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ORIGINAL RESEARCH ARTICLE

Dose Optimization of Elranatamab to Mitigate the Risk of Cytokine Release Syndrome in Patients with Multiple Myeloma

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Abstract

Background Elranatamab is a BCMA-CD3 bispecific antibody approved for the treatment of relapsed or refractory multiple myeloma. Cytokine release syndrome is one of the most common adverse events associated with bispecific antibodies.
Objective We aimed to determine the optimal elranatamab dosing regimen for mitigating cytokine release syndrome.
Patients and Methods Safety, pharmacokinetics, and exposure–response were analyzed across four clinical studies (MagnetisMM-1, MagnetisMM-2, MagnetisMM-3, and MagnetisMM-9). Different priming regimens evaluated across these studies included a one-step-up dose priming regimen of 44 mg with or without premedication, a two-step-up dose priming regimen of 12 mg on day 1 and 32 mg on day 4 with premedication, and a two-step-up dose priming regimen of 4 mg on day 1 and 20 mg on day 4 with premedication.
Results The maximum elranatamab serum concentration on day 1 was positively associated with any-grade and grade ≥ 2 cytokine release syndrome. A slower time to maximum serum concentration and a lower dose-normalized maximum serum concentration were observed with subcutaneous versus intravenous administration, supporting subcutaneous dosing to help mitigate cytokine release syndrome.
Conclusions Based on the incidence, severity, and predictable profile of cytokine release syndrome, the 12/32-mg priming-dose regimen with premedication was determined to be the optimal regimen before the first full dose of 76 mg on day 8.
Clinical Trial Registration ClinicalTrials.gov identifiers: NCT03269136, NCT04798586, NCT04649359, and NCT05014412.

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Key Points

Subcutaneous administration of elranatamab results in slower absorption, more gradual immune priming, and lower grade ≥ 2 cytokine release syndrome incidence versus intravenous administration.

Fixed subcutaneous elranatamab doses of 12 and 32 mg on days 1 and 4 then 76 mg on day 8 (with premedication) is the recommended priming regimen.

1 Introduction

Multiple myeloma (MM) is a plasma cell malignancy that is currently not curable in the majority of patients and is associated with poor clinical outcomes, especially in patients whose disease does not respond or becomes refractory to standard-of-care therapies, including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies [1–3]. Thus, therapies with novel modes of action, such as T-cell-engaging bispecific antibodies (BsAbs), are needed. Elranatamab, a BCMA/CD3-directed BsAb, induces cytotoxic T-cell responses against myeloma cells [4, 5]. Elranatamab is approved for relapsed or refractory MM (RRMM) and is in development for other MM settings [4–8].

Cytokine release syndrome (CRS), an inflammatory response induced by overactivation of immune cells and proinflammatory cytokine release, is a common toxicity with BsAbs [9–11]. Multiple strategies are used to reduce the CRS risk in the setting of BsAb therapy, including the use of alternative administration routes (e.g., subcutaneous [SC] vs intravenous [IV] administration), step-up dosing, and anti-inflammatory premedication regimens [12–14]. A subcutaneous route may provide slower and lower peak drug concentrations, reducing early and uncontrollable inflammatory responses, versus the IV route [12]. Step-up dosing, which involves increasing the dose of BsAb in a gradual manner to prime the immune system, is also used to mitigate CRS [12, 13]. Cytokine release syndrome risk is reduced with subsequent dosing, allowing full therapeutic doses to be administered without an increased risk of CRS. Administration of a premedication regimen, which typically includes corticosteroid, antipyretic, and antihistamine agents, may tamp down the exaggerated immune responses associated with initial doses of bispecific antibodies and thus further reduce the risk of CRS [13]. Identification of risk factors for CRS (e.g., body weight or biomarkers such as soluble BCMA [sBCMA]) may enable the use of pre-emptive individualized mitigation strategies [14–16].

Immune effector cell-associated neurotoxicity syndrome (ICANS) is another toxicity associated with BsAbs, generally occurring concurrently with or shortly after CRS. Immune effector cell-associated neurotoxicity syndrome involves peripheral immune overactivation, including cytokine release, leading to cerebral endothelial cell activation, blood–brain barrier dysfunction, and central nervous system inflammation [9, 17]. The impact of different dosing approaches on ICANS has not been evaluated. Here, we describe the impact of IV versus SC elranatamab, premedication, and different priming regimens on CRS and ICANS in patients with RRMM.

2 Subjects and Methods

2.1 Study Design and Participants

Cytokine release syndrome data across four clinical studies (MagnetisMM-1 [NCT03269136], MagnetisMM-2 [NCT04798586], MagnetisMM-3 [NCT04649359], and MagnetisMM-9 [NCT05014412]) in patients with RRMM who received IV or SC elranatamab were included in this report (Table 1 of the Electronic Supplementary Material [ESM]). Priming regimens assessed included: 1-step-up dose priming regimen of 44 mg (with or without premedication for CRS) on day 1, and two distinct 2-step-up dose priming regimens (with premedication) of 12 and 32 mg (12/32) or 4 and 20 mg (4/20) on days 1 and 4, respectively (Table 1). For all priming regimens, the first full dose of 76 mg was administered on day 8 (i.e., 1 week after the 44-mg dose in the 1-step-up dose regimens and 4 days after the second dose in the 2-step-up dose regimens). Blood samples were collected for the pharmacokinetic and sBCMA analyses in all studies. Cytokine release syndrome and ICANS were graded using the American Society for Transplantation and Cellular Therapy (all studies except MagnetisMM-1 IV cohort, where Common Terminology Criteria for Adverse Events criteria

