The prognostic value of the depth of response in multiple myeloma depends on the time of assessment, risk status and molecular subtype

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Supplementary Table 1. Schema of Total Therapy 3, 4, and 5.

Total Therapy 3	Total Therapy 4		Total Therapy 5
	Light	Standard	
Induction	**Induction**	**Induction**	**Induction**
VDT-PACE + collection of CD34+ cells	MEL-VDT-PACE + collection of CD34+ cells	MEL-VDT-PACE + collection of CD34+ cells MEL-VDT PACE	MEL10-VDT-PACE + collection of CD34+ cells
VDT-PACE			
ASCT	**ASCT**	**ASCT**	**ASCT**
MEL 200 mg/m2	VDT-MEL 200 mg/m2 (fractionated: 50mg/m2 d1-4)	MEL 200 mg/m2 (unfractionated)	MEL 20mg/m2-VRD-PACE
MEL 200 mg/m2	VDT-MEL 200 mg/m2 (fractionated: 50mg/m2 d1-4)	MEL 200 mg/m2 (unfractionated)	**Intertherapy**
			MEL 5mg/m2-VDT-PACE 75% MEL 5mg/m2-VDT-PACE 75%
Consolidation	**Consolidation**	**Consolidation**	**ASCT**
VDT-PACE (dose reduced) VDT-PACE (dose reduced)	VDT-PACE (dose reduced)	VDT-PACE (dose reduced) VDT-PACE (dose reduced)	MEL 20mg/m2-VRD-PACE
Maintenance	**Maintenance**	**Maintenance**	**Maintenance**
TT3A Year 1: VTD weekly Year 2-3: TD weekly	Years 1-3: VRD weekly	Years 1-3: VRD	Year 1: VRD/VMD alternating q month Years 2-3: VRD/VMD alternating q 2 months
TT3B Years 1-3: VRD weekly			

VDT-PACE: bortezomib (Velcade), dexamethasone, thalidomide, cisplatin (Platinum), doxorubicin (Adriamycin), cyclophosphamide, etoposide; MEL: melphalan; VTD: bortezomib (Velcade), thalidomide, dexamethasone; TD: thalidomide, dexamethasone; MEL-VDT-PACE: melphalan, bortezomib (Velcade), dexamethasone, thalidomide, cisplatin (Platinum), doxorubicin (Adriamycin), cyclophosphamide, etoposide; VDT-MEL: bortezomib (Velcade), dexamethasone, thalidomide, melphalan; VRD: bortezomib (Velcade), lenalidomide (Revlimid), dexamethasone; VMD: bortezomib (Velcade), melphalan, dexamethasone.

