Neoadjuvante immuuntherapie colorectaal carcinoom, anno 2026

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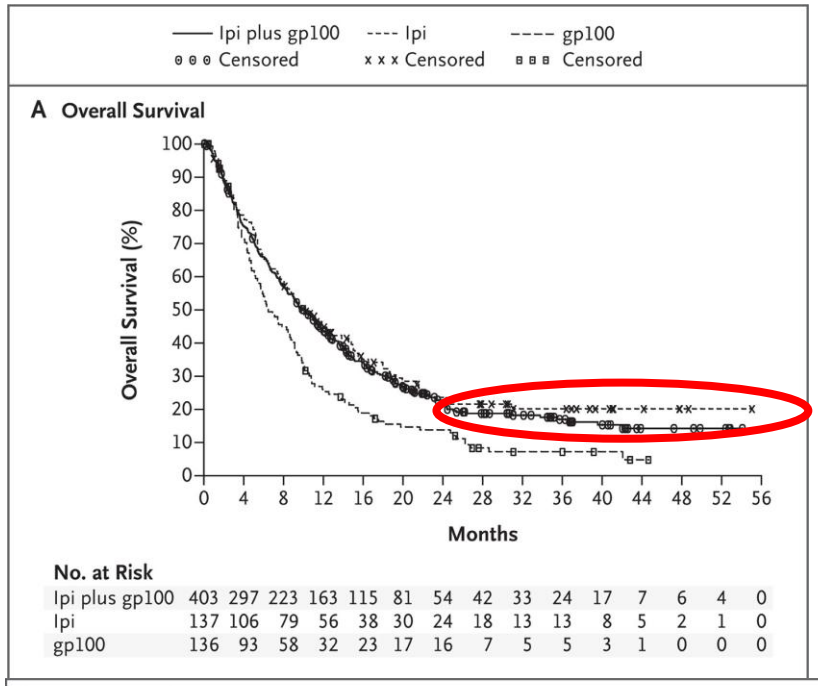
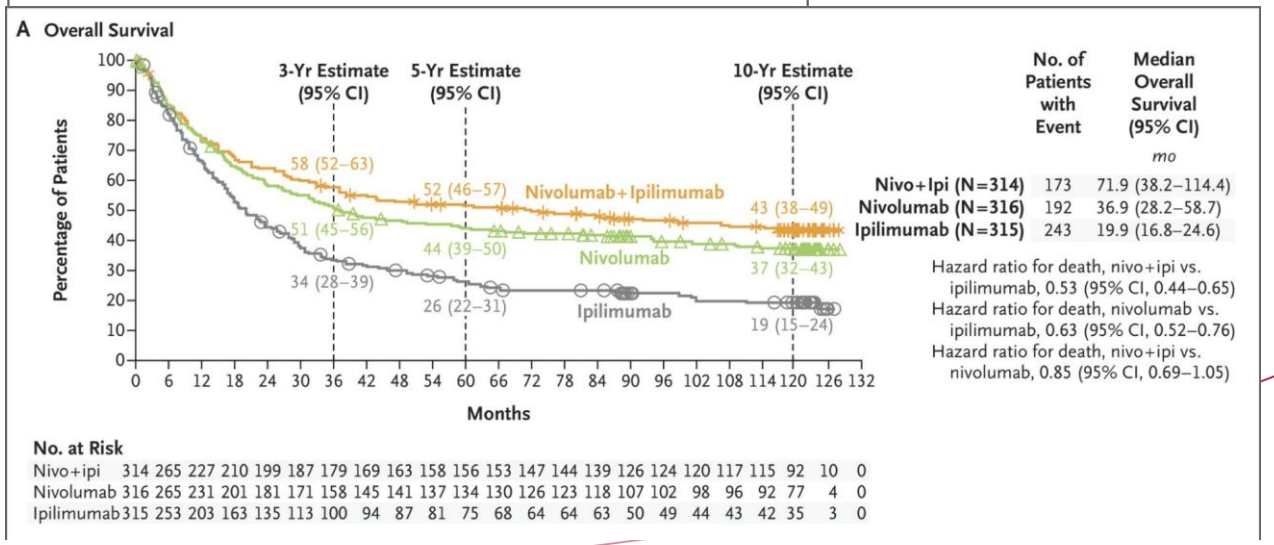
September 2026

Onderwerpen

- Introductie in immuuntherapie
- pMMR vs dMMR
- NICHE trial
- Lokaal irresectabel / gemetastaseerd dMMR coloncarcinoom

Immuuntherapie





3 Science 2013, Hodi et al 2010, Wolchok et al 2024

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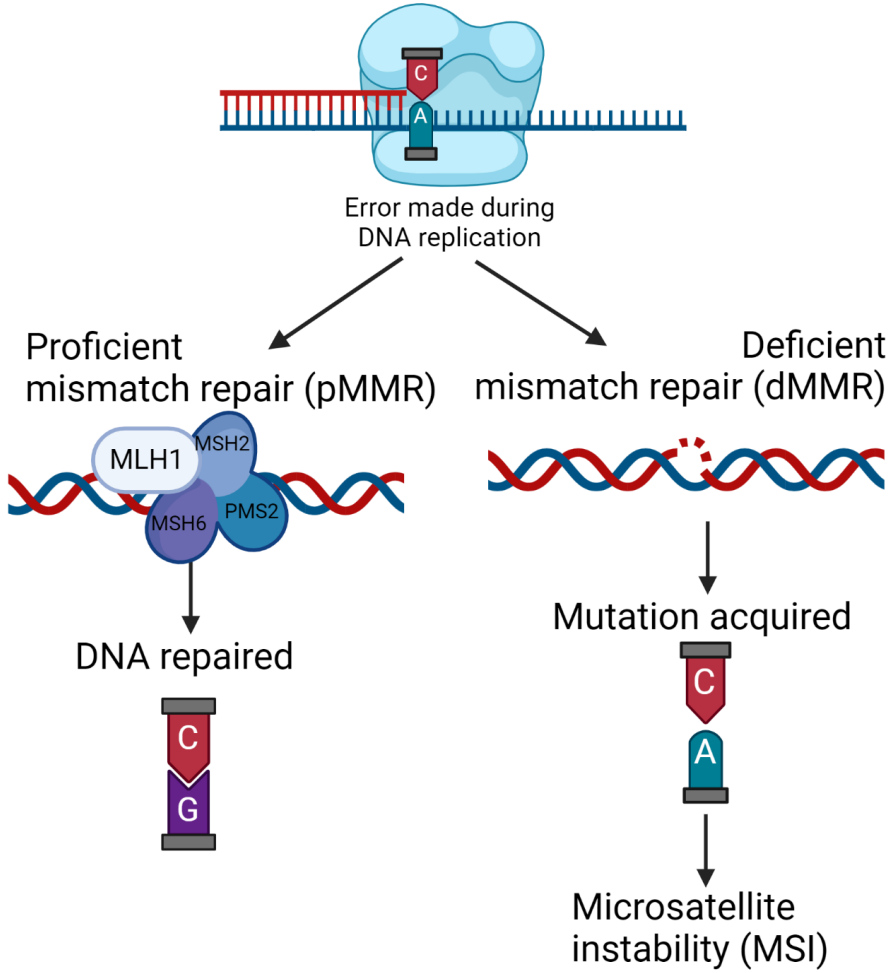
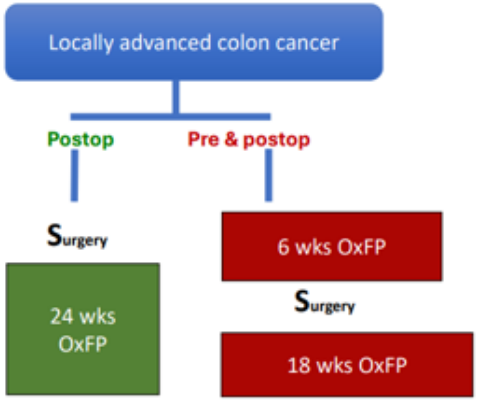
Coloncarcinoom

- Belangrijk verschil tussen MMR-deficiënte tumoren (dMMR) en MMR-proficiënte tumoren (pMMR) en de werkzaamheid van immuuntherapie

- dMMR leidt tot ophoping van “mutational load” en formatie van neo-antigenen
  - Loterij principe



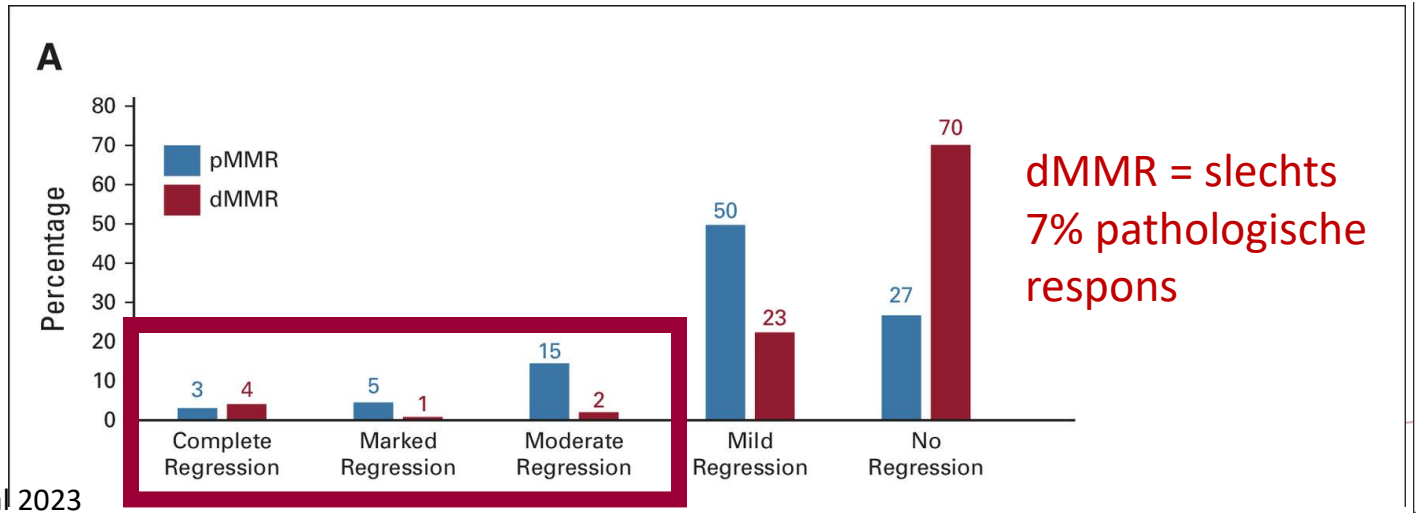
Niet-gemetastaseerd dMMR CRC



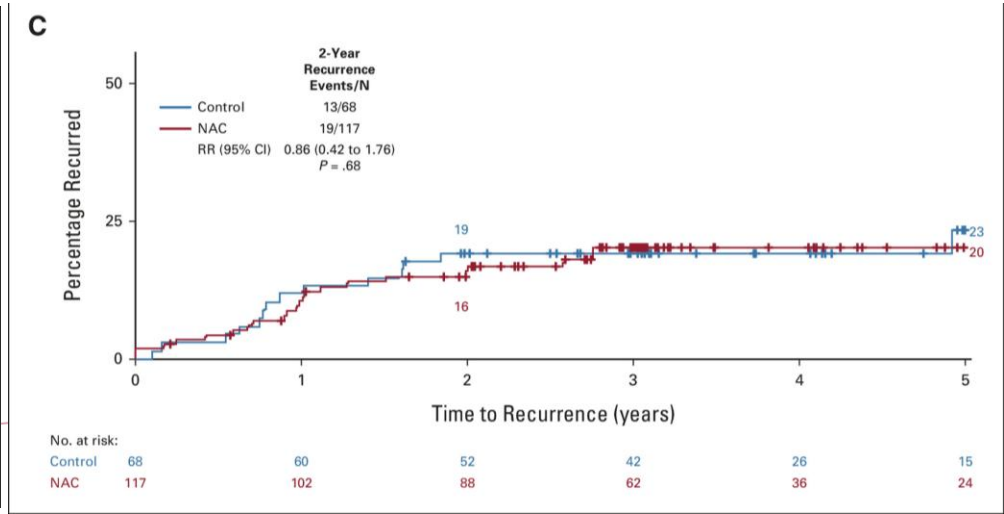
- 10–15% van de niet-gemetastaseerde colon carcinomen is mismatch-repair-deficiënt (dMMR)
- De huidige standaardbehandeling bestaat uit chirurgie, gevolgd door adjuvante chemotherapie, afhankelijk van het pathologisch stadium

