Immunotherapie in de oncologie

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22/11/2025

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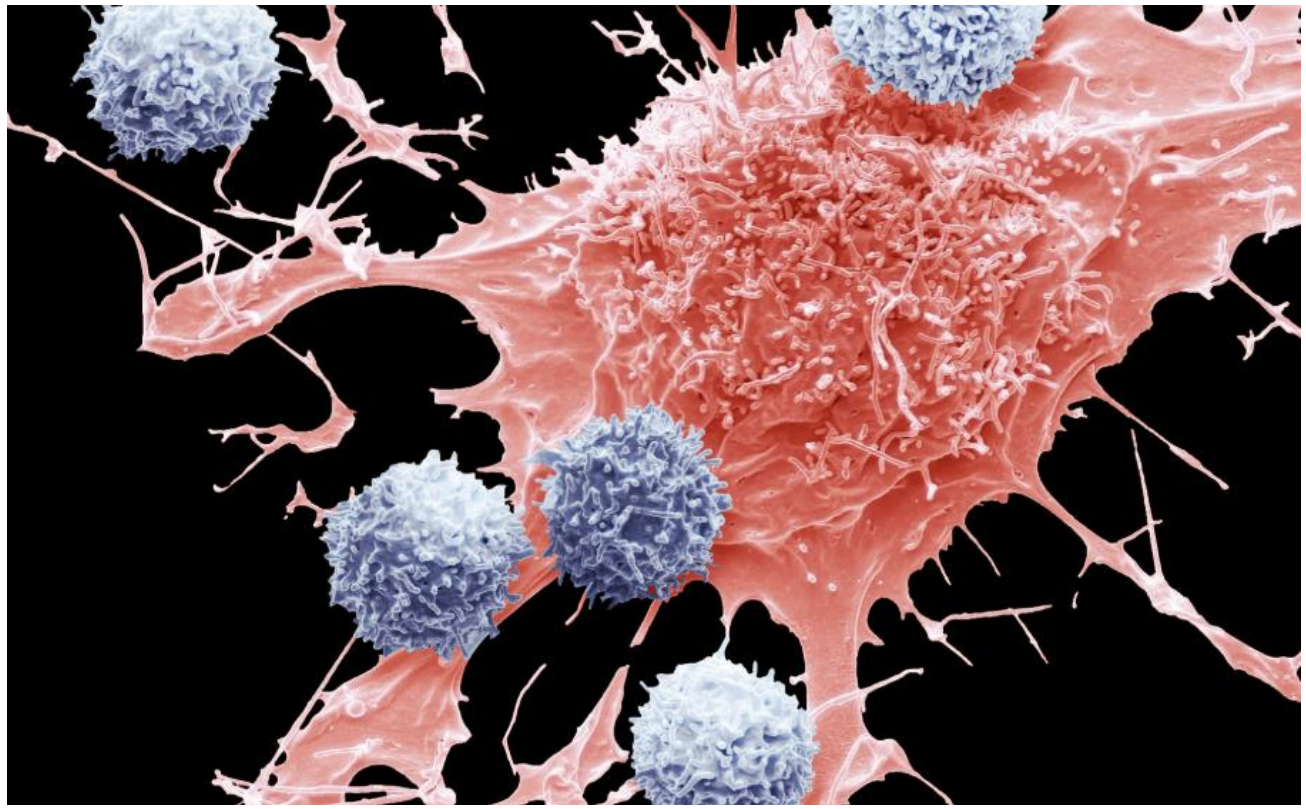
Universiteit Antwerpen

UZA

Overzicht

- Wat is immunotherapie?
  - Geschiedenis
  - Soorten
- Toepassingen in de oncologie
- Bijwerkingen
- Take home messages



Wat is immunotherapie?

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REVIEW

doi:10.1038/nature10673

Cancer immunotherapy comes of age

Ira Mellman[1], George Coukos[2] & Glenn Dranoff[3]

Activating the immune system for therapeutic benefit in cancer has long been a goal in immunology and oncology. After decades of disappointment, the tide has finally changed due to the success of recent proof-of-concept clinical trials. Most notable has been the ability of the anti-CTLA4 antibody, ipilimumab, to achieve a significant increase in survival for patients with metastatic melanoma, for which conventional therapies have failed. In the context of advances in the understanding of how tolerance, immunity and immunosuppression regulate antitumour immune responses together with the advent of targeted therapies, these successes suggest that active immunotherapy represents a path to obtain a durable and long-lasting response in cancer patients.

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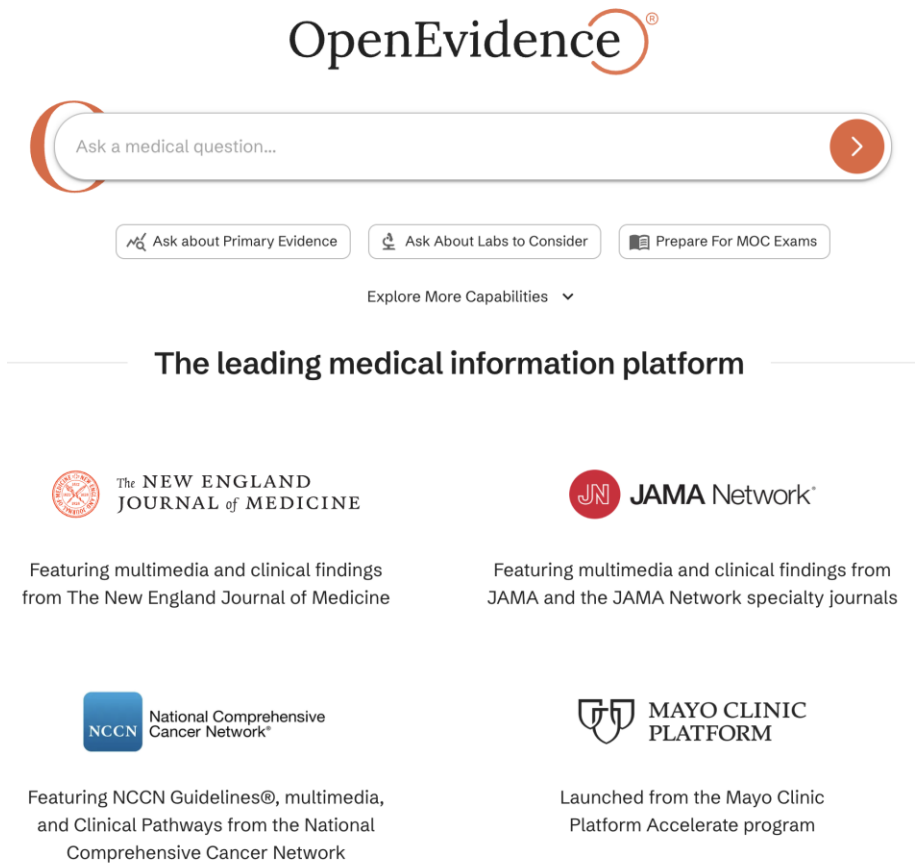
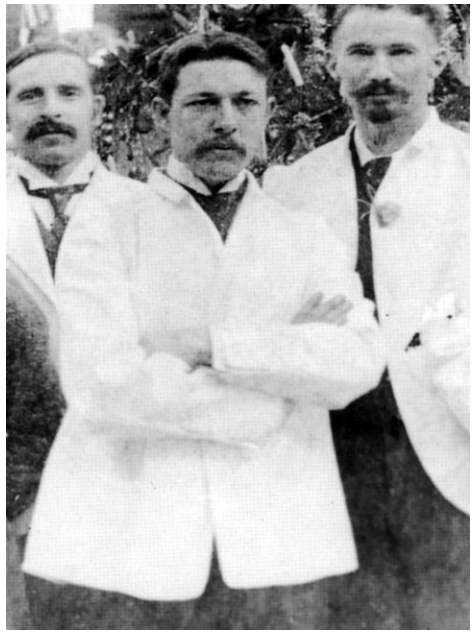
Wat is immunotherapie?



