Consensus recommendations for the management of colorectal cancer in older adults

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EORTC CRC Task Force Chair

ESMO/SIOG Cancer in the Elderly Task Force Member

COI

- Speaker: Merck Serono, Amgen, Roche, Servier, Ipsen, BMS
- Advisory Boards: Merck Serono, Novartis, Sanofi, BMS, Ipsen
- Travel grants: Merck Serono, Merck, Roche
- Research Funding: Merck, Astra Zeneca

Outline

- Introduction
- Adjuvant therapy
- Rectal Cancer
- Metastatic disease
- Conclusions

CONTROVERSIES REGARDING OLDER ADULTS

Largest group of patients with sparse available evidence

Often referred to as a “special population,” while most patients in clinical practice are older

Chronological age is often used for stratification instead of fitness/functional age

RCTs include selected fit and healthy adults – OA are underrepresented

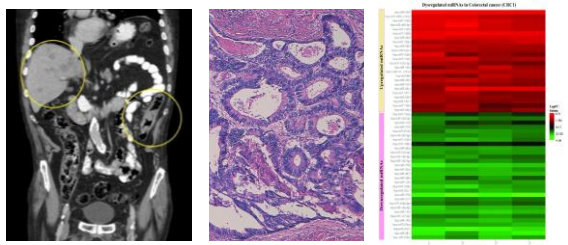
Few dedicated trials for older/vulnerable patients

Evidence based or evidence biased medicine?

Abbasi J. JAMA 2019;322(18):1751-3.

TUMOUR – KEY CONSIDERATIONS

TUMOUR



Stage

Prognosis – molecular characteristics

Synchronous or metachronous metastases

Tumour burden – metastatic sites

Is tumour biology different in older adults with CRC?

Right-sided ↑ (**>50%** in pts ≥80y vs 35% in pts <60 y)

CIMP + ↑ (**21-25%** in pts ≥75y vs 5-10% in pts <60 y)

MSI/dMMR ↑ (**15-20%** in pts ≥75y vs 5-10% in pts <65 y)

BRAF **V600E** ↑ (**12-25%** in pts ≥75y vs 5-15% in pts <60 y)

Van Herck Y, *et al.* Lancet Healthy Longev 2021;2(1

Oxaliplatin-based adjuvant chemotherapy in older patients with stage III colon cancer: an ACCENT/IDEA pooled analysis of 12 trials

		Age < 70 years *N*=13 569 (76%)	**Age ≥ 70 years** *N*=4 340 (24%)	***P*-value**
T stage	T1-T2	1812 (13.6%)	399 (9.3%)	**<0.001**[1]
	T3	9047 (68.1%)	2970 (69.4%)	
	T4	2418 (18.2%)	909 (21.2%)	
	Missing, N	292	62	
Sidedness	Proximal	3541 (41.0%)	1409 (52.3%)	**<0.001**[1]
	Distal	5088 (59.0%)	1287 (47.7%)	
	Missing, N	4940	1644	
MMR status	pMMR	2705 (90.0%)	406 (84.2%)	**<0.001**[1]
	dMMR	300 (10.0%)	76 (15.8%)	
	Missing, N	10564	3858	
BRAF status	MT	280 (9.4%)	93 (18.3%)	**<0.001**[1]
	WT	2711 (90.6%)	414 (81.7%)	
	Missing, N	10578	3833	

C Gallois … D Papamichael J Clin Oncol 2024

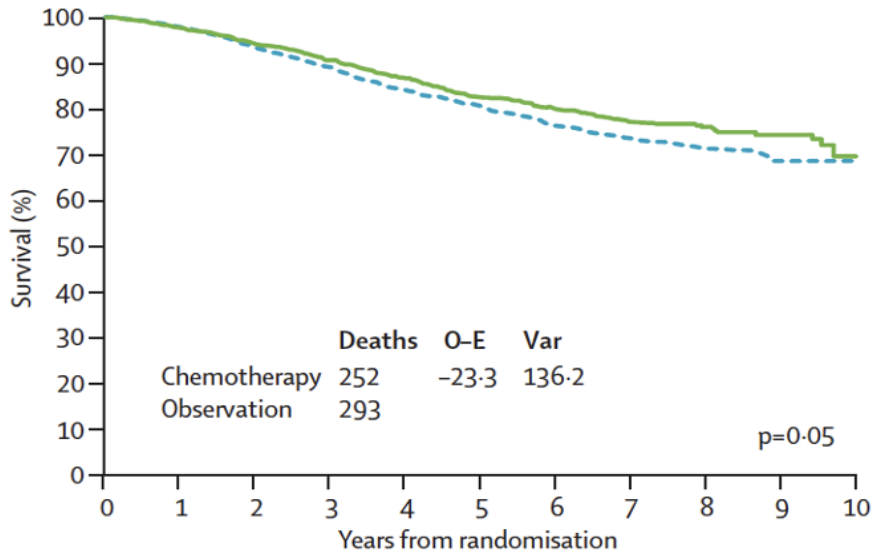
ADJUVANT THERAPY

STAGE II COLON CANCER

Adjuvant Therapy in Stage II

QUASAR TRIAL

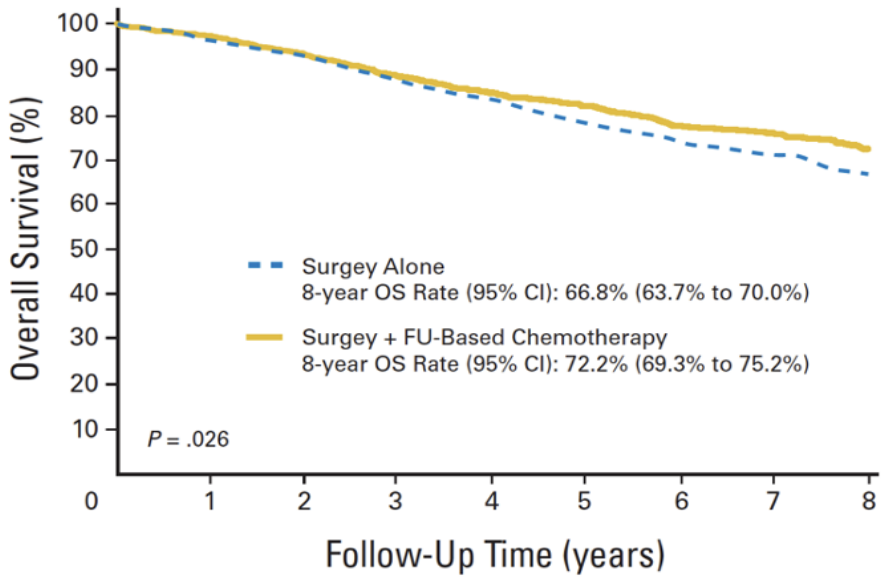
Absolute increase at 5 years OS: 3.6%



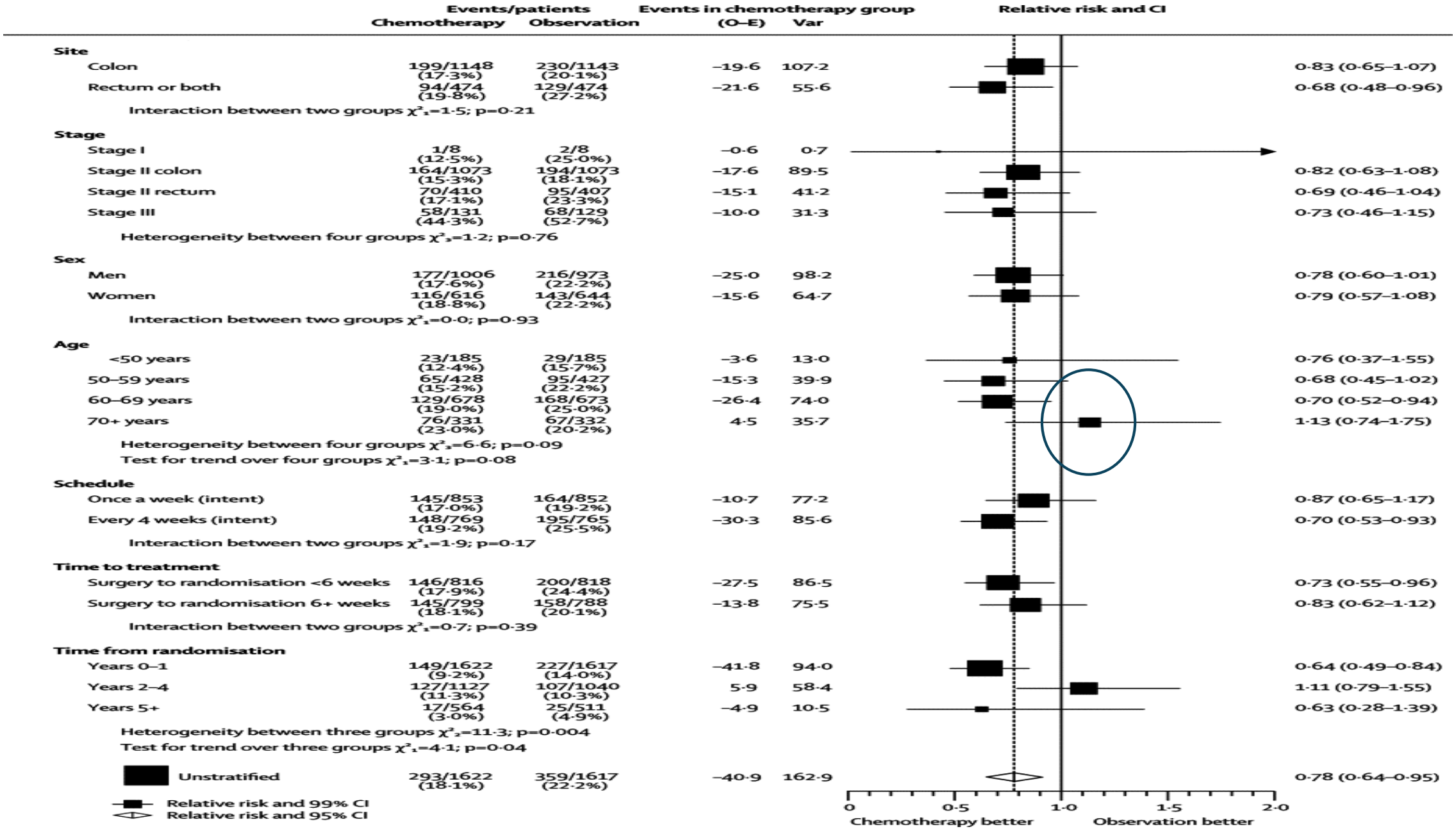
The QUASAR Collaborative Group. Lancet 2007; 370:2020.

ACCENT STUDY

Absolute increase at 8 years OS 5.4%



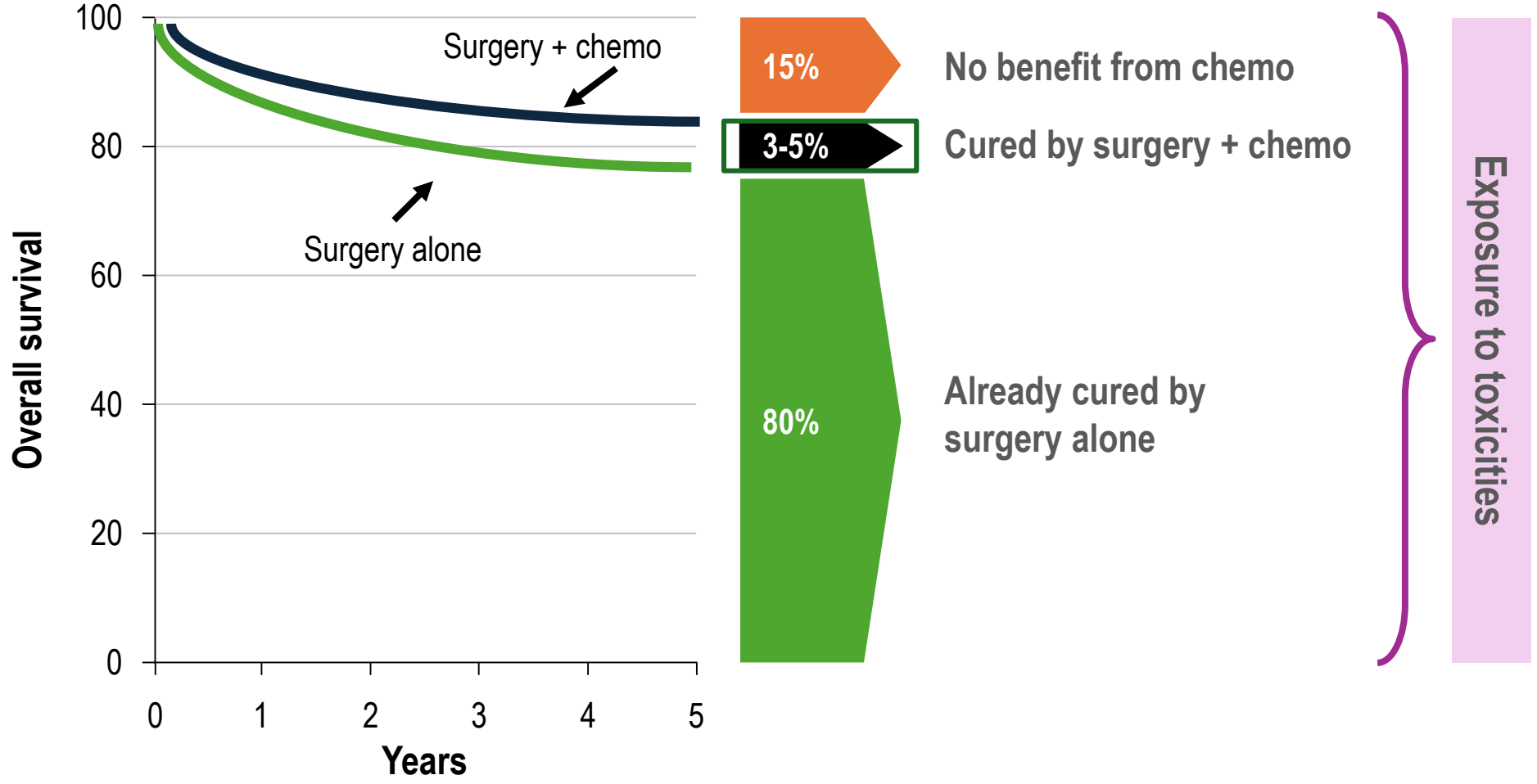
Sargent et al. J Clin Oncol 2009; 29:872-877



Gray R et al The Lancet 20

WHAT IS THE BENEFIT OF ADJUVANT CHEMO IN THE GENERAL POPULATION?

Stage II CRC

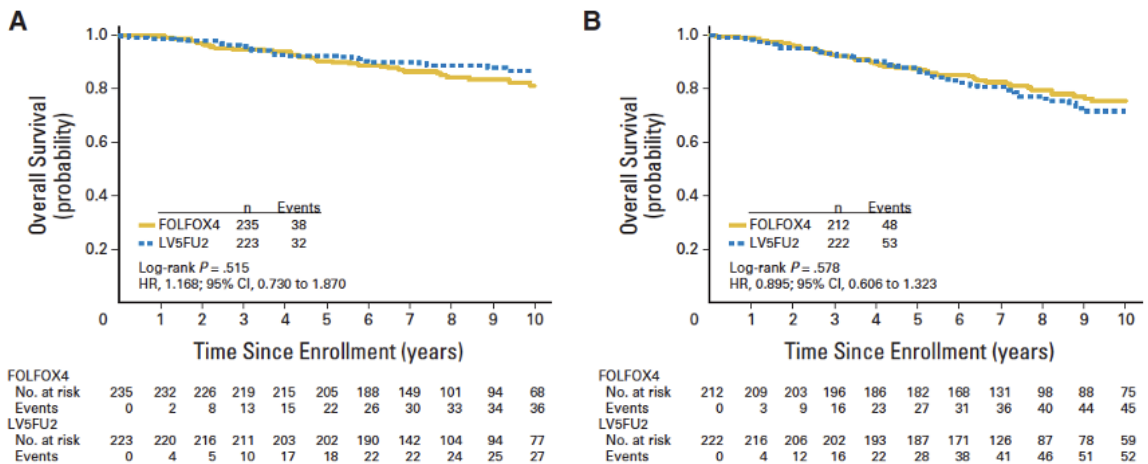


Adapted from Köhne CH. Ann Oncol 2012;23 (Supplement 10):x71–x76. © 2012 European Society for Medical Oncology.

