

ASH Review: Geriatric Hematology

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Nebraska
Medicine



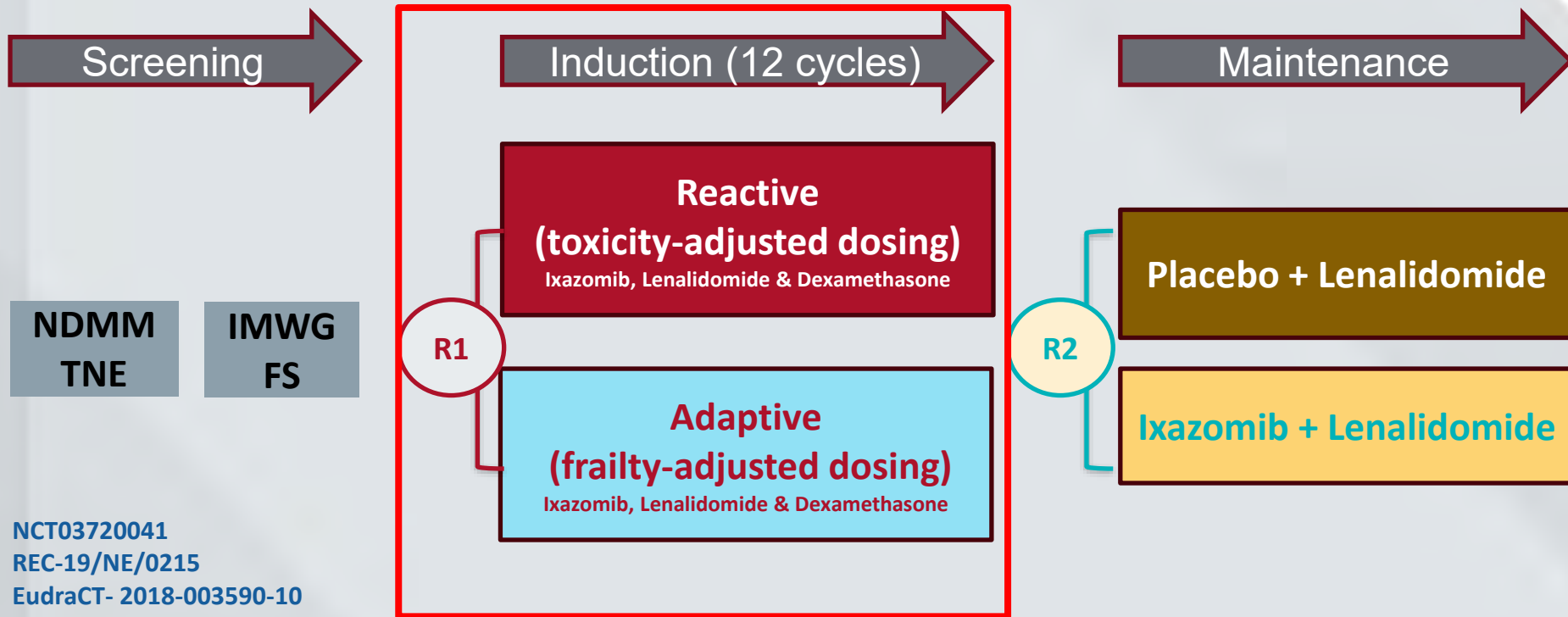
Myeloma



UK-MRA Myeloma XIV FiTNEss Trial Design



Chief Investigators: Gordon Cook, Graham Jackson



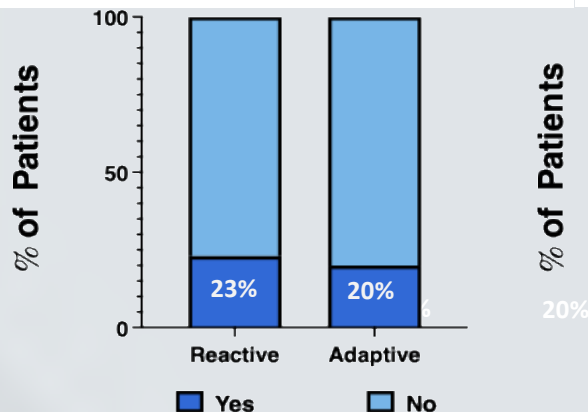
NCT03720041
REC-19/NE/0215
EudraCT- 2018-003590-10
ISRCTN17973108

