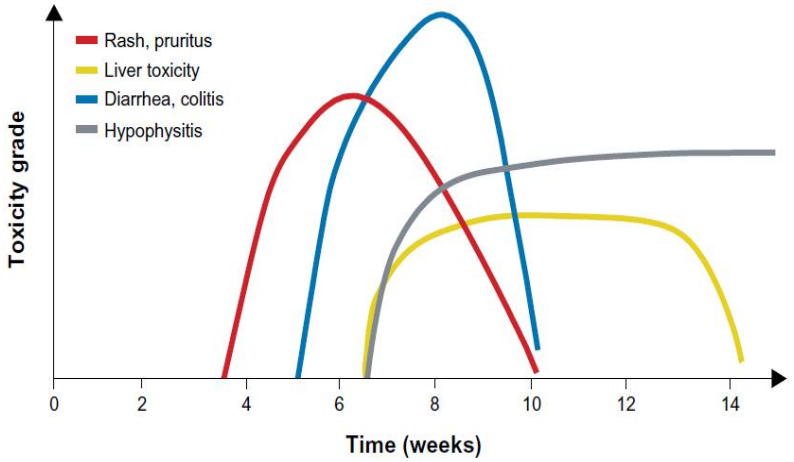
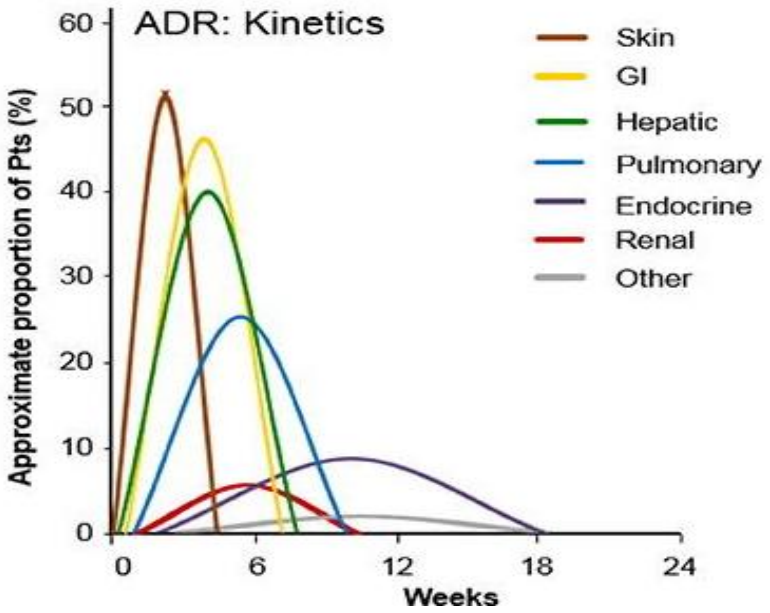
TIJDSTIP VAN OPTREDEN VAN DE BIJWERKINGEN

ipilimumab monotherapie



Weber et al. JCO 2012

combinatie immunotherapie



Hassel et al. Cancer Treatment Reviews. 2017

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IMMUUNTHERAPIE BIJWERKINGEN

REVERSIBEL

- colitis
- hepatitis
- dermatitis
- pneumonitis

NIET REVERSIBEL

- **Endocrinopathie** met hormonale substitutie
  - Thyroiditis; hypothyreoidie
  - Hypofysitis
    - Hypothyreoidie, hypocortisolisme
    - uitval gonadotrope as
  - Diabetes mellitus
- Restverschijnselen na eerdere ersntige toxiciteit
  - Neurologische toxiciteit → neuropathie
  - Hypocortisolisme/osteoporose na langdurig prednison gebruik
- Aanhoudende laaggradige toxicitiet
  - Gewrichtsklachten
  - Droge mond/droge ogen
  - Moeheid
  - Vitiligo
  - Jeuk/huidirritatie

