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RESEARCH ARTICLE

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Quality of life and symptoms among patients with relapsed/refractory AL amyloidosis treated with ixazomib-dexamethasone versus physician's choice

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Abstract

Patient-reported outcomes in AL amyloidosis have not been well-studied. We analyzed health-related quality of life (HRQOL) and AL amyloidosis symptoms data from the phase 3 TOURMALINE-AL1 trial (NCT01659658) (ixazomib-dexamethasone, $n = 85$; physician's choice of chemotherapy [PC], $n = 83$). HRQOL and symptom burden were measured with the SF-36v2, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity subscale (FACT/GOG-Ntx), and an amyloidosis symptom questionnaire (ASQ). Score changes during treatment were analyzed descriptively and using repeated-measures linear mixed models; analyses were not adjusted for multiplicity. Least-squares (LS) mean changes from baseline were significantly higher (better HRQOL) for ixazomib-dexamethasone at several cycles for SF-36v2 Role Physical and Vitality subscales ($p < .05$); no subscales demonstrated significant differences favoring PC. For FACT/GOG-Ntx, small but significant differences in LS mean changes

favored ixazomib-dexamethasone over PC at multiple cycles for seven items and both summary scores; significant differences favored PC for one item (trouble hearing) at multiple cycles. ASQ total score trended downward (lower burden) in both arms; significant LS mean differences favored ixazomib-dexamethasone over PC at some cycles ($p < .05$). Patients with relapsed/refractory AL amyloidosis treated with ixazomib-dexamethasone experienced HRQOL and symptoms that were similar to or trended better than patients treated with PC despite longer duration of therapy.

1 | INTRODUCTION

Systemic immunoglobulin light chain (AL) amyloidosis, a protein misfolding disease, is characterized by conversion of immunoglobulin light chains from their soluble states into amyloid fibril deposits, most commonly in the heart and kidneys, which in turn lead to organ dysfunction.[1] AL amyloidosis is a rare but serious disorder, affecting approximately 40 individuals per million annually, with an estimated incidence of 10.5 per million person-years.[2,3] AL amyloidosis is progressive, and early diagnosis is critical to prevent irreversible organ damage.[1]

Treatment of AL amyloidosis is particularly challenging, as it involves treatment directed against the plasma cell clone/dyscrasia that itself can cause deterioration of organ function, often in elderly and/or comorbid patients.[4] Drugs used to treat AL amyloidosis are derived from experience with multiple myeloma or other B-cell malignancies. Several classes of drugs, such as proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), as well as high-dose chemotherapy and autologous hematopoietic stem cell transplantation, have yielded effective suppression of production of amyloidogenic precursor protein for many patients. Recently, the combination of daratumumab with bortezomib, cyclophosphamide, and dexamethasone was approved as the first treatment ever for newly diagnosed patients.[5] However, no treatments are approved for AL amyloidosis in the relapsed/refractory setting, and effective therapies for patients with advanced cardiac involvement, in particular, represent an unmet need.

Although difficult to measure, health-related quality of life (HRQOL) can be profoundly affected in patients with systemic AL amyloidosis owing to multiorgan involvement and treatment.[1] Patient-reported outcomes (PROs) in AL amyloidosis are poorly understood and challenging to summarize given the heterogeneity of clinical characteristics and severity levels seen in patients presenting with the disease. Symptoms and outcomes may vary depending upon where the amyloid deposition occurs (e.g., heart, kidneys, liver, nervous system) but commonly include fatigue, weakness, dyspnea, neuropathy, edema, dizziness/lightheadedness, and gastrointestinal symptoms.[6] While no standardized disease-specific assessment tools or approaches with which to evaluate PROs in AL amyloidosis are available,[7] a literature review by the Amyloidosis Forum, a private-public partnership between the Amyloidosis Research Consortium and the US Food and Drug Administration (FDA), found that AL amyloidosis impacts daily activities, social functioning, and emotional well-being (*Sanchorawala* et al., *forthcoming*). More evidence is needed to understand the impact of treatment on HRQOL of patients with AL amyloidosis.

In the phase 3, open-label TOURMALINE-AL1 trial, patients with relapsed/refractory AL amyloidosis were randomized 1:1 to receive either oral ixazomib plus dexamethasone or physician's choice of chemotherapy (PC) in 28-day cycles and were followed until progression or unacceptable toxicity. An interim analysis demonstrated that ixazomib-dexamethasone was well-tolerated and, although the primary endpoint of overall hematologic response rate was not met, time-to-event efficacy analyses consistently favored ixazomib-dexamethasone.[8] Here, we report an analysis of PRO data on HRQOL and AL amyloidosis symptom severity from the phase 3 TOURMALINE- AL1 trial.

2 | METHODS

2.1 | Study design and population

The design and primary results of the phase 3, randomized, open-label TOURMALINE-AL1 trial (NCT01659658) have been reported previously.[8] Briefly, eligible participants were adults with a biopsy-confirmed AL amyloidosis with measurable major organ amyloid involvement (cardiac or renal) that was relapsed or refractory after 1 or 2 prior therapies. A total of 168 patients were randomized 1:1 to receive oral ixazomib (4 mg) on days 1, 8, and 15 plus oral dexamethasone 20 mg/day on days 1, 8, 15, and 22, or PC (dexamethasone alone or with an alkylating agent [melphalan or cyclophosphamide] or with an IMiD [thalidomide or lenalidomide]) in 28-day cycles. Randomization was stratified by Mayo 2004 cardiac risk stage, relapsed versus refractory disease, and prior PI exposure. Patients were treated until the first of the following: disease progression/death, unacceptable toxicity, or study termination. The study was conducted in accordance with Good Clinical Practice, and local ethics committees/institutional review boards approved the protocol.

