ICR The Institute of Cancer Research

in partnership with The ROYAL MARSDEN NHS Foundation Trust

UKMRA UK Myeloma Research Alliance

Goals of Myeloma Therapy

Aims of induction therapy in frail(er) myeloma patients

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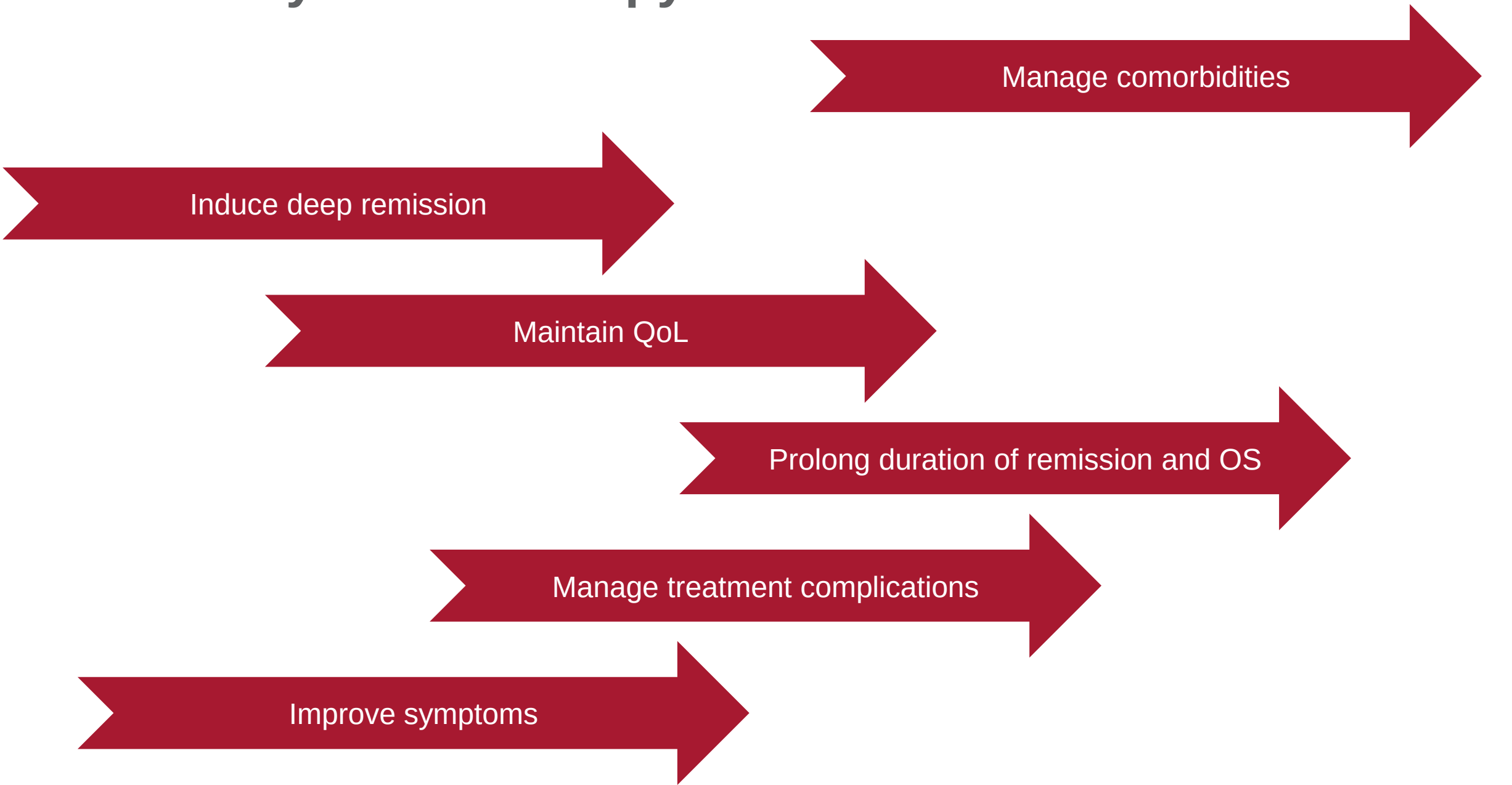
Disclosures: Charlotte Pawlyn

Abbvie	Consultancy, Honoraria
Amgen	Consultancy
Takeda Oncology	Consultancy
Janssen	Consultancy, Honoraria
Celgene/BMS	Consultancy, Honoraria
Sanofi	Consultancy, Honoraria
iTEOS	Consultancy
Pfizer	Consultancy
Menarini Stemline	Honoraria
Opna Bio	Honoraria

Goals of myeloma Therapy

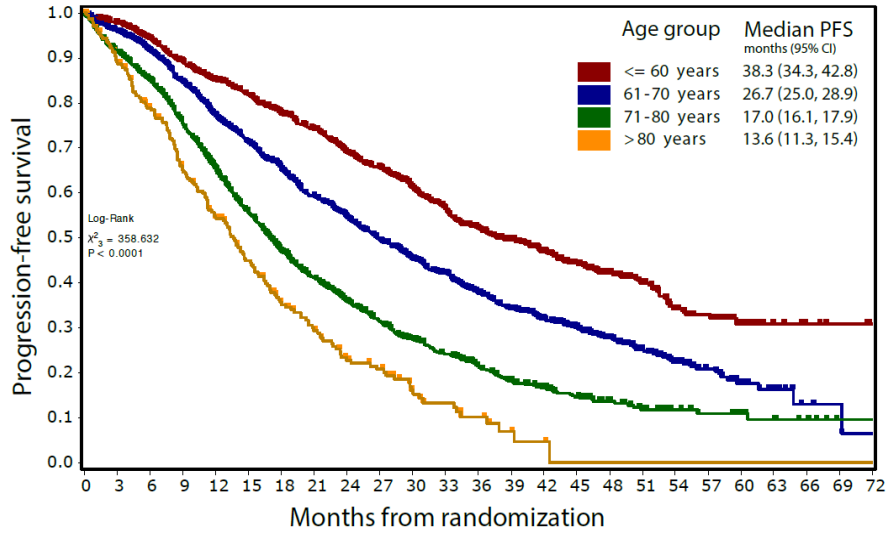


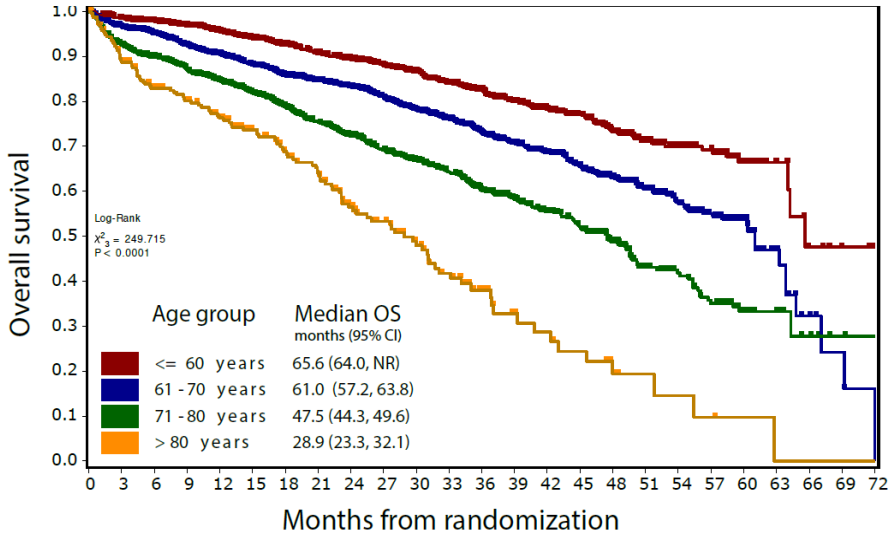
Goals of myeloma Therapy

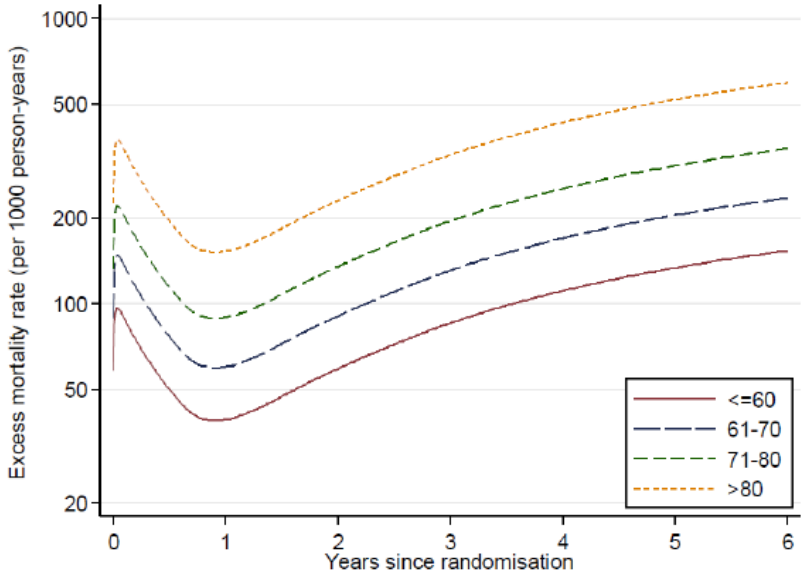
- Improve symptoms
- Manage comorbidities
- Manage treatment complications
- Maintain QoL
- Induce deep remission
- Prolong duration of remission and OS

More nuanced and multi-factorial than in younger patients

PFS and OS shorten with increasing patient age



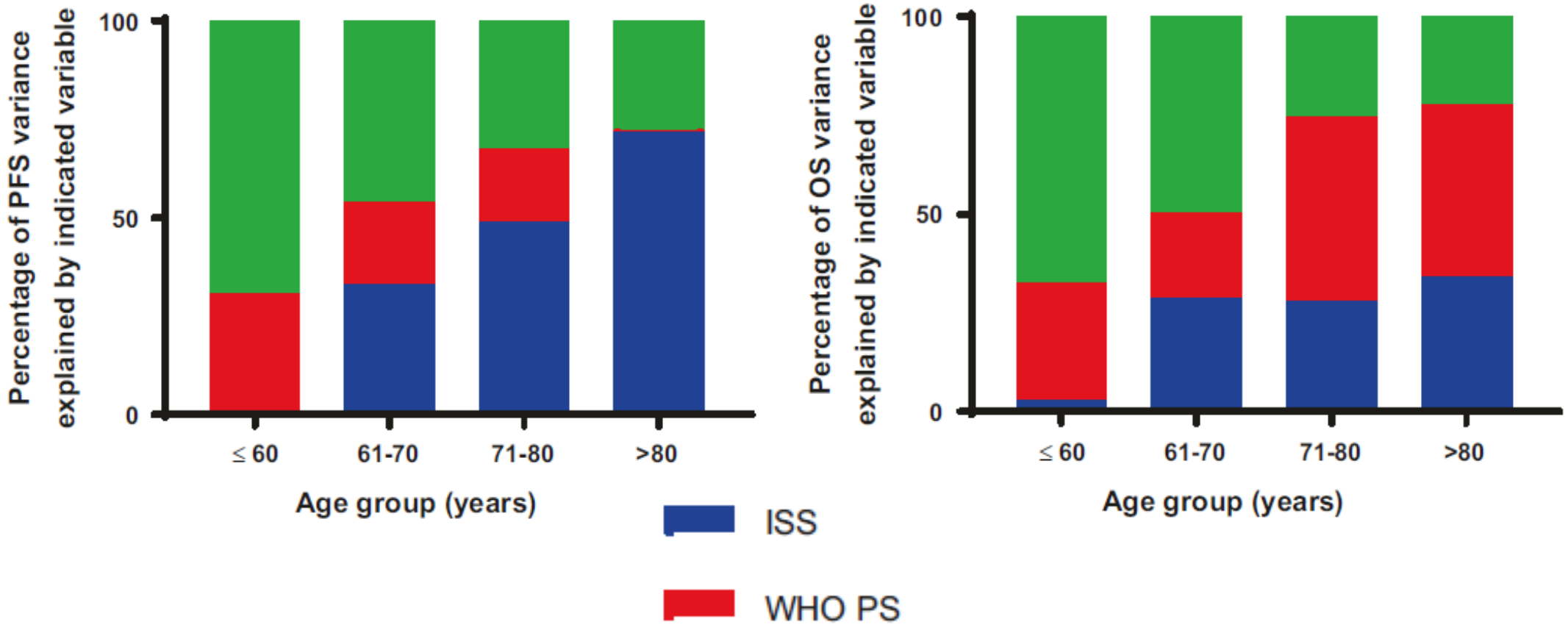




Excess mortality is greatest in oldest patients

Pawlyn C *et al*. *Leukemia.* 2020;34(2):604-612

The key driver of poor outcomes in older patients is not tumour genetics



In older patients features associated with **frailty** have a greater impact on outcome

