MonumenTAL·6

64407564MMY3009

European Hematology Association Investigator Meeting Discussion

Confidential information.

Information in this presentation is intended only for investigators and site personal participating in MonumenTAL-6 trial

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Agenda

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- Brief Updates on current enrollment and upcoming plans
- Updates on key changes in Protocol Amendment # 2
- Safety/efficacy updates for MonumenTAL-2 and RedirecTT-1
- Open forum discussion on best practices in AE management

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Updates

- Top Recruiting Countries
  - It's a TIE! (Australia and France)
- Top Recruiting Sites (again, a TIE !)
  - St Antonius Ziekenhuis Niewegein
  - Juravinski Cancer Center

Country	Total Screening	Total Randomized
Argentina	2	1
Australia	16	10
Austria	0	0
Belgium	6	5
Brazil	6	2
Canada	9	6
China	3	2
Czech Republic	6	3
Denmark	0	0
France	16	12
Germany	0	0
Greece	2	0
Hungary	0	0
India	1	1
Israel	6	5
Italy	13	9
Japan	3	3
Korea, Republic of	8	2
Netherlands	9	8
Poland	14	3
Saudi Arabia	0	0
Spain	10	7
Sweden	1	1
Turkey	5	0
United Kingdom	3	1
United States	0	0
Total	**139**	**81**

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Updates

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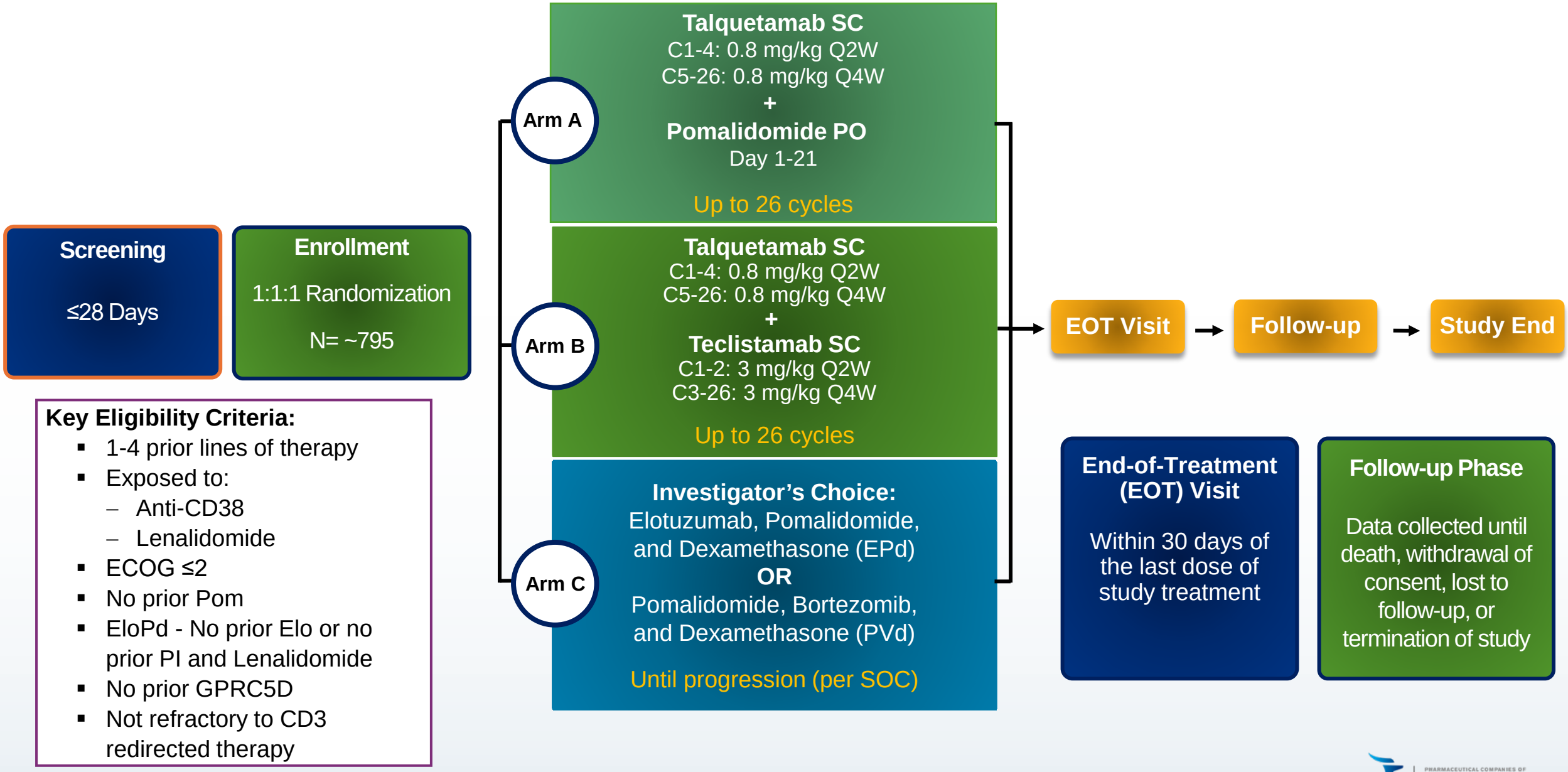
- IDMC Safety Review Meeting
  - 21st August 2024

