

AmphiA

Ontwikkelingen immuuntherapie

C. Steendam

C. van der Leest



Inhoud

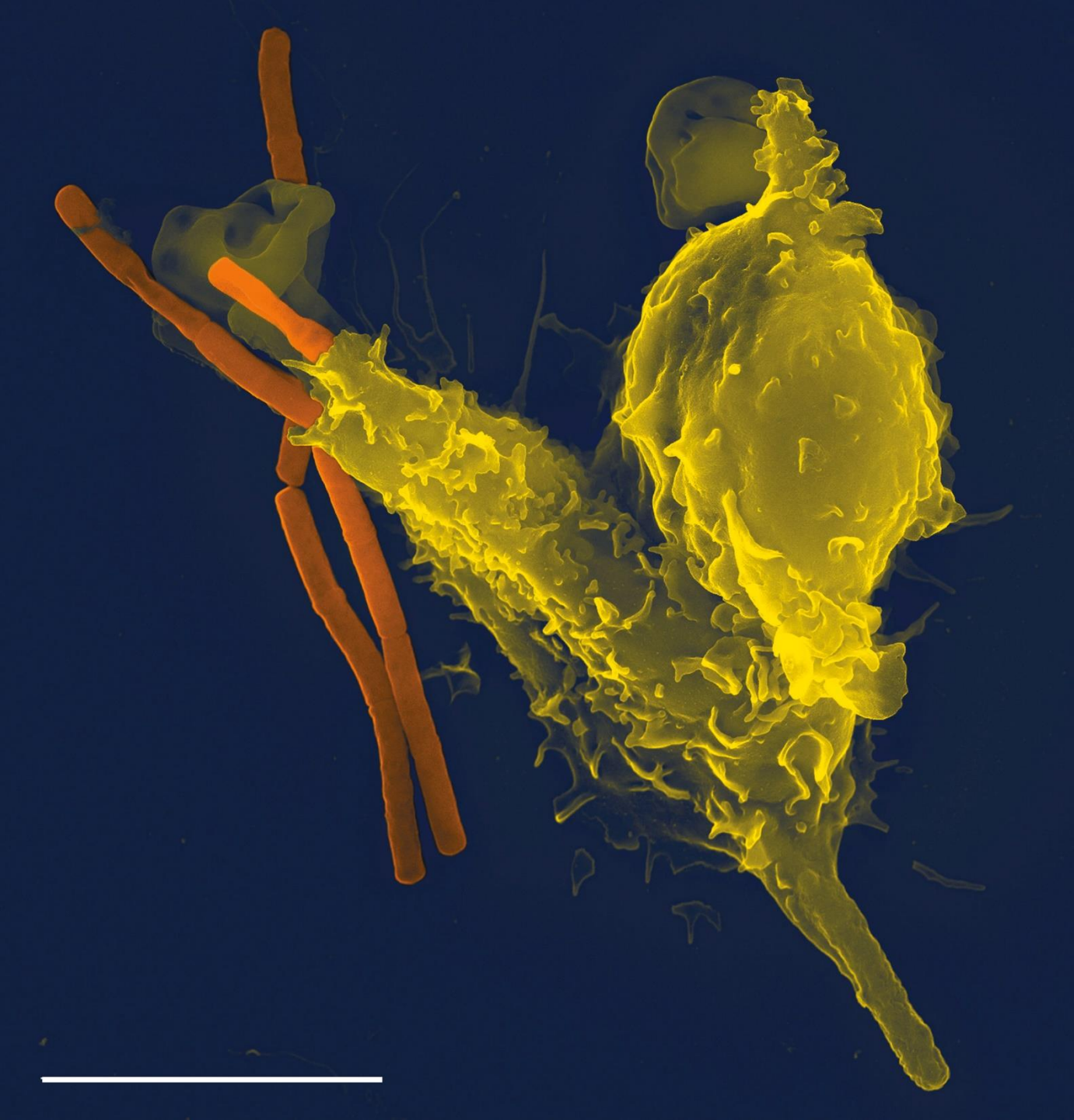
- Het immuunsysteem
- De kanker immuniteit cyclus
- Checkpoint remmers
 - Niet-kleincellige longkanker
 - Kleincellige longkanker (SCLC)
 - Longvlieskanker (mesothelioom)
- Ontwikkelingen in onderzoeksfase



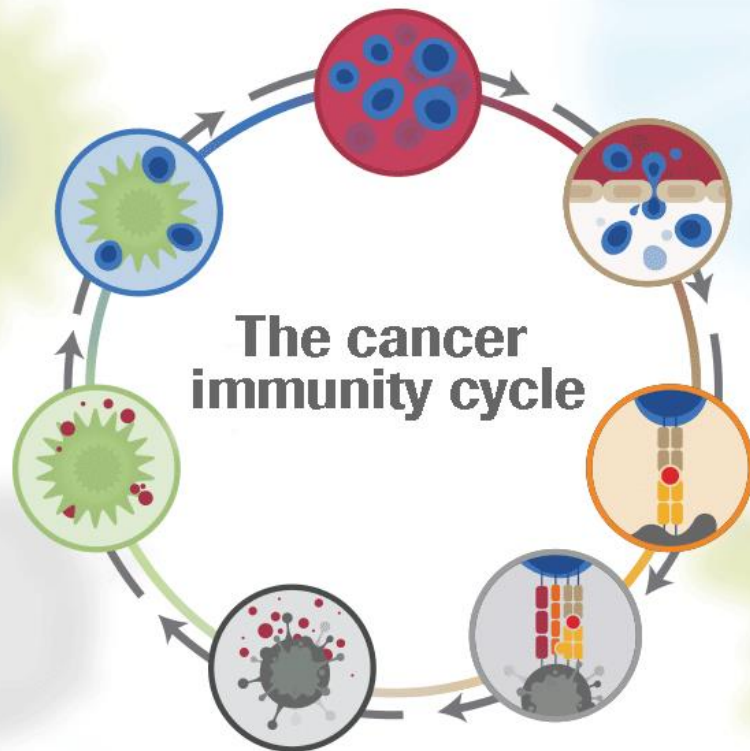
Het immuunsysteem

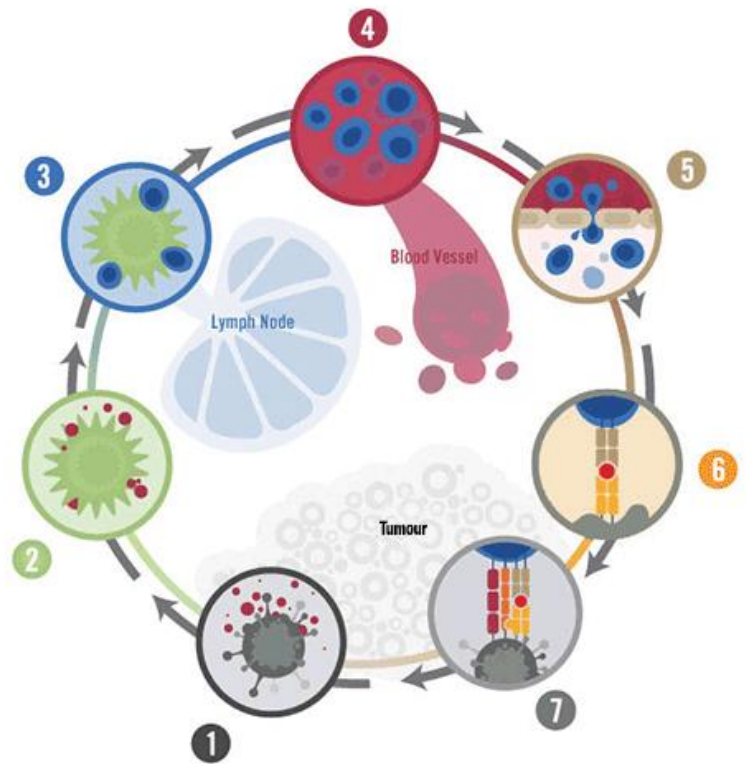
- Verdedigingssysteem tegen externe en interne ziekteverwekkers
- 1) Aangeboren deel (aspecifiek)
- 2) Verworven deel (specifiek, opbouw geheugen)