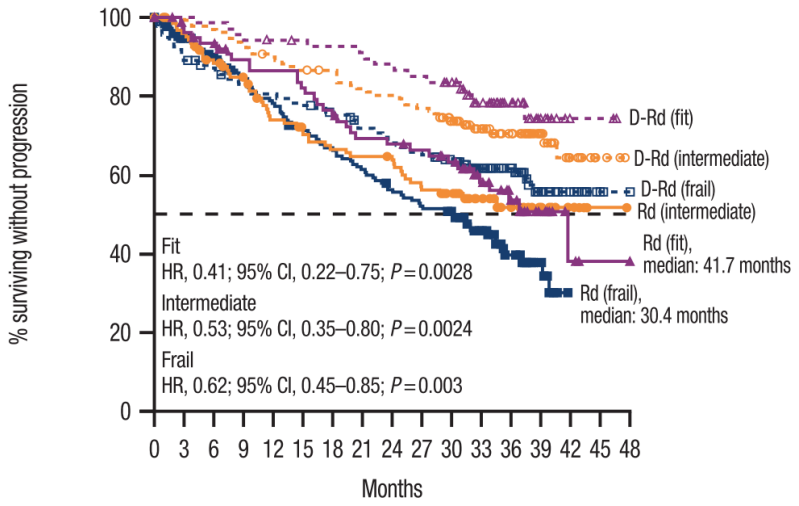
Pawlyn C *et al*. *Leukemia.* 2020;34(2):604-612

Toxicity increases with age

	CTDa					CRDa				
Age	**All**	≤70	71-75	76-80	>80	**All**	≤70	71-75	76-80	>80
Cycles Median (range)	**6 (1, 13)**	6 (1, 13)	6 (1, 11)	6 (1, 11)	5 (1, 10)	**6 (1, 12)**	6 (1, 10)	6 (1, 12)	6 (1, 12)	6 (1, 10)
Cycles Mean	**5.2**	5.4	5.5	5.0	4.6	**5.2**	5.6	5.4	5.1	4.2
Cessation due to tox % (n)	**12.2% (113)**	8.2% (16)	10.6% (36)	15.5% (41)	16.0% (20)	**11.0% (102)**	9.9% (22)	8.5% (26)	12.9% (36)	15.0% (18)

MAIA

n=737 TNE → DRd / Rd



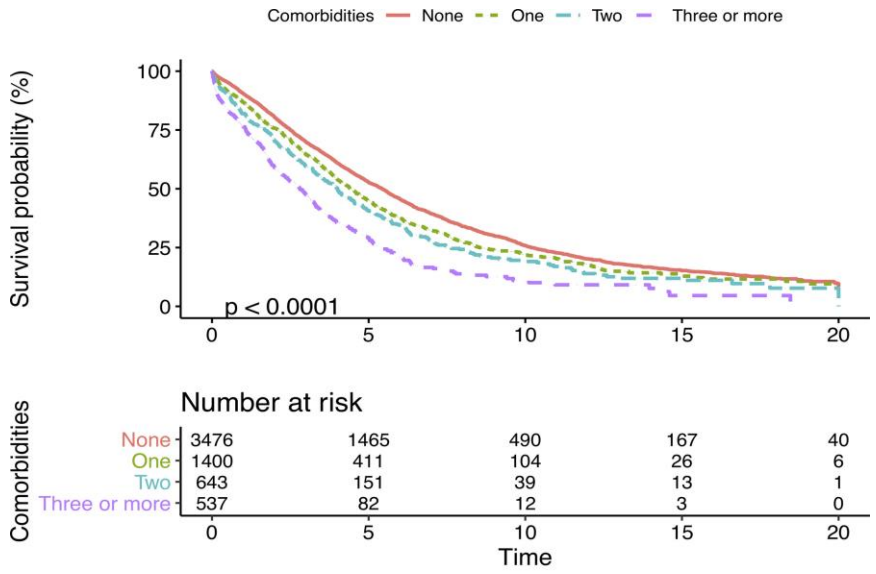
FRAIL patients:

- Shorter time on therapy
- More treatment emergent adverse events (serious and non-serious)
- More growth factor usage
- Higher rate of treatment discontinuation due to TEAEs

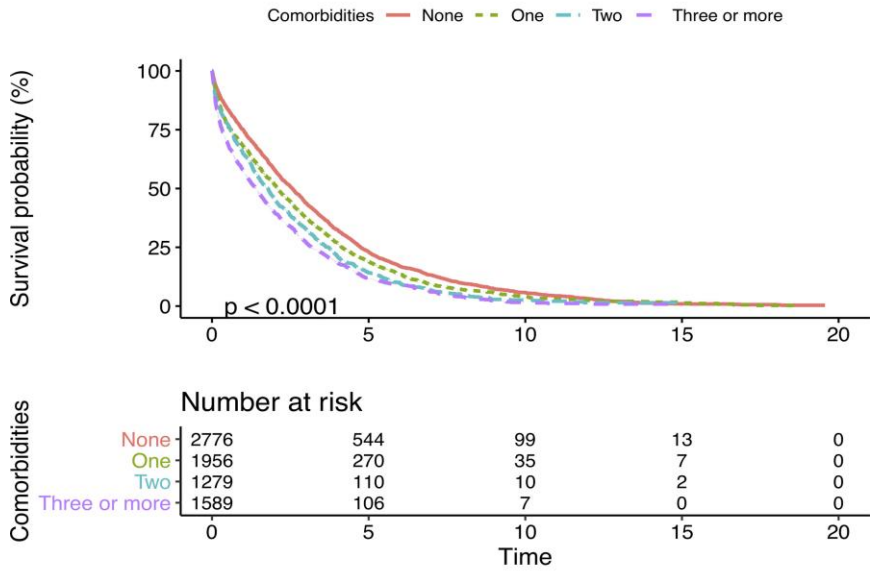
Pawlyn C et al ASH 2019
Kumar SK et al. ASH. 2022
Facon T *et al*. *Leukemia.* 2022;36:1066-1077

Co-morbidities

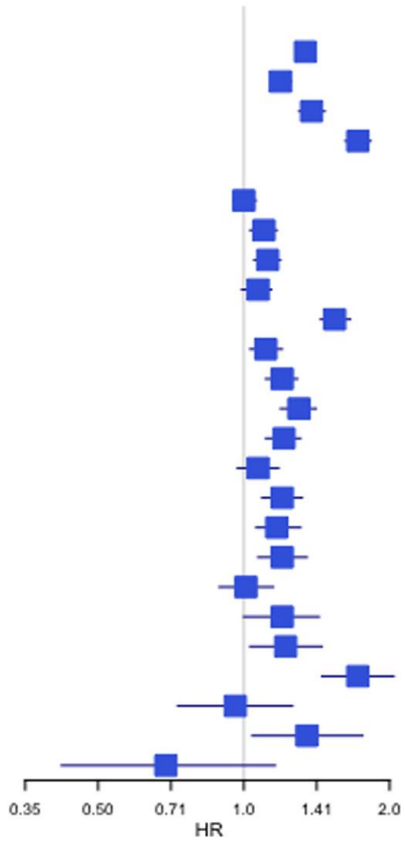
<70



>=70

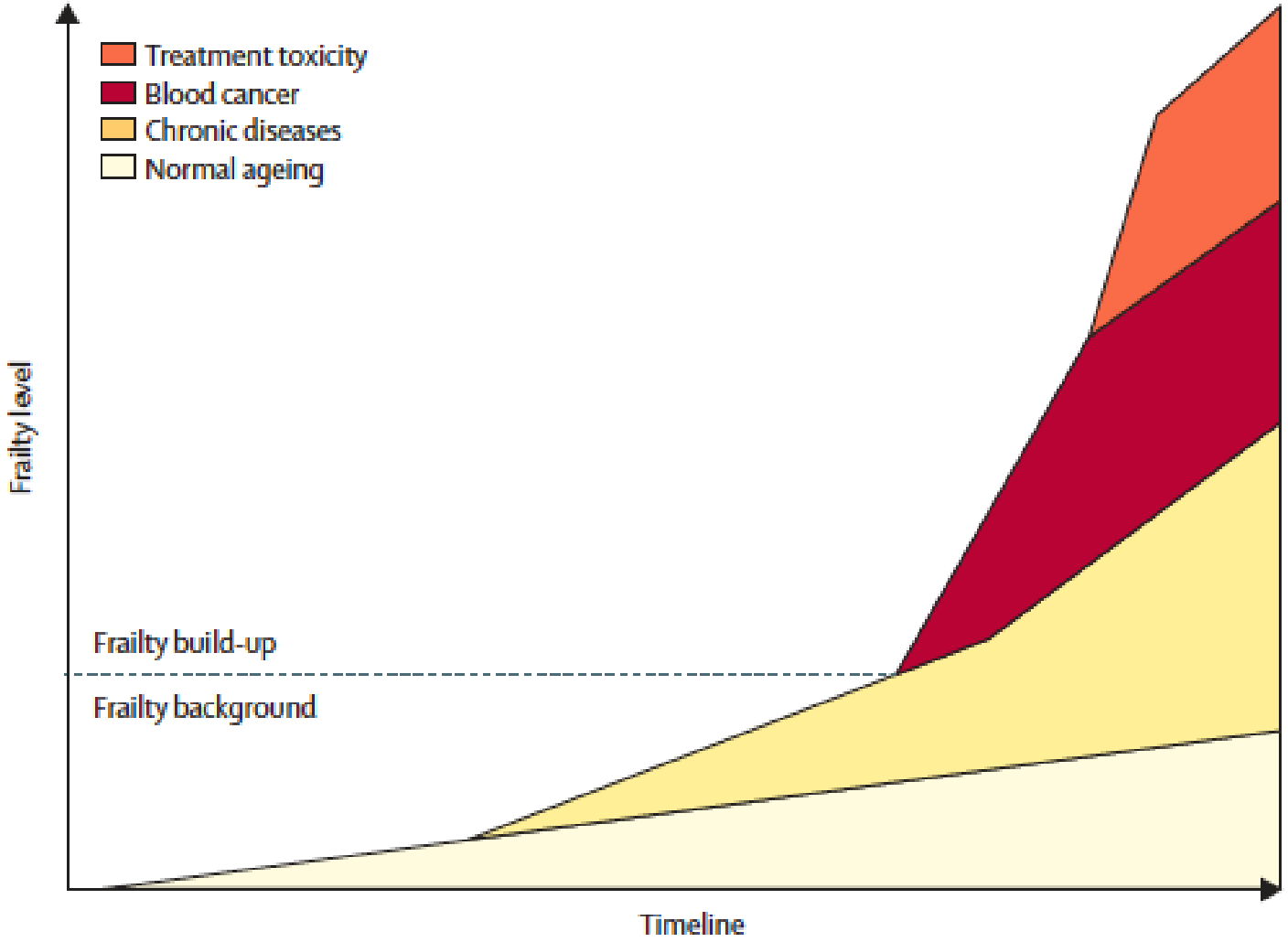


	No.	HR	95% CI
Number of Comorbidities			
None	6,252	1.00	
One or more	7,404	1.34	1.29-1.40
One	3,355	1.19	1.14-1.25
Two	1,922	1.38	1.30-1.47
Three or more	2,126	1.72	1.62-1.83
Comorbidities			
Hypertension	2,783	1.00	0.95-1.06
Arrhythmia	1,551	1.10	1.03-1.17
Cancer	1,544	1.12	1.05-1.19
Chronic ischaemic heart disease	1,254	1.07	0.99-1.14
Heart failure	1,242	1.54	1.44-1.66
Diabetes mellitus	1,144	1.11	1.03-1.20
Cerebrovascular disease	1,055	1.20	1.11-1.29
Psychological disease	832	1.30	1.19-1.41
Chronic lung disease	823	1.21	1.11-1.31
Endocrine disease	673	1.07	0.97-1.18
Peptic Ulcer	518	1.20	1.09-1.32
Neurological disease	473	1.17	1.06-1.31
Peripheral vascular disease	381	1.20	1.07-1.35
Rheumatological disease	374	1.01	0.89-1.15
Chronic kidney disease	184	1.20	1.00-1.43
Liver disease	181	1.22	1.03-1.45
Dementia	149	1.72	1.45-2.04
Obesity	103	0.96	0.73-1.26
Inflammatory bowel disease	83	1.35	1.04-1.76
Pancreatic disease	29	0.69	0.42-1.16



Sverrisdottir I. et al, *EJH.* 2021

Components of frailty



Frailty by treatment issues
Myelosuppression → Infection → Fatigue
Intestinal mucositis → Low food uptake → Weight loss
Neurotoxicity → Polyneuropathy → Weakness and falls

