First-in-Human Study of JNJ-79635322 (JNJ-5322), a Novel, Next-Generation Trispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Initial Phase 1 Results

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JNJ-5322 BCMA×GPRC5D×CD3 Trispecific: The Next Generation of Targeted Immunotherapies Reduces Side Effects and Enhances Efficacy

100 mg Q4W SC with 1 step-up dose selected as RP2D

- Dose escalation
- Dose and schedule optimization
- Step-up dose optimization

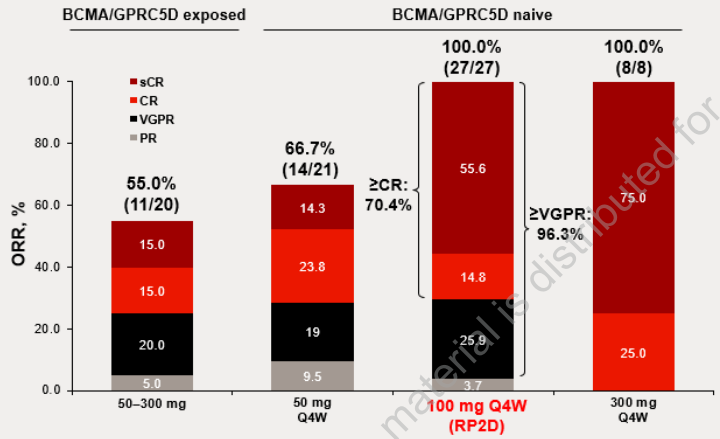
→ 100 mg Q4W SC (5 mg step-up dose)

Improved or similar GPRC5D TEAEs

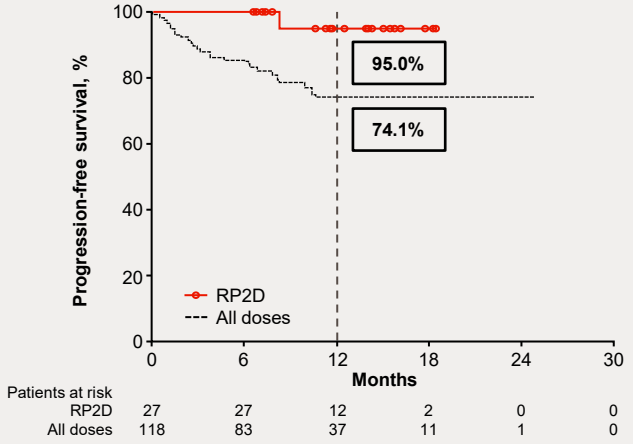
Taste ↓ Weight decrease ↓ Skin ↔ Nail

Low-grade GPRC5D TEAE profile

ORR 100% in patients naive to BCMA/GPRC5D at RP2D



12-month PFS rate 95% in patients naive to BCMA/GPRC5D at RP2D



JNJ-5322 Trispecific: Novel Binding Domains Targeting CD3, BCMA, and GPRC5D

Molecule

Dual-Targeted Molecule to Bind Both BCMA and GPRC5D

Novel CD3, BCMA, and GPRC5D Binding Domains

Implications

- Enhanced myeloma cell targeting due to **"double lock-down"** effect of binding 2 myeloma antigens
- **More comprehensive targeting of myeloma cells**
  - BCMA-/GPRC5D+, BCMA+/GPRC5D-, and dual BCMA+/GPRC5D+
- Prevention of antigen escape
- Potential to improve GPRC5D-related safety profile
- Manageable CRS profile with only 1 step-up dose needed

BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; GPRC5D, G protein–coupled receptor family C group 5 member D.

JNJ-5322 Trispecific: Study Design

Key eligibility criteria

- Triple-class exposed RRMM[a]

Key objectives

- Identify RP2D
- Safety, including DLTs
- Preliminary efficacy assessment

N=147 all doses investigated (all SC)

Dose Escalation

- 5 mg → 40–120 mg Q4W
- 3.6/5.0 mg → 10–30 mg Q2W
- MABEL 0.4 –10 mg Q2W

Dose Optimization

- 5 mg → 50 mg Q4W
- 5 mg → 100 mg Q4W
- 5 mg → 100 mg → 300 mg Q4W

Loading Dose/Schedule Optimization

- 5 mg → 200 mg Q4W[b] → 100 mg Q4W
- 5 mg → 100 mg Q8W
- 5 mg → 200 mg Q8W[c] → 100 mg Q8W

Optimization for Outpatient Dosing

- Lower (2.5 mg) vs higher (10 mg) SUD
- 2–4 vs 6–8 days between step-up and full dose
- Prophylactic tocilizumab

RP2D identification

- 5 mg → 100 mg Q4W SC

The RP2D with 1 SUD was determined based on safety-, PK-, and efficacy-guided endpoints; the MTD was not reached

[a]≥3 prior LOT or triple-class refractory in the United States. [b]200 mg given Q4W for 4 doses, then switched to 100 mg. [c]200 mg given Q8W for 2 doses, then switched to 100 mg. DLT, dose-limiting toxicity; LOT, line of therapy; MTD, maximum tolerated dose; PK, pharmacokinetics; Q2W, every other week; Q4W, every 4 weeks; Q8W, every 8 weeks; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; SUD, step-up dose.