Deliverable	Due Date
Clinical Cut-off (CCO)	26-Jun-2024
Data Entry up to CCO Completed	02-Jul-2024
Last Query Entered by Data Management	11-Jul-2024
Last Query Answered by Sites	15-Jul-2024
Critical Queries Answered by Sites	18-Jul-2024
IDMC Safety Review Meeting # 1	21-Aug-2024

Schematic Overview of the Study



Key Eligibility Criteria:

- 1-4 prior lines of therapy
- Exposed to:
  - Anti-CD38
  - Lenalidomide
- ECOG ≤2
- No prior Pom
- EloPd - No prior Elo or no prior PI and Lenalidomide
- No prior GPRC5D
- Not refractory to CD3 redirected therapy

ARM A: Talquetamab and Pomalidomide – 28-Day Cycle

Pretreatment for each dose of Cycle 1:

- **Dexamethasone 20 mg** or equivalent
- **Diphenhydramine 25-50 mg** or equivalent
- **Acetaminophen 650-1000 mg**
- Given in Cycles 2+ (pre-Talquetamab) if Grade 2+ CRS/sARRs related to talquetamab develop

Treatment:

- **Cycle 1**: **Talquetamab only (minimum of 2 days in between doses)**

	Talquetamab	Cycle Day
SC SU1	**0.01** mg/kg	C1D1
SC SU2	**0.06** mg/kg	C1D4 (Days 3-6)
SC treatment dose	**0.4** mg/kg	C1D8 (Days 5-10)
SC study treatment dose	**0.8** mg/kg	C1D15 (Days 7-15)

- **Cycle 2-6**: **Talquetamab + Pomalidomide**
  - Cycle 2-4 Dexamethasone **40 mg** (**20 mg** if <75 years of age with BMI <18.5 or ≥75 years of age)
  - Talquetamab **0.8** mg/kg SC treatment dose every 14d+/-3d
  - Pomalidomide **2** mg daily (D1-21/28 days) with option to increase to **4** mg depending on patient's tolerance
- **Cycle 7+: Talquetamab 0.8 mg/kg SC treatments** given as appropriate on D1 up to 26 cycles if no sign of PD or toxicity

	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7- 26
Talquetamab 0.8mg/kg Q2W	Q2W	Q2W	Q2W	Q4W if in ≥VGPR	Q4W if in ≥VGPR	Q4W if in ≥PR or Q2W until ≥PR

ARM B: Talquetamab and Teclistamab – 28-Day Cycle

Pretreatment for each dose of Cycle 1:

- **Dexamethasone 20 mg** or equivalent
- **Diphenhydramine 25-50 mg** or equivalent
- **Acetaminophen 650-1000 mg**
- Given in Cycles 2+ (on Day 1 and Day 15) if Grade 2+ CRS/sARRs related to talquetamab/teclistamab develop

Treatment: Talquetamab + Teclistamab

- **Cycle 1**

	Talquetamab	Teclistamab	Cycle/Day
SC SU1	**0.01** mg/kg	**0.06** mg/kg	C1D1
SC SU2	**0.06** mg/kg	**0.3** mg/kg	C1D4 (days 3-6)
SC treatment dose	**0.4** mg/kg	**1.5** mg/kg	C1D8 (Tal/Tec) and C1 D15 Tec only(days 5-10)
SC treatment dose	**0.8** mg/kg	**1.5** mg/kg	C1D15 Tal (days 7-15) C1D1 Tec only

- **Cycle 2-6:**
  - Talquetamab **0.8 mg/kg** and **teclistamab 3 mg/kg** SC 14d+/-3d
- **Cycle 7+:**
  - Treatment dose given as appropriate on D1 up to 26 cycles if no sign of PD or toxicity

	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7- 26
Talquetamab 0.8mg/kg Q2W	Q2W	Q2W	Q2W	Q4W if in ≥VGPR	Q4W if in ≥VGPR	Q4W if in ≥PR or Q2W until ≥PR
Teclistamab 3mg/kg Q2W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W

Schedule Change
Protocol Amendment 1 vs 2

	Talquetamab	Teclistamab	Cycle/Day
SC SU1	**0.01** mg/kg	**0.06** mg/kg	C1D1
SC SU2	**0.06** mg/kg	**0.3** mg/kg	C1D4 (days 3-6)
SC treatment dose	**0.4** mg/kg	**1.5** mg/kg	C1D8 (Tal/Tec) and C1 D15 Tec only(days 5-10)
SC treatment dose	**0.8** mg/kg	**1.5** mg/kg	C1D15 Tal (days 7-15) C1D1 Tec only

Initially was all, however its response based for PR or better

	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7- 26
Talquetamab 0.8mg/kg Q2W	Q2W	Q2W	Q2W	Q4W if in ≥VGPR	Q4W if in ≥VGPR	Q4W if in ≥PR or Q2W until ≥PR
Teclistamab 3mg/kg Q2W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W

Initially was Q2W Tec and change at Q4W by Cycle #3 for Partial Response

MonumenTAL-2 (Talquetamab-Pom) – EHA 2024

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Safety

- Cytopenias were mostly grade 3/4 and generally limited to the first few cycles
- Taste-, skin-, nail-, and rash-related GPRC5D AEs were mainly grade 1/2, with few discontinuations
- ICANS occurred in 3 pts; all were grade 1
- 9 pts had AEs that led to treatment discontinuation
- AEs led to dose reduction of tal or pom in 37.1% and 48.6% of pts, respectively; 65.7% and 77.1% of pts skipped doses of tal and pom due to AEs, respectively
  - The most common AEs that led to dose reduction of pom included neutropenia, peripheral neuropathy, and fatigue
  - Dose reduction and schedule changes were used to manage AEs
- In pts with and without oral toxicities, weight loss was evident early but stabilized and improved over time; a more gradual trend of improvement was noted in pts with oral toxicities
- The most common infections were pneumonia, upper respiratory tract infections, and COVID-19; infections were mostly grade1 and 2.
  - First-onset infections generally occurred in the first few cycles of treatment

Presented by E Searle at the European Hematology Association (EHA) 2024 Hybrid Congress; June 13–16, 2024; Madrid, Spain

