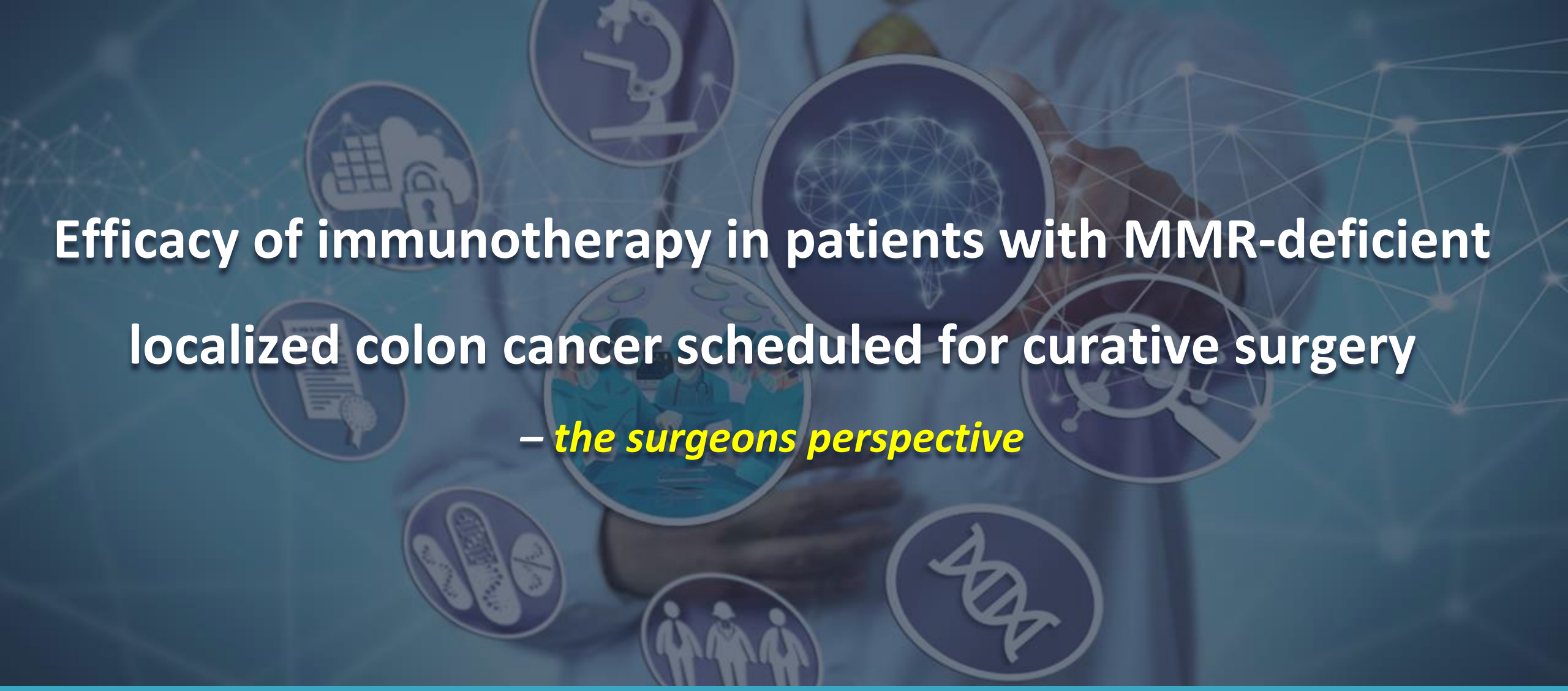

Efficacy of immunotherapy in patients with MMR-deficient localized colon cancer scheduled for curative surgery

– the surgeons perspective

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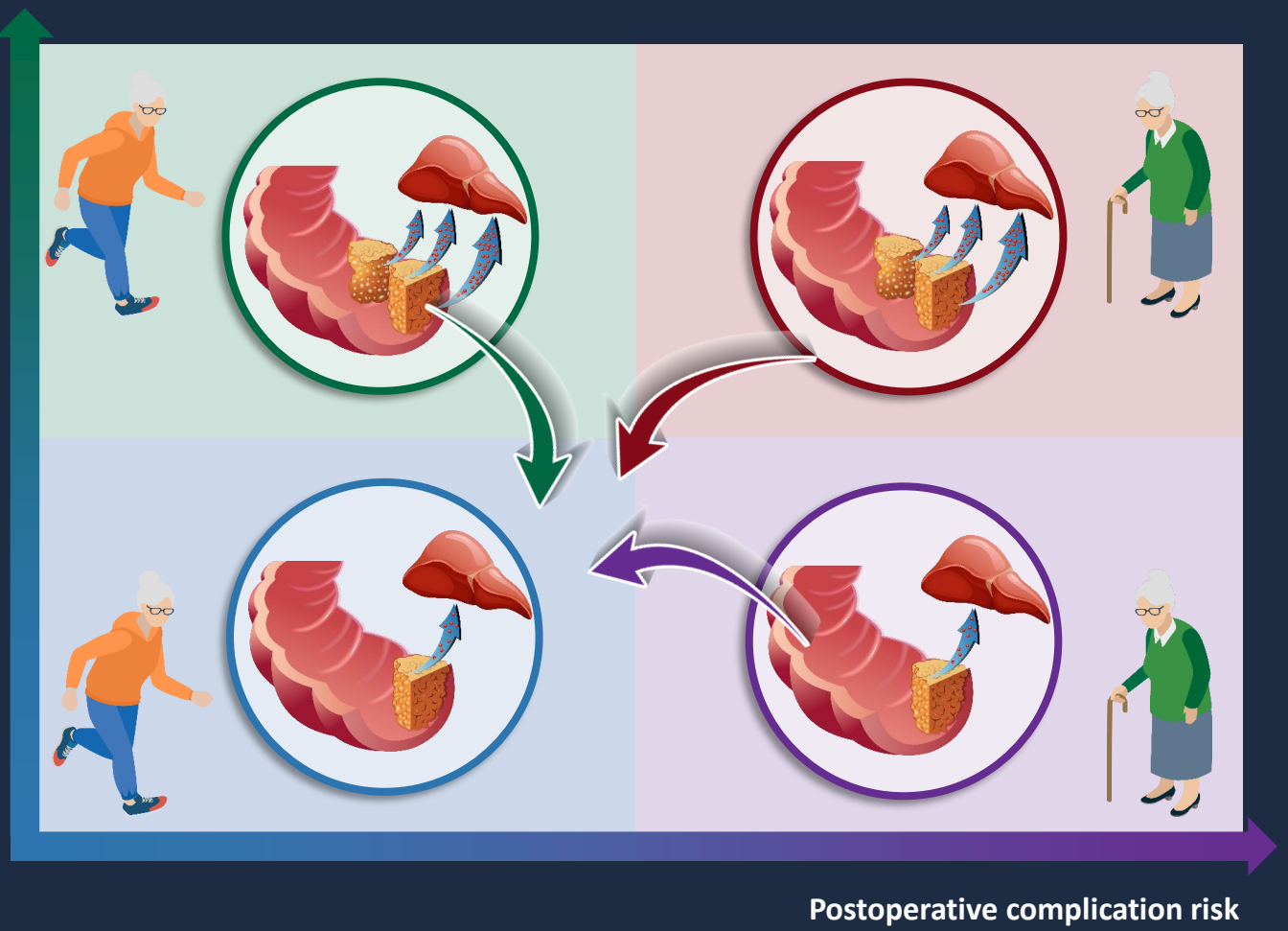
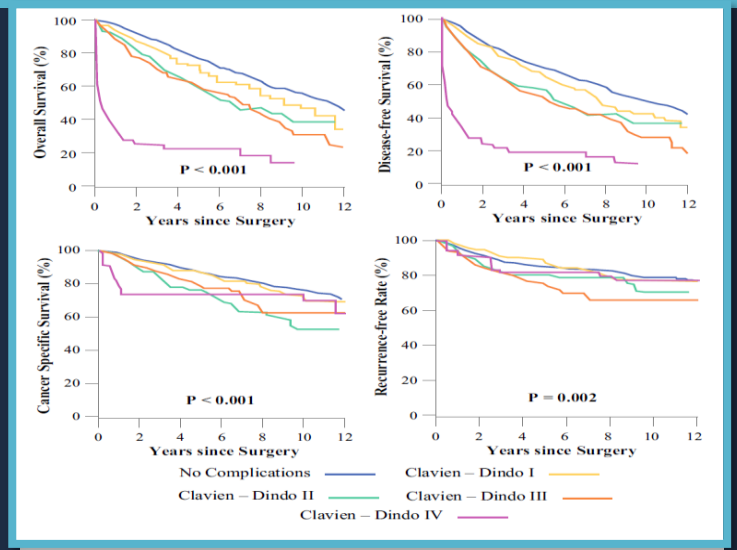
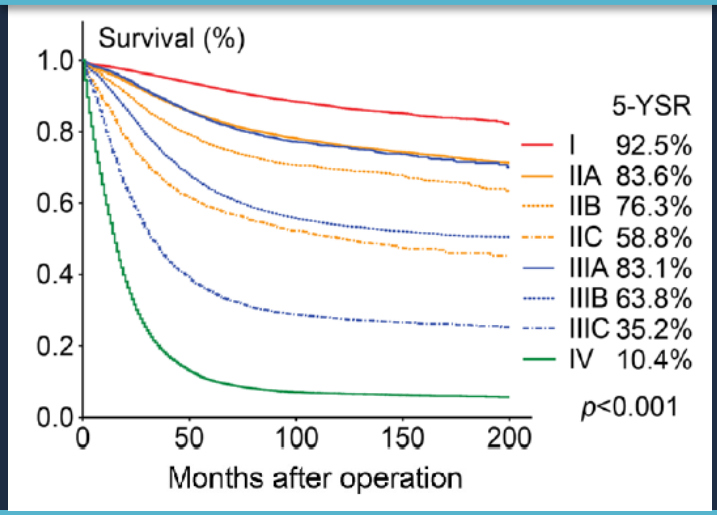
– vi er til for dig

Patients eligible for curative surgery for localized colon cancer – a spectrum of disease phenotypes







Duraes et al Ann Surg Oncol 2018

Gao et al. *BMC Cancer* 2013

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Quality improvements in surgical oncology through Enhanced Recovery AFTER surgery (ERAS)

REGION ZEALAND
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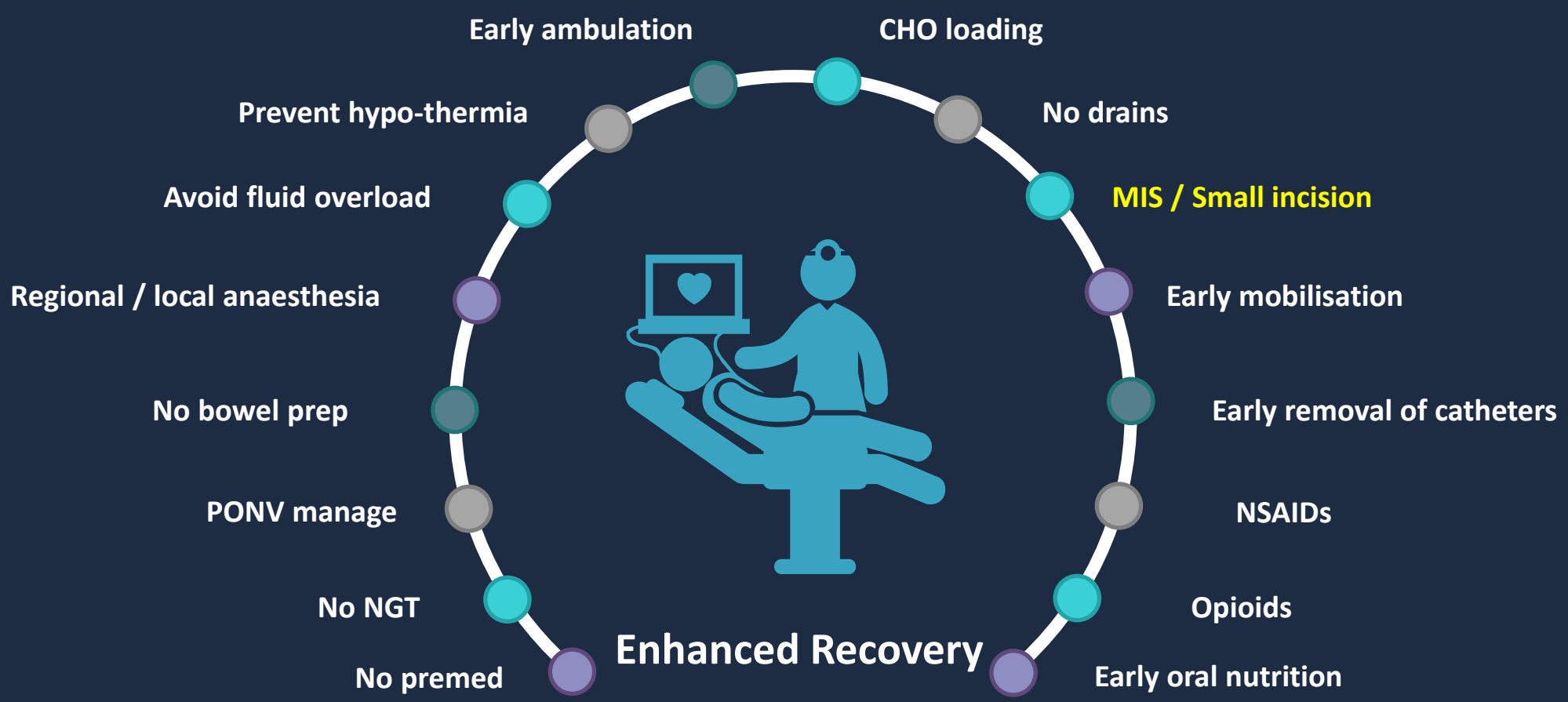

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Quality improvements in surgical oncology through Enhanced Recovery AFTER surgery (ERAS)

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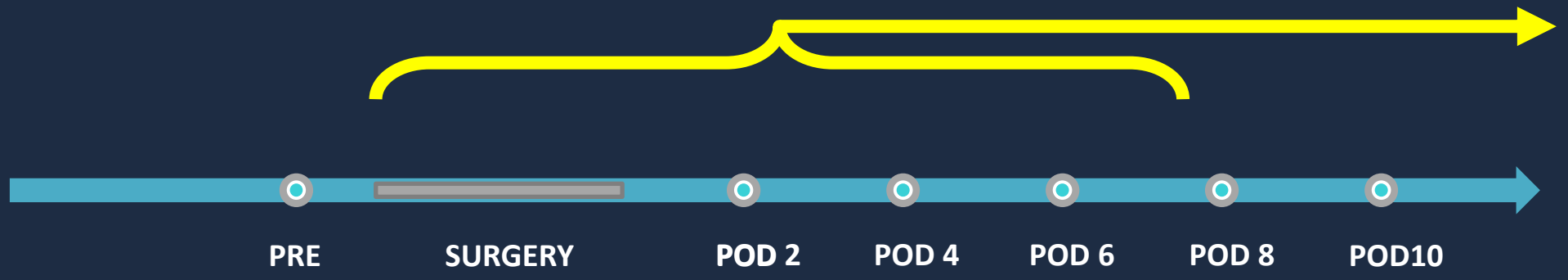