STAGE II COLON CANCER

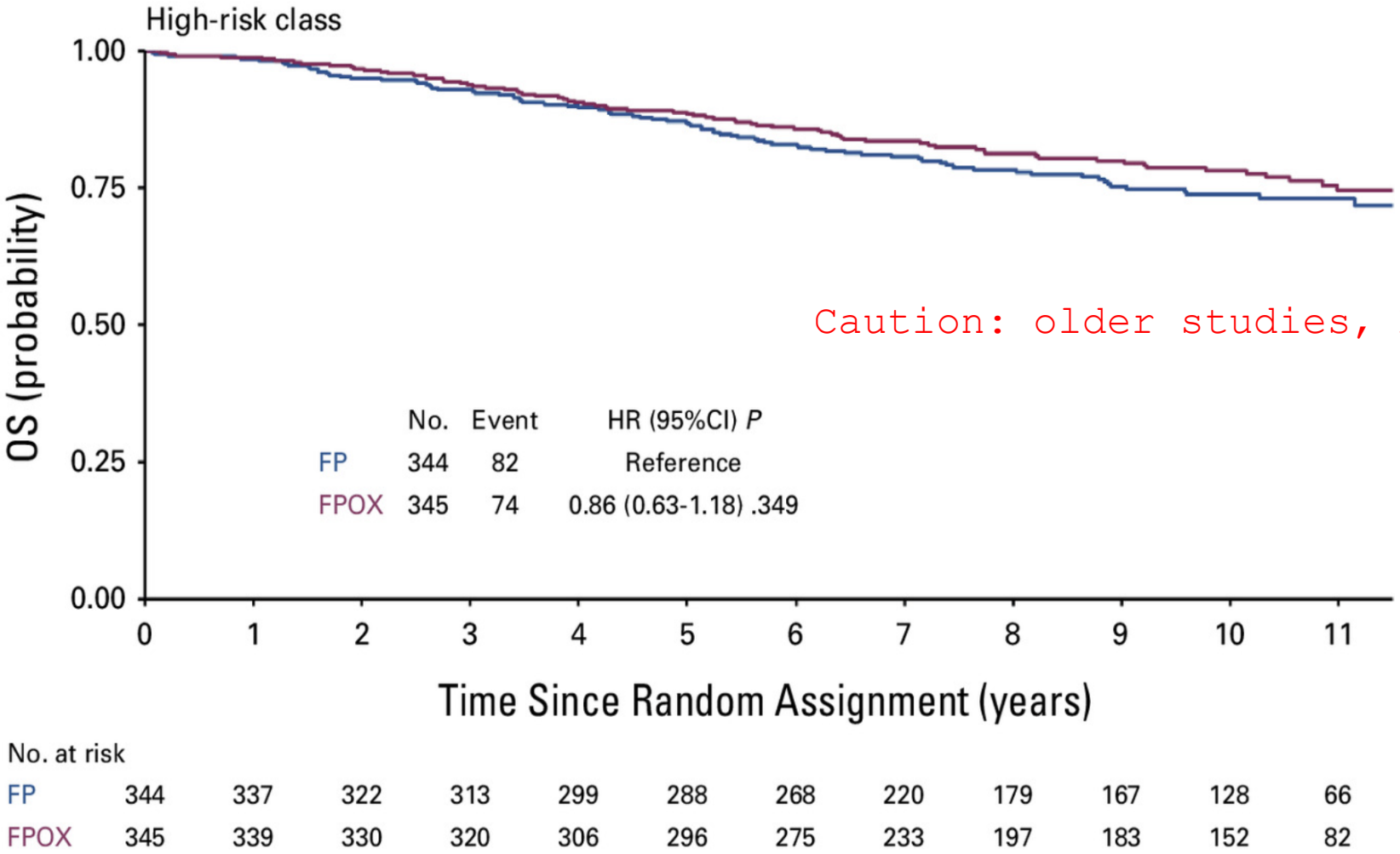
Oxaliplatin Yes vs No

- NSABP C-07 and MOSAIC investigated the value of the addition of ox to 5FU in stage II and III
- MOSAIC (10y follow-up):
  - ✓ Non significant improvement in DFS and OS in stage II high risk group
  - ✓ No benefit of oxaliplatin for low risk stage II patients



1. Kuebler JP, Wieand HS, O'Connell MJ et al. J Clin Oncol 2007; 25: 2198-2204.; 2. Andre T, Boni C, Mounedji-Boudiaf L et al. N Engl J Med 2004; 350: 2343-2351.; 3. André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. J Clin Oncol 2015 Dec 10;33(35):4176–87.

Assessment of the Addition of Oxaliplatin to Fluoropyrimidine-Based Adjuvant Chemotherapy in Patients With High-Risk Stage II Colon Cancer: An ACCENT Pooled Analysis



Caution: older studies, MSI, BRAF, RAS s

B Chibaudel et al JCO

Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial

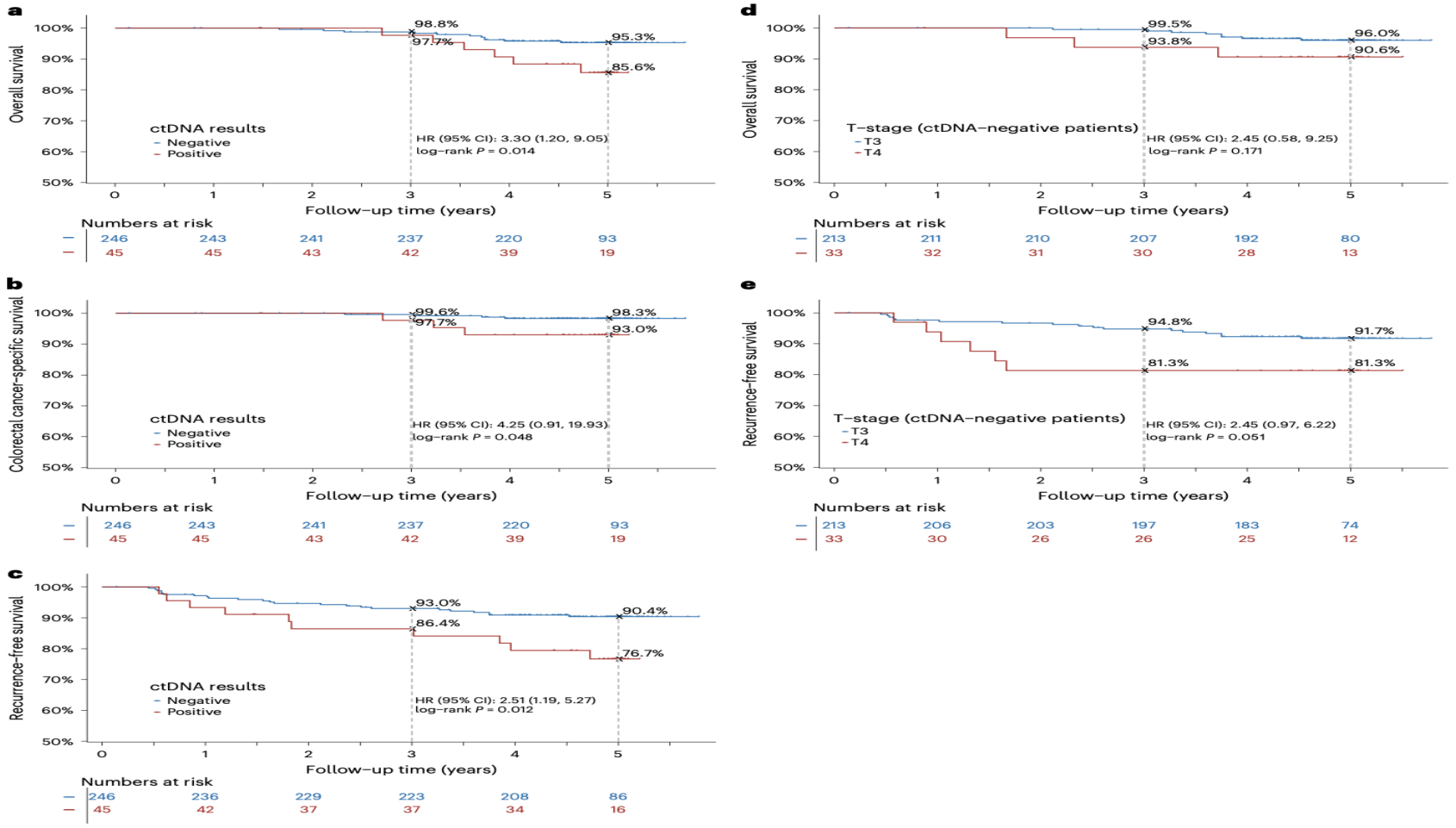
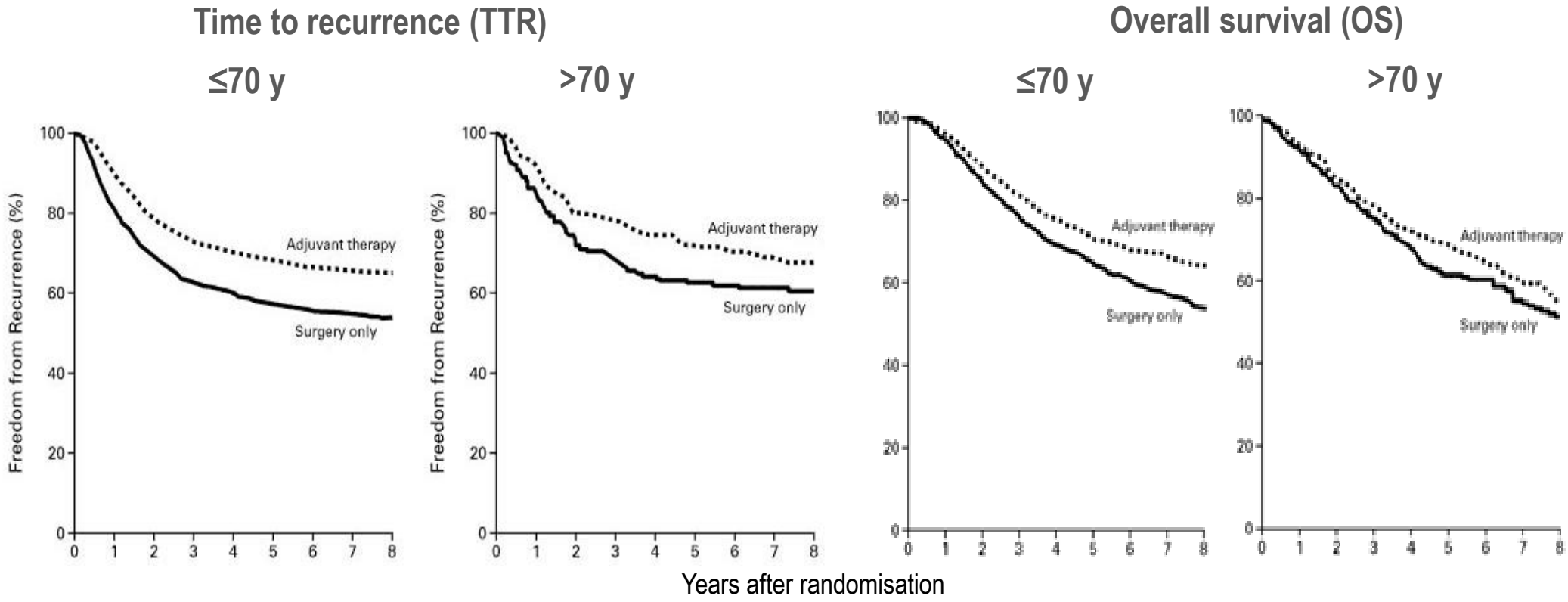


Fig. 3 | Kaplan-Meier estimates in the ctDNA-guided population. a–c, OS (**a**), DSS (**b**) and RFS (**c**) stratified by ctDNA status. **d**,**e**, OS (**d**) and RFS (**e**) in ctDNA-negative patients stratified by T stage.

'In DYNAMIC, the 5-year recurrence rate was 15% for the ctDNA-negative T4 tumors, similar to all clinical low-risk stage II patients combined, noting that there is no evidence supporting a survival benefit from adjuvant treatment in unselected T4 cases.'

Jeanne Tie et al. Nature Medicin

BENEFIT OF ADJUVANT 5-FLUOROURACIL (5-FU) IN OLDER PATIENTS >70 YR - STAGE II / III (3351 PTS)



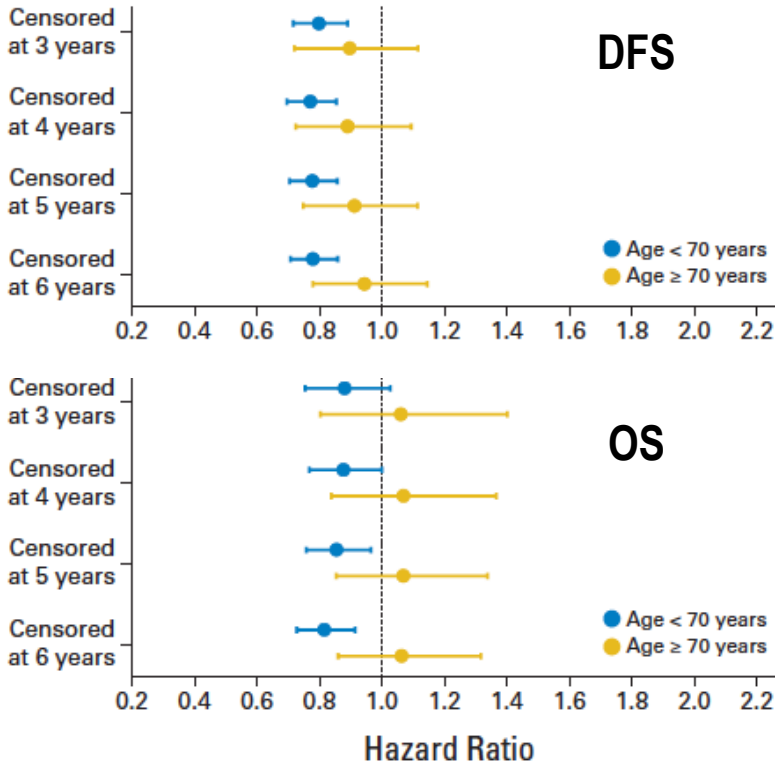
P-values for the test of interaction between age and treatment arm: 0.33 for TTR and 0.61 for OS

Patients over 70 benefit from adjuvant 5-FU with no increase in toxicities

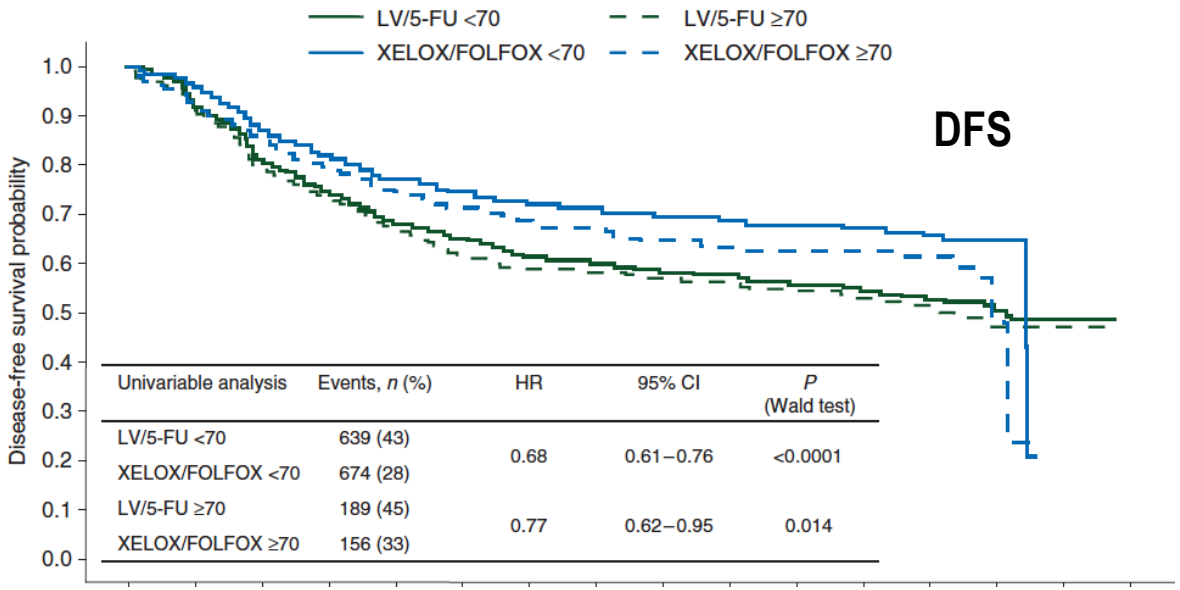
N Engl J Med 2001, Sargent DJ, *et al.* A Pooled Analysis of Adjuvant Chemotherapy for Resected Colon Cancer in Elderly, Patients, 345(15):1091-7,

BENEFIT OF OXALIPLATIN IN OLDER ADULTS >70 Y?

