CORRESPONDENCE OPEN

Check for updates

Real world outcomes with elotuzumab-based therapies for patients with relapsed refractory multiple myeloma: a Mayo Clinic experience

Blood Cancer Journal (2025)15:100; https://doi.org/10.1038/s41408-025-01310-z

Elotuzumab (Elo) is a monoclonal antibody (MoAb) targeting SLAMF7 that has improved overall survival (OS) in combination with the immunomodulatory drugs (IMiDs) lenalidomide (len) or pomalidomide (pom) and dexamethasone (D), in patients with relapsed/refractory multiple myeloma (RRMM) in the ELOQUENT 2 and 3 trials, respectively [1, 2]. However, in ELOQUENT 2, patients were not len-refractory or previously treated with daratumumab (Dara) and in ELOQUENT 3, <5% of patients were previously treated with Dara and none were pom-refractory [3, 4]. The majority of patients on these trials received 1–3 prior lines of therapy (LOT) and none were triple-class refractory (TCR). The efficacy of Elo+IMiD-based regimens in RRMM patients that are IMiD, Dara-, or TCR and have received >3 prior LOT are poorly characterized. Furthermore, clinical trials evaluating Elo-based regimens in heavily pretreated RRMM patients are lacking given the advent of highly efficacious T-cell mediated therapies such as chimeric-antigen receptor (CAR) T-cell and bispecific antibodies (BsAb) which have revolutionized the treatment of RRMM [5]. In this retrospective analysis, we aim to evaluate the real-world efficacy and the clinical outcomes of RRMM patients treated with Elo+ImiD+Dex regimens across the 3-site Mayo Clinic Comprehensive Cancer Center (MCCC).

We retrospectively analyzed the medical records of patients with RRMM treated with Elo+IMiD-based regimens between January 2016 and July 2023 at the MCCC. Patients were defined as being refractory to a treatment if they did not achieve a minimal response to therapy, progressed while on treatment or developed progressive disease within 60 days of the last treatment dose [6]. TCR RRMM was defined as patients refractory to an IMiD, a proteasome inhibitor (PI) and an anti-CD38 MoAb [7]. Clinical responses were assessed using the International Myeloma Working Group criteria [8]. Descriptive statistics were used to describe patient characteristics. Categorical variables were compared with Chi-square tests and continuous variables were compared with *t* tests. Outcomes were estimated using the Kaplan–Meier method.

Baseline patient characteristics are shown in Table 1. 135 patients were included in the analysis, 30 received Elo-Len-D (ERd) and 105 received Elo-Pom-D (EPd). Key differences between the ERd and EPd patient populations were that more patients treated with EPd were PI-exposed, pom-refractory, Dara-refractory and had extramedullary disease (EMM) compared to patients treated with ERd. The median time from MM diagnosis to start of an Elo-based regimen was 4.8 years. The median time to first response was 0.96 months for EPd and 1.2 months for ERd and the median time to best response was 1.8 months for both EPd and ERd. The median follow-up time for ERd treated patients was 20.5 months and 53.8 months for patients treated with EPd. At 2 years 38.8% and 53.7% of patients had ongoing sustained response for EPd and ERd, respectively. The median PFS for patients treated with EPd was 4.8 months and the median PFS for patients treated with ERd was 17.28 months (Fig. 1A). The median OS for patients treated with EPd was 2.55 years and was 5.64 years for patients treated with ERd. For Dara-refractory patients, the median time from Dara-progression to start of ERd and EPd was 3 months and 2.28 months, respectively. For Dara-refractory patients treated with EPd ($n = 94$), patients had received a median of 4 prior LOT and had a median PFS of 5.04 months compared to non-Dara refractory patients ($n = 11$) who had received a median of 3 prior LOT and had a median PFS of 2.64 mos, $p = 0.84$. For Dara-refractory patients treated with ERd ($n = 18$), patients had received a median of 4 prior LOT and had a median PFS of 7.68 months compared to non-Dara refractory patients ($n = 12$) who had received a median of 2 prior LOT and had a median PFS of 38.52 mos, $p = 0.015$. For patients treated with EPd that were Dara-refractory, the median OS was 30.6 months compared to an OS that was not reached for patients that were not Dara-refractory ($p = 0.80$). For patients treated with ERd that were Dara-refractory, the median OS was 13.56 months compared to a median OS of 80.16 months for patients that were not Dara-refractory ($p = 0.20$). For EPd treated patients who received ≥4 prior LOT the median PFS was 3.72 months compared to a median PFS of 5.88 months for patients who received ≤3 prior LOT ($p = 0.07$) (Fig. 1B). For EPd treated patients who received ≥4 prior LOT the median OS was 14.16 months compared to a median OS that was not reached for patients who received ≤3 prior LOT ($p = 0.04$). For ERd treated patients who received ≥4 prior LOT the median PFS was 5.16 months compared to a median PFS of 35.8 months for patients who received ≤3 prior LOT ($p < 0.001$) (Fig. 1C). For ERd treated patients who received ≥4 prior LOT the median OS was 10.2 months compared to a median OS that was not reached for patients who received ≤3 prior LOT ($p < 0.001$). For patients treated with EPd, the median PFS for TCR patients ($n = 52$) was 4.3 months compared to 5.04 months for non-TCR patients ($n = 53$), $p = 0.29$. For patients treated with ERd, the median PFS for TCR patients ($n = 11$) was 7.68 months compared to 28.56 months for non-TCR patients ($n = 19$), $p = 0.20$ (Fig. 1D). For patients that were pom-refractory and were treated with EPd ($n = 57$), their ORR was 28.7%, their median PFS was 3.72 months and their median OS was 27.12 months, compared to an ORR of 49.9% ($p = 0.03$), a median PFS of 8.16 months ($p < 0.001$) and a median OS that was not reached for patients that were not pom-refractory ($n = 48$) ($p = 0.07$). For patients that were len-refractory and were treated with ERd ($n = 19$), their ORR was 52.3%, their