Neoadjuvante chemotherapie (FOxTROT-studie) bij T3–4N0–2 tumoren
→ Een pathologische respons van 7% bij dMMR-tumoren

De driejaars recidiefkans bij lokaal gevorderde dMMR-colorectale carcinomen ligt tussen de 20–40%, ondanks adjuvante chemotherapie



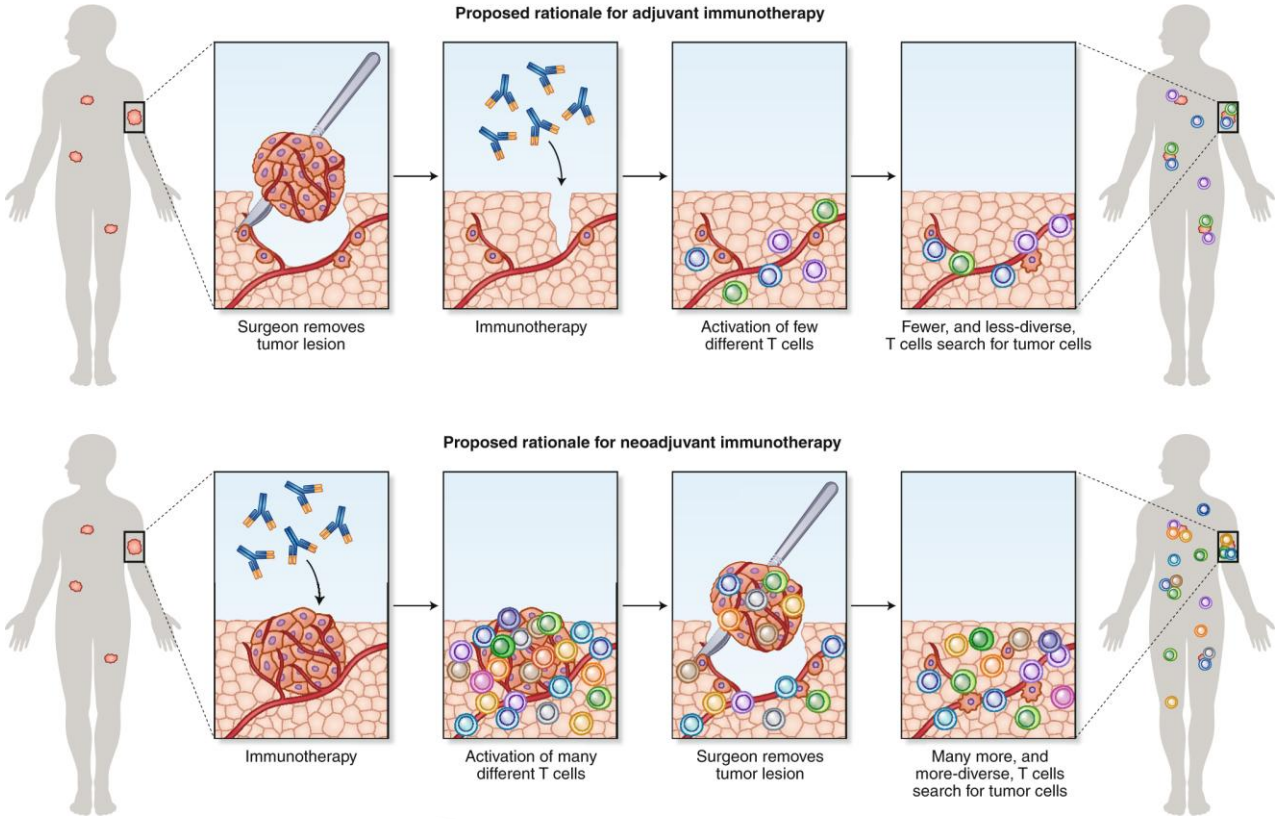
dMMR = slechts 7% pathologische respons



Morton et al 2023

Niet-gemetastaseerd dMMR CRC

Immuuntherapie neo-adjuvant versus adjuvant



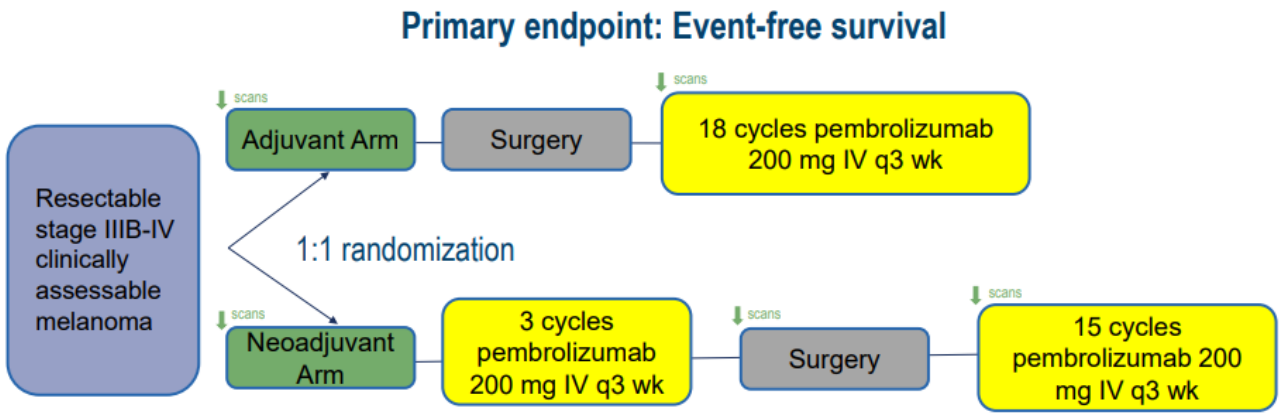
Verbeterde herkenbaarheid door het immuunsysteem door neoadjuvante immuuntherapie

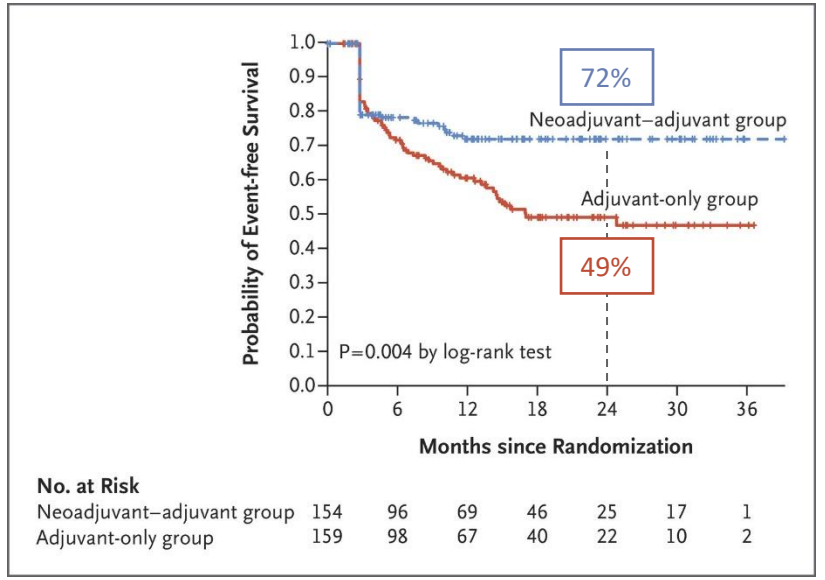
- Grotere hoeveelheid antigenen
- Tumordrainerende lymfeklieren blijven in situ
  → Hier worden T-cellen geprimed en geactiveerd
- Grotere pool van tumorreactieve T-cellen

Versluis et al 2020

Neoadjuvant vs adjuvant immuuntherapie bij melanoom

SWOG 1801





Patel, *NEJM*, 2023

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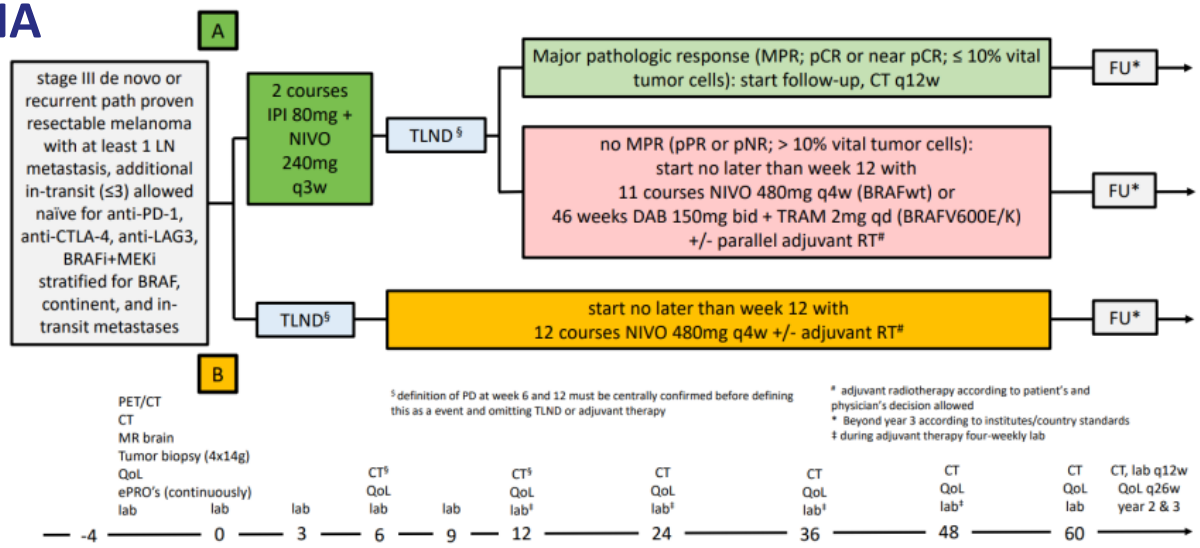
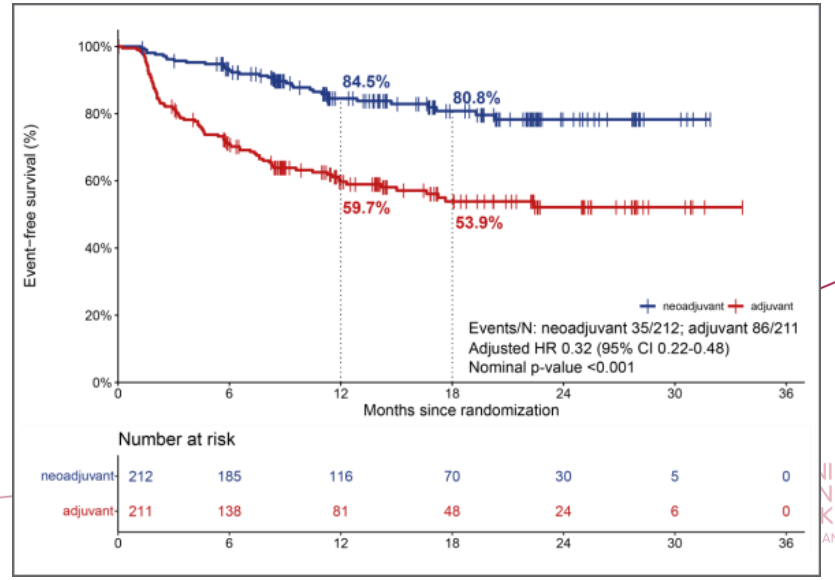