Results – Early Treatment Cessation (ETC)



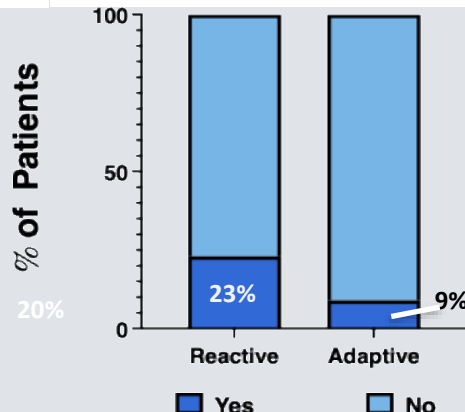
Unfit/Frail (n=535)

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



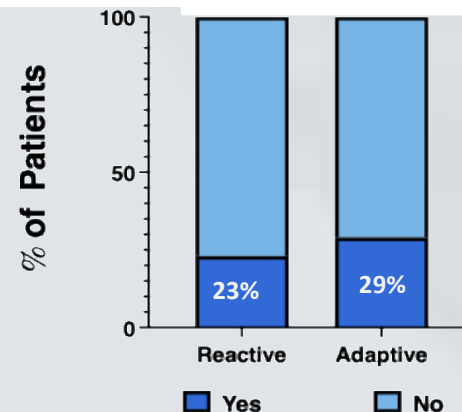
Unfit (n=240)

OR 0.34 (95% CI: 0.16, 0.72)



Frail (n=295)

OR 1.33 (95% CI: 0.79, 2.25)



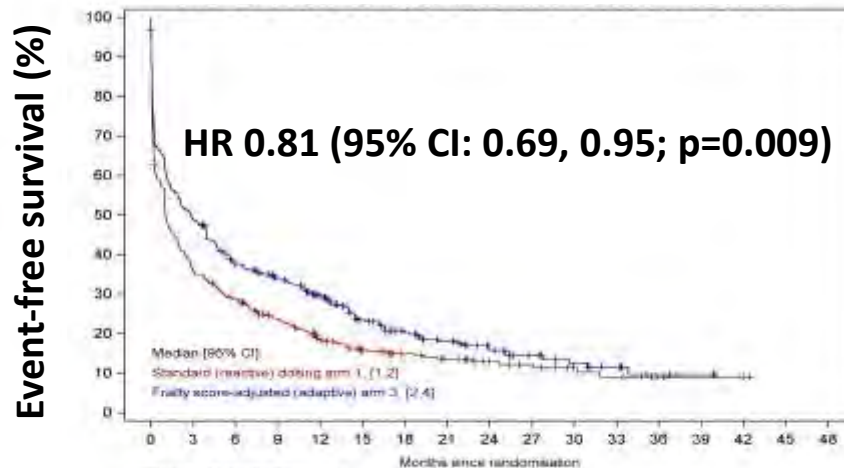
Reasons for stopping	Reactive	Adaptive
Death	26.9%	27.5%
Patient choice	28.8%	23.5%
Clinician choice	9.6%	15.7%
Toxicity	26.9%	21.6%

Results – Event-free survival (EFS)

