Optimizing Chemotherapy for Frail and Elderly Patients with Advanced Gastroesophageal Cancer:

The GO2 phase III trial

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on behalf of the GO2 Investigators

Background

- The median age of patients diagnosed with advanced (inoperable or metastatic) gastric or oesophageal (GO) cancer is >75 years.[1]
- Many patients are frail.
- …but international standard chemo schedules were developed in trials of mostly non-frail patients with median age <65 years.[2]
- Standard of care for advanced GO cancer in the UK has been EOCap.

1. Cancer Research UK. CancerStats. https://www.cancerresearchuk.org/health-professional/cancer-statistics/
2. Cunningham D, Starling N, Rao S, et al. New England Journal of Medicine 2008;358(1):36-46

Background

- In 2011 we audited 50 UK oncologists: 49 were using reduced chemo schedules in frail/elderly GO patients; high variation and non-evidence based.
- A randomised phase II trial (321GO) compared 3, 2 or 1-drug chemotherapy in frail/elderly GO cancer patients in a “pick-the-winner” (n=55) and found 2 drugs best.[3]

3. Hall et al. British Journal of Cancer British Journal of Cancer 2017 116(4):472-478

Aims

In frail or elderly patients with advanced GO cancer:

- Establish the dose of 2-drug chemotherapy achieving the best balance of cancer control, toxicity, patient acceptability and quality of life.

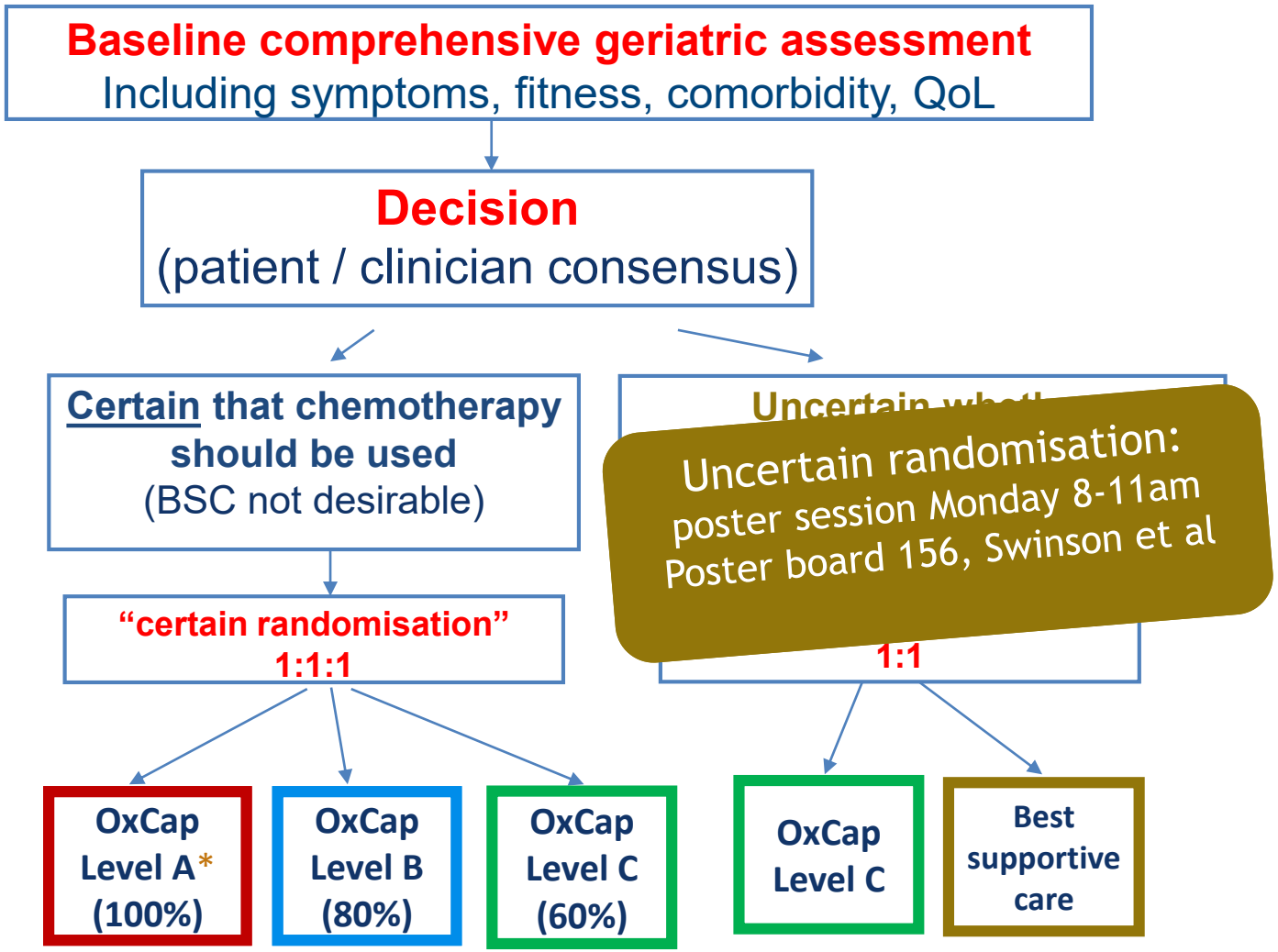
- Identify pre-treatment characteristics which predict for better or worse outcomes from different dose levels.

Trial design

Phase III, randomised, multi-centre, prospective, controlled, open label, non-inferiority trial

Eligibility
Not fit for full-dose 3-drug chemotherapy, but suitable for reduced intensity chemotherapy.

Follow-up
Total 1 year; 9 weekly imaging and PROMs



*Oxaliplatin 130mg/m^2 day 1 of a 21 day cycle Capecitabine 625mg/m^2 bd continuously - given until progression

Frailty assessment

Frailty model

Comprehensive Geriatric Assessment

9 domains pre-specified

Definition

Not frail	- impairment in 0 domains
Mildly frail	- impairment in 1-2 domains
Severely frail	- impairment in ≥3 domains

Domains	Assessment
Weight loss	Weight loss (> 3kg in 3m) | BMI (<18.5)
Mobility	Timed up and go test (>10 seconds)
Falls	2 or more falls in 6m (EORTC G8)
Neuropsychiatric	Dementia/depression diagnosis
Function	One or more impairment in IADL
Social	Place of residence (Requires 24 hour care)
Mood	EQ5D question (feelings today)
Fatigue	EORTC QLQ Fatigue Score
Polypharmacy	Prescribed regular medications (>4)

Statistical design

- **Step 1:** assess non-inferiority of lower doses compared with Level A
  - Primary endpoint: Progression Free Survival
    HR 1.34, 80% power; 1-sided 5% significance level (≈34 days median PFS*)
  - Secondary endpoint: overall survival

- **Step 2**: assess patient experience with lower doses
  - Key endpoint: Overall Treatment Utility (OTU)
  - Other endoints: toxicity, longitudinal QL