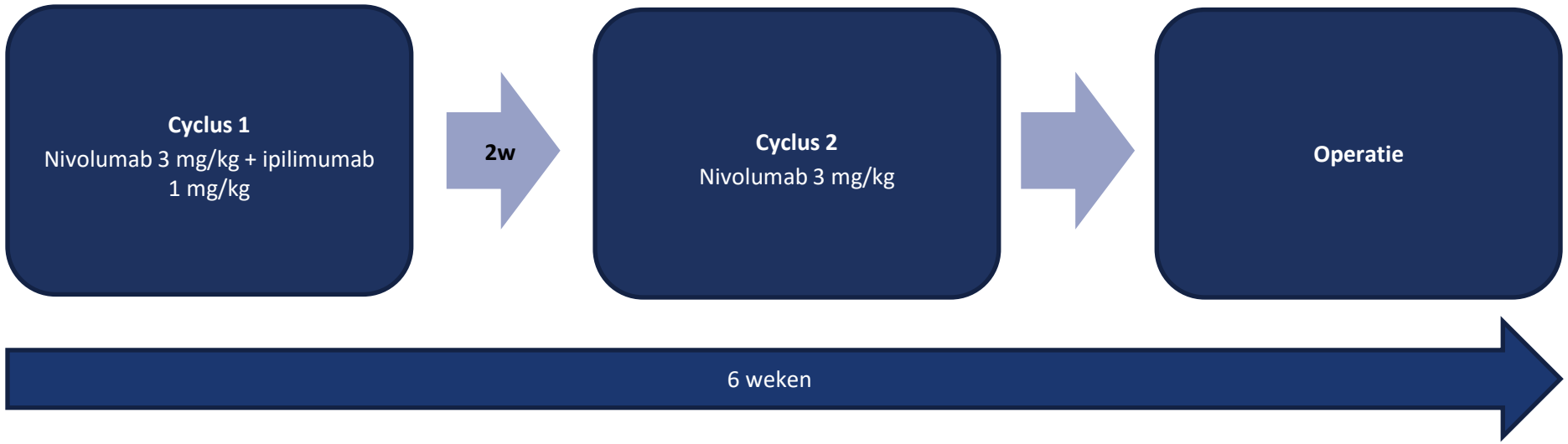
Lucas, *ESMO*, 2024

NICHE 2

Studie design

Belangrijkste inclusiecriteria

- Niet-gemetastaseerd **dMMR coloncarcinoom**, waarvoor nog geen eerdere behandeling heeft plaatsgevonden
- **cT3 en/of N+** op basis van radiologische stadiëring
- Geen klinische of radiologische aanwijzingen voor **obstructie of perforatie**



8 Chalabi et al 2024

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Objectives

Twee primaire eindpunten

- Veiligheid
- Driejaars ziektevrije overleving (DFS)

Secundaire eindpunten

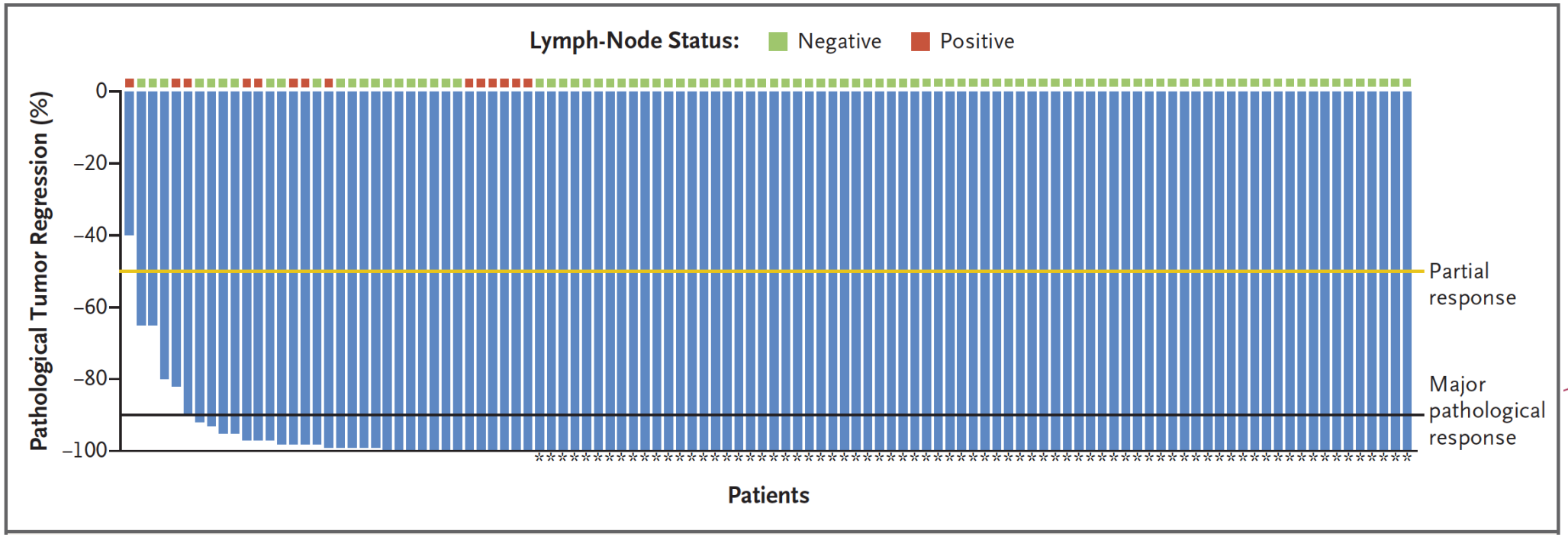
- Pathologische respons
- Translationeel onderzoek
- Circulerend tumor-DNA (ctDNA)

Baseline characteristics

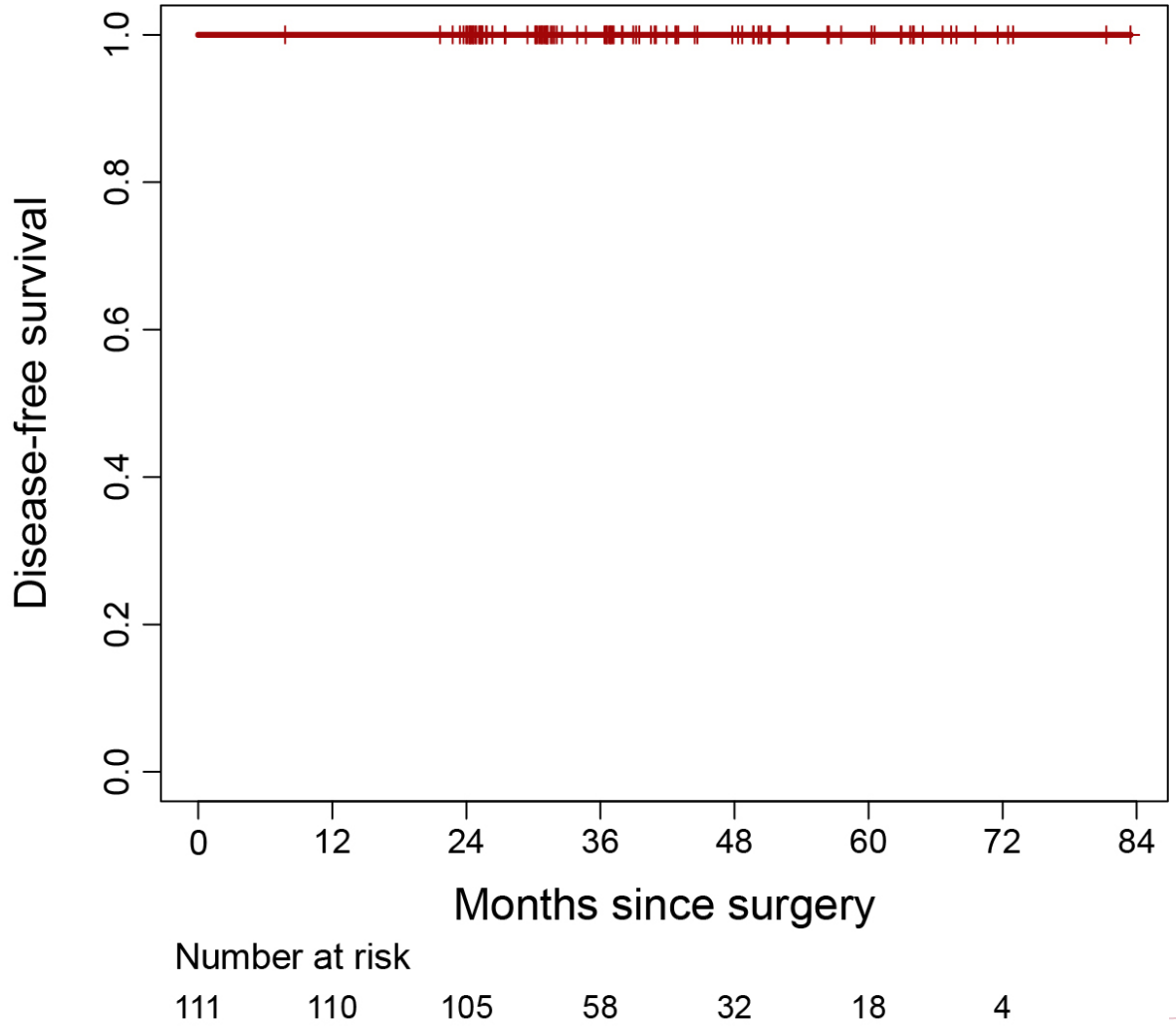
Characteristic	All patients, n = 115
Median age (range) – yr	60 (20-82)
Female sex – no. (%)	67 (58)
Tumor stage – no. (%)	
cT2	17 (15)
cT3 or cT3-4	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status – no. (%)	
cN0	38 (33)
cN+	77 (67)
Lynch syndrome – no. (%)	37 (33)

Pathologische respons in NICHE 2

- Een **pathologische respons** werd gezien bij **98% van de 111 patiënten** in de effectiviteitsanalyse
- **Major pathologische respons** (≤10% resterende vitale tumor): **95%**
- **Pathologische complete respons**: **68%**



Drie jaars ziektevrije overleving



- Median follow-up na chirurgie: 36,6 months (7,8 – 83,4)

Veiligheid

100% van de patiënten ontvingen beide cycli.

- Bij slechts **4% van de patiënten** trad graad 3–4-toxiciteit op.

Bij **2 patiënten (2%)** was er sprake van uitstel van de operatie.