Received: 20 March 2025 Revised: 6 May 2025 Accepted: 13 May 2025
Published online: 23 May 2025

Table 1. Baseline characteristics of relapsed/refractory myeloma patients treated with elotuzumab-based regimens ($N = 135$).

	Elotuzumab-lenalidomide-dexamethasone ($N = 30$)	Elotuzumab-pomalidomide-dexamethasone ($N = 105$)	*P* value
Age at MM diagnosis (years)			0.84
N	30	105	
Median	62.5	63.0	
Range	47.0–86.0	32.0–88.0	
Sex (male)	21 (70.0%)	59 (56.2%)	0.18
Race			0.078
Black	0 (0.0%)	11 (10.5%)	
Hispanic	2 (6.7%)	1 (1.0%)	
Other	1 (3.3%)	2 (1.9%)	
White	27 (90.0%)	91 (86.7%)	
ISS stage at diagnosis			0.35
Missing	1	1	
I/II	19 (65.5%)	55 (52.9%)	
III	6 (20.7%)	22 (21.2%)	
Unknown	4 (13.8%)	27 (26.0%)	
High-risk FISH			0.89
Missing	4	4	
No	13 (50%)	52 (51.5%)	
Yes	13 (50%)	49 (48.5%)	
1q			0.92
Missing	4	4	
No	17 (65.4%)	65 (64.4%)	
Yes	9 (34.6%)	36 (35.6%)	
Del 17p			0.53
Missing	4	4	
No	22 (84.6%)	90 (89.1%)	
Yes	4 (15.4%)	11 (10.9%)	
t(4;14)			0.74
Missing	4	4	
>No	24 (92.3%)	95 (94.1%)	
Yes	2 (7.7%)	6 (5.9%)	
t(14;16)			0.58
Missing	4	4	
No	24 (92.3%)	96 (95.0%)	
Yes	2 (7.7%)	5 (5.0%)	
t(14;20)			0.25
Missing	4	4	
No	26 (100.0%)	96 (95.0%)	
Yes	0 (0.0%)	5 (5.0%)	
Prior auto transplant	22 (73.3%)	54 (51.4%)	0.033
Number of prior lines prior to starting ELO			0.22
N	30	105	
Median	3.0	4.0	
Range	1.0–13.0	1.0–13.0	
1–3 prior lines of therapy	19 (63.3%)	45 (42.9%)	0.048
≥4 prior lines of therapy	11 (36.7%)	60 (57.1%)	0.048
IMiD exposed	30 (100.0%)	105 (100.0%)	
PI-exposed	25 (83.3%)	103 (98.1%)	0.001
Lenalidomide refractory	19 (63.3%)	65 (61.9%)	0.89
Pomalidomide refractory	9 (30.0%)	57 (54.3%)	0.019

