A new prognostic model for patients relapsing from upfront autologous transplantation for myeloma based on ISS and PFS1

Journal:	*British Journal of Haematology*
Manuscript ID	Draft
Manuscript Type:	Letters
Date Submitted by the Author:	n/a
Complete List of Authors:	Chavda, Selina; University College London Cancer Institute, Haematology Maciocia, Paul; University College London, Haematology; University College Hospital London, Department of Haematology Mesiri, Pavlina; CRUK & UCL Cancer Trials Centre, Haematology Counsel, Nicholas; CRUK & UCL Cancer Trials Centre, Haematology Kothari, Jaimal; University College Hospital, Haematology Bird, Antonia; University College Hospital, Cancer Services Mariner, Ciaran; University College London Hospitals NHS Foundation Trust, Haematology Chew, Anastasia; University College London Hospitals NHS Foundation Trust, Haematology Clesham, Katherine; University College London Hospitals NHS Foundation Trust, Haematology Moore, Sally; Royal United Hospital, Haematology Percy, Laura; Cancer Institute, University College London, Haematology Rismani, Ali; University College Hospital, Haematology D'Sa, Shirley; University College London Hospitals NHS Foundation Trust, Haematology Rabin, Neil; University College London Hospitals NHS Foundation Trust, Haematology Popat, Rakesh; University College London Hospitals NHS Foundation Trust, Haematology; Yong, Kwee; UCL, Haematology
Key Words:	MULTIPLE MYELOMA, STEM CELL TRANSPLANTATION, relapse

A new prognostic model for patients relapsing from upfront autologous transplantation for myeloma based on ISS and PFS1

Selina J Chavda[1], Paul Maciocia[1], Pavlina Mesiri[2], Nicholas Counsell[2], Jaimal Kothari[3], Antonia Bird[3], Ciaran Mariner[3], Anastasia Chew[3], Katherine Clesham[3], Sally Moore[3], Laura Percy[3], Ali Rismani[3], Shirley D'Sa[3], Neil Rabin[3], Rakesh Popat[1,3], Kwee Yong[1,3].

1 UCL Cancer Institute, 72 Huntley Street, London, WC1E 6DD.

2 CRUK & UCL Cancer Trials Centre, 90 Tottenham Court Road, London, W1T 4TJ.

3 University College London Hospitals NHS Foundation trusts, 235 Euston Road, London, NW1 2BU.

Running title: ISS stage and PFS1 at relapse from upfront ASCT in MM can be used to prognosticate outcomes

Correspondence: Dr Selina J Chavda UCL Cancer Institute, 72 Huntley street, London, WC1E 6DD.

Email: selina.chavda@nhs.net

The authors declare no relevant conflicts of interest

Word count: 993/1000

Multiple Myeloma (MM) is a common haematological malignancy, accounting for 10.0% of all bone marrow cancers in the UK (Velez *et al*, 2016). Chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard of care in transplant eligible newly diagnosed patients and has been shown to deepen

remission and improve overall survival (Kumar *et al,* 2008; Gay *et al*, 2017). However, most patients receiving ASCT will progress and require further treatment. Progression of disease remains heterogeneous and outcomes of salvage therapy are difficult to predict (Laubach *et al,* 2016). The choice of drugs used in salvage regimens has expanded recently, so that therapeutic decisions at relapse can be difficult. Improving understanding of factors affecting outcomes at relapse and responses to second line therapy will facilitate joint treatment decisions between clinicians and patients (Brioli 2016), and identify patient subgroups that fare poorly with current treatment options, and require new approaches.

The objective of our study was to explore factors influencing the outcomes of relapse. In a retrospective analysis of 474 patients undergoing ASCT between 2000-2014 at University College London Hospital, UK, 269 had relapsed at a median of 20 months post ASCT (95%CI 18-23). PFS1 was defined as time from ASCT to 1st progression or death from any cause; PFS2 as time from ASCT to second progression or death and second PFS as time from start of salvage regimen to second progression or death. Disease progression was defined as per IMWG criteria. Post relapse survival (PRS) was measured from date of progression and overall survival (OS) from date of ASCT. Time to event endpoints were estimated using Kaplan-Meier method; univariable and multivariable analysis performed using Cox regression models. Predictive accuracy of risk model systems were estimated using area under the survival curve of Cox models.

Characteristics of this group of 269 patients at diagnosis and relapse are shown in Supp Figure 1. With median follow up from relapse of 29 months, median PRS was

40 months (95% CI 35-44), and OS was 67 months (95% CI 57-73). PFS1 significantly affected PRS (HR 0.96 95% CI: 0.95-0.98, p<0.001), as well as OS: HR 0.87 (95%CI: 0.83-0.92, p<0.001), as may be expected in view of the contribution of PFS1 to OS. Higher ISS stage at relapse was also associated with shorter PRS (ISS 2/3 27 vs 50 months for ISS1, p<0.001) and OS (46 vs 82 months, p<0.001), as was presence of adverse FISH (t(4;14), t(14;16), t(14;20), del(17p), 1q gain or 1p loss) at relapse: PRS, 36 vs 65 months (p<0.001) and OS, 59 vs 97 months (p<0.001) (Supp Fig 2). We also explored features associated with early relapse. Early relapse (≤12 months from ASCT) was associated with shorter PRS (18 vs 49 months, p<0.001) and OS (27 vs 85 months; p<0.001) (Supp Fig 3). Comparisons of patient and disease characteristics revealed that a higher proportion of patients in the early relapse group had anaemia (p=0.01), hypercalcaemia (p=0.02), advanced ISS stage 2/3 (p=0.03), and had adverse cytogenetics at diagnosis (p<0.01) (Table 1).

