

Conceptual Approaches to Metastatic Disease:

When to “stop-and-go”?

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first
treatment for
inoperable
colorectal
metastases

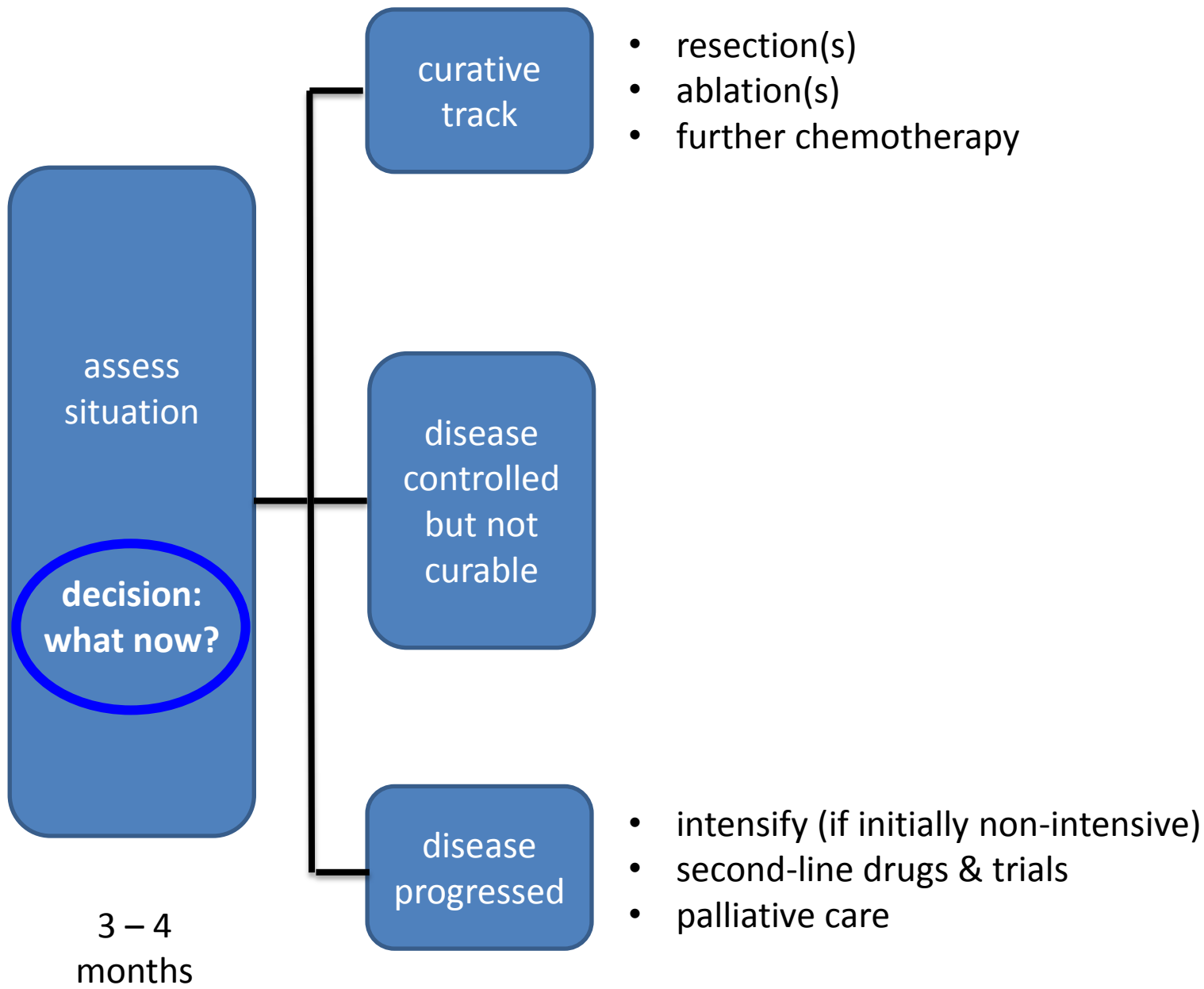
decision:
intensity



assess
situation

decision:
what now?

3 – 4
months



curative
track

disease
controlled
but not
curable

disease
progressed

continuous

fail

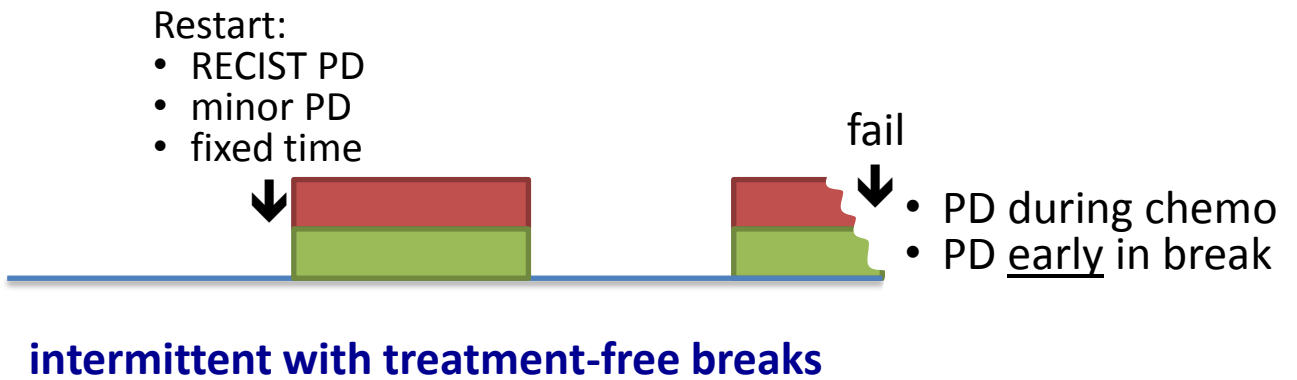
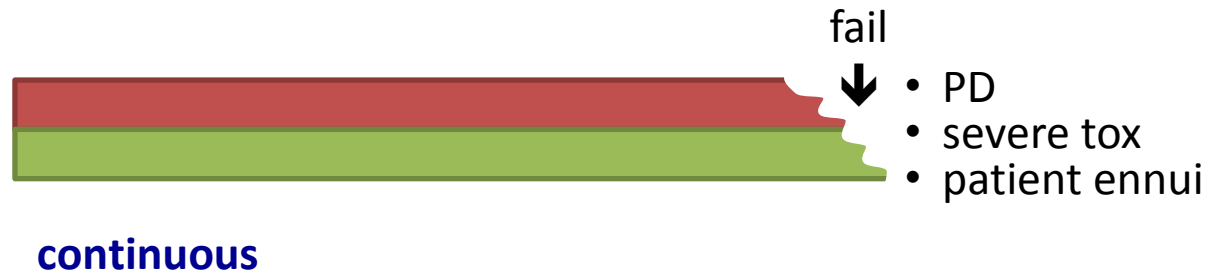


- PD
- severe tox
- patient ennui

curative
track

disease
controlled
but not
curable

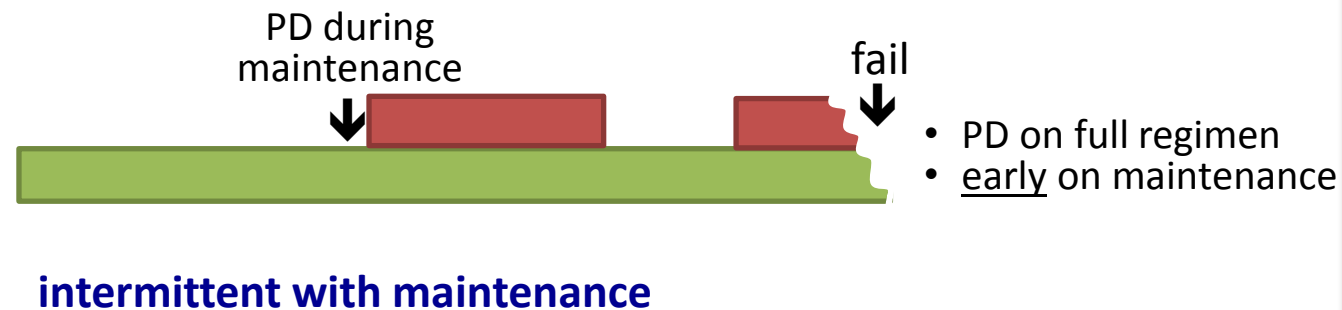
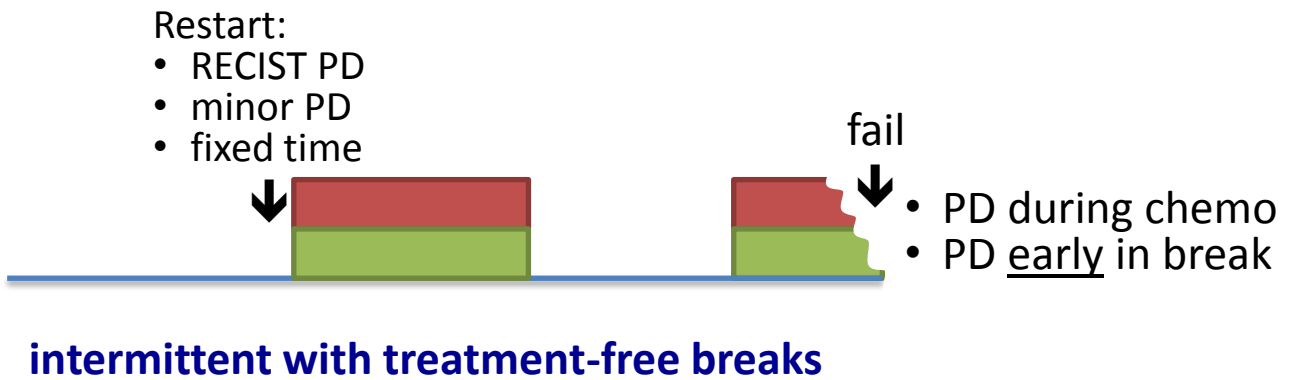
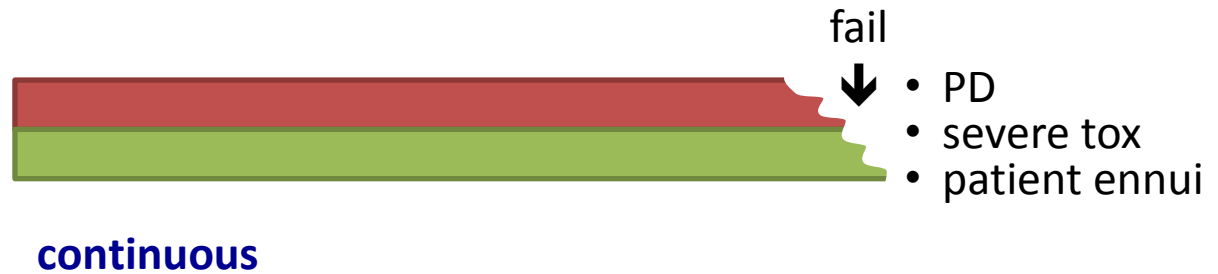
disease
progressed



curative
track

disease
controlled
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curable

disease
progressed





survival
time

time free of
cancer
symptoms

time free of
treatment
side-effects

time to live
life as
normal

wellbeing
and lethargy

- what are my priorities?
- let's discuss them
- informed choices
- trade-offs

impact on
carers

time free of
clinic visits &
treatments

financial
pressure

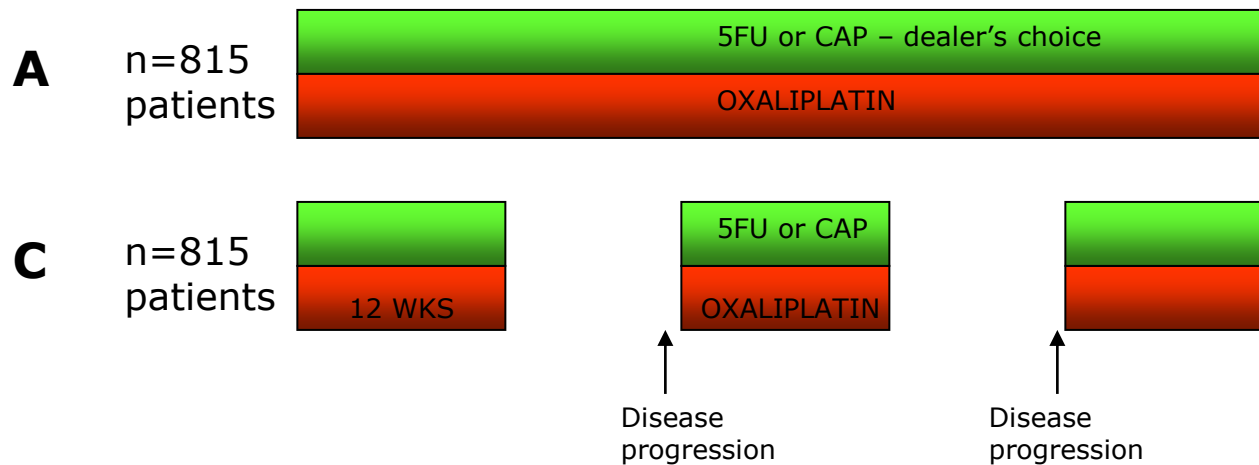
CT scan
results

Pressures and conflicts?

