

Supplementary Appendix

Progression-free survival as a surrogate endpoint in myeloma clinical trials: an evolving paradigm.

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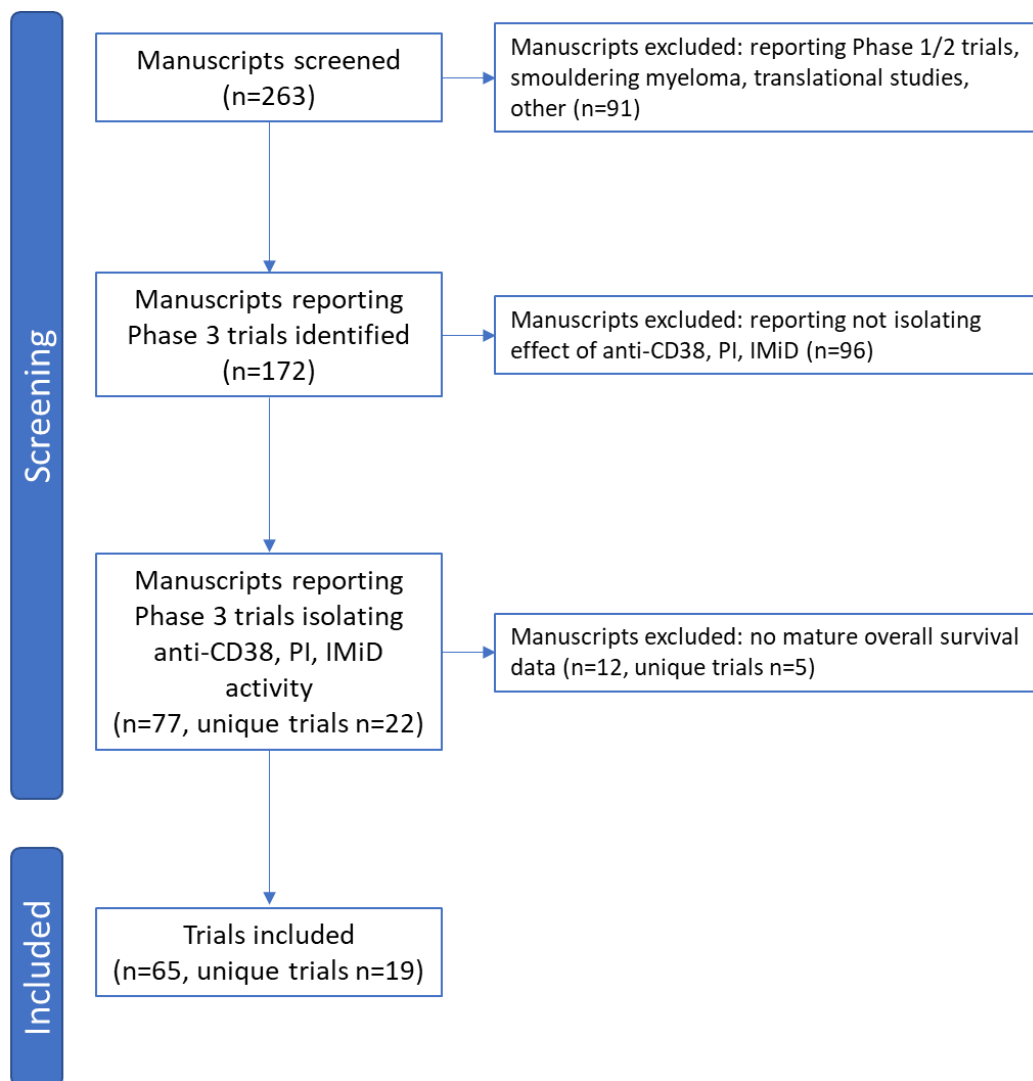
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Supplementary Methods

Pubmed was searched using the search term “(myeloma[Title]) AND ((lenalidomide[Title]) OR (ixazomib[Title]) OR (pomalidomide[Title]) OR (carfilzomib[Title]) OR (bortezomib[Title]) OR (daratumumab[Title]) OR (isatuximab[Title]) OR (elotuzumab[Title]))” for reports in the last decade.

