



Immuuntherapie in de GE-oncologie, wat is het en waar loop je tegenaan?



UMC Utrecht

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September 2024

oncomid
oncologie midden-nederland

Inhoud

- Wat is immuuntherapie?
 - Soorten
- Voor wie werkt het?
 - Orgaan vs moleculaire marker
 - RCT vs dagelijkse praktijk
 - Contra-indicaties
- Hoe meet je of immuuntherapie werkt?
 - Mediane OS? Tail of the curve?

Langer leven met immuuntherapie: 'Patiënt was vroeger kansloos'

Laatste nieuws

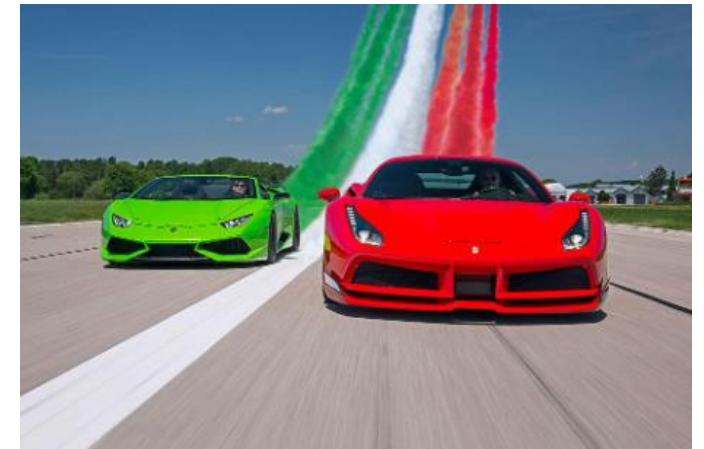
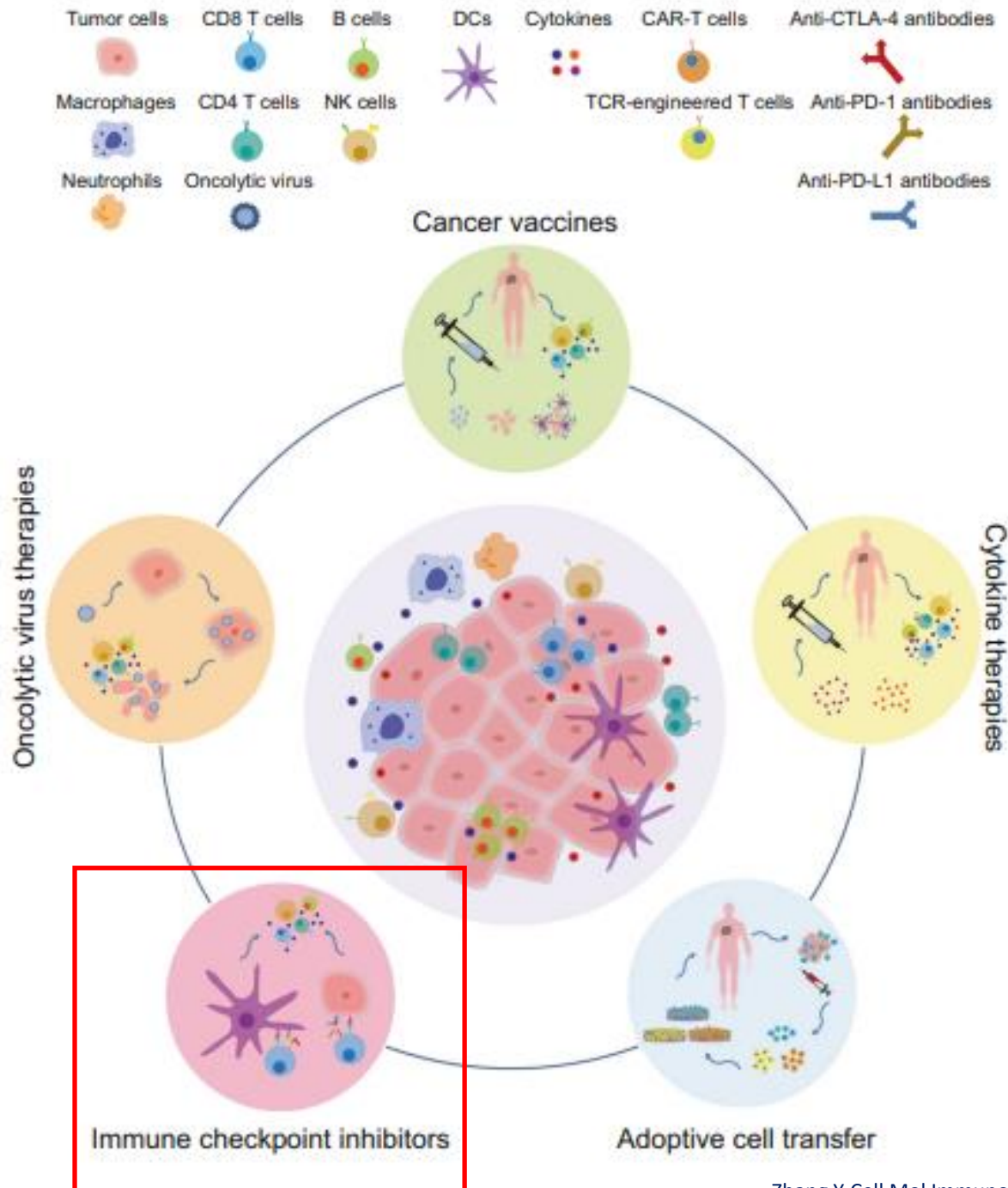


icht: Boulevard of

Veelbelovende nieuwe immuuntherapie tegen kanker gisteren

NOS Nieuws • Woensdag 5 juni, 23:00

Onderzoek: immuuntherapie zeer succesvol bij darmkanker



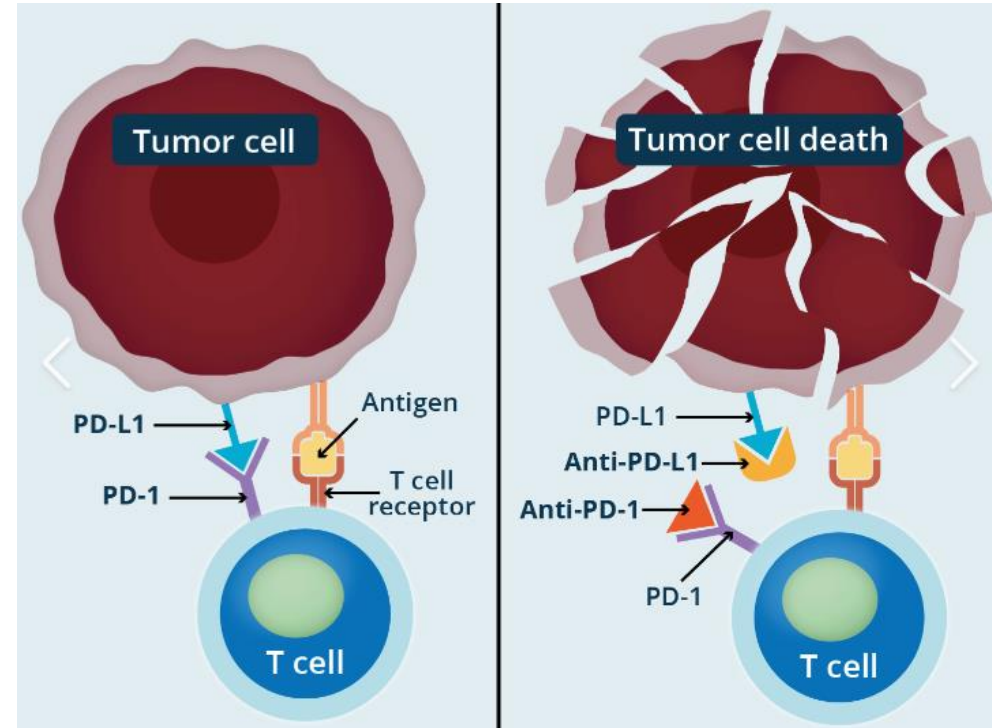
Checkmate studies:
Nivolumab

Keynote studies:
Pembrolizumab

Hoe werken checkpoint remmers?



Rem eraf--> afweer staat harder aan



Antenne PD: **P**rogrammed **D**eath

Voor wie werkt het/is het beschikbaar?

- Tumortype
- Moleculaire marker: CPS/TPS/MSI
- Conditie
- Overige ziekten

Voor welke indicaties binnen GE beschikbaar?