JNJ-5322 Trispecific: Baseline Characteristics

Characteristic	RP2D (n=36)	All doses (N=147)
Median follow-up, months (range)	11.6 (0.4–18.6)	9.3 (0.3–25.8)
Median age, years (range)	67.5 (43–87)	64.0 (39–87)
Male, n (%)	22 (61.1)	87 (59.2)
Race, n (%)		
White	28 (77.8)	110 (74.8)
Black/African American	1 (2.8)	13 (8.8)
Asian	1 (2.8)	7 (4.8)
Multiple	2 (5.6)	2 (1.4)
Unknown/not reported	4 (11.1)	15 (10.2)
Extramedullary plasmacytomas ≥1,[a] n (%)	3 (8.3)	16 (10.9)
High-risk cytogenetics,[b] n (%)	9 (27.3)	39 (31.2)
ISS stage,[c] n (%)		
I	19 (52.8)	77 (53.1)
II	12 (33.3)	50 (34.5)
III	5 (13.9)	18 (12.4)
Years since diagnosis,[d] median (range)	7.0 (0.9–18.7)	6.9 (0.7–31.9)

Characteristic	RP2D (n=36)	All doses (N=147)
Median prior LOT, n (range)	4.0 (2–11)	4.0 (1–11)
Exposure status, n (%)		
Triple-class[e]	36 (100.0)	147 (100.0)
Penta-drug[f]	15 (41.7)	72 (49.0)
BCMA/GPRC5D exposed	9 (25.0)	29 (19.7)
Prior BCMA	8 (22.2)	26 (17.7)
Prior GPRC5D	1 (2.8)	5 (3.4)
BCMA/GPRC5D naive	27 (75.0)	118 (80.3)
Antibody-drug conjugate	2 (5.6)	7 (4.8)
CAR-T therapy	4 (11.1)	12 (8.2)
Bispecific antibody	6 (16.7)	16 (10.9)
Refractory status, n (%)		
PI	19 (52.8)	86 (58.5)
IMiD	36 (100.0)	136 (92.5)
Anti-CD38	36 (100.0)	138 (93.9)
Triple-class[e]	19 (52.8)	79 (53.7)
Penta-drug[f]	2 (5.6)	10 (6.8)
To last LOT	34 (94.4)	132 (89.8)

Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with one 5 mg SUD.
[a]≥1 nonradiated, bone-independent lesion ≥2 cm. Patients with paraskeletal plasmacytomas were permitted but not counted as EMD. [b]FISH or karyotype testing in n=33 (RP2D) and n=125 (total). Defined as del(17p), t(4;14), or t(14;16). [c]In n=145 (total). [d]In n=35 (RP2D) and n=144 (total). [e]≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 mAb. [f]≥2 PIs, ≥2 IMiDs, and ≥1 anti-CD38 mAb. BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; FISH, fluorescence in situ hybridization; GPRC5D, G protein–coupled receptor family C group 5 member D; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; mAb, monoclonal antibody; PI, proteasome inhibitor; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SUD, step-up dose.

JNJ-5322 Trispecific: Treatment-Emergent Adverse Events

Most common TEAEs,[a] n (%)	RP2D (n=36)		All doses (N=147)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic TEAEs (≥10% of total)				
Neutropenia	15 (41.7)	11 (30.6)	72 (49.0)	61 (41.5)
Lymphopenia	16 (44.4)	15 (41.7)	55 (37.4)	52 (35.4)
Anemia	6 (16.7)	3 (8.3)	37 (25.2)	22 (15.0)
Thrombocytopenia	8 (22.2)	3 (8.3)	27 (18.4)	12 (8.2)
Leukopenia	5 (13.9)	3 (8.3)	19 (12.9)	11 (7.5)
Nonhematologic TEAEs (≥30% of total)				
Infections	29 (80.6)	12 (33.3)	111 (75.5)	42 (28.6)
Taste related[b]	21 (58.3)	NA	85 (57.8)	NA
CRS	19 (52.8)	0	83 (56.5)	0
Nail related[c]	22 (61.1)	0	81 (55.1)	0
Skin (non-rash)[d]	23 (63.9)	0	73 (49.7)	1 (0.7)
Hypogammaglobulinemia[e]	10 (27.8)	1 (2.8)	53 (36.1)	4 (2.7)
Diarrhea	11 (30.6)	1 (2.8)	49 (33.3)	5 (3.4)
Fatigue	13 (36.1)	3 (8.3)	48 (32.7)	4 (2.7)