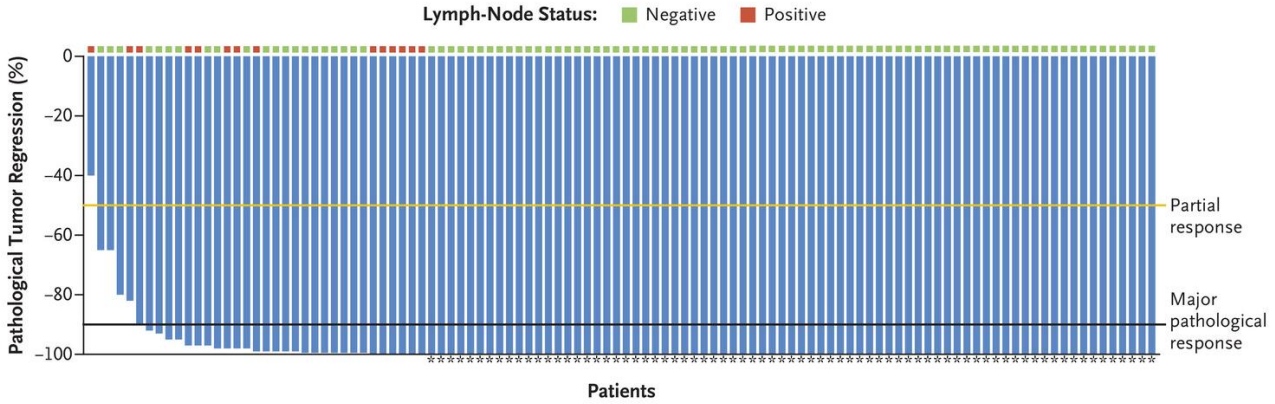
Ondanks de overwegend lage toxiciteitsgraad:

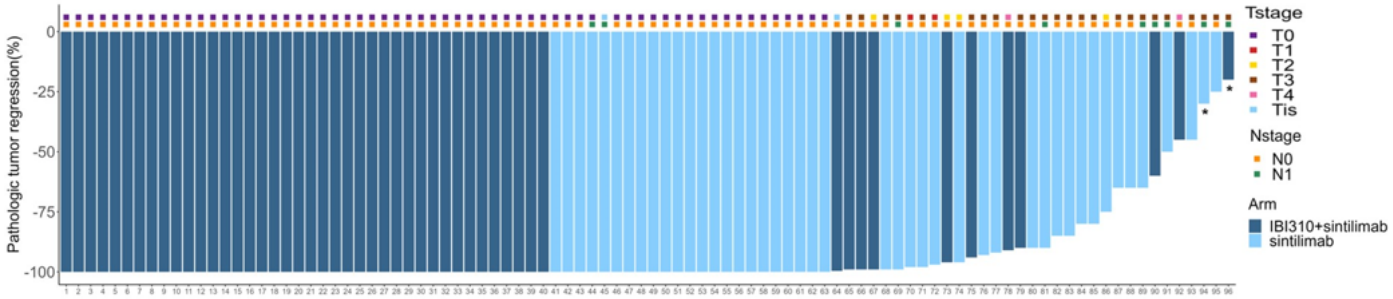
- **12% van de patiënten** ontwikkelde immuungerelateerde hypothyreoïdie.
- **3% van de patiënten** ontwikkelde immuungerelateerde hypocortisolisme.

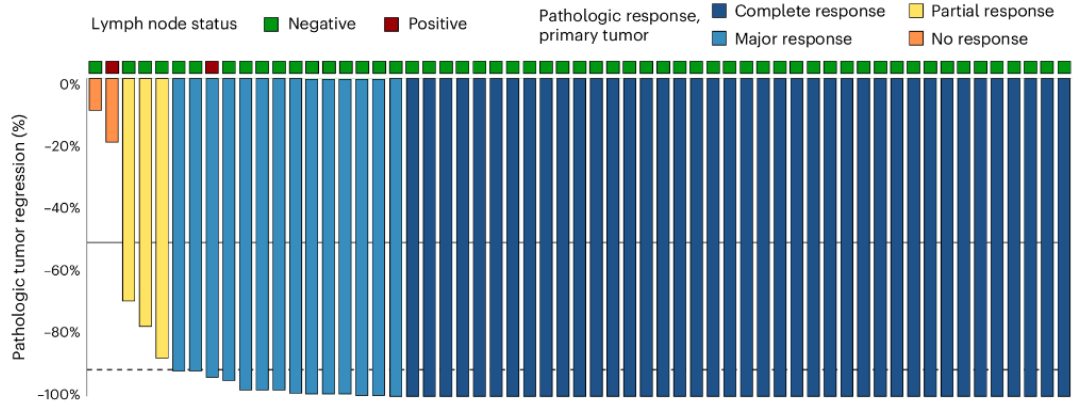
De mediane tijd tussen de laatste immuuntherapie en de operatie bedroeg **5,4 weken**.

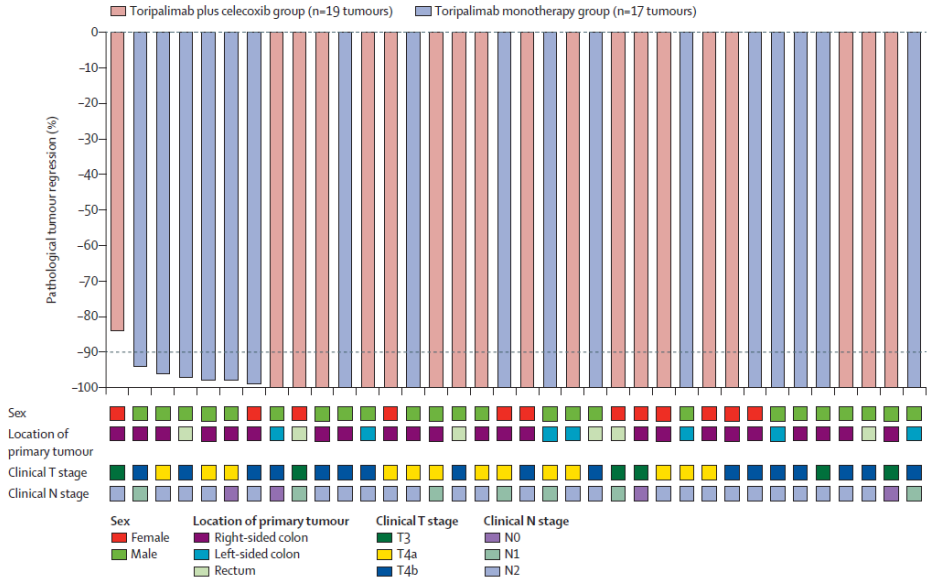
- Bij **100% van de patiënten** waren de resectiemarges vrij van tumor (**R0-resectie**).

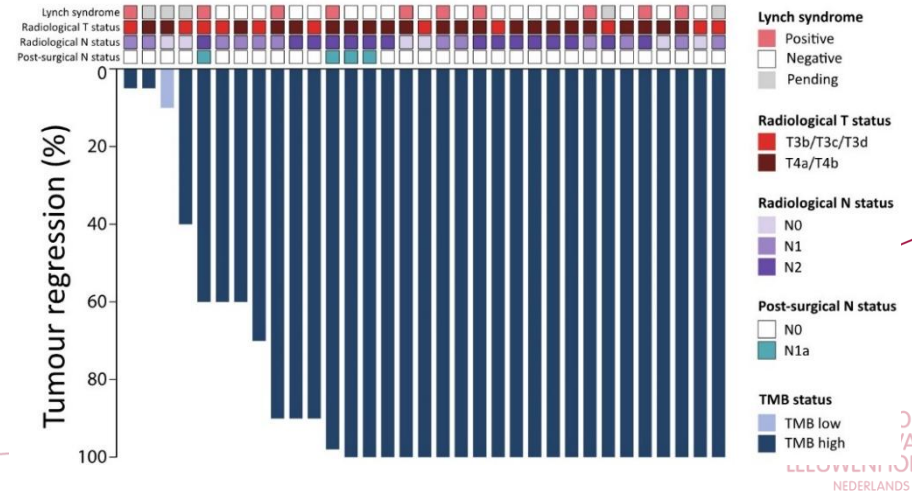
Overall high rates of deep pathological responses











Chalabi, *NEJM,* 2024; Xu, ASCO 2024; De Gooyer, *Nat Med*, 2024; Hu, *Lancet Gastroenterol Hepatol*, 2022; Shiu, ASCO 2024

Critici tegen implementatie van neo-adjuvante immuuntherapie in dagelijkse praktijk

- De aanname dat patiënten met **dMMR coloncarcinoom** na chirurgie een goede prognose hebben.

- Het ontbreken van een **controlegroep**.

- Bezorgdheid over mogelijke **selectiebias** in de NICHE-studie, waarbij een groep met een **gunstiger prognose** is geselecteerd.

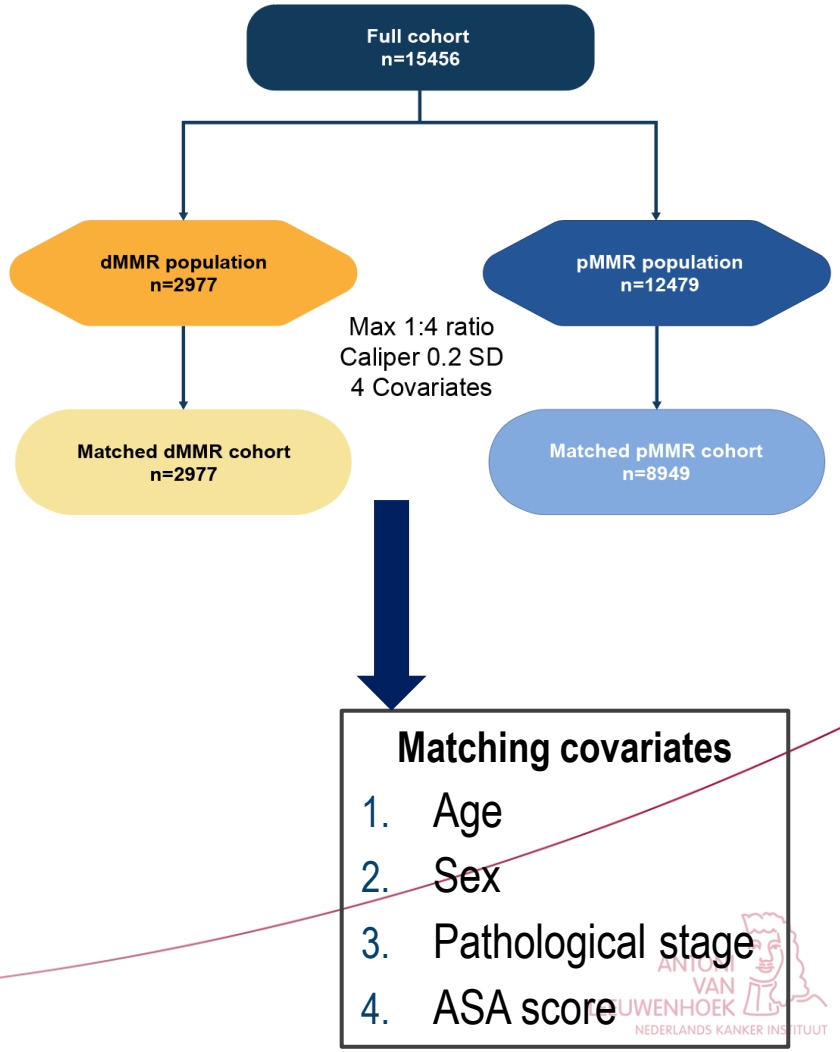
Real-world overleving verschil tussen gematchte stadium I-III dMMR en pMMR CRC patiënten