2.2 | Patient-reported outcomes measures

The following PRO measures were collected during the trial: the 36-item Short Form General Health Survey version 2 (SF-36v2)[9,10] was used to evaluate HRQOL, and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity subscale (FACT/

GOG-Ntx; Version 4)[11] and a novel amyloidosis symptom questionnaire (ASQ)[12] were used to evaluate AL amyloidosis symptom burden.

The SF-36v2 evaluates eight health-domain scales of functional health and well-being (Vitality, Physical Functioning, Bodily Pain, General Health, Role Physical, Role Emotional, Social Functioning, and Mental Health), as well as Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. All SF-36v2 scales and summary scores are transformed into a 0–100 scale, where higher scores indicate better health. The recall period is primarily the past 4 weeks, with some general health items referring to current health status, and one item comparing current health to health 1 year prior.

The FACT/GOG-Ntx is an 11-item questionnaire evaluating concerns with symptoms of neurotoxicity on a scale of 0 (not at all) to 4 (very much) within a recall period of the past 7 days. The 11 items (numbness or tingling in hands, numbness or tingling in feet, discomfort in hands, discomfort in feet, joint pain or muscle cramps, feeling weak all over, trouble hearing, ringing or buzzing in ears, trouble buttoning buttons, trouble feeling shape of small objects, trouble walking) yield two subscales: a sensory subscale with a score range of 0 to 44, and a neurotoxicity subscale with a score range of 0 to 16. For items and subscales, symptom scores are inverted so that higher scores indicate lower symptom burden.

In addition, the novel, study-specific ASQ was developed to evaluate symptom burden. The ASQ includes three items (swelling in the lower body, shortness of breath, dizziness or lightheadedness), each rated on an 11-point numerical scale (0 = least severe, 10 = most severe) of the worst symptom severity patients experienced in the previous 24 hours, yielding individual symptom scores as well as a total score ranging from 0 to 30. Higher values on the symptom scores and the total score indicate higher levels of symptomology or problems. The ASQ items were developed based on qualitative research that included a review of the published literature and social media; input from clinical experts; and interviews with patients with amyloidosis, involving both concept elicitation and cognitive debriefing of the draft ASQ[12]; no psychometric validation of the questionnaire has been performed thus far.

The SF-36v2 was assessed at screening, at day 1 of every third cycle, and at the end of treatment (EOT). The other PRO instruments were assessed at screening, at day 1 of every cycle, and at EOT. PRO analyses were conducted in patients with baseline and at least 1 postbaseline measurement in the intent-to-treat (ITT) population. For all measures, item-level missing data and scoring of the instruments were handled on the basis of the developers' guidelines. SF-36v2 scores were calculated by software provided by the instrument developer. For the FACT/GOG-Ntx, if at least 50% of subscale items were answered, subscale scores were prorated by multiplying the sum of the subscale by the number of items in the subscale and then dividing by the number of items actually answered. If fewer than 50% of subscale items were answered, proration was not allowed, and the subscale score was set to missing.

2.3 | Statistical analyses

To examine the impact of treatment for AL amyloidosis on QOL, using the PRO measures assessed in this trial, several descriptive and adjusted analyses were conducted. Compliance with each PRO measure was estimated at every cycle, and at EOT, and was defined as the percentage of patients remaining in the study who completed a PRO measure.

Summary statistics of mean (SD) observed values and changes from baseline in subscale scores over time, by treatment arm, were calculated. In addition, maximum improvements in subscale scores were summarized and compared using an analysis of covariance (ANCOVA) model, adjusted for cardiac risk stage, response to most recent prior therapy, and baseline use of PI (exposed or naïve), to compare treatment arms. Maximum improvement in a subscale score was defined as the difference between the best score while on study and the baseline score. For the SF-36v2 and ASQ, cumulative distribution function (CDF) plots of maximum improvement from baseline were developed with the maximum improvement on *x*-axis (where positive change in the SF-36v2 indicates improvement and negative change in the ASQ indicates improvement) and the cumulative proportion of patients experiencing a change less than or equal to that change on the *y*-axis, P(X < =x). To our knowledge, minimal clinically important differences for the included PRO measures have not been specifically established in AL amyloidosis.

Repeated measurements analysis using a linear mixed model with repeated measures was used to compare score changes from baseline between treatment arms. The model was adjusted for the following fixed effects: cardiac risk stage, response to most recent prior therapy, baseline use of PI (exposed or naïve), treatment group, visit, treatment by visit interaction, and baseline score. PROs were included as other secondary objectives and as such, no adjustment was made for multiple comparisons. *p* values are descriptive in nature. The data cut-off date for the HRQOL analyses was 20 February 2019.

3 | RESULTS

3.1 | Patient characteristics

All 168 patients who were enrolled and randomly assigned to receive ixazomib-dexamethasone or PC were included in the PRO analysis population. At study entry, demographic and disease characteristics were generally well-balanced between the ixazomib-dexamethasone ($n = 85$) and PC ($n = 83$) arms (Table 1). In both treatment arms, most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (91% in the ixazomib-dexamethasone arm and 87% in the PC arm), and 54% of patients in both arms were aged ≥65 years. More patients in the ixazomib-dexamethasone arm (71%) than in the PC arm (58%) had kidney involvement, whereas more patients in the PC arm (71%) than in the ixazomib-dexamethasone arm (62%) had heart involvement.

Patients in the ixazomib-dexamethasone arm completed up to 58 cycles of treatment, and those in the PC arm completed up to 43 cycles of treatment; median treatment duration was 11.7 versus 5.0 months respectively (data not shown). Compliance for all PRO measures was high at baseline (≥95%) and at all cycles before EOT (≥93%) (Table S1, Supplemental Material).

