2021 ESMO congress

Adjuvant Treatment for Colon Cancer

Stage III disease treatment:

When, how and for how long?

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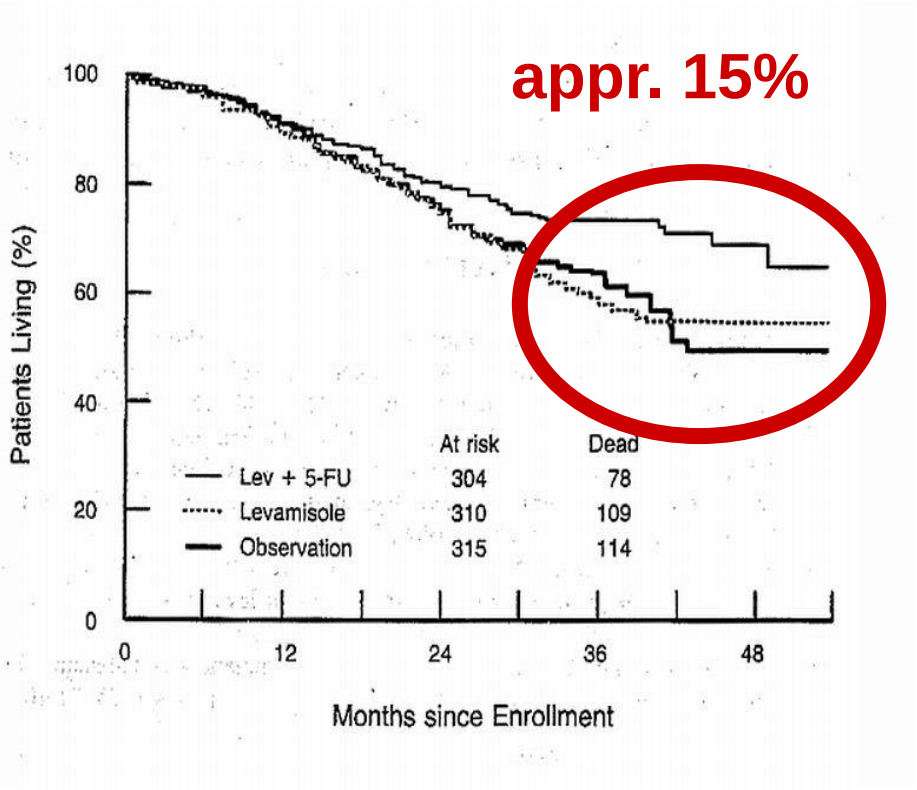
DECLARATION OF INTERESTS

study grant (to the institution):
Merck KGaA

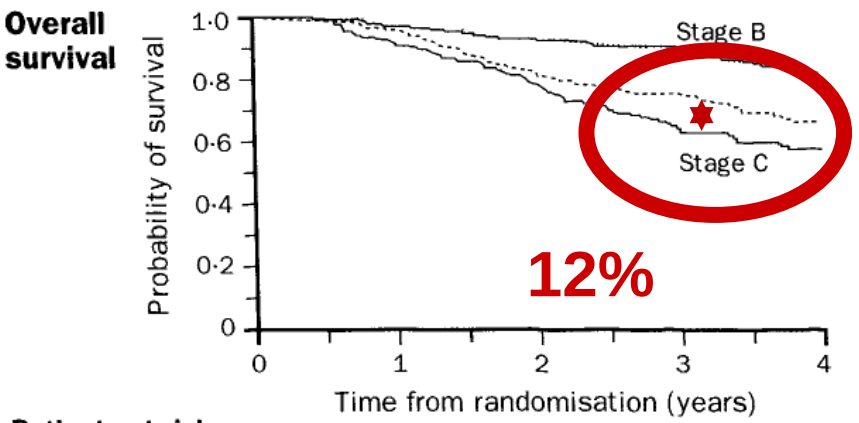
honoraries (lectures, ad-hoc advisory boards):
Amgen, Bayer, BMS, Falk FoundationMerck, MSD, Pierre Fabre, Roche / Genentech, Sanofi-Aventis, Servier, Shire

Stage III: Survival Benefit with 5-FU



Moertel et al NEJM 1990

6 mo 5-FU/FA vs. control



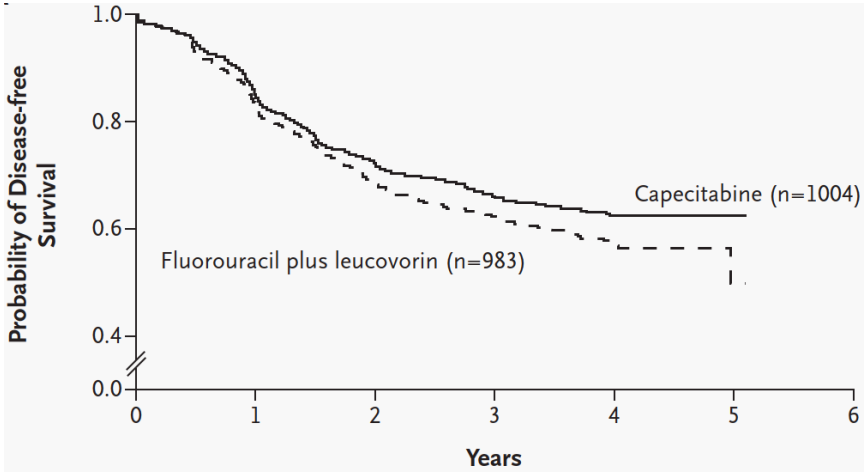
Patients at risk

Control, stage B	423	403	327	189	72
Fluorouracil/folinic acid, stage B	418	399	328	188	87
Control, stage C	334	298	225	125	53
Fluorouracil/folinic acid, stage C	318	300	231	161	63

IMPACT Meta analysis group Lancet 1995

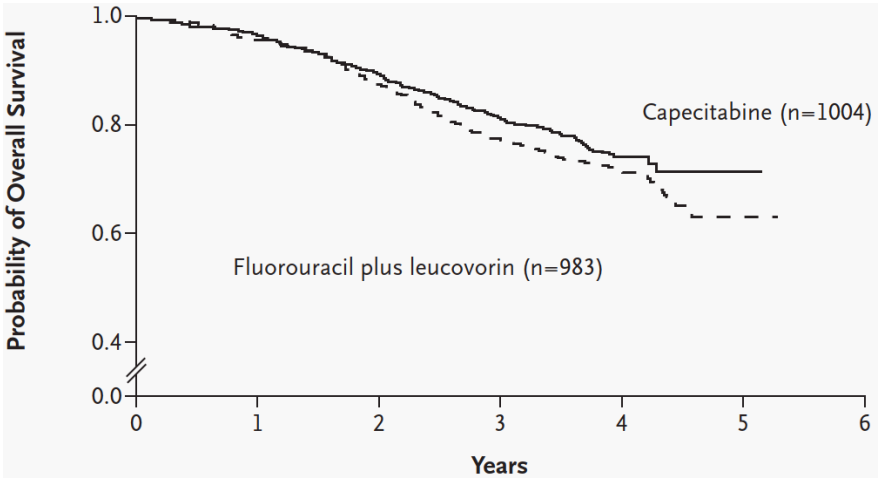
i.v. (bolus) 5-FU can be replaced by capecitabine

Disease free survival



HR 0.86 (0.74-0.99) p=0.04

Overall survival



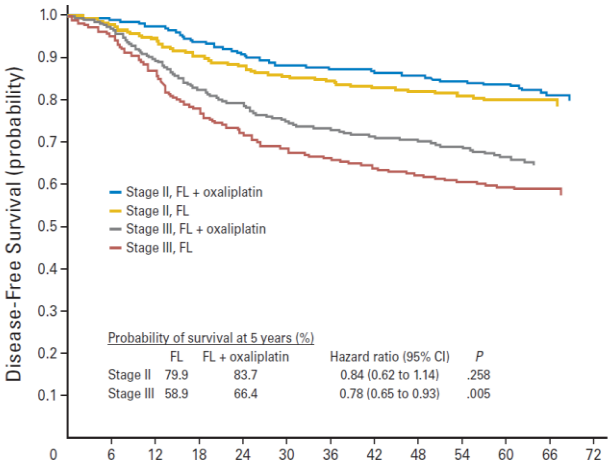
HR 0.84 (0.69-1.01) p=0.07

The study was designed to demonstrate non-inferiority which was shown with p<0.001
(margin for non-inferiority 1.20).

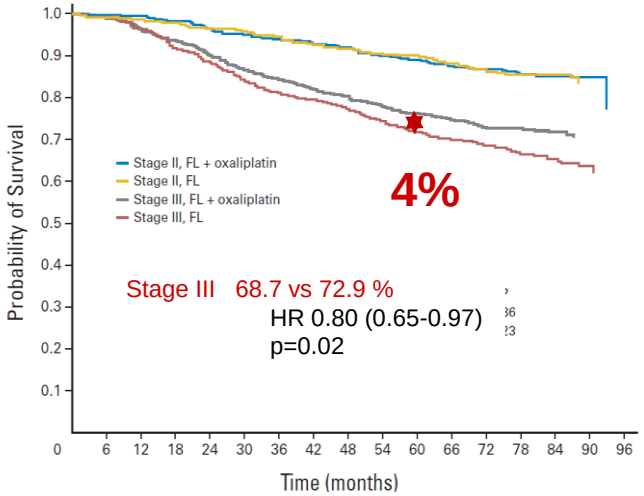
Twelves NEJM 2005

Current standard: Adding oxaliplatin to 5-FU

Disease free survival



Overall survival



Other positive trials:

NSABP C-07 5-FU bolus +/- oxaliplatin Kuebler JCO 2007

XELOXA, Cape/Ox vs. 5-FU bolus, Schmoll JCO 2015

FOLFOX vs. infusional 5-FU/FA

Andre NEJM 2004, JCO 2009

No (significant) improvement with...

