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Updated Efficacy and Safety Results of JNJ-5322, a Novel, Next-Generation BCMA×GPRC5D×CD3 Trispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma

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Key Takeaways

With longer follow-up, ramantamig (JNJ-5322), a trispecific antibody with novel B-cell maturation antigen (BCMA), G protein–coupled receptor class C group 5 member D (GPRC5D), and CD3 binding domains, continued to demonstrate deep and durable responses at the recommended phase 2 dose (RP2D), including high rates of complete response (CR) or better, and minimal residual disease (MRD) negativity

At the fixed RP2D of 100 mg every 4 weeks (Q4W), ramantamig demonstrated a favorable safety profile compared with BCMA- or GPRC5D-targeting bispecific antibodies (BsAbs) inclusive of oral adverse events (AEs), weight loss, and cytokine release syndrome (CRS), with a convenient, single step-up dose (SUD) suitable for use in an outpatient setting

Conclusions

Redesigned GPRC5D and CD3 binding domains, along with a single SUD and fixed Q4W dosing, may contribute to the overall safety profile at the RP2D of no grade ≥2 CRS with prophylaxis, no immune effector cell–associated neurotoxicity syndrome (ICANS) and no grade 3 oral AEs with minimal weight loss

Optimized infection management strategies incorporated into the study design resulted in a manageable infection profile (grade 3/4, 33.3%) and reduced risk of severe infections over time at the RP2D

Overall response rate (ORR) was 100.0% and responses continued to deepen (≥CR, 88.9%) at the RP2D in triple-class exposed patients naïve to T cell redirection therapies

MRD negativity at 10^{-5} and 10^{-6} was 100.0% in evaluable patients at the RP2D

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Poster

Supplementary material

https://www.congresshub.com/ASH2025/Oncology/Ramantamig/Krishnan

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Disclosures

AYK reports a consulting/advisory role for Celgene, GSK, 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 BMS; and has received research funding from Johnson & Johnson.

Introduction

- Ramantamig (JNJ-5322) is a next-generation, off-the-shelf immunotherapy with novel binding domains targeting dual myeloma antigens BCMA and GPRC5D, as well as a novel CD3-binding domain, which, when incorporated into one trispecific antibody, may overcome clonal heterogeneity and refractoriness associated with antigen escape[1,2]
- Initial data from the ongoing phase 1 study (NCT05652335) in patients with relapsed/refractory multiple myeloma (RRMM) demonstrated robust clinical efficacy with promising safety[3]:
  - An improved or similar safety profile of ramantamig compared with BCMA/GPRC5D BsAbs as monotherapy or in combination
  - ORR of 100.0% at the RP2D in triple-class exposed patients naïve to T-cell redirecting therapies

We present updated safety (N=36; median follow-up, 17.0 mo) and efficacy (in triple-class exposed patients naïve to T-cell redirecting therapies [N=27]; median follow-up, 17.8 mo) results at the RP2D from the ongoing phase 1 study; data cut-off Sept 2025

Methods

Phase 1 part 1 study design

Key eligibility criteria

Triple-class[a] exposed RRMM[b]

Dose escalation and optimization with final RP2D identification

RP2D identified as: 100 mg Q4W SC with 1 SUD (5 mg SC)

Key objectives

- Identify RP2D
- Safety[c]
- Preliminary efficacy (ORR, DOR, PFS)

[a]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [b]≥3 prior LOT or triple-class refractory in the United States. [c]TEAEs graded by CTCAE v5.0; CRS per ASTCT criteria. ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; IMiD, immunomodulatory drug; LOT, line of therapy; mAb, monoclonal antibody; PFS, progression-free survival; PI, proteasome inhibitor; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Extensive dose optimization based on safety-, pharmacokinetic-, and efficacy-guided endpoints supported selection of the optimal treatment regimen of the RP2D with a single SUD and monthly fixed dosing from the start of treatment (see Poster #4054)

Results

Baseline characteristics of patients who received the RP2D have been previously reported[3]

N=36 (RP2D)

Age[a] 67.5 (43–87)

Female 39%

Male 61%

High-risk cytogenetics,[b] n (%)
7/24 (29.2)

ISS stage III, n (%)
5 (13.9)

EMD,[c] n (%)
3 (8.3)

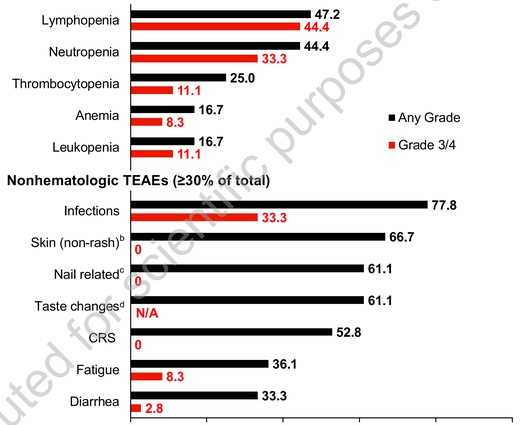
Prior LOT[a]
4 (2–11)

BCMA/GPRC5D exposure, n (%)
Naïve 27 (75.0)
Exposed[d] 9 (25.0)

Triple-class[e] refractory, n (%)
19 (52.8)

[a]Data are presented as median (range). [b]Defined as del(17p), t(4;14), or t(14;16). [c]≥1 nonradiated, bone-independent lesion ≥2 cm. Patients with parasketetal plasmacytomas were permitted but not counted as EMD. [d]Required washout periods included 90 and 21 days for CAR-T and BsAbs, respectively. [e]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. EMD, extramedullary disease; CAR, chimeric antigen receptor; ISS, International Staging System.

