PHARMACODYNAMICS OF SEA-BCMA, A NONFUCOSYLATED ANTIBODY TARGETING BCMA, IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

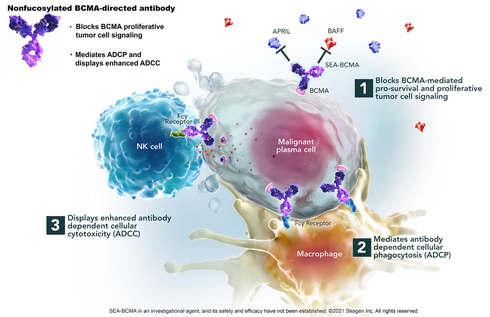
David Taft,[1] Clark Henderson, PhD,[1] Christine O'Day, PhD,[1] Changpu Yu,[1] Hong Li, PhD,[1] Phoenix Ho, MD,[1] Heather Van Epps, PhD[1]

[1]Seagen Inc., Bothell, WA, USA

Background

- SEA-BCMA is an investigational, humanized, nonfucosylated IgG1 monoclonal antibody targeting B-cell maturation antigen (BCMA) on malignant plasma cells.[1,2]
- Unconjugated antibodies that are well tolerated and can be combined with multiple modalities are an integral part of the multiple myeloma (MM) treatment landscape.
- Preclinical data show that SEA-BCMA blocks BCMA-mediated pro-survival and proliferative cell signaling, and mediates antibody-dependent cellular phagocytosis and enhanced antibody-dependent cellular cytotoxicity via increased binding to the activating Fc receptor FcγRIIIa (**Figure 1**).[2]
- A phase 1, open-label, multicenter study to evaluate the safety, tolerability, and antitumor activity of SEA-BCMA in adults with relapsed/refractory MM (SGNBCMA-001; NCT03582033) is ongoing.
- We investigated the binding and saturation pharmacodynamics (PD) of SEA-BCMA in patients enrolled in the dose-escalation and currently recruiting dose-expansion cohorts.

Figure 1. Proposed Mechanisms of Action of SEA-BCMA[2]



APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; NK, natural killer; SEA, sugar-engineered antibody.

Methods

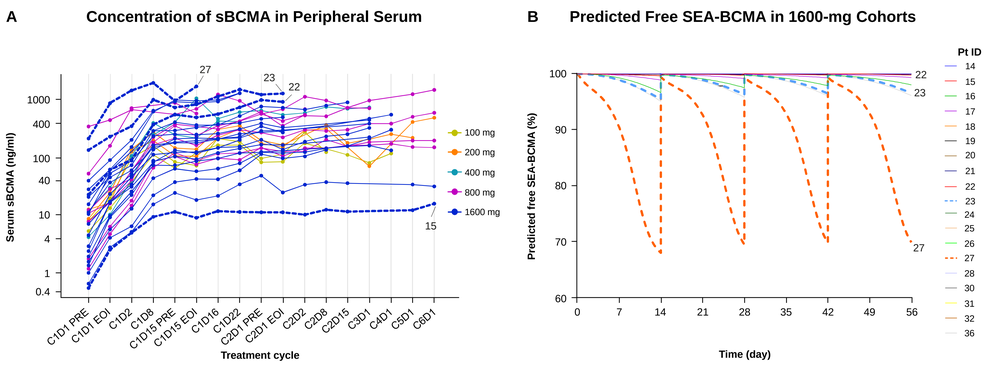
Novel Quantitative Assays Assessing BCMA and the Availability of SEA-BCMA

- Patient serum and/or bone marrow samples were collected at pre-dose and on-treatment timepoints.
- Novel quantitative assays were deployed to assess the BCMA target and the availability of SEA-BCMA:
  - A liquid chromatography-mass spectrometry (LC-MS) assay to detect total soluble BCMA (sBCMA) in serum.
  - A flow cytometry-based cell line binding capacity assay to assess the direct binding and saturation capacity of SEA-BCMA in serum.
  - A BCMA expression and receptor occupancy (RO) assay profiling malignant plasma cells in bone marrow aspirates by flow cytometry.