... irinotecan

PETACC3

5-FU +/- irinotecan

Van Cutsem JCO 2009

... cetuximab

PETACC8

FOLFOX +/- cetuximab

Taieb Lancet Oncol 2014

(KRAS ex 2 wt pts)

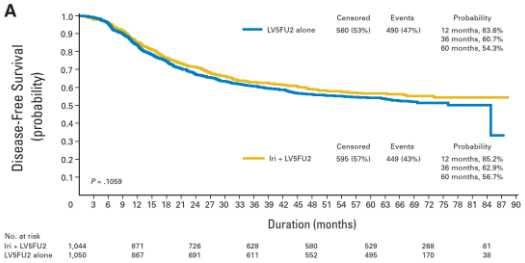
... bevacizumab

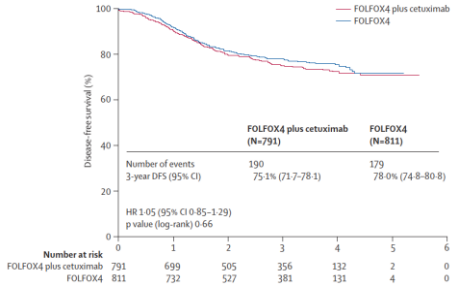
AVANT

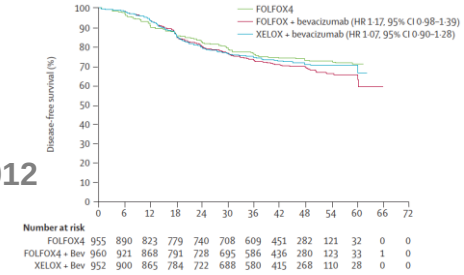
FU/OX +/- bevacizumab

de Gramont Lancet Oncol 2012

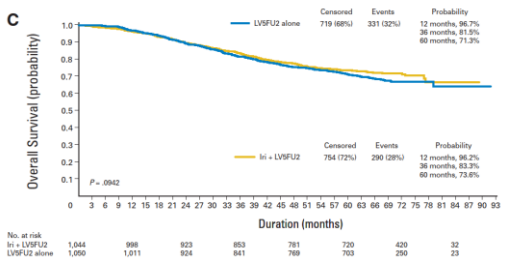
Disease free survival

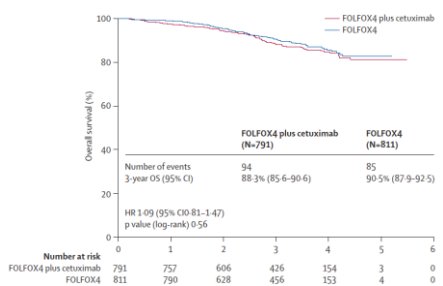


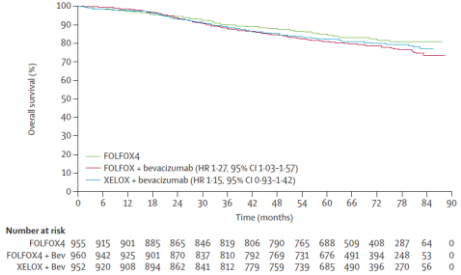




Overall survival







Further negative trials

CALGB 89803

5-FU bolus +/- irinotecan

Saltz JCO 2007

N0147

FOLFOX +/- cetuximab

Alberts JAMA 2012

NSABP C-08

FOLFOX +/- bevacizumab

Allegra JCO 2011 / 2013

Standard: oxaliplatin / fluoropyrimidine.

- Delta in overall survival 15 ... 20%
- i.v. 5-FU can be replaced by capecitabine

- **Problem with oxaliplatin: neurotoxicity**

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- Delta in overall survival 15 ... 20%
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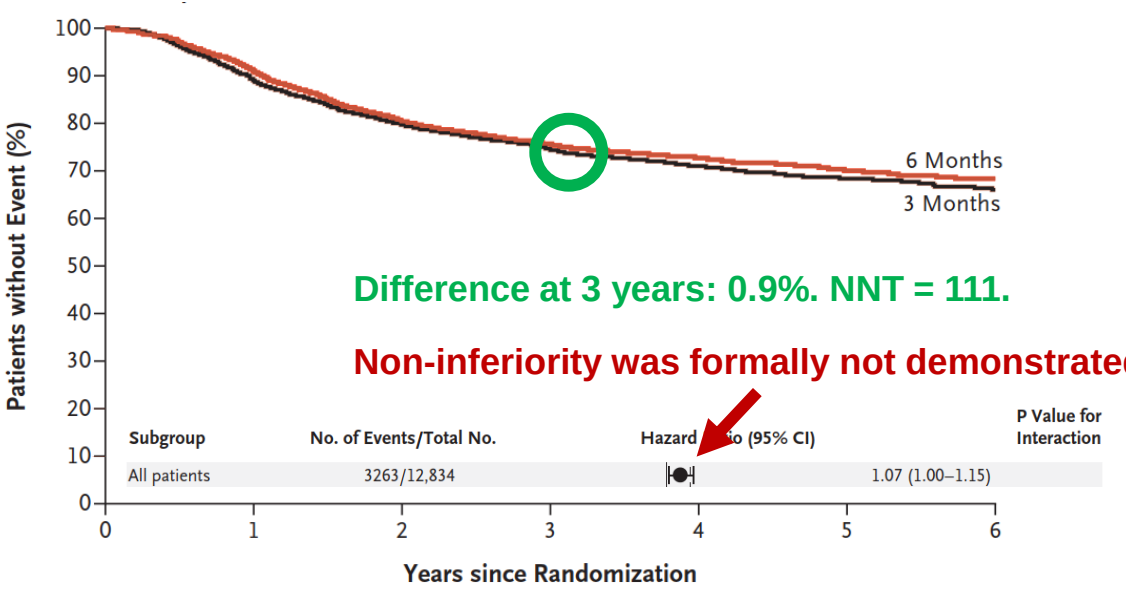
- **Problem with oxaliplatin: neurotoxicity**

IDEA initiative

Trial (Countries)	Regimen	# pts in stage III
TOSCA (Italy)	CapOx, FOLFOX (+/- Bevacizumab)	2402
SCOT (UK, Denmark, Spain, Sweden, Australia, New Zealand)	CapOx, FOLFOX	3983
IDEA France	CapOx, FOLFOX	2010
C80702 (US, Canada)	FOLFOX (+/- Celecoxib)	2440
HORG (Greece)	CapOx, FOLFOX	708
ACHIEVE (Japan)	CapOx, FOLFOX	1291

IDEA (Stadium III): 3 vs. 6 months, primary analysis

Disease free survival

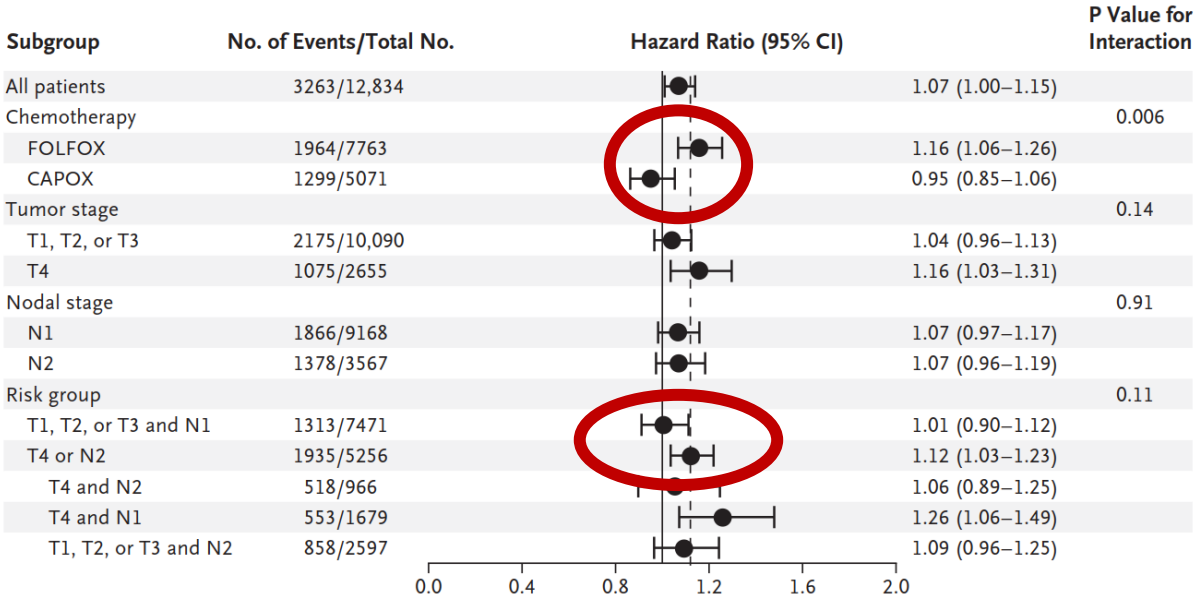


No. at Risk							
6 Months	6410	5530	4477	3065	1679	873	334
3 Months	6424	5446	4464	3000	1609	826	321