In this patient cohort, FISH data were available for 59.1% of patients at diagnosis and 52.0% of patients at relapse. Of patients tested at both time points (n=71), clonal evolution was seen in 20 (28.0%), with acquisition of adverse risk genetic markers at relapse (Supp Fig 4). 1q gain was the commonest aberration seen, followed by del 17p and t(4;14). Patients with del 17p at diagnosis and/or relapse had poorer outcomes compared to all other patients: PRS 31 vs 41 months (p=0.04), OS 59 vs 67 months, (p=0.02), or to those with other adverse cytogenetics (Supp Fig 5). Our results highlight the importance of acquiring genetic information at relapse.

At relapse, most patients were treated with proteasome inhibitors (59.1%), and 27.5% received immunomodulatory drugs. 24.5% of patients were entered into clinical trials. Achieving a deeper response to salvage treatment (CR/VGPR vs PR) was associated with a longer second PFS (Supp Fig 6), but not improved PRS or OS. PFS1 also correlated with second PFS (HR 0.98, 95% CI: 0.98-0.99, p<0.001). Use of novel agents, and entry into clinical trials was associated with deeper responses (p<0.05 for both).

Multivariable analysis was performed in order to identify independent prognostic factors for PRS. Variables included were PFS1, ISS stage at diagnosis and relapse, adverse cytogenetics at diagnosis and relapse, regimen received at relapse and response to salvage treatment, factoring in age at relapse and sex (Supp Fig 7). PFS1 retained independent prognostic significance- HR 0.91 (0.87-0.96, p=0.001), as did ISS stage 2/3 at relapse- HR 3.70 (1.58-8.66, p=0.003). Based on our results, we constructed a risk model to stratify patients at relapse post ASCT (Figure 1). Patients were divided into subgroups according to number of risk factors, defined as: relapse ≤12 months and ISS 2/3 stage at relapse. Patients with 0 vs 1 vs 2 risk factors had median PRS of 65 vs 34 vs 10 months and OS of 89 vs 50 vs 19 months, (p<0.001 for both). Statistical analysis performed using cumulative AUC modelling showed this model has significant discriminative accuracy when patients are risk stratified in this manner, with a probability of 72%.

Our real-world data echoes findings reported by other groups, indicating that early relapse is consistently associated with inferior outcomes (Jimenez-Zepeda *et al*, 2015; Gonsalves *et al*, 2016; Majithia *et al,* 2016; Ong *et al*, 2016; Kumar *et al*, 2018). Pending validation in other patient cohorts, our risk model will be useful to

stratify patients for clinical trials and may facilitate discussions with patients regarding prognosis at relapse. As development of increasingly efficacious induction regimens coupled with consolidation and maintenance post-ASCT will continue to increase PFS1, the poor prognostic impact of early relapse is likely to remain a challenge, especially when patients are relapsing on maintenance therapy. In this context, continued re-examination of disease biology at relapse and the outcomes of salvage regimens, including the validation of our risk model will help to optimise the management and counselling of these patients.

Acknowledgments:

This work was carried out at UCL/UCLH, which receives funding as an NIHR Biomedical Research Centre.
SJC, PM[1], JK, AB, CM, AC, KC, SM, LP, AR, SDS, NR, RP performed the research
KY designed the research study
SJC, PM[2], NC, KY analysed the data
SJC, PM[1], PM[2], RP, KY wrote the paper

References:

Brioli A. First line vs delayed transplantation in myeloma: Certainties and controversies. World J Transplant 2016; 6(2): 321-330.

Gay F, Oliva S, Petrucci MT et al. Autologous transplant vs oral chemotherapy and lenalidomide in newly diagnosed young myeloma patients: a pooled analysis. Leukemia 2017; 31(8):1727-1734

Gonsalves WI, Rajkumar SV, Gertz MA et al. Clinical course and outcomes of patients with multiple myeloma who relapse after autologous stem cell therapy. Bone Marrow Transplantation 2016; 51, 1156–1158.

Jimenez-Zepeda VH, Reece DE, Trudel S et al. Early relapse after single auto-SCT for multiple myeloma is a major predictor of survival in the era of novel agents. Bone Marrow Transplantation 2015; 50, 204–208.

Kumar SK, Rajkumar V, Dispenzieri A et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008; 111:2516-2520.

Kumar SK, Dispenzieri A, Fraser R et al. Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time. Leukemia 2018; 32, 986-995.

Laubach J, Garderet L, Mahindra A et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia 2016; 30(5):1005-17.

