

Appendix: characteristics of included studies

Table A1. Study characteristics of RCTs included in the surrogacy analysis

Study name (NCT number)	Trial phase	Region	Masking	Intervention	N	DCE, n (%)	TCE, n (%)	DCR, n (%)	TCR, n (%)	Prior LOTs, median (range)
ELOQUENT-3 (NCT02654132)	2	International	Open-label	Elotuzumab + Pomalidomide + Dexamethasone	60	59 (98)	--	41 (68)	--	3 (2-8)
				Pomalidomide + Dexamethasone	57	57 (100)	2 (4)	41 (72)	--	3 (2-8)
OCEAN (NCT03151811)	3	Europe, Australia, Asia	Open-label	Melflufen + Dexamethasone	246	--	--	162 (66)	39 (16)	3 (2-3)
				Pomalidomide + Dexamethasone	249	--	--	163 (65)	30 (12)	3 (2-3)
KEYNOTE-183 (NCT02576977)	3	International	Open-label	Pembrolizumab + Pomalidomide + Dexamethasone	125	> 119 (> 95)	3 (2)	51 (41)	--	3 (1-3)
				Pomalidomide + Dexamethasone	124	> 116 (> 94)	--	50 (40)	--	3 (1-3)
Dimopoulos et al. 2022 (NCT03170882)	2	International	Open-label	Ixazomib + Dexamethasone	73	73 (100)	14 (19)	--	--	--
				Pomalidomide + dexamethasone	49	49 (100)	7 (14)	--	--	--
MM-003/NIMBUS (NCT01311687)	3	International	Open-label	Pomalidomide + Dexamethasone	302	302 (100)	--	225 (75)	--	5 (2-14)
				Dexamethasone	153	153 (100)	--	113 (74)	--	5 (2-17)
Dimopoulos et al. 2021 (NCT01084252)	2	International	Open-label	Isatuximab	109	109 (100)	--	76 (70)	--	4 (2-10)
				Isatuximab + Dexamethasone	55	55 (100)	--	42 (76)	--	4 (2-10)
IFM2009-02 (NCT01053949)	2	France	Open-label	Pomalidomide 21/28+ Dexamethasone	43	32 (74)	--	32 (74)	--	5 (1-13)
				Pomalidomide 28/28+ Dexamethasone	41	32 (78)	--	32 (78)	--	5 (2-10)
FOCUS (NCT01302392)	3	International	Open-label	Carfilzomib	157	157 (100)	--	97 (62)	--	5 (3-15)
				Dexamethasone or equivalent + cyclophosphamide	158	158 (100)	--	100 (63)	--	5 (3-17)

-- indicates not reported. DCE, double-class exposed; DCR, double-class refractory; LOT, line of treatment; RCT, randomized controlled trial; TCE, triple-class exposed; TCR, triple-class refractory.

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MM-002 (NCT00833833)	2	USA, Canada	Open-label	Pomalidomide + Dexamethasone	113	113 (100)	--	70 (62)	--	5 (2-13)
				Pomalidomide	108	108 (100)	--	66 (61)	--	5 (1-12)
ICARIA-MM (NCT02990338)	3	International	Open-label	Isatuximab + Pomalidomide + Dexamethasone	154	154 (100)	--	72 (47)	--	3 (2-4)
				Pomalidomide + Dexamethasone	153	153 (100)	--	70 (46)	--	3 (2-4)
BELLINI (NCT02755597)	3	International	Double- blind	Venetoclax+ bortezomib + dexamethasone	194	--	--	78 (40)	--	--
				Bortezomib + dexamethasone	97	--	--	42 (43)	--	--
APOLLO/EMN14 (NCT03180736)	3	International	Open-label	Daratumumab + Pomalidomide + Dexamethasone	151	151 (100)	--	64 (42)	--	2 (1-5)
				Pomalidomide + Dexamethasone	153	153 (100)	--	65 (42)	--	2 (1-5)
ADMYRE (NCT01102426)	3	International	Open-label	Plitidepsin + Dexamethasone	171	--	--	65 (38)	--	--
				Dexamethasone	84	--	--	33 (39)	--	--
ARROW (NCT02412878)	3	International	Open-label	Carfilzomib QW + Dexamethasone	240	240 (100)	--	58 (24)	--	--
				Carfilzomib Q2W + Dexamethasone	238	238 (100)	--	21 (9)	--	--
CPT-MM301	3	China	Double- blind	CPT + Thalidomide + Dexamethasone	276	181 (66)	--	41 (15)	--	--
				Placebo + Thalidomide + Dexamethasone	139	83 (60)	--	13 (9)	--	--

-- indicates not reported. CPT, circularly permuted TRAIL; QW, every week; QW2, every 2 weeks.

