SUPPLEMENTARY INFORMATION

Predictors of early morbidity and mortality in newly diagnosed multiple myeloma: data from five randomized, controlled, phase III trials in 3700 patients

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SUPPLEMENTARY TABLES

Table S1. Characteristics and treatments in the trials included in the multi-cohort analysis.

	GMMG-HD4/HOVON-65	GMMG-MM5	GMMG-HD6	EMN02/HOVON-95	GMMG-HD7
Recruitment period	05/2005–05/2008	07/2010–11/2013	06/2015–09/2017	02/2011–04/2014	10/2018–09/2020
Induction regimen	**Arm B: PAD** bortezomib i.v. 1.3 mg/m^2 on days 1, 4, 8, 11 / doxorubicin i.v. 9 mg/m^2 on days 1–4 / dexamethasone p.o. 40 mg on days 1–4, 9–12, 17–20; repeated on day 29 (3x)	**Arms A1+B1: PAd** bortezomib i.v./s.c. 1.3 mg/m^2 on days 1, 4, 8, 11 / doxorubicin i.v. 9 mg/m^2 on days 1–4 / dexamethasone p.o. 20 mg on days 1–4, 9–12, 17–20; repeated on day 29 (3x) **Arms A2+B2: VCD** bortezomib i.v./s.c. 1.3 mg/m^2 on days 1, 4, 8, 11 / cyclophosphamide i.v. 900 mg/m^2 on day 1 / dexamethasone p.o. 40 mg on days 1–2, 4–5, 8–9, 11–12, repeated on day 22 (3x)	**Arms A1+A2: RVd** lenalidomide p.o. 25 mg on days 1–14 / bortezomib s.c. 1.3 mg/m^2 on days 1, 4, 8, 11 / dexamethasone 20 mg on days 1–2, 4–5, 8–9, 11–12; repeat on day 22 (4x) **Arms B1+B2: Elotuzumab-RVd** elotuzumab i.v. 10 mg/kg on days 1, 8, 15 (cycles 1+2) and on days 1 and 11 (cycles 3+4) / lenalidomide p.o. 25 mg on days 1–14 / bortezomib s.c. 1.3 mg/m^2 on days 1, 4, 8, 11 / dexamethasone 20 mg on days 1–2, 4–5, 8–9, 11–12 and 15 (only cycles 1+2); repeat on day 22 (4x)	**VCD:** bortezomib i.v. 1.3 mg/m^2 on days 1, 4, 8, 11 / cyclophosphamide i.v. 500 mg/m^2 on days 1 and 8 / dexamethasone p.o. 40 mg on days 1–2, 4–5, 8–9, 11–12; repeated on day 22 (3x *or* 4x)	**Arm IA: RVd** lenalidomide p.o. 25 mg on days 1–14 and 22–35 / bortezomib s.c. 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, 32 / dexamethasone 20 mg on days 1–2, 4–5, 8–9, 11–12, 15, 22–23, 25–26, 29–30, 32–33; repeat on day 43 (3x) **Arm IB: Isatuximab-RVd** isatuximab i.v. 10 mg/kg on days 1, 8, 15, 22, 29 (cycle 1) and on days 1, 15, 29 (cycles 2+3) / lenalidomide p.o. 25 mg on days 1–14 and 22–35 / bortezomib s.c. 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, 32 / dexamethasone 20 mg on days 1–2, 4–5, 8–9, 11–12, 15, 22–23, 25–26, 29–30, 32–33; repeat on day 43 (3x)

Anti-bacterial prophylaxis[a]	Recommended	Mandatory	Mandatory	Recommended	Recommended
***N* of patients per induction treatment**	192/218 (PAD only)	596 (PAd: 296; VCD: 300)	545 (RVd: 272; elotuzumab-RVd: 273)	1491 (VCD only)	658 (RVd: 328; isatuximab-RVd: 330)
CTCAE version	3.0	4.0	5.0	4.0	5.0
Trial registry	EudraCT No. 2004-000944-26	EudraCT No. 2010-019173-16	NCT 02495922	NCT 01208766	NCT 03617731

CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events, *EMN* European Myeloma Network, *GMMG* German-speaking Myeloma Multicenter Group, *HOVON* Dutch–Belgian Cooperative Trial Group for Hematology Oncology Foundation.
[a]Recommendations according to study protocols – HD4/HO-65: cotrimoxazol; MM5: cotrimoxazol or ciprofloxacin; HD6: cotrimoxazol or ciprofloxacin; EMN02/HO-95: not specified/according to local protocols; HD7: cotrimoxazol.

Table S2. Patient demographics and baseline characteristics in the trials included in the training cohort.