Table 1 Priming regimens evaluated in the CRS analysis

Priming regimen	CRS premedication	Clinical trials	Patients, *n*
Single dose of 600 µg/kg (day 1) followed by 1000 µg/kg (day 8)[a]	No	MagnetisMM-1 (Part 1.1)	20
Single dose of 44 mg (or 600 µg/kg; day 1) followed by 76 mg (or 1000 µg/kg; day 8)[a]	Yes	MagnetisMM-1 (Part 2A), MagnetisMM-2, first 4 enrolled patients in MagnetisMM-3	23
12 mg (day 1), 32 mg (day 4), followed by 76 mg (day 8)	Yes	MagnetisMM-3	183
4 mg (day 1), 20 mg (day 4), followed by 76 mg (day 8)	Yes	MagnetisMM-9	85

CRS cytokine release syndrome

[a]Patients from MagnetisMM-1 Part 1.1 and MagnetisMM-2 were treated with 600/1000 µg/kg or 44/76 mg

[Lee et al., 2014] were used) and were managed according to investigator discretion and published guidelines [18–20].

2.2 Exposure/Response Modeling

Binomial logistic regression analyses were performed using data from MagnetisMM-1 to correlate the predicted maximum serum concentration of elranatamab at 24 h ($C_{max\text{-}24h}$) to the probability of any-grade and grade ≥ 2 CRS. Individual $C_{max\text{-}24h}$ values were predicted using a population pharmacokinetic model [21]. Logistic regression models were used to predict any-grade and grade ≥ 2 CRS rates at the median exposure for different starting doses to inform the selection of priming regimens for further evaluation. Baseline body weight and sBCMA were analyzed as continuous variables and tested as covariates. Free (i.e., drug-unbound) sBCMA was measured in plasma samples using a fully validated, electrochemiluminescent ligand binding assay. Exposure–response analyses, data processing, and figure generation were performed in R software (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Patients

Overall, 364 patients were evaluated for this analysis. Baseline characteristics by study are summarized in Table 2.

3.2 Intravenous Versus Subcutaneous Elranatamab Administration Without Priming

In MagnetisMM-1, 23 and 65 patients received elranatamab intravenously or subcutaneously, respectively. The median time to maximum observed serum concentration was ~ 4 h for IV administration versus 3–7 days for SC administration. The dose-normalized maximum serum concentration (C_{max}) of elranatamab during dose escalation was 156.0–457.0 ng/mL/mg for IV administration versus 17.9–112.0 ng/mL/mg for SC administration. Geometric means (coefficient of variation %) for C_{max} after dose 1 (μg/mL) with the highest IV (50 μg/kg) and SC (1000 μg/kg) dose levels were 0.30 (75%) and 1.15 (38%), respectively.

Cytokine release syndrome was observed with IV administration (any grade, 47.8%; grade 2, 21.7%; grade ≥ 3, 0%), and the incidence increased with the dose (any grade, 0.1–3 μg/kg, 0%; 30–50 μg/kg, 80.0–100%). The incidence of grade 2 CRS in the 50-μg/kg cohort was 83.3%. The median time to onset of CRS was 1.0 day (with 76.5% of the events occurring on the same day of elranatamab dosing), and the median duration ranged from 1.5 to 2.0 days.

Most patients who received SC elranatamab in the dose-escalation cohorts (dose range 80–1000 μg/kg) without step-up dosing experienced CRS (any grade, 73.3%; grade 2, 20%; grade ≥ 3, 0%) and the CRS incidence increased with dose (data not shown). All patients who received the highest doses of 600 ($n = 6$) or 1000 ($n = 6$) μg/kg of elranatamab experienced CRS (all grade 1/2; Table 3). The median time to onset was 1.0 day with both doses (with 54.2% of the events occurring on the same day of elranatamab dosing);

Table 2 Patient demographics and baseline characteristics

	MagnetisMM-1 $n = 88$	MagnetisMM-2 $n = 4$	MagnetisMM-3 $n = 187$	MagnetisMM-9 $n = 85$	Total $N = 364$
Median age (range), years	65.0 (42–82)	68.5 (49–70)	68.0 (36–89)	64.0 (36-86)	66.0 (36–89)
Sex, *n* (%)					
Male	45 (51.1)	3 (75.0)	98 (52.4)	42 (49.4)	188 (51.6)
Female	43 (48.9)	1 (25.0)	89 (47.6)	43 (50.6)	176 (48.4)
Race, *n* (%)					
White	61 (69.3)	0	116 (62.0)	41 (48.2)	218 (59.9)
Black/African American	16 (18.2)	0	11 (5.9)	4 (4.7)	31 (8.5)
Asian	6 (6.8)	4 (100)	17 (9.1)	35 (41.2)	62 (17.0)
Unknown	0	0	3 (1.6)	3 (3.5)	6 (1.6)
Not reported	5 (5.7)	0	40 (21.4)	2 (2.4)	47 (12.9)
Median baseline body weight (range), kg	72.1 (42.0–121.9)	70.1 (61.4–73.5)	71.8 (36.5–159.6)	71.7 (44.5–149.0)[a]	71.8 (36.5–159.6)
Median baseline sBCMA (range), ng/mL[b]	33.8 (0.08–598)	53.0 (22–76)	48.3 (0.274–606)	41.8 (2.37–336)	44.35 (0.077–606)

sBCMA soluble B-cell maturation antigen

[a]Only 45 patients from MagnetisMM-9 had baseline body weight available

[b]Calculated from the number of patients with available sBCMA baseline measurements: a total of $N = 308$ ($n = 74$ in MagnetisMM-1, $n = 4$ in MagnetisMM-2, $n = 187$ in MagnetisMM-3, and $n = 43$ in MagnetisMM-9)

Table 3 Incidence and characteristics of CRS of SC elranatamab with and without priming doses and premedication for CRS