TABLE 1 Patient characteristics and descriptive subscale scores at baseline.

	Ixazomib–Dexamethasone ($n = 85$)	Physician's Choice ($n = 83$)
Patient characteristics		
Median age, years (range)	65 (38–84)	66 (33–82)
Age category, n (%)		
<65 years	39 (46)	38 (46)
65–75 years	37 (44)	35 (42)
≥75 years	9 (11)	10 (12)
Male, *n* (%)	51 (60)	46 (55)
Race[a], *n (%)*		
White	70 (82)	70 (84)
Black or African American	1 (1)	0
Asian	11 (13)	13 (16)
Region		
North America	29 (34)	22 (27)
Europe	37 (44)	39 (47)
Rest of the world	19 (22)	22 (27)
ECOG performance status, n (%)		
0	36 (42)	34 (41)
1	41 (48)	38 (46)
2	8 (9)	11 (13)
Sites of amyloid involvement[b], *n (%)*		
Heart	53 (62)	59 (71)
Liver	9 (11)	8 (10)
Kidney	60 (71)	48 (58)
Gastrointestinal tract	11 (13)	12 (14)
Lung	1 (1)	3 (4)
Autonomic nerve	5 (6)	5 (6)
Peripheral nerve	10 (12)	8 (10)
Skin	4 (5)	3 (4)
Muscle tissue	0	1 (1)
Tongue	6 (7)	6 (7)
Carpal tunnel syndrome	3 (4)	1 (1)
Other sites	13 (15)	13 (16)
Heart/kidney involvement, n (%)		
Both	28 (33)	24 (29)
Heart (no kidney)	25 (29)	35 (42)
Kidney (no heart)	32 (38)	24 (29)
Median sites of amyloid involvement at diagnosis, n (range)	2 (1–5)	2 (1–7)
Mayo cardiac risk stage, n (%)		
I	27 (32)	26 (31)
II	41 (48)	43 (52)
III	17 (20)	14 (17)
NYHA Class, n (%)		
0 and I	54 (64)	52 (63)
II and III	31 (36)	31 (37)
Serum creatinine clearance, n (%)		
<60 mL/min	37 (44)	30 (36)
≥60 mL/min	48 (56)	53 (64)
Median time from diagnosis, months (range)	34.5 (4.2–196.1)	32.6 (2.1–114.5)
Relapsed/refractory to last prior therapy, *n* (%)	68 (80)/17 (20)	66 (80)/17 (20)
Prior lines of therapy or SCT, n (%)		
≤1	50 (59)	50 (60)
≥2	35 (41)	33 (40)
PI-naïve/exposed, *n* (%)	46 (54)/39 (46)	44 (53)/39 (47)
Received prior transplant, *n* (%)	40 (47)	31 (37)
Type of prior therapy, n (%)		
Dexamethasone-containing	69 (81)	68 (82)
Prior IMiD	21 (25)	21 (25)
Thalidomide-containing	14 (16)	11 (13)
Lenalidomide-containing	7 (8)	12 (14)
Bortezomib-containing	40 (47)	39 (47)
Melphalan-containing	61 (72)	62 (75)
Cyclophosphamide-containing	29 (34)	29 (35)
Prednisolone-containing	3 (4)	4 (5)
Bendamustine-containing	1 (1)	0
Other	7 (8)	2 (2)
PRO subscale scores[c]		
SF-36v2[d]	$n = 81$	$n = 76$
Physical component summary	44.0; 42.3 (9.8)	43.6; 42.8 (10.0)
Mental component summary	53.3; 50.1 (10.4)	50.6; 49.3 (10.9)
Bodily Pain	51.5; 50.2 (11.1)	51.5; 50.1 (10.4)
General Health	40.4; 40.7 (9.4)	40.4; 41.7 (8.9)
Physical Functioning	46.1; 42.7 (9.8)	42.2; 42.1 (10.9)
Mental Health	53.5; 50.3 (9.9)	50.9; 49.1 (11.1)
Role Emotional	49.2; 46.6 (10.4)	50.9; 45.7 (11.9)
Role Physical	41.4; 41.7 (10.4)	42.6; 42.1 (11.6)
Social Functioning	47.3; 47.2 (9.6)	47.3; 46.2 (10.4)
Vitality	46.7; 47.2 (11.0)	49.6; 48.7 (11.2)
FACT/GOG-Ntx	$n = 82$	$n = 80$
Neurotoxicity subscale[e]	38.0; 35.5 (7.8)	38.0; 35.9 (6.9)
Sensory subscale[f]	14.0; 12.3 (3.9)	14.0; 12.8 (3.6)
NTX1: I have numbness or tingling in my hands	4.0; 3.2 (1.1)	4.0; 3.2 (1.0)
NTX2: I have numbness or tingling in my feet	3.0; 2.9 (1.3)	4.0; 3.1 (1.2)
NTX3: I feel discomfort in my hands	4.0; 3.3 (1.0)	4.0; 3.4 (0.9)

TABLE 1 (Continued)