Studieopzet
- Observationele **gematchte cohortstudie** op basis van de **Nederlandse Kankerregistratie (NKR)**

Populatie
- Patiënten met resectabel **stadium I–III colorectaal carcinoom**
- Resectie uitgevoerd in **2015–2019**

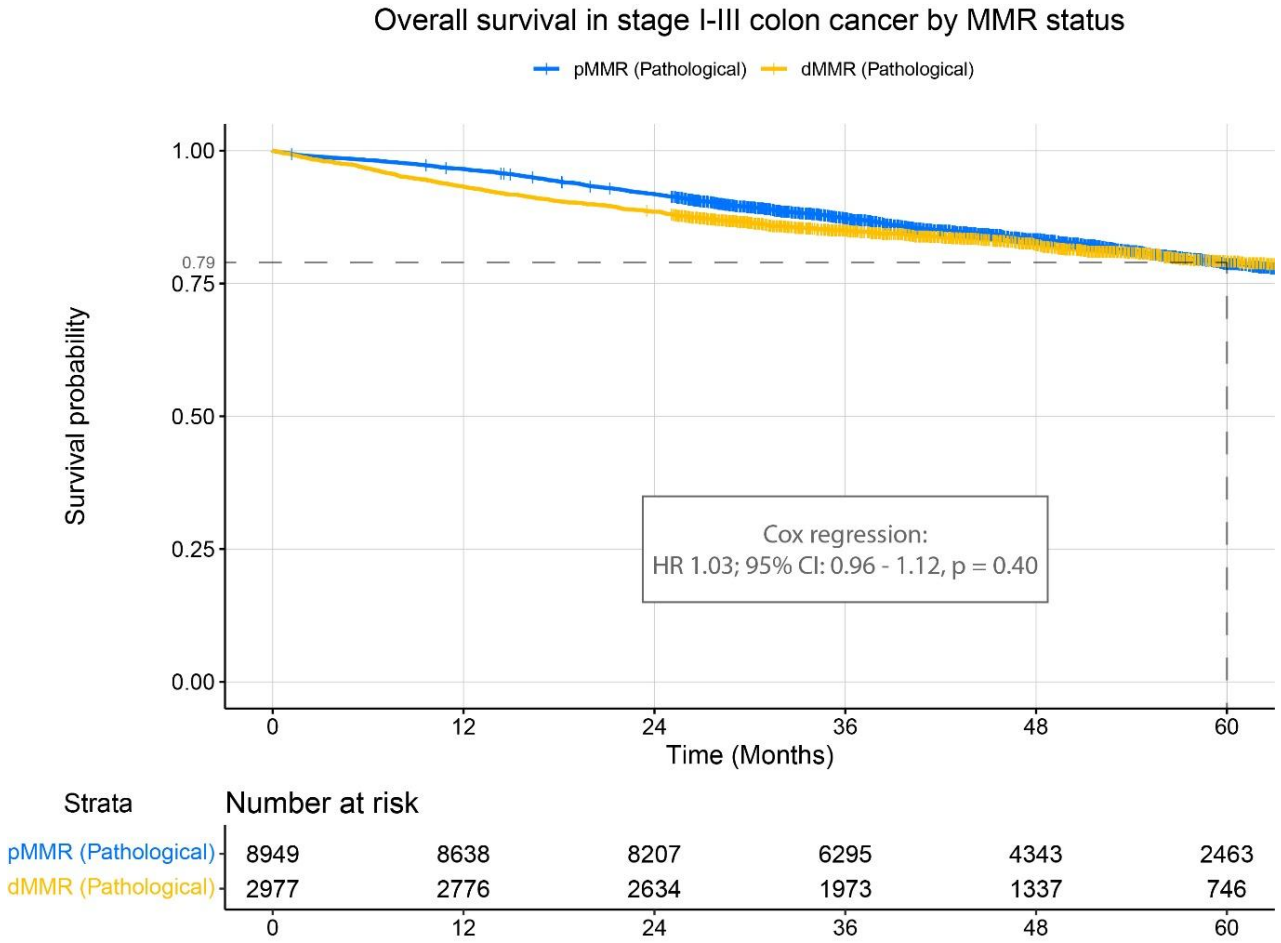
Overlevingsgegevens beschikbaar tot **2022**
Goedkeuring van **pembrolizumab** voor stadium IV colorectaal carcinoom in Nederland: **maart 2021**
Beperkte invloed van pembrolizumab op de **algehele overleving (OS)** van patiënten in dit cohort

Primair eindpunt: Algehele overleving (OS), gestratificeerd naar **MMR-status**



Vaessen et al. submitted

Overleving – matched cohorts dMMR vs pMMR



- Geen significant verschil in OS in dMMR and pMMR patiënten

- OS op 5 jaar
  - dMMR: 79% (95% CI: 77.5% - 80.8%)
  - pMMR: 79% (95% CI: 77.7% - 79.8%)

De Gooyer, Vaessen et al. Poster ESMO 2025

5 jaars OS per stadium en TNM volgens MMR-status

Stage group	Survival probability dMMR vs pMMR	
	5-year OS dMMR CC % (95% CI)	5-year OS pMMR CC % (95% CI)
Stage I-III	79% (78 - 81), *n* = 2977	79% (78 - 80), *n* = 8949
Pathological stage I	89% (86 - 92), *n* = 673	90% (89 - 92), *n* = 2062
Pathological stage II	82% (79 - 84), *n* = 1299	82% (81 - 84), *n* = 3445
pT3N0	84% (82 - 87), *n* = 1075	85% (83 - 87), *n* = 2790
pT4N0	**71% (65 - 78), n = 223**	**71% (67 - 75), n = 730**
Pathological stage III	**69% (66 - 72), n = 1005**	**68% (67 - 70), n = 3442**
pT1-3N+	77% (73 - 80), *n* = 732	75% (73 - 77), *n* = 2704
pT4N+	49% (43 - 56) *n* = 272	46% (41 - 50), *n* = 730
Clinical stage I	83% (79 – 88), *n* =494	86% (84 - 88), *n* = 1915
Clinical stage II	75% (72 - 79) *n* = 616	75% (72 -78), *n* = 1648
cT3N0	80% (76 - 85) n = 387	78% (75 - 81), n = 1191
cT4N0	**60% (51 - 70) n = 147**	**67% (61 - 73), n = 298**
Clinical stage III	77% (74 - 80) *n* = 967	75% (73 - 77), *n* = 1985
cT1-3N+	80% (76 - 84) *n* = 582	77% (74 - 80), *n* = 1244
cT4N+	**67% (60 - 75) n = 187**	**75% (58 - 72), n = 263**

- OS in dMMR en pMMR CRC is equal as per pathologic stage
- Pathologic stage III dMMR CRC has an unfavorable 5-year OS
- Pathologic T4 = irrespective of N status a negative prognostic factor
- Radiologic T4 = negative prognostic factor for OS, irrespective of pathologic stage

De Gooyer, Vaessen et al. Poster ESMO 2025

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Comparison of outcomes in clinical trials of locally advanced dMMR colon cancer: data from the FOxTROT and NICHE-2 trials

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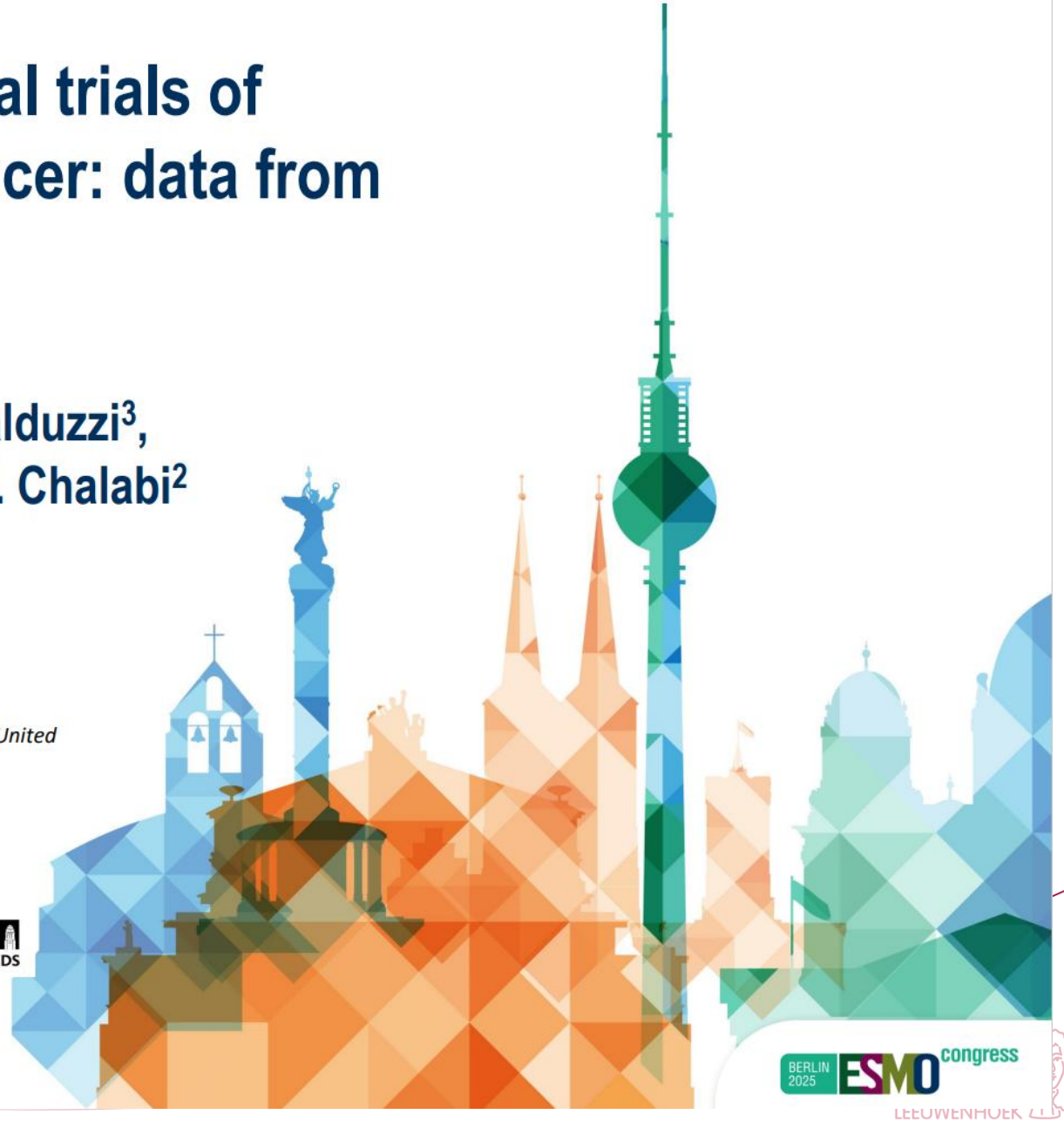
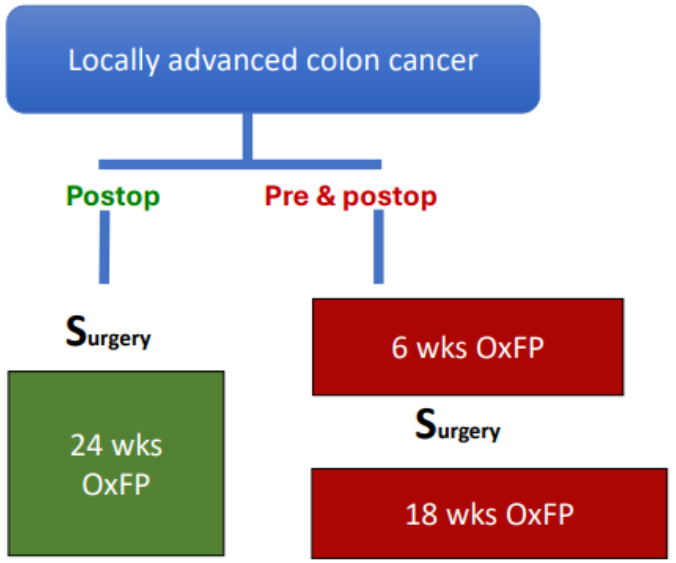
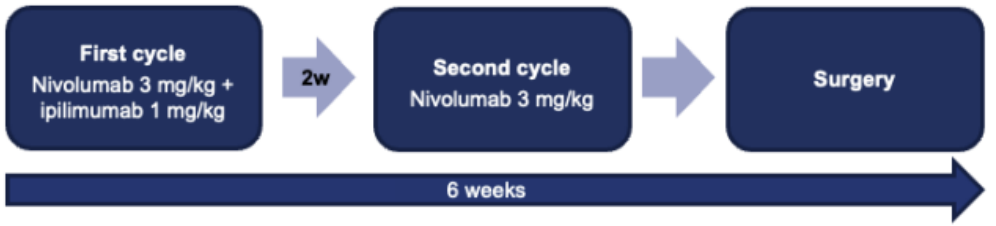