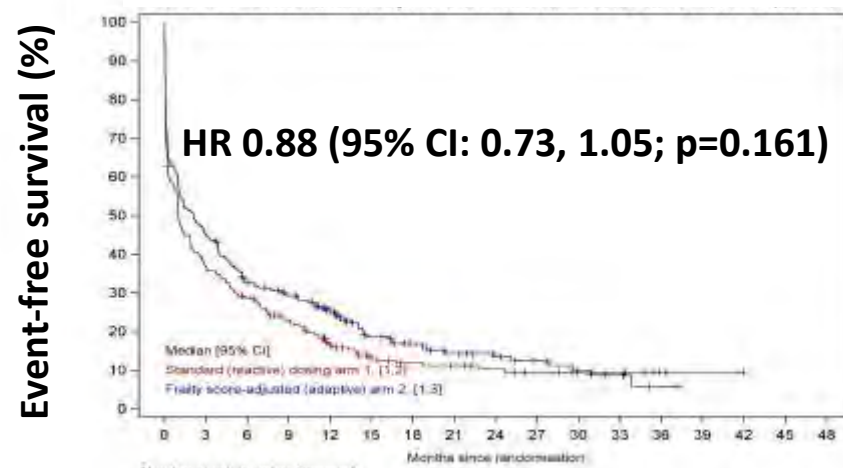


EFS defined as: PD, death from any cause, withdrawal from trial treatment, non-haematological (gd \geq 3) & haematological (gd \geq 4) toxicities

EFS ITT Population



EFS Unfit/Frail Population



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:

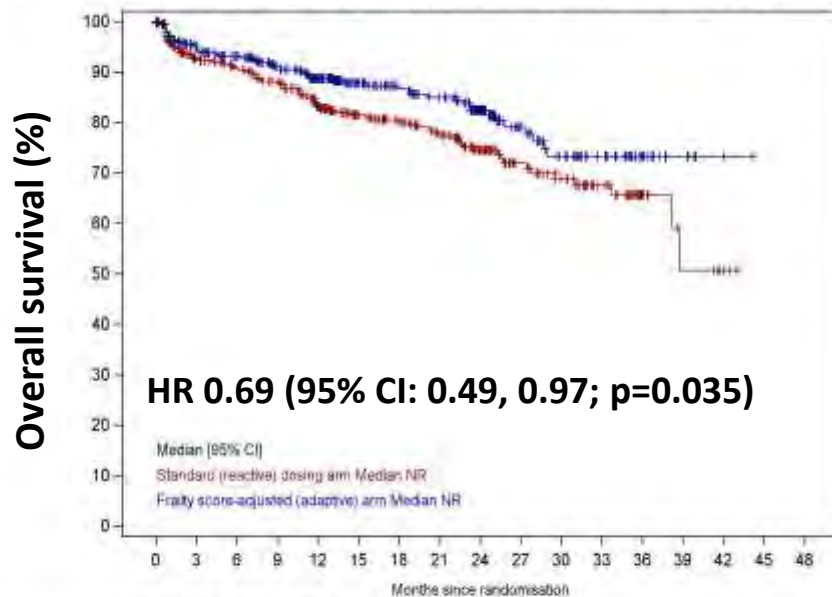
- Reactive arm 16.9% (95% CI: 12.6%, 21.8%)

- Adaptive arm 25.7% (95% CI: 20.6%, 31.1%)

Results – Overall survival (OS)



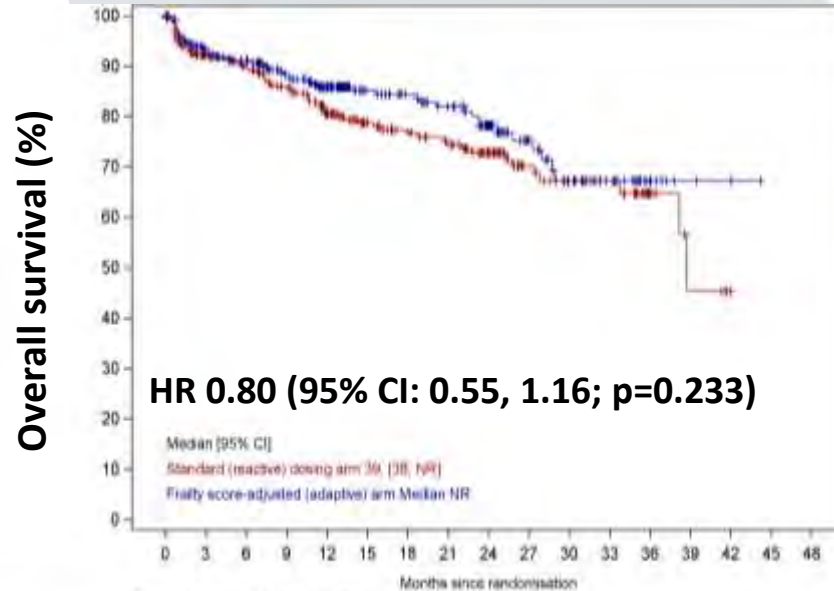
OS ITT Population



Number at risk (number censored)

