Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report

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Keypoints

- Elderly patients with myeloma are heterogeneous and assessment strategies are needed to define the frailty profile
- The proposed frailty score aims to better assess patients and provide them with more suitable therapies

ABSTRACT

We conducted a pooled analysis of 869 individual newly diagnosed elderly patient data from 3 prospective international trials. At diagnosis, a geriatric assessment had been performed to assess comorbidities, cognitive and physical status**.**

An additive scoring system (range 0-5), based on age, comorbidities, cognitive and physical conditions, was developed to identify 3 groups: fit (score=0, 39%); intermediate-fitness (score=1, 31%), and frail (score≥2, 30%). The 3-year overall survival was 84% in fit patients, 76% in intermediate-fitness patients (HR 1.61, 95%CI 1.02-2.56, p=0.042) and 57% in frail patients (HR 3.57 CI 95% 2.37-5.39, p<0.001). The cumulative incidence of grade ≥3 non-hematologic adverse events at 12 months was 22.2% in fit, 26.4% in intermediate-fitness (HR 1.23, 95%CI 0.89-1.71; p 0.217) and 34.0% (HR 1.74, 95%CI 1.28-2.38; p<0.001) in frail patients. The cumulative incidence of treatment discontinuation at 12 months was 16.5% in fit, 20.8% in intermediate-fitness (HR 1.41, 95%CI 1.00-2.01, p=0.052) and 31.2% (HR 2.21, 95%CI 1.57-3.09; p<0.001) in frail patients.

Our frailty score predicts mortality and the risk of toxicity in elderly myeloma patients. The International Myeloma Working group proposes this score for the measurement of frailty in designing future clinical trials.

INTRODUCTION

Multiple myeloma (MM) is a neoplastic disease which predominantly affects elderly patients,[1] with more than 60% of diagnoses and nearly 75% of deaths occurring in those over 65 years of age.[2] Although novel agents have substantially improved MM outcome,[3-7] patients over 70 years benefit less from new treatments,[8] probably due to an increased treatment-related toxicity and worse biology.[3,5,9-12] The well-known biologic and genetic prognostic factors, as well as age per se, are insufficient to explain this difference.[13-16] The elderly population is highly heterogeneous and assessment strategies are needed to define the frailty profile. Frail patients are underrepresented in clinical trials, and the role of new drugs in these patients is relatively unknown.[17] This prompted the European Medicines Agency to require post-marketing safety studies in the older population.[18] To date, the choice of MM treatment is primarily based on chronologic age and performance status.[19] However, among adults of the same age, physical and cognitive functions can be highly variable. In cancer patients, frailty and comprehensive geriatric assessment (CGA) are being incorporated to guide treatment decisions.[20] Frailty is a state of cumulative decline in many physiological systems, resulting in a diminished resistance to stressors, such as cancer and its treatment.[21-23] The CGA is a multidisciplinary, interdisciplinary patient evaluation with validated tools that can contribute to definition of the frailty profile.[24] In hematology, the CGA is not routinely performed because it is complex and time-consuming. The optimal tools for an appropriate geriatric assessment (GA) need to be established. Recently, three international guidelines have recommended the use of a GA to assess the patients' cognitive and functional status and comorbidities in the context of clinical trials.[25-27] To date, no study in MM has prospectively evaluated the predictive value of a GA, that may be more informative than age and performance status and it could better discriminate between fit and frail patients.

We assessed the predictive role of a baseline GA in 869 elderly newly diagnosed MM patients, to define a frailty score and assess its impact on clinical outcome and toxicity.