- are there external pressure to treat less?
- are there external pressures to treat more?
- are there pressures to satisfy regulators and research needs ahead of patients?
 - PFS is meaningless on intermittent therapy

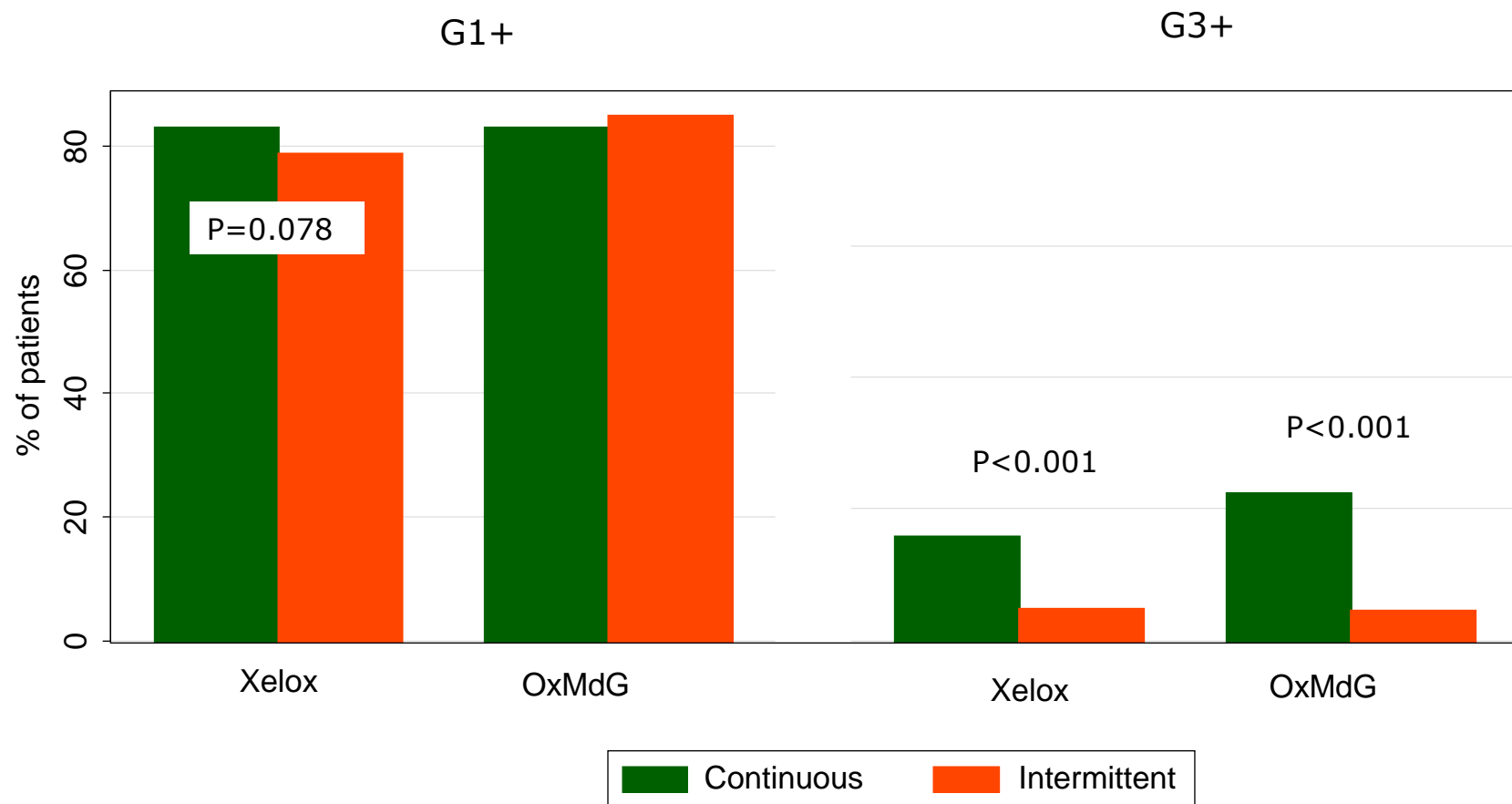
the data...

Intermittent vs continuous oxaliplatin-based combination chemotherapy

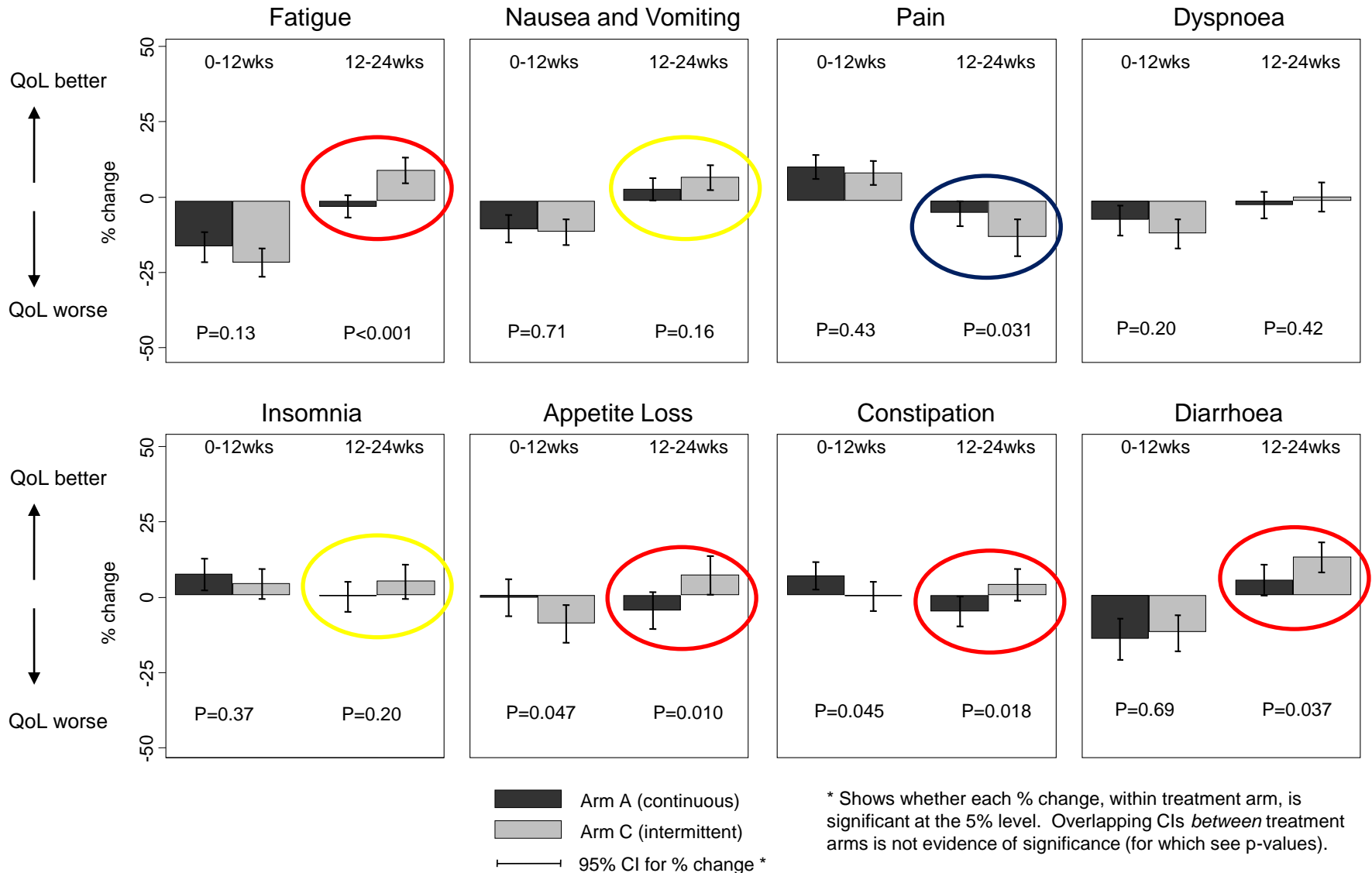


		Arm A continuous	Arm C intermittent
Total randomised		815	815
Choice of chemo at baseline	XELOX	66%	65%
	OxMdG	34%	35%
Sex	Male	64%	64%
	Female	36%	36%
Age	Median age	63	63
	75+	9%	8%
WHO PS	0	46%	46%
	1	46%	46%
	2	8%	8%
Prior adjuvant chemotherapy	No	75%	75%
	Yes	25%	25%

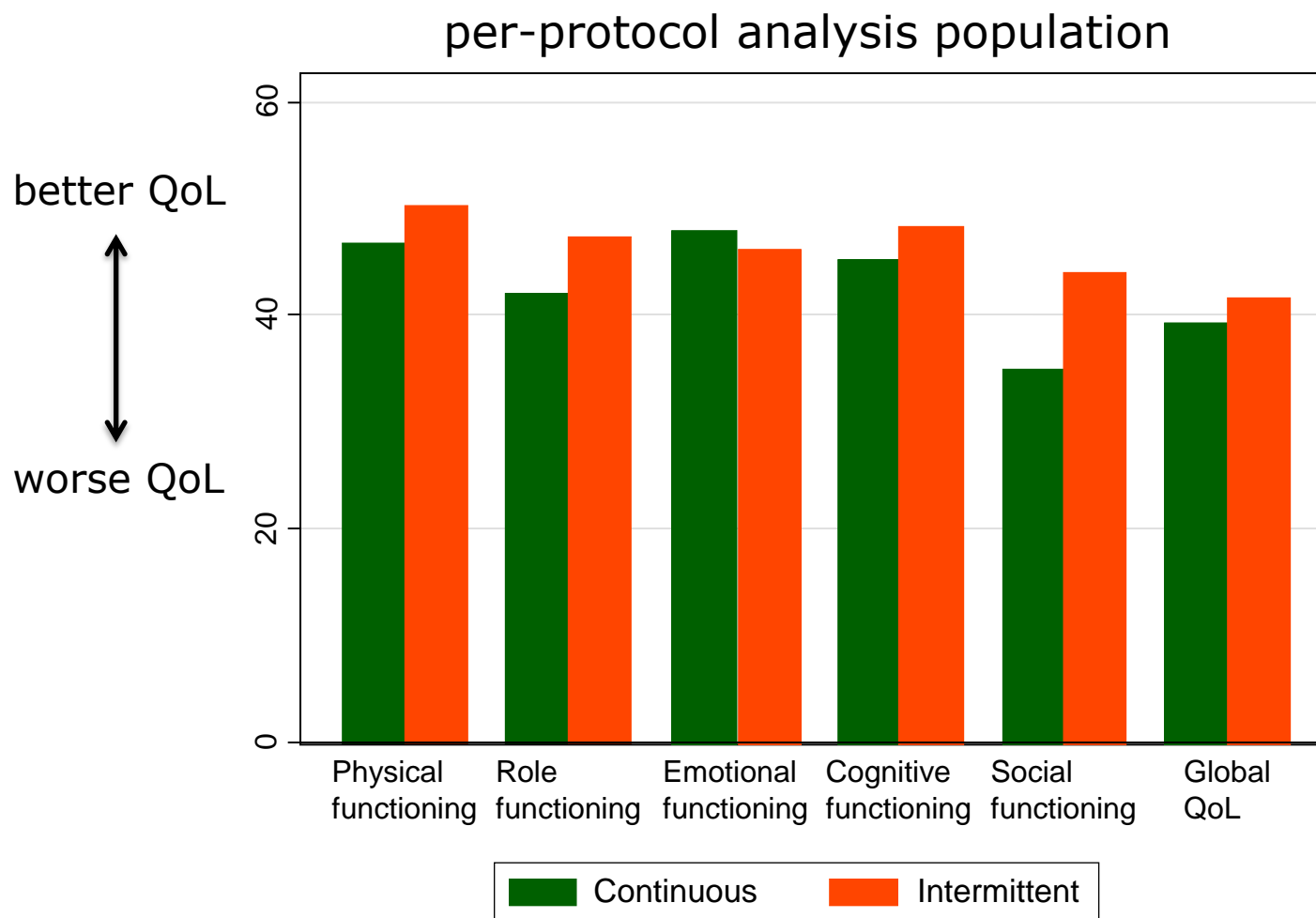
Worst grade peripheral neuropathy over entire treatment period (ITT)