- **Step 3**: explore whether optimum dose differs with baseline factors
  - Key endpoint: Overall Treatment Utility (OTU)
  - Baseline factors: **age, frailty, performance status**

*Non-inferiority boundary agreed by a patient focus group and clinician survey

"Overall Treatment Utility" (OTU) scored after 9 weeks:

good OTU

all of:

- clinician score "benefit"*

and

- patient satisfied

and

- no major toxicity

and

- no drop in QL¶

intermediate OTU

either:

- clinician score "no benefit"
- (but patient satisfied and no major toxicity or QL drop)

or

- either patient dissatisfied or major toxicity or QL drop
- (but clinician scores benefit)

poor OTU

both:

- clinician score "no benefit"

and any of

- patient dissatisfied
- major toxicity
- QL deterioration

or

- patient has died

NB: decision rules to ensure OTU can be scored in 100% patients

*clinician score of "benefit": no clinical/radiological evidence of cancer progression and no general health deterioration

¶ drop in QL defined as ≥16% fall (≥2 on the 12-point EORTC global QL scale). Cocks, K et al., Eur J Cancer (2012) 48, 1713–21

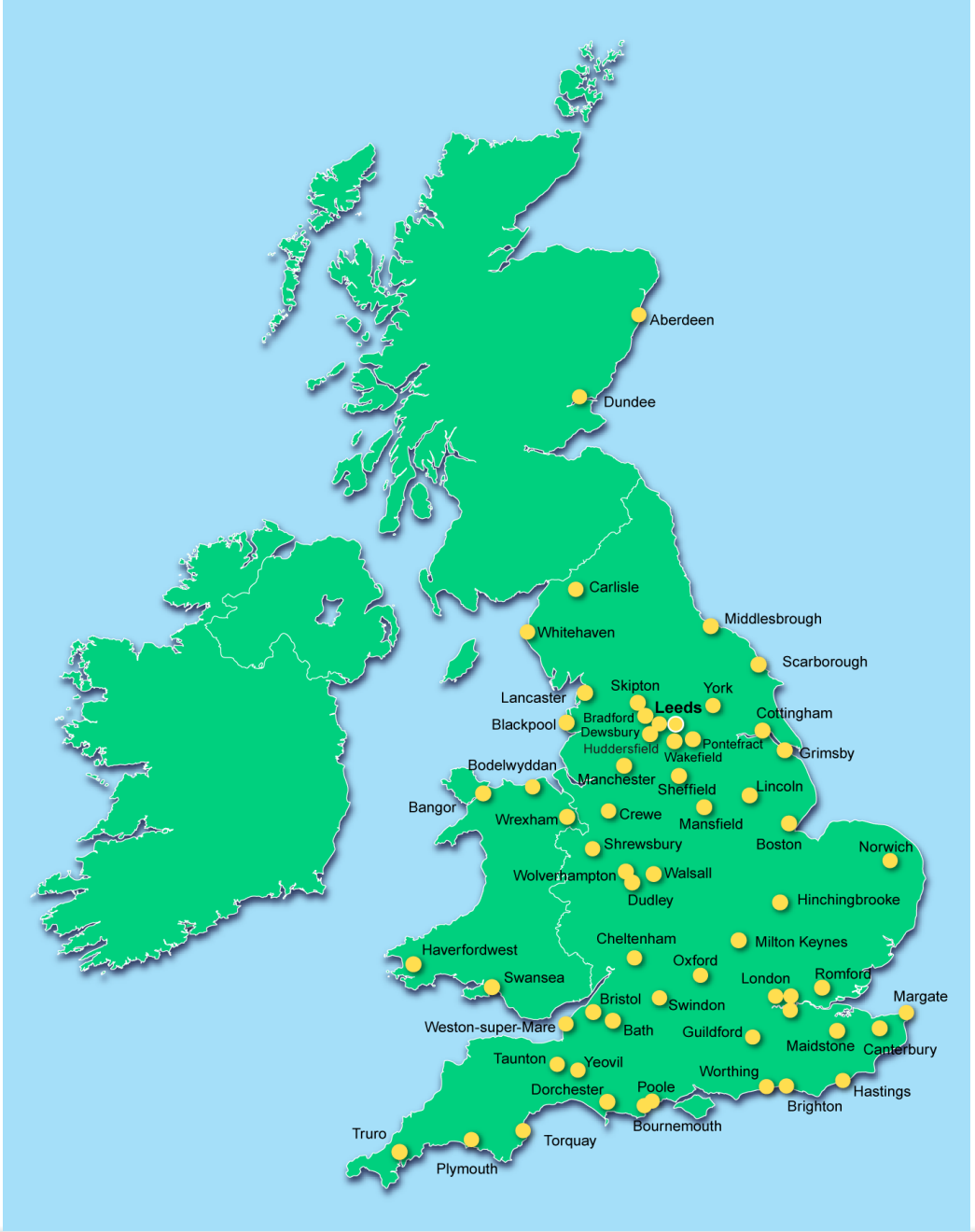
First developed in FOCUS2 trial [Seymour, et al (2011) The Lancet 377(9779): 1749-1759].

For more info see www.blogs.ed.ac.uk/canceroutcomes

Recruitment

(certain randomisation)

- 512 patients
- 2014 – 2017
- 61 UK hospitals



Patients

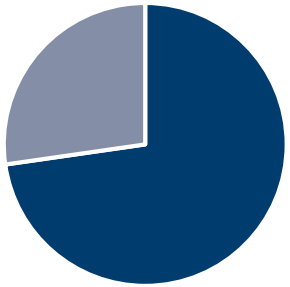
		Level A (n=170)	Level B (n=171)	Level C (n=173)	Total (n=512)
Median age (range)		76	76	77	76 (51 - 96)
Male gender		77%	75%	72%	75%
Site of primary	Oesophagus	32%	42%	39%	38%
	GO junction	29%	19%	22%	23%
	Gastric	38%	37%	37%	37%
Squamous histology		12%	11%	12%	11%
Trastuzumab treated		4%	6%	6%	5%
Distant metastases		68%	69%	70%	69%
Performance Status ≥2		31%	32%	31%	31%
Severely frail (≥3 domains)		61%	56%	58%	58%