Results

Figure 2. Interference by sBCMA Is Overcome Through Optimal Dosing at 1600 mg

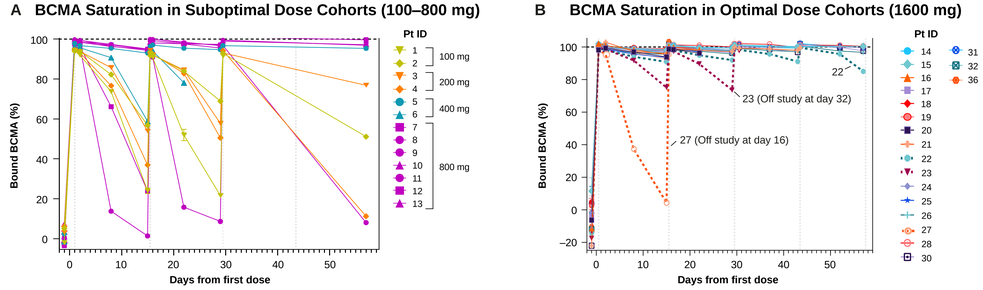
- sBCMA, produced through the clipping of extracellular membrane BCMA by γ-secretase, can be a decoy for BCMA-targeted antibodies.
- The median baseline sBCMA level in patients was 8.5 ng/mL (range, 0.5–352.0 ng/mL). After the first SEA-BCMA dose, a rapid and sustained increase in sBCMA was observed [median, 32-fold (range, 3–139-fold)] (**Figure 2A**).
- Binding of SEA-BCMA to sBCMA may result in the observed increase of sBCMA on treatment by:
  - Reduced clearance of sBCMA within the SEA-BCMA:sBCMA complex.
  - Diffusion of free sBCMA from tissue into the central blood compartment.
- A pharmacokinetic (PK)/PD model describing SEA-BCMA and sBCMA binding and clearance kinetics was used to predict "free" unbound SEA-BCMA per patient. Most patients in the 1600-mg cohorts are predicted to have >95% free SEA-BCMA (**Figure 2B**).
- Patients 27 and 23, who showed high sBCMA levels (**Figure 2A**, dashed lines), also displayed a lower predicted percent of unbound SEA-BCMA (**Figure 2B**, dashed lines).



BCMA, B-cell maturation antigen; C, cycle; D, day; EOI, end of infusion; PRE, pre-infusion; Pt, patient; sBCMA, soluble BCMA; SEA, sugar-engineered antibody.

Figure 3. BCMA Saturation Is Confirmed at the Optimal SEA-BCMA Dose

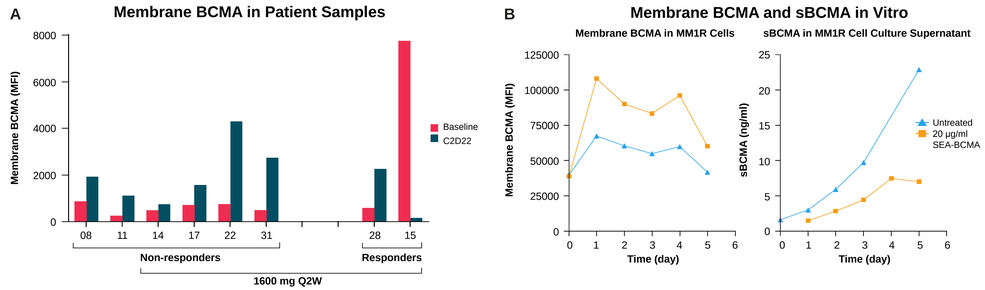
- BCMA saturation by SEA-BCMA was assessed in BCMA-expressing MM1R cells using a flow cytometry-based cell line binding capacity assay, and a dose-dependent ability of SEA-BCMA to saturate BCMA-expressing MM1R cells was observed.
  - In the 100- and 200-mg cohorts, BCMA saturation was not sustained through the first 2 cycles (4 total doses), while in the 800-mg cohort, 29% (2/7) patients did not sustain BCMA saturation (**Figure 3A**).
  - In the 1600-mg cohort, 84% (16/19) of patients sustained BCMA saturation (**Figure 3B**).
- The 3 patients at the 1600-mg dose (patients 27, 23, and 22) that did not sustain BCMA saturation had the highest levels of sBCMA (**Figure 2A**, dashed lines), which indicated sBCMA:SEA-BCMA complex formation may limit drug exposure and informed the decision to explore a more intensive weekly dosing regimen at the 1600-mg dose.



Dashed vertical lines represent dosing days with pre- and end-of-infusion timepoints.
BCMA, B-cell maturation antigen; Pt, patient.