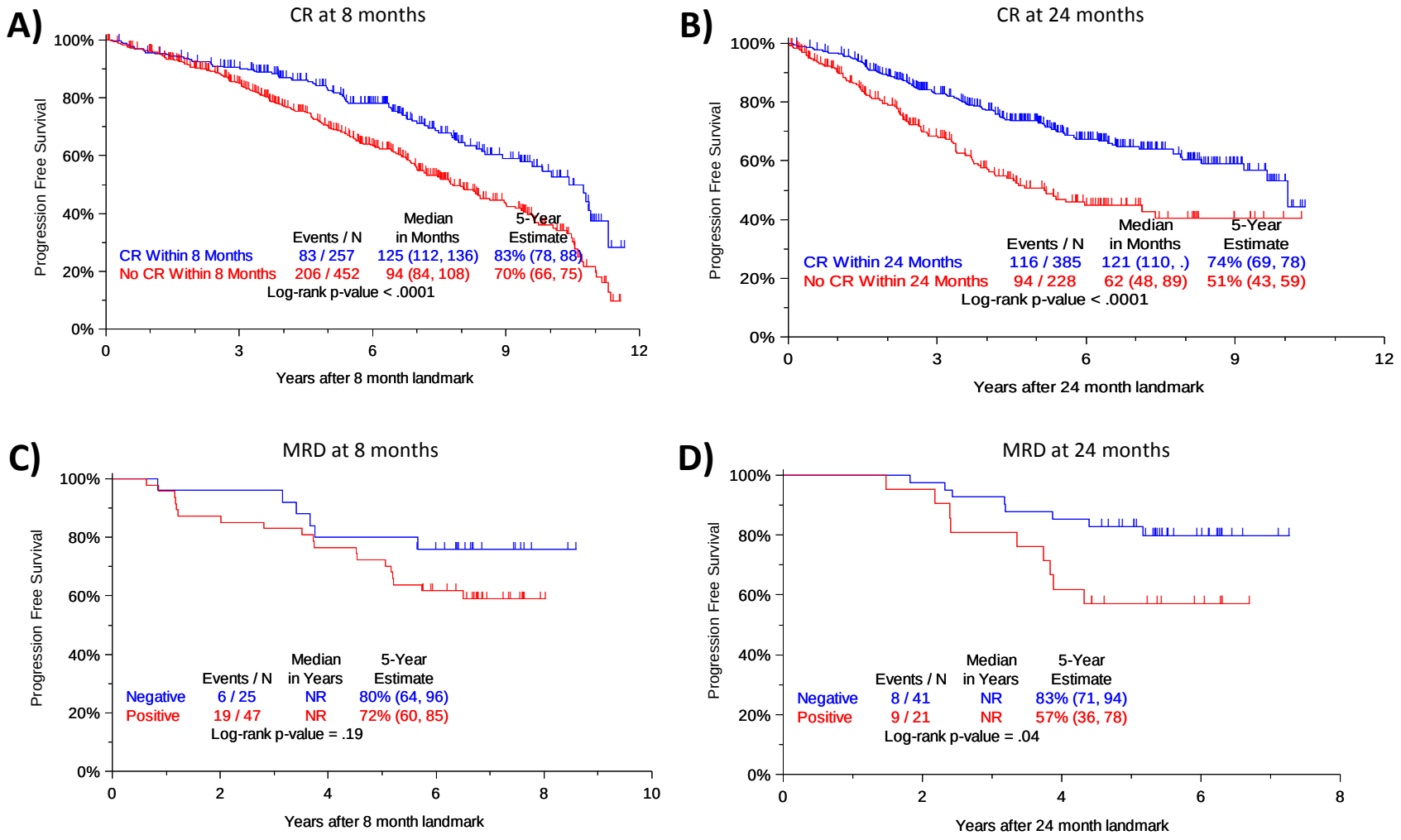
Supplemental Table 2. Baseline characteristics.