Table 1. continued

	Elotuzumab-lenalidomide-dexamethasone (*N* = 30)	Elotuzumab-pomalidomide-dexamethasone (*N* = 105)	*P* value
Carfilzomib refractory	8 (26.7%)	36 (34.3%)	0.43
Bortezomib refractory	16 (53.3%)	48 (45.7%)	0.46
ImiD AND PI refractory	13 (43.3%)	56 (53.3%)	0.33
Dara refractory	18 (60.0%)	94 (89.5%)	<0.001
Triple-class refractory	11 (36.7%)	52 (49.5%)	0.21
Extramedullary disease when Elo started	0 (0.0%)	17 (16.2%)	0.018
Number of Elo cycles			<0.001
N	29	104	
Median	7.3	4.0	
Range	1.0 –79.0	0.5–49.0	
Median time to first response (months)	1.2	0.96	
Median time to best response (months)	1.8	1.8	

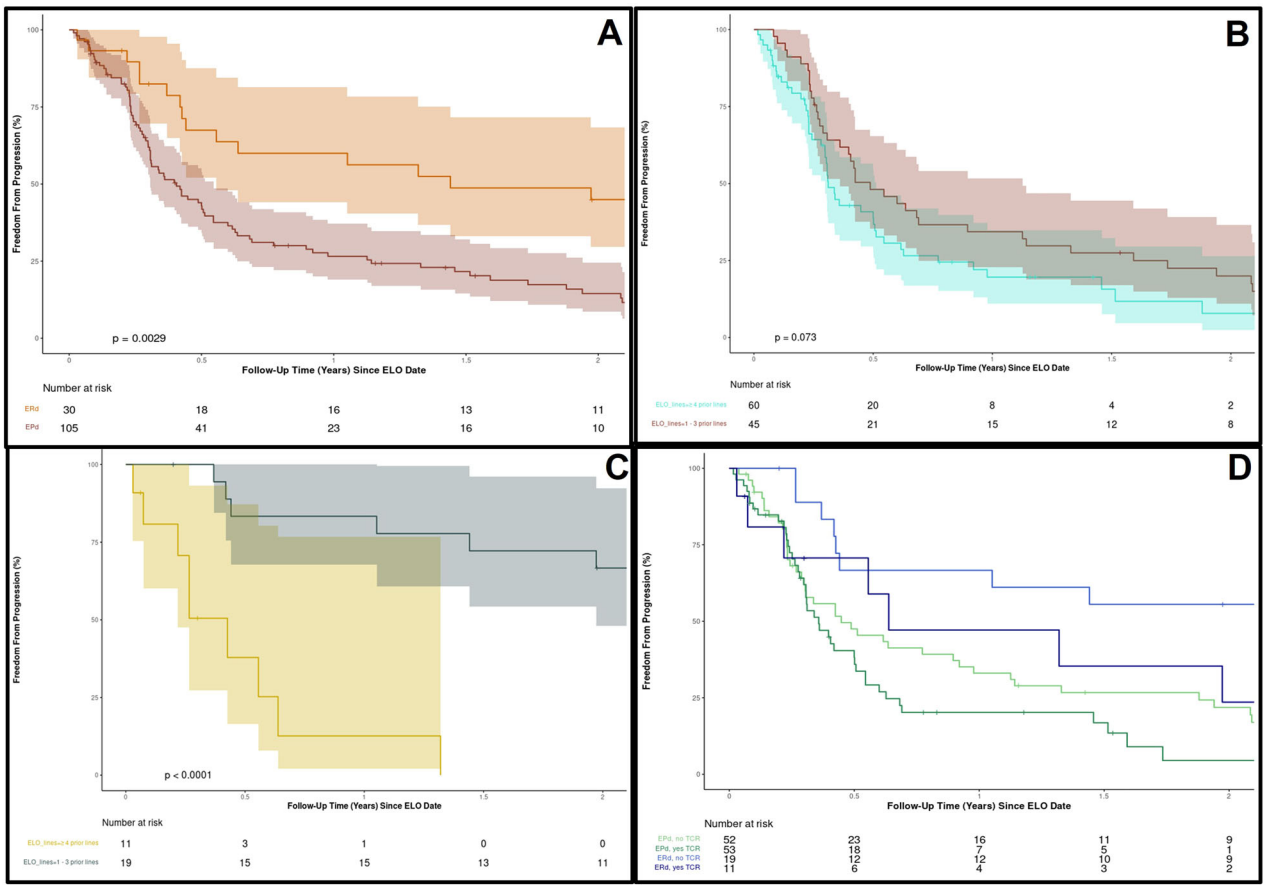

Fig. 1 Survival outcomes. A PFS of patients treated with ERd and EPd. **B** PFS of EPd-treated patients based on ≤3 prior LOT vs. ≥4 LOT. **C** PFS of-ERd treated patients based on ≤3 prior LOT vs. ≥4 LOT. **D** PFS of ERd and EPd-treated patients based on triple-class refractory status.

median PFS was 23.6 months and their median OS was 80.16 months, compared to an ORR of 54.5% ($p = 0.90$), a median PFS of 15.84 months ($p = 0.90$) and a median OS of 67.7 months for patients that were not len-refractory ($n = 11$) ($p = 0.90$).

The results of our study show the real-world efficacy of ERd and EPd in RRMM. Patients in ELOQUENT 2 treated with ERd had received a median of 2 prior LOT (none were TCR), achieved a median PFS of 19.4 months, and a median OS of 48.3 months [1, 3] whereas the patients treated with ERd in our study had received a median of 3 prior LOT (37% were TCR), achieved a median PFS of 17.3 months and a median OS of 67.7 months. Patients treated with ERd in our study had similar survival outcomes despite being more refractory and heavily pretreated compared to the patients in ELOQUENT 2 and in fact had superior OS which is likely due to

the advent of BCMA-directed immunotherapies which have improved the survival outcomes of patients with RRMM [9]. Patients in ELOQUENT 3 treated with EPd received a median of 3 prior LOT (none were TCR), achieved a median PFS of 10.3 months, and a median OS of 28.8 months [2, 4] whereas the patients treated with EPd in our study received a median of 4 prior LOT (49.5% were TCR), achieved a median PFS of 4.8 months, and a median OS of 30.6 months. Patients treated with EPd in our study had inferior PFS but similar OS compared to the