The FOxTROT & NICHE-2 Trial Designs

	Key Eligibility Criteria
FOxTROT	• CT assessed cT3+, cN0-2 • No metastatic disease • No clinical or radiological signs of obstruction
NICHE-2	• CT assessed cT3+ or N+ • No metastatic disease • No clinical or radiological signs of obstruction • Confirmed dMMR/ MSI-H status





Exclusion criteria:
- cT2 tumors in NICHE-2
- pMMR pts in FOxTROT

Jenny Seligmann

Morton, JCO, 2023; Chalabi, NEJM, 2024

Patient karakteristieken voor dMMR CRC FOxTROT vs NICHE-2

		FOxTROT N=185	NICHE-2 N=94
Median Age		65	57.5
Gender	Female	87 (47.0%)	58 (61.7%)
	Male	98 (53.0%)	36 (38.3%)
Tumor side	Right	160 (86.5%)	62 (66.0%)
	Left	25 (13.5%)	18 (19.1%)
Radiological T-stage	T3	120 (64.9%)	22 (23.4%)
	T4	65 (35.1%)	72 (76.6%)
Radiological N-stage*	N0	35 (19.3%)	24 (25.5%)
	N+	146 (80.7%)	70 (74.5%)

*missing information in 2 pts in FOxTROT; % excludes missing

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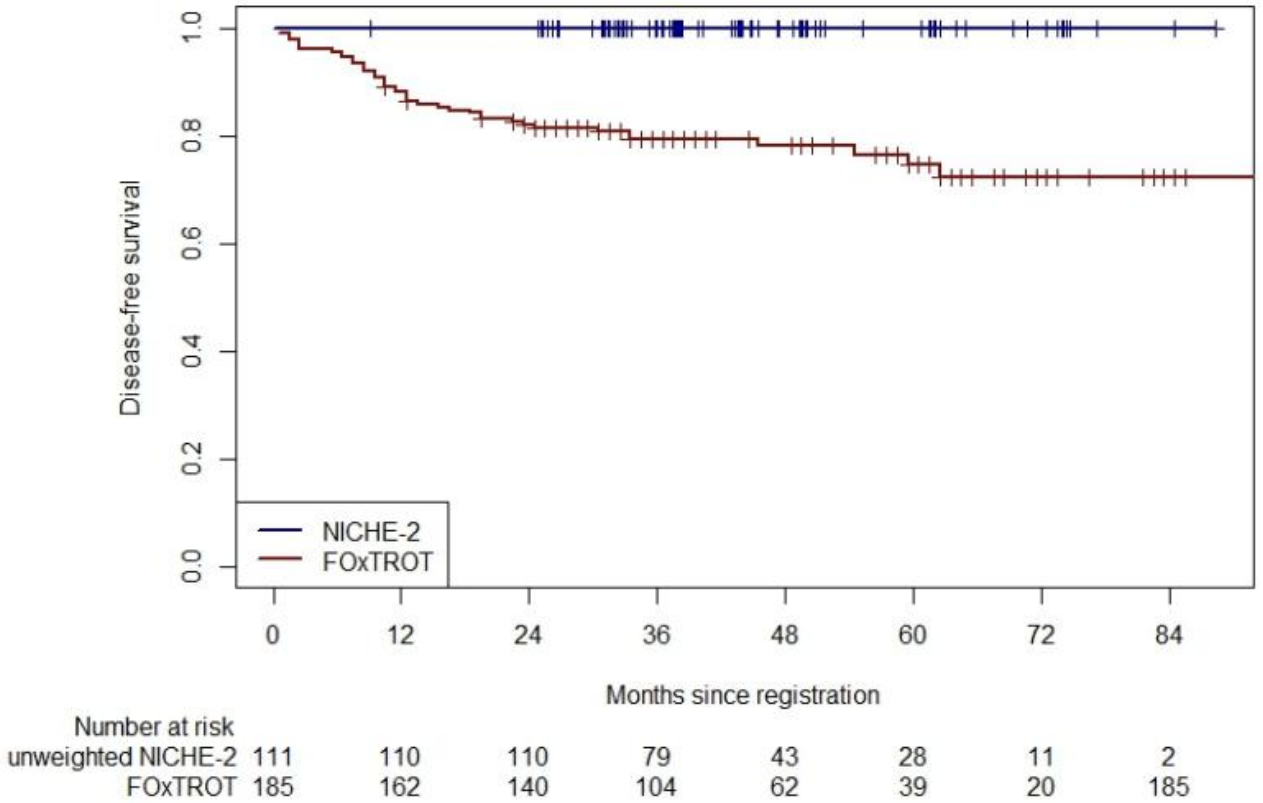
Primary analysis: 3 year Disease free survival

Neoadjuvant nivolimab and ipilimumab was superior to OxFp delivered before or after surgery



NICHE-2 (neoadjuvant nivolimab + ipilimumab)
DFS = 100%

FOxTROT (all strategies)
DFS = 80% (95%CI = 73-85%)

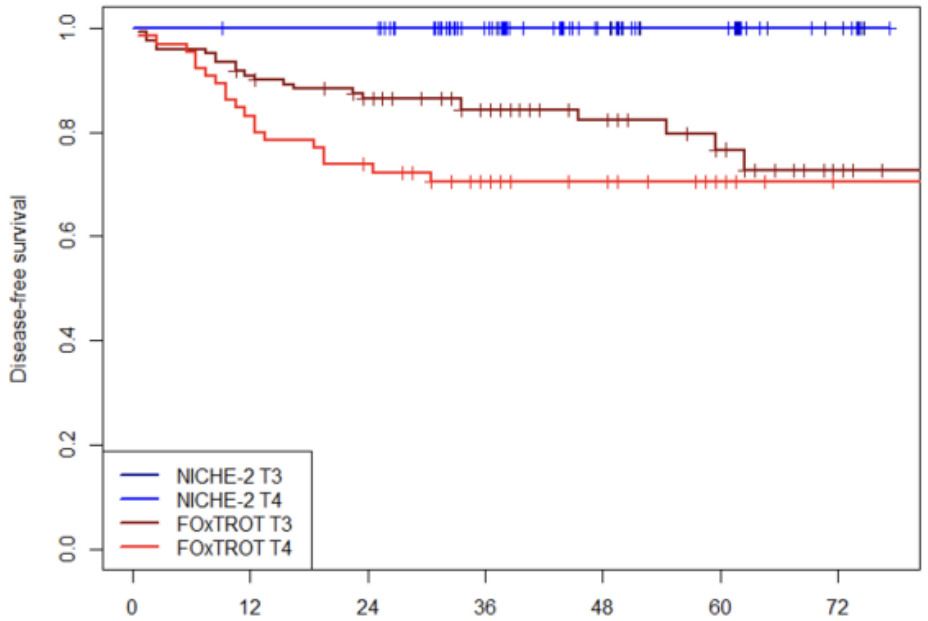
Log rank p<0.001

No differences observed in DFS between the 2 FOxTROT strategies (p=0.9)

Seligmann, ESMO 2025

Disease free survival by T-stage

Neoadjuvant nivolimab and ipilimumab was superior to OxFp delivered before or after surgery, especially for poor prognostic **clinical** T4 patients



Number at risk							
NICHE-2 T3	22	22	22	22	18	10	4
NICHE-2 T4	72	71	71	46	18	13	4
FOxTROT T3	120	108	95	71	39	24	10
FOxTROT T4	65	54	45	33	23	15	65

NICHE-2 cT3 DFS = 100%
NICHE-2 cT4 DFS = 100%

FOxTROT cT3 DFS = 84% (95% CI 76-90%)
FOxTROT cT4 DFS = 70% (95% CI 58-80%)

Log rank p<0.001

Seligmann, ESMO 2025

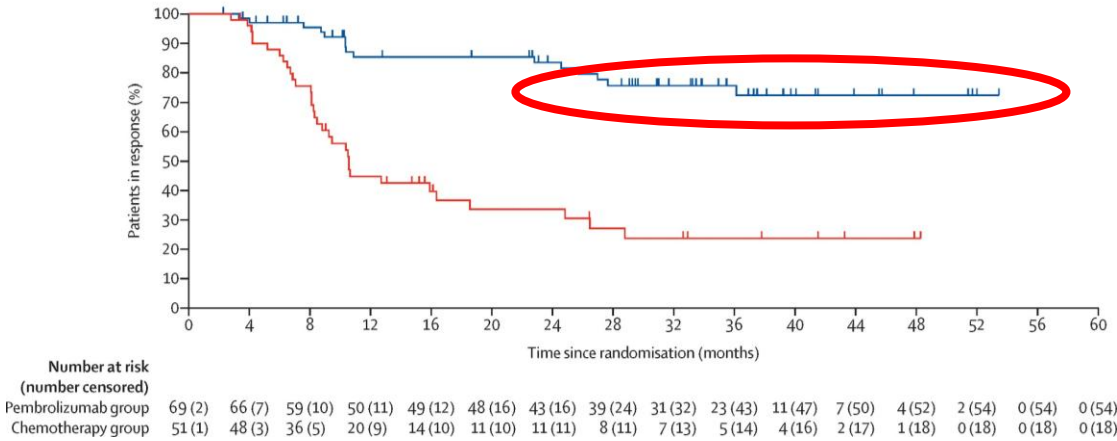
Conclusie NKR en NICHE / FOxTROT analyses