Grothey, NEJM 2018

IDEA: 3 vs. 6 months

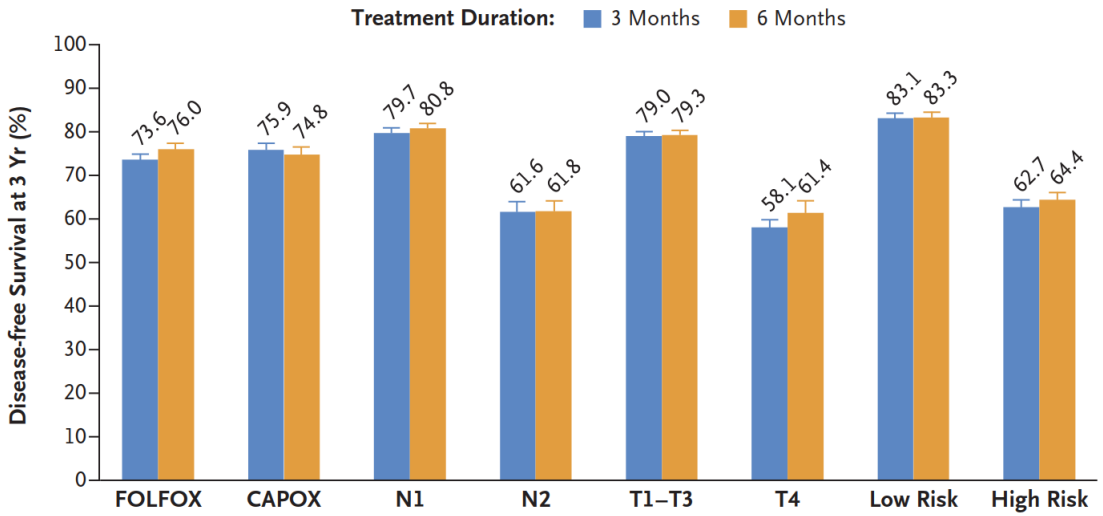
Disease free survival



Grothey, NEJM 2018

IDEA: 3 vs. 6 months

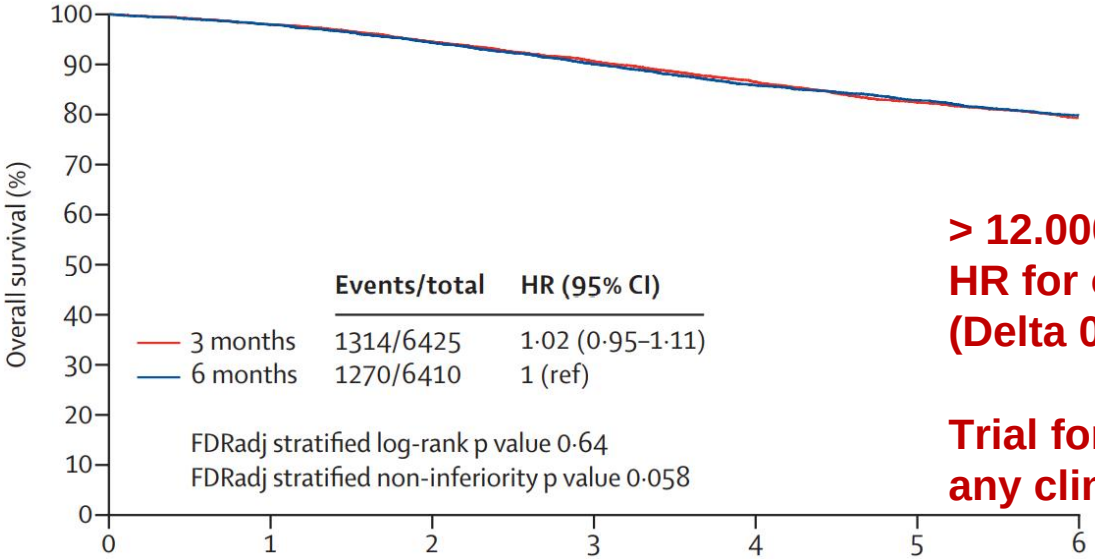
Disease free survival



No. of Patients	7763	5071	9168	3567	10,090	2655	7471	5256
Hazard Ratio 3 vs. 6 Mo (95% CI)	1.16 (1.06–1.26)	0.95 (0.85–1.06)	1.07 (0.97–1.17)	1.07 (0.96–1.19)	1.04 (0.96–1.13)	1.16 (1.03–1.31)	1.01 (0.90–1.12)	1.12 (1.03–1.23)

Grothey, NEJM 2018

IDEA (Stadium III): 3 vs. 6 months, overall survival



Number at risk							
3 months of therapy	6425	6177	5870	5413	4863	4023	2676
6 months of therapy	6410	6120	5790	5302	4729	3966	2686

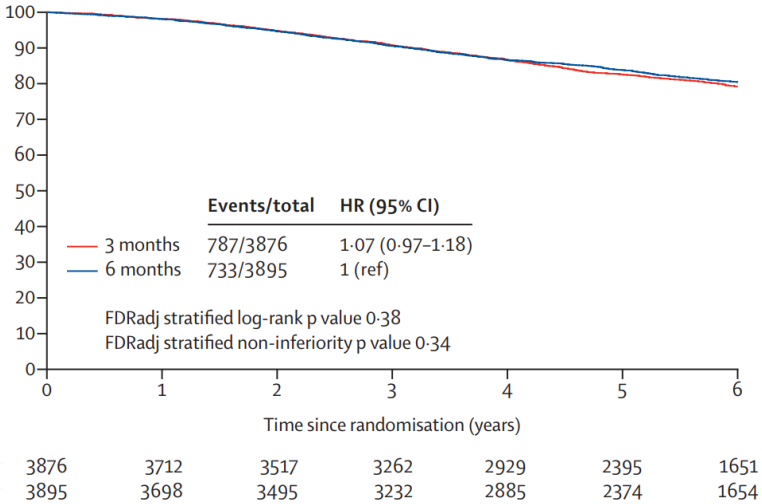
> 12.000 patients
HR for overall survival 1.02 (Delta 0.4%)

Trial formally negative, but: any clinical relevance?

Andre, Lancet Oncol 2020

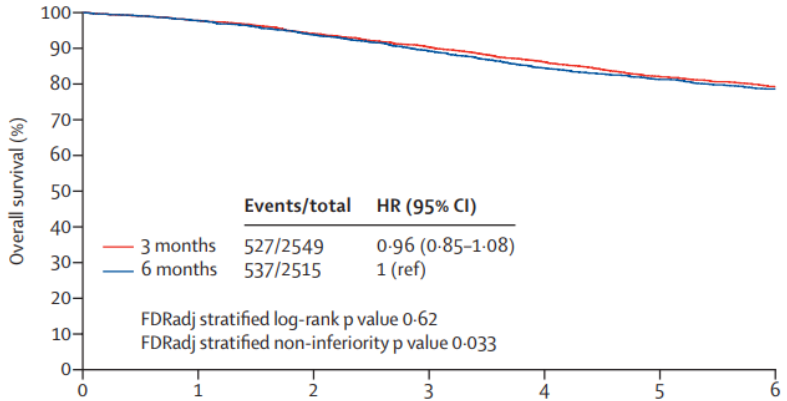
IDEA (Stadium III): 3 vs. 6 months, overall survival

FOLFOX



3876	3712	3517	3262	2929	2395	1651
3895	3698	3495	3232	2885	2374	1654

Capecitabin / Oxaliplatin



Number at risk							
3 months of therapy	2549	2465	2353	2151	1934	1628	1025
6 months of therapy	2515	2422	2295	2070	1844	1592	1032

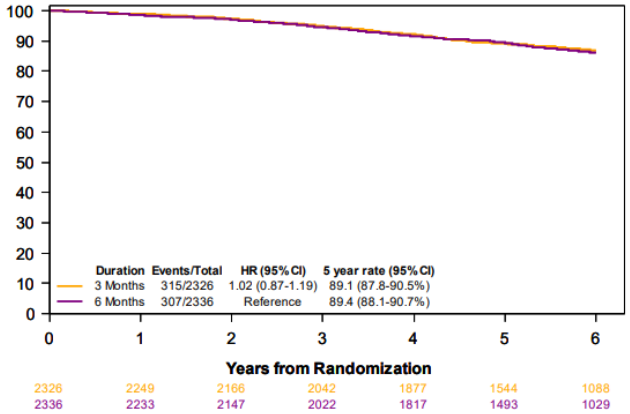
Andre, Lancet Oncol 2020

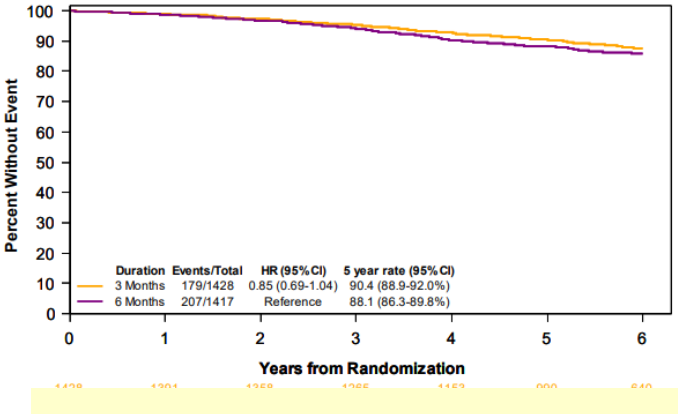
IDEA (Stadium III): 3 vs. 6 months, overall survival