patients in ELOQUENT 3 and a plausible explanation for this PFS difference is that the patients in our study were more heavily pretreated, TCR, and had EMM compared to patients on ELOQUENT 3. The similar OS outcomes between the ELOQUENT 3 patients and the patients on our study treated with EPd is likely due the use of BCMA-directed therapies. Having TCR disease or being Dara refractory did not appear to influence survival outcomes although non-Dara-refractory patients (median of 2 prior LOT) treated with ERd had a significantly longer PFS compared to Dara-refractory patients (median of 4 prior LOT) treated with ERd and this is likely due to the fact that the Dara-refractory patients were much more heavily pre-treated. These findings of the similar efficacy of EPd in TCR and Dara-refractory patients is consistent with reported clinical trial data [10] but is discordant with retrospective data showing that class/drug-refractory status better identifies patients with poor response to therapy, compared to LOT [11]. A plausible explanation for this might be that the modest efficacy of EPd did not allow for differences based on class/drug-refractory status to show in this heavily pre-treated patient population treated with EPd. Importantly, the results of our study show that the efficacy of Elo+IMiD-based regimens declines considerably when used after ≥4 prior LOT as patients who were treated with ERd or EPd and had received ≤3 prior LOT had a longer PFS and OS compared to patients who received ≥4 prior LOT. As expected, EPd showed greater efficacy and survival outcomes in patients that were not pom-refractory but there were no differences in outcomes amongst ERd-treated patients regardless of len-refractory status, likely due to the small number of ERd-treated patients on the study. A major limitation of our study is the small number of patients in the ERd cohort which may make the data from that cohort difficult to interpret, particularly the subgroup analyses within the ERd cohort. It appears that len-refractory patients treated with ERd had superior ORR, PFS, and OS compared to the non-len refractory patients treated with ERd. While the differences were not statistically signifiant, this is counterintuitive and likely represents a type II error due to the small number of patients treated with ERd and should be interpreted with caution.