QoL comparison



Quality of Life analysis: Functional scales at 24 weeks



*I'm off for
three months –
great!*

*I stop being a
cancer patient for
a few months*

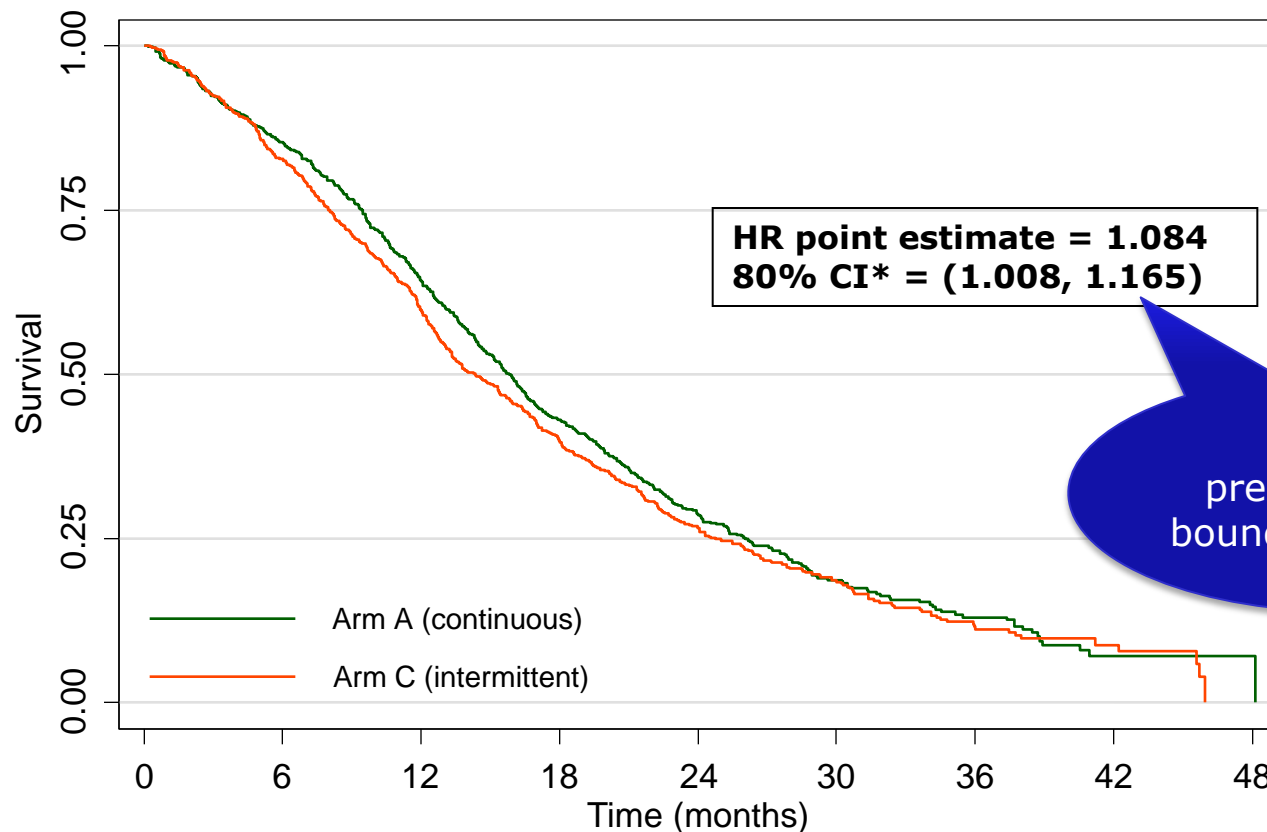
*So it's chemo and
more chemo until I
die? – no thanks!*

*I'm worried about
it spreading while
I'm off treatment*

*I don't think I could
have carried on
month after month*

*I was looking
forward to a break
but felt better on
chemo*

ITT analysis of Overall Survival



Number at risk

Arm A	815	688	513	297	151	73	32	4	1
Arm C	815	668	477	281	148	76	29	9	0

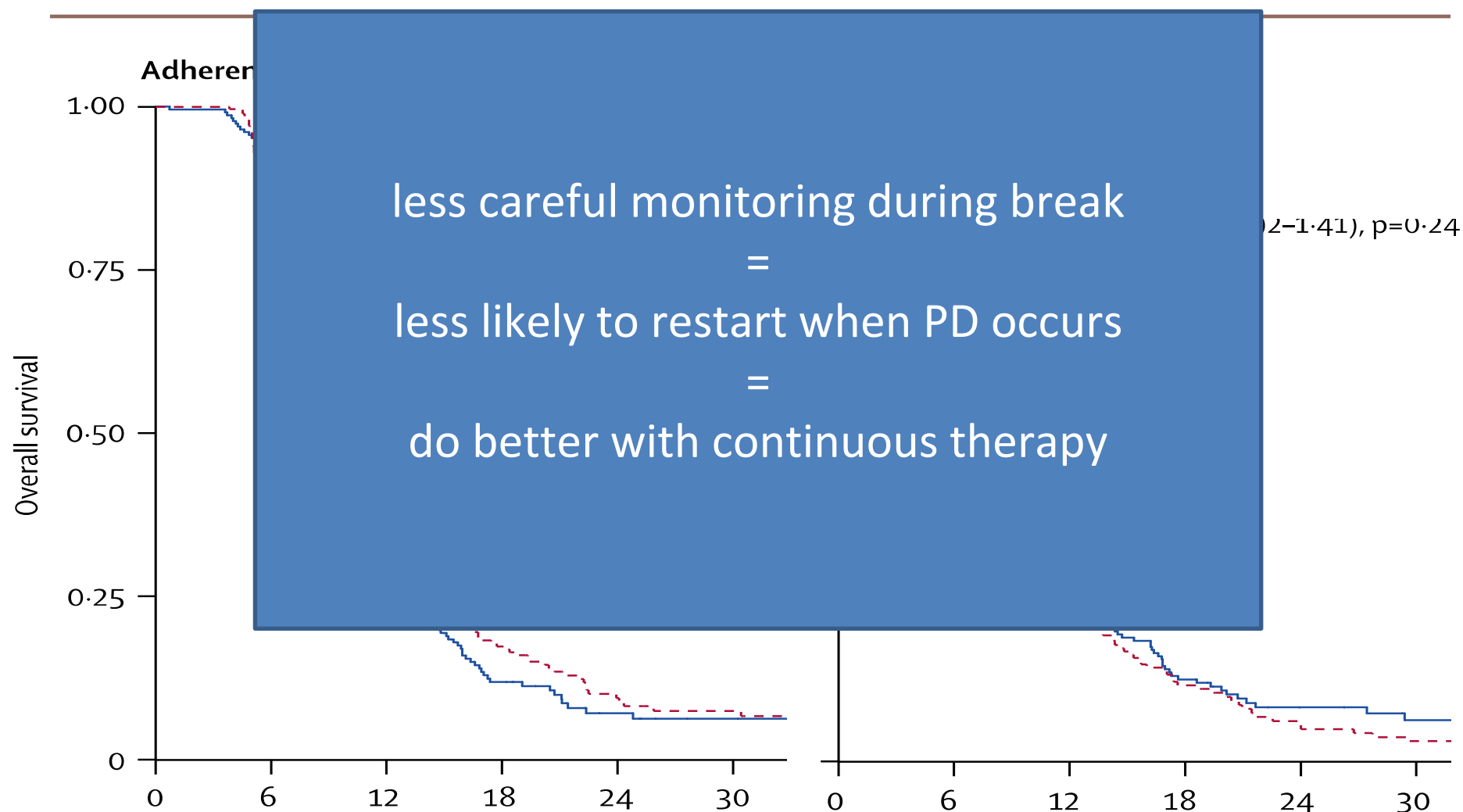
Chemotherapy-free intervals (intermittent arm)

N randomized		815
N (%) started CFI		511 (63%)
...of which N (%) restarted after first CFI		325 (64%)
Length of first CFI (weeks)	Median	16 weeks
	IQR	(14, 27)

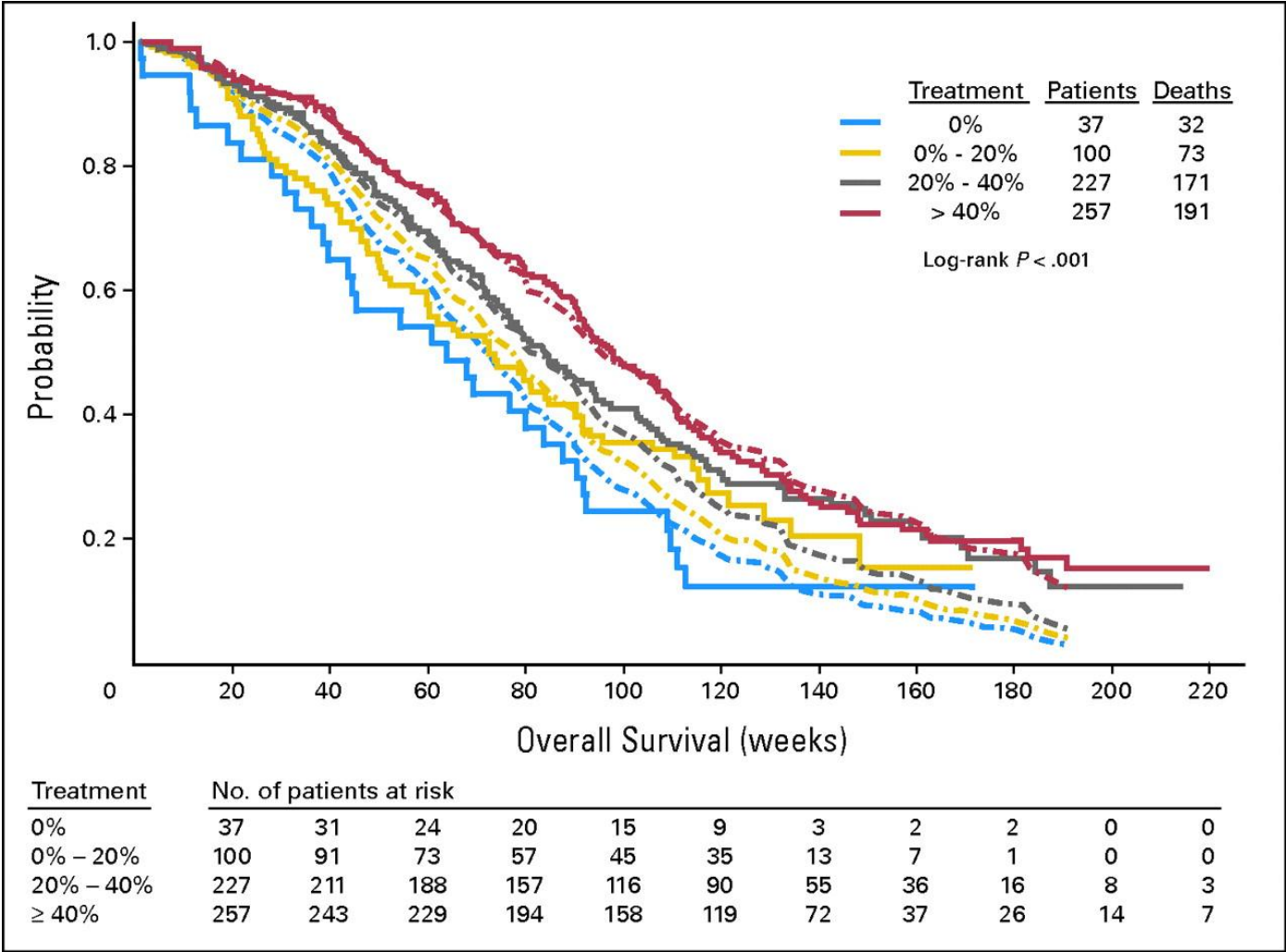
Wide variability in rate of restarting after treatment break

Centre code	n started break	n restarted chemo	% restarted
48	19	14	74%
17	18	10	56%
2	17	9	53%
54	16	10	63%
1	15	8	53%
46	15	5	33%
14	14	12	86%
16	14	12	86%
20	13	12	92%
26	11	6	55%
62	11	8	73%
68	11	8	73%
15	10	4	40%
59	9	3	33%
93	9	3	33%

