SUPPLEMENTARY MATERIAL

Treatment Regimens for Transplant-ineligible Patients with Newly Diagnosed Multiple Myeloma: A Systematic Literature Review and Network Meta-analysis

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Supplementary Table 1 Eligibility criteria used in the systematic literature review

Criteria	Inclusion criteria	Exclusion criteria	Brief rationale
Population	Patients with newly diagnosed multiple myeloma ineligible for autologous cell transplant (ASCT)	Indications other than MM; transplant-eligible population; relapsed/refractory MM	Only studies on newly diagnosed MM patients who are ASCT-ineligible are relevant for the purposes of this submission
Outcomes	Clinical outcomes, including OS, PFS, response (overall response, very good partial response, complete response etc.)	HRQoL, economic evaluation, other clinical outcomes, e.g. PFS2 etc.	Only studies that reported listed clinical outcomes, which will be used for indirect comparison, are regarded as relevant
Study design	Randomised controlled trials	Observational studies, single-arm trials, pharmacokinetic or pharmacodynamic studies	The study designs specified as eligible for inclusion were those considered most likely to report relevant data for this submission
Publication type	N/A	Editorials, reviews, letters	
Language restrictions	English	Any other language	The majority of the research in the field is published in English
Time	No time restriction for full-text publication; conference abstracts from 2018 onwards	N/A	Conference abstracts published 1 year ahead of search were included in Embase database. Manual search was conducted to ensure the latest publications were identified in the review

HRQoL, health-related quality of life; OS, overall survival; MM, multiple myeloma; N/A, not applicable; PFS, progression-free survival; PFS2, time from initial study randomization to second disease progression or death from any cause.

Supplementary Table 2 PFS and OS by age from the SWOG S0777 and ENDURANCE trials

Trial	Age subgroup	PFS HR (95% CI)	OS HR (95% CI)
SWOG S0777 (VRd vs Rd)	≥65 years	0.77 (0.55-–1.08)	0.77 (0.52–1.14)
	<65 years	0.68 (0.50–0.93)	0.64 (0.42–0.97)
ENDURANCE (KRd vs VRd)	≥65 years	1.18 (0.85–1.63)	Not reported
	<65 years	0.92 (0.66–1.27)	Not reported

CI, confidence interval; HR, hazard ratio; KRd, carfilzomib/lenalidomide/dexamethasone; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.

Supplementary Table 3 Overview of identified studies and their patient baseline characteristics

Trials	Location	Treatment arms	N	Median Age (years)	Female (%)	MM type-IgG (%)	ISS-stage III (%)	High-risk cytogenetic abnormality (%)[a]	ECOG ≥2 (%)
UPFRONT [1,2]	US	VD	168	74.5	40	62	33		
		VTD	167	73	58	58	32		
		VMP	167	72	46	62	36		
FIRST trial [3-14]	Multicountry; US, Canada, Asia Pacific, Europe	Rd continuous	535	73	45	62	40	17	22
		Rd18	541	73	50	61	40	20	21
		MPT	547	73	48	64	41	19	20
Palumbo et al. [15-21]	Italy; Europe	VMPT-VT[b]	254	71	49		19		
		VMP[b]	257	71	53		22		
		VMP-Lite[c]	191	71					
		VMP[d]	66	72					
San-Miguel et al. [22,23]	Multicountry; US, Europe, Asia Pacific	VMP-S	52	71		42	54	17	33
		VMP	54	70		68.5	54	10	24
VISTA trial [24-29]	Multicountry; US, Canada, Europe, Latin America, Asia Pacific	VMP	344	71	49	64	35		
		MP	338	71	51	62	34		
GEM05 [30-32]	Spain; Europe	VMP-Lite[e]	130	73	47	62	30	14	
		VTP	130	73	53	55	37	7	
		VT maintenance	91	71	47	62	29	17	
		VP maintenance	87	72	53	55	30	15	
MM-015 [33-38]	Multicountry; Asia Pacific, Europe	MPR-R	152	71	53.3		48.7		
		MPR	153	71	46.4		48.4		
		MP	154	72	51.3		50.6		
Sacchi et al. [39]	Italy; Europe	MP	54	79	52	63	30		9
		MPT	64	76	55	73	22		12

