

Clinical Management of Patients With Relapsed/Refractory Multiple Myeloma Treated With Talquetamab

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Abstract

Talquetamab had a unique pattern of T-cell- and GPRC5D-associated AEs in MonumenTAL-1. Dermatologic toxicities were managed with corticosteroids and emollients, oral AEs with dose modification, and infections per standard of care. Cytokine release syndrome/immune effector cell-associated neurotoxicity syndrome were managed consistent with other T-cell redirection therapies. GPRC5D-associated adverse events may improve or resolve over time. Overall, the safety profile was manageable with minimal discontinuations due to AEs.

Background: Talquetamab is a bispecific antibody targeting the multiple myeloma-associated antigen G protein-coupled receptor family C group 5 member D (GPRC5D). In the phase 1/2 MonumenTAL-1 trial (NCT03399799/NCT04634552), overall responses rates were > 71% in patients with triple-class exposed relapsed/refractory multiple myeloma (RRMM). Due to the distribution of the target antigen, a unique pattern of GPRC5D-associated adverse events (AEs) was observed, together with T-cell redirection-associated AEs. Management strategies for talquetamab-associated AEs are described. **Discussion:** GPRC5D-associated AEs included dermatologic (rash, nonrash, and nail toxicities) and oral AEs (dysgeusia, dysphagia, and dry mouth). The incidence of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were consistent with other T-cell redirection therapies. The incidence of high-grade infections was lower than observed with B-cell maturation antigen-targeting bispecific antibodies, with less frequent use of intravenous immunoglobulin required. GPRC5D-associated AEs were mostly low

Abbreviations: AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GPRC5D, G protein-coupled receptor family C group 5 member D; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; IMiD, immunomodulatory agents; IVIG, intravenous immunoglobulin; LOT, line of therapy; MM, multiple myeloma; ORR, overall response rate; PET/CT, positron emission tomography/computed tomography; PI, proteasome inhibitor; QW, weekly; Q2W, every other week; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous.

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grade and led to few discontinuations. Skin toxicities were managed with emollients, topical corticosteroids, and oral corticosteroids (for high-grade, persistent, or AEs that progress). Nail toxicities were commonly managed with emollients. Based on investigator experience, dose modification may be effective for controlling oral events. Observation for potential weight changes is required. Infections were managed per standard of care. CRS and ICANS were effectively managed, consistent with other trials of T-cell redirection therapies. **Conclusion:** Although talquetamab had a distinct safety profile, AEs were considered clinically manageable and mostly low grade. With appropriate education and support, health care practitioners can ensure patients with RRMM maintain quality of life and treatment adherence.

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Introduction

Treatment outcomes for patients with relapsed/refractory multiple myeloma (RRMM) have improved due to the introduction of immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), anti-CD38 antibodies, and more recently, B-cell maturation antigen (BCMA)-directed therapies.^{1–6} However, almost all patients eventually relapse on standard therapies,² emphasizing the need for treatments with novel mechanisms of action.

Talquetamab is a T-cell–redirecting bispecific antibody targeting the multiple myeloma (MM)-associated antigen, G protein-coupled receptor family C group 5 member D (GPRC5D) on myeloma cells and CD3 on T cells.^{7,8} In MonumenTAL-1, a first-in-human, phase 1/2 trial (NCT03399799/NCT04634552) of talquetamab in patients with RRMM, 2 recommended phase 2 doses (RP2Ds) were identified: subcutaneous 0.4 mg/kg weekly (QW) and 0.8 mg/kg every other week (Q2W).⁹ Talquetamab demonstrated overall response rates (ORR) of 74.1% and 71.7% in patients who received the QW and Q2W dosing schedules, respectively, and 64.7% in a cohort of patients who had received either dosing schedule and had received prior T-cell redirection with bispecific antibodies or chimeric antigen receptor T-cell (CAR-T) therapies.⁷ Responses were durable across the 3 cohorts.⁷ ORRs were similar to those achieved with anti-BCMA bispecific antibodies in patients with triple-class exposed RRMM.^{1,3,6,7} The safety profile of talquetamab was distinct compared with other myeloma therapies.⁷ Dermatologic and oral adverse events (AEs) were observed, consistent with other GPRC5D-targeting agents.^{7,10–13} Any-grade and grade 3/4 infections were experienced by fewer patients than in trials of BCMA-directed bispecific antibodies,^{1,3,6,7} which may be due to little to no expression of GPRC5D on normal B cells and plasma cells,^{14–17} resulting in no observed B-cell depletion over time with talquetamab.^{7,18} Relatively low rates of neutropenia were also observed with talquetamab.^{7,9} Consistent with other T-cell redirection therapies, AEs associated with talquetamab also included cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).^{1,3–5,7,10,11,13} Based on the results from MonumenTAL-1, the U.S. Food and Drug Administration (FDA) approved talquetamab for the treatment of patients with RRMM who have received ≥ 4 prior lines of therapy (LOT), including a PI, IMiD, and anti-CD38 monoclonal antibody.¹⁹ The European Medicines Agency (EMA) has also approved talquetamab in patients with RRMM who have received ≥ 3 prior LOT, including an IMiD, a PI, and an anti-CD38

monoclonal antibody, and have demonstrated disease progression on the last therapy.²⁰

The introduction of new therapies with novel mechanisms of action into the treatment arsenal for RRMM creates a need for guidance on AE management.^{21,22} Although talquetamab had a distinct safety profile, AEs associated with talquetamab are clinically manageable and rarely led to discontinuation with appropriate education and support. We report further details on AEs associated with talquetamab and provide strategies for mitigating, monitoring, and managing toxicities.

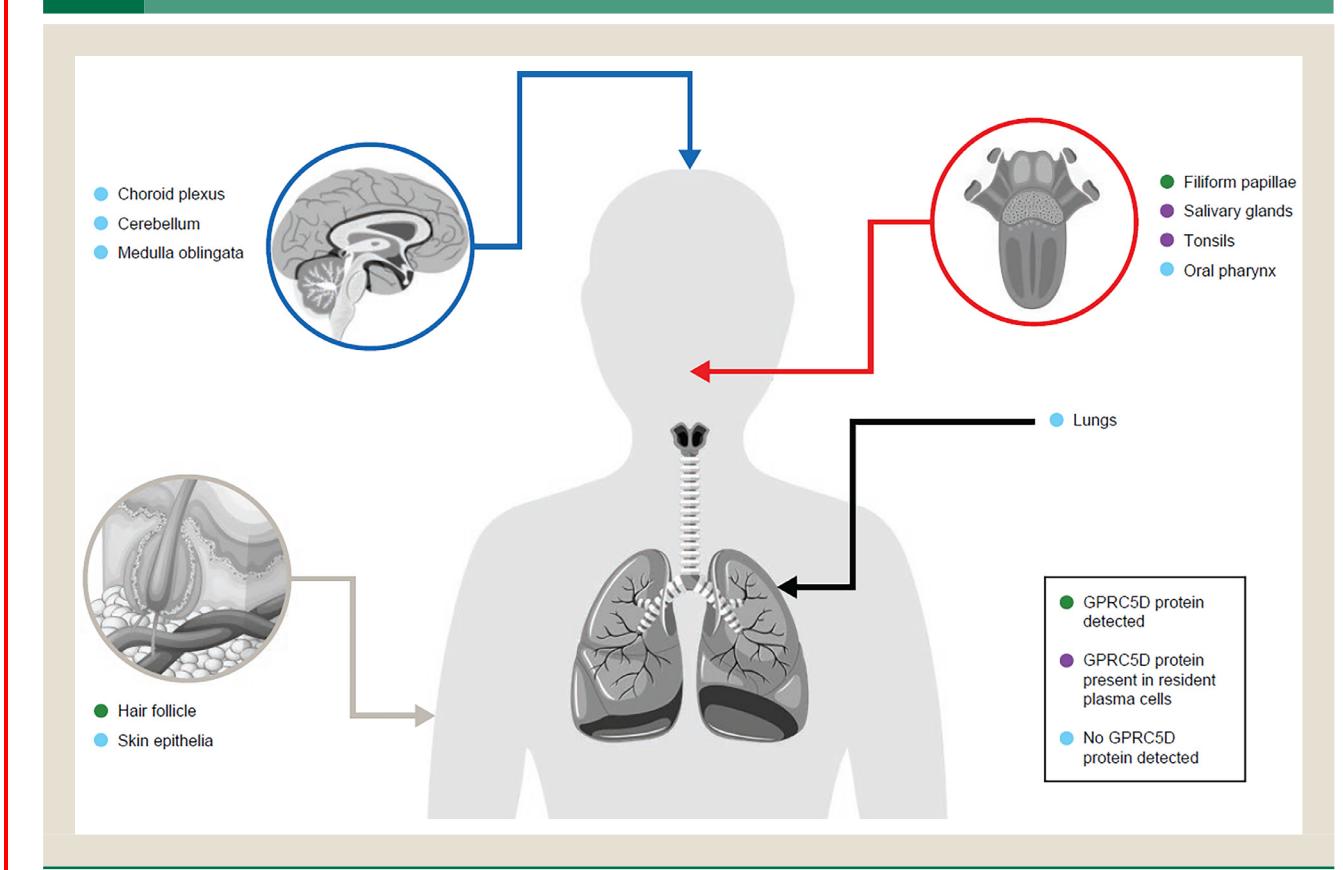
Pathophysiology

GPRC5D is a type-C 7-pass transmembrane receptor of unknown function that is predominantly expressed in cells with a plasma cell phenotype and is upregulated on clonal plasma cells from patients with monoclonal gammopathy of undetermined significance, plasma cell leukemia, and MM compared with normal plasma cells.^{8,15,17} Among immune cells, GPRC5D is predominantly expressed on cells with a plasma cell phenotype, with little to no expression in normal B cells, T cells, natural killer cells, monocytes, granulocytes, and bone marrow progenitors.^{8,14–17} This is unlike BCMA, an established therapeutic target in MM, and Fc receptor-like 5, which are expressed on normal B cells and plasma cells,^{23–25} as well as CD38, which is expressed by natural killer cells, T cells, and dendritic cells.²⁶ Although there is relatively limited expression in other healthy tissues, GPRC5D expression has been observed in skin, particularly in hair follicles, with a high correlation between expression levels of GPRC5D and hair follicle-specific genes (Figure 1)^{9,27}; GPRC5D expression also has been detected in eccrine glands.¹³ However, the mechanism by which GPRC5D-targeting therapies cause skin AEs remains unclear. GPRC5D expression has been shown in the keratogenous zone of the nail in mice, suggesting that nail toxicity is an on-target, off-tumor effect.^{9,27} GPRC5D expression in the oral cavity is limited to the filiform papillae of the tongue, which do not contain taste receptors, and residential/interstitial plasma cells.^{9,28} Dysgeusia has now been established as a commonly reported AE associated with GPRC5D-targeting therapies,^{9–11,13} although its etiology is unclear, and the nature of the taste disturbance may vary between patients.

Talquetamab Safety Profile

As of January 17, 2023, 339 patients received subcutaneous talquetamab at the RP2Ds in MonumenTAL-1 (0.4 mg/kg QW

Figure 1 Map of GPRC5D protein expression by immunohistochemistry in tissues with GPRC5D-positive gene expression.
Abbreviations: GPRC5D = G protein-coupled receptor family C group 5 member D.



[n = 143] and 0.8 mg/kg Q2W [n = 145]), including 51 patients who received prior T-cell redirection therapies.⁷ The most common AEs included CRS, dermatologic toxicities (skin and nail disorders), and oral events (dysgeusia, dysphagia, and dry mouth), consistent with other GPRC5D-targeting therapies (Table 1, Figure 2).^{7,10-13} Cytopenia events were common, generally reversible, and limited to the first few cycles. In the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, AEs resulted in treatment discontinuation in 4.9%, 8.3%, and 7.8% of patients, respectively, and dose reductions in 14.7%, 8.3%, and 9.8% of patients, respectively. Among all patients, 51.6% had at least 1 serious AE and 3.2% had grade 5 AEs (COVID-19 and general physical health deterioration, both n = 2; fungal sepsis, infection, septic shock, respiratory failure, acute respiratory failure, pulmonary embolism, and basilar artery occlusion, all n = 1).

Prevention and Management Strategies for Adverse Events Associated With Talquetamab Oral Events.

Dysgeusia.

i. Data from MonumenTAL-1

Dysgeusia is an alteration in the quality and/or sensitivity of taste sensation.^{29,30} In MonumenTAL-1, dysgeusia, ageusia (loss of taste),

hypogeusia (reduced ability to taste), and general taste disorders were included under the term dysgeusia and are reported in these analyses.⁷ As per Common Terminology Criteria for Adverse Event (CTCAE) classification, dysgeusia has a maximum severity of grade 2, defined as altered taste with a change in diet and presence of noxious, unpleasant, or loss of taste, with grade 1 defined as altered taste with no change in diet. It should be noted that a robust evaluation method for dysgeusia has not yet been established and the grading system currently used in clinical settings is highly subjective. In total, 72.0% (n = 103), 71.0% (n = 103), and 76.5% (n = 39) of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, had dysgeusia⁷; most events were grade 1 (59.2%, 58.3%, and 66.7%, respectively). Of patients who experienced dysgeusia, dysgeusia events occurred concurrently with decreased appetite in 10.7%, 11.7%, and 2.6% of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, concurrently with dry mouth in 19.4%, 16.5%, and 20.5%, respectively, and concurrently with weight decrease of ≥ 10% from baseline in 20.4%, 15.5%, and 10.3%, respectively. Median time to onset was 20.0, 15.0, and 12.5 days in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively (Table 2), although some investigators have reported that patients experienced dysgeusia shortly after talquetamab dosing, even as early as the first day or a few

Table 1 AEs of interest in MonumenTAL-1 Compared With Other GPRC5D-Targeting Therapies in Clinical Development.

	Talquetamab ^a (N = 339)		Forimtamig ^b (N = 108)				MCARH109 ^c (N = 17)		OriCAR-017 ^d (N = 10)		BMS-986393 ^e (N = 33)	
			IV Cohort (n = 51)		SC Cohort (n = 57)							
AEs of interest, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anemia	155 (46)	99 (29)	17 (33)	8 (16)	28 (49)	22 (39)	15 (88)	7 (41)	8 (80)	7 (70)	12 (36)	7 (21)
Neutropenia	119 (35)	103 (30)	12 (24)	6 (12)	10 (18)	9 (16)	17 (100)	17 (100)	10 (100)	10 (100)	22 (67)	20 (61)
Lymphopenia	91 (27)	83 (24)	NR	NR	NR	NR	17 (100)	17 (100)	3 (30)	2 (20)	NR	NR
Thrombocytopenia	101 (30)	71 (21)	16 (31)	7 (14)	15 (26)	11 (19)	15 (88)	11 (65)	9 (90)	9 (90)	13 (39)	7 (21)
CRS	260 (77)	5 (1)	42 (82)	1 (2)	45 (79)	1 (2)	15 (88)	1 (6)	10 (100)	0	21 (64)	2 (6)
ICANS ^f	26 (10)	6 (2)	5 (10)	1 (2)	7 (12)	2 (4)	1 (6)	1 (6)	0	0	2 (6)	0
Skin-related AEs ^{g,h,i,j,k}	221 (65)	1 (0)	40 (78)	6 (12)	49 (86)	13 (23)	1 (6)	0	3 (30)	0	10 (30)	0
Hair and nail changes	NR	NR	12 (24)	0	16 (28)	0	NR	NR	NR	NR	NR	NR
Nail-related AEs ^{l,m,n}	188 (55)	0 (0)	NR	NR	NR	NR	11 (65)	0	3 (30)	0	3 (9)	0
Dysgeusia ^o	245 (72)	NA	NR	NR	NR	NR	2 (12)	0	NR	NR	5 (15)	0
Dry mouth	122 (36)	0 (0)	NR	NR	NR	NR	1 (6)	0	NR	NR	NR	NR
Dysphagia	82 (24)	3 (1)	NR	NR	NR	NR	NR	NR	NR	NR	1 (3)	0
Mucosal toxicity ^p	NR	NR	37 (73)	0	44 (77)	3 (5)	NR	NR	NR	NR	NR	NR
Rash-related AEs ^q	118 (35)	12 (4)	NR	NR	NR	NR	3 (18)	0	NR	NR	NR	NR
Infections	217 (64)	63 (19)	31 (61)	11 (22)	26 (46)	15 (26)	3 (18)	2 (12)	NR	NR	NR	NR
Cerebellar AEs	1 (0.3) ^r	1 (0.3) ^r	NR	NR	NR	NR	2 (12)	0	NR	NR	0	0

Data cutoff: January 17, 2023 (talquetamab); April 5, 2022 (forimtamig); June 30, 2022 (OriCAR-017); patients were enrolled between September 15, 2020 and June 16, 2021 (MCARH109); September 7, 2022 (BMS-986393). For talquetamab, AEs were graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.03; CRS and ICANS were reported according to American Society for Transplantation and Cellular Therapy guidelines.

Abbreviations: AE = adverse event; CAR-T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; GI = gastrointestinal; GPRC5D = G protein-coupled receptor family C group 5 member D; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous; NA = not applicable; NR = not reported; Q2W = every other week; QW = weekly; RP2D = recommended phase 2 dose; SC = subcutaneous.

^a Includes patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts. In phase 1, 0.405 mg/kg SC QW was 1 of the 2 RP2Ds; 0.4 mg/kg SC QW was selected as the final dosing concentration in phase 2 for operational convenience.

^b Administered 18 to 10,000 µg in the IV cohort and 1200 to 7200 µg in the SC cohort.

^c 3 patients received 25×10^9 CAR-T cells and 50×10^9 CAR-T cells, 6 patients received 150×10^6 CAR-T cells, and 5 patients received 450×10^6 CAR-T cells.

^d 3 patients each received 1×10^6 CAR-T cells per kg, 3×10^6 CAR-T cells per kg, 6×10^6 CAR-T cells per kg, respectively, in the dose-escalation phase. In the expansion phase, 1 patient received the RP2D of 3×10^6 CAR-T cell per kg.

^e 33 patients received doses of BMS-986393 at 25 (n = 6), 75 (n = 9), 150 (n = 11), 300 (n = 6), and 450 (n = 1) $\times 10^6$ CAR-T cells.

^f As ICANS was only assessed in phase 2 of the talquetamab trial, the number of patients included in the analysis were 122, 109, and 34 in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively. For forimtamig, numbers are reported for AEs consistent with ICANS.

^g Includes skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome in patients who received talquetamab.

^h Includes rash, skin exfoliation erythema, skin toxicity, dermatitis, dermatitis exfoliative, toxic skin, eruption, eczema, rash erythematous, rash macular, and rash maculopapular with forimtamig treatment.

ⁱ Includes pruritus with MCARH109 treatment.

^j Includes pruritus and dry skin with OriCAR-017 treatment.

^k Includes pruritus, maculopapular rash, pain from skin, erythema, and vesicular rash with BMS-986393 treatment.

^l Includes nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging with talquetamab treatment.

^m Includes nail disorder with OriCAR-017 treatment.

ⁿ Includes nail bed disorder, nail discoloration, and nail disorder with BMS-986393 treatment.

^o Includes dysgeusia, ageusia, hypogesia, and general taste disorders with talquetamab treatment.

^p Includes dysgeusia, dry mouth, ageusia, stomatitis, salivary hypersecretion, mucosal inflammation, anosmia, dry lip, lip oedema, mucosal dryness, mucosal toxicity, and paraesthesia oral for forimtamig.

^q Includes rash, maculopapular rash, erythematous rash, and erythema in patients treated with talquetamab and rash in patients who received MCARH109.

^r Reported as ataxia with talquetamab treatment.

Figure 2**Summary of key AEs associated with talquetamab.**

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; QW = weekly; Q2W = every other week.

^aIncludes dysgeusia, ageusia, hypogeusia, and general taste disorders.