Factor	All Patients	TT3a	TT3b	TT4	TT5
Median Age (Years)	59.8 (N=883) (30.4 - 75.9)	59.6 (N=276) (32.5 - 74.7)	59.2 (N=168) (30.7 - 74.7)	60.4 (N=365) (30.4 - 75.9)	60.5 (N=74) (32.8 - 74.0)
Cytogenetic abnormalities	352/864 (41%)	90/267 (34%)	67/164 (41%)	145/359 (40%)	50/74 (68%)
Cytogenetic abnormalities 13	174/864 (20%)	49/267 (18%)	35/164 (21%)	58/359 (16%)	32/74 (43%)
Hypodiploid	148/864 (17%)	39/267 (15%)	27/164 (16%)	57/359 (16%)	25/74 (34%)
Hyperdiploid	200/864 (23%)	51/267 (19%)	42/164 (26%)	85/359 (24%)	22/74 (30%)
Female	331/883 (37%)	95/276 (34%)	64/168 (38%)	140/365 (38%)	32/74 (43%)
Age at Registration	0/883 (0%)	0/276 (0%)	0/168 (0%)	0/365 (0%)	0/74 (0%)
Age >= 65 yr	249/883 (28%)	79/276 (29%)	42/168 (25%)	107/365 (29%)	21/74 (28%)
IgA Isotype	186/876 (21%)	66/276 (24%)	37/168 (22%)	63/358 (18%)	20/74 (27%)
IgG Isotype	506/876 (58%)	158/276 (57%)	84/168 (50%)	229/358 (64%)	35/74 (47%)
Albumin < 3.5 g/dL	352/883 (40%)	75/276 (27%)	74/168 (44%)	167/365 (46%)	36/74 (49%)
B2M >= 3.5 mg/L	474/878 (54%)	128/276 (46%)	96/166 (58%)	192/362 (53%)	58/74 (78%)
B2M > 5.5 mg/L	240/878 (27%)	59/276 (21%)	49/166 (30%)	99/362 (27%)	33/74 (45%)
CRP >= 8 mg/L	521/881 (59%)	275/275 (100%)	120/168 (71%)	97/364 (27%)	29/74 (39%)
Creatinine >= 2 mg/dL	56/883 (6%)	21/276 (8%)	11/168 (7%)	17/365 (5%)	7/74 (9%)
Hemoglobulin < 10 g/dL	330/883 (37%)	82/276 (30%)	52/168 (31%)	148/365 (41%)	48/74 (65%)
LDH >= 190 U/L	198/883 (22%)	74/276 (27%)	42/168 (25%)	52/365 (14%)	30/74 (41%)
Platelet Count < 150 x 10^9/L	140/883 (16%)	33/276 (12%)	26/168 (15%)	52/365 (14%)	29/74 (39%)
ISS Stage 1	291/878 (33%)	123/276 (45%)	48/166 (29%)	108/362 (30%)	12/74 (16%)
ISS Stage 2	347/878 (40%)	94/276 (34%)	69/166 (42%)	155/362 (43%)	29/74 (39%)
ISS Stage 3	240/878 (27%)	59/276 (21%)	49/166 (30%)	99/362 (27%)	33/74 (45%)
CD-1 subgroup	63/883 (7%)	15/276 (5%)	18/168 (11%)	21/365 (6%)	9/74 (12%)
CD-2 subgroup	132/883 (15%)	35/276 (13%)	27/168 (16%)	67/365 (18%)	3/74 (4%)
HY subgroup	296/883 (34%)	86/276 (31%)	51/168 (30%)	149/365 (41%)	10/74 (14%)
LB subgroup	114/883 (13%)	49/276 (18%)	13/168 (8%)	50/365 (14%)	2/74 (3%)
MF subgroup	51/883 (6%)	22/276 (8%)	9/168 (5%)	11/365 (3%)	9/74 (12%)
MS subgroup	116/883 (13%)	36/276 (13%)	23/168 (14%)	38/365 (10%)	19/74 (26%)
PR subgroup	111/883 (13%)	33/276 (12%)	27/168 (16%)	29/365 (8%)	22/74 (30%)
GEP 70 High Risk	129/883 (15%)	40/276 (14%)	37/168 (22%)	2/365 (1%)	50/74 (68%)