- At the RP2D, 1 DLT (neutropenia) and 1 grade 5 TEAE (pneumonia)
- Across all other doses, 4 DLTs (maculopapular rash, palmar-plantar erythrodysesthesia syndrome, pneumonia, and respiratory failure) and 4 grade 5 TEAEs (adenoviral encephalitis [drug related], embolic stroke, multiple organ dysfunction syndrome, and pulmonary hemorrhage)

Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with one 5 mg SUD. [a]TEAEs graded by CTCAE v5.0; CRS per ASTCT criteria. [b]Dysgeusia, ageusia, hypogeusia, and taste disorder; maximum grade is 2 per CTCAE. [c]Nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxicity, and nail ridging. [d]Skin exfoliation, dry skin, pruritus, and palmar-plantar erythrodysesthesia syndrome. [e]Presented as a TEAE only. ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; NA, not applicable; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SUD, step-up dose; TEAE, treatment-emergent adverse event.

JNJ-5322 Trispecific: CRS, With or Without Prophylactic Tocilizumab, and ICANS

Parameter	100 mg without prophylactic tocilizumab (n=26)	100 mg with prophylactic tocilizumab (n=20)
Patients with CRS,[a] n (%)	18 (69.2)	4 (20.0)
Grade 1	14 (53.8)	4 (20.0)
Grade 2	4 (15.4)	0
Grade 3	0	0
Onset of CRS,[b] days, median (range)	2 (1–4)	1 (1–2)
Duration of CRS, days, median (range)	2 (1–5)	2 (2–2)
Timing of CRS,[c] n (%)		
SUD 1	12 (46.2)	2 (10.0)
First full dose	10 (38.5)	2 (10.0)
≥Second full dose	0	1 (5.0)
Supportive measures for CRS,[d] n (%)	17 (65.4)	4 (20.0)
Tocilizumab	12 (46.2)	2 (10.0)
Oxygen	3 (11.5)	0
Corticosteroids	1 (3.8)	2 (10.0)
Other	14 (53.8)	4 (20.0)
CRS recovered or resolved	18 (100.0)	4 (100.0)

- No ICANS at RP2D

Prophylactic tocilizumab decreased CRS incidence and severity

Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with one 5 mg SUD.
[a]CRS and ICANS graded per ASTCT criteria. [b]Relative to the most recent dose. [c]Patients could experience ≥1 event. [d]Patients could receive ≥1 supportive therapy. ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SUD, step-up dose.

JNJ-5322 Trispecific: Infections Summary

Most common infections (≥10% of total)[a] and hypogammaglobulinemia,[b] n (%)	RP2D (n=36)		All doses (N=147)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Infections	29 (80.6)	12 (33.3)	111 (75.5)	42 (28.6)
Upper respiratory tract infection	14 (38.9)	1 (2.8)	44 (29.9)	4 (2.7)
Pneumonia	6 (16.7)	4 (11.1)	28 (19.0)	21 (14.3)
COVID-19	5 (13.9)	0	21 (14.3)	1 (0.7)
Nasopharyngitis	4 (11.1)	0	15 (10.2)	0
Urinary tract infection	5 (13.9)	1 (2.8)	15 (10.2)	1 (0.7)
Hypogammaglobulinemia	18 (50.0)		90 (61.2)	
Patients receiving ≥1 dose of IVIG[c]	17 (47.2)		83 (56.5)	

- 2 patients died due to infections (adenoviral encephalitis, pneumonia, n=1 each) in setting of hypogammaglobulinemia (<200 mg/dL)

