Supplementary Table 1A. Hematological SAEs in pts with no (Ø) / with DR & impact on subsequent therapy continuation

	Entire cohort	Fit	Intermediate	Frail	<60 years	60-69 years	≥70 years
Pts **Ø DR : with DR** (%)	148 (59) : 102 (41)	59 (81) : 14 (19)	80 (55) : 65 (45)	9 (28) : 23 (72)	80 (79) : 21 (21)	43 (57) : 33 (43)	25 (34) : 48 (66)
SAEs in pts **with Ø DR : with DR** (per pt)	92 (0.6) : 65 (0.6)	15 (0.3) : 2 (0.1)	66 (0.8) : 39 (0.6)	11 (1.2) : 24 (1.0)	46 (0.6) : 8 (0.4)	23 (0.5) : 21 (0.6)	23 (0.9) : 36 (0.8)
Therapy adaptations*[1] in pts after SAEs **with Ø DR : with DR** (%)	5 (5) : 8 (12)	0 (0) : 0 (0)	2 (3) : 5 (13)	3 (27) : 3 (13)	0 (0) : 1 (13)	2 (9) : 2 (10)	3 (13) : 5 (14)

Supplementary Table 1B. Non-hematological SAEs in pts with no (Ø) / with DR & impact on subsequent therapy continuation

	Entire cohort	Fit	Intermediate	Frail	<60 years	60-69 years	≥70 years
Pts **Ø DR : with DR** (%)	148 (59): 102 (41)	59 (81): 14 (19)	80 (55) : 65 (45)	9 (28) : 23 (72)	80 (79): 21 (21)	43 (57): 33 (43)	25 (34) : 48 (66)
SAEs in pts **with Ø DR : with DR** (per pt)	53 (0.4): 70 (0.7)	15 (0.3) : 2 (0.1)	33 (0.4) : 37 (0.6)	5 (0.6) : 31 (1.4)	29 (0.4) : 5 (0.2)	15 (0.4) : 29 (0.9)	9 (0.4) : 36 (0.8)
Therapy adaptations*[1] in pts after SAEs **with Ø DR : with DR** (%)	14 (26) : 14 (20)	3 (20) : 0 (0)	8 (24) : 6 (16)	3 (60) : 8 (26)	5 (17) : 0 (0)	5 (33) : 4 (14)	4 (44) : 10 (28)

Abbreviations:
DR: Dose Reduction; SAE: Serious Adverse Event; pt.: patient; Ø: No;
*[1] Adaptations: DR, therapy pause or -discontinuation

Supplementary Table 2. Therapy-discontinuation in MM patients (n=8) during induction

Patients	Age (years)	R-MCI score	Initial DR: Yes/No	Reason for therapy discontinuation	Therapy cycle of discontinuation	Possible avoidance of therapy discontinuation and/or SAE diminution with better tailored therapy?	R-MCI helpful in tailored therapy decisions: Yes/No
1	67	3 = fit	Yes	Persisting neutropenia	4th VCD cycle	No	No
2	58	3 = fit	No	Acute heart and renal failure (MM with concomitant AL-amyloidosis); unsuccessful in-hospital resuscitation	3rd VCD cycle	Yes	Yes*[1]
3	62	5 = interm.	Yes	Acute respiratory insufficiency with opiate overdose; reduced general condition	1st VCD cycle	Yes	Yes
4	78	7 = frail	Yes	Reduced general condition; multifactorial-induced reduced vigilance	1st VCD cycle	Yes	Yes
5	77	7 = frail	Yes	Sepsis	4th VCD cycle	Yes	Yes
6	84	7 = frail	Yes	Acute heart failure; infection	4th RD cycle	Yes	Yes
7	77	8 = frail	Yes	Acute renal failure; MM progression	3rd VCD cycle	Yes	Yes
8	63	8 = frail	Yes	Reduced vigilance; metabolic acidosis; transfer to intensive care unit	1st VCD cycle	Yes	Yes
∑ *Median (range)*	*Median:72 (58-84)*	*Median:7 (3-8)*	7/8 = most with DR	Pt constitution-, MM and/or therapy-induced complications	*Median:3 (1-4)*	In 7/8 = most induction protocols were overdosed, suggesting this rather than underdosing the larger clinical challenge*[2]	In 7/8 deemed helpful