FOLFOX

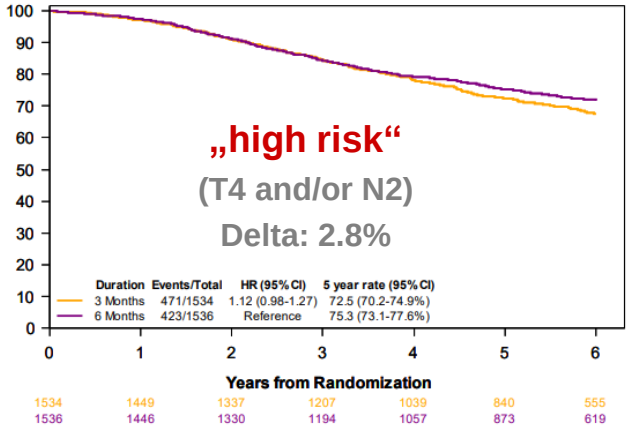
Capecitabin / Oxaliplatin

„low risk“
(not T4, not N2)





„high risk“
(T4 and/or N2)

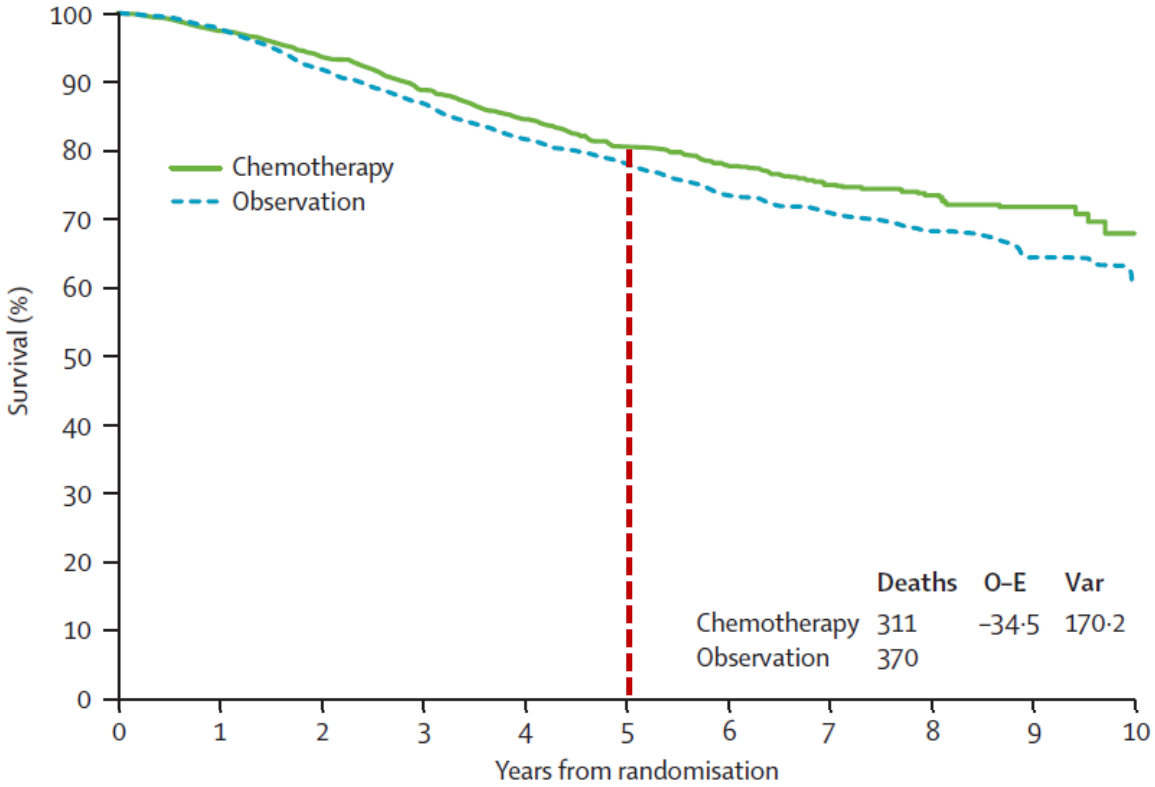


No visible difference in OS for low risk or CapOx

In „high risk“ > 90 % effect with 3 months

Andre,
Lancet Oncol 2020
suppl. mat.

Stage II: QUASAR trial



2 ... 3 % overall survival difference in stage II do not justify a general treatment recommendation...

QUASAR Collaborative Group, Lancet 2007

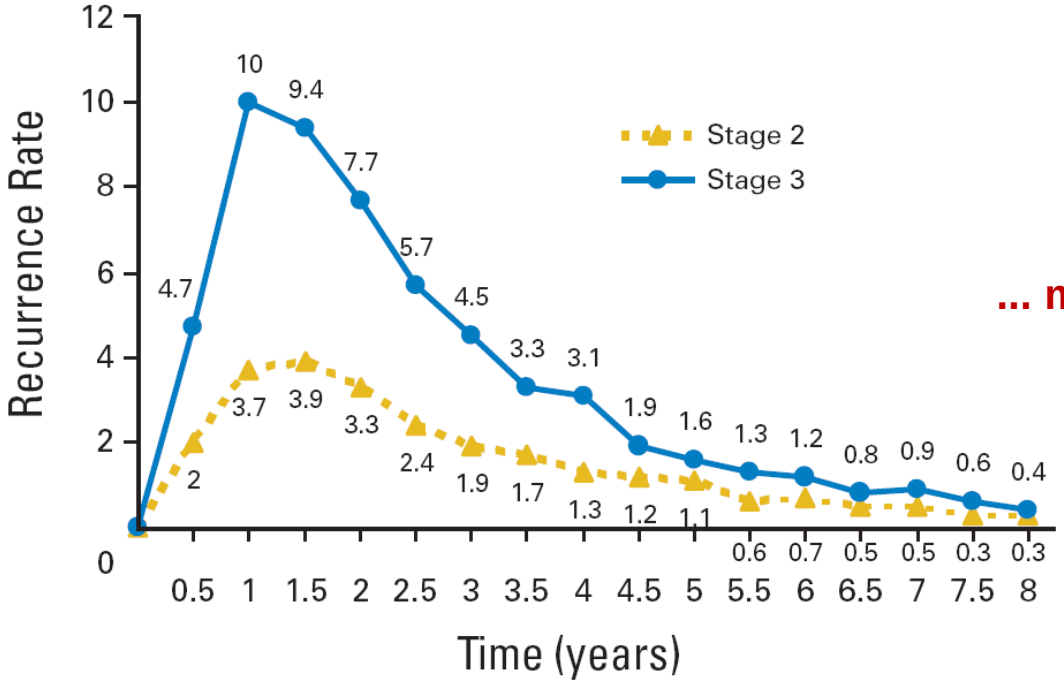
Standard: oxaliplatin / fluoropyrimidine.

- Delta in overall survival 15 ... 20%
- i.v. 5-FU can be replaced by capecitabine

Much more than 90% of the treatment effect in the first 3 months.

- low risk (no T4, no N2): 3 months CapOx
- high risk (T4 or N2): guidelines differ (6 months FOLFOX, 3 months CapOx)
- ESMO recommendation: 6 months treatment for high risk

