Outcomes for unselected, newly diagnosed multiple myeloma patients

Many clinical trials have reported survival outcomes for newly diagnosed multiple myeloma (NDMM) patients. Notably, these are selected patients and, thus, do not reflect a population of unselected NDMM patients. Therefore, we conducted a retrospective study for this population treated at a single clinic specializing in the treatment of MM. We showed a median progression-free survival (PFS) of 22 months. The median overall survival (OS) was 152 months, which is the longest reported in the world to date. It was found that Revised-International Staging System (RISS) stage and cytogenetic risk predicted longer PFS, but the only predictor of OS was age at diagnosis.

Multiple myeloma is the second most common hematologic malignancy, accounting for 9.4% of blood-based cancers in the United States.[1] It is characterized by the abnormal proliferation of clonal plasma cells in the bone marrow (BM), leading to excessive production of monoclonal immunoglobulins. Advancements in the use of combination therapies that include glucocorticosteroids, immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies (mAb) have substantially improved survival rates.[2,3]

The Second Revised International Staging System[4] (R2-ISS) utilizes serum β_2 microglobulin, albumin, lactate dehydrogenase, and cytogenetic profiles to determine staging.[5] High-risk cytogenetic abnormalities (HRCA) include deletion 17p (del[17p]), translocation t(4;14)(p16;q32), t(14;16)(q32;q23), and 1q gain/amplification detected by interphase fluorescent *in situ* hybridization (FISH) from BM samples. The presence of these markers is associated with a worse prognosis.[6]

Studies assessing outcomes among NDMM patients have been conducted as part of clinical trials that have strict inclusion and exclusion criteria.[7] As a result, trial participants are under-representative of the broader NDMM population who have inferior outcomes because of poor performance status, impaired renal dysfunction, low blood counts, and advanced disease.[7] Limited data are available among NDMM patients outside of clinical trials, highlighting the need for real-world evidence to better inform clinical decision-making. This retrospective study aimed to analyze outcomes among NDMM patients treated at a clinic specializing in this B-cell malignancy.

Although 1,269 new patients were seen between August 15, 2006, and February 2024, 22 could not consent and were excluded from analysis, and 1,072 initiated front-line treatment elsewhere. Thus, 175 NDMM patients who began their front-line treatment in this clinic were included and provided informed consent in accordance with local institutional review board requirements and the Declaration of Helsinki. Data analysis was based on an observation cut-off date of July 7, 2024.

Progression-free survival and OS were compared using log-rank comparison of Kaplan-Meier survival curves. International Myeloma Working Group (IMWG) criteria were used to define responses and progressive disease.[8] R2-ISS was used for disease staging. Univariate analysis was performed using Cox proportional hazard ratios. $P<0.05$ was considered statistically significant.

Table 1 shows patient baseline characteristics (N=175). The median age at diagnosis was 65.8 years and there were 55.4% males and 44.6% females. Using R2-ISS staging,

Table 1. Patient baseline characteristics.

Characteristic	All patients	IgA	IgG	Light chain	Non-secretory	Other
N	175	32	101	36	2	4
Sex, male/female	97/78	19/13	55/46	20/16	1/1	2/2
Median age at diagnosis, years (range)	65.8 (31.5-97.9)	70.1 (47.7-86.7)	65.5 (35.4-97.9)	66.6 (35.4-97.9)	42.8 (37.4-87.7)	62.8 (43.4-78.0)
Race, Caucasian/African American/Hispanic/Asian/Middle Eastern	134/4/11/16/10	26/0/4/1/1	77/4/5/9/6	28/0/1/4/3	1/0/0/1/0	2/0/1/1/0
Median follow-up, months (range)	46.7 (1.4-316.0)	46.5(4.1-200.7)	40.9 (1.4-316.0)	52.4 (5.4-110.7)	106.6 (86.9-126.3)	42.5 (4.3-117.8)
R-ISS, I/II/III/unknown	31/84/21/39	6/18/4/4	14/50/12/25	10/14/5/7	0/0/0/2	2/2/0/0
Cytogenetic risk, standard/high/unknown	61/38/76	13/5/14	29/23/49	18/9/9	0/0/2	1/1/2

N: number; R-ISS: Revised International Staging System.

