Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen / Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	Geen disclosures

State of the Art

Urogenitale en blaastumoren

- Focus op immuun checkpoint inh -

Harm Westdorp, MD, PhD

Internist-oncoloog
Afdeling Medische Oncologie
Radboudumc, Nijmegen

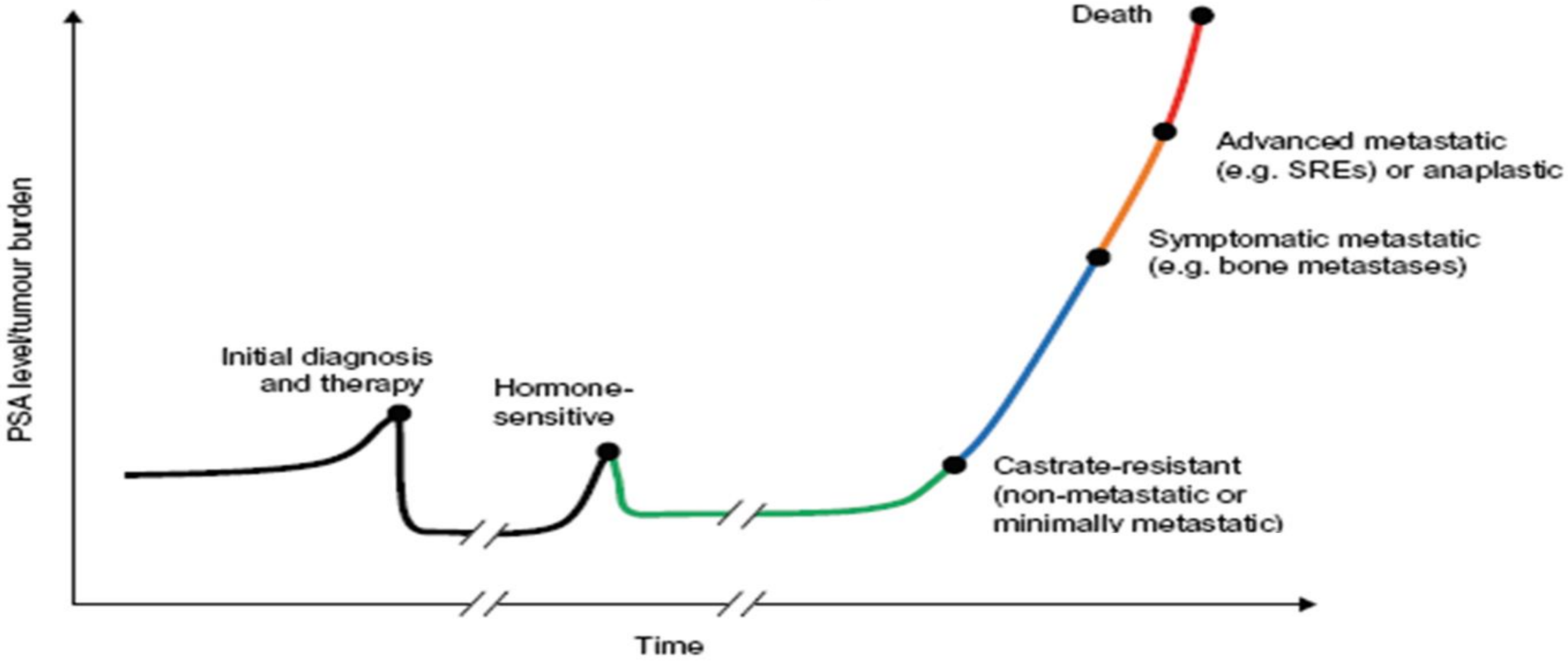
Dinsdag 27 september 2022, Antropia, Driebergen

Radboud University

Radboudumc
university medical center

Prostaatcarcinoom

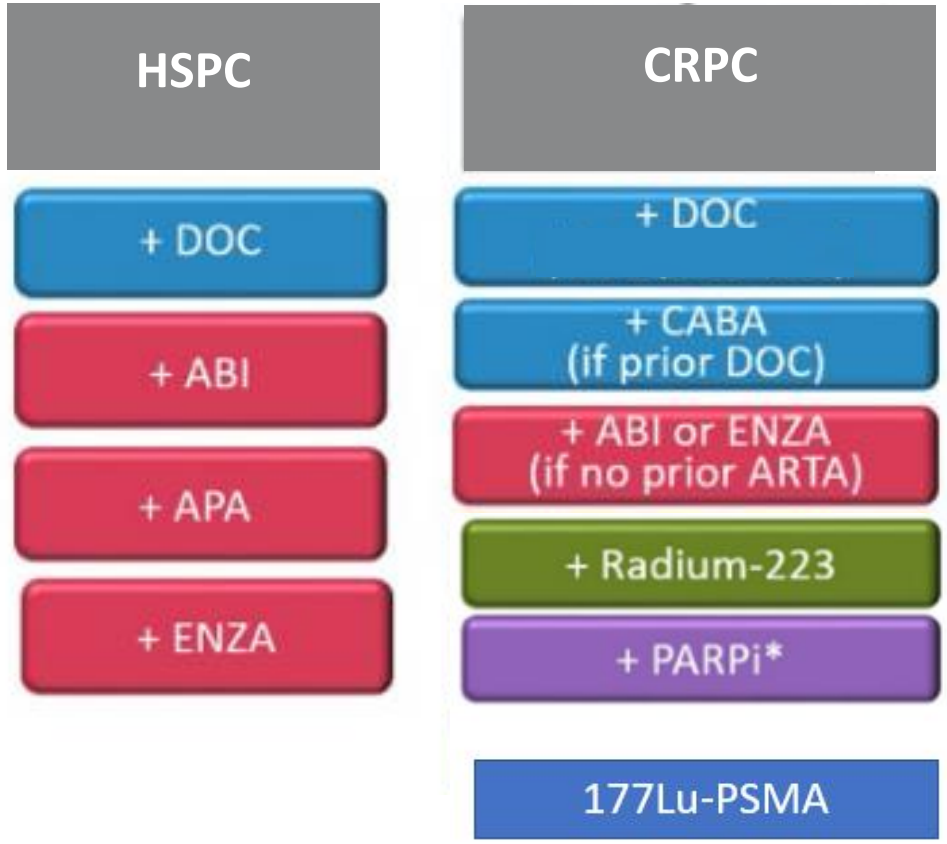
Het beloop bij gemetastaseerd prostaatcarcinoom



Oudard et al. Cancer Treatment Reviews 2013

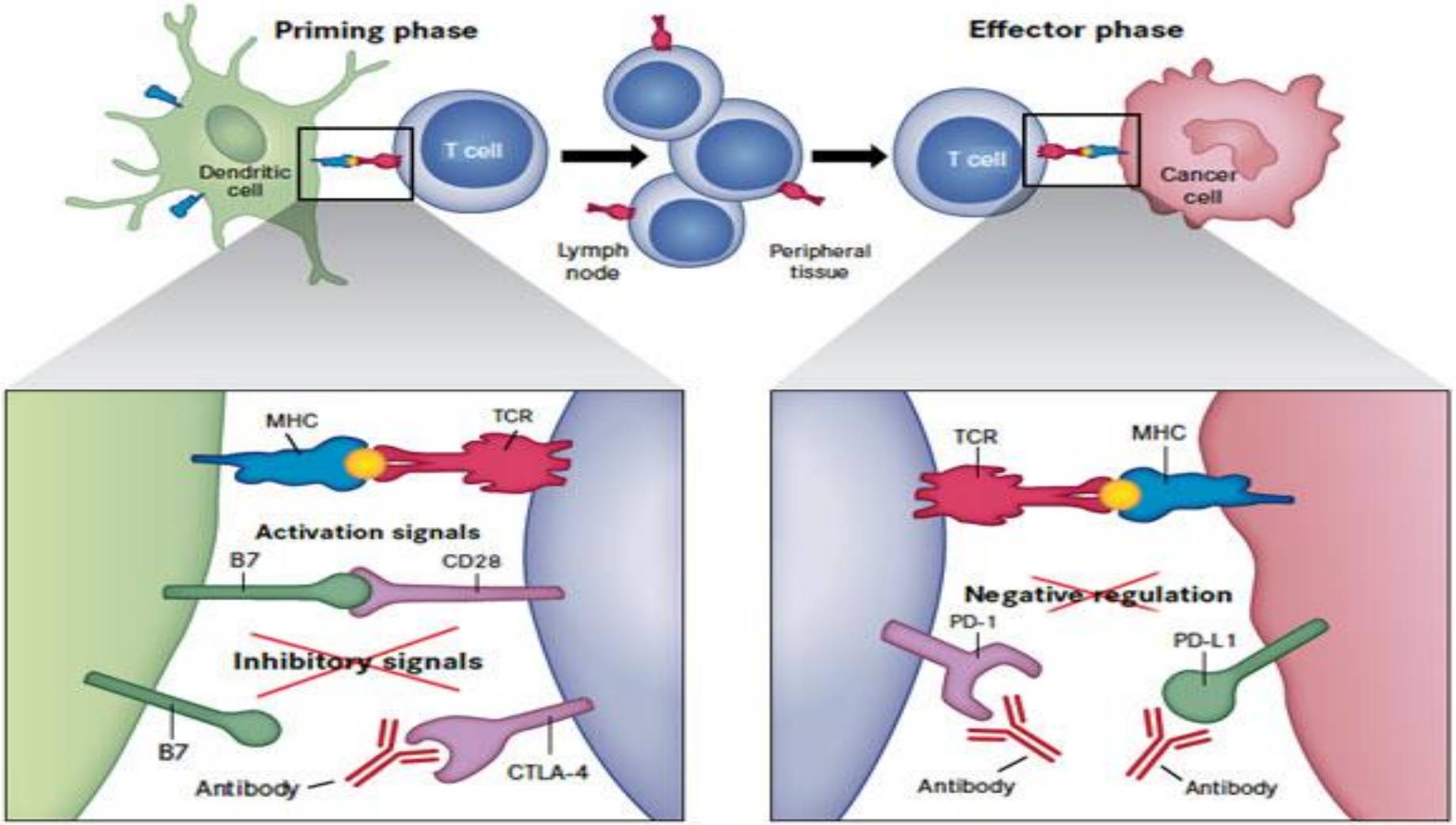
Radboudumc

Uitbreiding van het therapeutisch arsenaal bij gemetastaseerd hormoon-sensitief PC en castratie-resistant PC