TEAE ≥25%, n (%)	All patients (N=35)	
	Any grade	Grade 3/4
Hematologic AEs		
Neutropenia	22 (62.9)	20 (57.1)
Anemia	13 (37.1)	9 (25.7)
Thrombocytopenia	10 (28.6)	7 (20.0)
Nonhematologic AEs		
Taste-related[a]	30 (85.7)	0
Infections	28 (80.0)	8 (22.9)
CRS	26 (74.3)	1 (2.9)
Skin-related[b]	26 (74.3)	2 (5.7)
Nail-related[c]	24 (68.6)	0
Dry mouth	19 (54.3)	0
Fatigue	19 (54.3)	5 (14.3)
Pyrexia	14 (40.0)	1 (2.9)
Nausea	13 (37.1)	0
Diarrhea	11 (31.4)	0
Headache	10 (28.6)	1 (2.9)
Rash-related[d]	10 (28.6)	1 (2.9)
Back pain	9 (25.7)	1 (2.9)
Cough	9 (25.7)	0
Weight decreased	9 (25.7)	2 (5.7)

[a]Includes dysgeusia, ageusia, taste disorder, and hypogeusia. Per CTCAE v5.0, the maximum grade of dysgeusia is 2. [b]Includes skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome. [c]Includes nail discoloration, nail disorder, nail toxicity, nail dystrophy, nail ridging, onychoclasis, onycholysis, and onychomadesis. [d]Includes rash, rash maculopopular, rash erythematous, and erythema.
TEAE, treatment-emergent adverse event.

MonumenTAL-2 (Talquetamab-Pom) – EHA 2024

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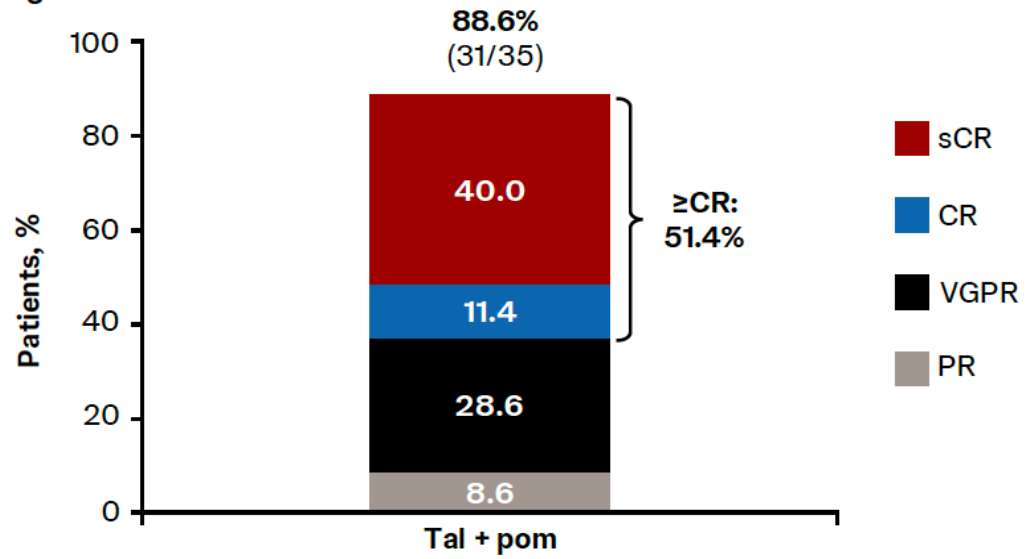
Figure 2: ORR



CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Table 1: Efficacy outcomes

	Tal + pom (N=35)
Median follow-up (range), months	16.8 (1.2–25.1)
Median time to first response (range), months	1.1 (0.0–3.3)
Median DOR, months (95% CI)	NR (12.0–NE)
12-month DOR rate, % (95% CI)	74.4 (53.5–86.9)
Median PFS, months (95% CI)	NR (12.9–NE)
12-month PFS rate, % (95% CI)	72.6 (53.9–84.7)

NE, not estimable; NR, not reached.