Chen & Mellman kanker – immuniteit cyclus

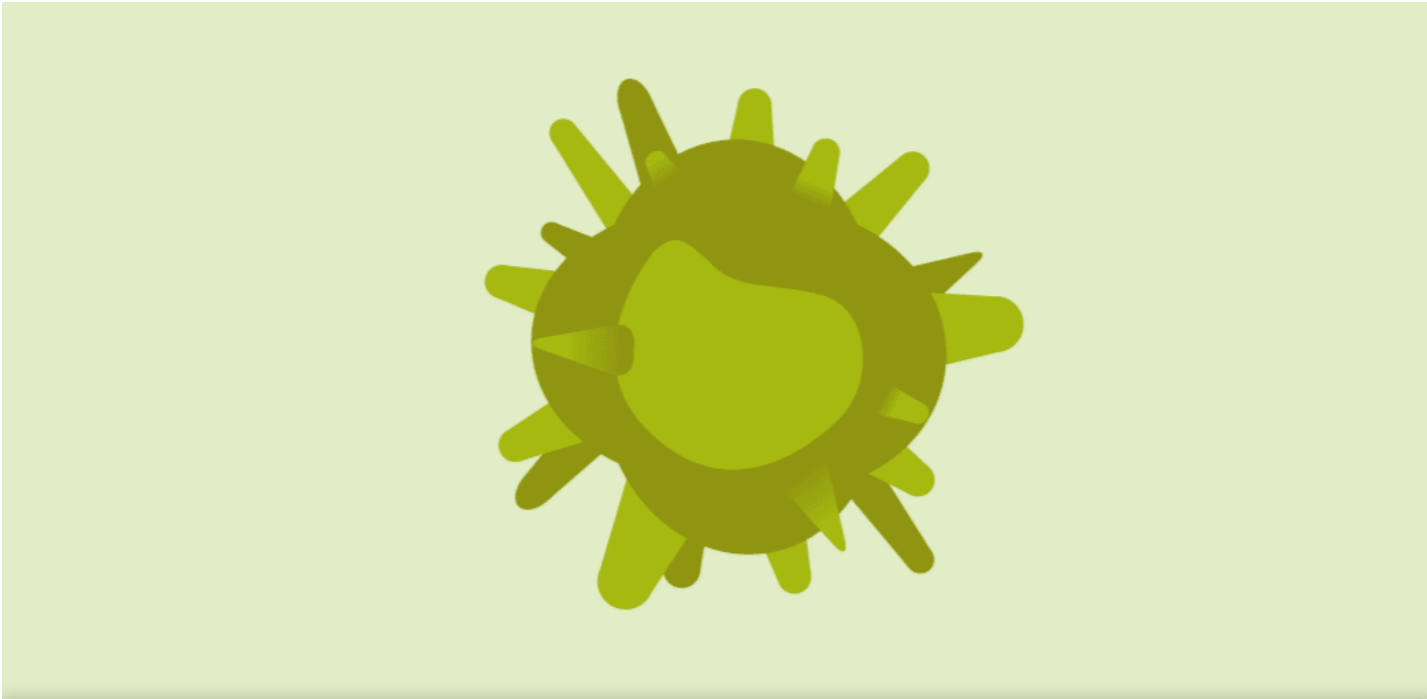






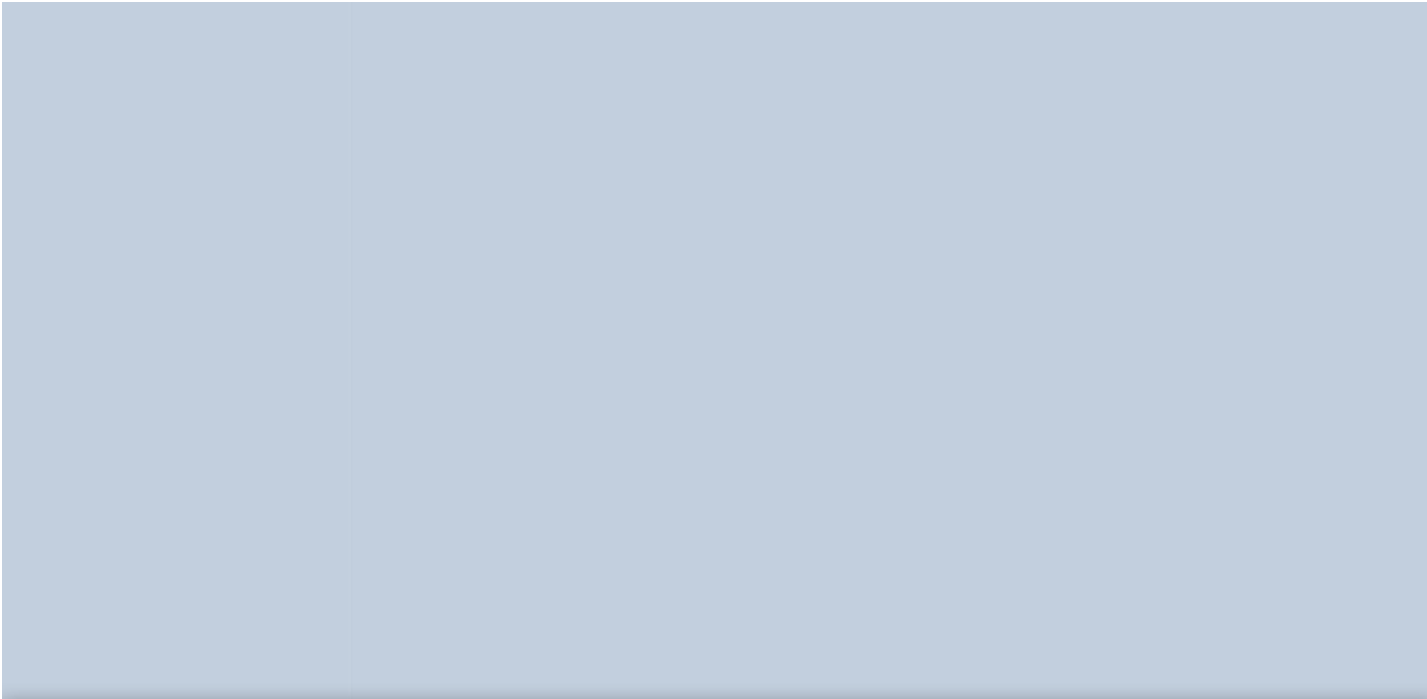
In step 1, mutations in cancer cells cause the release of substances called 'antigens' that show that cancer cells are different from normal cells. This allows the immune system to recognise them.





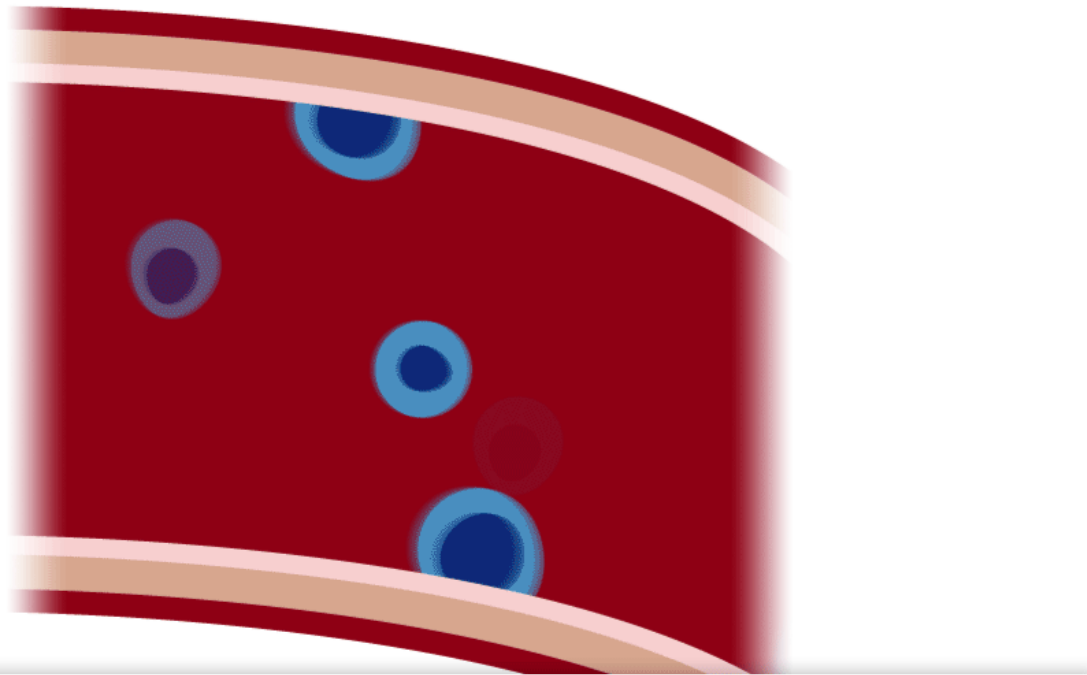
In step 2, immune cells that specialise in finding antigens and take them to T cells, located in the lymph nodes. Immunotherapy can boost immunity at this step and others.





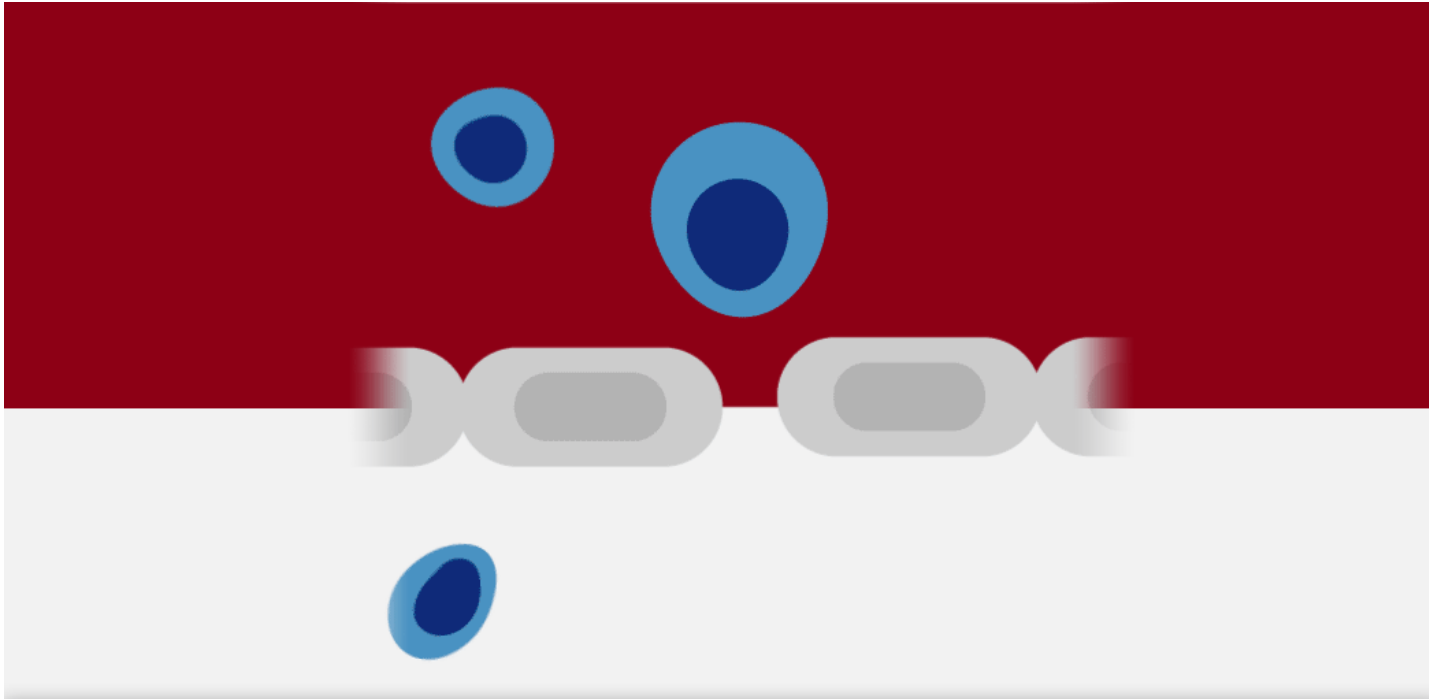
In step 3, T cells become 'primed' or 'activated' by these foreign antigens, which begins the immune response against cancer cells.





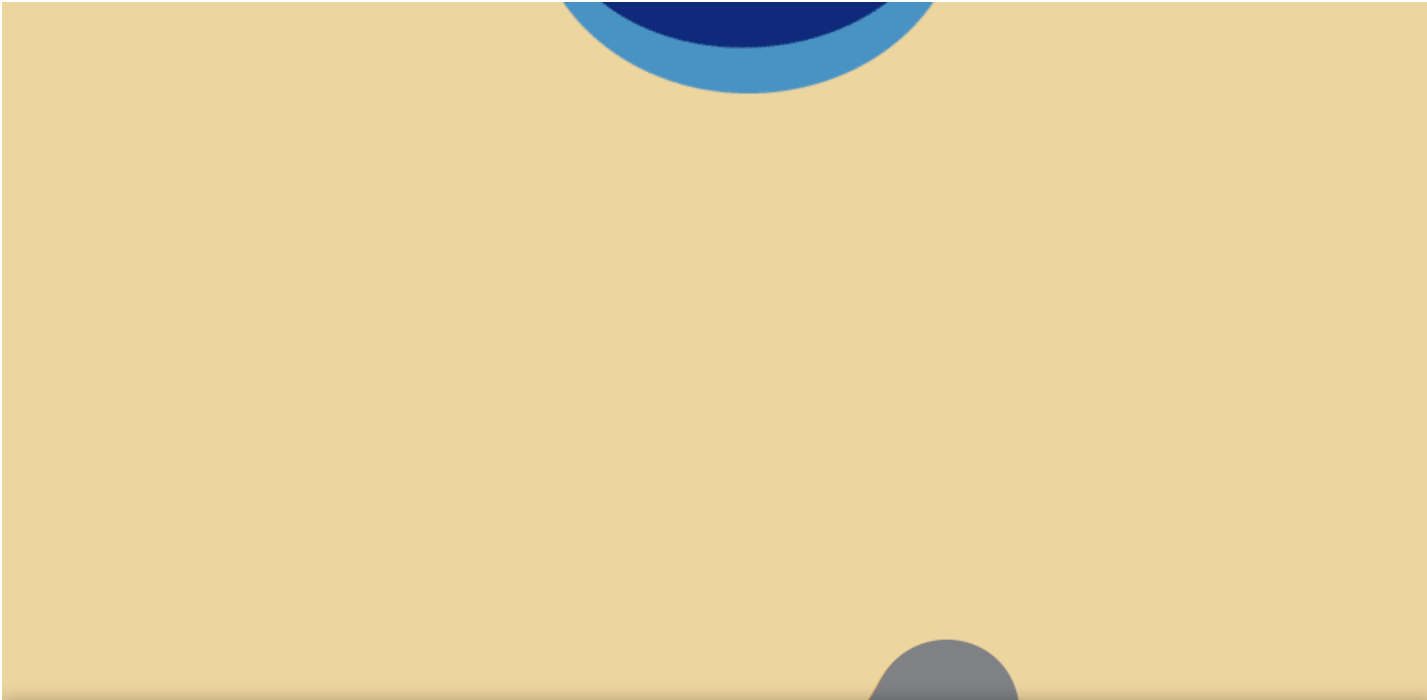
In step 4, activated T cells travel through blood vessels towards the location of the tumour.