	600 µg/kg[a] ($n = 6$)	1000 µg/kg[a] ($n = 6$)	44/76 mg without premedication[b] ($n = 20$)	44/76 mg with premedication[c] ($n = 23$)	12/32/76 mg with premedication ($n = 183$)	4/20/76 mg with premedication ($n = 85$)
Patients with CRS, *n* (%)[d]	6 (100.0)	6 (100.0)	20 (100.0)	18 (78.3)	106 (57.9)	54 (63.5)
Grade 1	5 (83.3)	4 (66.7)	10 (50.0)	7 (30.4)	80 (43.7)	41 (48.2)
Grade 2	1 (16.7)	2 (33.3)	10 (50.0)	10 (43.5)	25 (13.7)	12 (14.1)
Grade ≥3	0	0	0	1 (4.3)	1 (0.5)	1 (1.2)
Patients with >1 CRS event, *n* (%)[e]	0	0	2 (10.0)	0	23 (12.6)	15 (17.6)
Time to onset of CRS, median (range), days	1.0 (1.0–2.0)	1.0 (1.0–3.0)	1.0 (1.0–3.0)	2.0 (1.0–2.0)	2.0 (1.0–9.0)	2.0 (1.0–7.0)
Duration of CRS, median (range), days	2.5 (1.0–5.0)	4.0 (1.0–10.0)	3.0 (2.0–7.0)	3.0 (1.0–4.0)	2.0 (1.0–19.0)	2.0 (1.0–19.0)

ASTCT American Society for Transplantation and Cellular Therapy, *CRS* cytokine release syndrome, *SC* subcutaneous

[a]Patients from MagnetisMM-1 dose-escalation cohort

[b]Patients from MagnetisMM-1 Part 1.1 and MagnetisMM-2 who received a single priming dose of 600 µg/kg followed by 1000 µg/kg (body weight-based equivalent of 44 mg followed by 76 mg for a 75-kg patient) without premedication

[c]Patients from MagnetisMM-1 Part 2A, MagnetisMM-2, and MagnetisMM-3 who received a single priming dose of 44 mg followed by 76 mg or a single priming dose of 600 µg/kg followed by 1000 µg/kg with premedication

[d]According to ASTCT criteria

[e]Refers only to recurrent CRS events observed with elranatamab doses 1–4

the median duration ranged from 2.5 to 4.0 days. Two patients in the 1000-µg/kg cohort experienced prolonged CRS (10 days each).

3.3 CRS with a 1-Step-Up Dose Priming Regimen With or Without Premedication

All 20 patients (100%) who received the 1-step-up dose priming regimen of elranatamab before the 76-mg full dose (i.e., 44/76 mg) without premedication developed CRS (all grade 1/2; Table 3, Fig. 2A). Two patients (10.0%) had recurrent CRS after dose 2 (76 mg). Any-grade CRS rate was 78.3% for the 23 patients who received 44/76 mg with premedication (grade ≥ 2 CRS, 47.8%). One patient (4.4%) given 44/76 mg with premedication experienced grade 3 CRS. All CRS events were observed after dose 1; no CRS events were observed after dose 2 (Fig. 2B). The median time to onset with versus without premedication was 2.0 versus 1.0 days, respectively; the median CRS duration was 3.0 (range 1.0–4.0 days) versus 3.0 days (range 2.0–7.0 days; Fig. 1 of the ESM), respectively.

3.4 Association of Elranatamab Exposure with CRS

To further reduce the risk of CRS, exposure–response modeling of MagnetisMM-1 data ($N = 88$) was used to select priming doses for further investigation. As CRS is mainly observed after the initial doses with a median onset of 1.0 day, the correlation between $C_{max\text{-}24h}$ and the probability of any-grade and grade ≥ 2 CRS was assessed to inform the selection of priming regimens for further evaluation. Maximum serum concentration of elranatamab at 24 h was found to be significantly associated with both any-grade and grade ≥ 2 CRS (Fig. 1, Table 2 of the ESM). The model predicted that an initial priming dose of 12 mg of elranatamab would be associated with any-grade and grade ≥ 2 CRS rates of 60.1% and 16.3%, respectively, and an initial priming dose of < 12 mg (i.e., 4 mg) with any-grade and grade ≥ 2 CRS rates of 40.7% and 11.1%, respectively (vs the predicted any-grade and grade ≥ 2 rates of 93.4% and 41.6%, respectively, with the 44-mg dose; Fig. 1; Table 3 of the ESM).

3.5 CRS with Two Distinct 2-Step-Up Dose Priming Regimens with Premedication

The 12/32-mg regimen with premedication ($n = 183$) resulted in any-grade (57.9%) and grade ≥ 2 (14.2%) CRS rates consistent with modeling predictions (Table 3). Most events with the 12/32-mg regimen occurred after doses 1 (43.2%) and 2 (19.4%) of elranatamab, with few events after doses 3 (7.4%) and 4 (1.2%; Fig. 2C). Recurrent CRS was observed in 12.6% of patients. One patient (0.5%)