Reduced complications and mortality

Long-term outcomes of laparoscopic vs open colectomy in T4 colon cancer

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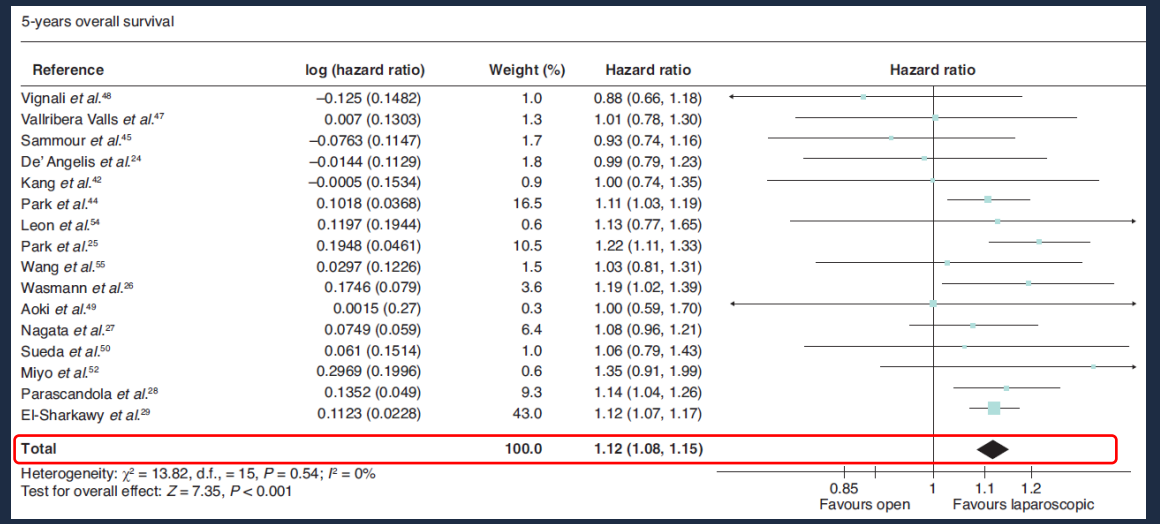
Meta-analysis of 24 studies (n=18,123)

No significant difference in 3-yr and 5-yr DFS as well as recurrence rates

Improved 5-yr OS with laparoscopic surgery (HR: 1.12, 1.08 – 1.15, p<0.001)



Podda et al. *Br J Surg* 2022

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What about BEFORE surgery - prehabilitation

REGION ZEALAND
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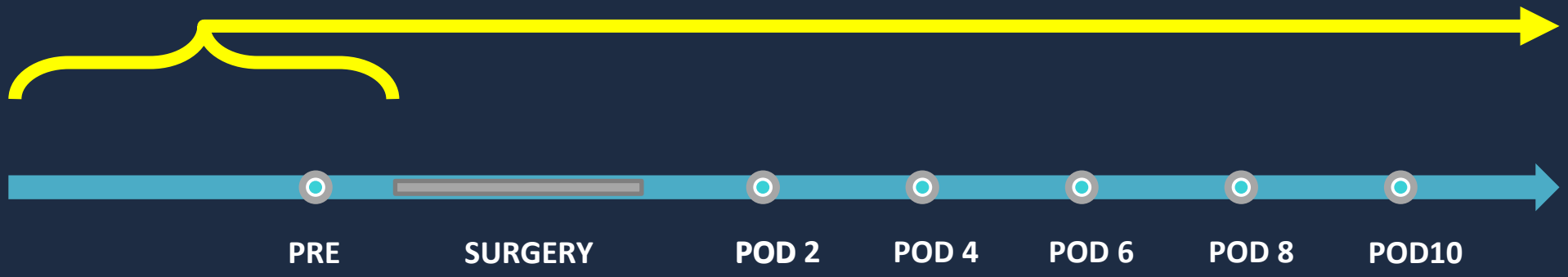

MORBIDITY ⬆

MORTALITY ⬆

First of the 'Large' RCT´s

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JAMA Surgery | Original Investigation

Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery

The PREHAB Randomized Clinical Trial

JAMA Surg. Published online March 29, 2023. doi:10.1001/jamasurg.2023.0198

INTERVENTIONS The 4-week in-hospital supervised multimodal prehabilitation program consisted of a high-intensity exercise program 3 times per week, a nutritional intervention, psychological support, and a smoking cessation program when needed.

MAIN OUTCOMES AND MEASURES Comprehensive Complication Index (CCI) score, number of patients with CCI score more than 20, and improved walking capacity expressed as the 6-minute walking distance 4 weeks postoperatively.

First of the 'Large' RCT´s

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Figure 1. CONSORT Flow Diagram

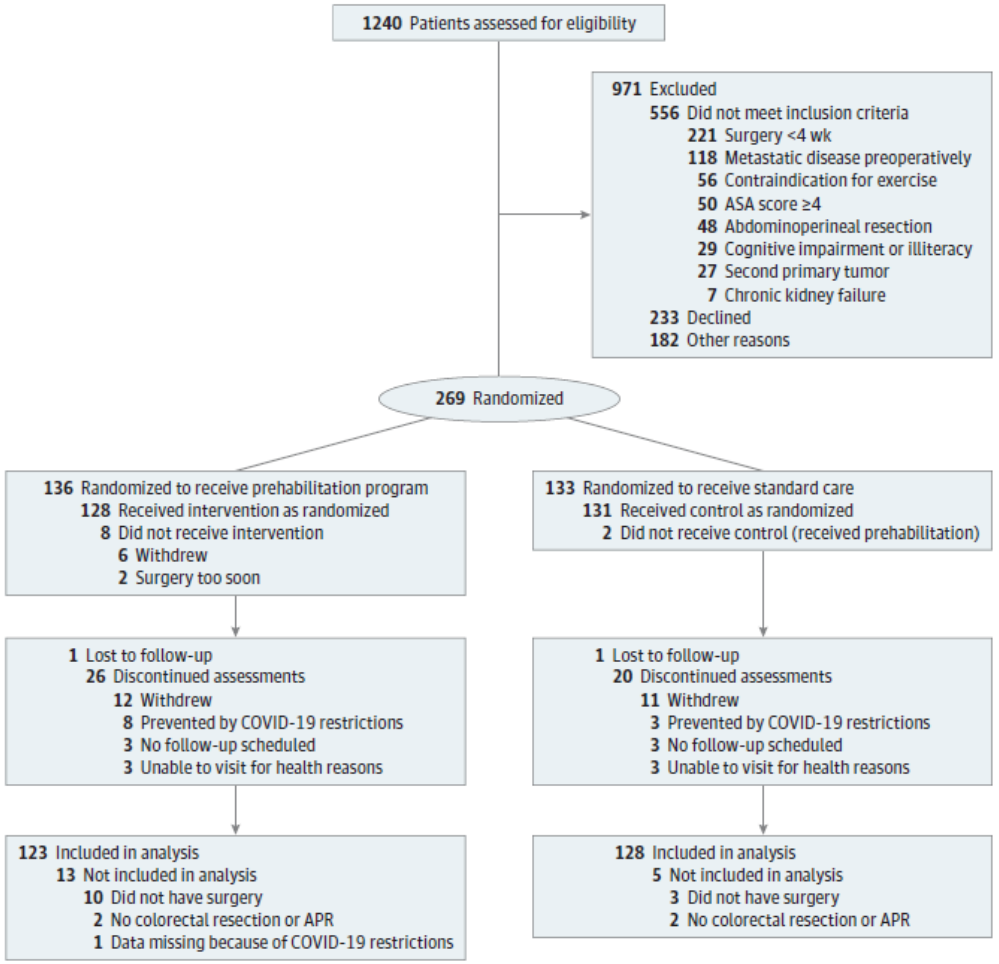

Table 1. Baseline and Clinical Characteristics[a] (continued)

Characteristic	No. (%) Prehabilitation group (n = 123)	Control group (n = 128)
Type of surgery		
Hemicolectomy		
Right	62 (50.4)	63 (49.2)
Left	10 (8.1)	10 (7.8)
Colectomy		
Transverse	2 (1.6)	0
Subtotal	2 (1.6)	3 (2.3)
Sigmoid	17 (13.8)	24 (18.8)
TaTME	7 (5.7)	8 (6.3)
TEM	1 (0.8)	1 (0.8)
Low anterior resection	22 (17.9)	19 (14.8)
Minimal invasive surgery[c]	118 (95.9)	116 (90.6)
Stoma creation	13 (10.6)	14 (10.9)
Duration of surgery, median (IQR), min	160.0 (130.0-201.0)	171.5 (137.0-201.5)
Intraoperative blood loss, median (IQR), mL[d]	0 (0-50)	0 (0-50)
Missing	88 (71,5)	95 (74.2)
6-MWD, median (IQR), m	514.0 (450.0-578.0)	512.5 (435.0-572.0)
Missing	1 (0.8)	2 (1.6)
6-MWD ≥400 m	100 (81.3)	106 (82.8)
Missing	1 (0.8)	2 (1.6)
$\dot{V}O_2$AT, median (IQR), mL × kg^{-1} × min^{-1}	12.3 (10.9-15.0)	12.9 (10.3-15.0)
Missing	14 (11.4)	17 (13.3)
Peak $\dot{V}O_2$, median (IQR), mL × kg^{-1} × min^{-1}	18.0 (15.0-21.9)	19.0 (15.0-22.3)
Missing	10 (8.1)	13 (10.2)

JAMA Surg. Published online March 29, 2023. doi:10.1001/jamasurg.2023.0198

First of the 'Large' RCT´s

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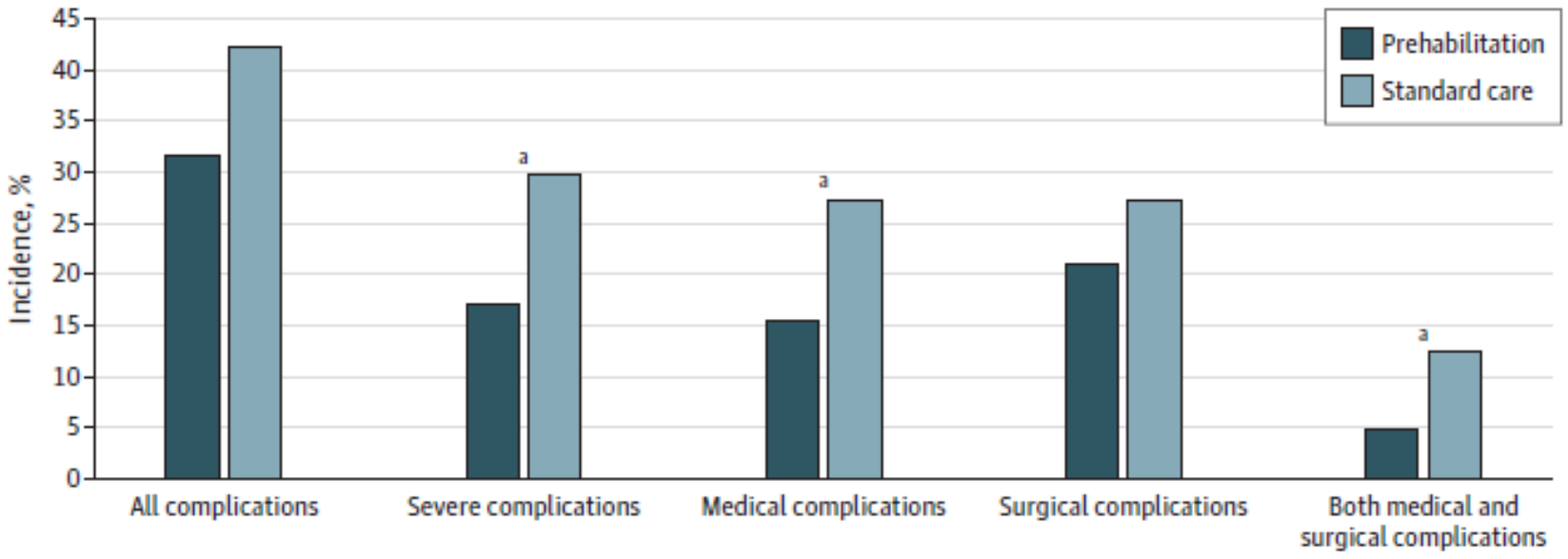
Research Original Investigation

Effect of Prehabilitation on Postoperative Complications and Functional Capacity for Colorectal Cancer Surgery

Figure 2. Complications Within 30 Days After Surgery



Complications in the intention-to-treat population (n = 251) are reported as percentage of patients having at least 1 complication, a severe complication (Comprehensive Complication Index score >20), at least 1 medical or surgical complication, and having at least 1 medical and 1 surgical complication.

[a] $P < .05$.

JAMA Surg. Published online March 29, 2023. doi:10.1001/jamasurg.2023.0198

What about immune-oncological treatment BEFORE surgery

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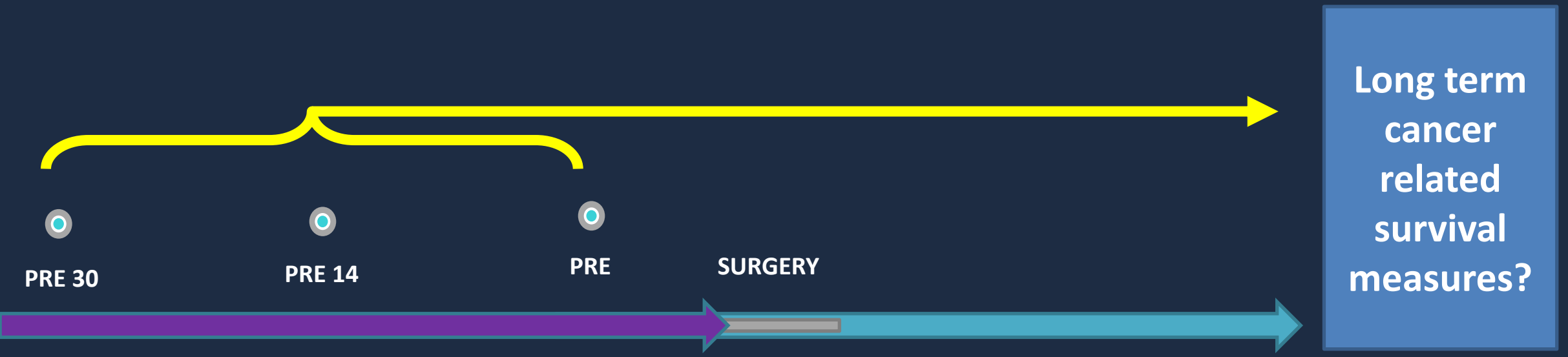