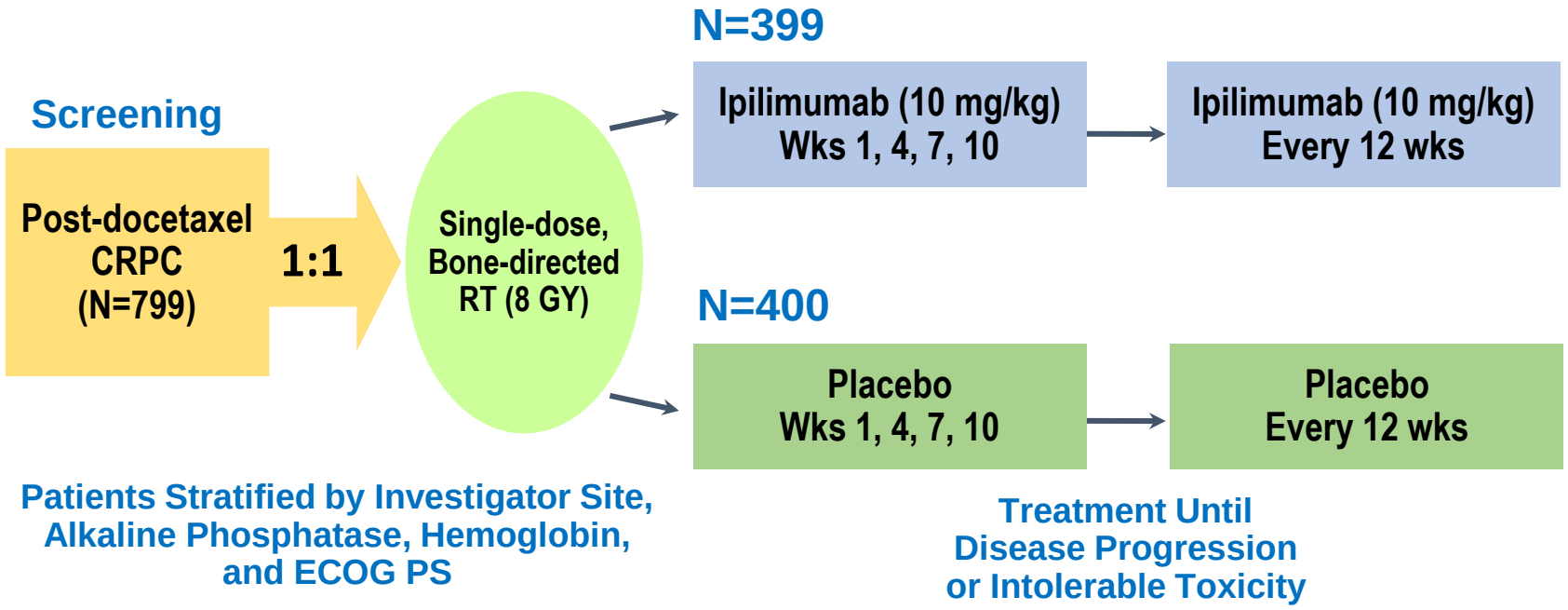
Hoe zit het met immuun checkpoint inh bij PCa?

Immune checkpoint inhibitors (ICIs)



CRPC: immunotherapie

CA184-043: Study Design

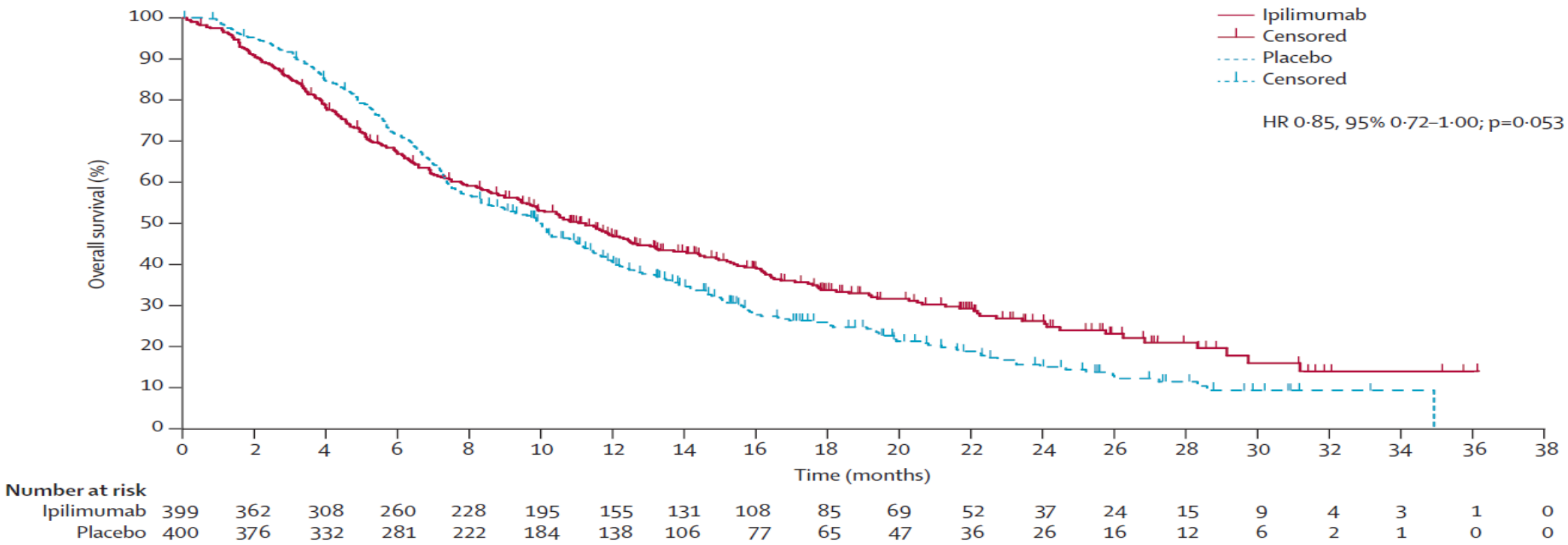


- Primary endpoint: overall survival (OS)
- Secondary endpoints: progression-free survival, safety
- Exploratory endpoint: PSA response rate

Kwon et al. Lancet Oncol 2014

Radboudumc

CRPC: ipilimumab (post-docetaxel)

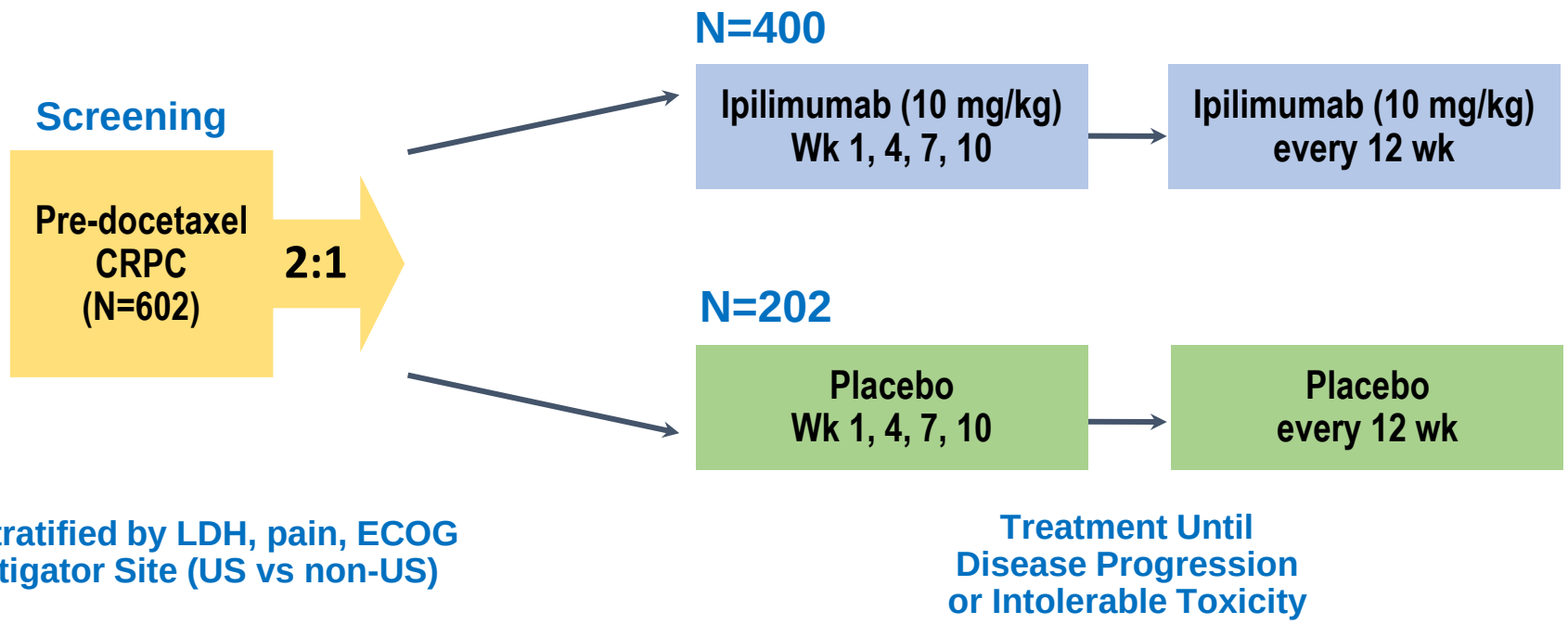


Kwon et al. Lancet Oncol 2014

Radboudumc

CRPC: ipilimumab (pre-docetaxel)