17.7%, 48.0%, 12.0%, and 22.3% of patients were stage I, II, III, and unknown staging, respectively. Additionally, 21.7% of patients showed HRCA, 34.9% of patients tested negative for HRCA, and 43.4% of patients had unknown cytogenetic abnormalities; thus, 38.3% of patients with evaluable cytogenetics and FISH had HRCA.

Regimens used in the front-line setting are shown in Table 2. The majority (N=128, 73.2%) received dexamethasone, bortezomib, and pegylated liposomal doxorubicin (PLD) with (N=11) or without (N=117) lenalidomide (Table 2). One hundred and twenty-six patients received at least one other regimen following front-line therapy; overall, 561 follow-up treatments were administered to these patients. Excluding glucocorticosteroids, the most common medications used in the 561 treatments administered after front-line therapy were lenalidomide (N=142, 25.3% of regimens), bortezomib (N=112, 20.0%), elotuzumab (N=100, 17.8%), PLD (N=72, 12.8%), and pomalidomide (N=69, 12.3%). Only one patient underwent an autologous stem cell transplantation (ASCT) which was in the second-line setting and no patients were treated with BsAb or chimeric antigen receptor (CAR) T-cell therapies.

The overall response rate (ORR) to front-line treatment was 71.4% (Figure 1A); furthermore, 96% of patients had at least a 25% reduction in their monoclonal protein level in this setting. The median PFS and OS for lines 1 through 7 are shown in Figure 1B. The median PFS for front-line treatment was 22 months (range: 0.2-155.2 months; 95% Confidence Interval [CI]: 19.5-26.9) (Figure 1C) and the median OS was 152 months (range: 1.5-320.6 months; 95% CI: 99.3-173.5) (Figure 1D). The median follow-up for living patients was 58.7 months. The 1-, 3-, 5-, and 10-year OS rates were 95.8%, 83.9%, 77.2%, and 59.9%, respectively. Only 3% (N=5) of patients died within six months of beginning treatment. The median number of lines of therapy for all patients was 3 (range: 1-26). The median number of lines of therapy received among patients who died was 6 (range: 1-26).

Patients that attained at least a partial response (PR) in front-line therapy had a longer PFS than those that did not (27 *vs.* 14 months, P=0.0004), but did not show evidence of longer OS (174 *vs.* 152 months, P=0.5487). Similarly, those who attained complete remission (CR) had a longer PFS than those that did not (42 *vs.* 18 months, P<0.0001), but still did not live longer (Undefined *vs.* 135 months, P=0.3592). Those who achieved CR showed a longer PFS with a larger effect size than achievement of partial response (PR), with CR attainment extending PFS by a median of 24 months while PR attainment extended PFS by 13 months.

Potential predictor variables were investigated for their effect on PFS and OS. Variables included sex, age, RISS score, and cytogenetic risk as defined by the IMWG, as well as baseline serum monoclonal protein, sFLC difference, creatinine, calcium, and hemoglobin. Cytogenetic risk (Hazard Ratio [HR]: 2.22; 95% CI: 1.30-3.79), R2-ISS stage I *vs.* III (HR: 2.45; 95% CI: 1.22-4.92), and R2-ISS stage II *vs.* III (HR: 1.82; 95% CI: 1.00-3.29) significantly predicted a longer PFS. Notably, age at diagnosis was the only significant predictor (HR: 1.04; 95% CI: 1.01-1.08) of OS among the variables investigated.