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
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 (288)	2 (311)	0 (313)								

OS Unfit/Frail Population



Number at risk (number censored)

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Standard (reactive) dosing arm	269 (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 (60)	104 (130)	66 (161)	29 (192)	9 (212)	2 (218)	0 (221)								

Median Follow-up: 14.7 mns (7.6,24,4)

Frailty and Outcomes in Multiple Myeloma Patients Eligible for Autologous Hematopoietic Cell Transplantation



How is frailty evaluated? HCT frailty scale	Who performs the evaluation?
Clinical frailty score (CFS): ≥3 (Frail) [vs 1-3 (Not frail)]	Median time: 5-6 minutes
Instrumental activities of daily living (IADL) score: ≥1 Limitation [vs no limitation]	Medical doctor
Timed up and go test (TUGT): Abnormal >10 seconds [vs normal]	Nurse coordinator
Grip strength (GS): Abnormal [vs normal] If female less than 16 kg If male less than 26 kg	Laboratory (bloodwork)
Self-rated health question (SRH-Q) Fair, poor [vs excellent, very good, good]	When?
Fall in last 6 months: Yes [vs no]	Before HCT: first consultation
Albumin serum level (Alb): Abnormal (<38 g/L) [vs normal]	Costs
C-reactive protein (CRP): Abnormal (≥11 mg/L) [vs normal]	Hand dynamometer
	No other recurrent costs



N=296

Median age 57 (range 31-75)

	Fit	Intermediate	Frail	P-value
	23.2%	48%	18%	
Hospitalization, days	14	15	15	
Readmission	2.0%	8.6%	13.5%	0.06
1-Yr relapse	8.9%	5.6%	6.5%	0.903
1-Yr OS	98.9%	95.8%	84.3%	<0.01



Simplified Frailty Scale

Table 1 ECOG proxy of IMWG algorithm of frailty

Category	Score
Age	
≤75 years	0
76–80 years	1
>80 years	2
Charlson Comorbidity Index	
≤1	0
>1	1
ECOG performance status	
0	0
1	1
≥2	2
Sum of scores	
Nonfrail	0–1
Frail	≥2

ECOG Eastern Cooperative Oncology Group, *IMWG* International Myeloma Working Group

Frailty and Outcomes after Bispecific T-Cell Engager Therapy for Patients with Relapsed/Refractory Multiple Myeloma



- Single institution retrospective cohort study
- Treatment: Teclistimab, talquetamab, elranatamab
- N= 112
- Age range 40 - 88
- 83 (74%) frail at the time of BsAb treatment
- Frailty measure used: Simplified (IFM) frailty score (=age, ECOG PS, Charlson comorbidity Index)

	Frail N=83	Nonfrail N=29	P- value
CRS (all grades)	62%	62%	1
ICANS (all grades)	14%	3%	0.21
Treatment-related mortality	14%	7%	0.46
Overall response rate	72%	62%	0.43
Median PFS (months)	6.5	4.6	0.45
Median OS (months)	7.5	7.3	0.16



Frailty-Based Outcomes with Bispecific Antibodies in Older Patients with Multiple Myeloma

- Retrospective cohort study, single-institution
- Treatment: Teclistimab, talquetamab or investigational
- N= 99
- Age range 65-89 years
- 71% frail at the time of BsAb treatment
- Frailty measure used: Simplified (IFM) frailty score (=age, ECOG PS, Charlson comorbidity Index)

	Frail N=70	Nonfrail N=29	P-value
All-grade CRS	59%	66%	NS
Grade 3-4 CRS	3%	7%	NS
ICANS	9%	3%	NS
Early mortality (90 days)	23%	10%	P=0.17
Overall response rate	52%	62%	NS
1-Yr PFS	36%	48%	P=0.26
1-Yr OS	57%	61%	P=0.30