Abbreviations:
MM: Multiple myeloma; R-MCI: Revised-Myeloma Comorbidity Index; interm.: intermediate-fit; DR: Dose Reduction; SAE: Serious Adverse Event; pt: patient; VCD: Bortezomib, Cyclophosphamide, Dexamethasone; Rd: Lenalidomide, Dexamethasone

*[1] R-MCI-score results in AL-amyloidosis vs.MM patients have proven to be similar, albeit amyloidosis patient constitution was generally more impaired, suggesting that via R-MCI-fitter deemed amyloidosis patients must be regarded much sicker and treated with utmost care as compared to MM patients; see details in Schoeller K, Ihorst G, Engelhardt M et al. Blood 2019; 134 (Supplement_1): 3474. doi: https://doi.org/10.1182/blood-2019-127030

*[2] Engelhardt M, Domm AS, Wäsch R et al. Haematologica. 2017 May;102(5):910-921

Supplementary Table 3. Number of patients who suffered ≥1 SAE CTC 3-5 divided in R-MCI groups

	Entire cohort	Fit	Intermediate	Frail	*p-value*
Patients	250	73	145	32	
≥1 hematological and/or non-hematological SAE (%)	120 (48)	18 (25)	80 (55)	22 (69)	*<0.0001*
≥1 hematological SAE (%)	101 (40)	14 (19)	67 (46)	20 (63)	*<0.0001*
Anemia (%)	76 (30)	9 (12)	50 (34)	17 (53)	*<0.0001*
Leukocytopenia (%)	56 (22)	5 (7)	42 (29)	9 (28)	*0.0015*
Thrombocytopenia (%)	25 (10)	3 (4)	13 (9)	9 (28)	*0.0007*
≥1 non-hematological SAE (%)	67 (27)	8 (11)	41 (28)	18 (56)	*<0.0001*
≥1 infectious SAE (%)	56 (22)	8 (11)	35 (24)	13 (41)	*0.0006*
≥1 renal SAE (%)	19 (8)	2 (3)	10 (7)	7 (22)	*0.0020*
≥1 pulmonary SAE (%)	15 (6)	2 (3)	9 (6)	4 (13)	*0.0587*
≥1 cardiac SAE (%)	12 (5)	2 (3)	5 (3)	5 (16)	*0.0193*
Leukocytopenia & ≥1 infectious SAE (%)	25 (10)	1 (1)	18 (12)	6 (19)	*>0.05*

Abbreviations:
R-MCI: Revised-Myeloma Comorbidity Index; SAE: Serious Adverse Event

Supplementary Table 4. First response after start of induction in R-MCI subgroups

R-MCI subgroups	CR	vgPR	PR	SD	PD	Sum
Fit pts (%)	1 (1%)	19 (26%)	33 (45%)	16 (22%)	4 (6%)	73
Intermediate-fit pts (%)	1 (1%)	32 (22%)	79 (54%)	26 (18%)	7 (5%)	145
Frail pts (%)	1 (3%)	8 (25%)	13 (40.5%)	6 (19%)	4 (12.5%)	32

Abbreviations:
R-MCI: Revised-Myeloma Comorbidity Index; CR: Complete Remission; vgPR: very good Partial Remission; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease; Sum: summary

Supplementary figure legends

Supplementary Figure 1. R-MCI with via multivariate analysis generated prognostic factors

Abbreviations: R-MCI: Revised-Myeloma Comorbidity Index; FEV 1: Forced expiratory volume in 1 second; KPS: Karnofsky Performance Status, TUG: Timed Up and Go; IADL: Instrumental Activities of Daily Living; eGFR: estimated Glomerular Filtration Rate;

*[1] Lung dysfunction: Mild: FEV1 <80%; moderate: FEV1 ≤60% or diffusion capacity ≤61%, severe: FEV1 <50%; mild: 0/1 parameter is correct; moderate: 2 parameters are correct; severe: >2 parameters are correct