Pooled analysis MOSAIC/NSABP C07/XELOXA[1]
Stage II/III



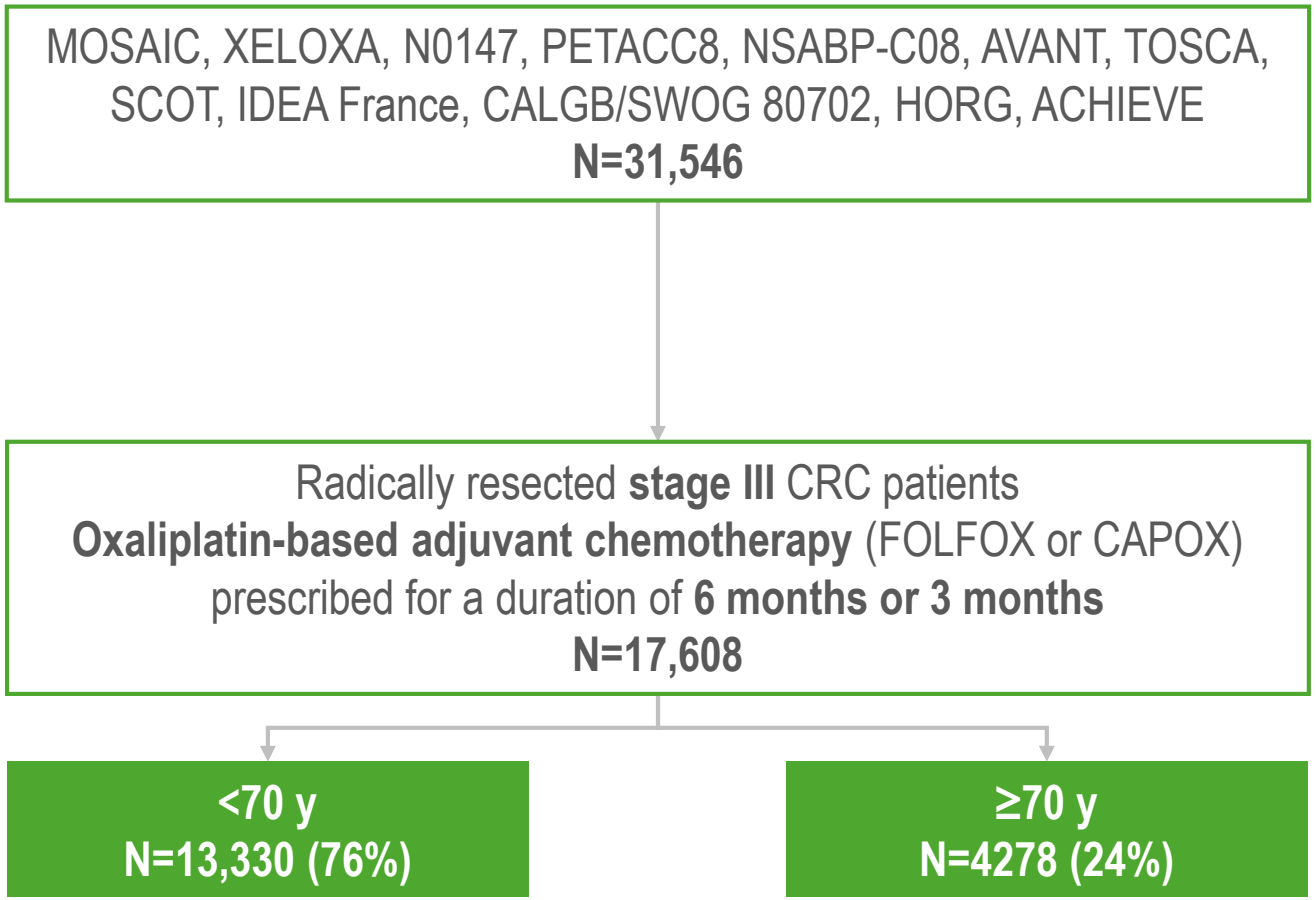
Pooled analysis NSABP C07/XELOXA/X ACT/AVANT[2]
Stage III



Univariable analysis	Events, *n* (%)	HR	95% CI	*P* (Wald test)
LV/5-FU <70	639 (43)	0.68	0.61–0.76	<0.0001
XELOX/FOLFOX <70	674 (28)			
LV/5-FU ≥70	189 (45)	0.77	0.62–0.95	0.014
XELOX/FOLFOX ≥70	156 (33)			

1. McCleary NJ, Impact of Age on the Efficacy of Newer Adjuvant Therapies in Patients With Stage II/III Colon Cancer: Findings From the ACCENT Database, J Clin Oncol, 2013, 31(20), 2600-6. 2. Haller DG, *et al.* Ann Oncol 2015;26(4):715-24

ACCENT/IDEA POOLED ANALYSIS OF 12 TRIALS



Exclusion criteria

Treatment with:

- Fluoropyrimidine alone arms
- Targeted therapies (cetuximab, bevacizumab [BEV])

Stages II, IV

Lower-middle rectal cancer

Patients who did not receive any chemotherapy

Gallois C, *et al.* J Clin Oncol 2024

ACCENT/IDEA POOLED ANALYSIS OF 12 TRIALS

Compliance

Worse treatment adherence in patients ≥70 y vs <70 y:

- **More early treatment discontinuation** (= ≤75% of cycles[1]): 21.9% vs 15.2%; p<0.001
- **Decreased relative dose intensity (RDI)**, especially for 6-month regimens

  RDI <80% for fluoropyrimidine: 39.6% vs 28.6%; p<0.001

  for oxaliplatin: 52.7% vs 42.9%; p<0.001

Tolerance

Higher grade 3-4 adverse events in patients ≥70 y vs <70 y (but not always clinically relevant)

FOLFOX:

Thrombocytopenia: 2.5% vs 1.7% (p=0.04)

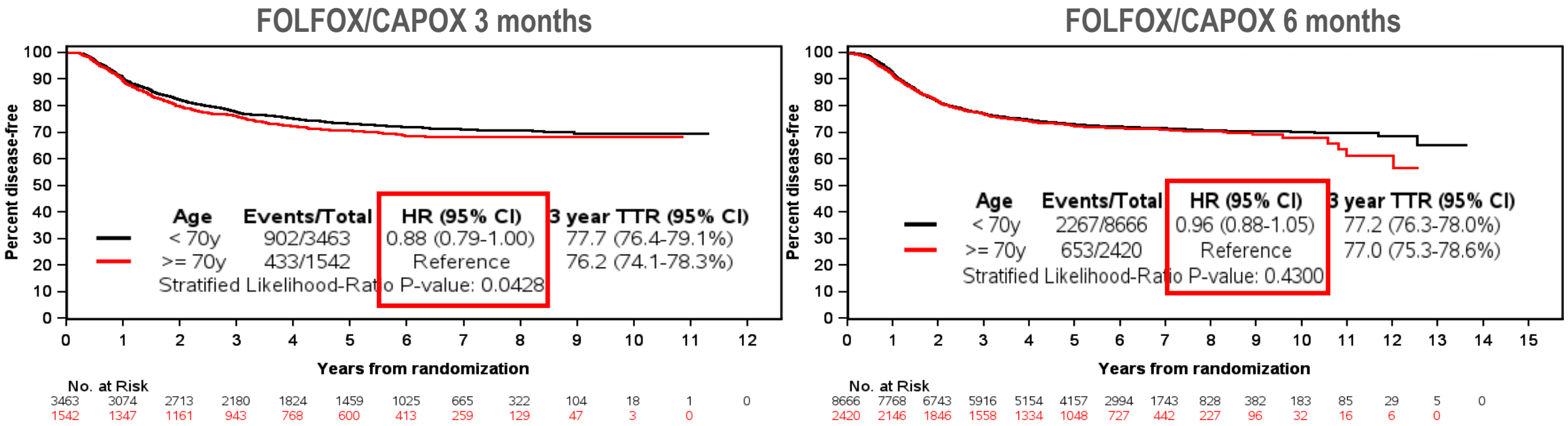
CAPOX:

Diarrhoea:	14.2% vs 11.3% (p=0.02)
Mucositis:	1.1% vs 0.3% (p=0.02)
Neutropenia:	12.1% vs 9.6% (p=0.03)

Gallois C, *et al.* J Clin Oncol 2024

ACCENT/IDEA POOLED ANALYSIS OF 12 TRIALS

TTR according to age and treatment duration

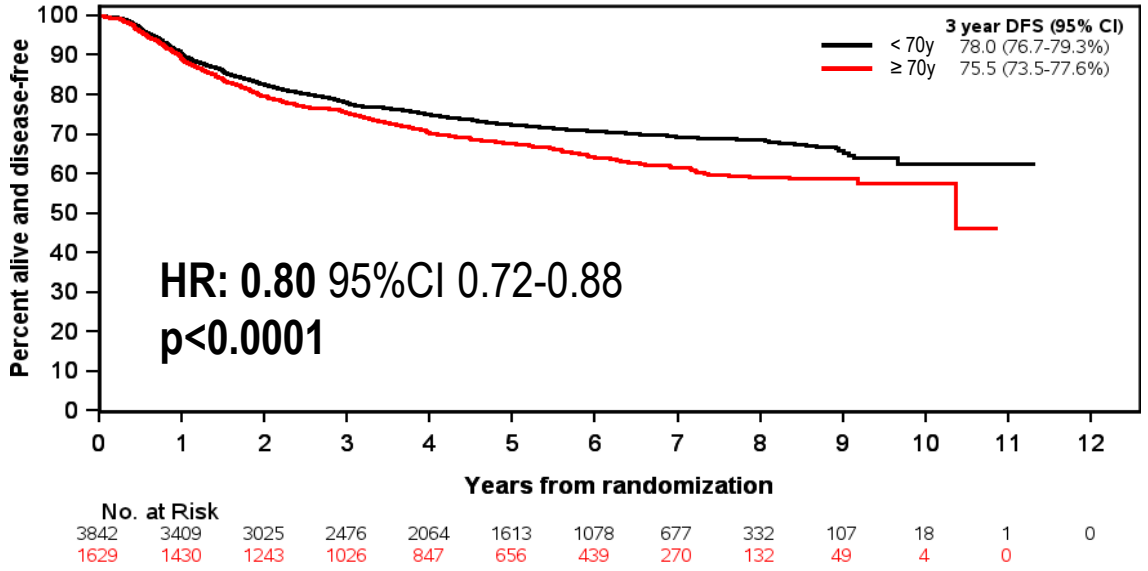


Kaplan-Meier curves adjusted for: sex, performance status (PS), T stage, N stage, year of enrolment

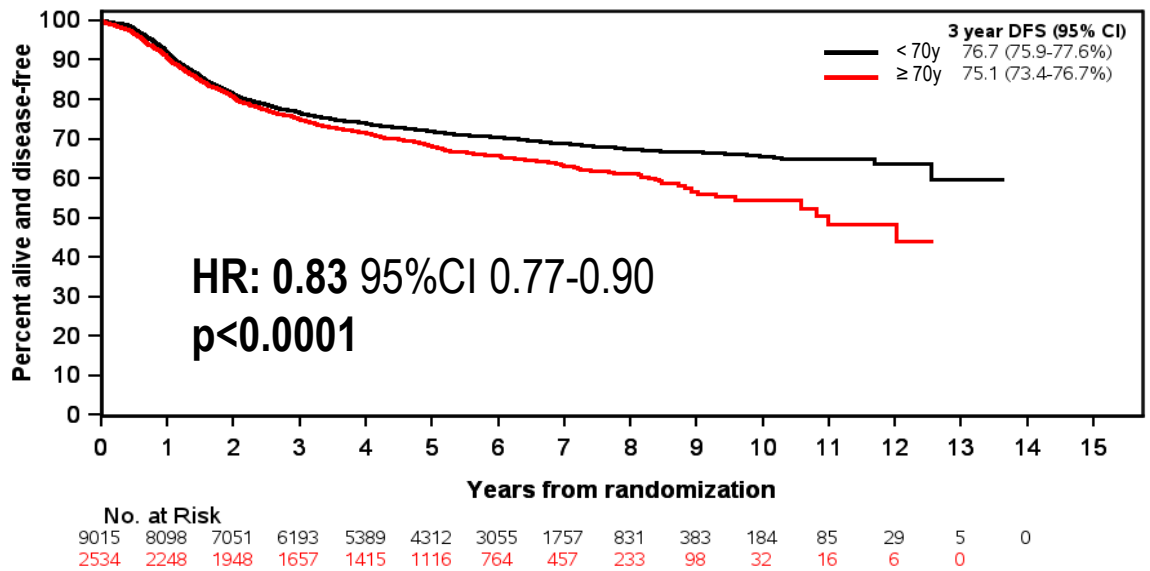
ACCENT/IDEA POOLED ANALYSIS OF 12 TRIALS

Disease-free survival according to age and treatment duration

FOLFOX/CAPOX 3 months



FOLFOX/CAPOX 6 months



Kaplan-Meier curves adjusted for: sex, PS, T stage, N stage, year enrollment

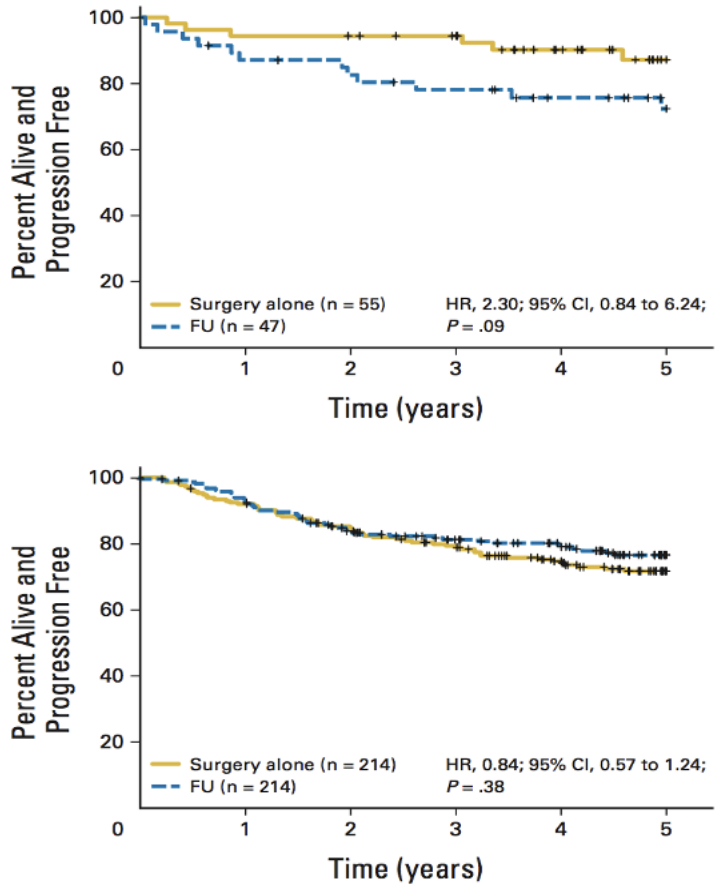
OS, survival after recurrence (SAR), cancer-specific survival:
Significant decrease in patients ≥70 y compared with <70 y

Gallois C, *et al.* J Clin Oncol 20

TUMOR BIOLOGY

MICROSATTELLITE STATUS

- Validated prognostic factor with positive impact on survival in early stage disease
- Stage II-MSI patients:
  - ✓ Low recurrence rates without CT[1,2]
  - ✓ Adjuvant FU-based CT do not decrease distant relapses in these patients[3]
  - ✓ The potential detrimental effect of 5FU has not been confirmed[4]
- Current data in MSI stage II CC support observation



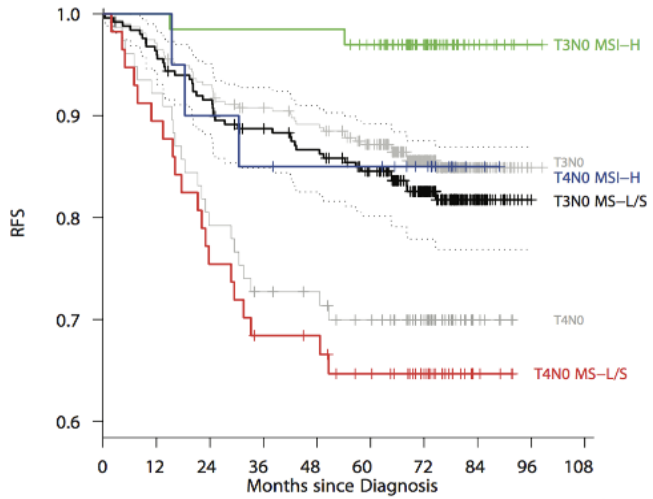
1. Hutchins G et al. J Clin Oncol 2011 , 2. Sinicrope FA et al. J Clin Oncol 2013, 3. Sinicrope et al. JNCI 2011, 4. Sargent et al. J Clin Oncol 2010

TUMOR BIOLOGY

MICROSATTELLITE STATUS

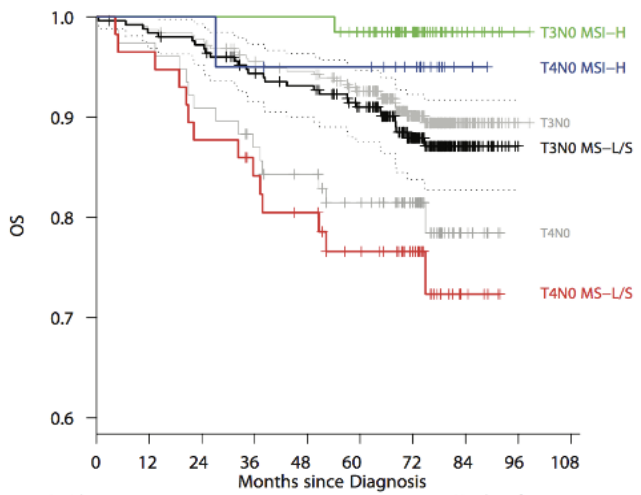
Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage II/III Colon cancer

Recurrence free survival



At risk:									Number of events
T3N0 MS–L/S	251	240	227	216	209	194	130	30	43
T3N0 MSI–H	66	66	65	65	65	61	35	9	2
T4N0 MS–L/S	57	51	43	38	37	32	23	4	20
T4N0 MSI–H	20	20	18	17	16	16	12	2	3

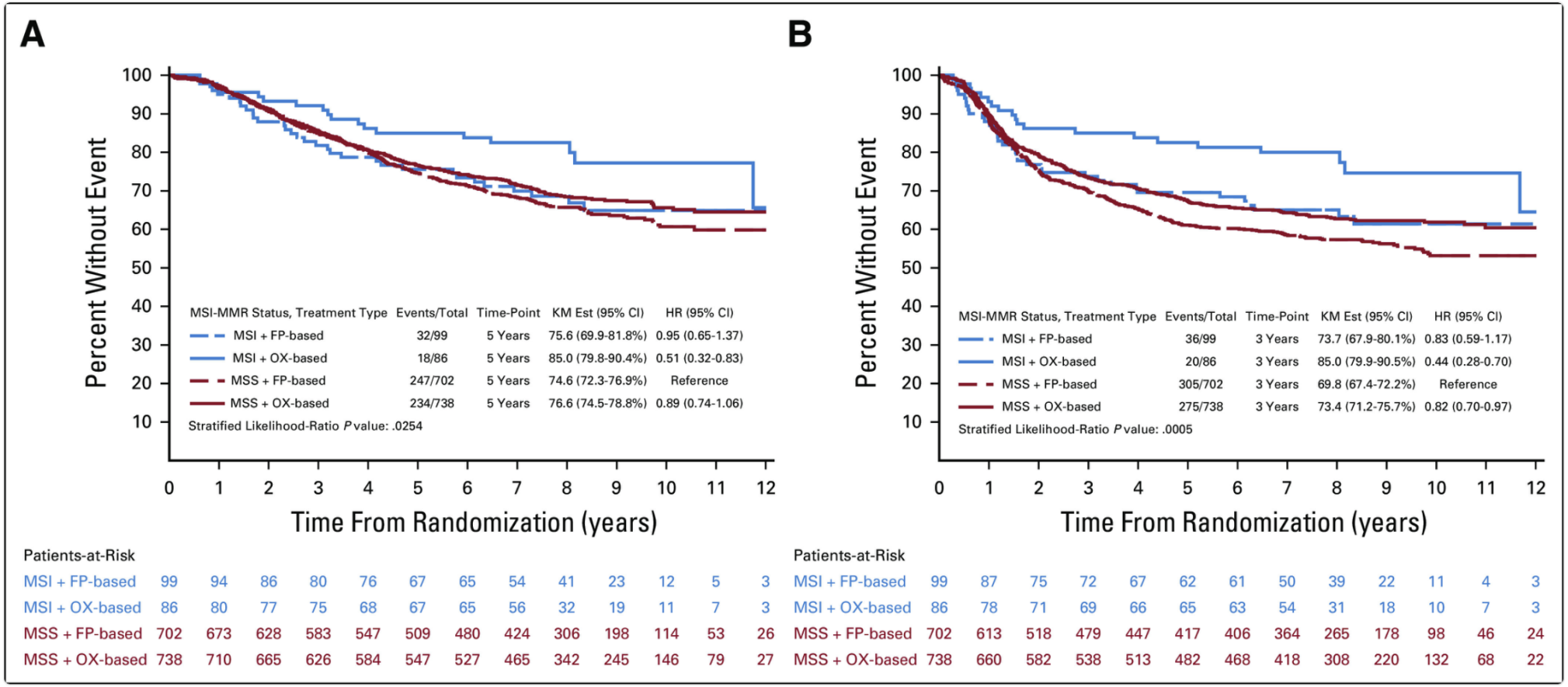
Overall survival



At risk:									Number of events
T3N0 MS–L/S	251	246	242	230	225	209	138	31	29
T3N0 MSI–H	66	66	66	66	66	61	35	9	1
T4N0 MS–L/S	57	55	50	46	43	37	26	5	14
T4N0 MSI–H	20	20	20	19	18	18	14	2	1

Roth AD, Delorenzi M, Tejpar S et al. Integrated analysis of molecular and clinical prognostic factors in stage II/III colon cancer. J Natl Cancer Inst. 2012 Nov 7;104(21):1635-46

Microsatellite Instability in Patients With Stage III Colon Cancer Receiving Fluoropyrimidine With or Without Oxaliplatin: An ACCENT Pooled Analysis of 12 Adjuvant Trials



Effect of FP-based and oxaliplatin-based adjuvant treatment according to the MSI/dMMR status. Overall survival (A) and disease-free survival (B) of patients treated with FP or FP plus oxaliplatin therapy. dMMR, mismatch repair system deficiency; FP, fluoropyrimidine; HR, hazard ratio; KM, Kaplan-Meier; MSI, microsatellite instability; OX, oxaliplatin.