***n* (%)**		**GMMG-HD4**	**GMMG-MM5**	**GMMG-HD6**	**All**
Evaluable	Yes	192 (100)	596 (100)	545 (100)	1333 (100)
Completed IT	Yes	180 (93.8)	567 (95.1)	514 (94.3)	1261 (94.6)
Median age	Years (range)	55 (31–65)	58 (32–70)	58 (32–70)	58 (31-70)
Age > 60 years	No	140 (72.9)	347 (58.2)	312 (57.2)	799 (59.9)
	Yes	52 (27.1)	249 (41.8)	233 (42.8)	534 (40.1)
	Missing	-	-	-	-
Sex	Female	121 (63.0)	348 (58.4)	309 (56.7)	778 (58.4)
	Male	71 (37.0)	248 (41.6)	236 (43.3)	555 (41.6)
	Missing	-	-	-	-
WHO performance status	0–1	177 (92.2)	533 (90.5)	496 (91.0)	1206 (91.0)
	> 1	15 (7.8)	56 (9.5)	49 (9.0)	120 (9.0)
	Missing	-	7	-	7
Body mass index	≤ 30 kg/m^2	162 (84.4)	488 (81.9)	438 (81.0)	1088 (81.9)
	> 30 kg/m^2	30 (15.6)	108 (18.1)	103 (19.0)	241 (18.1)
	Missing	-	-	4	4
White blood cell count	≥ 4.0/nL	169 (88.0)	487 (81.7)	436 (80.0)	1092 (81.9)
	< 4.0/nL	23 (12.0)	109 (18.3)	109 (20.0)	241 (18.1)
	Missing	-	-	-	-
Hemoglobin	≥ 10.0 g/dL	121 (63.0)	394 (66.1)	385 (70.6)	900 (67.5)
	< 10.0 g/dL	71 (37.0)	202 (33.9)	160 (29.4)	433 (32.5)
	Missing	-	-	-	-
Platelets	≥ 150/nL	172 (89.6)	520 (87.2)	489 (89.7)	1181 (88.6)
	< 150/nL	20 (10.4)	76 (12.8)	56 (10.3)	152 (11.4)
	Missing	-	-	-	-
Creatinine	≤ 2.0 mg/dL	173 (90.1)	530 (88.9)	512 (93.9)	1215 (91.2)
	> 2.0 mg/dL	19 (9.9)	66 (11.1)	33 (6.1)	118 (8.8)
	Missing	-	-	-	-
Calcium	≤ 2.75 mmol/L	176 (92.6)	554 (93.0)	525 (96.3)	1255 (94.3)
	> 2.75 mmol/L	14 (7.4)	42 (7.0)	20 (3.7)	76 (5.7)
	Missing	2	-	-	2
C-reactive protein	≤ 5.0 mg/L	120 (65.2)	340 (57.7)	351 (65.0)	811 (61.8)

	> 5.0 mg/L	64 (34.8)	249 (42.3)	189 (35.0)	502 (38.2)
	Missing	8	7	5	20
Lactate dehydrogenase	Normal	151 (83.4)	489 (82.3)	451 (83.2)	1091 (82.8)
	> ULN	30 (16.6)	105 (17.7)	91 (16.8)	226 (17.2)
	Missing	11	2	3	16
International Staging System	I/II	141 (78.3)	433 (72.7)	423 (77.6)	997 (75.5)
	III	39 (21.7)	163 (27.4)	122 (22.4)	324 (24.5)
	Missing	12	-	-	12
Cytogenetics	Standard risk	126 (75.5)	387 (73.3)	322 (72.0)	835 (73.1)
	High risk	41 (24.6)	141 (26.7)	125 (28.0)	307 (26.9)
	Missing	25	68	98	191
Anti-bacterial prophylaxis	No	21 (35.6)	67 (11.2)	9 (1.6)	97 (8.1)
	Yes	38 (64.4)	529 (88.8)	536 (98.3)	1103 (91.9)
	Missing	133	-	-	133

GMMG German-speaking Myeloma Multicenter Group, *IT* induction therapy, *ULN* upper limit of normal, *WHO* World Health Organization.

Table S3. Study endpoints in the training cohort.

***n* (%)**	**GMMG-HD4**	**GMMG-MM5**	**GMMG-HD6**	**All**
Evaluable	192 (100)	596 (100)	545 (100)	1333 (100)
Severe infection (grade ≥ 3)	52 (27.1)	60 (10.1)	46 (8.4)	158 (11.8)
Death	4 (2.1)	8 (1.3)	12 (2.2)	24 (1.8)
Severe infection/death	53 (27.6)	64 (10.7)	50 (9.2)	167 (12.5)
Cause of death	(*n* = 4)	(*n* = 8)	(*n* = 12)	(*n* = 24)
Infection	2 (50.0)	4 (50.0)	9 (75.0)	15 (62.5)
Multiple myeloma	1 (25.0)	2 (25.0)	2 (16.7)	5 (20.8)
Thromboembolic event	-	2 (25.0)	1 (8.3)	3 (12.5)
Unknown	1 (25.0)	-	-	1 (4.2)

GMMG German-speaking Myeloma Multicenter Group.