Recurrences / metastases in adjuvant trials



... mostly during the first few years

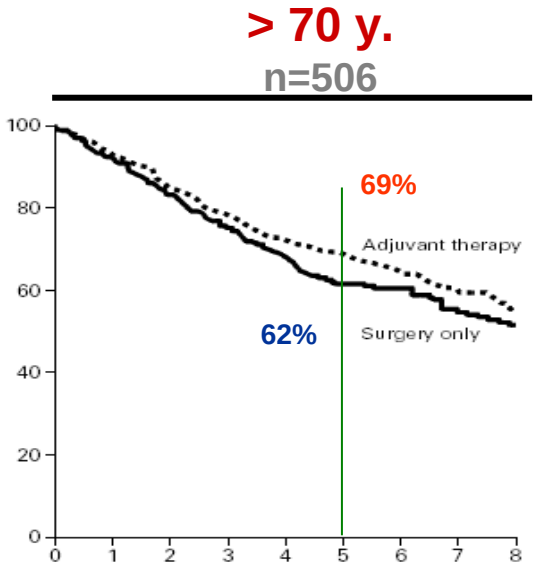
ACCENT database, Sargent JCO 2007

Adjuvant 5-FU in elderly patients

Table 1. Distribution of Patients by Age

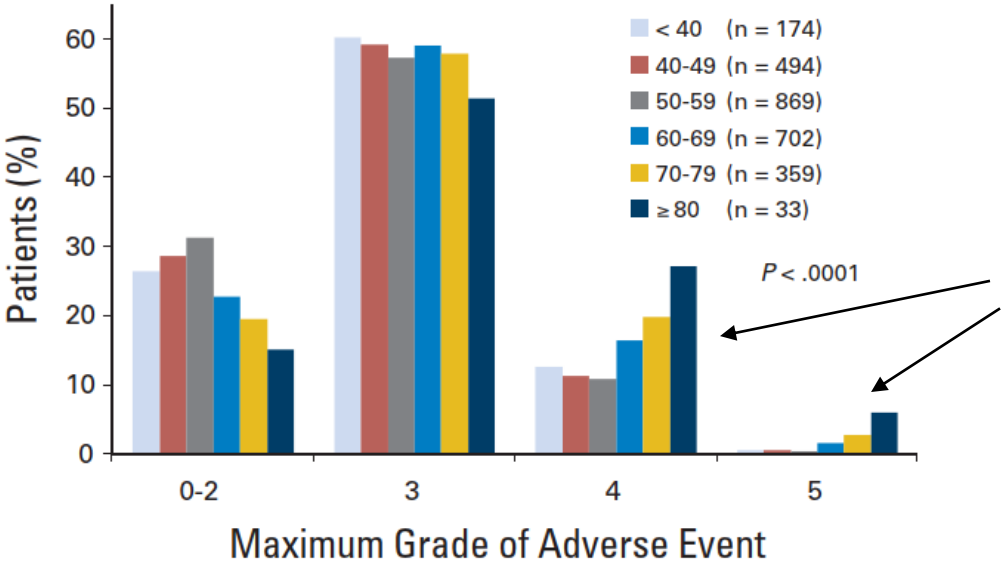
Patient Age (years)	No. of Patients	%
< 30	299	0.9
30-34	503	1.5
35-39	956	2.9
40-44	1,549	4.6
45-49	2,510	7.4
50-54	3,818	11.4
55-59	5,056	15.1
60-64	6,188	18.4
65-69	6,610	19.7
70-74	4,488	13.4
75-79	1,334	3.9
≥ 80	263	0.8
Total	33,574	100

Hubbart, JCO 2012



Sargent, NEJM 2001

Adverse events in NSABP C-08 according to age



Grade 4 / 5 events and age...

grade 4 – life threatening;
grade 5 – fatal

These patients were fit enough to be enrolled in clinical trials

The trial studied FOLFOX +/- bevacizumab in stage II/III, Allegra, JCO 2009

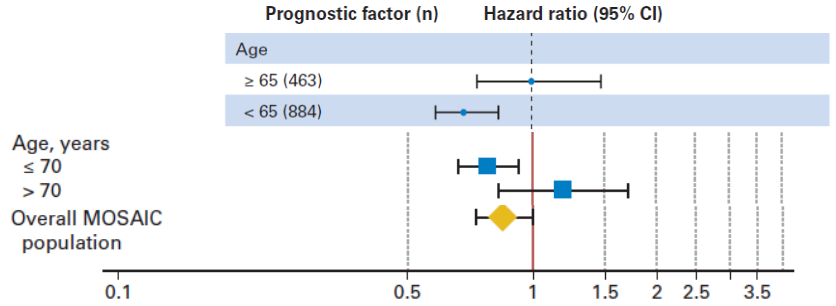
Oxaliplatin: Sub group analyses for age

MOSAIC

FOLFOX vs. 5-FU

Andre

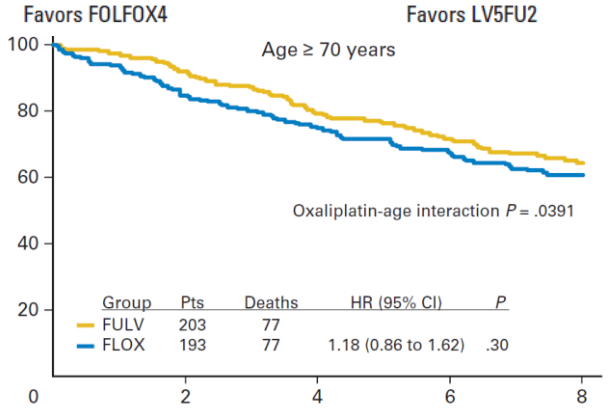
JCO 2009/2016



NSABP-C07

FLOX vs. 5-FU

Yothers JCO 2011



XELOXA

Cape/Ox vs. 5-FU

Schmoll JCO 2015

< 70 y HR 0.82 (0.67-1.01)

≥ 70 y HR 0.91 (0.66-1.26)

Standard: oxaliplatin / fluoropyrimidine.

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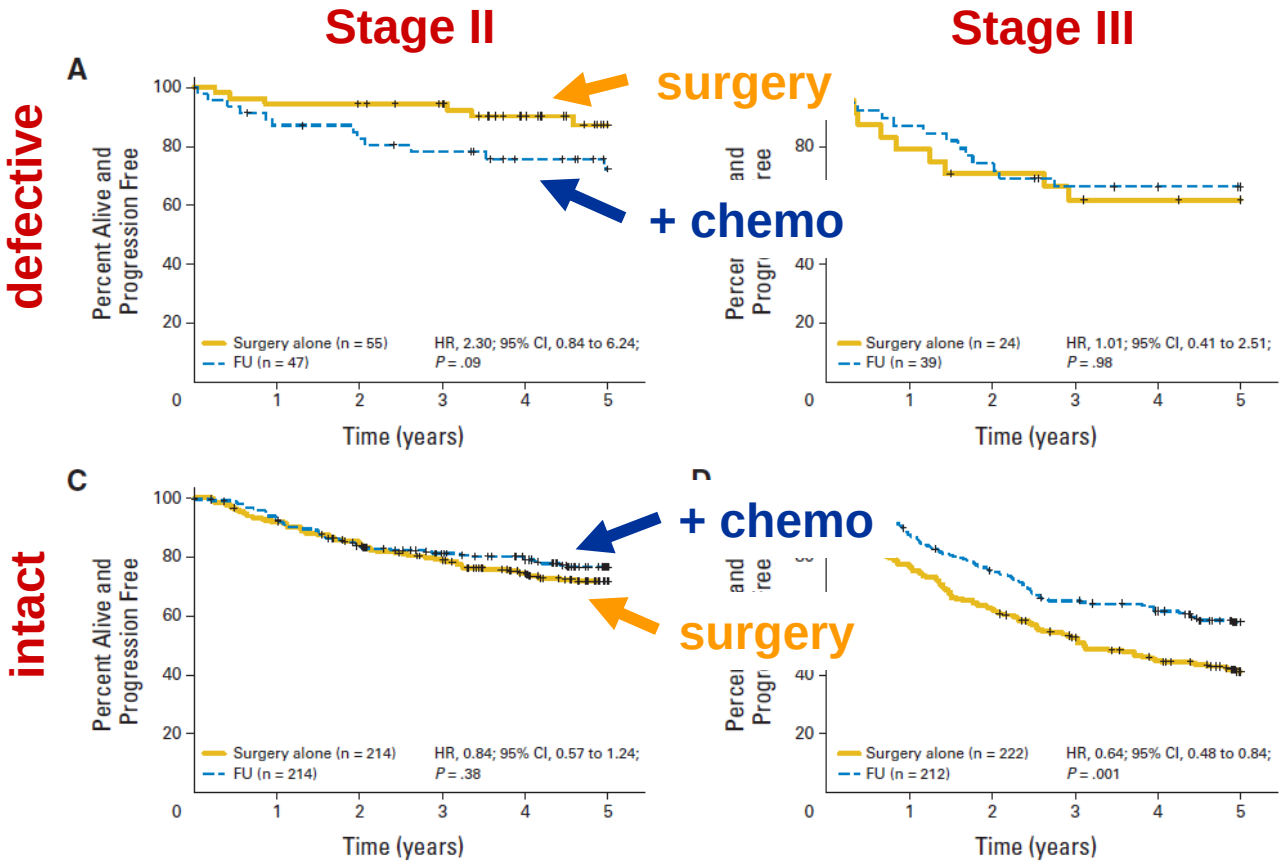
Much more than 90% of the treatment effect in the first 3 months.

- low risk (no T4, no N2): 3 months CapOx
- high risk (T4 or N2): guidelines differ (6 months FOLFOX, 3 months CapOx)
- ESMO recommendation: 6 months treatment for high risk

Elderly patients should be offered adjuvant therapy.

- For patients with > 75 years limited evidence.
- Limited/no benefit from oxaliplatin > 70 years → rather 6 months fluoropyrimidine.