Efficacy of neoadjuvant IO

Treatment regimen	Patient population (all dMMR/MSI)	No. of patients	Gr. 3-4 irAEs	Time to surgery	pCR rate
Chalabi et al, NEJM 2024, ESMO 2024 (NICHE-2)					
Nivolumab 3mg/kg Q2W x 2 + ipilimumab 1mg/kg x 1	Colon cancer Locally advanced	115	**5%**	**5.4 weeks**	**68%**
Xu et al, ASCO 2024					
Sintilimab 200mg Q3W x 2 +/- IBI310 1mg/kg x 1	Colon cancer Locally advanced	101 (49 vs 52)	**18% (mono) 27% (dual)**	**7 weeks vs 6.3 weeks**	**78% vs 47%**
De Gooyer et al, ESMO 2024, NatMed 2024 (NICHE-3)					
Nivolumab 480mg + Relatlimab 480mg Q2W x 2	Colon cancer Locally advanced	59	**10%**	**7.6 weeks**	**68%**
Chen et al, Lancet Gastr Hepat 2022 (PICC)					
Toripalimab 3mg/kg Q2W x 6 +/- celecoxib	Colorectal cancer Locally advanced	34	**3%**	**13.1 weeks**	**88% (+celec) 65% (-celec)**
Shiu et al, ASCO 2024 (NEOPRISM)					
Pembrolizumab 200mg Q2W x 3	Colorectal cancer Locally advanced	32	**6.2%**	**11.9 weeks**	**58%**
De la Fouchardiere, ESMO 2024 (IMHOTEP)					
Pembrolizumab 400mg Q4W x 1-2	Colorectal cancer	77	**13%**	**6.8 weeks**	**47% (1 cycle) 68% (2 cycles)**

BARCELONA 2024 ESMO congress

Dual ICI

Mono ICI

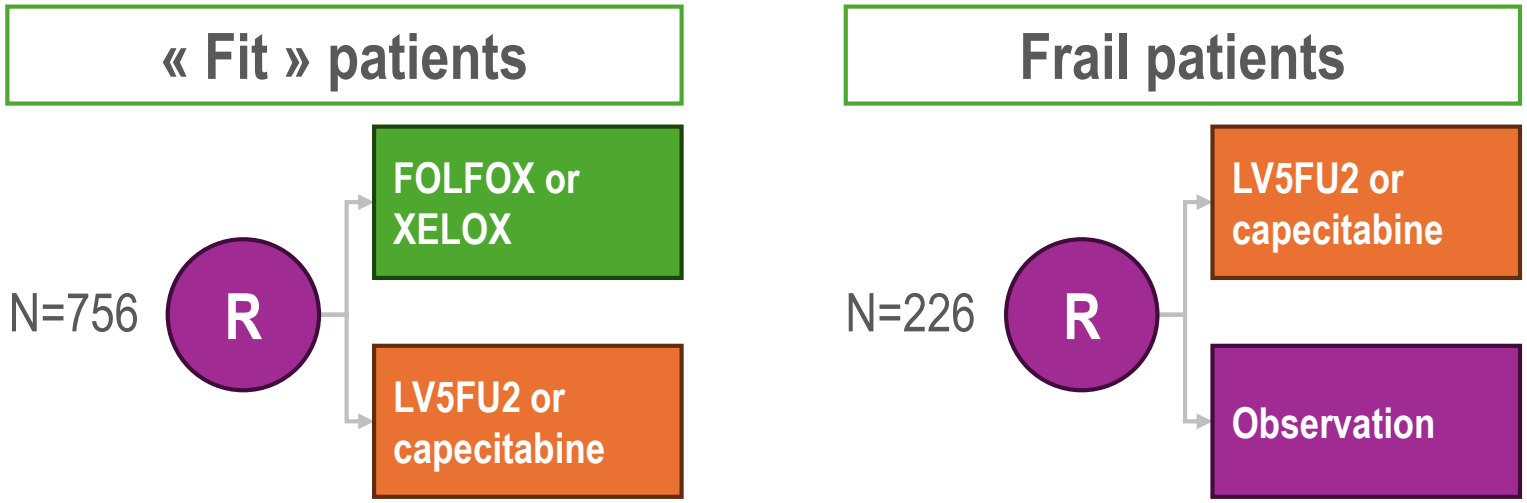
High pCR rates across studies

- The evidence for the use of neoadjuvant IO in MSI-H LACC is consistent and accumulating
- Impressive short-term efficacy and (likely) long-term cancer control (NICHE-2)
- Need to exercise caution with patient selection / toxicity
- Organ preservation will be a paradigm shift but needs to be balanced against the standard of care approach for good prognosis patients
- Neo-adjuvant IO is still not standard of care

ADAGE – PRODIGE 34

FFCD – GERCOR – UNICANCER – GERICO – BGDO

Adjuvant patients ≥70 y, Stage III



Objective: 3 yr-DFS:

Group 1: +7% in oxaliplatin arm

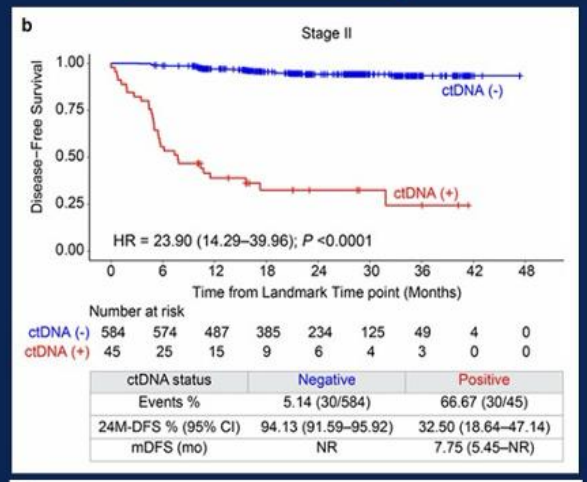
Group 2: +15% in chemo arm

Aparicio T, *et al.* Dig Liver Dis 2020;52(5):493-5

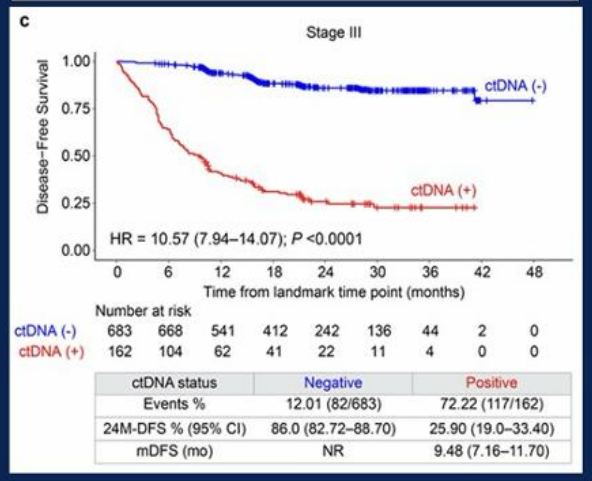
ctDNA is Prognostic in Resected Stage II-III Colon Cancer

ctDNA during MRD Window

GALAXY[1]

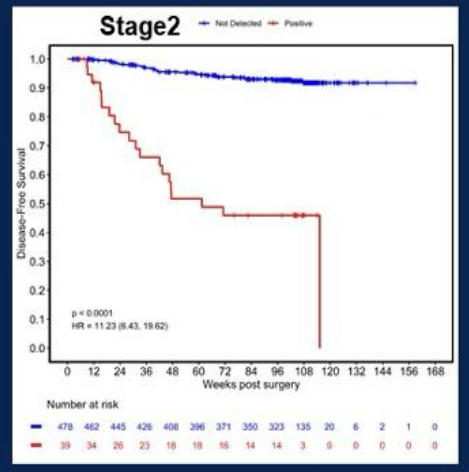


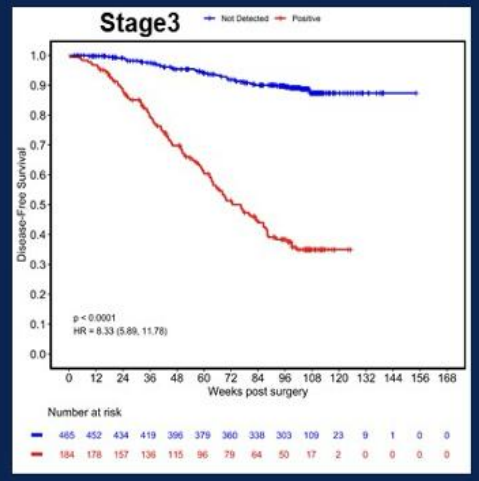
ctDNA status	Negative	Positive
Events %	5.14 (30/584)	66.67 (30/45)
24M-DFS % (95% CI)	94.13 (91.59–95.92)	32.50 (18.64–47.14)
mDFS (mo)	NR	7.75 (5.45–NR)



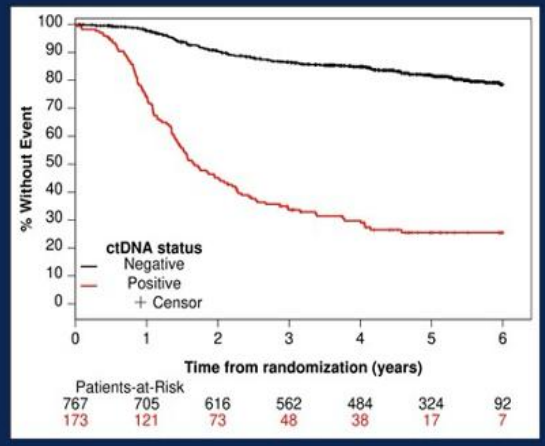
ctDNA status	Negative	Positive
Events %	12.01 (82/683)	72.22 (117/162)
24M-DFS % (95% CI)	86.0 (82.72–88.70)	25.90 (19.0–33.40)
mDFS (mo)	NR	9.48 (7.16–11.70)

BESPOKE[2]

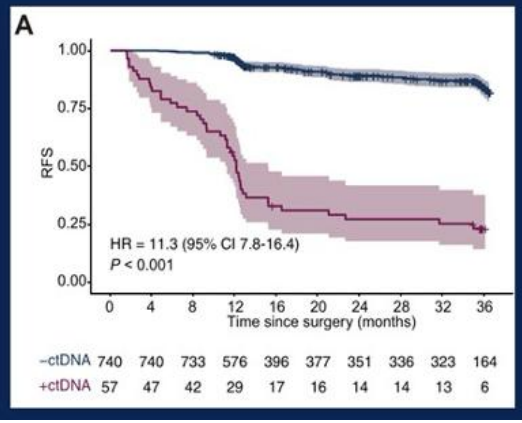




CALGB/SWOG 80702[3]



Nationwide Danish cohort[4]



STAGE II CRC

Pragmatic approach patients >70 y

Geriatric screening – e.g. Geriatric 8 (G8)

High competing risk for death* or low risk for relapse: surveillance

High risk of relapse: 6 mo FP

(3 months of CAPOX if MSS and T4 and 'fit' ? ? ? - very scarce evidence)

→ **Patient preferences and shared decision-making**

ctDNA guided de-intensification or intensification, watch this space!

*Lee Schonberg index calculator. Available at https://eprognosis.ucsf.edu/leeschonberg.php. accessed Apr 2024.

STAGE III CRC

Potential approach for patients >70 y

Geriatric screening – e.g., G8

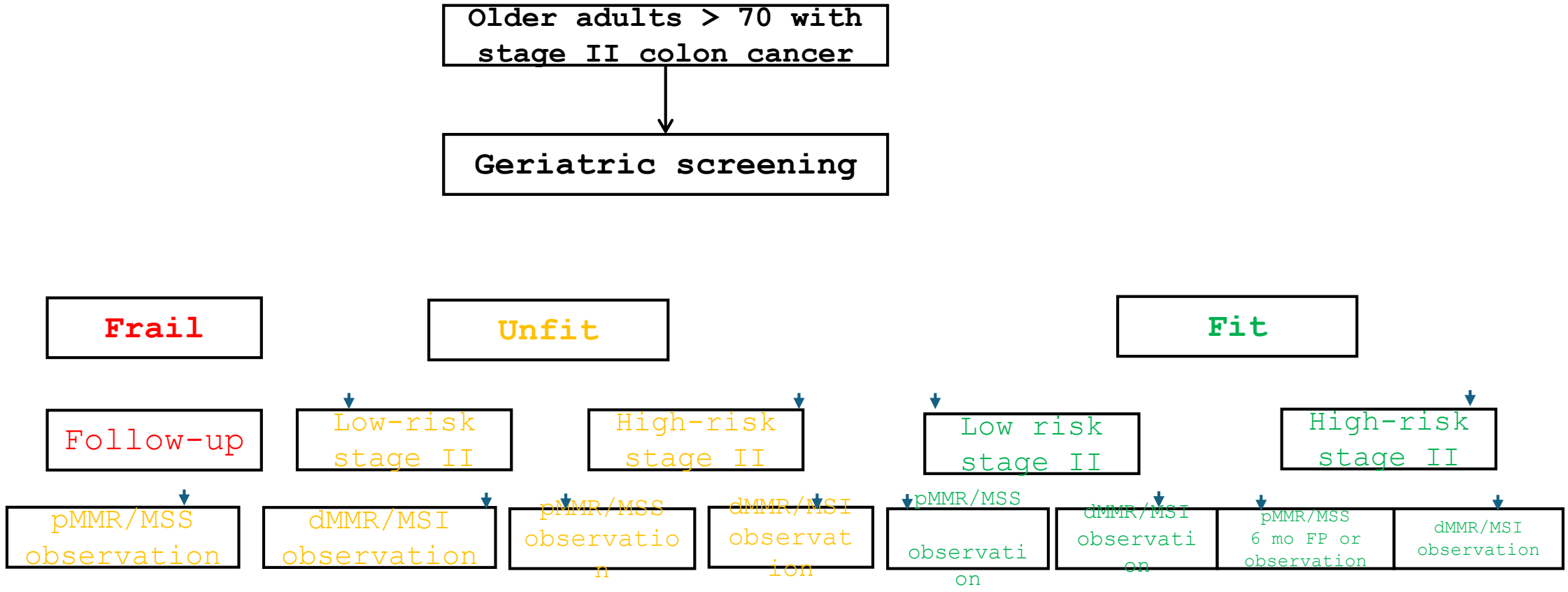
Patients **« fit » for doublet chemotherapy:** CAPOX 3 months in the majority of cases (or FOLFOX 6 months with discontinuation of oxaliplatin after 3 months)*