Majithia N, Rajkumar SV, Lacy MQ et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. Leukemia 2016; 1–6.

Ong SY, De Mel S, Chen XY Early relapse post autologous transplant is a stronger predictor of survival compared with pretreatment patient factors in the novel agent era: analysis of the Singapore Multiple Myeloma Working Group. Bone Marrow Transplantation 2016; 51, 933–937

Velez R, Turesson I, Landgren O et al. Incidence of multiple myeloma in Great Britain, Sweden, and Malmö, Sweden: the impact of differences in case ascertainment on observed incidence trends. BMJ Open 2016;6:e009584.

Table and Figure for Manuscript

Table I Patient characteristics at relapse (relapse < 12 months and >12 months post ASCT).

(Abbreviations: sCR/CR-stringent complete response/complete response, VGPR- very good partial remission, PR- partial remission. ISS Stage 1: B2 microglobulin < 3.5 and Albumin>35g/L, ISS Stage 3: B2 microglobulin>5.5, ISS stage 2: patients not fulfilling criteria for Stage 1 or 3)

Patient characteristics	≤ 12 months post ASCT	> 12 months post ASCT	p value (chi squared) excluding unknown patients
Number of patients	73	196	
Sex	**M** 48 (65.8%) **F** 25 (34.2%)	**M** 129 (65.8%) **F** 67 (34.2%)	p=0.99
Median age at relapse	57 (30-71)	61 (38-73)	p=0.96
Haemoglobin levels **<110g/l** **>110g/L** **Unknown**	 34 (46.6%) 30 (41.1%) 9 (12.3%)	 64 (32.6%) 116 (59.2%) 16 (8.1%)	**p=0.01**
Creatinine **<100mmmol/L** **>100mmol/L** **Unknown**	 49 (67.1%) 14 (19.2%) 10 (13.7%)	 144 (73.5%) 36 (18.4%) 16 (8.1%)	p=0.71
Calcium levels **>2.75mmol/L** **<2.75mmol/L** **Unknown**	 16 (21.9%) 55 (75.3%) 2 (2.8%)	 26 (13.3%) 162 (82.6%) 8 (4.1%)	**p=0.02**
Bony disease **No bony disease** **Unknown**	11 (15.1%) 62 (84.9%) 0 (0%)	37 (18.9%) 158 (80.6%) 1 (0.5%)	p=0.46
ISS stage **ISS stage 1** **ISS stage 2/3** **Unknown**	 25 (34.2%) 25 (34.2%) 23 (31.6%)	 91 (46.4%) 43 (21.9%) 62 (31.7%)	**p=0.03**
FISH at diagnosis **Standard risk** **High risk** **Unknown**	 21 (28.8%) 17 (23.3%) 35 (47.9%)	 96 (49.0%) 25 (12.8%) 75 (38.2%)	**p<0.01**
FISH at relapse **Standard risk** **High risk** **Unknown**	 19 (26.5%) 23 (31.5%) 31 (42.5%)	 49 (25.0%) 49 (25.0%) 98 (50.0%)	p=0.61
Therapy at induction **No treatment** **IMiD** **PI** **Other (Chemo, radiotherapy)** **Unknown**	 0 (0%) 10 (All thalidomide) (13.7%) 11 (15.1%) 52 (71.2%) 0 (0%)	 0 (0%) 37 (18.9%) 23 (11.7%) 135 (68.9%) 1(0.5%)	**p<0.01**
Therapy at relapse **No treatment** **2nd ASCT** **IMiD** **PI** **Other (Chemo, radiotherapy)** **Unknown**	 3 (4.1%) 3 (4.1%) 29 (39.7%) 28 (38.4%) 6 (8.2%) 7(9.6%)	 6 (3.1%) 31 (15.8%) 45 (23.0%) 131 (66.8%) 11 (5.6%) 3(1.5%)	**p<0.01**