*'**Immunotherapy** is a therapeutic approach that modulates or harnesses the immune system to treat disease.'*

Geschiedenis

- William B. Coley - 1891
  - Opzettelijk bacteriële toxinen geïnjecteerd bij patiënten met sarcoom, waarbij tumorregressie werd waargenomen
  - Eerste succesvolle immunologische interventie voor kanker



- Dobosz P, et al..Frontiers in Immunology. 2019

Geschiedenis

- Tasuka Honjo - 1992

The EMBO Journal vol.11 no.11 pp.3887 – 3895, 1992

Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death

Yasumasa Ishida, Yasutoshi Agata, Keiichi Shibahara and Tasuku Honjo[1]

Department of Medical Chemistry, Kyoto University Faculty of Medicine, Yoshida, Sakyo-ku, Kyoto 606, Japan

[1]Corresponding author

Communicated by J.Tooze

of actinomycin D or cycloheximide on the death of nerve growth factor (NGF)-deprived rat neurons (Martin *et al.*, 1988) and that of mouse thymocytes induced by glucocorticoids (Cohen and Duke, 1984) or by an endogenous superantigen (MacDonald and Lees, 1990). These facts suggest that at least a few genes, if not specific ones, must be expressed to cause programmed cell death.

Geschiedenis

- James Allison - 1995

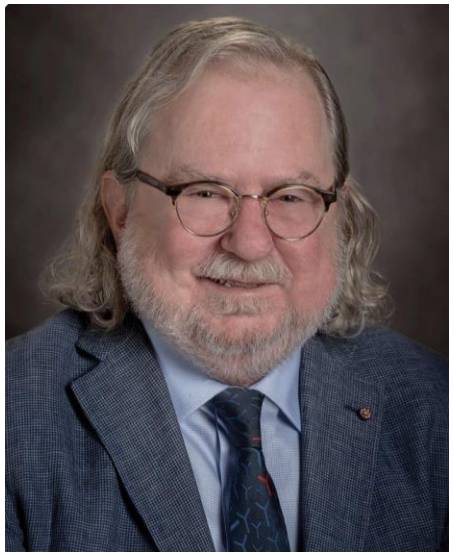
CD28 and CTLA-4 Have Opposing Effects on the Response of T cells to Stimulation

By Matthew F. Krummel and James P. Allison

From the Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, Berkeley, California 94720

Summary

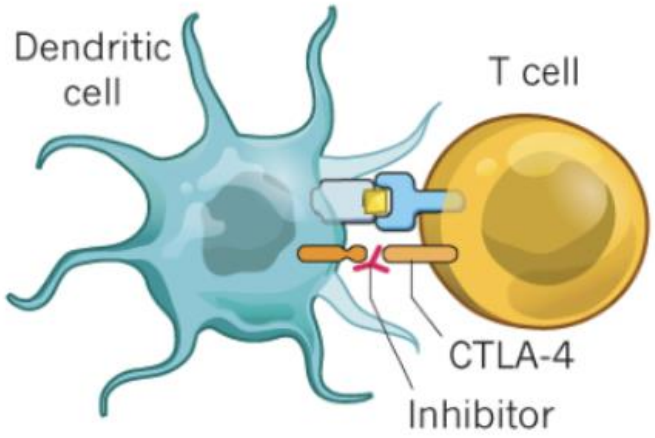
The importance of the B7/CD28/CTLA-4 molecules has been established in studies of antigen-presenting cell–derived B7 and its interaction with the T cell costimulatory molecule CD28. CTLA-4, a T cell surface glycoprotein that is related to CD28, can also interact with B7-1 and B7-2. However, less is known about the function of CTLA-4, which is expressed at highest levels after activation. We have generated an antibody to CTLA-4 to investigate the consequences of engagement of this molecule in a carefully defined system using highly purified T cells. We show here that the presence of low levels of B7-2 on freshly explanted T cells can partially inhibit T cell proliferation, and this inhibition is mediated by interactions with CTLA-4. Cross-linking of CTLA-4 together with the TCR and CD28 strongly inhibits proliferation and IL-2 secretion by T cells. Finally, results show that CD28 and CTLA-4 deliver opposing signals that appear to be integrated by the T cell in determining the response to activation. These data strongly suggest that the outcome of T cell antigen receptor stimulation is regulated by CD28 costimulatory signals, as well as inhibitory signals derived from CTLA-4.



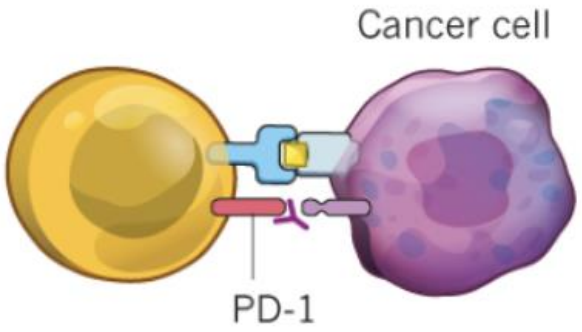
Geschiedenis

CHECKPOINT INHIBITOR DRUGS

'Checkpoint' proteins block T-cell activity. Inhibitor drugs can release the brakes on T cells at different stages.



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.



The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

©nature

Ledford, H. Cancer treatment: The killer within. Nature 508, 24–26 (2014).

Geschiedenis

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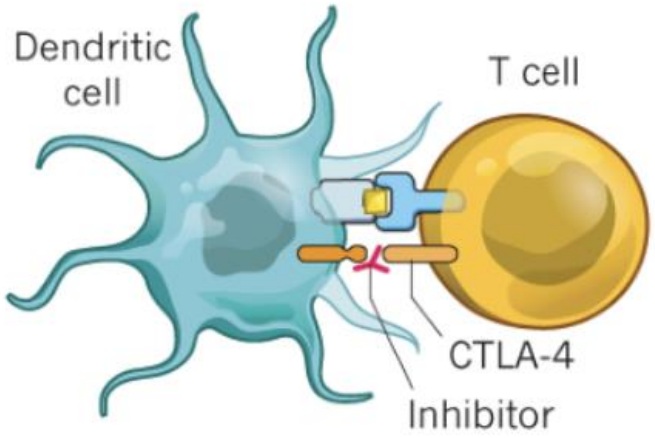

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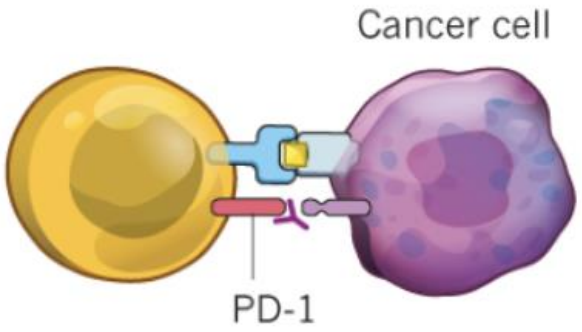