	Ixazomib–Dexamethasone ($n = 85$)	Physician's Choice ($n = 83$)
NTX4: I feel discomfort in my feet	3.5; 2.9 (1.4)	4.0; 3.1 (1.2)
NTX5: I have joint pain or muscle cramps	3.0; 3.0 (1.3)	3.0; 3.1 (1.1)
HI12: I feel weak all over	3.0; 2.9 (1.1)	3.0; 2.8 (1.1)
NTX6: I have trouble hearing	4.0; 3.5 (0.9)	4.0; 3.4 (1.1)
NTX7: I get a ringing or buzzing in my ears	4.0; 3.4 (1.1)	4.0; 3.5 (1.0)
NTX8: I have trouble buttoning buttons	4.0; 3.6 (0.9)	4.0; 3.6 (0.9)
NTX9: Trouble feeling shape of small objects	4.0; 3.8 (0.7)	4.0; 3.7 (0.7)
AN6: I have trouble walking	3.5; 3.0 (1.3)	4.0; 3.1 (1.1)
ASQ[g]	$n = 82$	$N = 79$
Item 1: Swelling in the lower body	1.5; 2.2 (2.5)	1.0; 2.6 (2.8)
Item 2: Shortness of breath	2.0; 2.6 (2.6)	1.0; 2.1 (2.5)
Item 3: Dizziness or lightheadedness	0.0; 1.1 (1.8)	0.0; 1.3 (2.0)
Total score	5.0; 5.9 (4.9)	4.0; 6.0 (5.6)

Abbreviations: ASQ, amyloidosis symptom questionnaire; ECOG, Eastern Cooperative Oncology Group; EQ-5D-3L, EuroQol 5-Dimension 3-Level; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity; IMiD, immunomodulatory drug; NYHA, New York Heart Association; PI, proteasome inhibitor; SCT, stem cell transplant; SF-36v2, 36-item Short Form General Health Survey version 2.
[a]Race not reported in three patients in the ixazomib–dexamethasone arm.
[b]Patients could report multiple sites of amyloid involvement.
[c]Scores are among patients with baseline and at least one postbaseline assessment in the intent-to-treat population.
[d]SF-36v2 scores are transformed into a 0–100 scale, where higher scores indicate better health.
[e]FACT/GOG-Ntx items range from 0 to 4. Neurotoxicity subscale scores range from 0 to 44; symptom scores were inverted so that higher scores on items and subscales indicate higher quality of life or functioning.
[f]FACT/GOG-Ntx items range from 0 to 4. Sensory subscale scores range from 0 to 16; symptom scores were inverted so that higher scores on items and subscales indicate higher quality of life or functioning.
[g]ASQ scores range from 0 to 10 for each item, with higher scores indicating greater severity; range 0 to 30 for total score.

3.2 | Changes during treatment in PRO measure subscale scores

3.2.1 | HRQOL

Baseline HRQOL, as measured by the SF-36v2, was similar between treatment arms (Table 1). During the treatment period, descriptive SF-36v2 PCS and MCS scores remained stable relative to baseline and were similar between arms (Figure S1, Supplemental Material). The eight subscale scores were also generally maintained over time and were mostly similar between arms, although descriptive mean changes from baseline in the Role Physical and Vitality scales showed small but consistent differences in favor of ixazomib-dexamethasone compared with PC during most of the treatment period after the beginning cycles (Figure 1; Figure S2, Supplemental Material). In the repeated-measures analyses, least-squares (LS) mean changes from baseline were significantly higher (indicating better HRQOL) for ixazomib-dexamethasone compared with PC at multiple cycles in the SF-36v2 Role Physical subscale (at cycles 6 and 15) and Vitality subscale (at cycles 3, 6, 9, and 24) and at single cycles for the General Health subscale (at cycle 27) and PCS score (at cycle 27) ($p < .05$) (data not shown). No subscales demonstrated significant differences favoring PC. Based on the ANCOVA model, estimated differences between treatment arms in maximum improvement from baseline (i.e., difference between baseline score and best score on a subscale) were 3.1 (95% confidence interval [CI], 0.9–5.2) for the Role Physical subscale, 4.5 (95% CI, 2.2–6.8) for the Vitality Subscale, 2.4 (95% CI, 0.5–4.3) for the PCS score, and 2.7 (95% CI, 0.4–5.0) for the MCS score, and ranged from 1.2 to 2.6 for all other subscales (data not shown). In addition, CDFs for maximum improvement in SF-36v2 subscale scores showed that differences between the treatment arms were generally small and variable, except for Role Physical and Vitality subscales, which showed a small but consistent separation in favor of ixazomib-dexamethasone (Figure S3, Supplemental Material). Maximum improvement on the two summary scores, PCS and MCS, ranged from −10 to +15 points for almost all patients (Figure S3).

3.2.2 | Symptom burden

Baseline scores on the FACT/GOG-Ntx revealed low symptom burden at baseline, leaving little room for improvement (Table 1). The three items with slightly higher burden (lower mean [SD] scores) for both treatment arms at baseline were "I have numbness or tingling in my feet" (ixazomib–dexamethasone, 2.9 [1.32]; PC, 3.1 [1.21]), "I have joint pain or muscle cramps" (ixazomib–dexamethasone, 3.0 [1.25]; PC, 3.1 [1.05]), and "I feel weak all over" (ixazomib–dexamethasone, 2.9 [1.12]; PC, 2.8 [1.11]). During the treatment period, FACT/GOG-Ntx subscale scores were generally maintained over time (Figure S4, Supplemental Material). There were slight differences favoring ixazomib-dexamethasone for the items "I have joint pain or muscle cramps," "I have trouble walking," and "I feel weak all over" (Figure 2; Figure S5, Supplemental Material). In the repeated-measures analyses, there were small but significant differences in LS mean changes from baseline favoring ixazomib-dexamethasone over PC at multiple cycles for 7 of the 11 individual items, as well as for the sensory summary score (at cycles 6, 21, and 22) and neurotoxicity summary score (at cycles 2, 6, 7, 15, 21, and 24) (data not shown). Differences favoring ixazomib-dexamethasone were most pronounced for the items "I have joint pain or muscle cramps," "I have trouble walking," and "I feel weak all over." There were small but significant differences favoring PC over ixazomib-dexamethasone for one individual item (trouble hearing) at multiple later cycles. Estimated mean differences in maximum improvement from baseline based on the ANCOVA model were 0.6 (95% CI, −0.1 to 1.3) for the sensory subscale and 2.0 (95% CI, 0.7 to