Baseline frailty

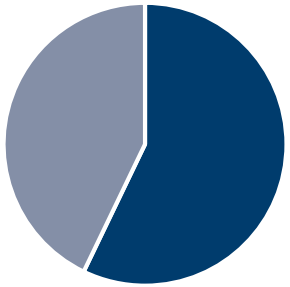
impaired

not impaired

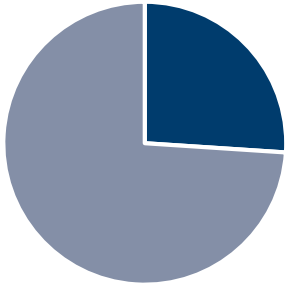
Polypharmacy



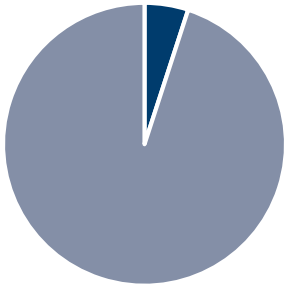
Mobility



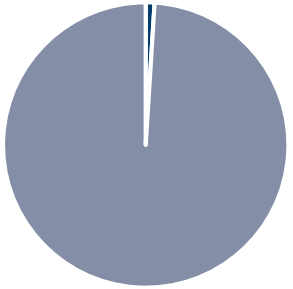
Fatigue



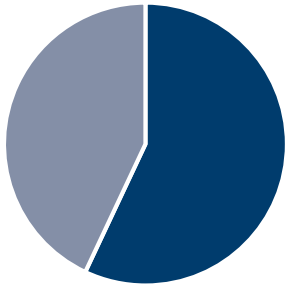
Falls



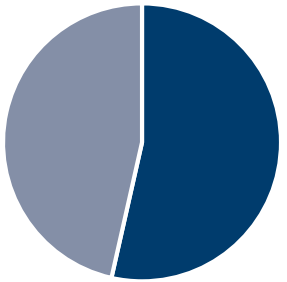
Social care



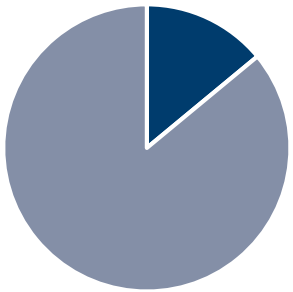
Daily activities



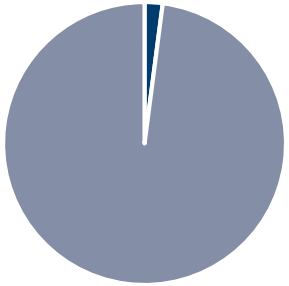
Weight loss



Neuropsychiatric



Mood



Results: step 1 - non-inferiority is confirmed

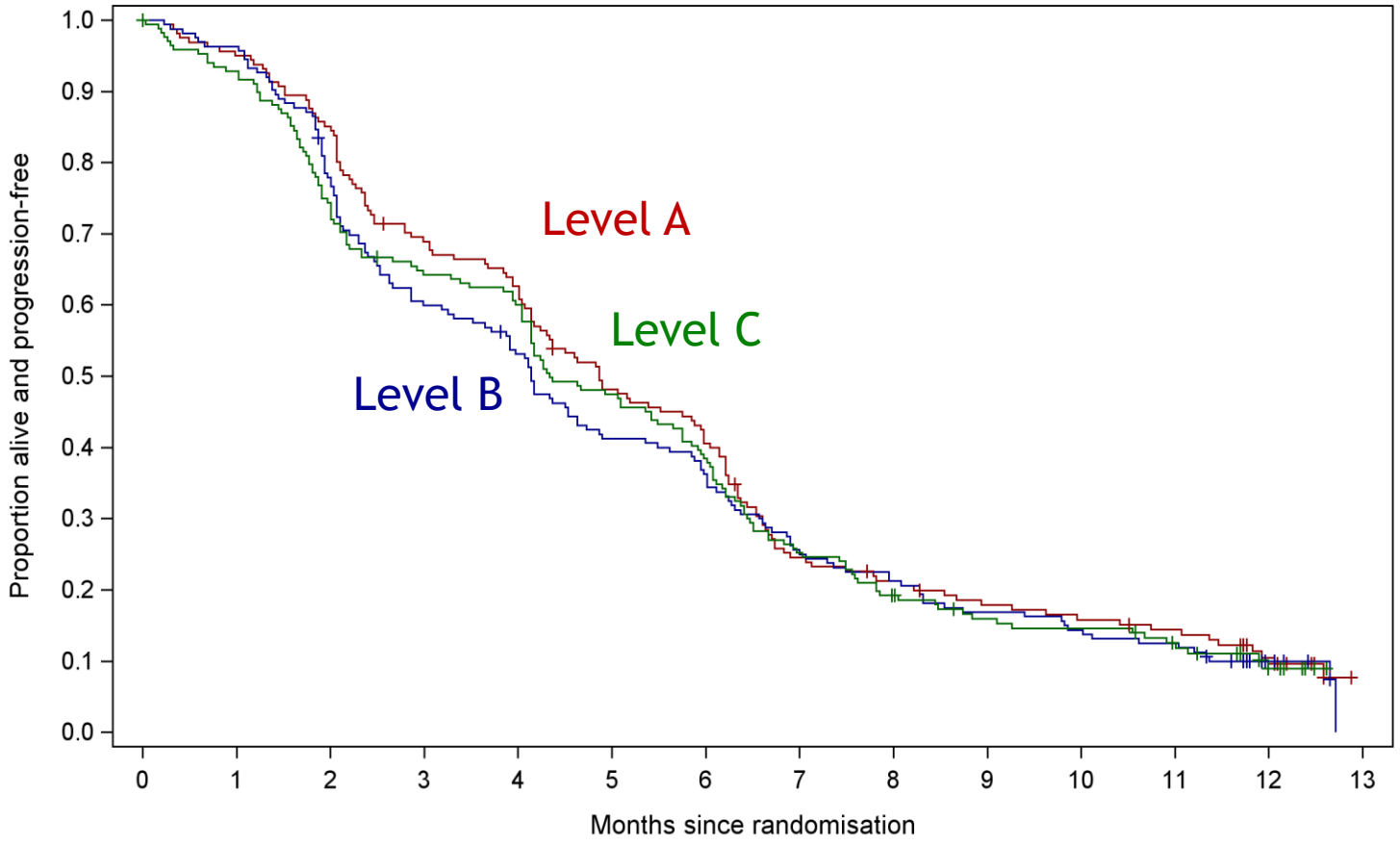
Primary endpoint

Progression Free Survival

Adjusted hazard ratios

Level B vs A 1.09 [95% CI 0.89 – 1.32]

Level C vs A 1.10 [95% CI 0.90 – 1.33]



The non-inferiority boundary of 1.34 is excluded, so non-inferiority is confirmed