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CANDOR (NCT03158688)	3	International	Open-label	Carfilzomib + Daratumumab + Dexamethasone	312	--	--	37 (12)	--	--
				Carfilzomib + Dexamethasone	154	--	--	18 (12)	--	--
VANTAGE-088 (NCT00773747)	3	International	Double- blind	Vorinostat + bortezomib	317	--	--	17 (5)	--	2 (--)
				Bortezomib	320	--	--	20 (6)	--	2 (--)
COLUMBA (NCT03277105)	3	International	Open-label	Daratumumab SC	263	263 (100)	--	--	--	4 (2-12)
				Daratumumab IV	259	259 (100)	--	--	--	4 (1-15)
ELOQUENT-2 (NCT01239797)	3	International	Open-label	Elotuzumab + Lenalidomide + Dexamethasone	321	--	--	--	--	2 (1-4)
				Lenalidomide + Dexamethasone	325	--	--	--	--	2 (1-4)
ENDEAVOR (NCT01568866)	3	International	Open-label	Carfilzomib + Dexamethasone	464	--	--	--	--	2 (1-2)
				Bortezomib + Dexamethasone	465	--	--	--	--	2 (1-2)
LEPUS (NCT03234972)	3	China	Open-label	Daratumumab + Bortezomib + Dexamethasone	141	102 (72)	--	--	--	2 (1-11)
				Bortezomib + Dexamethasone	70	51 (73)	--	--	--	2 (1-7)
CASTOR (NCT02136134)	3	International	Open-label	Daratumumab + Bortezomib + Dexamethasone	251	112 (45)	--	--	--	2 (1-9)
				Bortezomib + Dexamethasone	247	129 (52)	--	--	--	2 (1-10)

-- indicates not reported. IV, intravenous; SC, subcutaneous.

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POLLUX (NCT02076009)	3	International	Open-label	Daratumumab + lenalidomide + dexamethasone	286	125 (44)	--	--	--	1 (1-11)
				Lenalidomide + Dexamethasone	283	125 (44)	--	--	--	1 (1-8)
Raje et al. 2017 (NCT01602224)	2	International	Open-label	Tabalumab 100 mg + Dexamethasone + Bortezomib	74	--	--	--	--	1 (1-3)
				Tabalumab 300 mg + Dexamethasone + Bortezomib	74	--	--	--	--	1 (0-3)
				Dexamethasone + Bortezomib	72	--	--	--	--	1 (1-3)
SWOG S1304 (NCT01903811)	2	USA	Open-label	Low-dose Carfilizomib + Dexamethasone	64	--	--	--	--	3 (--)
				High-dose Carfilizomib + Dexamethasone	57	--	--	--	--	3 (--)
BOSTON (NCT03110562)	3	International	Open-label	Selinexor + Bortezomib + Dexamethasone	195	--	--	--	--	2 (--)
				Bortezomib + Dexamethasone	207	--	--	--	--	2 (--)
PANORAMA-1 (NCT01023308)	3	International	Double- blind	Panobinostat + bortezomib + dexamethasone	387	--	--	--	--	--
				Bortezomib + dexamethasone	381	--	--	--	--	--
TOURMALINE-MM1 (NCT01564537)	3	USA, Canada	Double- blind	Ixazomib + lenalidomide + dexamethasone	360	--	--	--	--	--
				Lenalidomide + dexamethasone	362	--	--	--	--	--