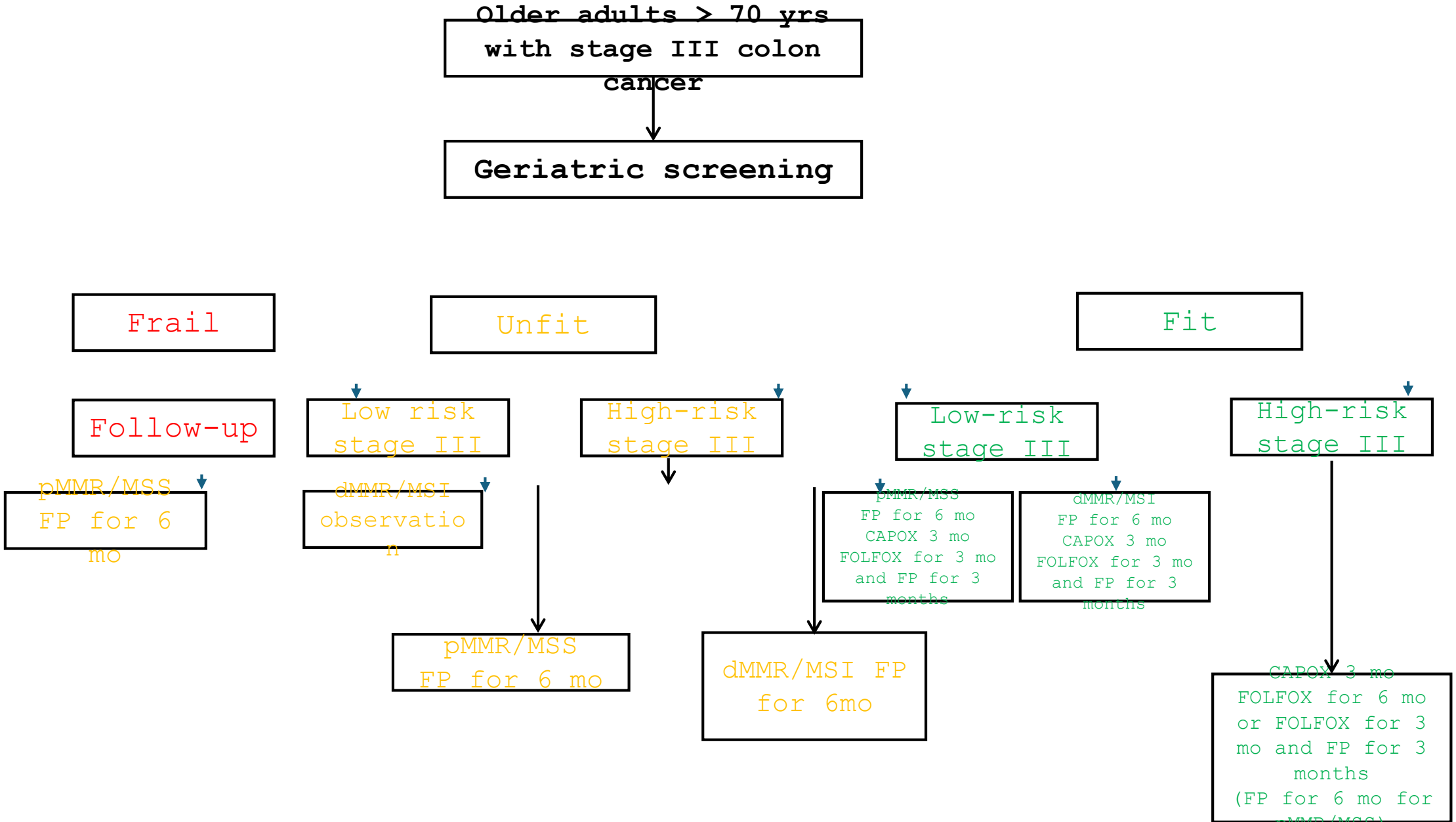
In **high-risk patients « fit » for doublet chemotherapy:** CAPOX for 3-6 months or FOLFOX 6 month[illegible]er 3 months*

→ **Patient preference and shared decision-making**

Patients **unfit for doublet chemotherapy:** fluoropyrimidine 6 months

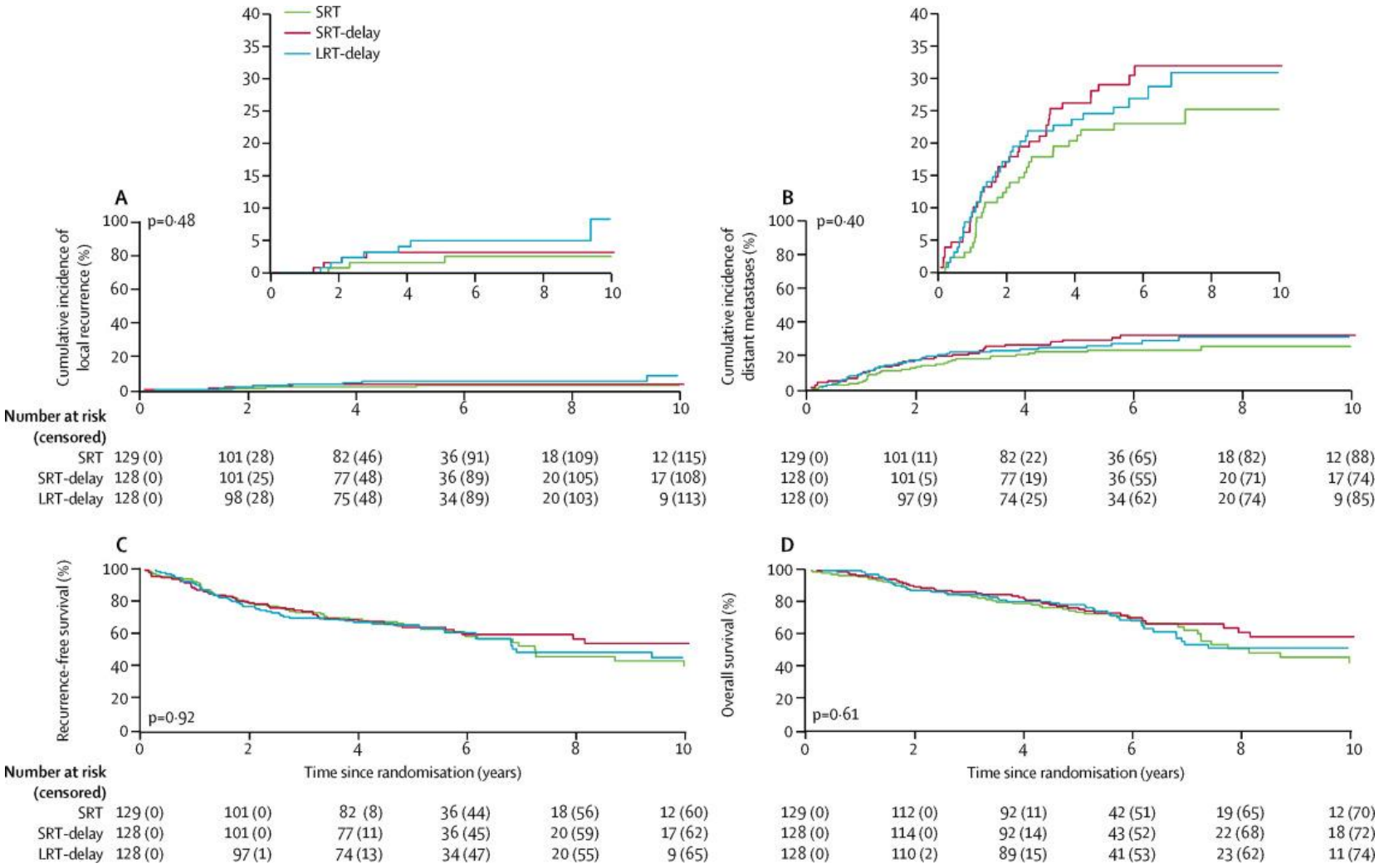
*Aiming for an improvement in TTR


Older adults > 70 with stage II colon cancer
Geriatric screening
Frail
Unfit
Fit
Follow-up
Low-risk stage II
High-risk stage II
Low risk stage II
High-risk stage II
pMMR/MSS observation
dMMR/MSI observation
pMMR/MSS observation
dMMR/MSI observation
pMMR/MSS observation
dMMR/MSI observation
pMMR/MSS 6 mo FP or observation
dMMR/MSI observation


Older adults > 70 yrs with stage III colon cancer
Geriatric screening
Frail
Unfit
Fit
Follow-up
Low risk stage III
High-risk stage III
Low-risk stage III
High-risk stage III
pMMR/MSS FP for 6 mo
dMMR/MSI observation
pMMR/MSS FP for 6 mo
pMMR/MSS FP for 6 mo CAPOX 3 mo FOLFOX for 3 mo and FP for 3 months
dMMR/MSI FP for 6 mo CAPOX 3 mo FOLFOX for 3 mo and FP for 3 months
dMMR/MSI FP for 6mo
CAPOX 3 mo FOLFOX for 6 mo or FOLFOX for 3 mo and FP for 3 months (FP for 6 mo for

RECTAL CANCER

Role of CRT vs SCRT: Stockholm III

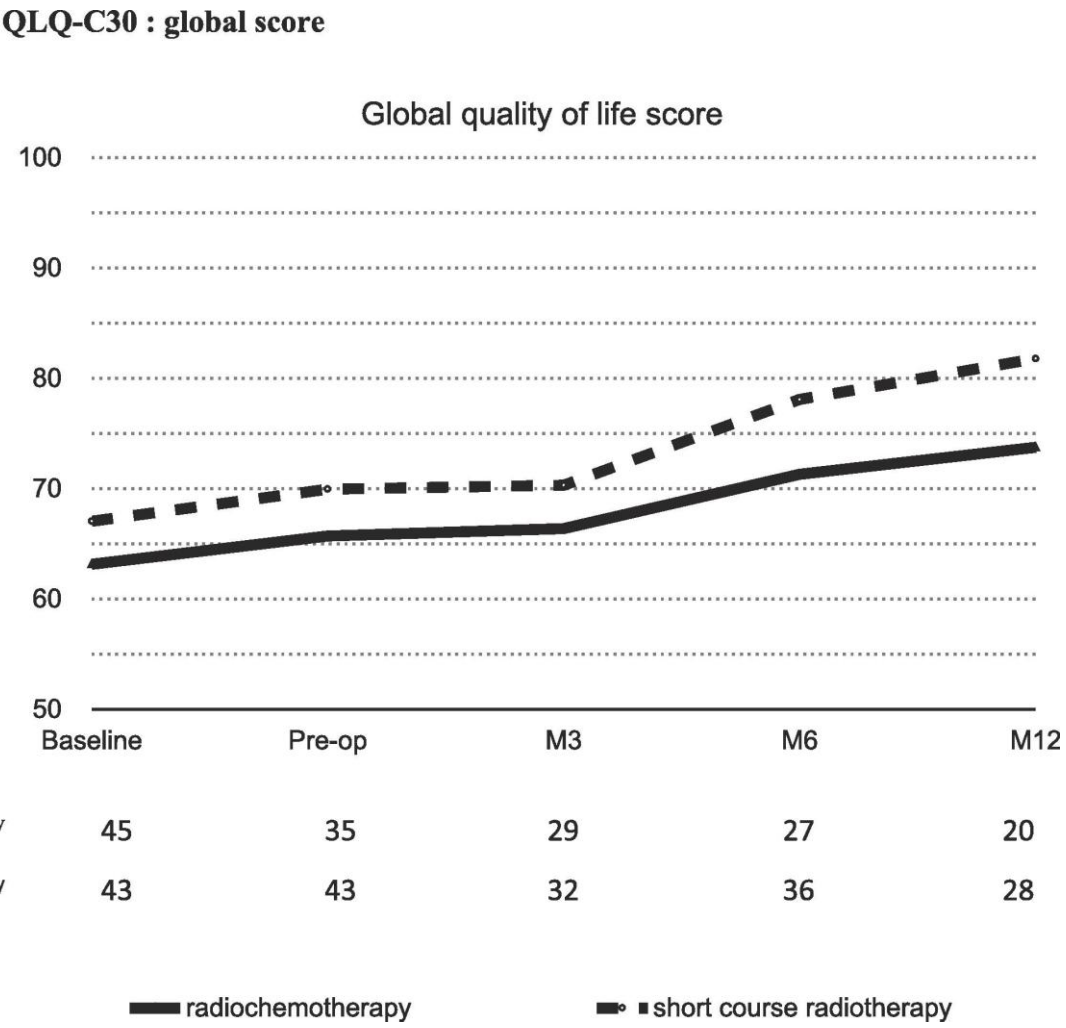


840 patients
LARC

Erlandsson et al. Lancet C

Role of CRT vs SCRT: PRODIGE 42/GERICO 12

- QoL



François et al. Radioth Onc

Role of brachytherapy to avoid TME

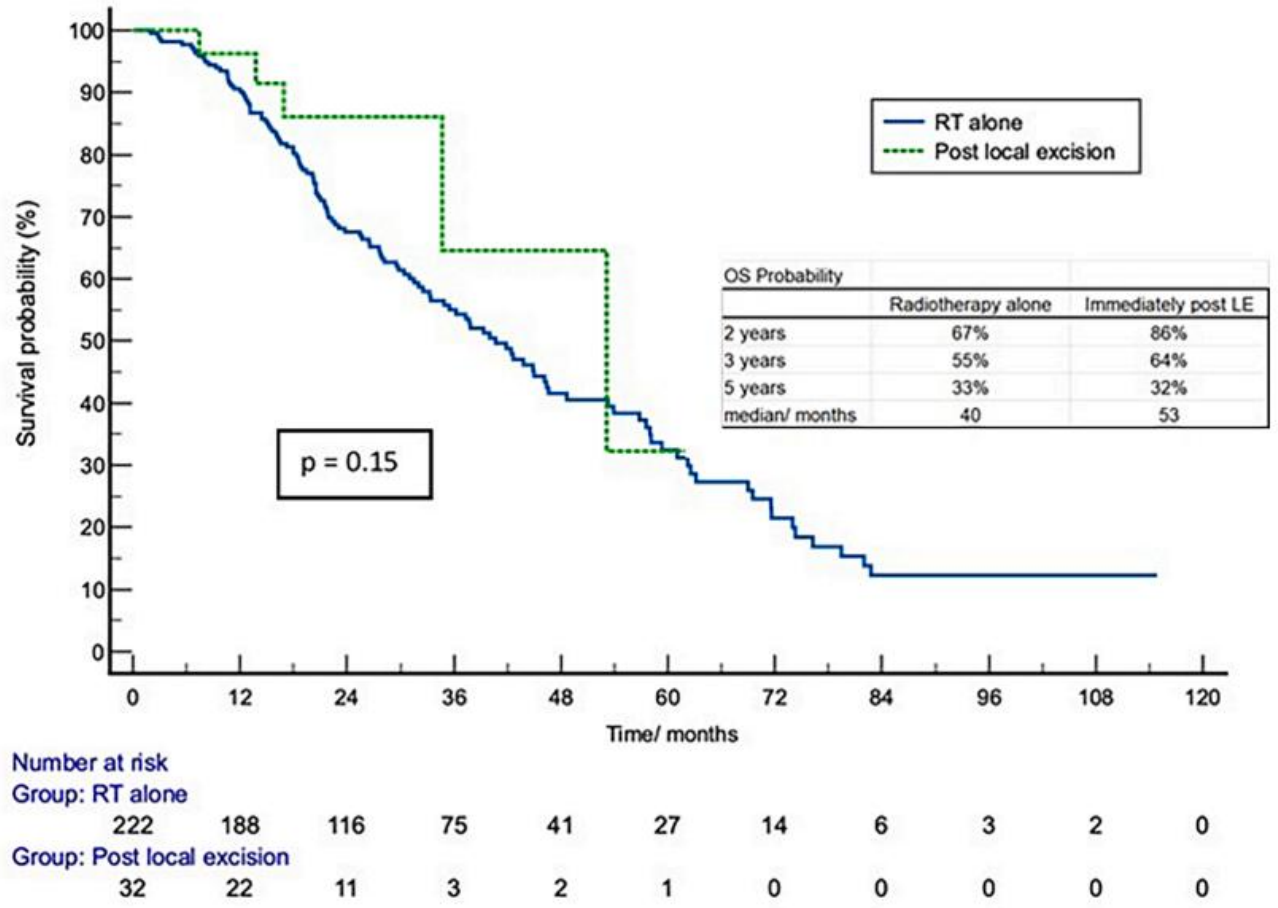
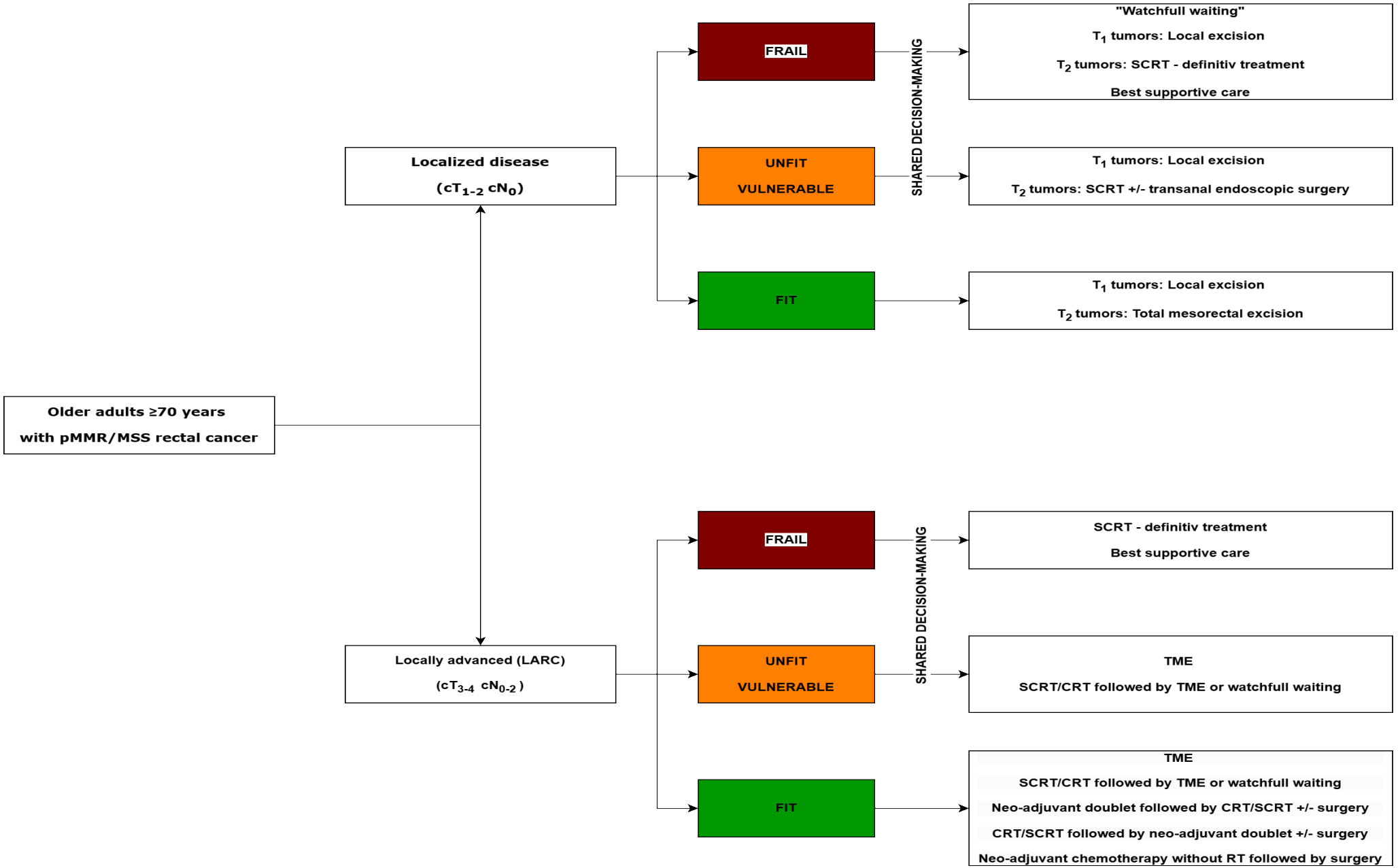


Fig. 1. Kaplan Meier Survival Curves for OS comparing RTA and ILE groups.

