Early, Deep, and Durable Responses, and Low Rates of Cytokine Release Syndrome with REGN5458, a BCMAxCD3 Bispecific Antibody, in a Phase 1/2 First-in-Human Study in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

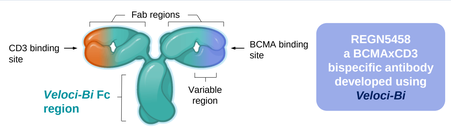
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Background

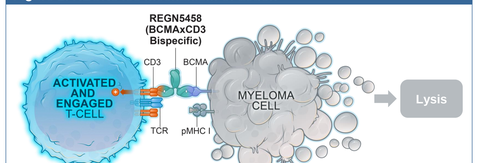
- REGN5458 is a BCMAxCD3 bispecific antibody that targets T-cell effector function to induce cytotoxicity of BCMA-expressing MM cells (Figures 1 and 2)
- Poor outcomes are observed in patients with MM who are refractory to multiple classes of therapies, with a median PFS of ~3–5 months and OS of 6–15 months[1,2]
- Here, we report results from an ongoing phase 1 study of REGN5458 IV in patients with relapsed/refractory MM

Figure 1. REGN5458 molecular structure



The *Veloci-Bi* platform allows for creation of bispecific antibodies that closely resemble natural human antibodies.

Figure 2. REGN5458 mechanism of action



First-in-human study design

Primary objectives (Phase 1)

- Safety, tolerability, and DLTs
- Recommended Phase 2 dose (RP2D)

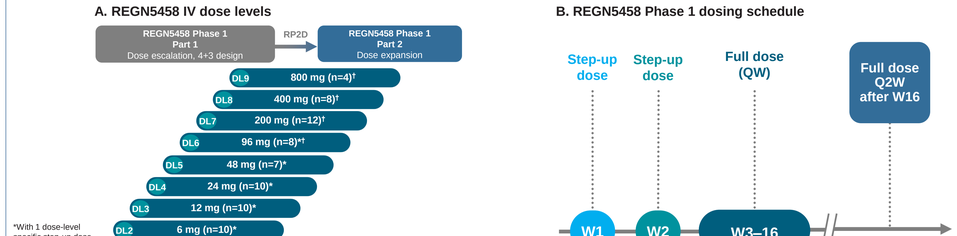
Secondary objectives (Phase 1)

- ORR, DOR, PFS, MRD status, and OS

Patient eligibility

- Active MM by IMWG; non-secretory MM allowed
- Relapsed/refractory (or intolerance) to ≥3 lines of therapy including an IMiD, a PI, and an anti-CD38 Ab, or double-refractory to an IMiD and PI and progressed on or after an anti-CD38 Ab

Figure 3. First-in-human study design



Baseline characteristics

Table 1. Baseline characteristics

Patient and disease characteristics	Total (N=73)
Median age, years (range)	64 (41–81)
Age ≥75 years, n	15 (21%)
Male, n	34 (47%)
ECOG performance status, n	
0	21 (29%)
1	51 (70%)
2	1 (1%)
Revised ISS stage at study entry, n	
I	11 (15%)
II	42 (58%)
III	17 (23%)
Prior autologous transplant, n*	47 (64%)
Plasma cell burden – BMPC ≥50, n	17/44 (39%)†
Cytogenetic high risk‡, n	10/57 (18%)†
Prior systemic treatment	**Total (N=73)**
Refractory status, n	
Proteasome inhibitor	70 (96%)
Anti-CD38 Ab (daratumumab/isatuximab)	70 (96%)
Immunomodulatory drug	69 (95%)
Median prior lines of therapy, n (range)	5 (2–17)
Progressed-refractory, n	
Triple-refractory§	65 (89%)
Quad-refractory‖	51 (70%)
Penta-refractory¶	28 (38%)
Refractory to last line of therapy#, n	66 (90%)

*Includes 2 patients who underwent tandem autologous transplant; †Among patients with available samples; ‡Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16); §Refractory to 1 anti-CD38, ≥1 IMiD, ≥1 PI; ‖Refractory to 1 anti-CD38, 2 IMiDs, ≥1 PI OR 1 anti-CD38, ≥1 IMiDs, 2 PIs; ¶Refractory to 1 anti-CD38, 2 IMiDs, 2 PIs; #Includes patients with a lack of response or relapse within 60 days of last line of therapy.