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TOURMALINE-MM1 China continuation study (NCT01564537)	3	China	Double- blind	Ixazomib + lenalidomide + dexamethasone	57	--	--	--	--	--
				Lenalidomide + dexamethasone	58	--	--	--	--	--
OPTIMISMM (NCT01734928)	3	International	Open-label	Pomalidomide + Bortezomib + Dexamethasone	281	--	--	--	--	--
				Bortezomib + Dexamethasone	278	--	--	--	--	--
ASPIRE (NCT01080391)	3	International	Open-label	Carfilzomib + Lenalidomide + Dexamethasone	396	--	--	--	--	2 (1-3)
				Lenalidomide + Dexamethasone	396	--	--	--	--	2 (1-3)
APEX (NCT00048230)	3	International	Open-label	Bortezomib	332	--	--	--	--	2 (--)
				Dexamethasone	336	--	--	--	--	2 (--)
MM-010 (NCT00424047)	3	Europe, Australia, Israel	Double- blind	Lenalidomide + Dexamethasone	176	--	--	--	--	--
				Dexamethasone	175	--	--	--	--	--
MM-009 (NCT00056160)	3	USA, Canada	Double- blind	Lenalidomide + Dexamethasone	177	--	--	--	--	--
				Dexamethasone	176	--	--	--	--	--
AMBER (NCT00473590)	2	USA, Canada	Open-label	Bevacizumab + Bortezomib	49	--	--	--	--	--
				Bortezomib	53	--	--	--	--	--
MUK Five (ISRCTN17354232)	2	UK	--	Carfilzomib + Cyclophosphamide + Dexamethasone	201	--	--	--	--	--
				Bortezomib + Cyclophosphamide + Dexamethasone	99	--	--	--	--	--

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DOXIL-MMY-3001 (NCT00103506)	3	International	Open-label	Bortezomib	322	--	--	--	--	--
				Pegylated Liposomal Doxorubicin + Bortezomib	324	--	--	--	--	--
CA204-009 (NCT01478048)	2	USA, Europe	Open-label	Elotuzumab + Bortezomib + Dexamethasone	77	--	--	--	--	--
				Bortezomib + Dexamethasone	75	--	--	--	--	--
Orlowski et al. 2015 (NCT00401843)	2	International	Double- blind	Siltuximab + Bortezomib	142	--	--	--	--	--
				Bortezomib	144	--	--	--	--	--
OPTIMUM (NCT00452569)	3	International	Open-label	Dexamethasone	126	--	--	--	--	--
				Thalidomide 100	121	--	--	--	--	--
				Thalidomide 200	122	--	--	--	--	--
				Thalidomide 400	130	--	--	--	--	--
Kropff et al. 2017 (NCT00813150)	3	Germany	Open-label	Bortezomib + Dexamethasone	46	--	--	--	--	--
				Bortezomib + Dexamethasone + Cyclophosphamide	47	--	--	--	--	--
JCOG0904 (UMIN000003135)	2	Japan	--	Bortezomib + Dexamethasone	22	--	--	--	--	--
				Thalidomide + Dexamethasone	22	--	--	--	--	--
Richardson et al. 2020 (NCT01002248)	3	International	Open-label	Perifosine + Bortezomib + Dexamethasone	69	--	--	--	--	--
				Bortezomib + Dexamethasone	66	--	--	--	--	--

-- indicates not reported.

Appendix: search strategies for the umbrella review

Table A2. Embase search strategy (search date: July 7, 2022)