While it is reported that the main mechanisms of resistance to IMiDs involve alterations in cereblon which inhibit the ability of IMiDs induce myeloma cell death, the role of cereblon alterations on IMiDs' immunomodulatory functions remain unknown [12]. It is purported that immune cell exhaustion mediates resistance to IMiDs' immunomodulatory functions [12], however, combining IMiDs with an immunostimulatory MoAb such as Dara, can enhance the adaptive immune response and overcome IMiD resistance [13]. Given Elo's known ability to enhance innate immune responses [14], it is therefore plausible that using ERd or EPd in IMiD-refractory patients can yield clinical responses. It has been reported that CD16/CD226^{Low} NK cells with reduced effector functions accumulate in patients with MM and negatively impact clinical outcomes [15] and this NK-cell dysfunction may explain the modest responses seen with Elo-based regimens in heavily pretreated RRMM.

It is becoming increasingly more difficult to justify the use of Elo+IMiD-based regimens in RRMM. Len and pom can be used in combination with anti-CD38 MoAbs and PIs which induce deeper and more durable responses than EPd and ERd. Furthermore, with the multitude of highly efficacious therapies available for RRMM such as BCMA/GPRC5d-directed immunotherapies, selinexor, and venetoclax-based combinations (for [t;11:14]) which can also be combined with IMiDs [5] and also induce more durable responses, using ERd or EPd have fallen out of favor. In TCR MM patients, there is essentially no role for ERd and while EPd has activity in this patient population, the aforementioned novel therapies lead to deeper and more durable responses [5]. Nonetheless, in regions where access to BCMA/GPRC5d-directed immunotherapies, selinexor, or venetoclax is limited, there is a role for Elo+IMiD-based regimens as they show modest clinical activity even in TCR, heavily pretreated myeloma patients and can serve as a bridge to a clinical trial or a salvage transplant. Additionally, there is the potential to use elotuzumab in combination with bortezomib, pomalidomide, and dexamethasone (Elo-VPd) in RRMM as a recent phase II clinical trial demonstrated an ORR of 56.3% and a median PFS of 10 months in 48 RRMM patients that had received a median of 3 prior LOT [16]. However, in triple-class exposed patients that were refractory to anti-CD38 mAb ($n = 14$), the ORR was 35.7% and the median PFS was 5.82 months [16]. There are ongoing clinical trials evaluating Elo in combination with the next generation IMiDs iberdomide (NCT05560399) and mezigdomide (NCT03989414) and with belantamab mafodotin (NCT05002816). In the CC-92480-MM-002 trial, 20 patients received Elo-mezigdomide-D at 0.3 mg ($n = 11$) or 0.6 mg ($n = 9$) and ORRs were 36% and 56%, respectively [17].

Ricardo D. Parrondo[1]✉, Saurav Das[1], Hanna Sledge[1], Leif Bergsagel[2], Rafael Fonseca[2], Nelson Leung[3], Prashant Kapoor[3], Morie Gertz[3], Francis Buadi[3], Angela Dispenzieri[3], Jamie Elliott[1], Andre Fernandez[1], Caitlin Flott[1], Asher A. Chanan-Khan[1], Vivek Roy[1] and Sikander Ailawadhi[1]

[1]*Division of Hematology-Oncology, Mayo Clinic Florida, Jacksonville, FL, USA.* [2]*Division of Hematology-Oncology, Mayo Clinic, Phoenix, AZ, USA.* [3]*Division of Hematology, Mayo Clinic, Rochester, MN, USA.*
✉*email: Parrondo.Ricardo@mayo.edu*

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

1. Dimopoulos MA, Lonial S, White D, Moreau P, Weisel K, San-Miguel J, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomized ELOQUENT-2 study. Blood Cancer J. 2020;10:91.
2. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus pomalidomide and dexamethasone for relapsed/refractory multiple myeloma: final overall survival analysis from the randomized phase II ELOQUENT-3 trial. J Clin Oncol. 2023;41:568–78.
3. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015;373:621–31.
4. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med. 2018;379:1811–22.
5. Costa LJ, Hungria V, Mohty M, Mateos MV. How I treat triple-class refractory multiple myeloma. Br J Haematol. 2022;198:244–56.
6. Anderson KC, Kyle RA, Rajkumar SV, Stewart AK, Weber D, Richardson P. Clinically relevant end points and new drug approvals for myeloma. Leukemia. 2008;22:231–9.
7. Stalker ME, Mark TM. Clinical management of triple-class refractory multiple myeloma: a review of current strategies and emerging therapies. Curr Oncol. 2022;29:4464–77.
8. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328–e46.