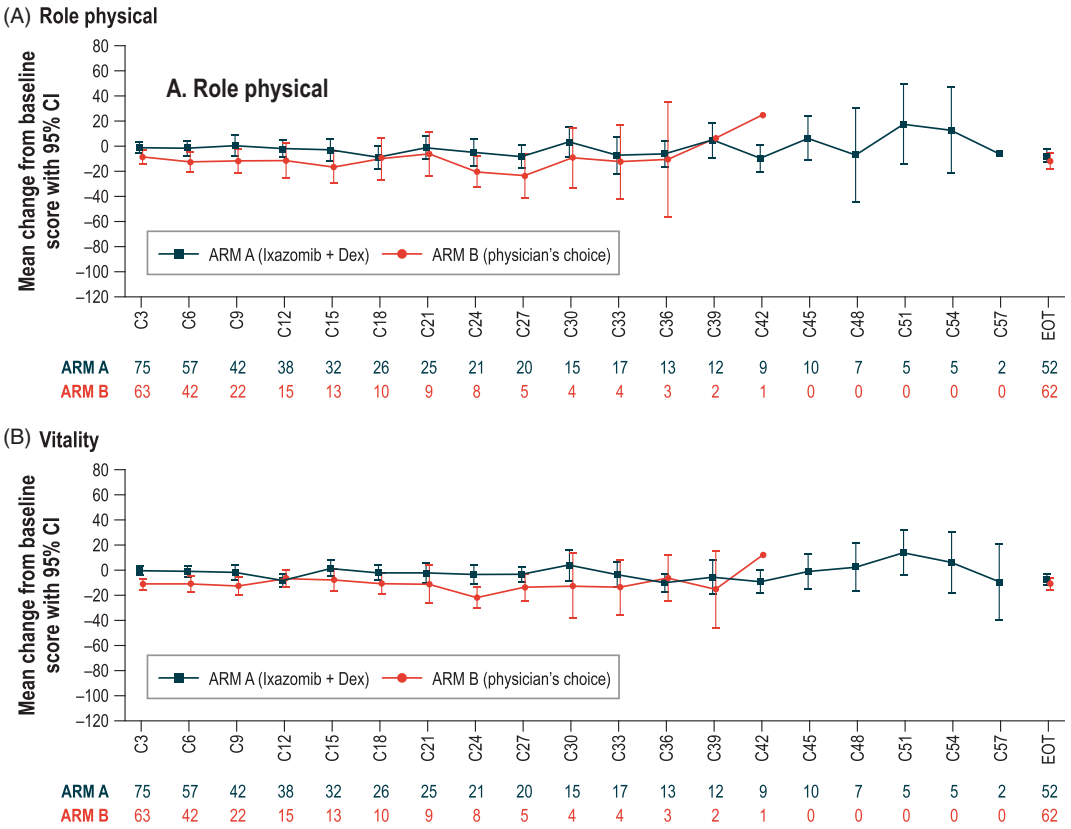

FIGURE 1 Mean changes from baseline in SF-36v2 Role Physical and Vitality scores over time. CI = confidence interval; SF-36v2 = Short Form Health Survey. The SF-36v2 consists of eight health-domain scales of functional health and well-being (Vitality, Physical Functioning, Bodily Pain, General Health, Role Physical, Role Emotional, Social Functioning, and Mental Health), as well as Physical Component Summary and Mental Component Summary scores. All scale and summary scores are transformed into 0–100 scales, where higher scores are associated with less disability and better quality of life. Figure S2 in the Supplemental Material presents mean changes from baseline for the SF-36v2 summary scores and other subscale scores.

3.3) for the neurotoxicity summary score. The items with the highest estimated mean difference between the ixazomib-dexamethasone and PC arms were "I have joint pain or muscle cramps" (0.3; 95% CI, 0.1–0.5); "I feel weak all over" (0.3; 95% CI, 0.1–0.6); and "I have trouble walking" (0.3; 95% CI, 0.1–0.5). Small differences in favor of ixazomib-dexamethasone were observed for all other items except "I have trouble hearing" (0.0; 95% CI, −0.1 to 0.2).

Low symptom burden at baseline was also evident in the ASQ scores (Table 1). Of a possible range of 0 to 30 for the ASQ total score, median scores were 5.0 for ixazomib-dexamethasone and 4.0 for PC. In both arms, ASQ total score trended downward slightly during treatment after the first few cycles, indicating diminishing symptom burden, but with small increases indicating worsening at EOT (Figure S6, Supplemental Material). In the repeated-measures analyses, there were significant differences during treatment favoring ixazomib-dexamethasone over PC at cycles 7 and 21 for total score; at cycles 15, 21, and 35 for swelling; at cycle 7 for shortness of breath, and at cycles 7 and 16 for dizziness or lightheadedness ($p < .05$) (Figure 3). Estimated differences in maximum improvement from baseline based on the ANCOVA, where negative change from baseline indicates improvement, were − 0.8 (95% CI, −1.8 to 0.2) for ASQ total score, −0.2 (95% CI, −0.6 to 0.3) for swelling, −0.4 (95% CI, −0.9 to 0.1) for shortness of breath, and −0.3 (95% CI, −0.7 to 0.1) for dizziness or lightheadedness. The CDF plot for maximum improvements from baseline in ASQ total score showed a slight separation in favor of ixazomib-dexamethasone versus PC, reflecting slight decreases in symptoms (Figure S7, Supplemental Material); the shortness of breath item showed the most consistent separation in favor of ixazomib-dexamethasone, as the proportion of patients with an improvement from baseline was at almost all time points.