DELAYING CURATIVE TREATMENT

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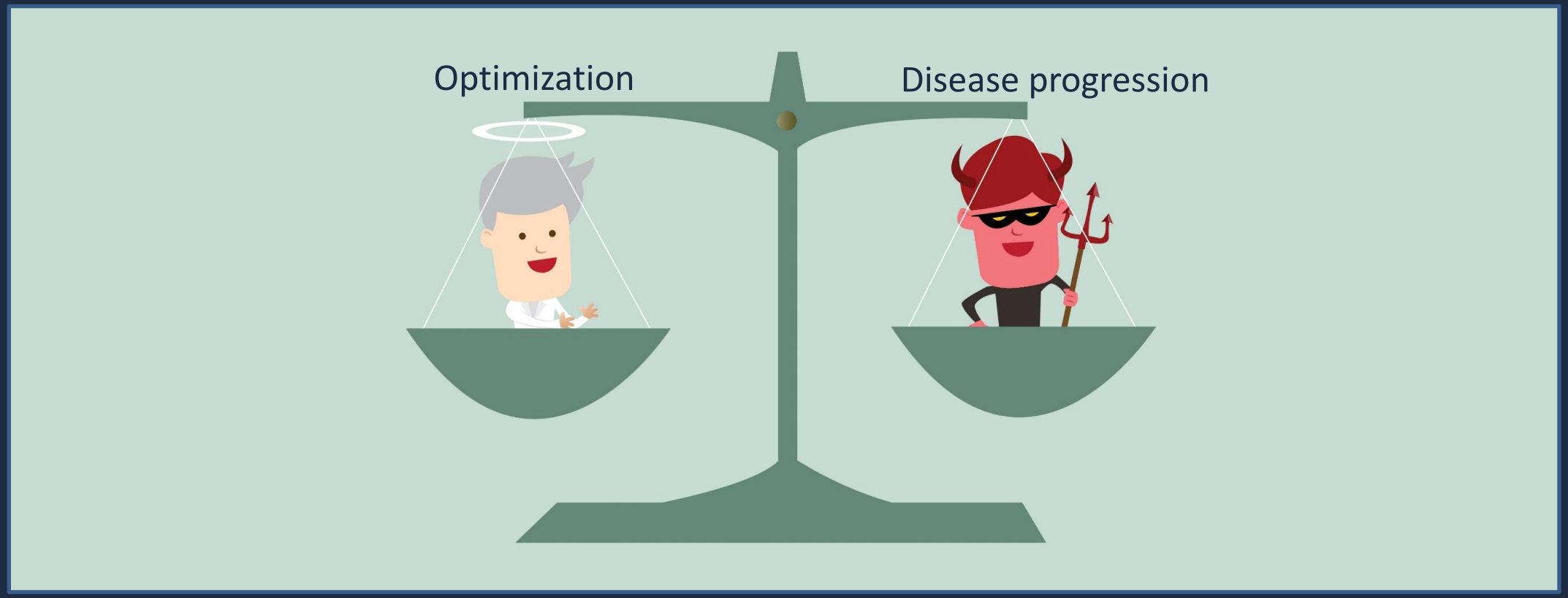
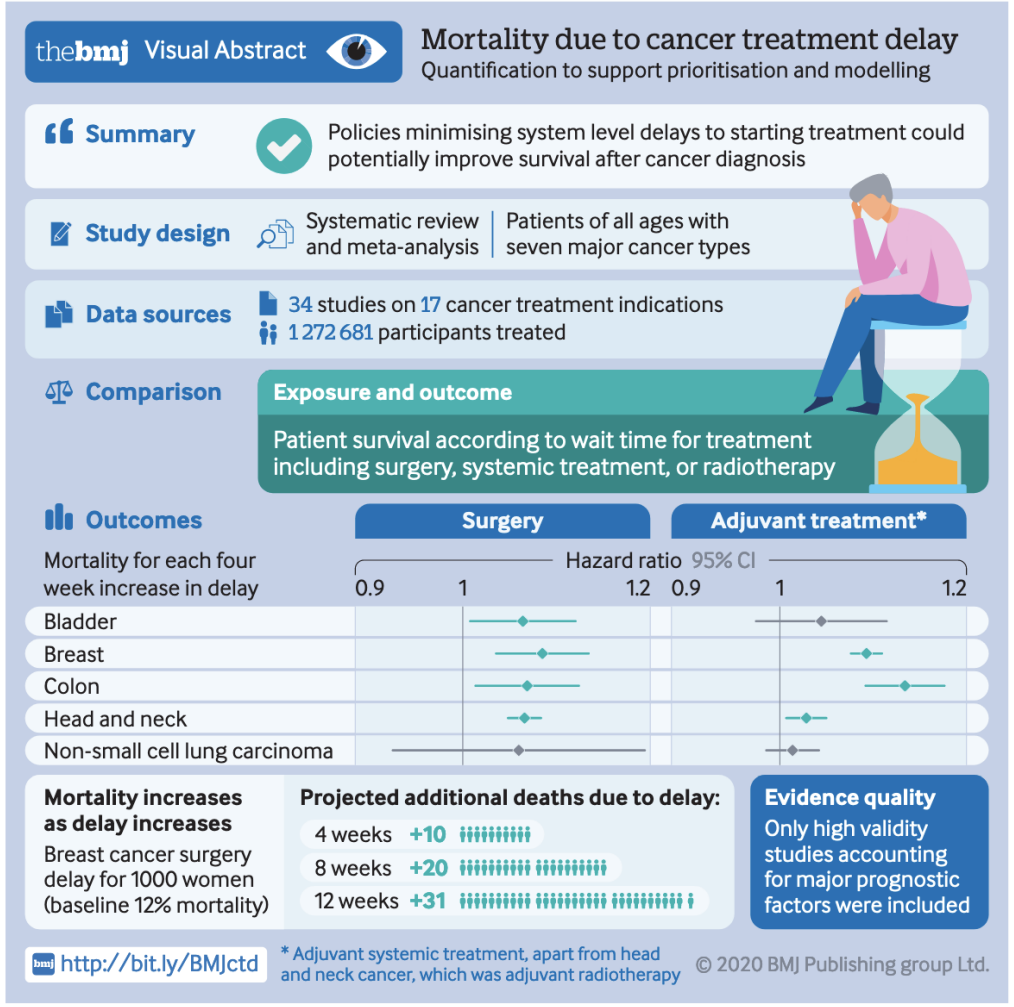


Mortality due to cancer treatment delay: systematic review and meta-analysis

Timothy P Hanna,[1,2,3] Will D King,[3] Stephane Thibodeau,[2] Matthew Jalink,[1,2] Gregory A Paulin,[2] Elizabeth Harvey-Jones,[4] Dylan E O'Sullivan,[3] Christopher M Booth,[1,2,3,5] Richard Sullivan,[6] Ajay Aggarwal[4,6,7]



Indication: surgery	Source	Study design	Dataset (dates)	Median age (years)	Stage	Other study details
Bladder	Chu 2019[13]	Retrospective observational comparison	SEER Medicare database (2004-2012)	75.2 (mean)	II	—
	Gore 2009[14]	Retrospective observational comparison	SEER Medicare database (1992-2001)	≤12 weeks=73.8, >12 weeks=73.6 (mean)	II	—
	Kulkarni 2009[15]	Retrospective observational comparison	Ontario Cancer Registry (1992-2004)	≤90 days 67.4, >90 days 69.2 (mean)	Tx, T0, Ta, Tis, T1-T4	—
Breast	Bleicher 2016[16]	Retrospective observational comparison	SEER Medicare database (1992-2009), NCDB (2003-2005) databases	75.2 (mean), 60.3 (mean)	I-III, I-III	Both cohorts were included in meta-analysis as overlap was limited owing to years considered in two cohorts, wider geographical population coverage of NCDB with ≥18 years represented (SEER was ≥66 years)
	Eaglehouse 2019[17]	Retrospective observational comparison	CCR, MDR databases (1998-2010)	54.5 (mean)	I-III	—
	Polverini 2016[18]	Retrospective observational comparison	NCDB (2004-2012)	59.4 (mean)	I-III	—
	Shin 2013[19]	Retrospective observational comparison	KCCR database (2006)	49.3 (mean)	Local and regional (SEER)	—
	Mateo 2020[20]	Retrospective observational comparison	NCDB (2010-2014)	NR	I-III	—
Colon	Bagaria 2019[21]	Retrospective observational comparison	Multicentre, US (1990-2012)	71 (range 18-99)	I-IV (pathological)	—
	Flemming 2017[22]	Retrospective observational comparison	OCR, CIHI DAD, OHIP databases (2002-2008)	71 (IQR 62-78)	I-IV (pathological)	—
NSCLC	Kanarek 2014[23]	Retrospective observational comparison	Institutional US (2003-2009)	61% ≥65	1A, 1B/2A, 2B	—
	Samson 2015[24]	Retrospective observational comparison	NCDB (1998-2010)	<8 weeks: 67.63 (±10.1), ≥8 weeks: 68.73 (±9.8) (mean (±SD))	I (clinical)	—
Cervix	No high validity data found					
Head and neck	Murphy 2016[25]	Retrospective observational comparison	NCDB (2003-2005)	NR	I-IVB	Oral tongue, oropharynx, larynx, hypopharynx
	Liao 2017[26]	Retrospective observational comparison	Taiwanese Cancer Registry database (2004-2010)	52.8 (mean)	I-IVB (clinical)	Oral cavity

CCR=Department of Defence Central Cancer Registry; CIHI DAD=Canadian Institute for Health Information Discharge Abstract Database; IQR=interquartile range; KCCR=Korean Central Cancer Registry; MDR=Military Health System Data Repository; NCDB=National Cancer Database (US); NR=not reported; NSCLC=non-small cell lung cancer; OCR=Ontario Cancer Registry; OHIP=Ontario Health Insurance Plan; SEER=Surveillance, Epidemiology, and End Results.

Details of the papers involved in the meta-analysis

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Flemming et al 2017

Association between the time to surgery and survival among patients with colon cancer: A population-based study

J.A. Flemming [a,b,e,*], S. Nanji [c,d], X. Wei [e], C. Webber [b,e], P. Groome [b,e], C.M. Booth [a,b,d,e]

[a] Department of Medicine, Queen's University, Kingston, Canada
[b] Department of Public Health Sciences, Queen's University, Kingston, Canada
[c] Department of Surgery, Queen's University, Kingston, Canada
[d] Department of Oncology, Queen's University, Kingston, Canada
[e] Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Kingston, Canada

Accepted 26 April 2017
Available online ■ ■ ■

Abstract

Factors associated with time-to-surgery (TTS) and survival in colon cancer has not been well studied. Cancer Care Ontario recommends surgery within 42 days of diagnosis and that 90% of patients meet this benchmark. We describe factors associated with TTS and survival in routine clinical practice.

Methods: Retrospective population-based cohort study of patients receiving elective colonic resection after diagnosis of colon cancer in Ontario, Canada from 2002 to 2008 followed until 2012. Factors associated with TTS were identified using multivariate log-binomial and Quantile regression at 42 days and 90th percentiles. The association between TTS and cancer-specific (CSS) and overall survival (OS) were examined using multivariate Cox regression.

Results: 4326 patients; median age 71 years and 52% male. Median TTS was 24 days (IQR 14–37); at the 90th percentile 56 days. Factors associated with TTS ≥ 42 days and >90th percentile included older age, co-morbid illness, surgeon volume, and stage I disease ($P < 0.05$ for all). In patients whose TTS was either at 42 days or 90th percentile, those ≥80 years old waited two weeks longer than those <60 years, individuals with co-morbid illness waited 10 days longer than without co-morbidity, and patients with stage I disease waited 10 days longer than those with stage IV disease ($P < 0.05$ for all). Delay in TTS > 42 days or >90th percentile was not associated with OS or CSS.

Conclusion: Age, co-morbidity, and stage of cancer are associated with TTS. There was no association between TTS and CSS or OS.

Keywords: Time-to-surgery; Overall survival; Cancer-specific survival; Institute for Clinical Evaluative Sciences; Ontario Cancer Registry

Bagaria et al 2019

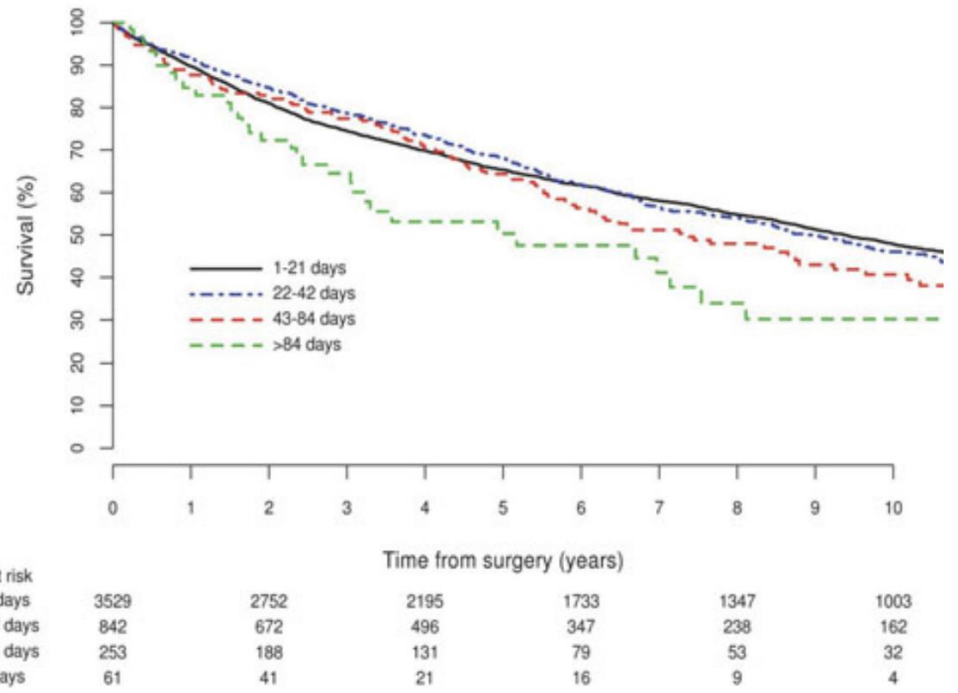
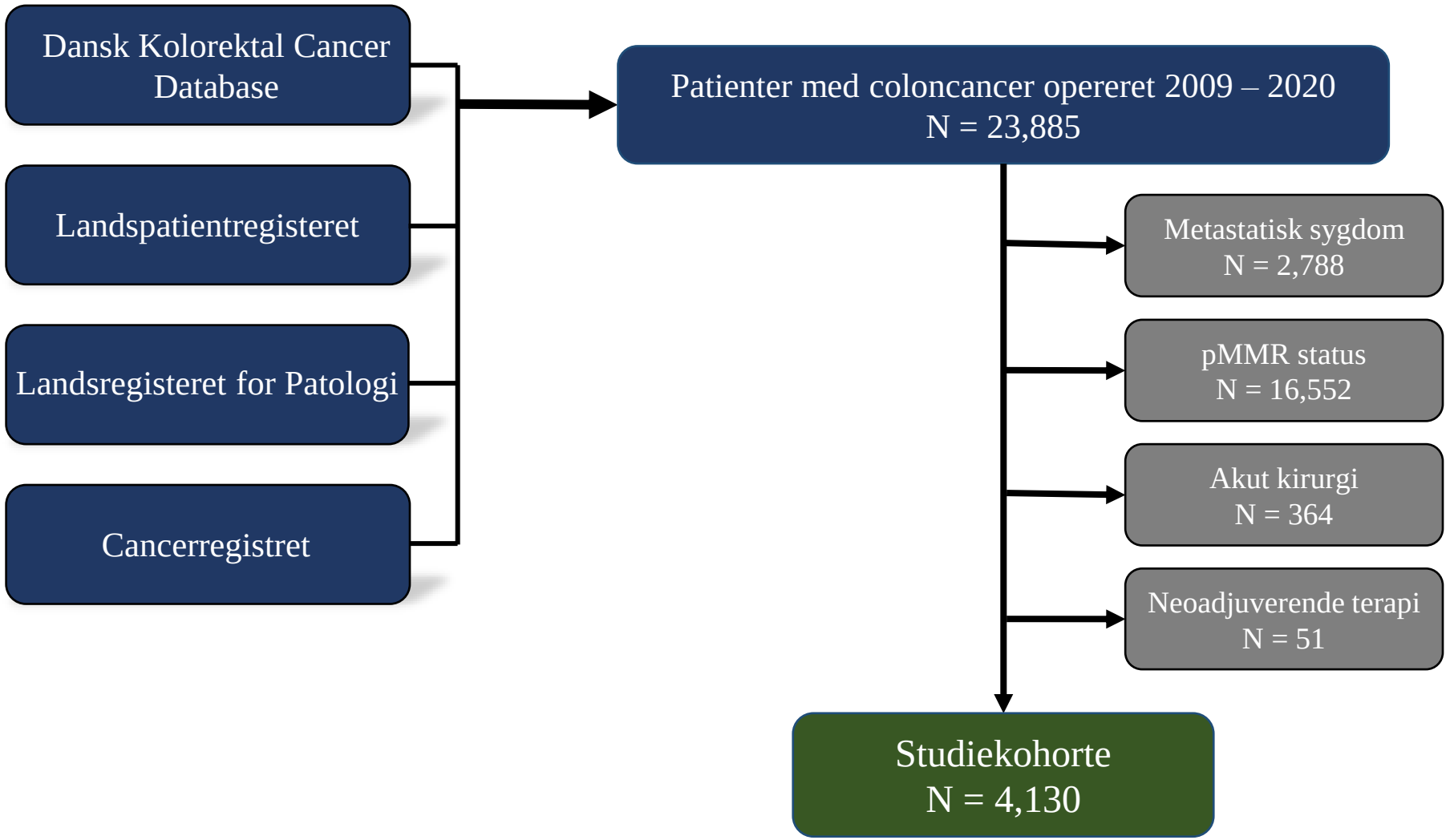
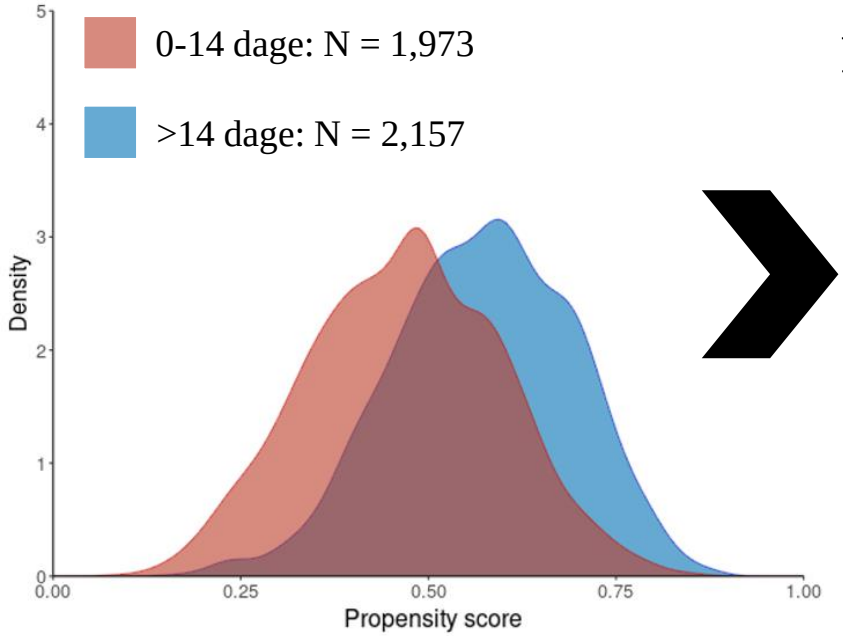