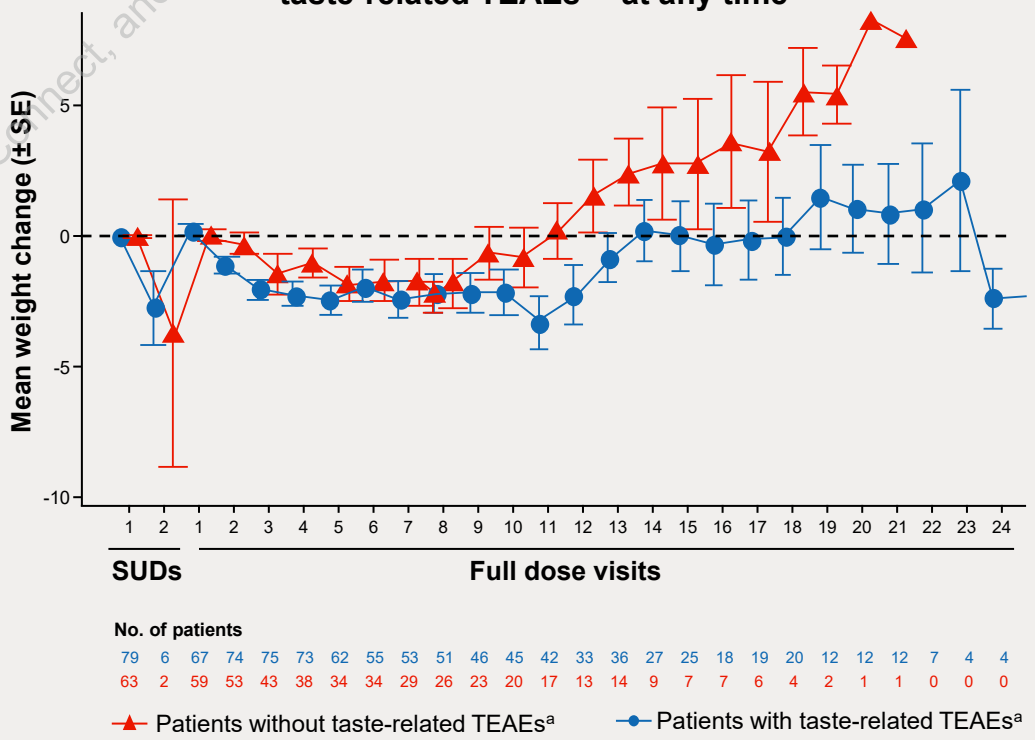
Infections can be managed with monthly IgG monitoring and Ig replacement to maintain IgG ≥400 mg/dL

Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with one 5 mg SUD. [a]TEAEs graded by CTCAE v5.0. TEAEs listed by descending order of frequency in the total population. [b]Patients with ≥1 TEAE or postbaseline IgG value <400 mg/dL. [c]Includes patients who started IVIG prior to treatment. CTCAE, Common Terminology Criteria for Adverse Events; IgG, Immunoglobulin G; IVIG, intravenous immunoglobulin; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SUD, step-up dose; TEAE, treatment-emergent adverse event.

JNJ-5322 Trispecific: GPRC5D Oral TEAEs and Weight Changes

Oral TEAEs, n (%)	RP2D (n=36)				All doses (N=147)			
	All Grade	Grade 1	Grade 2	Grade 3/4	All Grade	Grade 1	Grade 2	Grade 3/4
Taste-related[a]	21 (58.3)	15 (41.7)	6 (16.7)	NA	85 (57.8)	62 (42.2)	23 (15.6)	NA
Non-taste–related								
Dry Mouth	9 (25.0)	9 (25.0)	0	0	26 (17.7)	25 (17.0)	1 (0.7)	0
Dysphagia	0	0	0	0	5 (3.4)	1 (0.7)	4 (2.7)	0
Glossitis	1 (2.8)	0	1 (2.8)	0	1 (0.7)	0	1 (0.7)	0
Stomatitis	1 (2.8)	1 (2.8)	0	0	5 (3.4)	3 (2.0)	2 (1.4)	0
Decreased appetite	5 (13.9)	2 (5.6)	2 (5.6)	1 (2.8)	19 (12.9)	12 (8.2)	5 (3.4)	2 (1.4)