Outcomes of Frailty Subgroups Treated with Teclistamab in the Real-World: An International Myeloma Foundation Study Database Analysis

- Retrospective analysis, 7 institutions
- Treatment: Teclistimab
- N= 81
- Age: Median 76 yrs (range 70-91)
- 73% frail at the time of BsAb treatment
- Frailty measure used: Simplified (IFM) frailty score (=age, ECOG PS, Charlson comorbidity Index)

	Frail N=59	Nonfrail N=22	P-value
All-grade CRS	47%	55%	
Grade 2 CRS	29%	8%	0.23
ICANS	14%	9%	0.72
Infection	59%	45%	0.32
Overall response rate	66%	50%	0.61
1-Yr PFS	42.4%	47.6%	
1-Yr OS	61.5%	64.9%	



Lymphoma



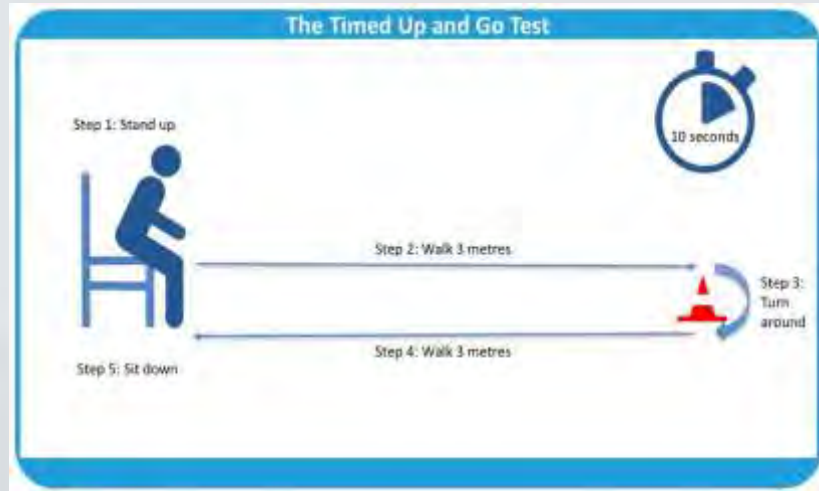
Frailty's Impact on CAR T-Cell Therapy Outcomes in Patients with Lymphoproliferative Disorders: Insights from a Spanish Multicenter Pilot Study Conducted on Behalf of the Geth-CT

- N=36
- Frailty measure: HCT frailty scale
- median age 61 (range 28-76)

	Fit N=7	Intermedi ate N=22	Frail N=7	P-value
N=36	19%	62%	19%	
Grade 2-4 CRS	50%	33%	50%	0.874
Grades 2-4 ICANS	20%	33%	67%	0.065
ICU admission	24%	26.7%	50%	P=0.354
Relapse	12.5%	26.7%	50.0%	0.026
Death	12.5%	13.2%	50.0%	0.050



A Prospective Geriatric Assessment (GA) Study Predicting Toxicities in Older Adults (OA) with Non-Hodgkin Lymphoma (NHL): Timed up and Go Test (TUG) Time Emerges As a Functional Vital Sign