Results: step 1 - non-inferiority

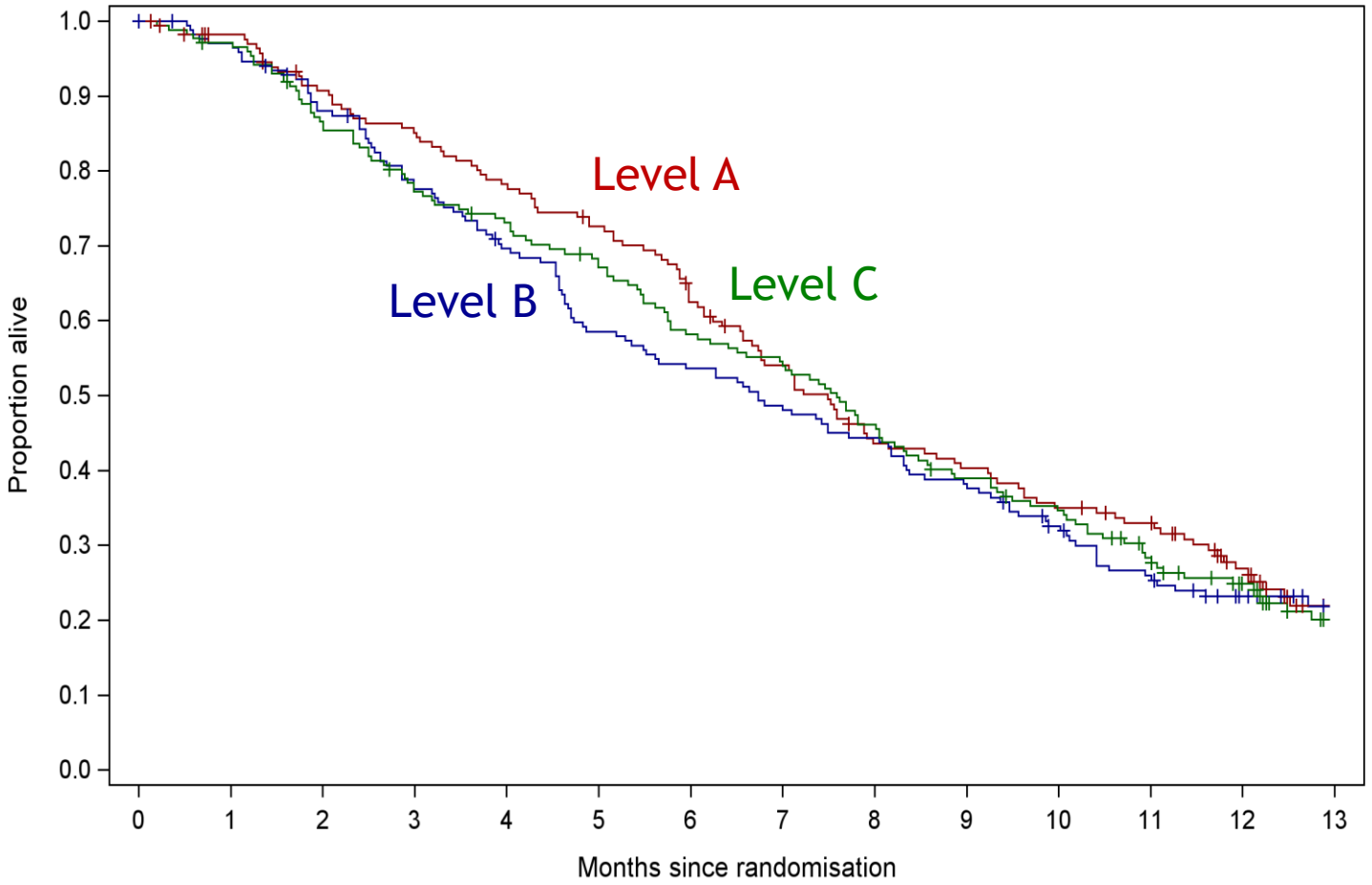
Overall survival

Median survival

Level A 7.5 months

Level B 6.7 months

Level C 7.6 months



Results step 2: the patient experience

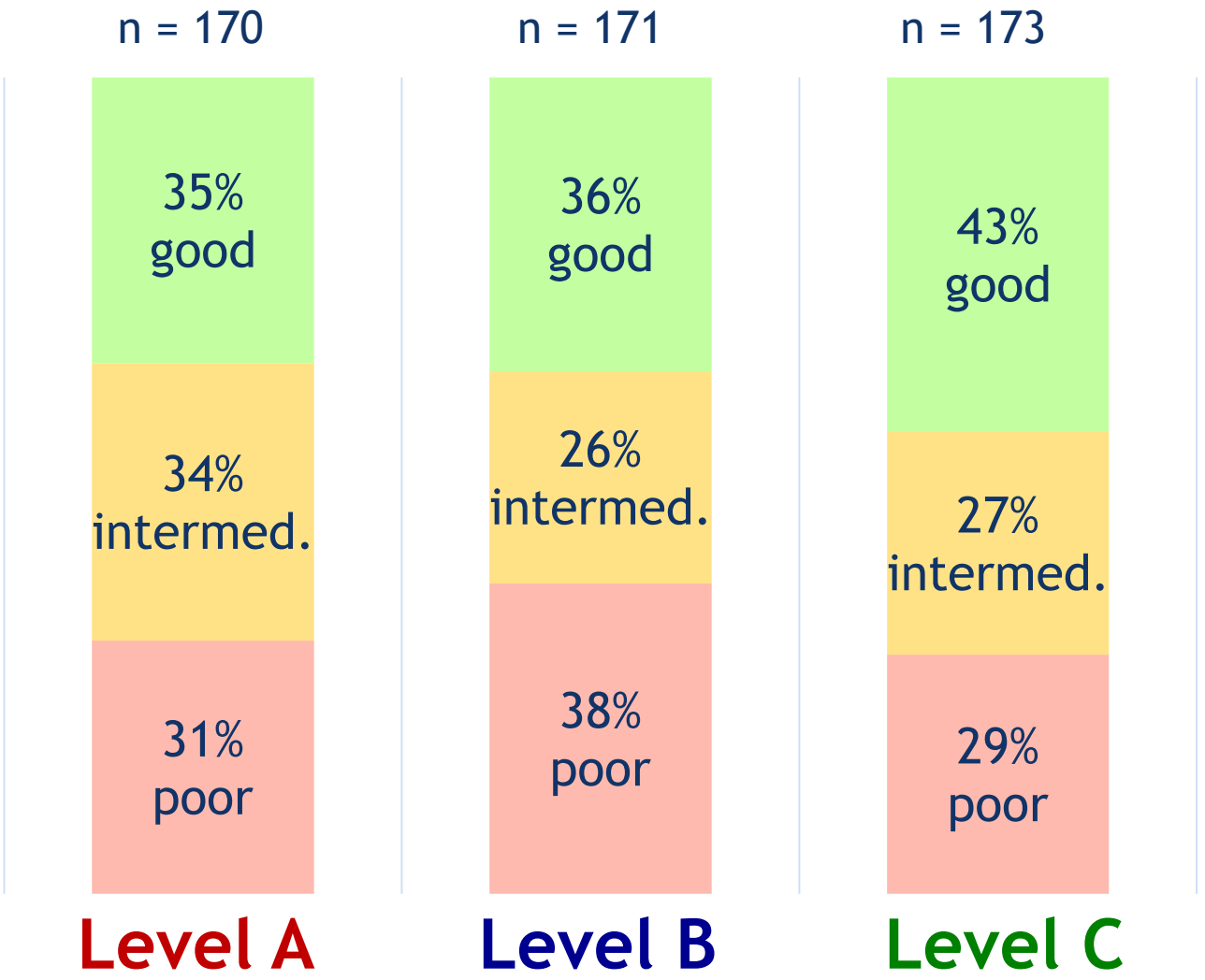
Overall Treatment Utility

Overall treatment utility favours **Level C**, which had the highest percentage of Good and lowest percentage of Poor OTU scores

Adjusted odds ratios (trend for better OTU)