In step 5, T cells reach the cancer cells and 'infiltrate' the tumour in order to attack it.





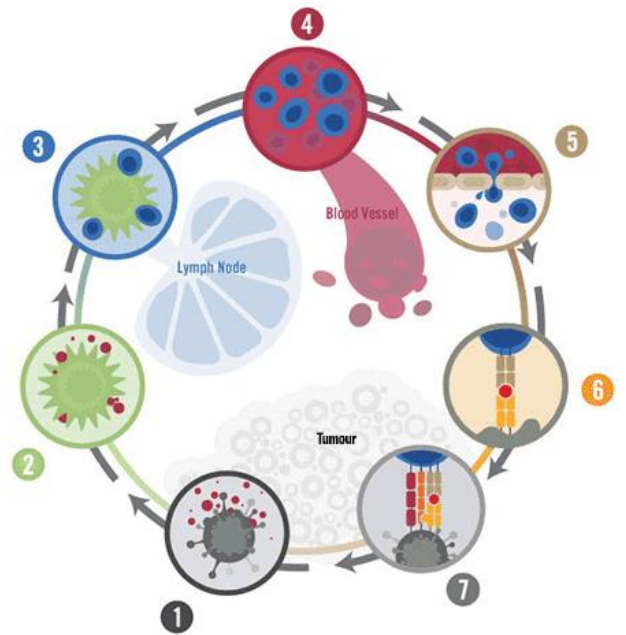
In step 6, T cells are able to recognise foreign cancer cells based on the antigens they released earlier.





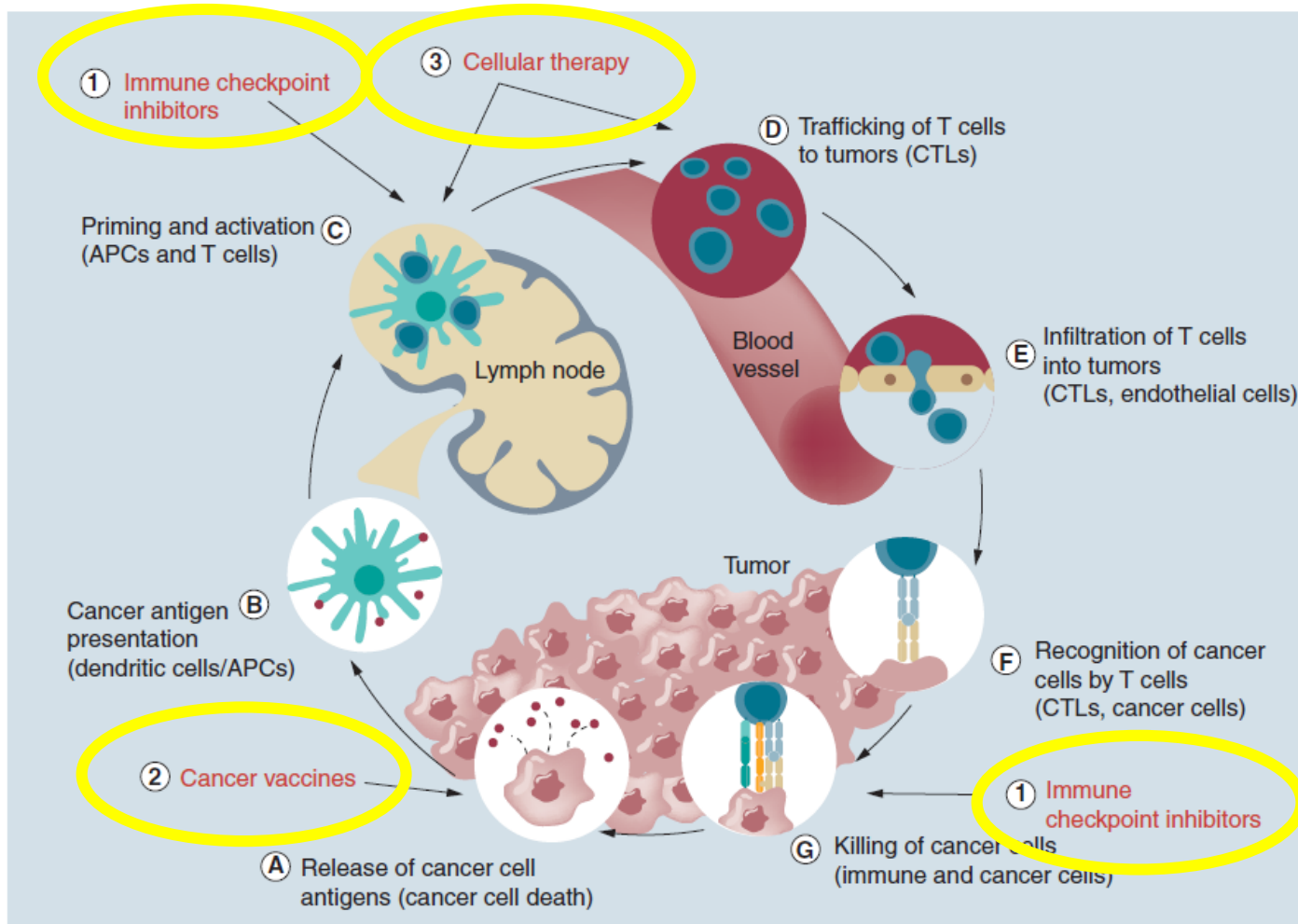
In step 7, T cells destroy cancer cells by activating a series of steps that lead to cell death. This is where immunotherapy can effect PD-L1 or PD-1, enhancing immunity.





Killing cancer cells releases more antigens and the cancer-immunity cycle starts all over again.





Checkpoint remmers



Checkpoint remmers

- Controle momenten in immuunrespons
- Check of alles naar behoren loopt
- Mogelijkheid tot remming reactie



Immune checkpoints

Immunotherapeutic strategies in NSCLC: the present & the future Review

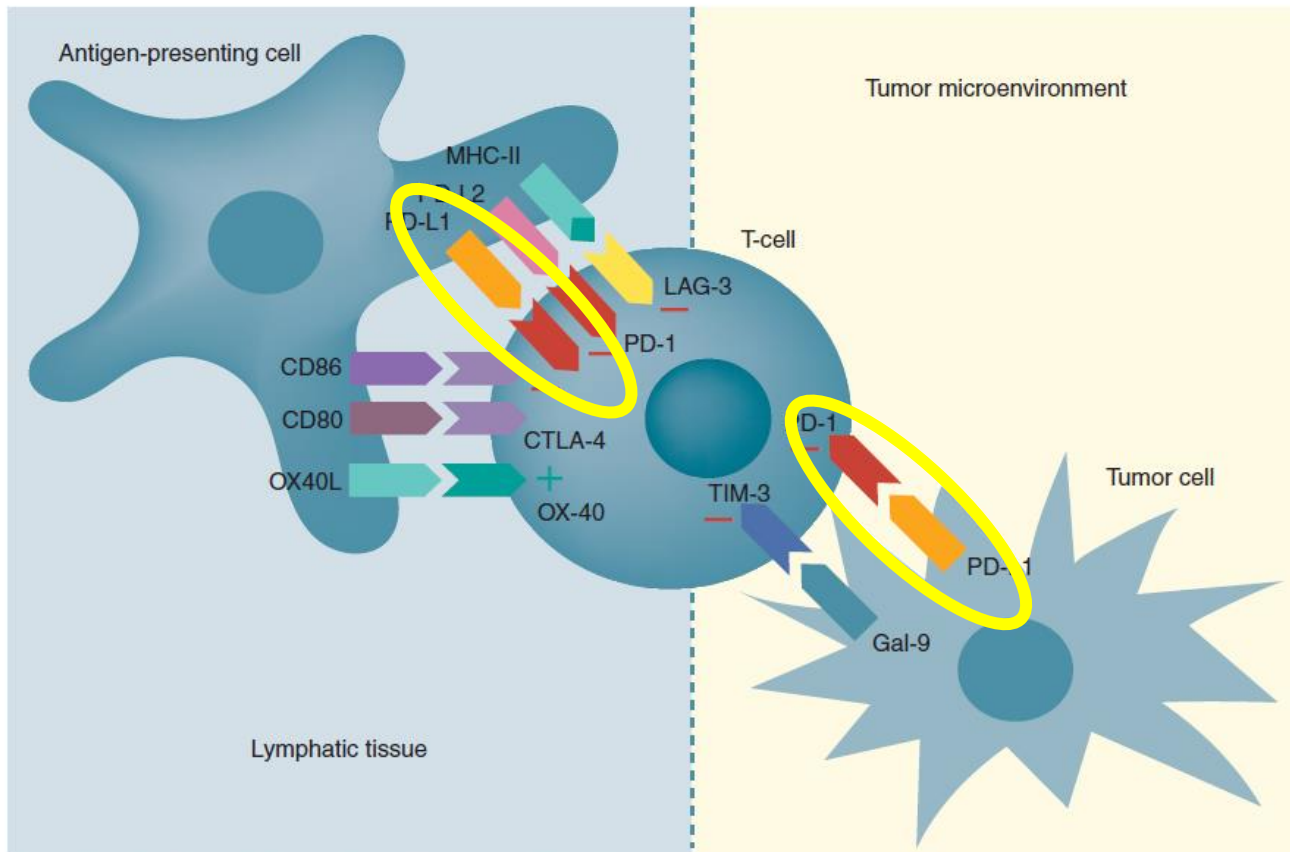
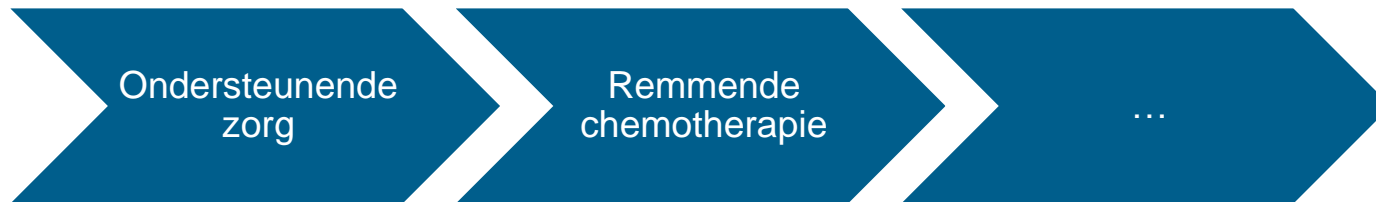


Figure 2. Overview of the relevant immune checkpoints.