- Tal + pom showed rapid, deep, and durable responses; a trend for longer DOR with deeper response was observed, which suggests that pts with a ≥VGPR may have more durable responses
- Neutropenia was worse with the combination than with tal monotherapy, but its frequency was comparable to pom monotherapy; there was no evidence of additive hematologic or CRS toxicities
- Similar rates of GPRC5D-related AEs were observed as with tal monotherapy, and the majority were grade 1/2, with few discontinuations; dose reductions were used to manage AEs

RedirecTT-1 (Talquetamab-Teclistamab)

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	Tec 3.0mg/kg Q2W Tal 0.8mg/kg Q2W	All patients
Number	44	94
Hematological AE (All grades) • Neutropenia • Febrile Neutropenia • Anemia • Thrombocytopenia	 25 (56.8%) 3 (6.8%) 11 (25.0%) 9 (20.5%)	 64 (68.1%) 12 (12.8%) 36 (38.3%) 28 (29.8%)
Infections (All grades)	21 (47.7%)	60 (63.8%)
CRS • Grade 1 • Grade 2 • Grade 3 or 4	 23 (52.3%) 10 (22.7) 0	 50 (53.2%) 22 (23.4%) 2 (2.1%)
ICANS • Grade 1 • Grade 2 • Grade 3 or 4	 2 (4.5%) 0 0	 2 (2.1%) 1 (1.1%)
Neurotoxicity • Grade 1 • Grade 2 • Grade 3 or 4	 18 (40.9%) 14 (31.8%) 0	 37 (39.4%) 34 (36.2%) 5 (5.4%)

How can the risk of infection be reduced?
Immunoglobulin Repletion

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- **IVIG use** was associated with a significantly lower risk of serious infections among patients receiving Teclistamab treatment
- Cumulative incidence of infections at 6 months: 5.3% with IVIG vs 54.8% with observation only [P < .001])