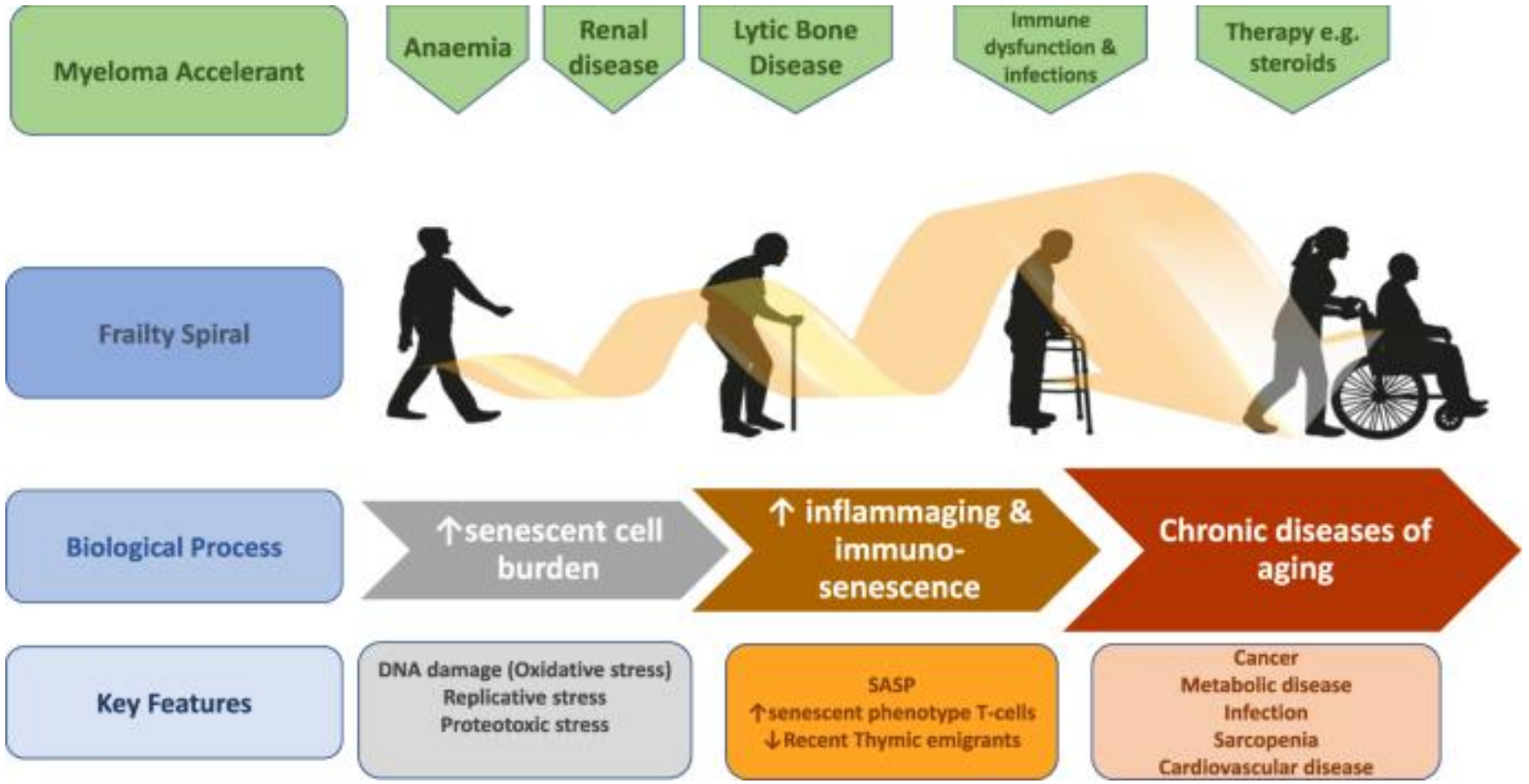
Frailty by cancer issues
Anaemia → Weakness
Immunosuppression → Infection → Fatigue
Tumour pain → Pain-related posture → Sarcopenia

Frailty by chronic multimorbidity and polypharmacy
Congestive heart failure → Low cardiopulmonary reserve
Osteoarthritis→ Immobility → Sarcopenia → Weakness
Diabetic neuropathy → Impaired proprioception → Fall risk
Drug–drug interaction→ Intestinal side-effect → Weight loss

Frailty by senescence of cells and organs or inflammaging
Cardiopulmonary → Decline of VO_2 max
Muscles → Sarcopenia → Loss of strength and power
Metabolism → Lower energy uptake → Undernutrition

Goede et al, *Lancet Healthy Longev*, 2021, 2; e736-45

Frailty

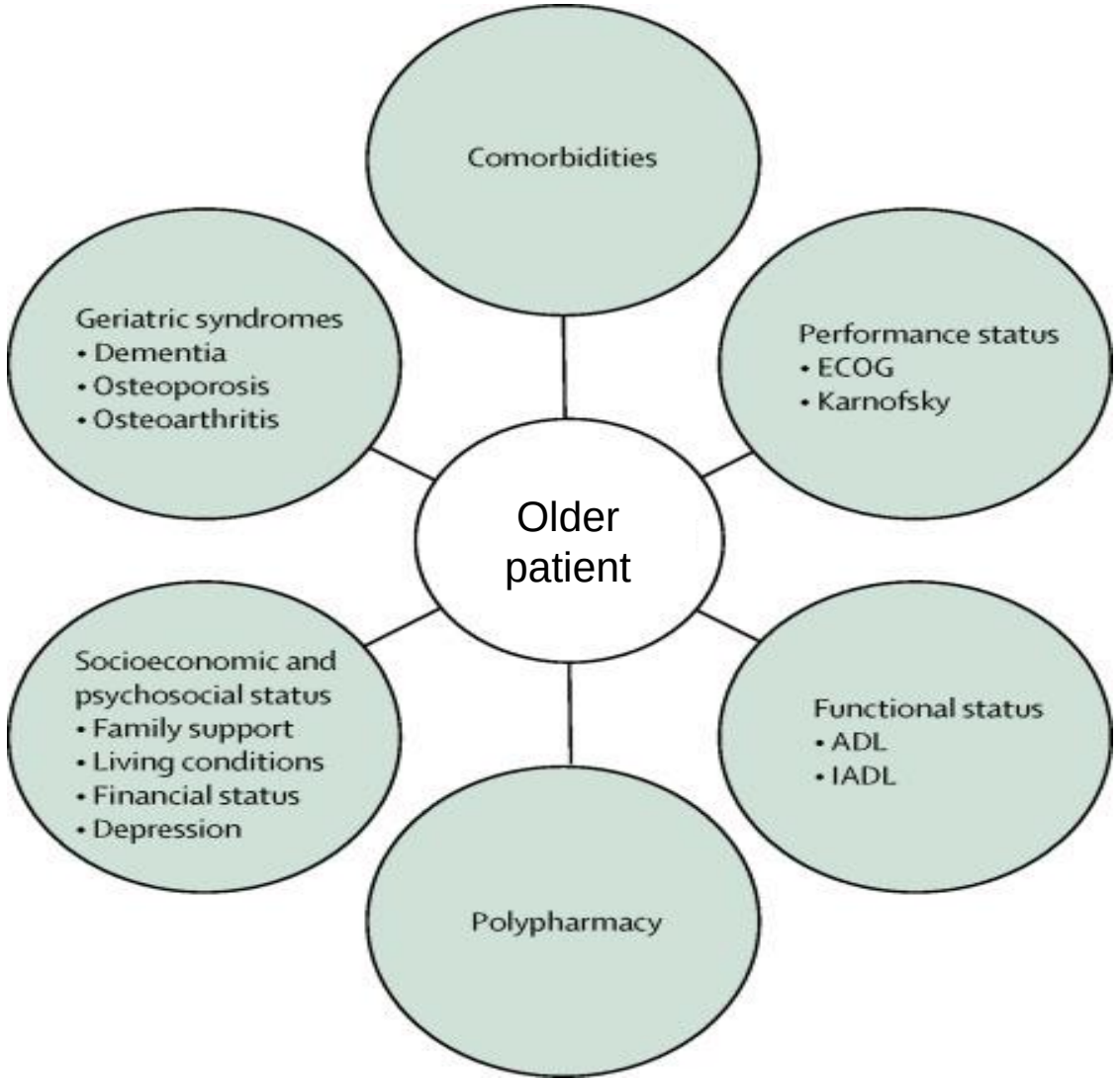


Cook G *et al*. *Leukemia.* 2020;34:2285-2294

Frailty / co-morbidity

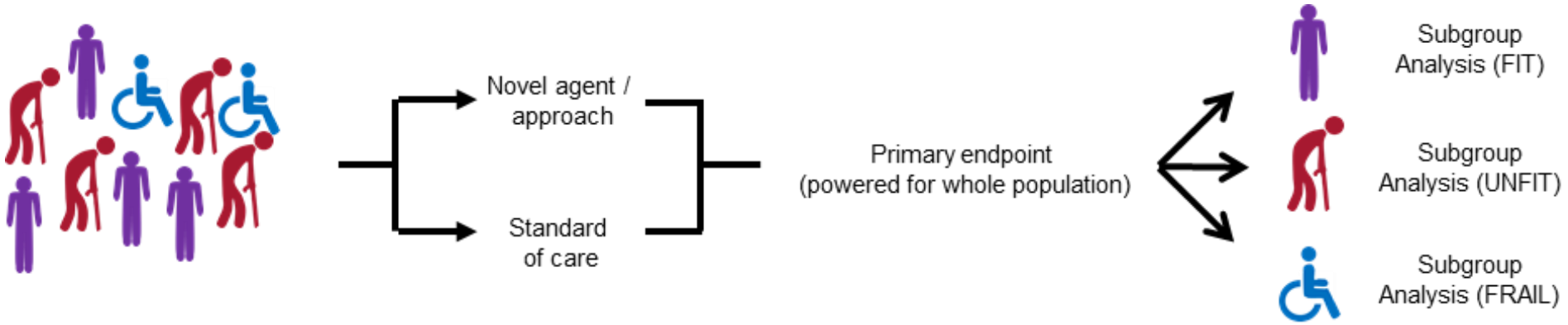
High unmet need

- Frail patients often excluded from clinic trials, both academic and industry
- Multiple domains to address:



Porceddu *et al*. *Lancet Oncology.* 2017

Assessment of frailty in clinical trials



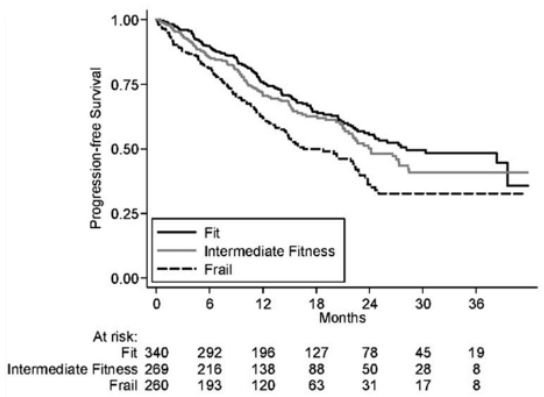
Frailty scores in newly diagnosed myeloma patients

	HR (95% CI)	p-value	Score
Age (years)			
≤75	1		0
76–80	1.13 (0.76–1.69)	0.549	1
>80	2.40 (1.56–3.71)	<0.001	2
CCI			
≤1	1		0
≥2	1.37 (0.92–2.05)	0.125	1
ADL			
>4	1		0
≤4	1.67 (1.08–2.56)	0.020	1
IADL			
>5	1		0
≤5	1.43 (0.96–2.14)	0.078	1

FIT 0
UNFIT 1
FRAIL ≥2

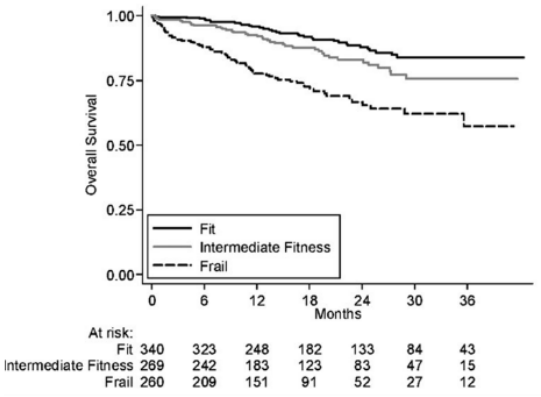
PFS

	3-year PFS	HR, 95% CI	*P* value
Fit	48%		
Unfit	41%	1.18, 0.91–1.53	0.211
Frail	33%	1.68, 1.31–2.15	<0.001



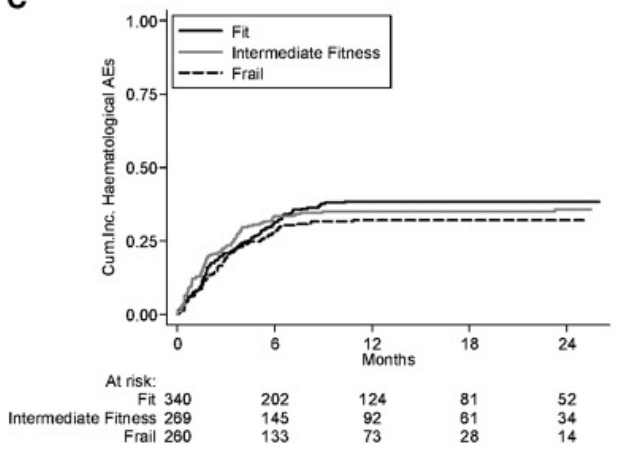
OS

	3-year OS	HR, 95% CI	*P* value
Fit	84%		
Unfit	76%	1.61, 1.02–2.56	0.042
Frail	57%	3.57, 2.37–5.39	<0.001



Higher non-haem toxicity and discontinuation rates were observed in frail patients

C



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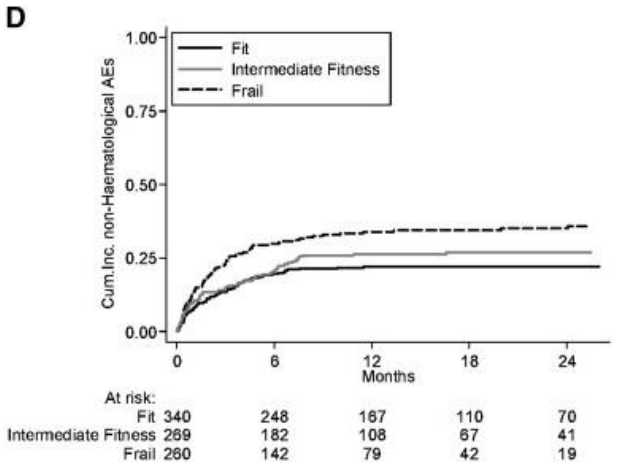