DNA mismatch repair and chemo (5-FU)



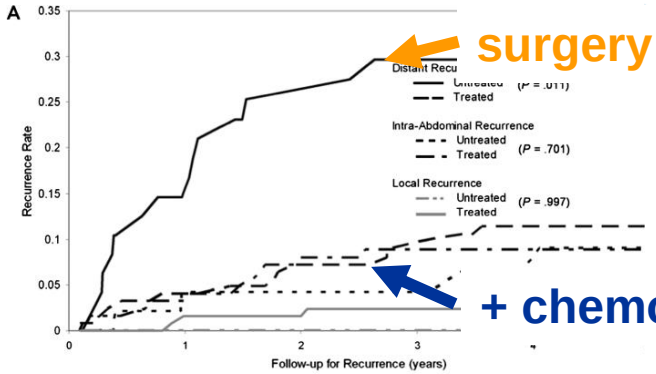
Sargent, JCO 2010

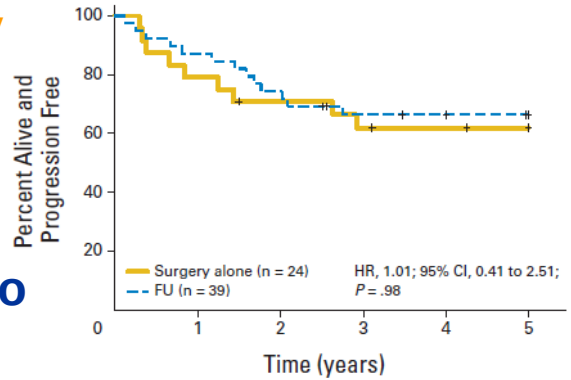
DNA mismatch repair and chemo (5-FU)

Recurrences Stage III

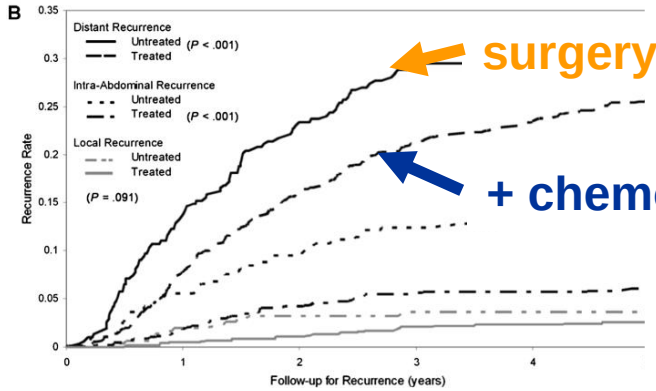
Stage III

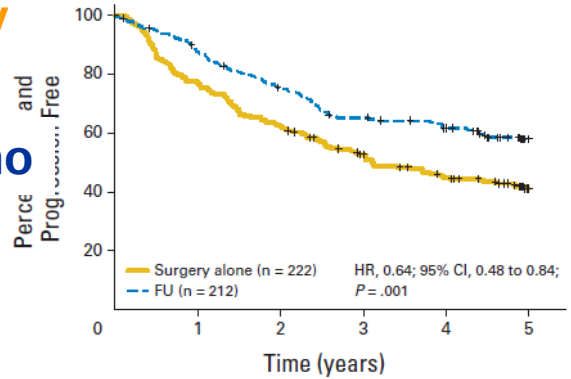
defective





intact



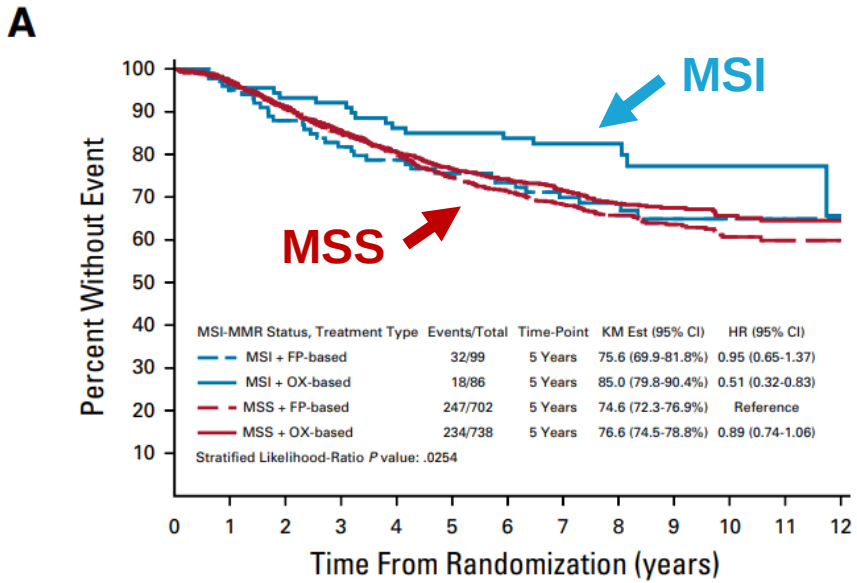


Sinicrope, JNCI 2011

Sargent, JCO 2010

DNA mismatch repair and adding oxaliplatin

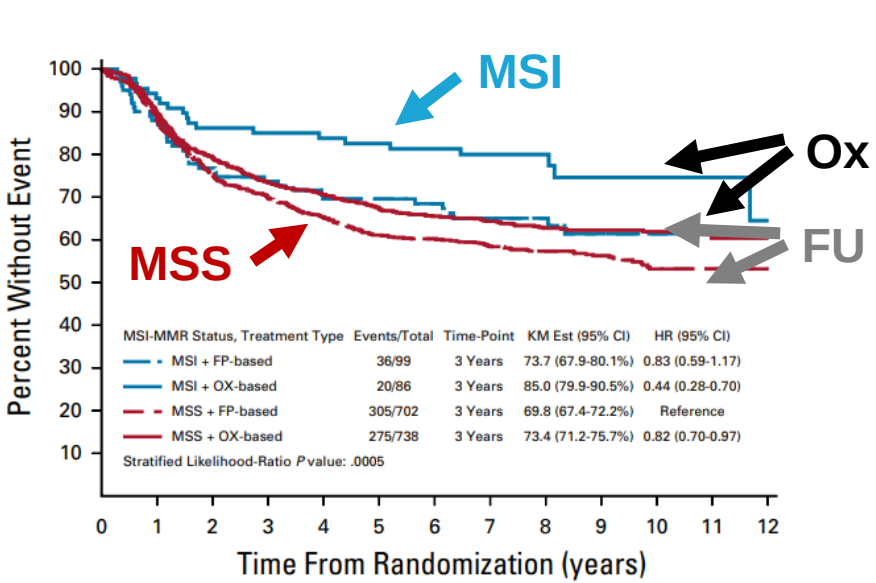
Overall survival



Patients-at-Risk

MSI + FP-based	99	94	86	80	76	67	65	54	41	23	12	5	3
MSI + OX-based	86	80	77	75	68	67	65	56	32	19	11	7	3
MSS + FP-based	702	673	628	583	547	509	480	424	306	198	114	53	26
MSS + OX-based	738	710	665	626	584	547	527	465	342	245	146	79	27

Disease free survival



Patients-at-Risk

MSI + FP-based	99	87	75	72	67	62	61	50	39	22	11	4	3
MSI + OX-based	86	78	71	69	66	65	63	54	31	18	10	7	3
MSS + FP-based	702	613	518	479	447	417	406	364	265	178	98	46	24
MSS + OX-based	738	660	582	538	513	482	468	418	308	220	132	68	22

Cohen, JCO 2020

Standard: oxaliplatin / fluoropyrimidine.

- Delta in overall survival 15 ... 20%
- i.v. 5-FU can be replaced by capecitabine

Much more than 90% of the treatment effect in the first 3 months.

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- high risk (T4 or N2): guidelines differ (6 months FOLFOX, 3 months CapOx)
- ESMO recommendation: 6 months treatment for high risk

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- For patients with > 75 years limited evidence.
- Limited/no benefit from oxaliplatin > 70 years → rather 6 months fluoropyrimidine.

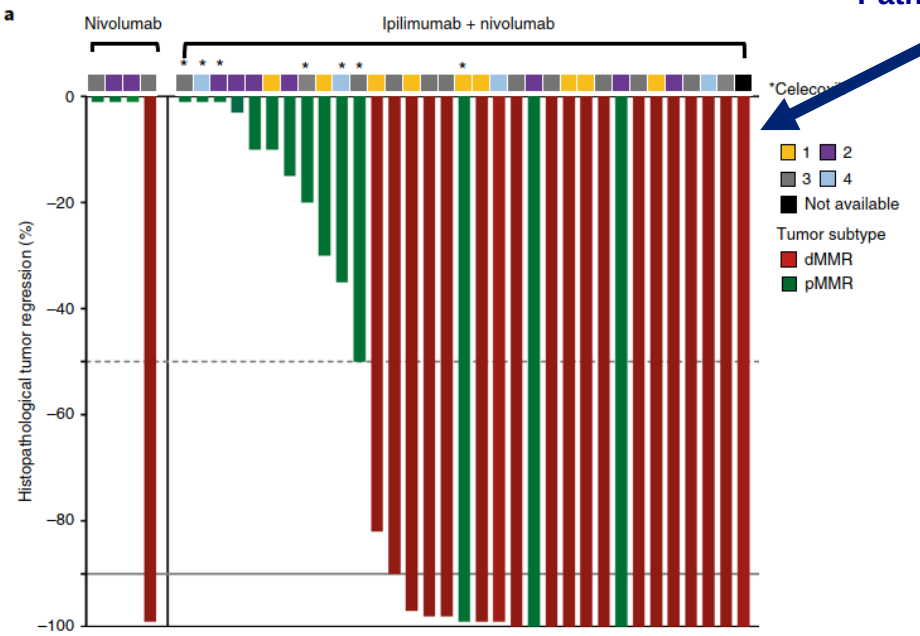
Do not use MSI / dMMR for adjuvant chemotherapy decision in stage III.