Behandeling stadium IV NSCLC tot 2015



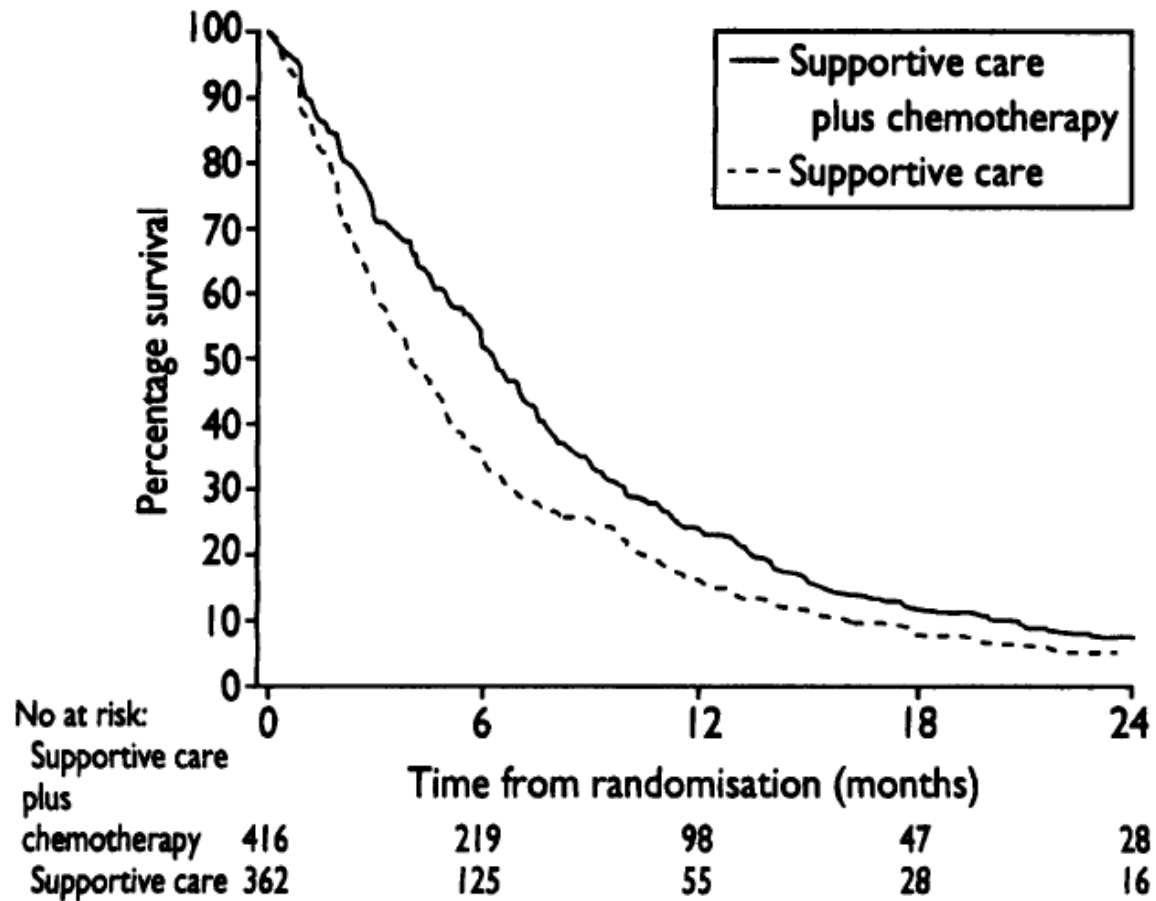


FIG 8—Survival in trials of supportive care versus supportive care plus chemotherapy (only trials using regimens based on cisplatin)



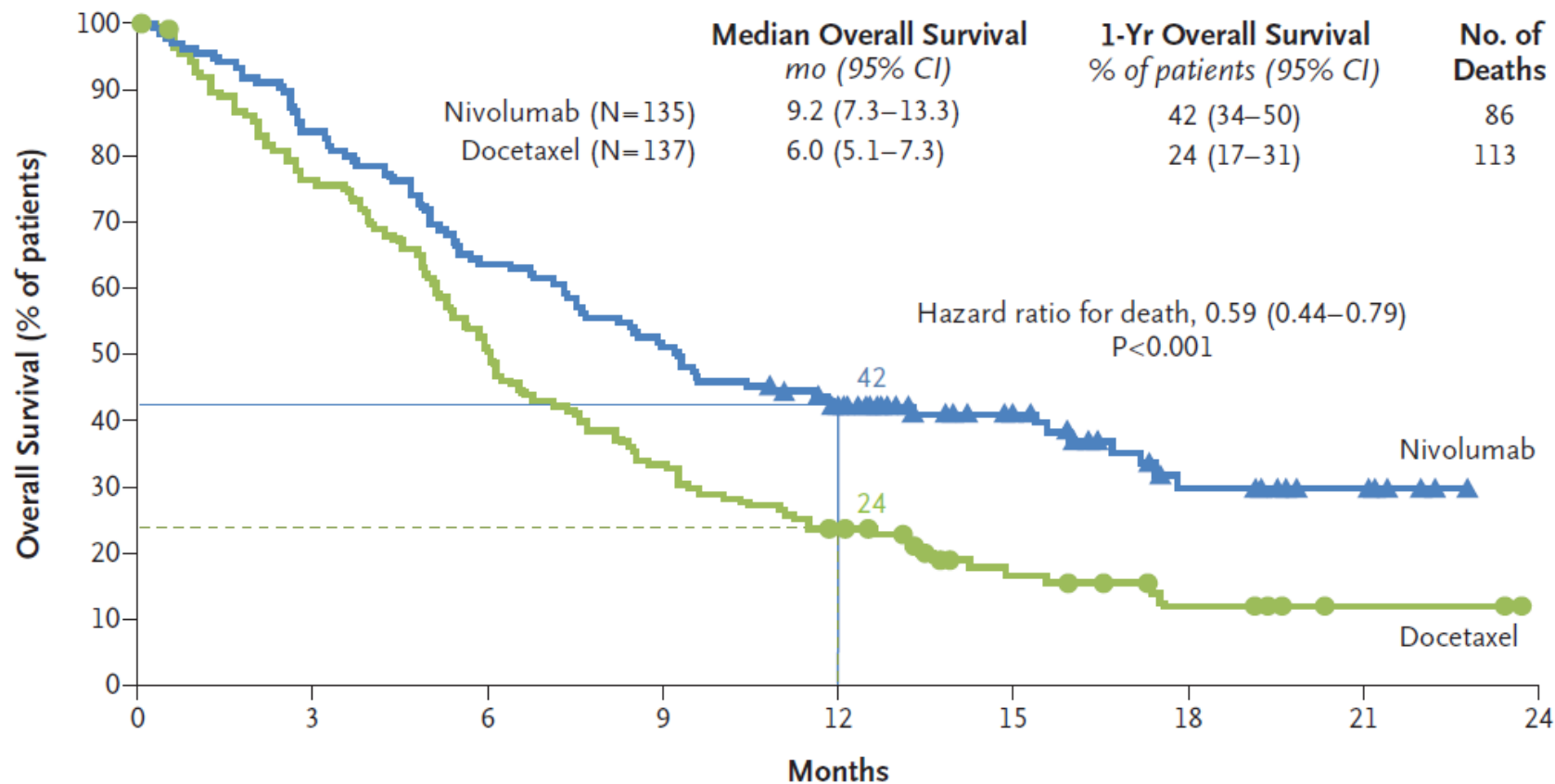
Stadium IV NSCLC

(teruggekeerde lokaal gevorderde/uitgezaaide longkanker)

- Tot 2015: remmende platinum combinatie chemotherapie, als het nadien terugkwam eventueel nog een keer remmende docetaxel chemotherapie
- In 2015: resultaten onderzoek met nivolumab vergeleken met docetaxel chemotherapie bij patiënten bij wie de kanker weer terug kwam na de eerste platinum combinatie chemotherapie



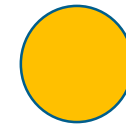
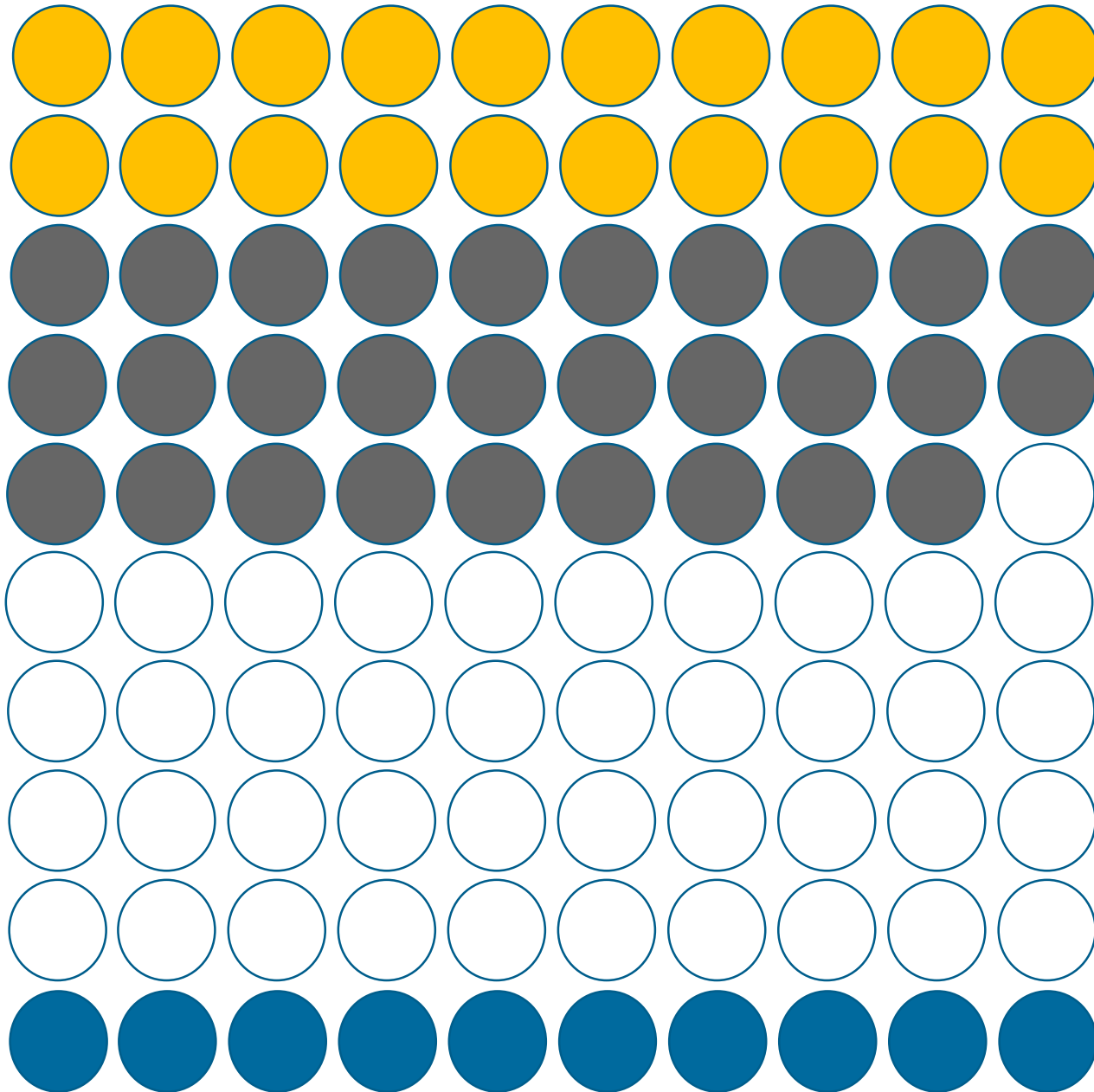
Nivolumab 2015: placeiselcelcarcinoom