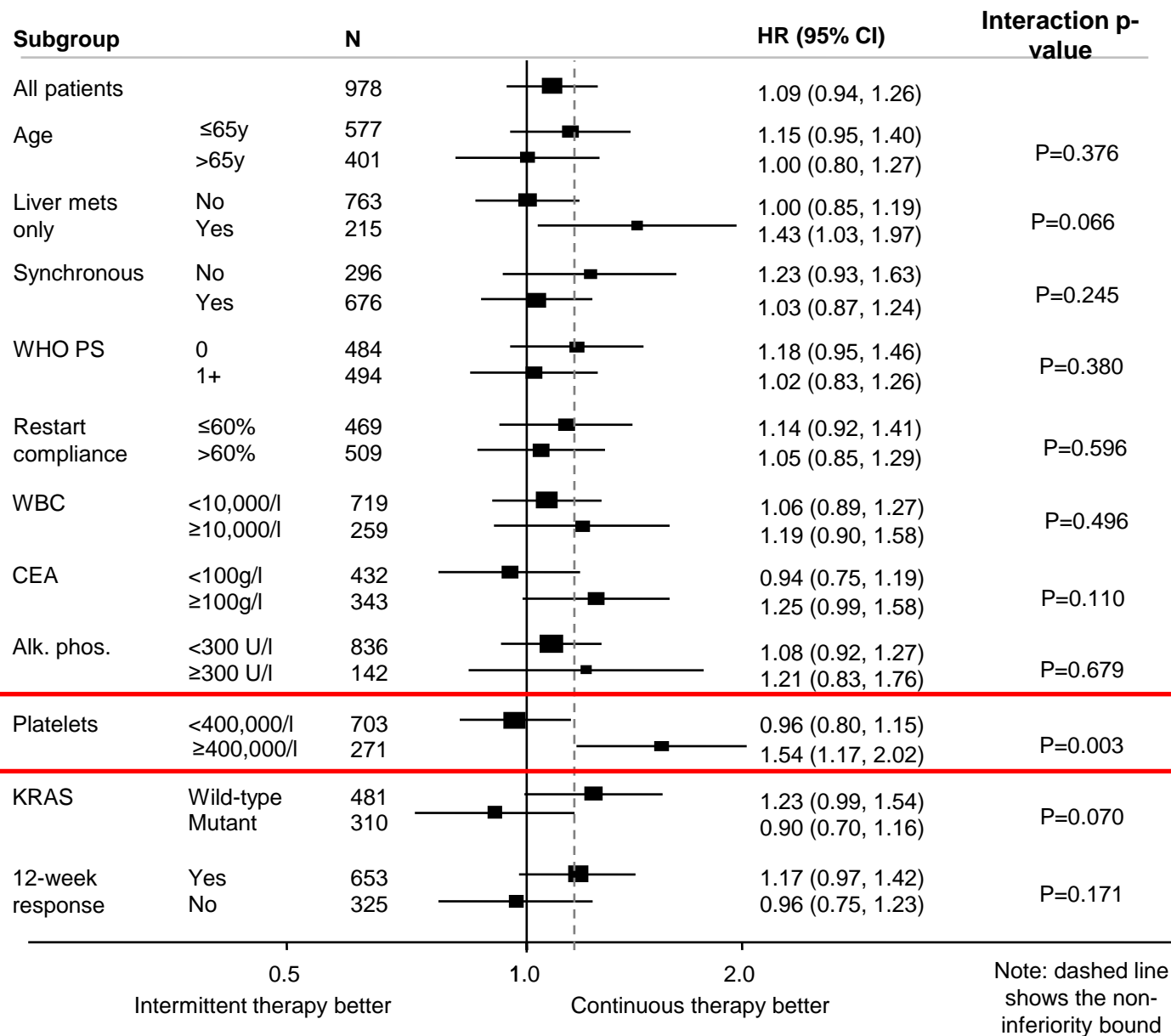
Impact of treatment breaks in non-adherent vs adherent centres



Overall survival curves by percentage of patients with oxaliplatin reintroduction – OPTIMOX-1 study

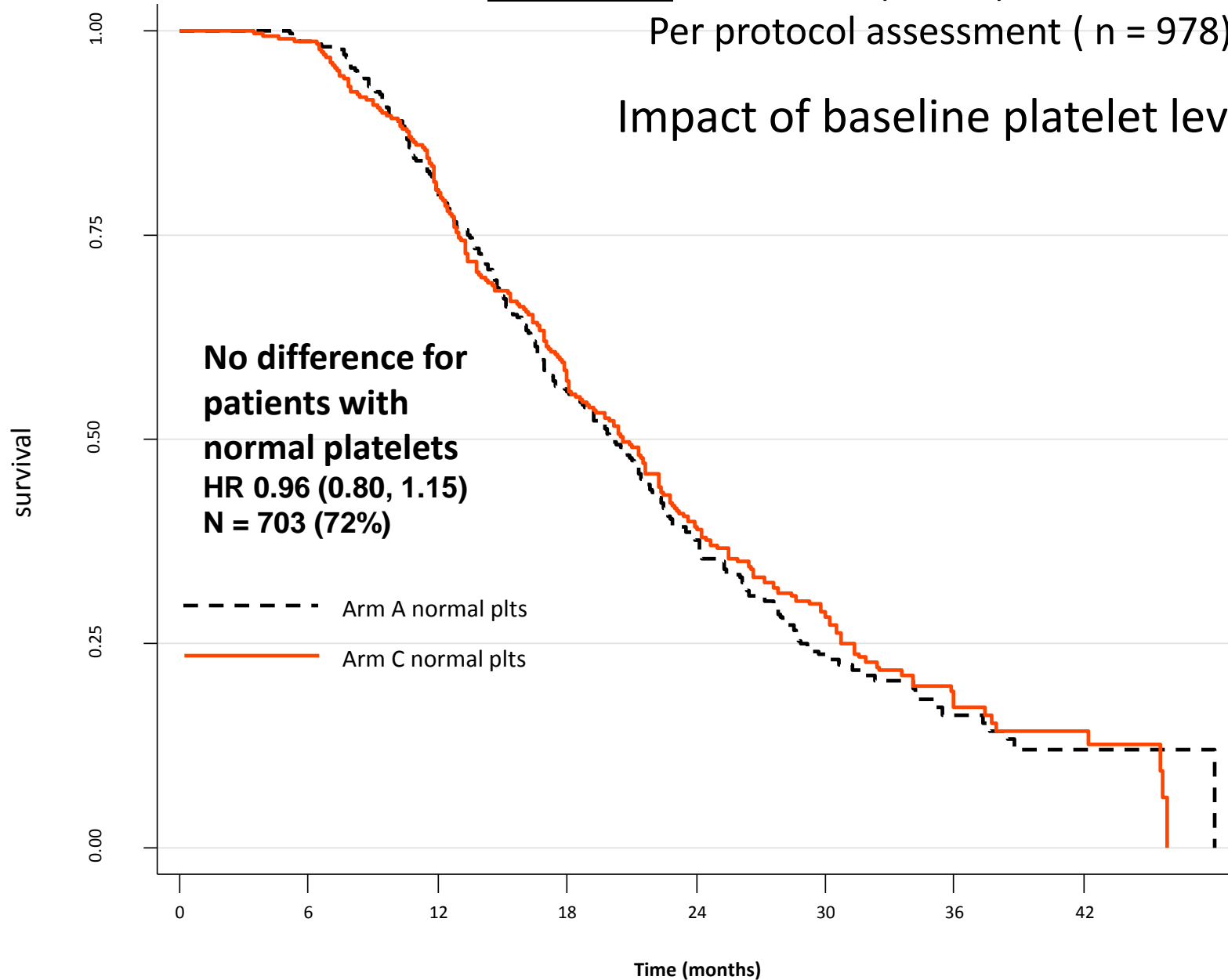


de Gramont, A. et al. J Clin Oncol; 25:3224-3229 2007

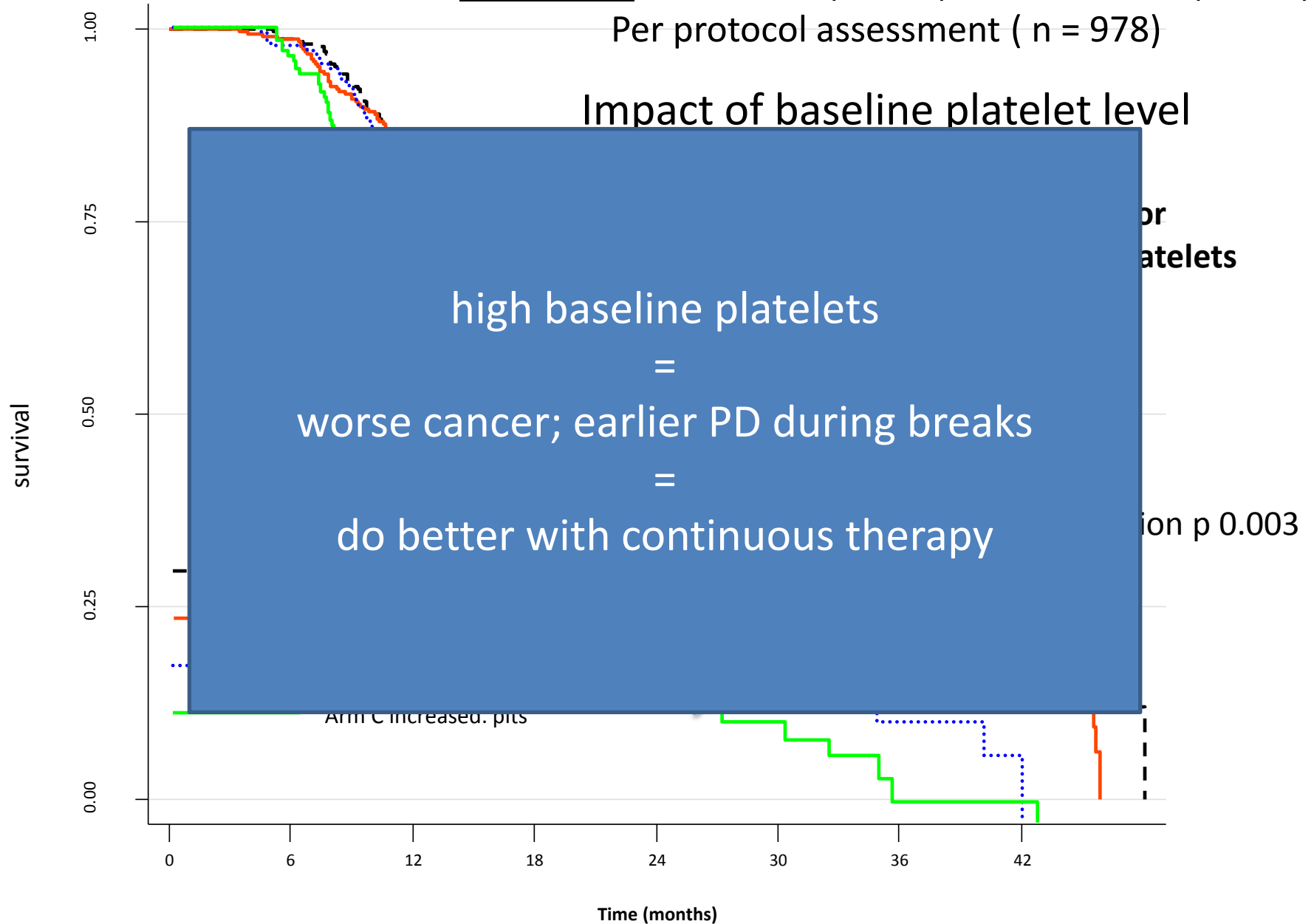


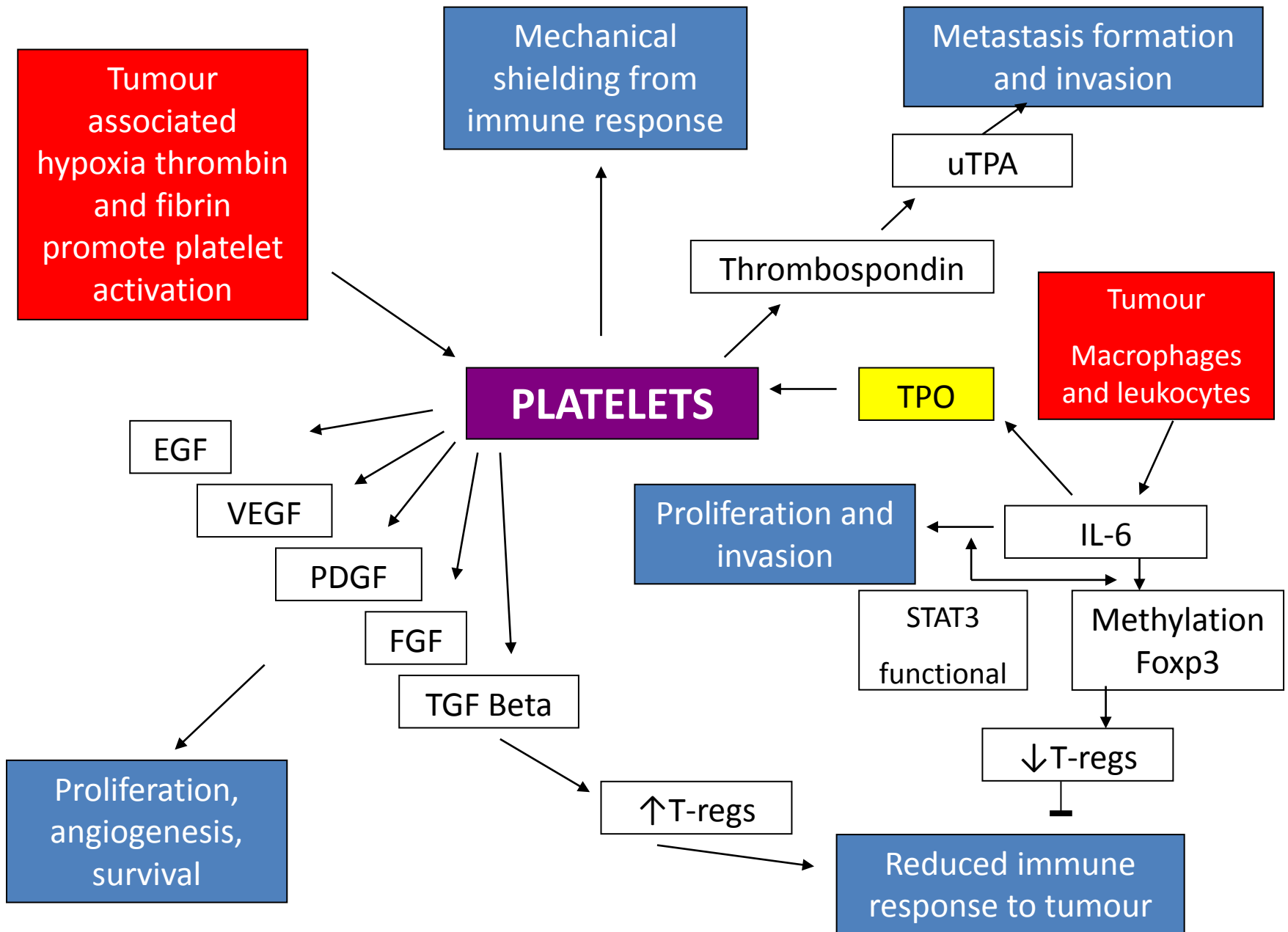
COIN trial: Continuous (Arm A) v Intermittent (Arm C)
Per protocol assessment (n = 978)