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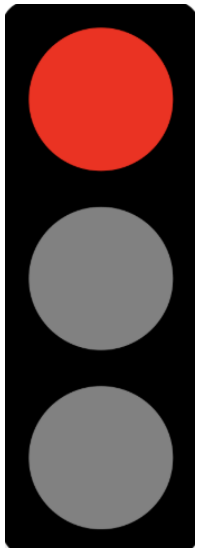

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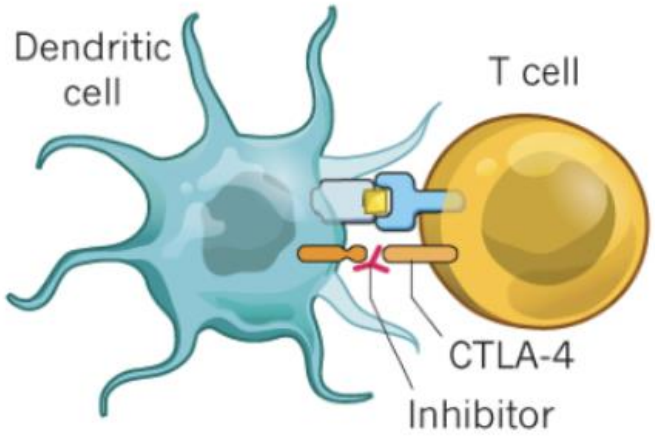

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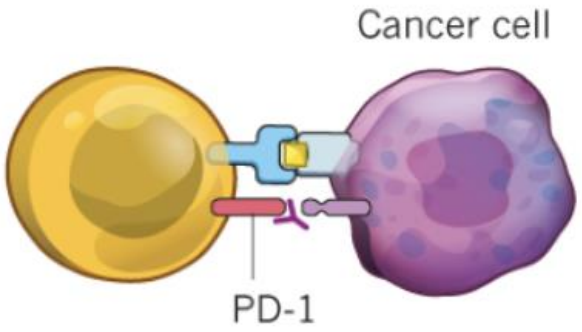

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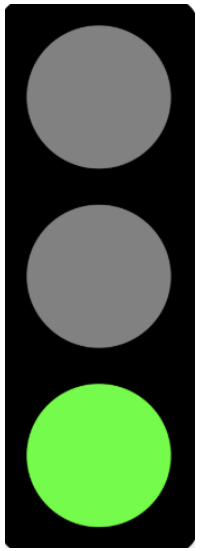


Ledford, H. Cancer treatment: The killer within. Nature 508, 24–26 (2014).

Geschiedenis

The NEW ENGLAND JOURNAL of MEDICINE

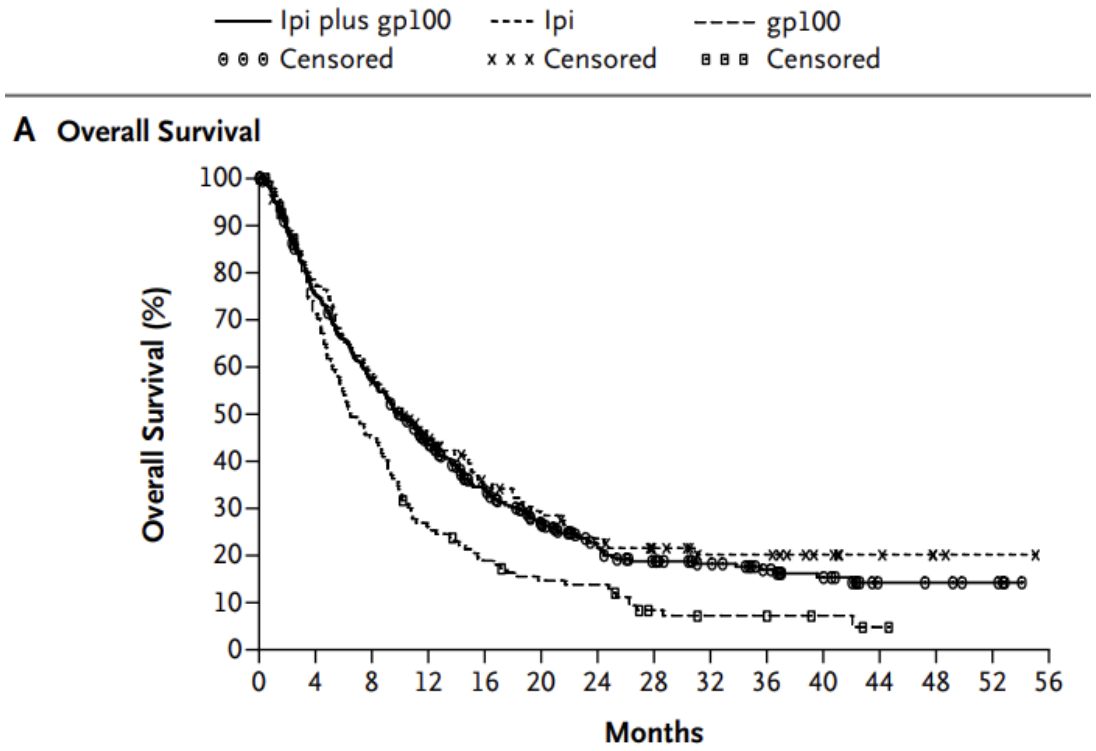
ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