Level B vs A 0.87 [95% CI 0.59 – 1.29]

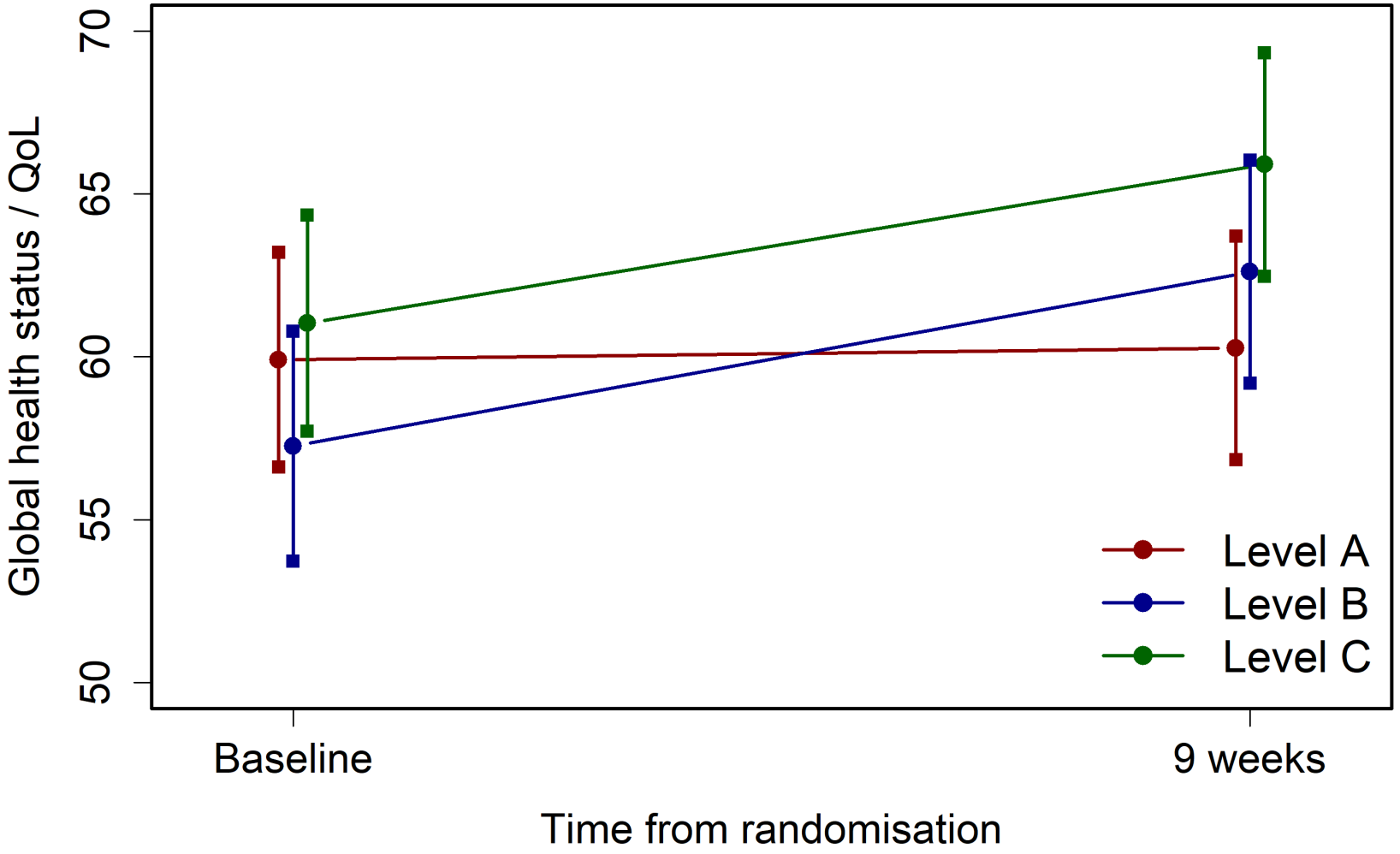
Level C vs A 1.24 [95% CI 0.84 – 1.84]



Results step 2: the patient experience

Quality of life

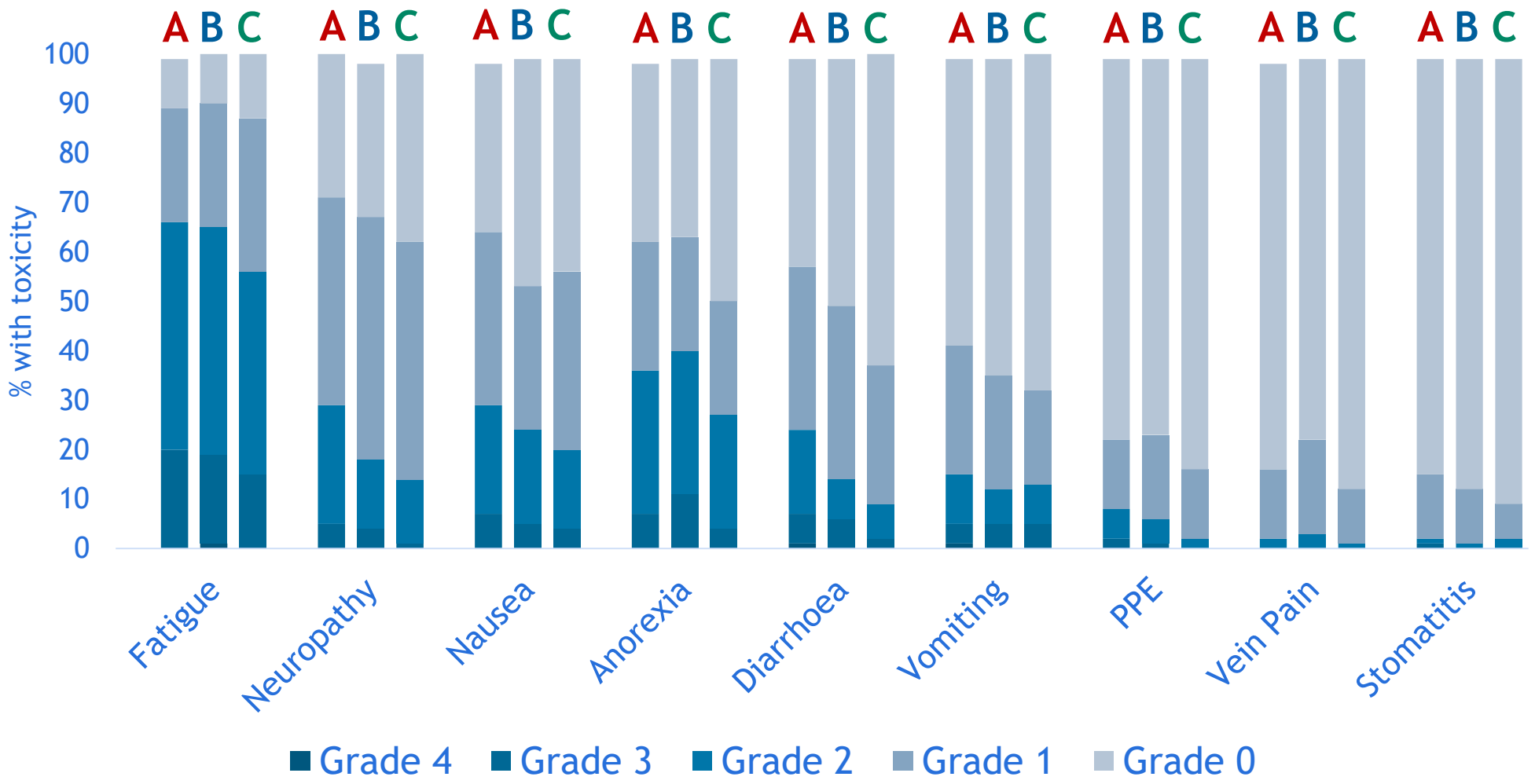
Mean QL improved from baseline to 9 weeks with Level B and Level C