FIGURE 3 Overall survival according to wait-time for colectomy for all patients.

Time to surgery in dMMR colon cancer



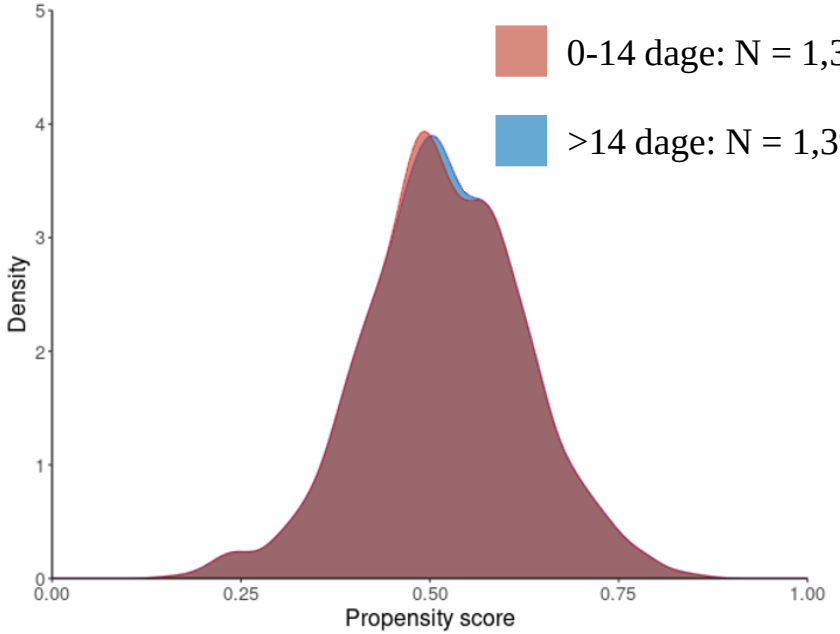
Matching



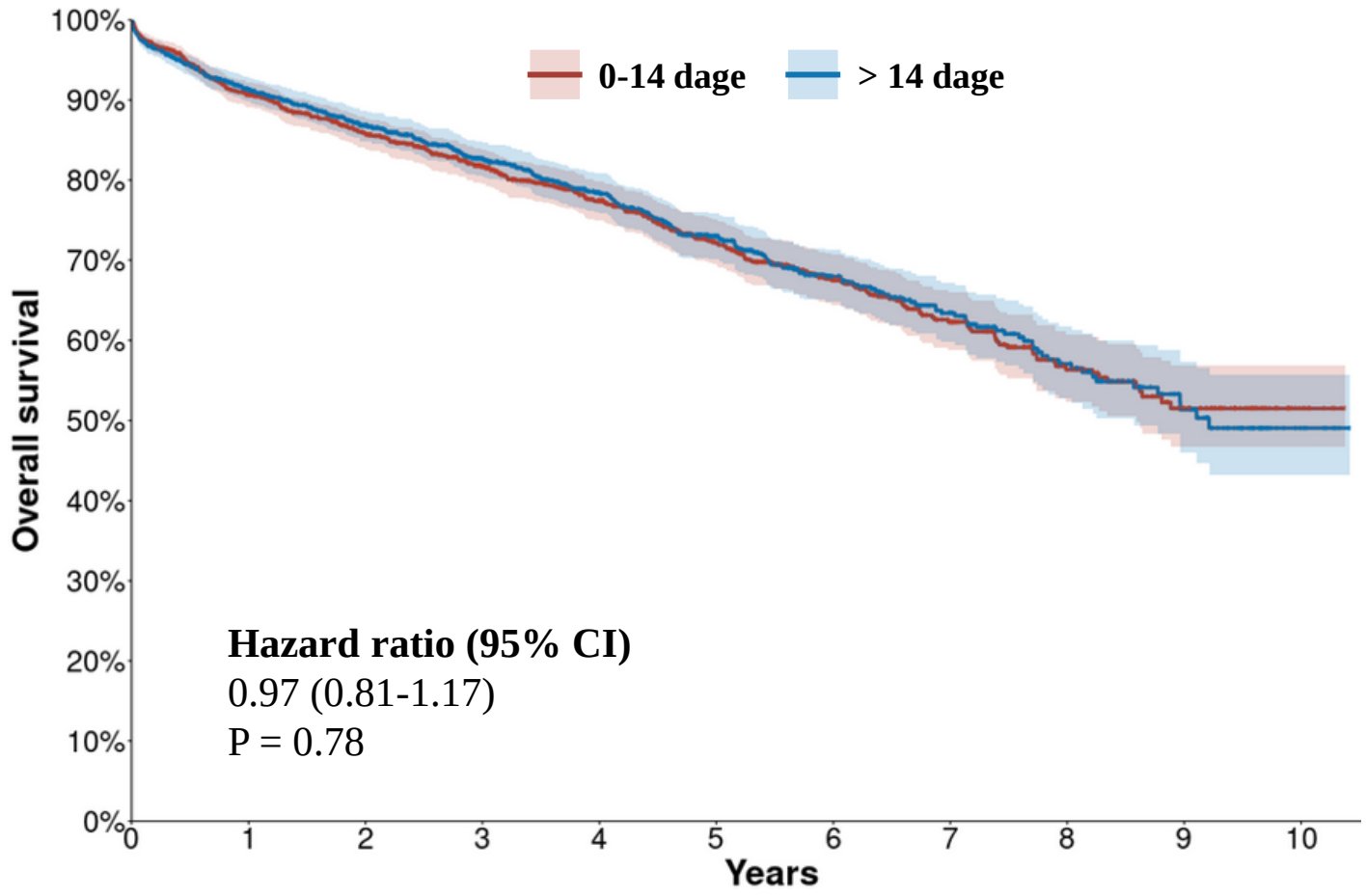
Propensity score matching 1:1

Kovariater > 12,000

- Demografidata
- Diagnoser
- Målinger
- Procedurer



Overall survival

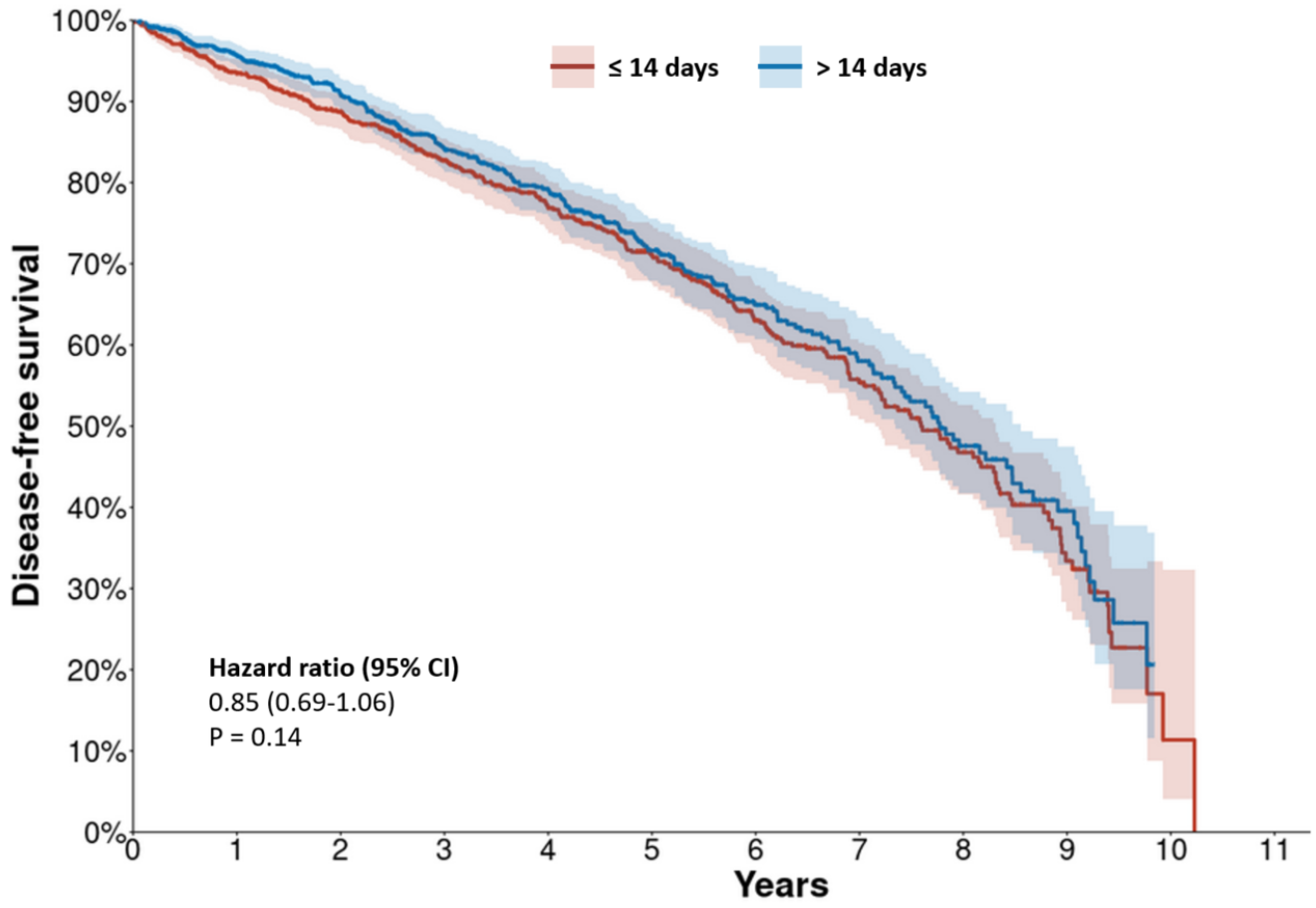


No. at risk

0-14 dage	1397	1165	978	809	616	462	323	222	128	62	10
> 14 dage	1397	1142	937	757	581	432	277	185	110	53	9

T. Justesen et al. European Journal of Surgical Oncology, 2023

Disease-free survival



No. at risk

≤ 14 days	899	757	647	503	404	301	211	140	83	33	< 6	0
> 14 days	899	747	633	478	386	258	174	117	63	27	0	0