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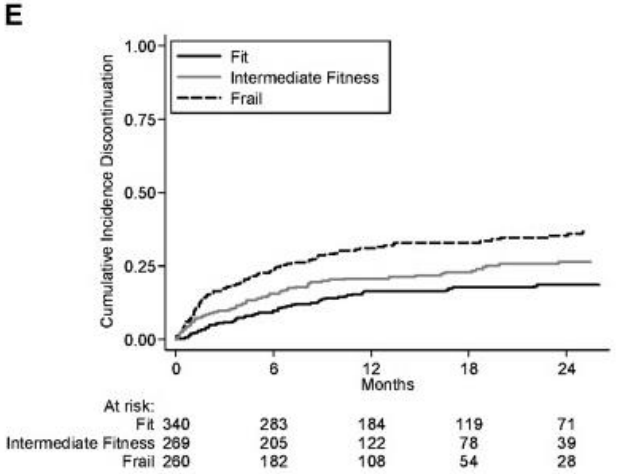


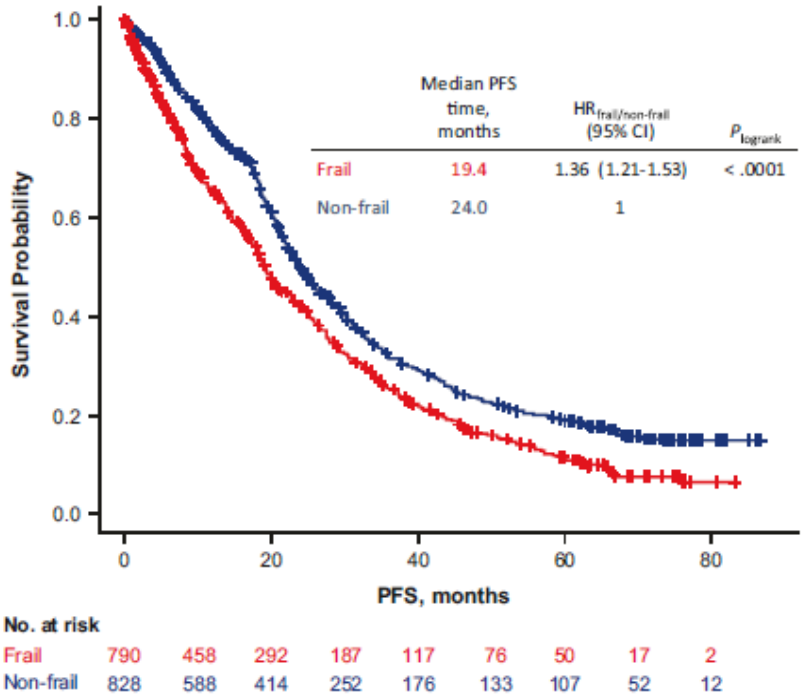
Palumbo A, *et al. Blood* 2015;125:2068–74

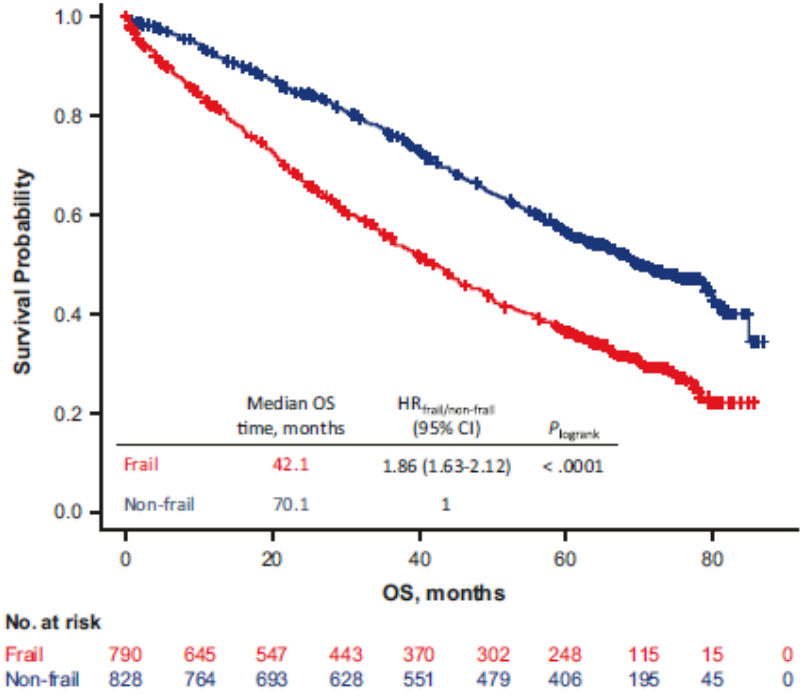
Frailty scores – simplified IMWG

	Score
Age (years)	
≤75	0
76–80	1
>80	2
CCI	
≤1	0
≥2	1
ECOG	
0	0
1	1
2	2

Non-FRAIL 0-1
FRAIL ≥2

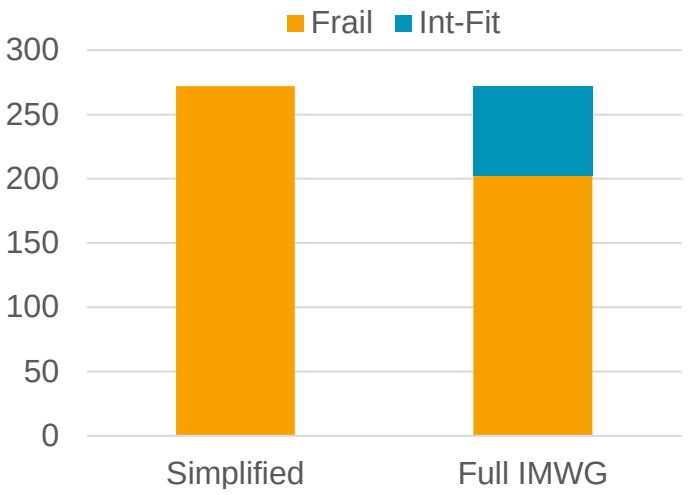
FIRST (MM-020)

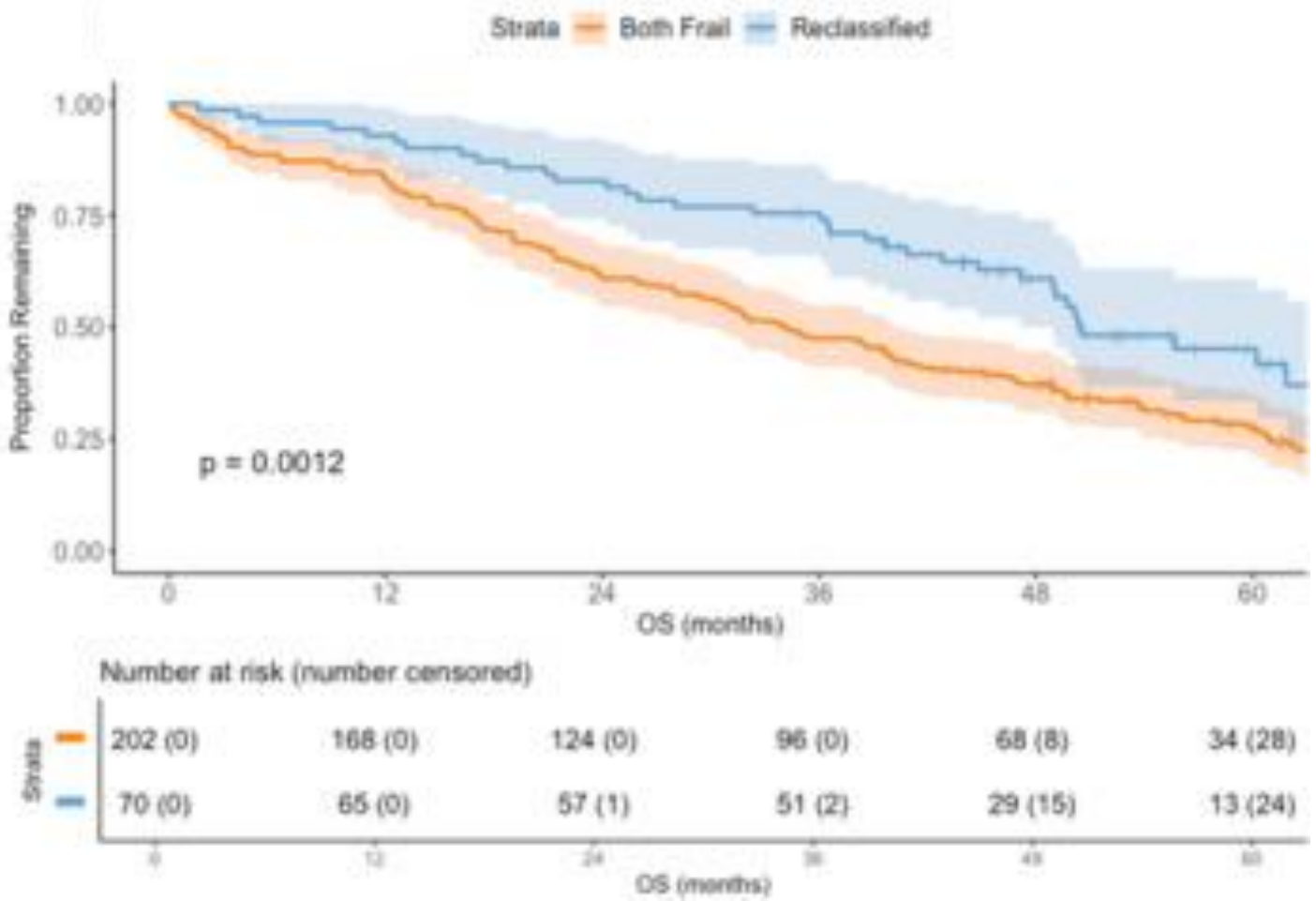




Facon T, *et al*. *Leukemia* 2020;34:224-233

Caution with simplification





Groen K, Smits F, Nasserinejad K, *et al*. *Hemasphere.* 2024

Frailty scores in newly diagnosed myeloma patients

IMWG Frailty Score

	HR (95% CI)	p-value	Score
Age (years)			
≤75	1		0
76–80	1.13 (0.76–1.69)	0.549	1
>80	2.40 (1.56–3.71)	<0.001	2
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FIT 0
UNFIT 1
FRAIL ≥2

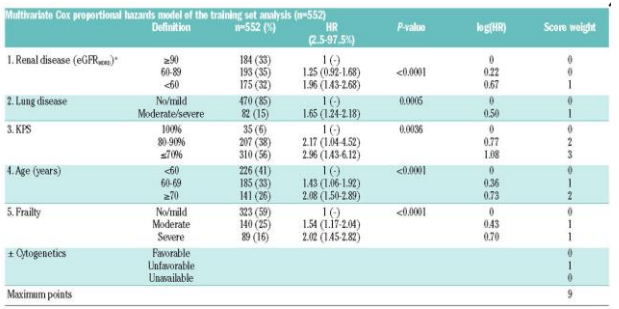
Palumbo A, et al. *Blood.* 2015

Simplified IMWG

	Score
Age (years)	
≤75	0
76–80	1
>80	2
CCI	
≤1	0
≥2	1
ECOG	
0	0
1	1
2	2

Facon T, et al. *Leukemia.* 2020

R-MCI



Multivariate Cox proportional hazards model of the training set analysis (n=552)	Definition	n=552 (%)	HR (2.5-97.5%)	P-value	log(HR)	Score weight
1. Renal disease (eGFR$_{MDRD}$)*	≥90	184 (33)	1 (-)		0	0
	60-89	193 (35)	1.25 (0.92-1.68)	<0.0001	0.22	0
	<60	175 (32)	1.96 (1.43-2.68)		0.67	1
2. Lung disease	No/mild	470 (85)	1 (-)	0.0005	0	0
	Moderate/severe	82 (15)	1.65 (1.24-2.18)		0.50	1
3. KPS	100%	35 (6)	1 (-)	0.0036	0	0
	80-90%	207 (38)	2.17 (1.04-4.52)		0.77	2
	≤70%	310 (56)	2.96 (1.43-6.12)		1.08	3
4. Age (years)	<60	226 (41)	1 (-)	<0.0001	0	0
	60-69	185 (33)	1.43 (1.06-1.92)		0.36	1
	≥70	141 (26)	2.08 (1.50-2.89)		0.73	2
5. Frailty	No/mild	323 (59)	1 (-)	<0.0001	0	0
	Moderate	140 (25)	1.54 (1.17-2.04)		0.43	1
	Severe	89 (16)	2.02 (1.45-2.82)		0.70	1
± Cytogenetics	Favorable					0
	Unfavorable					1
	Unavailable					0
Maximum points						9

Engelhardt M, et al. *Haematologica.* 2017

UK-MRP

- Only data available in all baseline assessments:
  - WHO PS
  - Age
  - ISS
  - CRP
- Age not defined as a cohort but continuous
- No questionnaires

Cook G, et al. *Lancet Haem.* 2019

Mayo

	Score
Age	
<70	0
≥70	1
PS	
0–1	0
≥2	1
NT BNP	
<300 mg/L	0
≥300 mg/L	1

Milani P, et al. *AJH* 2016

Improving outcomes for older patients in clinical trials

Novel agent / approach

Standard of care

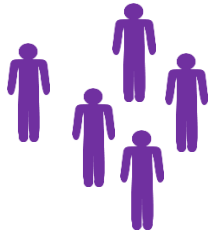
Primary endpoint (powered for whole population)