9. Rees MJ, Kumar S. BCMA-directed therapy, new treatments in the myeloma toolbox, and how to use them. Leuk Lymphoma. 2024;65:287–300.
10. Parrondo RD, LaPlant BR, Elliott J, Fernandez A, Flott CJ, Arrington D, et al. Phase II trial of elotuzumab with pomalidomide and dexamethasone for daratumumab-refractory multiple myeloma. Blood Cancer J. 2024;14:152.
11. Goel U, Charalampous C, Kapoor P, Binder M, Buadi FK, Dingli D, et al. Defining drug/drug class refractoriness vs lines of therapy in relapsed/refractory multiple myeloma. Blood Cancer J. 2023;13:11.
12. Bird S, Pawlyn C. IMiD resistance in multiple myeloma: current understanding of the underpinning biology and clinical impact. Blood. 2023;142:131–40.
13. Gavriatopoulou M, Kastritis E, Ntanasis-Stathopoulos I, Fotiou D, Roussou M, Migkou M, et al. The addition of IMiDs for patients with daratumumab-refractory multiple myeloma can overcome refractoriness to both agents. Blood. 2018;131:464–7.
14. Kurdi AT, Glavey SV, Bezman NA, Jhatakia A, Guerriero JL, Manier S, et al. Antibody-dependent cellular phagocytosis by macrophages is a novel mechanism of action of elotuzumab. Mol Cancer Ther. 2018;17:1454–63.
15. Blanquart E, Ekren R, Rigaud B, Joubert M-V, Baylot V, Daunes H, et al. NK cells with adhesion defects and reduced cytotoxic functions are associated with a poor prognosis in multiple myeloma. Blood. 2024;144:1271–83.
16. Yee AJ, Laubach JP, Campagnaro EL, Lipe BC, Nadeem O, Friedman RS, et al. Elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in relapsed and refractory multiple myeloma. Blood Adv. 2025;9:1163–70.
17. Richardson PG, Sandhu I, Hofmeister CC, Orlowski RZ, White D, Belotti A, et al. Mezigdomide (MEZI) plus dexamethasone (DEX) and daratumumab (DARA) or elotuzumab (ELO) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): results from the CC-92480-MM-002 trial. Blood. 2023;142:1013.

AUTHOR CONTRIBUTIONS

Parrondo designed the study and wrote the manuscript. Sledge performed the statistical analysis. Das collected the data. Parrondo, Das, Bergsagel, Fonseca, Leung, Kapoor, Gertz, Dispenzieri, Buadi, Elliott, Fernandez, Flott, Chanan-Khan, Roy, and Ailawadhi analyzed the data for the study. All authors critically revised the manuscript and approved the final version.

COMPETING INTERESTS

Parrondo serves on the advisory board for Sanofi Aventis and Astra Zeneca and has received research funding from Bristol Myers Squibb Foundation and GlaxoSmithKline. Ailawadhi has provided consultancy for Celgene, Amgen, Janssen, and Takeda, and has received research funding from Pharmacyclics, Cellectar, and Janssen. Chanan-Khan has received research funding from Xencor Pharmacyclics, Merck, Janssen, Ascentage, and Millennium. Kapoor received research funding from Takeda Pharmaceuticals, Celgene, and Amgen. Dispenzieri received research funding from Celgene, Millennium Pharmaceuticals, Pfizer, and Janssen and received a travel grant from Pfizer. Gertz served as a consultant for Millennium Pharmaceuticals and received honoraria from Celgene, Millennium Pharmaceuticals, Onyx Pharmaceuticals, Novartis, GlaxoSmithKline, Prothena, Ionis Pharmaceuticals, and Amgen. Leung serves on an advisory board for Takeda Pharmaceuticals. Fonseca served as a consultant for Amgen, BMS, Celgene, Takeda, Bayer, Janssen, Novartis, Pharmacyclics, Sanofi, Karyopharm, Merck, Juno, Kite, Aduro, OncoTracker, Oncopeptides, GSK, and AbbVie, and is on the scientific Advisory Board for Adaptive Biotechnologies, Caris Life Sciences and OncoTracker. The remaining authors declare no competing financial interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol and all amendments were reviewed and approved by the Institutional Review Board at Mayo Clinic Florida (IRB # 23-001194) as an IRB-exempt study. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the principles originating from the Declaration of Helsinki.

CONSENT TO PARTICIPATE

Individual informed consent was obtained per institutional requirements and guidelines.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Ricardo D. Parrondo.