SURVIVAL TRENDS IN MULTIPLE MYELOMA BY TREATMENT ERA IN THE UNITED STATES

Isherwood A[1], Bolger F[1], Morris J[1], Rollmann D[2], Griffin A[3], Spencer M[3], Hickson S[2]

[1]Clarivate, London, UK [2]Johnson & Johnson, Raritan, NJ, USA, [3]Johnson & Johnson, High Wycombe, UK*

Rationale

The progression of innovation in medicines can lead to significant shifts in how diseases are treated, ultimately transforming health outcomes for patients. For example, in Multiple Myeloma (MM) the treatment paradigm has evolved greatly from chemotherapy in the '70s and '80s to stem cell transplantation in the 90s, and into an era of innovative medicines including targeted treatments such as proteasome inhibitors and immunomodulatory drugs in the 2000s. The continuing advancement of treatment options in MM today including CD38 monoclonal antibodies, CAR T-cell therapies, antibody-drug conjugates, and bispecific therapies offer realistic hope for a cure.

Objective

The aim of this study was to investigate the impact of medicine treatment eras on patient survival in Multiple Myeloma in the United States (US).

Methods

Data source: Overall survival (OS) for 1-year through 10-year (2000 to 2021) and median OS (mOS) (1975-2016, median not reached past 2016) were taken from the US Surveillance, Epidemiology, and End Results (SEER) Program (8–17 Registries, 1975–2021)[1] for MM.

Median Overall Survival (mOS): mOS represents the time point at which 50% of patients have died. Due to the high overall survival rates reported in patients with MM diagnosed within the last 10 years, mOS data in SEER is only available up to 2016.

Forecasted mOS: 1-year to 10-year OS was forecasted by fitting polynomial curves ($R^2 > 0.9$ for all curves) to raw OS data from 2000 to 2020. Median OS was subsequently estimated for diagnosis years 2017–2025 by applying logarithmic curve fitting ($R^2 > 0.9$ for all curves) to the corresponding 1-year to 10-year OS values. The SEER Program reports 95% confidence intervals (CI95%) for the OS data used in this analysis. To generate an upper-range forecast estimate, the same modeling steps were repeated using the upper bounds of the CI95% OS values reported by SEER.

Treatment availability: the timing of the availability of new treatments for MM was determined as the date of first launch of the molecule in the US and was overlaid on Figure 1.

Changes in OS and mOS were calculated for each era (1975–1991, 1992–1999, and 2000–2021). The McNemar test was used to assess significant changes in OS, and the one-way Z-test within SEER was applied to evaluate significant differences in mOS. These eras were defined based on the timing of second registry reporting to avoid artifacts in OS differences caused by changes in the denominator, such as the number of registries. The selected eras closely aligned within a few years to major treatment milestones: chemotherapy in 1975, stem-cell transplant in 1992, and immunomodulatory or CAR-T therapies in 2001. Since 1975, SEER expanded its coverage twice, with new registries added in 1992 and 2000:

- 1975–1991: 8 state registries
- 1992–1999: 12 state registries
- 2000–2022: 17 state registries

Results

Median overall survival (mOS)

Based on SEER data, patients diagnosed with MM in 2000 had an mOS of approximately 20 months, compared with 6 months for those diagnosed in 2015. Using the one-sided Z-test, statistically significant changes in mOS were observed for the 2000-2021 era. mOS increased ~3-fold from 1975 to 2016. The greatest increase was seen from 2000 onwards (124%, 29.3 to 65.8months). Forecasted mOS in 2025 was 78.0–94.7 months (Figure 1).