ABSTRACT

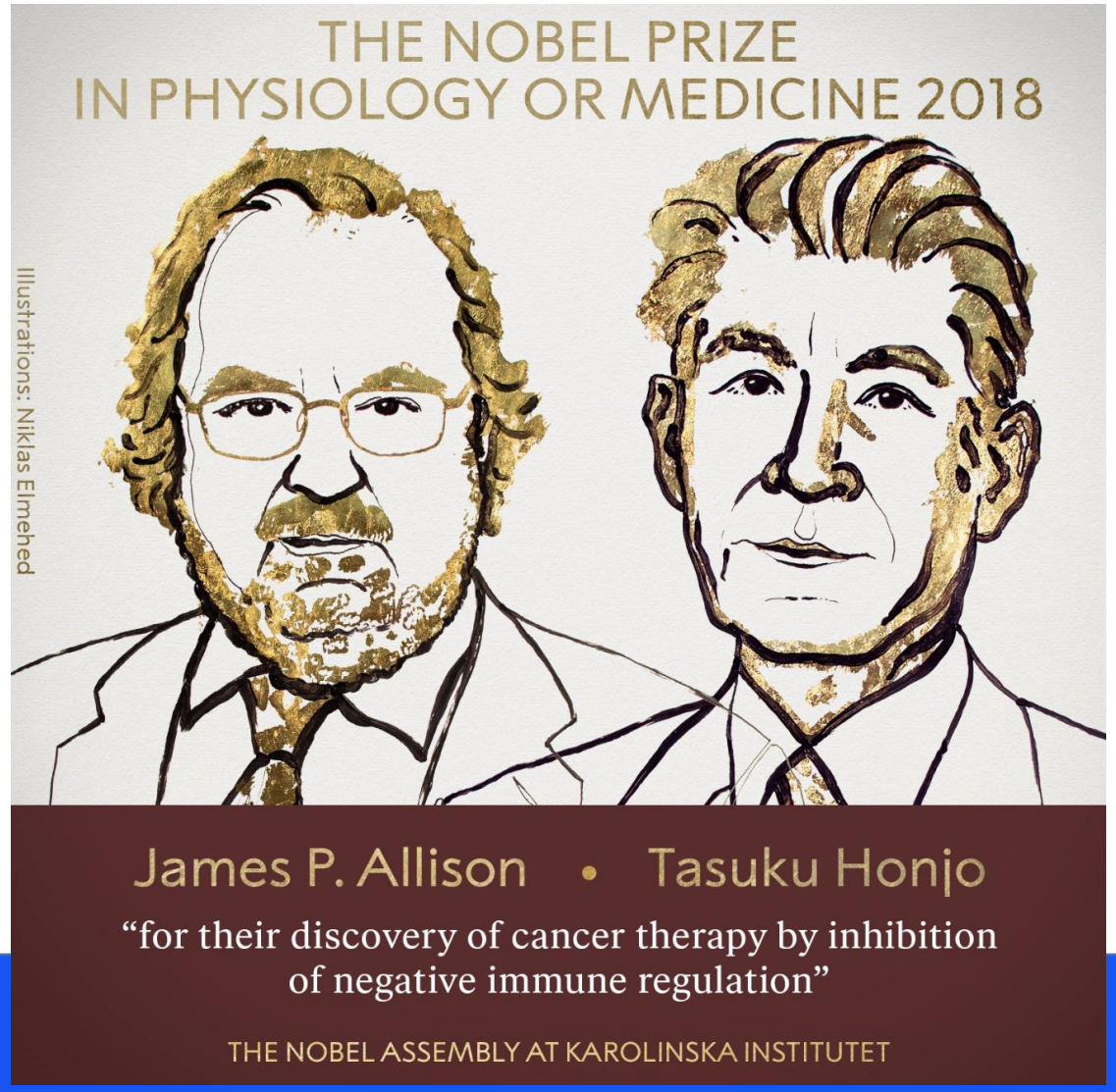
Geschiedenis



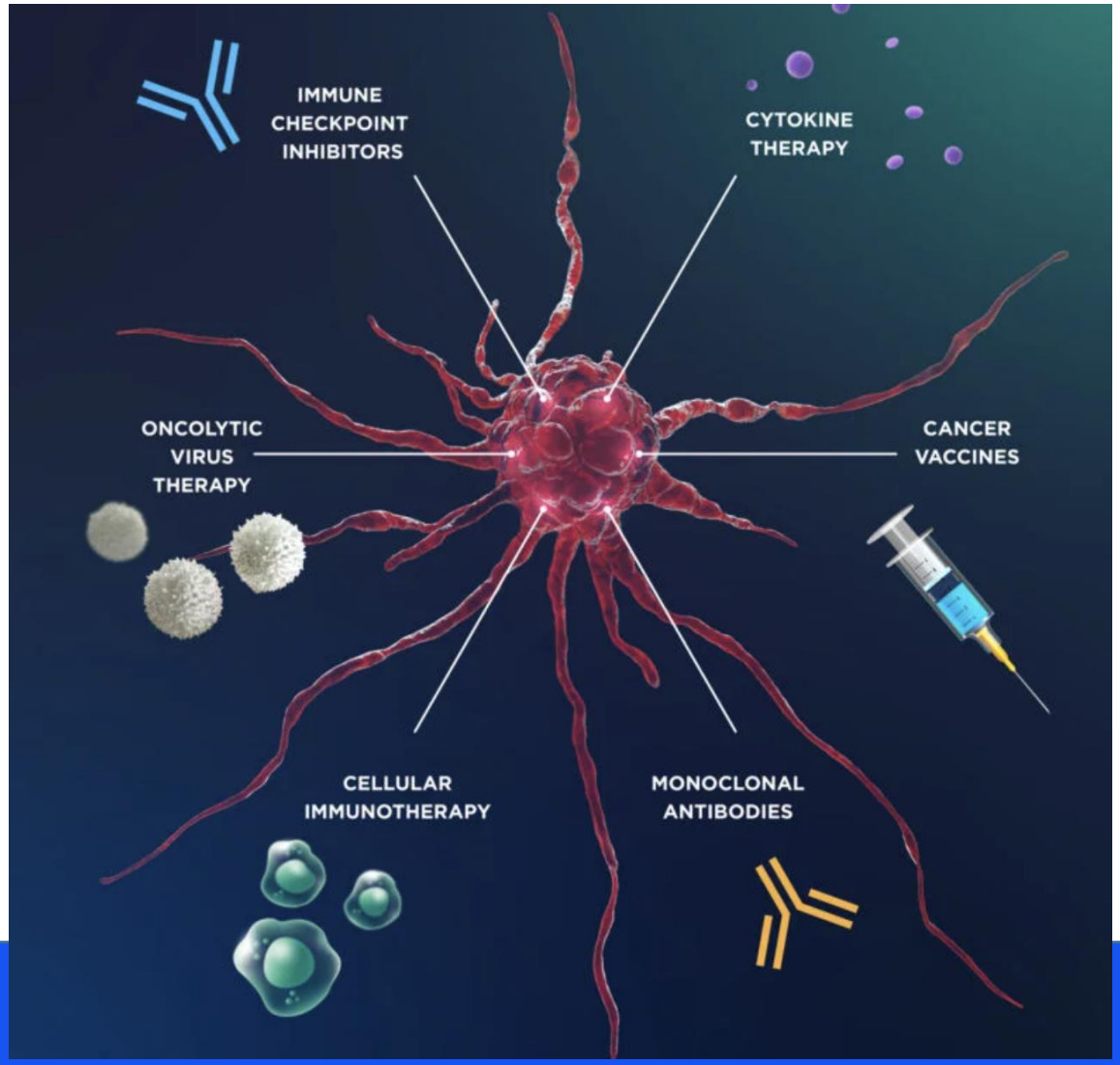
No. at Risk

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

Nobelprijs voor Geneeskunde 2018



Soorten immunotherapie



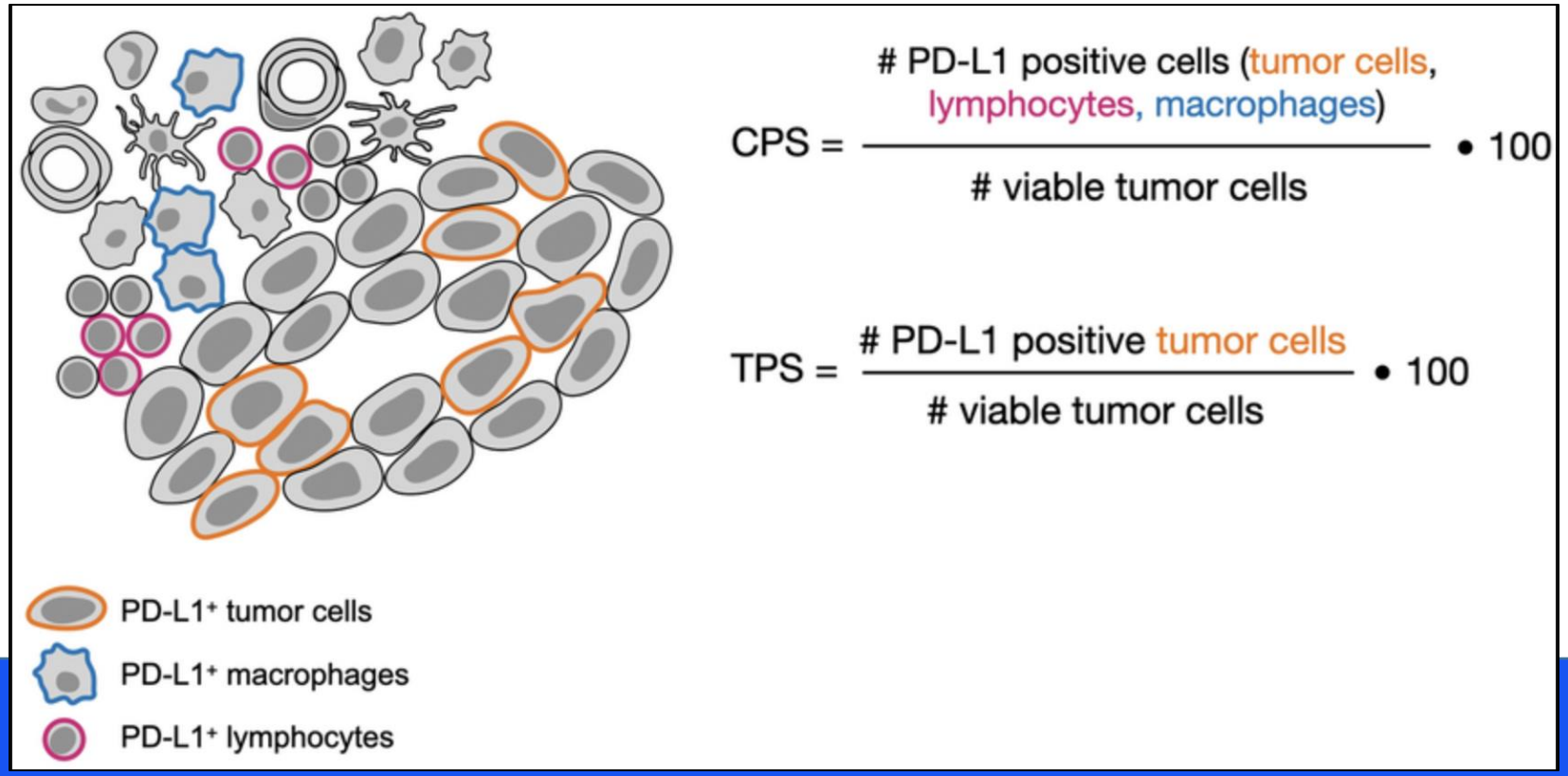
Toepassingen

Voorbeelden uit de kliniek

- Immune checkpoint inhibitors
  - Anti-PD-1
    - Pembrolizumab
    - Nivolumab
    - …
  - Anti-PD-L1
    - Durvalumab
    - Atezolizumab
    - …
  - Anti-CTLA-4