Table S4. Odds ratio and 95% confidence interval estimates comparing risk score stages for endpoints severe infection, death, and severe infection/death in the training cohort.

	Odds ratio	**95% Confidence interval**	***p***
Severe infection			
High vs low risk	3.40	1.99–5.79	< 0.001
High vs intermediate risk	2.25	1.39–3.66	< 0.001
Intermediate vs low risk	1.51	0.91–2.50	0.06
Death			
High vs low risk	15.67	2.68–91.56	< 0.001
High vs intermediate risk	4.70	1.58–13.99	< 0.001
Intermediate vs low risk	3.33	0.51–21.57	0.13
Severe infection/death			
High vs low risk	3.63	2.15–6.13	< 0.001
High vs intermediate risk	2.34	1.46–3.76	< 0.001
Intermediate vs low risk	1.55	0.94–2.55	0.04

Comparison of risk groups for endpoints severe infection, death, or combined endpoint of severe infection/death.

Table S5. Distribution of baseline and risk factors in the validation cohorts.

***n* (%)**		**HOVON-65**	**EMN02/HOVON-95**	**GMMG-HD7**
Evaluable	Yes	218 (100)	1491 (100)	658 (100)
Completed IT	Yes	197 (90.3)	1340 (89.9)	605 (92.0)
Age > 60 years	No	157 (72.0)	970 (65.1)	372 (56.5)
	Yes	61 (28.0)	521 (34.9)	286 (43.5)
	Missing	-	-	-
WHO performance status	0–1	184 (84.8)	1270 (85.2)	592 (90.2)
	> 1	33 (15.2)	221 (14.8)	62 (9.8)
	Missing	1	-	2
Platelets	≥ 150/nL	189 (87.1)	1263 (85.9)	592 (90.0)
	< 150/nL	28 (12.9)	208 (14.1)	66 (10.0)
	Missing	1	20	-
International Staging System	I/II	153 (78.9)	1163 (78.0)	516 (78.2)
	III	41 (21.1)	328 (22.0)	142 (21.6)
	Missing	24	-	-
Anti-bacterial prophylaxis	No	27 (25.7)	361 (24.5)	16 (2.4)
	Yes	78 (74.3)	1112 (75.5)	642 (97.6)
	Missing	113	18	-

EMN European Myeloma Network, *GMMG* German-speaking Myeloma Multicenter Group, *HOVON* Dutch–Belgian Cooperative Trial Group for Hematology Oncology Foundation, *IT* induction therapy, *WHO* World Health Organization.

Table S6. Study endpoints in the validation cohorts.

***n* (%)**	**HOVON-65**	**EMN02/HOVON-95**	**GMMG-HD7**
Evaluable	218	1491	658
Severe infection (grade ≥ 3)	56 (25.7)	101 (6.8)	77 (11.7)
Death	13 (6.0)	25 (1.7)	12 (1.8)
Severe infection/death	61 (28.0)	118 (7.9)	81 (12.3)

EMN European Myeloma Network, *GMMG* German-speaking Myeloma Multicenter Group, *HOVON* Dutch–Belgian Cooperative Trial Group for Hematology Oncology Foundation.

Table S7. Odds ratio and 95% confidence interval estimates comparing risk score stages for endpoints severe infection, death, and severe infection/death in the HO65 trial.

	Odds ratio	**95% Confidence interval**	***p***
Severe infection			
High vs low risk	3.12	1.15–8.45	0.007
High vs intermediate risk	2.23	0.80–6.20	0.07
Intermediate vs low risk	1.40	0.56–3.53	0.39
Death			
High vs low risk	6.67	0.89–49.86	0.03
High vs intermediate risk	1.49	0.33–6.70	0.54
Intermediate vs low risk	4.47	0.64–31.38	0.07
Severe infection/death			
High vs low risk	3.24	1.21–8.65	0.005
High vs intermediate risk	1.96	0.72–5.31	0.11
Intermediate vs low risk	1.65	0.68–4.02	0.19

Comparison of risk groups for endpoints severe infection, death, or combined endpoint of severe infection/death.

Table S8. Odds ratio and 95% confidence interval estimates comparing risk score stages for endpoints severe infection, death, and severe infection/death in the EMN02/HO95 trial.