Subgroup Analysis (FIT)

Subgroup Analysis (UNFIT)

Subgroup Analysis (FRAIL)

FIT



Novel agent / approach

Standard of care

Primary endpoint (powered for FIT population)

UNFIT

Novel agent / approach

Standard

Primary endpoint (powered for UNFIT population)

Identify patients upfront and adapt therapy based on frailty

FRAIL

Novel agent / approach

Standard of care

Primary endpoint (powered for FRAIL population)

Trial Design

FiTNEss
UK-MRA Myeloma XIV

Induction (12 cycles) → Maintenance (to PD or intolerance)

R1

"REACTIVE"
(Standard dosing)

	All patients	Days
Ixazomib	4mg	1,8,15
Lenalidomide	25mg	1-21
Dexamethasone	40mg (<=75y) 20mg (>75y)	1,8,15,22

"ADAPTIVE"
(IMWG frailty score adjusted dosing)

	FIT	UNFIT	FRAIL	Days
Ixazomib	4mg	4mg	4mg	1,8,15
Lenalidomide	25mg	15mg	10mg	1-21
Dexamethasone	40mg	20mg	10mg	1,8,15,22

R2

- Lenalidomide + placebo
- Lenalidomide + ixazomib

Chief Investigators:
Gordon Cook
Graham Jackson

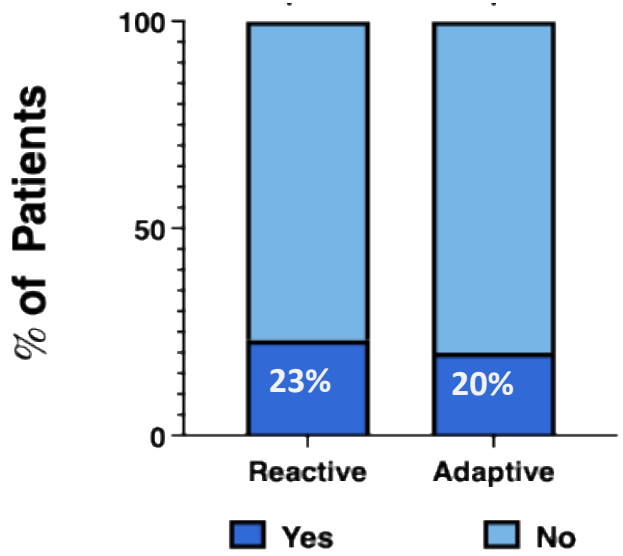
Coulson A. et al, BMJ Open 2022

Results – Early Treatment Cessation (ETC)

UKMRA
UK Myeloma
Research Alliance

Unfit/Frail (n=535)

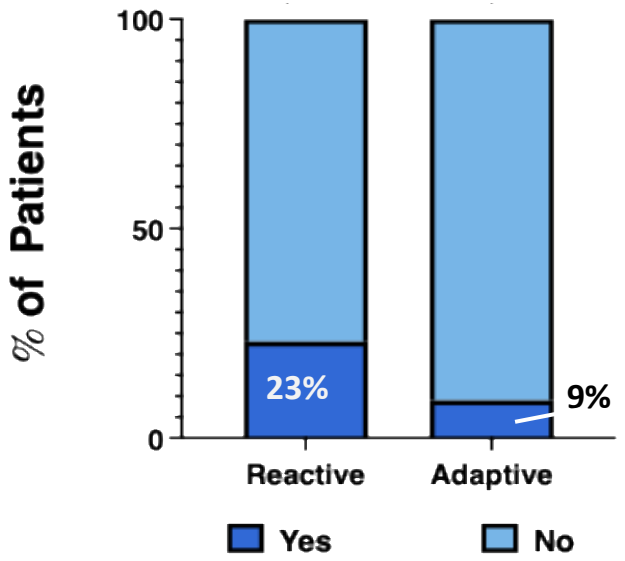
OR 0.83 (95% CI: 0.54, 1.25, p=0.3678)



Reasons for stopping	Reactive	Adaptive
Death	26.9%	27.5%
Patient choice	28.8%	23.5%
Clinician choice	9.6%	15.7%
Toxicity	26.9%	21.6%

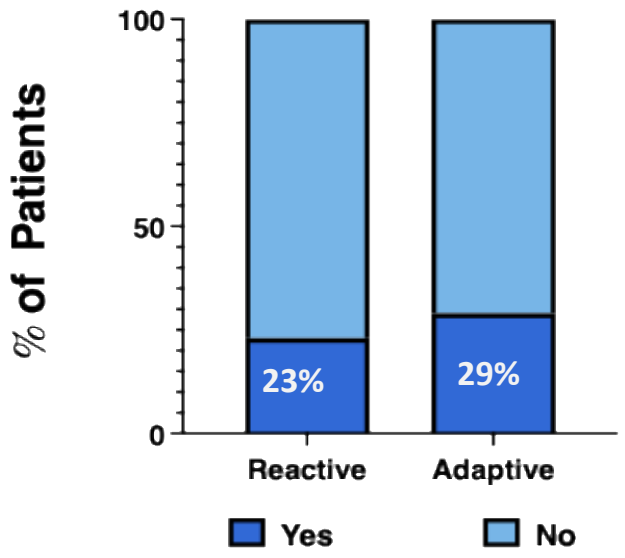
Unfit (n=240)

OR 0.34 (95% CI: 0.16, 0.72)



Frail (n=295)

OR 1.33 (95% CI: 0.79,2.25)



FiTNESs UK-MRA Myeloma XIV g.cook@leeds.ac.uk

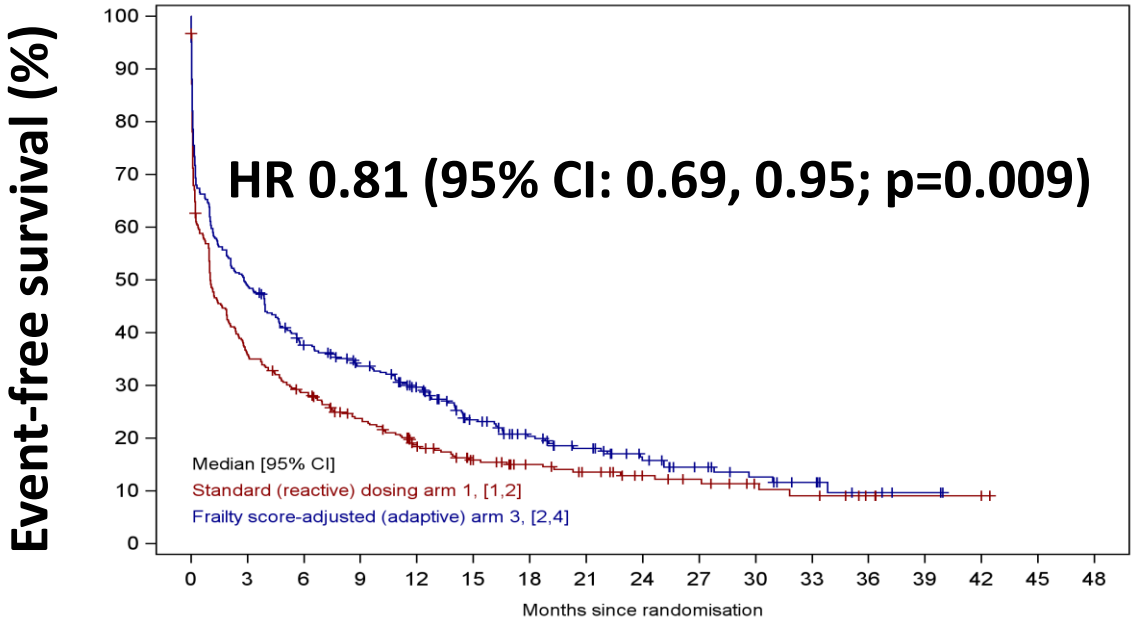
Cook G. et al, ASH 2024

Results – Event-free survival (EFS)

UKMRA
UK Myeloma Research Alliance

EFS defined as: PD, death from any cause, withdrawal from trial treatment, non-haematological (gd≥3) & haematological (gd≥4) toxicities

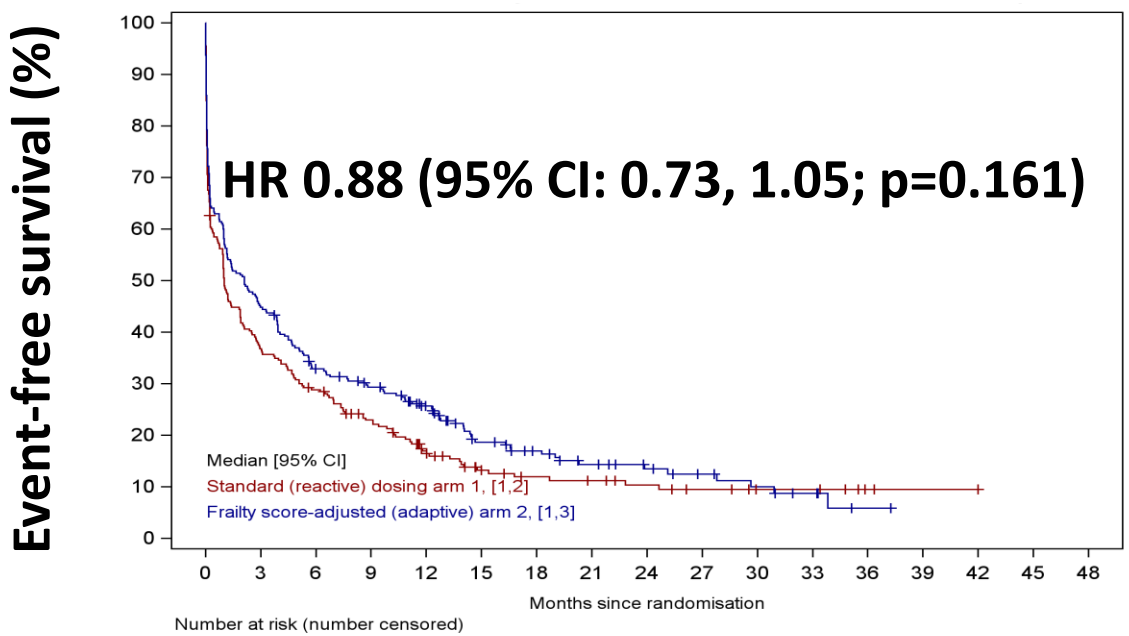
EFS ITT Population



Number at risk (number censored)

Standard (reactive) dosing arm	365 (1)	102 (4)	55 (18)	31 (32)	18 (41)	10 (47)	4 (51)	1 (54)	0 (55)
Frailty score-adjusted (adaptive) arm	368 (0)	134 (5)	91 (21)	47 (39)	26 (51)	13 (60)	4 (67)	0 (71)	

EFS Unfit/Frail Population



Number at risk (number censored)

Standard (reactive) dosing arm	265 (0)	75 (2)	35 (13)	17 (22)	12 (25)	6 (30)	2 (34)	0 (36)	
Frailty score-adjusted (adaptive) arm	270 (0)	86 (3)	56 (15)	27 (27)	15 (34)	8 (38)	1 (43)	0 (44)	

1-year EFS:

- **Reactive arm 18.8% (95% CI: 14.8%, 23.0%)**
- **Adaptive arm 29.7% (95% CI: 25.0%, 34.5%)**

1-year EFS:

- **Reactive arm 16.9% (95% CI: 12.6%, 21.8%)**
- **Adaptive arm 25.7% (95% CI: 20.6%, 31.1%)**

FiTNEss UK-MRA Myeloma XIV g.cook@leeds.ac.uk

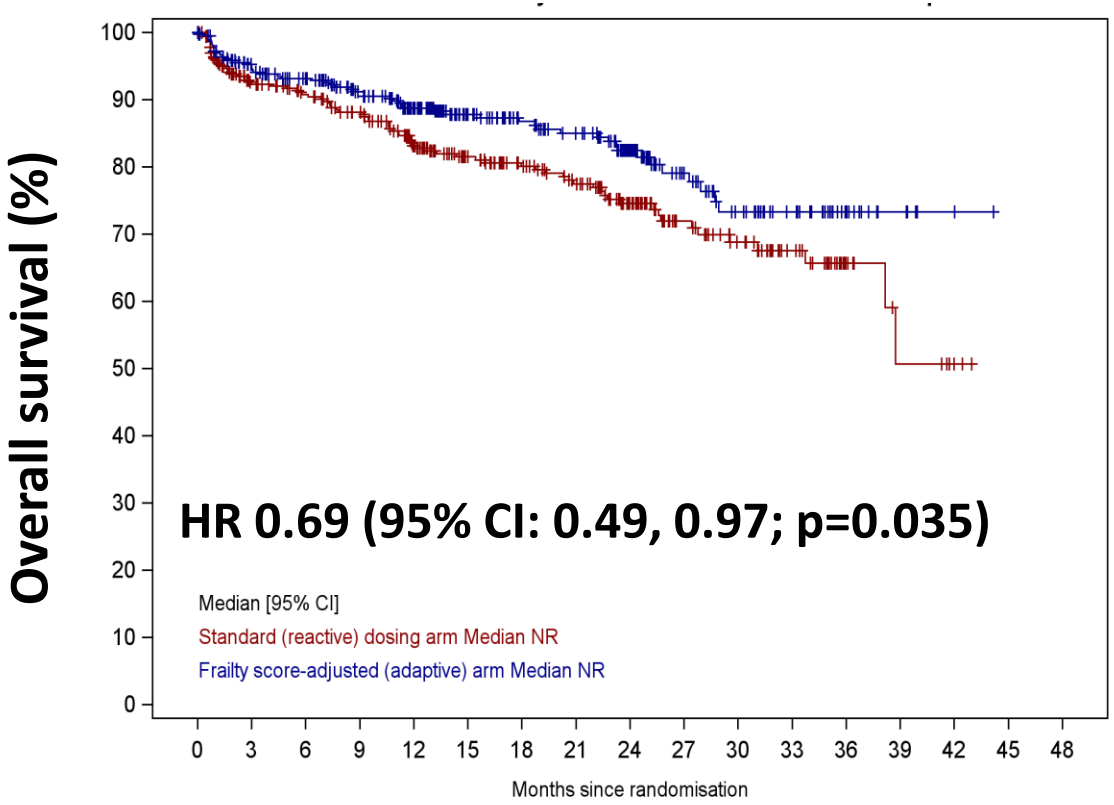
Median Follow-up: 14.7m (7.6,24.4)