METHODS

Patient population and study design

The European Myeloma Network (EMN) and Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) groups introduced a baseline GA in all trials for newly diagnosed MM patients, ineligible for autologous stem cell transplantation due to age or coexisting comorbidities. Three prospective multicenter trials (EMN01-NCT01093136; 26866138MMY2069-NCT01190787; IST-CAR-506-NCT01346787) were included in this analysis.[28-30] Besides Italy, Czech Republic enrolled patients in the EMN01 study, and the Netherlands participated in the 26866138MMY2069 and IST-CAR-506 studies. Briefly, patients in the EMN01 trial were randomized to lenalidomide with either dexamethasone (Rd) or with cyclophosphamide-prednisone (RCP) or with melphalan-prednisone (MPR). Patients enrolled in the 26866138MMY2069 trial received bortezomib with either prednisone (VP) or with cyclophosphamide-prednisone (VCP) or with melphalan-prednisone (VMP). Patients in the IST-CAR-506 trial received carfilzomib with cyclophosphamide-dexamethasone. Inclusion and exclusion criteria are reported in supplementary table S1. All patients provided written informed consent to participate in the studies, which had been approved by the institutional ethics committees. The studies were conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

The primary objective of this analysis was to identify a simple scoring system based on geriatric parameters to predict overall survival (OS). The secondary objectives included the impact evaluation of the frailty scoring system on treatment-related toxicity and progression-free survival (PFS).

Assessment

The GA consisted of three tools: Katz's Activity of Daily Living (ADL), Lawton's Instrumental Activity of Daily Living (IADL) and Charlson comorbidity index (CCI) (Tables S2-S3). The ADL

and the IADL scales were adopted to assess self-care activities, tasks of household management and independence status (Supplementary table S2).[31] The CCI estimates the number and the severity of comorbidities (Supplementary table S3).[32] Performance status, Beta-2-microglobulin, Albumin, International Staging System (ISS)[33] and chromosomal abnormalities [t(4:14), t(11:14), t(14;16), del13, and del17p13] were assessed. OS was calculated from the time of treatment start until the date of death for any cause or the date the patient was last known to be alive. PFS was calculated from the time of treatment start until the date of progression, relapse, death for any cause, or the date the patient was last known to be in remission. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 or 4.0. Cumulative incidence of grade ≥3 hematologic and non-hematologic events and drug discontinuation were calculated from the time of treatment start until the date of first toxicity or drug discontinuation due to cause other than progression or death, that were considered as competing events. For all the time-to-event endpoints, times of observation were censored on April 22nd, 2013.

Statistical Analysis

Patients were analyzed on an intention-to-treat basis. OS and PFS were estimated using the Kaplan-Meier method, while cumulative incidence of grade ≥3 toxicity and treatment discontinuation were estimated accounting for competing events using the method of Gooley et al.[34] The frailty score was built combining age, ADL and IADL scales and CCI, evaluating their prognostic role on OS. To define a categorisation of these variables, to simplify the score calculation and inspect the potential non-linear relationship with OS, the variables were previously evaluated in a Cox Model using restricted cubic splines transformation. The prognostic role of age, ADL, IADL and CCI was evaluated in a Cox Model including also ISS, unfavorable chromosome profile (defined as t(4;14) or t(14;16) or del17p13), performance status and type of treatment. Variables included in the final model were identified through a backward selection based on the Akaike Information Criterion

(AIC), choosing the final with the lowest AIC. The discrimination ability of the model was evaluated calculating the Harrell's C statistic. Group differences according to the final classification were investigated using the Cox proportional hazard model for OS and PFS, accounting for ISS, chromosome abnormalities, type of treatment and type of regimens, whereas the cumulative incidences of discontinuation and toxicities were calculated using the Fine & Gray model. Finally, as explorative analysis, the CHAID (CHi-squared Automatic Interaction Detector) method was used as an iterative decision tree to determine patient classification based on ISS and frailty score, according to the linear prediction of Cox Model adjusted for chromosome abnormalities and type of treatment.

RESULTS

Cohort characteristics

The three trials included 869 newly diagnosed MM patients. The median age was 74 years and 46% of patients were older than 75 years (Table 1). One-hundred nineteen patients (14%) had an ADL score ≤4, 156 (18%) an IADL score ≤5 and 144 (17%) a CCI ≥2. The most frequent co-morbidities are diabetes without organ damage (13.2%), mild renal failure (7.4%), cardio-pulmonary disease (10.4%) and peripheral vascular disease (5.8%). The most frequent parameters that were abnormal in ADL are those linked to the independence in bathing (19.6%), transferring (13.7%) and dressing (12.1%). Similarly, the most frequent parameters that were abnormal in IADL are those related to mode of transportation (38.0%), housekeeping (37.3%), shopping (33.9%) and laundry (31%).