	Odds ratio	**95% Confidence interval**	***p***
Severe infection			
High vs low risk	2.36	1.25–4.46	0.002
High vs intermediate risk	1.48	0.83–2.66	0.11
Intermediate vs low risk	1.59	0.87–2.91	0.07
Death			
High vs low risk	5.11	1.05–24.97	0.02
High vs intermediate risk	1.17	0.40–3.43	0.73
Intermediate vs low risk	4.37	0.96–19.79	0.02
Severe infection/death			
High vs low risk	2.56	1.41–4.66	< 0.001
High vs intermediate risk	1.50	0.87–2.59	0.08
Intermediate vs low risk	1.70	0.97–3.01	0.03

Comparison of risk groups for endpoints severe infection, death, or combined endpoint of severe infection/death.

Table S9. Odds ratio and 95% confidence interval estimates comparing risk score stages for endpoints severe infection, death, and severe infection/death in the HD7 trial.

	Odds ratio	**95% Confidence interval**	***p***
Severe infection			
High vs low risk	3.38	1.62–7.04	< 0.001
High vs intermediate risk	2.47	1.25–4.90	0.002
Intermediate vs low risk	1.37	0.66–2.82	0.31
Death			
High vs low risk	5.08	0.71–36.52	0.05
High vs intermediate risk	2.56	0.52–12.54	0.17
Intermediate vs low risk	1.98	0.26–15.19	0.43
Severe infection/death			
High vs low risk	3.68	1.78–7.62	< 0.001
High vs intermediate risk	2.49	1.28–4.84	0.001
Intermediate vs low risk	1.48	0.73–3.02	0.20

Comparison of risk groups for endpoints severe infection, death, or combined endpoint of severe infection/death.

SUPPLEMENTARY FIGURE

Fig. S1. Logistic regression analyses of factors influencing risk of severe infection, death, or combined endpoint of severe infection/death during induction therapy for each trial included in the training cohort.

A Forest plots on factors associated with risk of severe infection. **B** Forest plots on factors influencing risk of death. **C** Forest plots on factors influencing risk of severe infection and/or death. Analyses are presented for each trial in the training cohort (HD4, MM5, and HD6) and overall. All logistic regression analyses including the complete training cohort accounted for trial effects. *P* values from univariable analysis were adjusted for multiple testing.

BMI body mass index, *CI* confidence interval, *ISS* International Staging System, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *WHO* World Health Organization.