Steinke et al. ctRC


Older adults ≥70 years
with pMMR/MSS rectal cancer
Localized disease
(cT_{1-2} cN_0)
Locally advanced (LARC)
(cT_{3-4} cN_{0-2})
FRAIL
UNFIT
VULNERABLE
FIT
SHARED DECISION-MAKING
"Watchfull waiting"
T_1 tumors: Local excision
T_2 tumors: SCRT - definitiv treatment
Best supportive care
T_1 tumors: Local excision
T_2 tumors: SCRT +/- transanal endoscopic surgery
T_1 tumors: Local excision
T_2 tumors: Total mesorectal excision
SCRT - definitiv treatment
Best supportive care
TME
SCRT/CRT followed by TME or watchfull waiting
TME
SCRT/CRT followed by TME or watchfull waiting
Neo-adjuvant doublet followed by CRT/SCRT +/- surgery
CRT/SCRT followed by neo-adjuvant doublet +/- surgery
Neo-adjuvant chemotherapy without RT followed by surgery

METASTATIC SETTING

DEDICATED RCT FOR OLDER ADULTS – CHEMOTHERAPY

First-line chemotherapy without targeted agents in molecularly unselected treatment naïve older adults with mCRC										
Prospective RCTs	**Design**	**Eligibility**	**GA**	**mAge (range)**	**RR (%)**	**mPFS (months)**	**mOS (months)**	**Older adult specific endpoints**	**Conclusion**	**Context**
Rosati et al. 2010 Phase II n=94	Dose-reduced CAPOX vs CAPIRI	≥70 years	No	74 (74-94)	38 vs 36	8.0 vs 7.0 p=0.195	19.3 vs 14.0 p=0.165	N/A	Comparable efficacy, CAPOX had improved tolerability	Weekly adm. of Ox/Iri days 1+8. Fit pts. (ECOG 0-1)
Seymour et al. 2011 MRC FOCUS2 Phase III n=457	5FU/Cap→ 5FU/Cap+Ox vs 5FU/Cap+Ox 80% start dose	Not eligible for standard doublet	MNA MMSE CCI ADL HADS 20m walk	74 (35-87)	13 vs 35 p<0.01	3.5/5.2 vs 5.8/5.8 Adding Ox: HR: 0.84 (0.69-1.01)	10.1/11.0 vs 10.7/12.4 Adding Ox: HR: 0.99 (0.81-1.18)	Overall treatment utility (OUT) Composite endpoint	Combination tends to increase PFS/RR Ox: neuropathy Cap: gr. 3+ PPE and diarrhea	ECOG PS 2=29% Methodology: QoL
Aparicio et al. 2016 FFCD 2001-02 Phase III n=282	5FU+LV/FOLF vs 5FU+LV/FOLF+Iri	≥75 years	IADL CCI MMSE GDS	80 (75-92)	21 vs 42 p<0.01	5.2 vs 7.3 p=0.15 Adding Iri: HR: 0.84 (0.66-1.07)	14.2 vs 13.3 p=0.77 Adding Iri: HR: 0.96 (0.75-1.24)	N/A	Combination tends to increase PFS/RR Iri: neutropenia and diarrhea	ECOG PS 2=32%
Winther et al. 2019 Liposits et al. 2021, '22, '23 NORDIC9 Phase II n=160	100% S1→Iri vs 80% SOx→IRIS Bevacizumab: optional	≥70 years Not eligible for full-dose standard doublet	CCI G8 VES-13 HGS TUG	78 (70-88) IQR: (76-81)	33 vs 42 p=0.257	5.3 vs 6.2 p=0.047 HR: 0.72 (0.52-0.99)	11.5 vs 14.5 p=0.302 HR: 0.82 (0.57-1.19)	QoL Prognostic value of plasma biomarkers, functional status, *RAS/BRAF* status	Combination: - increased PFS - less toxicity - fewer hospital. - better QoL Progn. value of: - systemic infl. - physical funct. - m*BRAF*^{V600E}	ECOG PS 2=20% 25% received Bev S1 is not widely used in Europe

CONCLUSIONS – RANDOMISED TRIALS FOR OLDER ADULTS

- Common approach tested – full-dose fluoropyrimidine vs reduced-dose doublet
- Reduced-dose doublet results in higher RR and PFS benefit
- No OS benefit

Limitations

- Most included patients have ECOG 0-1
- Few older adult specific/patient-centred endpoints
- GA is used for exploring prognostic factors

DEDICATED TRIALS FOR OLDER ADULTS –CHEMOTHERAPY ± BEVACIZUMAB

First-line chemotherapy with Bevacizumab in treatment naïve older adults with mCRC										
Prospective RCTs	**Design**	**Eligibility**	**GA**	**mAge (range)**	**RR (%)**	**mPFS (months)**	**mOS (months)**	**Older adult specific endpoints**	**Conclusion**	**Context**
Kabinnavar et al. 2005 **Phase II** **n=209**	5FULV vs 5FULV + Bev	Not eligible for doublet + ≥65 years or ECOG 1-2	No	71 (NA)	15 vs 26 p=0.055	5.5 vs 9.2 p=0.0002 HR: 0.50 (0.34-0.73)	12.9 vs 16.6 p=0.16 HR: 0.79 (0.56-1.10)	No	PFS increased No OS benefit gr. 3 HT No diff. in QoL	ECOG PS 2= 7% Mostly fit patients
Cunningham et al. 2013 **AVEX** **Phase III** **n=280**	CAP vs CAP+Bev	Not eligible for standard doublet ≥70 years	No	76 (70-87)	10 vs 19 p=0.04	5.1 vs 9.1 p<0.001 HR: 0.53 (0.41-0.69)	16.8 vs 20.7 p=0.18 HR:0.79 (0.57-1.09)	No	Combination increases: PFS RR gr. 3-4 toxicity	ECOG PS 2=8% Fit patients
Aparicio et al. 2018 **PRODIGE 20** **Phase II** **n=91**	CT vs CT+Bev	≥75 years	G8, IADL, QoL, MNA-SF, Energy, Mini-COG Mini-GDS Social support Köhne index	80 (75-90)	The study was not designed for comparing differences in efficacy endpoints. 32 vs 37	7.8 vs 9.7	19.8 vs 21.7	Composite endpoint: Efficacy +Safety +QoL	Combination is safe (60%) and efficient (50%) Bev: HT increased	ECOG PS 2=20% Efficacy and safety do not differ between arms.
Hamaguchi et al. 2022 **RESPECT** **Phase III** **n=251**	5FULV/CAP + Bev vs FOLFOX/ CAPEOX + Bev	70-74 years + ECOG 2 or ≥75 years + ECOG 0-2	CCI G8 VES-13 HGS TUG	79 82% (75-84)	29.5 vs 47.7	9.4 vs 10.0 p=0.086 HR: 0.84 (0.67-1.04)	21.3 vs 19.7 p=0.302 HR: 1.05 (0.81-1.34)	QoL No diff.	Combination: No PFS or OS benefit	Recruitment: 2012-2019 ECOG PS 2=7% Japanese pts.
André et al. 2022 **SOLSTICE** **Phase III** **n=856**	TT+Bev vs CAP+Bev	Ineligible for full-dose doublet/triplet No age limit	G8 CCI	73 IQR 65-80 45% ≥75		9.4 vs 9.3 p=0.0464 HR: 0.87 (0.75–1.02)	19.7 vs 18.6 HR: 1.08 (0.92-1.28)	QoL no diff. Fit patients (G8, CCI, NLR) benefit most	No PFS and OS difference Grade ≥3 tox: TT: neutropenia CAP: HFS	ECOG PS 2=20% 7% m*BRAF*^{V600E} QoL methodology

CONCLUSIONS – CHEMOTHERAPY ± BEVACIZUMAB

- Addition of BEV as first-line results in higher RR and PFS benefit
- No OS benefit
- Fluoropyrimidine + BEV is well tolerated
- Addition of BEV – risk/benefit assessment – shared decision making

Be aware of increase in ATEs

Limitations:

- Most included patients have ECOG 0-1
- Few older adult specific/patient-centred endpoints

DEDICATED RCT TO OA – EGFR INHIBITORS

First-line chemotherapy with EGFRi in treatment naïve older adults with mCRC									
Prospective RCTs	**Design**	**Eligibility**	**GA**	**mAge (range)**	**RR (%)**	**mPFS (months)**	**mOS (months)**	**Older adult specific endpoints**	**Conclusion Context**
Lonardi et al. 2023 **Phase II n=183**	m5FULV + Panit. vs mFOLFOX + Panit. Initial 12 cycles followed by Panit. maintenance	70-75 years & ECOG ≤2 or >75 years & ECOG ≤1	G8 CRASH score	77 (70-86) IQR (73-79)	52 vs 69 p=0.182 DCR 86 vs 92 p=0.163	9.0 vs 9.6 p<0.001 against the null hypothesis (PFS≤ 6 m) Comparison of arms: HR: 1.08 (0.80-1.46) p=0.611	22.0 vs 23.5 p=0.986 HR: 1.00 (0.73-1.38)	Fit pts (G8> 14) had longer PFS (p=0.049) and OS (p<0.001) compared to those with G8≤ 14	Comparable efficacy: PFS, OS More gr.3 toxicity for mFOLFOX Better outcome: 70-75 years: mFOLFOX >75: 5FULV p for interaction: 0.026

CONCLUSIONS – CHEMOTHERAPY + EGFR INHIBITORS

- Fluoropyrimidine + panitumumab is a reasonable choice
- Doublet + panitumumab results in comparable efficacy and safety
- Fit patients (G8 >14) had significantly improved OS (mOS, 32.8 vs 18.7 months; HR: 0.54, p<0.001)
- Few older adult specific/patient-centred endpoints

EPIDERMAL GROWTH FACTOR RECEPTOR-1 INHIBITOR (EGFRi) TO DOUBLET CHEMOTHERAPY

Addition of EGFRi to doublet CT as first-line in *RAS/BRAF*wt

ARCAD database – pooled analysis of 7 RCTs (n=1920)

CT + EGFRi vs CT alone – efficacy in patients <70 vs ≥70 years

Median age: 73 years

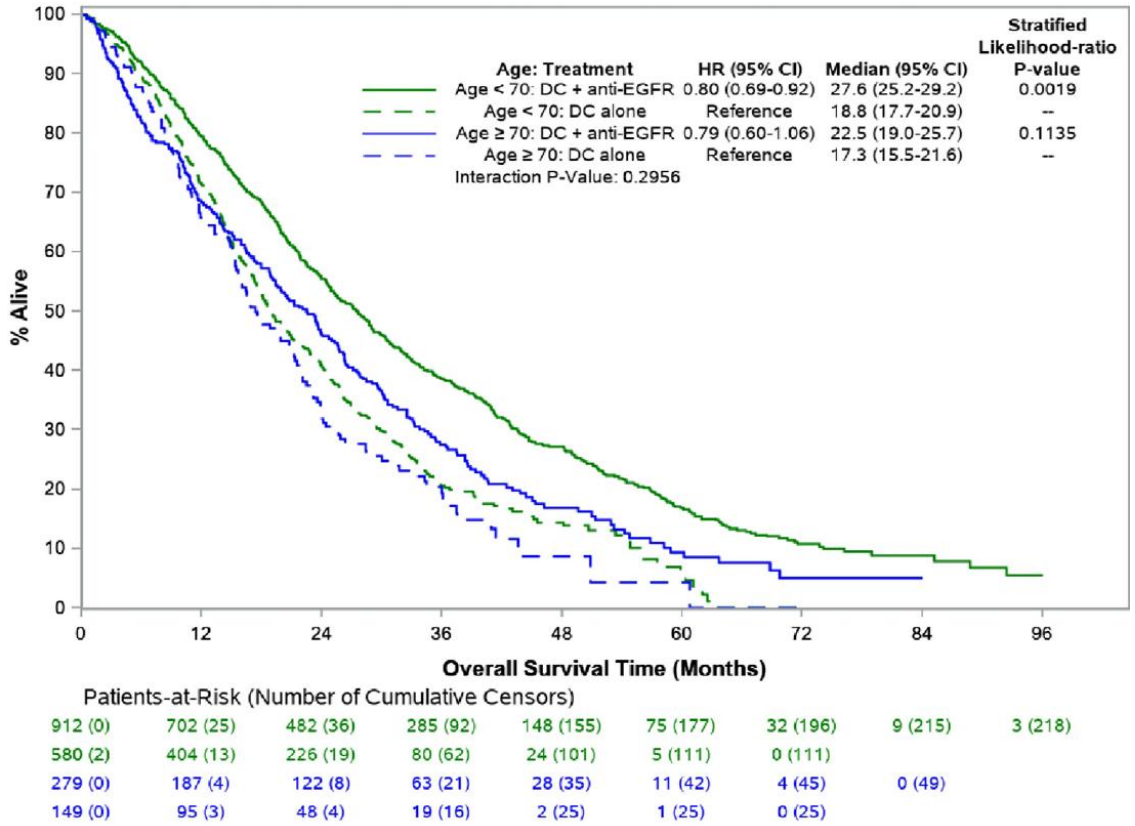
ECOG 0 = 47%, ECOG ≥1 = 53%

Conclusion:

Patients <70 years benefit of EGFRi + CT as first line compared with CT alone

Patients ≥70 years: no significant PFS or OS benefit of CT + EGFRi compared with CT alone

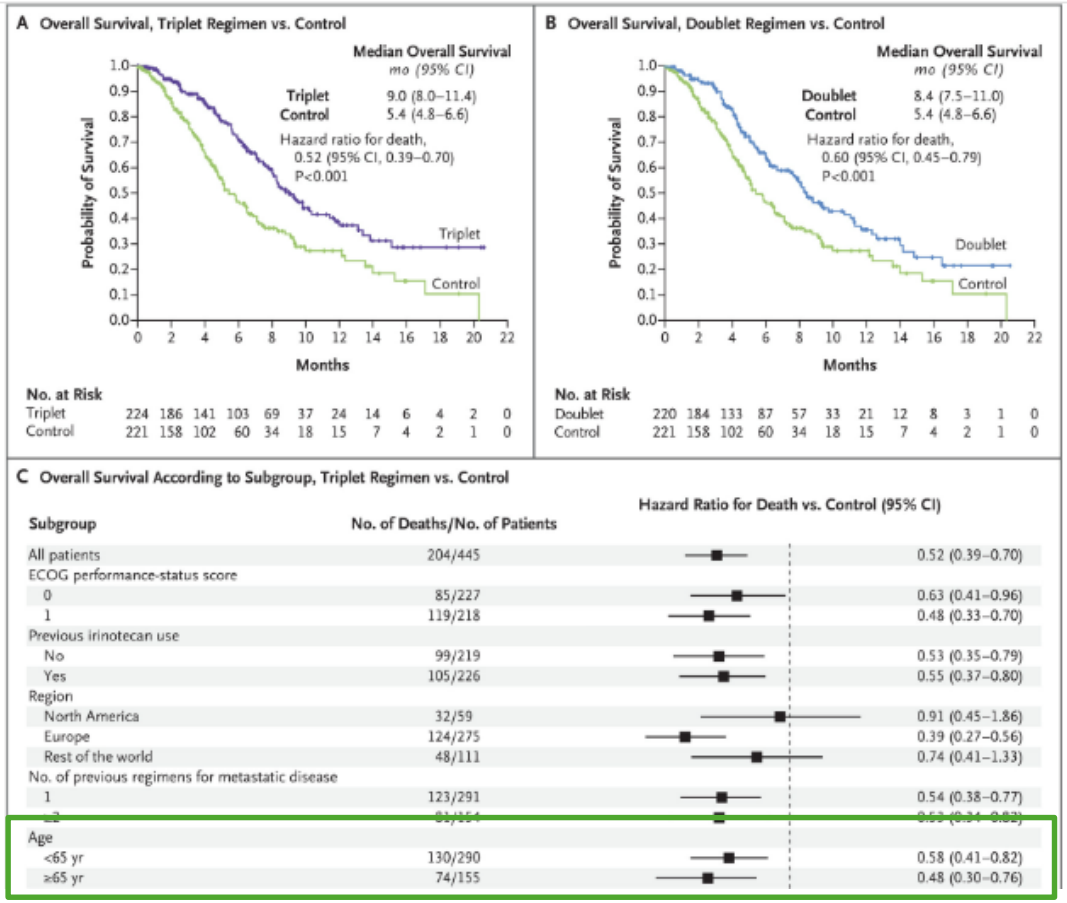
Patients ≥70 years with left-sided primary: significant PFS and OS benefit