Overall survival (OS) probability

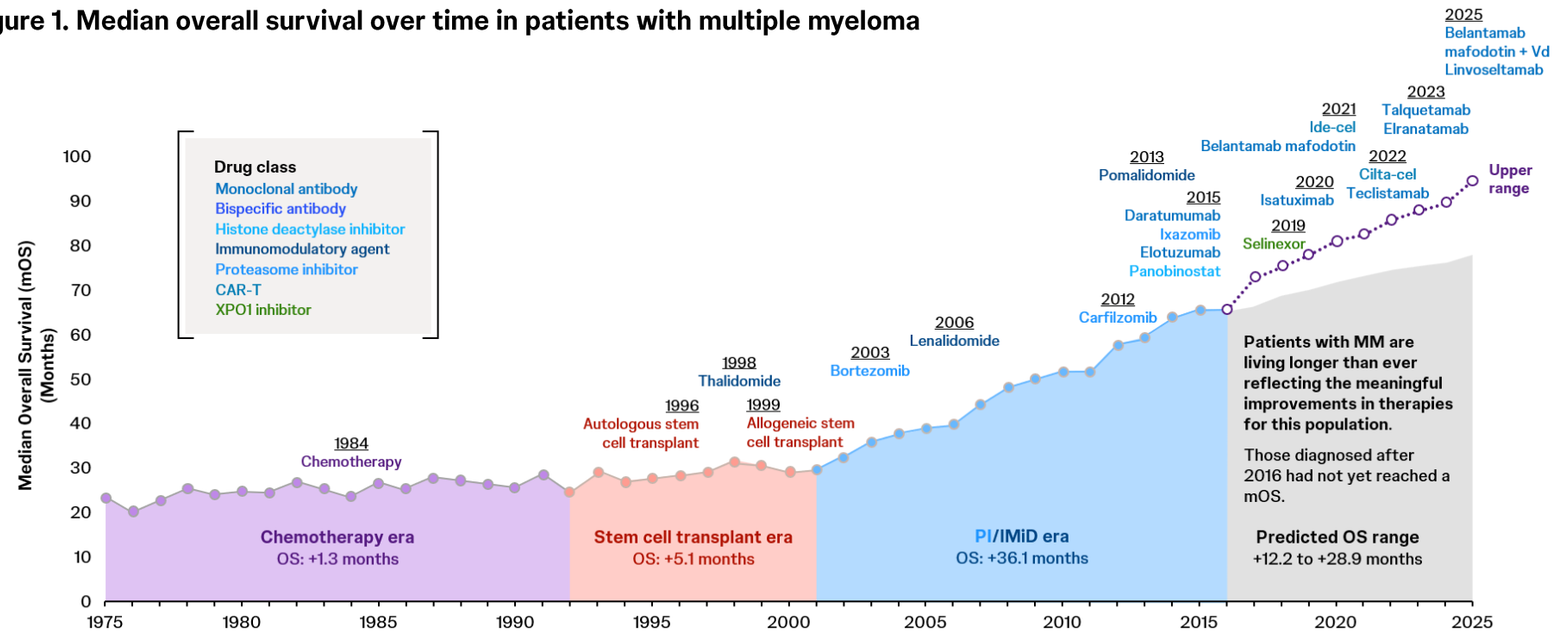
For patients with MM, the 1- to 10-year OS probability increased significantly, with McNemar test $p<0.05$ across all eras, with the greatest increases occurring since 2000, coinciding with the availability of novel and targeted medicines.

1-year survival for patients with MM increased 17.2% from 2000 to 2021 (69.9% to 81.9%). The greatest improvements in OS were seen for 7-year to 10-year survival.

- 30% of patients diagnosed with MM in 2012 could expect to live at least 10 years vs. only 13.8% in 2000 (117.4% increase) and 6.1% in 1975.
- 42.9% of patients diagnosed with MM in 2015 could expect to live at least 7 years vs. only 21.1% in 2000 (a 103.3% increase) and 11.3% in 1975.

*A Griffin and M Spencer were employed by J&J when this study was performed and are no longer with the company.

Figure 1. Median overall survival over time in patients with multiple myeloma



Note: The predicted curve (dotted line) is considered a conservative forecast. The drug approval and adoption process in conjunction with the time to deployment of a drug in the frontline setting may result in a lag that negatively affects median OS. When drugs are deployed in the frontline setting, they carry more weight, and the OS curve will improve. Dates correspond to molecule first launch in the US.