Fig. 1A

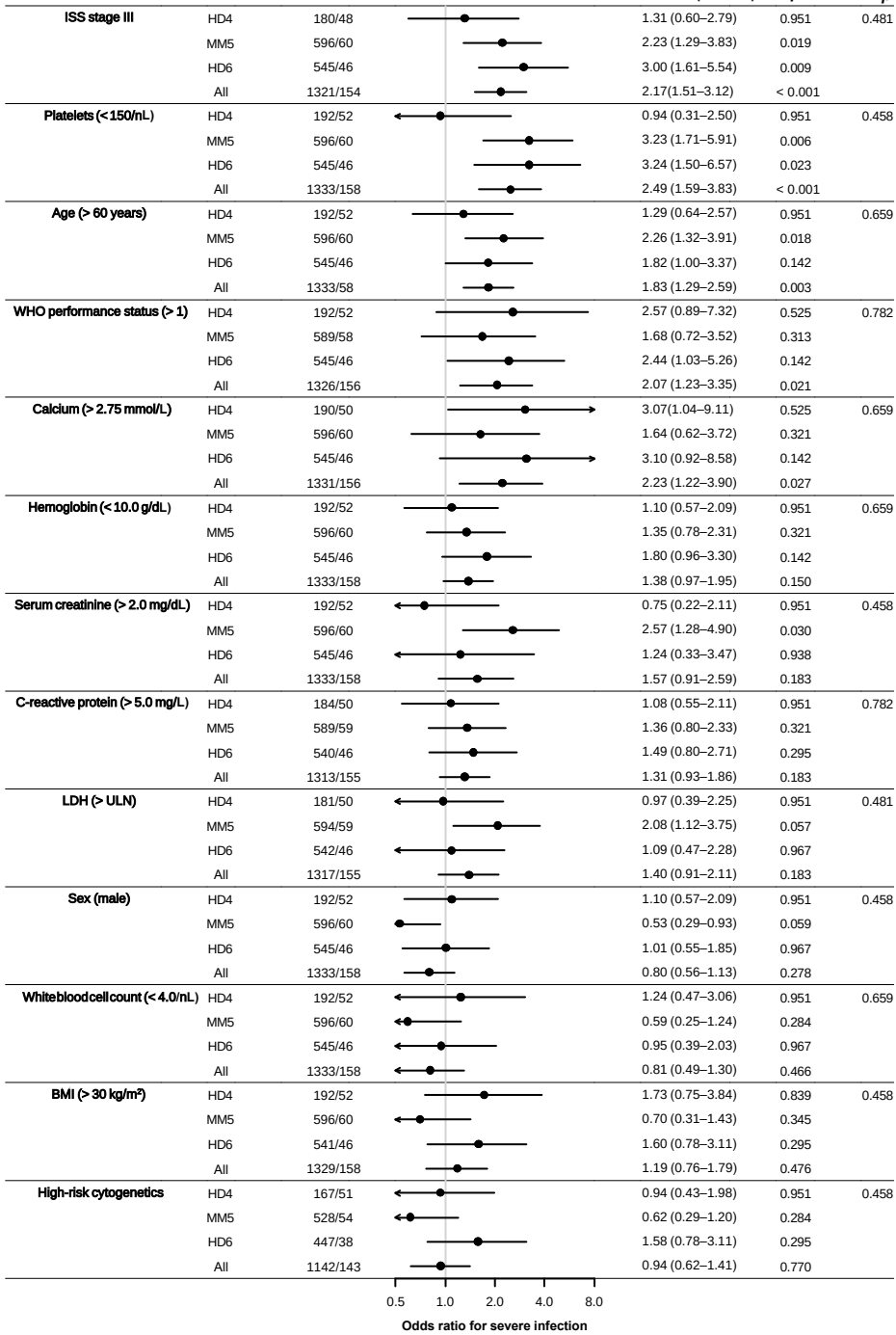

Variable
Trial
N/Severe infections
Odds ratio (95% CI)
p
IA p
ISS stage III
HD4 180/48 1.31 (0.60–2.79) 0.951 0.481
MM5 596/60 2.23 (1.29–3.83) 0.019
HD6 545/46 3.00 (1.61–5.54) 0.009
All 1321/154 2.17(1.51–3.12) < 0.001
Platelets (< 150/nL)
HD4 192/52 0.94 (0.31–2.50) 0.951 0.458
MM5 596/60 3.23 (1.71–5.91) 0.006
HD6 545/46 3.24 (1.50–6.57) 0.023
All 1333/158 2.49 (1.59–3.83) < 0.001
Age (> 60 years)
HD4 192/52 1.29 (0.64–2.57) 0.951 0.659
MM5 596/60 2.26 (1.32–3.91) 0.018
HD6 545/46 1.82 (1.00–3.37) 0.142
All 1333/58 1.83 (1.29–2.59) 0.003
WHO performance status (> 1)
HD4 192/52 2.57 (0.89–7.32) 0.525 0.782
MM5 589/58 1.68 (0.72–3.52) 0.313
HD6 545/46 2.44 (1.03–5.26) 0.142
All 1326/156 2.07 (1.23–3.35) 0.021
Calcium (> 2.75 mmol/L)
HD4 190/50 3.07(1.04–9.11) 0.525 0.659
MM5 596/60 1.64 (0.62–3.72) 0.321
HD6 545/46 3.10 (0.92–8.58) 0.142
All 1331/156 2.23 (1.22–3.90) 0.027
Hemoglobin (< 10.0 g/dL)
HD4 192/52 1.10 (0.57–2.09) 0.951 0.659
MM5 596/60 1.35 (0.78–2.31) 0.321
HD6 545/46 1.80 (0.96–3.30) 0.142
All 1333/158 1.38 (0.97–1.95) 0.150
Serum creatinine (> 2.0 mg/dL)
HD4 192/52 0.75 (0.22–2.11) 0.951 0.458
MM5 596/60 2.57 (1.28–4.90) 0.030
HD6 545/46 1.24 (0.33–3.47) 0.938
All 1333/158 1.57 (0.91–2.59) 0.183
C-reactive protein (> 5.0 mg/L)
HD4 184/50 1.08 (0.55–2.11) 0.951 0.782
MM5 589/59 1.36 (0.80–2.33) 0.321
HD6 540/46 1.49 (0.80–2.71) 0.295
All 1313/155 1.31 (0.93–1.86) 0.183
LDH (> ULN)
HD4 181/50 0.97 (0.39–2.25) 0.951 0.481
MM5 594/59 2.08 (1.12–3.75) 0.057
HD6 542/46 1.09 (0.47–2.28) 0.967
All 1317/155 1.40 (0.91–2.11) 0.183
Sex (male)
HD4 192/52 1.10 (0.57–2.09) 0.951 0.458
MM5 596/60 0.53 (0.29–0.93) 0.059
HD6 545/46 1.01 (0.55–1.85) 0.967
All 1333/158 0.80 (0.56–1.13) 0.278
White blood cell count (< 4.0/nL)
HD4 192/52 1.24 (0.47–3.06) 0.951 0.659
MM5 596/60 0.59 (0.25–1.24) 0.284
HD6 545/46 0.95 (0.39–2.03) 0.967
All 1333/158 0.81 (0.49–1.30) 0.466
BMI (> 30 kg/m²)
HD4 192/52 1.73 (0.75–3.84) 0.839 0.458
MM5 596/60 0.70 (0.31–1.43) 0.345
HD6 541/46 1.60 (0.78–3.11) 0.295
All 1329/158 1.19 (0.76–1.79) 0.476
High-risk cytogenetics
HD4 167/51 0.94 (0.43–1.98) 0.951 0.458
MM5 528/54 0.62 (0.29–1.20) 0.284
HD6 447/38 1.58 (0.78–3.11) 0.295
All 1142/143 0.94 (0.62–1.41) 0.770
0.5
1.0
2.0
4.0
8.0
Odds ratio for severe infection