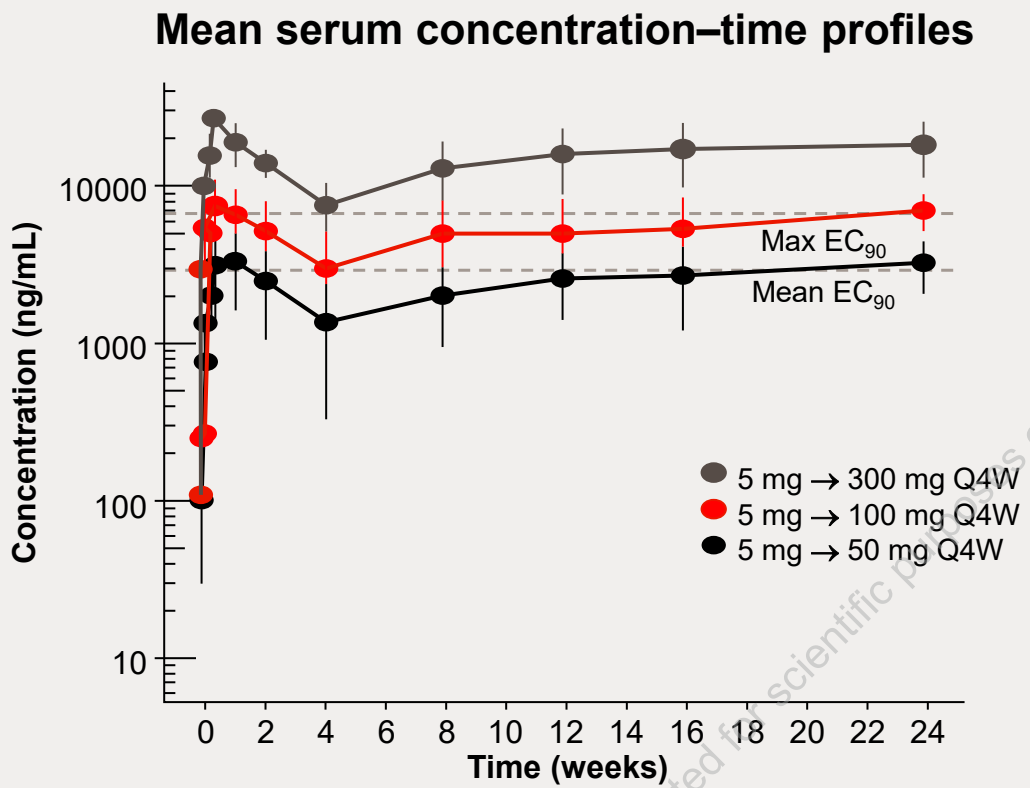
Weight change from baseline according to taste-related TEAEs[a,b] at any time



Grade 1/2 weight loss is usually transient and occurred in 6% (RP2D) and 12% (all doses). No grade ≥3 events

Data cut-off date: April 15, 2025. Median follow-up: 11.6 months (RP2D) and 9.3 months (all doses). RP2D selected as 100 mg Q4W with one 5 mg SUD.
[a]Includes dysgeusia, ageusia, hypogeusia, and taste disorder. [b]Weight measurements were used to assess weight loss, and then the percentage change from baseline was graded per CTCAE. CTCAE, Common Terminology Criteria for Adverse Events; GPRC5D, G protein–coupled receptor family C group 5 member D; NA, not applicable; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SE, standard error; SUD, step-up dose; TEAE, treatment-emergent adverse event.