Abbreviations: CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory drug; mOS, median overall survival; OS, overall survival; PI, proteasome inhibitor; Vd, bortezomib and dexamethasone; XPO1, enhanced exportin 1.
Individual drugs/therapies are color-coded as per their drug class. The combination of the full circles and the unbroken trendline depict observed data. The full trendline depicts the predicted data. The combination of the hollow circles and the dotted trendline depict the upper range of the predicted data.

Figure 2. 1- to 10-year survival probability for patients diagnosed with multiple myeloma (1975-2021)

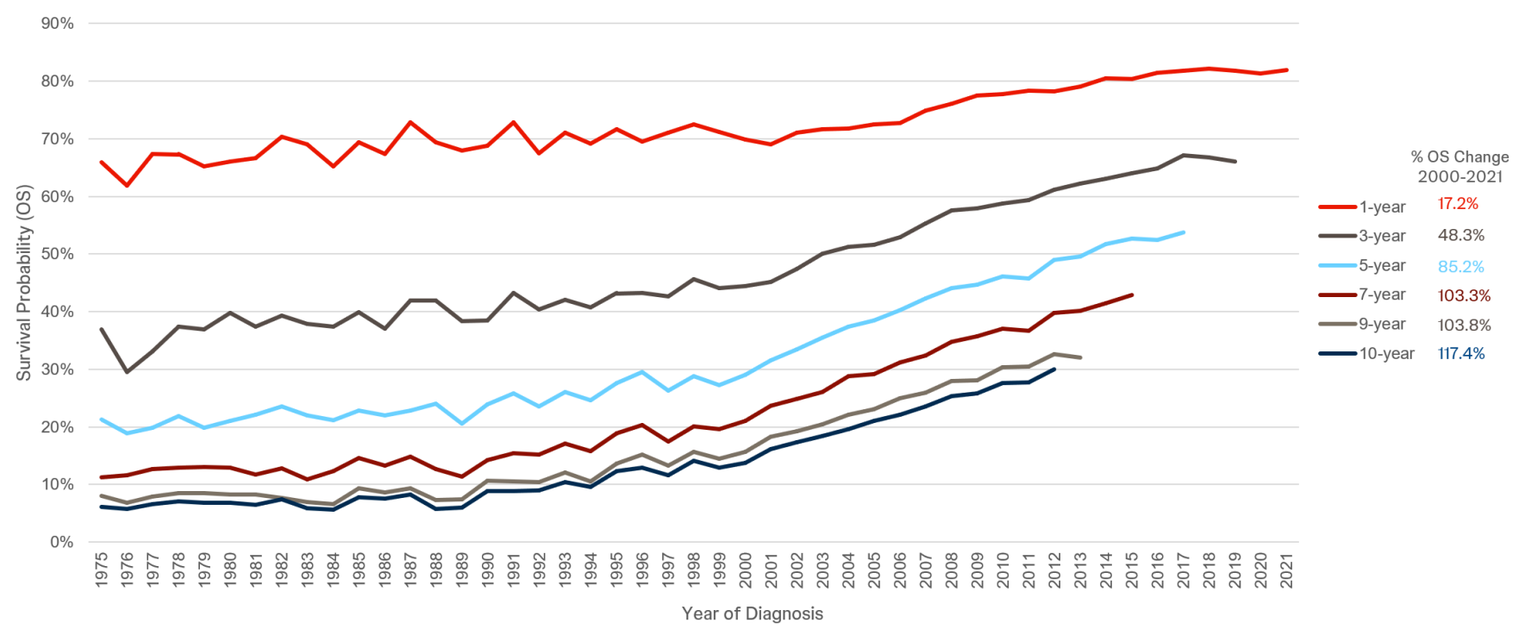


Table 1. Overall survival (OS) and mOS by treatment era

	1975-1991 Chemotherapy era	1992-1999 Stem cell transplant era	2000-2021* Targeted Medicines era
OS increase, % (range), [years of data availability]**			
1-year	10.5 (65.9%-72.8%)	5.5 (67.5%-71.2%)	17.2 (69.9%-81.9%) [2000-2021]
3-year	17.1 (36.9%-43.2%)	9.2 (40.4%-44.1%)	48.3 (44.5%-66.0%) [2000-2019]
5-year	21.1 (21.3%-25.8%)	15.3 (23.6%-27.2%)	85.2 (29.0%-53.7%) [2000-2017]
7-year	37.2 (11.3%-15.5%)	28.9 (15.2%-19.6%)	103.3 (21.1%-42.9%) [2000-2015]
10-year	45.9 (6.1%-8.9%)	43.3 (9.0%-12.9%)	117.4 (13.8%-30%) [2000-2012]
mOS increase, months (range)			
	23.4 (23.3-28.8)	25.4 (24.6-30.8)	124.1 (29.3-65.8)***

*Date range varies due to data availability
**All OS increases were statistically significant (McNemar p-value less than 0.05)
***mOS increase was statistically significant in targeted medicines era only (Z-test greater than +1.6)

Discussion

The treatment landscape for MM has evolved substantially since the chemotherapy era of the 1980s and 1990s, leading to a nearly threefold increase in mOS.

As patients are living longer, mOS had not been reached for those diagnosed from 2016 and long-term outcomes can only be projected.

The strong increase in mOS projected to 2025 is considered a conservative forecast as it is based on trends from already established medicines.

- The full survival benefits of treating patients in the frontline (1L) setting with recently launched innovative medicines are not yet reflected, as these therapies are initially introduced in later lines of treatment. At that stage, more than 50% of patients[2] will have died without the opportunity to receive them