No. at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

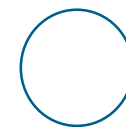




Afname van de tumor



Tumor blijft stabiel

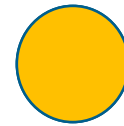
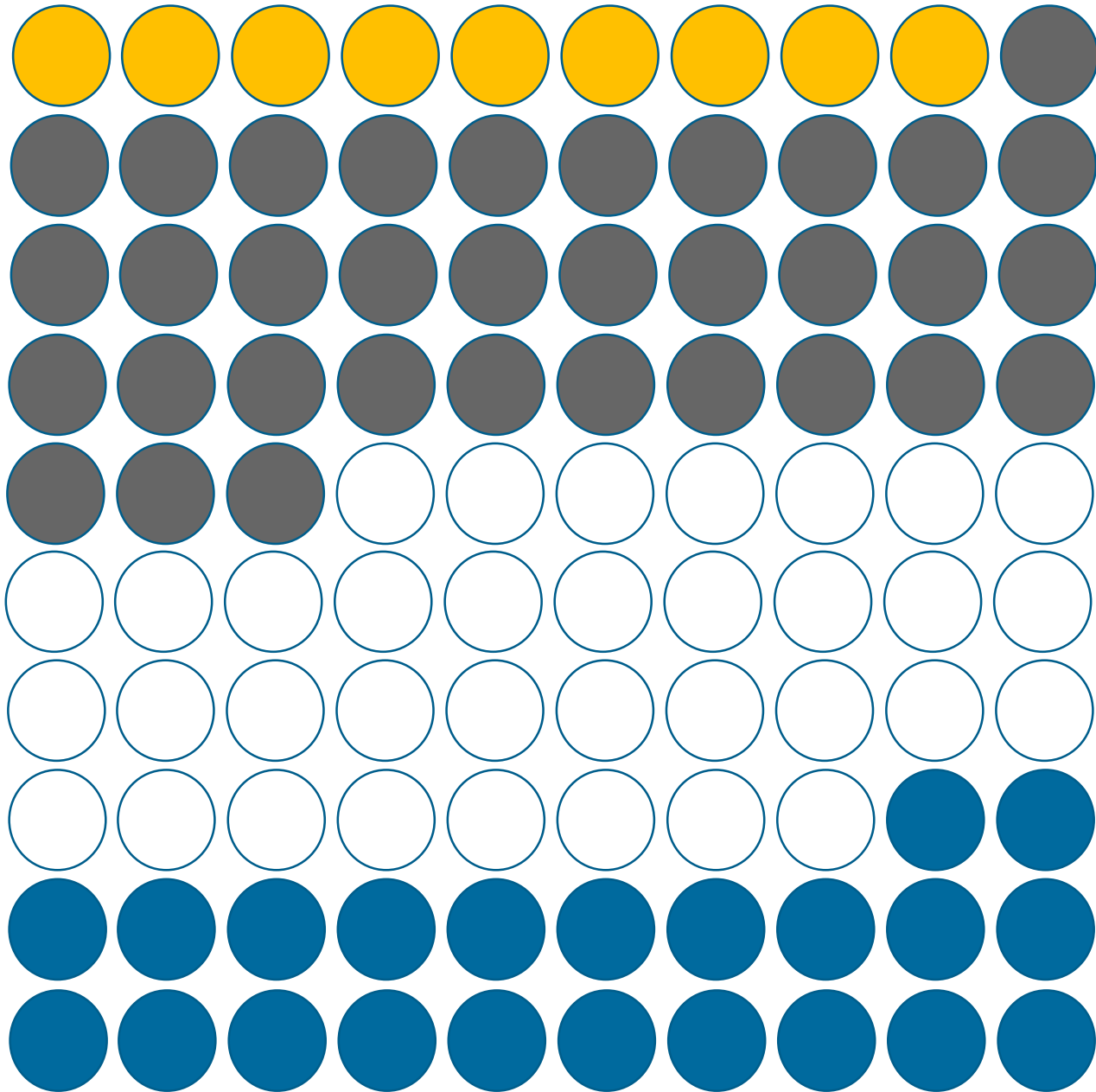


Tumor groeit door



Onduidelijk

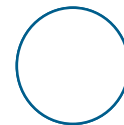




Afname van de tumor



Tumor blijft stabiel



Tumor groeit door

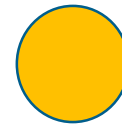
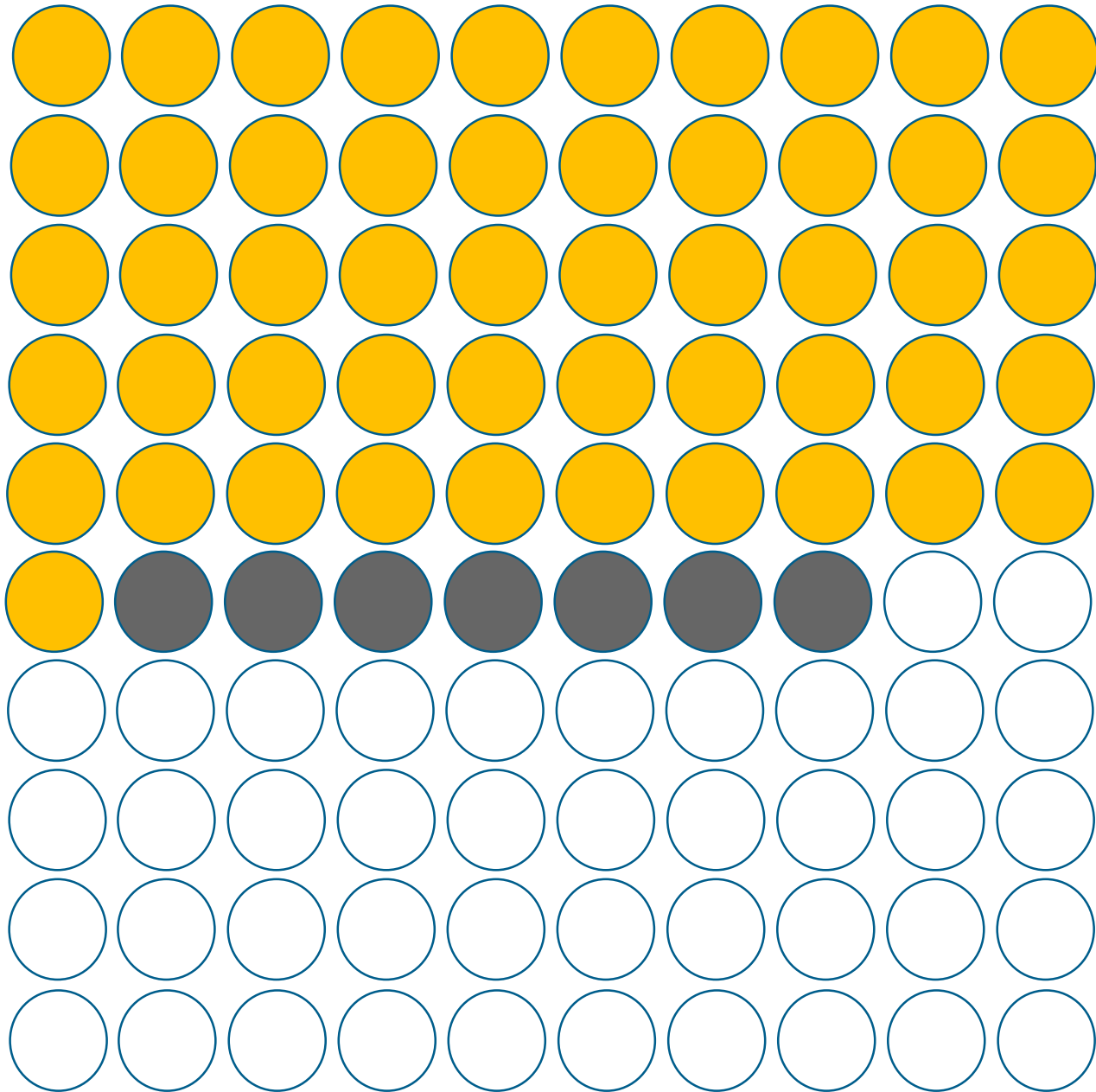


Onduidelijk

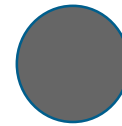


Bijwerkingen

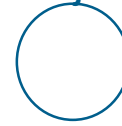




Milde bijwerkingen

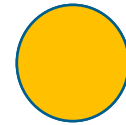
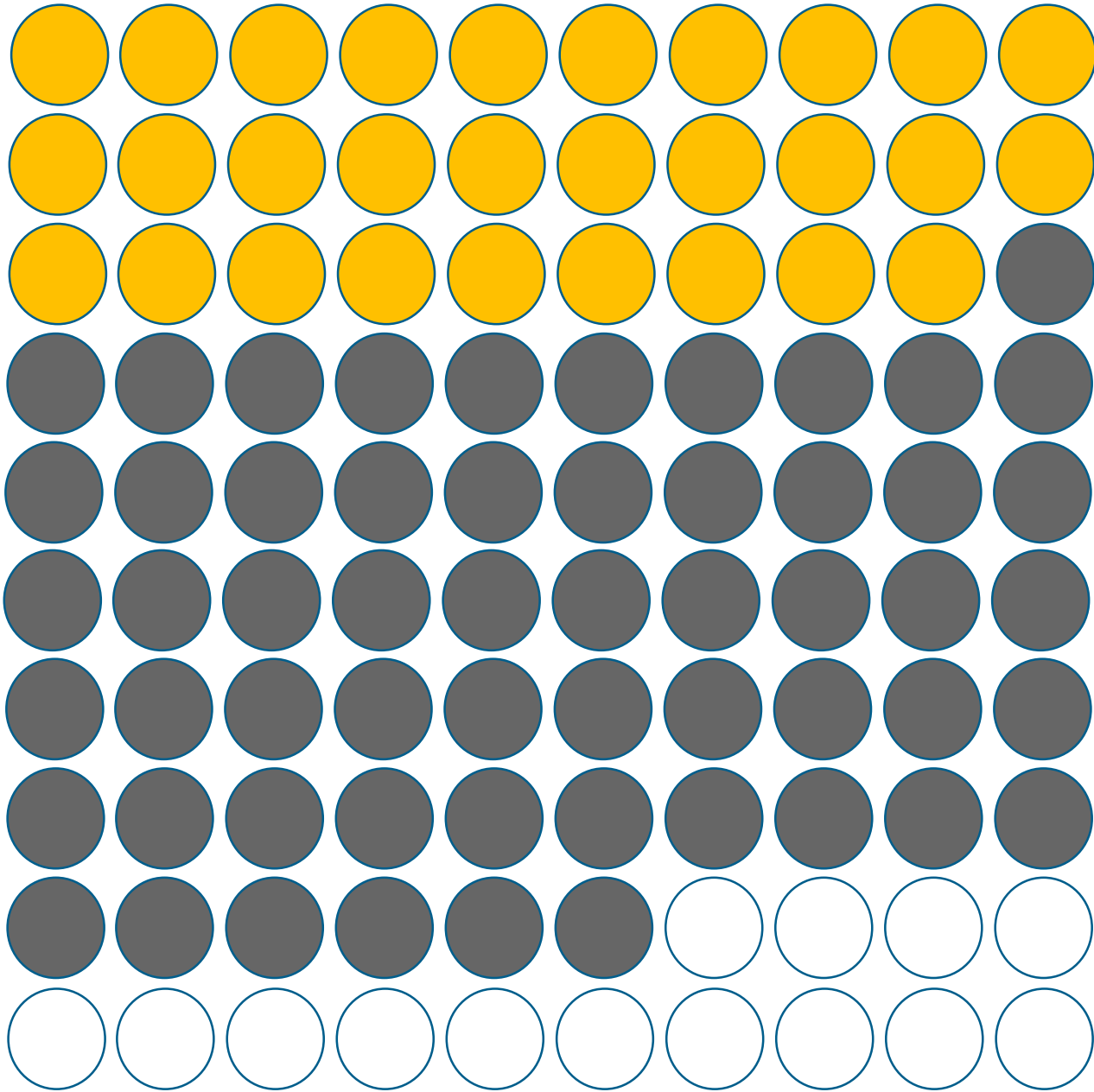