Figure 1: Patient stratification by number of risk factors at relapse

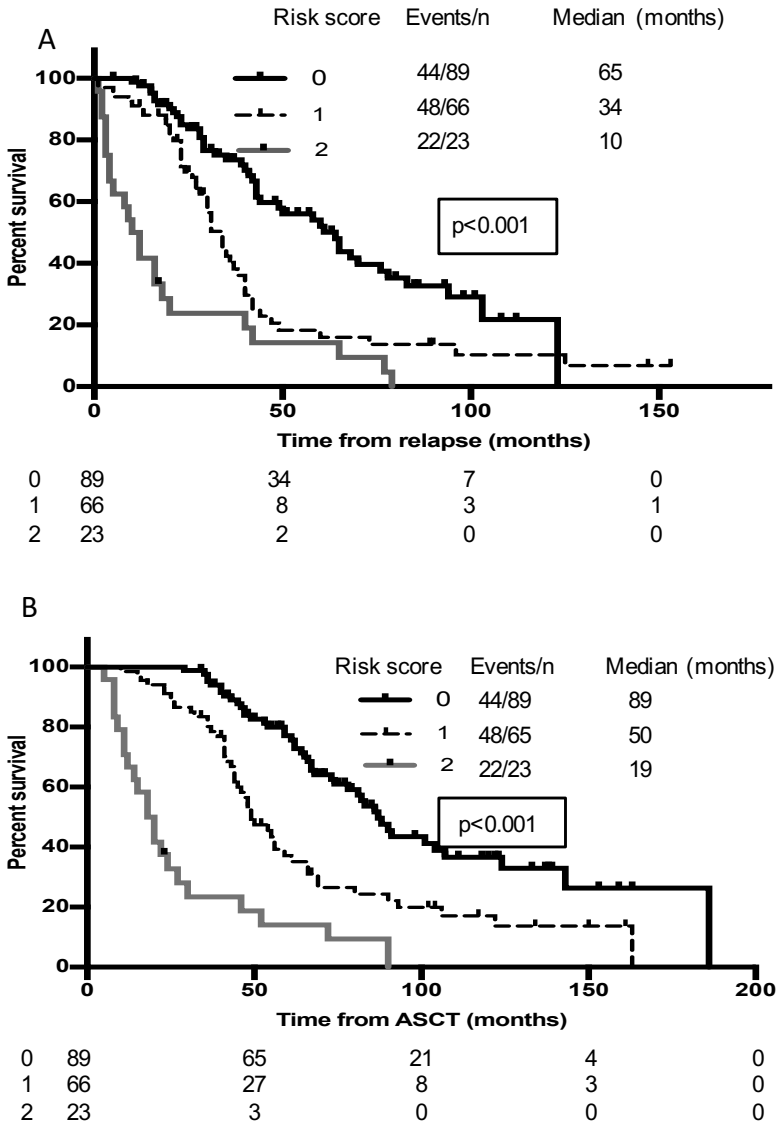


Figure 1. Assessment of survival based on risk score. Risk factors were relapse ≤ 12 months post ASCT, and ISS 2 or 3. A score was developed based on 0, 1 or 2 risk factors.
PRS (A) and OS (B) of patients in each risk group.