Cook G. et al, ASH 2024

Results – Overall survival (OS)

UKMRA
UK Myeloma
Research Alliance

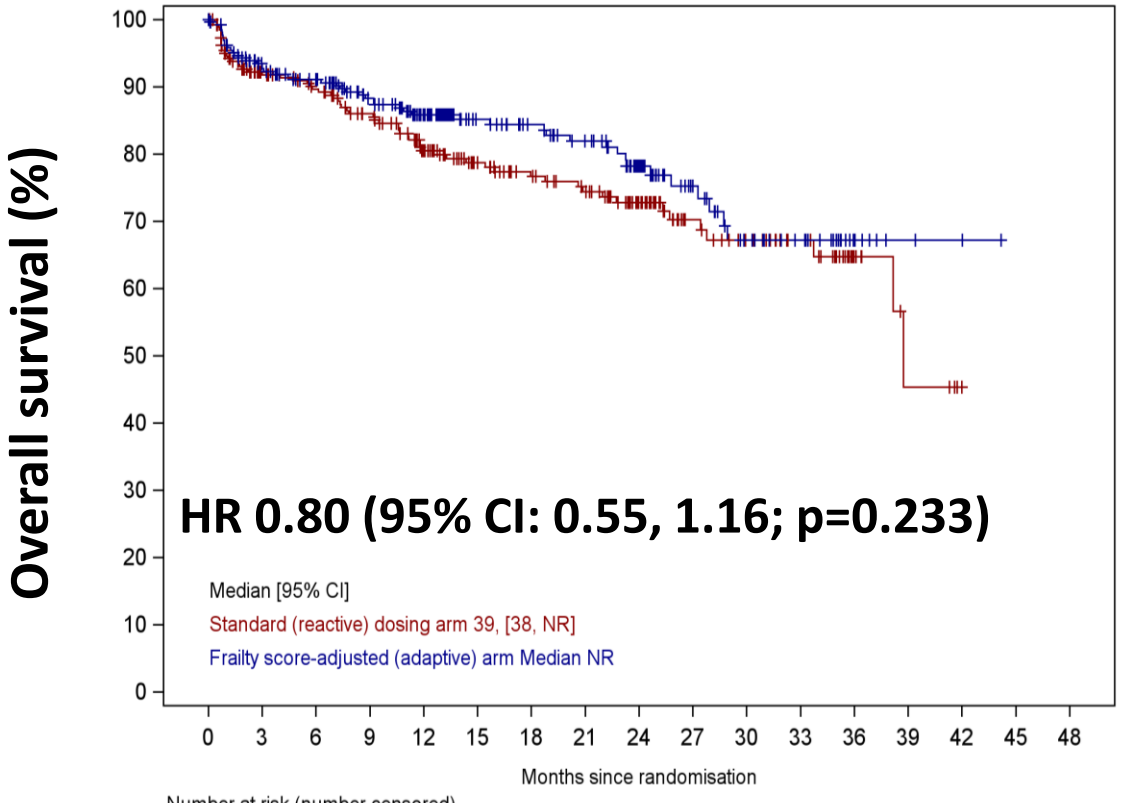
OS ITT Population



Number at risk (number censored)

Standard (reactive) dosing arm	365 (1)	285 (48)	217 (94)	161 (143)	106 (188)	58 (230)	16 (270)	2 (282)	0 (284)
Frailty score-adjusted (adaptive) arm	368 (2)	302 (42)	229 (102)	155 (172)	96 (224)	43 (270)	15 (298)	2 (311)	0 (313)

OS Unfit/Frail Population



Number at risk (number censored)

Standard (reactive) dosing arm	265 (0)	204 (35)	148 (72)	107 (107)	72 (137)	39 (166)	11 (193)	0 (202)	
Frailty score-adjusted (adaptive) arm	270 (2)	213 (34)	156 (80)	104 (130)	66 (161)	29 (192)	9 (212)	2 (219)	0 (221)

FiTNEss UK-MRA Myeloma XIV g.cook@leeds.ac.uk

Median Follow-up: 14.7m (7.6, 24.4)

Cook G. et al, ASH 2024

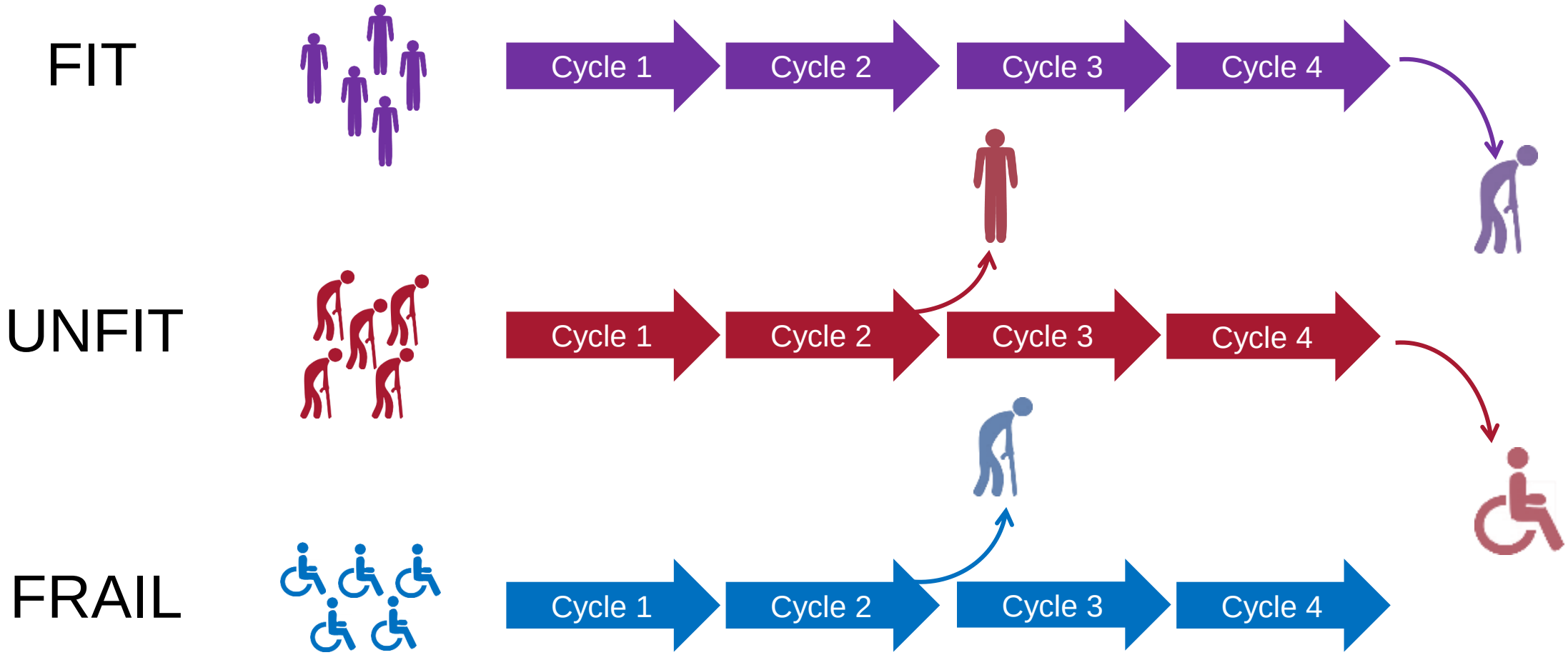
Possible dose modifications

	FIT	UNFIT	FRAIL
Prospectively evaluated in FiTNEss:			
Dexamethasone	40mg weekly	20mg weekly	10mg weekly
Lenalidomide	25mg	15mg	10mg
Ixazomib	4mg	4mg* / 3mg	4mg* / 2.3mg
Not prospectively evaluated:			
Pomalidomide	4mg	3mg	2mg
Bortezomib	1.3mg/m2 twice weekly / weekly	1.3mg/m2 weekly	1mg/m2 weekly
Carfilzomib	Depending on schedule		
Daratumumab	No modification recommended		

*dose in FiTNEss

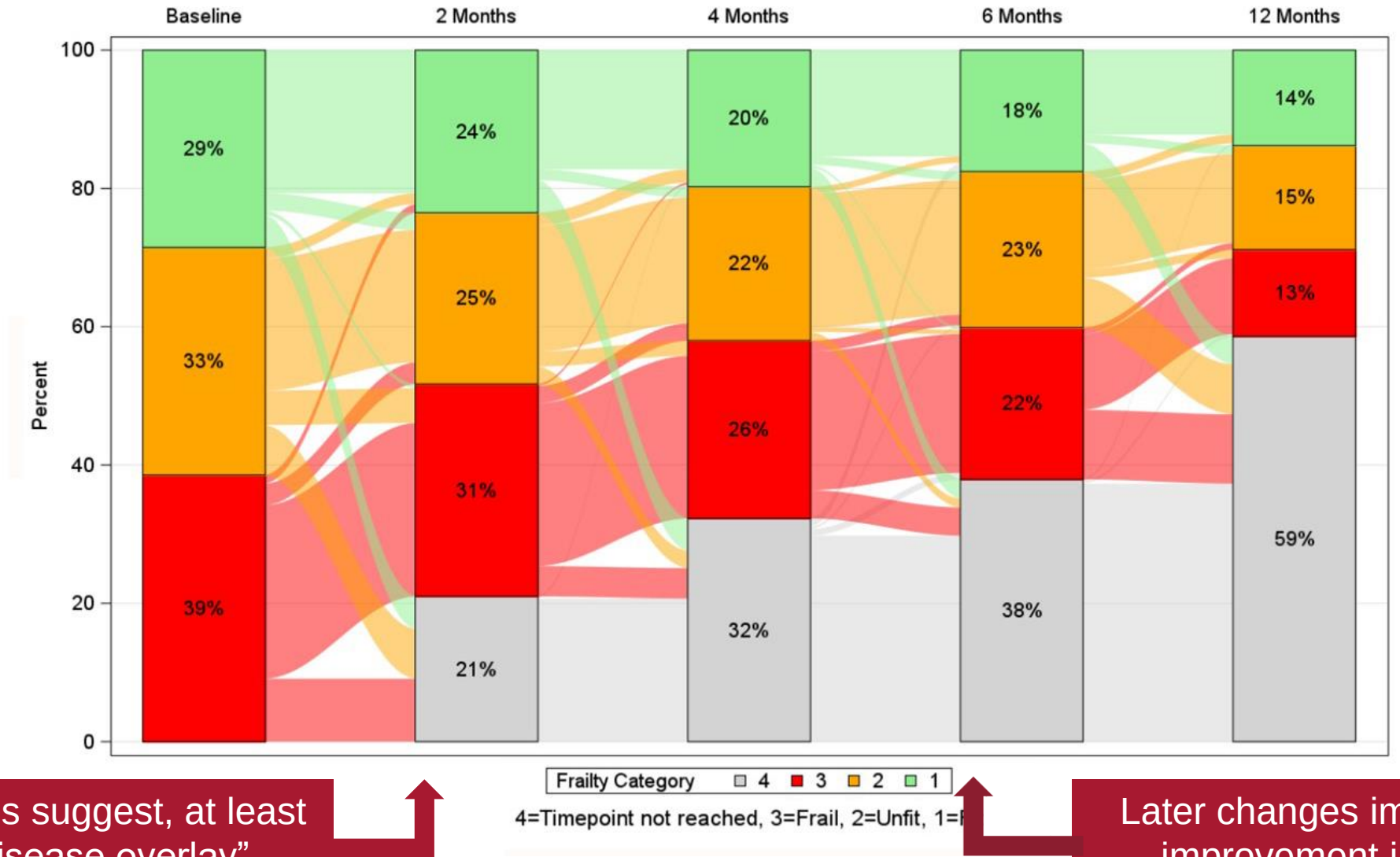
Based on EHA/ESMO guidelines and Zweegman S, Current Opinion in Oncology 2017

Frailty as a dynamic/modifiable risk factor



Pawlyn C, et al *Hematology Am Soc Hematol Educ Program*. 2022

Frailty as a dynamic biomarker in FiTNEss (REACTIVE/standard arm only)



Early changes suggest, at least in part, “disease overlay”