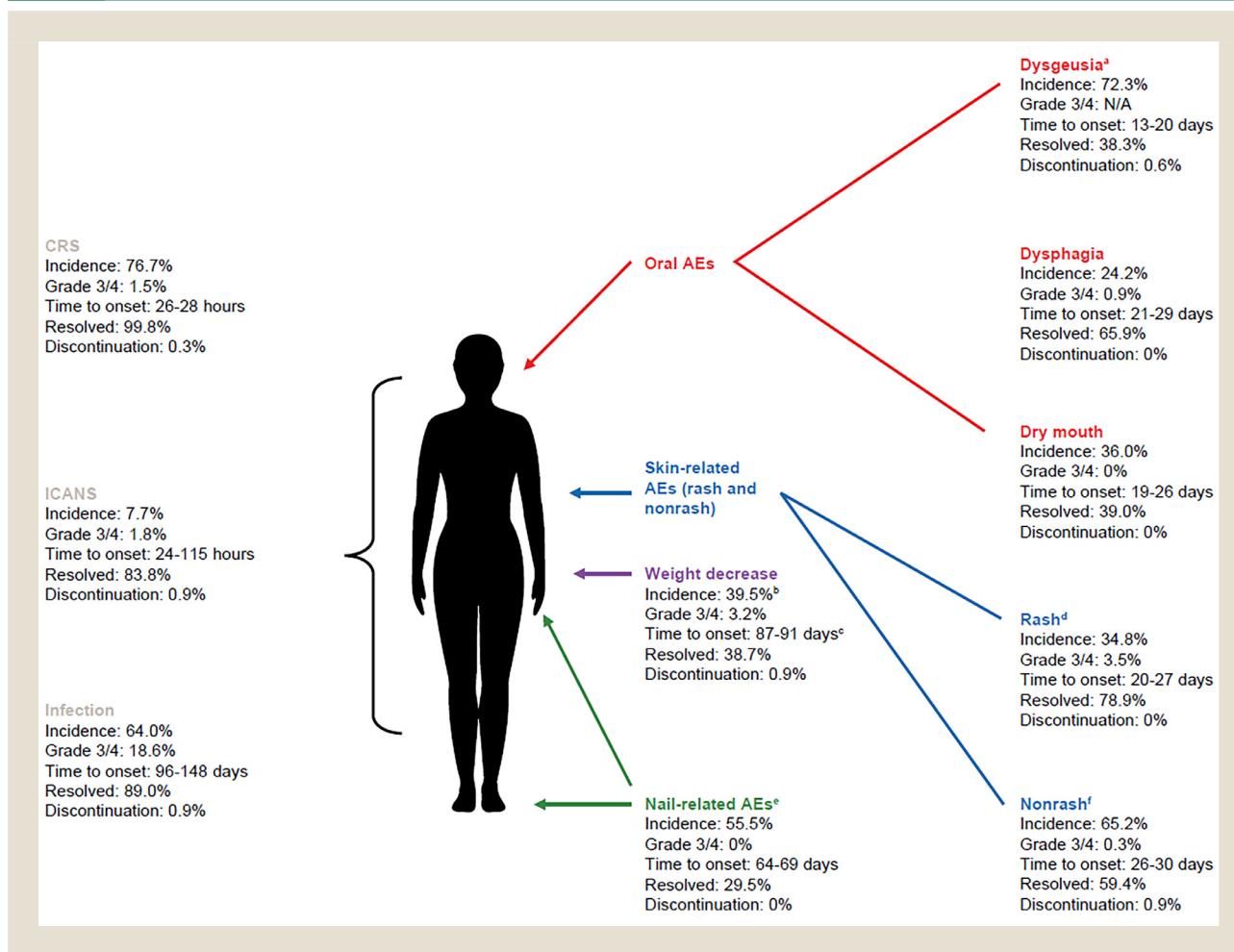
^bThe number of patients with a ≥ 10% decrease in weight from baseline in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts was 37.1%, 32.4%, and 29.4%, respectively.

^cTime to onset for weight loss is reported for patients with a ≥ 10% decrease in weight from baseline.

^dIncludes rash, maculopapular rash, erythematous rash, and erythema.

^eIncludes nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasia, nail dystrophy, nail toxicity, and nail ridging.

^fIncludes skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome.



days following initiation of step-up dosing. Median duration of each dysgeusia event was 95.0-130.0 days across the 3 cohorts (Table 2), and the median total duration that patients experienced dysgeusia across all events was 235.5 days (range, 1-870). Resolution rates of dysgeusia are shown in Table 2; experiences varied across patients, with some events resolving completely or partially, defined as a reduction in severity from grade 2 to grade 1; however, a proportion of events did not partially or completely resolve, suggesting that optimal management strategies are still evolving (Figure 3A and B, and Supplemental Figure 1A). Dose modifications were implemented in 26 patients (7.7%) across all 3 cohorts due to dysgeusia (Table 3). In total, 2 patients discontinued due to dysgeusia, both in the 0.8 mg/kg Q2W cohort.

ii. Management

The MonumenTAL-1 protocol specified that oral events (dysgeusia, dysphagia, and dry mouth) should be managed with mouth rinses, such as salt water or liquid corticosteroids, pain medications, and short courses of oral corticosteroids. In MonumenTAL-1, the most concomitant medications used by investigators to manage dysgeusia were dexamethasone, triamcinolone, and nystatin, administered orally (Table 4); however, investigators also used mineral and vitamin support with zinc and biotin, salivary stimulants, and hydration. Although the efficacy of these measures was not formally assessed, investigator experience suggests that these measures appeared to be of limited effectiveness for the manage-

Table 2 Median Time to Onset, Duration, and Resolution Rates for AEs of Interest in MonumenTAL-1.

AE	Talquetamab 0.4 mg/kg QW (n = 143)	Talquetamab 0.8 mg/kg Q2W (n = 145)	Prior T-Cell Redirection (n = 51)
Dysgeusia			
Median time to onset (days) ^a	20.0	15.0	12.5
Median duration (days) ^b	95.0	102.0	130.0
Resolved ^c , n (%)	58 (45.7)	36 (30.8)	17 (37.0)
Dysphagia			
Median time to onset (days) ^a	20.5	28.5	27.5
Median duration (days) ^b	109.0	73.0	174.0
Resolved ^c , n (%)	25 (69.4)	29 (72.5)	4 (33.3)
Dry mouth			
Median time to onset (days) ^a	26.0	22.0	18.5
Median duration (days) ^b	57.0	89.0	58.5
Resolved ^c , n (%)	20 (50.0)	20 (31.3)	13 (40.6)
Skin (rash-related)			
Median time to onset (days) ^a	20.0	22.0	27.0
Median duration (days) ^b	28.0	26.0	15.0
Resolved ^c , n (%)	66 (88.0)	47 (72.3)	22 (71.0)
Skin (nonrash-related)			
Median time to onset (days) ^a	29.5	27.0	26.0
Median duration (days) ^b	36.0	39.0	32.0
Resolved ^c , n (%)	90 (60.0)	99 (57.2)	45 (63.4)
Nail			
Median time to onset (days) ^a	68.5	67.5	64.0
Median duration (days) ^b	88.5	74.0	122.0
Resolved ^c , n (%)	32 (32.7)	25 (25.5)	13 (31.7)
Infections			
Median time to onset (days) ^a	148.0	108.0	96.0
Median duration (days) ^b	11.5	12.0	12.0
Resolved ^c , n (%)	207 (90.4)	166 (87.4)	82 (89.1)
CRS			
Median time to onset (hours) ^a	25.9	28.0	26.3
Median duration (hours) ^b	14.5	18.0	20.4
Resolved ^c , n (%)	188 (99.5)	189 (100.0)	57 (100.0)
ICANS ^d			
Median time to onset (hours) ^a	23.6	31.9	115.5
Median duration (hours) ^b	15.5	7.8	48.5
Resolved ^c , n (%)	18 (85.7)	12 (80.0)	1 (100.0)

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; QW = weekly; Q2W = every other week.

^a Median time to onset calculated relative to the most recent dose received.

^b Median duration is based on events with both start and end time/dates available.

^c Patients could have more than 1 event. Percentages are calculated with the number of events as the denominator.

^d As ICANS was only assessed in phase 2 of the trial, the number of patients included in the analysis were 122, 109, and 34 in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively.

ment of dysgeusia. In contrast, investigator experience indicated that dose modifications, including reductions, delays, or skips were the most effective management strategy for dysgeusia. Based on emerging data in patients who switched to a lower dose (0.8 mg/kg Q2W to 0.4 mg/kg Q2W) or to a less frequent dose (0.8 mg/kg Q2W to 0.8 mg/kg monthly), patients who received dose modifications are expected to maintain responses to talquetamab.³¹

The effect of dose modification on oral events is consistent with analyses showing that increased talquetamab exposure can result

in a higher incidence of dysgeusia.³² Therefore, dose modifications allow patients to continue therapy to maintain clinical benefit while potentially reducing the severity of dysgeusia and other oral events based on investigator experience.³¹ Nutritional monitoring, such as for iron deficiencies, should be undertaken with appropriate supplementation. High caloric shakes should be considered to ensure adequate nutritional intake and to prevent weight loss due to dysgeusia or other oral events. Patients with weight loss may require adjustments to weight-based medications, including talquetamab,

Table 3 Dose Modifications for Treatment-Emergent AEs in MonumenTAL-1.

AE, n (%)	Talquetamab 0.4 mg/kg QW (n = 143)	Talquetamab 0.8 mg/kg Q2W (n = 145)	Prior T-Cell Redirection (n = 51)
Dysgeusia			
Dose modification	12 (8.4)	8 (5.5)	6 (11.8)
Delayed	0	0	0
Skipped ^a	7 (4.9)	4 (2.8)	5 (9.8)
Reduced ^b	10 (7.0)	5 (3.4)	4 (7.8)
Dysphagia			
Dose modification	2 (1.4)	2 (1.4)	3 (5.9)
Delayed	0	0	0
Skipped ^a	2 (1.4)	1 (0.7)	1 (2.0)
Reduced ^b	0	1 (0.7)	2 (3.9)
Dry mouth			
Dose modification	2 (1.4)	4 (2.8)	3 (5.9)
Delayed	0	0	0
Skipped ^a	2 (1.4)	2 (1.4)	2 (3.9)
Reduced ^b	1 (0.7)	3 (2.1)	2 (3.9)
Skin (rash-related)			
Dose modification	9 (6.3)	6 (4.1)	2 (3.9)
Delayed	1 (0.7)	1 (0.7)	0
Skipped ^a	7 (4.9)	5 (3.4)	2 (3.9)
Reduced ^b	1 (0.7)	1 (0.7)	0
Skin (nonrash-related)			
Dose modification	12 (8.4)	1 (0.7)	3 (5.9)
Delayed	1 (0.7)	0	0
Skipped ^a	9 (6.3)	1 (0.7)	3 (5.9)
Reduced ^b	5 (3.5)	0	1 (2.0)
Nail			
Dose modification	1 (0.7)	0	1 (2.0)
Delayed	0	0	0
Skipped ^a	1 (0.7)	0	1 (2.0)
Reduced ^b	1 (0.7)	0	0
Infections			
Dose modification	32 (22.4)	29 (20.0)	10 (19.6)
Delayed	1 (0.7)	9 (6.2)	0
Skipped ^a	31 (21.7)	20 (13.8)	9 (17.6)
Reduced ^b	0	1 (0.7)	1 (2.0)
CRS ^c			
Dose modification	18 (12.6)	21 (14.5)	3 (5.9)
Delayed	17 (11.9)	21 (14.5)	3 (5.9)
Skipped ^a	2 (1.4)	2 (1.4)	0
Reduced ^b	1 (0.7)	1 (0.7)	0
ICANS ^{c, d}			
Dose modification	2 (1.6)	2 (1.8)	0
Delayed	0	2 (1.8)	0
Skipped ^a	2 (1.6)	0	0
Reduced ^b	1 (0.8)	0	0

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; QW = weekly; Q2W = every other week.

^aDefined as patients who had at least 1 dose skip before resuming on the same dosing level and schedule thereafter.

^bDefined as changes to either a reduced dose or a less frequent dosing schedule.

^c≥ 1 treatment-emergent symptoms of CRS/ICANS leading to dose modification.

^dAs ICANS was only assessed in phase 2 of the trial, the number of patients included in the analysis was 122, 109, and 34 in 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively.

Clinical Lymphoma, Myeloma & Leukemia

Table 4 Most Common Supportive Measures and Concomitant Treatments for Treatment-Emergent AEs in MonumenTAL-1.

AEs, n (%)	Talquetamab 0.4 mg/kg QW (n = 143)	Talquetamab 0.8 mg/kg Q2W (n = 145)	Prior T-Cell Redirection (n = 51)
Dysgeusia			
Local oral concomitant medications (\geq 3 patients in any cohort) ^a	15 (10.5)	13 (9.0)	5 (9.8)
Dexamethasone	1 (0.7)	4 (2.8)	2 (3.9)
Triamcinolone	4 (2.8)	0	0
Nystatin	0	3 (2.1)	1 (2.0)
Dysphagia			
Concomitant medications (\geq 2 patients in any cohort) ^a	9 (6.3)	11 (7.6)	4 (7.8)
Sodium bicarbonate	0	4 (2.8)	0
Sodium chloride	1 (0.7)	2 (1.4)	1 (2.0)
Fluconazole	1 (0.7)	2 (1.4)	0
Nutrients	0	2 (1.4)	0
Omeprazole	0	2 (1.4)	0
Dry mouth			
Local oral concomitant medications (\geq 4 patients in any cohort) ^a	18 (12.6)	18 (12.4)	11 (21.6)
Xylitol	6 (4.2)	1 (0.7)	3 (5.9)
Glycerol	4 (2.8)	0	3 (5.9)
Glucose oxidase	1 (0.7)	4 (2.8)	2 (3.9)
Lactoferrin	1 (0.7)	4 (2.8)	2 (3.9)
Lactoperoxidase	1 (0.7)	4 (2.8)	2 (3.9)
Lysozyme	1 (0.7)	4 (2.8)	2 (3.9)
Sorbitol	3 (2.1)	0	4 (7.8)
Artificial saliva	0	4 (2.8)	0
Skin (rash-related)			
Concomitant medications (\geq 5 patients in any cohort) ^a	42 (29.4)	32 (22.1)	15 (29.4)
Topical medication	32 (22.4)	23 (15.9)	11 (21.6)
Corticosteroids	28 (19.6)	22 (15.2)	9 (17.6)
White soft paraffin	11 (7.7)	4 (2.8)	1 (2.0)
Liquid paraffin	8 (5.6)	2 (1.4)	1 (2.0)
Glycerol	7 (4.9)	1 (0.7)	0
Ammonium lactate	1 (0.7)	5 (3.4)	1 (2.0)
Oral medications	21 (14.7)	17 (11.7)	8 (15.7)
Cetirizine	8 (5.6)	3 (2.1)	1 (2.0)
Corticosteroids	5 (3.5)	7 (4.8)	4 (7.8)
Desloratadine	5 (3.5)	1 (0.7)	0
Skin (nonrash-related)			
Concomitant medications (\geq 5 patients in any cohort) ^a	50 (35.0)	57 (39.3)	22 (43.1)
Topical medication	37 (25.9)	46 (31.7)	20 (39.2)
Triamcinolone	9 (6.3)	18 (12.4)	7 (13.7)
Ammonium lactate	4 (2.8)	12 (8.3)	2 (3.9)
White soft paraffin	7 (4.9)	10 (6.9)	1 (2.0)
Clobetasol	8 (5.6)	9 (6.2)	1 (2.0)
Propylene glycol	2 (1.4)	9 (6.2)	1 (2.0)
Liquid paraffin	8 (5.6)	5 (3.4)	3 (5.9)
Macrogol	1 (0.7)	8 (5.5)	1 (2.0)
Simethicone	1 (0.7)	8 (5.5)	1 (2.0)

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Table 4 (continued)

AEs, n (%)	Talquetamab 0.4 mg/kg QW (n = 143)	Talquetamab 0.8 mg/kg Q2W (n = 145)	Prior T-Cell Redirection (n = 51)
Sorbic acid	1 (0.7)	8 (5.5)	1 (2.0)
Sorbitol	1 (0.7)	8 (5.5)	1 (2.0)
Betamethasone	7 (4.9)	0	0
Oral medications	23 (16.1)	10 (6.9)	9 (17.6)
Cetirizine	5 (3.5)	2 (1.4)	0
Nail			
Topical concomitant medications (\geq 3 patients in any cohort) ^a	10 (7.0)	11 (7.6)	6 (11.8)
Ammonium lactate	0	5 (3.4)	1 (2.0)
Glycerol	3 (2.1)	1 (0.7)	0
Liquid paraffin	3 (2.1)	1 (0.7)	0
White soft paraffin	3 (2.1)	1 (0.7)	0
Infections			
Concomitant medications (\geq 5 patients in any cohort) ^a	76 (53.1)	86 (59.3)	35 (68.6)
Amoxicillin	34 (23.8)	22 (15.2)	6 (11.8)
Clavulanate	26 (18.2)	14 (9.7)	5 (9.8)
Azithromycin	9 (6.3)	14 (9.7)	8 (15.7)
Nirmatrelvir/ritonavir	1 (0.7)	14 (9.7)	1 (2.0)
Fluconazole	6 (4.2)	13 (9.0)	2 (3.9)
Levofloxacin	12 (8.4)	11 (7.6)	5 (9.8)
Paracetamol	11 (7.7)	10 (6.9)	6 (11.8)
Vancomycin	8 (5.6)	9 (6.2)	1 (2.0)
Ciprofloxacin	9 (6.3)	1 (0.7)	7 (13.7)
Salbutamol	4 (2.8)	8 (5.5)	2 (3.9)
Piperacilllin/tazobactam	7 (4.9)	7 (4.8)	2 (3.9)
Nystatin	7 (4.9)	4 (2.8)	1 (2.0)
Meropenem	4 (2.8)	6 (4.1)	2 (3.9)
Dexamethasone	3 (2.1)	6 (4.1)	1 (2.0)
Ipratropium bromide	5 (3.5)	5 (3.4)	1 (2.0)
Moxifloxacin	2 (1.4)	5 (3.4)	3 (5.9)
Cefepime	1 (0.7)	5 (3.4)	3 (5.9)
Metronidazole	3 (2.1)	5 (3.4)	0
CRS			
Supportive measures	106 (74.1)	103 (71.0)	39 (76.5)
Paracetamol	80 (55.9)	77 (53.1)	30 (58.8)
Tocilizumab	50 (35.0)	55 (37.9)	26 (51.0)
Intravenous fluids	16 (11.2)	25 (17.2)	12 (23.5)
Oxygen	8 (5.6)	10 (6.9)	3 (5.9)
Corticosteroids	5 (3.5)	5 (3.4)	8 (15.7)
Vasopressors	2 (1.4)	1 (0.7)	1 (2.0)
Other	51 (35.7)	50 (34.5)	17 (33.3)
ICANS ^b			
Supportive measures	9 (7.4)	9 (8.3)	1 (2.9)
Corticosteroids	8 (6.6)	3 (2.8)	1 (2.9)
Dexamethasone	7 (5.7)	3 (2.8)	1 (2.9)
Methylprednisolone	1 (0.8)	0	0

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Table 4 (continued)

AEs, n (%)	Talquetamab 0.4 mg/kg QW (n = 143)	Talquetamab 0.8 mg/kg Q2W (n = 145)	Prior T-Cell Redirection (n = 51)
Tocilizumab	3 (2.5)	5 (4.6)	1 (2.9)
Levetiracetam	1 (0.8)	2 (1.8)	0
Anakinra	0	1 (0.9)	0

Includes any prescribed concomitant medications or treatments deemed necessary to provide adequate supportive care. All medications (including prescriptions and over-the-counter products, and transfusions of blood products) different from the study drug were recorded throughout the study until 100 days after the last dose of study drug during phase 1 and up to 30 days after the last dose of study drug during phase 2 or until the start of subsequent systemic anticancer treatment, if earlier. Supportive medications and concomitant medications ordered per the highest number in any of the 3 cohorts.

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; QW = weekly; Q2W = every other week.

^a Patients could receive ≥ 1 concomitant medication.

^b As ICANS was only assessed in phase 2 of the trial, the number of patients included in the analysis was 122, 109, and 34 in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively.

and other conditions, such as hypotension and diabetes mellitus, should be monitored.

Dry Mouth/Xerostomia

i. Data from MonumenTAL-1

Xerostomia is clinically defined as the subjective complaint of having a dry mouth.³³ In MonumenTAL-1, 26.6% (n = 38), 40.0% (n = 58), and 51.0% (n = 26) of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, had dry mouth, which were all grade 1/2.⁷ Of patients who experienced dry mouth, a dry mouth event occurred concurrently with

decreased appetite in 7.9%, 12.1%, and 15.4% of patients in each of the 3 cohorts, respectively; with dysgeusia in 23.7%, 31.0%, and 38.5%, respectively; with dysphagia in 5.3%, 9.0%, and 16.7%, respectively; and with decreased weight of ≥ 10% from baseline in 13.2%, 6.9%, and 11.5%, respectively. Median time to onset was 26.0, 22.0, and 18.5 days in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, and the median duration of each dry mouth event was 57.0–89.0 days across the 3 cohorts (Table 2). The median total duration that patients experienced dry mouth across all events was 216 days (range, 4–628). In the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, 50.0%, 31.3%, and 40.6% of dry

Figure 3 Resolution of AEs of interest during treatment (A) and course of (B) dysgeusia, (C) dry mouth, (D) dysphagia, (E) rashes, (F) nonrash skin toxicities, (G) nail toxicities, (H) infections, (I) CRS, and (J) ICANS in individual patients who experienced each adverse event during treatment. Weight loss was assessed as per vital signs.