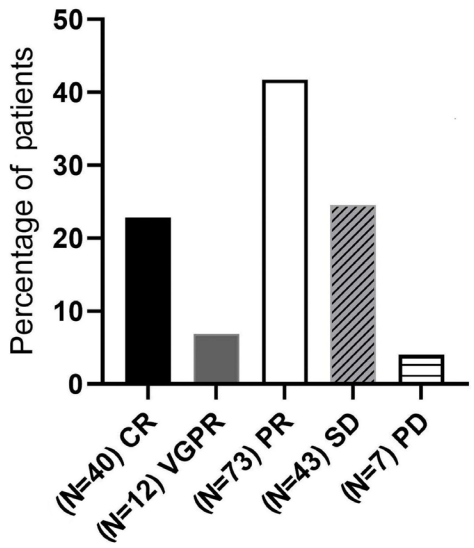
In this retrospective study, outcomes were determined for an unselected population of 175 NDMM patients who started their treatment between August 2006 and February 2024. These patients showed a median age and proportion of males similar to NDMM data from the Surveillance, Epidemiology, and End Results (SEER) program.[9] We report the longest median OS (152 months) to date which surpasses results (136 months) from our previous report[10] that included data among patients who initiated treatment between August 2006 until February 2022, which is two years earlier than the current study. The continued improvement in OS among NDMM patients reflects the growing number of therapeutic options available to treat our MM patients, as shown in this study. Most patients (73.1%) were initially treated with PLD, bortezomib, and dexamethasone with or without lenalidomide, and those treated with these regimens had an ORR of 83.3% and a median PFS of 22 months.-Notably, our long OS was

Table 2. Frontline treatment regimens.

Front-line treatment	N of patients
Dexamethasone / Bortezomib / Pegylated Liposomal Doxorubicin	117
Dexamethasone / Bortezomib / Pegylated Liposomal Doxorubicin / Lenalidomide	11
Elotuzumab / Lenalidomide / Dexamethasone	9
Dexamethasone / Bortezomib / Lenalidomide	7
Bortezomib / Vitamin C / Melphalan	5
Lenalidomide / Methylprednisolone	4
Cyclophosphamide / Carfilzomib / Dexamethasone	4
Bortezomib / Vitamin C / Cyclophosphamide	3
Dexamethasone / Daratumumab / Bortezomib / Lenalidomide	3
Dexamethasone / Bortezomib	3
Daratumumab / Bortezomib / Dexamethasone	2
Bortezomib / Vitamin C / Cyclophosphamide / Dexamethasone	2
Daratumumab / Lenalidomide / Dexamethasone	2
Bortezomib / Vitamin C / Cyclophosphamide / Dexamethasone / Lenalidomide	1
Cyclophosphamide / Bortezomib / Dexamethasone	1
Ruxolitinib / Methylprednisolone	1

N: number.

A

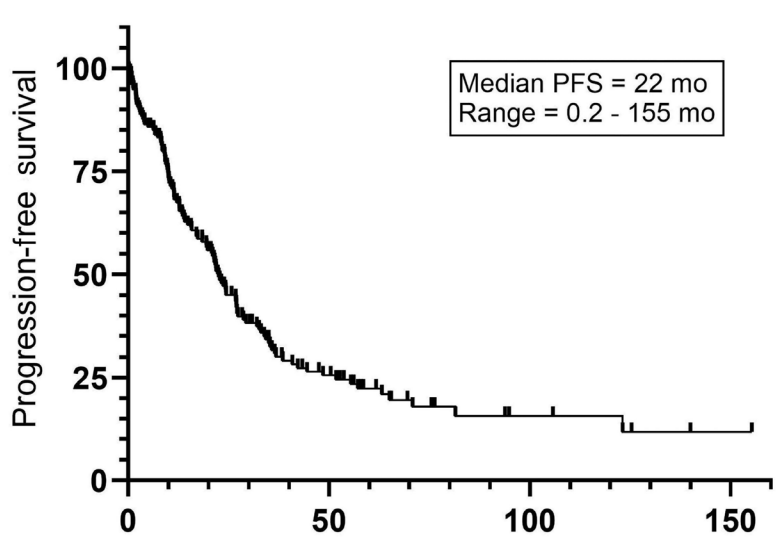


B

Survival according to line of treatment

Line of treatment	Number of patients	Median PFS (months)	Median OS (months)
1	175	22	152
2	126	8	108
3	103	9	81
4	69	5	49
5	55	4	47
6	49	2	32
7	37	5	30

