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Safety and Preliminary Clinical Activity of REGN5458, an Anti-BCMA x Anti-CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma

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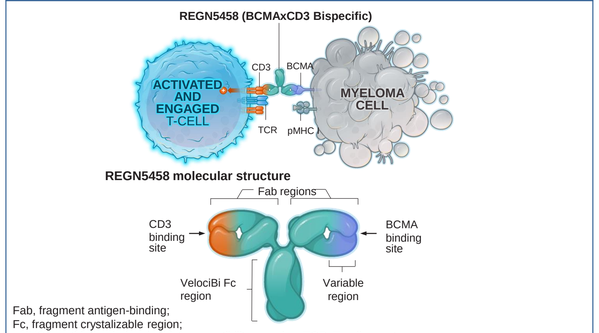
Introduction

- Multiple myeloma (MM) is characterized by the expansion of malignant plasma cells which express the cell surface protein B-cell maturation antigen (BCMA).
- REGN5458, an anti-BCMA x anti-CD3 bispecific antibody (BCMAxCD3 bsAb), is designed to closely resemble natural human antibodies, using Regeneron's proprietary 'human antibody mouse' technology (*VelocImmune®*) and 'full-length bispecific antibody' platform (*VelociBi™*).
- REGN5458 binds to both BCMA on plasma cells and to CD3 on T-cells, thereby utilizing BCMA to redirect T-cell effector function to multiple myeloma (MM) cells (**Figure 1**).

Figure 1. REGN5458 mode of action and molecular structure



Fab, fragment antigen-binding;
Fc, fragment crystalizable region;
pMHC, peptide-loaded major histocompatibility complex; TCR, T-cell receptor.

Preclinical data

- REGN5458 mediates killing of MM cell lines and primary human plasma cells **(Figure 2A-C).**
- REGN5458 (BCMAxCD3 bsAb) demonstrates anti-tumor efficacy in a dose-dependent manner in xenogenic MM tumor models with variable BCMA levels (**Figure 3A-B**).

Figure 2. T-cell mediated killing of cell lines

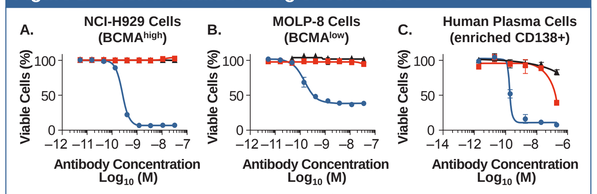


Figure 3. BCMAxCD3 bsAb antitumor efficacy in mice

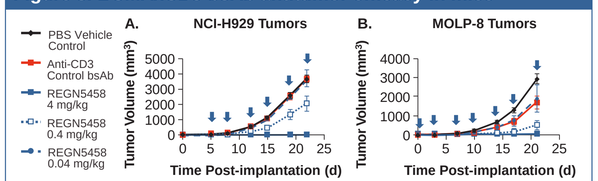


Figure 2. Adherent cell-depleted peripheral blood mononuclear cells (PBMC) were incubated with BCMA^{high} NCI-H929 (A) or BCMA^{low} MOLP-8 MM cells (B), or enriched CD138+ human bone marrow plasma cells were cultured with autologous PBMC (C). Either REGN5458 (BCMAxCD3 bsAb), CD3-binding control bsAb, or parental anti-BCMA monoclonal antibody (mAb) was added and the cells were cultured for 48 hours before cell viability was measured by flow cytometry analysis. Values represent mean (± SD) frequencies of viable target cells from duplicate samples. **Figure 3**. NSG mice were co-implanted subcutaneously with a mixture of human PBMC and either NCI-H929 (A) or MOLP-8 (B) MM cells. Mice were dosed with the indicated antibody twice weekly starting on day 5 (A) or day 0 (B).

Methods

Clinical study design

- This is a Phase 1/2, open-label, first-in-human study of REGN5458 (NCT03761108) in patients with relapsed/refractory (R/R) MM.
- The Phase 1 portion enrolls patients with R/R MM in a 4+3 dose-escalation design.
- REGN5458 is administered according to the treatment schedule shown in **Figure 4.**

Phase 1 Primary objectives

- To assess safety, tolerability, and dose-limiting toxicities (DLTs) and to determine the recommended Phase 2 dose of REGN5458 as monotherapy in patients with R/R MM.

Phase 1 Secondary objectives

- To evaluate pharmacokinetics, characterize immunogenicity, assess preliminary anti-tumor activity.

Figure 4. Patient flow diagram

Screening period	REGN5458 treatment period		Follow-up	
Up to 28 days	QW x 16 IV doses	Q2W x 12 IV doses	Core follow-up (6 months)	Extended follow-up (9 months)

IV, intravenously; QW, every week; Q2W, every 2 weeks.

Key inclusion criteria*

- Age ≥18 years.
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1.
- Progression on or after ≥3 prior lines of therapy including proteasome inhibitor (PI), immunomodulatory agent (IMiD), and anti-CD38 Ab; or progression on or after an anti-CD38 Ab and double refractory to a PI and an IMiD.
- Patients with non-secretory MM may be considered for enrollment after discussion with the sponsor that includes feasibility of response assessment according to International Myeloma Working Group (IMWG) guidelines[1].

Key exclusion criteria*

- History of any allogeneic stem cell transplantation, or autologous stem cell transplantation within 12 weeks of the start of study treatment.
- Prior treatment with any anti-BCMA antibody (including antibody drug conjugate or bispecific antibody) or BCMA-directed CAR T therapy.

*Expanded list of key inclusion and exclusion criteria are available at clinicaltrials.gov.