Identification of prognostic variables and frailty score development

For all geriatric components, no strong evidence of linear association was found and their impact on OS was explored using the recorded categorical variables (figure S1). Advanced age, functional decline on ADL and IADL, and the presence of comorbidities showed a trend toward a progressive

worsening of OS (figure S1A). Their impact on OS was investigated in a multivariate Cox regression model (figure S1B). A reduced OS was observed in patients aged 75-80 years (HR 1.35) and was more pronounced in those >80 years (HR 2.68), in those with ADL ≤4 (HR 1.58) and IADL ≤5 (HR 1.81) and in patients with CCI ≥2 (HR 1.58). No difference was found with respect to reference category for ADL 5, IADL 6-7 and CCI 1 (p>0.500). The final stratification of variables was defined according to the following cut-off: ADL (>4,≤4), IADL (>5, ≤5) and CCI (<2, ≥2). After the backward selection, performance status was removed from the final model (with ECOG PS, AIC=1750.62; without ECOG PS, AIC=1748.92). In a multivariate analysis, adjusted for ISS, chromosome abnormalities and type of therapy, a higher risk of death was observed for patients aged 75-80 years (HR 1.13; 95% CI 0.76-2.40) and >80 years (HR 2.4; 95% CI 1.56-3.71), for those with an ADL score ≤4 (HR 1.67; 95% CI 1.08-2.56), an IADL ≤5 (HR 1.43; 95% CI 0.96-2.14) and a CCI ≥2 (HR 1.37; 95% CI 0.92-2.05) (Table 2). An additive frailty score based on the integer part of HRs (HR=1-2, score=1; HR>2.00, score=2) was then calculated. By combining the risk scores (range 0-5) for these variables, patients were stratified into three distinctive risk groups for OS: fit (score=0); intermediate-fitness (score=1), and frail (score≥2). Table 3 indicates the proportion of patients in each risk group, their OS and their treatment discontinuation and toxicities requiring dose modifications. Among the 260 frail patients, 123 (47%) were older than 80 years and only 50 (19%) were categorized as frail only for age.

Prognostic characteristics of the frailty score

The median follow-up was 18 months (IQR, 11-28 months). By applying the proposed frailty score, the 3-year OS was 84% in fit, 76% in intermediate-fitness (HR 1.61, 95%CI 1.02-2.56, p=0.042) and 57% in frail patients (HR 3.57, 95%CI 2.37-5.39, p<0.001) (Figure 1A). In the multivariate analysis, frailty profiles were associated with a shorter OS, regardless of staging and treatment administered (Table 4). One-hundred forty-three (16%) out of the 869 patients died, 34 (10%) in the fit, 39 (14%) in the intermediate-fitness and 70 (27%) in the frail group. The causes of death were:

disease progression [18 (5%) in fit, 22 (8%) in intermediate-fitness and 35 (13%) in frail patients] and toxicity [11 (3%), 10 (4%) and 21 (8%), respectively]. The higher risk of death for disease-progression, especially in frail patients, was related with the lower dose-intensity as a consequence of the higher rate of drug discontinuation and/or dose reduction (Table S4). The most frequent reasons of toxicity-related death were cardiac events [3 (1%) in fit, 2 (1%) in intermediate-fitness, 11 (4%) in frail patients] and infections [2 (1%), 2 (1%) and 8 (3%), respectively]. The prognostic impact of the frailty profile on OS was similar in different subgroups defined by ISS, chromosomal abnormalities, type of treatment (lenalidomide-based and proteasome inhibitor-based therapies) and type of regimens (doublet and triplet regimens) (Figure S2).

By applying the proposed frailty score, the 3-year PFS was 48% in fit, 41% in intermediate-fitness (HR 1.18, 95%CI 0.91-1.53 p 0.211) and 33% in frail patients (HR 1.68, 95%CI 1.31-2.15 p<0.001) (Figure 1B). These data were confirmed in a Cox model (Table 4)

Grade ≥3 hematologic AEs were documented in 130 (38%) fit, 94 (35%) intermediate-fitness and 79 (30%) frail patients. The cumulative incidences of grade ≥3 hematologic AEs were 24.1% in fit, 29.3% in intermediate-fitness and 23.2% in frail patients at 4 months, and 38.4% in fit, 35.1% in intermediate-fitness and 32.2% in frail patients at 12 months (Figure 1C). The risk of grade ≥3 hematologic AE was not significantly higher in intermediate-fitness (HR 0.97, 95% CI 0.74-1-28, p=0.831) and in frail patients (HR 0.94, 95% CI 0.71-1.26, p=0.698) compared with fit ones (table 4).