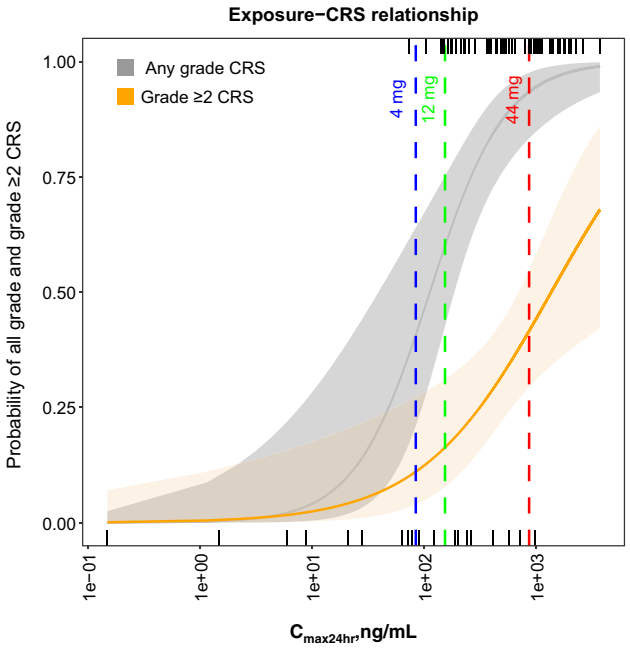

Fig. 1 Relationship between elranatamab exposure and cytokine release syndrome (CRS) based on data from patients treated with elranatamab in MagnetisMM-1. Two binomial logistic regression analyses, one for any-grade CRS and another for grade ≥ 2 CRS, were performed. The gray solid line and the gray shaded area represent the median and 95% confidence interval predicted probability of any-grade CRS. The orange solid line and the orange shaded area represent the median and 95% confidence interval predicted probability of grade ≥ 2 CRS. Vertical (dashed) lines represent the geometric mean maximum elranatamab serum concentration on day 1 ($C_{max\text{-}24h}$) at the corresponding doses of 4 mg (blue), 12 mg (green), and 44 mg (red), respectively. Rug lines on the top and bottom of the plot indicate $C_{max\text{-}24h}$ values for participants who did (top) and did not (bottom) experience CRS. American Society for Transplantation and Cellular Therapy grading was used for CRS and immune effector cell-associated neurotoxicity syndrome grading for all cohorts except the intravenous cohort where the Common Terminology Criteria for Adverse Events criteria (Lee et al., 2014) grading system [37] was used because American Society for Transplantation and Cellular Therapy grading was not available

with grade 3 CRS after dose 1 did not have a CRS recurrence after subsequent doses. The median time to onset was 2.0 (range 1.0–9.0) days, and the median CRS duration was 2.0 (range 1.0–19.0) days.

A priming regimen with lower initial doses and premedication (4/20 mg; $n = 85$) resulted in any-grade and grade ≥ 2 CRS in 63.5% and 15.3% of patients, respectively (Table 3). Cytokine release syndrome events were almost equally distributed across doses 1 (29.4%), 2 (27.4%), and 3 (21.7%), with 4.9% of patients developing CRS after dose 4 (2 [2.5%] with grade 2 CRS; Fig. 2D). Recurrent CRS occurred in 17.6% of patients. The median time to onset was 2.0 (range 1.0–7.0) days, and the median CRS duration was 2.0 (range 1.0–19.0) days.

3.6 Impact of Baseline Body Weight on CRS

The analysis dataset included patients with available baseline body weight: the median was 71.5 (range 36.5–159.6) kg (Table 2). Body weight was not a statistically significant covariate on any-grade or grade ≥ 2 CRS in the logistic regression analysis from MagnetisMM-1 ($N = 88$). In patients receiving full elranatamab doses (1000 µg/kg or 76 mg, $n = 265$), no clinically relevant differences in CRS were seen in those with a body weight of < 72 kg ($n = 141$) versus ≥ 72 kg ($n = 124$) [data not shown]. With the 12/32-mg priming regimen, no significant trends on CRS incidence or severity were observed across different body weight quartiles (Fig. 3A). Cytokine release syndrome rates were 55.6% (grade ≥ 2, 20%), 63.0% (grade ≥ 2, 8.7%), 52.2% (grade ≥ 2, 17.4%), and 60.9% (grade ≥ 2, 10.9%) for body weight quartiles 1, 2, 3, and 4, respectively.

3.7 Relationship Between sBCMA Levels and CRS

A univariable exposure–response logistic regression analysis from MagnetisMM-1 showed that baseline sBCMA levels were negatively correlated with the probability of any-grade but not grade ≥ 2 CRS. In a multivariable analysis including both $C_{max\text{-}24h}$ and baseline sBCMA as covariates, baseline sBCMA was not significant. With the 12/32-mg regimen, a trend was observed for lower any-grade CRS rates in quartiles 3 and 4 versus quartiles 1 and 2 (Fig. 3B). The rates of any-grade CRS events were 66.7%, 67.4%, 57.8%, and 59.6% for sBCMA quartiles 1, 2, 3, and 4, respectively. No trend was observed for the incidence of grade ≥ 2 CRS (13.3%, 15.2%, 20%, and 8.5% for sBCMA quartiles 1, 2, 3, and 4, respectively). However, a shifted CRS profile was observed in patients with the highest sBCMA levels (i.e., quartile 4); events were less frequent with dose 1 (19.1%) but occurred at a higher incidence with dose 2 (23.9%).