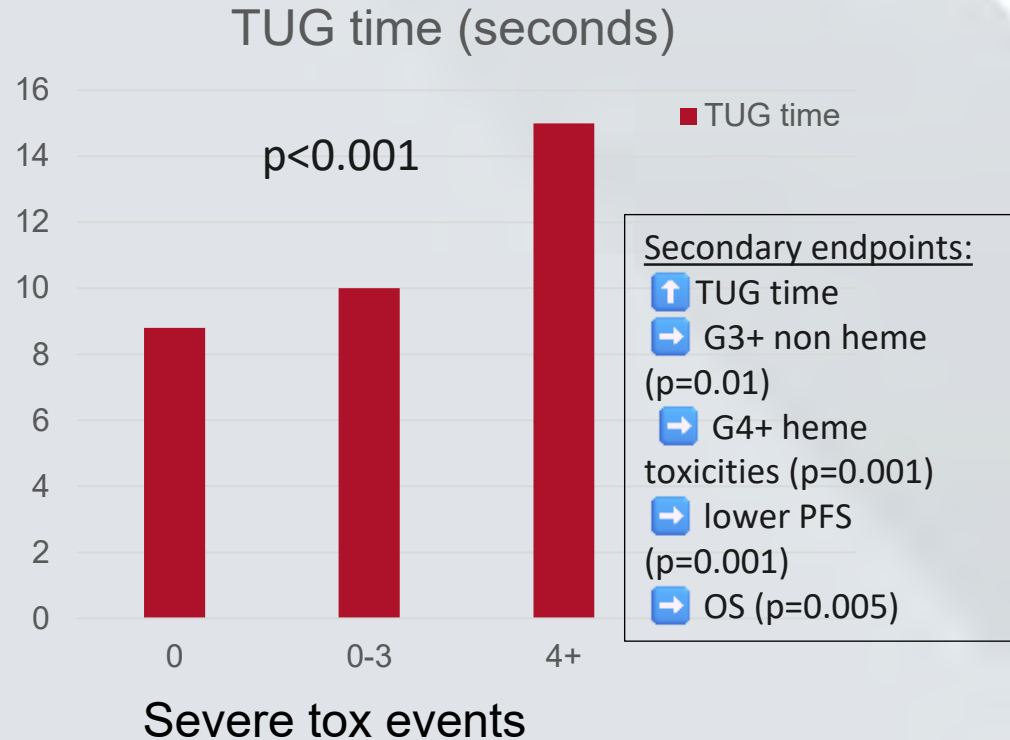


N=194

Median age 74 yrs (range 60-93 yrs)

72% DLBCL/R-CHOP

Endpoint: Severe Tox (hospitalization/<80% dose intensity/treatment discontinuation/death)





Myeloid Neoplasms



Impact of Frailty in a Prospective Cohort of Patients with MDS Treated with Hypomethylating Agents

MDS-specific frailty scale

CLINICAL FRAILTY SCALE		
	1	VERY FIT People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
	2	FIT People who have no active disease symptoms but are less fit than not enjoy 1. Often, they exercise or are very active occasionally, e.g., seasonally.
	3	MANAGING WELL People whose medical problems are well controlled, even if occasionally symptomatic, but often are not regularly active beyond routine walking.
	4	LIVING WITH VERY MILD FRAILTY Previously "vulnerable," this category marks early transition from complete independence. While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up" and/or being tired during the day.
	5	LIVING WITH MILD FRAILTY People who often have more evident slowing, and need help with high order instrumental activities of daily living (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
	6	LIVING WITH MODERATE FRAILTY People who need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (sitting, standing) with dressing.
	7	LIVING WITH SEVERE FRAILTY Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within 6 months).
	8	LIVING WITH VERY SEVERE FRAILTY Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
	9	TERMINALLY ILL Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise living with severe frailty. (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question many and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seem to remember their past life events well. They can't do personal care with prompting.

In severe dementia, they cannot do personal care without help.

In very severe dementia they are often bedfast. Many are virtually mute.

Clinical Frailty Scale ©2005-2020 Bevan, Fowler & Cella. All rights reserved. For permission, see www.geriatricsmedicine.com or the download of a printed clinical response of Blood and Frailty in elderly people. 2004; 2005; 273-449-490

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Element	Definition of deficit	Weighting
RDW	Deficit if out of hospital lab range	2
LDH	Deficit if out of hospital lab range	2
WBC	Deficit if out of hospital lab range	1
MCV	Deficit if out of hospital lab range	1
Ferritin	Deficit if out of hospital lab range	1
Reticulocyte count	Deficit if out of hospital lab range	1
ALP	Deficit if out of hospital lab range	1
ALT	Deficit if out of hospital lab range	1
Bilirubin	Deficit if >1.5 x ULN of normal hospital range	1
Creatinine clearance (ml/min)		<30:1 30-59:0.5 ≥60:0
BMI		<18.5 or ≥30:1 25-29.9:0.5 18.5-24.9:0
Any cancer history	Deficit if current or in the past	1
Plans, prepares, and serves adequate meals independently	Deficit if unable	1
Global fatigue score (0-10, 10 is the highest degree of fatigue)		≥7:1 4-6:0.5 0-3:0
4-m walk test (time to walk 4 m in seconds)		>6.67:1 4-6.67:0.5 ≤4:0