Grade ≥3 non-hematologic AEs were reported in 62 (18%) fit, 60 (22%) intermediate-fitness and 77 (30%) frail patients. The cumulative incidences of non-hematologic grade ≥3 AEs were 16.6% in fit, 16.7% in intermediate-fitness and 26.5% in frail patients at 4 months, and 22.2% in fit, 26.4% in intermediate-fitness and 34.0% in frail patients at 12 months (Figure 1D, table 3). The risk of grade ≥3 non-hematologic AE was slightly increased in intermediate-fitness (HR 1.13, 95%CI 0.81-1.58;

p 0.462) and significantly increased in frail patients (HR 1.57, 95%CI 1.12-2.19; p=0.008) compared with fit ones (table 4).

Drug discontinuation for any cause, excluding progression and death, was reported in 58 (17%) fit, 58 (22%) intermediate-fitness and 66 (25%) frail patients. The cumulative incidence of treatment discontinuation was 7.4% in fit, 11.9% in intermediate-fitness and 19.2% in frail patients at 4 months, and 16.5% in fit, 20.8% in intermediate-fitness and 31.2% in frail patients at 12 months (Figure 1E, table 3). The risk of drug discontinuation was significantly higher in intermediate-fitness (HR 1.41, 95%CI 1.00-2.01, p=0.052) and in frail patients (HR 2.21, 95%CI 1.57-3.09; p<0.001) compared with fit ones (table 4).

Integration of the frailty score into the International Staging System

Combining the frailty score with the ISS stage, 6 groups were identified: 128 (14.7%) fit patients with ISS stage I, 212 (24.4%) fit patients with ISS stage II or III, 177 (20.4%) intermediate-fitness patients with ISS stage I or II, 92 (10.6%) intermediate-fitness patients with ISS stage III, 161 (18.5%) frail patients with ISS stage I or II and 99 (11.4%) frail patients with ISS stage III (Figure S3). Survival curves for these 6 categories are shown in Figure S4: 11% were considered very high risk patients, with a 3-year OS of 55%; 19% were high risk patients, with a 3-year OS of 61%; 55% were considered intermediate risk patients, with a 3-year OS of 75-77%; and 15% were low risk patients, with a 3-year OS of 94%.

DISCUSSION

This analysis showed that a frailty score that combines age, functional status and comorbidities can predict survival and toxicity, and is useful to determine the feasibility of a treatment regimen. The frailty profile was associated with an increased risk of death, progression, non-hematologic AEs and treatment discontinuation, regardless of ISS stage, chromosome abnormalities and type of treatment.

The global population is rapidly aging, the number of people >80 years is expected to quadruple between 2000 and 2050.[35] The standard approved treatments for newly diagnosed elderly MM include nine 6-week cycles of VMP with twice-weekly bortezomib and twelve 6-week cycles of MPT with 200 mg/day thalidomide. No changes in dose and schedule are approved according to age or performance status. Unfortunately, these standard schedules induced a high rate of grade 3-4 non-hematologic AEs (91% with VMP and 75% with MPT),[3,9] with survival benefit inferior in patients >75 years. Most clinical trials include fit patients, while the majority of frail patients are excluded. In these studies, approximately 10% of patients are >75 years of age. In contrast, approximately 40% of patients who receive treatment for malignancies are frail.[18]

In a community-based population randomized phase 3b study comparing VMP with bortezomib-thalidomide-dexamethasone and bortezomib-dexamethasone,[36] no difference was detected between doublet and triplet regimens. Similarly, continuous treatment with oral Rd significantly improved outcome and reduced the toxicities compared with the standard MPT.[6] These data indirectly suggest that, when frail patients are adequately represented in clinical trials, doublet regimens can be as effective as triplet combinations with a better safety profile.