*[2] Frailty[8,17,23]: Karnofsky Index ≤70%; Time Up/Go >10 seconds; IADL ≤4 points; subjective fitness grade E or F

*[3] Unfavorable: del17p13, t(4;14), t(14;16), t(14;20), chromosome 1 abnormalities, c-myc, del(13q14), hypodiploidy

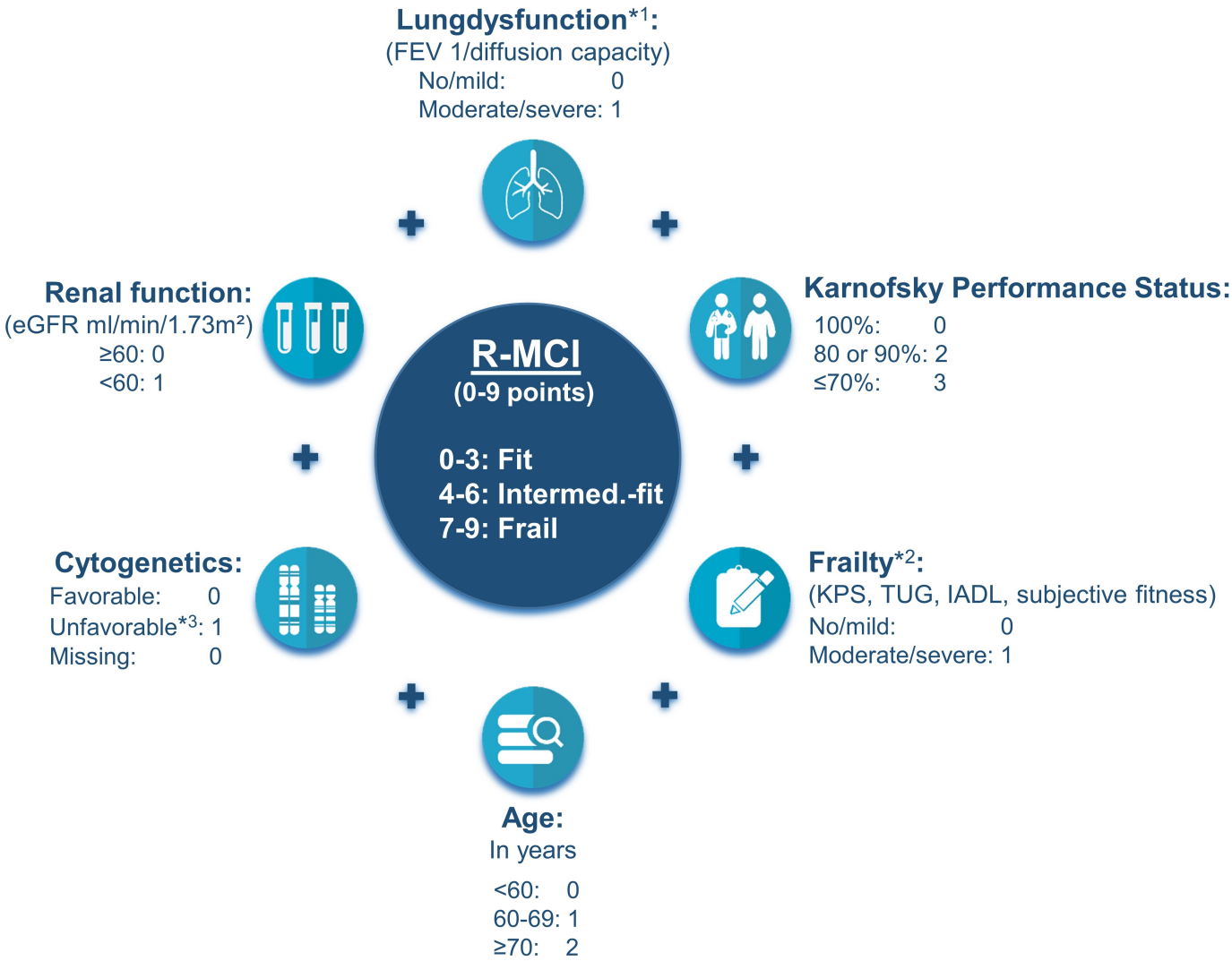
Supplementary Figure 2. Consort flow diagram: study design