CA184-095: Study Design

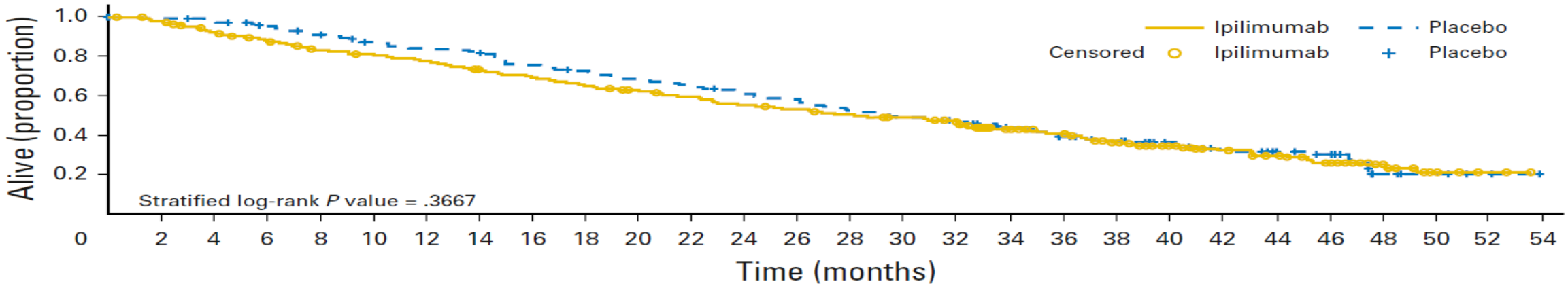


- Primary endpoint: OS
- Secondary endpoint PFS, time to next therapy, pain progression

Beer JCO 2017

Radboudumc

CRPC: ipilimumab (pre-docetaxel)

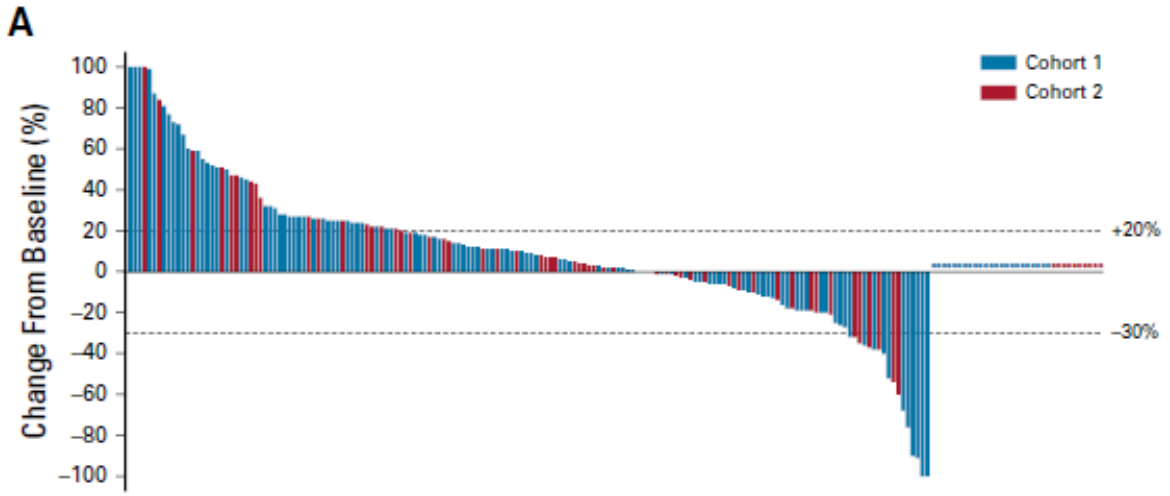


No. at risk																											
Ipilimumab	400	389	364	342	320	310	298	279	265	250	236	223	208	197	186	179	166	136	116	94	78	64	46	32	18	7	3	0
Placebo	202	198	195	186	175	166	161	155	142	136	128	122	113	108	98	92	85	74	59	53	41	33	25	19	6	4	2	0

Beer et al. JCO 2017

Radboudumc

Keynote-199 trial: pembrolizumab bij mCRPC



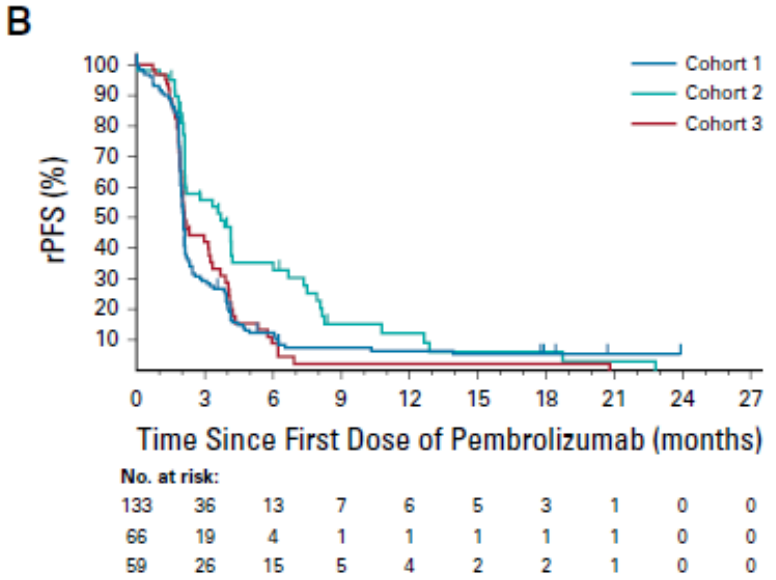


TABLE 2. Summary of Responses

Variable	Cohort 1 (PD-L1 positive)	Cohort 2 (PD-L1 negative)	Cohort 3 (bone predominant)	Cohorts 1 and 2 Combined	Cohorts 1, 2, and 3 Combined
Response assessed per RECIST v1.1 by central radiology review					
No. of patients	133	66	59	199	258
ORR, No. (%; 95% CI)	7 (5; 2 to 11)	2 (3; < 1 to 11)	—	9 (5; 2 to 8)	—

Cohort 1: RECISTable ziekte en PD-L1+

Cohort 2: RECISTable ziekte en PD-L1-

Cohort 3: bone-predominant, onafh van PD-L1 status

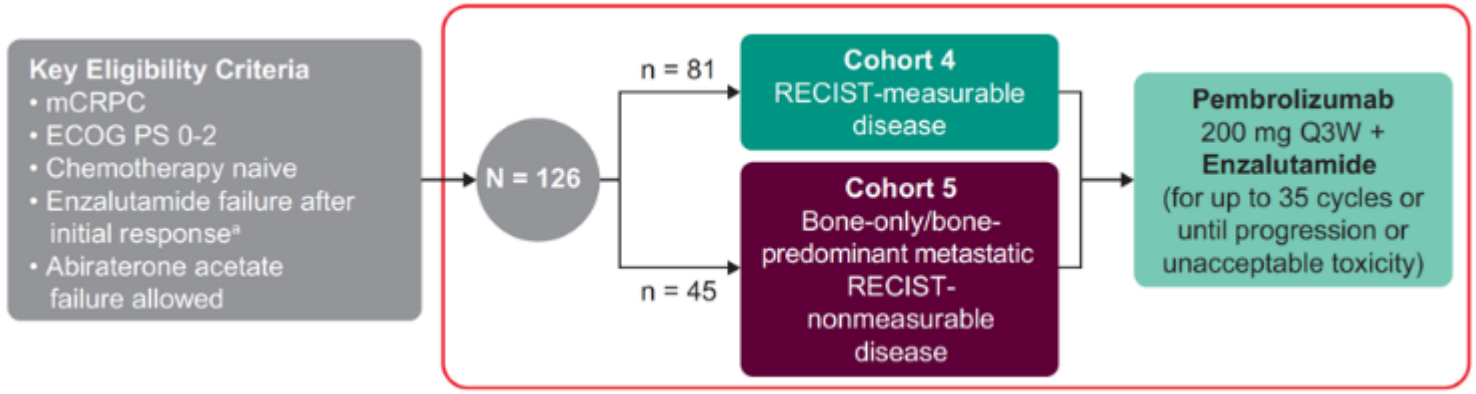
Antonarakis et al. J Clin Oncol 2020

Radboudumc

Keynote-199 trial: pembrolizumab bij mCRPC

623P

KEYNOTE-199 Phase 2 Study of Pembrolizumab Plus Enzalutamide for Enzalutamide-Resistant Metastatic Castration-Resistant Prostate Cancer: Cohorts 4 and 5 Update