No.	Description	Terms	Hits
1	Population terms	exp multiple myeloma/	88788
2		(myeloma or (multiple adj2 myeloma\$) or plasmacytom\$ or plasmocytom\$ or mgus or (monoclonal adj2 gammopath\$)).ti,ab.	104444
3		1 or 2	122716
4		(refractor* or recurr* or relaps* or resist* or fail* or rescue or pretreated or pre-treated or previously treated or re-treated or second line or second-line or 2nd line or 2L or 2 L or 2 line or third line or third-line or 3rd line or 3L or 3 L or 3 line or fourth line or fourth-line or 4th line or 4L or 4 L or 4 line* or prior treatment or prior therapy or later line or subsequent line or (progress* adj2 (after* or post*))).ti,ab.	4490321
5		exp cancer recurrence/ or exp relapse/ or exp therapy resistance/ or exp tumor recurrence/ or exp recurrent disease/ or exp cancer resistance/ or exp drug resistance/ or exp treatment failure/ or exp salvage therapy/	1168061
6		('Re oc?ur*' or reoc?ur* or recrudescen* or (post* adj (chemo* or line or therap* or treat*)) or ((pre* or prio* or prev* or post* or heav* or late* or receiv* or subsequ*) adj4 (treat* or therap* or regim* or progress* or fail* or relaps* or resis* or refract* or line* or chemo* or target*)) or ((lack* or inadequa*) adj2 respon*) or nonrespon* or 'non respon*' or unrespon* or 'un respon*' or 'no respon*' or 'not respond*').ab,ti.	3038573
7		or/4-6	6634896
8	Population terms, combined	3 and 7	52259
9	Study design terms	exp network meta-analysis/	5641
10		((network adj (meta-analy* or metaanaly* or metanaly* or met-analy*)) or (indirect adj4 (comparison* or analy* or eval* or evidence or method*)) or ((mixed-treatment* or multiple treatment*) adj1 comparison*) or ((match* or population) adj4 comparison*) or (simulated adj2 (control* or comparison*)) or outcome regression or (historical control* or historical comparison*) or Bayesian or frequentist or (network adj4 (analy* or evidence)) or propensity scor* weigh* or MAIC or STC or ITC or MTC or NMA or bucher*).ti,ab.	214568
11	Study design terms, combined	or/9-10	214828
12	Intersection study design terms and population terms	8 and 11	733
13	Term for language restriction	limit 12 to English language	723
14	Term for date restriction	limit 13 to yr="2017-current"	375

Umbrella review represents an update to a previously published systematic literature review (Cope S, et al. *Value Health* 2020;23:441-450.)

Appendix: search strategies for the umbrella review

Table A3. MEDLINE search strategy (search date: July 7, 2022)

No.	Description	Terms	Hits
1	Population terms	exp multiple myeloma/	45703
2		(myeloma or (multiple adj2 myeloma\$) or plasmacytom\$ or plasmocytom\$ or mgus or (monoclonal adj2 gammopath\$)).ti,ab.	66341
3		1 or 2	74622
4		(refractor* or recurr* or relaps* or resist* or fail* or rescue or pretreated or pre-treated or previously treated or re-treated or second line or second-line or 2nd line or 2L or 2 L or 2 line or third line or third-line or 3rd line or 3L or 3 L or 3 line or fourth line or fourth-line or 4th line or 4L or 4 L or 4 line* or prior treatment or prior therapy or later line or subsequent line or (progress* adj2 (after* or post*))).ti,ab.	3274597
5		exp relapse/ or exp drug resistance/ or exp treatment failure/ or exp salvage therapy/	602354
6		('Re oc?ur*' or reoc?ur* or recrudescen* or (post* adj (chemo* or line or therap* or treat*)) or ((pre* or prio* or prev* or post* or heav* or late* or receiv* or subseque*) adj4 (treat* or therap* or regim* or progress* or fail* or relaps* or resis* or refract* or line* or chemo* or target*)) or ((lack* or inadequa*) adj2 respon*) or nonrespon* or 'non respon*' or unrespon* or 'un respon*' or 'no respon*' or 'not respond*').ab,ti.	2043901
7		or/4-6	4771950
8	Population terms, combined	3 and 7	22007
9	Study design terms	exp network meta-analysis/	3896
10		((network adj (meta-analy* or metaanaly* or metanaly* or met-analy*)) or (indirect adj4 (comparison* or analy* or eval* or evidence or method*)) or ((mixed-treatment* or multiple treatment*) adj1 comparison*) or ((match* or population) adj4 comparison*) or (simulated adj2 (control* or comparison*)) or outcome regression or (historical control* or historical comparison*) or Bayesian or frequentist or (network adj4 (analy* or evidence)) or propensity scor* weigh* or MAIC or STC or ITC or MTC or NMA or bucher*).ti,ab.	174124
11	Study design terms, combined	or/9-10	174402
12	Intersection study design terms and population terms	8 and 11	174
13	Term for language restriction	limit 12 to English language	167
14	Term for date restriction	limit 13 to yr="2017-current"	82

Umbrella review represents an update to a previously published systematic literature review (Cope S, et al. *Value Health* 2020;23:441-450).