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome.

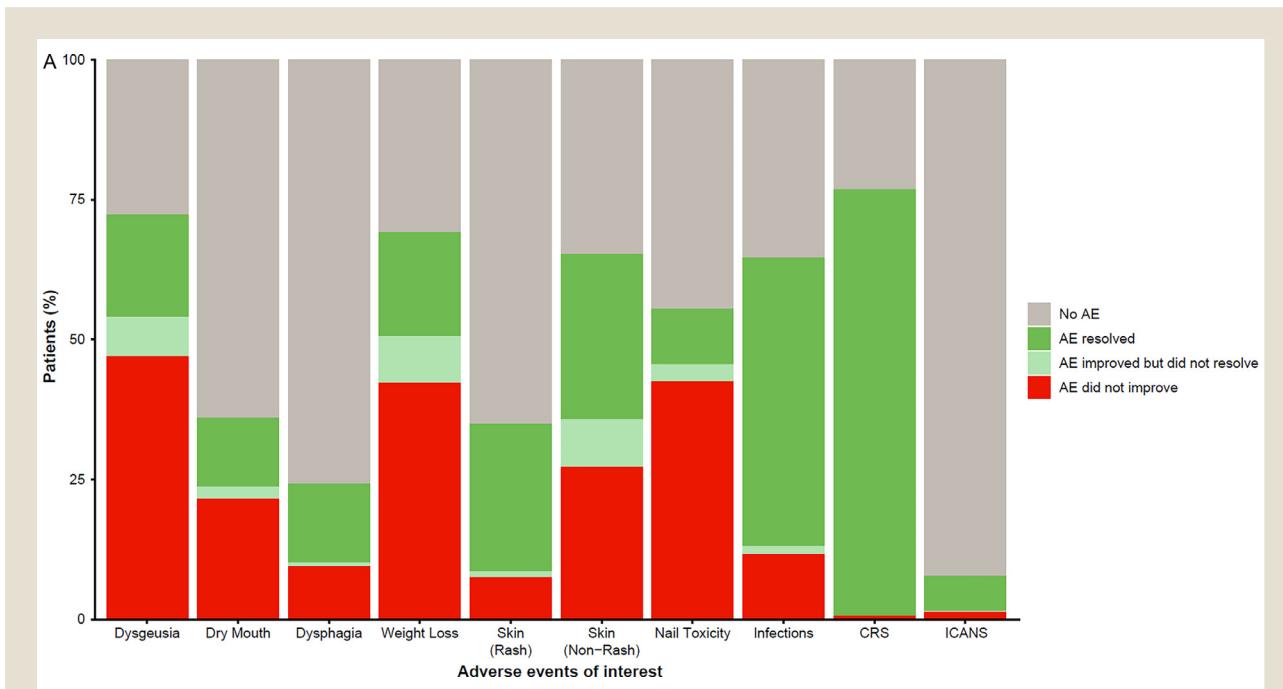


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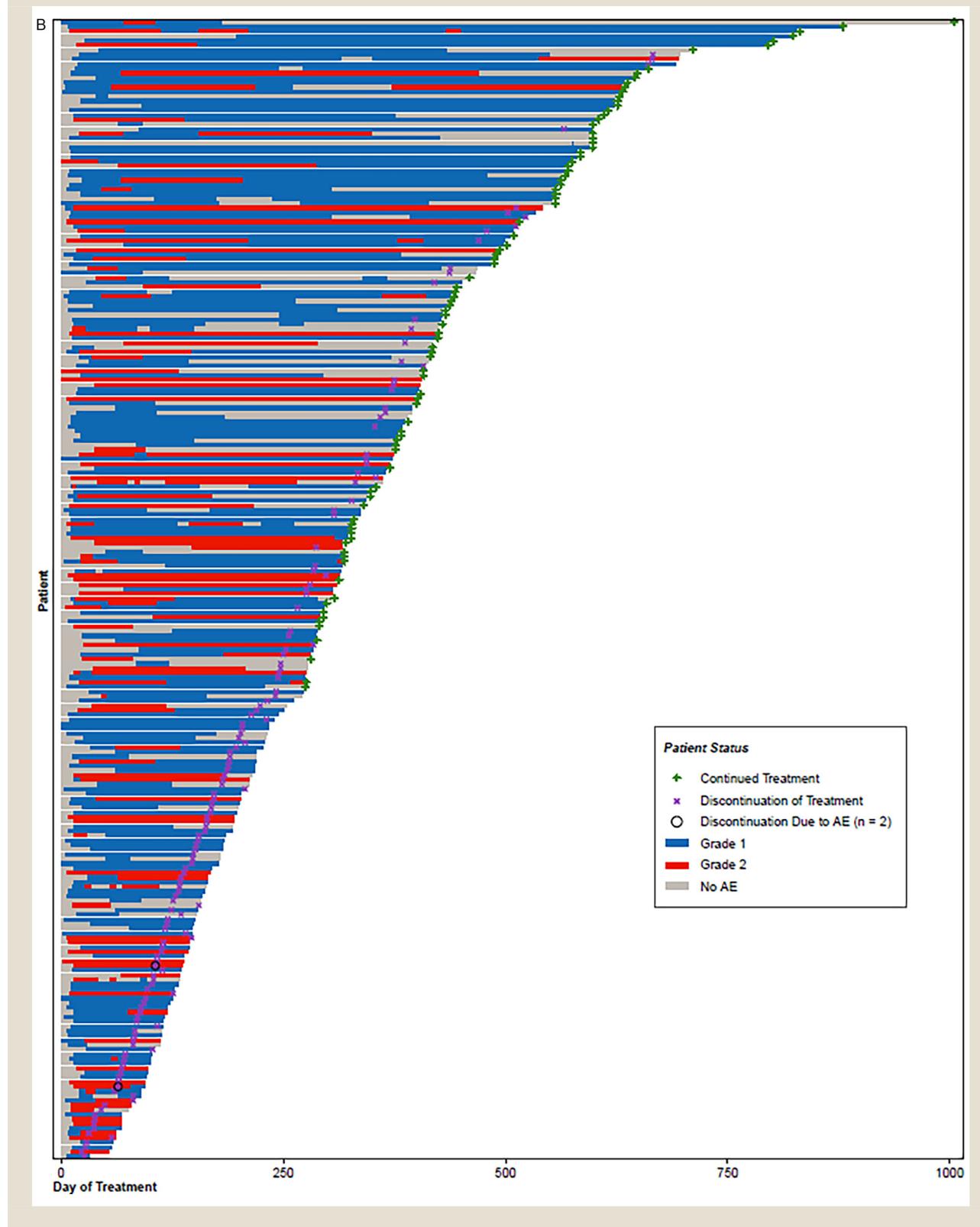


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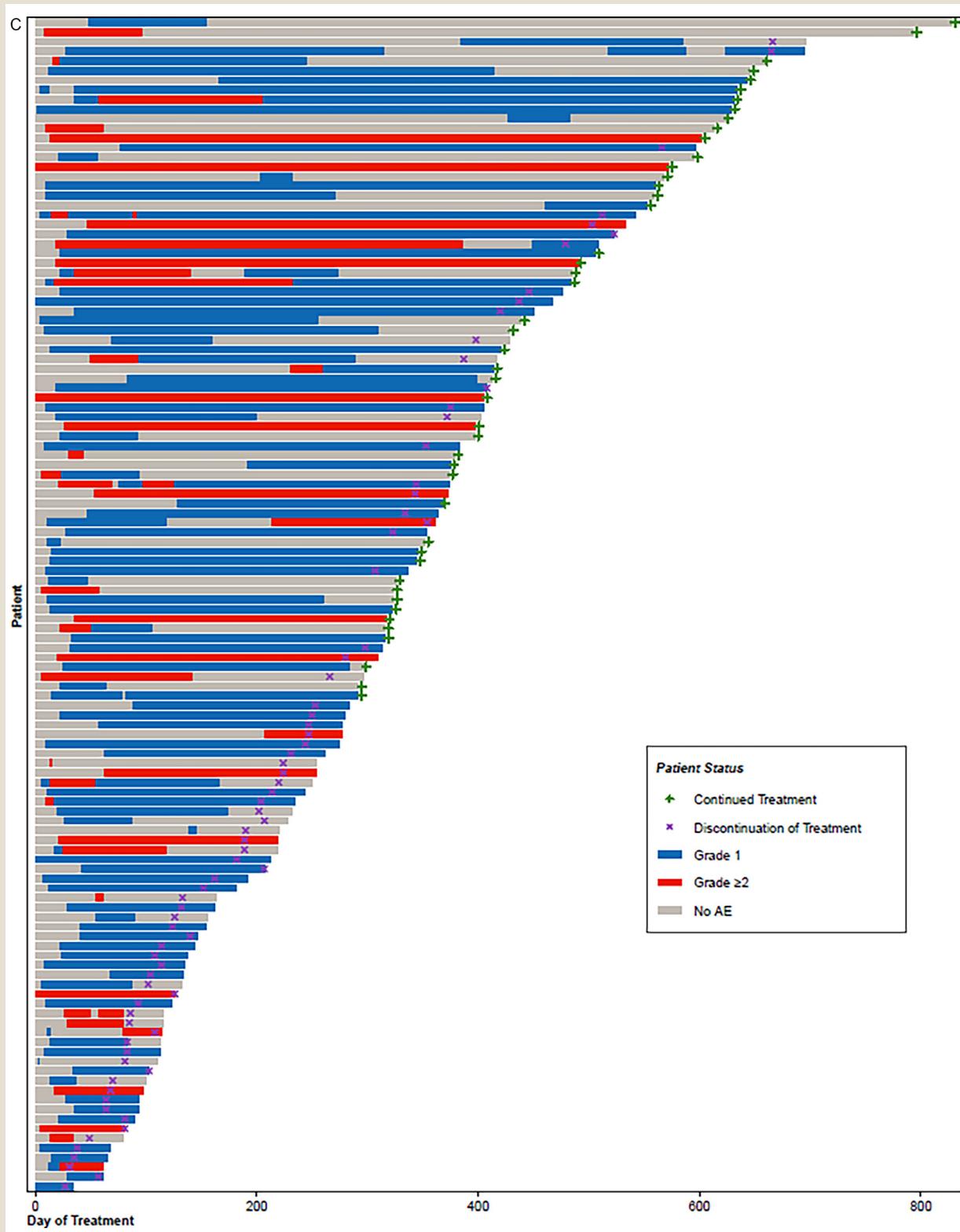


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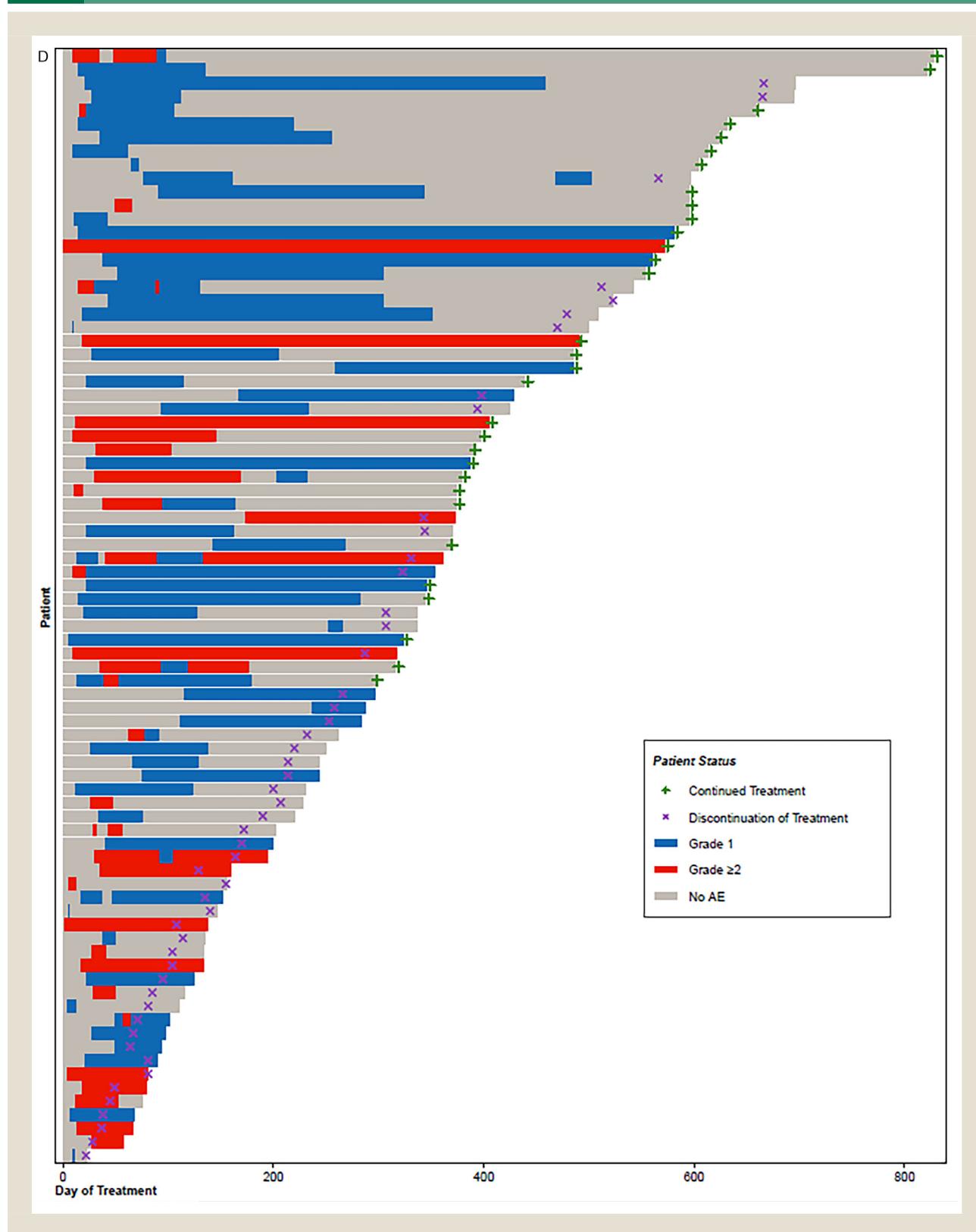


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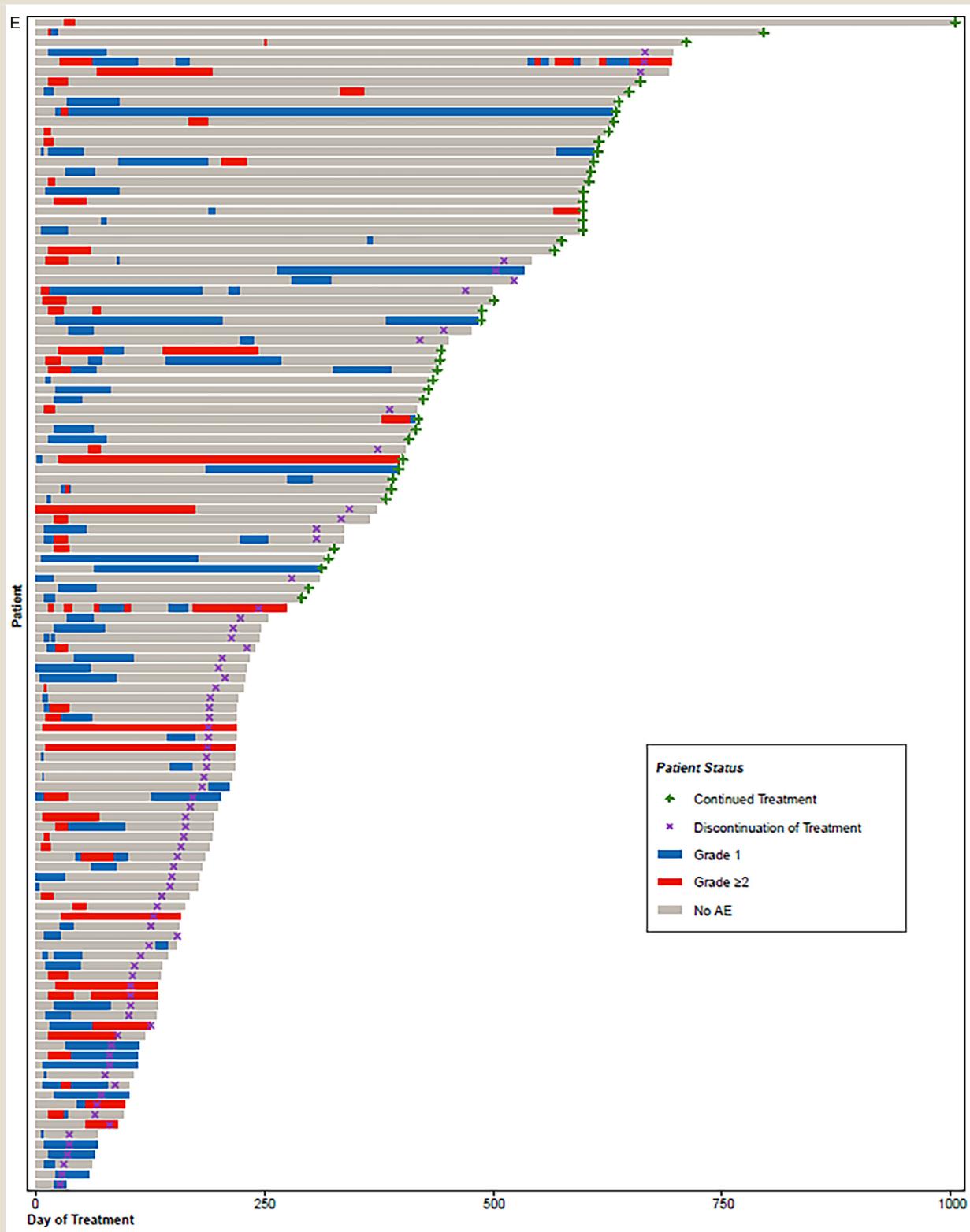


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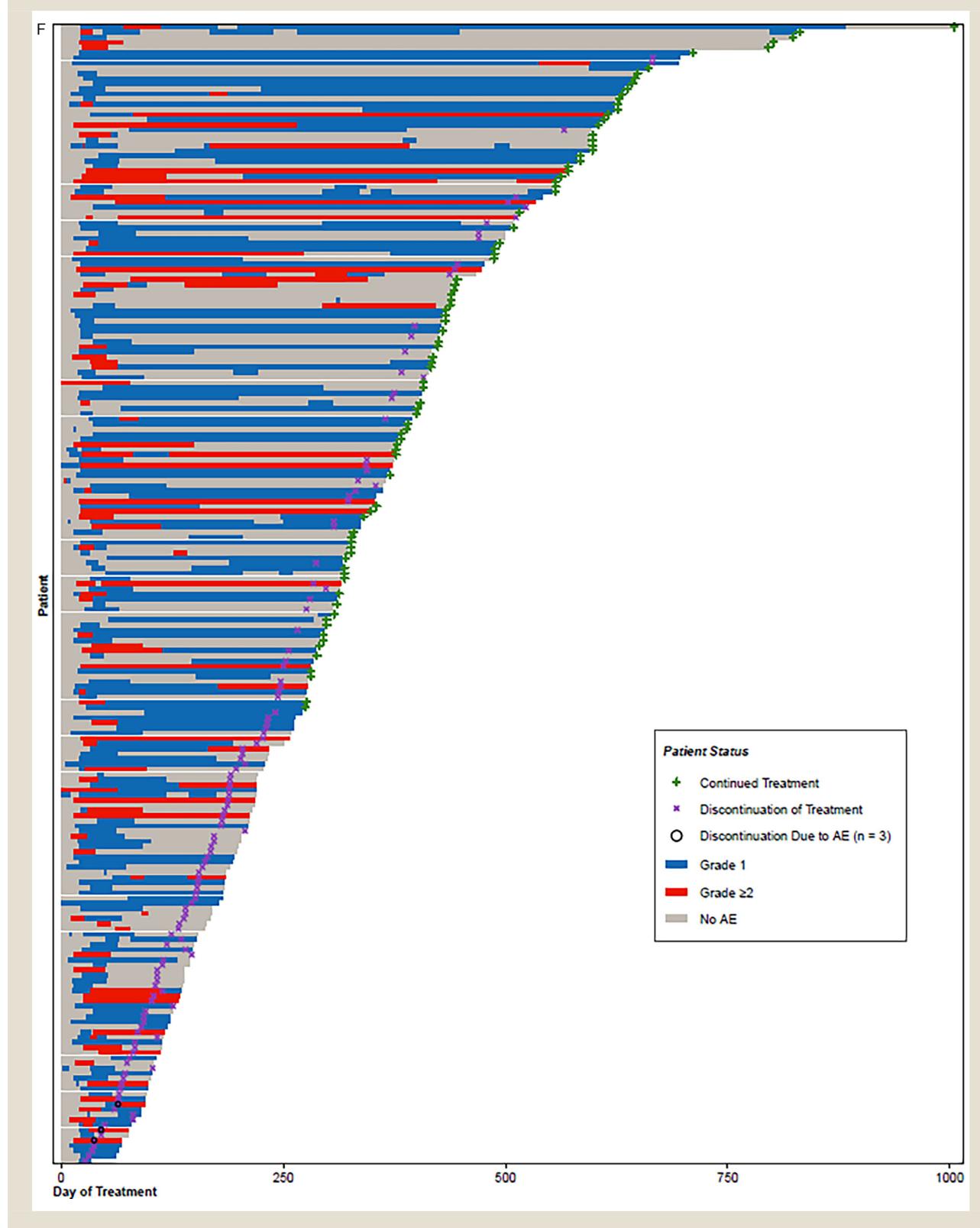