T. Justesen et al. European Journal of Surgical Oncology, 2023

ICI for dMMR colon cancer – early experiences

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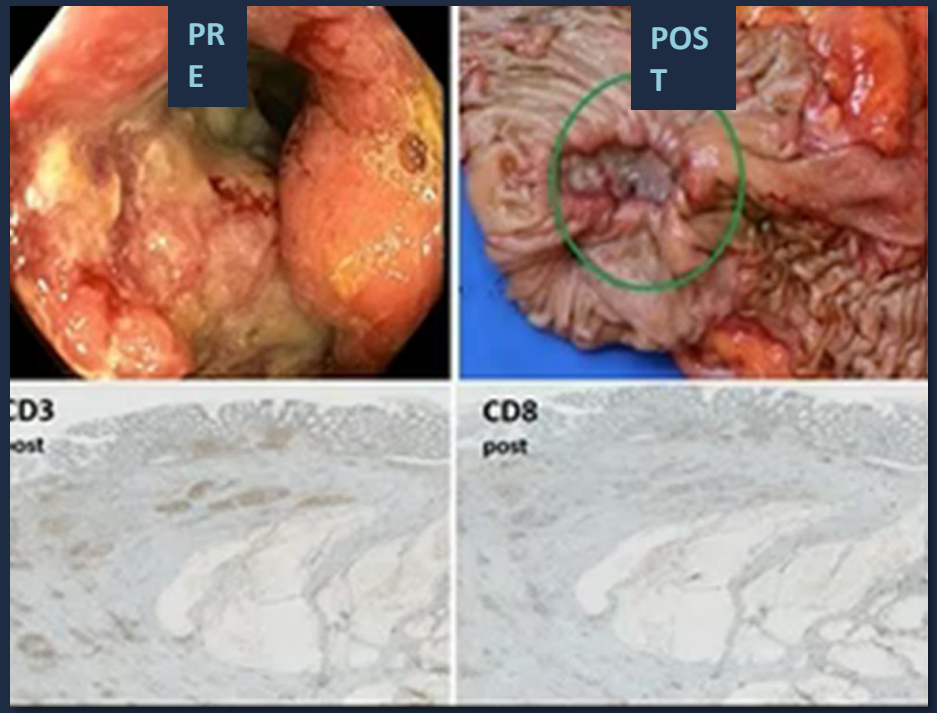
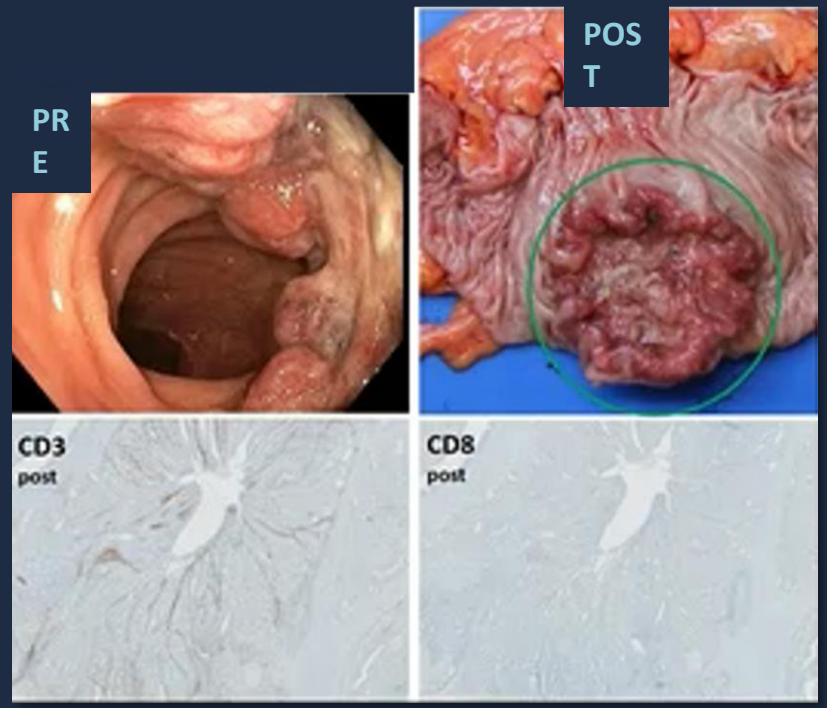
dMMR & pMMR tumor in single patient

MMR deficient tumor coecum; cT3N2



MMR proficient tumor sigmoid; cT3N0



Chalabi et al Nat med 2019

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-020-0805-8
Check for updates

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi[1,2,3]✉, Lorenzo F. Fanchi[2,4,17], Krijn K. Dijkstra[2,4,17], José G. Van den Berg[5,17], Arend G. Aalbers[6], Karolina Sikorska[7], Marta Lopez-Yurda[7,8], Cecile Grootscholten[1], Geerard L. Beets[6,9], Petur Snaebjornsson[5], Monique Maas[10], Marjolijn Mertz[11], Vivien Veninga[2,4], Gergana Bounova[4,12], Annegien Broeks[13], Regina G. Beets-Tan[9,10], Thomas R. de Wijkerslooth[1], Anja U. van Lent[14], Hendrik A. Marsman[15], Elvira Nuijten[7], Niels F. Kok[6], Maria Kuiper[1], Wieke H. Verbeek[1], Marleen Kok[3,16], Monique E. Van Leerdam[1], Ton N. Schumacher[2,4], Emile E. Voest[1,2,4,17]✉ and John B. Haanen[2,3,17]

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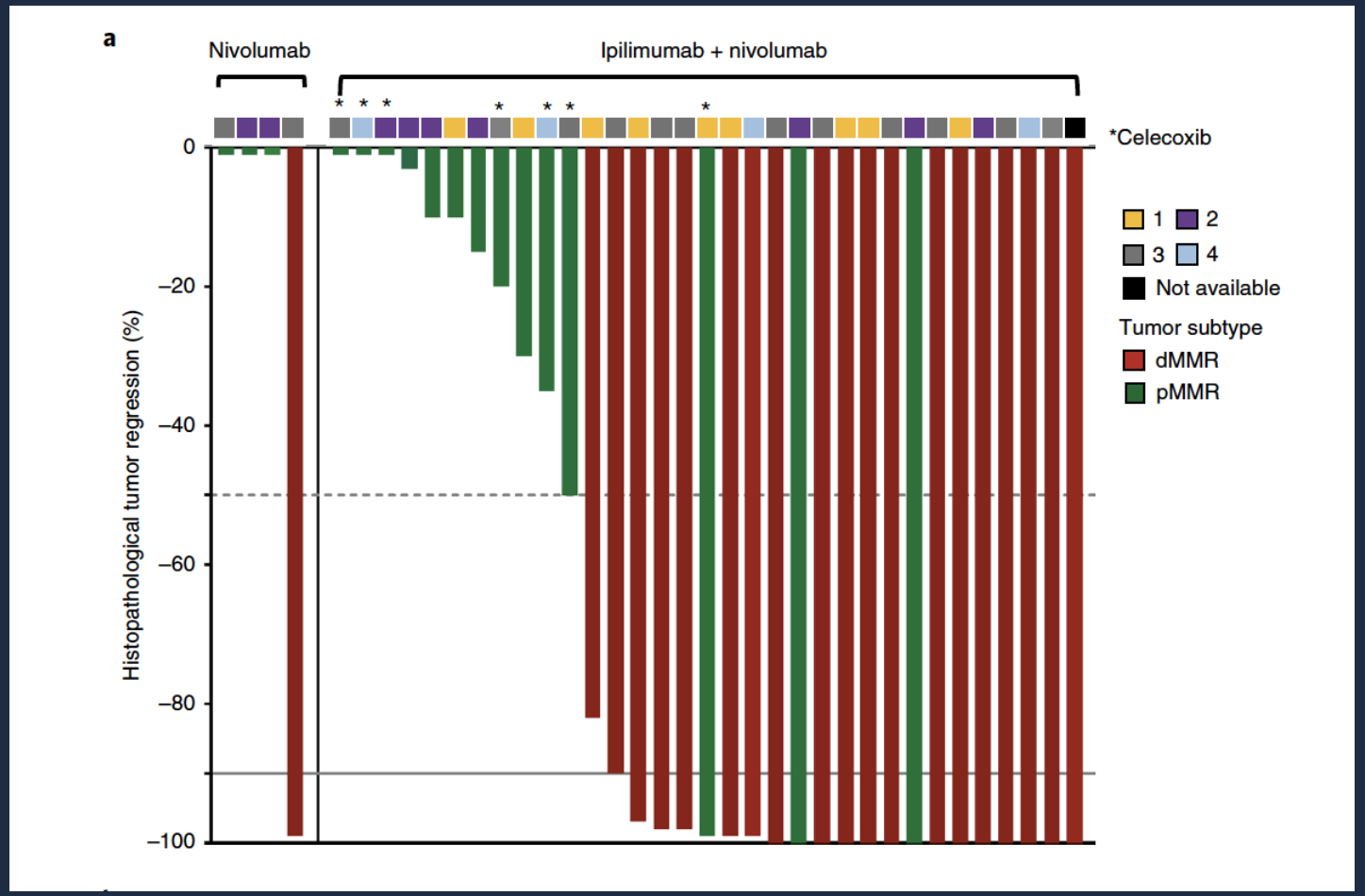


Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR- deficient colon cancers: Final clinical analysis of the NICHE study.

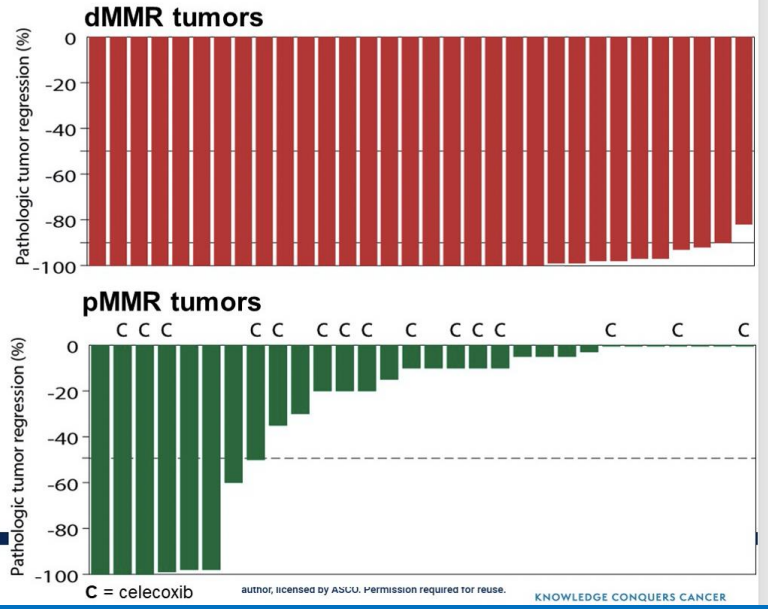
Responses in 29% of pMMR and 100% of dMMR tumors

Pathologic response	dMMR *n*= 32	pMMR *n*= 31
Major (≤10% VTR)	31 (97%)	7 (23%) *
Complete	22 (69%)	4 (13%) *
Partial (≤50% VTR)	1 (3%)	2 (6%)
Nonresponse (>50% VTR)	0 (0%)	22 (71%)

- **dMMR: 32/32 (100%) responders**
  - Lynch: 13/13 MPR, 12 pCR
  - Non-Lynch: 18/19 MPR, 10 pCR; 1 PR
- **pMMR: 9/31 (29%) responders**

*1 patient has not undergone surgery, now 1 year after treatment completion and no longer evidence of intraluminal or radiological disease, incl neg biopsies

VTR= viable tumor rest; MPR = major pathologic response; pCR = pathologic complete response; PR= partial response

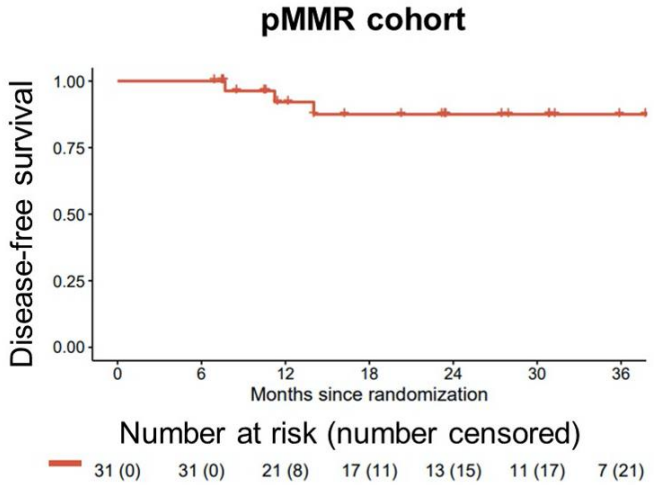


3511: Neoadjuvant nivolumab, ipilimumab, and celecoxib in MMR-proficient and MMR-deficient colon cancers: Final clinical analysis of the NICHE study.

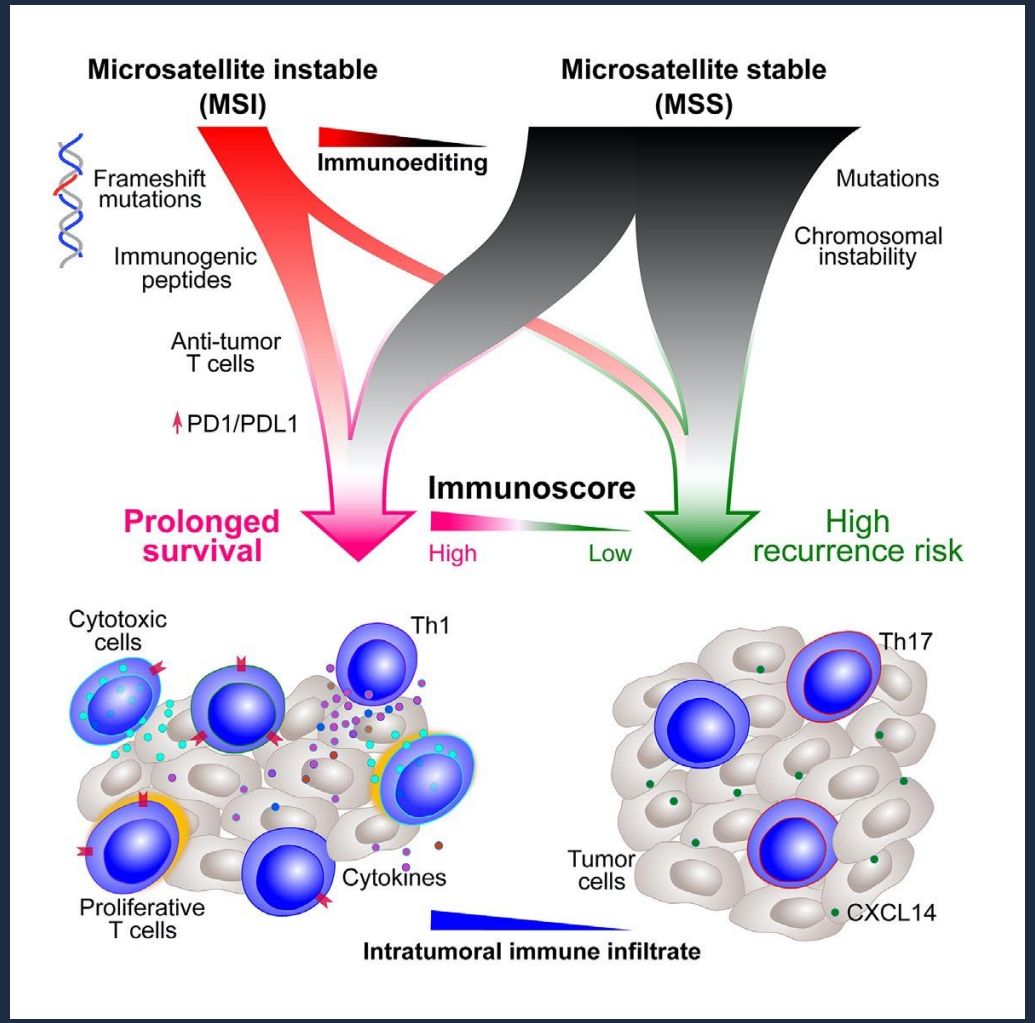
Adjuvant chemotherapy and disease recurrences

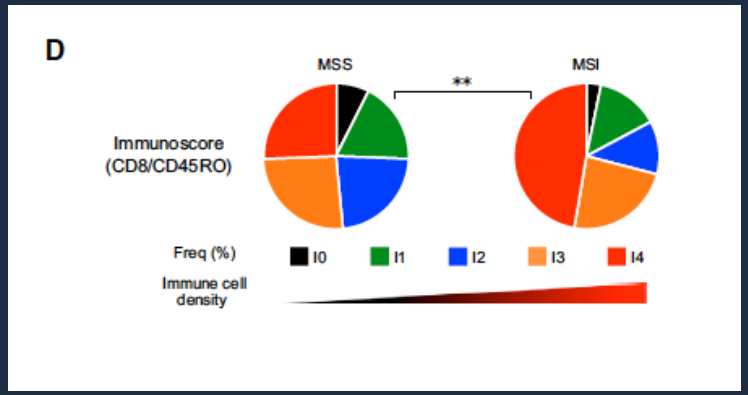
- **Adjuvant chemotherapy**
  - 2 dMMR patients with post-treatment positive lymph nodes (1 MPR, 1 PR)
  - 8 pMMR patients (all NR)