    - Ipilimumab
    - Tremelimumab

Voorbeelden uit de kliniek

- Immune checkpoint inhibitors
  - Niet voor iedereen!



Bill R, Faquin WC, Pai SI. Assessing PD-L1 Expression in Head and Neck Squamous Cell Carcinoma: Trials and Tribulations. *Head Neck Pathol.* 2023;17(4):969-975. doi:10.1007/s12105-023-01590-6

Voorbeelden uit de kliniek

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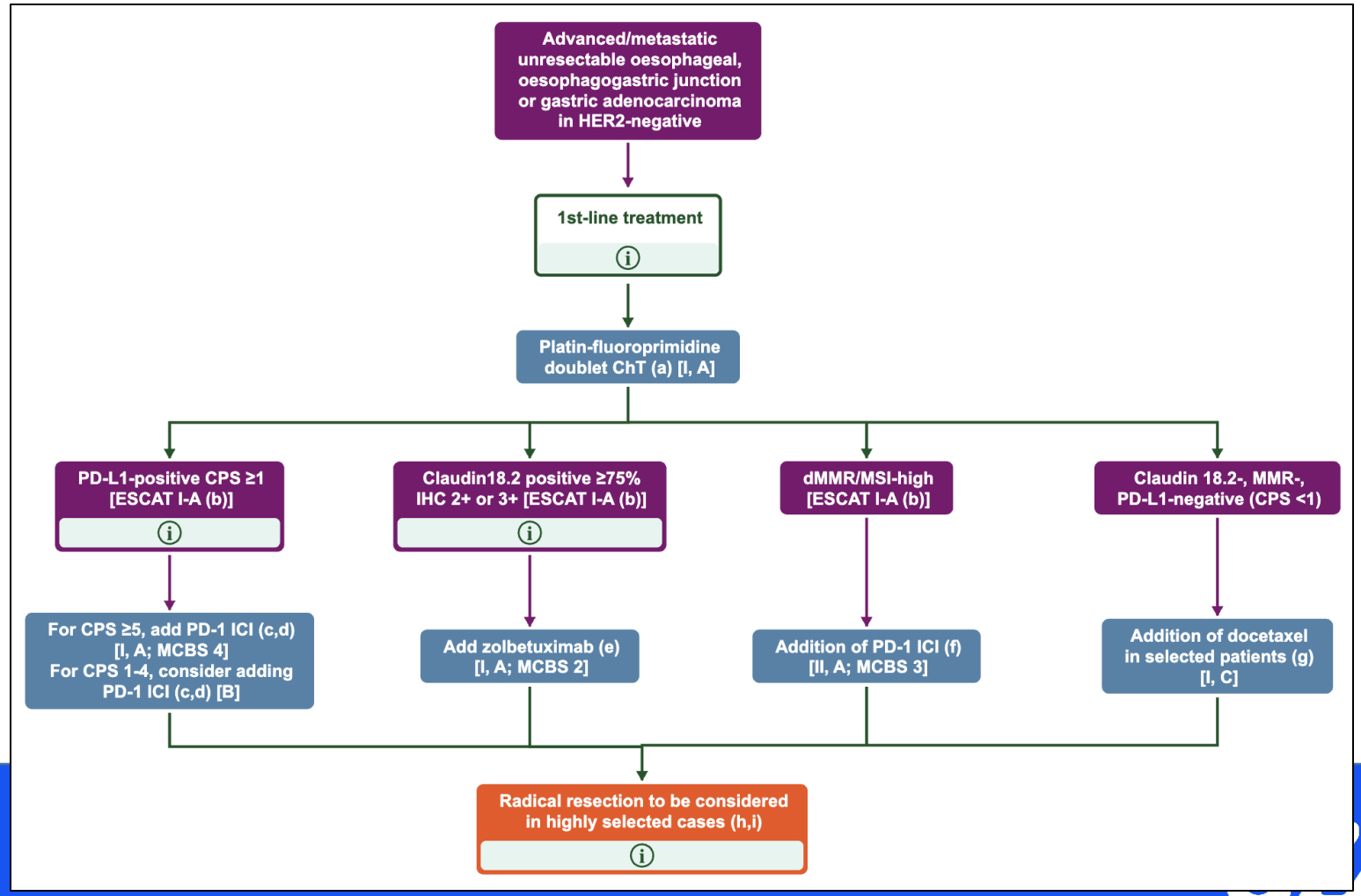

- ESMO Gastric cancer living guidelines.