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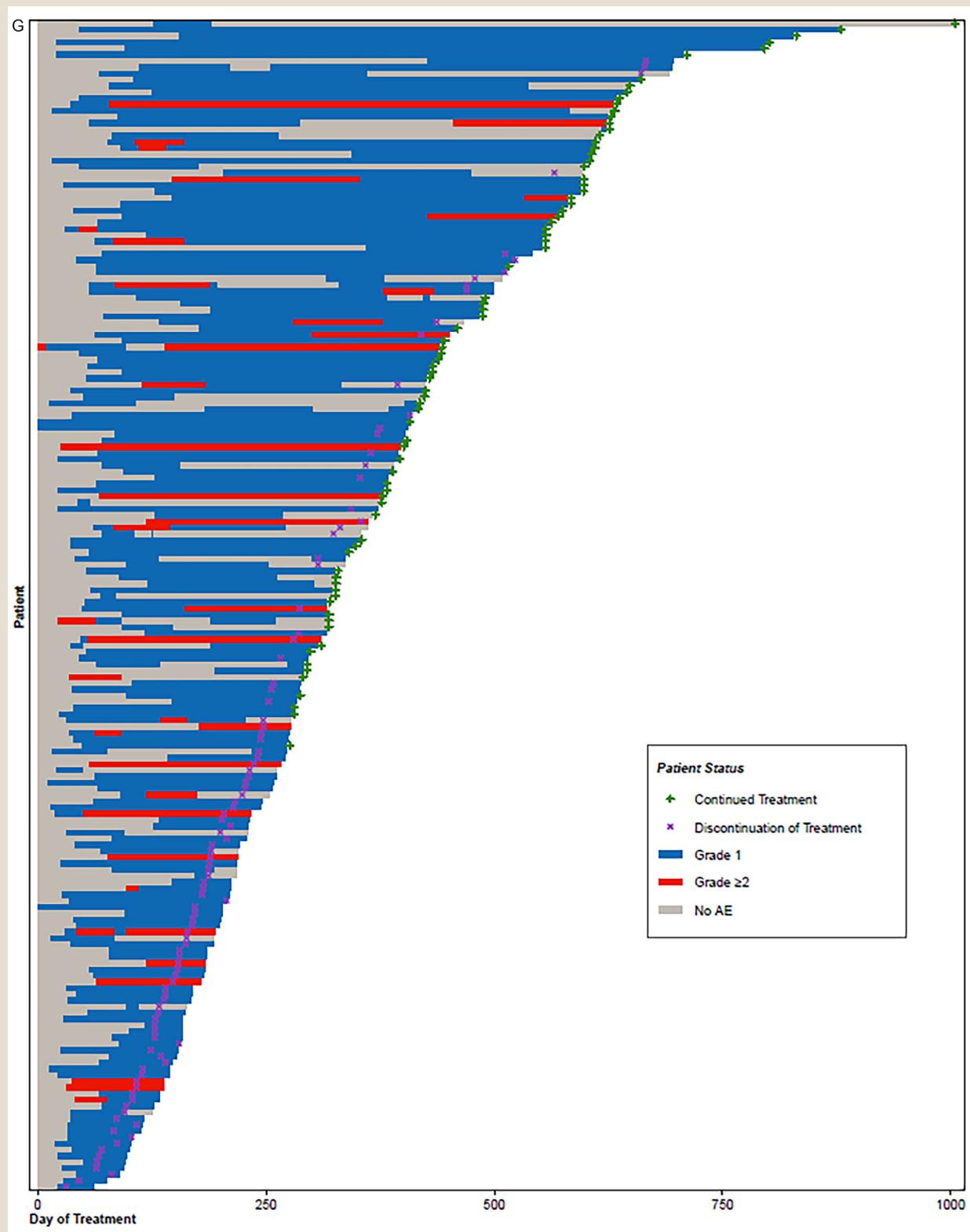


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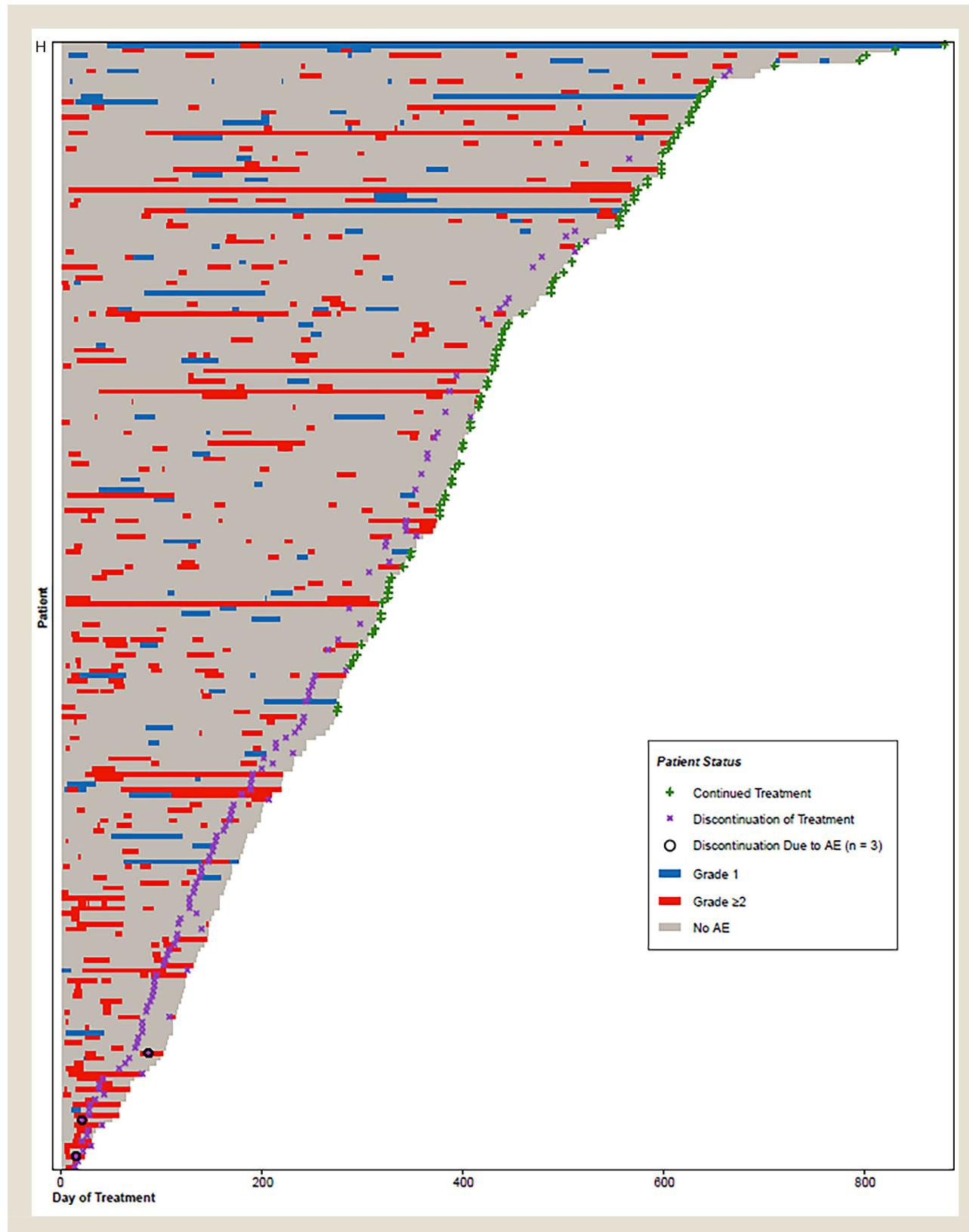


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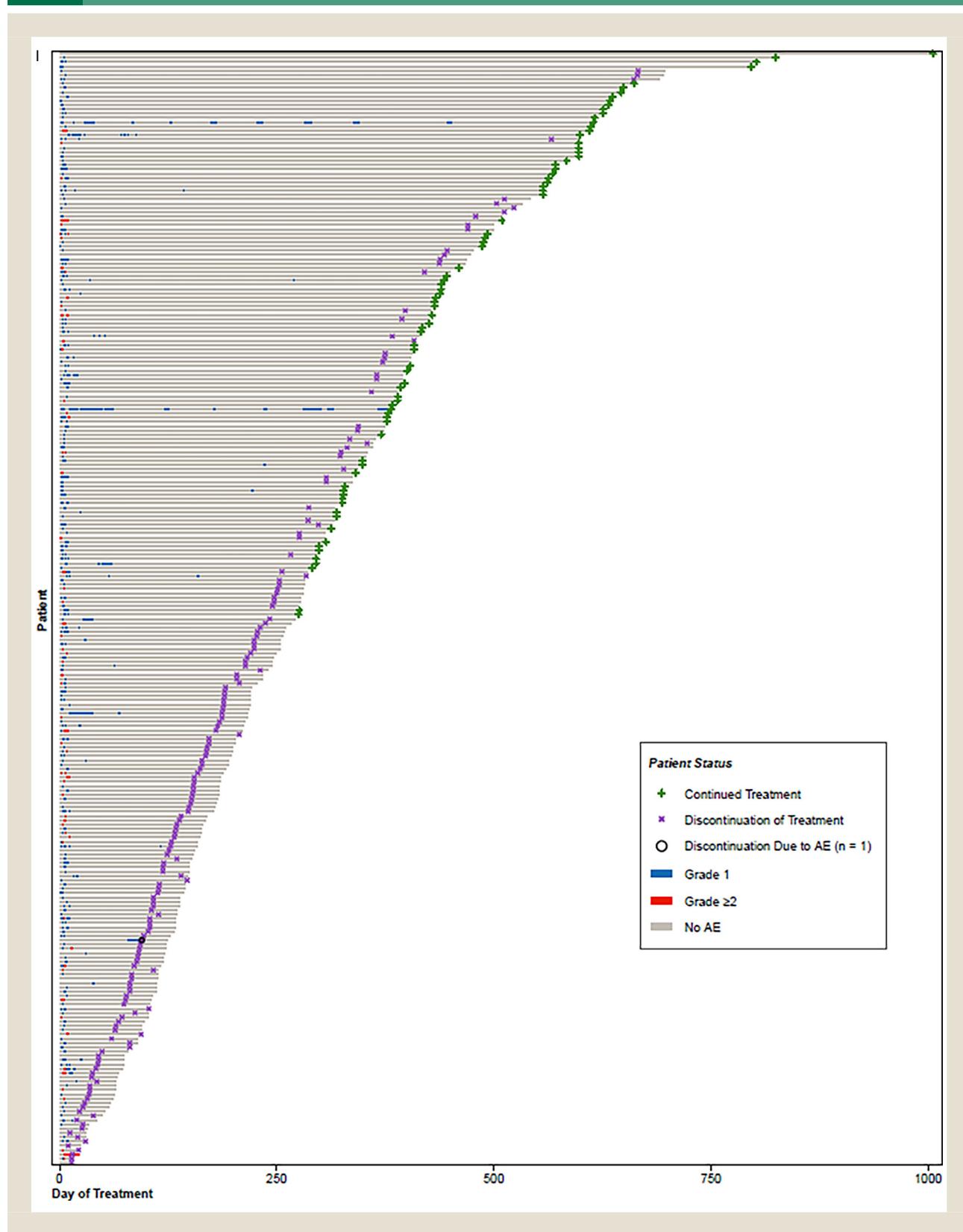
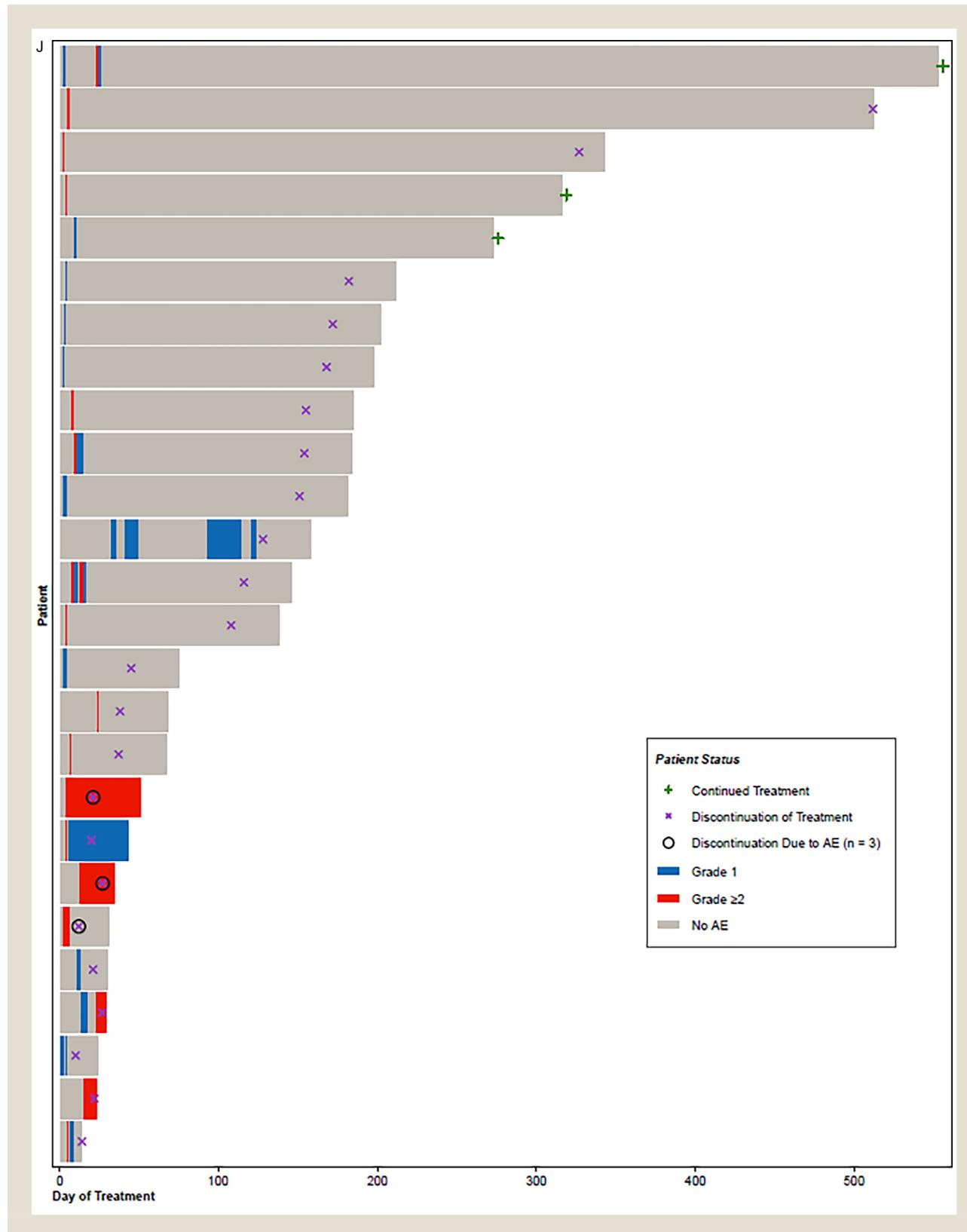


Figure 3 | Continued



Clinical Lymphoma, Myeloma & Leukemia

mouth events resolved (*Table 2*), showing that a high proportion of events did not partially or completely resolve (*Figure 3A* and C, and Supplemental Figure 1B). Dose modifications were implemented in 9 patients with dry mouth (*Table 3*); no patients discontinued treatment due to dry mouth.

ii. Management

In MonumenTAL-1, some of the most common concomitant medications given to patients by investigators for dry mouth included xylitol and sorbitol to support dental health; glycerol and artificial saliva to aid lubrication of foods; and glucose oxidase, lysozyme, lactoferrin, and lactoperoxidase as antibacterial agents (*Table 4*). Although these measures were not assessed for efficacy, investigator experience suggests that dry mouth can be managed with increased hydration (sipping water throughout the day) and intraoral topical agents, such as topical saliva sprays or sugar-free chewing gum, to stimulate saliva flow. These measures are consistent with the role that saliva has in oral health, providing lubrication and antimicrobial properties.³⁴ Sodium lauryl sulfate-free toothpastes may be better tolerated than other toothpastes. These supportive measures may in turn help with managing dysgeusia and dysphagia. As for the guidance outlined for dysgeusia, dose reductions, delays, or skips were also reported by investigators to be a potentially effective management strategy for dry mouth.

Dysphagia

i. Data from MonumenTAL-1

Dysphagia describes the symptom of patients having trouble swallowing.³⁵ It is often described as a sensation of food being stuck in the esophagus or chest.³⁶ Saliva is necessary to swallow, and based on the experience of investigators in the MonumenTAL-1 trial, dysphagia appeared to be secondary to dry mouth. Dysphagia occurred in 23.8% (n = 34), 24.8% (n = 36), and 23.5% (n = 12) of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively. The majority were low grade. In total, 3 (2.1%) patients, all in the 0.8 mg/kg Q2W cohort, had grade 3 dysphagia. Of patients who experienced dysphagia, a dysphagia event occurred concurrently with decreased appetite in 14.7%, 19.4%, and 8.3% of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, concurrently with dry mouth in 17.6%, 16.7%, and 25.0%, respectively, and concurrently with weight decrease of $\geq 10\%$ from baseline in 17.6%, 19.4%, and 8.3%, respectively. Median time to onset of dysphagia was 20.5, 28.5, and 27.5 days in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively; median duration was 109.0, 73.0, and 174.0 days, respectively (*Table 2*). The median total duration that patients experienced dysphagia across all events was 165.5 days (range, 20-572). In the 0.4 mg/kg QW and 0.8 mg/kg Q2W cohorts, most dysphagia events resolved, although the resolution rate was lower in the prior T-cell redirection cohort (*Table 2*, *Figure 3A* and D, and Supplemental Figure 1C). Dose modifications due to dysphagia were implemented in < 6% of patients across all 3 cohorts (*Table 3*); no patients discontinued due to dysphagia.

ii. Management

In MonumenTAL-1, the most common concomitant medications administered to manage dysphagia were sodium bicarbonate, sodium chloride, fluconazole, nutritional support (use of total parenteral nutrition/feeding tubes was rarely required), and omeprazole (*Table 4*). Investigators also advised that they used tramadol and oxycodone to manage pain and corticosteroids to control inflammation. “Magic mouthwash” (which contains at least 3 of an antihistamine, anesthetic, antacid, antifungal, corticosteroid, or antibiotic) was also used to manage pain and inflammation. These measures were not assessed for efficacy, and based on the experience of investigators, dose reductions, delays, or skips were the most effective management strategy for dysphagia, consistent with the guidance outlined for dysgeusia and dry mouth. As dysphagia appeared to be secondary to dry mouth, frequent intake of liquids, particularly while consuming food, and use of artificial saliva may be beneficial to patients.

Value of Specialist Referral for Oral Events

Early referral to a dietitian or nutritionist at the onset of therapy should be encouraged to provide guidance on maintaining a balanced diet and weight, irrespective of the presence of oral events. Specialist referral to oral medicine or otorhinolaryngology is of limited value for dysgeusia due to the lack of specific therapeutic interventions. Routine dentist visits, including regular cleanings, should be maintained due to the increased risk of dental/periodontal disease and oral mucosa issues associated with dry mouth. Specialist referral to gastroenterology may be advisable to rule out other upper aero-digestive track abnormalities, such as candida esophagitis or cytomegalovirus infections, for patients who have high-grade or increasingly severe dysphagia or an event that is unresponsive to oral treatments or dose modifications. Specialist referral may also be advisable if other symptoms develop that suggest a structural or neuromuscular cause of dysphagia.