**Irresectabel
gemetastaseerd
Slokdarm- en
maagcarcinoom**



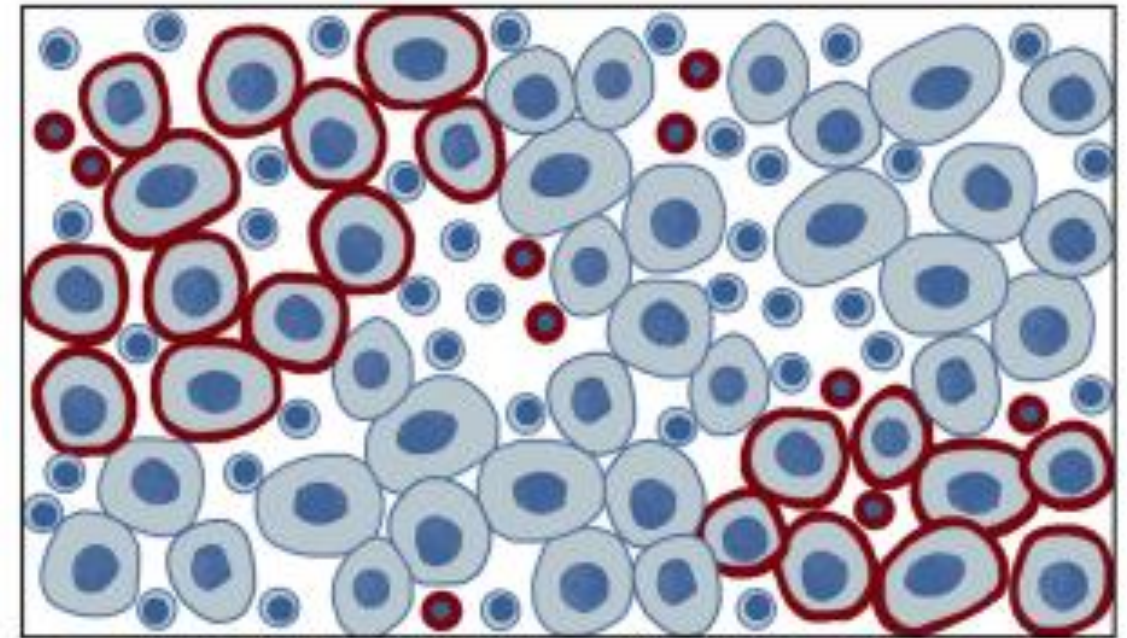
**Niet lokaal te
behandelen
Hepatocellulair
carcinoom**



**Irresectabel
gemetastaseerd
Coloncarcinoom
dMMR**

Moleculaire marker

- Expressie van programmed cell death ligand 1 (PD-L1)
- Predictor voor effectiviteit checkpoint blokkade?
- Intratumorale heterogeniteit
- Assay/patholoog van invloed



$$\text{TPS} = \frac{\text{No. PD-L1 positive tumor cells}}{\text{Total No. of viable tumor cells}} \times 100$$

$$\text{CPS} = \frac{\text{No. PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

Biomarker

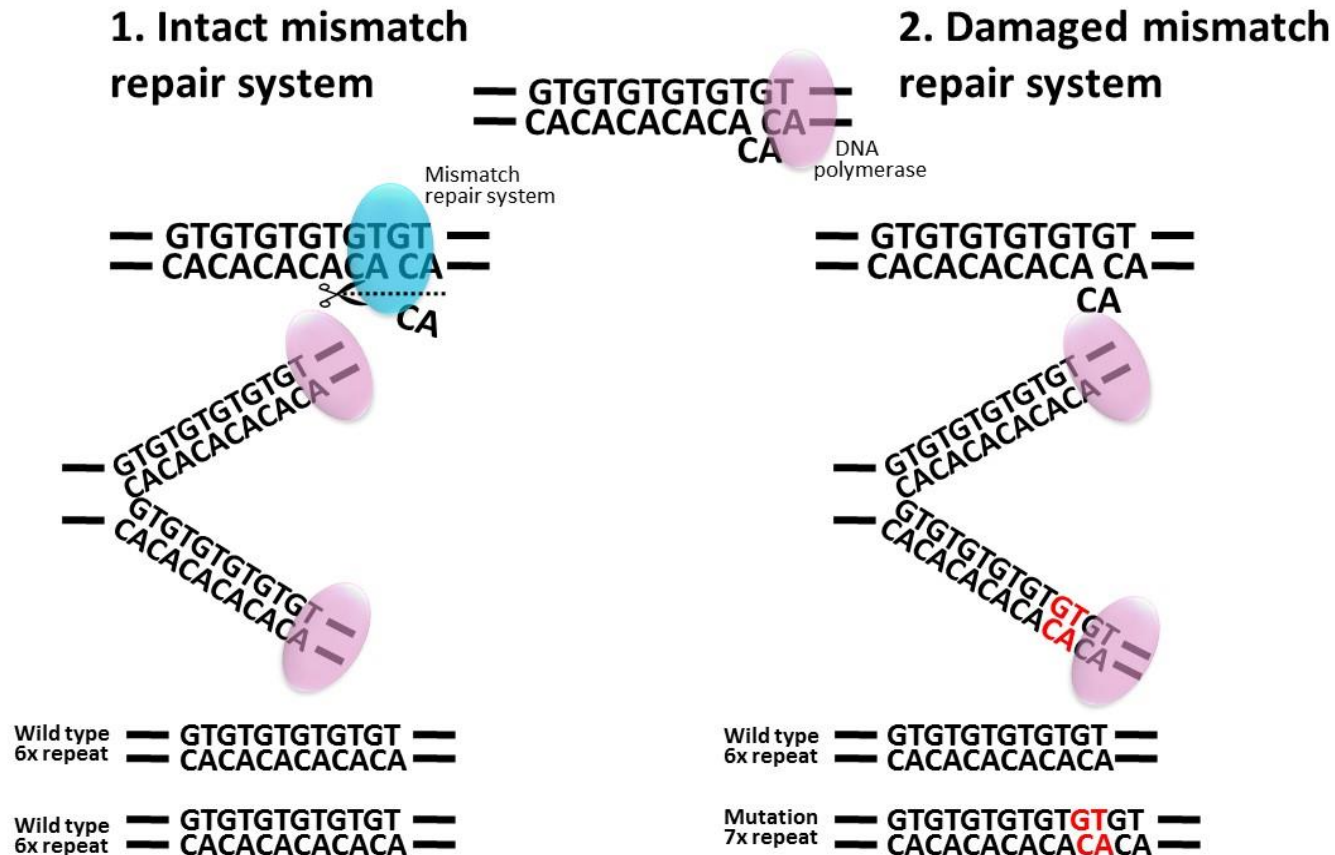
Combined Positive Score (CPS)

Measures the number of PD-L1 staining cells, including tumor cells, lymphocytes, and macrophages, divided by total number of viable tumor cells multiplied by 100

$$\text{CPS} = \frac{\# \text{ PD-L1 staining cells}}{\text{total \# viable tumor cells}} \times 100$$

Mismatch repair eiwitten

Mutaties worden gerepareerd door mismatch repair system
Proficient of deficiënt mismatch repair systeem (pMMR of dMMR)



Irresectabel gemetastaseerd slokdarm- en maag carcinoom

Irresectabel/gemetastaseerd adeno
1e lijn CPS \geq 5: nivolumab + CAPOX

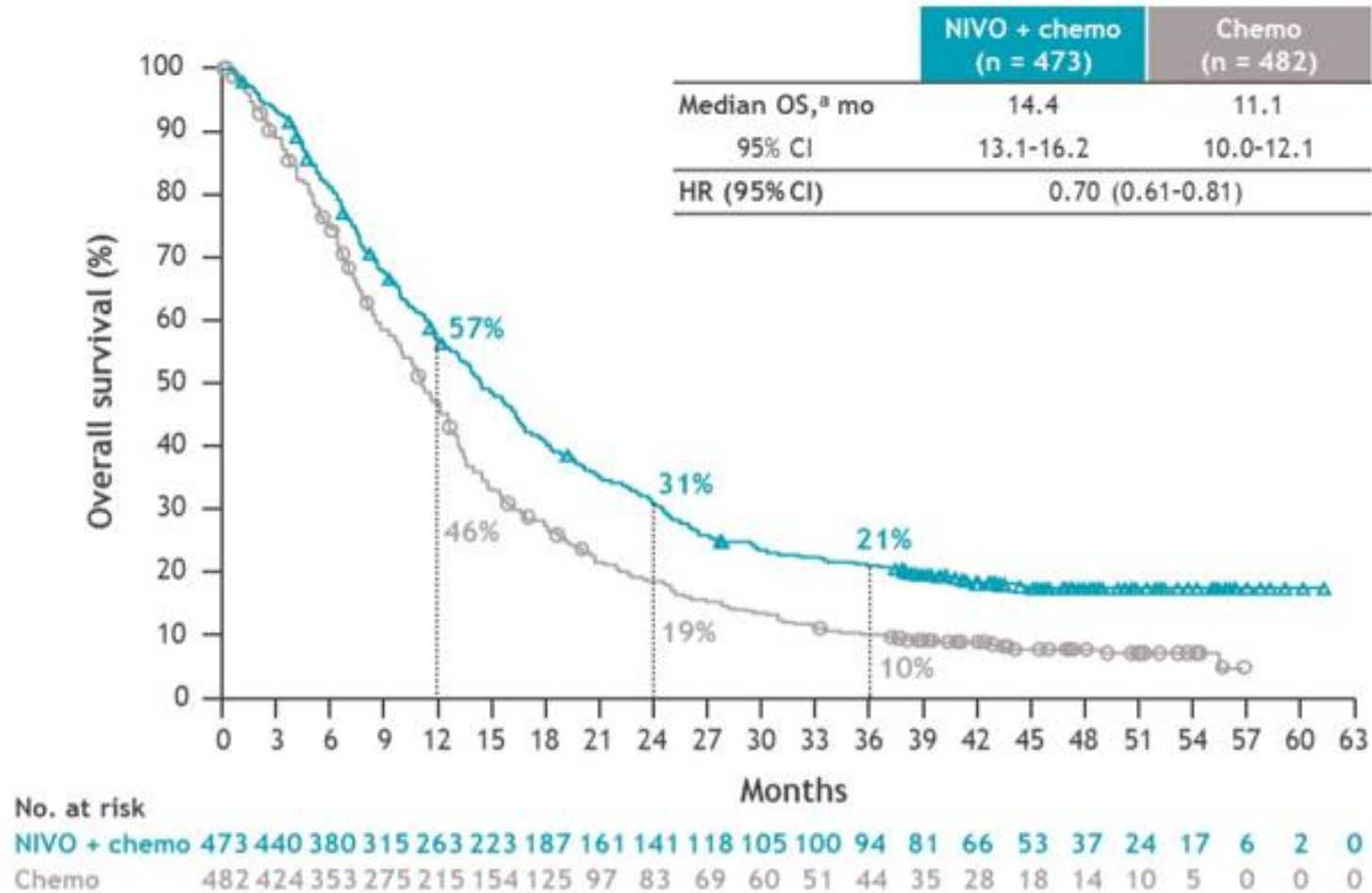
Irresectabel/gemetastaseerd plaveisel
1e lijn TPS \geq 1: nivolumab + CAPOX