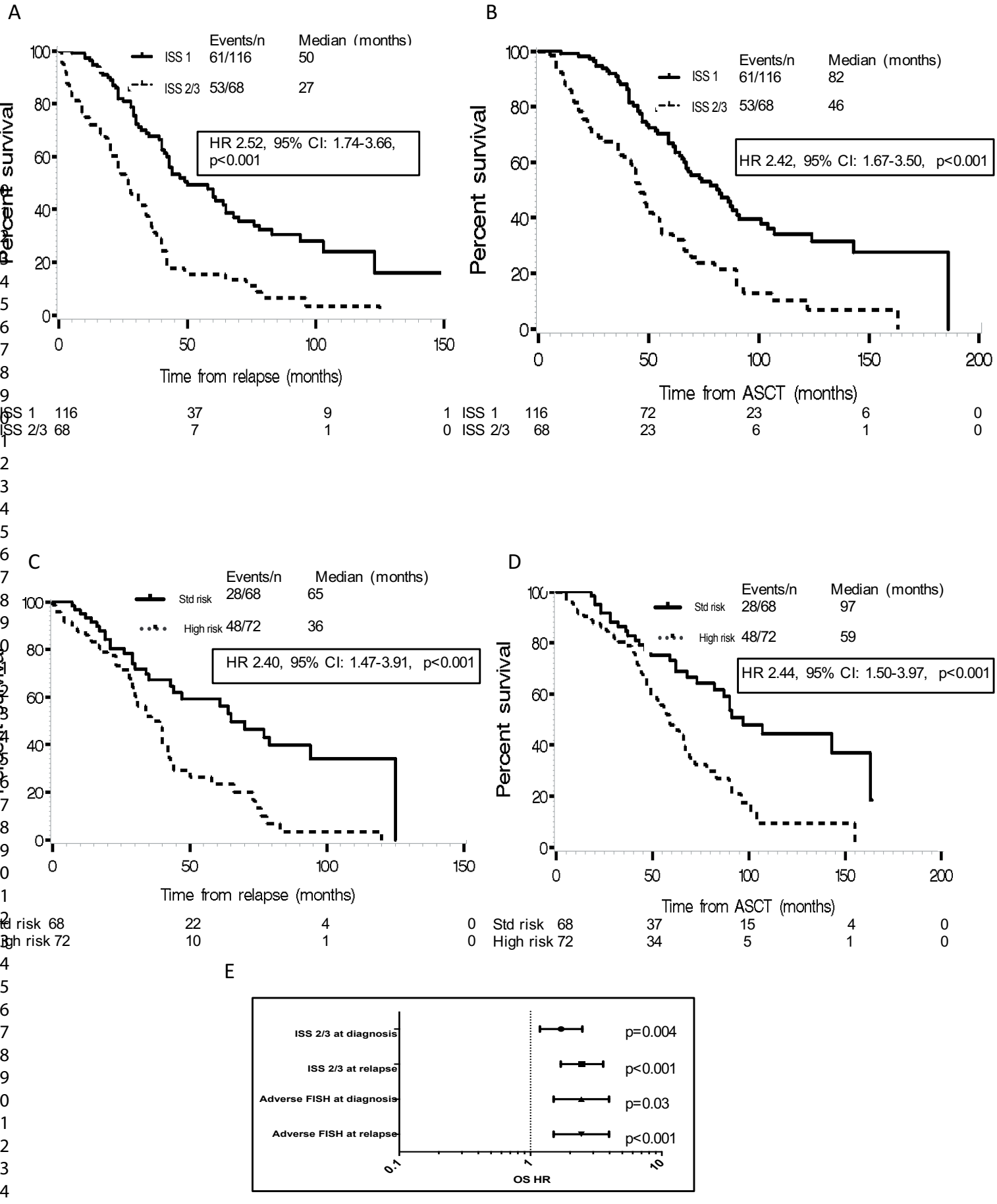
Supplementary Figures

Supplementary Figure 1: Baseline patient characteristics at diagnosis and relapse

(Abbreviations: sCR/CR-stringent complete response/complete response, VGPR- very good partial remission, PR- partial remission. ISS Stage 1: B2 microglobulin < 3.5 and Albumin>35g/L, ISS Stage 3: B2 microglobulin>5.5, ISS stage 2: patients not fulfilling criteria for Stage 1 or 3)

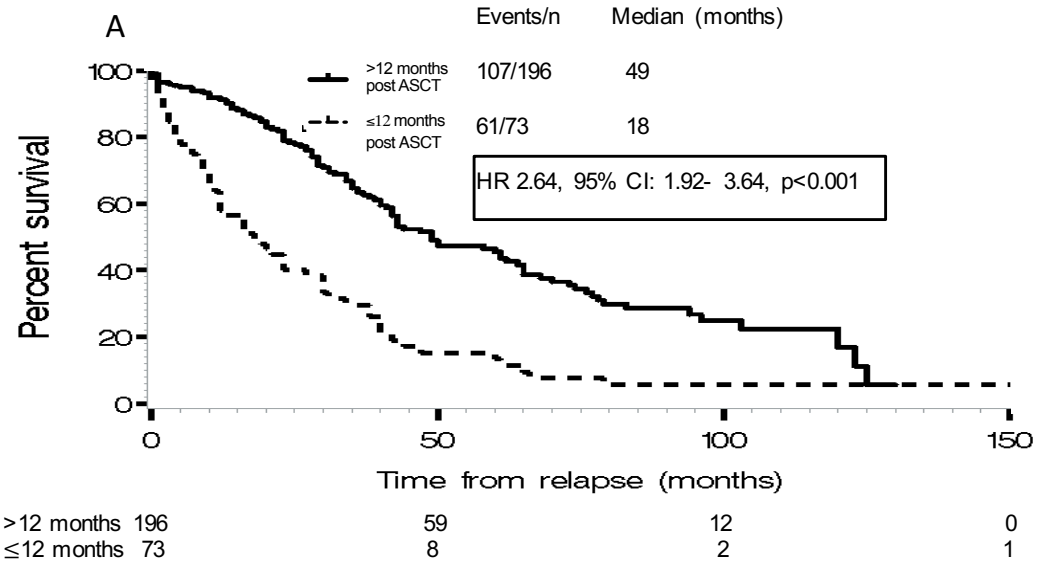
	Patient characteristics at diagnosis	**Patient characteristics at relapse**
Sex	**M** 177 (65.8%) **F** 92 (34.2%)	
Median age	57 years (28-70)	60 years (range 30-73)
Median age at ASCT	58 years (29-70)	
MM Isotype		
IgG	153 (56.9%)	
IgA	62 (23.0%)	
Light chain only	42 (15.6%)	
Other	IgD 4 (1.5%) IgM 2 (0.7%) Non-secretory 5 (1.9%)	
Unknown	1 (0.4%)	
ISS		
Stage 1	86 (32.0%)	116 (43.1%)
Stage 2/3	105 (39.0%)	68 (25.3%)
Unknown	78 (29.0%)	85 (31.6%)
FISH		
Standard risk	117 (43.5%)	68 (25.3%)
High risk	42 (15.6%)	72 (26.8%)
Unknown	110 (40.9%)	129 (47.9%)
Regimens used:		
IMiD	47 (17.5%)	74 (27.5%)
PI	34 (12.6%)	159 (59.1%)
Other:(Chemotherapy/ steroids/radiotherapy)	187 (69.5%) (chemotherapy n=171)	17 (6.4%)
Unknown	1 (0.4%)	10 (3.7%)
No treatment	0 (0%)	9(3.3%)
Best response pre-ASCT		
sCR/CR	12 (4.5%)	
VGPR	66 (24.5%)	
PR	168 (62.5%)	
<PR	21 (7.8%)	
Unknown	2 (0.7%)	
Best response post ASCT		
sCR/CR	40 (14.9%)	
VGPR	139 (51.7%)	
PR	76 (28.3%)	
<PR	13 (4.7%)	
Unknown	1 (0.4%)	