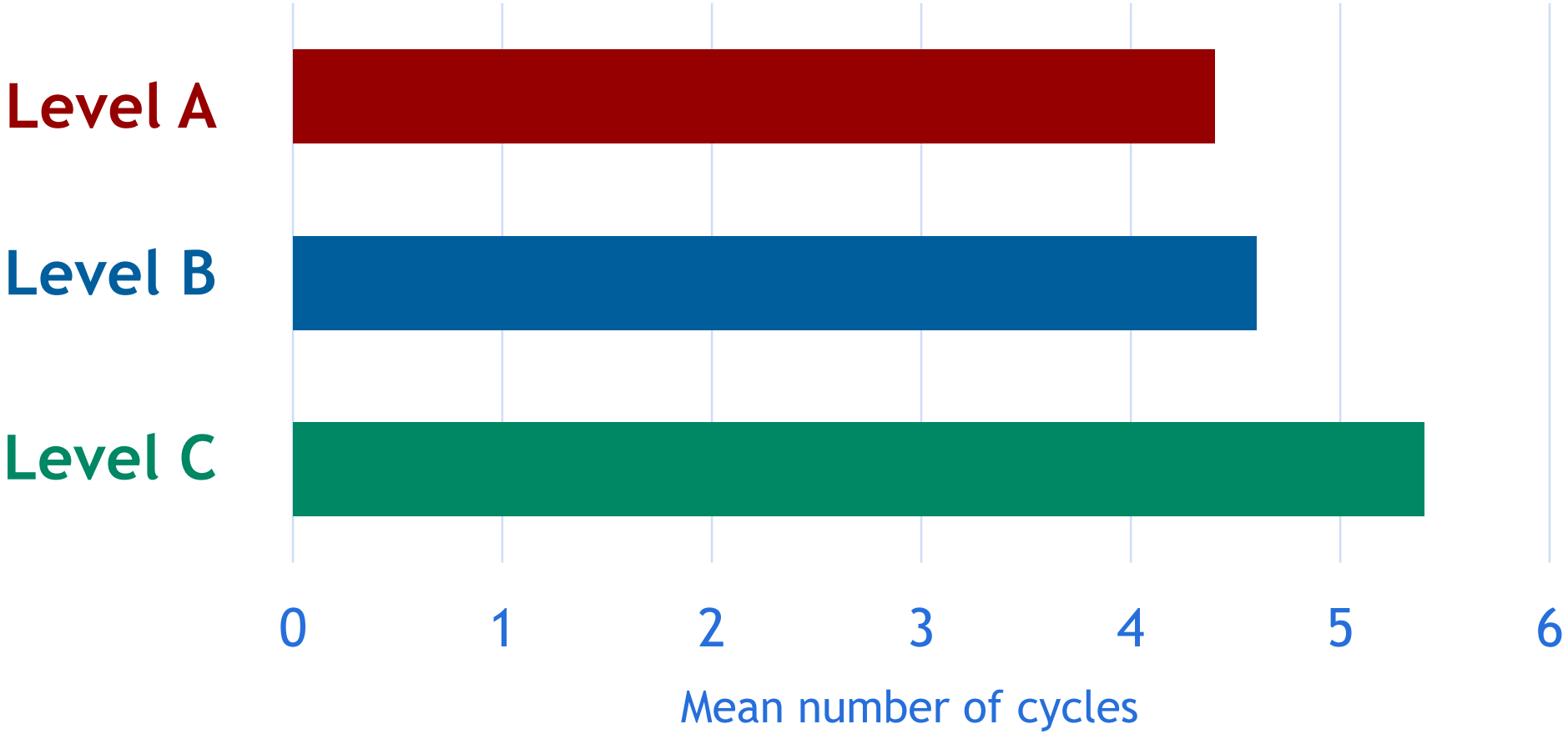
Complete case analysis, adjusted for baseline QoL