Irresectabel/gemetastaseerd oesophagus
1e lijn CPS \geq 10: pembrolizumab + CAPOX



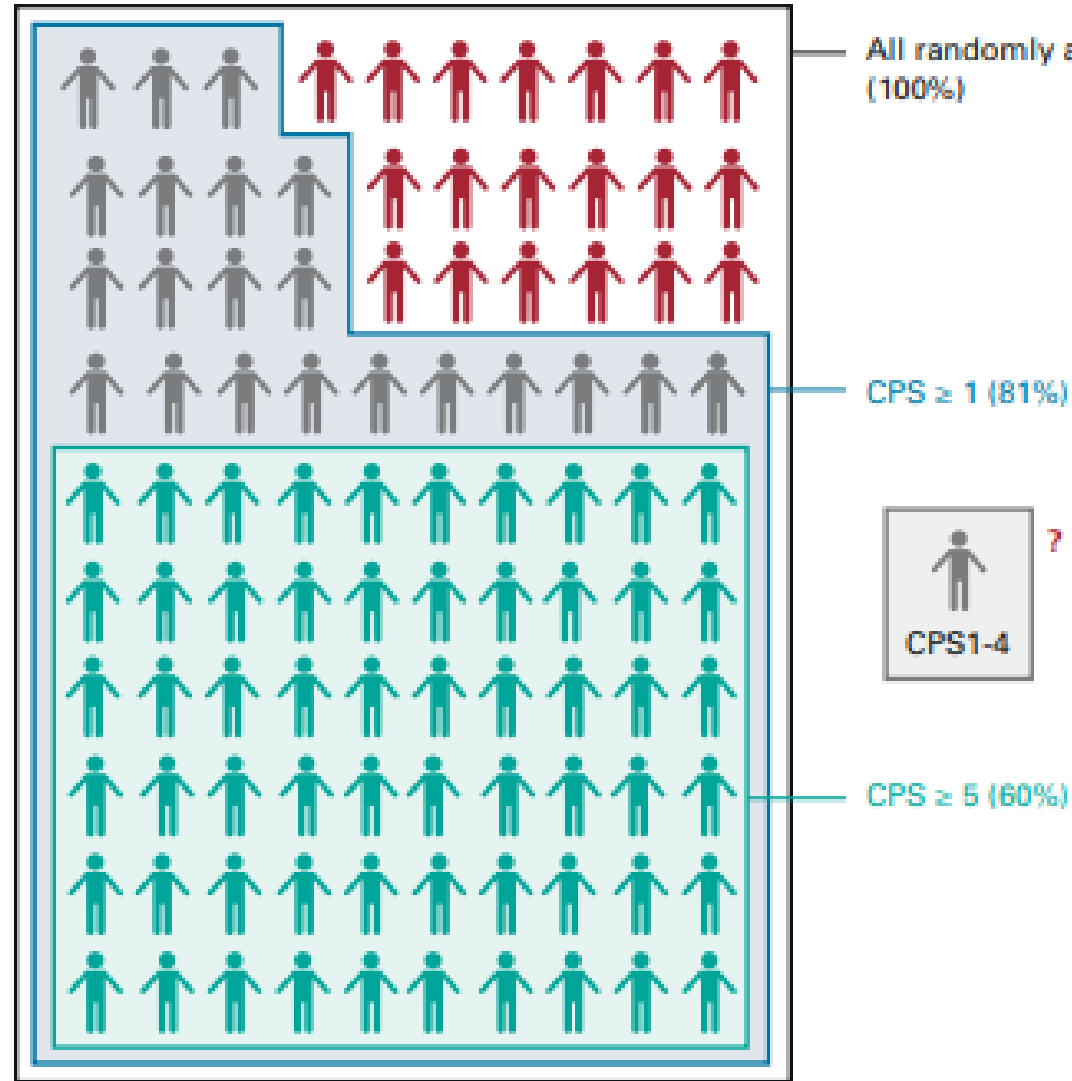
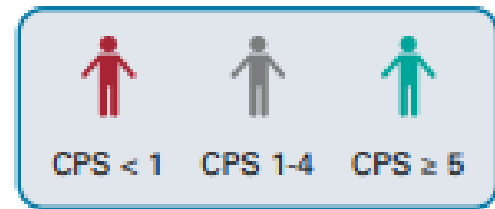
Checkmate 649

PD-L1 CPS ≥ 5



CheckMate-649

Nivolumab plus chemotherapy v chemotherapy
for first-line treatment of advanced gastroesophageal adenocarcinoma

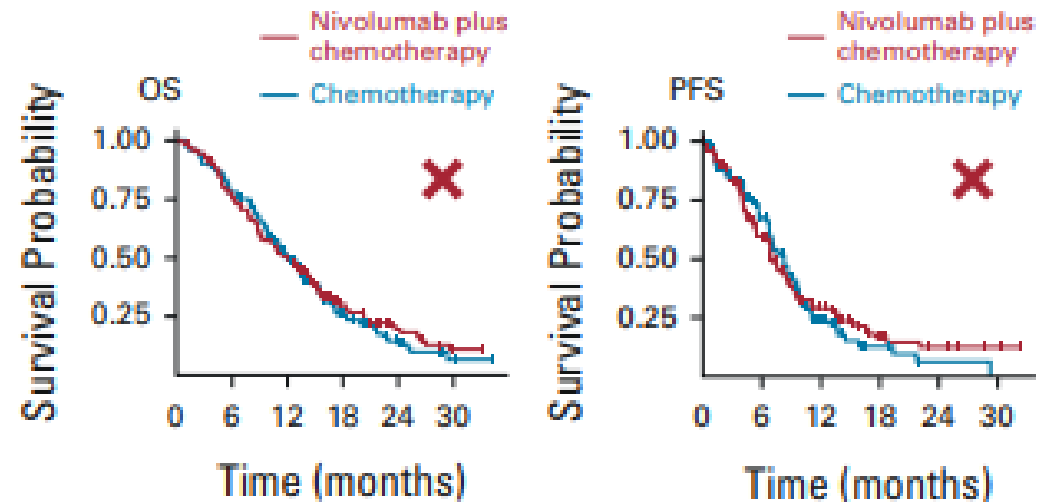


CheckMate-649 end points

- OS and PFS benefit of nivolumab plus chemotherapy shown in
- ✓ All randomly assigned
- ✓ CPS ≥ 1
- ✓ CPS ≥ 5

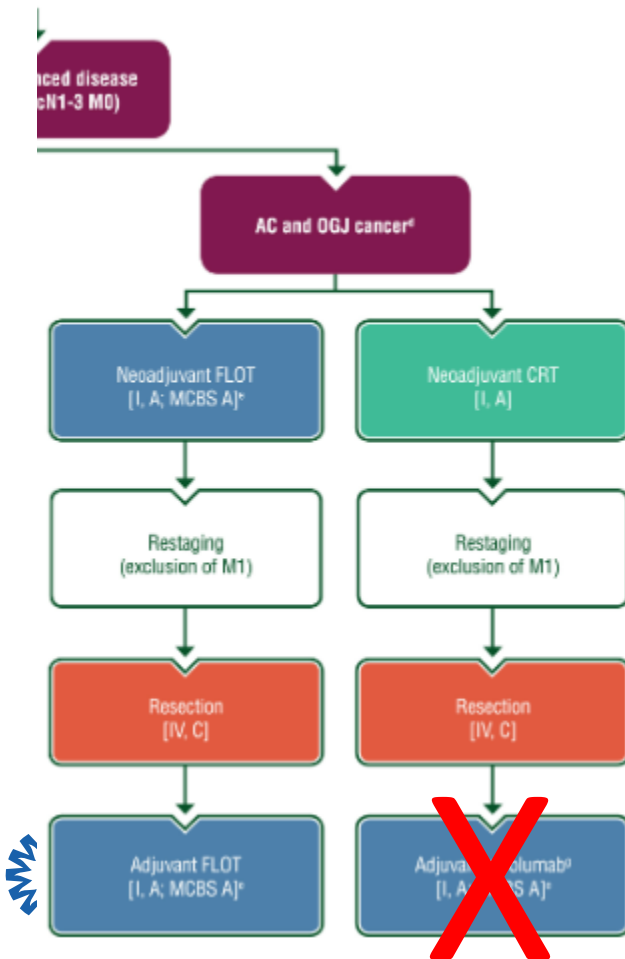
However, it is unclear if the benefit seen in the all randomly assigned and CPS ≥ 1 population was driven by the CPS ≥ 5 population