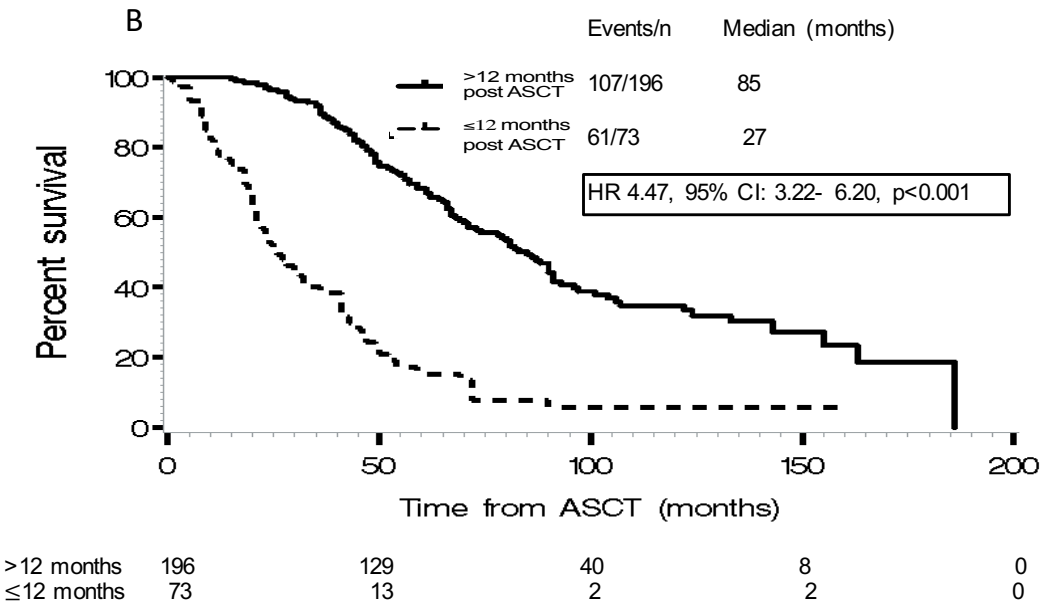
Supplementary Figure 2: Effect of biological risk factors at relapse on survival



Supplementary Figure 3. Effect of biological factors at diagnosis and relapse on PRS and OS. PRS (A) and OS (B) in patients according to ISS stage at relapse, PRS (C) and OS (D) according to adverse cytogenetic risk at relapse. (E) Forest plot illustrating hazard ratio (HR) for OS according to risk factors at diagnosis and relapse