Fig. 1B

Variable	Trial	*N*/Deaths	Odds ratio (95% CI)	*p*	IA *p*
Severe infections	HD4	192/4	6.58 (1.05–69.06)	0.488	0.747
	MM5	596/8	9.42 (2.37–37.45)	0.017	
	HD6	545/12	24.31 (7.68–87.73)	< 0.001	
	All	1333/24	15.21 (6.58–36.85)	< 0.001	
WHO performance status (> 1)	HD4	192/4	5.16 (0.48–33.99)	0.488	0.963
	MM5	589/7	7.70 (1.68–32.45)	0.055	
	HD6	545/12	8.07 (2.44–25.19)	0.009	
	All	1326/23	7.10 (2.96–16.30)	< 0.001	
ISS stage III	HD4	180/4	3.72 (0.56–24.83)	0.488	0.963
	MM5	596/8	4.27 (1.12–18.59)	0.100	
	HD6	545/12	4.94 (1.62–16.04)	0.028	
	All	1321/24	4.57 (2.05–10.51)	0.001	
Severe thromboembolic events	HD4	192/4	2.10 (0.02–22.11)	0.896	0.747
	MM5	596/8	40.80 (6.42–211.91)	0.008	
	HD6	545/12	6.63 (1.22–25.16)	0.080	
	All	1333/24	7.86(2.33–21.79)	0.008	
Platelets (< 150/nL)	HD4	192/4	0.91 (0.01–9.05)	0.952	0.747
	MM5	596/8	4.46 (1.02–17.12)	0.119	
	HD6	545/12	4.86 (1.36–15.23)	0.065	
	All	1333/24	3.53 (1.39–8.18)	0.030	
Hemoglobin (< 10.0 g/dL)	HD4	192/4	0.72 (0.07–4.48)	0.919	0.747
	MM5	596/8	3.12 (0.82–13.55)	0.201	
	HD6	545/12	3.38 (1.1–10.94)	0.080	
	All	1333/24	2.53 (1.14–5.72)	0.057	
BMI (> 30 kg/m²)	HD4	192/4	2.32 (0.22–14.70)	0.712	0.747
	MM5	596/8	4.64 (1.18–18.23)	0.100	
	HD6	541/12	1.57 (0.39–5.07)	0.629	
	All	1329/24	2.36 (0.97–5.34)	0.123	
C-reactive protein (> 5.0 mg/L)	HD4	184/3	3.19 (0.41–35.38)	0.518	0.747
	MM5	589/8	0.87 (0.20–3.28)	0.903	
	HD6	540/12	2.59 (0.85–8.37)	0.198	
	All	1313/23	1.84 (0.81–4.19)	0.268	
Sex (male)	HD4	192/4	1.72 (0.26–11.36)	0.829	0.963
	MM5	596/8	2.23 (0.59–9.69)	0.401	
	HD6	545/12	1.32 (0.43–4.06)	0.629	
	all	1333/24	1.66 (0.75–3.74)	0.352	
Serum creatinine (> 2.0 mg/dL)	HD4	192/4	3.95 (0.37–25.60)	0.518	0.963
	MM5	596/8	1.60 (0.17–7.48)	0.848	
	HD6	545/12	2.01 (0.21–8.86)	0.629	
	All	1333/24	1.79 (0.47–5.05)	0.500	
Calcium (> 2.75 mmol/L)	HD4	190/4	5.51 (0.51–36.51)	0.488	0.747
	MM5	596/8	0.76 (0.01–6.25)	0.903	
	HD6	545/12	3.44 (0.36–15.65)	0.385	
	All	1331/24	1.95 (0.39–6.24)	0.500	
LDH (> ULN)	HD4	181/3	0.70 (0.01–7.44)	0.927	0.747
	MM5	594/8	0.92 (0.10–4.29)	0.929	
	HD6	542/12	2.68 (0.76–8.31)	0.221	
	All	1317/23	1.45 (0.50–3.57)	0.562	
High-risk cytogenetics	HD4	167/3	5.30 (0.68–59.13)	0.488	0.747
	MM5	528/6	0.74 (0.08–3.76)	0.903	
	HD6	447/9	1.39 (0.33–4.99)	0.629	
	All	1142/18	1.41 (0.51–3.57)	0.562	
Age (> 60 years)	HD4	192/4	2.74 (0.41–18.19)	0.518	0.747
	MM5	596/8	2.21 (0.58–9.62)	0.401	
	HD6	545/12	0.70 (0.20–2.15)	0.629	
	All	1333/24	1.30 (0.57–2.89)	0.563	
White blood cell count (< 4.0/nL)	HD4	192/4	0.78 (0.01–7.71)	0.929	0.923
	MM5	596/8	1.72 (0.31–6.84)	0.732	
	HD6	545/12	0.65 (0.07–2.77)	0.629	
	All	1333/24	0.83 (0.22–2.29)	0.737	