Primary end points: ORR by RECIST v1.1 by blinded independant central review

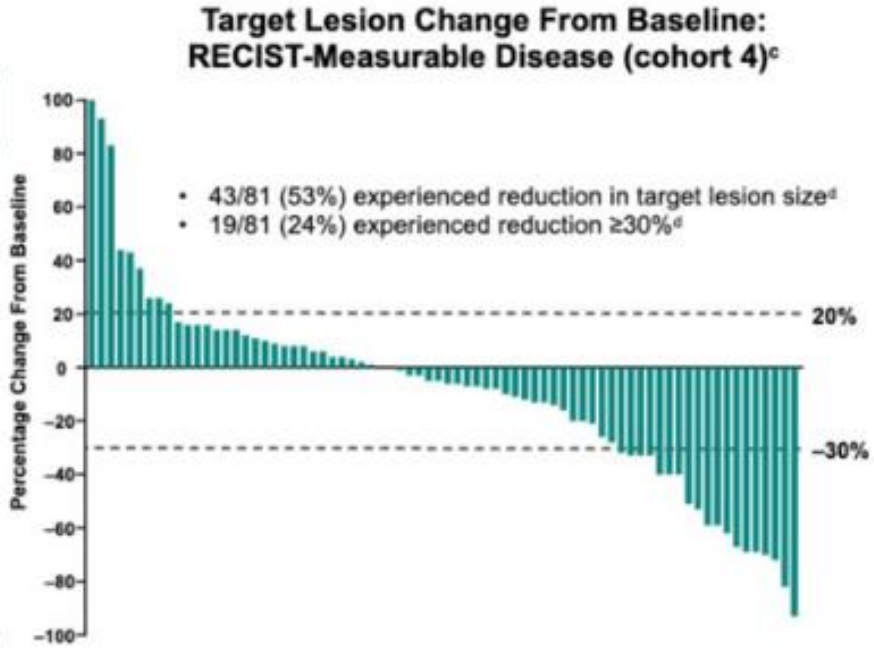
Keynote-199 trial: pembrolizumab in mCRPC

623P

KEYNOTE-199 Phase 2 Study of Pembrolizumab Plus Enzalutamide for Enzalutamide-Resistant Metastatic Castration-Resistant Prostate Cancer: Cohorts 4 and 5 Update

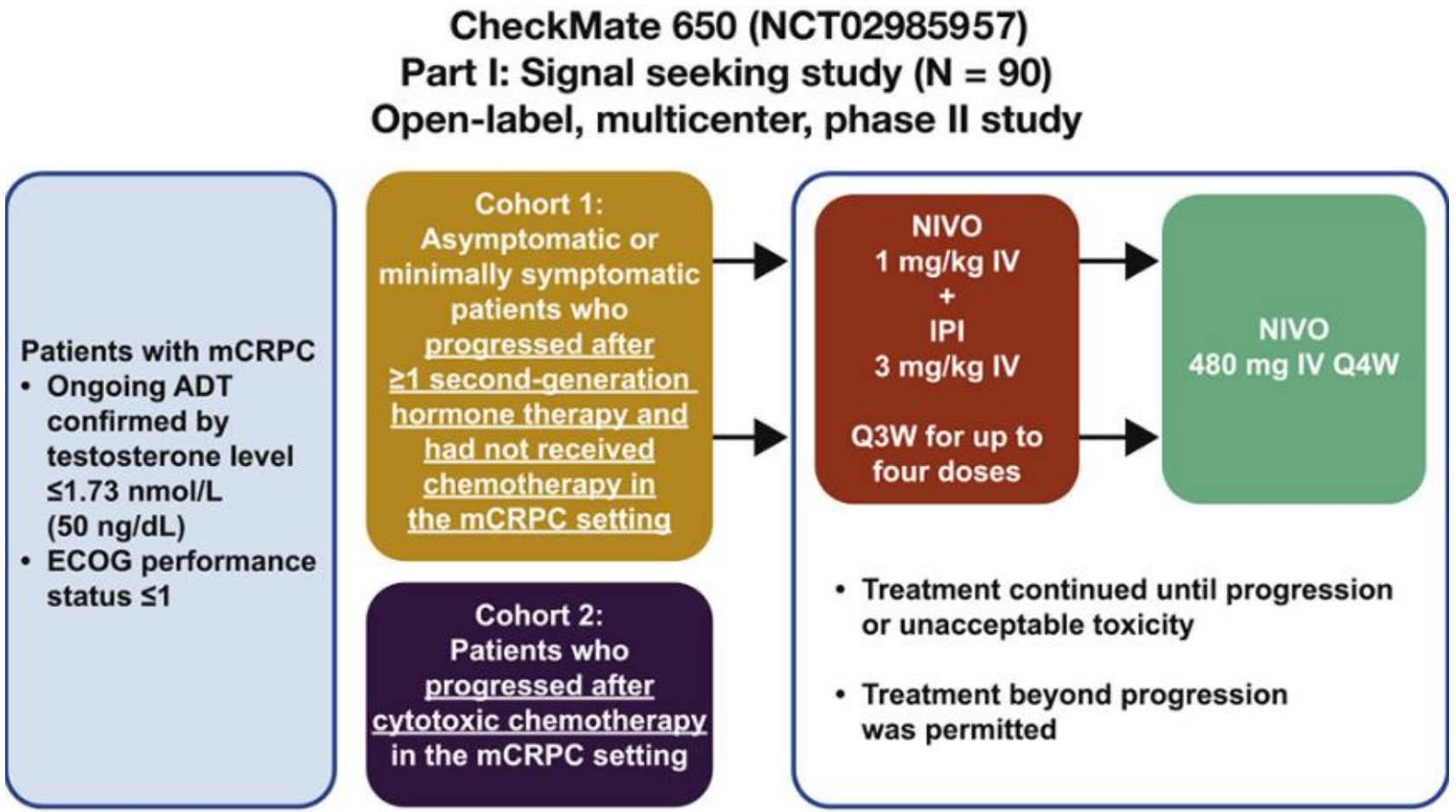
Best Confirmed Response by BICR per RECIST v1.1

n (%)	Cohort 4 n = 81	Cohort 5 n = 45
ORR	**10 (12)**	**NA**
CR	2 (2)	NA
PR	8 (10)	NA
SD of any duration	31 (38)	0 (0)
Non-CR/non-PD of any duration	0 (0)	23 (51)
DCR (CR + PR + SD or non-CR/non-PD)	**41 (51)**	**23 (51)**
PD	31 (38)	20 (44)
Nonevaluable[a]	2 (2)	1 (2)
No assessment[b]	7 (9)	1 (2)



Radboudumc

Ipilimumab en nivolumab bij mCRPC (Checkmate 650)



Sharma et al. Cancer Cell 2020

Radboudumc

Ipilimumab en nivolumab bij mCRPC (Checkmate 650)

Endpoints	Cohort 1 (n = 45)	Cohort 2 (n = 45)
Co-primary		
Investigator assessed ORR	25.0%	10.0%
rPFS	Median 5.5 months (95% CI, 3.5–7.1)	Median 3.8 months (95% CI, 2.1–5.1)
Secondary		
OS	Median 19.0 months (95% CI, 11.5–not evaluable)	Median 15.2 months (95% CI, 8.4–not evaluable)
Safety	Grade 3–4 treatment-related AEs in 42.2% of patients	Grade 3–4 treatment-related AEs in 53.3% of patients
Exploratory		
PSA response rate	17.6%	10.0%
Correlation of biomarkers with efficacy	Preliminary evidence of potential biomarkers of response	

Sharma et al. Cancer Cell 2020

Radboudumc

Ipilimumab en nivolumab bij mCRPC (Checkmate 650)

ipilimumab-induced increase in tumor-infiltrating T cells. Here, we report the largest trial to date in mCRPC with anti-CTLA-4 plus anti-PD-1 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; CheckMate 650, NCT02985957). With median follow-ups of 11.9 and 13.5 months in cohorts 1 (pre-chemotherapy; n = 45) and 2 (post-chemotherapy; n = 45), objective response rate was 25% and 10%, and median overall survival was 19.0 and 15.2 months, respectively. Four patients, two in each cohort, had complete responses. Exploratory studies identify potential biomarkers of response. Grade 3–4 treatment-related adverse events have occurred in ~42%–53% of patients, with four treatment-related deaths. Therefore, dose/schedule modifications have been implemented.

- Slechts 29% kreeg 4x ipi/nivo
- 48% gestopt vanwege tox

Sharma et al. Cancer Cell 2020

Radboudumc

Ipilimumab (1 mg/kg) en nivolumab (3 mg/kg) bij geselecteerde mCRPC patienten

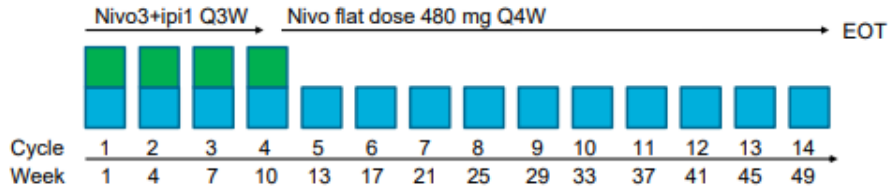
Key inclusion criteria
mCRPC with one of the following molecular subtypes:
- Microsatellite instability (MSI) and/or mismatch repair deficiency (MMRd);
- High TMB (> 7 mutations per megabase);
- BRCA2 inactivation or BRCAness signature;
- CDK12 inactivation and/or a tandem duplication signature (TDS).

ECOG performance score 0-1

Study cohorts (n=75)
- A1: ICB-naïve, measurable disease (main cohort; n=50)
- A2: ICB-naïve, non-measurable disease
- A3: Prior ICB, measurable disease

Primary endpoint
Disease control rate at 6 months

- This interim analysis was performed in 25 patients with at least 17 weeks of follow up and **aimed at < 35% toxicity-related discontinuations in the first 17 weeks**.