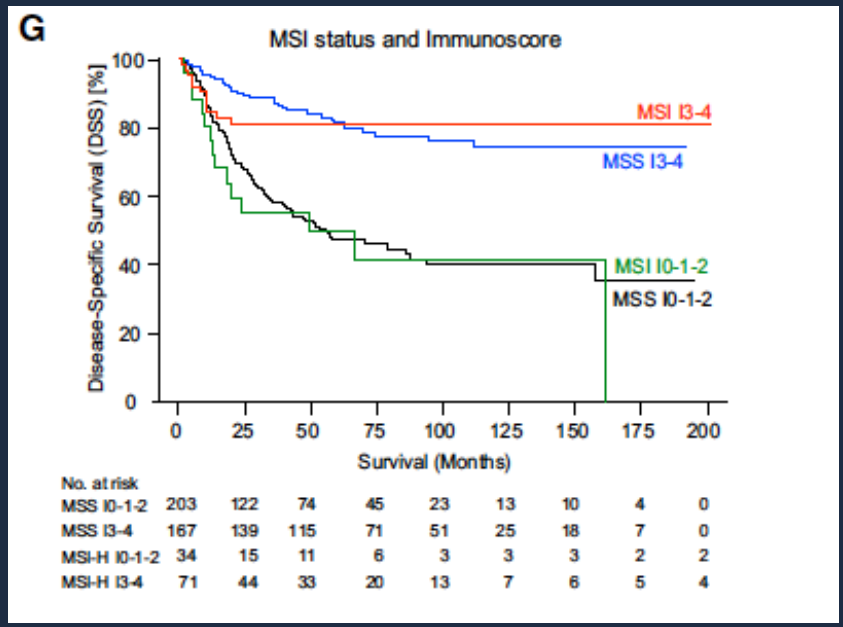
- Median follow-up time **pMMR** cohort **28 months**; disease recurrence in 2/31 (6%) patients, both nonresponders*
- Median follow-up time **dMMR** cohort **32 months**: no recurrences to date



Different clinical phenotypes of patients with MSI-high tumors







Mlecnik et al Immunity 2016

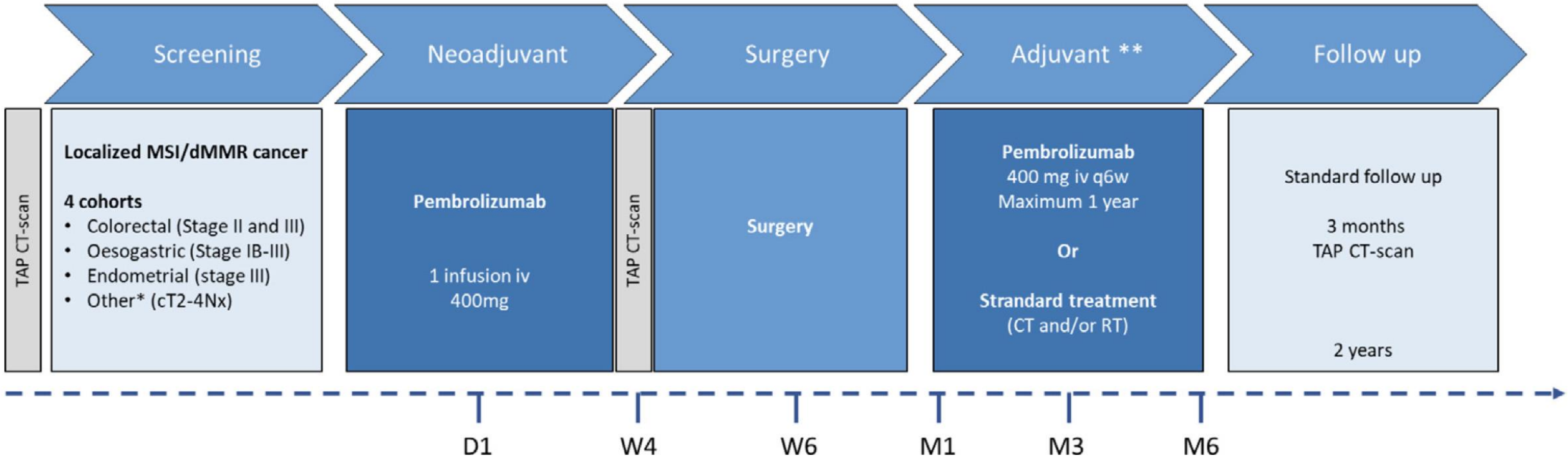
Different clinical phenotypes of patients with MSI-high tumors

For patients with Lynch syndrome, the risk of developing CRC before the age of 75 have been shown to vary drastically depending on the mutated MMR gene:

approximately 11-12%, 15-20%, 43-51%, and 46-57% for mutations in *PMS2*, *MSH6*, *MSH2*, and *MLH1,* respectively

Møller et al Gut 2018
Dominiquez-Valentin et al Genet Med 2020
Broeke et al JCO 2018

IMHOTEP TRIAL



Coutzac et al Dig Liv Dis 2022

2591: Immunotherapy for localized dMMR/MSI tumors: First interim analysis of the IMHOTEP trial.

Immunotherapy for localized dMMR/MSI tumors: first interim analysis of the IMHOTEP trial.

s: C. de la Fouchardière[1], A. Zaanan[2], R. Cohen[3], S. Le Sourd[4], D. Tougeron[5], E. Soularue[6], O. Dubreuil[7], N. Willet[8], E. Samalin[9], G. Piessen[10], V. Hautefeuille[11], M. Jary[12], M. Ben Abdelghani[13], L. Evesque[14], P. Rochigneux[15], E. Blanc[1], A. de Montfort[1], F. Bibeau[16],C. Coutzac[1]

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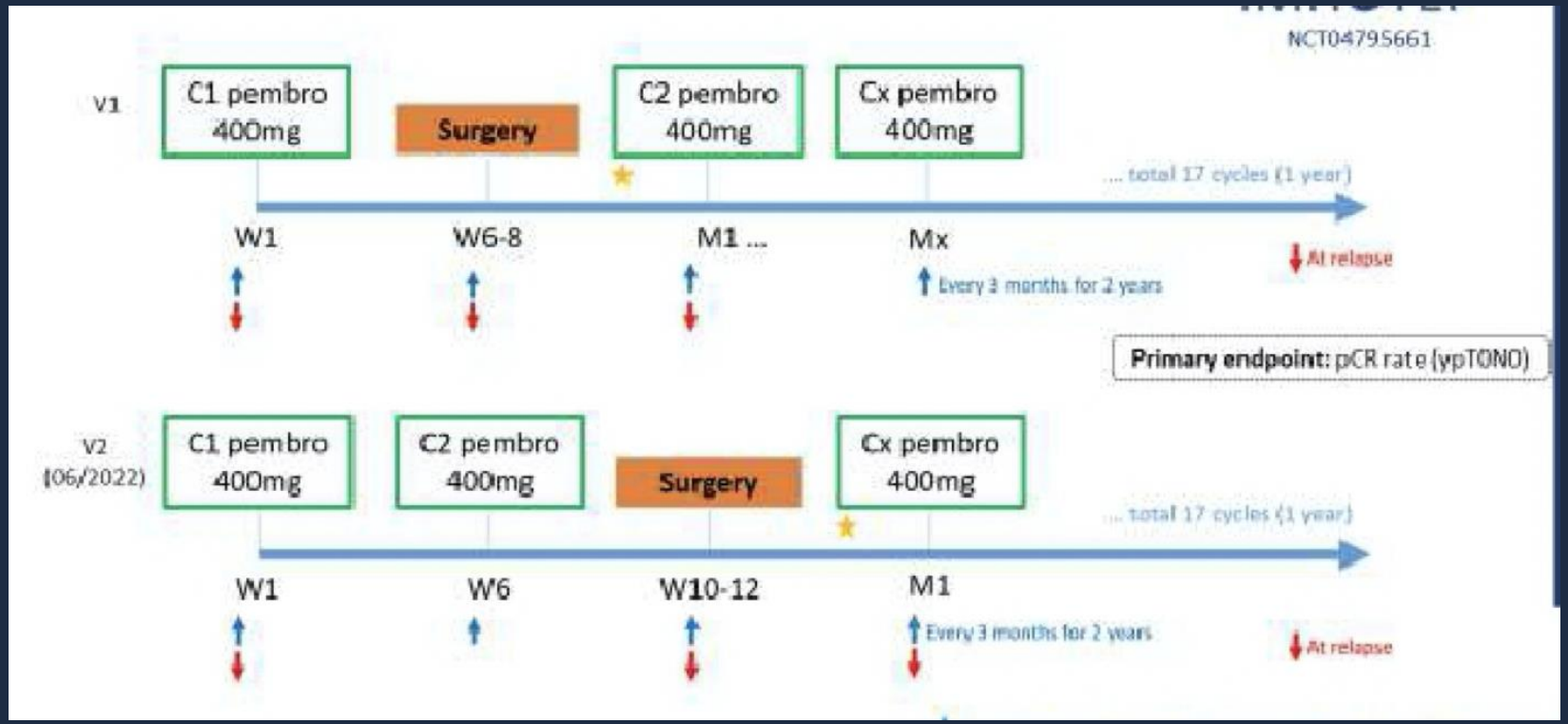

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- 35 pt's with CRC
- 1/3 PS 0

Patients' characteristics	Cohort				All Cohorts
	Colorectal	Gastroesophageal	Endometrial	Other	
	N=35	N=21	N=5	N=9	N=70
Median age (min; max)	66.0 (26.0; 89.0)	73.0 (55.0; 87.0)	68.0 (56.0; 88.0)	59.0 (38.0; 72.0)	67.5 (26.0; 89.0)
Sex male, N (%)	22 (62.9%)	11 (52.4%)	0 (0.0%)	5 (55.6%)	38 (54.3%)
ECOG-PS 0	13 (37.1%)	8 (38.1%)	1 (25.0%)	7 (77.8%)	29 (42.0%)

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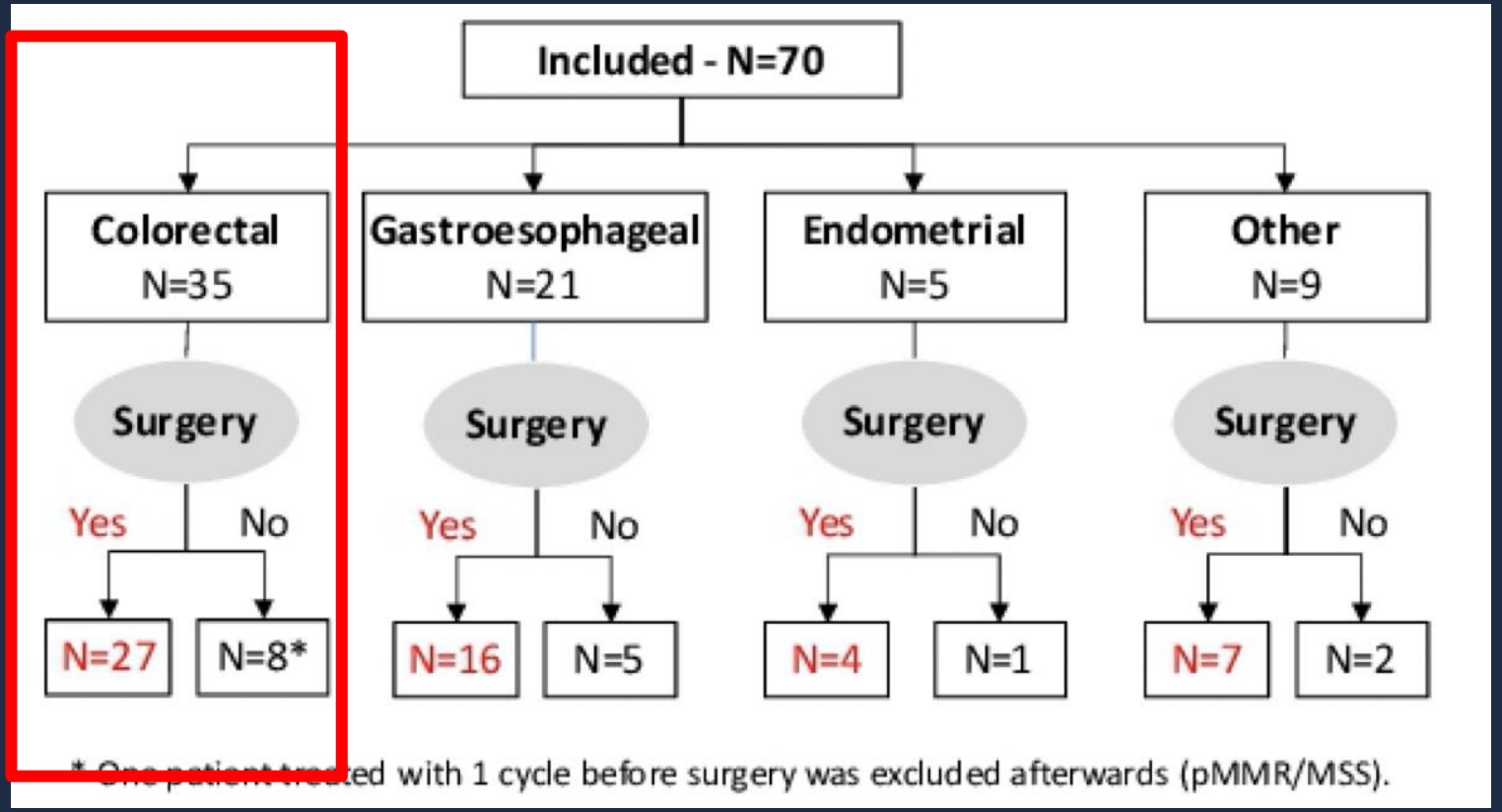
- 27 out of 35 operated
- 8 not operated



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Pre-operative pembrolizumab cycles number (n=54)

P cycles		Colorectal N=27	Gastroesophageal N=16	Endometrial N=14	Other N=7	All cohorts N=54
1	N (%)	17 (63.0)	11 (68.8)	1 (25.0)	2 (28.6)	31 (57.4)
2	N (%)	10 (37.0)	5 (31.3)	3 (75.0)	5 (71.4)	23 (42.6)

Reasons for omitting surgery (N=16)

- **Partial or complete clinical response after 1 or 2 injections (N=8)**
- Disease progression (N=1)
- Death before surgery (N=4)*
- Excluded (N=1)
- Toxicity (N=2)

*Tumor-related complications (n=2) (endometrial hemorrhage; colon perforation). **Suspicion of disease progression** (n=2) (radiological review ongoing).

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- a lower number with complete response compared with NICHE-2
- Dose-response relationship

Primary endpoint: pCR (ypT0N0) rate (N=54)

	Colorectal N=27	Gastroesophageal N=16	Endometrial N=4	Other N=7	All Cohorts N=54
ypT0N0 N (%)	**11** (40.7)	4 (25.0)	**0** (0.0)	6 (85.7)	**21 (38.9)**

pCR according to pembrolizumab cycles number

1 cycle	6 (35.3)	2 (18.2)	**0** (0.0)	**2** (100.0)	**10 (32.3)**
2 cycles	5 (50.0)	2 (40.0)	**0** (0.0)	**4** (80.0)	**11 (47.8)**

+ 15,5%

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IMHOTEP

Conclusions

In this interim analysis, we observed a **limited pathologic complete response rate with short-course neoadjuvant pembrolizumab (400mg flat dose, 1 or 2 cycles)**.

