

Total Therapy 1 (August 1990 – June 1995)	Total Therapy 2 (October 1998 – February 2004)	Total Therapy 3 (February 2004 - August 2009)	Total Therapy 4 (June 2008 – January 2019)	
	Randomization ± Thal		Light	Standard
<b>Induction</b>	<b>Induction</b>	<b>Induction</b>	<b>Induction</b>	<b>Induction</b>
VAD x 3 HD CTX + HPC Collection EDAP	VAD ± Thal DCEP 1 & 2 CAD + HPC Collection	VDT-PACE + collection of CD34+ cells VDT-PACE	MEL-VDT-PACE + collection of CD34+ cells	MEL-VDT-PACE + collection of CD34+ cells MEL-VDT PACE
<b>Transplant</b>	<b>Transplant</b>	<b>Transplant</b>	<b>Transplant</b>	<b>Transplant</b>
MEL 200 mg/m2 MEL 200 mg/m2	MEL 200 mg/m2 MEL 200 mg/m2	MEL 200 mg/m2 MEL 200 mg/m2	VDT-MEL 200 mg/m2 (fractionated: 50mg/m2 d1-4) VDT-MEL 200 mg/m2 (fractionated: 50mg/m2 d1-4)	MEL 200 mg/m2 (unfractionated) MEL 200 mg/m2 (unfractionated)
<b>Consolidation</b>	<b>Consolidation</b>	<b>Consolidation</b>	<b>Consolidation</b>	<b>Consolidation</b>
Not Applicable	DPACE x 4 cycles ± Thal	VDT-PACE (dose reduced) VDT-PACE (dose reduced)	VDT-PACE (dose reduced)	VDT-PACE (dose reduced) VDT-PACE (dose reduced)
<b>Maintenance</b>	<b>Maintenance</b>	<b>Maintenance</b>	<b>Maintenance</b>	<b>Maintenance</b>
IFN TIW	Year 1: Dex + IFN ± Thal Year 2-3: IFN ± Thal	TT3A Year 1: VTD weekly Year 2-3: TD weekly TT3B Years 1-3: VRD weekly	Years 1-3: VRD weekly	Years 1-3: VRD

Total Therapy 5 (November 2008 - January 2019)	Total Therapy 5b (November 2008 - January 2019)	Total Therapy 6 (April 2009 - January 2019)	Total Therapy 7 (August 2017 - )
<b>Induction</b>	<b>Induction</b>	<b>Induction</b>	<b>Induction</b>
MEL10-VDT-PACE + collection of CD34+ cells	MEL 10-CFZ-TD-PACE + PBSC collection	MEL-10-VTD-PACE + PBSC collections	KTD-Dara-PACE + PBSC Harvest
<b>Transplant 1</b>	<b>Transplant 1</b>	<b>Transplant 1</b>	<b>Transplant 1</b>
MEL-80 + VRD-PACE	MEL-80 + CFZ-TD-PACE	MEL-80 - VRD-PACE	fMEL 200
<b>Intertherapy</b>	<b>Intertherapy</b>	<b>Intertherapy</b>	<b>Intertherapy</b>
MEL-20 (5mg/m2/d x 4d) + VTD-PACE (75%) 2 cycles	MEL-20 (5mg/m2/d x 4d) + CFZ- TD-PACE (75%)	MEL 5mg/m2-VDT-PACE 75% MEL 5mg/m2-VDT-PACE 75%	Immunological-Consolidation 1 Daratumumab
<b>Transplant 2</b>	<b>Transplant 2</b>	<b>Transplant 2</b>	<b>Consolidation 1</b>
MEL-80 + VRD-PACE	MEL-80 + CFZ-TD-PACE	MEL-80 - VRD-PACE	Daratumumab + KD
	<b>Consolidation</b>		<b>Transplant 2</b>
	CFZ-TD-PACE		fMEL 200
<b>Maintenance</b>	<b>Maintenance</b>	<b>Maintenance</b>	<b>Maintenance</b>
Year 1: VRD/VMD alternating q month Years 2-3: VRD/VMD alternating q 2 months	Year 1: CRD monthly Years 2-3: CD monthly	Year 1: VRD alternating q month Years 2-3: VRD alternating q 2 months	Daratumumab (monthly) + KD* Daratumumab (monthly) + RD (alternating 3-month blocks)

## Appendix Figure 1: Total Therapy Schemas

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; CRD: carfilzomib, Revlimid®, dexamethasone; CD: carfilzomib + dexamethasone; fMEL: fractionated melphalan; KD: carfilzomib and dexamethasone; RD: lenalidomide and dexamethasone.

**Supplemental Table 1. Minimal Residual Disease (MRD) Patterns According to Treatment**

Treatment Protocol	MRD Status		Median Time to MRD Conversion (range)	
	MRD Negative	MRD conversion	From Dx	From ASCT
Off-TTP (n = 223)	133 (59.6)	90 (40.4)	7.9 (1.4 – 27.1)	7.6 (1.0 – 24.5)
TTP1 (n = 4)	3 (75.0)	1 (25.0)	24.1 (21.8 – 30.9)	23.3 (21.0 – 27.8)
TTP2 (n = 64)	38 (59.4)	26 (40.6)	16.1 (9.5 – 21.0)	15.6 (8.8 – 21.0)
TTP3a (n = 46)	28 (60.9)	18 (39.1)	13.4 (7.1 – 15.5)	13.0 (6.9 – 15.1)
TTP3b (n = 36)	27 (75.0)	9 (25.0)	11.2 (4.8 – 12.9)	11.0 (4.5 – 12.6)
TTP4 (n = 135)	86 (63.7)	49 (36.3)	7.2 (1.8 – 17.5)	6.5 (1.4 – 10.7)
TTP5 (n = 20)	13 (65.0)	7 (35.0)	6.1 (1.2 – 10.2)	5.9 (0.9 – 9.9)
TTP5b (n = 1)	1 (100.0)	0 (0.0)	5.4 (N/A)	5.1 (N/A)
TTP6 (n = 39)	15 (38.5)	24 (61.5)	5.4 (1.5 – 10.5)	5.1 (1.1 – 10.2)

NOTE. Data are no. (%) unless otherwise noted. Median time to MRD conversion is provided in years. Abbreviations: TTP, Total Therapy Protocol; Dx, diagnosis; ASCT, autologous stem cell transplant; N/A, non-applicable