Impact of baseline platelet level



COIN trial: Continuous (Arm A) v Intermittent (Arm C)
Per protocol assessment (n = 978)



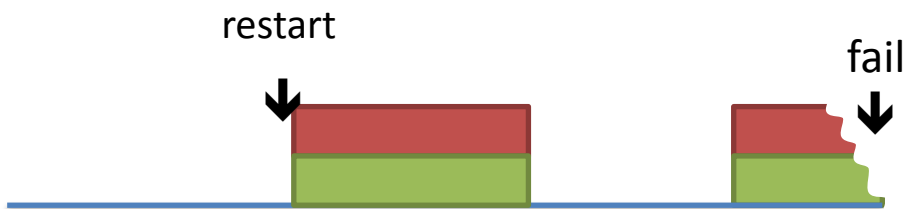


curative
track



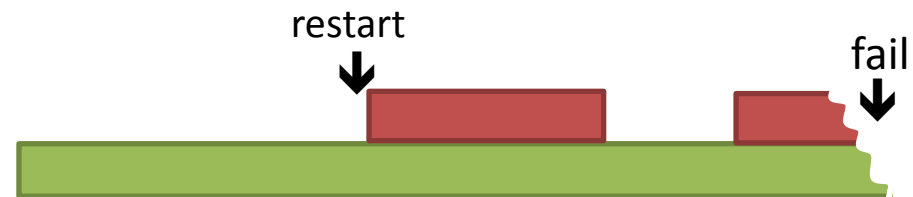
continuous

disease
controlled
but not
curable



intermittent with treatment-free breaks

disease
progressed

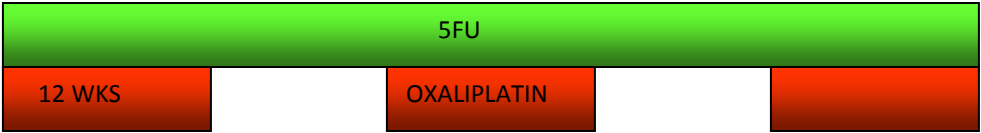


intermittent with maintenance

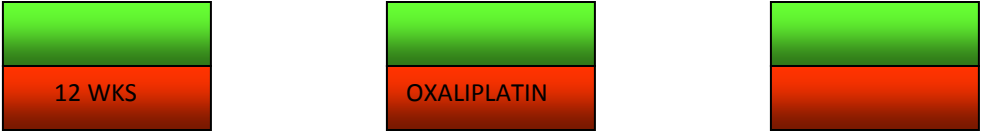
OPTIMOX-2

202 pts

A

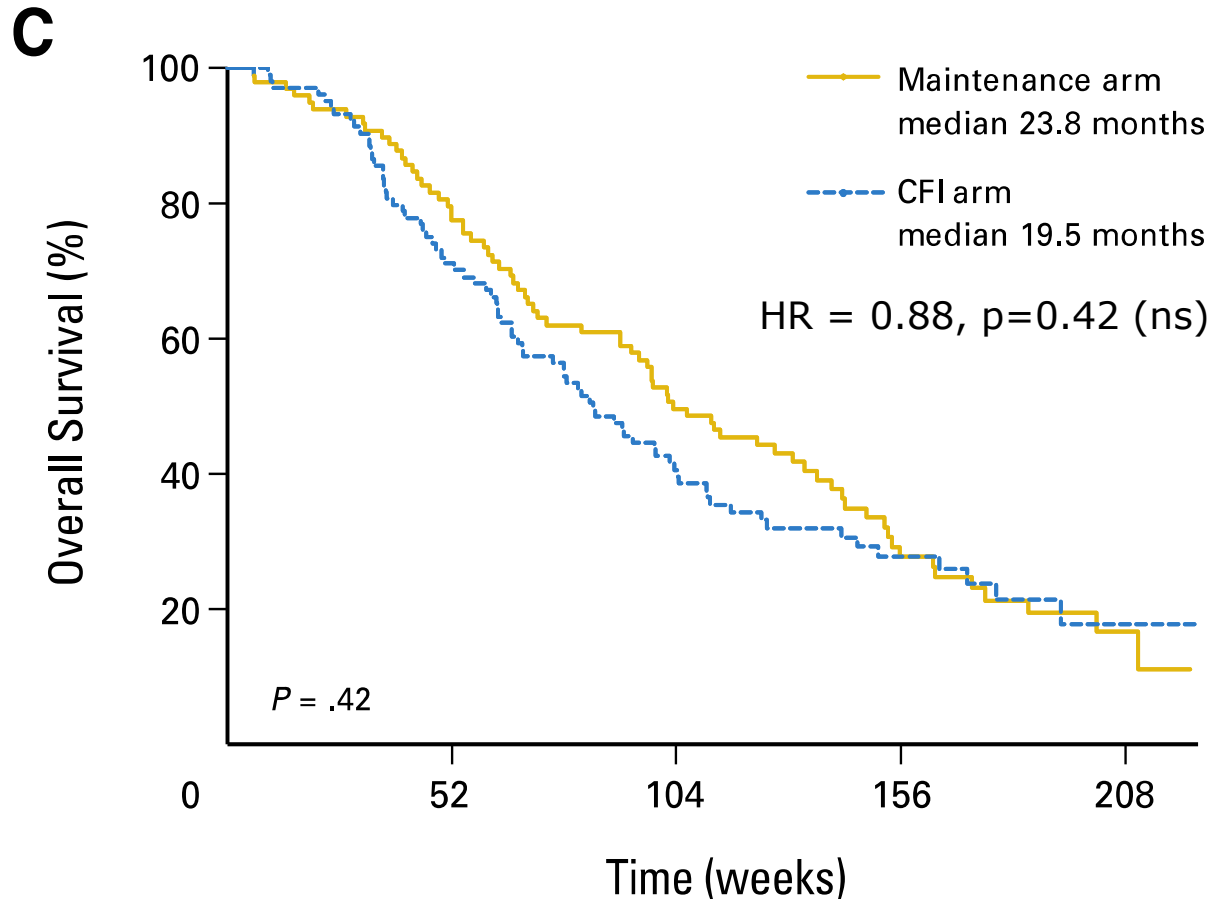


B



Results from OPTIMOX-2

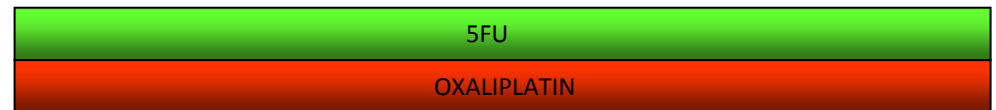
Chibaudel et al., JCO 27:5727, 2009



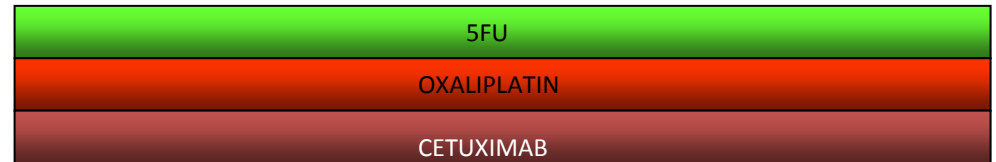
NB 56/202 (28%) of the patients in this analysis had come off study for surgery, death or other reasons before treatments separated

NORDIC VII

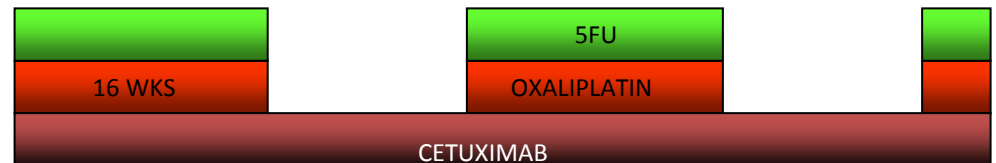
A



B



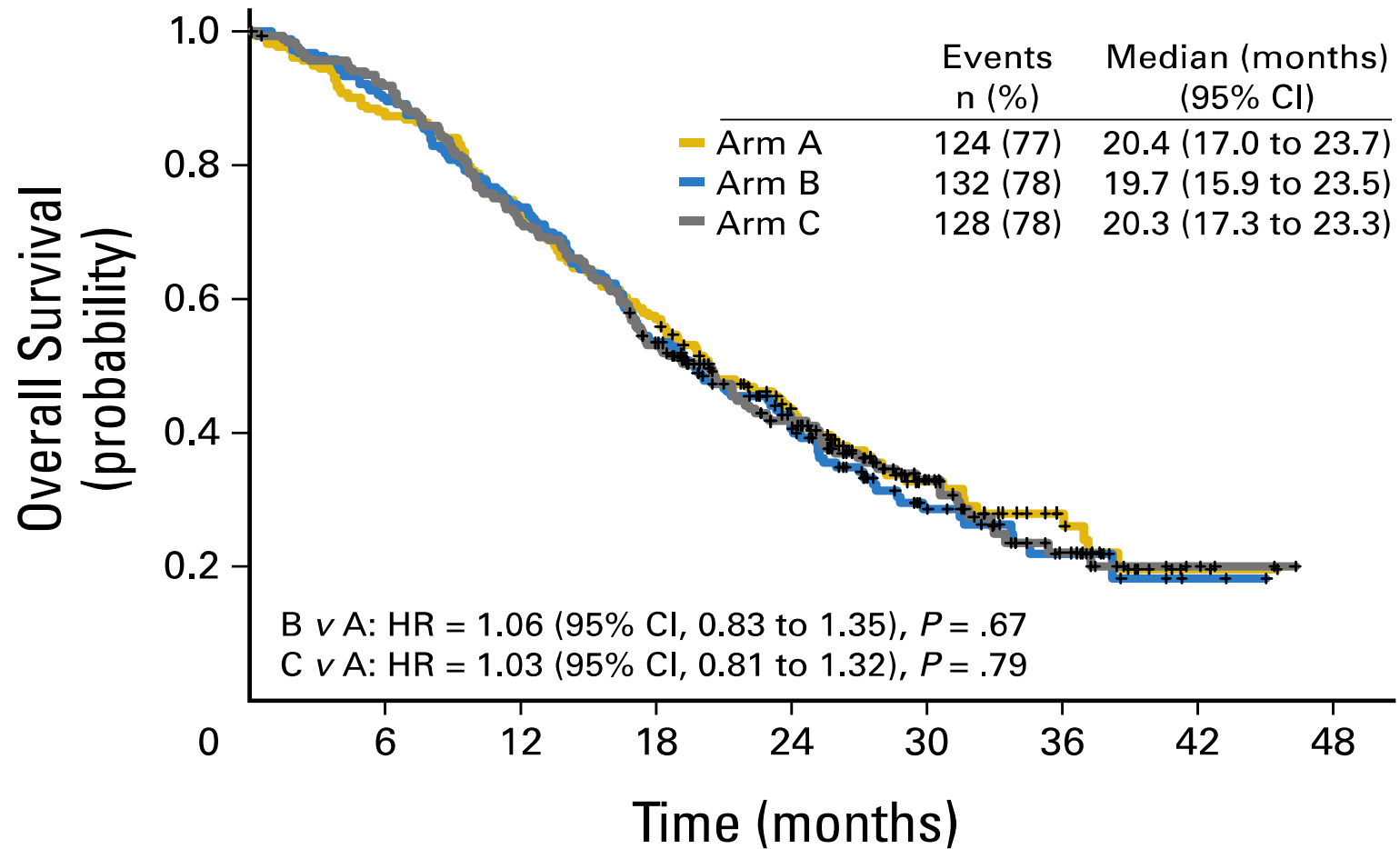
C



Nordic VII

Tveit et al, J Clin Oncol on-line, 2012

Overall Survival, ITT population (includes KRAS-wt, -mut and -unknown patients)