Trials	Location	Treatment arms	N	Median Age (years)	Female (%)	MM type-IgG (%)	ISS-stage III (%)	High-risk cytogenetic abnormality (%)[a]	ECOG ≥2 (%)
MRC Myeloma IX [40]	Multicountry; Asia Pacific, Africa, Europe	MP CTD	423 426	73 73	45.4 43.2	60.8 58.2	39 39.4	41.9 42.7	
TMSG study [41]	Turkey; Europe	MPT-T MP	58 57	69 72	39.7 52.6	83 71.4			
HOVON 49 [42]	Netherlands; Europe	MP MPT-T	168 165	73 72	45.2 43	61.3 58.8	17.3 19.4		
NMSG [43]	Multicountry; Europe	MPT-T MP	182 175	74.6 74.1	49 39		36 30		
IFM 01/01 [44]	Multicountry; Europe	MP MPT	116 113	78.5	47 62		30 35		
GIMEMA [45,46]	Italy; Europe	MPT-T MP	167 164	72 72		65 63	29 29		
Ludwig et al. [47]	Multicountry; Europe	VMC(P) with conv.(P)[f] VMCP with cont.(P)[g]	144 148	66.5 67.5	54 49	63 62	67 68		
HOVON87/NMSG18 [48-50]	Multicountry; Europe	MPT-T MPR-R	318 319	72 73	49 42	64 63	26 26		
IFM 95-01 [51]	Multicountry; Europe	MP M-DEX DEX DEX-IFN	122 118 127 121	70 69 70 69	43 53 50 50	58 60 65 57			
Magarotto et al. [52-57]	Multicountry; Europe	MPR CPR Rd-9	218 222 222	74 73 74	50 52 51		27 27 27	17 22 25	
		RP maintenance R maintenance	198 204	73 73	47 58		23 23	19 18	
Hungria et al. [58]	Multicountry; Latin America	MPT CTD TD	32 32 18	72.2 70 71.6	53.1 65.6 44.4	51.7 55.2 55.6	46.7 41.9 27.8		53.4 50.4 44.4
GEM10 [59,60]	Spain; Europe	Seq. VMP-Lite[h]+ Rd	118 115	75 73		44 47	30 25	16 11	

Trials	Location	Treatment arms	N	Median Age (years)	Female (%)	MM type-IgG (%)	ISS-stage III (%)	High-risk cytogenetic abnormality (%)[a]	ECOG ≥2 (%)
		Alt. VMP-Lite[h]+ Rd							
E1A06 [61,62]	Multicountry; US, Asia Pacific	MPT-T MPR-R	154 152	75.8 76.6	44.2 46.7	71.3 72.6	32.2 30.3		18.8 19.1
Song et al. [63] [i]	Korea; Asia Pacific	MPT CTD	74 83	69 69	45.9 39.8	47.3 51.8	52.7 55.4		
Ludwig et al. [64]	Multicountry; Europe	TD MP	145 143	72 72	49 51	62.7 65.7			
IFM 99–06 [65][j]	Multicountry; Europe	MP MPT	196 125		44 50		30 29		
Dimopoulos et al. [66-69]	Multicountry; Asia Pacific, Europe, US	ICD-300 ICD-400	36 34	72.5 75.5	58 47	58 53			17 21
Takezako et al. [70,71]	Japan; Asia Pacific	ERd Rd continuous	40 42	72 73	57.5 47.6	78 69	20 21	3 0	
CLARION trial [72,73]	Multicountry; Asia Pacific, Europe, Latin America, North America	VMP CMP	477 478	72 72	49.9 49.2		37.7 38.1	14 11.3	21.2 18.6
KEYNOTE 185 trial [74,75]	NA	Pembro-Rd Rd continuous	151 150	74 74	54 53		29 21	16 7	0 1
ALCYONE trial [76-82]	Multicountry; Asia Pacific, Europe, Latin America, North America	D-VMP VMP-lite[k]	350 356	71	54 53	40.9 39.3	40.6 36.2	16.9 14.9	25.7 23.6
IMPROVE MPB-study [83]	Japan; Asia Pacific	modified PETHEMA-VMP[l] JCOG-VMP[m]	45 46	72 72	46.7 37	62 63	20 15		
MAIA [84-87][n]	Multicountry; North America, Europe, Asia Pacific	D-Rd Rd continuous	368 369	73 74	48.6 47.2	61.1 62.6	29.1 29.8	15 13.6	17.1 16
RV-MM-PI-0752 [88-90]	Italy; Europe	Rd9-R	101	75			21	13	11