Patient Counseling/Patient Education for Oral Events

Patients should be advised that dysgeusia is a commonly reported AE with talquetamab and that its onset may occur during early treatment cycles; although some events may partially or completely resolve, a substantial proportion of patients are expected to experience ongoing issues with altered taste. However, patients are expected to experience improvements in health-related quality of life with talquetamab after cycles 4 and 5 once disease control is achieved (as of January 17, 2023, median time to first response was 1.1-1.3 months across the 3 cohorts, and time to complete response or better was 2.6-4.7 months).³⁷ Given the median time to response and emerging data showing maintenance of response with dose modification strategies, patients should be informed that if dysgeusia or an oral event is affecting their quality of life, a dose may be omitted and then reduced.^{31,37} Patients therefore should be encouraged to report any taste disturbances or changes in appetite during treatment. Patients should also be encouraged to experiment with foods of different textures and tastes; loss or alteration of specific tastes, such as salty, sweet, bitter, and umami, may be differentially affected, and reports of anosmia (loss of smell) were infrequent. Enhancement with spicy, sour, or other aromatic flavor additives may be encouraged as tolerated and indicated by overall

dietary needs or preferences. Although the incidence and severity of dysgeusia was captured during the MonumenTAL-1 trial, and the rate of discontinuations due to this AE were low, the effect of taste-related changes requires additional evaluation to determine the specific effect on quality of life. The effect of taste changes during talquetamab treatment on quality of life is the subject of ongoing studies, with specific tools to better assess the character and effect of taste change on patients beyond standard CTCAE and quality of life questionnaires under investigation. Further characterization of the resolution or improvement in taste changes upon dose reduction is also under further assessment. Based on investigator experience, taste-related changes are expected to improve after discontinuation of talquetamab over a number of months.

With regards to dry mouth, patients should be encouraged to take small sips of liquids regularly, particularly while consuming food. Stomatitis had a relatively low incidence in MonumenTAL-1, occurring in 13.3%, 5.5%, and 13.7% of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively. Patients who develop dry mouth resulting from stomatitis should be encouraged to use sodium lauryl sulfate-free toothpastes and corticosteroid mouthwash. As with other oral events, patient education and discussion should be encouraged to raise patient awareness of dry mouth to ensure that symptoms are reported to their physician.

Patients should be advised that dysphagia may develop during treatment, and some patients may have persistent symptoms and experience issues with texture when eating certain items, such as bread, meat, rice, or other low-moisture foods. This may be partly managed through alterations of foods with sauces or broths, taking care to be mindful of total fat and sodium intake. As for dry mouth, drinking water during meals may help to alleviate symptoms of dysphagia, as might taking smaller bites of food and experimenting with different food types.

Complications of Oral Events

Changes in diet due to oral events can result in weight loss for patients, which requires close monitoring, especially for those with a low body weight at baseline. Additionally, comorbidities that may affect weight should be managed. Nutritional deficiencies and hypoferritinemia have been observed, which required supplementation in some cases. It should also be noted that changes in diet in response to oral events may result in gastrointestinal complications, such as changes in stool consistency. For patients with taste disturbances, it may be helpful to encourage patients to set reminders to eat and hydrate regularly. Weight-based dosing of talquetamab and other medications may also need to be adjusted in response to weight changes; this is particularly important for antihypertensive, diabetes, and thyroid medications. Nutritionist consultation should be considered at talquetamab initiation to provide nutritional support throughout treatment and to encourage active patient and caregiver engagement in the management of oral events affecting diet and food consumption.

Dermatologic Toxicity

Skin Toxicity

i. Data from MonumenTAL-1

The description of skin toxicities may vary across sites and trials of GPRC5D-targeting therapies. This section focuses on rash (inclusive of rash, maculopapular rash, erythematous rash, and erythema) and nonrash skin toxicities (inclusive of skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome); alopecia is described below in the rare AE section. Rashes were experienced by 39.9% (n = 57), 29.7% (n = 43), and 35.3% (n = 18) of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively.⁷ Nonrash skin toxicities were experienced by 55.9% (n = 80), 73.1% (n = 106), and 68.6% (n = 35) of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively.⁷ Most skin toxicities were grade 1/2: there were 12 (3.5%) grade 3 rash AEs and 1 (0.3%) grade 3 nonrash AE across the 3 cohorts. Median time to onset of rashes was 20.0–27.0 days, and median duration of each rash event was 15.0–28.0 days across the 3 respective cohorts; median time to onset of nonrash skin toxicities was 26.0–29.5 days and median duration of each nonrash skin toxicity was 32.0–39.0 days across the 3 cohorts (Table 2). Together with the resolution and median duration data, the experience from the MonumenTAL-1 trial suggests that rashes occur earlier, have a shorter duration, and are more likely to resolve compared with nonrash skin toxicities (Table 2). The median total duration that patients experienced rash-related and nonrash skin toxicities across all events was 73 days (range, 6–610) and 196.5 days (range, 3–688), respectively. Most rash-related and nonrash skin toxicities never reached grade 2, and the majority partially or completely resolved (Figure 3A, E, and F, and Supplemental Figure 1D and E). Dose modifications were few for both rash and nonrash skin toxicities (Table 3). No patients discontinued treatment due to rash, and 3 patients discontinued due to nonrash skin toxicities (2 patients in the 0.4 mg/kg QW cohort due to skin exfoliation and 1 patient due to dry skin in the 0.8 mg/kg Q2W cohort).

ii. Management

The MonumenTAL-1 protocol specified that rashes should be managed as per institutional guidelines, with topical corticosteroids used for rashes occurring during the first treatment cycle; early consideration should be given to a short course of oral corticosteroids to reduce the risk of rash progression. The most common concomitant medications patients received for skin toxicities in the MonumenTAL-1 trial are shown in Table 4. Based on the experiences from the MonumenTAL-1 trial, prophylaxis is not needed; however, management of skin toxicities should begin with early intervention, at the start of treatment and before development of symptoms, with liberal use of emollients and adequate hydration, such as with ammonium lactate cream, heavy moisturizers, and systemic hydration, ideally applied multiple times per day, especially after bathing. Rash and desquamation may become severe in some cases; the extent of exfoliation tends to wax and wane over time. Based on investigator experience, exfoliation occurred mainly on the palms of hands and the soles of feet. For skin toxicity, low-potency topical corticosteroids were used by investigators, with different potencies administered based on the site and severity of the event, per protocol recommendations. For generalized rashes that are not controlled by topical corticosteroids and/or for rashes occurring

Clinical Lymphoma, Myeloma & Leukemia

over a large surface area, short pulses of oral corticosteroids should be considered. If patients experience persistent or high-grade skin toxicities, particularly after cycle 2, or if their rashes are refractory to emollients or low-potency corticosteroids, dermatological consultation may be considered. This will be particularly applicable if a treatment center, including its dermatology consultants, have limited experience of using talquetamab. Photographic records may be useful to monitor skin toxicities over time.

Nail toxicity

i. Data from MonumenTAL-1

In MonumenTAL-1, nail toxicities (occurred on fingers and toes and included nail discoloration, nail disorder, onycholysis [separation of the nail from its nail bed], onychomadesis [detachment of the nail from its nail bed], onychoclasia [nail breakage], nail dystrophy, nail toxicity, and nail ridging) were observed in 54.5% (n = 78), 53.8% (n = 78), and 62.7% (n = 32) of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively.⁷ All events were grade 1/2.⁷ Median time to onset of nail toxicities was similar in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts at 68.5, 67.5, and 64.0 days, respectively, and median duration of each nail toxicity event was 74.0–122.0 days across the 3 cohorts (Table 2). The median total duration that patients experienced nail toxicities across all events was 220.5 days (range, 6–832). Resolution rates are shown in Table 2 and many events persist over the course of treatment (Figure 3A and G, and Supplemental 1F). There were very few dose modifications (Table 3) and no discontinuations due to nail-related toxicities.

ii. Management

The MonumenTAL-1 protocol recommends that nail toxicities may be managed with nail soaks, topical moisturizers, and topical corticosteroids. Emollients were a commonly used concomitant medication (Table 4); vitamin E oil, as well as systemic hydration, biotin, triamcinolone 0.025% ointment, and protective nail coverings, such as wearing socks and gloves at night, were also considered and used by investigators. Occlusion may be used to concentrate the effect of topical corticosteroids and/or moisturizers on nails. Nail hardeners, acrylics, and gels should be avoided as they may potentiate fungal infections. Based on anecdotal experience from investigators, dose reductions, delays, or skips may help to resolve or improve nail toxicities. At the outset of talquetamab therapy, the health care team should conduct nail assessments as part of their physical examination to help with monitoring of nail health.

Value of Specialist Referral for Dermatologic Toxicity

Hematologic oncologists may effectively manage early skin toxicities without specialist referral if they are familiar with talquetamab and the required management strategies; however, referral to dermatology may be warranted in cases in which patients experience persistent or grade 3/4 skin toxicities. Referral to a specialist may also be warranted to rule out other rare etiologies of rashes; a case report recently published described a patient who presented with a 3-week history of nonpruritic rash on week 3 of talquetamab Q2W but was later diagnosed as having talquetamab-induced Grover's disease,

which is a rare and transient dermatosis.³⁸ With regards to nail toxicities, referral to podiatry may be required for patients who find it difficult to maintain toenail hygiene, for those who develop infections related to compromised nail beds, or for those for whom standing and wearing footwear or comfortable coverings are a challenge.

Patient Counseling/Patient Education for Dermatologic Toxicity

Patients should be advised that occurrence of rashes is expected to peak during early treatment cycles and decrease during subsequent treatment cycles, whereas occurrence of nonrash skin toxicities is expected to plateau after an initial increase during early treatment cycles. Patients should be encouraged to keep their skin clean and dry throughout the course of treatment, as well as to take short lukewarm showers and use a heavy lotion or moisturizer throughout the day,³⁹ such as soft paraffin, glycerin- and panthenol-containing healing ointments, or aqua glycolic skin cream. Additionally, patients with anhidrosis (occurring in 2 patients [1.4%], both in the 0.8 mg/kg Q2W cohort) should avoid hot weather and use misting sprays, as necessary. Patients who report photosensitivity should be encouraged to use sunscreen to ensure proper skin protection from sunlight.

For nail toxicities, patients should be made aware of nail disorders at the outset of therapy. Patients should be educated that nail toxicities may wax and wane over time and that some events may take time to resolve due to the slow nature of nail growth; overall, nail toxicities are expected to be mostly low grade and not affect treatment adherence. Based on the experience of investigators in the MonumenTAL-1 trial, some patients reported concerns regarding changes in nail appearance and nail loss. Practicing good personal general hygiene to reduce the risk of nail infections should be encouraged. Patients should also be encouraged to avoid activities that heighten the chances of nail breakages and should keep their nails short to avoid nail manipulation⁴⁰; for patients for whom frequent use of their hands is a key part of their day-to-day activities, the use of implements or aides that avoid exacerbating nail damage should be encouraged. Patients may also be advised to wear gloves overnight and when performing activities in water. Finally, it may be advisable to wear socks overnight, and comfortable shoes should be worn to avoid impacting the toenails.

Infections

i. Data from MonumenTAL-1

Infections are a key complication of MM and may be due to patient-, disease-, or treatment-related factors.⁴¹ In MonumenTAL-1, 58.7% (n = 84), 66.2% (n = 96), and 72.5% (n = 37) of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, had infections, which were grade 3/4 in 19.6%, 14.5%, and 27.5% of patients.^{7,18} The most common any-grade infections were COVID-19, upper respiratory tract infections, nasopharyngitis, urinary tract infections, bronchitis, and pneumonia.¹⁸ The most common grade 3/4 infections, defined as requiring invasive or urgent intervention per CTCAE classification, were pneumonia, urinary tract infections, COVID-19, sepsis, and cellulitis.¹⁸ Median time to onset of infections was

148.0, 108.0, and 96.0 days in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, and most high-grade infections occurred during the first 100 days of treatment (Table 2, Figure 3H, and Supplemental Figure 1G). Median duration of each infection event was 11.5, 12.0, and 12.0 days, respectively, although median duration may vary owing to the wide range of infections experienced during treatment; > 87% of infections resolved across all 3 cohorts (Table 2 and Figure 3A). Opportunistic infections occurred in 5 (3.5%) patients in the 0.4 mg/kg QW cohort (esophageal candidiasis, n = 2; adenovirus infection, fungal sepsis, and viral retinitis, all n = 1), 8 (5.5%) patients in the 0.8 mg/kg Q2W cohort (esophageal candidiasis, n = 3; adenovirus infection, herpes ophthalmic, cytomegalovirus infection, cytomegalovirus viremia, and human herpesvirus 6 infection, all n = 1), and 3 (5.9%) patients in the prior T-cell redirection cohort (esophageal candidiasis, adenovirus infection, and disseminated varicella zoster virus infection, all n = 1).¹⁸ There were no cases of pneumocystis pneumonia. Infections occurred concurrently with grade 3/4 neutropenia in 13.1%, 3.1%, and 24.3% of patients in the 3 respective cohorts. Although there was no additional decrease in immunoglobulin G (IgG) levels during talquetamab treatment, hypogammaglobulinemia by IgG was common: 64.3% (0.4 mg/kg QW), 67.6% (0.8 mg/kg Q2W), and 72.5% (prior T-cell redirection); intravenous immunoglobulin use was 14.7%, 13.1%, and 15.7%, respectively, which is lower than the rates in BCMA-targeting bispecific antibodies.^{1,3,18} Dose modifications due to infections are listed in Table 3. Infections led to discontinuation of 2 patients in the 0.4 mg/kg QW cohort and 1 patient in the prior T-cell redirection cohort. In total, 5 (1.5%) patients died from infections (COVID-19 pneumonia, n = 2; septic shock, fungal sepsis, and infection, all n = 1).¹⁸

ii. Prevention and Management

Prophylaxis for infections was commonly used in MonumenTAL-1. The prevention of herpes infections was the most common reason for prophylaxis. Acyclovir was the most common prophylactic medication, with use in 52.4% of patients in the 0.4 mg/kg QW cohort, 71.7% in the 0.8 mg/kg Q2W cohort, and 74.5% in the prior T-cell redirection cohort. Valaciclovir was the second most common form of prophylaxis, with use in 37.1%, 11.0%, and 17.6% of patients in each cohort, respectively. In patients who are deemed to have an elevated risk of developing infections, antibacterial prophylaxis may be beneficial. Antifungal prophylaxis should be considered if patients have undergone treatment with high-dose or prolonged use of corticosteroids. New-onset infections were typically observed in earlier treatment cycles, so more aggressive infection prevention management strategies may be considered during this period, particularly until cytopenias recover.¹⁸ As patients treated with talquetamab showed preservation of humoral immune function and no decreases in B cells or polyclonal IgG, vaccinations are still expected to be effective.¹⁸ However, vaccines should preferentially be given before treatment initiation, although this may not be possible in all instances, such as for annual influenza and COVID-19 vaccinations.

Testing for cytomegalovirus and Epstein–Barr virus is advisable for patients who have an unexplained fever or unexplained

symptoms, such as weight loss, extreme fatigue, and diarrhea. Monitoring for hypogammaglobulinemia and administration of intravenous immunoglobulin (IVIG) have also been recommended as key elements of preventing and managing infections during novel antibody treatment,^{41–44} including talquetamab.

In MonumenTAL-1, the most common concomitant medications given for infections are shown in Table 4; these were mostly antibiotics, although antifungal, anticholinergic, and glucocorticoid medications were also used. Relatively few infections were observed in patients treated with talquetamab compared with BCMA-targeting bispecific antibodies^{1,3}; however, as is common practice in the management of MM patients, IVIG should be considered for those patients with hypogammaglobulinemia and recurrent infections, and based on investigator experience, can be administered to patients on the same day as talquetamab after the CRS risk period has elapsed. During step-up doses and early treatment cycles, it is important to rule out CRS if a patient has a fever because symptoms associated with infections may overlap with those of CRS. Filgrastim should be considered to manage neutropenia. An important part of infection management may also be to temporarily interrupt dosing to allow the infections to resolve before continuing talquetamab.

iii. Patient counseling/patient education

Patients should be counseled on the signs and symptoms of infection and encouraged to actively report them during their treatment to ensure prompt intervention. Additionally, patients should be informed that infection prevention measures should be followed, such as nonpharmacological inventions (wearing face masks and maintaining distance) and ensuring that people they are likely to interact with are vaccinated for infectious diseases.

CRS

i. Data from MonumenTAL-1

CRS is an acute systemic inflammatory syndrome that is associated with CAR-T therapies and bispecific antibodies.^{1,3,4,7,10–13,45,46} In MonumenTAL-1, 79.0% (n = 113), 74.5% (n = 108), and 76.5% (n = 39) of patients had CRS per American Society for Transplantation and Cellular Therapy (ASTCT) criteria in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively.⁷ The rates of CRS in the MonumenTAL-1 trial are broadly comparable with rates observed with other T-cell–redirecting bispecific antibodies.^{1,3,6,7,45} Median time to onset of CRS was 25.9, 28.0, and 26.3 hours in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, and median duration of each CRS event was 14.5–20.4 hours across the 3 cohorts (Table 2). Most CRS events were grade 1/2, occurred with step-up doses and the first full dose, and almost all events resolved (Table 2, Figure 3A and I, and Supplemental Figure 1H). Patients rarely had CRS at or beyond cycle 2, with 5 patients each in the 0.4 mg/kg QW and 0.8 mg/kg Q2W cohorts and 2 patients in the prior T-cell redirection cohort having a CRS event at or beyond cycle 2. The number of patients who required dose modifications due to CRS in MonumenTAL-1 is shown in Table 3. One patient in the 0.8 mg/kg Q2W cohort discontinued treatment due to CRS;

Clinical Lymphoma, Myeloma & Leukemia

there were no CRS-related discontinuations in the 0.4 mg/kg QW or prior T-cell redirection cohorts.

ii. Management

The MonumenTAL-1-defined guidelines for managing CRS are shown in Supplemental Table 1. Supportive measures for CRS in the MonumenTAL-1 trial are shown in **Table 4** and included tocilizumab, oxygen, corticosteroids, and vasopressors, the latter of which was used rarely, consistent with the literature⁴⁷⁻⁵⁰ and protocol guidelines. Early experience with CRS led to incorporation of premedication and modifications to dosing to mitigate CRS events with T-cell–redirecting therapies. Talquetamab administration includes step-up doses before the first full dose (0.01 mg/kg and 0.06 mg/kg for step-up doses 1 and 2, respectively, for both schedules, and 0.3 mg/kg for the step-up dose 3 in the Q2W group in MonumenTAL-1, which was changed in the FDA and EMA labels to 0.4 mg/kg to ensure that the first 3 doses are the same for both dosing schedules) as well as pretreatment with a glucocorticoid, antihistamine, and antipyretic.^{7,9,19,20} Patients in MonumenTAL-1 were also required to be hospitalized for at least 48 hours from the start of each step-up dose injection and the first full dose. The entire health care team, including nurses, front-line inpatient providers, physicians in hematology-oncology, as well as emergency room physicians, hospitalists, neurologists, and intensive care unit consultants should be aware of signs and symptoms of CRS, which include fever, tachypnea, headache, tachycardia, hypotension, rash, hypoxia, and/or multi-organ system dysfunction,^{51,52} during treatment with talquetamab, particularly during step-up dosing and the first dosing cycle. During initiation of talquetamab, patients should be monitored frequently for signs of a fever ($\geq 38.3^{\circ}\text{C}$) that may suggest CRS.⁵³ It is important to distinguish early symptoms of CRS from those that may be related to infection and consider hemophagocytic lymphohistiocytosis in those patients, particularly if they have high disease burden and are not responding to initial CRS management. A detailed medical history should be taken in conjunction with physical work-up, and additional imaging may be required to rule out infection and to help differentiate CRS from other causes of fever. It is also important to distinguish CRS from injection-site reactions and systemic administration-related reactions. Once CRS has been confirmed, the patient should be monitored closely and treated per institutional protocols, CRS treatment guidelines and the label.^{19,20,54,55}

Talquetamab treatment should be held until CRS has fully resolved and in cases of severe CRS, discontinuation may be considered. Treatment with these measures was effective based on the experience in MonoumenTAL-1. Tocilizumab use reduced the likelihood of CRS recurrence. Across the 3 cohorts, 23-26% of patients treated with tocilizumab had a subsequent CRS event compared with 42-52% of patients who did not receive tocilizumab. However, the effect of prophylactic use of tocilizumab before commencing talquetamab on the incidence of CRS has not been assessed. The timing of intervention for CRS depends on several factors, including whether patients have high tumor burden, other comorbidities, or frailty⁵²; for these patients, close monitoring and urgent care for any signs or symptoms of CRS is required. Management of patients who develop severe CRS requires multidepartmental

collaboration between hematology/oncology, neurology, radiology, and critical care units⁵²; however, based on experiences with talquetamab in MonumenTAL-1, these cases are expected to be rare. With talquetamab, almost all events fully resolved with appropriate and timely management.

iii. Patient counseling/patient education

Patients should be made aware of the symptoms of CRS and should be encouraged to report them to their health care teams, particularly during step-up dosing and the first dosing cycle. Patients should also be advised that management strategies for CRS are effective.