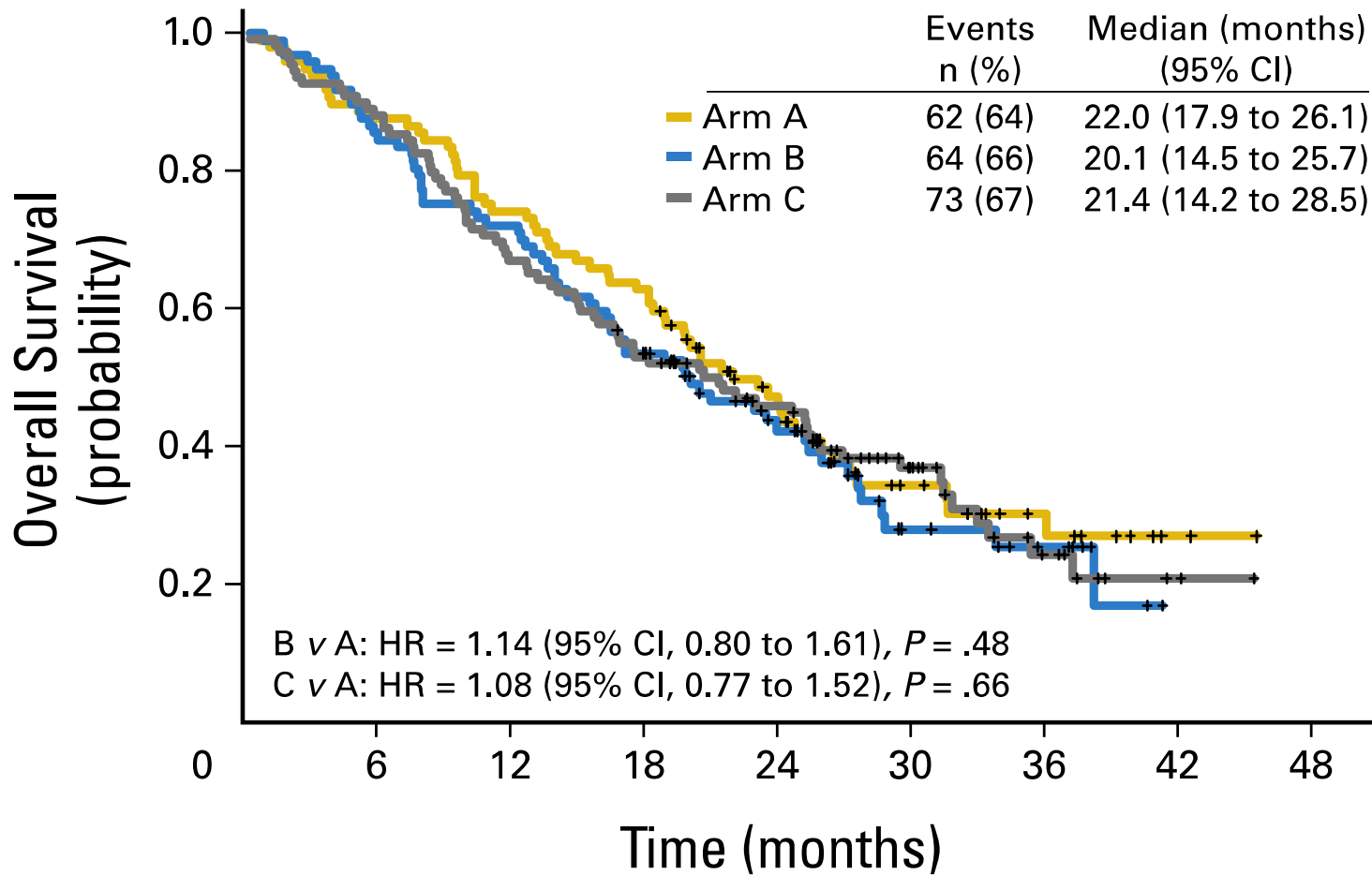
No. at risk

Arm A	185	161	135	105	68	30	15	2	0
Arm B	194	175	143	101	59	27	12	2	0
Arm C	187	171	133	98	64	34	14	4	0

Nordic VII

Tveit et al, J Clin Oncol on-line, 2012

Overall Survival, KRAS-wt patients)

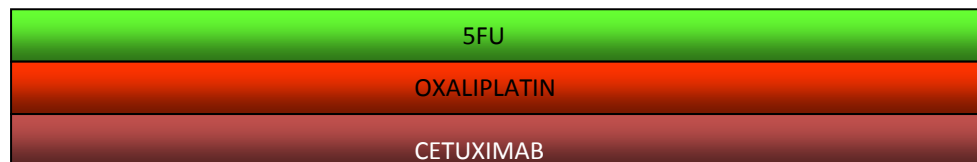


No. at risk

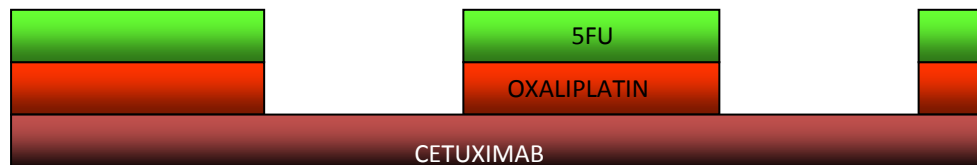
Arm A	97	85	72	61	38	18	9	2	0
Arm B	97	83	70	51	29	12	7	0	0
Arm C	109	96	73	57	44	23	9	2	0

NORDIC VII

B

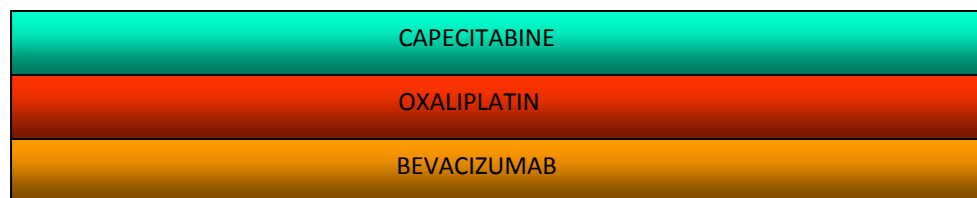


C

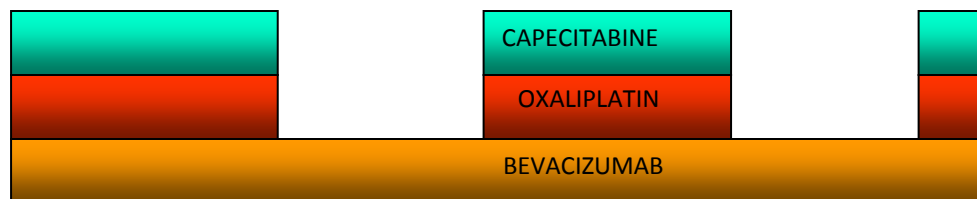


16 WKS

A



B



18 WKS

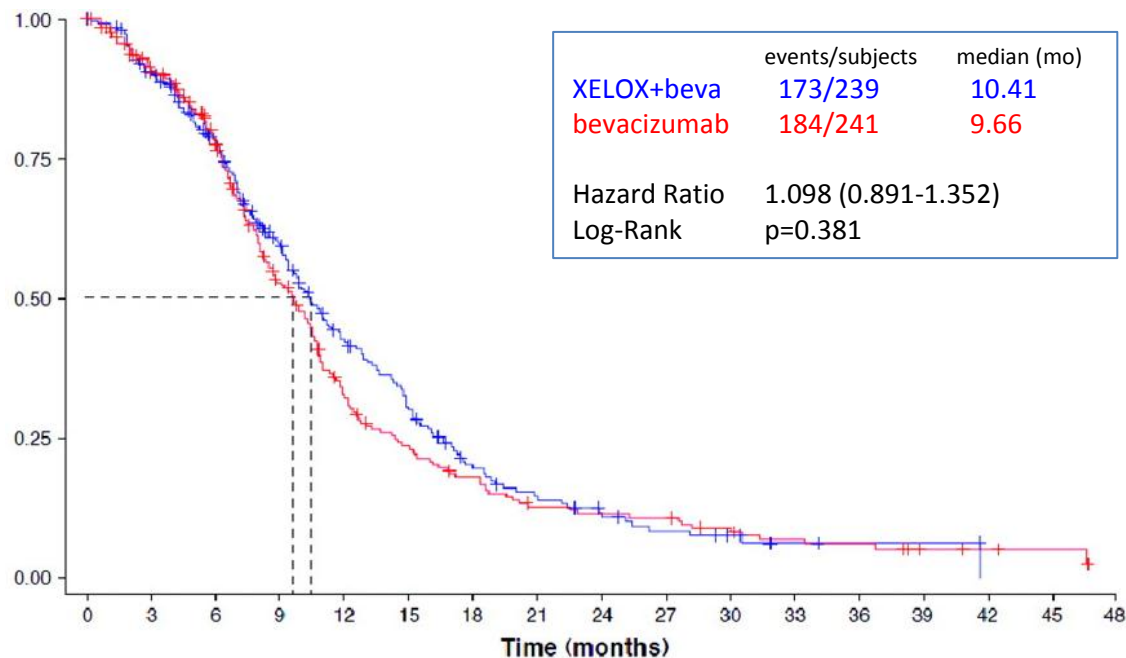
TTD

MACRO

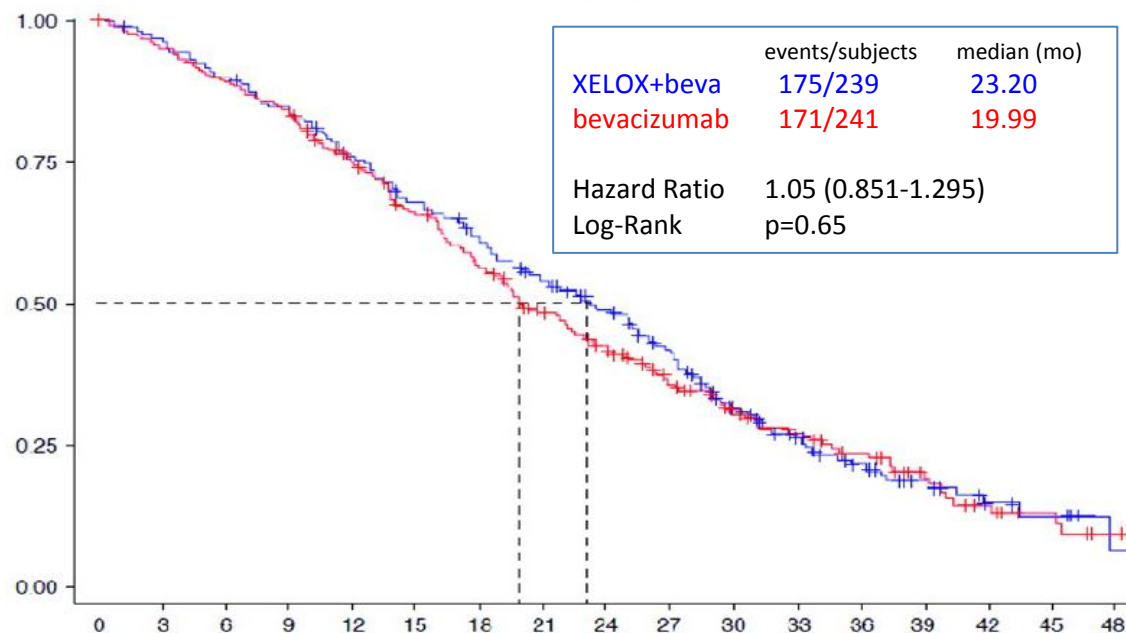
470 pts

TTD MACRO

Progression-Free
Survival



Overall
Survival



Díaz-Rubio E et al.