Supplementary Figure 3: Survival according to timing of relapse



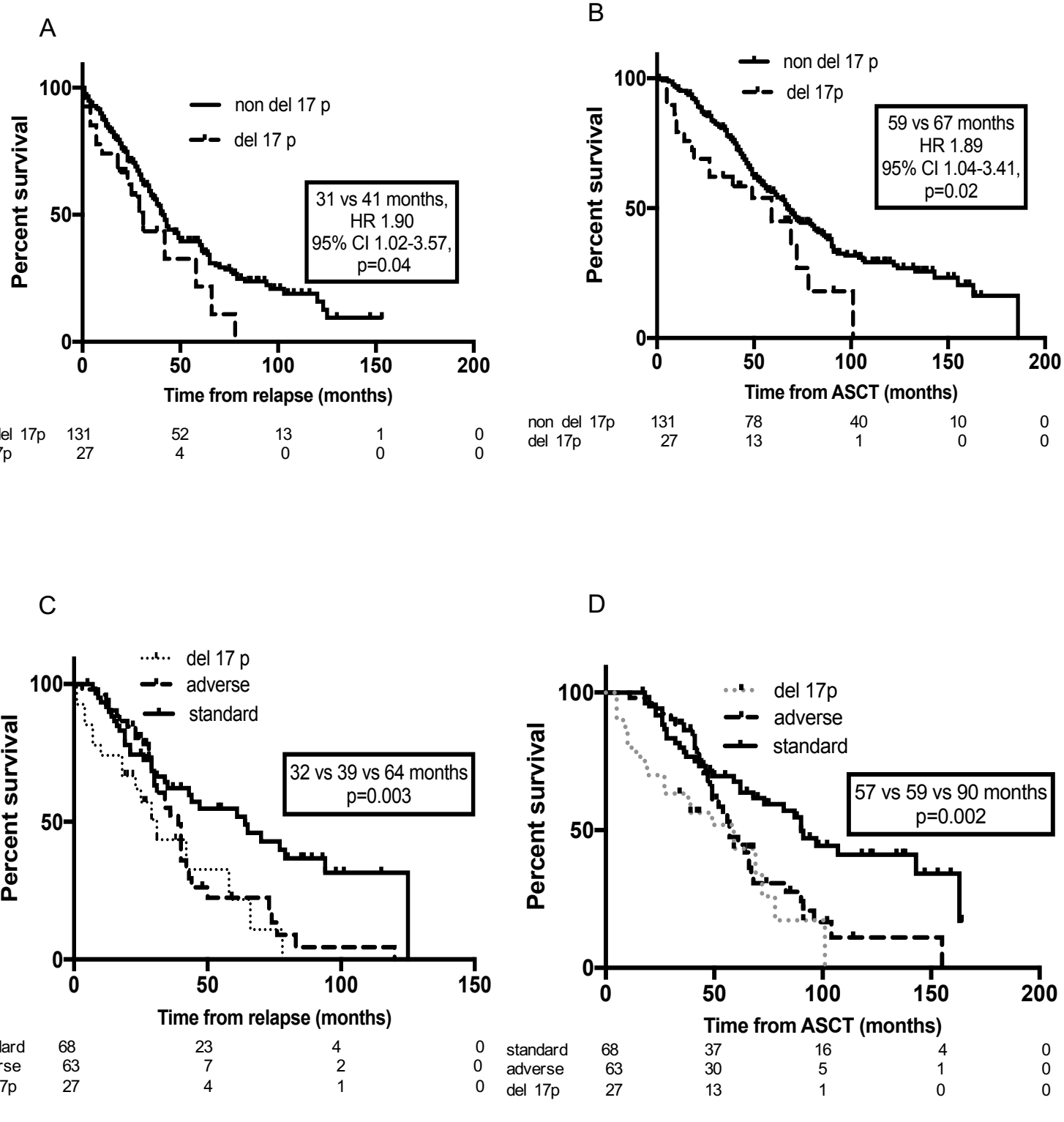


Supplementary Figure 3. Assessment of survival based on timing of relapse. PRS (A) and OS (B) for patients relapsing within 12 months of ASCT or thereafter

Supplementary Figure 4: Clonal evolution between diagnosis and relapse

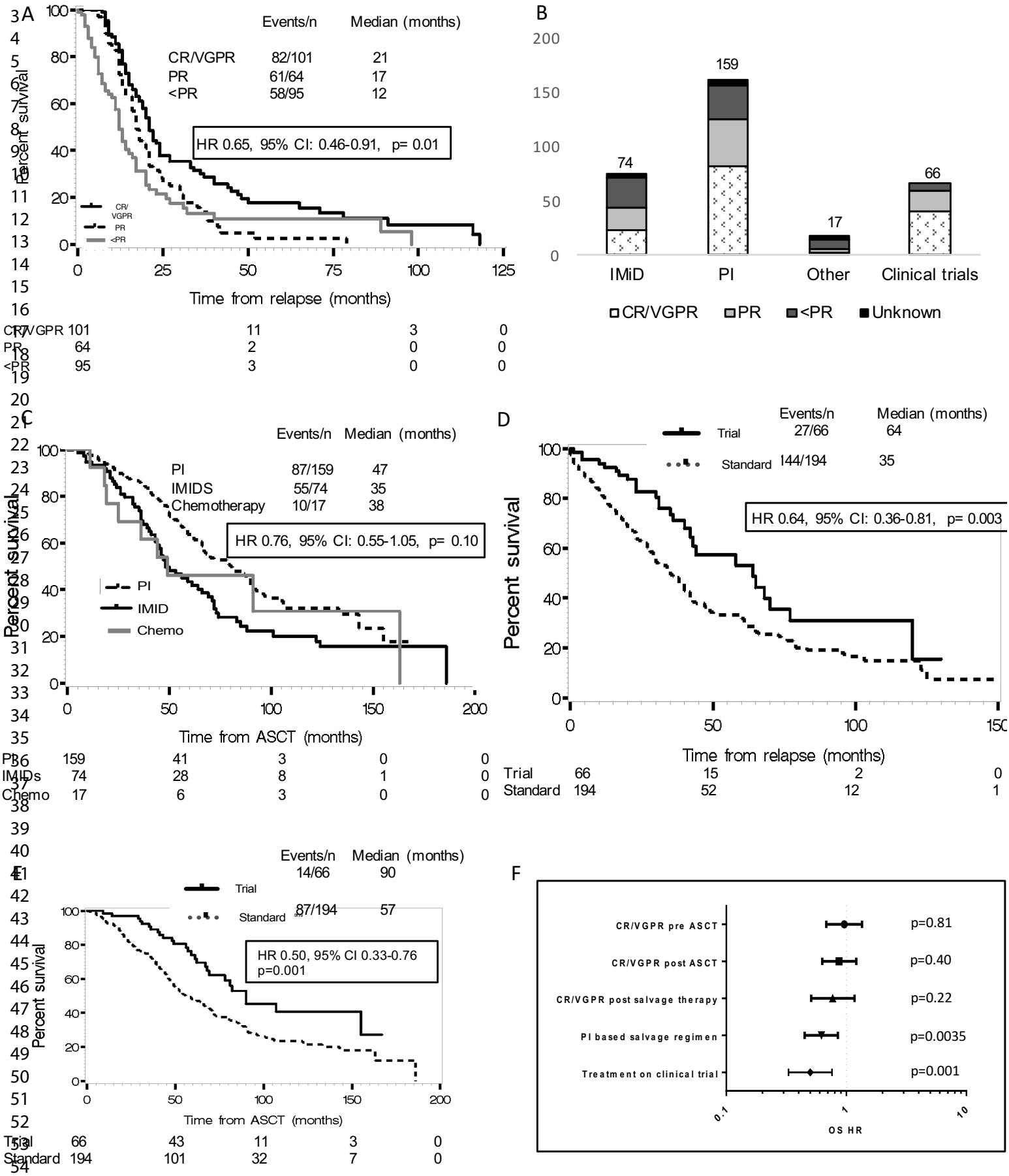
Patient no.	Patient characteristics	Sex	Age at ASCT	PFS1 (months)	Cytogenetics at diagnosis	Cytogenetics at relapse	PRS (months)	OS (months)
#1	IgG K	F	54	35	Hyperdiploidy	1q gain	120	155
#2	K light chain	M	67	34	Nil abnormalities	Del 17p	25	59
#3	K light chain	M	64	83	Nil abnormalities	Del 17p	30	114
#4	IgG λ	M	63	43	Nil abnormalities	1q gain, 1p loss	59	102
#5	IgA K	M	58	14	Nil abnormalities	t(4;14)	76	91
#6	K light chain	F	59	17	Nil abnormalities	1q gain	73	90
#7	IgG K	M	59	17	Nil abnormalities	1q gain	42	59
#8	IgG K	M	48	18	Nil abnormalities	Del 17p, RB1 loss	29	47
#9	λ light chain	M	43	20	t(11;14)	t(11;14) 1p loss	58	78
#10	IgG K	M	61	37	Del 13q	Del 13q, Del 17p	31	69
#11	K light chain	M	63	11	Del 13q	Del 13q, Del 17p, 1q gain	24	35
#12	IgG K	M	59	38	1q gain	t(4;14), 1q gain	36	74
#13	IgG K	F	52	28	Nil abnormalities	1q gain	40	68
#14	IgA λ	M	57	14	Nil abnormalities	1q gain, 1p loss, loss of FGFR3	36	51
#15	IgG λ	M	49	15	Nil abnormalities	1p loss	23	39
#16	IgG K	F	67	16	t(11;14)	t(11;14), Del 17p	23	40
#17	IgA K	M	45	25	Nil abnormalities	t(4;14)	17	43
#18	IgA K	F	60	25	Nil abnormalities	1q gain, del 17p	13	38
#19	IgG λ	F	28	11	Nil abnormalities	1p loss, RB1 loss, del 17p	22	34
#20	IgA K	F	49	4	Nil abnormalities	1q gain, del 17p	1	5