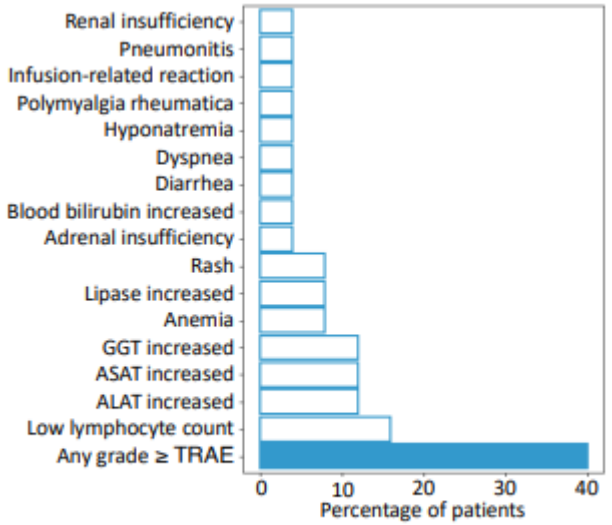
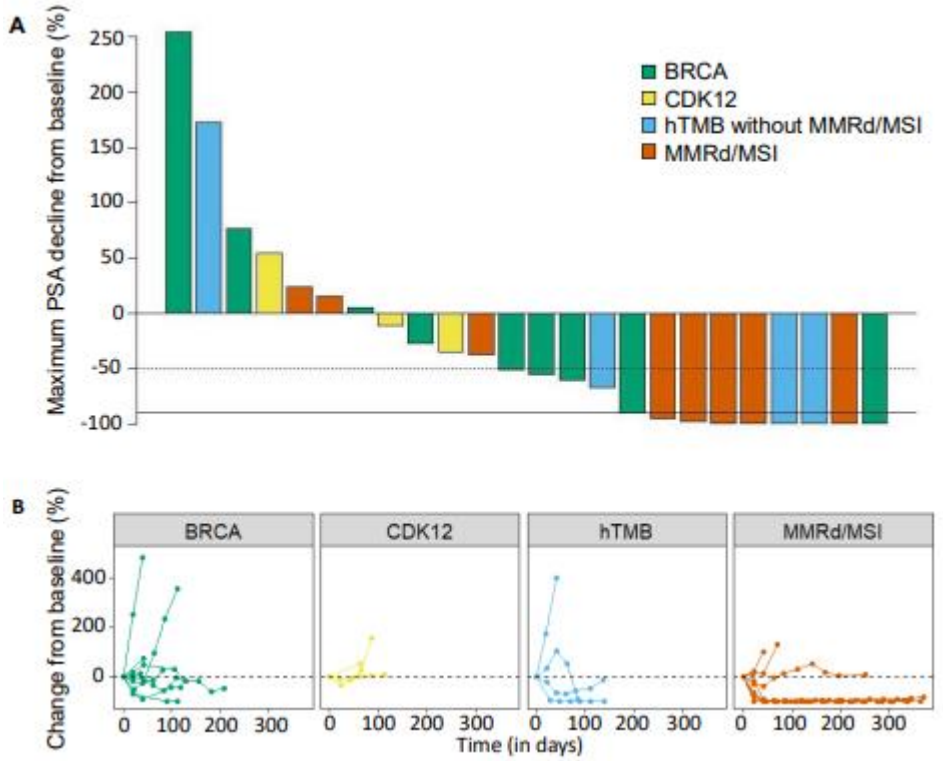