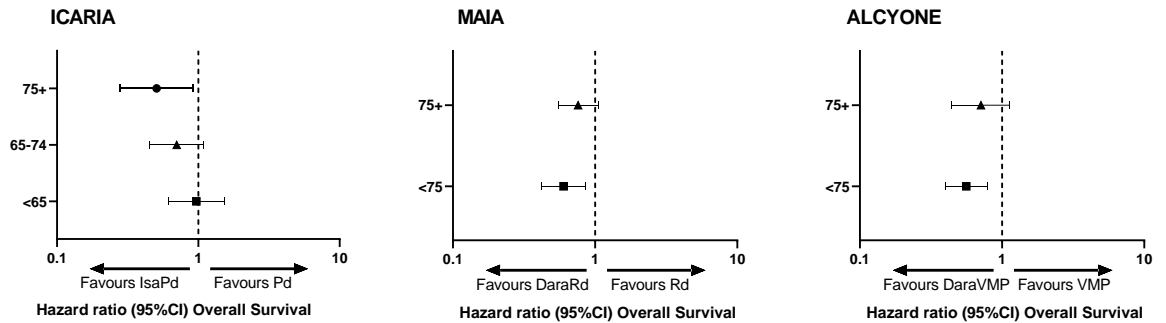
Supplementary Figure 1. Study selection. The PFS and OS data were extracted from the most recent publication or presentation related to each trial including hazard ratio (HR) and 95% CI as well as the median age of patients enrolled. If data included in FDA/EMA analyses were available in the form of trial reports [1-3], and were not available as published papers, these were also included.

EMA, European Medicine Agency; FDA, Food and Drug Administration; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

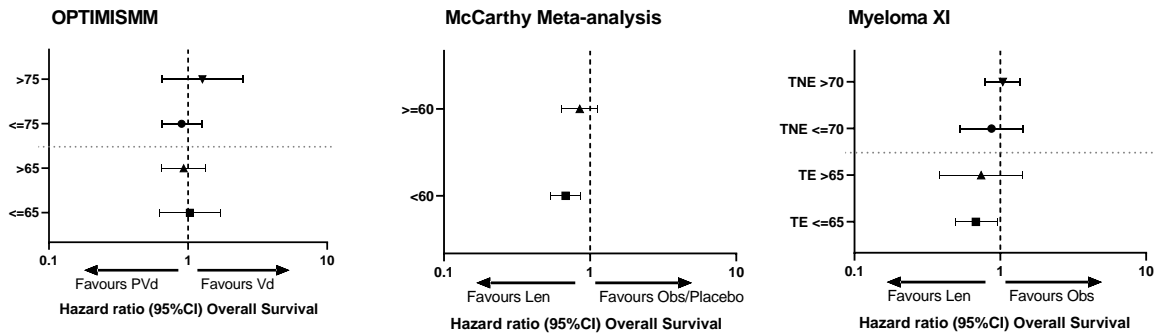


Supplementary Figure 2. Heterogeneity by age in the ICARIA [4], MAIA [5], and ALCYONE [6] trials by different anti-myeloma agents. Ab, anti-CD38 antibody; IMiD, immunomodulatory agent; PI, proteasome inhibitor.