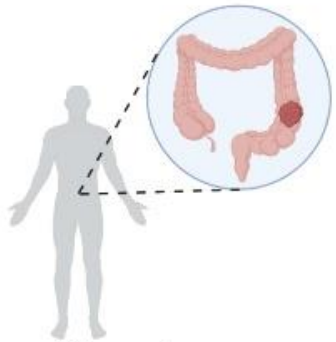
(I) When we added the number of non-operated patients (due to clinical response) to the pCR rate, our results were comparable with previous reports.

(II) We demonstrated that preoperative anti-PD-1 duration has an impact on pCR rate.

(III) Overall, tolerance of pembrolizumab was acceptable without new safety signal.

Next steps toward organ preservation. - the RESET C trial!

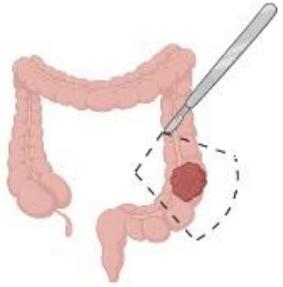
Study design
- Multicenter: 10 hospitals
- Number of patients: 85
  - dMMR colon cancer
  - Stage I-III



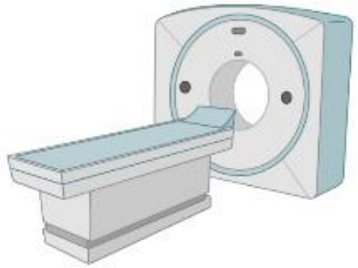
Diagnosis
If eligible then inclusion

Pembrolizumab
4mg/kg (max 400mg)

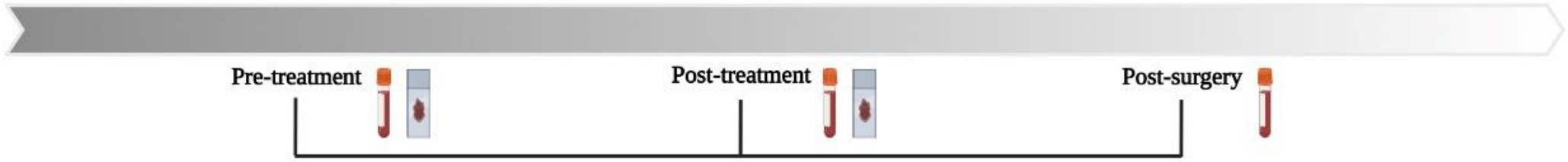
Tumour restaging
CT scan and colonoscopy



Surgery
3-5 weeks after pembrolizumab



Follow-up
CT scans 1 and 3 years



NAC for the patient with a dMMR tumor phenotype

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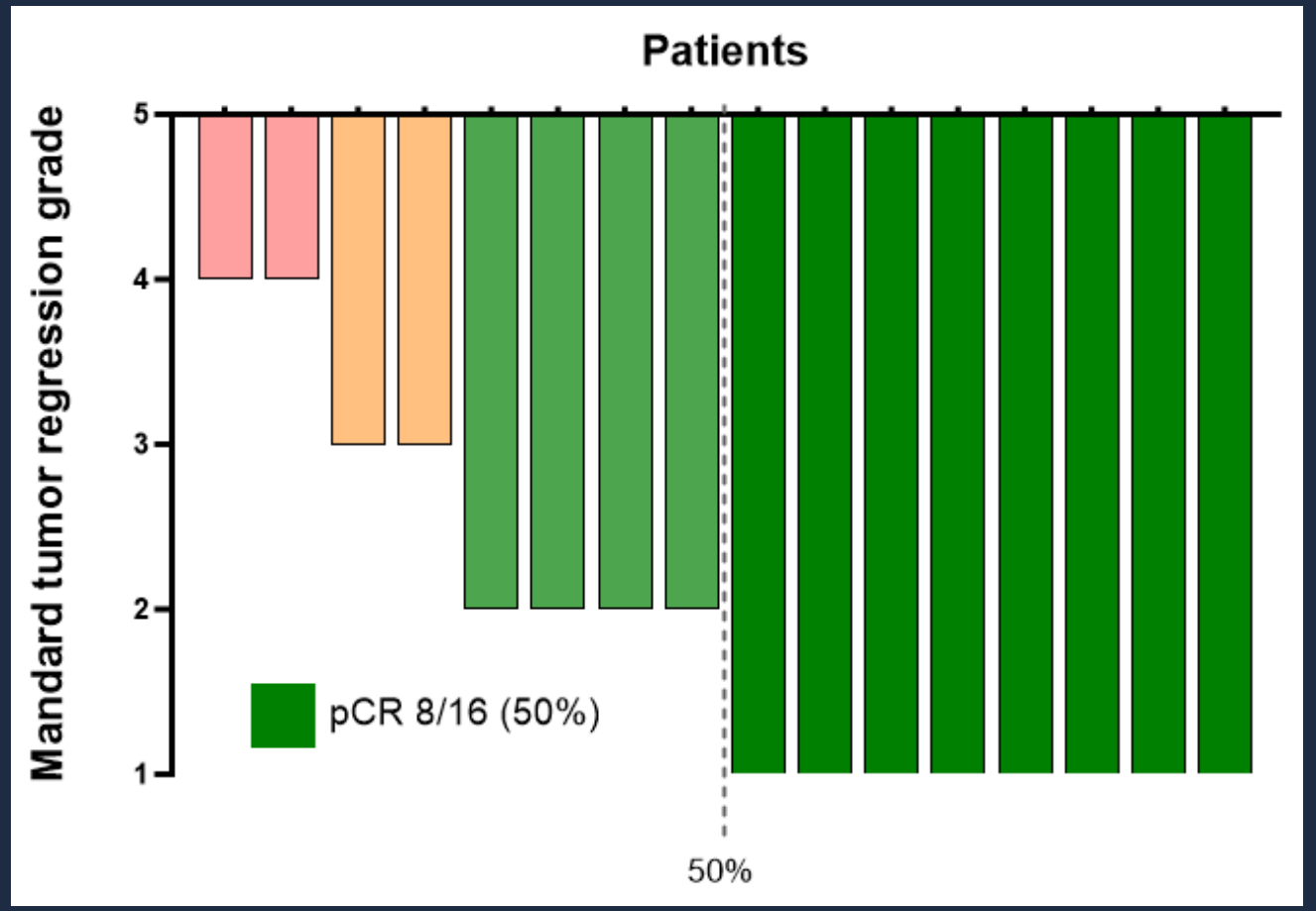

3610: Immunotherapy for localized MSI-H colorectal cancer: Characterizing endoscopic and imaging response

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Immunotherapy for Localized MSI-H Colorectal Cancer: Characterizing Endoscopic and Imaging Response

Daniel A. Fox,[1] Tsuyoshi Konishi,[2] Harmeet Kaur,[2] Y. Nancy You,[2] Kanwal P.S.Raghav,[2] Phillip S. Ge,[2] Craig Messick,[2] Benny Johnson,[2] Van K. Morris II,[2] Jane V Thomas,[2] Preksha Shah,[2] Brian K. Bednarski,[2] Scott Kopetz,[2] George J. Chang,[2] Kaysia Ludford,[2] Victoria Higbie,[2] Michael J. Overman,[2] Deepak Bhamidipati[2]
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Baylor College of Medicine

- Challenge of the future – monitoring response in IO-treatments

- Complete response (CR)
- Near CR
- Partial Response/Stable disease
- Progressive Disease

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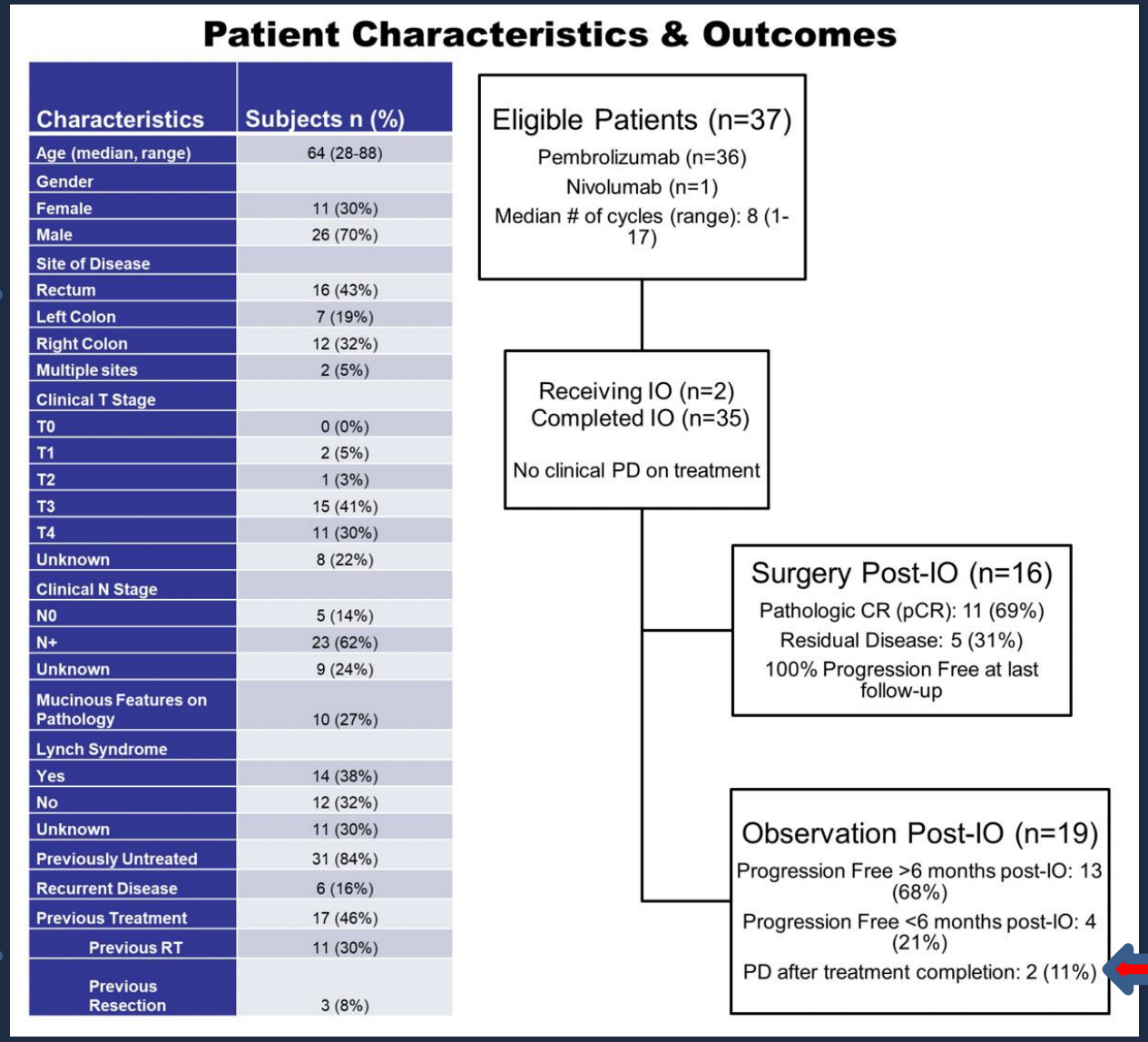
Patient Characteristics & Outcomes

Characteristics	Subjects n (%)
Age (median, range)	64 (28-88)
Gender	
Female	11 (30%)
Male	26 (70%)
Site of Disease	
Rectum	16 (43%)
Left Colon	7 (19%)
Right Colon	12 (32%)
Multiple sites	2 (5%)
Clinical T Stage	
T0	0 (0%)
T1	2 (5%)
T2	1 (3%)
T3	15 (41%)
T4	11 (30%)
Unknown	8 (22%)
Clinical N Stage	
N0	5 (14%)
N+	23 (62%)
Unknown	9 (24%)
Mucinous Features on Pathology	10 (27%)
Lynch Syndrome	
Yes	14 (38%)
No	12 (32%)
Unknown	11 (30%)
Previously Untreated	31 (84%)
Recurrent Disease	6 (16%)
Previous Treatment	17 (46%)
Previous RT	11 (30%)
Previous Resection	3 (8%)



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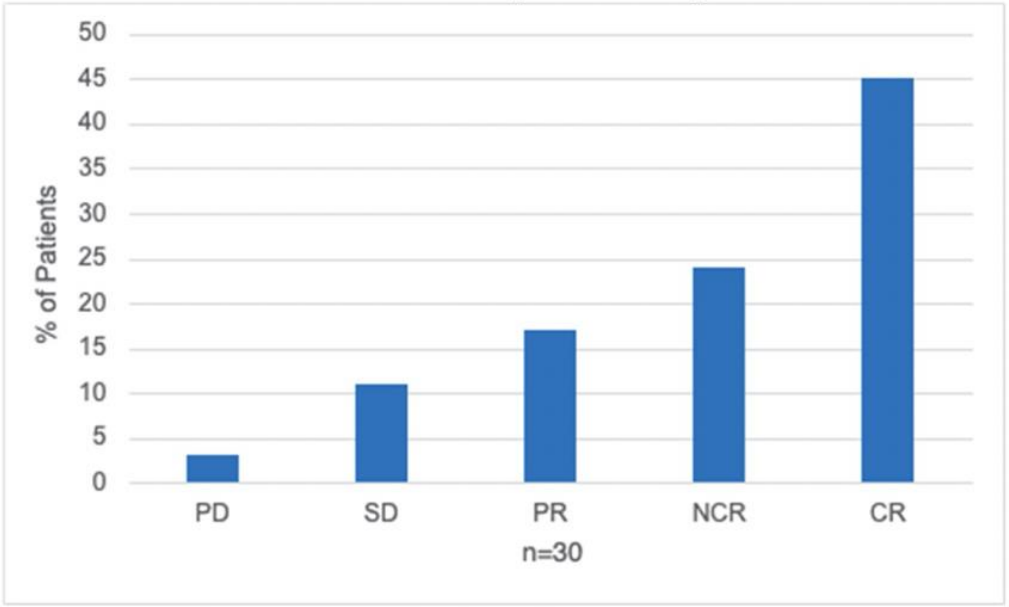
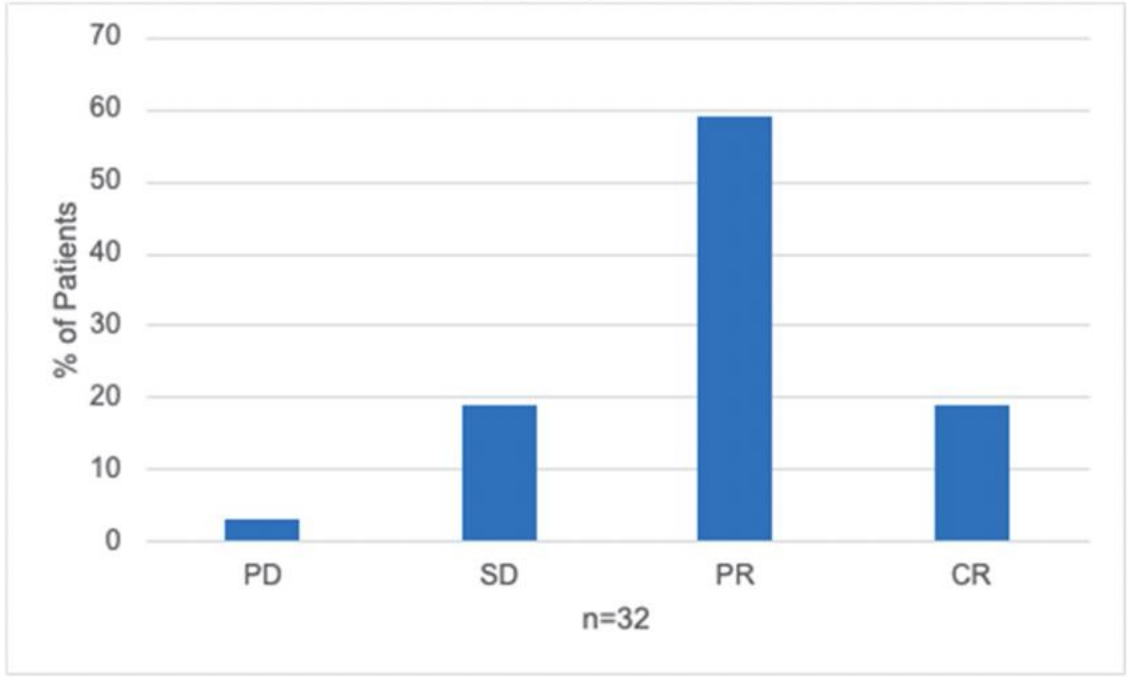
Results

Best Endoscopic Response



This bar chart shows the distribution of best endoscopic response for each patient. The best endoscopic response was CR in 13 of 30 (43%) patients, which was achieved after a median of 6 cycles.