Figure 2. Incidence of grade ≥ 3 TRAEs

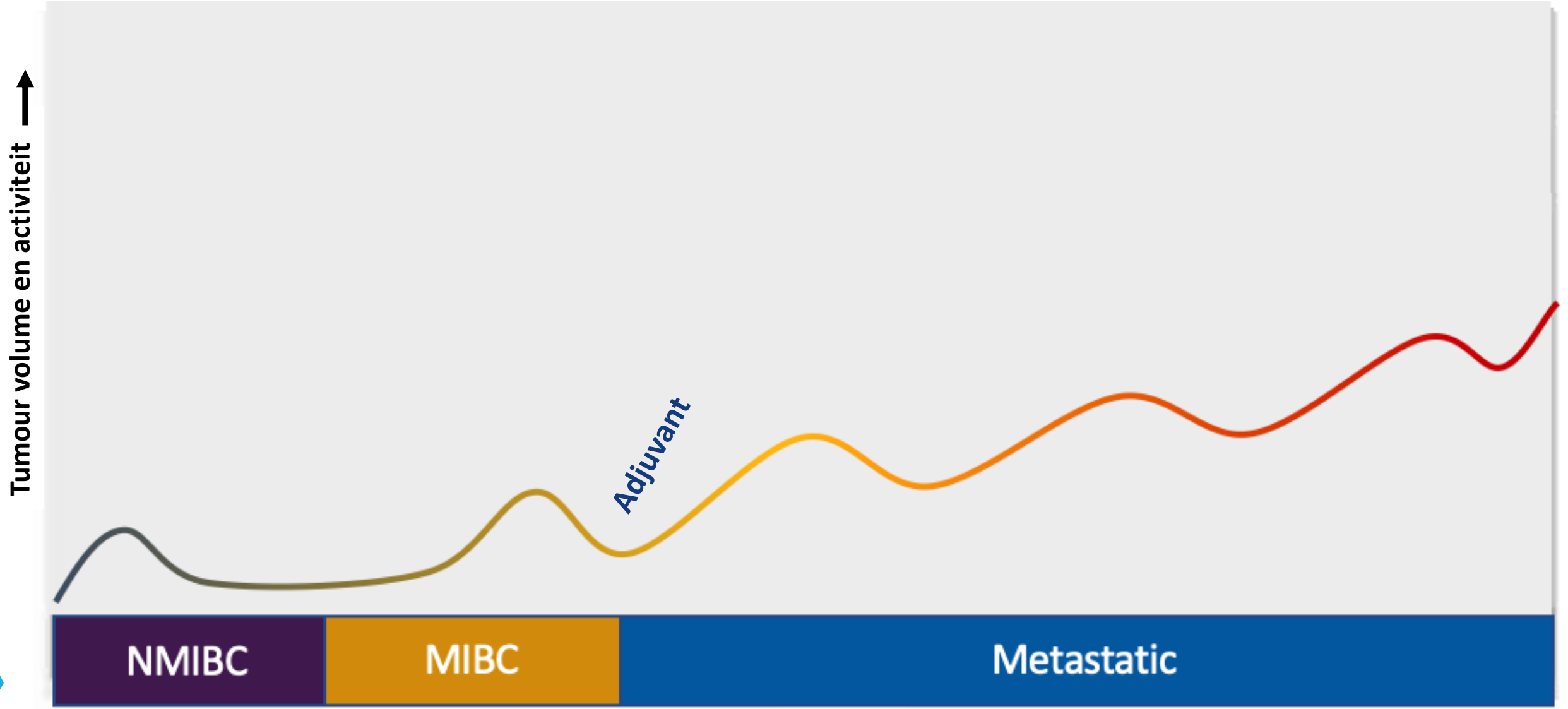


v Wilpe, Westdorp, …. Mehra. Poster presentatie ESMO 2022

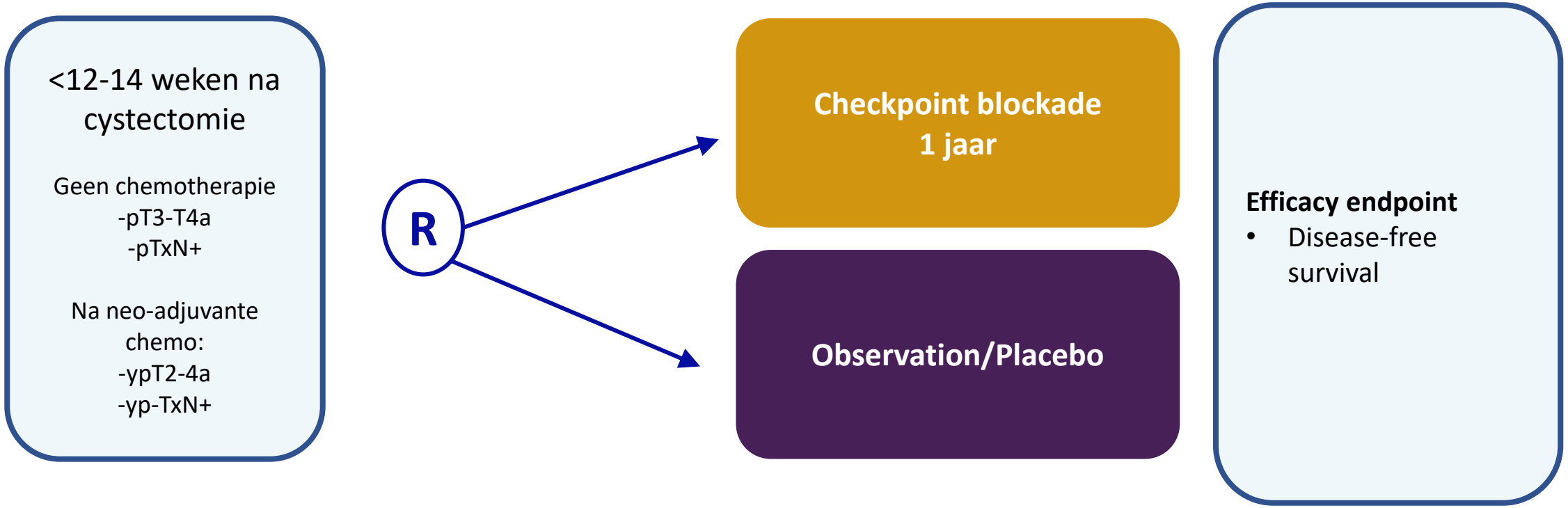
Radboudumc

Blaaskanker

Blaaskanker



Adjuvante studies



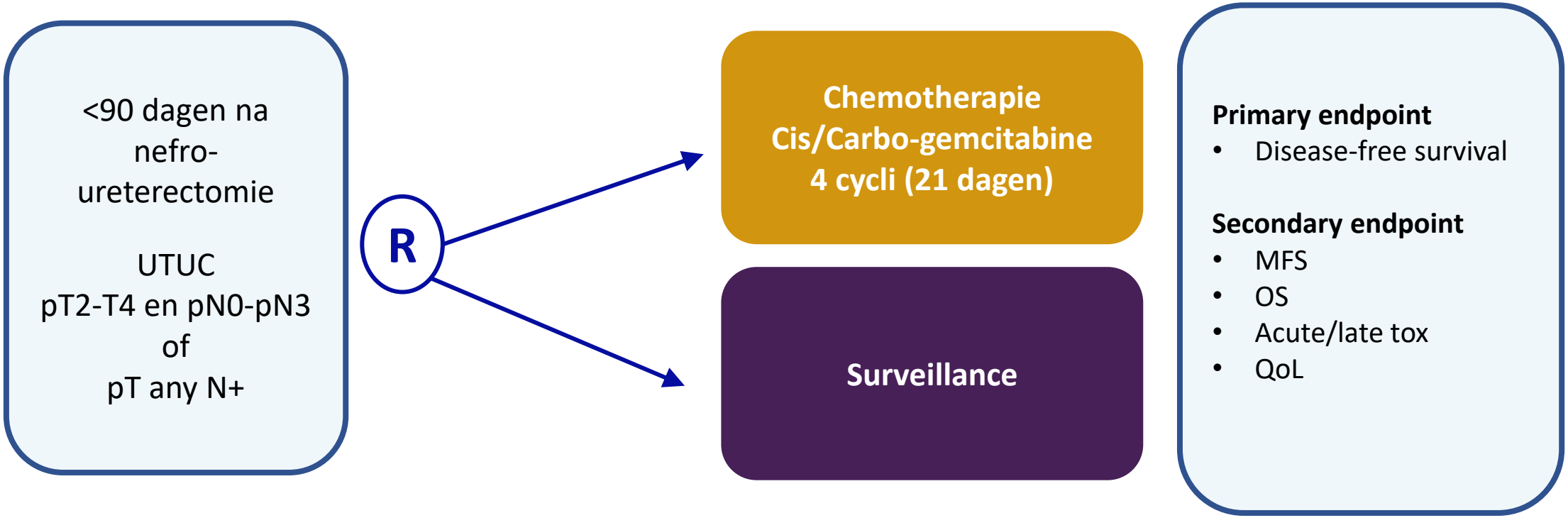
Mediane DFS van 21,0 mnd vs 10,9 mnd; HR 0.70 (0.54-0.90);
Echter, dit is vooralsnog niet regulier beschikbaar.

Bajorin, Witjes et al. NEJM 2021

Adjuvante studies

POUT

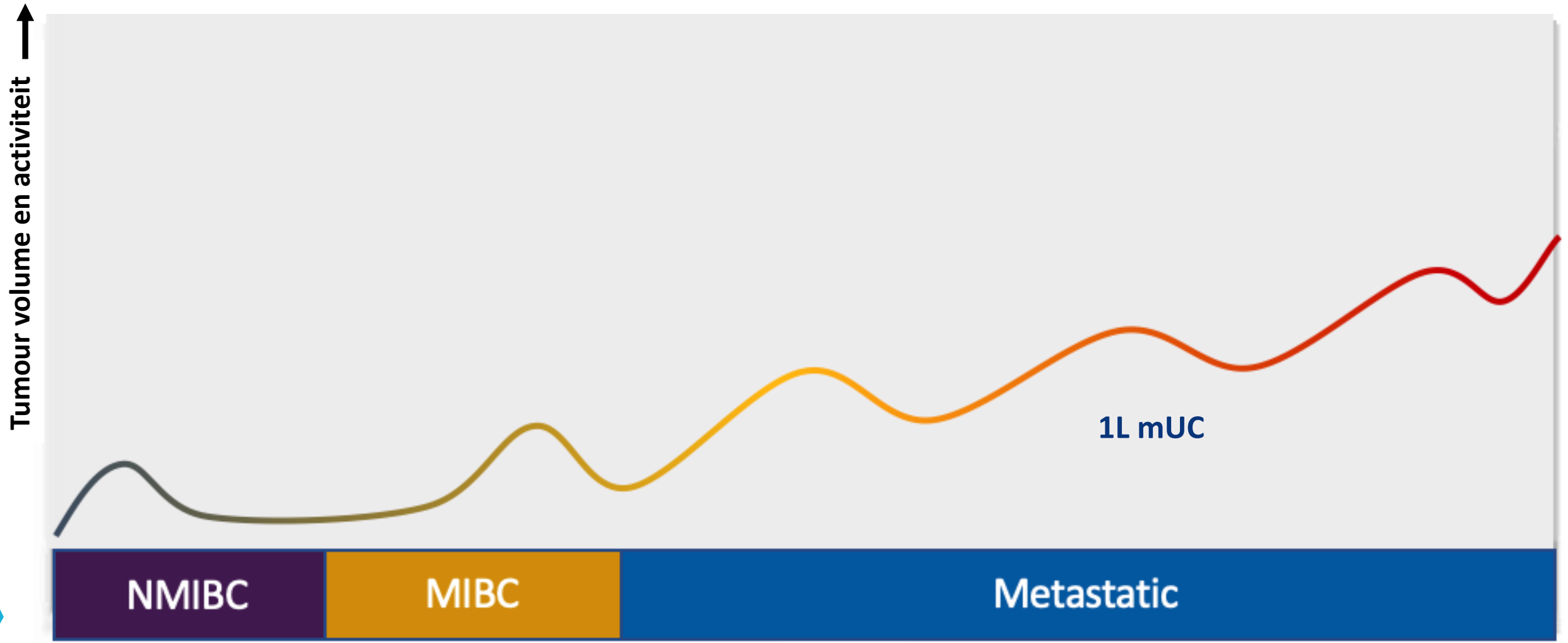
- N=800
- ASCO 2018: interim



Significante winst ten opzichte van follow-up (3-jr DFS 71% vs. 50%, HR 0.51 (0.35-0.76) en 3-jr metastase-free survival 72% en 53%, HR 0.52 (0.36-0.77)). De voorlopige OS data zijn niet significant: 3-jr OS 79% vs. 67% (HR 0.70 (0.46-1.06)

Birtle et al. Lancet 2020

mUC 1e lijn

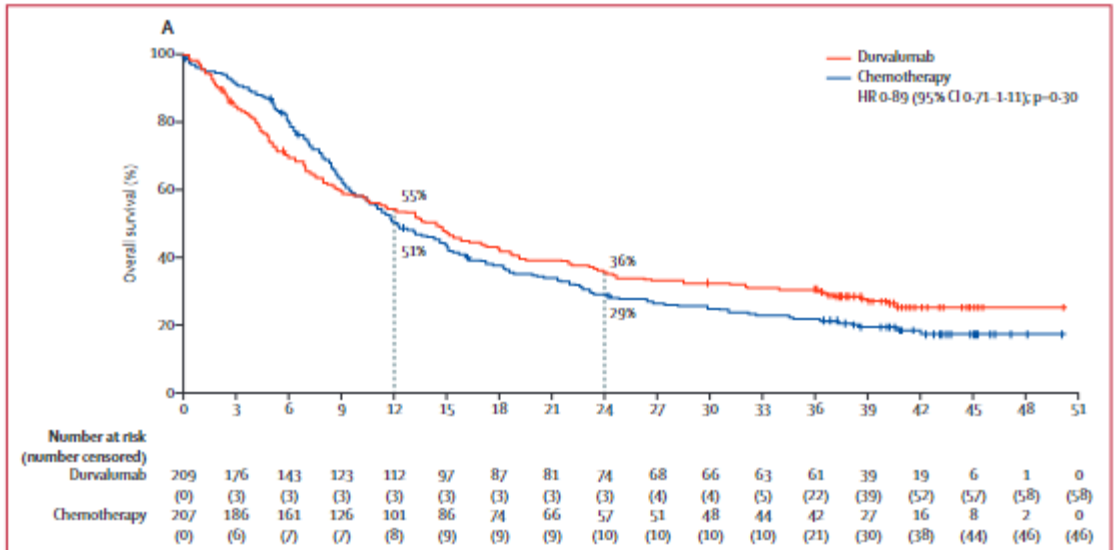


DANUBE fase 3 trial negatief

- Indicatie:
  - Onbehandeld, niet-resectabel locally advanced of gemetastaseerd UCC
  - 1:1:1 randomisatie
    - Durvalumab monotherapie 1500 mg a 4 weken iv
    - Durvalumab 1500 mg + tremulimumab 75 mg (max 4x); beide a 4 weken iv + maintenance durvalumab 1500 mg a 4 weken
    - SOC (gem/cis of gem/carbo)