4 | DISCUSSION

The TOURMALINE-AL1 trial population with relapsed or refractory AL amyloidosis had generally good HRQOL and low symptom burden at baseline that remained stable during treatment. Treatment with ixazomib-dexamethasone had an impact on HRQOL that was comparable with, and for some subscales and timepoints more favorable than, treatment with the physician's choice of chemotherapy, despite a longer duration of therapy. Mean baseline scores on the SF-36v2 PCS (42.3 for the ixazomib–dexamethasone arm and 42.8 for the PC

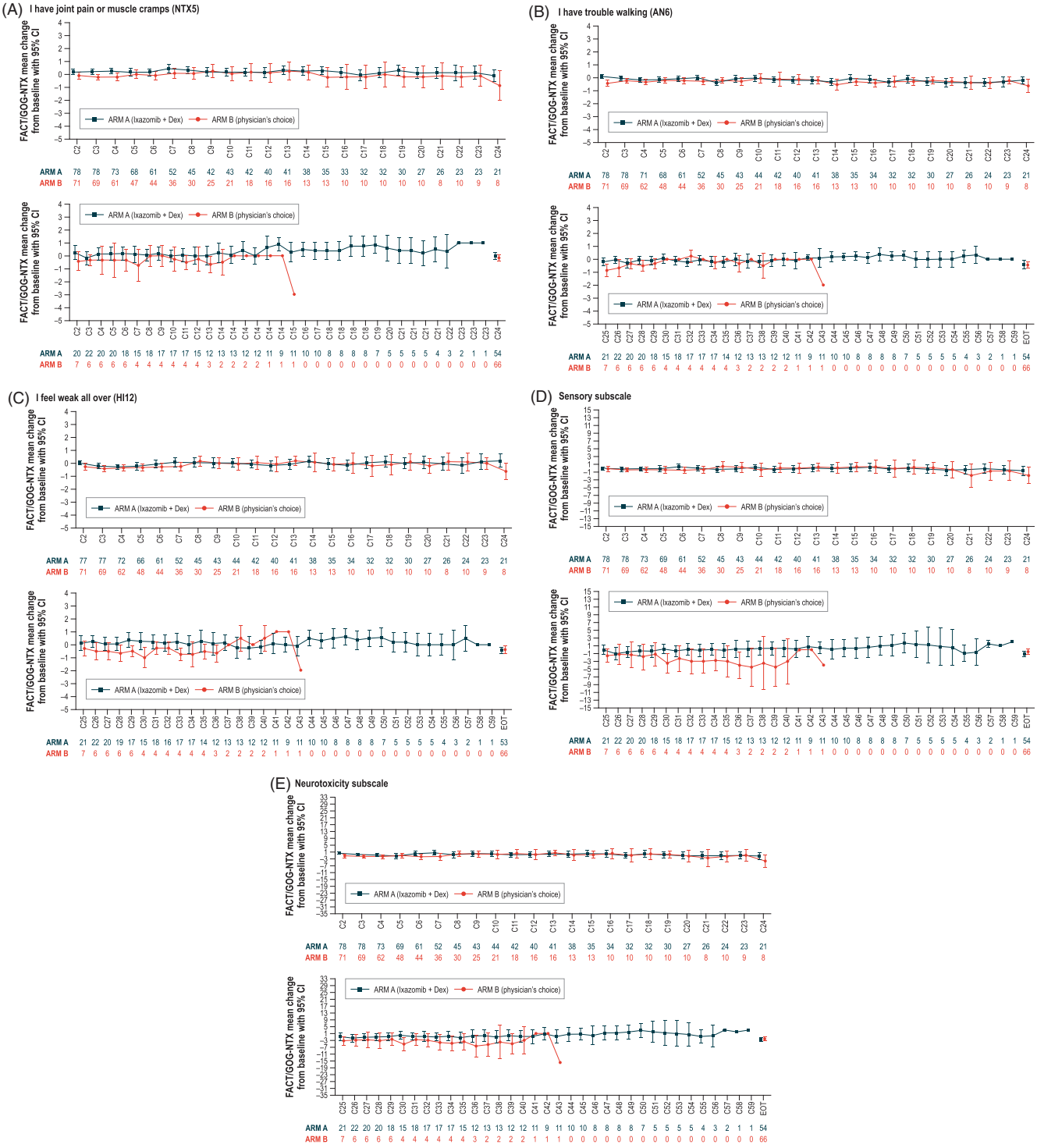

FIGURE 2 Mean changes from baseline in FACT/GOG-Ntx scores over time. CI = confidence interval; FACT/GOG-Ntx = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity. The FACT/GOG-Ntx consists of 11 individual items evaluating symptoms of neurotoxicity on a scale of 0 (not at all) to 4 (very much). The FACT-GOG-Ntx Sensory subscale is the sum of items NtX1-4, ranging 0 to 16. The FACT/GOG-Ntx Neurotoxicity subscale is the sum of all Ntx items, ranging 0 to 44. Symptom scores on items and subscales are then inverted so that higher scores of FACT/GOG-Ntx indicate higher quality of life or functioning. Figure S5 in the Supplemental Material presents mean changes from baseline for the other FACT/GOG-Ntx item scores.

arm) were modestly lower than the general population norm (46.8), whereas mean baseline scores on the MCS (50.1 and 49.3, respectively) were generally comparable with the general population norm (51.5).[13] During treatment, SF-36v2 scores remained generally stable, with small but statistically significant improvements in the Role Physical and Vitality subscales for ixazomib-dexamethasone relative to PC