ICANS

i. Data from MonumenTAL-1

ICANS is a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.⁵⁶ In MonumenTAL-1, ICANS was graded per ASTCT criteria, based on the most severe event experienced, including depressed level of consciousness, seizures, motor findings, raised intracranial pressure, intraocular pressure, or cerebral edema, and immune effector cell-associated encephalopathy (ICE) score. In total, 10.7% (n = 13), 11.0% (n = 12), and 2.9% (n = 1) of patients had ICANS in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively (ICANS was reported only in phase 2 of the MonumenTAL-1 study).⁷ Most cases of ICANS were observed concurrently with CRS (66.7%, 66.7%, and 100.0% in each cohort, respectively). In each of the 3 respective cohorts, 4.1%, 3.7%, and 2.9% of patients had serious ICANS. Median time to onset of ICANS was 23.6, 31.9, and 115.5 hours in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, and median duration of each ICANS event was 7.8-48.5 hours across the 3 cohorts (**Table 2**). Most events were grade 1/2, occurred during step-up dosing or the first full dose, and most events resolved (**Table 2**, **Figure 3A** and J, and Supplemental Figure 1I). Two patients each in the 0.4 mg/kg QW and 0.8 mg/kg Q2W cohorts required dose modifications due to ICANS (**Table 3**). In total, 2 patients in the 0.4 mg/kg QW and 1 patient in the 0.8 kg/mg Q2W cohorts discontinued due to ICANS.

ii. Management

The MonumenTAL-1-defined guidelines for managing ICANS per ICE score are shown in Supplemental Table 2. The list of supportive measures given to patients to manage ICANS is shown in **Table 4** and are consistent with those listed in the literature, including corticosteroids, tocilizumab, levetiracetam, and anakinra.⁴⁹ Due to the overlapping symptoms, the differential diagnosis of ICANS often involves infections, stroke, seizures, intracranial hemorrhage, or progression in the central nervous system.⁵⁷ ICANS typically develops in patients who have CRS, usually after the first fever, but can also develop independently of CRS or after CRS resolution.⁵⁶ For isolated ICANS, corticosteroids have been suggested as the first-line therapy, whereas tocilizumab and corticosteroids have been advised for cases that are concurrent with CRS (Supplemental Table 2).⁴⁹ For grade 1 events, which are expected to

resolve quickly with supportive care, close monitoring is advised while other potential etiologies for symptoms are excluded by diagnostic tests.⁴⁹ Corticosteroids are used routinely for grade ≥ 2 events.⁴⁹ Severe cases of ICANS should be treated in a critical care unit and should include potential airway protection by intubation as well as neurology consultation. In cases where there are signs of cerebral edema, elevation of the head and hyperosmolar therapy with mannitol or hypertonic saline and hyperventilation are advised, together with high-dose corticosteroids.⁴⁹ For patients with a history of seizures or central nervous system disease, primary seizure prophylaxis is advised with levetiracetam.⁴⁹ Based on experience with talquetamab in MonumenTAL-1, severe ICANS events are expected to be rare and resolve with appropriate and timely management.^{7,9,19,20}

iii. Patient counseling/patient education

Patients and caregivers should be educated on the symptoms of ICANS, which include aphasia, altered level of consciousness, agitation, delirium, encephalopathy, impairment of cognitive skills, lethargy, and motor weakness. Caregivers should be advised to check for these symptoms, particularly during early treatment cycles. Patients receiving talquetamab should also be advised that ICANS symptoms are most likely to develop during hospitalized doses, be mostly transient, and typically resolve quickly.

Other Clinical Considerations

Rare Adverse Events. In MonumenTAL-1, several AEs occurred rarely but are of clinical significance. Health care teams should be aware that these events may occur in rare instances during talquetamab treatment. Grade 3/4 tumor lysis syndrome occurred in 1 patient with a bone marrow plasma cell percentage of 90% via biopsy and 60% via aspirate in the 0.8 mg/kg Q2W cohort. Prophylaxis with hydration and rasburicase may be beneficial for patients deemed to be at high risk of developing tumor lysis syndrome, such as those with high tumor burden or renal impairment. One patient had hemophagocytic lymphohistiocytosis in the prior T-cell redirection cohort, which was grade 2. Consistent with the GPRC5D expression profile, alopecia occurred in 7.0%, 10.3%, and 7.8% of patients in the 0.4 mg/kg QW, 0.8 mg/kg Q2W, and prior T-cell redirection cohorts, respectively, which were mostly grade 1, with no grade 3/4 events. Facial hair loss was observed in some patients; however, no clinical intervention was required, and no patients discontinued due to alopecia. One patient treated in the 0.8 mg/kg Q2W cohort had any-grade ataxia; however, cerebellar toxicities have been reported more frequently with CAR-T therapies compared with bispecific antibodies.¹⁰ Health care teams should also be aware that potential immune-mediated AEs have been reported by investigators, such as pneumonitis, colitis, hypophysitis, and hypothyroidism. Lastly, physicians should be aware of the need to manage anemia and other nutritional deficiencies, although a causative relationship to talquetamab has not been established.

Tumor Flare and Pseudoprogression. Tumor flare reaction is a clinical syndrome that is caused by an influx of T cells into tumor sites.^{58,59} Symptoms may be similar to those associated with early disease progression, such as bone pain.^{58,59} Radiologic

imaging may show pseudoprogression, a phenomenon associated with immunotherapies, including checkpoint inhibitors and T-cell redirection therapies, in which an increase in tumor size may occur due to the influx of immune cells.⁶⁰⁻⁶² This has been observed with talquetamab. In a case report of a 61-year-old woman with RRMM who had a single osteolytic hypermetabolic focal bone lesion treated with talquetamab, 2-[18 F]FDG positron emission tomography/computed tomography (PET/CT) imaging showed early tumor flare at Day 28; however, at Day 84, bone marrow aspirate, M-component assessment, and 2-[18 F]FDG PET/CT demonstrated complete response.⁶⁰ Pseudoprogression, and thus tumor flare reactions, can be misinterpreted in the clinic as disease progression or AEs, such as bone pain, and lead to early discontinuation of a drug, resulting in poor patient outcomes.⁶¹ Treatment for tumor flare reactions should include management of the associated pain with analgesics, including opioids, and corticosteroids to control MM- and inflammation-related symptoms.⁵⁸ Tumor flare reactions should be confirmed before adjusting the treatment regimen to ensure patients remain on effective therapy.⁶⁰ For talquetamab, worsening pain during step-up or early doses should prompt repeat disease assessment. A reduction in the serum free light-chain ratio, with worsening pain or imaging findings showing increased tumor size, should provide reassurance that the patient is in response and the associated pain or imaging results are likely due to robust T-cell infiltration at focal disease sites.

Practical Administration of Talquetamab

In MonumenTAL-1, talquetamab administration was proceeded by step-up dosing to mitigate against the risk of severe CRS, as outlined in the CRS section.^{7,9,19,20} Patients are encouraged to carry wallet cards or medical identification cards so as to be identifiable to health care professionals as undergoing talquetamab treatment, to mitigate the risks of infections, ICANS, and CRS. Patient education will be an important component of effectively preparing patients for the AEs that they are likely to experience during talquetamab treatment. The patient's health care team, including nurses, will be instrumental in supporting patients throughout their treatment journey and will therefore require education of talquetamab-associated AEs. Crucially, knowing what to expect will allow patients to report symptoms immediately and health care teams to manage AEs effectively, thereby ensuring treatment adherence and maintaining patients' quality of life.

Discussion

Talquetamab is a novel therapy providing deep and durable responses in patients with RRMM.^{7,9} Although patients treated with talquetamab report sustained clinically meaningful improvements in health-related quality of life, a proportion of patients are expected to have a more difficult time remaining on therapy due to the AEs described here.³⁷ Although GPRC5D-associated AEs were often low grade, these toxicities still negatively affect quality of life and require timely management. With the management strategies described here, GPRC5D-associated AEs were not treatment limiting, led to few discontinuations, and generally did not require specialist referral (Supplementary Table 3). Additionally, as median time to response was 1.1-1.3 months with talque-

Clinical Lymphoma, Myeloma & Leukemia

tamab in MonumenTAL-1, a dose may be omitted and then reduced to mitigate the effect of GPRC5D-associated AEs; responses were maintained in patients who prospectively and retrospectively reduced dose intensity in MonumenTAL-1, providing support for dose reduction strategies.³¹ Given the efficacy observed with talquetamab, most patients are expected to experience improvements in quality of life during over the course of treatment. For patients who experience more severe AEs, the strategies outlined should help to maintain patient quality of life during treatment.^{31,37}

Oral events, such as dysgeusia, were not anticipated when clinical trials of agents targeting this novel antigen began, as GPRC5D expression in the oral cavity is limited to the filiform papillae of the tongue.^{9,28} During the phase 1 dose-escalation phase of MonumenTAL-1, only a few oral events were reported; however, based on clinical experience in MonumenTAL-1 and other trials of GPRC5D-targeting agents,^{7,9-11,13,45} dysgeusia is a commonly reported AE with these agents, suggesting that it may be dose-related and an on-target off-tumor AE. As oral AEs were not expected at the time of trial initiation, many of the current tools to assess these events are rudimentary, and the grading or grouping of these AEs are not standardized across sites and clinical trials. Further work is required to understand the pathophysiology of oral events, which may be facilitated by taking biopsies of the tongue and/or salivary glands during treatment with T-cell–redirecting GPRC5D-targeting therapies, and to better characterize the symptoms and patient experience of these events. Based on the experiences from MonumenTAL-1, dose modifications may be the most effective strategy to manage oral events. For other AEs related to GPRC5D expression, skin toxicities generally started within the first month of treatment and were managed with the early use of emollients and hydration, followed by topical or oral corticosteroids. Nail toxicities often appeared within 2 months of treatment initiation, were generally cosmetic in nature (not severe or painful), tended to persist throughout treatment, and were commonly managed with emollients.

CRS was the most common AE associated with talquetamab and was managed based on published guidelines, including the use of tocilizumab. Data from MonumenTAL-1 underline the importance of preemptive step-up dosing, premedication, and prompt intervention for the management of CRS.^{7,9} With these measures, almost all patients fully recovered from CRS in MonumenTAL-1. ICANS is also associated with T-cell redirection therapies, including talquetamab, and often occurred in association with CRS. The incidence, severity, time to onset, and duration of ICANS was broadly consistent with approved BCMA-directed T-cell redirecting therapies.^{1,3,5,6,63} ICANS was generally transient and reversible based on the data from MonumenTAL-1. Infection rates, particularly high-grade and fatal events, were lower with talquetamab compared with BCMA-targeting T-cell–redirecting therapies.^{1,3,7} Most infections in MonumenTAL-1 were grade 1/2; however, all infections affect the burden of disease generally and patient quality of life,^{64,65} and require general preventative measures, close monitoring and management to prevent symptoms from worsening.

Overall, the safety profile of talquetamab does not overlap with other antimyeloma therapies,^{1-6,66} and is manageable with the strategies outlined, suggesting that it may be a versatile combina-

tion partner, which has been demonstrated by combinations with daratumumab, teclistamab, and pomalidomide.⁶⁷⁻⁶⁹

Conclusion

AEs associated with talquetamab are distinct but clinically manageable with appropriate education and support. In some patients the occurrence of GPRC5D-associated AEs either persisted over the course of treatment or reoccurred multiple times. However, for a substantial proportion of patients, these events are expected to improve over time and may become more tolerable when disease control is achieved^{7,70} due to the possibility of implementing dose modifications, which are under investigation.³¹ It is important to note that the current experience of talquetamab is based on clinical trial patients, and not those who will enter the clinic in real-world settings. Health care practitioners should be cognizant of new AEs that may be observed in real-world settings.

CRediT authorship contribution statement

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Disclosure

Ajai Chari reports a consulting/advisory role for AbbVie, Antogene, Bristol Myers Squibb, Genentech, Genzyme, GlaxoSmithKline, Janssen Oncology, Karyopharm Therapeutics, Oncopeptides, Seagen, Secura Bio, Shattuck Bio, Shattuck Labs, and Takeda; and has received research funding from Amgen, Celgene, Janssen, Pharmacyclics, Seagen, and Takeda. Amrita Krishnan reports a consulting/advisory role for Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Pfizer, and Regeneron; has served in a leadership role for Sutro Biopharma; has served on speakers' bureaus for Amgen, Celgene, and Takeda; has stock/other ownership interests in Bristol Myers Squibb; and has received research funding from Janssen. Leo Rasche has received honoraria from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, and Sanofi; reports a consulting or advisory role with Bristol Myers Squibb, Janssen, GlaxoSmithKline, Pfizer, and Sanofi; and has received research funding from Bristol Myers Squibb and SkylineDx. Jing Christine Ye reports a consulting or advisory role for Bristol Myers Squibb, Sanofi and Janssen; and has received research funding from Celgene, Genmab, GlaxoSmithKline, MingSight, Novartis, Pfizer, and Regeneron. Alfred Garfall reports a consulting/advisory role for Amgen, CDR-Life, GlaxoSmithKline, and Janssen; has patents, royalties, other intellectual property in the field of CAR-T cell therapy; has stock/other ownership interests in Cabaletta Bio; and has received research funding from CRISPR Therapeutics, Janssen, Novartis, and Tmunity Therapeutics, Inc. Rakesh Popat reports a consulting/advisory role for BeiGene, Celgene, GlaxoSmithKline, Janssen, and Roche; has received travel, accommodations, and expenses from GlaxoSmithKline and Janssen; received honoraria from AbbVie, Celgene, GlaxoSmithKline, Janssen, and Sanofi; and has received research funding from GlaxoSmithKline. Brea Lipe reports a consulting or advisory role with Bristol Myers Squibb, GlaxoSmithKline, Janssen Oncology, Karyopharm Therapeutics, Sanofi, and Takeda; and has received research funding from Amgen, Celgene, Celllectar, Janssen, Karyopharm Therapeutics, and Seagen. Xiang Qin is an employee of Janssen Research and Development and reports stock and other ownership interests in Johnson & Johnson/Janssen. Michela Campagna is an employee of Janssen Research and Development and reports stock and other ownership interests in Johnson & Johnson/Janssen. Tara Masterson is an employee of Janssen Research and Development and reports stock and other ownership interests in Johnson & Johnson. Chalmer Tomlinson is an employee of Janssen Research and Development. Brandi Hilder is an employee of Janssen Oncology and reports stock and other ownership interests in Johnson & Johnson/Janssen. Jaszianne Tolbert is an employee of Johnson & Johnson and reports stock and other ownership in Johnson & Johnson; and has received research funding from Janssen Research and Development. Thomas Renaud is an employee of Janssen Oncology and reports stock and other ownership interests in Johnson & Johnson/Janssen. M. Damiette Smit was an employee of Janssen Research and Development at the time this work was performed, is a current employee of

Enliven Therapeutics; and reports patents at Janssen Research and Development/Janssen and Amgen. Kathleen Gray is an employee of Janssen Oncology and reports stock and other ownership interests in Johnson & Johnson/Janssen. Colleen Kane is an employee of Janssen Oncology and reports stock and other ownership interests in Johnson & Johnson/Janssen. Christoph Heuck is an employee of Janssen Research and Development; reports stock and other ownership interests in Janssen Research and Development; and reports patents, royalties, and other intellectual property in Janssen Research and Development. Niels WCJ van de Donk has received research funding from Amgen, Bristol Myers Squibb, Celgene, Celllectis, Janssen, and Novartis; and reports a consulting or advisory role with AbbVie, Adaptive Biotechnologies, Amgen, Bayer, Bristol Myers Squibb, Celgene, Janssen, Novartis, Pfizer, Roche, Servier, and Takeda.

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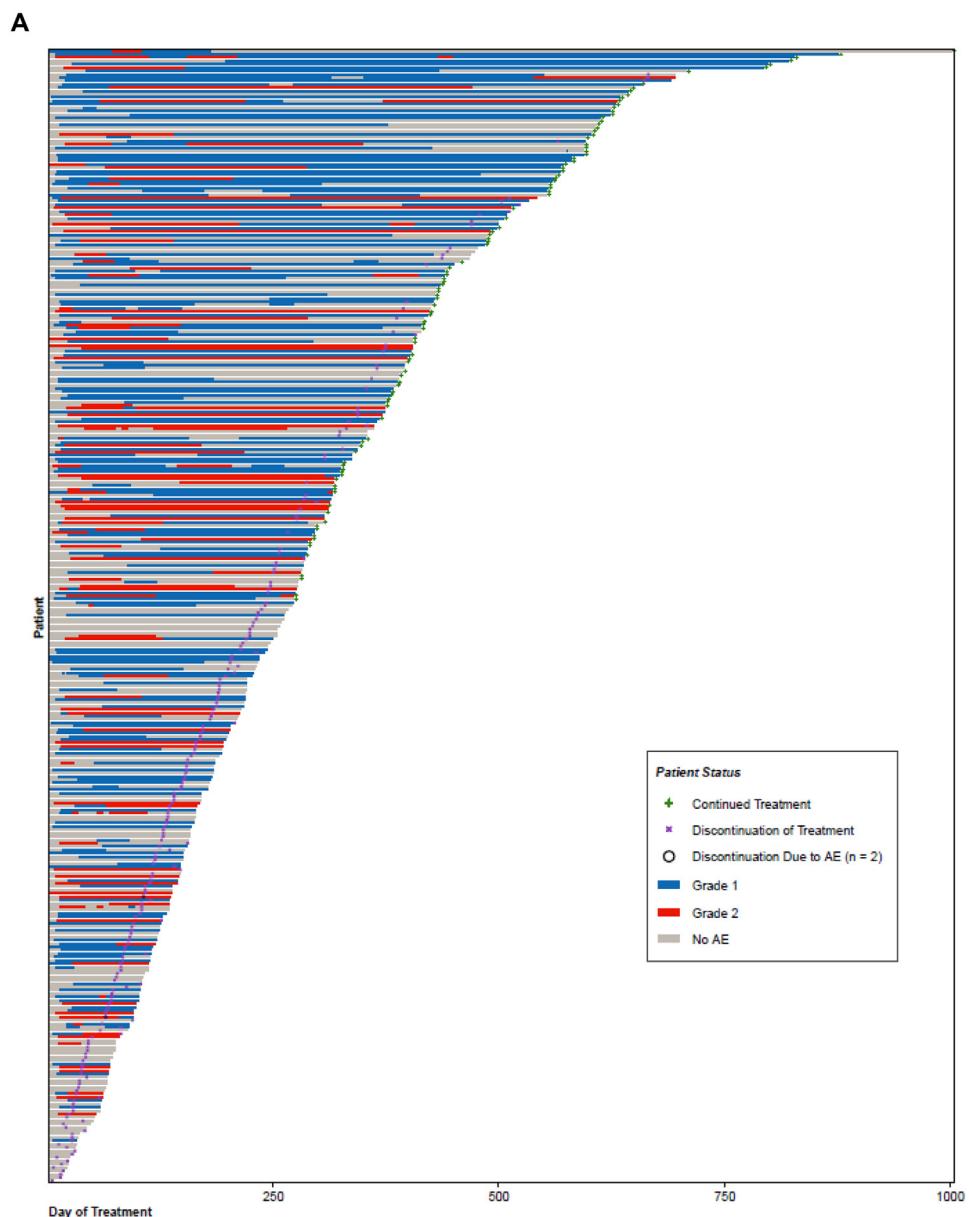
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Supplementary material

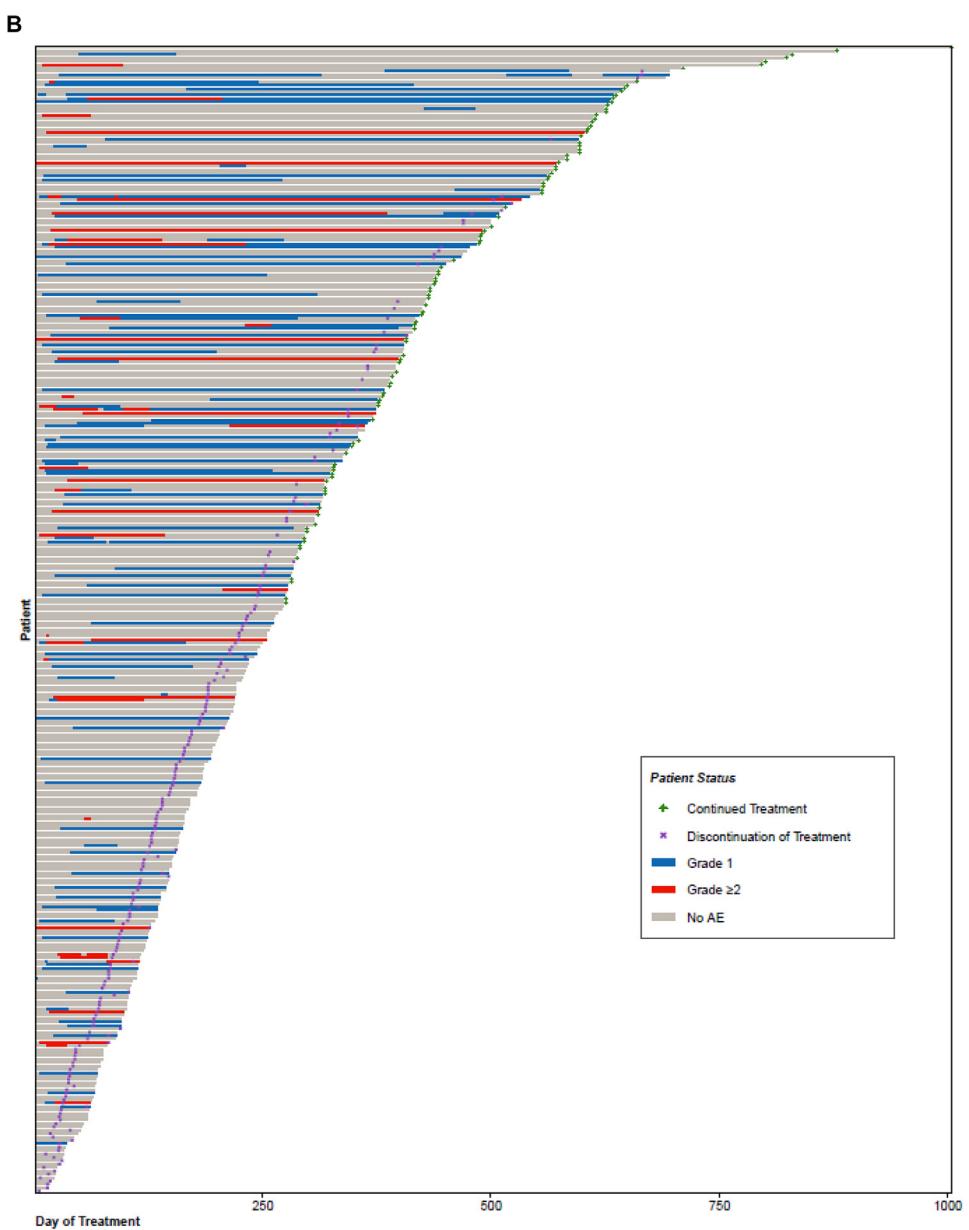
Supplementary Figure 1

Course of (A) dysgeusia, (B) dry mouth, (C) dysphagia, (D) rashes, (E) nonrash skin toxicities, (F) nail toxicities, (G) infections, (H) CRS, and (I) ICANS in individual patients who did and did not experience each adverse event during treatment.