Although this analysis is based on patients enrolled in clinical trials, the less strict inclusion/exclusion criteria allowed 30% of frail patients to be treated. In our analysis, the 3-year OS rate was 84% in fit, 76% in intermediate-fitness and 57% in frail patients. The OS for fit patients compares favorably with the standard treatments;[3,4] similarly, the survival of frail patients is comparable to that of the community-based population previously reported.[36] A significantly higher cumulative incidence of non-hematologic toxicities and drug discontinuation was reported in frail compared with fit patients, and severe non hematologic AEs and drug discontinuation induced a shorter survival.[12] Unexpectedly, the performance status did not affect OS, whereas the frailty status increased the risk of death by approximately 3 fold, thus confirming the need for a more sophisticated evaluation of elderly patients before starting therapy. Our findings suggest that the cut-off age of 80 years instead of 75 years should be used for the definition of frail conditions.

Indeed, the risk of death is only slightly increased in patients 75-80 years of age, while it is 2.4 times higher in patients >80 years. Besides age, the most common reasons for an increase in frailty were losing independence in self-care activities, household management and transferring/transportation.

By combining the frailty score with the established ISS, the 3-year OS rate was 55% in the frail-ISS 3 group, and 94% in the fit-ISS 1 group. The combination of these two independent parameters significantly improved the prognostic value of the single ones, therefore this is an important strategy in the future for predicting outcome.

Chronologic age, performance status, and physician's clinical judgment are not sufficient to characterize the frail population. The GA is a more sensitive predictor of clinical outcomes, and the proposed score may be adopted as a valid new standard to evaluate patients' frailty. It could be used in everyday clinical practice as well as in the context of research to ensure an adequate representation of elderly patients and to allow more precise cross-trial comparisons. Although evidence-based GA-tailored treatments are still lacking, fit patients could receive full-dose, triplet therapies or even more intensive approach including stem cell transplant. Intermediate-fitness patients may benefit from doublet treatments or less intense triplets.[37] Frail patients could benefit from a gentler, reduced-dose doublet approach or even a palliative/supportive treatment, since the benefits of low toxicity on survival should be considered carefully, especially in the very frail. Future trials comparing full-dose therapy and adjusted schedules in elderly patients will support these recommendations and validate our approach.

The GA is a time and manpower-consuming procedure. To overcome this limitation, an ICT application for computers may significantly reduce the time required to perform the GA to only 5-7 minutes. Of note, the time invested in this procedure should be balanced against the advantage of reducing the subsequent risk of severe AEs by approximately one-third.

The strength of this analysis lies in the large, broadly representative and fairly homogenous set of data provided by 72 European institutions. The applicability of the frailty score in a multicenter

setting is a prerequisite for its use in the clinical practice. Furthermore, the GA was prospectively obtained prior to initiation of chemotherapy and reflects the patient's baseline health rather than the toxicities induced by the therapy.

The major limitation of this study is the absence of an independent validation cohort of patients, since the GA is not routinely performed in an external cohort of patients, and our sample size is inadequate for an internal validation. The presence of patients exclusively enrolled in experimental trials may be another limitation, yet this allows more homogeneous treatment, thus avoiding the bias of different treatments. Furthermore, although population-based data also include the most frail patients and consequently may give the opportunity to investigate the role of frailty in the population, such databases typically lack the level of detail captured in clinical trials, limiting the possibility to conduct a risk factor analysis.

In summary, this study supports the systematic, prospective use of a GA as important additional tool in the clinical evaluation. Our findings point out some relevant issues of patients' functional and health status that have a prognostic importance similar to that of myeloma-related risk factors, such as ISS and chromosomal abnormalities. Prospective studies to validate our findings as well as a unique score reflecting both the reserve capacity of patients and established disease-specific risk factors are needed to provide comprehensive algorithms for therapeutic decision-making.