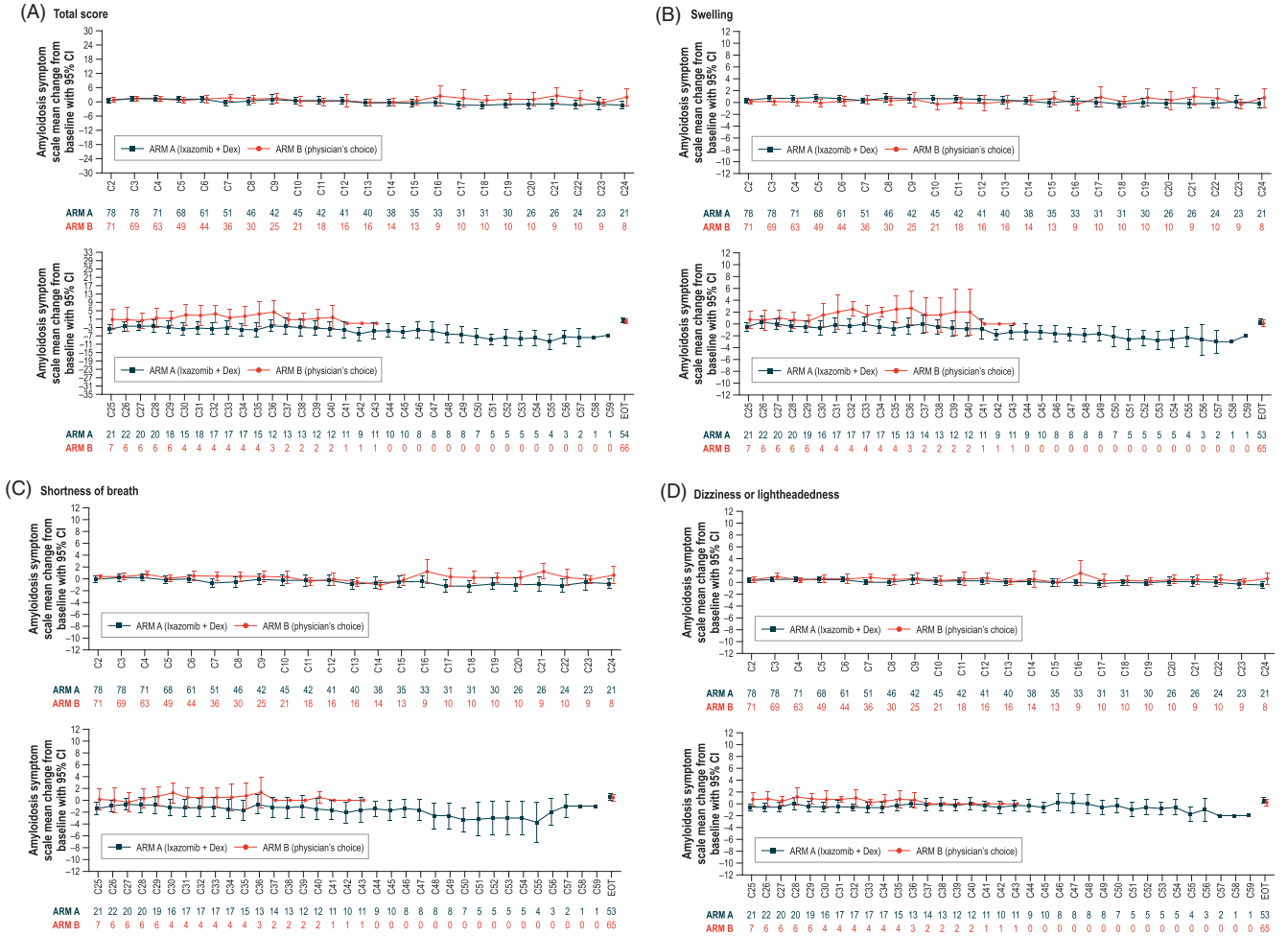

FIGURE 3 Mean changes from baseline in amyloidosis symptom questionnaire scores over time. CI = confidence interval; ASQ = amyloidosis symptom questionnaire. The ASQ consists of three items, each rated on an 11-point numerical scale of symptom severity from 0 (least severe) to 10 (most severe). Total score is the sum of all item scores, ranging from 0 to 30.

at multiple treatment cycles. This finding suggests that treatment with ixazomib-dexamethasone enabled patients to at least maintain their energy levels and carry on with their daily activities. Baseline FACT/GOG-Ntx and ASQ scores revealed low symptom burden, leaving little room for improvement. Nonetheless, on the FACT/GOG-Ntx, small but significant improvements in neurotoxicity and sensory summary scores, as well as seven individual items, were observed in favor of ixazomib-dexamethasone relative to PC. It is possible that these measures may not be sufficiently sensitive to detect symptom burden or true decrements in underlying disease in patients with relapsed/refractory AL amyloidosis.

A prior analysis of PROs from the phase 3 ANDROMEDA trial evaluating daratumumab, bortezomib, cyclophosphamide, and dexamethasone (D-VCd) versus VCd alone with newly diagnosed AL amyloidosis found that patients with clinical improvement following systemic therapy for AL amyloidosis experience small but meaningful improvements in HRQOL and symptoms.[14] During treatment, score changes from baseline in PRO measures including the SF-36, EQ-5D, and EORTC QLQ-C30, albeit small in magnitude, generally favored D-VCd over VCd alone.[14] Patients treated with D-VCd experienced more meaningful improvements in HRQOL and symptoms and a shorter median time to improvement, particularly for EORTC QLQ-C30 Global Health Status, than patients treated with VCd alone.