Ernstige
bijwerkingen

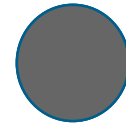


Geen bijwerkingen

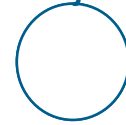




Milde bijwerkingen



Ernstige
bijwerkingen



Geen bijwerkingen



Uitkomsten onderzoek nivolumab in tweede lijn

- Langere tijd zonder tumorgroei
- Gemiddeld langere overleving
- Minder ernstige bijwerkingen

- → registratie en verzoek tot vergoeding
- → eerste 12 immuuntherapie centra in NL starten met nivolumab bij longkanker

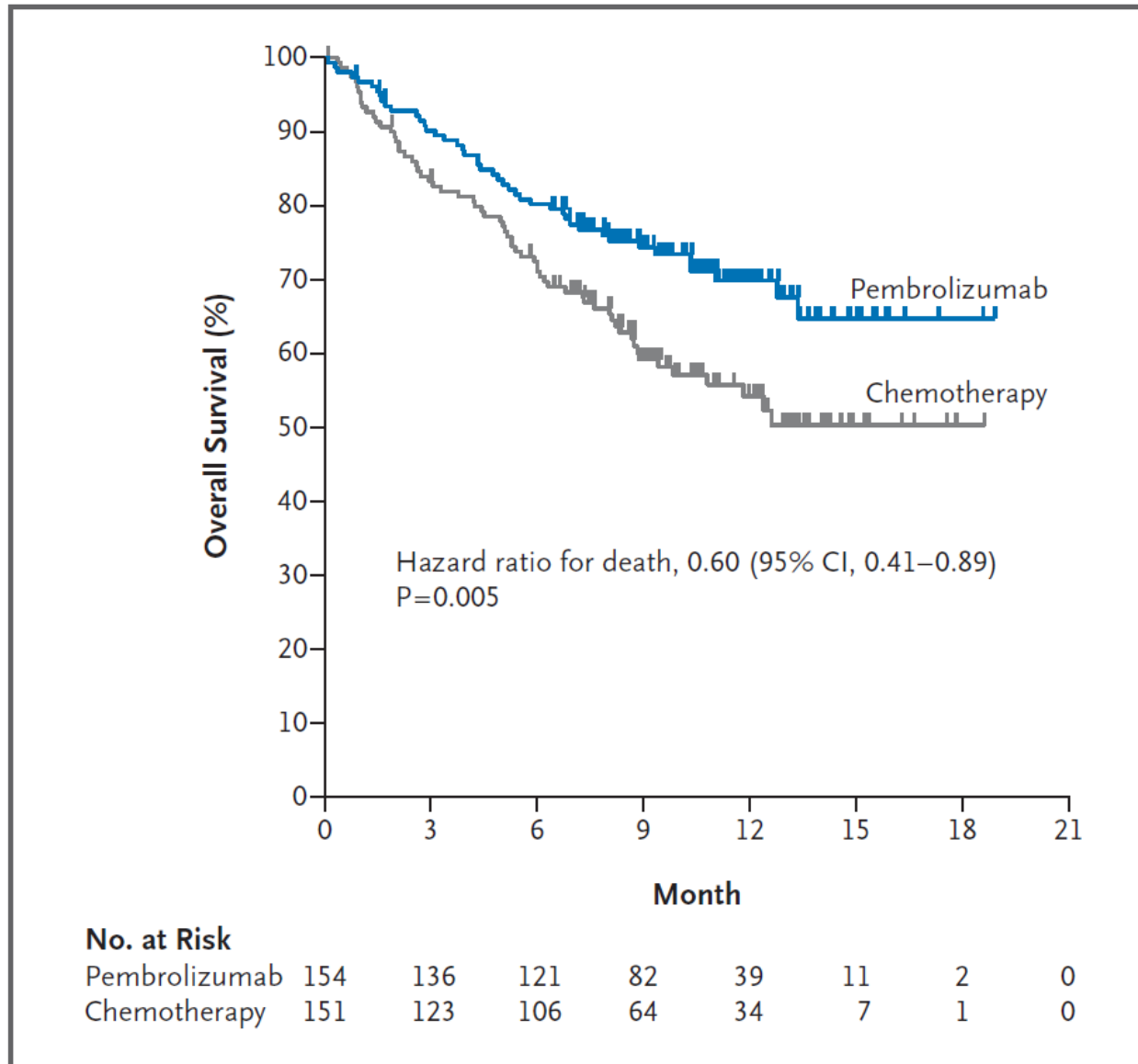


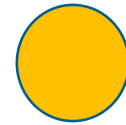
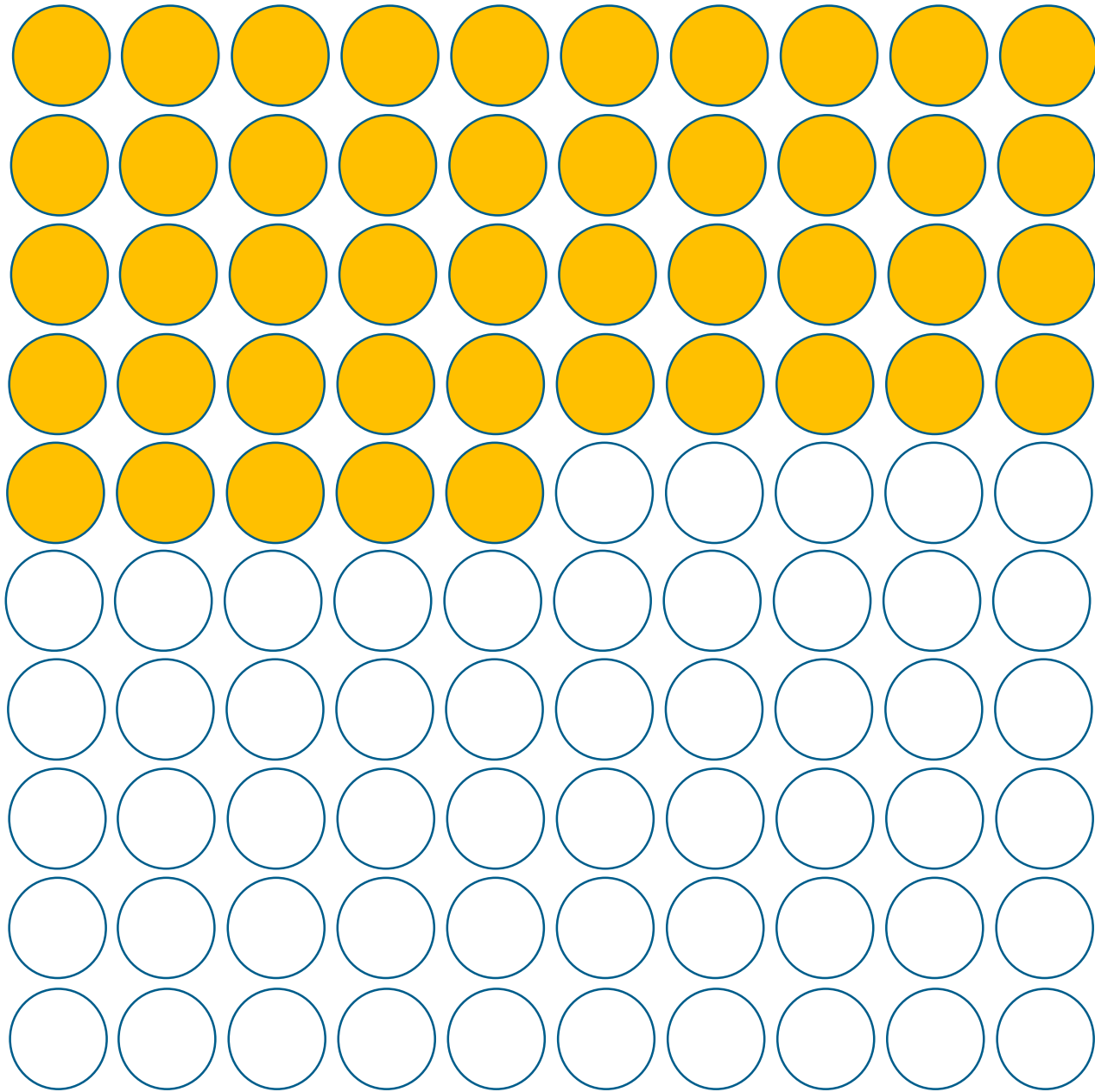
Pembrolizumab 1^e lijn

- 2017 registratie voor NSCLC PD-L1 >50%

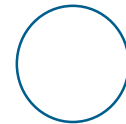


Pembrolizumab 1^e lijn



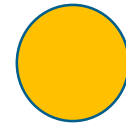
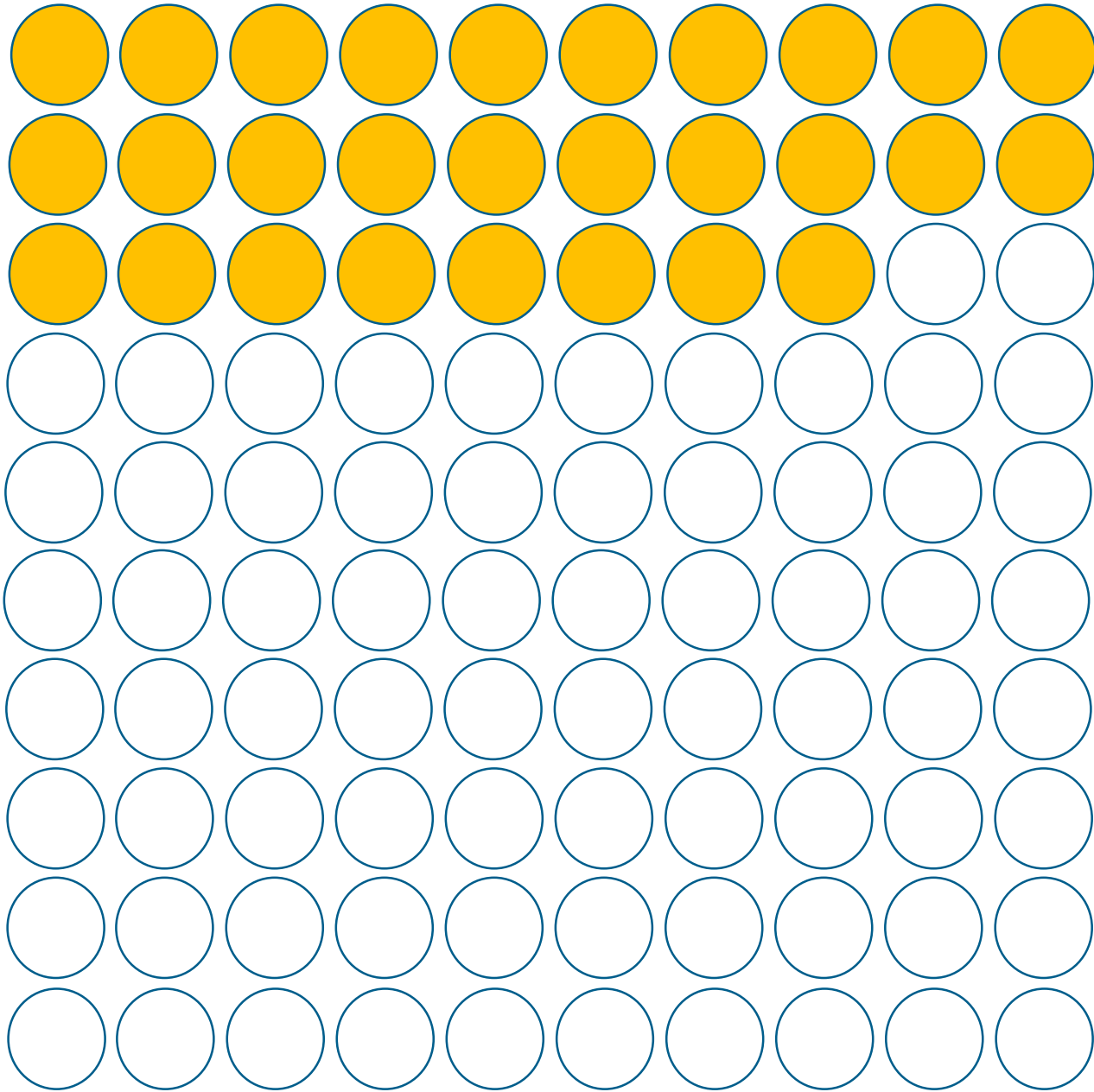