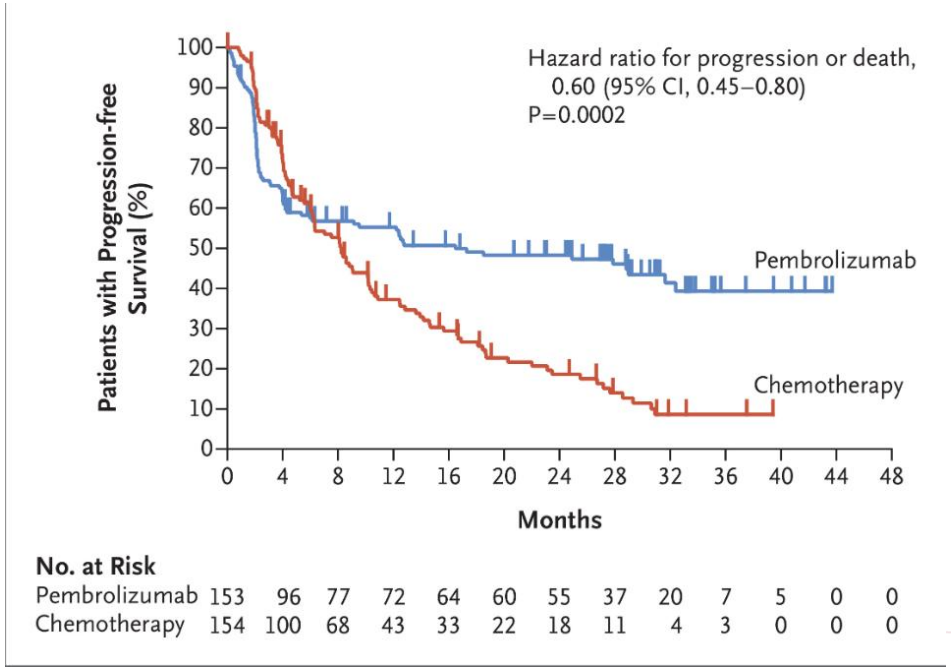
- Overleving is gelijk voor patiënten met een dMMR and pMMR CRC in gematchte cohorten

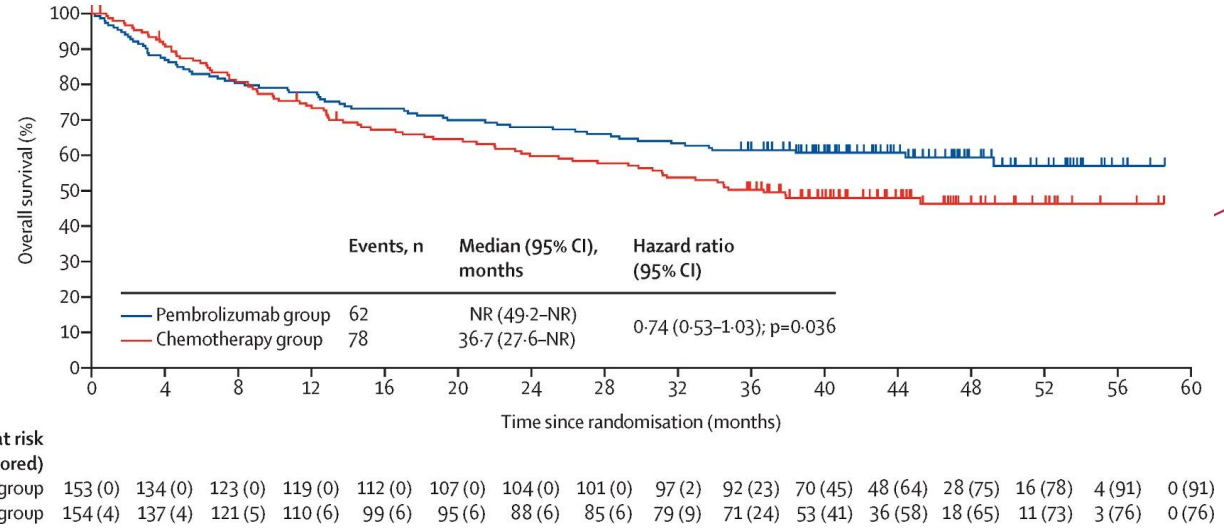
- T4 tumoren zijn zowel pathologisch als radiologisch een sterke negatieve prognostische factor

Gemetastaseerd CRC; dMMR

- Keynote-177
  - RCT; Pembrolizumab vs chemotherapie
  - Cross over was toegestaan bij progressie
  - Geleid tot registratie pembrolizumab





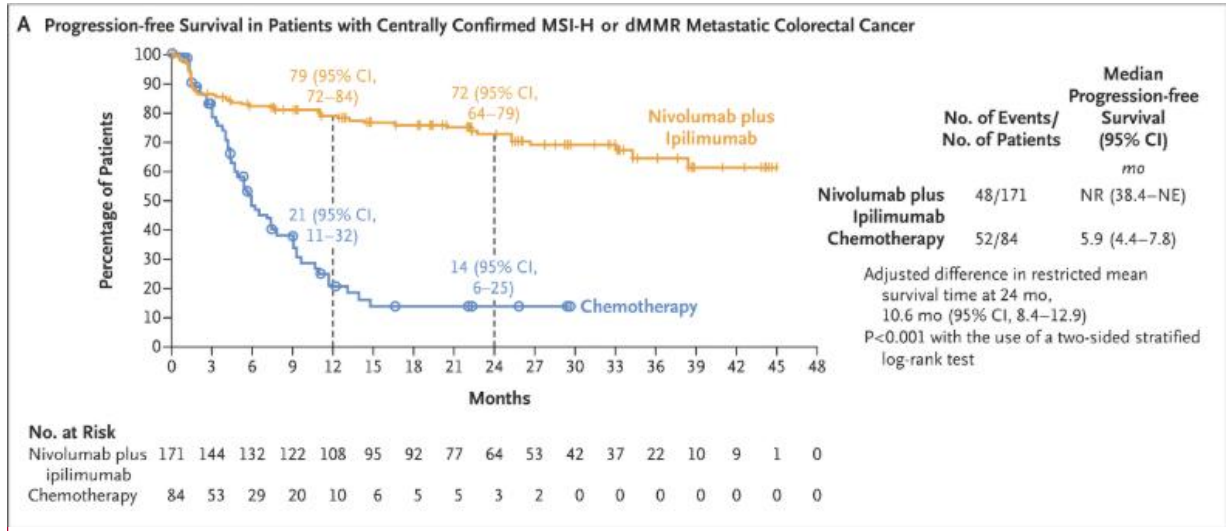


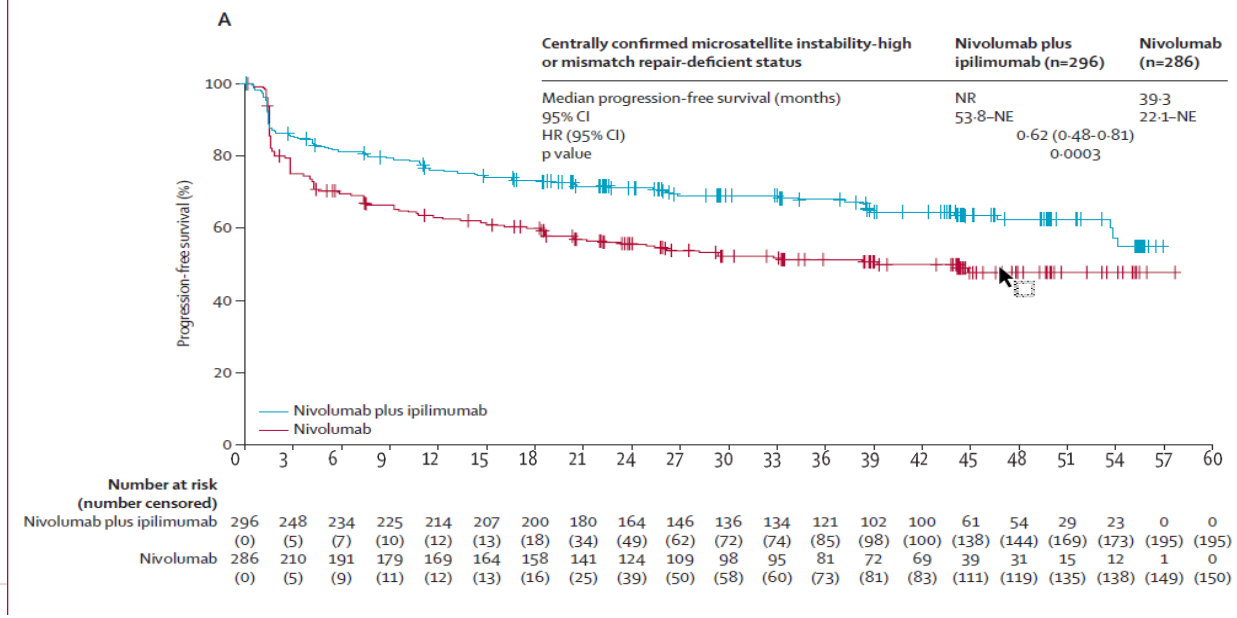
Gemetastaseerd CRC; dMMR

- Checkmate 8HW
  - RCT; Nivolumab+ipilimumab vs nivolumab vs chemotherapie
  - Gemetastaseerd **<u>OF niet-resectabel</u>**

Beschikbaar in Nederland sinds april 2026 (niet alle ziekenhuizen)

	Nivolumab plus ipilimumab group (n=296)	Nivolumab group (n=286)
Objective response rate (95% CI)	209 (71%) [65–76]	165 (58%) [52–64]
Best overall response		
Complete response	90 (30%)	80 (28%)
Partial response	119 (40%)	85 (30%)
Stable disease	40 (14%)	53 (19%)
Progressive disease	30 (10%)	54 (19%)
Unevaluable	17 (6%)	14 (5%)





26 Andre et al NEJM 2024, Andre et al Lancet 2025

Take home message

- Het begint bij jullie

- Vraag altijd MMR status aan de patholoog bij het afnemen van biopten van voor maligniteit verdachte afwijking in het colon / rectum

- Als dMMR overleg met de oncoloog ten aanzien van mogelijkheden tot behandeling met immuuntherapie

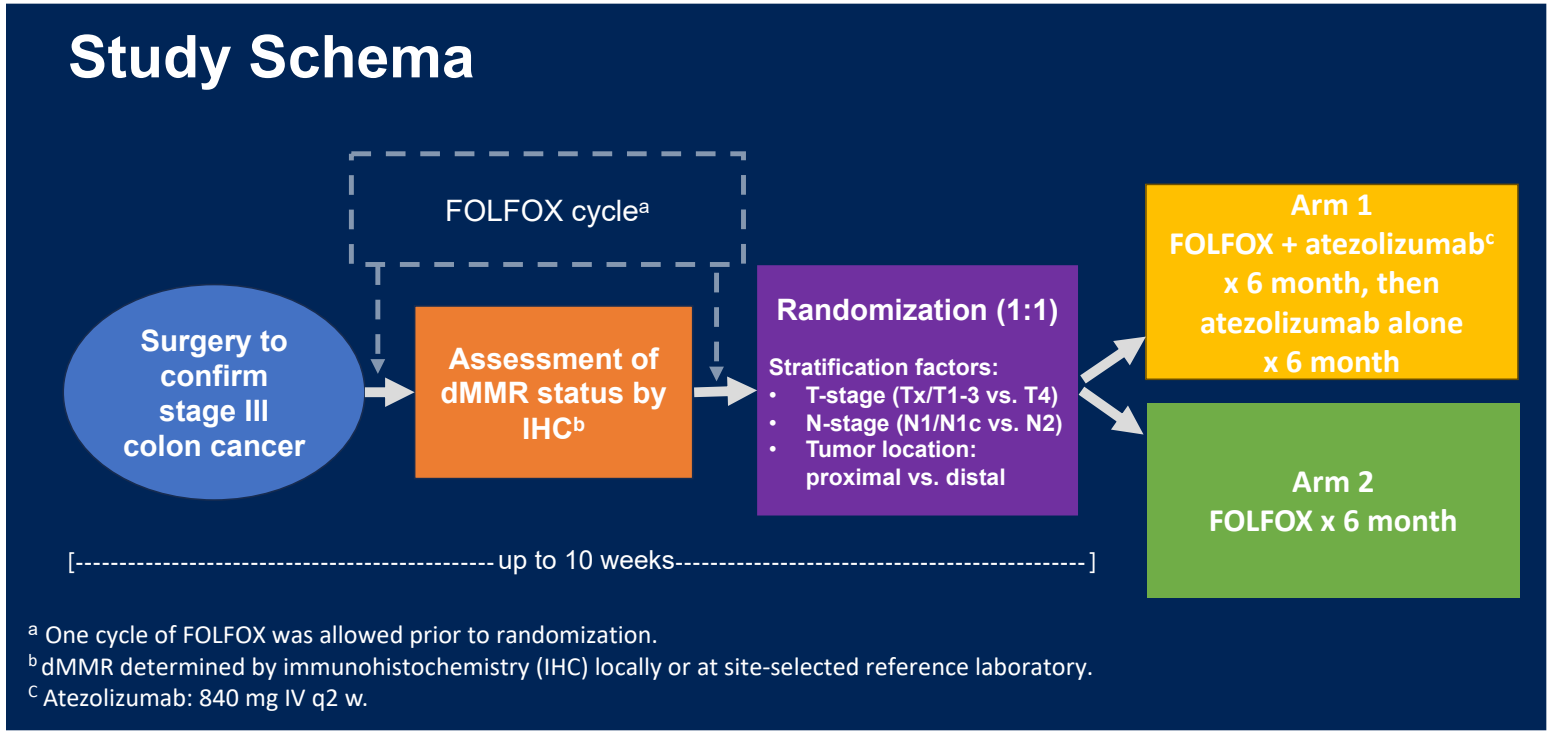
Momenteel lopende neo-adjuvante studies met immuuntherapie (AvL)