Voorbeelden uit de kliniek

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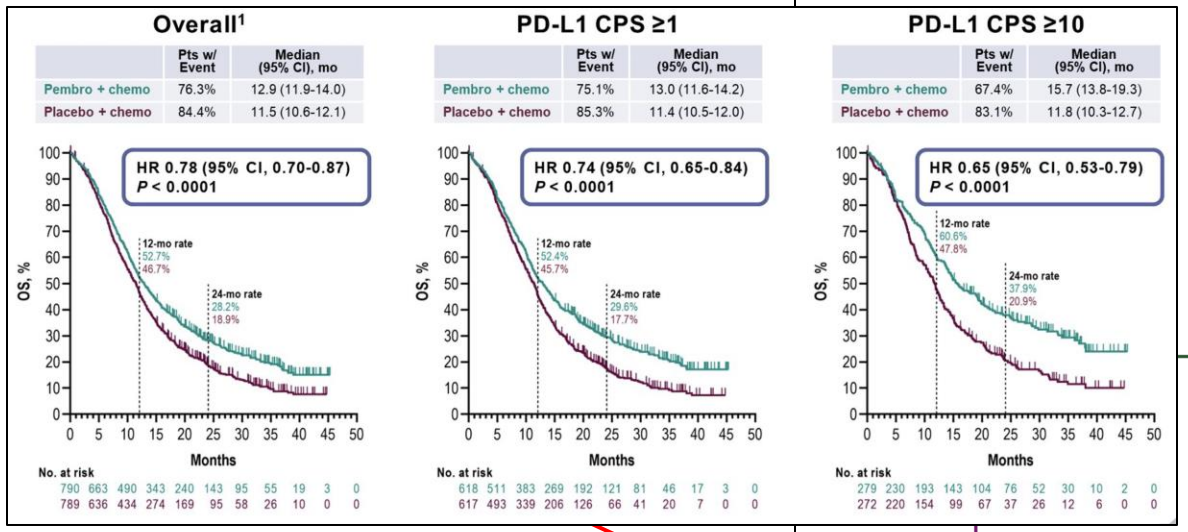
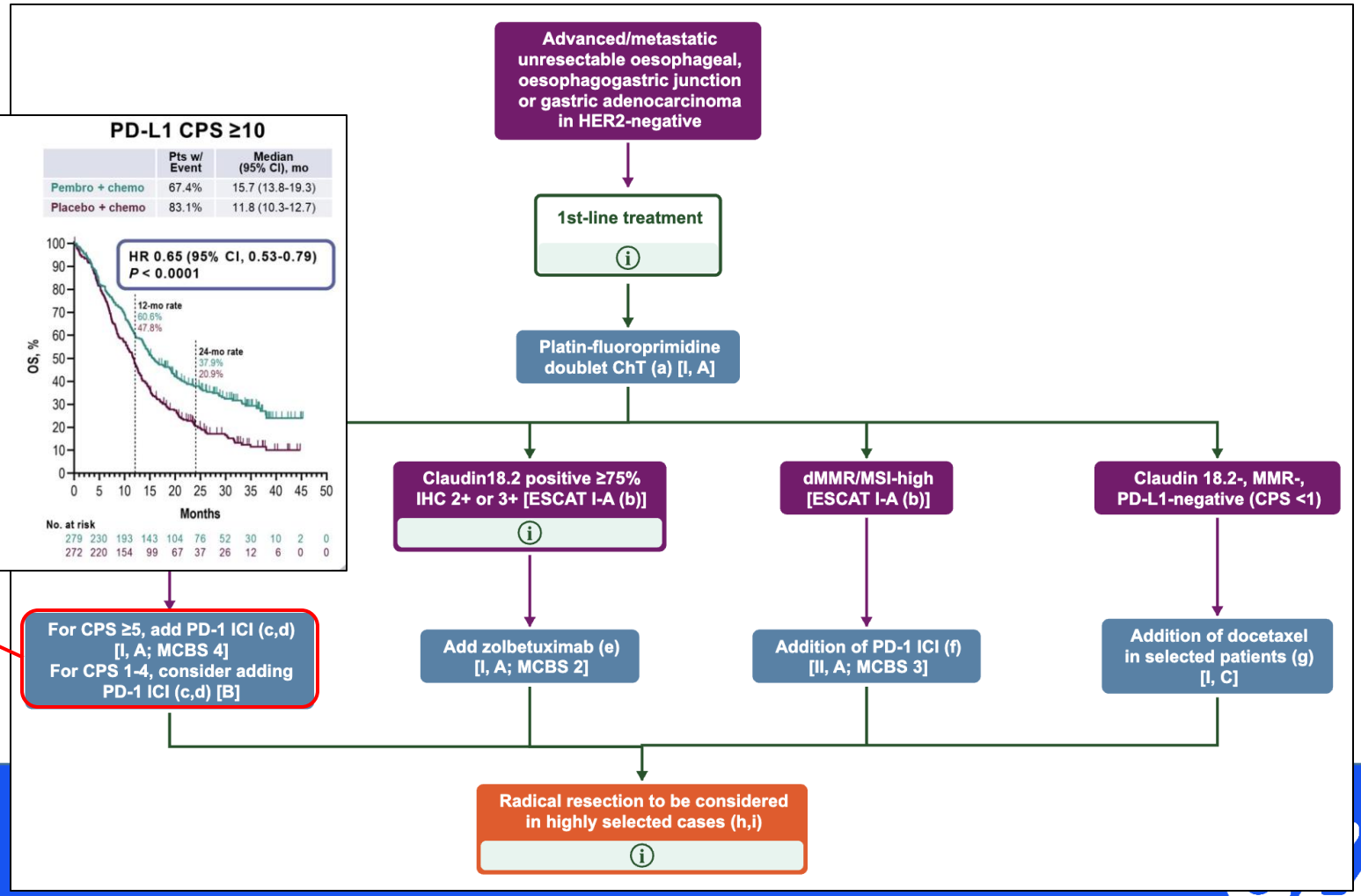
  - Niet voor iedereen!



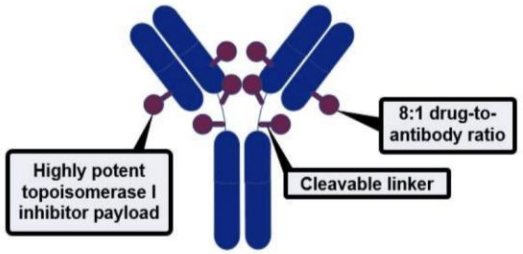
KEYNOTE-859 trial

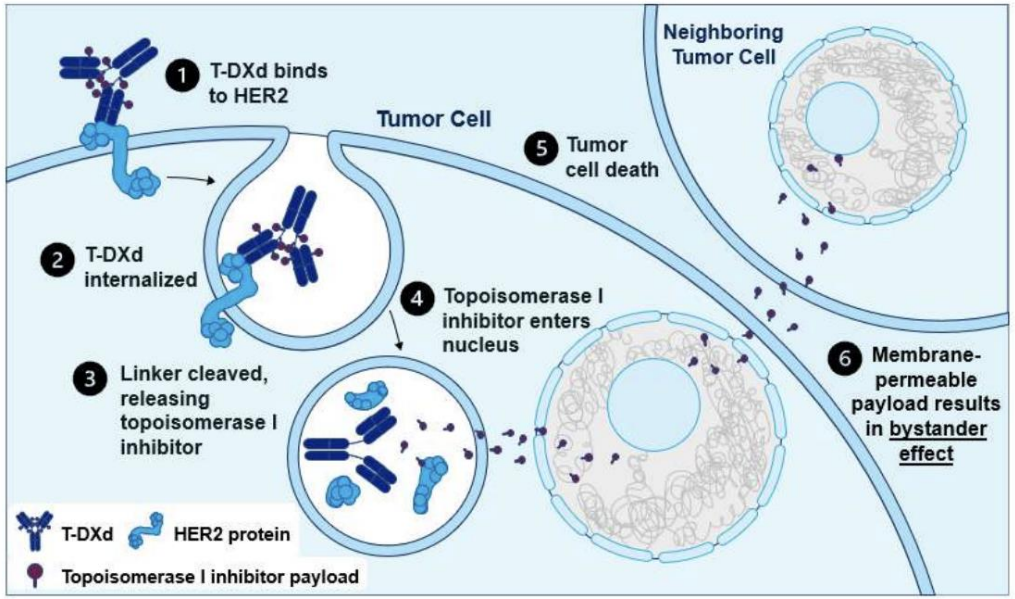


- ESMO Gastric cancer living guidelines.
- Rha S.Y., et al. Ann Oncol. 2025

Voorbeelden uit de kliniek

- Monoclonal antibodies & antibody-drug conjugates (ADC)
  - Anti-HER2
    - Trastuzumab
    - Trastuzumab-deruxtecan
    - …
  - Anti-VEGF
    - Bevacizumab
    - Ramucirumab
    - …
  - Anti-EGFR
    - Panitumumab
    - Cetuximab
    - …
  - …