Results step 2: the patient experience

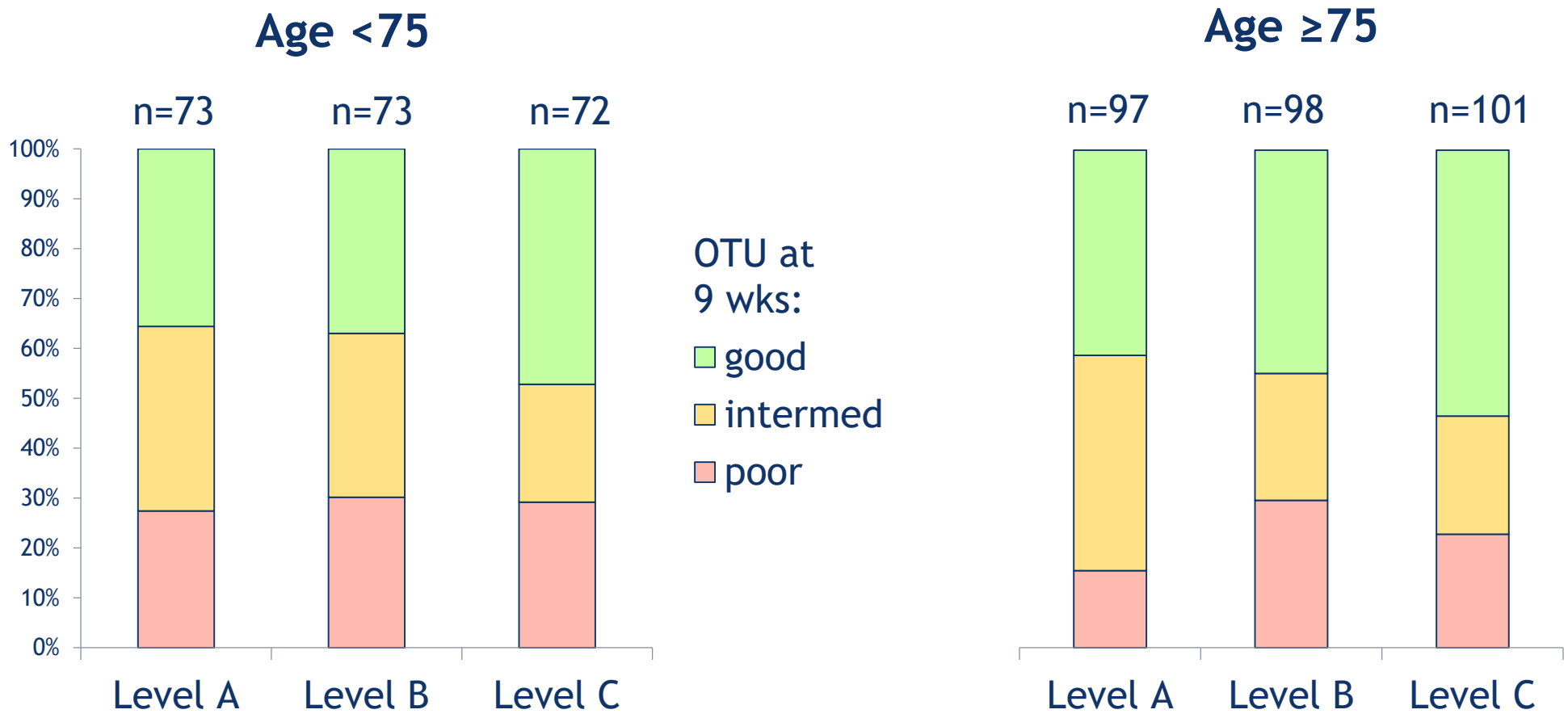
Toxicity



Treatment duration

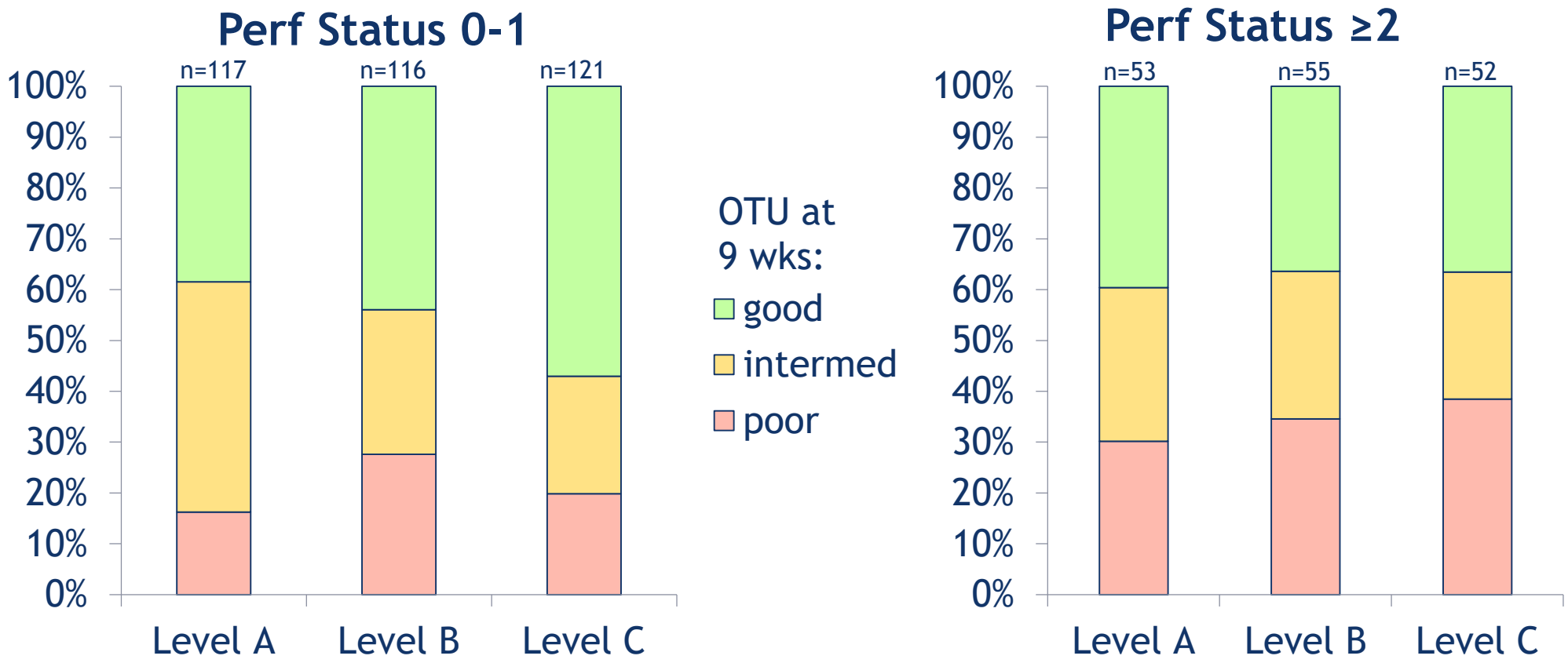


Step 3: Effect of baseline factors - age



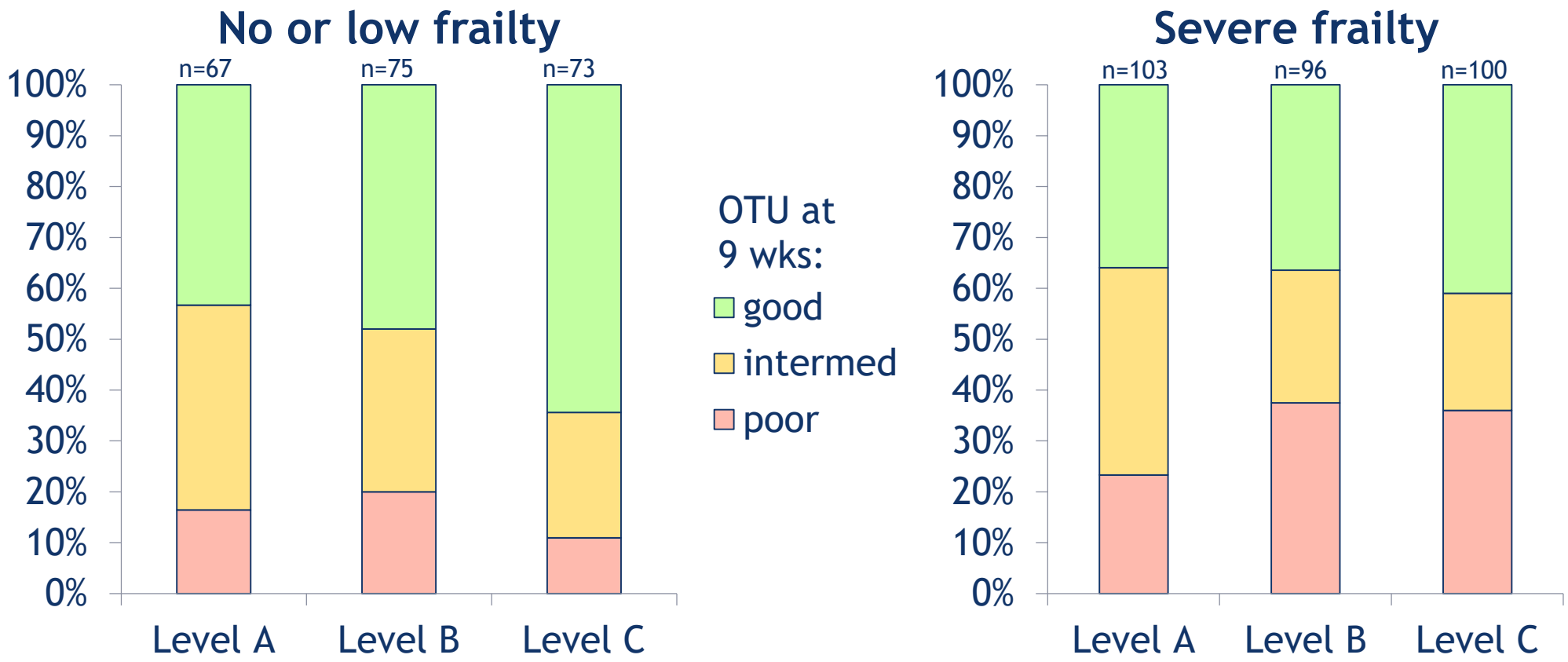
Tests for heterogeneity not significant (A/B/age: p=0.47; A/C/age: p=0.81)