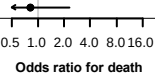
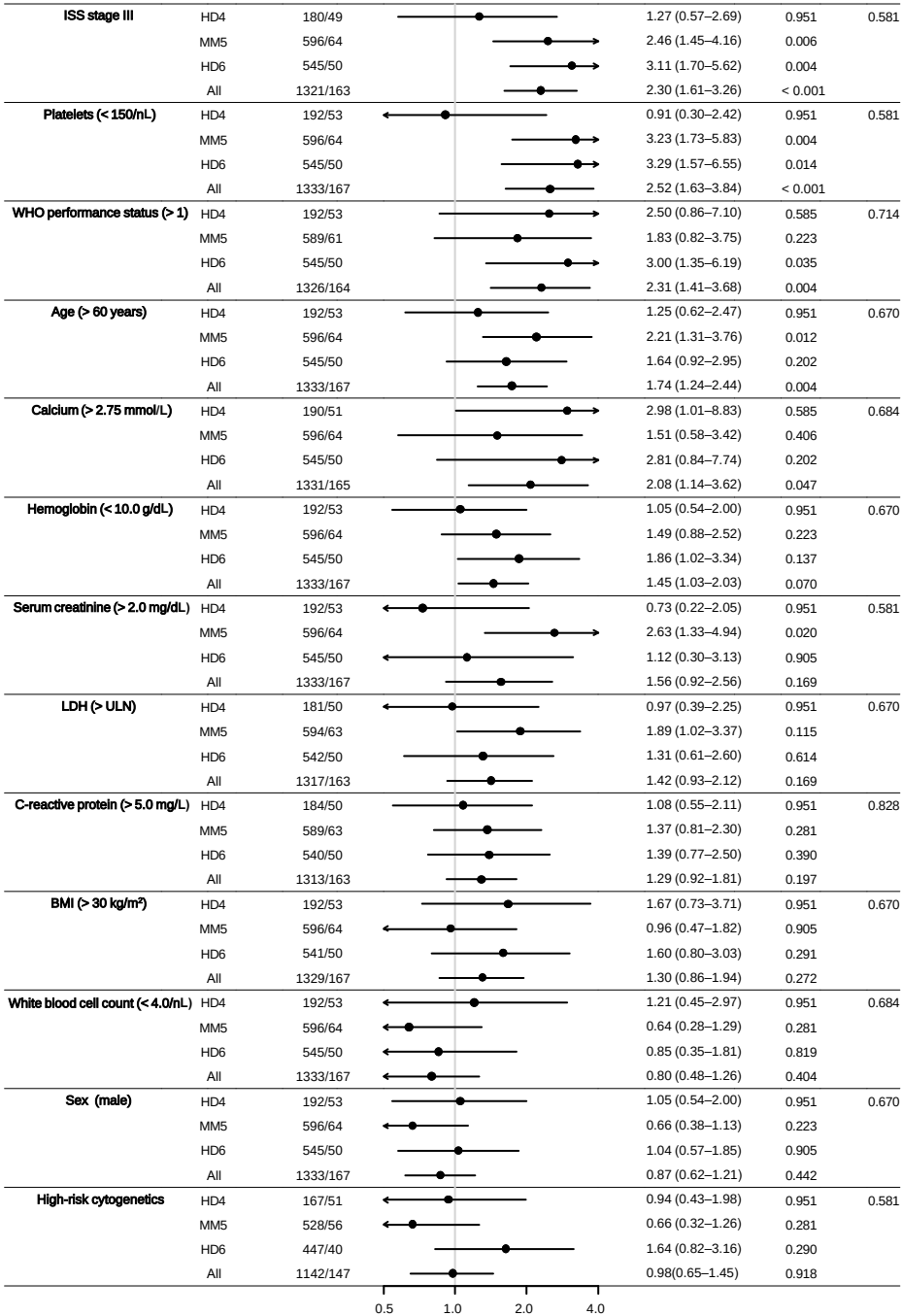