- But change of the standard is likely.

Neoadjuvant immunotherapy in CRC (mostly MMR-d / MSI-H)

Nivolumab monotherapy or ipilimumab/nivolumab

Pathological response



Chalabi et al, Nature Medicine 2020

FOxTROT: peri- vs postoperative chemotherapy

3 x FOLFOX → OP → 9 x FOLFOX

vs.

OP → 12 x FOLFOX

Seymour, ASCO 2019 / Morton, ESMO 2019

FOxTROT: peri- vs postoperative chemotherapy

3 x FOLFOX → OP → 9 x FOLFOX vs. OP → 12 x FOLFOX

1. **Not more complications**

Underwent surgery	Pre&post n=684	Post n=351	
Procedure involved a stoma	11.7%	9.0%	p=0.18
Wound infection	8.5%	8.9%	p=0.85
Bronchopneumonia	1.8%	3.1%	p=0.16
PE ± DVT	1.6%	0.6%	p=0.18
Anastomotic leak or intra-abdo abscess	4.7%	7.4%	p=0.07
complication requiring further surgery	4.3%	7.1%	p=0.05
complication prolonging hospital stay	11.6%	14.3%	p=0.21
Death within 30 days	0.6%	0.6%	p=0.98

Seymour, ASCO 2019 / Morton, ESMO 2019

FOxTROT: peri- vs postoperative chemotherapy

3 x FOLFOX → OP → 9 x FOLFOX vs. OP → 12 x FOLFOX

1. Not more complications
2. **Downsizing/downstaging**

Local pathology	neoadj. chemo n=682	Straight to surgery n=347	
pT0	4.1%	0%	p<0.0001
pT1-2	11.7%	5.8%	
pT3	63.7%	64.5%	
pT4	20.5%	29.8%	
Max tumour diameter – median	35mm	50mm	p<0.0001
Spread beyond muscularis – median	4mm	5mm	p=0.005
EMVI+	32.3%	45.0%	p<0.0001
pN0	59.4%	48.7%	p<0.0001
pN1	25.4%	25.1%	
pN2	15.2%	25.9%	
Apical node positive	3.8%	7.5%	p=0.013

Seymour, ASCO 2019 / Morton, ESMO 2019

FOxTROT: peri- vs postoperative chemotherapy

3 x FOLFOX → OP → 9 x FOLFOX vs. OP → 12 x FOLFOX

1. **Not more complications**
2. **Downsizing/downstaging**
3. **More R0 resections**

	periop	postop	
R1/R2/no resection	**4.8%**	**11.1%**	**p=0.001**

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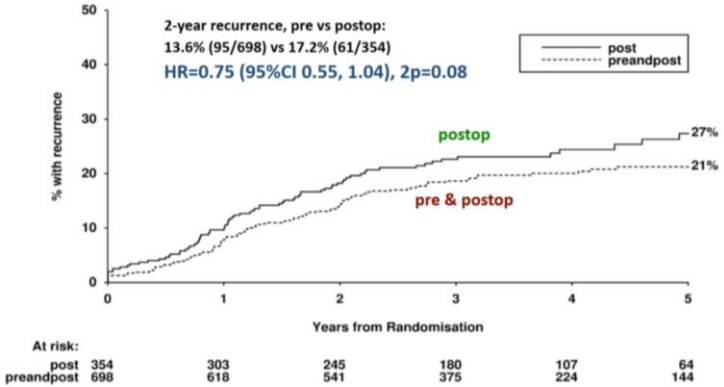
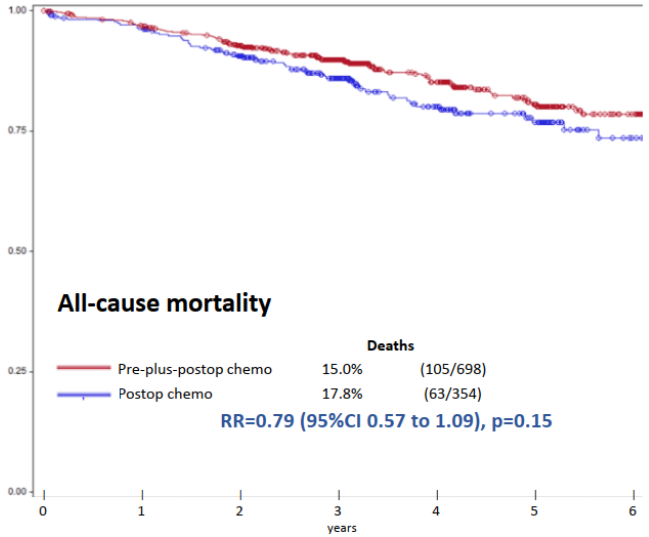
4. **Trend: less recurrences / better survival**





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Potential risk of overtreatment

Local pathology	neoadj. chemo n=682	Straight to surgery n=347	
pT0	4.1%	0%	p<0.0001
pT1-2	11.7%	5.8%	
pT3	63.7%	64.5%	
pT4	20.5%	29.8%	
Max tumour diameter – median	35mm	50mm	p<0.0001
Spread beyond muscularis – median	4mm	5mm	p=0.005
EMVI+	32.3%	45.0%	p<0.0001
pN0	59.4%	48.7%	p<0.0001
pN1	25.4%	25.1%	
pN2	15.2%	25.9%	
Apical node positive	3.8%	7.5%	p=0.013

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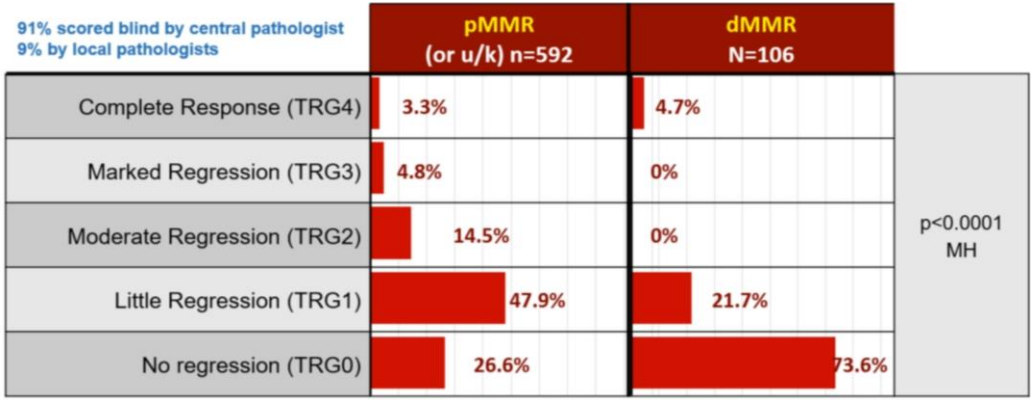
MSI-H patients might not benefit.



Seymour, ASCO 2019 / Morton, ESMO 2019

Standard: oxaliplatin / fluoropyrimidine.

- Delta in overall survival 15 ... 20%
- i.v. 5-FU can be replaced by capecitabine

Much more than 90% of the treatment effect in the first 3 months.

- low risk (no T4, no N2): 3 months CapOx
- high risk (T4 or N2): guidelines differ (6 months FOLFOX, 3 months CapOx)
- ESMO recommendation: 6 months treatment for high risk

Elderly patients should be offered adjuvant therapy.

- For patients with > 75 years limited evidence.
- Limited/no benefit from oxaliplatin > 70 years → rather 6 months fluoropyrimidine.