Tumor neemt af

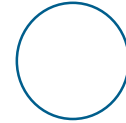


Tumor neemt niet af





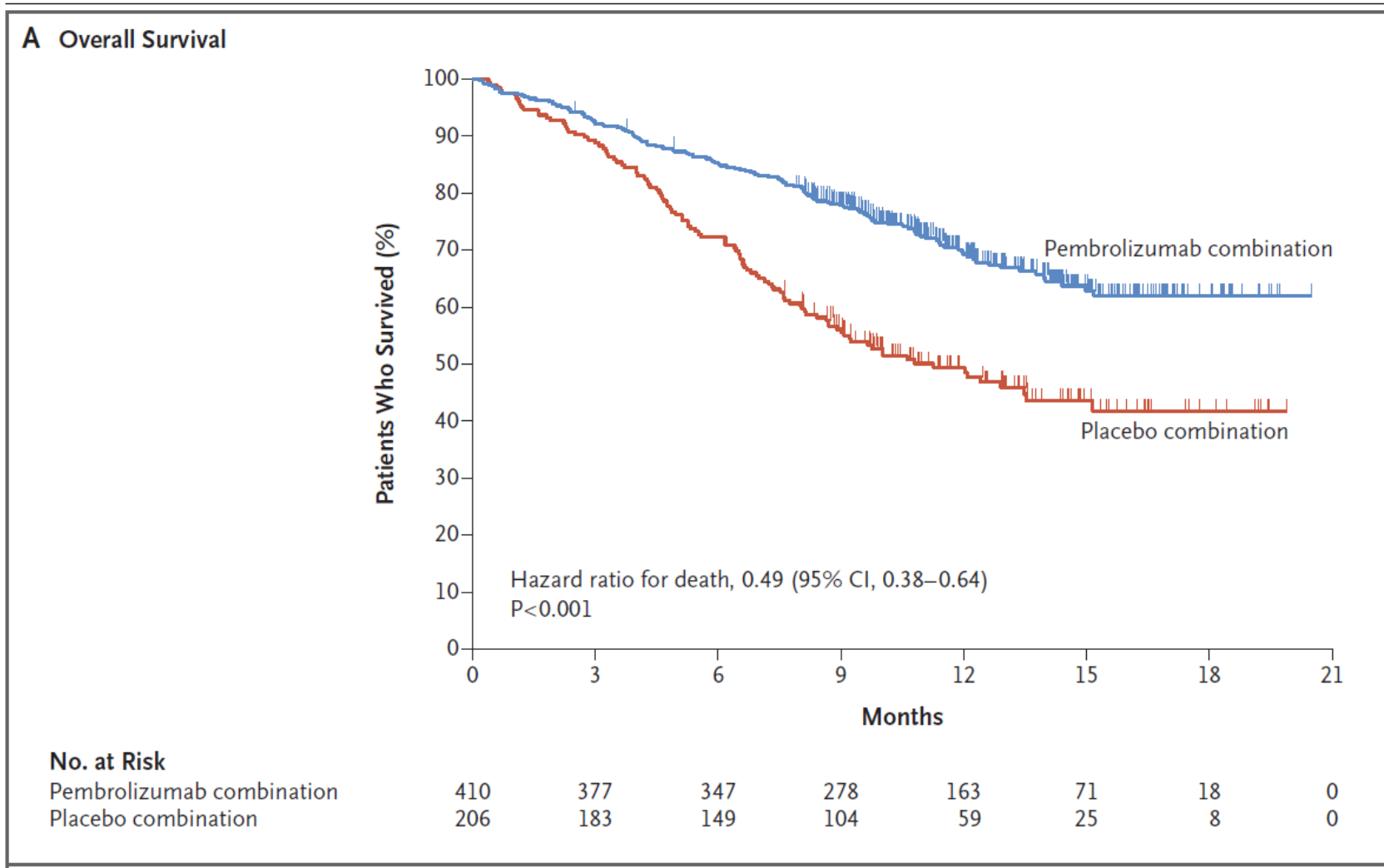
Tumor neemt af
($\geq 30\%$)



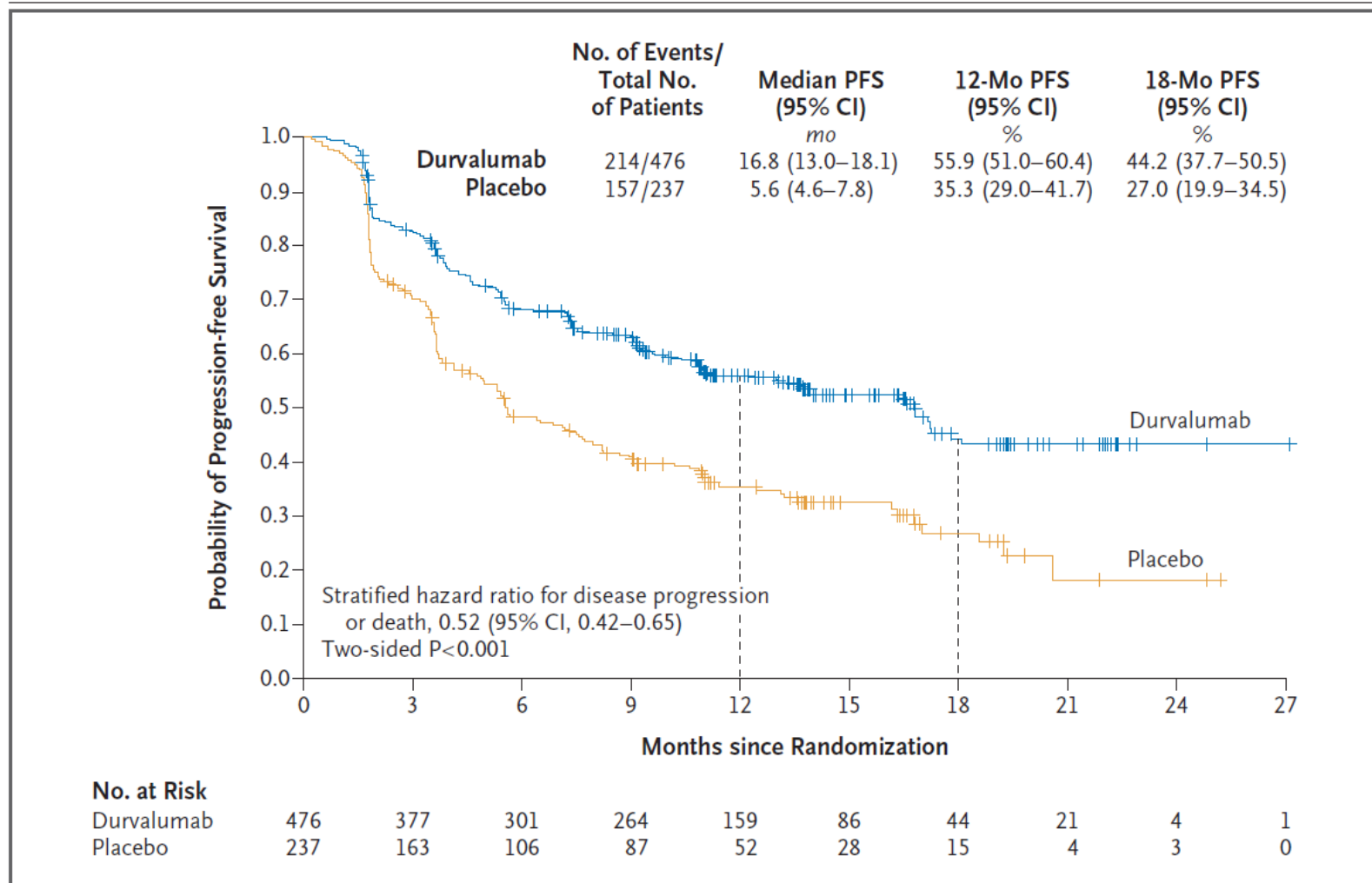
Tumor neemt
niet af



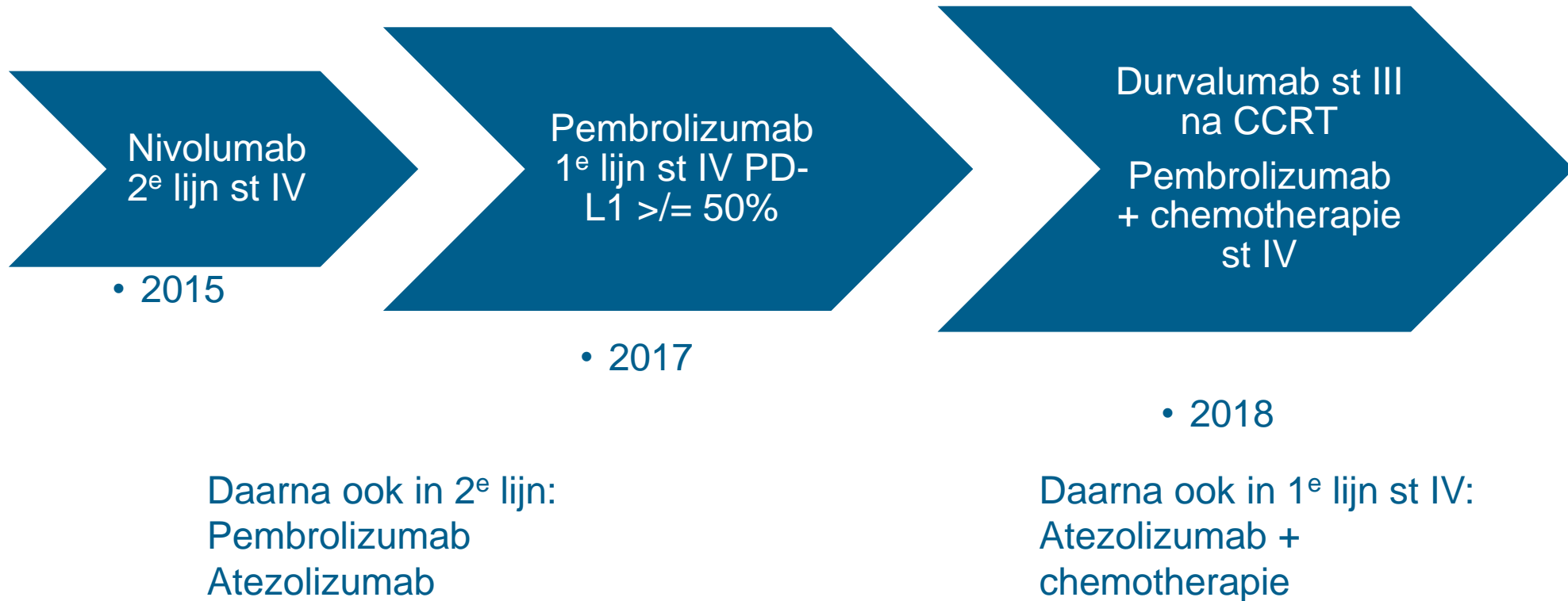
Pembrolizumab + chemotherapie



Durvalumab na chemo+bestraling



Registratie, beoordeling en vergoeding bij NSCLC



Eerder geen gunstige resultaten:

- Vaccinatie met tumordeeltjes (na operatie)
- T-cellen opladen/vervormen (CAR-T)



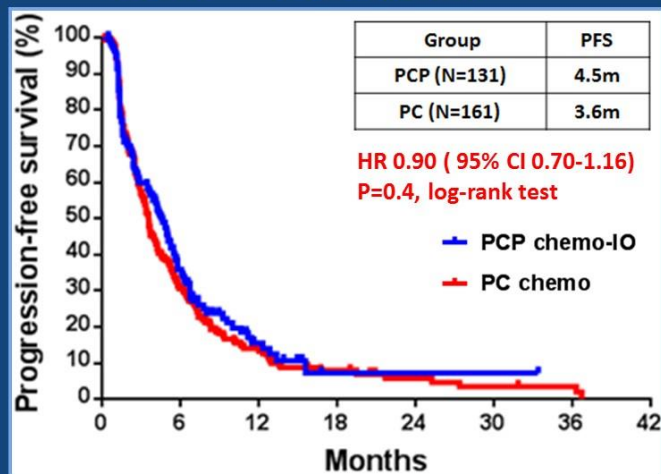
In de pijplijn (onderzoeksfase)

- Stadium I/II:
 - Checkpoint remmer na operatie (adjuvant, na chemotherapie)
 - Checkpoint remmer voor operatie (neoadjuvant)
- Stadium III:
 - Checkpoint remmer tijdens chemoradiotherapie
 - Checkpoint remmer in plaats van chemotherapie bij radiotherapie
- Stadium IV:
 - Checkpoint remmers in ander toedieningsschema
 - Onderzoek naar biomarkers om gunstig effect te voorspellen

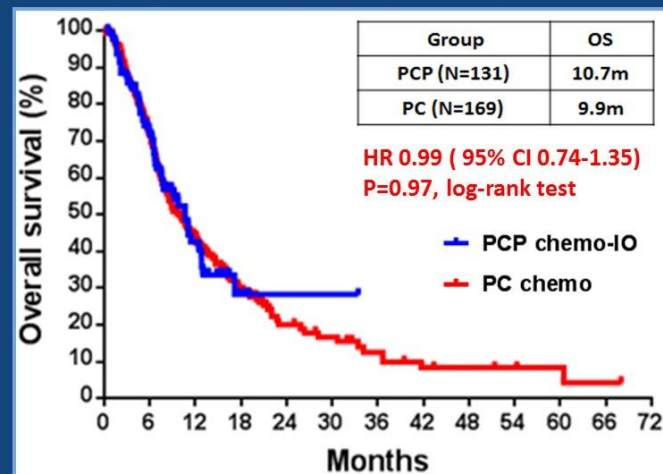


Lack of benefit from addition of pembrolizumab to CP chemotherapy in *STK11* and/or *KEAP1*-mutant non-squamous NSCLC

STK11^{MUT} and/or *KEAP1*^{MUT}



STK11^{MUT} and/or *KEAP1*^{MUT}



Kleincellige longkanker

- Bescheiden effect van toevoegen atezolizumab aan standaard chemotherapie bij uitgezaaide ziekte
 - Gemiddelde tijd van uitblijven progressie +4 weken
 - Gemiddelde overleving +8 weken
 - Bij effect hield dit meestal wel langdurig aan (bij die patiënten)
 - Geen duidelijke voorspellende factoren gevonden voor effect
-
- Niet beoordeeld of vergoed, nog in onderzoeksverband



Mesotheliom (longvlieskanker)

- Enig effect van pembrolizumab en nivolumab na eerdere chemotherapie (respons bij 19-29% van de patiënten) in nog vroege studies
- Nog geen registratie/beoordeling/vergoeding → alleen in onderzoeksverband

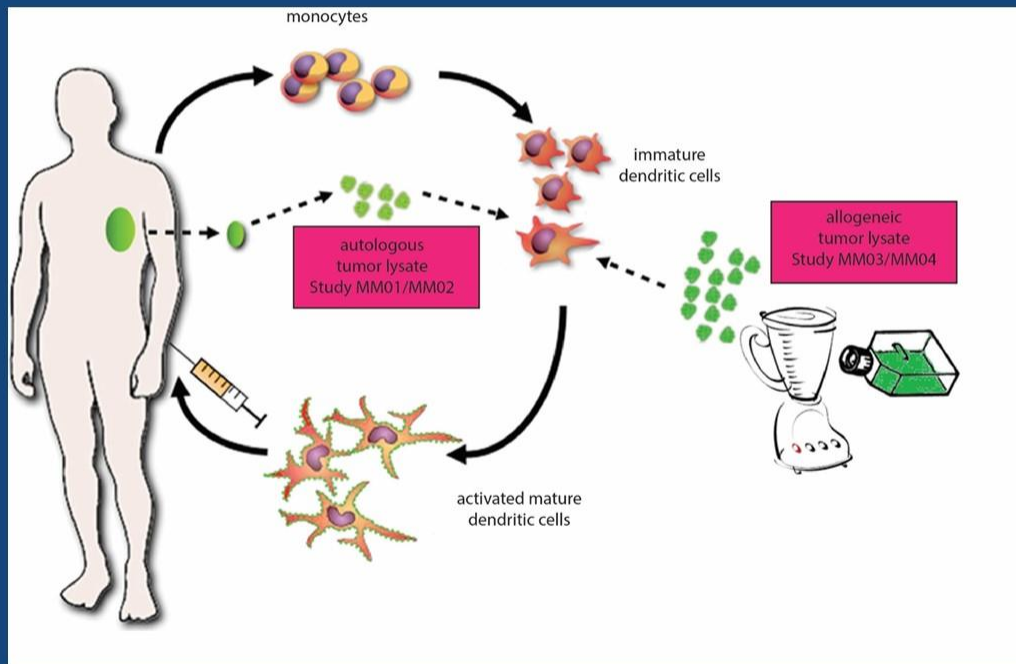


Dendritische celtherapie

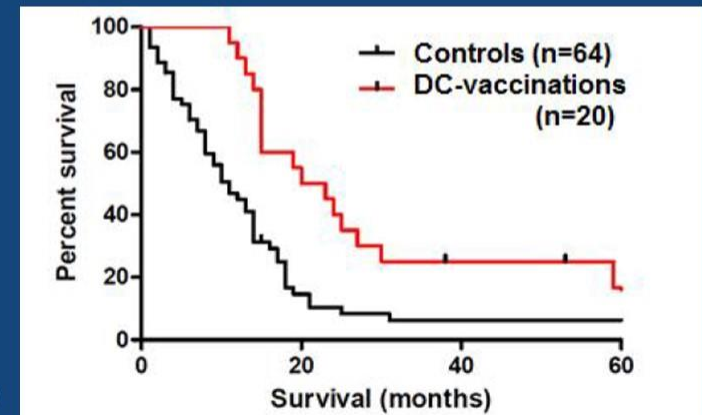
- In het laboratorium 'opladen' van dendritische cellen met kanker antigenen
- Geactiveerde dendritische cellen terugplaatsen in het lichaam



Dendritic Cells therapy with autologous or allogeneic tumor cell lysate as maintenance in unresectable, non-progressing MPM patients after standard first line chemotherapy



First studies (MM01/MM02) showed a survival effect of autologous lysate based DC therapy in 20 patients after 1st line chemotherapy compared to a concurrent control group of 64 pts receiving the same chemo only



Hegmans, J. P. *et al*, AJRCCM 2010

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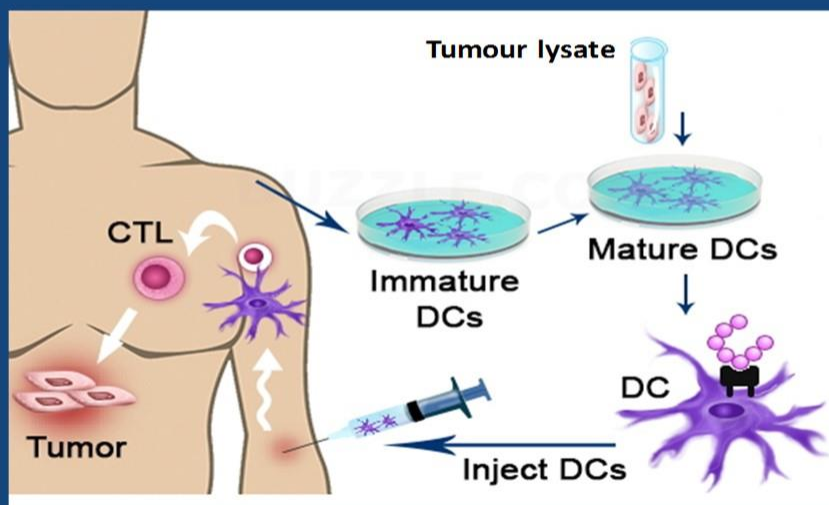
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Ongoing European randomized Phase 3 trial (MM04; “DENIM”): DC therapy with allogeneic tumor cell lysate (“Mesopher”) as Maintenance (+BSC) versus BSC alone after standard 1st line chemotherapy in unresectable, non-progressing MPM

(NCT03610360) - European Union H2020 funding



Accrual (May 2019): 45 / 230 planned patients (8/2018-)

Centers: Rotterdam* (J Aerts, PI; Cornelissen), Antwerp* (J van Meerbeeck), Lille* (A Scherpereel), Amsterdam* (P Baas), Leicester (D Fennell), Ancona (R Berardi); *recruiting

First endpoint: mOS - hypothesis = 21 months after randomization for the MesoPher group vs 12 months for the control group (HR of 0.57)

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Wat moet er nog gebeuren?

- Een hoop!
- Uitzoeken welke soorten immuuntherapie behalve al bekende checkpoint remmers kunnen helpen
- Uitzoeken in welke situaties (stadium/operatie/bestraling) immuuntherapie kan helpen
- Uitzoeken bij welke specifieke patiënten immuuntherapie kan helpen
 - Betere biomarkers voor effect



Vragen?