KMSubtraction-derived KM plots for CPS 1-4

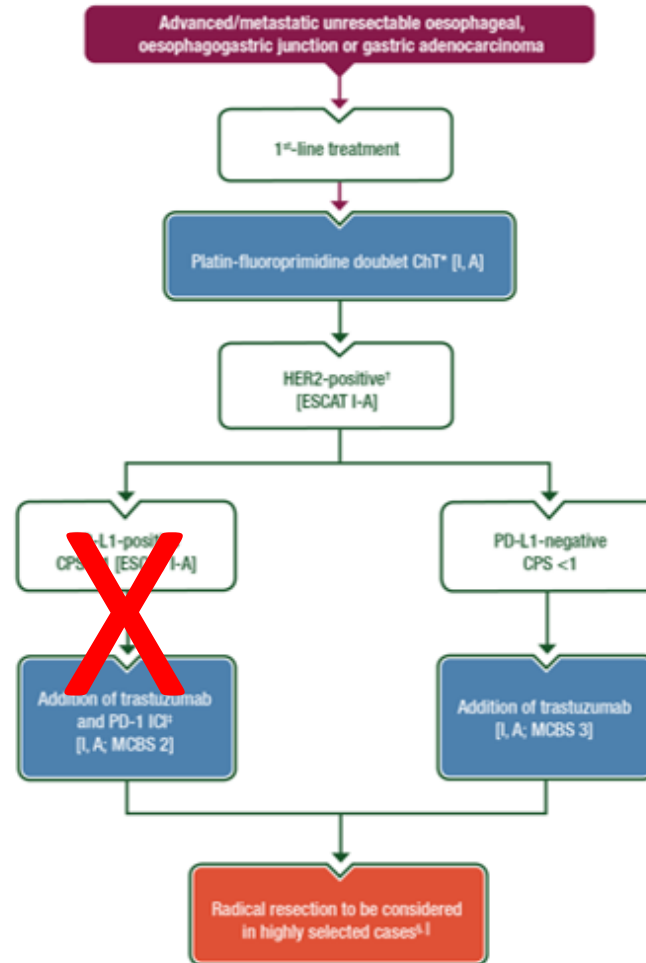


Geen indicatie afwijkend tov Europa

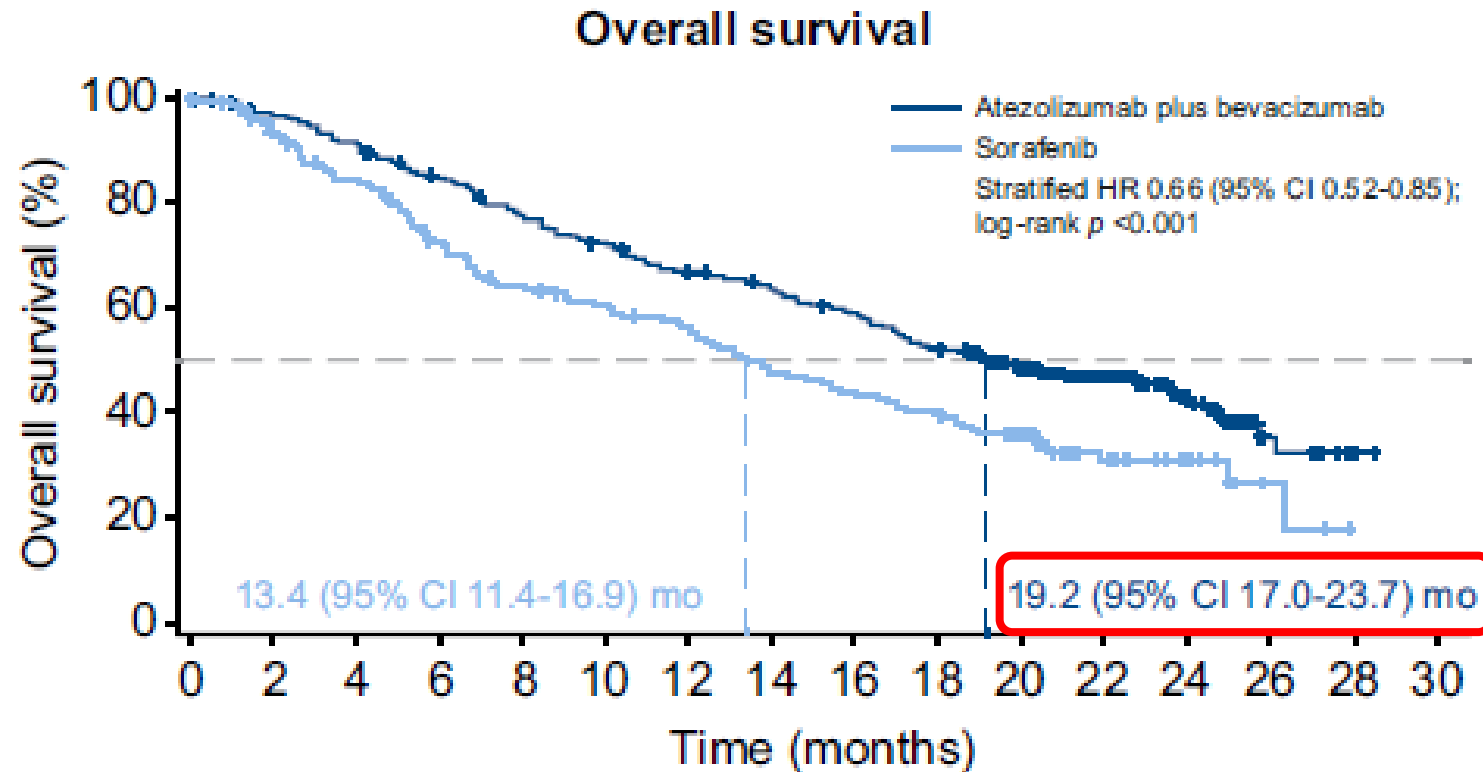
Adjuvant nivolumab na CROSS bij tumorrest



HER2 pos en CPS ≥ 1 : CAPOX-trastuzumab + pembrolizumab



Hepatocellulair carcinoom



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

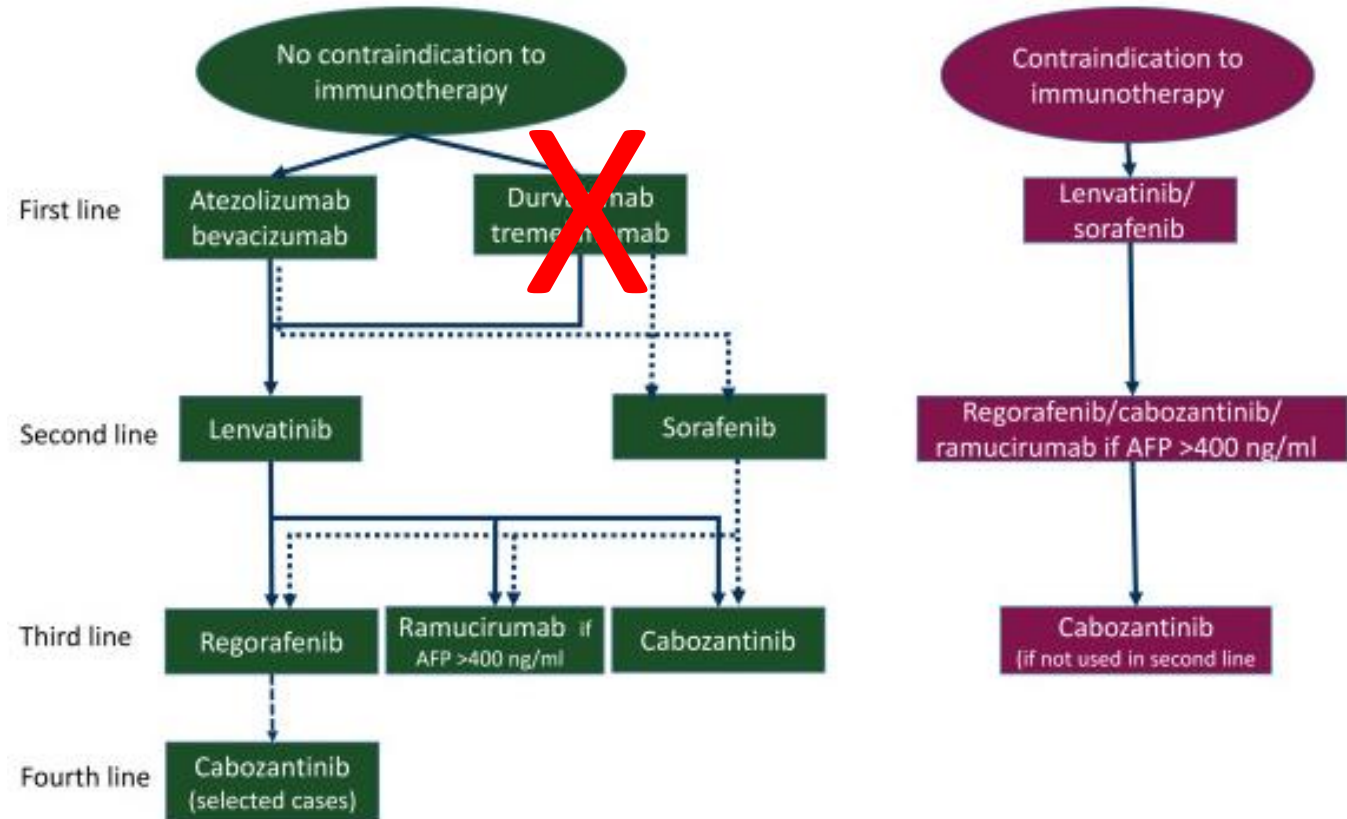
Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D.,
Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D.,
Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D.,
Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D.,
Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D.,
Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D.,
for the IMbrave150 Investigators*