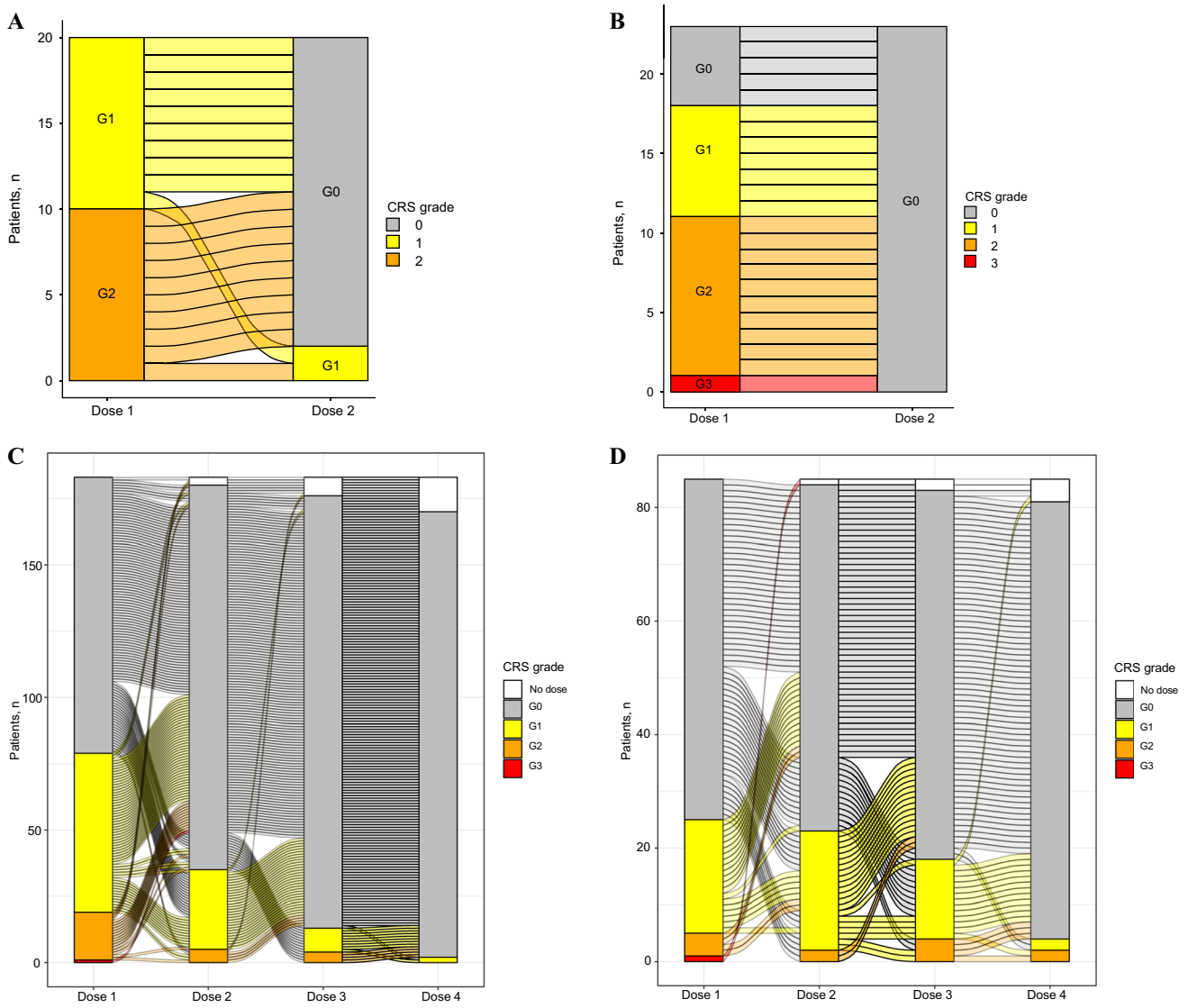

Fig. 2 Cytokine release syndrome (CRS) profile in patients who received a 1-step-up dose priming regimen of 44 mg without (**A**) or with (**B**) premedication or the 2-step-up dose priming regimen of 12/32 mg with premedication (**C**) or 4/20 mg with premedication (**D**). Sankey plot demonstrating the CRS profile in patients who received a 1-step-up dose priming regimen of 44 mg of elranatamab either with or without premedication or a 2-step-up dose priming regimen of either 12 and 32 mg or 4 and 20 mg with premedication. *G* grade

3.8 Impact of Different Dosing Regimens on ICANS

No ICANS was reported in the IV dose-escalation cohorts where lower doses were explored (0.1–50 µg/kg). In the SC dose-escalation cohorts, no ICANS were reported in the two lower SC dose cohorts (80 µg/kg and 130 µg/kg). Immune effector cell-associated neurotoxicity syndrome was reported in the 360 (n = 1/4, 25.0%) and 600 µg/kg (n = 1/6, 16.7%) cohorts (both grade 2) and in the 1000 µg/kg (n = 2/6, 33.3%; both grade 1) cohort. The rate of ICANS was 15% (n = 3/20; all grade ≤ 2) in patients who received 44/76 mg without premedication and 17.4% (n = 4/23; all grade ≤ 2) in those who received 44/76 mg with premedication. In patients receiving 2-step-up dose priming regimens, ICANS occurred in 3.3% (n = 6/183; grade 3, 1.1%) of patients who received 12/32 mg and 4.7% (n =4/85, grade ≥ 3, 0%) of patients who received 4/20 mg. Immune effector cell-associated neurotoxicity syndrome occurred only in patients who experienced CRS, although the timing of ICANS was not always concurrent with CRS. A trend showing higher