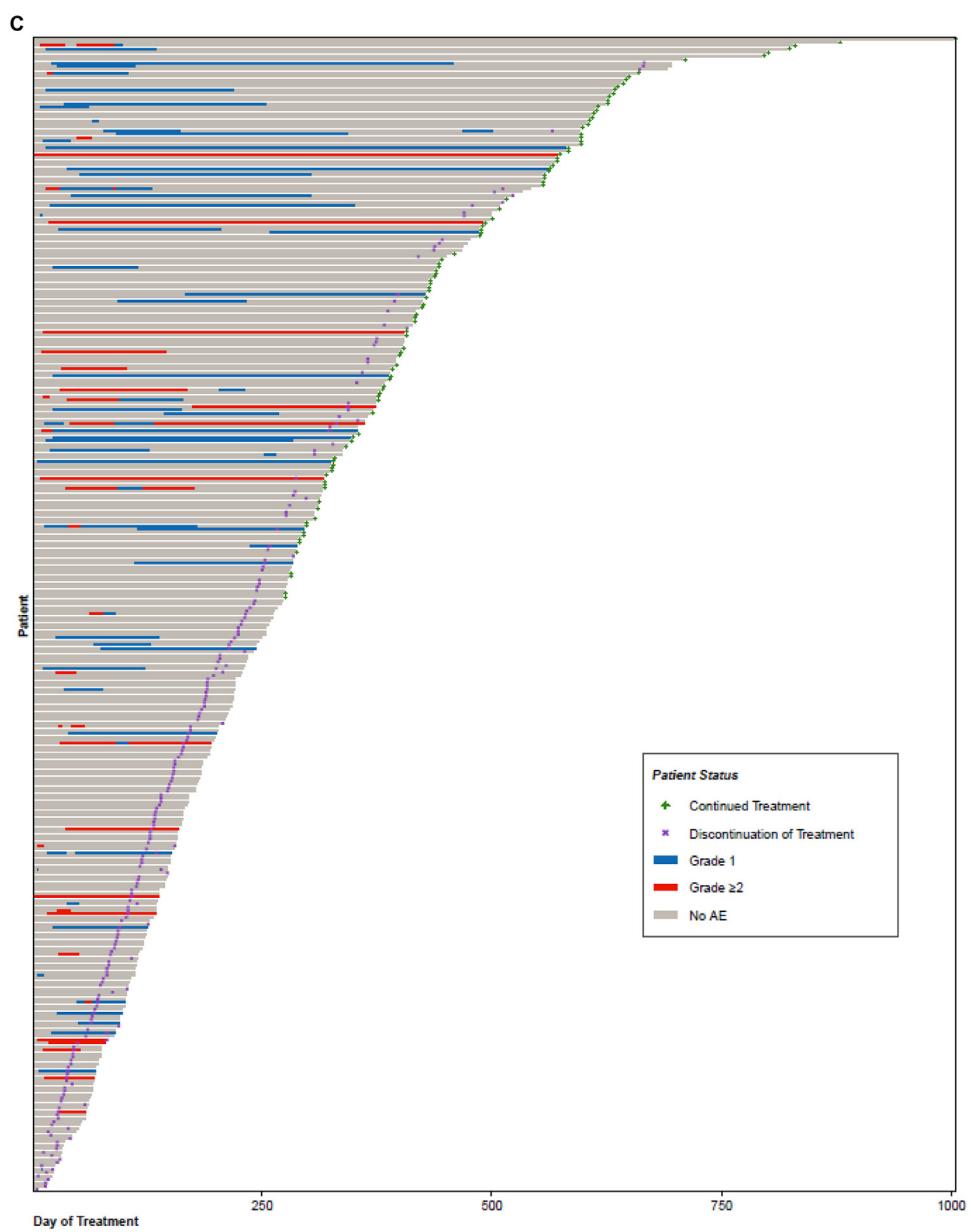
Abbreviations: AE = adverse event; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome.



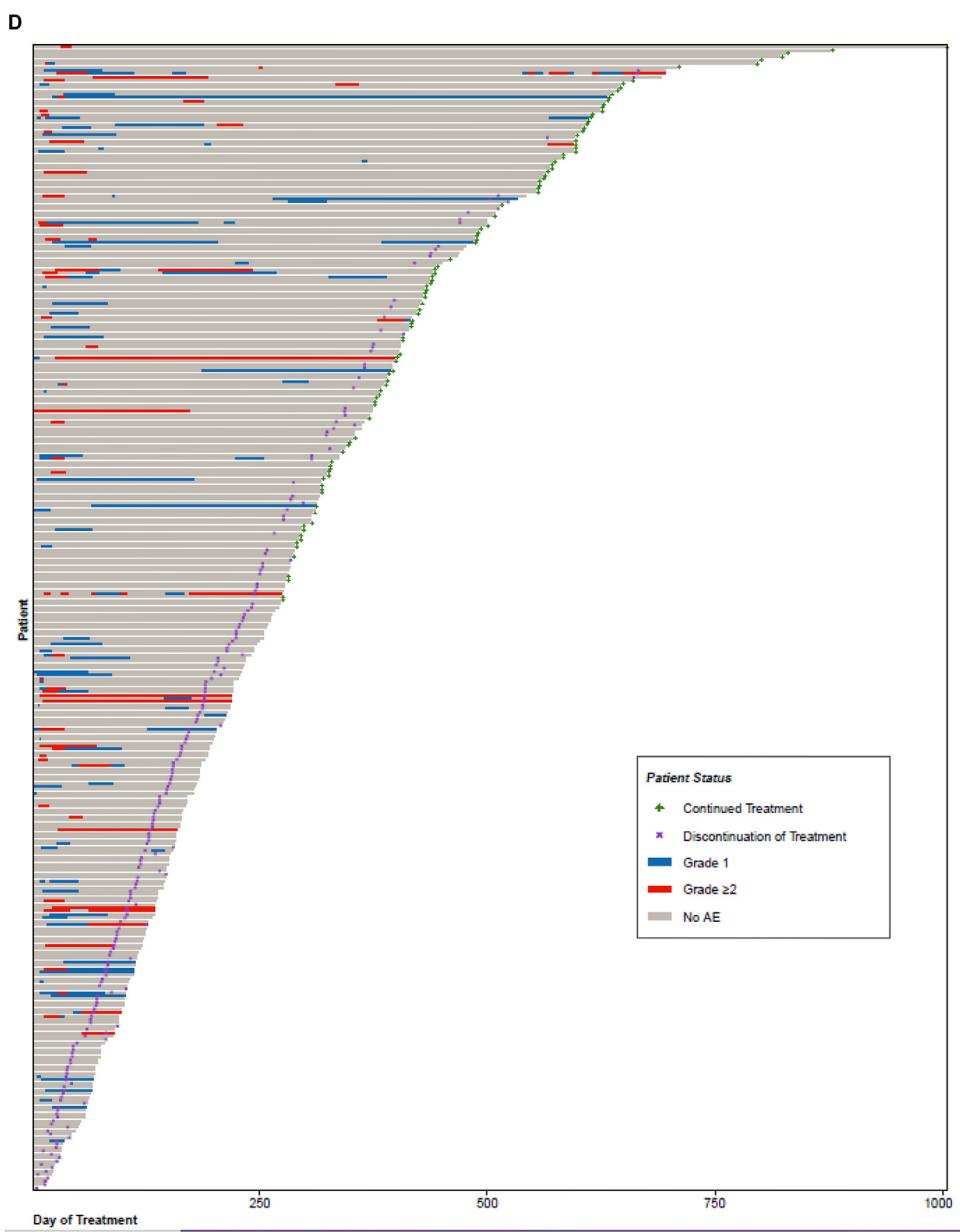
Supplementary Figure 1 | Continued



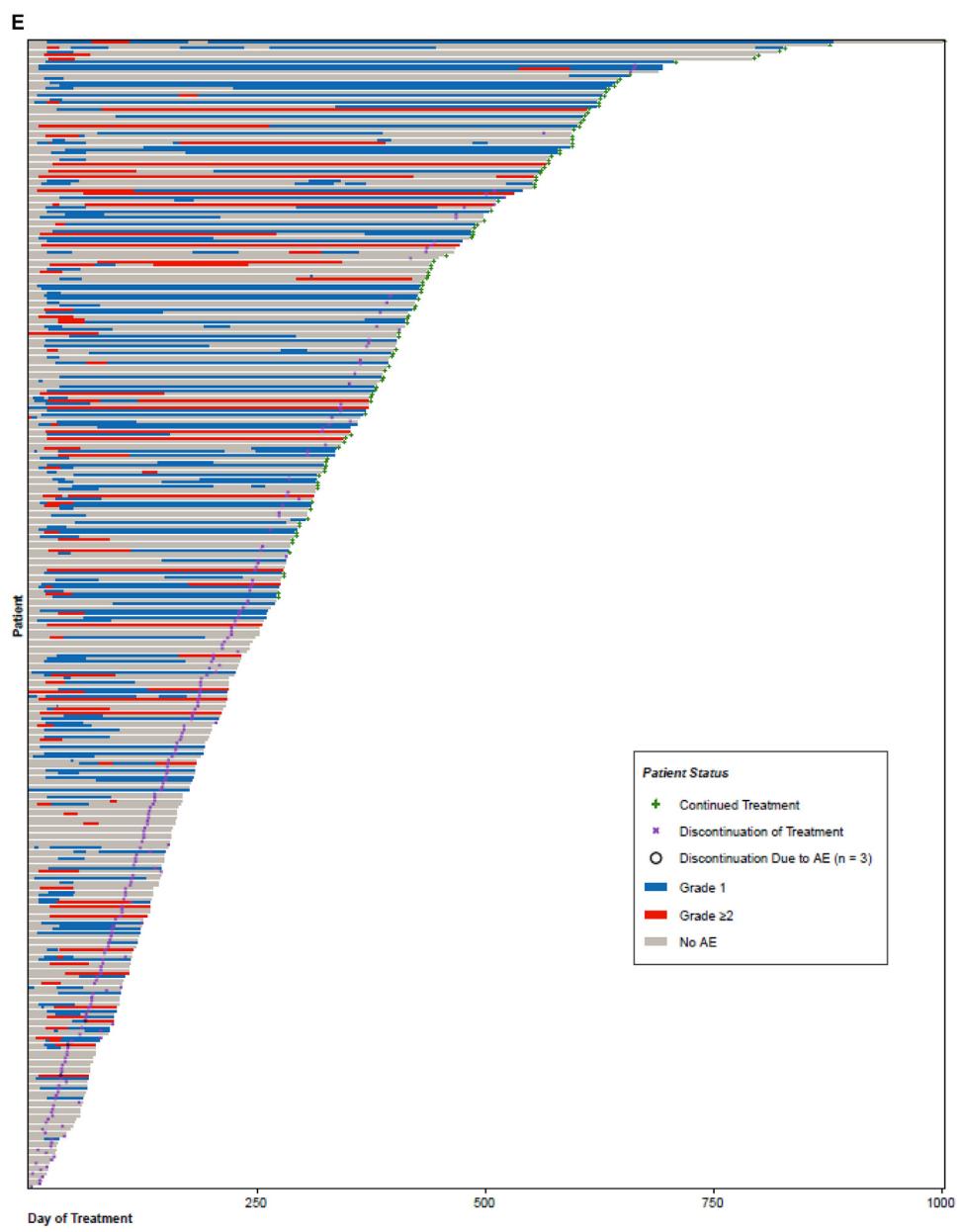
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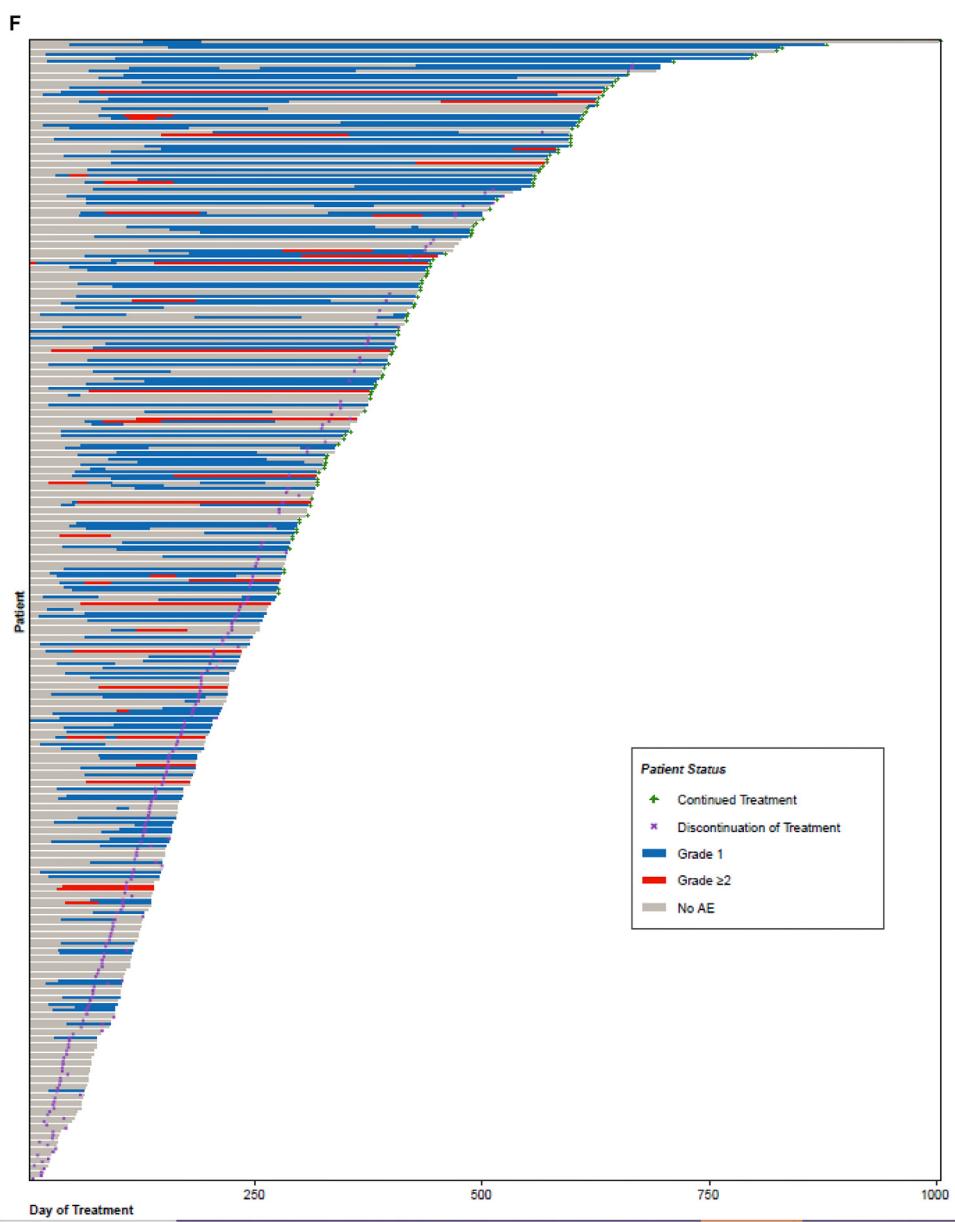
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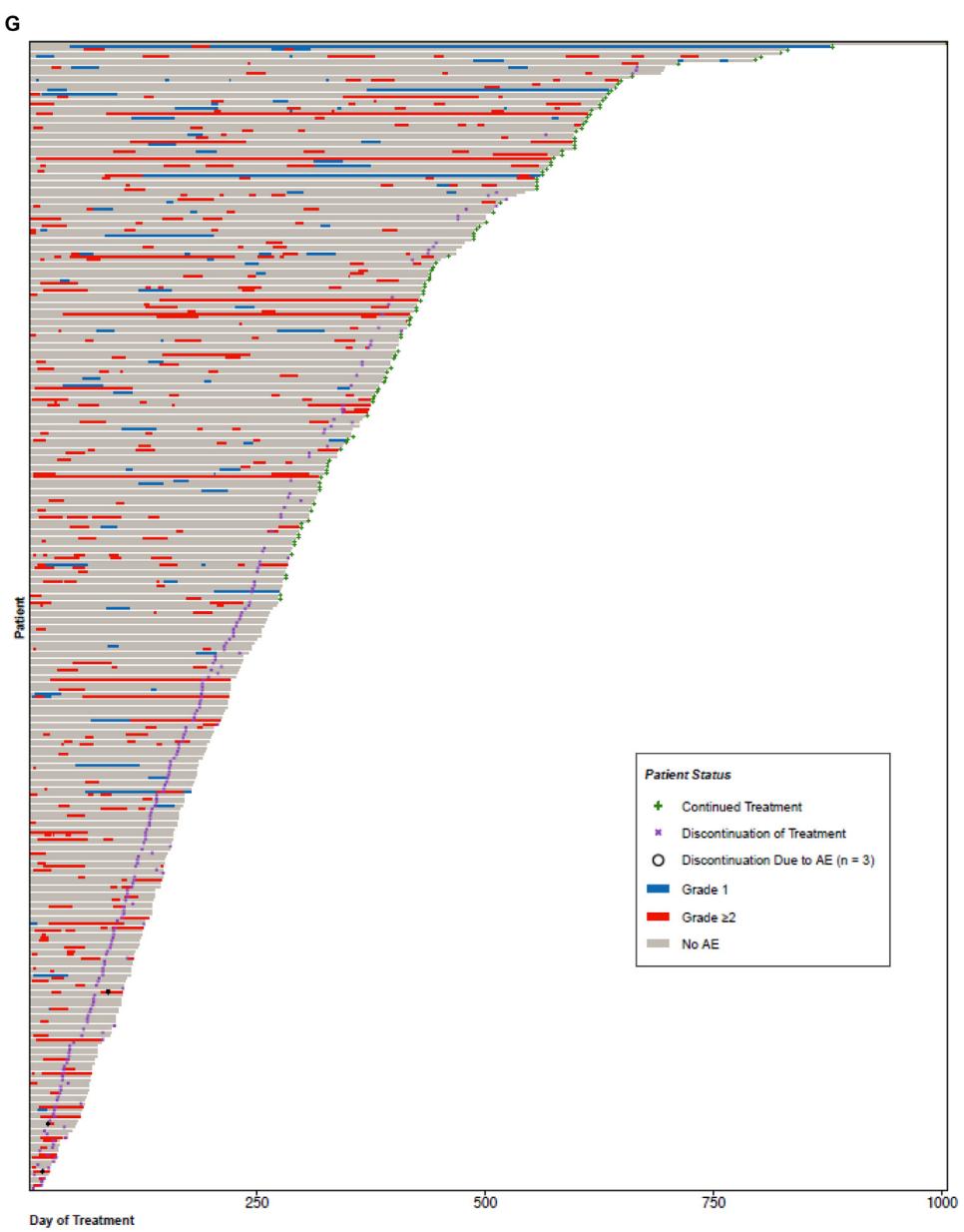
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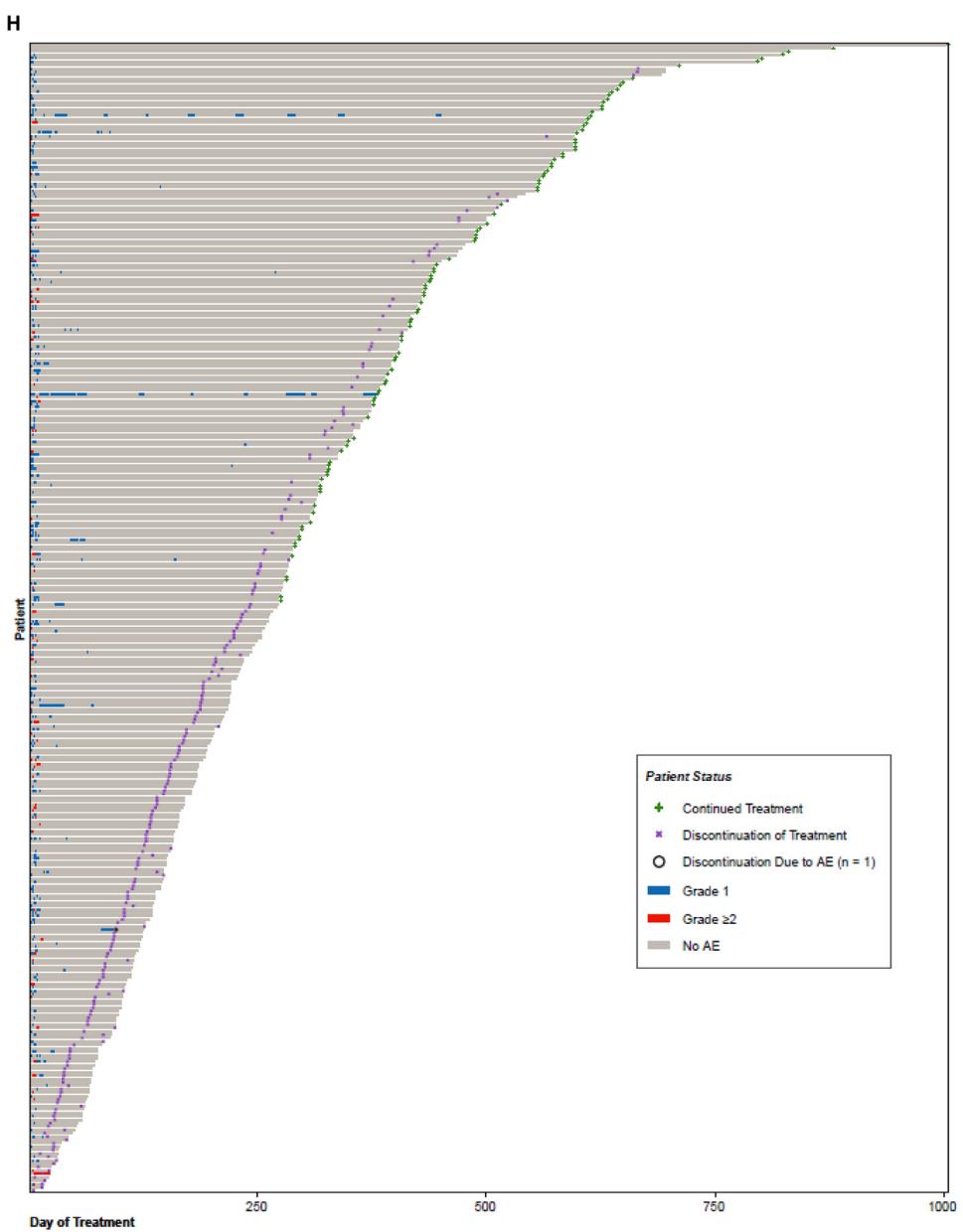
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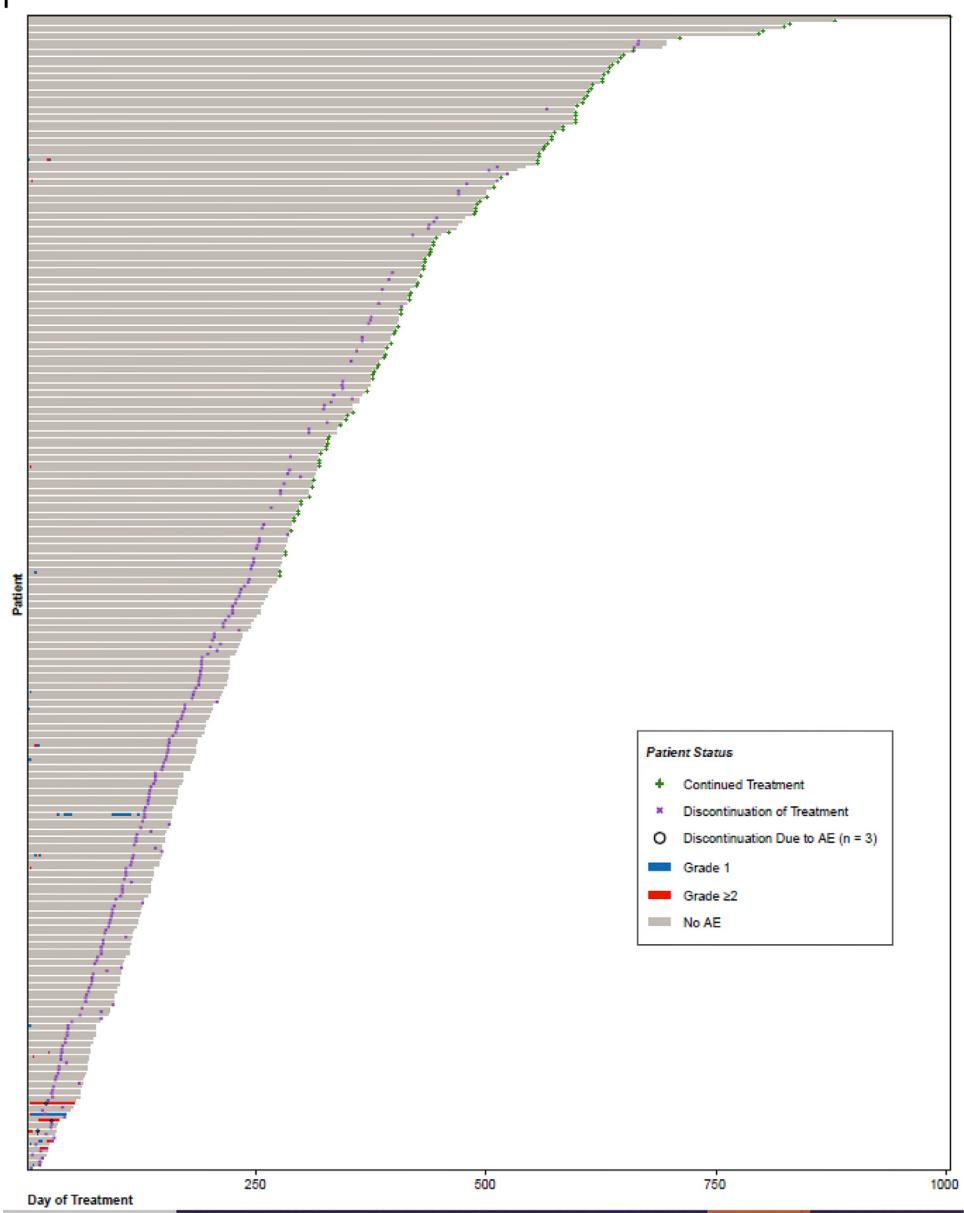