Abbreviations: MM: Multiple Myeloma; SAE: Serious Adverse Event; OS: Overall Survival; PFS: Progression Free Survival; R-MCI: Revised-Myeloma Comorbidity Index; y: years

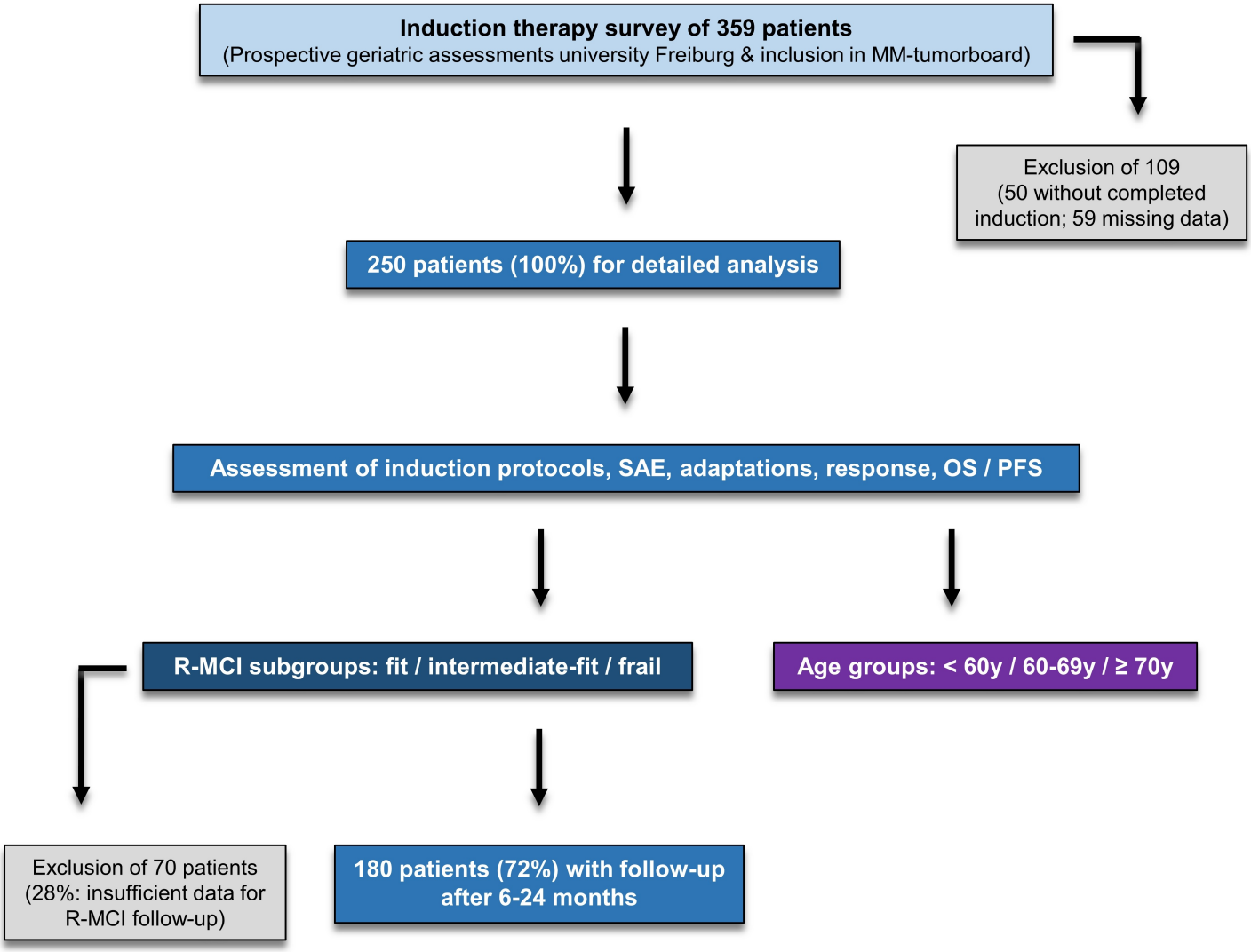
Supplementary Figure 3. VCD vs. non-VCD distribution in entire cohort and in follow-up cohort with R-MCI changes from start of induction (T0) to 6-24 months after first R-MCI assessment (T1)