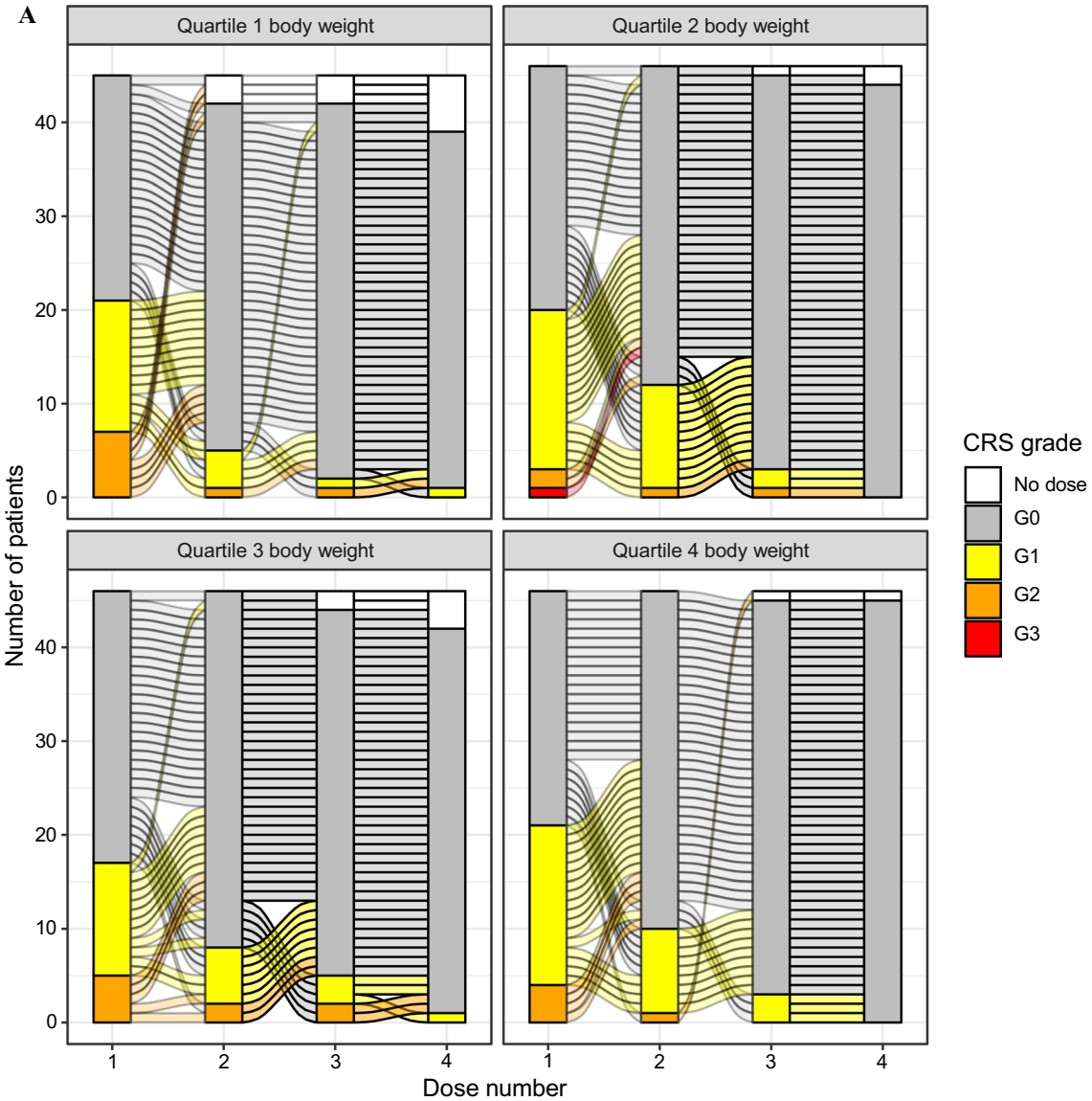

Fig. 3 Cytokine release syndrome (CRS) profile per body weight quartiles (**A**) and per baseline soluble B-cell maturation antigen (sBCMA) levels (**B**) in patients who received the 12/32-mg priming regimen. Sankey plots demonstrating the CRS profile in patients with varying baseline body weights using quartiles (quartile 1, < 62 kg; quartile 2, 62 to < 72 kg; quartile 3, 72 to < 84.5 kg, quartile 4, ≥ 84.5 kg) and varying baseline sBCMA levels (quartile 1, free baseline sBCMA < 13.9 ng/mL; quartile 2, 13.9 to < 48.3 ng/mL; quartile 3, 48.3 to < 149 ng/mL; quartile 4, ≥ 149 ng/mL) who received a 2-step-up dose priming regimen of either 12 and 32 mg or 4 and 20 mg with premedication. *G* grade