Table S1 Guidelines for the Management of Cytokine Release Syndrome as Defined in the MonumenTAL-1 Clinical Protocol.

Presenting Symptoms	Treatment Options	
	Tocilizumab	Corticosteroids
Temperature $\geq 38^{\circ}\text{C}$ ^a Temperature $\geq 38^{\circ}\text{C}$ ^a with either: hypotension responsive to fluids and not requiring vasopressors, or oxygen requirement of low-flow nasal cannula ^b or blow-by	May be considered Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses	Not applicable Manage per guidance below if no improvement within 24 hours of starting tocilizumab
Temperature $\geq 38^{\circ}\text{C}$ ^a with either: hypotension requiring 1 vasopressor with or without vasopressin, or oxygen requirement of high-flow nasal cannula ^b , facemask, non-rebreather, or venturi mask	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses	If no improvement, administer methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone (eg, 10 mg IV every 6 hours). Continue corticosteroids use until the event is grade 1 or less, then taper over 3 days
Temperature $\geq 38^{\circ}\text{C}$ ^a with either: hypotension requiring multiple vasopressors (excluding vasopressin), or oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses	As above or administer methylprednisolone 1000 mg IV per day for 3 days per investigator discretion. If no improvement or if condition worsens, consider alternative immunosuppressants ^c

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; IV = intravenous.

^a Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (eg, tocilizumab or steroids).

^b Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is > 6 L/min.

^c Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

Table S2 Guidelines for the Management of Immune Effector Cell-Associated Neurotoxicity Syndrome as Defined in the MonumenTAL-1 Clinical Protocol.

Presenting Symptoms	Treatment Options	
	Concurrent With CRS	Not Concurrent With CRS
ICE score 7-9 ^a or depressed level of consciousness ^b : awakens spontaneously	Management of CRS as appropriate. Monitoring of neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion	Monitor neurologic symptoms and consider neurology consultation and evaluation, per investigator discretion
ICE score 3-6 ^a or depressed level of consciousness ^b : awakens to voice	Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis Administer tocilizumab per management guidelines for CRS. If no improvement after starting tocilizumab, administer dexamethasone 10 mg IV every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is grade 1 or less, then taper	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is grade 1 or less, then taper
ICE score 0-2 ^a or depressed level of consciousness ^b : awakens only to tactile stimulus or seizures ^b either: <ul style="list-style-type: none">• Any clinical seizure, focal or generalized, which resolves rapidly, or• Nonconvulsive seizures on EEG that resolve with intervention, or• Raised ICP: focal/local edema on neuroimaging^b	Administer tocilizumab per management guidelines for CRS. In addition, administer dexamethasone 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is grade 1 or less, then taper	Administer dexamethasone 10 mg IV every 6 hours. Continue dexamethasone use until the event is grade 1 or less, then taper
ICE score 0 ^a or depressed level of consciousness ^b either: <ul style="list-style-type: none">• Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or• Stupor or coma, or seizures^b, either:• Life-threatening prolonged seizure (> 5 min), or• Repetitive clinical or electrical seizures without return to baseline in between, Or motor findings ^b : <ul style="list-style-type: none">• Deep focal motor weakness such as hemiparesis or paraparesis, Or raised ICP/cerebral edema ^b , with signs/symptoms such as: <ul style="list-style-type: none">• Diffuse cerebral edema on neuroimaging, or• Decerebrate or decorticate posturing, or• Cranial nerve VI palsy, or• Papilledema, or• Cushing's triad	Administer tocilizumab per management guidelines for CRS. As above, or consider administration of methylprednisolone 1000 mg IV per day with first dose of tocilizumab and continue methylprednisolone 1000 mg IV per day for 2 or more days, per investigator discretion	As above, or consider administration of methylprednisolone 1000 mg IV per day for 3 days; if improves, then manage as above
	Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists (ie, intensivists) for further evaluation, as needed. In case of raised ICP/cerebral edema: <ul style="list-style-type: none">• Elevate head of patient's bed to an angle of 30 degrees• If patient has Ommaya reservoir, drain cerebrospinal fluid to target opening pressure of < 20 mmHg• Hyperventilation to achieve target PaCO₂ of 28 to 30 mmHg but maintained for no longer than 24 hours• Consider neurology and/or neurosurgery consultation• Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended above• Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%)• Consider IV anesthetics for burst-suppression pattern on electroencephalography	

Abbreviations: CRS = cytokine release syndrome; EEG = electroencephalogram; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; IV = intravenous.

^a If patients are arousable and able to perform mental status assessment, the following domains should be tested: orientation, naming, following commands, writing, and attention.

^b Attributable to no other cause.

Table S3 Summary of Guidance for GPRC5D-Associated Adverse Events Compared With the United States FDA Label and EMA Summary of Product Characteristics.

AE of Interest	Management Guidelines per FDA Label and EMA Summary of Product Characteristics		Management Advice per Investigator Experience
	FDA	EMA	
Oral Toxicity and Weight Loss Grade 1/2	<ul style="list-style-type: none"> Provide supportive care Consider withholding talquetamab if not responsive to supportive care 	<ul style="list-style-type: none"> Supportive care may include saliva stimulating agents, corticosteroid mouth wash, or consultation with a nutritionist Weight change should be monitored regularly during therapy Interrupt talquetamab until stabilization or improvement, and consider restarting on modified schedule 	<p>Dysgeusia</p> <ul style="list-style-type: none"> Consider dose modification strategies, including reductions, delays, or skips Salivary stimulants may be considered and adequate hydration should be maintained Consider enhancement of food with spicy, sour, or other aromatic flavor additives, ensuring overall dietary needs or preferences <p>Dry mouth</p> <ul style="list-style-type: none"> Consider initiation of increased hydration (sipping water throughout the day) and intraoral topical agents, such as topical saliva sprays or sugar-free chewing gum, to stimulate saliva flow Patients who develop dry mouth resulting from stomatitis should be encouraged to use sodium lauryl sulphate-free toothpastes and corticosteroid mouthwash Consider dose modification strategies, including reductions, delays, or skips <p>Dysphagia</p> <ul style="list-style-type: none"> Consider use of frequent intake of liquids, particularly while consuming food, and use of artificial saliva Consider advising patients to take smaller bites of food and encourage experimentation with foods with different textures Consider dose modification strategies, including reductions, delays, or skips Specialist referral to gastroenterology may be advisable to rule out other upper aero-digestive track abnormalities, such as candida esophagitis or cytomegalovirus infections, for patients who have high-grade or increasingly severe dysphagia or an event that is unresponsive to oral treatments or dose modifications Specialist referral may also be advisable if other symptoms develop that suggest a structural or neuromuscular cause of dysphagia <p>Weight loss</p> <ul style="list-style-type: none"> Consider initiation of nutritional monitoring Nutritional support is encouraged, with use of vitamins, minerals, and high caloric shakes to help maintain weight <p>General guidance for oral events</p> <ul style="list-style-type: none"> Early referral to a dietitian or nutritionist at the onset of therapy should be encouraged to provide guidance on maintaining a balanced diet and weight, irrespective of the presence of oral events Routine dentist visits, including regular cleanings, should be maintained due to the increased risk of dental/periodontal disease and oral mucosa issues associated with dry mouth and other oral AEs Patients with weight loss may require adjustments to weight-based medications; this is particularly important for anti-hypertensive, diabetes, and thyroid medications

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Table S3 (continued)

AE of Interest	Management Guidelines per FDA Label and EMA Summary of Product Characteristics		Management Advice per Investigator Experience
	FDA	EMA	
Grade 3	<ul style="list-style-type: none"> Withhold talquetamab until resolution to grade 1 or better and provide supportive care 		
Grade 4	<ul style="list-style-type: none"> Permanently discontinue talquetamab 		
Patient counseling	<ul style="list-style-type: none"> Discuss the signs and symptoms of oral toxicities including dysgeusia, dry mouth, dysphagia, and stomatitis Counsel patients to seek medical attention should signs or symptoms of oral toxicity occur Advise patients that they may experience weight loss and to report weight loss Advise patients that they may be referred to a nutritionist for consultation 	<ul style="list-style-type: none"> Patients should be counseled to seek medical attention should signs or symptoms of oral toxicity occur 	<ul style="list-style-type: none"> Inform patients that they should report taste disturbances, changes in appetite, or other oral events during treatment Given the median time to response and emerging data showing maintenance of response with dose modification strategies, patients should be informed that if dysgeusia or an oral event is affecting their quality of life, a dose may be omitted and then reduced
Dermatologic AEs			
Grade 1/2	<ul style="list-style-type: none"> Monitor for skin toxicity, including rash progression Consider early intervention and treatment to manage skin toxicity 	<ul style="list-style-type: none"> Skin reactions, including rash progression, should be monitored for early intervention and treatment with corticosteroids For worsening grade 1 or 2 rashes, oral corticosteroids should also be administered For nonrash skin reactions, dose modification may be considered (applicable to events of any grade) 	<p>Skin toxicities</p> <ul style="list-style-type: none"> Consider early intervention with liberal use of emollients and adequate hydration Consider use of low-potency topical corticosteroids, with different potencies administered based on the site and severity of the event For generalized rashes that are not controlled by topical corticosteroids and/or for rashes occurring over a large surface area, consider short pulses of oral corticosteroids If patients experience persistent or high-grade skin toxicities, particularly after cycle 2, or if their rashes are refractory to emollients or low-potency corticosteroids, dermatological consultation should be considered <p>Nail toxicities</p> <ul style="list-style-type: none"> Conduct nail assessments as part of physical examinations to help with monitoring nail health Consider dose modification strategies, including reductions, delays, or skips Consider nail soaks, topical moisturizers, including emollients, and topical corticosteroids Occlusion may be used to concentrate the effect of topical corticosteroids and/or moisturizers on nails Consider advising patients to use protective nail coverings, such as wearing socks and gloves at night <p>Specialist referral</p> <ul style="list-style-type: none"> Referral to dermatology may be warranted in cases in which patients experience persistent or grade 3/4 skin toxicities Referral may also be warranted to rule out other rare etiologies of rashes Referral to podiatry may be required for patients who find it difficult to maintain toenail hygiene, for those who develop infections related to compromised nail beds, or for those for whom standing and wearing footwear or comfortable coverings is challenging
Grade 3/4	<ul style="list-style-type: none"> Withhold talquetamab until adverse reaction improves to grade 1 or baseline Withhold talquetamab as recommended based on severity 	<ul style="list-style-type: none"> For grade 3 or higher events, oral corticosteroids should be administered Withhold talquetamab until adverse reaction improves to grade 1 or baseline For skin reactions and nail disorders, talquetamab should be withheld based on severity and institutional guidelines should be followed 	

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Table S3 (continued)

AE of Interest	Management Guidelines per FDA Label and EMA Summary of Product Characteristics		Management Advice per Investigator Experience
	FDA	EMA	
Patient counseling	<ul style="list-style-type: none"> Discuss the signs and symptoms of skin reactions 	<ul style="list-style-type: none"> No specific guidance listed 	<p>Skin toxicities</p> <ul style="list-style-type: none"> Patients should be encouraged to keep their skin clean and dry throughout the course of treatment, as well as to take short lukewarm showers and use a heavy lotion or moisturizer throughout the day Patients with anhidrosis should avoid hot weather and use misting sprays In patients who report photosensitivity, patients should also be encouraged to use sunscreen to ensure proper skin protection from sunlight <p>Nail toxicities</p> <ul style="list-style-type: none"> Patients should be educated that nail toxicities may increase and decrease over time and that some events may take a while to resolve due to the slow nature of nail growth Patients should be educated to practice good personal general hygiene to reduce the risk of nail infections Patients should be encouraged to avoid activities that heighten the chances of nail breakages and should keep their nails short to avoid nail manipulation Patients for whom frequent use of their hands is a key part of their day-to-day activities should be encouraged to use implements or aides that avoid exacerbating nail damage Patients should be advised to wear gloves overnight and when performing activities in water, as well as wearing socks overnight and comfortable shoes

Abbreviations: AE = adverse event; EMA = European Medicines Agency; FDA = Food and Drug Administration; GPRC5D = G protein-coupled receptor family C group 5 member D.