Trials	Location	Treatment arms	N	Median Age (years)	Female (%)	MM type-IgG (%)	ISS-stage III (%)	High-risk cytogenetic abnormality (%)[a]	ECOG ≥2 (%)
		Rd continuous	98	76			26	16	10
SWOG S0777 [91,92][o]	Multicountry; North America, Asia Pacific	VRd Rd continuous	91 106						
Myeloma XI [93-96][p]	Multicountry; Europe	CTDa[q] CRDa[q]	924 926	74 75	42 44.9	63.5 62.5	35.9 35.2	37.3 35.2	
		CVD[r] No active treatment[r]	106 110						
		CTDa-R[s] CTDa[s] CRDa-R[s] CRDa[s]	194 150 213 166	73.5 73.5 74 73	40.7 36 42.7 37.3	64.9 56.7 63.4 62.7	34.5 28.7 31.5 28.9	43.2 46 31.7 43.1	
Suzuki et al. [97]	Japan; Asia Pacific	MPT MP	52 51	78 76	46.2 51	67.3 51	23.1 23.5		13.5 7.8
GERMAIN [98]	Germany; Europe	VMP-R VMP-placebo	19 21	73 76	37 29	53 48	37 5		
ENDURANCE [99,100]	Multicountry; North America	VRd KRd	542 545	64 65	42 40		26 29	28 28	11 10
GEM-CLARIDEX [101,102]	Spain; Europe	CRd Rd	143 143	76				15.6	
UNITO-EMN10 [103,104]	Italy; Europe	Id ICd ITd IBd	41 59 60 11	74					
Кирилл Белоусов et al. [105]	Russia; Europe	VMP VRP	45 38						
AGMT MM-02 [99,106]	Austria, Germany	KTd KRd	87						
TOURMALINE-MM2 [107]	Multicountry	IRd Placebo-Rd	351 354	73 74			16 17		
HOVON126 [108]	Europe	ITd-I ITd-placebo	39 39	72 73			21 28	18 18	

Trials	Location	Treatment arms	N	Median Age (years)	Female (%)	MM type-IgG (%)	ISS-stage III (%)	High-risk cytogenetic abnormality (%)[a]	ECOG ≥2 (%)
SWOG 1211 [109]	US	VRd-Elo VRd	48 52	62 66	40 40		31 27		
TOURMALINE-MM4 [110][t]	Multicountry; Africa, Asia, Europe, North America, Asia Pacific	Ixazomib Placebo	425 281	72 73			35 36	17 17	

ADL, activity of daily living; ASCT, autologous stem cell transplant; BMP, bortezomib/melphalan/prednisone; BMPS, BMP plus siltuximab; BMPT-VT, bortezomib/melphalan/prednisone/thalidomide followed by maintenance with bortezomib plus thalidomide; CMP, carfilzomib/melphalan/prednisone; cont., continuous; conv., conventional; CPR, cyclophosphamide/prednisone/lenalidomide; CRd, cyclophosphamide/lenalidomide/dexamethasone; CRDa, attenuated cyclophosphamide/lenalidomide/dexamethasone; CTDa, attenuated cyclophosphamide/thalidomide/dexamethasone; CTDa-L/CRDa-L, CTDa/CRDa plus lenalidomide maintenance; DBMP, daratumumab plus BMP; DEX-IFN, dexamethasone-Interferon alpha; DRd, daratumumab plus Rd; ERd, elotuzumab plus Rd; ICd, ixazomib/cyclophosphamide/dexamethasone; IADL, instrumental ADL; Id, ixazomib/dexamethasone; IRd, ixazomib/lenalidomide/dexamethasone; ITd, ixazomib/thalidomide/dexamethasone; ITd-I, ITd plus ixazomib maintenance; IVD, ixazomib/bortezomib/dexamethasone; JCOG, Japan Clinical Oncology Group; KRd, carfilzomib/lenalidomide/dexamethasone M-DEX, melphalan/dexamethasone; MM, multiple myeloma; MP, melphalan/prednisone; MPR, melphalan/prednisone/lenalidomide; MPR-R, MPR plus lenalidomide