Later changes imply ongoing improvement in function

Dynamic frailty better predicts overall survival

HOVON 143

Dara-Ixa-dex

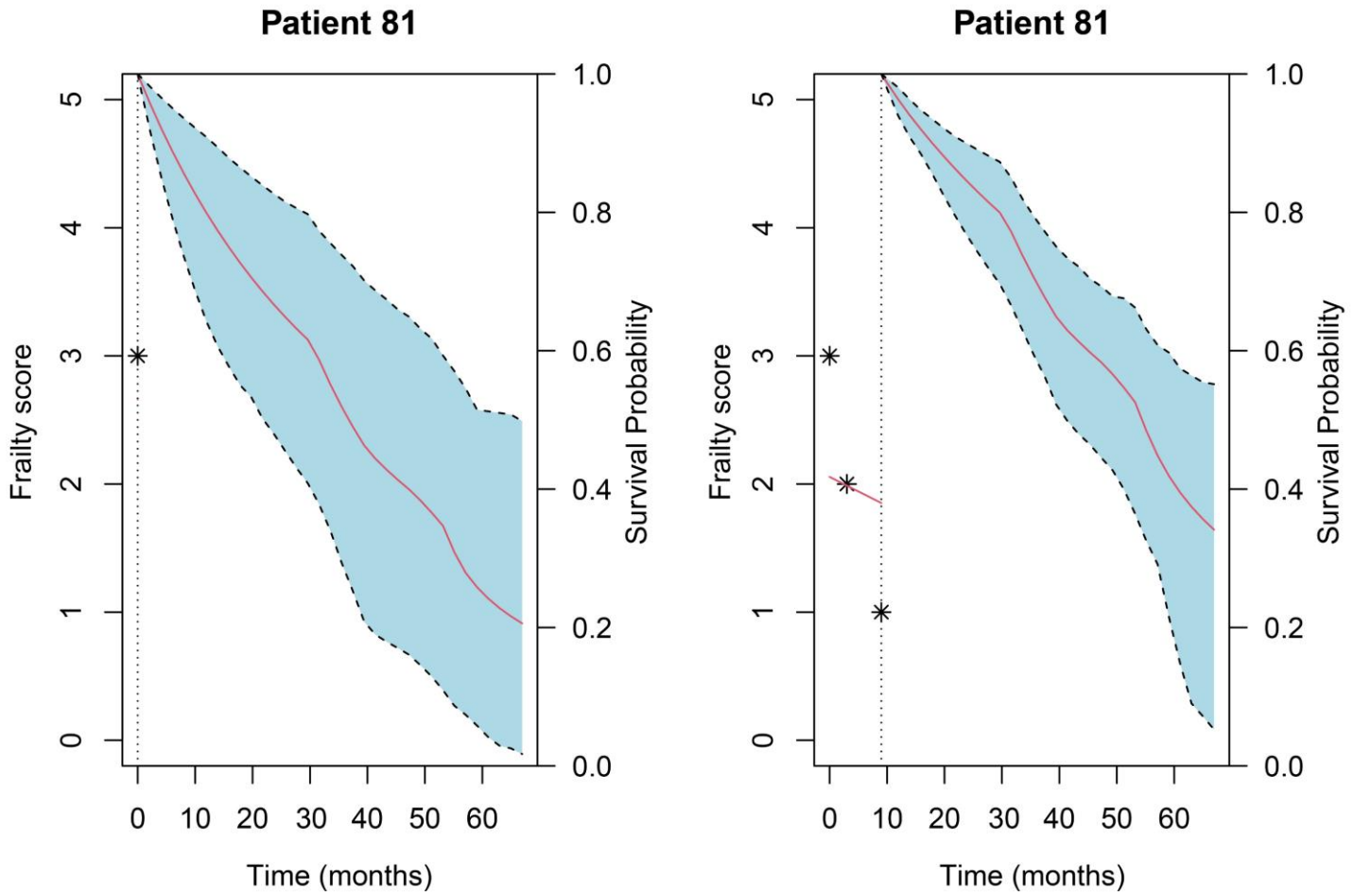
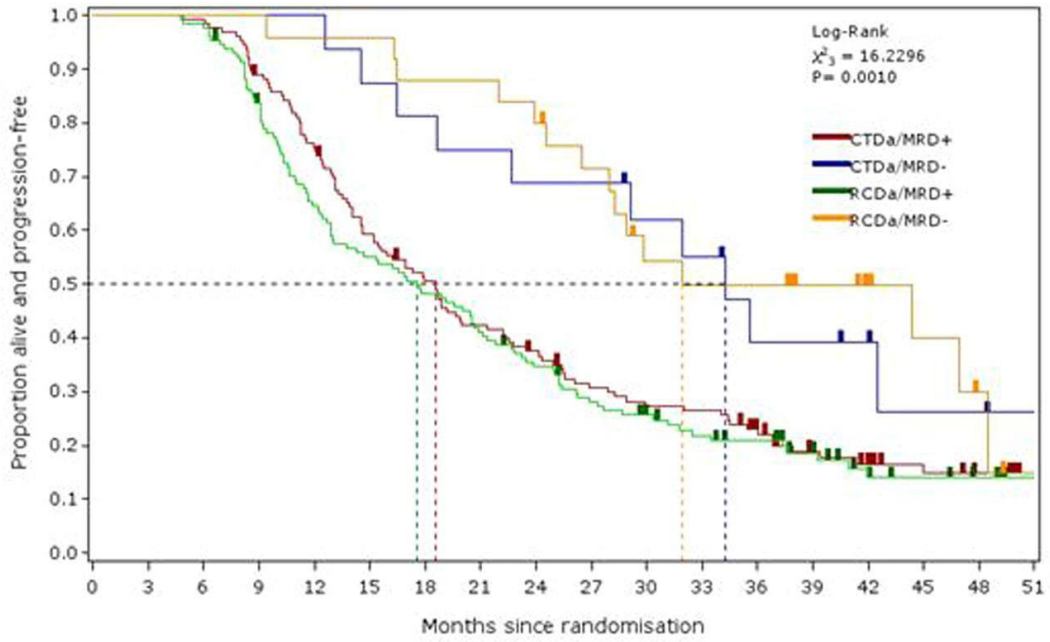


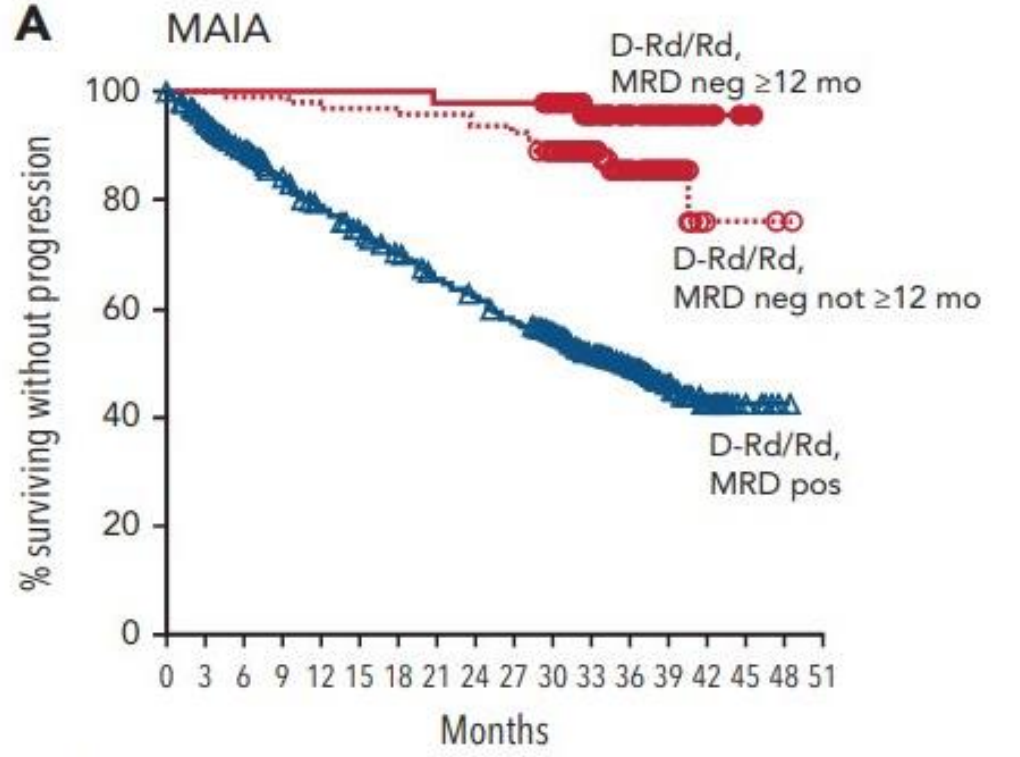
Figure 1. Survival probability based on frailty assessment at baseline (**left**), versus survival probability based on incorporating dynamic frailty assessments over time (**right**). A representative patient case demonstrates the impact of improvement in frailty score from 3 at baseline, to 2 at three months and 1 at nine months, on survival probability.