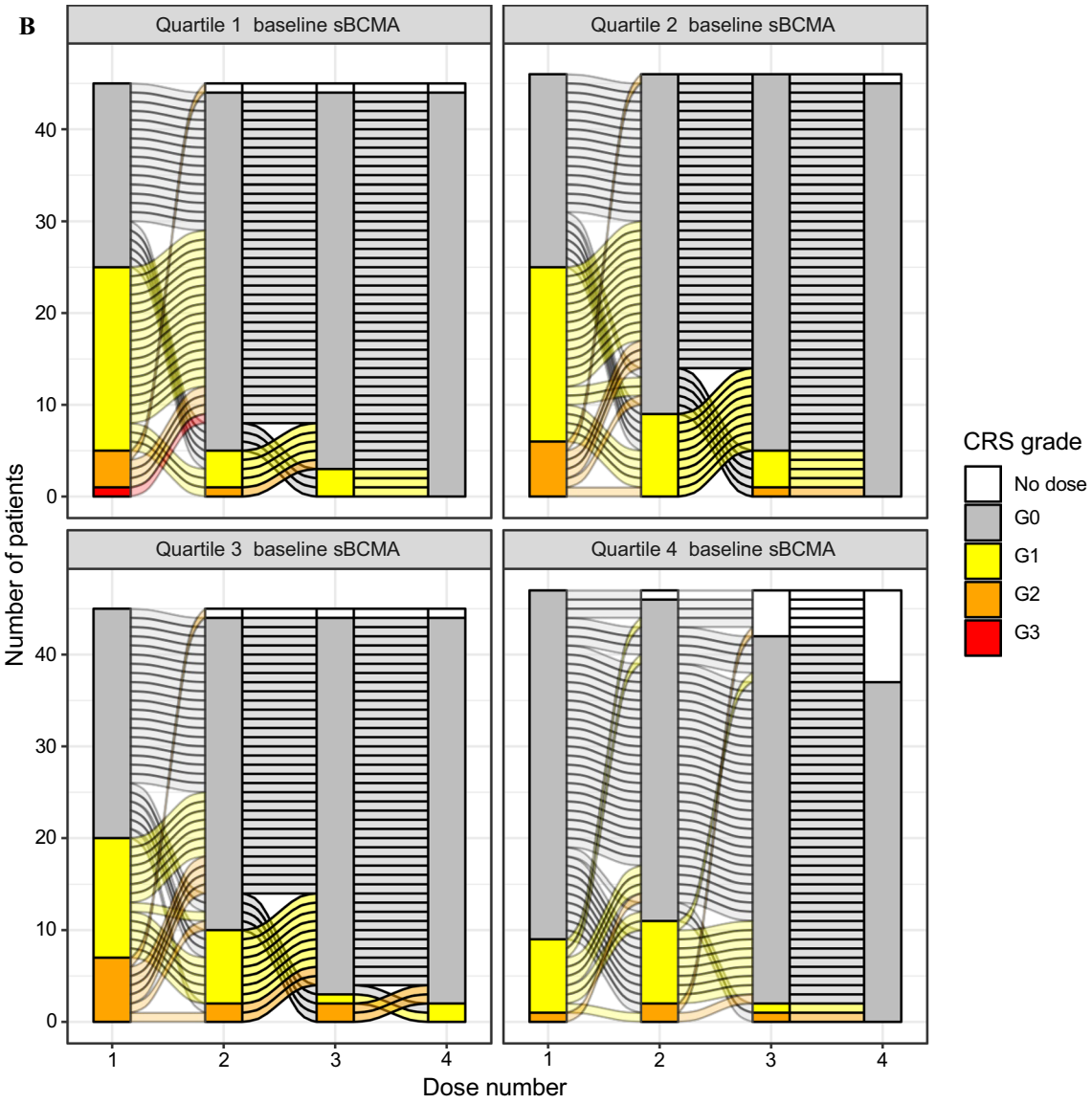

Fig. 3 (continued)

elranatamab $C_{max\text{-}24h}$ in patients experiencing ICANS was observed (data not shown).

4 Discussion

Subcutaneous administration of BsAbs is a more convenient route and may mitigate the development of early, rapid, and uncontrollable immune responses and thus CRS. [12, 13] Subcutaneous elranatamab delayed C_{max} and resulted in lower dose-normalized C_{max} than IV elranatamab, leading to a lower grade ≥ 2 CRS incidence with the highest dose of SC elranatamab (1000 µg/kg; 33.3%) versus IV elranatamab (50 µg/kg; 83.3%), even though C_{max} was higher with SC administration. The slower absorption with SC administration results in more gradual sensitization to initial immune stimulation versus IV administration [13]. The time to maximum observed serum concentration was delayed with the SC route (3–7 days) versus the IV route (~ 4 h, i.e., shortly after the end of infusion). The median time to onset of CRS tended to be later for SC cohorts and cohorts using priming regimens versus IV cohorts; CRS events occurring on the same day of elranatamab dosing were less frequent with SC versus IV administration. The CRS profile associated with SC dosing is consistent with the results of a recent meta-analysis of BCMA-targeting BsAbs [13]. The pharmacokinetic and CRS profile of IV and SC elranatamab during dose escalation in MagnetisMM-1 led to the selection of the SC route for subsequent studies.

Several elranatamab SC regimens for CRS mitigation were evaluated across four studies. The regimens spanned different approaches, including regimens without step-up doses, a 1-step-up dose priming regimen (44 mg), and two distinct 2-step-up dose priming regimens (12/32 mg and 4/20 mg). In the 1-step-up dose priming regimen cohorts, premedication reduced CRS incidence and was associated with a longer median time to onset and a shorter maximum CRS duration compared with the 1-step-up dose priming regimen without premedication. Although studies with elranatamab have not been performed, premedication is expected to have a minimal impact on the efficacy of elranatamab, given that corticosteroids are only administered with the initial doses. Therefore, premedication was implemented in subsequent cohorts/studies. However, the impact of premedication on grade ≥ 2 CRS appeared minimal, highlighting the need for an additional strategy, such as the 2-step-up dose priming regimen, to reduce the CRS risk.

Exposure–response modeling predicted that, compared with 44 mg, initial doses of 12 or 4 mg would result in lower CRS rates. These predications were confirmed via evaluation of the 12/32-mg and the 4/20-mg regimens. For the 12/32-mg regimen, the predicted rates agreed with the observed rates; however, the predicted rates for 4/20-mg regimen were underestimated, owing to the assumption that CRS events were driven by exposure after dose 1 (i.e., $C_{max,\ 24h}$), which might not be valid if there is an inadequate stimulation of the immune system with dose 1. Alternative modeling strategies capturing CRS evolution and accounting for multiple events over time might better predict CRS with too low initial doses [22].

Cytokine release syndrome rates after dose 1 were higher with the 12/32-mg versus 4/20-mg priming regimen; however, CRS incidence and severity after subsequent doses were higher with the 4/20-mg regimen. Recurrent CRS events were also more frequent with the 4/20-mg regimen. Thus, an initial elranatamab dose of 4 mg may provide insufficient immune stimulation, leading to more CRS events with the second priming dose of 20 mg and the first full and later doses of 76 mg. The more predictable CRS profile observed with the 12/32 priming regimen led to the selection of this priming regimen for future use.