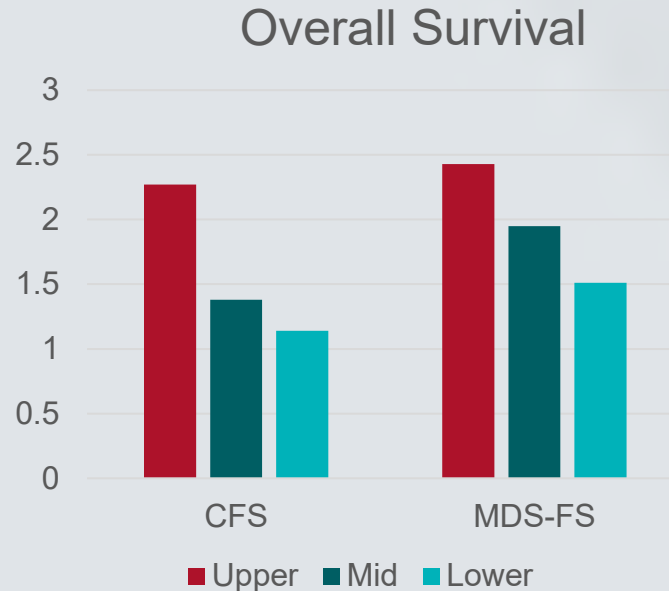
RDW red blood cell distribution width, LDH lactate dehydrogenase, WBC white blood cell, MCV mean corpuscular volume, ALP alkaline phosphatase, ALT alanine aminotransferase, BMI body mass index.

Wan et al Leukemia 2020 34:3434-3438



Impact of Frailty in a Prospective Cohort of Patients with MDS Treated with Hypomethylating Agents

- N=513
- Median age 72.7 (66-81)
- Treatment: Azacitidine and Decitabine
- Frailty measures used:
 - Clinical Frailty Scale
 - MDS-specific frailty scale



Lower MDS FS-15 scores predictive of completing ≥ 4 cycles of HMA



Allogeneic Stem Cell Transplant

The Composite Health Risk Assessment Model (CHARM) Predicts Risks of Toxicities, Functional and Cognitive Decline Among Survivors of Allogeneic Hematopoietic Cell Transplantation (allo-HCT): A Prospective BMT-CTN Study 1704

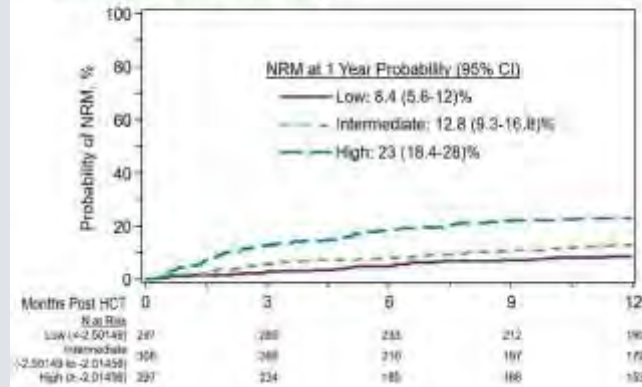
- Development and validation of the CHARM model: (*Artz et al ASH 2023*)
 - Comorbidities
 - C-reactive protein
 - Albumin
 - Weight loss

Table: Covariates selected by multivariate analysis influencing NRM within 1 year

Variable (continuous)	Subdistribution Hazard Ratio (95% CI)	95% CI	p-value
HCT-CI	1.163	1.092 - 1.243	<0.0001
LOG (CRP) ^a , mg/L	1.142	1.020 - 1.278	0.0188
Albumin, g/dL	0.491	0.347 - 0.683	<0.0001
% Weight loss, squibb ^{b,c,d}	1.001	1.002 - 1.002	0.0023