Smits F. et al, ASH 2023

Induce deep remission – MRD as a goal

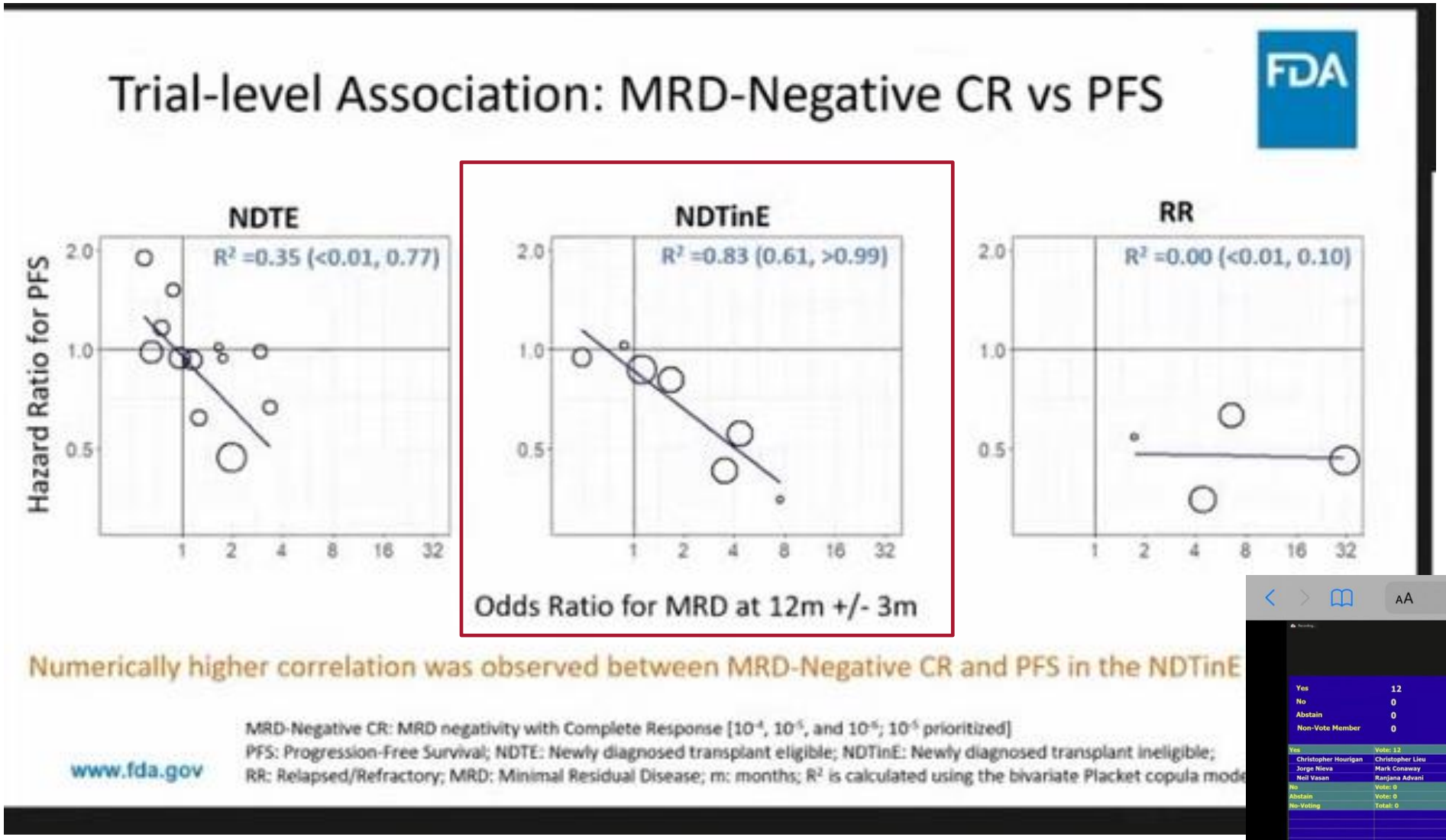


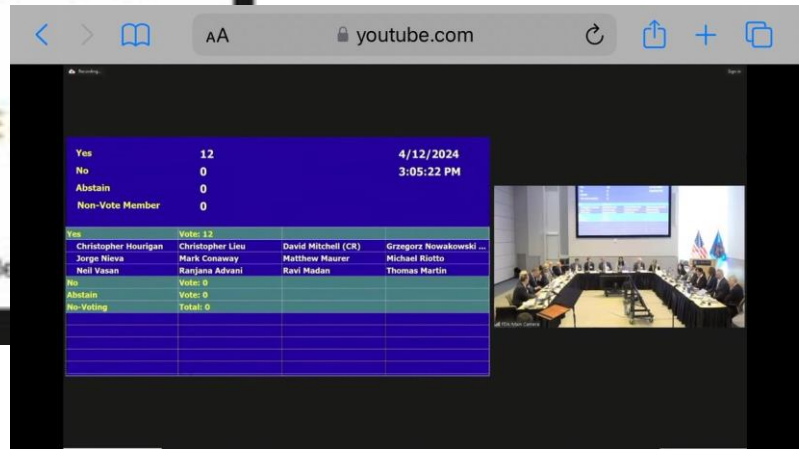
De Tute R, ASH, 2016



San Miguel J, Blood, 2022

Induce deep remission – MRD as a goal

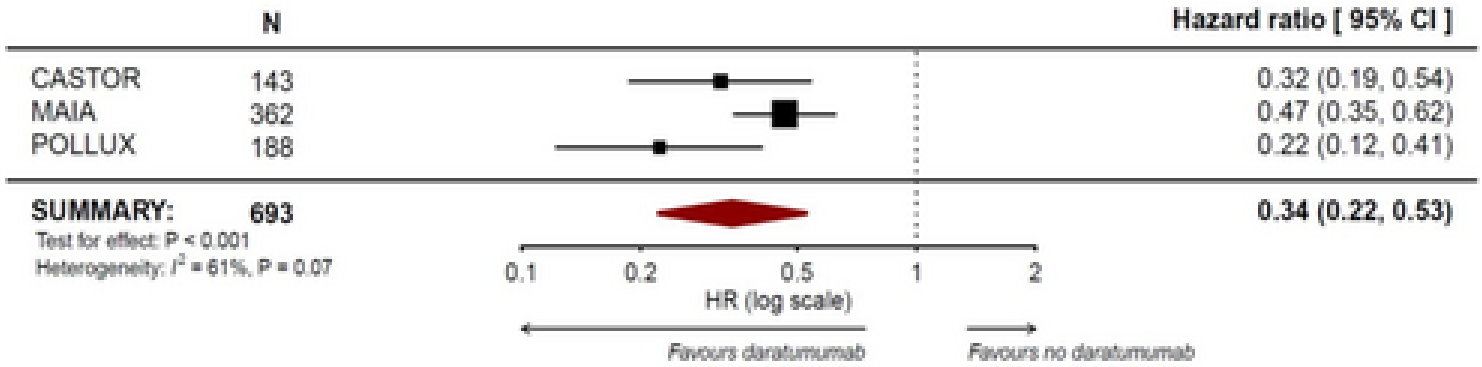




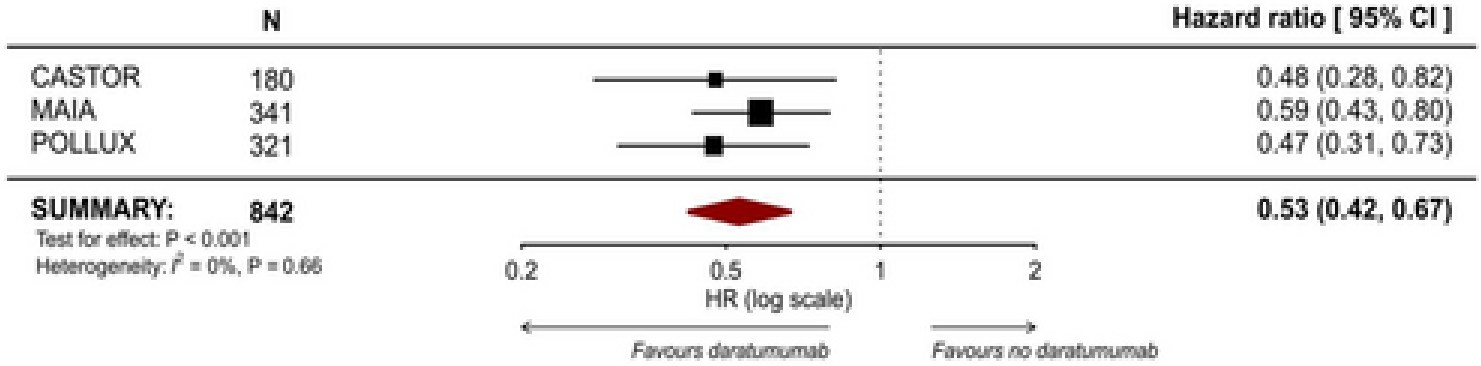
FDA, ODAC, 2024

Inducing deeper remission improves outcomes even in patient with lower physical function

A) Low physical function – Progression Free Survival

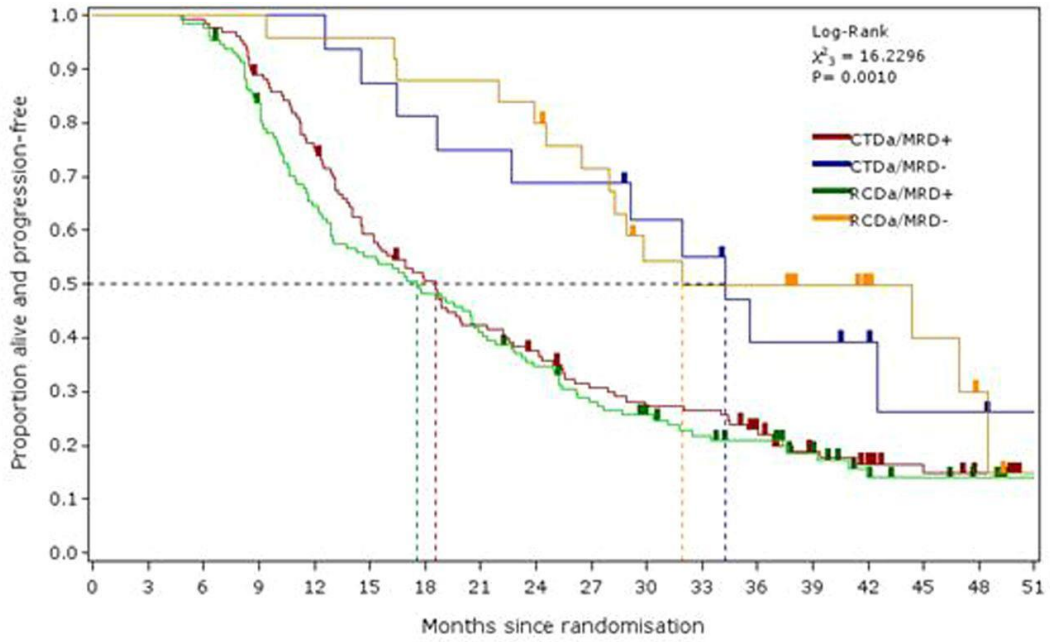


B) High physical function – Progression Free Survival

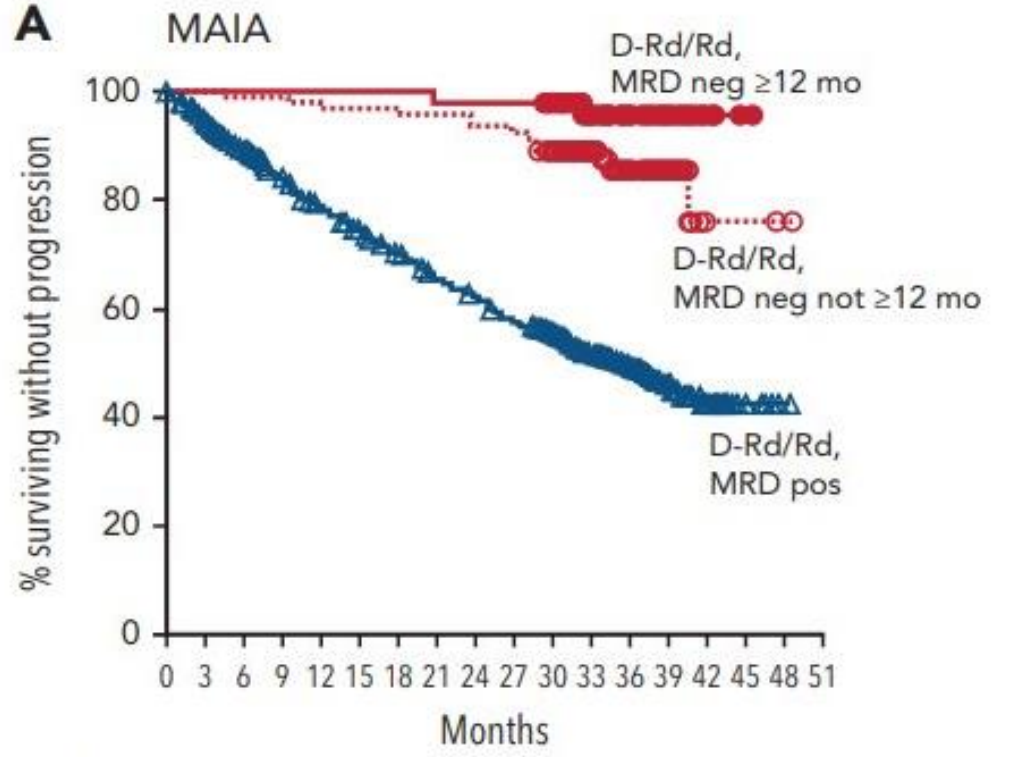


Abuhella, EJH, 2025

Induce deep remission – MRD as a goal



De Tute R, ASH, 2016

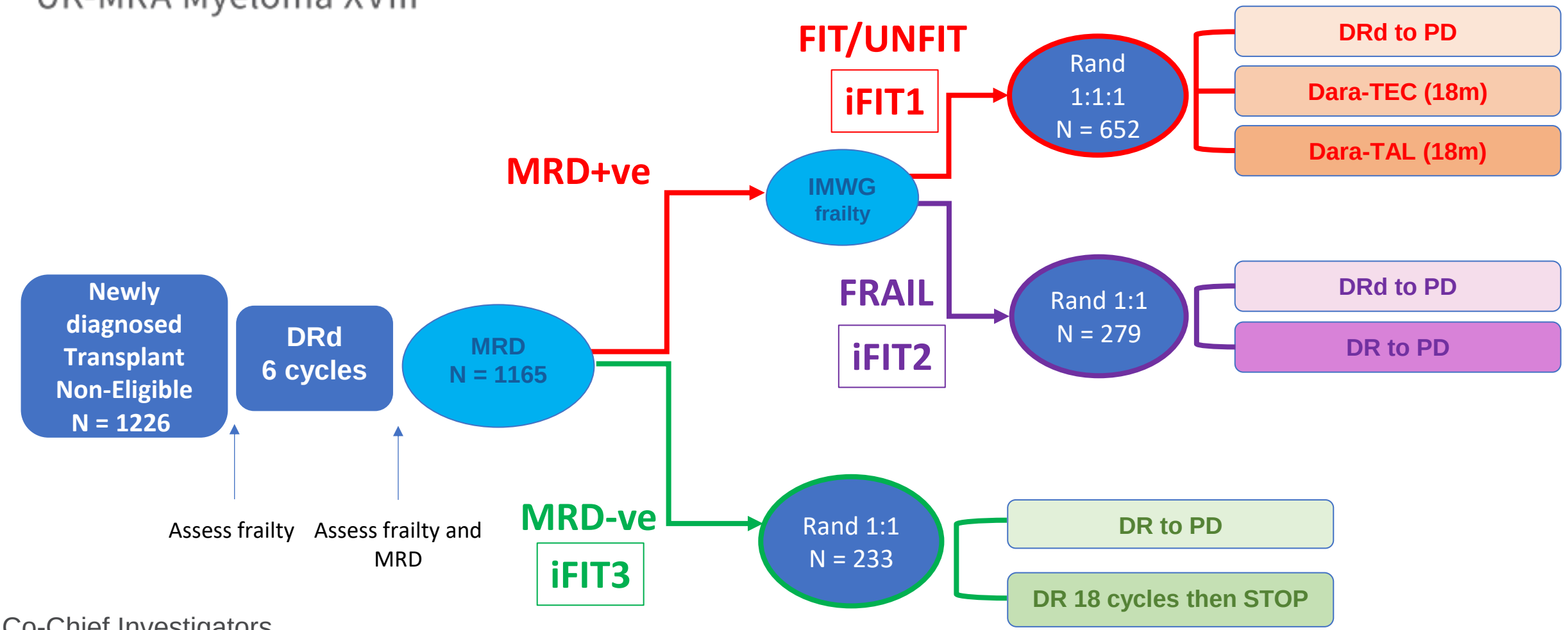


San Miguel J, Blood, 2022

iFIT

UK-MRA Myeloma XVIII

iFIT: Immunotherapy approaches adapted for Fitness In newly diagnosed transplant ineligible patients with myeloma



Co-Chief Investigators
Dr Charlotte Pawlyn
Professor Gordon Cook

Summary

- *Excess* deaths are highest in older myeloma patients
- Stratified medicine in this group should focus on frailty not genetics
- Several frailty scores published and validated in different patient cohorts
  - Prospective validation of treatment mofification based on frailty score
  - Limitations of frailty scores – ongoing work to define ‘frailty biomarkers’
- Important to recognise potentially dynamic nature of frailty – this may change suitability for different treatment modalities over time
- Achieving the deepest, MRD negative remissions is critical

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Myeloma XI

FiTNEss UK-MRA Myeloma XIV

Chief Investigators:
Gordon Cook and Graham Jackson

iFIT UK-MRA Myeloma XVIII

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UKMRA UK Myeloma Research Alliance