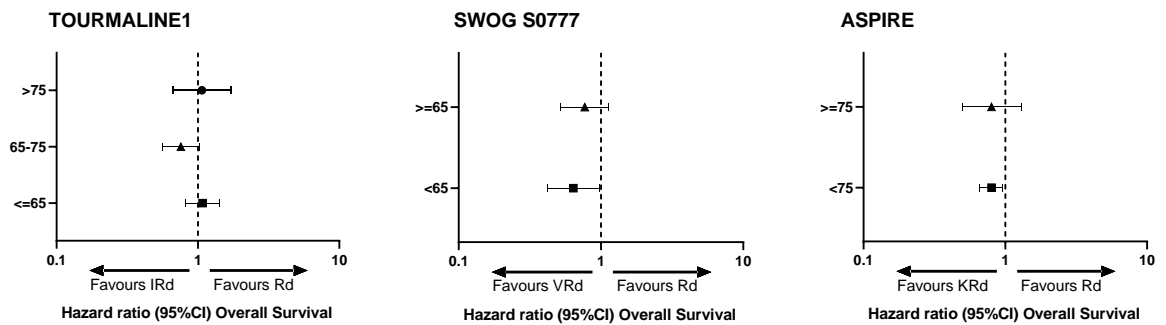
A) Anti-CD38



B) IMiD



C) PI



Supplementary Table 1: Summary of trial reports included in the analysis

Trial	Ref for PFS	Ref for OS	Comparison	Median age (years)	PFS HR	LL 95% CI	UL 95% CI	Median F/U (months)	OS HR	LL 95% CI	UL 95% CI	Median F/U (months)
Trials isolating anti-CD38 therapy												
CASTOR	[7]	[8]	Vd +/- Dara	64	0.31	0.25	0.4	40	0.74	0.59	0.92	73
POLLUX	[9]	[10]	Rd +/- Dara	65	0.44	0.35	0.55	44.3	0.73	0.58	0.91	80
ICARIA	[4]	[4]	Pd +/- Isa	67	0.6	0.44	0.81	11.6	0.76	0.57	1.01	35
ALCYONE	[6]	[6]	VMP +/- Dara	71	0.42	0.34	0.51	40.1	0.60	0.46	0.8	40
MAIA	[5]	[5]	Rd +/- Dara	73	0.53	0.43	0.66	56.2	0.68	0.53	0.86	56
Trials isolating IMiD therapy												
GIMEMA RV-MM-PI-209	[11]	[11]	Obs vs Len	57	0.47	0.33	0.65	51	0.64	0.36	1.15	51
IFM 2005-02	[12]	[12]	Placebo vs Len	58	0.57	0.47	0.68	86	0.899	0.717	1.127	86
CALGB Alliance 100104	[13]	[13]	Placebo vs Len	59	0.57	0.46	0.71	91	0.61	0.46	0.8	91
Myeloma XI TE	[14]	[14]	Obs vs Len	61	0.48	0.4	0.58	31	0.69	0.52	0.93	31
MM-009	[1]	[1]	Dex +/- Len	63	0.39	0.29	0.55	NR*	0.48	0.33	0.71	NR*
MM-010	[2]	[2]	Dex +/- Len	63	0.33	0.24	0.48	NR*	0.75	0.51	1.1	NR*
OPTIMISMM/MM-007	[15]	[3]	Vd +/- Pom	68	0.61	0.49	0.77	15.9	0.98	0.73	1.32	NR*
Myeloma XI TNE	[14]	[14]	Obs vs Len	74	0.44	0.37	0.53	31	1.02	0.8	1.29	31
Trials isolating PI therapy												
GIMEMA-MMY-3006	[16]	[16]	Td +/- V	56	0.62	0.5	0.77	124	0.68	0.51	0.9	124
TOURMALINE3	[17]	[18]	Obs vs Ixa	58	0.72	0.58	0.89	31	1.008	0.744	1.367	64
SWOG S0777	[19]	[19]	Rd +/- V	63	0.742	0.594	0.928	84	0.709	0.543	0.926	84
ASPIRE	[20]	[21]	Rd +/- K	64	0.69	0.57	0.83	32	0.79	0.67	0.95	67
TOURMALINE1	[22]	[23]	Rd +/- Ixa	66	0.74	0.59	0.94	14.7	0.939	0.784	1.125	85
TOURMALINE4	[24]	[18]	Obs vs Ixa	73	0.659	0.542	0.801	21.2	1.136	0.853	1.514	36
TOURMALINE2	[25]	[25]	Rd +/- Ixa	73	0.83	0.676	1.018	54	0.998	0.79	1.261	58

*Minimum follow-up referenced as median f/u not reported (NR).

Dara, daratumumab; dex, dexamethasone; F/U, follow-up; HR, hazard ratio; isa, isatuximab; ixa, ixazomib; K, carfilzomib; Len, lenalidomide; LL, lower limit; NR, not reported; obs, observation; OS, overall survival; Pd, pomalidomide-dexamethasone; PFS, progression free survival; pom, pomalidomide; Rd, lenalidomide-dexamethasone; Td, thalidomide-dexamethasone; TE, transplant eligible; TNE, transplant non-eligible; UL, upper limit; V, bortezomib; Vd, bortezomib-dexamethasone; VMP, bortezomib-melphalan-prednisone.