Best Imaging Response



This bar chart shows the distribution of best imaging response for each patient. The best imaging response was CR in 6 of 32 (19%) of patients. **In cases where imaging and endoscopy were available (n=24), discrepancy in best response was noted in 14 (58%) cases. The most common discrepancy was partial response on imaging when endoscopic CR was noted (n=6 cases).**

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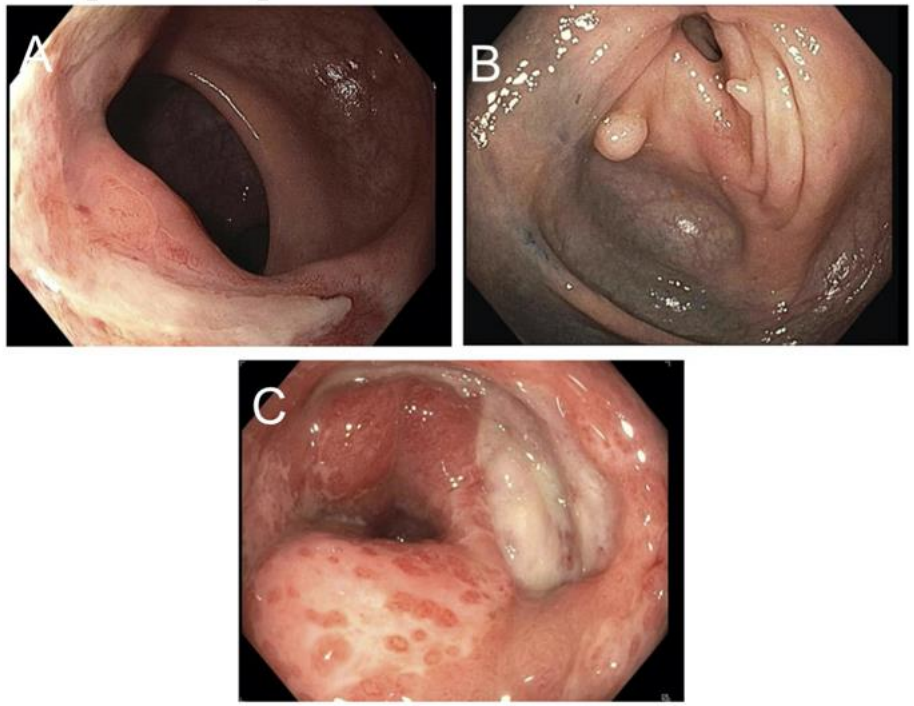
Endoscopic Reports of Residual Disease with pCR



Endoscopic findings indicating residual disease prior to surgery included findings such as ulceration, scarring, strictures, and an obstructing mass in one case. The report descriptions of the example images: **(A)** “single solitary 15mm ulcer…in the mid-rectum” after 2 cycles of IO, **(B)** “malignant appearing, intrinsic moderate stenosis in ascending colon“ after 8 cycles of IO, **(C)** “ulcerated mucosa, edema, and erythema of rectum” after 12 cycles of IO.

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RESEARCH SUMMARY

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Cercek A et al. DOI: 10.1056/NEJMoa2201445

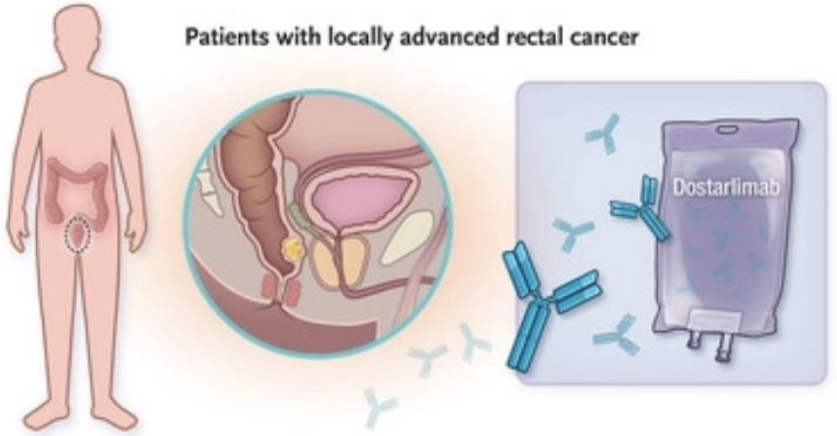
CLINICAL PROBLEM

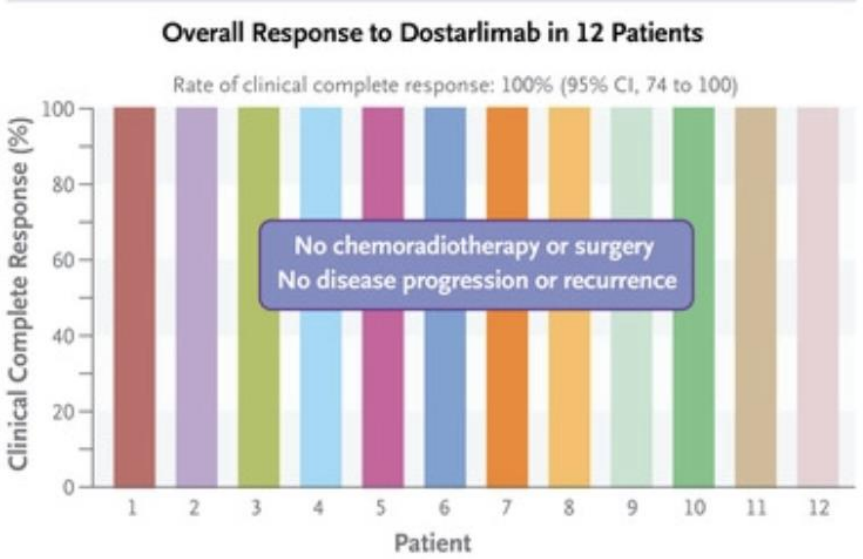
Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

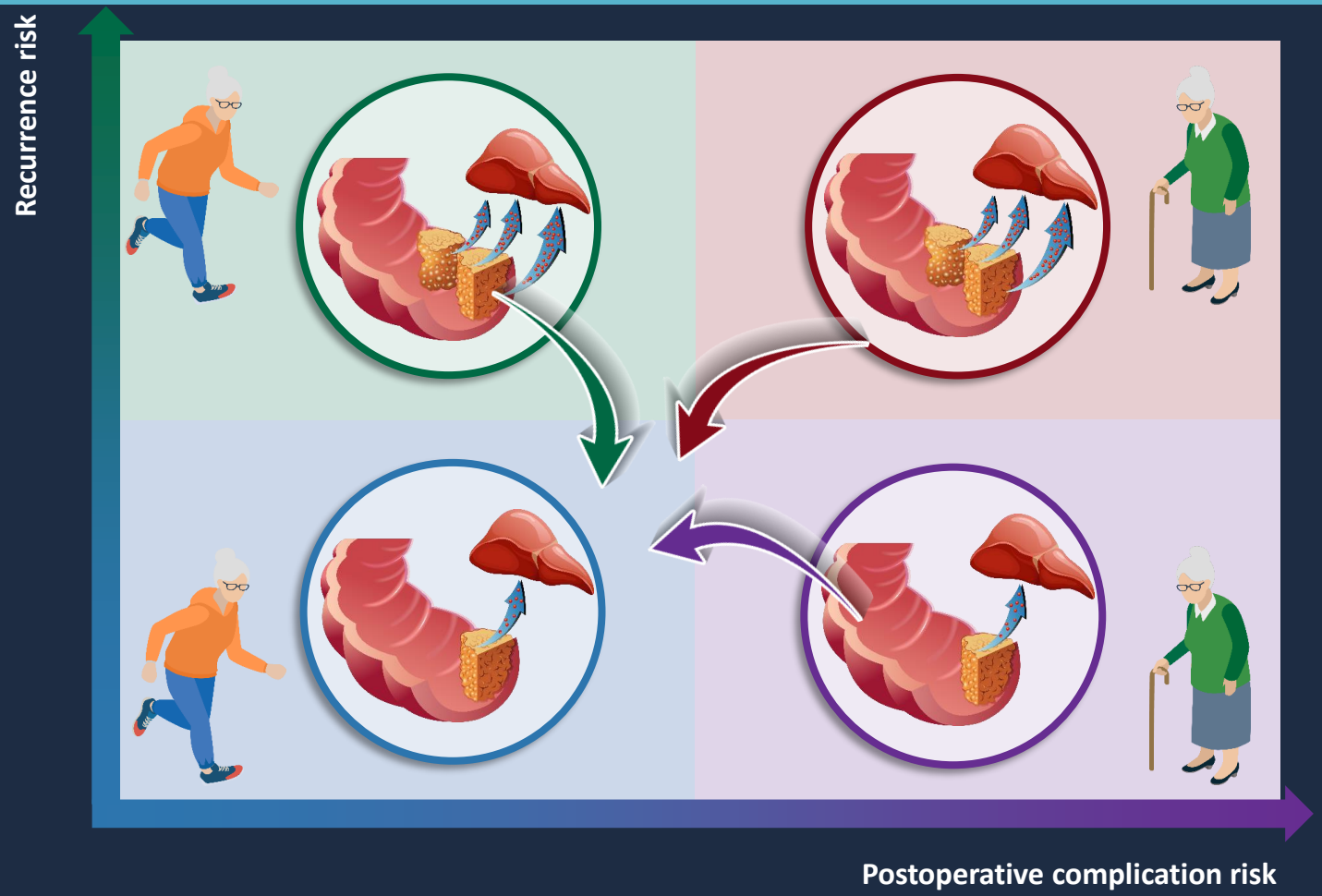
Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.

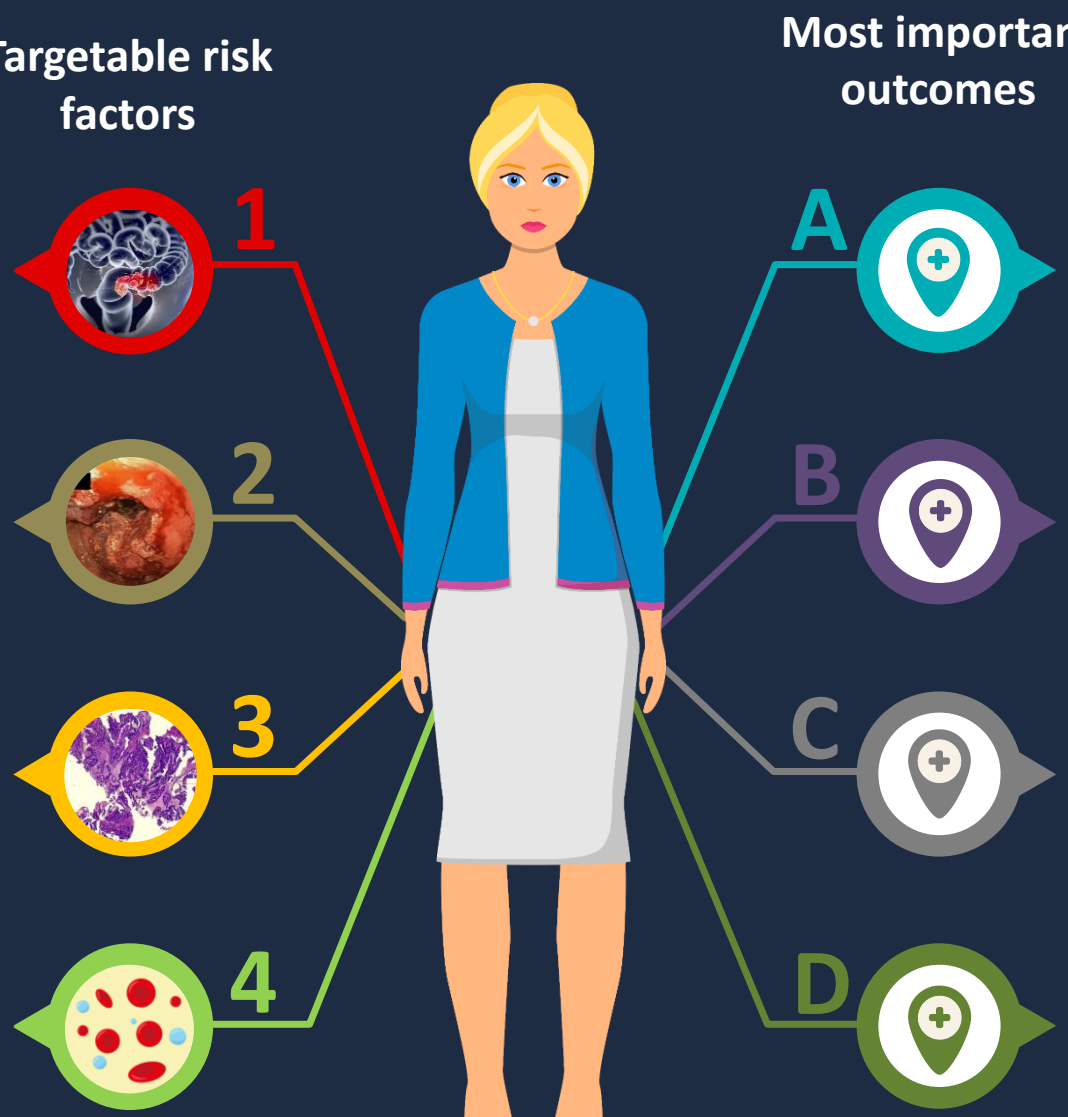




A spectrum of disease phenotypes – has the time come for organ preservation in colon cancer



Understanding the variation between patients and most important outcomes for the patient is crucial



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