Results

- Seven patients, with a median of seven lines of prior systemic therapy, all failing anti-CD38 antibody treatment, were enrolled in two dose groups with REGN5458 (3 mg and 6 mg weekly doses) and had opportunity for assessment at 4 weeks; clinical cut-off date: October 11, 2019.
- Responses were observed in four of seven (57%) patients, including three of four (75%) in the 6 mg dose group. Two patients (50%) in the 6 mg dose group were minimal residual disease (MRD) negative, meaning that no cancer cells were detectable in the bone marrow.
- With a duration of follow-up ranging from 1.8–7.5 months, three responders have ongoing responses (duration of response range 1–5.2 months) (**Figure 5**)**.**

Adverse events

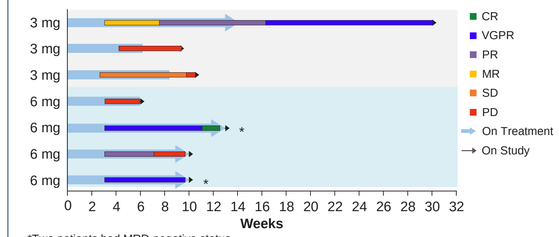
- Adverse events (AEs) are summarized in **Table 2**.
- No patient had a Grade 5 treatment-emergent AE (TEAE).
- One patient experienced three serious TEAEs of febrile neutropenia, pain in extremity, and septic shock.
- Three patients experienced Grade 1 cytokine release syndrome; no patient experienced infusion-related reactions.
- No DLTs were reported**.**

Table 1. Patient demographics and baseline characteristics

	3 mg (N=3)	6 mg (N=4)	Total (N=7)
Median age, years (range)	78 (76–81)	74 (59–79)	78 (59–81)
Age ≥70, n	3	2	5
Male, n	1	3	4
ECOG PS 1, n	3	3	6
Revised ISS at study entry, n			
II	3	3	6
III	0	1	1
Median prior lines of systemic therapy, (range)	6 (4–7)	9.5 (2–17)	7 (2–17)
Progressed-Refractory, n			
Lenalidomide	2	4	6
Bortezomib	2	4	6
Carfilzomib	3	3	6
Pomalidomide	3	2	5
Daratumumab	3	4	7

ISS, International Staging System

Figure 5. Duration of response in individual patients



*Two patients had MRD negative status.
The arrow for 'on study' is plotted to the last overall response assessment.
CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

Table 2. Summary of AEs

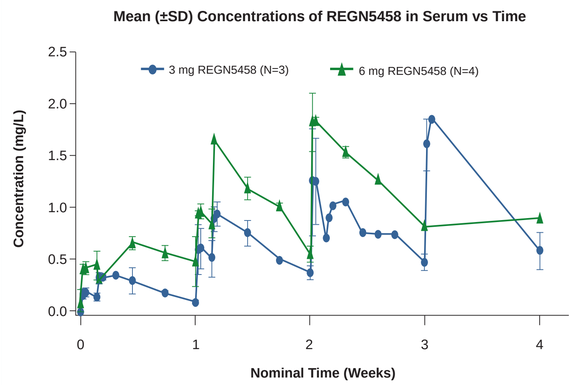
N, patients	Any Grade	Grade ≥3
At least one TEAE	7	5
Serious AE	1	1
TEAE*		
Lymphopenia†	5	3
Anemia	4	1
Thrombocytopenia§	3	1
CRS	3	0
Hypertension	2	2
Fatigue	2	1
Pain in extremity	2	1
Atrial fibrillation	1	1
Febrile neutropenia	1	1
Septic shock	1	1

*Data shown are limited to TEAEs that had n ≥3 patients for any Grade or n ≥1 patient for Grade 3 or higher; †Composite term also includes lymphocyte count decreased; §Composite term also includes platelet count decreased. CRS, cytokine release syndrome.

Pharmacokinetics and biomarkers

- Preliminary data suggest that the mean concentrations of REGN5458 in serum in patients with MM appear increased with dose from 3 mg to 6 mg (**Figure 6**).
- Time to peak cytokine concentration varied within a dose and across dose levels (data not shown).

Figure 6. Pharmacokinetics



Summary

- **A total of seven patients (median age 78 years) with R/R MM (median seven lines of prior systemic therapies, all of whom failed anti-CD38 treatment) have been treated with REGN5458, an anti-BCMA x anti-CD3 bispecific antibody (NCT03761108).**
- **As of data cut-off, no DLTs were reported.**
- **Antitumor activity of REGN5458 observed at initial dose levels in patients with primarily medullary and secretory MM.**
  - **Responses were observed in four of seven (57%) patients, including three of four (75%) in the 6 mg dose group.**
  - **Two patients (50%) in the 6 mg dose group were MRD negative.**
  - **Three responders had ongoing responses at the time of the data cut-off.**
- **Enrollment into the Phase 1 dose escalation portion is ongoing.**

Disclosures

DC: There are no relationships to disclose; **DM**: Consultant for Foundation Medicine, AbbVie, Celgene and Takeda; **SL**: Consultant for Janssen, BMS, Takeda, Abbvie, Bayer, Sanofi, Proclara; equity ownership and board member for Caelum Biosciences; Research funding from Karyopharm and Sanofi; honoraria from International Myeloma Foundation, Multiple Myeloma Research Foundation, Physician Education Resources (PER); patent Columbia University; 11-1F4mAb as Anti-Amyloid Strategy; speaker bureau for Clinical Care Options; **SJ**: Consultant for Celgene Corporation, Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck & Co, Karyopharm Therapeutics, AbbVie; **JL, AB, LA, DC, MZ, WZ, KO, DD, IL, DMW, GDY, MS, MK**, **DS**: Employees and shareholders of Regeneron Pharmaceuticals, Inc.

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1. Rajkumar et al. *Lancet Oncol.* 2014;15:e538–48

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