Safety

Dose-limiting toxicity (DLT)

- DLTs were reported in 2 patients
  - DL4 (24 mg) and DL6 (96 mg)
- Maximum-tolerated dose not reached

CRS

- No Grade ≥3 CRS (Figure 4)
  - The majority of patients did not develop CRS
  - Majority of CRS events were Grade 1
  - Only 3 patients (4%) experienced Grade 2 CRS
  - CRS onset most common in first 2 weeks (Table 3)
- No relationship was observed between CRS and dose level, or CRS and response

Potential ICANS events

- No Grade 3 ICANS events reported
- Grade 2 events occurred in 3 patients (4%)

Deaths

- 5 (7%) Grade 5 AEs were reported [sepsis (n=3); COVID (n=1); pneumonia (n=1)]
- All Grade 5 events were not related to study treatment

Pharmacokinetics

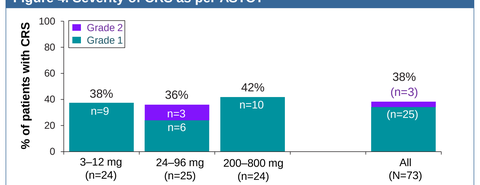
- REGN5458 serum concentration increased with dose, approximately dose proportionally

Table 2. Treatment-emergent adverse events

	Total (N=73)		
	Any grade	Grade 3	Grade 4
All treatment-emergent adverse events (TEAEs) n (%)			
Any	73 (100)	31 (42)	24 (33)
Hematologic TEAEs, *in ≥20% of patients (any grade)* **n (%)**			
Anemia	23 (32)	17 (23)	0
Lymphopenia	17 (23)	7 (10)	7 (10)
Neutropenia	17 (23)	5 (7)	11 (15)
Thrombocytopenia	15 (21)	6 (8)	4 (5)
Non-hematologic TEAEs, *in ≥20% of patients (any grade)* **n (%)**			
Fatigue	33 (45)	2 (3)	0
CRS	28 (38)	0	0
Pyrexia	26 (36)	3 (4)	0
Nausea	24 (33)	0	0
Dyspnea	19 (26)	0	0
Diarrhea	18 (25)	2 (3)	0
Back pain	18 (25)	4 (5)	0
Vomiting	18 (25)	0	0
Pneumonia	17 (23)	8 (11)	0
Chills	16 (22)	1 (1)	0
Cough	16 (22)	0	0
Headache	15 (21)	2 (3)	0

All AEs were TEAEs irrespective of causality and were evaluated based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) except CRS which was graded per ASTCT.[3] Composite terms include neutropenia (neutrophil count decreased, neutropenia), thrombocytopenia (platelet count decreased, thrombocytopenia), lymphopenia (lymphocyte count decreased, lymphopenia), leukopenia (white blood cell count decreased, leukopenia), anemia (hemoglobin decreased, anemia), sepsis SMQ narrow (MedDRA 24.0 SMQ [narrow]). Total patient number represents the total number of patients treated.

Figure 4. Severity of CRS as per ASTCT*



*The highest severity of CRS per ASTCT[3] from each patient was included.

Table 3. Incidence, timing, and management of CRS

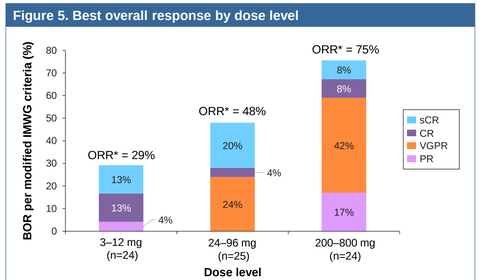
Study population	Total (N=73)
Patients with CRS, n	28 (38%)
Median time to first CRS* onset†, hours (range)	10.1 (6–47)
Median duration of CRS, hours (range)	14.7 (0–96)
Patients with supportive measures to treat CRS, n	Total patients with CRS (n=28)
Tocilizumab	12 (43%)
Steroids	6 (21%)

*The highest severity of CRS per ASTCT[3] from each patient was included.
†From the start of infusion of the most recent prior dose.