maintenance; MPT, melphalan/prednisone/thalidomide; MPT-T, MPT plus thalidomide maintenance; placebo-Rd, placebo followed with Rd maintenance; Rd, lenalidomide/dexamethasone; NDMM, newly diagnosed MM; Rd 18, lenalidomide/dexamethasone 18 months; Rd 9, lenalidomide/dexamethasone 9 months; Rd 9-R, Rd 9 with lenalidomide maintenance; Rd continuous, lenalidomide/dexamethasone continuous; SLR, systematic literature review; TIE, transplant ineligible; VD, bortezomib/dexamethasone; VMCP, vincristine/melphalan/cyclophosphamide and prednisolone; VMP-S, bortezomib/melphalan/prednisone/siltuximab; VRd, bortezomib/lenalidomide/dexamethasone; VRd-Elo, VRd plus elotuzumab; VTD, bortezomib/thalidomide/dexamethasone.

[a]Defined as translocations (4;14) or (14;16) or deletion 17p in the trials; (gain(1q), t(4;14), 71t(14;20), t(14;16), and del(17p) in MRC Myeloma IX study).

[b]No distinction between patients who received bortezomib with 9 once-weekly cycles/4 twice-weekly and 5 once-weekly cycles.

[c]Subgroup of the VMP arm (*N* = 257), patients who received the modified VMP schedule; 9 once-weekly cycles.

[d]Subgroup of the VMP arm (*N* = 257), patients who received the original VMP schedule; 4 twice-weekly and 5 once-weekly cycles.

[e]Bortezomib twice weekly during cycle 1, once weekly during cycles 2-6.

[f]14 days of prednisolone treatment in the induction phase per cycle.

[g]28 days of prednisolone treatment in the induction phase per cycle.

[h]Bortezomib twice weekly during cycle 1, once weekly during cycles 2–9.

[i]MM patients with renal impairment; outcomes relating to different subgroups of patients (as determined by glomerular filtration rate cut-off levels) per treatment arm were reported, thus outcome variables haven't been presented in this report.

[j]MEL100 arm not reported.

[k]Bortezomib is administered twice weekly at weeks 1, 2, 4, and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4, and 5 in cycles 2 to 9

[l]Bortezomib is administered twice weekly in cycle 1 (6-week cycle) followed by 4 weekly doses in cycles 2 to 9; 5-week cycles.

[m]Bortezomib is administered in 3 weekly doses in cycles 1 to 9; 4-week cycles.

[n]Intermediate-fit NDMM patients, with a total frailty score (age, Charlson Index, ADL and IADL) of 1. To better approximate a real-world older population, patients usually excluded from clinical trials or with abnormal laboratory values could be included in the trial.

[o]Patients without an intent for immediate ASCT were included. A subgroup analysis of patients 65–75 and >75 years old is provided and outcomes of these subgroups are included in this SLR as ASCT-ineligible patients.

[p]Outcomes related to TIE patients are included in this SLR. Patients considered ineligible for transplantation at trial entry were randomly assigned (1:1) to induction with either attenuated CTD or attenuated CRD. Patients with a suboptimal response to induction treatment were randomly assigned (1:1) to cyclophosphamide, bortezomib, and dexamethasone (CVD) or no CVD. Patients completing induction and intensification treatment (where applicable) and eligible were randomly assigned (1:1) to lenalidomide maintenance or observation.

[q]Represents patients who entered the induction randomisation.

[r]Represents patients who entered the maintenance randomisation.

[s]Represents TIE patients who entered the consolidation randomisation.

[t]The TOURMALINE-MM4 trial is designed to compare single-agent ixazomib maintenance to placebo for patients who received a major positive response to initial therapy and have not undergone SCT.

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