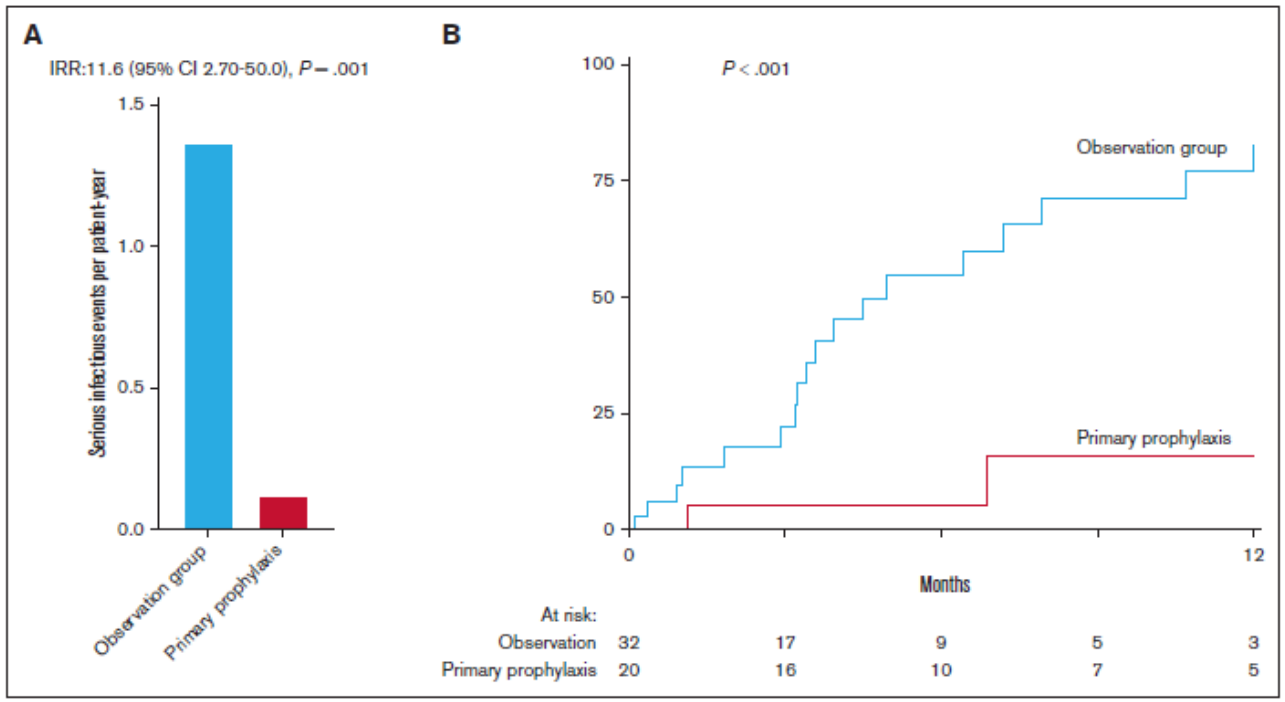

Figure 4. IVIG supplementation reduces the frequency of serious infections in patients treated with teclistamab. (A) Serious (grade ≥ 3) infectious events per patient-year in patients treated with teclistamab according to treatment with IVIG (primary prophylaxis) or without IVIG (observation group). (B) Cumulative incidence plot of time to first serious infection in patients treated with teclistamab according to treatment with IVIG (primary prophylaxis) or without IVIG (observation group). IRR, incidence rate ratio.

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Frerichs et al Blood Advances 2024; Lancman et al Blood Cancer Discov 2023

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IVIG/SCIG Administration Guidance

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- **For all participants, *regardless of cohort*, it is recommended to give IVIG/SCIG prophylactically, *regardless of IgG level or history of active or past infection*:**

IMWG guideline: Consider an early start of IVIG replacement regardless of a particular cutoff, considering that the first infection event typically occurs early after the start of bispecific antibodies therapy[1]

prior to first dose of study treatment
(eg, during screening)

-OR-

initiate replacement therapy ASAP during treatment
(eg, Cycle 1 Day 15, after completion of Step-Up Doses)

Note: Due to the potential for reactions to IVIG administration, it should be avoided for a minimum of 48 hours after each step-up dose and also after the first treatment dose of teclistamab or talquetamab, as well as during any event of CRS

It is recommended to **administer IV immunoglobulin 0.4 g/kg every 3 to 6 weeks.**

1. International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma Lancet Oncol 2024; 25: e205–16

CRS/ICANS Management

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OPTec: A Phase 2 Study to Evaluate Outpatient Administration of Teclistamab, a BCMA-targeting Bispecific Antibody, in Patients with Multiple Myeloma

Treatment Phase

Tocilizumab:

- 8 mg/kg IV, 2-4 hours prior to 1st step-up dose

Teclistamab:

- Step-up dose 1: 0.06 mg/kg SC
- Step-up dose 2[a]: 0.3 mg/kg SC
- Treatment dose[b]: 1.5 mg/kg SC (once weekly)

Safety

Stopping criteria (Grade >3 CRS or neurotoxicity/immune effector cell-associated neurotoxicity syndrome [ICANS]) were not met by the first 11 patients.

The most common adverse events were headache (5), nausea (5), neutropenia (4), and injection site reaction (4).

No patient required hospitalization due to tocilizumab or teclistamab.

No patient experienced CRS or ICANS.

One patient had Grade 2 infections of the upper respiratory tract and urinary tract, and 2 patients had 1 infection each (Grade 2 candida infection/Grade 2 viral upper respiratory tract infection).

GPRC5D Related Toxicity Management

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- The Mainstay of Mx is supportive care. Dose interruptions or reductions might be required in severe or persistent cases.
- Cutaneous Adverse Events:
  - Prevention: early or prophylactic use of emollients (eg, urea 10% cream or ammonium lactate 12% cream) and sunscreen
  - Treatment: Low-potency topical corticosteroids (e.g., hydrocortisone and triamcinolone) are recommended, with an escalation to medium-potency corticosteroids.
  - For more extensive (ie, grade ≥3) rashes or rashes refractory to topical therapies, short courses of oral steroids (eg, prednisone or prednisolone) can be used.
- Oral symptoms:
  - Xerostomia can be managed with increased hydration (saliva substitutes), or sugar-free chewing gum to stimulate saliva flow.
  - Sulfate-free toothpaste might be better tolerated.
  - Nutritional supplements are recommended to optimize oral intake and limit body weight loss.
  - The treatment of oral comorbidities (eg, Candida or thrush or nutritional deficiencies leading to glossitis)