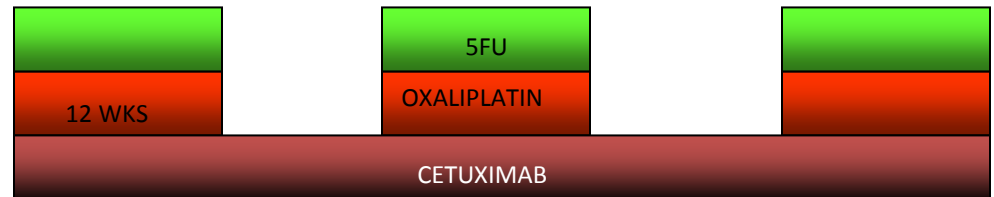
The Oncologist
2012;17:15-25

COIN-B

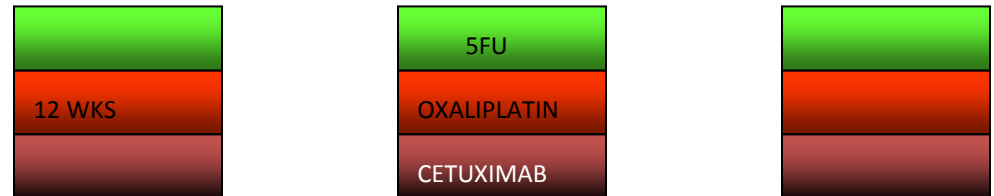
169 pts

KRAS-wt

D

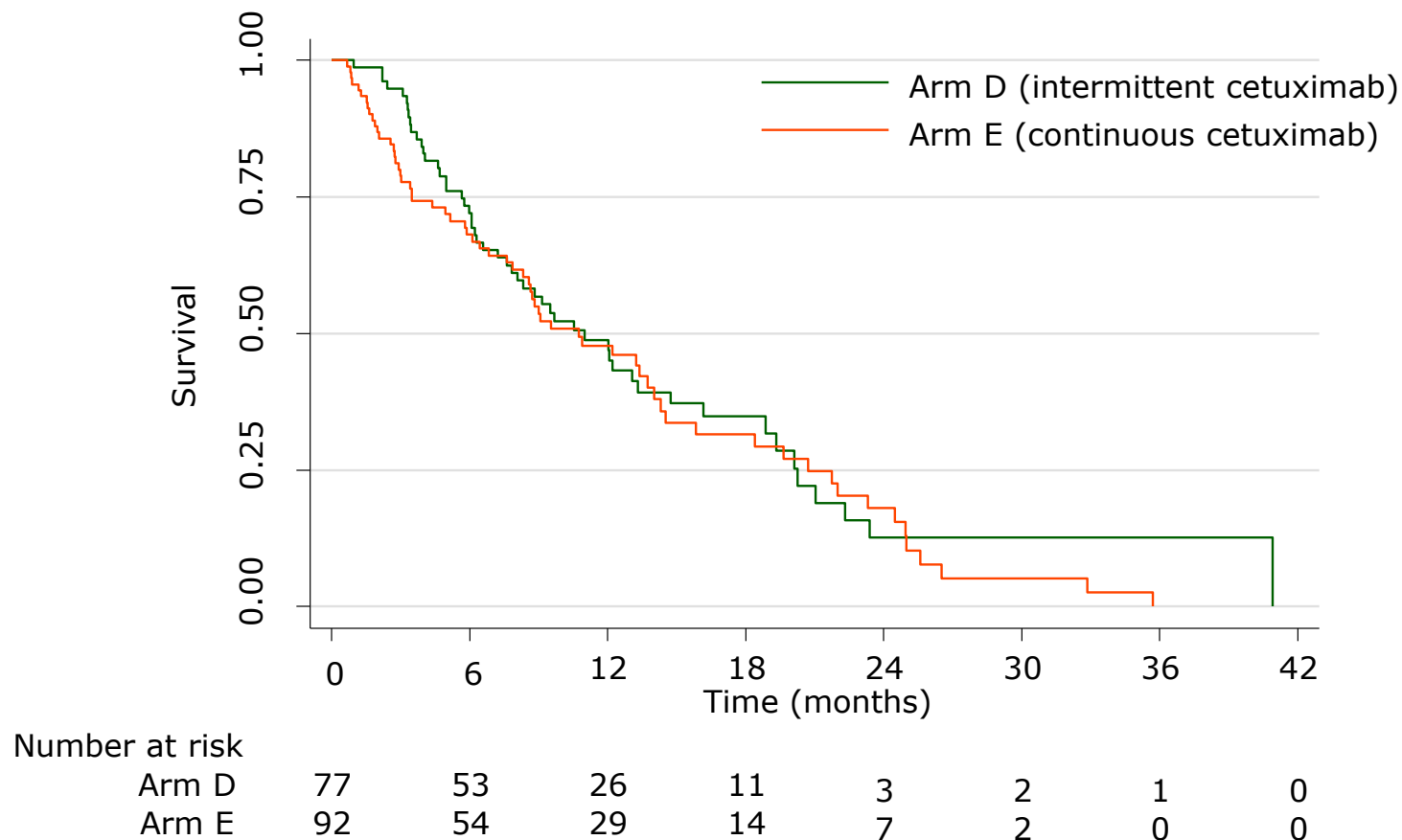


E



FFS from randomisation

(All randomised KRAS^{wt} patients ITT)

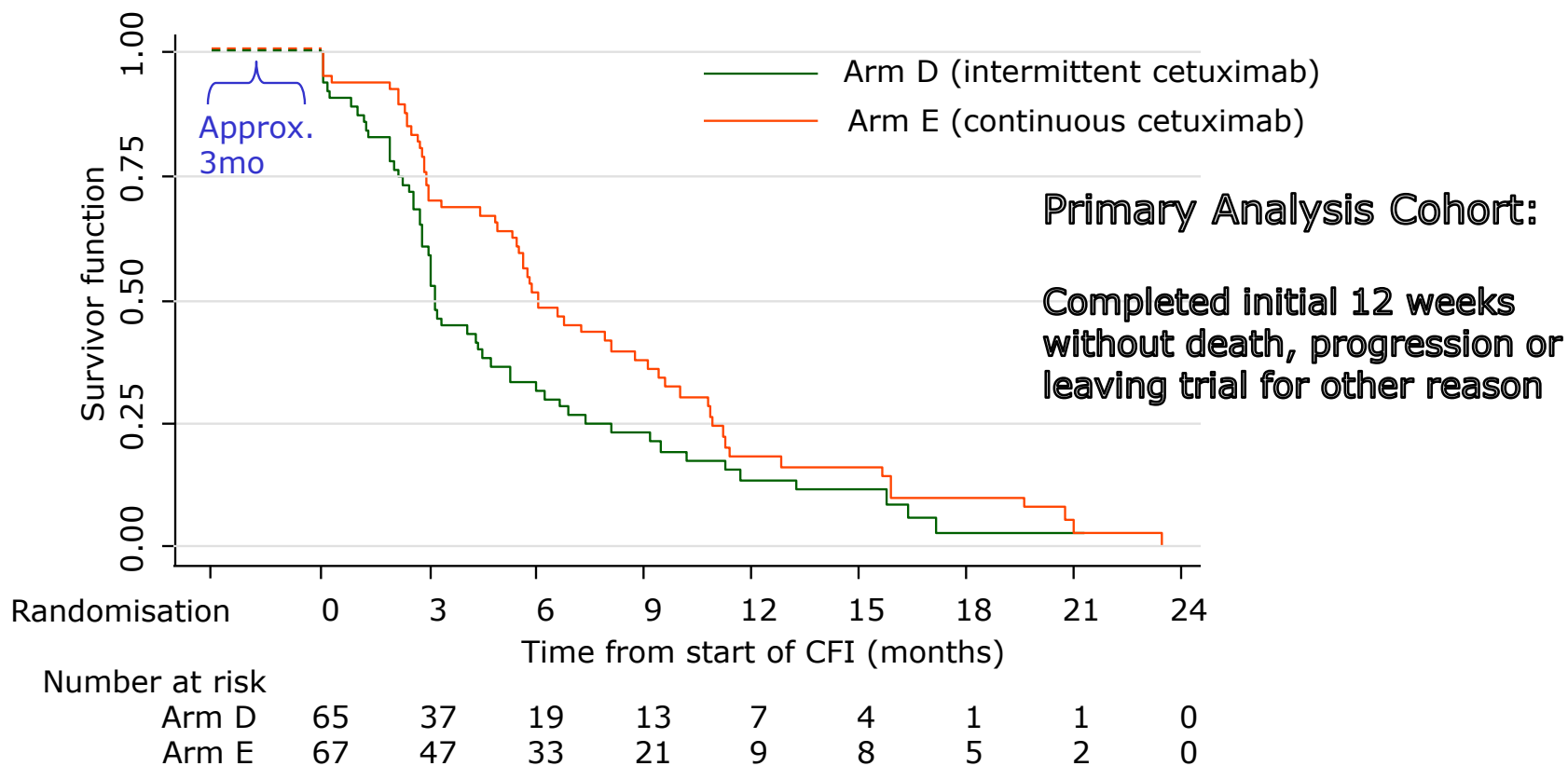


Median FFS (months):

Arm D: 11.0 (IQR 5.7 to 20.3)

Arm E: 10.7 (IQR 3.5 to 20.7)

PFS from start of first Chemotherapy-Free Interval (KRAS^{wt} patients still on trial after 12 weeks)



Median PFS (months):

Arm D: 3.1 (IQR 2.1 to 8.1)

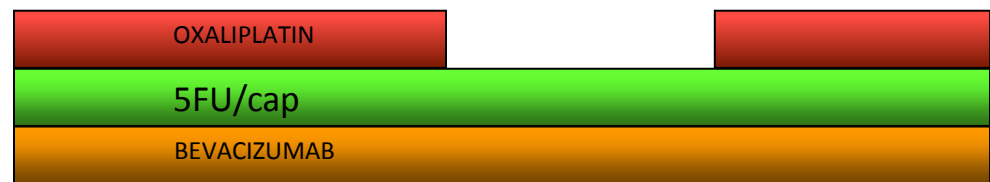
Arm E: 6.0 (IQR 2.9 to 10.9)

Hazard ratio (Arm E vs Arm D): 0.67 (95% CI 0.46 to 0.98); p=0.039

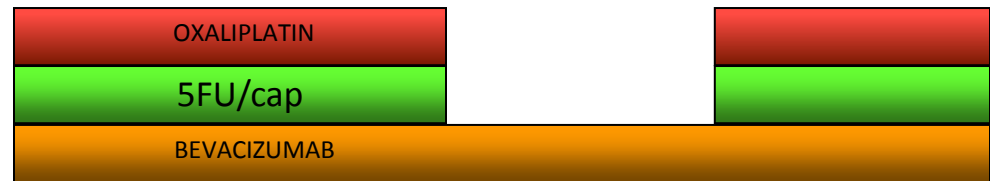
AIO-KRK 0207

456 pts

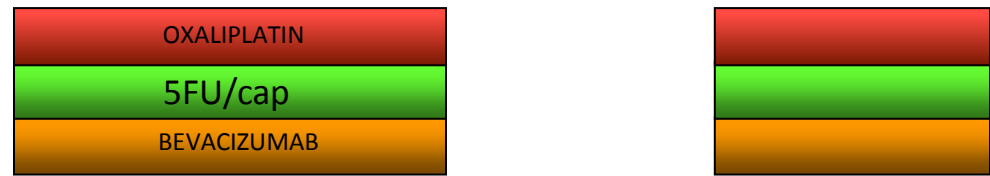
A



B



C

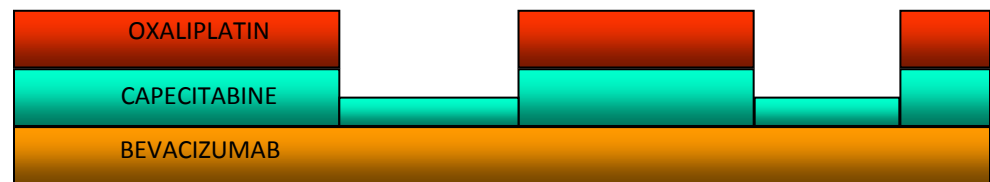


24 WKS

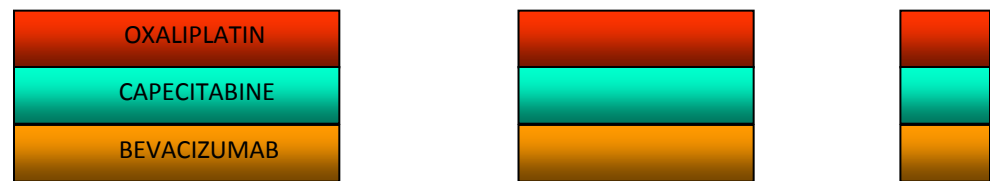
CAIRO-3

635pts

A



B



18 WKS

...so where does this leave us?