- NICHE momenteel vol
  - Wel bezig met nieuw orgaansparend cohort

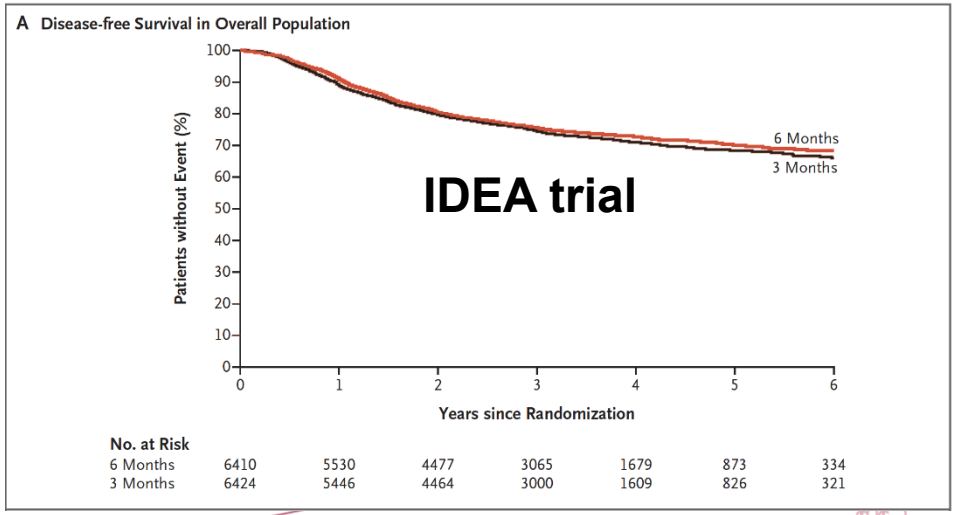
- NEOASIS
  - Basket trial voor zowel pMMR als dMMR tumoren (zonder metastasen) (bijv. mamma, endometrium, slokdarm/maag, rectum, Merkelcel, sarcoom).
  - Behandeling met botensilimab+balstilimab
  - dMMR CRC vol, wel nog opties voor dMMR upper-GI tumoren (slokdarm, maag, dunnedarm)
  - dMMR rectumcarcinoom; orgaansparend cohort

Vragen?

ATOMIC study: adjuvant chemotherapy +/- atezolizumab for stage III dMMR colon cancer



- stage 3 dMMR tumors
  - R0 resections
- Post-surgery MMR status testing
- 6 months of adjuvant folfox in both arms



Grothey et al, NEJM 2018

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High-risk vs low-risk tumors in de ATOMIC studie

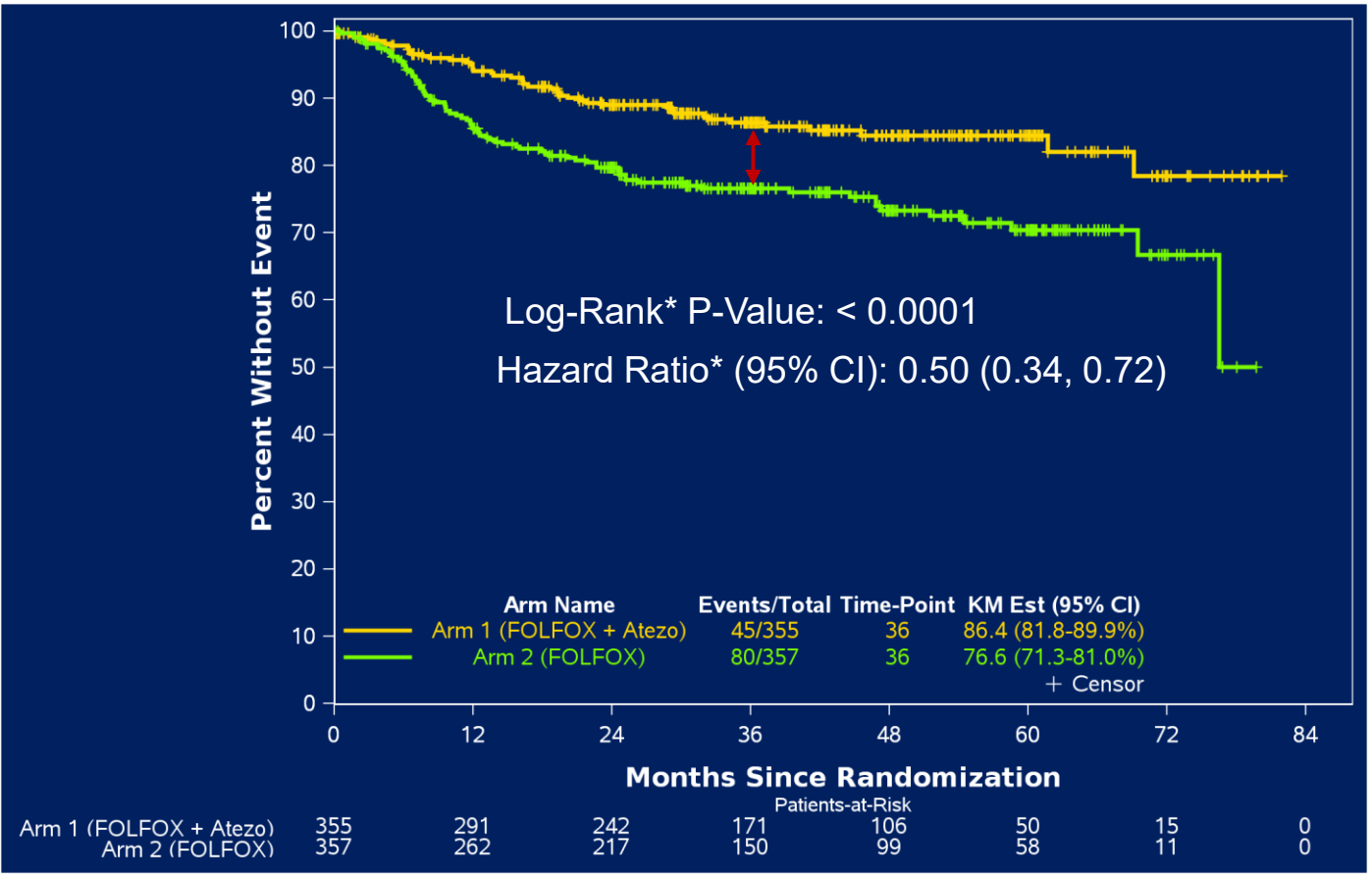
	mFOLFOX6 + Atezo (N=355)	mFOLFOX6 (N=357)
Age (years)		
Median	65	63
Q1, Q2	51.0, 73.0	48.0, 73.0
Sex, n (%)		
Median	186 (52.4%)	206 (57.7%)
Median	169 (47.6%)	151 (42.3%)
Race, n (%)		
White	302 (85.1%)	305 (85.4%)
Black	28 (7.9%)	22 (6.2%)
Other	25 (6.0%)	30 (8.4%)
Primary Tumor Site, n (%)		
Proximal	301 (84.8%)	296 (82.9%)
Distal	53 (14.9%)	57 (16.0%)
Multiple	1 (0.3%)	4 (1.1%)

	mFOLFOX6 + Atezo (N=355)	mFOLFOX6 (N=357)
T-Stage, n (%)		
T_x	0	1 (0.03%)
T_1	11 (3.1%)	4 (1.1%)
T_2	30 (8.5%)	22 (6.2%)
T_3	202 (56.9%)	216 (60.5%)
T_4	112 (31.5%)	114 (31.9%)
N-Stage, n (%)		
N_1/N_{1c}	226 (63.7%)	225 (63.0%)
N_2	129 (36.3%)	132 (37.0%)
Risk Group, n (%)		
Low (T_x-T_3 and N_1/N_{1c})	164 (46.2%)	164 (45.9%)
High (T_4 and/or N_2)	191 (53.8%)	193 (54.1%)
ECOG, n (%)		
0	238 (67.0%)	225 (63.0%)
1	111 (31.3%)	127 (35.6%)
2	6 (1.7%)	5 (1.4%)

High-risk (T4 and/or N2) tumors well balanced between arms

46% low-risk tumors in each arm

Primary endpoint: 3-year DFS



10% improvement in 3-year DFS: statistically significant and clinically meaningful

13% recurrences <u>despite</u> 6 months of folfox + 1 year atezo

How many, and which, patients are cured with surgery alone?

Safety and tolerability

Characteristics	mFOLFOX6 + Atezo (N=346)#	mFOLFOX6 (N=334)#
Median treatment duration	5.5 months (mFOLFOX6); 10.9 months (Atezo)	5.4 months
Any Grade AE, % (n) Treatment-related	100% (346) 99.7% (345)	95.1% (329) 94.2% (326)
Grade 3-4 AE, % (n) Treatment-related	83.8% (290) 72.3% (250)	69.1% (239) 59.2% (205)
Grade 5 AE, % (n) Treatment-related	1.7% (6) 0.6% (2)*	0.6% (2) 0.0% (0)

- Higher rate of grade 3-4 AEs with folfox + atezo
- **Expected**: hypothyroidism; diarrhea
- **Unexpected**: grade 4 neutropenia in atezo arm (14% vs 7%); neuropathy
- **Patient deaths**: 6 (1.7%) in atezo arm, vs 2 (0.6%) in control arm

- Vraag bij presentatie MH Geukes Foppen
-
- Welke tumoreigenschap is van belang voor de mogelijke werkzaamheid van neoadjuvante immuuntherapie bij het coloncarcinoom?
- A: pMMR
- B: RAS-mutatie
- C: dMMR
- D: BRAF-mutatie
-
- Juiste antwoord: C — dMMR (deficiënt mismatch repair)