- As the development of medicines shifts to earlier lines of therapy, where absolute survival benefits are typically greater, improved patient survival is expected.

With the launch of new targeted innovative medicines greater survival outcomes for patients can be expected.[6,7]

Recent clinical studies of new medicines in MM have shown OS well beyond what can be seen in the SEER data.[3,4,5]

The advancement of innovative treatment options for MM such as cell therapies offers realistic hope for a cure.

Conclusion

Survival for patients with MM has progressively increased over the last decades as new and better treatments become available. Forecasted mOS is likely to be a conservative estimate since new medicines are typically first available in later-lines of treatment and then shift to earlier lines where the absolute beneficial impact is expected to be greater. Additionally, clinical trials beyond the period of study have shown even greater survival benefits,[3,8] progressing hope towards a cure. Success in extending patient survival highlights the challenge for future waves of innovative medicines to demonstrate OS benefit within the range of randomized clinical trials (RCTs). New approaches and novel endpoints are needed to appropriately measure clinically meaningful patient benefits.

References

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 17 Registries, Nov 2023 Sub (1975-2021), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2024, based on the November 2023 submission.
2. Fonseca R et al. BMC Cancer. 2020;20:1087.
3. Facon T et al. Abstract P968. Final survival analysis of daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma: MAIA study. Poster presented at EHA2024
4. Usmani S Z, et al. Daratumumab + bortezomib/lenalidomide/dexamethasone in patients with transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: results of the phase 3 CEPHEUS. Oral presentation. 21st International Myeloma Society (IMS) Annual Meeting. September 25 – 28, 2024.
5. Rodríguez-Otero P, et al. Daratumumab (DARA) + (VRd) in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM): analysis of minimal residual disease (MRD) in the PERSEUS trial. 2024 American Society for Clinical Oncology (ASCO) Annual Meeting. June 3, 2024.
6. Munshi N et al. N Engl J Med. 2021;384:705-716
7. Martin T, et al. J Clin Oncol. 2022;41:1265-1274.
8. Moreau, et al. ASCO, 2025