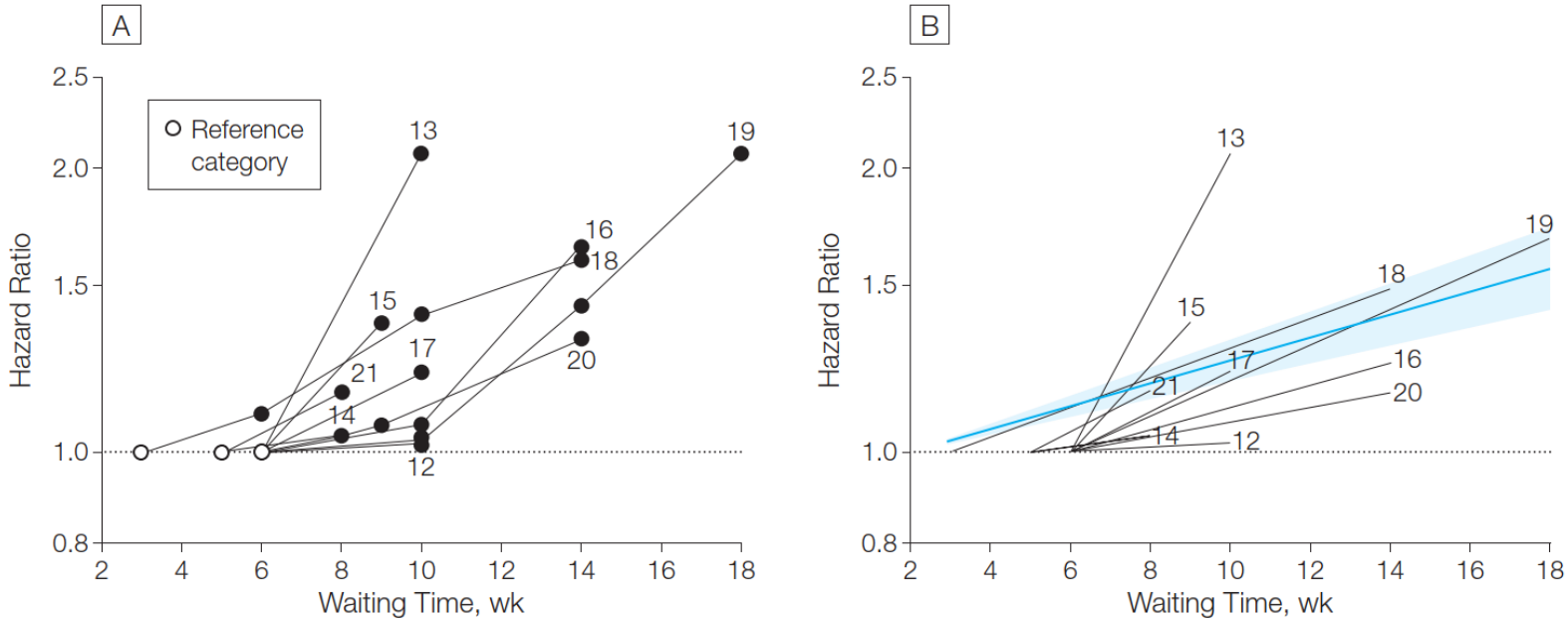
Do not use MSI / dMMR for adjuvant chemotherapy decision in stage III.

- But change of the standard is likely.

Neoadjuvant treatment may improve R0 rates and survival.

- To be confirmed
- Currently option for locally advanced tumours

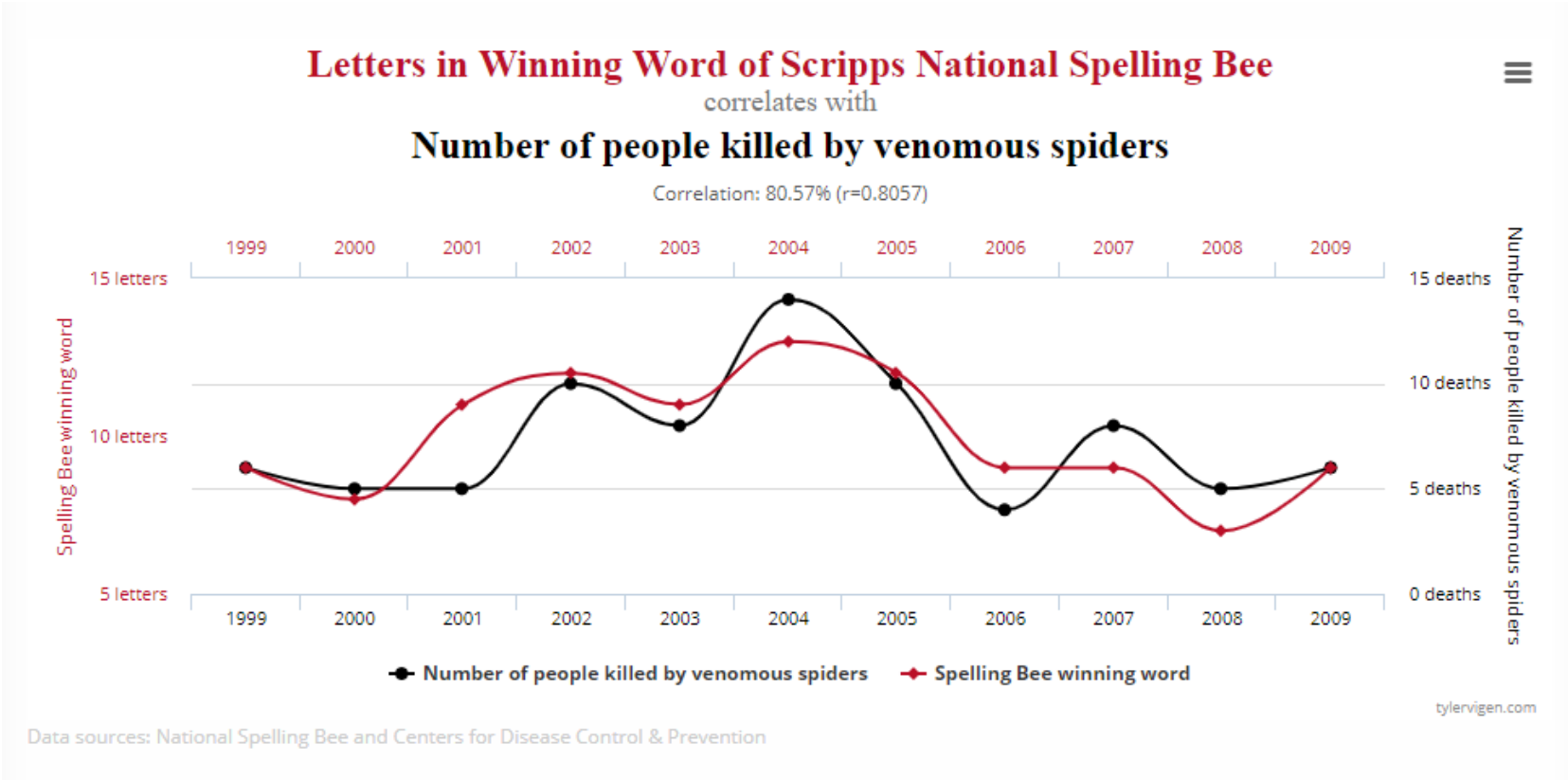
Later treatment start associated with worse prognosis



(Try to) start early.

Biagi JAMA 2011

Be careful: correlation is not always causality



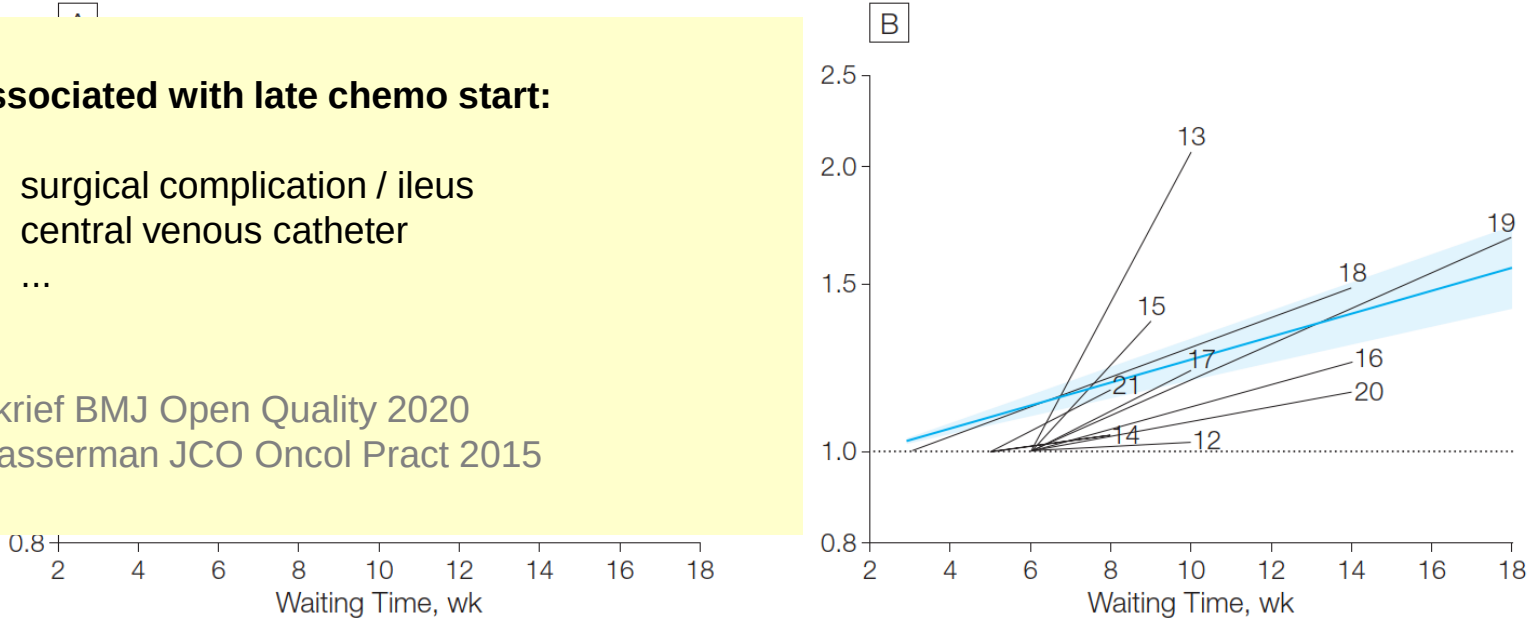
https://www.tylervigen.com/spurious-correlations

Later treatment start associated with worse prognosis

Associated with late chemo start:

- surgical complication / ileus
- central venous catheter
- ...

Elkrief BMJ Open Quality 2020
Wasserman JCO Oncol Pract 2015



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Start as soon as possible.

- But not earlier.