Results for the ANDROMEDA population with newly diagnosed AL amyloidosis are not directly comparable with those from our study conducted with a relapsed/refractory population with lower disease burden. In particular, mean baseline SF-36v2 PCS and MCS scores were somewhat higher for our population than for the ANDROMEDA population (PCS: 40.2 for the D-VCd arm and 41.8 for the VCd arm; MCS: 47.0 and 46.2, respectively), although both AL amyloidosis populations still scored lower than the population norm. Patients with relapsed AL amyloidosis receiving second-line therapy typically tend to have better functional status than newly diagnosed patients. This may be because patients receiving second-line therapy responded to and experienced symptomatic improvements with first-line therapy. Patients receiving second-line therapy also commonly begin treatment upon biochemical relapse, before there is organ deterioration. Thus, the sensitivity to detect HRQOL changes in patients receiving second-line therapy is likely modest. Nevertheless, results of both the current study in a relapsed or refractory population and the

ANDROMEDA study in a newly diagnosed population support that HRQOL and symptom burden are stable to modestly improved while on treatment for AL amyloidosis. Prior research has shown that treatment of AL amyloidosis with high-dose melphalan or stem cell transplantation produces measurable and sustained improvements in HRQOL, particularly in those patients who achieve hematologic complete response.[13] The current analysis provides insight into the HRQOL impact of regimens other than stem cell transplantation for patients with relapsed AL amyloidosis.

As with many rare diseases, no validated disease-specific PRO measure exists to evaluate amyloidosis-specific symptom burden. The challenges of developing and using PRO measures to capture the experiences of patients with rare diseases are well-documented.[15,16] Based on preliminary qualitative evidence, the study-specific ASQ employed in this study to evaluate amyloidosis symptom burden was well-received by patients,[12] but may not be sensitive enough to pick up symptom burden level and change in relapsed/refractory patients, particularly among a population in which treatment response was not evaluated. Additional research is needed to further establish the content validity of the measure and evaluate its measurement properties and further applications in clinical research. In addition, no minimally important differences specific to AL amyloidosis have been established for any of the measures used in this analysis. Future research should define minimally important differences to aid in interpreting quality of life analyses in this disease area.

Importantly, these analyses did not explore whether patients' clinical characteristics, treatment experiences, or response to therapy were significantly associated with HRQOL outcomes and symptom burden. Baseline characteristics such as performance status may have influenced the treating physician's chosen chemotherapy regimen and dosing among patients in the PC arm, and PC regimen in turn may have had an effect on patients' HRQOL and symptom burden during treatment. In addition, these analyses did not explore whether organ response and hematologic response were associated with significant improvements in HRQOL and symptom burden, nor was any potential effect of prior treatment regimens on these outcomes analyzed. Evaluating the degree to which prior treatment history and hematologic and organ response in the AL amyloidosis population contribute to significant improvements in HRQOL are all important directions for future research.

Limitations of this analysis are acknowledged. Owing to the open-label study design, results should be interpreted with caution. In addition, the statistical tests performed as part of this PRO analysis were not corrected for multiple comparisons; hence, any conclusions based on observed statistical significance between the treatment arms should be made with caution. The measurement properties of the ASQ have not yet been validated; thus, there is uncertainty about whether the measure fully captures relevant symptom changes for this patient population.

In conclusion, patients with relapsed/refractory AL amyloidosis who were treated with ixazomib-dexamethasone experienced HRQOL and symptom impacts that were similar to or trended better than patients treated with PC. These data suggest that treatment with ixazomib-dexamethasone, although given for a substantially longer treatment duration than PC, does not have a negative impact on HRQOL in patients with relapsed/refractory AL amyloidosis, a population with no approved treatment options.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Vaishali Sanchorawala has received research funding from Celgene, Millennium-Takeda, Janssen, Prothena, Sorrento, Karyopharm, Oncopeptide, and Caelum; has been a consultant for Pfizer, Janssen, and Attralus; and has served on advisory committees for Proclara, Caelum, AbbVie, Janssen, Regeneron, Protego, Pharmatrace, Telix, and Prothena. Ashutosh Wechalekar has served on advisory boards for Janssen, Alexion, Prothena, and Attralus and has received honoraria from Takeda and BMS. Stefan Schönland has served on advisory committees for Janssen, Telix, and Prothena; has received honoraria from Janssen and Takeda; has received research funding from Janssen, Prothena, and Sanofi; and has received travel and congress participation grants from Janssen, Prothena, Celgene, Binding Site, and Jazz. Heather Landau has received honoraria from Pfizer and Genzyme; has received consulting fees from Legend Biotech, Prothena, Genzyme, Karyopharm, Caelum Biosciences, Pfizer, and Celgene; and has received research funding from Takeda, Janssen, and Caelum Biosciences. Kenshi Suzuki has received honoraria from Takeda, ONO, Amgen, Novartis, Sanofi, BMS, AbbVie, and Janssen; has received consulting fees from Amgen, Takeda, and BMS; and has received research funding from BMS. Angela Dispenzieri has served on an advisory board and independent review committee for Janssen and data monitoring safety committees for Oncopeptides and Sorrento and has received research funding from Alynlam, Pfizer, Takeda, Pfizer, and BMS. Raymond Comenzo has served on advisory committees for Sanofi and Janssen and holds a patent for an AL amyloidosis treatment. Dasha Cherepanov, Vanessa C Hayden, Arun

Kumar, Richard Labotka, and Douglas V. Faller were employees of Takeda Pharmaceuticals, Inc. at the time of this research, and may have owned Takeda stocks. Efstathios Kastritis has received honoraria from Amgen, Janssen, Takeda, Genesis Pharma, Pfizer, GSK, and Prothena and has received research funding from Amgen, Janssen, and Pfizer. Kihyun Kim, Fiona Kwok, and Giampaolo Merlini have no conflicts to disclose.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan, and data supporting the results reported in this article, will be made available to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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