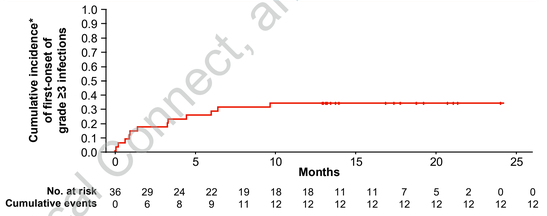
Figure 1: The safety profile of the RP2D was consistent with previous results[3,a]; CRS occurred in 53% of patients (grade 1, 42%; grade 2, 11%), inclusive of patients who received prophylactic tocilizumab



[a]1 patient died while in very good partial response (VGPR) (due to pneumonia in the setting of hypogammaglobulinemia <200 mg/dL). [b]Skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome. [c]Nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging. [d]Dysgeusia, ageusia, hypogeusia, and taste disorder; maximum grade is 2 per CTCAE.

- **Prophylactic tocilizumab decreased CRS incidence (from 69.2% to 20.0%) and severity (no grade ≥2 events) in patients who received ramantamig 100 mg (Supplemental Table 1)**
- **No ICANS was reported at the RP2D**

Figure 2: The cumulative incidence of grade ≥3 infections plateaued within the first year of therapy at the RP2D



*Kaplan-Meier method was used to account for patient censoring.

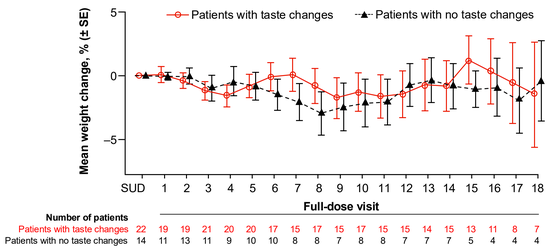
- **Across all doses, no additional deaths due to infections occurred during the subsequent follow-up period**
- **91% of patients received immunoglobulin replacement irrespective of hypogammaglobulinemia (Supplemental Table 2)**

Table: Compared with Tal[4] and Tal + Tec,[5] a relatively low incidence and severity of oral TEAEs and short median duration of taste changes (57 days) were reported for ramantamig at the RP2D

Oral TEAEs, n (%)	All Grade	Grade 1	Grade 2	Grade 3/4
Taste changes[a]	22 (61.1)	16 (44.4)	6 (16.7)	NA
Non–taste-related				
Dry mouth	9 (25.0)	9 (25.0)	0	0
Dysphagia	0	0	0	0
Glossitis	1 (2.8)	0	1 (2.8)	0
Stomatitis	2 (5.6)	1 (2.8)	1 (2.8)	0

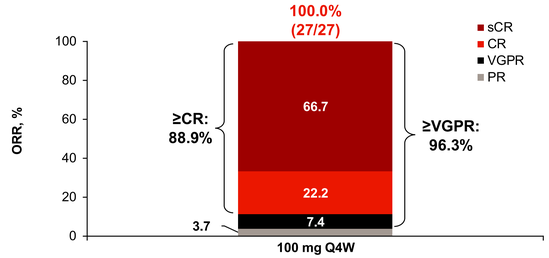
[a]Dysgeusia, ageusia, hypogeusia, and taste disorder; maximum grade is 2 per CTCAE. NA, not applicable; Tal, talquetamab; Tec, teclistamab.

Figure 3: Unlike Tal, mean weight loss was minimal over time at the RP2D. Consistent with Tal, changes in mean weight were similar irrespective of taste changes[4]



At the RP2D: ORR of 86.1% (n=31/36), ≥CR rate of 75.0%, and MRD-negativity rate of 100.0% at 10^{-5} (n=10/10) and 10^{-6} (n=7/7)

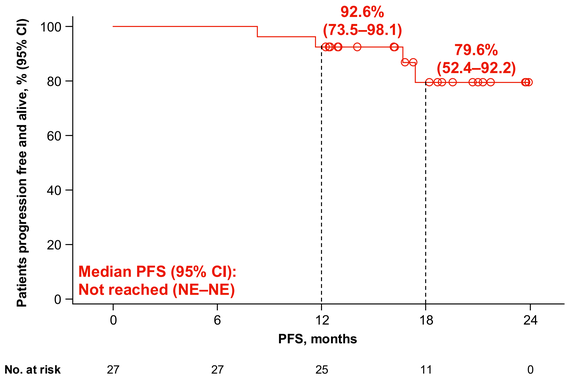
Figure 4: At the RP2D, triple-class exposed patients naïve to T cell redirection therapies achieved an ORR of 100.0% with deepening responses since the last report[3]



PR, partial response; sCR, stringent complete response.

Responses were durable in triple-class exposed patients naïve to T cell redirection therapies who received the RP2D; 24 of 27 patients were alive and in response at 17.8 mo of median follow-up (Supplemental Figure)

Figure 5: In triple-class exposed patients naïve to T cell redirection therapies treated with the RP2D, 92.6% and 79.6% remained progression free and alive at 12 months and 18 months, respectively



NE, not estimable.

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Multiple Myeloma

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