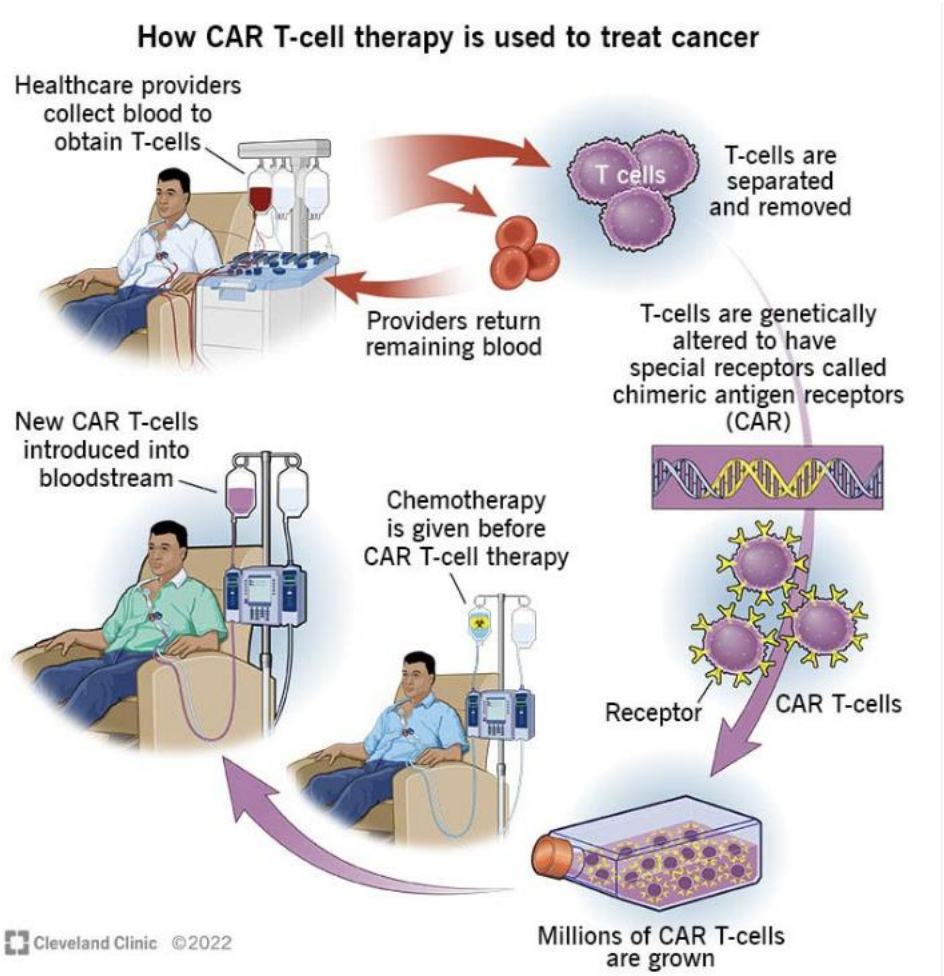




- Modi S., et al. J Clin Oncol. 2020

Voorbeelden uit de kliniek

- Cellular immunotherapy
  - Chimeric Antigen Receptors (CAR) - T cells
- Cancer vaccines
  - Bacillus Calmette-Guérin (BCG)
- Oncolytic virus therapy
  - Talimogene laherparepvec (T-VEC)
- Cytokine therapy
  - Interleukin 2 (IL-2)



Bijwerkingen

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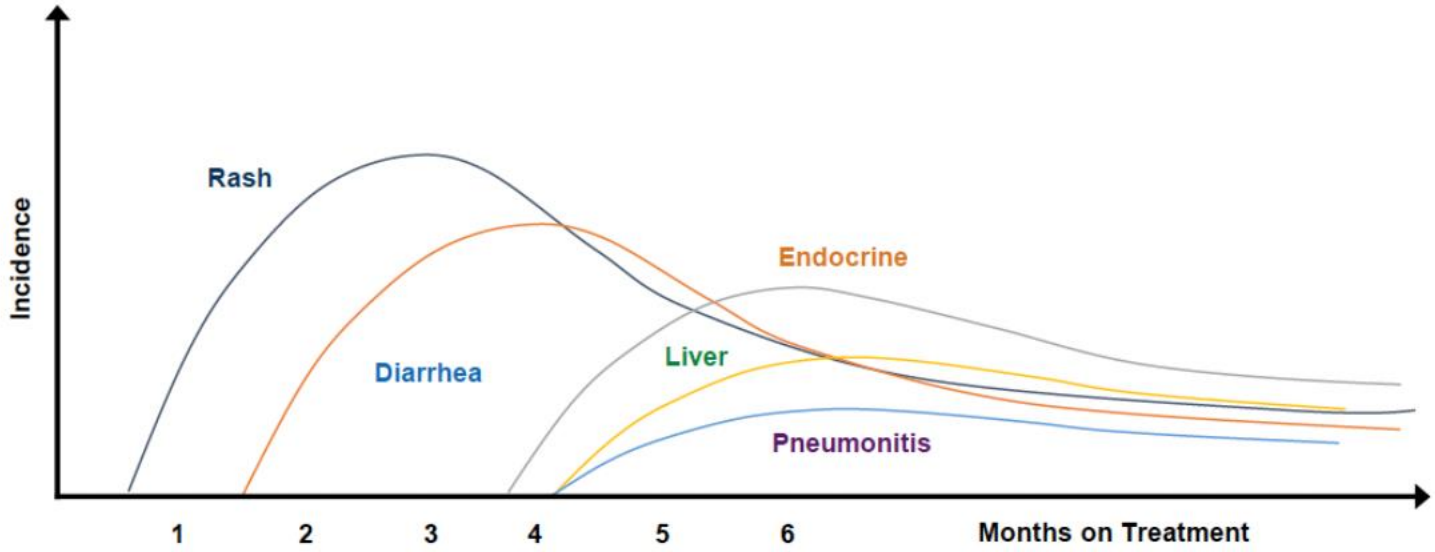
- Meestal mild tot matig
- **MAAR!**