JNJ-5322 Trispecific: Pharmacokinetics

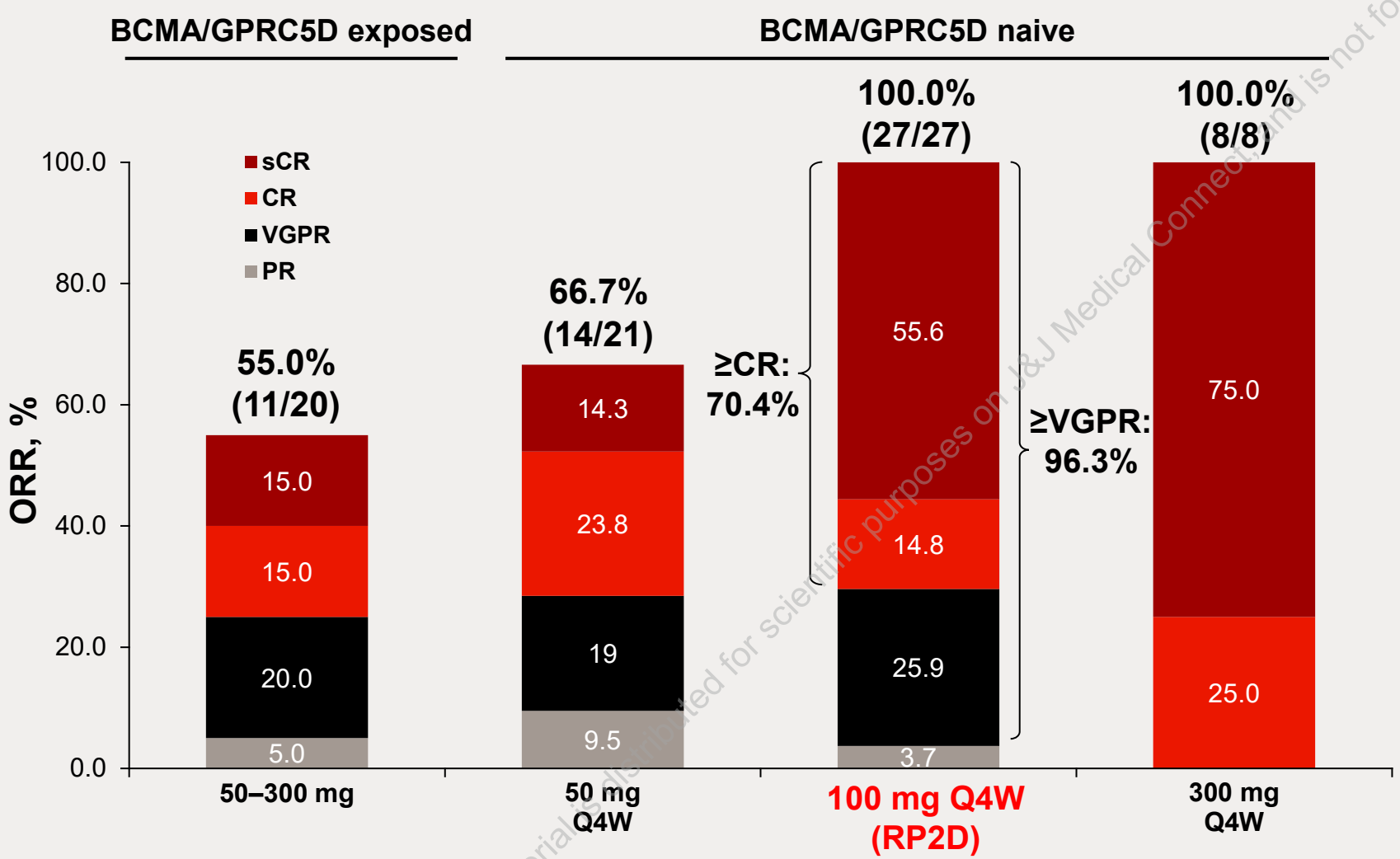


- Exposure increased in an approximately dose-proportional manner across all doses
- Steady state was reached after 12 weeks, with an estimated steady state half-life of ~17 days
- After first dose administration, the mean serum concentration slowly increased across all doses, reaching a median maximum observed serum concentration after 7 days for Q4W dosing

At the RP2D, the mean serum concentration was maintained above the mean EC_{90}

RP2D selected as 100 mg Q4W with one 5 mg SUD.
EC_{90}, 90% maximal effective concentration; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SUD, step-up dose.

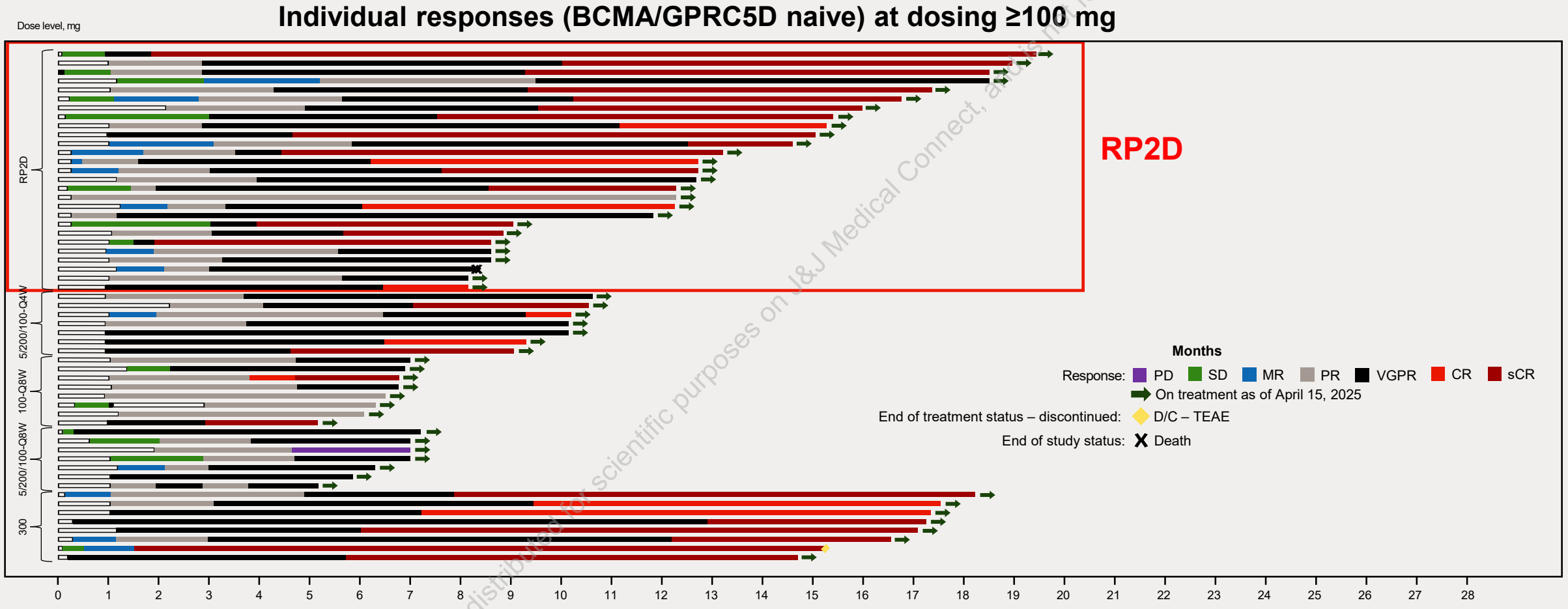
JNJ-5322 Trispecific: ORR in Patients Naive or Exposed to BCMA/GPRC5D Therapies