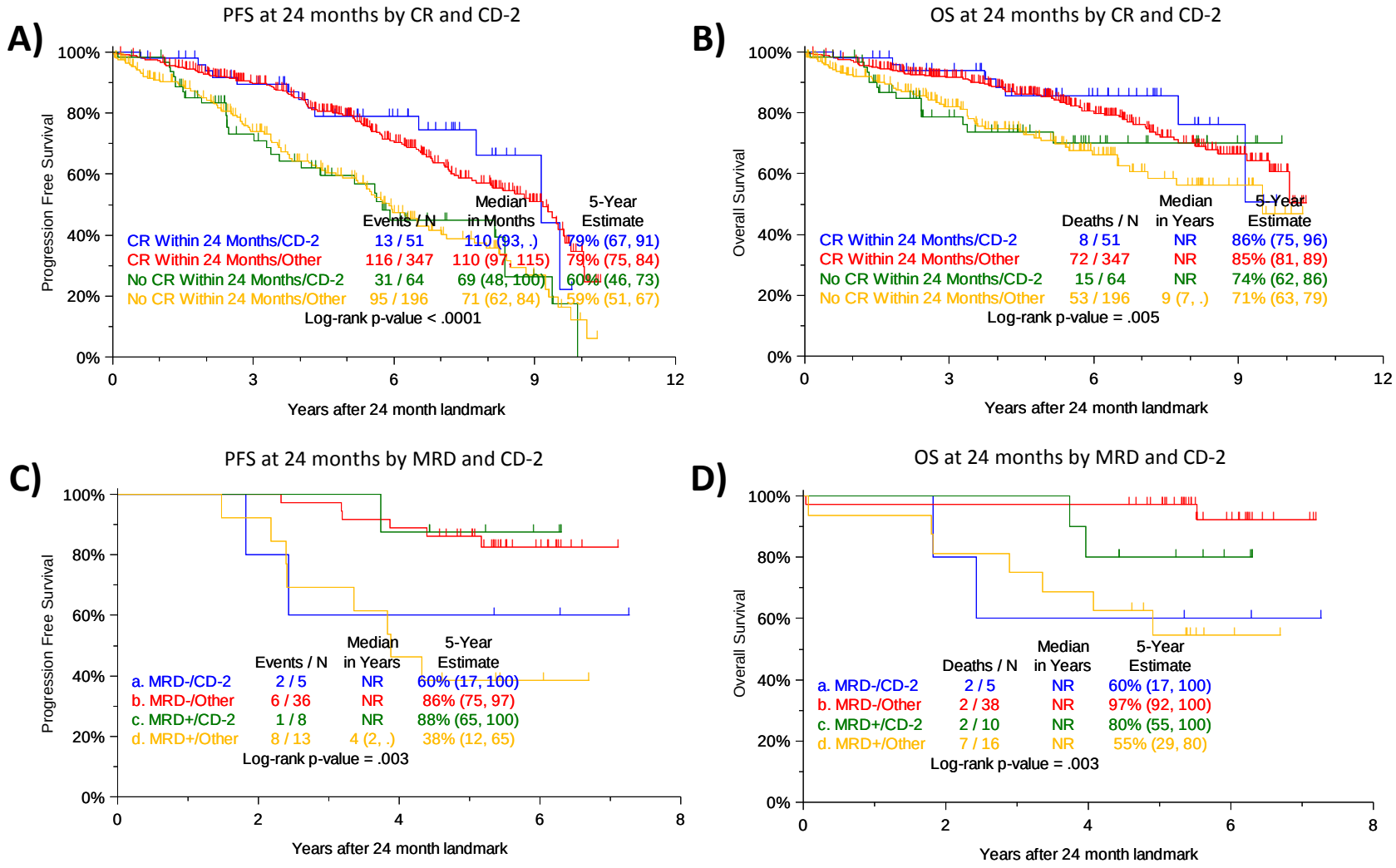
n/N (%): n- Number with factor, N- Number with valid data for factor
ND: No valid observations for factor

Supplementary Table 3. MRD status in long term survivors who have achieved a conventional CR. MRD by 8 color MFC was assessed in 162 who had completed treatment and remained relapse free at 4-8 years after protocol enrollment. The percentage of MRD negativity increased yearly with all patients being negative after 7 years of enrollment.