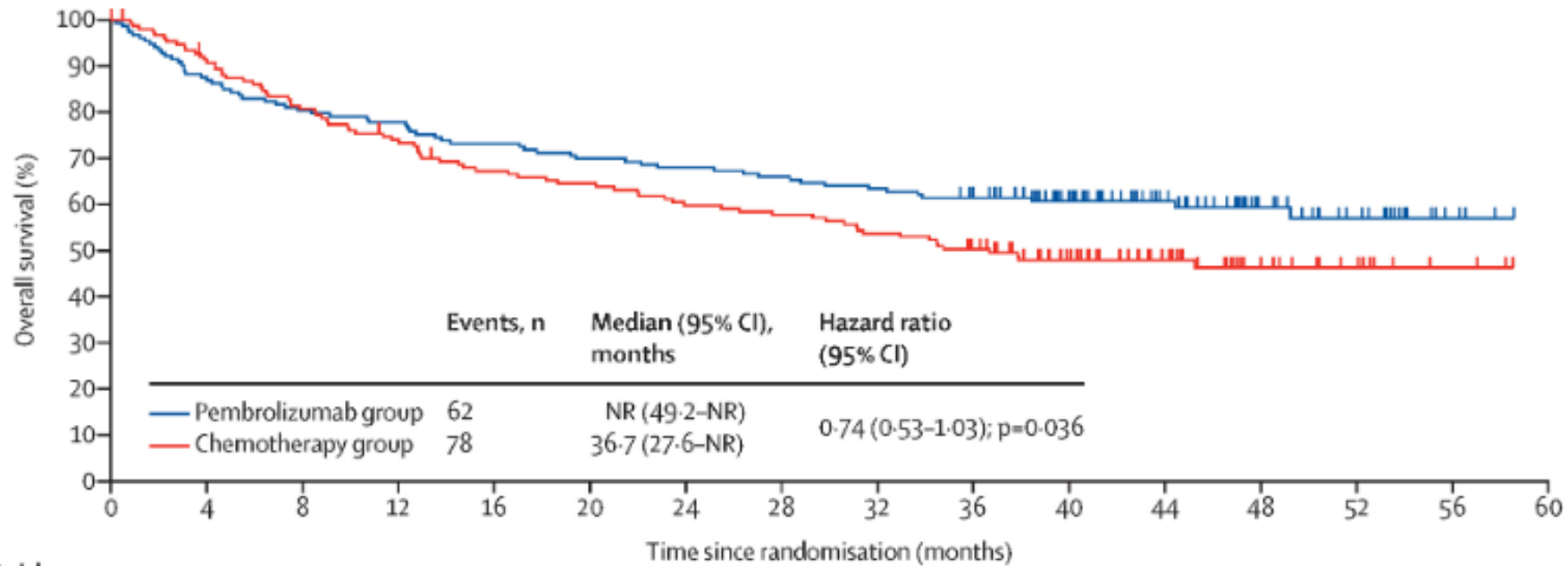
Geen indicatie afwijkend tov Europa

Niet lokaal te behandelen
hepatocellulair carcinoom
Tremelimumab+ durvalumab

Gemetastaseerd
galwegkanker
GEMCIS + durvalumab



Coloncarcinoom MSI



Number at risk
(number censored)

| | | | | | | | | | | | | | | | | |
|---------------------|---------|---------|---------|---------|---------|---------|---------|---------|--------|---------|---------|---------|---------|---------|--------|--------|
| Pembrolizumab group | 153 (0) | 134 (0) | 123 (0) | 119 (0) | 112 (0) | 107 (0) | 104 (0) | 101 (0) | 97 (2) | 92 (23) | 70 (45) | 48 (64) | 28 (75) | 16 (78) | 4 (91) | 0 (91) |
| Chemotherapy group | 154 (4) | 137 (4) | 121 (5) | 110 (6) | 99 (6) | 95 (6) | 88 (6) | 85 (6) | 79 (9) | 71 (24) | 53 (41) | 36 (58) | 18 (65) | 11 (73) | 3 (76) | 0 (76) |

Conditie



Overige ziekten: auto-immuunziekten

nature reviews rheumatology

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[nature](#) > [nature reviews rheumatology](#) > [review articles](#) > article

Review Article | Published: 05 October 2022

Immune-checkpoint inhibitor use in patients with cancer and pre-existing autoimmune diseases

[Alice Tison](#), [Soizic Garaud](#), [Laurent Chiche](#), [Divi Cornec](#) & [Marie Kostine](#) 

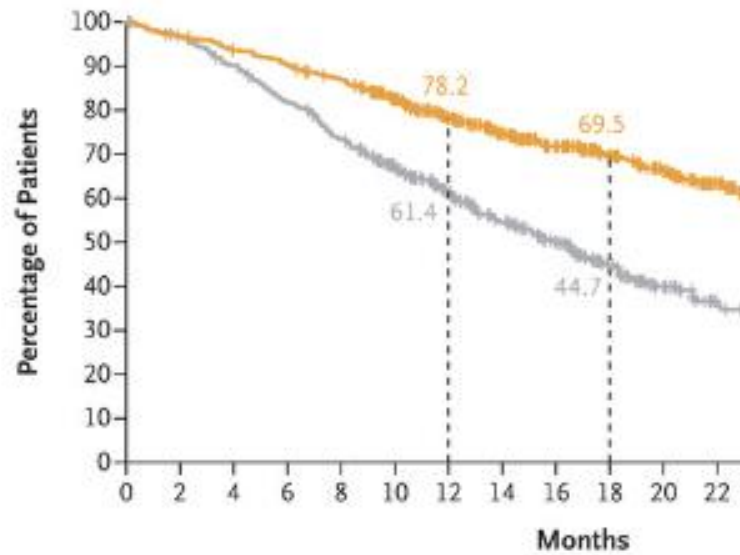
Nature Reviews Rheumatology **18**, 641–656 (2022) | [Cite this article](#)

6806 Accesses | 62 Citations | 33 Altmetric | [Metrics](#)

- Gerandomiseerde studies exclusie onderliggende auto-immuunziekten
- Retrospectieve studies: acceptabel risico met kans op flare-up 75%
- Hoe om te gaan met immunosuppressiva?
 - Balans onderliggende ziekte en goede tumor respons