Supplementary Figure 5: Del 17p is associated with poorer outcomes at diagnosis or relapse, irrespective of other cytogenetic abnormalities



Supplementary Figure 5. Del 17p is associated with poorer outcomes at diagnosis or relapse, irrespective of other cytogenetic abnormalities. PRS (A) and OS (B) in patients with del17p at diagnosis or relapse, PRS (C) and OS (D) in patients with del 17p vs other adverse cytogenetics vs standard risk disease.

Supplementary Figure 6: Effect of salvage regimens and response on survival



Supplementary Figure 6. Assessment of survival based on salvage regimen and responses to salvage regimens at relapse.

2nd PFS (A) for CR/VGPR compared to PR (B) Responses according to regimen type. PRS (C) for treatment with PI at relapse compared to other systemic regimens. PRS (D) and OS (E) for patients treated in clinical trials compared to standard therapies. (F) Forest plot illustrating hazard ratio (HR) for OS according to depth of response, use of proteasome inhibitor (PI) and treatment in clinical trial

Supplementary Figure 7:

Multivariable analysis

	HR	95% CI		p value (<0.05 considered statistically significant
PFS1	0.89	0.83	0.95	<0.001
Year of relapse (prior or after 2008)	2.04	0.73	5.84	0.18
ISS stage at diagnosis	0.82	0.35	1.93	0.65
ISS stage 2/3 at relapse	7.89	2.21	28.16	0.0015
Cytogenetics at diagnosis	0.39	0.11	1.34	0.13
Cytogenetics at relapse	2.50	0.66	9.47	0.18
Regimen received at relapse	1.28	0.43	3.86	0.66
Response to salvage therapy	2.73	0.79	9.49	0.11

Stepwise Cox regression model taking significant variables from above:
PFS1 and ISS stage at relapse retain significance.

	HR	95% CI		p value (<0.05 considered statistically significant
PFS1	0.91	0.87	0.96	0.001
ISS stage 2/3 at relapse	3.70	1.58	8.66	0.003

UCL CANCER INSTITUTE
72 HUNTLEY STREET
LONDON WC1E

DEPARTMENT OF HAEMATOLOGY, UCLH
1ST FLOOR CENTRAL
250 EUSTON ROAD, LONDON NW1 2PG

20 May 2018

Dear Finbarr,

As discussed, here is our paper "A new prognostic model for patients relapsing from upfront autologous transplantation for myeloma based on ISS and PFS1" now re-formatted into a letter for the British Journal of Haematology. I hope you find this suitable for publication, it proposes a new risk model to assess these patients, based on multivariable analysis of several risk factors.

With best wishes,

Kwee L Yong
Professor of Haematology and Consultant