Currently approved BCMA-targeting T-cell redirecting therapies for RRMM include the chimeric antigen receptor T-cell therapies ciltacabtagene autoleucel (cilta-cel) and idecabtagene vicleucel (ide-cel) and the BsAbs elranatamab and teclistamab [4, 5, 23–25]. As with BsAbs, CRS is a common toxicity with chimeric antigen receptor T-cell therapies [10, 11]. Although the analysis is limited by cross-trial comparisons, CRS incidence (84–95%) and severity (grade ≥ 3, 5%; grade 5, ≤1%) with cilta-cel and ide-cel were higher and events lasted longer (median duration, 4.0–5.0 days) than those observed with elranatamab and teclistamab. [26–29] Differences in CRS premedication regimens (e.g., exclusion of corticosteroids for chimeric antigen receptor T-cell therapy) and a lack of fractionated dosing regimens may explain these differences [13].

Priming and full dosing regimens of approved BsAbs for cancer treatment have been previously summarized and discussed [14, 30]. Cytokine release syndrome with other bispecific antibodies approved for treating RRMM [25, 31], including teclistamab (any grade, 72%; grade 1, 50%; grade 2, 21%; grade 3, < 1%) and talquetamab, a GPRC5D-targeting BsAb (SC 400 µg/kg once weekly: any grade, 79%; grade 1, 62%; grade 2, 15%, grade 3, 2%), both utilizing 2 step-up dose priming regimens (teclistamab: 0.06 mg/kg and 0.3 mg/kg; talquetamab: 0.01 mg/kg and 0.06 mg/kg) and premedication, appear higher than those observed with elranatamab [28, 32]. After dose 1, CRS rates were similar between teclistamab and elranatamab (44% and 43%, respectively) and were lower with talquetamab (34%) [28, 32]. However, after dose 2, the CRS rate with elranatamab (19%) was lower than that with teclistamab (35%) and talquetamab (49%) [28, 32]. Similarly, the CRS incidence after the initial full dose of elranatamab [dose 3] (7%) was lower than that with teclistamab (24%) and talquetamab (27%) [28, 32]. The recurrent CRS rate was also lower with elranatamab (12.6%) than with teclistamab (33%) and talquetamab (32%) [28, 32]. Patients given the 12-mg priming dose of elranatamab initially received a higher percentage of the full dose (16%) and likely experienced a greater immune stimulation compared with teclistamab and talquetamab (4% and 2.5% of full dose, respectively), potentially explaining the reduced CRS incidence with later doses of elranatamab.

Fixed dosing was supported by similar CRS rates and profiles across a wide range of body weights and is preferred for drugs with a wide therapeutic window because of convenience, a reduced risk for medical errors, and cost effectiveness because of lower drug waste [33, 34]. Additionally, body weight was not a statistically significant covariate on elranatamab exposure and therefore, a fixed dosing approach is expected to result in less inter-individual variability in drug exposure and consequently the CRS profile [21].

Baseline sBCMA levels were negatively associated with the probability of any-grade CRS in a univariable analysis, possibly owing to sBCMA acting as a sink that reduces drug exposure [15], which is consistent with sBCMA not being a significant covariate in the multivariable analysis with exposure. Additional research is needed to establish the value of sBCMA as a biomarker for CRS.

Immune effector cell-associated neurotoxicity syndrome, another toxicity observed with T-cell redirecting therapies, is generally associated with CRS [9]. Immune effector cell-associated neurotoxicity syndrome was observed with the three highest doses of 360, 600, and 1000 µg/kg of SC elranatamab. The incidence of ICANS was similar in patients

who received the 1-step-up dose priming regimen of 44 mg with or without premedication. Immune effector cell-associated neurotoxicity syndrome rates were lower with the 12/32 and 4/20 regimens, suggesting that lower starting doses are associated with a lower incidence of ICANS. However, the interpretation of the relationship between ICANS and the different priming regimens may be limited by the small number of events. The incidence and severity of ICANS were higher with cilta-cel (any grade, 17%; grade ≥ 3, 2%) [29] and ide-cel (reported as neurologic toxicity; any grade, 18%; grade ≥ 3, 3%) [27] versus the 12/32-mg priming regimen (any grade, 3.3%; grade 3, 1.1%), which could be related to the higher CRS rates and the inability/difficulty to implement fractionated dosing regimens with CAR T-cell therapies. Immune effector cell-associated neurotoxicity syndrome rates were similar between elranatamab (3.3%) and teclistamab (3%) but appeared higher with talquetamab (11%) [35, 36].

The limitations of this study include the small sample size of some of the cohorts and the low incidence of certain events per cohort, in particular ICANS. Additionally, the different priming regimens were not evaluated through a randomized comparison. However, the baseline characteristics for participants receiving theses regimens were generally comparable between groups. Despite these limitations, this analysis is the first describing multiple approaches to mitigate CRS and ICANS and may provide useful insights for the development of BsAbs.

5 Conclusions

SC administration, 2-step-up dose priming regimens, and premedication, may reduce CRS and potentially ICANS with BsAbs. Subcutaneous elranatamab administered at fixed doses of 12 and 32 mg on days 1 and 4, respectively, followed by 76 mg on day 8 (with premedication for the first three doses), was selected as the recommended priming regimen for patients with RRMM and for subsequent studies.

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Declarations

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Conflicts of interest/competing interests Mohamed Elmeliegy, Andrea Viqueira, Erik Vandendries, Anne Hickman, Umberto Conte, Donald Irby, Jennifer Hibma, Hoi-Kei Lon, Joseph Piscitelli, Pooneh Soltantabar, Athanasia Skoura, Sibo Jiang, and Diane Wang report employment and stock ownership at Pfizer.

Ethics approval All studies reported here were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. The study protocols and relevant documents were approved by independent institutional review boards or ethics committees at each investigative center.

Consent to participate All patients provided written informed consent.

Consent for publication Not applicable.

Availability of data and material Upon reasonable request and subject to review, Pfizer will provide the data that support the findings of this article. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizeroncologydevelopment.com/trials for more information.

Code availability Not applicable.

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