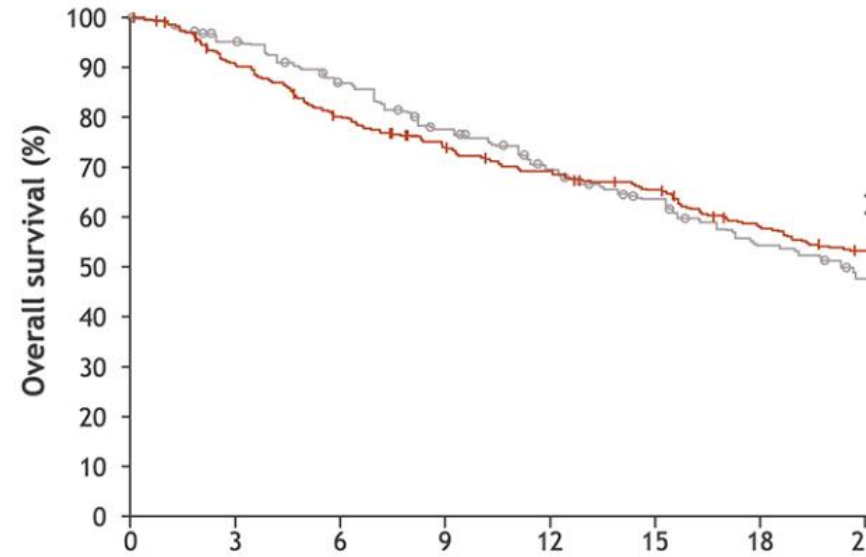
Effectiviteit bepalen

A Overall Survival



No. at Risk

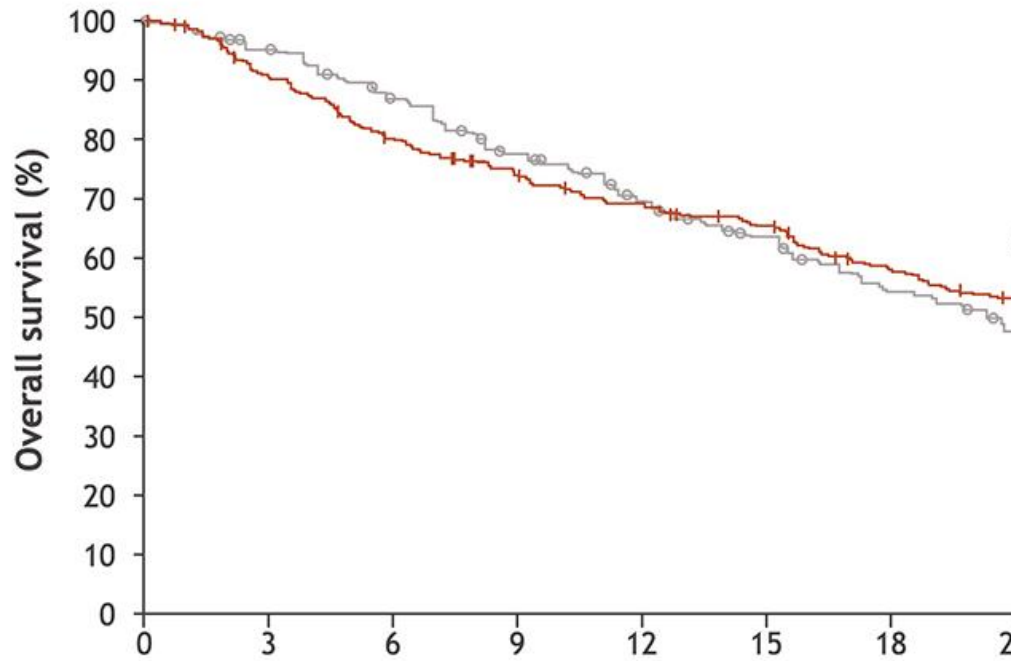
| | | | | | | | | | | | | |
|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| Enfortumab vedotin-pembrolizumab | 442 | 426 | 409 | 394 | 376 | 331 | 270 | 222 | 182 | 141 | 108 | 67 |
| Chemotherapy | 444 | 423 | 393 | 356 | 317 | 263 | 209 | 164 | 125 | 90 | 60 | 37 |



No. at risk

| | | | | | | | | |
|-------------------|-----|-----|-----|-----|-----|-----|-----|----|
| NIVO + IPI | 335 | 300 | 264 | 239 | 220 | 206 | 179 | 16 |
| LEN/SOR | 333 | 310 | 280 | 245 | 216 | 194 | 164 | 14 |

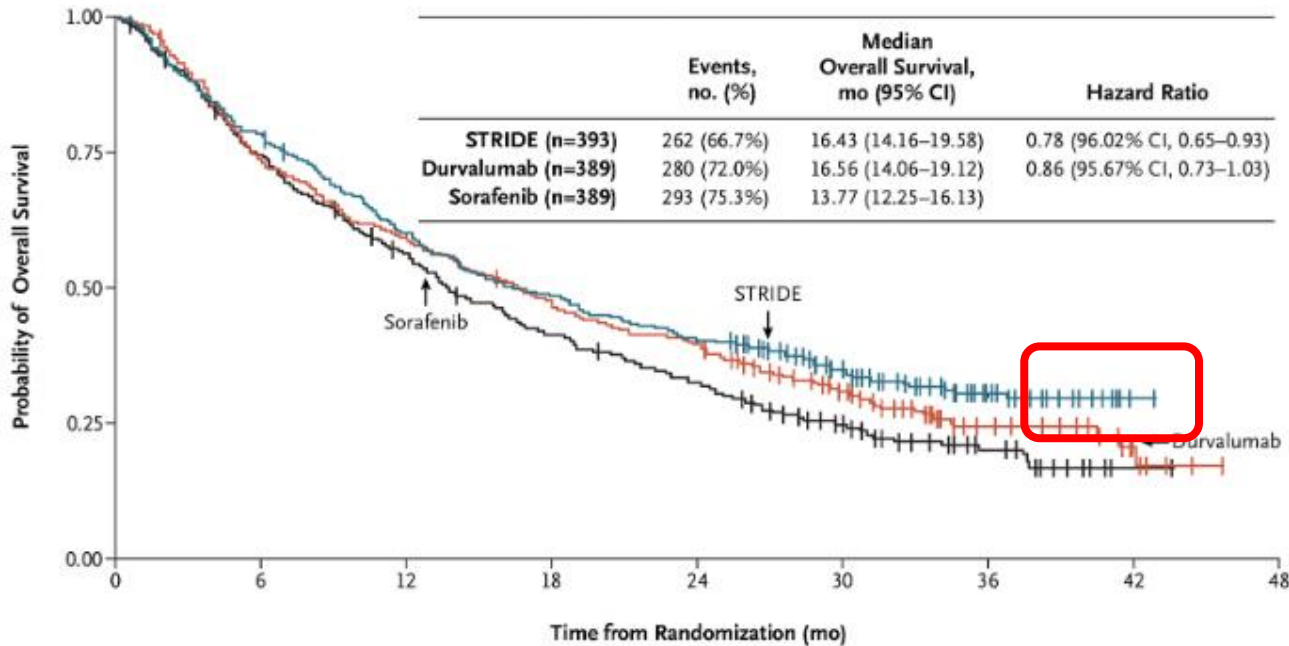
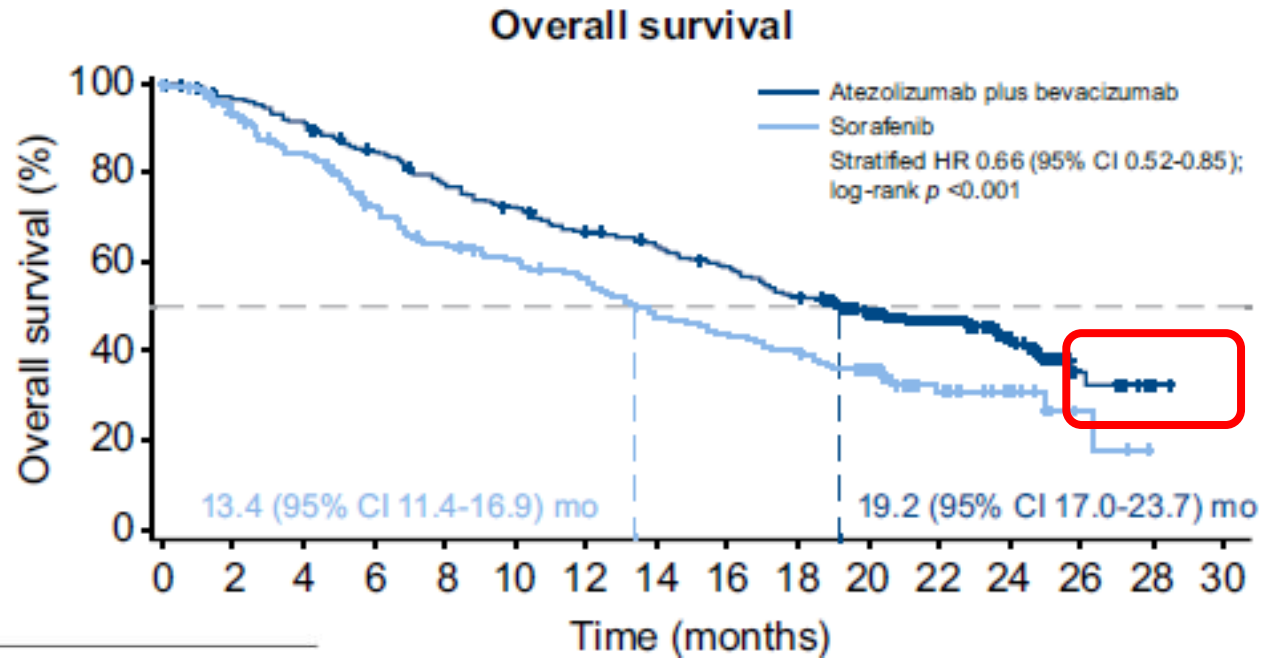
Tail of the curve/plateau



No. at risk

| | | | | | | | | |
|-------------------|-----|-----|-----|-----|-----|-----|-----|---|
| NIVO + IPI | 335 | 300 | 264 | 239 | 220 | 206 | 179 | 1 |
| LEN/SOR | 333 | 310 | 280 | 245 | 216 | 194 | 164 | 1 |

Tail of the curve/plateau



PASKWIL-criteria 2023: palliatieve behandeling

Palliatief, effectiviteit

| | | | |
|--|--|---|------------|
| mOS in controlegroep \leq 12 maanden | • winst totale overleving (OS) | > 12 weken en HR < 0,70 óf toename van 2 jaar OS winst \geq 10% (mits > 20% van de patiënten in de interventiegroep na 2 jaar nog in leven is)* | + + |
| mOS in controlegroep > 12 maanden | • winst totale overleving (OS) | > 16 weken en HR < 0,70 óf toename van 3 jaar OS winst \geq 10% (mits > 20% van de patiënten in de interventiegroep na 3 jaar nog in leven is)* | + + |
| | • winst progressievrije overleving (PFS) | > 16 weken en HR < 0,70 | + |

CASUS

**84 jarige man
naar de lymfeklieren uitgezaaid slokdarmkanker**

Wat wil je weten?