Papamichael D, *et al. EJC 2022*

BRAF^{V600E} MUTATED METASTATIC CRC 2ND OR 3RD LINE

Similar efficacy and safety in fit, younger and older

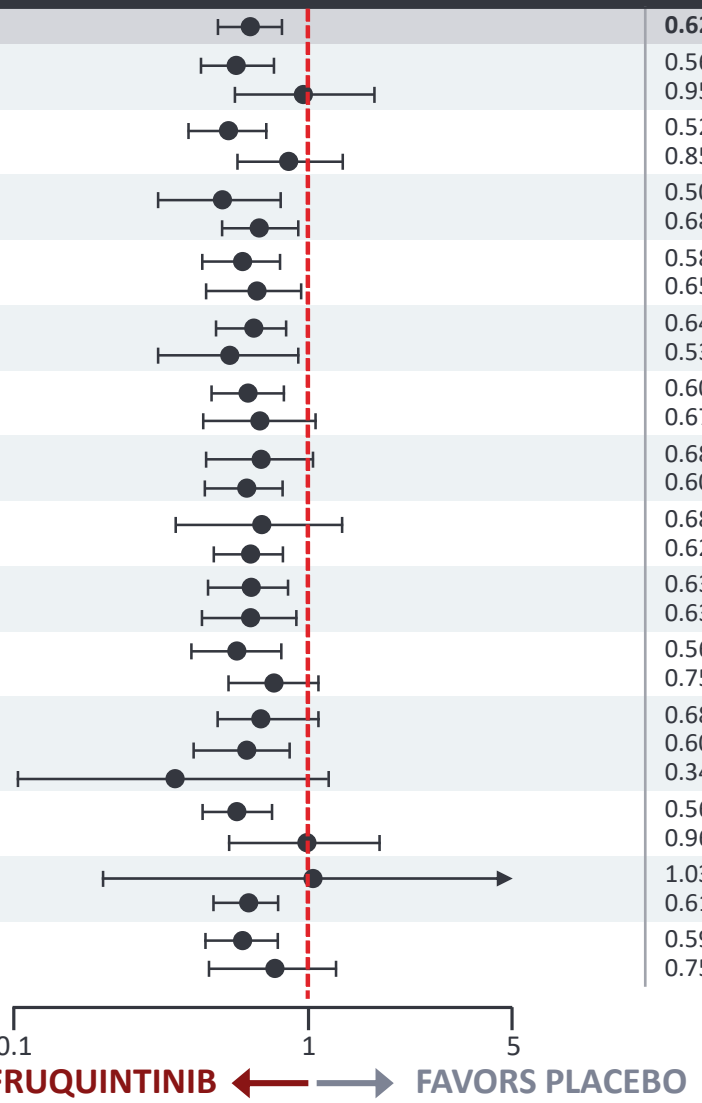


AEs, n (%)	By age group		
	<70 years (n=166)	≥70 years (n=50)	P-value
Any AE	162 (97.6)	50 (100.0)	0.7475
Dermatological toxicity	128 (77.1)	35 (70.0)	0.3058
Arthralgia/myalgia	92 (55.4)	29 (58.0)	0.7475
Nausea/vomiting	71 (42.8)	30 (60.0)	0.0323
Diarrhoea	63 (38.0)	20 (40.0)	0.7941
Abdominal pain	54 (32.5)	21 (42.0)	0.2176
Nephrotoxicity	5 (3.0)	2 (4.0)	0.7295
Fatigue/asthenia	87 (52.4)	34 (68.0)	0.0515

From N Engl J Med 2019, Kopetz S, *et al.* Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer, 381(17)::1632-43,
Taieb J, *et al.* Clin Colorectal Cancer 2023;22(1):59-66.

Fruquintinib efficacy: FRESCO
OS subgroup analysis (ITT population)

SUBGROUP		FRUQUINTINIB + BSC, n		PLACEBO + BSC, n		HR	(95% CI)
		DEATHS	TOTAL	DEATHS	TOTAL		
ITT population		**188**	**278**	**109**	**138**	**0.62**	**(0.49, 0.79)**
Age	<65 years	151	228	88	110	0.56	(0.43, 0.73)
	≥65 years	37	50	21	28	0.95	(0.55, 1.63)
Sex	Male	108	158	77	97	0.52	(0.39, 0.70)
	Female	80	120	32	41	0.85	(0.57, 1.29)
Baseline ECOG performance status	0	50	77	28	37	0.50	(0.31, 0.79)
	1	138	201	81	101	0.68	(0.52, 0.90)
Time from first metastatic diagnosis to randomization	≤18 months	115	163	64	75	0.58	(0.43, 0.79)
	>18 months	73	115	45	63	0.65	(0.45, 0.94)
No. of prior treatment lines on metastatic disease	≤3	146	221	86	107	0.64	(0.49, 0.83)
	>3	42	57	23	31	0.53	(0.31, 0.90)
Previous chemotherapy lines	2 or 3	126	190	80	98	0.60	(0.46, 0.80)
	>3	62	88	29	40	0.67	(0.43, 1.05)
Prior use of VEGF inhibitors	Yes	60	84	35	41	0.68	(0.45, 1.03)
	No	128	194	74	67	0.60	(0.45, 0.80)
Prior use of EGFR inhibitors	Yes	31	40	14	19	0.68	(0.35, 1.30)
	No	157	238	95	119	0.62	(0.48, 0.80)
Prior targeted treatments	No anti-VEGF and no anti-EGFR	109	167	63	83	0.63	(0.46, 0.86)
	Anti-VEGF or anti-EGFR	79	111	46	55	0.63	(0.43, 0.90)
***KRAS* status**	Wild type	103	157	56	74	0.56	(0.40, 0.78)
	Mutated	85	121	53	64	0.75	(0.53, 1.07)
Primary tumor site	Colon	98	147	55	70	0.68	(0.49, 1.07)
	Rectum	84	125	46	60	0.60	(0.41, 0.86)
	Colon and rectum	6	6	7	7	0.34	(0.10, 1.18)
Primary tumor site at the time of diagnosis	Left side	141	214	91	115	0.56	(0.43, 0.73)
	Right side	41	56	16	21	0.96	(0.53, 1.75)
Metastasis	Single	5	13	2	4	1.03	(0.20, 5.37)
	Multiple	183	265	107	134	0.61	(0.48, 0.78)
Liver metastasis	Yes	134	185	85	102	0.59	(0.45, 0.77)
	No	54	93	24	36	0.75	(0.46, 1.21)



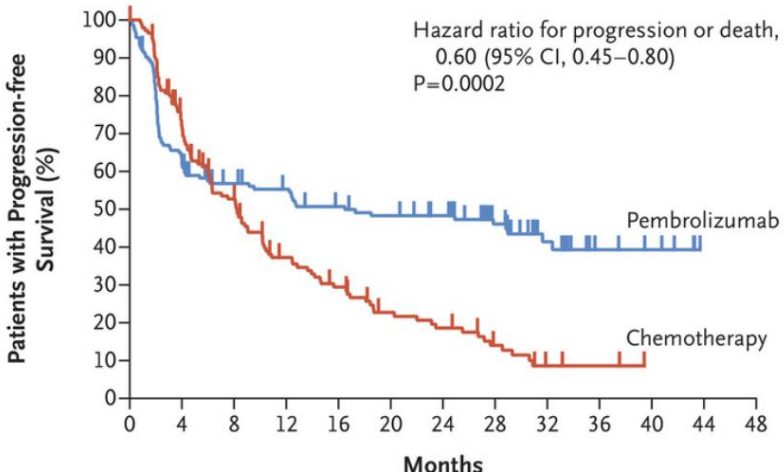
Note: This study was not powered to detect statistically significant differences between arms in subgroups

BSC, best supportive care; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; VEGF, vascular endothelial growth factor

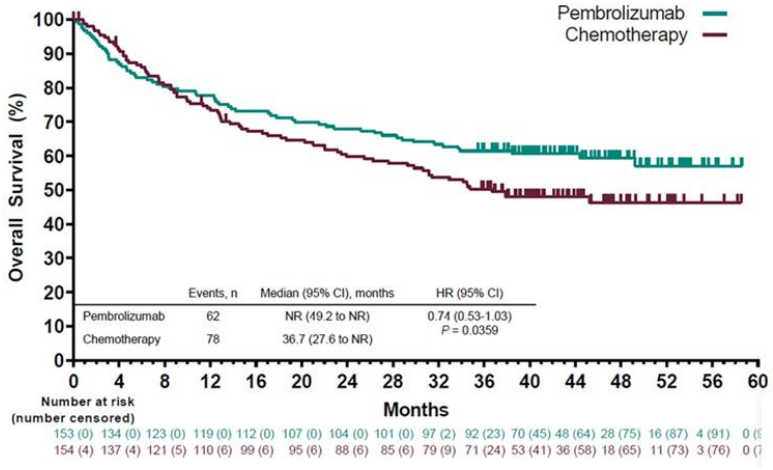
Li J, et al. JAMA 2018;319:2486–96

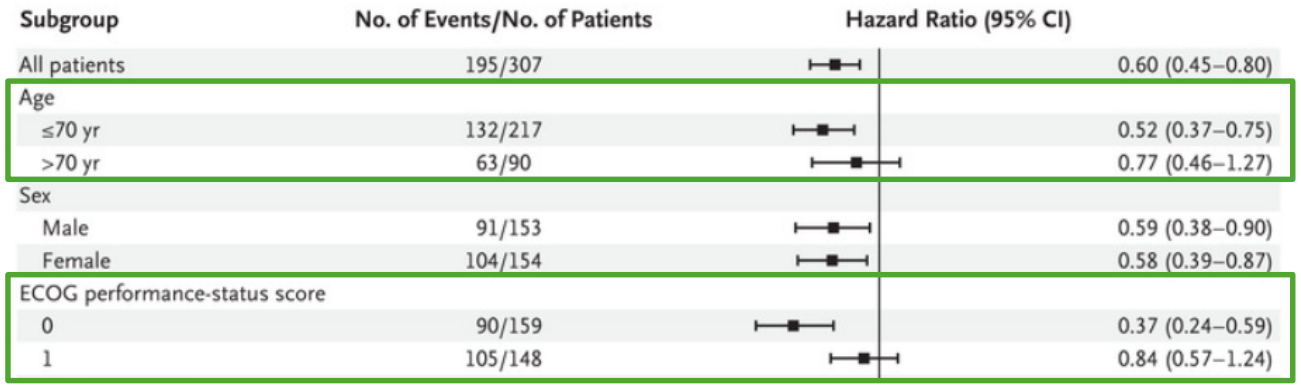
KEYNOTE 177 – PEMBROLIZUMAB VS CHEMOTHERAPY

PFS

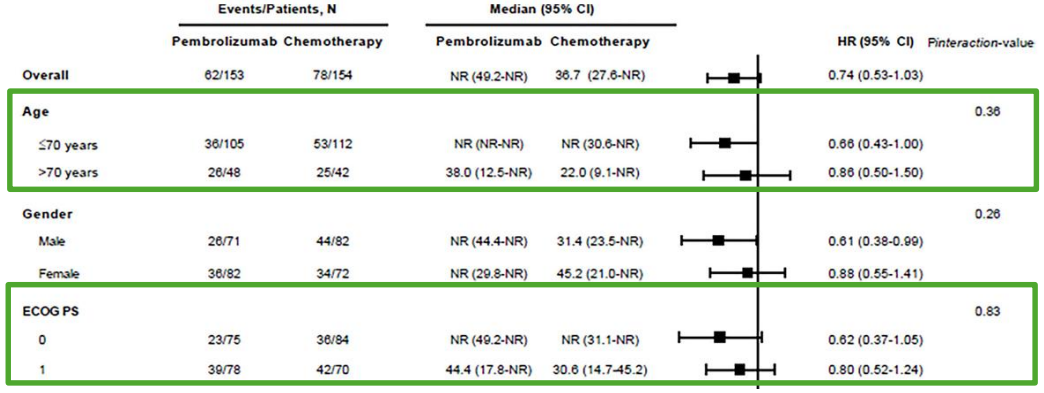


OS





Subgroup	No. of Events/No. of Patients	Hazard Ratio (95% CI)
All patients	195/307	0.60 (0.45–0.80)
Age		
≤70 yr	132/217	0.52 (0.37–0.75)
>70 yr	63/90	0.77 (0.46–1.27)
Sex		
Male	91/153	0.59 (0.38–0.90)
Female	104/154	0.58 (0.39–0.87)
ECOG performance-status score		
0	90/159	0.37 (0.24–0.59)
1	105/148	0.84 (0.57–1.24)



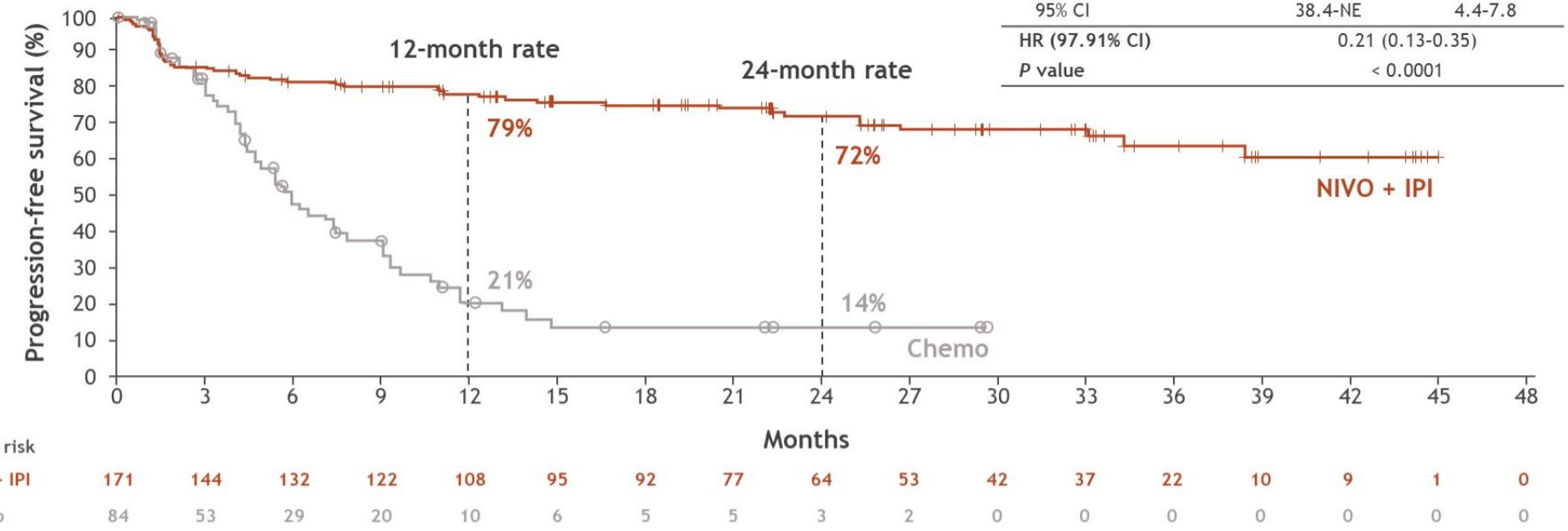
	Events/Patients, N		Median (95% CI)		HR (95% CI)	Pinteraction-value
	Pembrolizumab	Chemotherapy	Pembrolizumab	Chemotherapy		
Overall	62/153	78/154	NR (49.2-NR)	36.7 (27.6-NR)	0.74 (0.53-1.03)	
Age						0.36
≤70 years	36/105	53/112	NR (NR-NR)	NR (30.6-NR)	0.66 (0.43-1.00)	
>70 years	26/48	25/42	38.0 (12.5-NR)	22.0 (9.1-NR)	0.86 (0.50-1.50)	
Gender						0.26
Male	26/71	44/82	NR (44.4-NR)	31.4 (23.5-NR)	0.61 (0.38-0.99)	
Female	36/82	34/72	NR (29.8-NR)	45.2 (21.0-NR)	0.88 (0.55-1.41)	
ECOG PS						0.83
0	23/75	36/84	NR (49.2-NR)	NR (31.1-NR)	0.62 (0.37-1.05)	
1	39/78	42/70	44.4 (17.8-NR)	30.6 (14.7-45.2)	0.80 (0.52-1.24)	

1. From N Engl J Med 2020, André T, *et al.* Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer, 383(23): 2207–18, Copyright © 2020, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 2. Reprinted from The Lancet Oncol, 23(5), Diaz LA, *et al.* Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study, 659-70. Copyright © 2022, with permission from Elsevier Ltd. All rights reserved.

PROGRESSION-FREE SURVIVAL

CheckMate 8HW: first results of first-line nivolumab (NIVO) + ipilimumab (IPI) vs chemo

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR as first line, all randomised patients (HR 0.32; 95% CI, 0.23, 0.46)

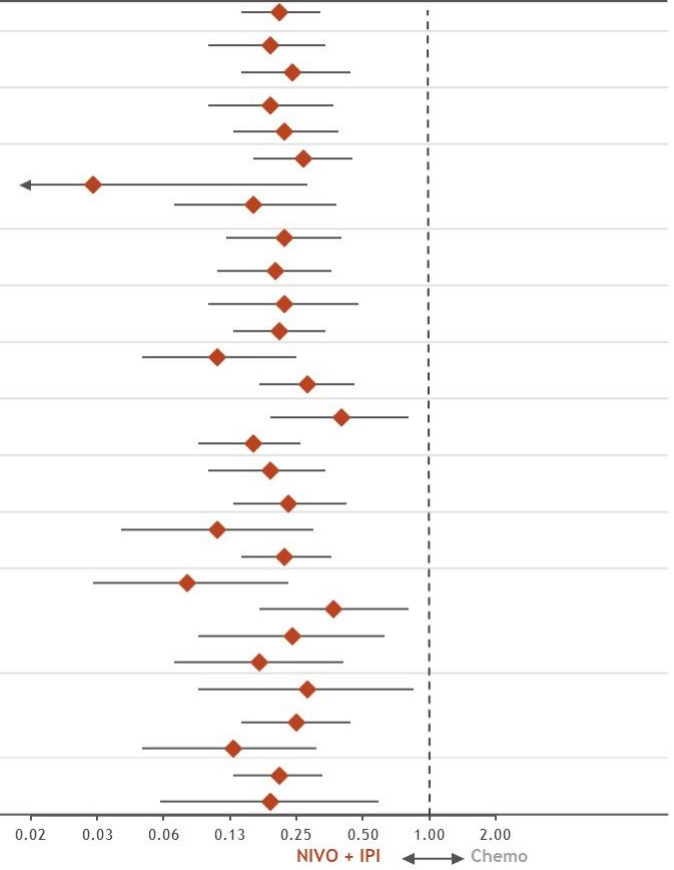
[a]Per BICR; [b]Median follow-up, 24.3 months.
BICR, blinded independent central review.
André T, *et al.* ASCO Gastrointestinal Cancers Symposium 2024; abstract LBA768. Reproduced with permission from Prof Thierry André.