Fig. 1C


Variable
Trial
N/Events
Odds ratio (95% CI)
p
IA p
ISS stage III
HD4 180/49 1.27 (0.57–2.69) 0.951 0.581
MM5 596/64 2.46 (1.45–4.16) 0.006
HD6 545/50 3.11 (1.70–5.62) 0.004
All 1321/163 2.30 (1.61–3.26) < 0.001
Platelets (< 150/nL)
HD4 192/53 0.91 (0.30–2.42) 0.951 0.581
MM5 596/64 3.23 (1.73–5.83) 0.004
HD6 545/50 3.29 (1.57–6.55) 0.014
All 1333/167 2.52 (1.63–3.84) < 0.001
WHO performance status (> 1)
HD4 192/53 2.50 (0.86–7.10) 0.585 0.714
MM5 589/61 1.83 (0.82–3.75) 0.223
HD6 545/50 3.00 (1.35–6.19) 0.035
All 1326/164 2.31 (1.41–3.68) 0.004
Age (> 60 years)
HD4 192/53 1.25 (0.62–2.47) 0.951 0.670
MM5 596/64 2.21 (1.31–3.76) 0.012
HD6 545/50 1.64 (0.92–2.95) 0.202
All 1333/167 1.74 (1.24–2.44) 0.004
Calcium (> 2.75 mmol/L)
HD4 190/51 2.98 (1.01–8.83) 0.585 0.684
MM5 596/64 1.51 (0.58–3.42) 0.406
HD6 545/50 2.81 (0.84–7.74) 0.202
All 1331/165 2.08 (1.14–3.62) 0.047
Hemoglobin (< 10.0 g/dL)
HD4 192/53 1.05 (0.54–2.00) 0.951 0.670
MM5 596/64 1.49 (0.88–2.52) 0.223
HD6 545/50 1.86 (1.02–3.34) 0.137
All 1333/167 1.45 (1.03–2.03) 0.070
Serum creatinine (> 2.0 mg/dL)
HD4 192/53 0.73 (0.22–2.05) 0.951 0.581
MM5 596/64 2.63 (1.33–4.94) 0.020
HD6 545/50 1.12 (0.30–3.13) 0.905
All 1333/167 1.56 (0.92–2.56) 0.169
LDH (> ULN)
HD4 181/50 0.97 (0.39–2.25) 0.951 0.670
MM5 594/63 1.89 (1.02–3.37) 0.115
HD6 542/50 1.31 (0.61–2.60) 0.614
All 1317/163 1.42 (0.93–2.12) 0.169
C-reactive protein (> 5.0 mg/L)
HD4 184/50 1.08 (0.55–2.11) 0.951 0.828
MM5 589/63 1.37 (0.81–2.30) 0.281
HD6 540/50 1.39 (0.77–2.50) 0.390
All 1313/163 1.29 (0.92–1.81) 0.197
BMI (> 30 kg/m²)
HD4 192/53 1.67 (0.73–3.71) 0.951 0.670
MM5 596/64 0.96 (0.47–1.82) 0.905
HD6 541/50 1.60 (0.80–3.03) 0.291
All 1329/167 1.30 (0.86–1.94) 0.272
White blood cell count (< 4.0/nL)
HD4 192/53 1.21 (0.45–2.97) 0.951 0.684
MM5 596/64 0.64 (0.28–1.29) 0.281
HD6 545/50 0.85 (0.35–1.81) 0.819
All 1333/167 0.80 (0.48–1.26) 0.404
Sex (male)
HD4 192/53 1.05 (0.54–2.00) 0.951 0.670
MM5 596/64 0.66 (0.38–1.13) 0.223
HD6 545/50 1.04 (0.57–1.85) 0.905
All 1333/167 0.87 (0.62–1.21) 0.442
High-risk cytogenetics
HD4 167/51 0.94 (0.43–1.98) 0.951 0.581
MM5 528/56 0.66 (0.32–1.26) 0.281
HD6 447/40 1.64 (0.82–3.16) 0.290
All 1142/147 0.98(0.65–1.45) 0.918
0.5
1.0
2.0
4.0
Odds ratio for severe infection / death