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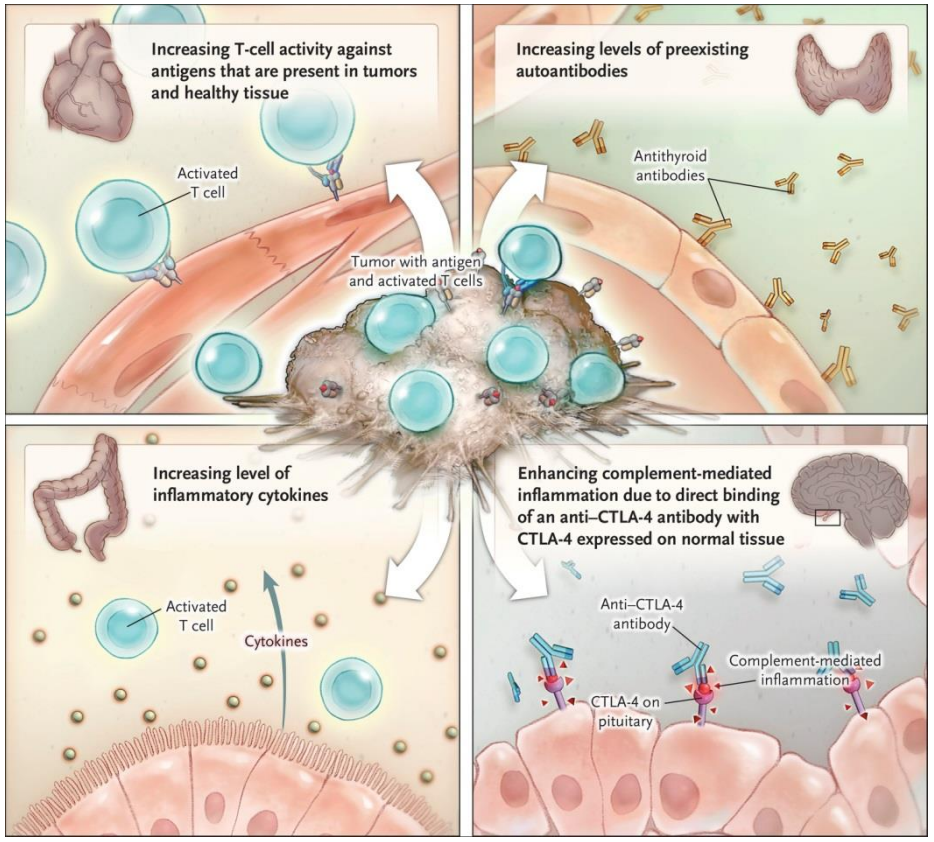
MOGELIJKE MECHANISMEN IMMUUNGERELATEERDE BIJWERKINGEN



Postow et al. NEJM 2018

1 BEHANDELING VAN BIJWERKINGEN

immunotherapie

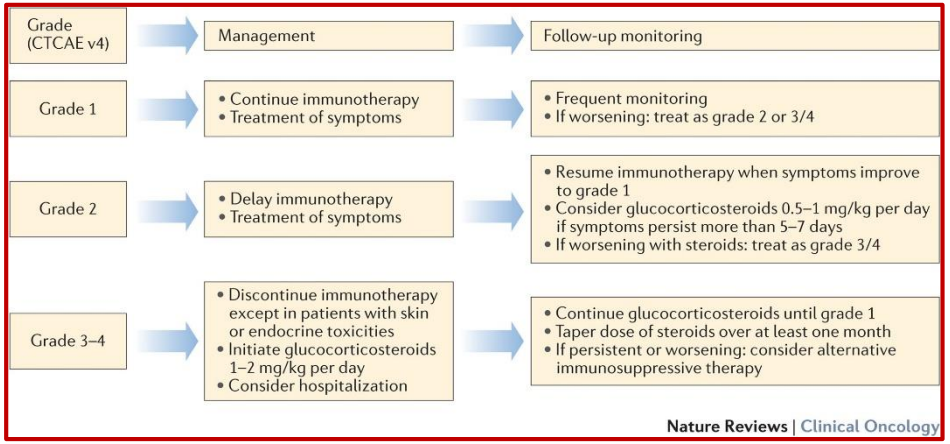
- (Tijdelijk) staken van immunotherapie
- Immunosuppressiva:
  - glucocorticoïden (oraal/intraveneus)
  - anti-TNF-alpha (infliximab)
  - mycofenolaatmofetil
  - tacrolimus

ESMO

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*



Boutros, C. et al. Nat. Rev. Clin. Oncol. 2016

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VRAGEN