C



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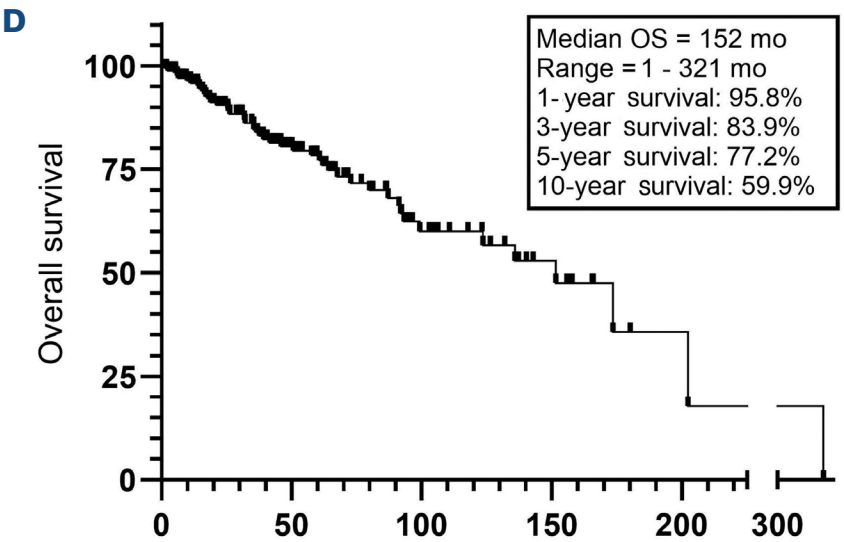

Figure 1. Survival and response rates for all patients. (A) Proportion of patients by response to front-line therapy. (B) The median progression-free survival (PFS) and overall survival (OS) for patients based on treatment number for lines 1 through to 7. (C) Kaplan-Meier analysis of PFS for all patients. (D) Kaplan-Meier analysis of OS for all patients as well as 1-, 3-, 5-, and 10-year survival rates. CR: complete response; mo: months; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response.

achieved among patients who did not undergo SCT except for one patient as part of second-line treatment. A recent randomized phase III study has shown no OS advantage with autologous SCT to treat NDMM patients.[11] Also, none of the patients in this study received either BsAb or CAR T-cell therapy. These novel therapeutic approaches achieve high CR rates but are hampered by significant short- and long-term side effects.[12]

Many of the predictive findings from our previous report[10] remained the same in the current study except for some key differences. Baseline serum free light chain (sFLC) differences between the involved and uninvolved sFLC no longer predicted a longer PFS. Attaining at least a PR became predictive of a longer PFS. Cytogenetic risk became a more significant predictor of PFS, and R2-ISS stage II was a predictor of a longer PFS when compared to stage III. Despite this, neither cytogenetic risk nor RISS stage were predictive of a longer OS. Notably, the only factor that significantly predicted OS was age at diagnosis.