International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma Lancet Oncol 2024; 25: e205–16

Talquetamab Safety and Efficacy Milestones

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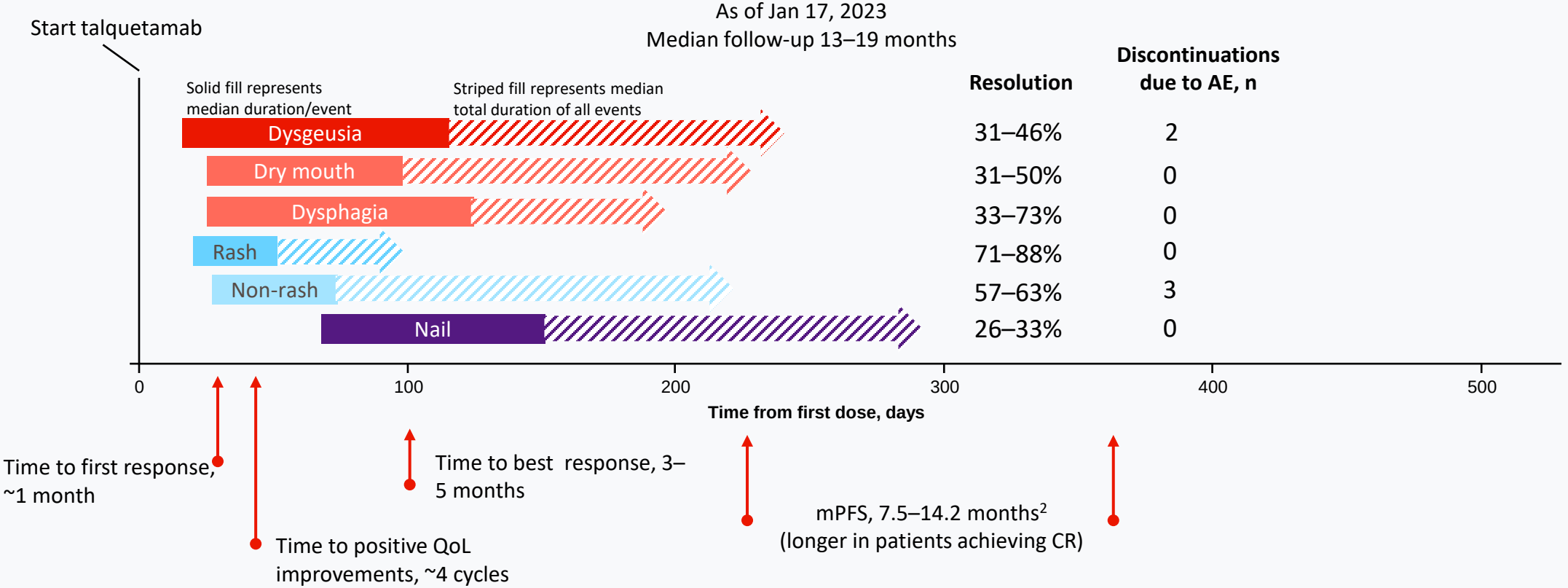
On-target, off-tumor AE onset, duration, and resolution over time[1]

As of Jan 17, 2023
Median follow-up 13–19 months



	Resolution	Discontinuations due to AE, n
Dysgeusia	31–46%	2
Dry mouth	31–50%	0
Dysphagia	33–73%	0
Rash	71–88%	0
Non-rash	57–63%	3
Nail	26–33%	0

- 6 discontinuations were due to AEs related to T-cell redirection: 2 due to infection, 1 due to CRS, and 3 due to ICANS

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1. Chari A, et al. Clin Lymphoma Myeloma Leuk. Online ahead of print. Mar 2024. doi: XX.
2. Touzeau C, et al. Presented at EHA 2023; June 8-11, 2023; Frankfurt, Germany.

AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

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