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Table 1. Baseline patient characteristics

	No. of patients (N=869)	% of patients	Median (IQR)
Age (years)			74 (70-78)
≤65	16	2	
65-74	451	52	
≥75	402	46	
≥80	161	19	
Creatinine (mg/dl)			0.98 (0.80-1.22)
<2	802	92	
≥2	37	5	
Missing	30	3	
ECOG Performance status			
0	258	30	
1	398	46	
2	166	19	
3	14	2	
International Staging System			
I	239	28	
II	361	42	
III	269	31	
Chromosome abnormalities			
t(4;14)	80	9	
t(14;16)	22	3	
del17p13	105	12	
Missing	147	17	
Unfavorable profile	329	38	
ADL			6 (5-6)
>4	750	86	
≤4	119	14	
IADL			8 (6-8)
>5	713	82	
≤5	156	18	
Charlson Comorbidity Index			0 (0-1)
≤1	725	83	
≥2	144	17	
Therapy			
Lenalidomide-containing regimens	659	76	
Proteasome inhibitors-containing regimens	210	24	

Abbreviations : IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living. Unfavorable profile defined as t(4;14) or t(14;16) or del17p13.

Table 2. The final Cox regression model*

	HR (95% CI)	p-value	Score
Age			
≤ 75 years	1	-	0
76-80 years	1.13 (0.76-1.69)	0.549	1
> 80 years	2.40 (1.56-3.71)	<0.001	2
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
Charlson Comorbidity Index			
≤1	1	-	0
≥2	1.37 (0.92-2.05)	0.125	1
International Staging System			
I	1	-	-
II	2.37 (1.38-4.09)	0.002	-
III	3.21 (1.85-5.58)	<0.001	-
Chromosome abnormalities			
Favorable	1	-	-
Unfavorable	1.79 (1.23-2.60)	0.002	-
Missing	1.13 (0.69-1.83)	0.036	-
Therapy			
Proteasome inhibitors	1	-	-
Lenalidomide	0.74 (0.50-1.11)	0.142	-

Harrell's C index=0.7069 AIC=1748.918.

*Hazard ratios and relative risks are for overall survival in patients with the factors as compared with those without the factors. The model was adjusted for International Staging System, chromosome abnormalities and therapy.

Abbreviations: HR, hazard ratio; CI, confidence interval; ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living. Unfavorable profile defined as t(4;14) or t(14;16) or del17p13.

Table 3. Additive total score and related rate of overall survival and progression-free survival at 3 years.

Additive total score	Patient Status	Number of patients	Overall Survival	Progression-free Survival	Treatment discontinuation	Grade 3-4 non-hematologic AEs
		(%)	% (95% CI)	% (95% CI)	Cumulative incidence at 12 months - %	Cumulative incidence at 12 months - %
0	Fit	340 (39)	84 (78-89)	48 (41-56)	16	22
1	Intermediate-fitness	269 (31)	76 (67-82)	41 (32-49)	21	26
≥ 2	Frail	260 (30)	57 (45-68)	33 (25-41)	31	34

In univariate Cox model the Harrell's C index=0.6608 and the AIC= 1766.077**.** In multivariate Cox model the Harrell's C index=0.7092 and the AIC=1743.353. Abbreviations: 95% CI, 95 percent confidence interval; AEs, adverse events

Table 4: Univariate and multivariate analysis of the impact of the frailty profile of patients on overall survival, progression-free survival, discontinuation rate and incidence of grade 3 or higher toxicity.

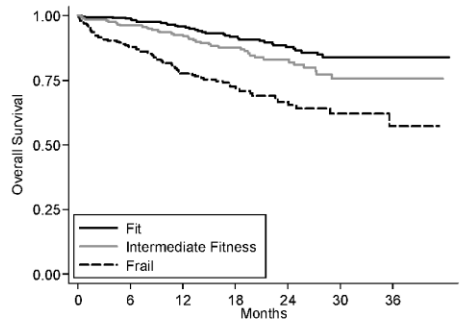
	Overall survival		**Progression-free survival**		**Discontinuation**		**Grade ≥3 hematologic toxicity**		**Grade ≥3 non-hematologic toxicity**	
Crude:	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Fit	1	-	1	-	1	-	1	-	1	-
Intermediate-fitness	1.61 (1.02-2.56)	0.042	1.18 (0.91-1.53)	0.211	1.48 (1.05-2.10)	0.026	0.97 (0.74-1.27)	0.808	1.23 (0.89-1.71)	0.217
Frail	3.57 (2.37-5.39)	<0.001	1.68 (1.31-2.15)	<0.001	2.27 (1.64-3.14)	<0.001	0.83 (0.62-1.09)	0.181	1.74 (1.28-2.38)	<0.001
Adjusted*:	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Fit	1	-	1	-	1	-	1	-	1	-
Intermediate-fitness	1.37 (0.86-2.18)	0.181	1.08 (0.83-1.40)	0.583	1.41 (1.00-2.01)	0.052	0.97 (0.74-1.28)	0.831	1.13 (0.81-1.58)	0.462
Frail	2.88 (1.88-4.40)	<0.001	1.48 (1.15-1.92)	0.003	2.21 (1.57-3.09)	<0.001	0.94 (0.71-1.26)	0.698	1.57 (1.12-2.19)	0.008