Phase 1 efficacy

- Observed median duration of follow-up (range): 3 months (0.7–22.1)
- Responses have been observed across all dose levels, with a trend for higher response rates at higher doses
  - 51% ORR among all enrolled patients (full analysis set – includes all patients who had opportunity for response assessment at 4 weeks)
- 75% ORR and 58% ≥VGPR with REGN5458 200–800 mg (Figure 5)
- Among all responders, 86% achieved ≥VGPR, 43% ≥CR
- Among CR/sCR with available MRD data:
  - 4/10 MRD negative at 10^{-5}

Figure 5. Best overall response by dose level

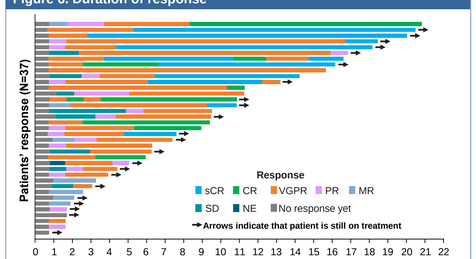


Data cut-off: 30 September 2021.
*Full analysis set - includes all patients who had opportunity for response assessment at 4 weeks.

Duration of response

- Responses occurred early, were durable, and deepened with time (Figure 6)
  - Median time to response is <1 month
  - 70% of responses occurred within the first 2 months
- Estimated median DOR was not reached (includes patients who had opportunity for response assessment at 4 weeks; estimated Kaplan-Meier method)
  - Using the estimated Kaplan-Meier method, the probability of responders being in response at 8 months was 90.2% (95% CI: 72.6, 96.7)
- The longest responses are ongoing for 19+ months at the latest data cut-off

Figure 6. Duration of response



Data cut-off: 30 September 2021.

REGN5458: Conclusions

- **Early, deep, and durable responses are observed with REGN5458 in patients with RRMM who are at least triple refractory to prior treatment**
  - ORR of 75% and 58% ≥VGPR at higher doses (200–800 mg)
  - 86% of responders achieved VGPR or better; 43% ≥CR
  - Estimated median DOR was not reached
  - Probability of responders being event free at 8 months was 90.2% (95% CI: 72.6, 96.7)
- **REGN5458 shows an acceptable safety and tolerability profile**
  - Maximum-tolerated dose has not been reached
  - CRS was reported in 38% of the patients
    - The majority of events were Grade 1, occurred within the first 2 weeks and resolved within 1 day
    - No Grade ≥3 CRS
    - No correlation between CRS and dose level was observed
- **REGN5458 showed promising efficacy and an acceptable safety profile in patients with heavily pretreated RRMM**
- **These results support further development as monotherapy. Phase 2 portion of the study is recruiting**

References

1. Gandhi U, et al. *Leukemia*. 2019;33:2266–75. 2. Kumar SK, et al. *Leukemia*. 2017;31:2443–48.
3. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625–38.

Disclosures

ClinicalTrials.gov ID: NCT03761108. This study was funded by Regeneron Pharmaceuticals, Inc. The data described in the presentation will report on the investigational use of REGN5458 in a first-in-human trial in patients with multiple myeloma. REGN5458 has not been approved or evaluated by any regulatory authority. This study is compliant with the Declaration of Helsinki for Studies involving Human Subjects

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Ab, antibody; AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cells; BOR; best overall response; CD, cluster of differentiation; CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DL, dose level; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Fab, fragment antigen-binding; Fc, fragment crystallizable region; ICANS, immune effector cell-associated neurotoxicity syndrome by preferred term and each National Cancer Institute [NCI] grade-core treatment based on sponsor-provided list; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; ISS, International Staging System; IV, intravenous; MM, multiple myeloma; MR, minimal response; MRD, minimal residual disease; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; pMHC, peptide-loaded major histocompatibility complex; PR, partial response; QW, weekly; Q2W, every 2 weeks; RP2D, recommended Phase 2 dose; RR, relapsed/refractory; sCR, stringent CR; SD, stable disease; SMQ, standardized MedDRA queries; TCR, T-cell receptor; TEAE, treatment-emergent adverse events; VGPR, very good partial response; W, week.

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