- Oncodaily
- Dolladill et al. JAMA Oncol. 2020

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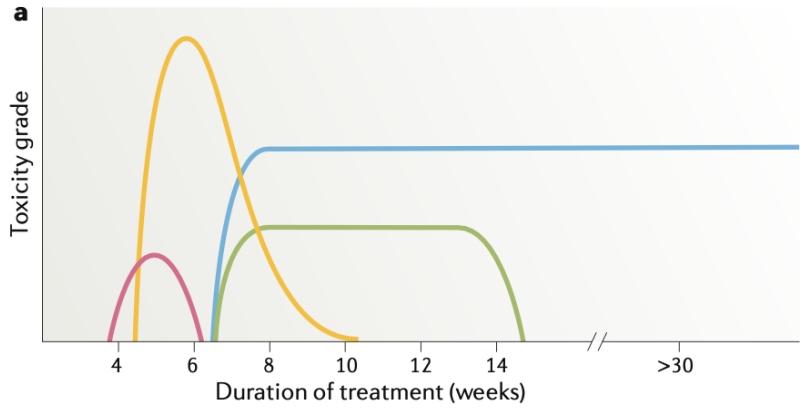
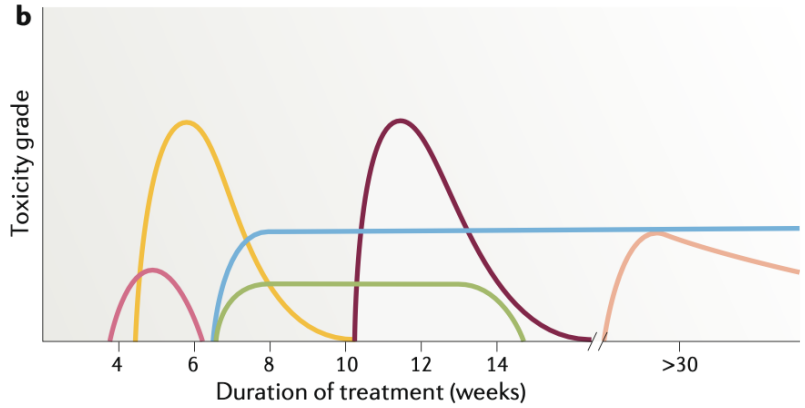
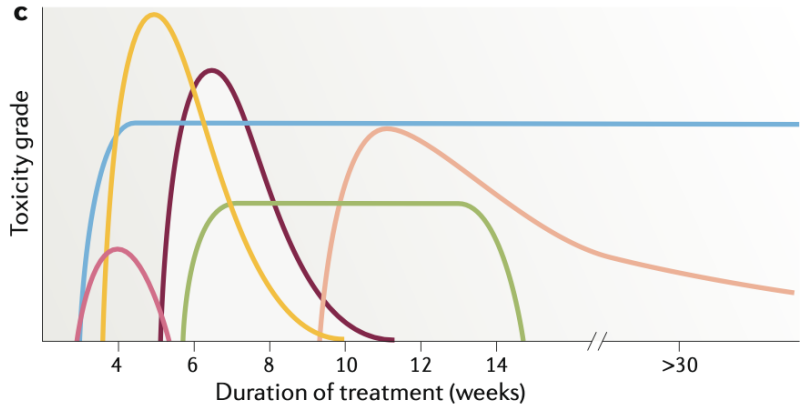
Anti-CTLA-4

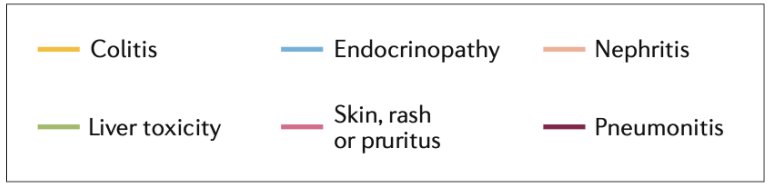


Anti-PD-1/PD-L1



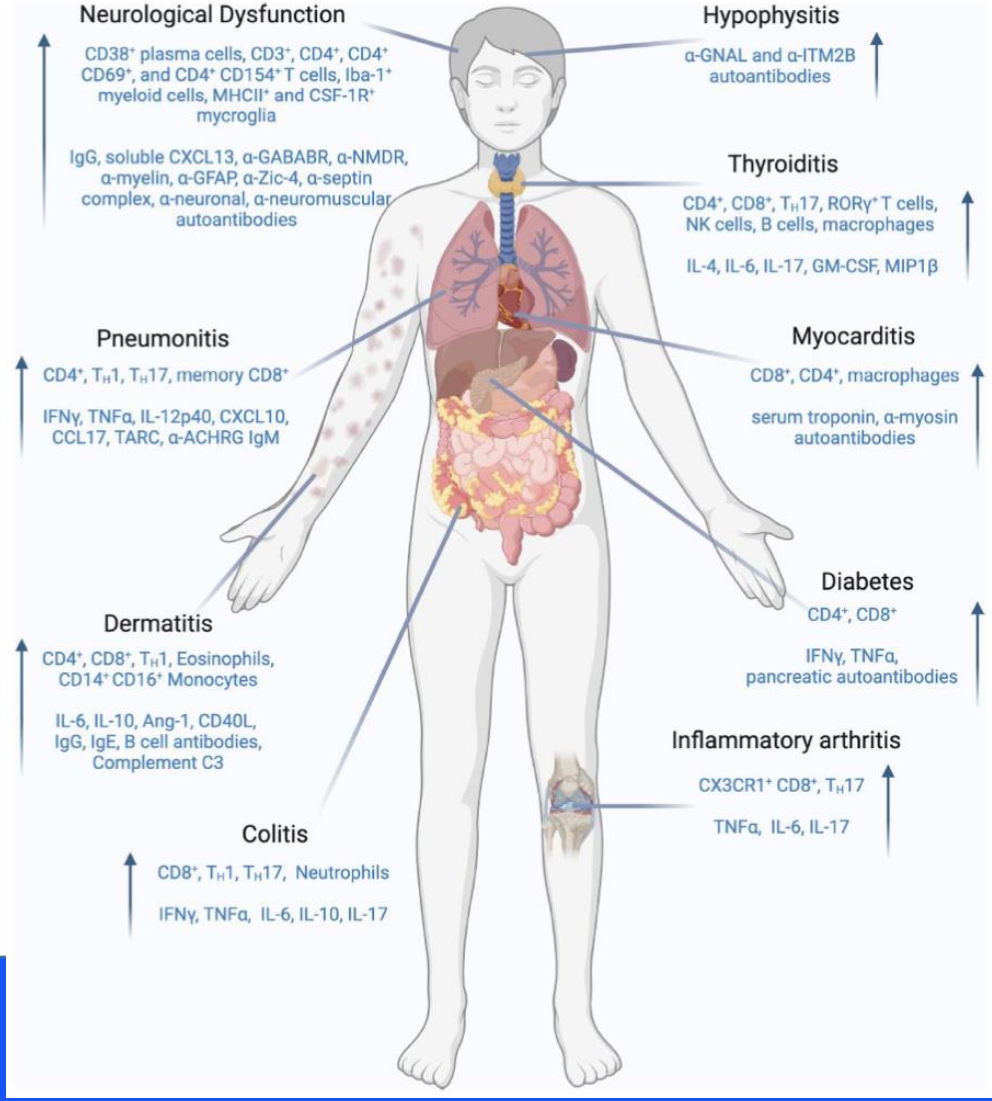
Anti-CTLA-4
+
Anti-PD-1/PD-L1





- Oncodaily
- Martins F. et al. Nat Rev Clin Oncol. 2019

Pathofysiologie onduidelijk



- Keam et al. Frontiers in Immunology 2024

Take home messages

- Revolutie – still ongoing – in de oncologie
  - Indicaties ↗
    - Neo-adjuvant, adjuvant, onderhoudsbehandeling, …
- Soms spectaculaire en duurzame respons, maar geen remedie “for all”
- Niet voor alle kankerpatiënten
  - Belang van biomerkers ↗
- Goede tolerantie maar kans op (ernstige) bijwerkingen!

Dank voor u aandacht!

Vragen?