Powles et al. Lancet Oncol 2020

DANUBE fase 3 trial negatief



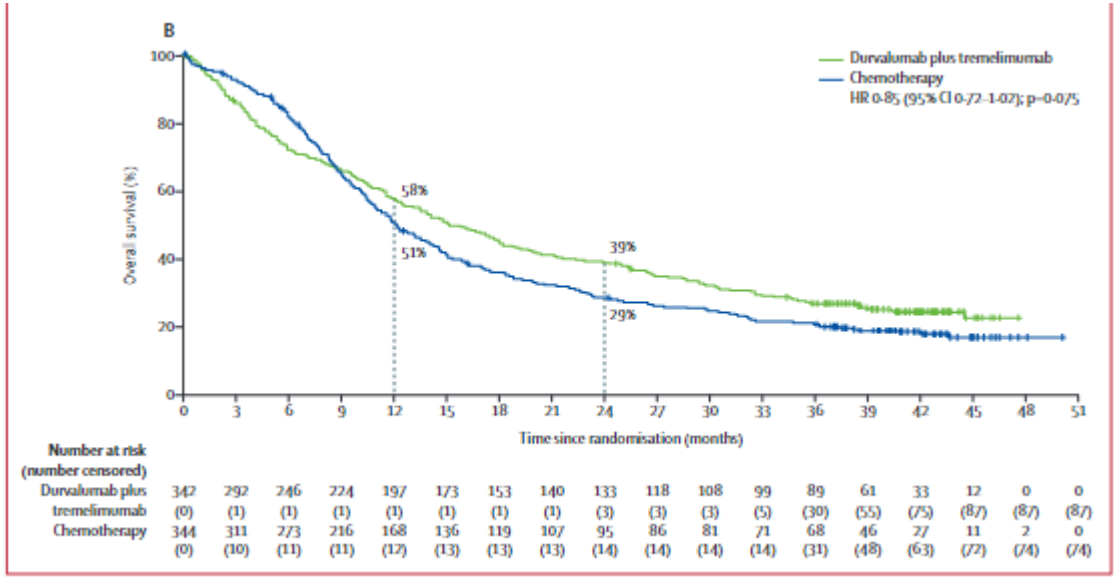
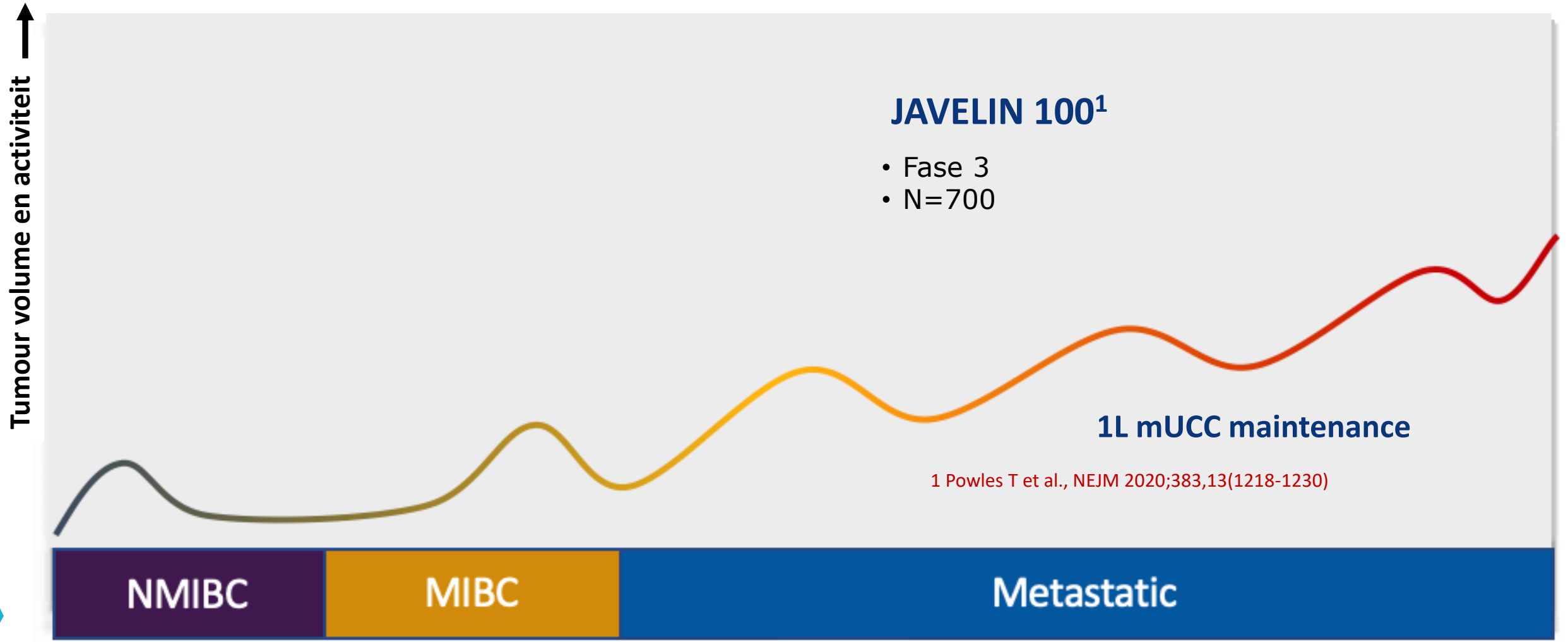


Figure 2: Overall survival (coprimary endpoints)

Powles et al. Lancet Oncol 2020

Radboudumc

mUCC 1e lijn maintenance PD-L1



Avelumab maintenance

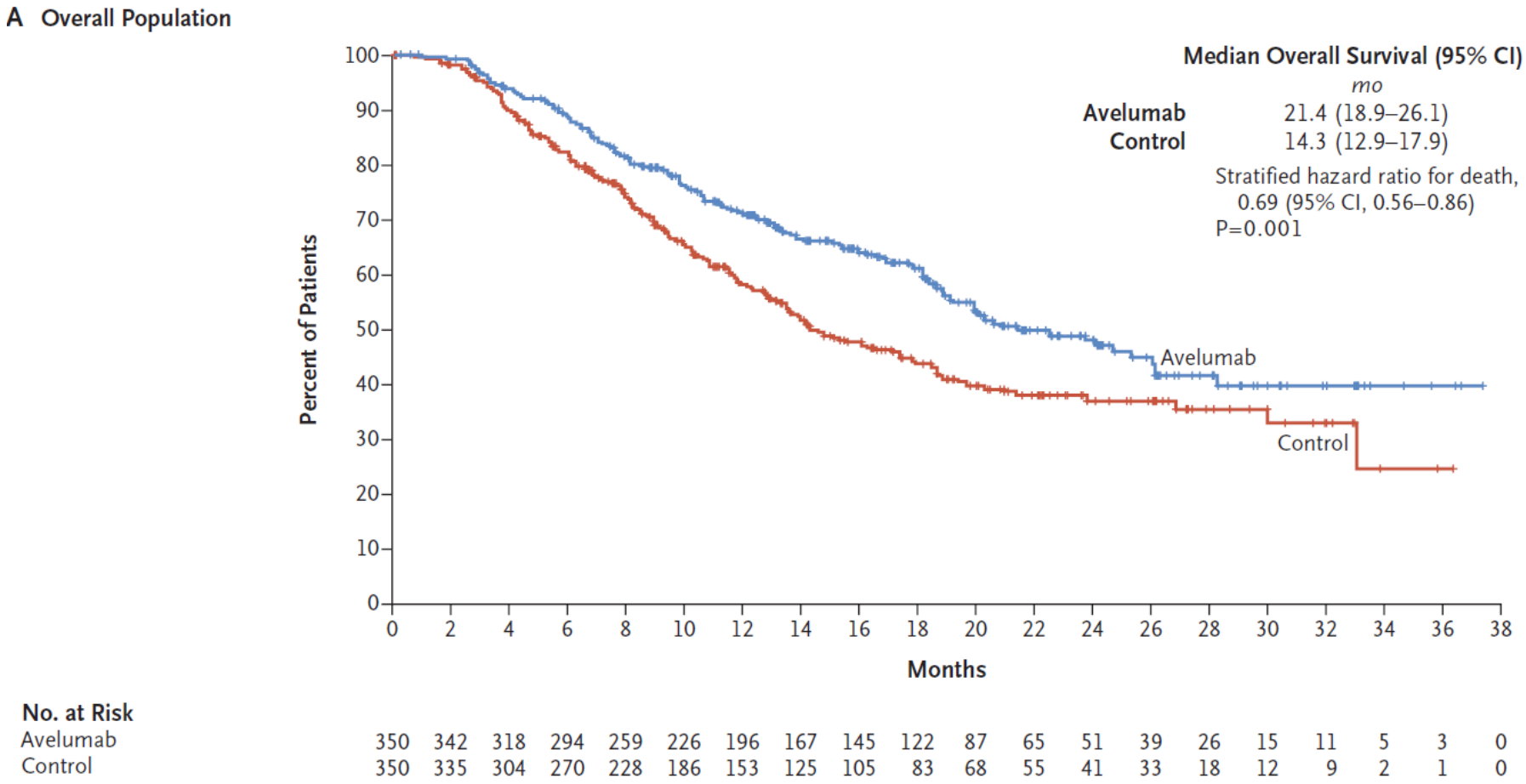
- Indicatie:
  - Niet-resectabel locally advanced of gemetastaseerd UC
  - Geen PD na 4-6 cycli gem/cis of gem/carbo

- Studie armen:
  - Avelumab 10 mg/kg iv a 2 weken tot PD of uncontrolled tox
  - BSC