Abbreviations: VCD: Bortezomib, Cyclophosphamide, Dexamethasone; RAD: Lenalidomide, Adriamycin, Dexamethasone; VRd: Bortezomib, Lenalidomide, Dexamethasone; RD: Lenalidomide, Dexamethasone; IdaD: Idarubicin, Dexamethasone

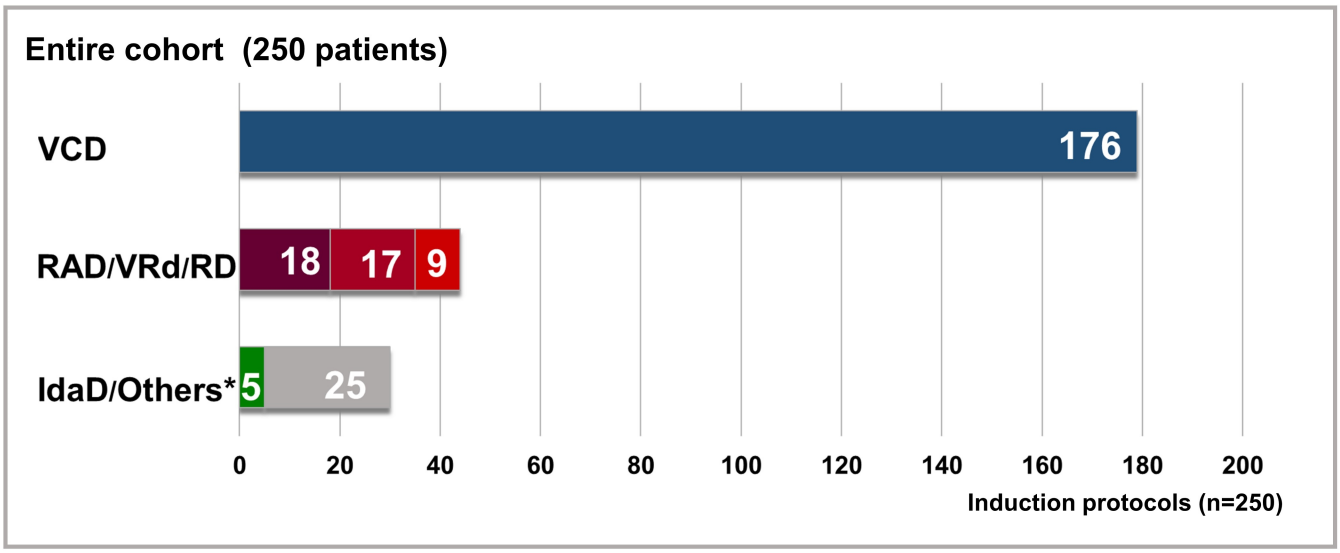
*Others: Vd: Bortezomib, Dexamethasone; RCD: Lenalidomide, Cyclophosphamide, Dexamethasone; CD: Cyclophosphamide, Dexamethasone; TD: Thalidomide, Dexamethasone; MVP: Melphalan, Bortezomib, Prednisolone; VTD: Bortezomib, Thalidomide, Dexamethasone; Elo-VRd: Elotuzumab, Bortezomib, Lenalidomide, Dexamethasone



Supplementary Figure 1



Supplementary Figure 2



Follow-up cohort (180 patients)			
Treatment induction: VCD vs. non-VCD	**Median / mean (range) R-MCI T0**	**Median / mean (range) R-MCI T1**	**Mean difference R-MCI T0→T1 (range)**
VCD (n=127)	5 / 4.6 (0-9)	4 / 3.9 (0-8)	-0.7 (4↓ - 3↑)
Non-VCD (n=53)	3 / 3.5 (0-7)	3 / 3.2 (0-7)	-0.3 (2↓ - 3↑)
p-value	*<0.0001*	*<0.0051*	*<0.0535*

Supplementary Figure 3