CASUS

Wensen

Gemotiveerd voor palliatieve systeemtherapie
Grootste klacht: passagestoornissen

Conditie

Wandelt elke dag 45 minuten
ADL zelfstandig geen hulp

- Informatie huisarts opvragen
- Geriater ICC

CASUS

Uitgebreidheid ziekte

Beperkt gemetastaseerd naar enkele lymfklieren en longen

Moleculaire markers

CPS \geq 5

MSS

HER2 neg

CASUS

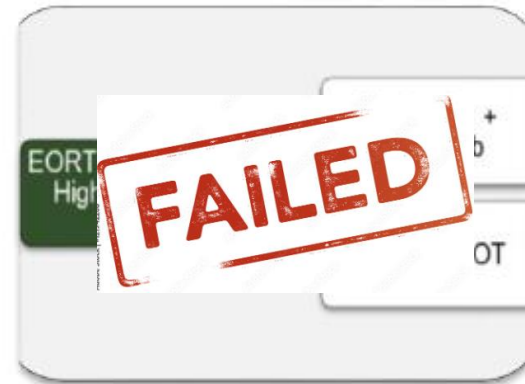
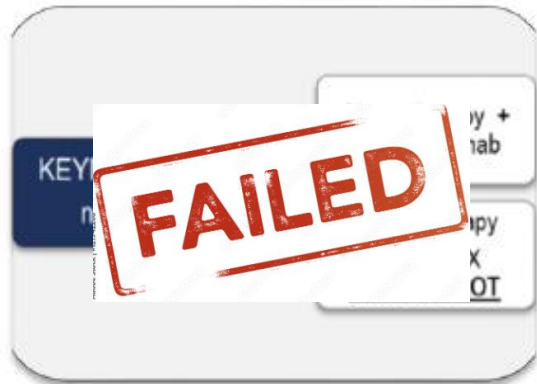
Eerst radiotherapie met als doel verbeteren passagestoornissen

Daarna opnieuw bespreken CAPOX(-NIVOLUMAB)

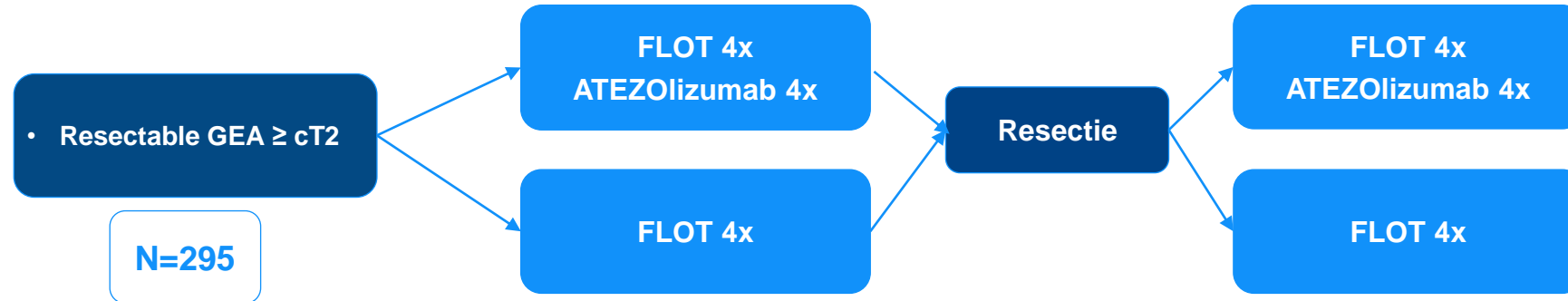
Toekomst selectie

Immune checkpoint inhibitors in operable GEA

International clinical trials



Toekomst: Fase 2 studie AIO-DANTE

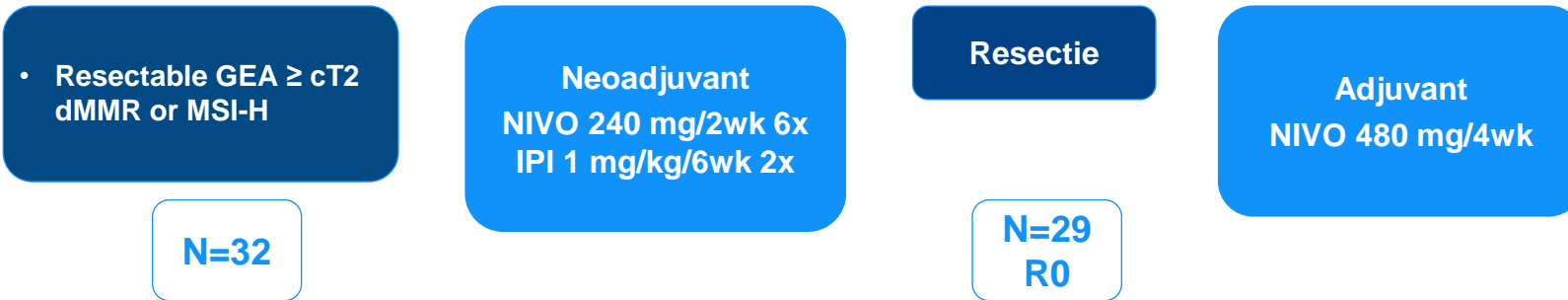


Path. regression by PD-L1 expression and MSI status for arms A vs B.

| Path. reg. for arms A vs B | Local assessment | | Central assessment* | |
|-------------------------------|------------------|------------|---------------------|------------|
| | TRG1a | TRG1a/b | TRG1a | TRG1a/b |
| All pts (n=295) | 24% vs 15% | 48% vs 39% | 25% vs 24% | 49% vs 44% |
| PD-L1 CPS ≥1 (n=146) | 26% vs 16% | 53% vs 49% | 27% vs 25% | 54% vs 50% |
| PD-L1 CPS ≥5 (n=67) | 30% vs 24% | 58% vs 47% | 36% vs 27% | 55% vs 50% |
| PD-L1 CPS ≥10 (n=45) | 38% vs 14% | 71% vs 38% | 46% vs 24% | 71% vs 52% |
| MSI high (n=25) | 50% vs 27% | 70% vs 47% | 50% vs 27% | 70% vs 47% |

↑pCR bij ↑CPS

Fase 2 studie: NEONIPIGA zie ook NICHE



Pathological
complete
response
rate



| TRG Mandard | |
|---|---------------------|
| TRG 1: complete regression/fibrosis without tumor cells | 17 (59) |
| TRG 2: fibrosis with scattered tumor cells | 4 (14) ^a |
| TRG 3: fibrosis and tumor cells with a dominance of fibrosis | 2 (7) |
| TRG 4: fibrosis and tumor cells with dominance of tumor cells | 4 (14) |
| TRG 5: tumor without evidence of regression | 2 (7) |

Resectie wel nodig?

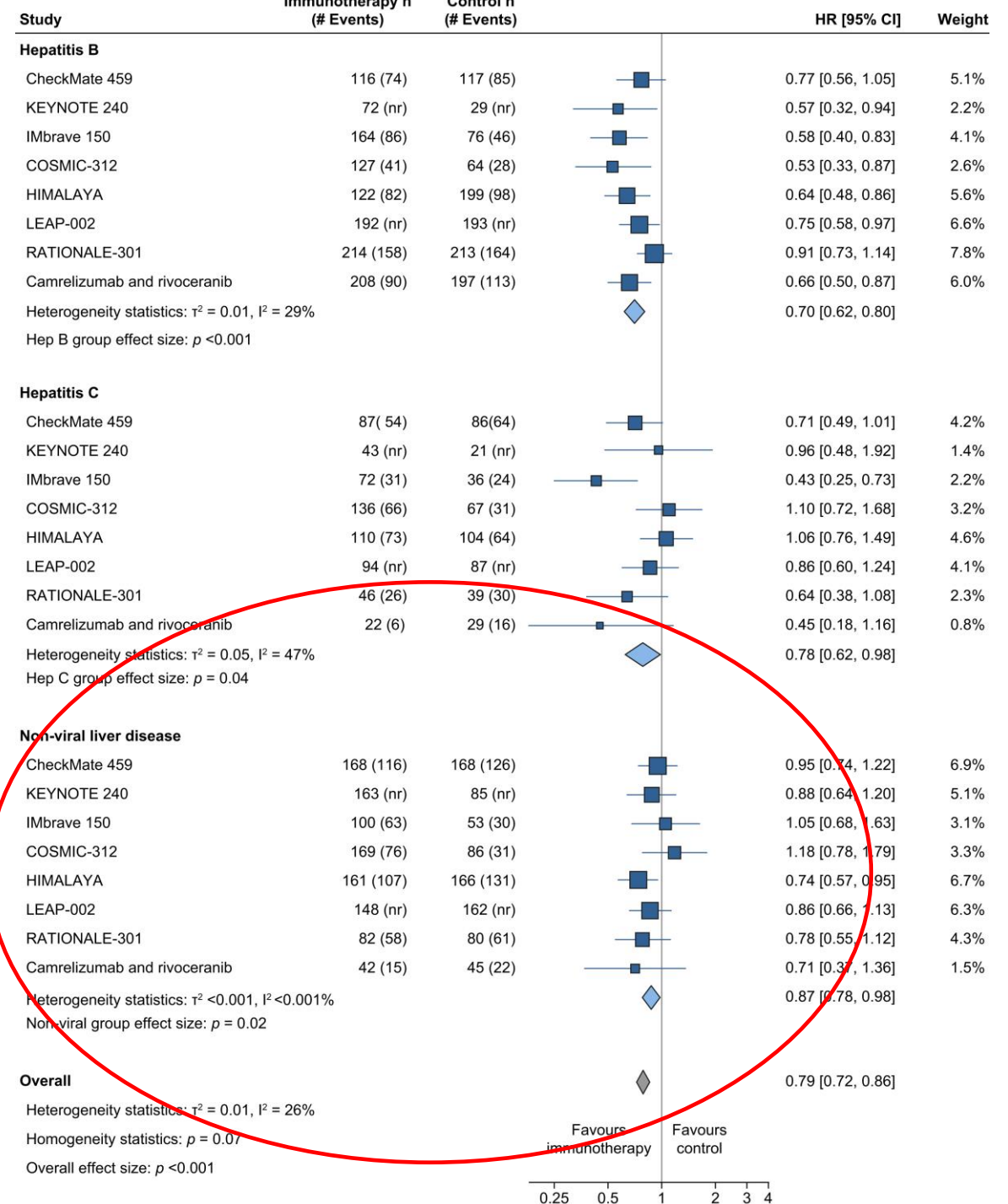
Hepatocellulair carcinoom

Onderliggende oorzaak cirrose is niet predictief voor effect van immunotherapie

Pfister D, NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature. 2021 Apr;592(7854):450-456.