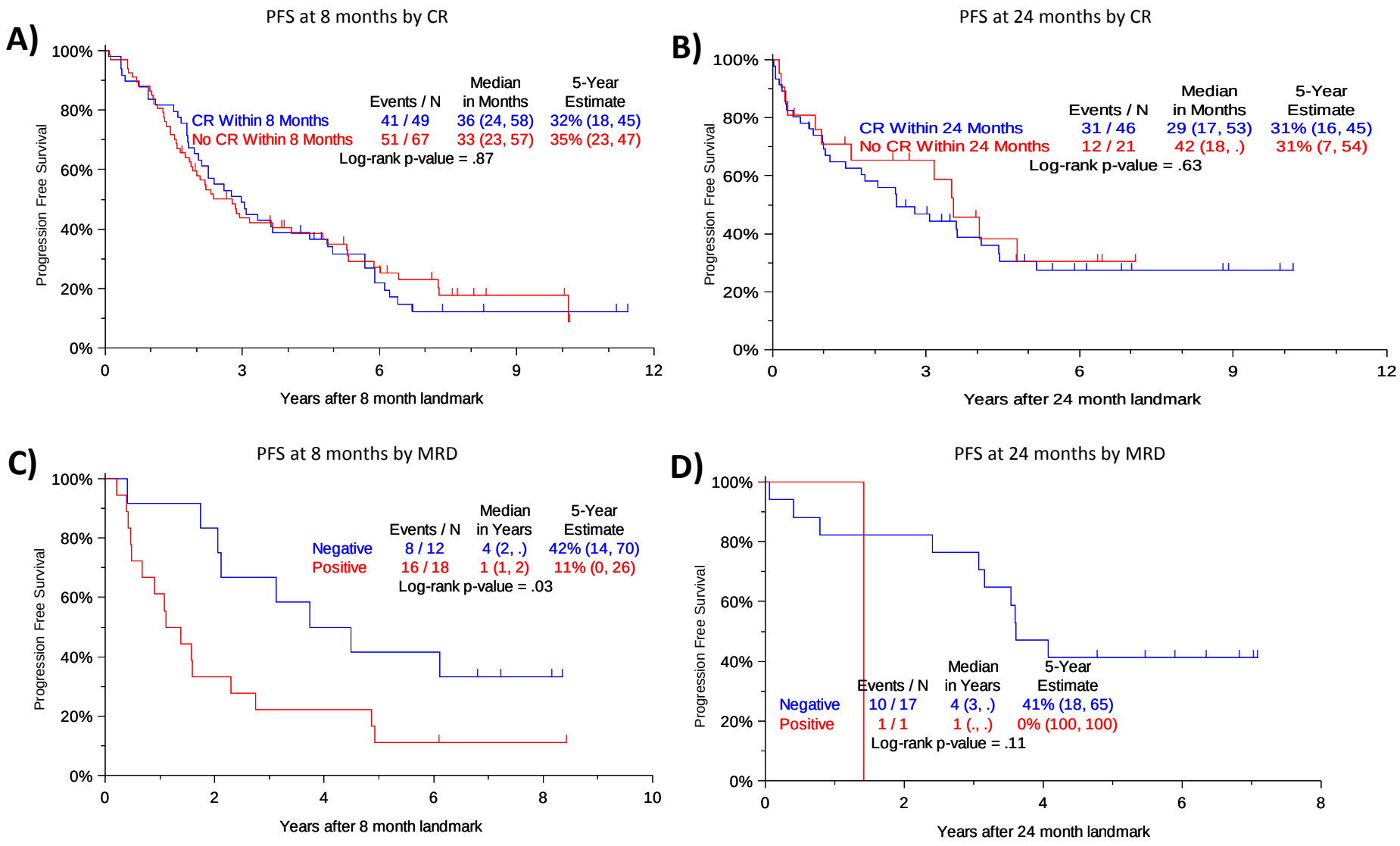
Year after enrollment	10^{-5} MRD negative	10^{-5} MRD positive	Total
4	40 (58%)	29 (42%)	69
5	31 (84%)	6 (16%)	37
6	18 (95%)	1 (5%)	19
7	6 (100%)	0	6
8	1 (100%)	0	1



Supplementary Figure 1. Progression free survival at different landmarks by CR and MRD measured by NGS for Low Risk patients. At 8 month landmark, LR patients with CR had a significantly better PFS compared to non CR patients, **A)** ($p<0.0001$). There was a trend for improved PFS in MRD negative patients, **C)** ($p=0.19$). At 24 month landmark, PFS was significantly better in patients with CR, **B)** $p<0.0001$, and MRD negativity, **D)** $p= 0.04$.



Supplementary Figure 2. PFS and OS by CR and MRD status for the favorable CD-2 subgroup at 24 month landmark. CD-2 patients that did not achieve a CR tended to have better OS than patients of other molecular subgroups who did not achieve a CR, **B)** while PFS was similar between these groups, **A)**. For CD2 patients with at least a VGPR, MRD negativity did not seem to be necessary for achievement of long term PFS, **C)** and OS, **D)**.



Supplementary Figure 3. PFS from different landmarks by CR and MRD measured by NGS for High Risk patients. There was no difference in PFS in HR patients with CR at 6 month landmark, **A)** or 24 month landmark, **B)**. MRD negativity was significantly associated with improved PFS after ASCT at 8 month landmark, **C)** p=0.03. **D)** At 24 month follow up, all but one HR patient were MRD negative and 5 year PFS from that landmark was 41%.