At the RP2D in patients naive to BCMA/GPRC5D (n=27)	
Median follow-up, months (range)	12.2 (7.4–18.6)
Median time to first response, months (range)	1.2 (0.3–5.2)
Median time to best response, months (range)	5.9 (0.3–11.1)

Data cut-off date: April 15, 2025. Median follow-up 16.4 months in the 300 mg Q4W cohort. RP2D selected as 100 mg Q4W with one 5 mg SUD. BCMA, B-cell maturation antigen; CR, complete response; GPRC5D, G protein–coupled receptor family C group 5 member D; ORR, overall response rate; PR, partial response; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; sCR, stringent complete response; SUD, step-up dose; VGPR, very good partial response.

JNJ-5322 Trispecific: Individual Response in Patients Naive to BCMA/GPRC5D Therapies

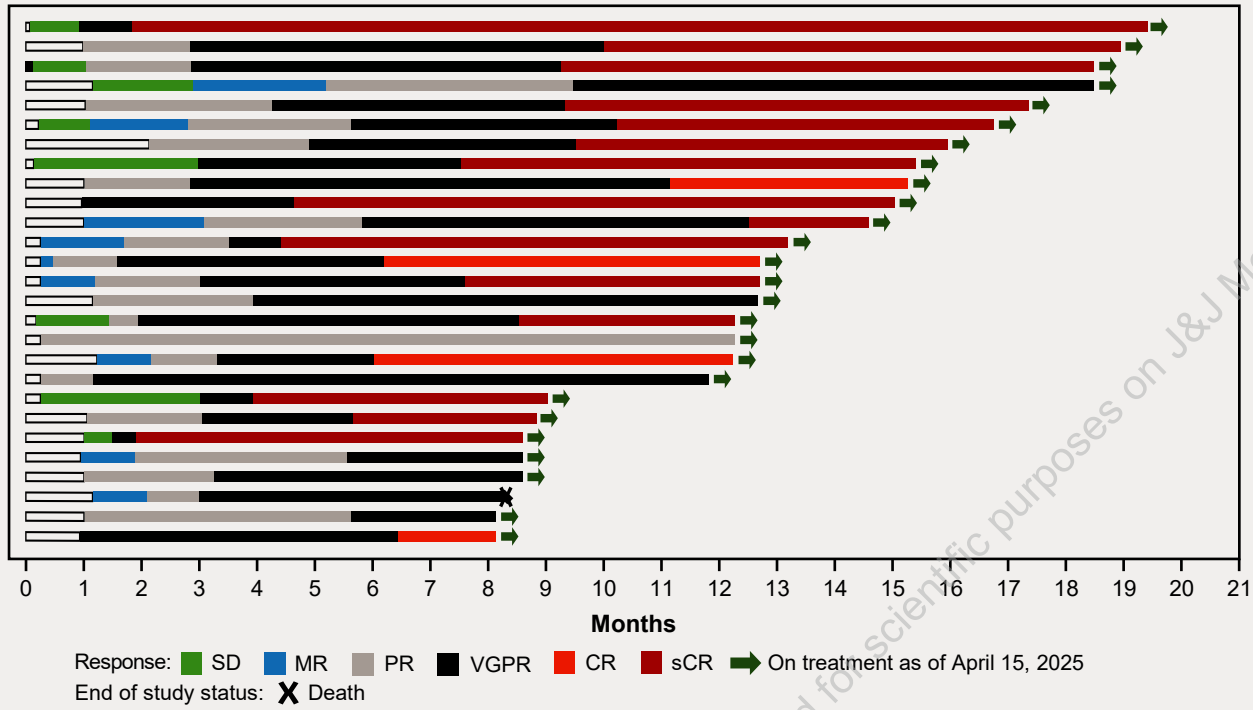


Almost all patients remain in response with 12 months of follow-up[a]