*adjusted for International Staging System, chromosome abnormalities and therapy. Abbreviations: HR, hazard ratio; 95% CI, 95 percent confidence interval.

FIGURES LEGEND:

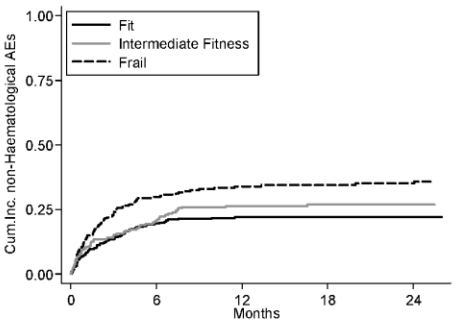
Figure 1: Long-term outcomes. Overall survival (A); progression-free survival (B) and cumulative incidence of haematological adverse events (C), non-haematological adverse events (D) and discontinuation (E) in the intention-to-treat population

A



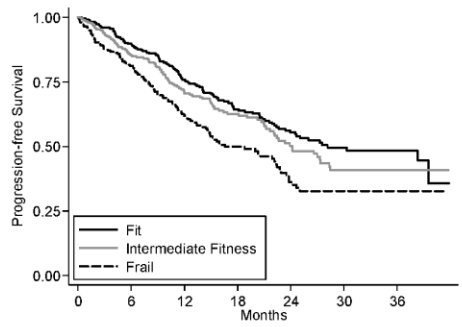
At risk:							
Fit	340	323	248	182	133	84	43
Intermediate Fitness	269	242	183	123	83	47	15
Frail	260	209	151	91	52	27	12

D



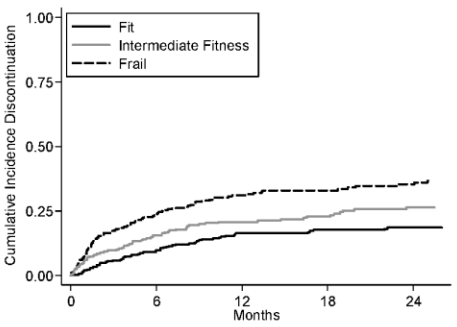
At risk:						
Fit	340	248	167	110	70	
Intermediate Fitness	269	182	108	67	41	
Frail	260	142	79	42	19	

B



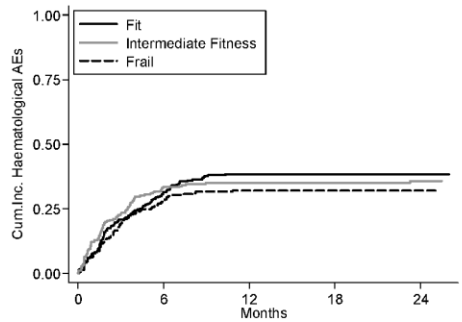
At risk:							
Fit	340	292	196	127	78	45	19
Intermediate Fitness	269	216	138	88	50	28	8
Frail	260	193	120	63	31	17	8

E



At risk:						
Fit	340	283	184	119	71	
Intermediate Fitness	269	205	122	78	39	
Frail	260	182	108	54	28	

C



At risk:					
Fit	340	202	124	81	52
Intermediate Fitness	269	145	92	61	34
Frail	260	133	73	28	14