- Behandeling na PD:
  - Na avelumab: 6,3% anti-PD-1
  - Na BSC: 43,7% anti-PD-1

Powles et al. NEJM 2020

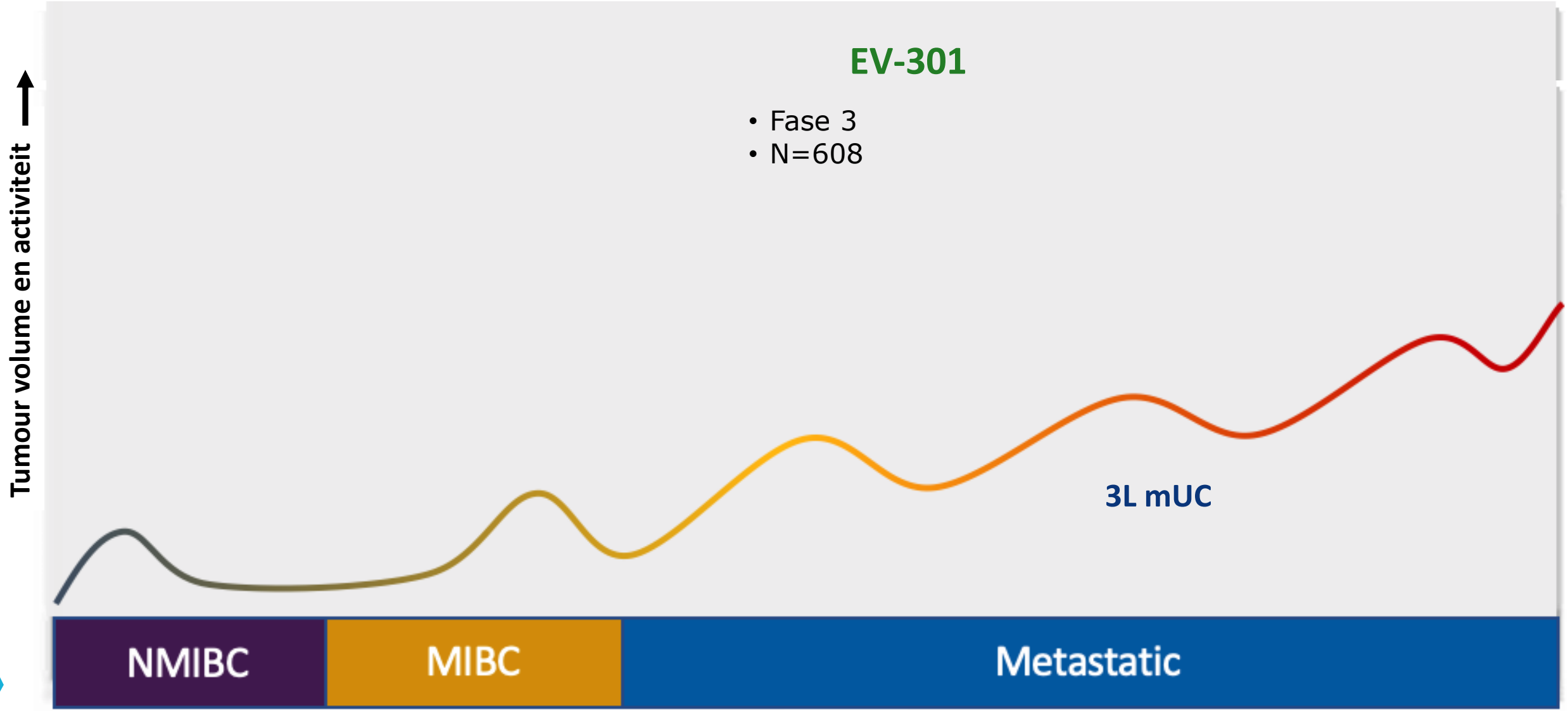
Avelumab maintenance



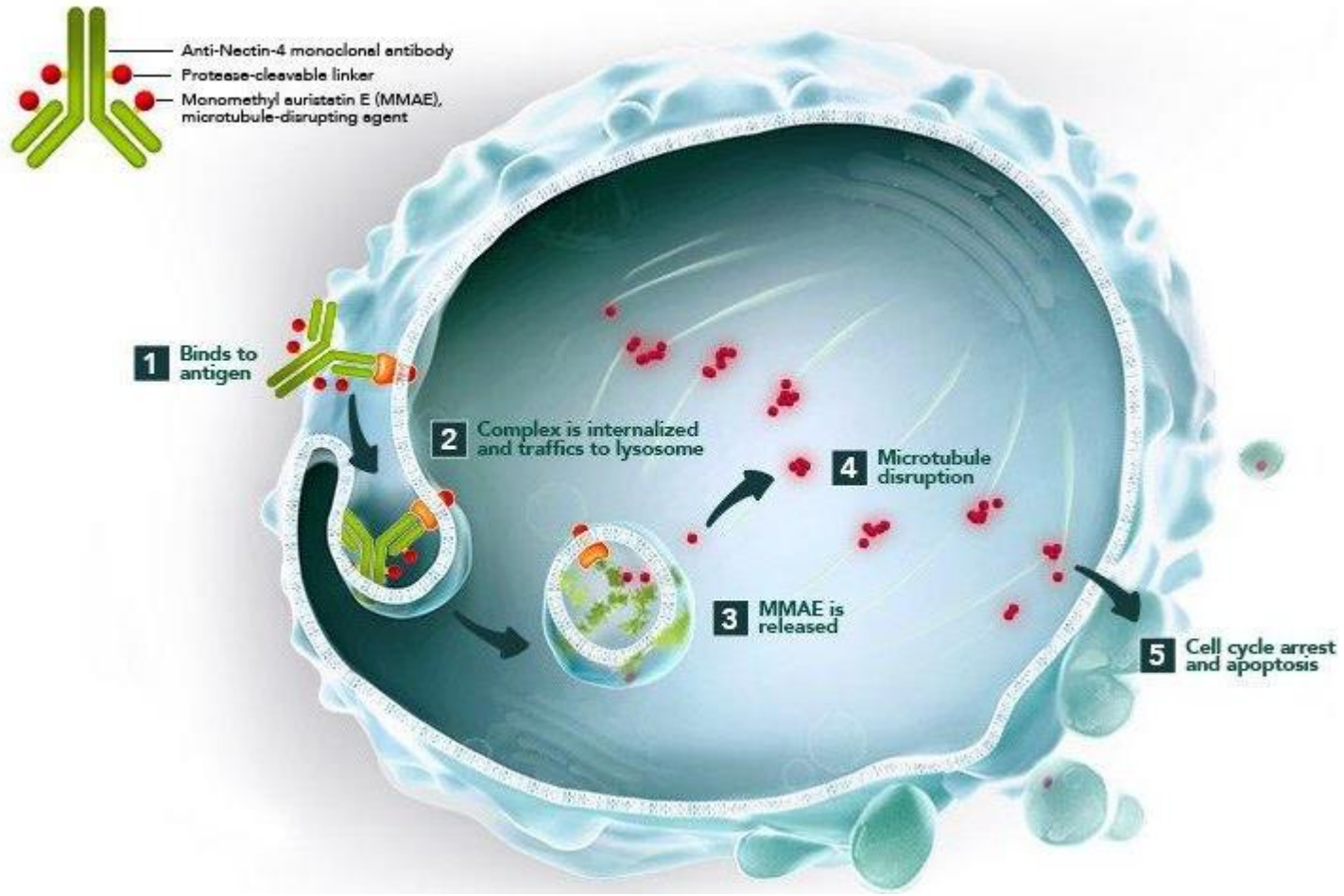
Powles et al. NEJM 2020

Radboudumc

mUC 3e lijn: enfortumab vedotin (EV)



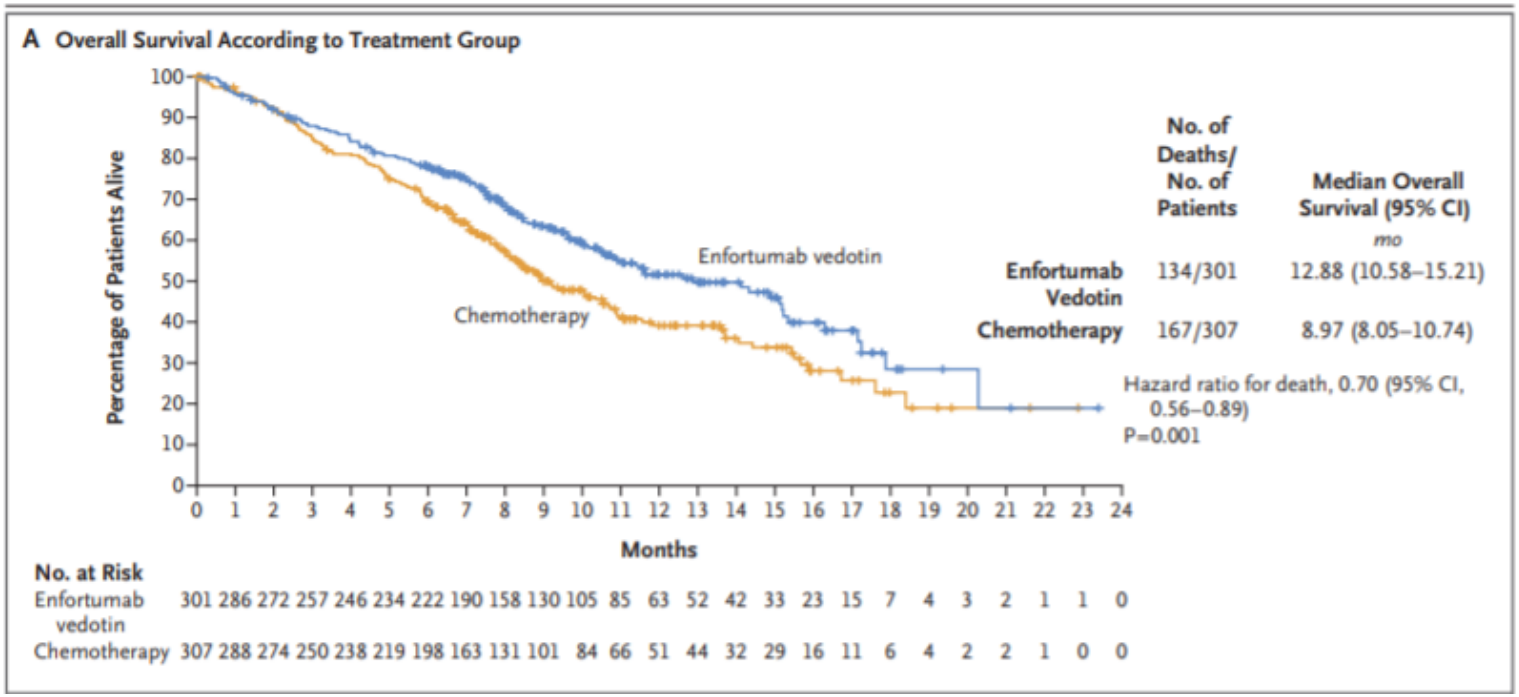
Hoe werkt EV: antibody-drug conjugate



mUC – 3L – positief commissie BOM advies

Lijn	Drug	Comparator	PFS	HR	ΔMo	OS	HR	ΔMo
EV-301	Enfortumab vedotin	CT	ITT	0.61 (0.50-0.75)	1.9	ITT	0.70 (0.56-0.89)	3.9

The NEW ENGLAND JOURNAL of MEDICINE



Powles et al. NEJM 2021

Radboudumc

Vragen?