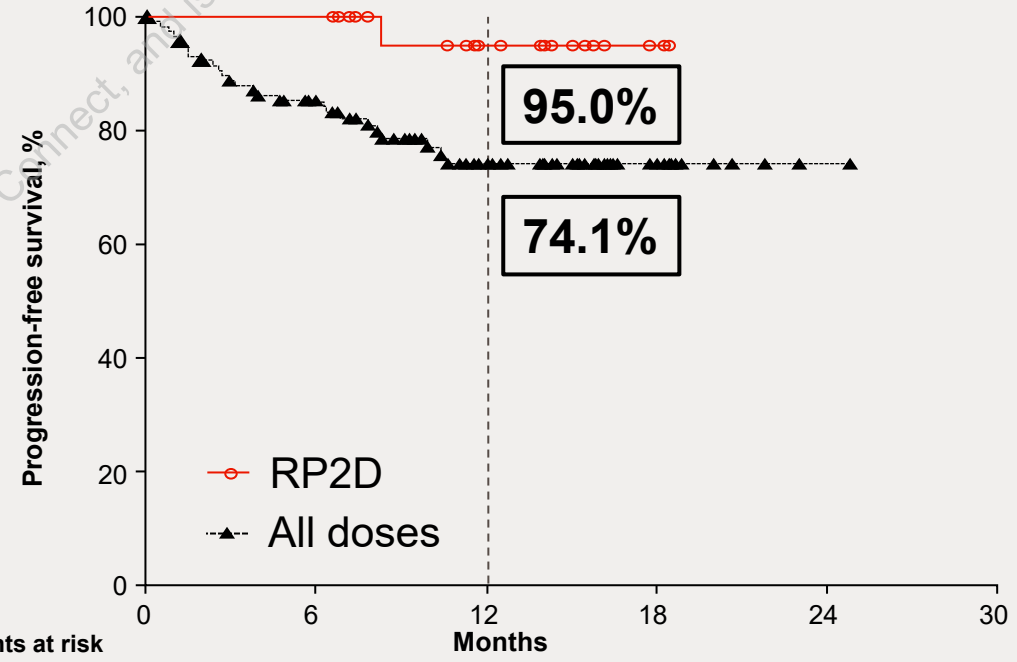
Data cut-off date: April 15, 2025. RP2D selected as 100 mg Q4W with one 5 mg SUD. [a]One patient was in response at time of death. BCMA, B-cell maturation antigen; CR, complete response; D/C, discontinued; GPRC5D, G protein–coupled receptor family C group 5 member D; MR, minimal response; PD, progressive disease; Q4W, every 4 weeks; Q8W, every 8 weeks; RP2D, recommended phase 2 dose; sCR, stringent complete response; SD, stable disease; SUD, step-up dose; TEAE, treatment-emergent adverse event; VGPR, very good partial response.

JNJ-5322 Trispecific: Individual Response and PFS at the RP2D (100 mg Q4W With One 5 mg SUD)

Individual responses (BCMA/GPRC5D naive) at RP2D



PFS (BCMA/GPRC5D naive)



Patients at risk						
RP2D	27	27	12	2	0	0
All doses	118	83	37	11	1	0

1 discontinuation at the RP2D
(death while in VGPR)
No progression or other discontinuations at RP2D to-date

12-month PFS 95.0% at the RP2D
(74.1% across all doses)
PFS data support the RP2D

Data cut-off date: April 15, 2025. BCMA, B-cell maturation antigen; CR, complete response; GPRC5D, G protein–coupled receptor family C group 5 member D; MR, minimal response; PFS, progression-free survival; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; sCR, stringent complete response; SD, stable disease; SUD, step-up dose; VGPR, very good partial response.

JNJ-5322 Trispecific: Potential Paradigm Shift With ORR Comparable to CAR-T

- **JNJ-5322 100 mg Q4W SC with 1 SUD (2–8 days before first full dose) of 5 mg was selected as the RP2D**
- **JNJ-5322 appeared to have an improved or similar safety profile compared with bispecific antibodies targeting BCMA/GPRC5D**
  - Grade 3/4 infection rate of 28.6% with appropriate infection management
  - Improved oral TEAE profile, with minimal to no weight loss
  - CRS events were low grade with only 1 SUD; prophylactic tocilizumab data support option for outpatient dosing
- **ORR at the RP2D in patients naive to BCMA/GPRC5D of 100% (≥CR, 70.4%)**
  - 12-month PFS of 95.0% at the RP2D in BCMA/GPRC5D-naive patients

JNJ-5322, a BCMA×GPRC5D T-cell engaging trispecific antibody, demonstrated manageable safety and an ORR comparable to CAR-T, with convenient, off-the-shelf, Q4W dosing with 1 SUD to facilitate outpatient dosing

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; GPRC5D, G protein–coupled receptor family C group 5 member D; ORR, overall response rate; PFS, progression-free survival; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous; SUD, step-up dose; TEAE, treatment-emergent adverse event.

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