Step 3: effect of baseline factors - Perf. status



n=514. Tests for heterogeneity not significant (A/B/PS: p=0.84; A/C/PS: p=0.15)

Step 3: effect of baseline factors - frailty



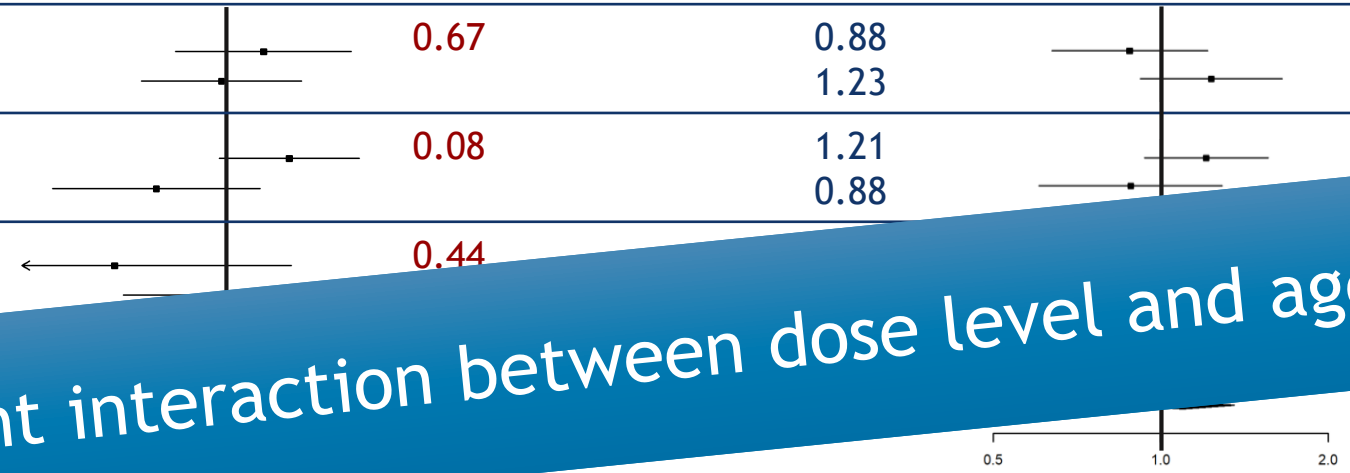
n=514. Tests for heterogeneity not significant (A/B/frailty: p=0.10; A/C/frailty: p=0.06)

Step 3: Effect of baseline factors - PFS and OS

A versus B

PFS

Subgroup		PFS HR	p(het)
Age	<75	1.13	0.67
	≥75	0.98	
PS	0-1	1.23	0.08
	≥2	0.79	
Frailty	No	0.68	0.44
	Slight	1.07	
	Severe		

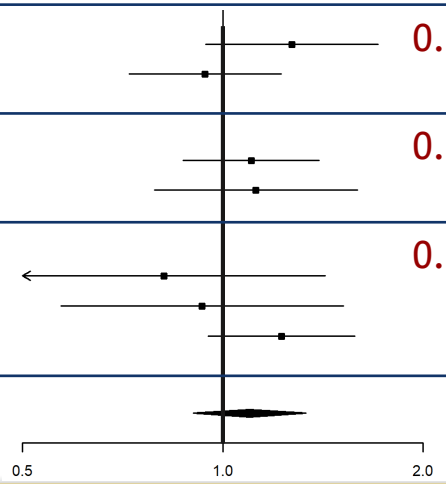


OS

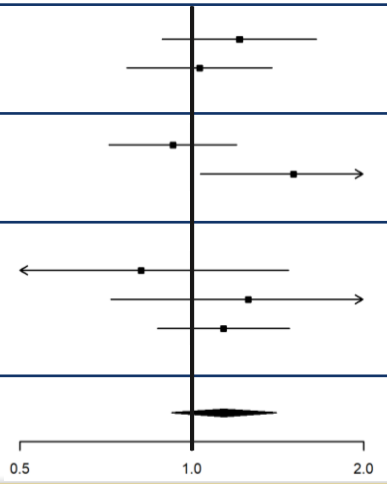
OS HR	p(het)
0.88	0.18
1.23	
1.21	0.22
0.88	

No significant interaction between dose level and age, PS or frailty

Subgroup		PFS HR	p(het)
Age	<75	1.27	0.24
	≥75	0.94	
PS	0-1	1.10	0.98
	≥2	1.12	
Frailty	No	0.82	0.66
	Slight	0.93	
	Severe	1.23	
Overall		**1.10**	



OS HR	p(het)
1.21	0.45
1.03	
0.93	0.04
1.51	
0.82	0.82
1.26	
1.14	
1.14	



Summary

- This is the largest RCT to date specifically investigating frail/elderly advanced GO cancer patients.

- The lowest dose tested provided
  - non-inferior cancer control (PFS and OS)
  - the best patient experience (OTU, toxicity and QoL)

- No subgroup clearly benefited from higher dose treatment
  - Further work is investigating personalised dose selection based on CGA

Conclusions

- Low-dose treatment may be offered to patients too frail or elderly for a full-dose regimen, in the confidence that it may give a better patient experience without compromising cancer control or survival

- Overall Treatment Utility is a useful clinical trial outcome measure that reflects the goals of palliative therapy

Acknowledgements

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Trial Management Group

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Trial Steering Committee

Gareth Griffiths (chair), Sally Clive, Vanessa Potter, Jean Gall

Patients and their families

My family and I would like to say thank you for such a lovely letter, it is so good to know what happens after taking part in a trial and you are not forgotten.

I lost my dear husband of nearly 60 years in May 2015, when he was asked if he would take part in the trial he already knew he was terminaly ill but he said "it will be too late for me but if it would help others he would be very please" and we hope this too.

Thank you once again for thinking of us and Good Luck with the out come.

"...thank you for thinking of us."

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