- ‘stop & go’ strategy not significantly inferior in any individual trial
 - non-inferiority not proven – small OS loss not excluded
 - careful adherence to protocol may avoid this
 - baseline \uparrow platelets may identify who needs continuous (needs validation)
 - “Jury still out” on lower-intensity maintenance
- clear advantages in PROMs etc
 - improved QL
 - less toxicity
 - less resource usage
 - valued by most (though not all) patients

treatment break = research opportunity



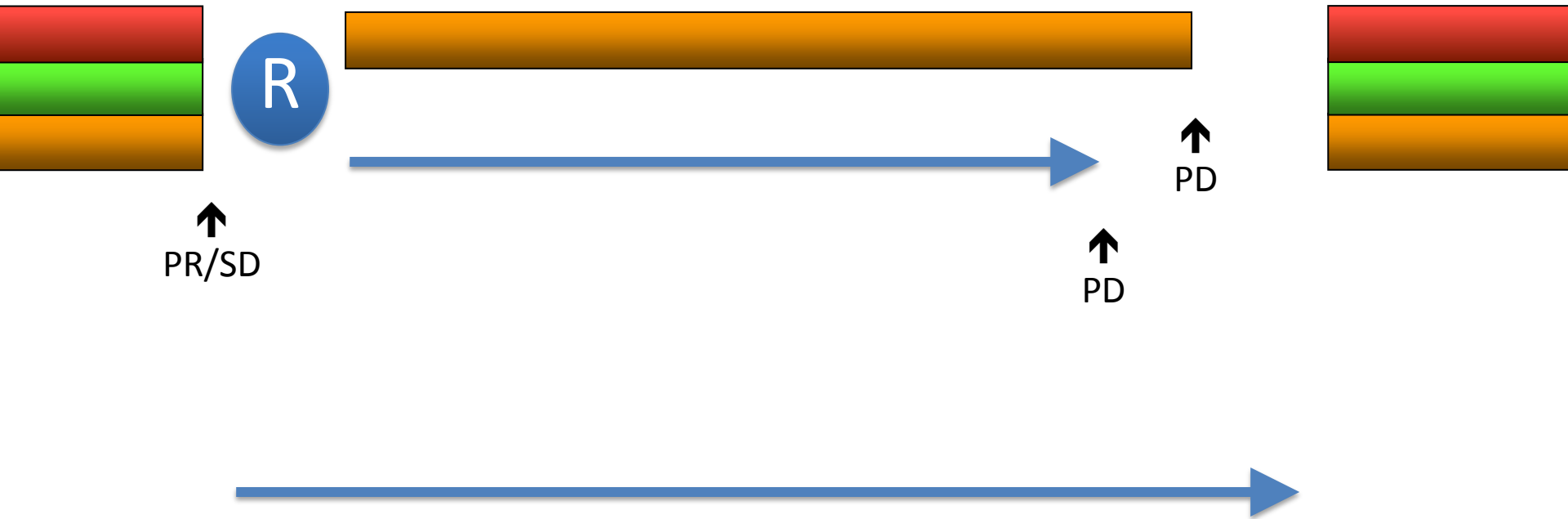
↑
PR/SD



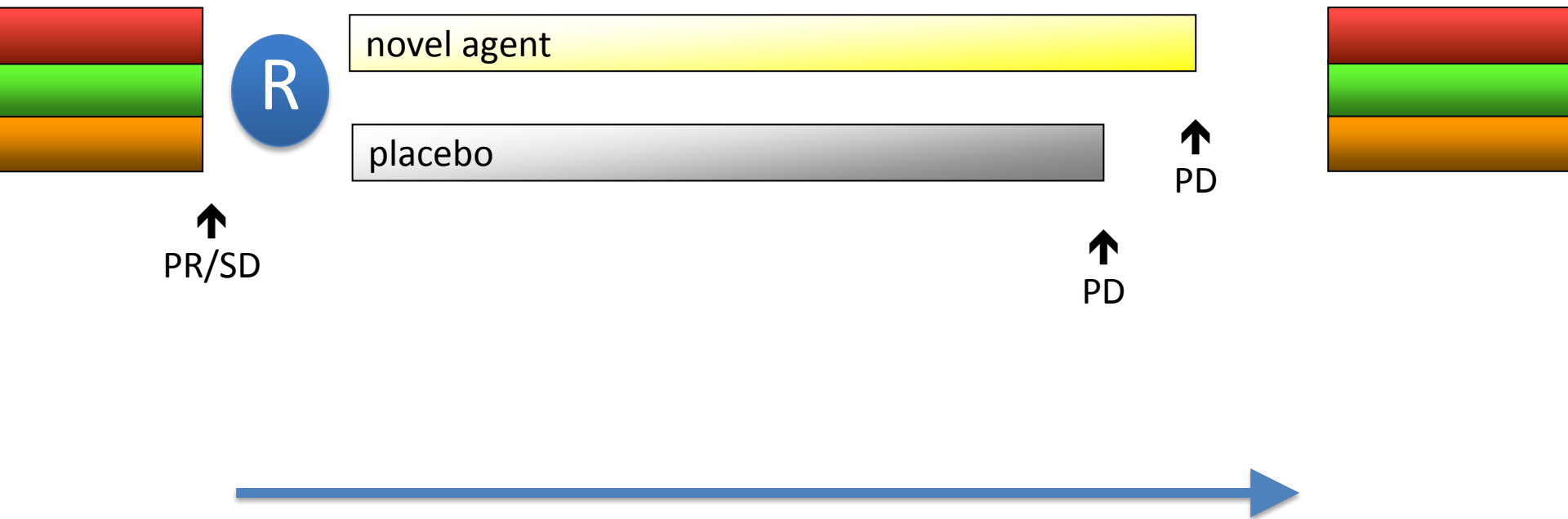
↑
PD



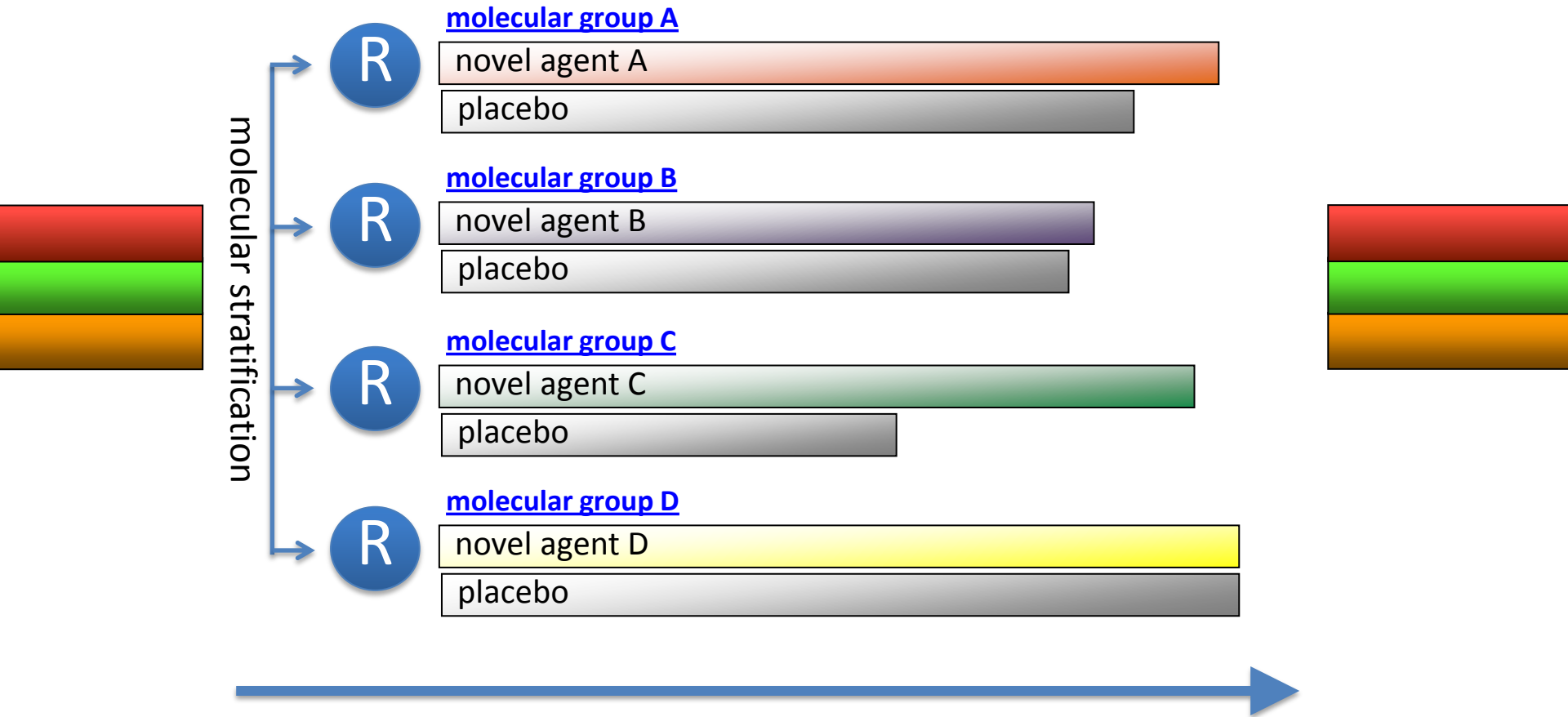
treatment break = research opportunity



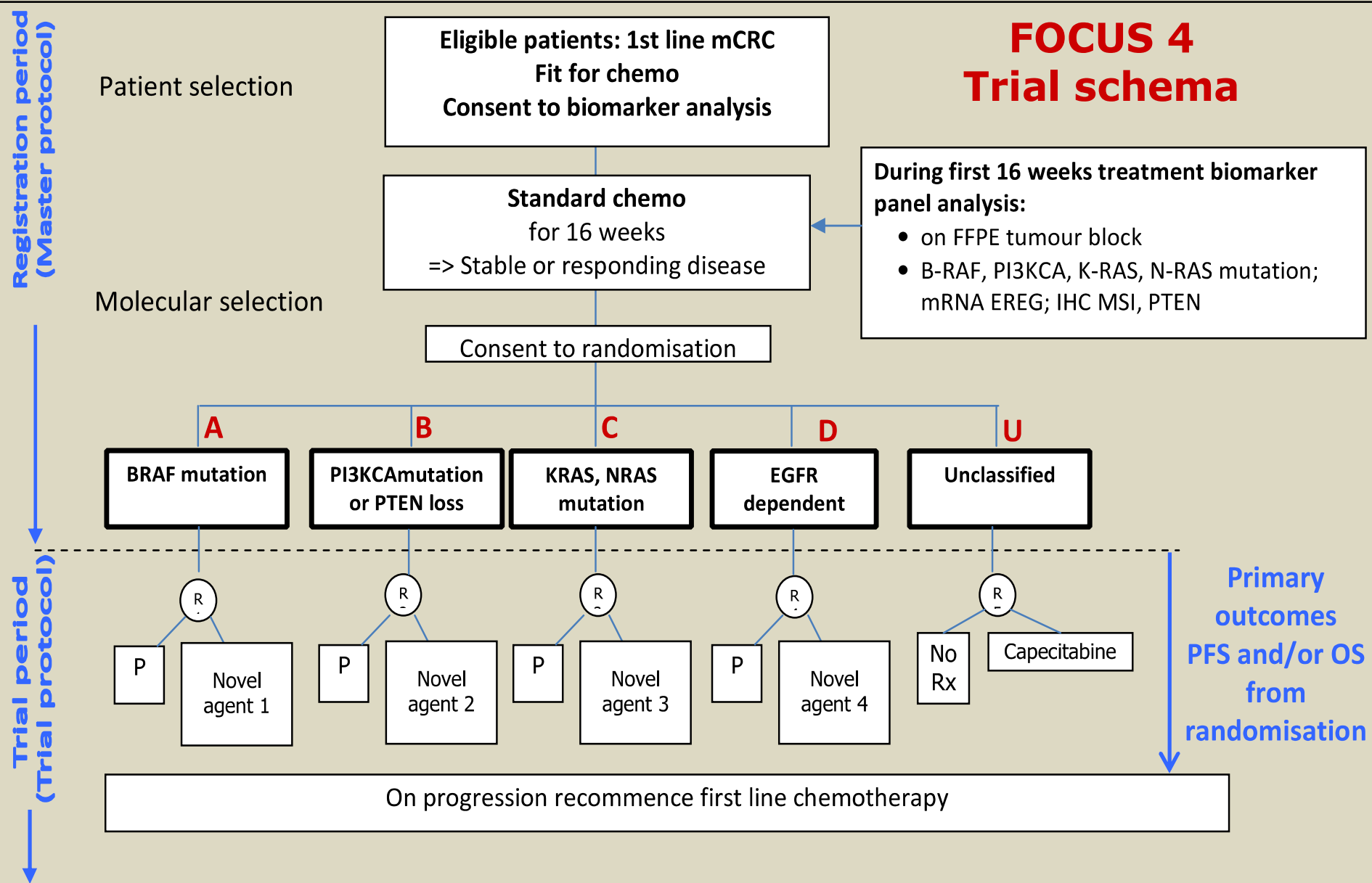
treatment break = research opportunity



treatment break = research opportunity



FOCUS 4 Trial schema



NCRI Colorectal Cancer Clinical Studies Group: Tim Maughan, Rick Kaplan, Phil Quirke, Richard Wilson, Richard Adams, Harpreet Wasan, Gary Middleton, et al.

Conclusions

- treatment breaks should be discussed with patients
- many patients may take time off all treatment with minimal compromise to survival
 - need to validate platelets and other selection factors
- progression during breaks should be anticipated, detected and treated
- maintenance low-toxicity chemo or targeted therapy is of interest but further evidence is awaited
- this is an excellent and ethical opportunity to test novel therapies

Thank you