In contrast to our patients who received a median of 6 lines of therapy from diagnosis to death, a recent study from the University of Kansas showed that their MM patients received a median of only 3 lines of therapy.[13] A similar recent report from France also reported a median of only 3 lines of therapy prior to death.[14] This suggests that the extended OS achieved in our clinic is likely in part due to exposure to more lines of treatment and the use of an increased number of novel therapies in our clinic. Multiple retrospective studies have shown that improvements in OS for MM patients during the past three decades have coincided with the approval and usage of novel therapeutic agents and combinations.[15]

One of the strengths of this study is the long and accurate follow-up of a population of unselected, newly diagnosed MM patients. We achieved a long OS with the use of diverse classes of drugs used in a multitude of combinations. As therapies that are more efficacious at eliciting deeper responses are made more tolerable with fewer long-term and high-grade side effects, healthcare professionals will have even better treatment options

available for improving survival as well as quality of life for MM patients in the future.

Authors

Jonathan T. Moore,[1,2] Sarah M. Mettias,[1] Jamie Cheung,[1] Regina Swift,[1] Benjamin Eades,[1] Shahrooz Eshaghian,[1] Gary Schwartz[1] and James R. Berenson[1,2,3]

[1]Berenson Cancer Center; [2]Institute for Myeloma & Bone Cancer Research and [3]ONCOtherapeutics, West Hollywood, CA, USA

Correspondence:
J. BERENSON - jberenson@Berensoncancercenter.com

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Disclosures

No conflicts of interest to disclose.

Contributions

JRB designed the study. JM, SM, JC and JRB wrote the manuscript. JM and JRB organized and analyzed the data. JRB, RS, BE, SE and GS helped to run the study.

Data-sharing statement

For original data, please contact James R. Berenson.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49. [Erratum in: CA Cancer J Clin. 2024;74(2):203].
2. Mettias S, ElSayed A, Moore J, Berenson JR. Multiple myeloma: improved outcomes resulting from a rapidly expanding number of therapeutic options. Target Oncol. 2025;20(2):247-267.
3. Chacon A, Leleu X, Bobin A. 30 years of improved survival in non-transplant-eligible newly diagnosed multiple myeloma. Cancers (Basel). 2023;15(7):1929.
4. Greipp PR, San Miguel J, Durie BG, et al. International Staging System for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420. [Erratum in: J Clin Oncol. 2005;23(25):6281].
5. D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second Revision of the International Staging System (R2-ISS) for overall survival in multiple myeloma: a European Myeloma Network (EMN) report within the HARMONY project. J Clin Oncol. 2022;40(29):3406-3418. [Erratum in: J Clin Oncol. 2022;40(34):4032].
6. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127(24):2955-2962.
7. Klausen TW, Gregersen H, Abildgaard N, et al. The majority of newly diagnosed myeloma patients do not fulfill the inclusion criteria in clinical phase III trials. Leukemia. 2019;33(2):546-549.
8. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-1473. [Erratum in: Leukemia. 2006;20(12):2220. Erratum in: Leukemia. 2007;21(5):1134].
9. SEER*Explorer: an interactive website for SEER cancer statistics [Internet]. Expected Survival Life Tables by Socio-Economic Standards. Surveillance Research Program, National Cancer Institute; 2024 Apr 17. https://seer.cancer.gov/statistics-network/explorer/Accessed 20 March 2025.
10. Jew S, Bujarski S, Regidor B, et al. Clinical outcomes and serum B-cell maturation antigen levels in a real-world unselected population of newly diagnosed multiple myeloma patients. Target Oncol. 2023;18(5):735-747.
11. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. N Engl J Med. 2022;387(2):132-147.
12. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022;387(6):495-505.
13. McInturf G, Younger K, Sanchez C, et al. Palliative care utilization, transfusion burden, and end-of-life care for patients with multiple myeloma. Eur J Haematol. 2022;109(5):559-565.
14. Sesques P, Karlin L, Massy E, et al. End-of-life management of multiple myeloma patients in the era of CD38 and immunotherapy. Front Oncol. 2024;14:1436587.
15. Harwood M, Dunn N, Moore J, Mollee P, Hapgood G. Trends in myeloma relative survival in Queensland by treatment era, age, place of residence, and socioeconomic status. Leuk Lymphoma. 2020;61(3):721-727.