^anatural log. ^bvalue > 3.3 indicate a positive association with risk of NRM.
^cweight gain or no weight loss is scored as 4 0.
 CHARM formula = $0.15310 * \text{HCT-CI} + 0.13247 * \text{LOG}(\text{CRP}) + 0.71227 * (\text{ALBUMIN}) + 0.00119 * (\% \text{ Weight Loss})^2$

Non-Relapse Mortality





The Composite Health Risk Assessment Model (CHARM) Predicts Risks of Toxicities, Functional and Cognitive Decline Among Survivors of Allogeneic Hematopoietic Cell Transplantation (allo-HCT): A Prospective BMT-CTN Study 1704

N=1105 Allo
HCT candidates

Models adjusted
for conditioning
intensity , GVHD
prophylaxis,
disease-risk
index, etc

**Higher
CHARM
score**

Serious organ
toxicity
(OR 2.05)

Worsening
cognition
(OR 1.55/2 pts on
MOCA)

Greater disability
(IADL)

PROMIS physical
function

Depression

Mortality after
GVHD



The Composite Health Risk Assessment Model (CHARM) Predicts Risks of Toxicities, Functional and Cognitive Decline Among Survivors of Allogeneic Hematopoietic Cell Transplantation (allo-HCT): A Prospective BMT-CTN Study 1704

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Mortality after
GVHD

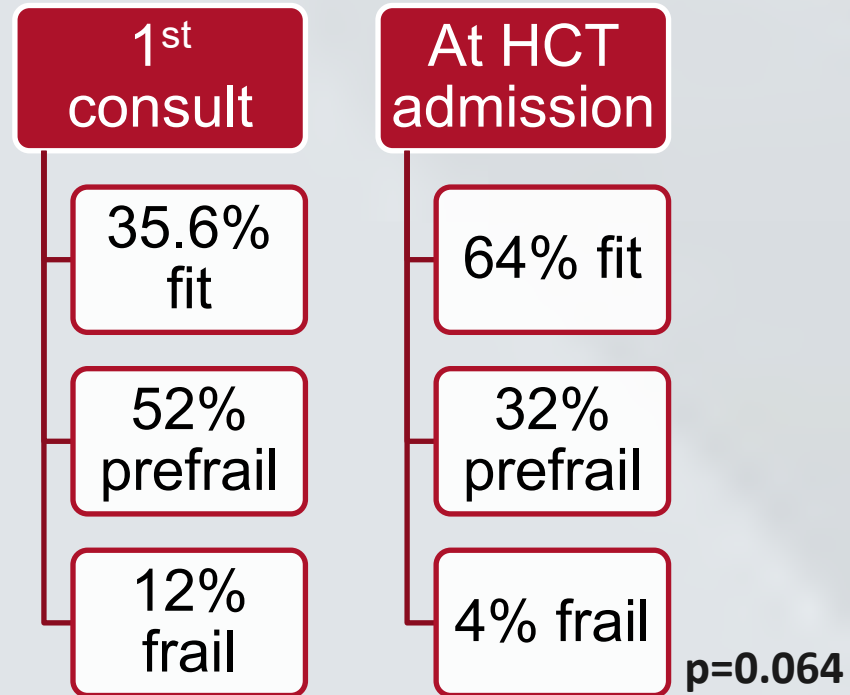
NOT

Chronic GVHD



Transforming Frailty Care in Allo-HCT Candidates: A Prospective Assessment of a Tele-Prehabilitation Project

- Intervention: **T-PreHab**
- PM&R physician
- Tailored, home-based exercise program
- Nutritional consult + supplements
- N=25
- Adherence >80%
- Comparison: Historical controls (N=59): fitness level unchanged





Recurring themes & summary

- Many frailty measures in use
 - Some disease-specific, others adopted from geriatrics
- Considering frailty in dosing treatment for myeloma improves EFS and OS
- Frailty measures can be predictive and prognostic
 - More simplified frailty measures may miss opportunity to identify individuals at greater risk
 - More comprehensive or physical performance based measures tend to show differences in outcomes
- Frailty can be reversed with intervention (exercise)



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