Supplementary References

1. Celgene. *Clinical Study Report CC-5013-MM-009*. Retrieved from European Medicines Agency. Report release date September 26, 2005.
2. Celgene. *Clinical Study Report CC-5013-MM-010*. Retrieved from European Medicines Agency. Report release date September 9, 2005.
3. Celgene. *Clinical Study Report CC-4047-MM-007*. Retrieved from European Medicines Agency.
4. Richardson PG, Perrot A, San-Miguel J, Beksac M, Spicka I, Leleu X, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. *Lancet Oncol*. 2022;23(3):416-27.
5. Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(11):1582-96.
6. Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet*. 2020;395(10218):132-41.
7. Mateos MV, Sonneveld P, Hungria V, Nooka AK, Estell JA, Barreto W, et al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in patients with previously treated multiple myeloma: Three-year follow-up of CASTOR. *Clin Lymphoma Myeloma Leuk*. 2020;20(8):509-18.
8. Sonneveld P, Chanan-Khan A, Weisel K, Nooka A, Masszi T, Beksac M, et al. P04: Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone alone in patients with previously treated multiple myeloma : Overall survival results from the phase 3 CASTOR trial. *HemaSphere*. 2022;6:12.
9. Bahlis NJ, Dimopoulos MA, White DJ, Benboubker L, Cook G, Leiba M, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia*. 2020;34(7):1875-84.
10. Dimopoulos M, Oriol A, Nahi H, San-Miguel J, Bahlis N, Usmani S, et al. P05: Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with previously treated multiple myeloma: Overall survival results from the phase 3 POLLUX trial. *HemaSphere*. 2022;6:13.
11. Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D, Petrucci MT, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371(10):895-905.
12. EMA. Assessment report: Revlimid January 2017 [Available from: https://www.ema.europa.eu/en/documents/variation-report/revlimid-h-c-717-ii-0089-g-epar-assessment-report-variation_en.pdf].
13. Holstein SA, Jung SH, Richardson PG, Hofmeister CC, Hurd DD, Hassoun H, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol*. 2017;4(9):e431-e42.
14. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2019;20(1):57-73.
15. Richardson PG, Oriol A, Beksac M, Liberati AM, Galli M, Schjesvold F, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(6):781-94.
16. Tacchetti P, Pantani L, Patriarca F, Petrucci MT, Zamagni E, Dozza L, et al. Bortezomib, thalidomide, and dexamethasone followed by double autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GIMEMA-MMY-3006): long-term follow-up analysis of a randomised phase 3, open-label study. *Lancet Haematol*. 2020;7(12):e861-e73.

17. Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019;393(10168):253-64.
18. Dimopoulos MA, Rajkumar SV, Lonial S, Chng W-J, Iida S, Mateos M-V, et al. Interim analyses of overall survival (OS) from the TOURMALINE MM3 & MM4 studies of ixazomib maintenance following primary therapy in multiple myeloma (MM). *Blood*. 2021;138 (Supplement):1656.
19. Durie BGM, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J*. 2020;10(5):53.
20. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-52.
21. Siegel DS, Dimopoulos MA, Ludwig H, Facon T, Goldschmidt H, Jakubowiak A, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2018;36(8):728-34.
22. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621-34.
23. Richardson PG, Kumar SK, Masszi T, Grzasko N, Bahlis NJ, Hansson M, et al. Final overall survival analysis of the TOURMALINE-MM1 phase III trial of ixazomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2021;39(22):2430-42.
24. Dimopoulos MA, Špička I, Quach H, Oriol A, Hájek R, Garg M, et al. Ixazomib as postinduction maintenance for patients with newly diagnosed multiple myeloma not undergoing autologous stem cell transplantation: The phase III TOURMALINE-MM4 trial. *J Clin Oncol*. 2020;38(34):4030-41.
25. Facon T, Venner CP, Bahlis NJ, Offner F, White DJ, Karlin L, et al. Oral ixazomib, lenalidomide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood*. 2021;137(26):3616-28.