Copil FD, No correlation between MASLD and poor outcome of Atezolizumab-Bevacizumab therapy in patients with advanced HCC. Liver Int. 2024 Apr;44(4):931-943.

Meyer T. Aetiology of liver disease and response to immune checkpoint inhibitors: An updated meta-analysis confirms benefit in those with non-viral liver disease. J Hepatol. 2023 Aug;79(2):e73-e76.



CLINICAL CANCER RESEARCH

ABOUT ▾ ARTICLES ▾ FOR AUTHORS ▾ ALERTS NEWS CANCER HALLMARKS WEBUI

Volume 27, Issue 12

15 June 2021



CLINICAL TRIALS: IMMUNOTHERAPY | JUNE 15 2021

Neoadjuvant Chemoradiotherapy Combined with Atezolizumab for Resectable Esophageal Adenocarcinoma: Single-arm Phase II Feasibility Trial (PERFECT) ✓

Tom van den Ende ; Nicolien C. de Clercq; Mark I. van Berge Henegouwen ; Suzanne S. Gisbertz ; E.D. I. R.H.A. Verhoeven; Sybren L. Meijer; Sandor Schokker ; M.P.G. Dings; Jacques J.G.H.M. Bergman; Nadia Haj M. Jelle P. Ruurda ; Richard van Hillegersberg ; Stella Mook; Max Nieuwdorp; Tanja D. de Gruijl; Tanya T.D. Soere Bauke Ylstra ; Nicole C.T. van Grieken ; Maarten F. Bijlsma; Maarten C.C.M. Hulshof; H.W.M. van Laarhoven

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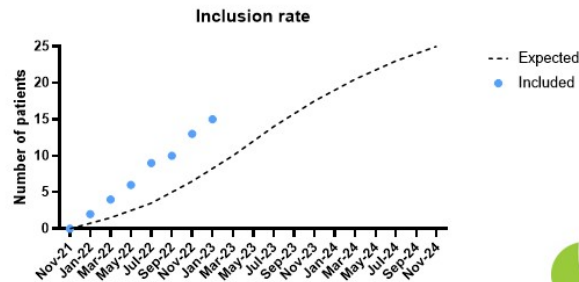
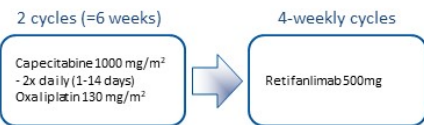
Clin Cancer Res (2021) 27 (12): 3351–3359.

<https://doi.org/10.1158/1078-0432.CCR-20-4443> [Article history](#)



Anti-PD-1, Capecitabine, and Oxaliplatin for the first-line treatment of dMMR esophagogastric cancer (Auspicious-dMMR): a proof-of-principle

- Investigator initiated
- Chemo- and immunotherapy in advanced dMMR esophagogastric cancer
- 7 Treatment sites
- 11 Screening sites



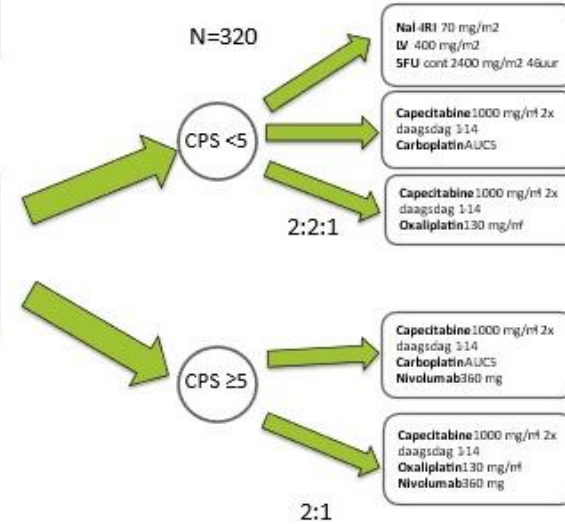
Study coordinator: JorisBos, auspicious@amsterdamumc.nl, 020 44 40506



Gerandomiseerde multicenter fase 2 studie

1^e lijns behandeling gemetastaseerd oesophagus- en maagcarcinoom

Adenocarcinoom RECIST meetbaar
Her2 negatief WHO 0-2

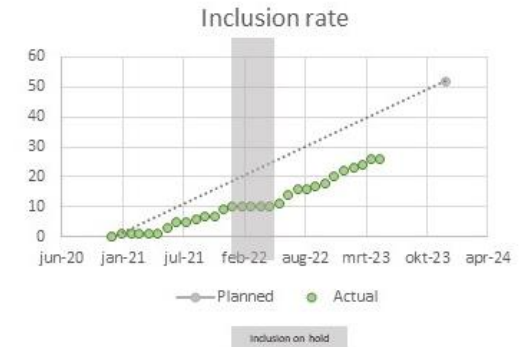


TGF-β And PD-L1 inhibition with Bintrafusp alfa in Esophageal Squamous Cell carcinoma combined with chemoradiation TheRapY

- Single-arm open label feasibility studie
- Definitieve chemoradiatie in plaveiselcelcarcinoom + bintrafusp alfa



Chemotherapie: paclitaxel 50 mg/m² en carboplatin AUC = 2 iv
Radiotherapie: 28 fracties van 1.8 Gy, 5 fracties per week
Bintrafusp alfa: 2400 mg iv

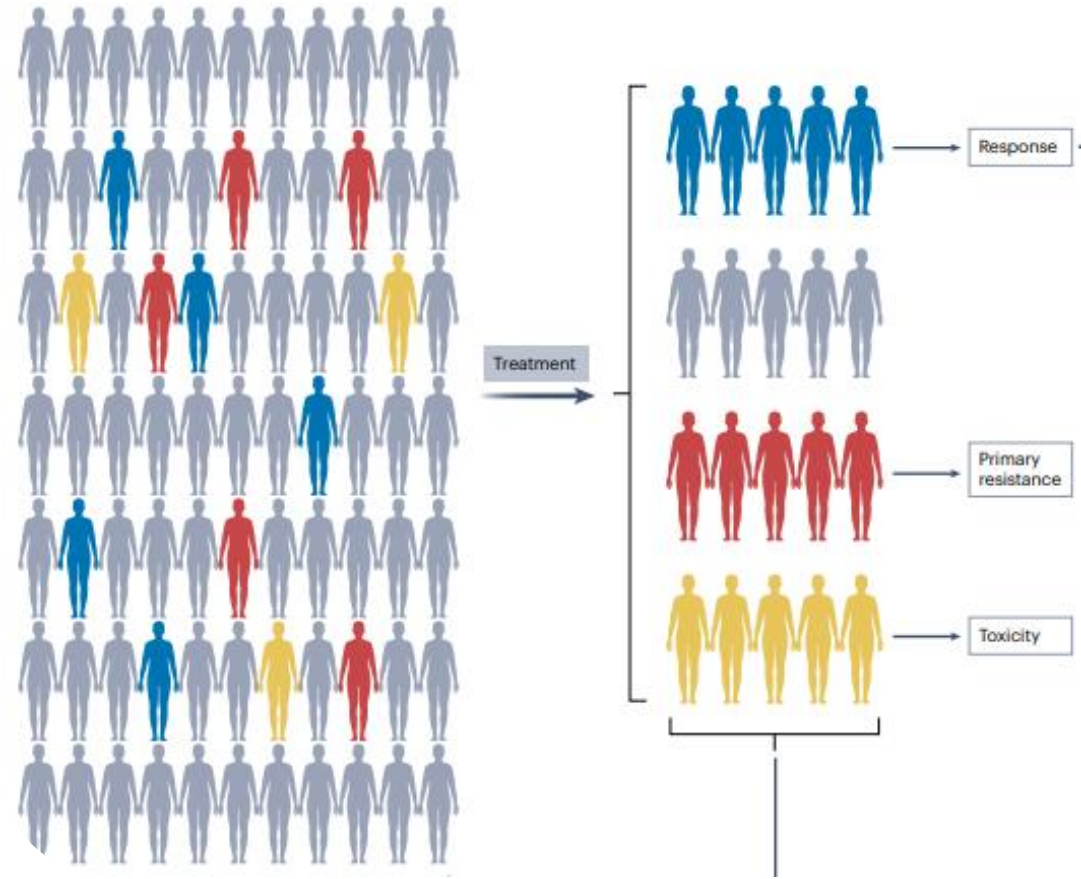


Samenvatting

Immuuntherapie: checkpoint
blokkade in reguliere behandeling
GE-oncologie

Afhankelijk van tumorsoort,
CPS,TPS,MSI, conditie/comorbiditeit

Onderzoek: op zoek naar juiste
biomarker





Bijwerkingen van immuuntherapie