PROGRESSION-FREE SURVIVAL SUBGROUP ANALYSIS

CheckMate 8HW: first results of first-line NIVO + IPI vs chemo

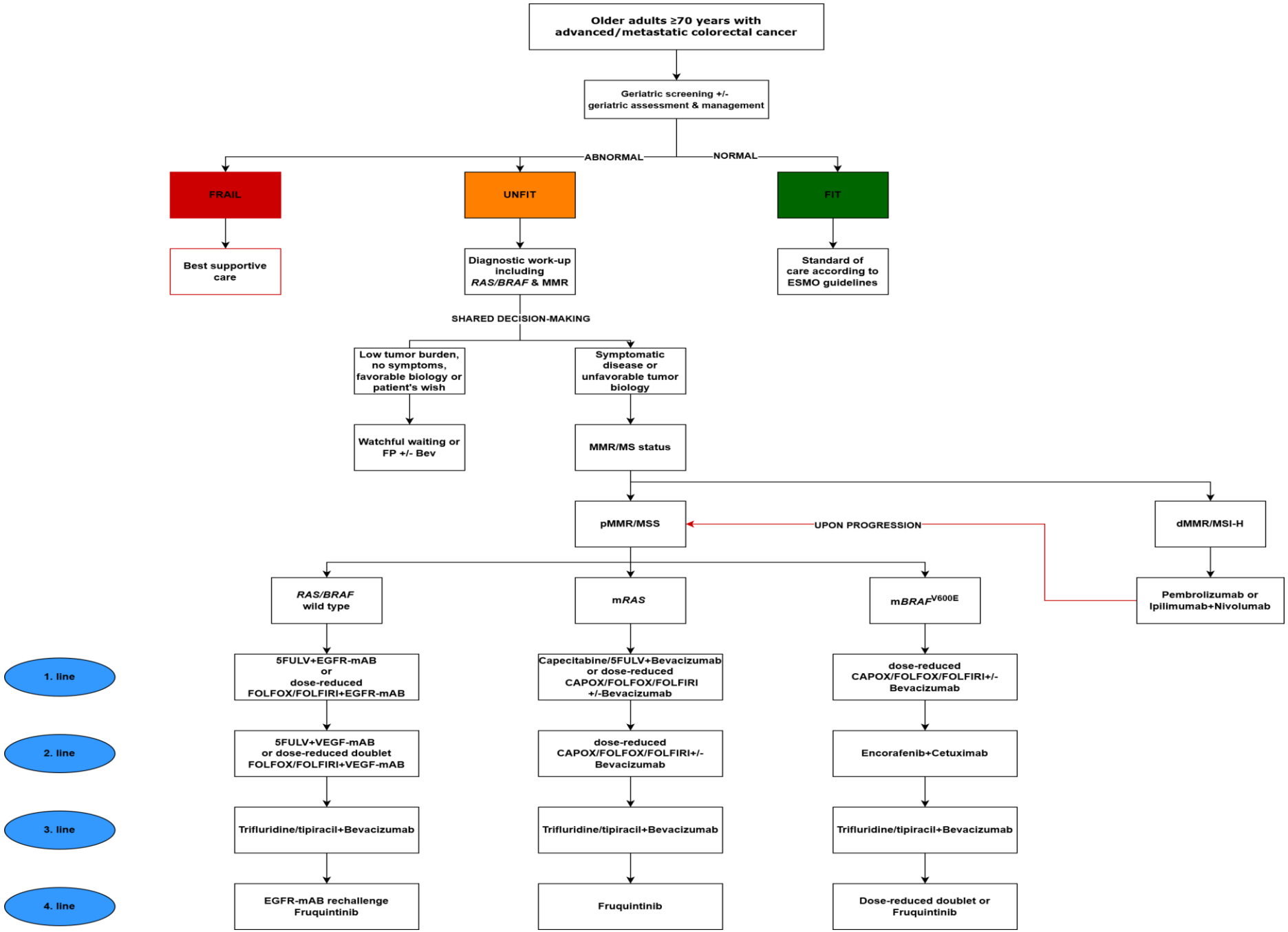
Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	≥ 1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
	Unknown (n = 66)	NR	5.5	0.13
Prior surgery related to current cancer	Yes (n = 222)	NR	7.1	0.21
	No (n = 33)	NR	3.0	0.19

[a]Per BICR.



[a]Per BICR

André T, et al. ASCO Gastrointestinal Cancers Symposium 2024; abstract LBA768. Reproduced with permission from Prof Thierry André.


Older adults ≥70 years with advanced/metastatic colorectal cancer
Geriatric screening +/- geriatric assessment & management
ABNORMAL
NORMAL
FRAIL
UNFIT
FIT
Best supportive care
Diagnostic work-up including RAS/BRAF & MMR
Standard of care according to ESMO guidelines
SHARED DECISION-MAKING
Low tumor burden, no symptoms, favorable biology or patient's wish
Symptomatic disease or unfavorable tumor biology
Watchful waiting or FP +/- Bev
MMR/MS status
pMMR/MSS
UPON PROGRESSION
dMMR/MSI-H
RAS/BRAF wild type
mRAS
mBRAFV600E
Pembrolizumab or Ipilimumab+Nivolumab
1. line
2. line
3. line
4. line
5FULV+EGFR-mAB or dose-reduced FOLFOX/FOLFIRI+EGFR-mAB
Capecitabine/5FULV+Bevacizumab or dose-reduced CAPOX/FOLFOX/FOLFIRI +/-Bevacizumab
dose-reduced CAPOX/FOLFOX/FOLFIRI+/- Bevacizumab
5FULV+VEGF-mAB or dose-reduced doublet FOLFOX/FOLFIRI+VEGF-mAB
dose-reduced CAPOX/FOLFOX/FOLFIRI+/- Bevacizumab
Encorafenib+Cetuximab
Trifluridine/tipiracil+Bevacizumab
Trifluridine/tipiracil+Bevacizumab
Trifluridine/tipiracil+Bevacizumab
EGFR-mAB rechallenge Fruquintinib
Fruquintinib
Dose-reduced doublet or Fruquintinib

CONCLUSIONS

Still low number of RCTs dedicated to OA

Most OA included are fit

GA and GA-guided interventions are not systemically used

Subgroup analyses of RCTs including fit OA have limited value for daily clinical practice

Real value of cancer drugs in actual users remain unclear

High quality real-world data collected with strict methodology are limited yet

PERSPECTIVES – IMPROVEMENT OF THE EVIDENCE BASE

Dedicated RCTs are needed to evaluate the real value of cancer drugs in unselected/vulnerable OA

Patient-centred endpoints (QoL, independence, functional status) should be (co)-primary endpoint(s)

Patient stratification based on geriatric assessment

Geriatric assessment guided interventions to optimise deficits are feasible*

*Mohile SG, *et al*, Lancet 2021;398(10314):1894-04; Li D, *et al*, JAMA Oncol 2021;7(11):e214158; Lund CM, *et al*, Br J Cancer 2021;124(12):1949-58; Soo WK, *et al*, Lancet Healthy Longev 2022;3(9):e617-27.

Thank you

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IDEA – INTERNATIONAL DURATION EVALUATION OF ADJUVANT CHEMOTHERAPY

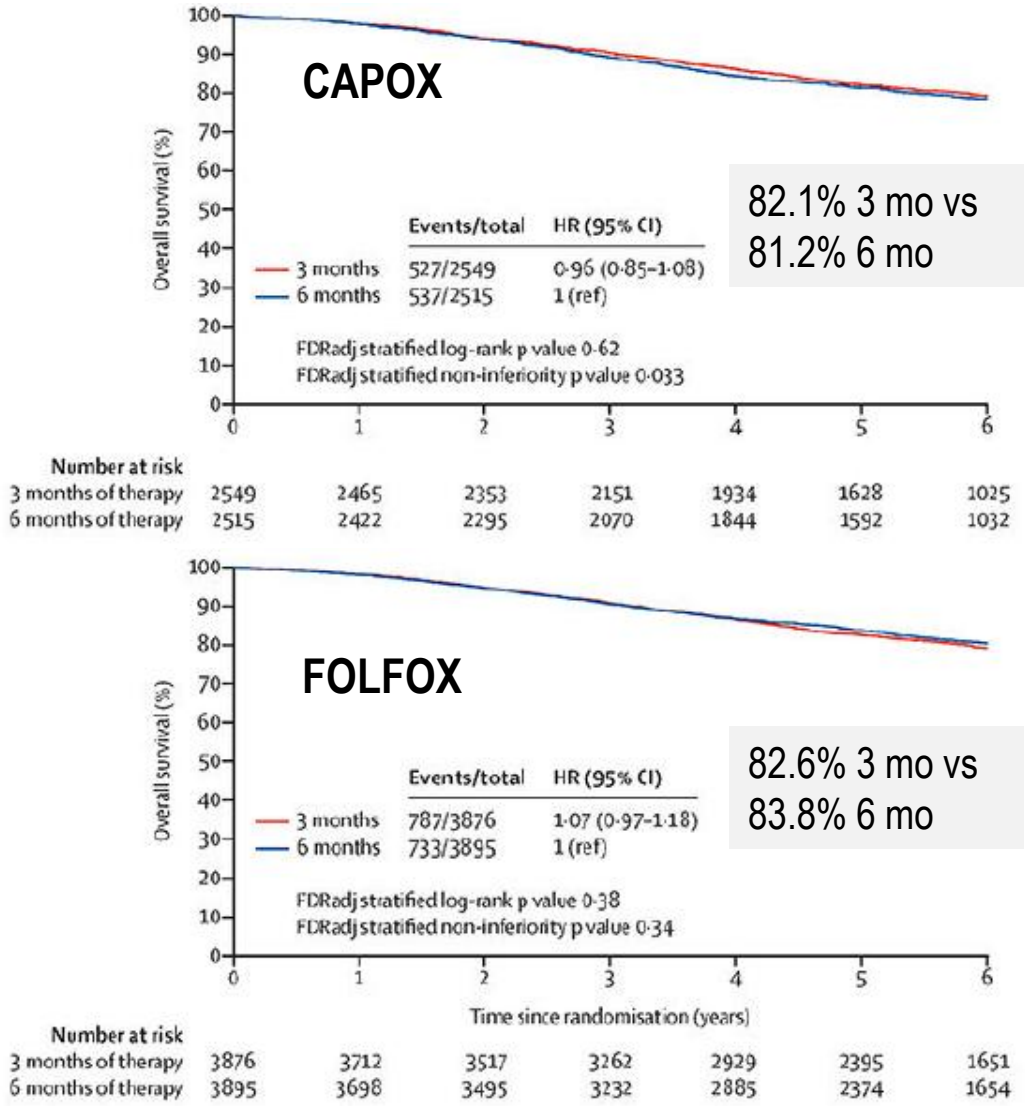
Updated results: 5-year OS

Non-inferiority not confirmed for OS but...

The absolute difference is

0.4%

(82.4% vs 82.8%)

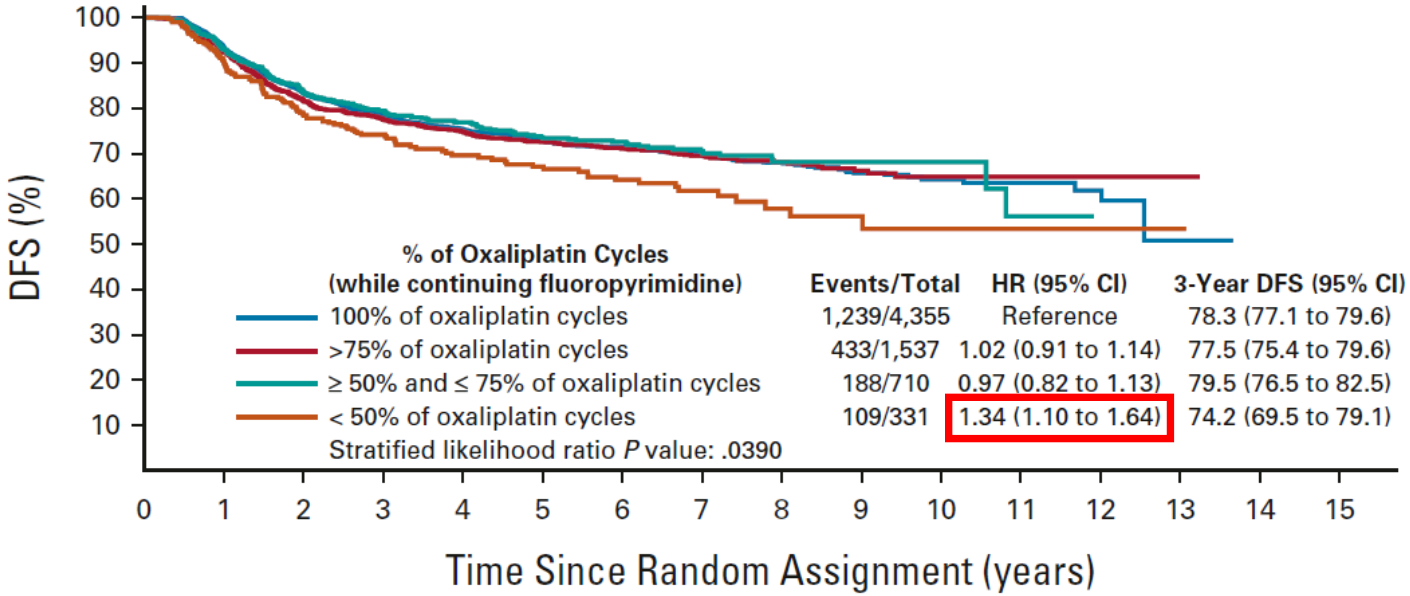


The Lancet Oncol, 21(12), André T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials, 1620–9.

FOR 6-MONTH DURATION: REDUCE THE DURATION OF OXALIPLATIN?

ACCENT/IDEA pooled analysis of 11 adjuvant trials

DFS according to the number of oxaliplatin cycles received (while continuing fluoropyrimidine)



No. at risk:

4,355	4,032	3,544	3,107	2,685	2,109	1,538	917	475	223	97	48	20	1	0
1,537	1,407	1,229	1,076	920	745	574	418	237	116	49	27	5	2	0
710	659	580	474	396	320	239	167	90	40	22	5	0		
331	297	256	196	152	129	99	62	32	17	11	7	3	1	0

Adjusted Kaplan-Meier curves

Adjustment variables:

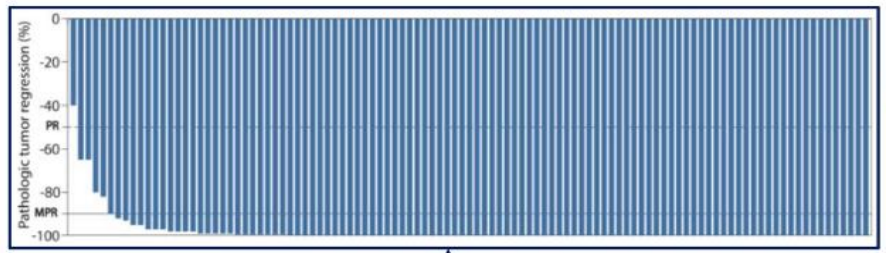
- Age
- Gender
- Year of enrollment
- ECOG performance status (PS)
- T and N stage

After 3 months of doublet chemotherapy in patients having grade 1-2 neurotoxicity: **stopping oxaliplatin** is a likely valid option for **not impairing clinical outcomes**

Gallois C, *et al.* Prognostic Impact of Early Treatment and Oxaliplatin Discontinuation in Patients With Stage III Colon Cancer: An ACCENT/IDEA Pooled Analysis of 11 Adjuvant Trials. J Clin Oncol 2022, 41(4):803-815.

The evolution of neoadjuvant IO in dMMR colon cancer

First results NICHE @ESMO



Chalabi et al, ESMO 2022

NEOPRISM @ASCO Sintilimab +/- anti-CTLA4 @ASCO

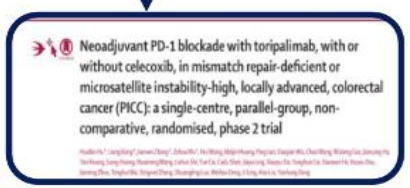
NICHE-2 (3-year DFS) NICHE-3 IMHOTEP

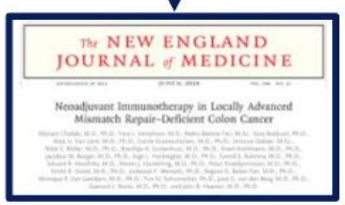
2018 | 2020 | 2022 | ASCO2024 | ESMO 2024


ARTICLES

nature medicine

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


Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial


The NEW ENGLAND JOURNAL of MEDICINE

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer


nature medicine

Article

Neoadjuvant nivolumab and relatlimab in locally advanced MMR-deficient colon cancer: a phase 2 trial