Figure 4. Membrane BCMA Increases on Treatment

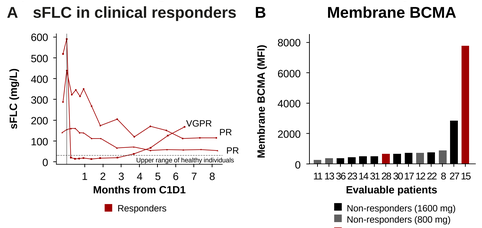
- Membrane BCMA expression was assessed on malignant plasma cells in patient bone marrow aspirates.
- An increase in membrane BCMA from baseline was observed across most evaluable patients at cycle 2, day 22 (C2D22) (**Figure 4A**).
- To support the clinical findings, in vitro experiments were performed to assess membrane BCMA expression and sBCMA release in BCMA-expressing MM1R cells treated with SEA-BCMA (**Figure 4B**).
- These data demonstrate that membrane BCMA increases and sBCMA production is reduced in response to SEA-BCMA treatment, confirming the clinical findings shown in Figure 4A.
- The apparent ability of SEA-BCMA to increase membrane BCMA levels is hypothesized to result from SEA-BCMA blocking the recognition of BCMA by γ-secretase, leading to reduction in γ-secretase–induced cleavage and accumulation of the full-length receptor on the cell surface.



BCMA, B-cell maturation antigen; C2D22, cycle 2, day 22; MFI, mean fluorescence intensity; Q2W, once every 2 weeks; sBCMA, soluble BCMA; SEA, sugar-engineered antibody.

Figure 5. Responding Patients Show a Range of BCMA Characteristics; High BCMA Expression and Full RO Are Not Required for Response

- Clinical responders achieved a >50% reduction in serum free light chain (sFLC) levels, contributing to the total response assessment (**Figure 5A**).
- Membrane BCMA expression at baseline was assessed in evaluable patients (**Figure 5B**).
  - Two responders (patients 15 and 28) showed variable BCMA expression, with patient 28 showing comparable BCMA expression to several non-responders.
- RO was calculated at C2D22. Two evaluable responders achieved 58% and 98% RO, whereas non-responders achieved comparable levels (**Figure 5C**).
  - Although full membrane BCMA saturation is hypothesized to facilitate a maximal clinical response, it is not required across responders.
  - High RO in an evaluable responder (patient 15) showing a reduction in free membrane BCMA at C2D22 relative to baseline, as a component of RO (**Figure 5D**).
- Patient 15, with the highest membrane BCMA expression observed (**Figure 5B**), also had the lowest baseline and on-treatment sBCMA levels (**Figure 2A**), suggesting reduced γ-secretase activity and a pharmacological target for increased SEA-BCMA activity.



BCMA, B-cell maturation antigen; C1D1, cycle 1, day 1; C2D22, cycle 2, day 22; MFI, mean fluorescence intensity; PR, partial response; RO, receptor occupancy; sBCMA, soluble BCMA; SEA, sugar-engineered antibody; sFLC, serum free light chain; VGPR, very good partial response.

Conclusions

- While sBCMA is a potential sink for therapeutic antibodies targeting BCMA, SEA-BCMA at the current 1600-mg dosing maintained high ratios of free SEA-BCMA to complexed SEA-BCMA, even as sBCMA accumulated in circulation.
- The in vitro cell binding assay was informative for dose selection. At lower doses, incomplete binding was observed for most patients. At higher doses in the dose-escalation and dose-expansion cohorts, complete target binding was observed for most patients. To ensure complete BCMA ligand blocking, we are now exploring a more intensive weekly dosing regimen at the 1600-mg dose.
- Current data suggest that response does not require high BCMA expression.
- Most evaluable patients achieved 50%–95% BCMA occupancy on plasma cells, but full RO was not required for response.
- Interestingly, membrane BCMA increased on treatment. In vitro nonclinical data support the hypothesis that binding of SEA-BCMA inhibits recognition of BCMA by γ-secretase, resulting in reduced sBCMA and accumulation of full-length membrane BCMA.
- In summary, this PD assessment of SEA-BCMA has guided the clinical dose and schedule for the phase 1 study. SEA-BCMA is clinically active in monotherapy for relapsed/refractory MM patients. Additional phase 1 monotherapy (Part B) and standard-of-care combination cohorts (Part C dexamethasone; Part D pomalidomide + dexamethasone) are currently recruiting.[3]

References

1. Yu C, et al. Presented at: European Hematology Association Virtual Congress, June 11, 2021; Poster EP944.
2. Van Epps H, et al. (2018). Cancer Res 78(13 Suppl): Abstract 3833.
3. Hoffman J, et al. (2021). To be presented at: American Society of Hematology Hybrid Congress. Session 653: Myeloma and plasma cell dyscrasias: clinical prospective therapeutic trials; 6:00 PM–8:00 PM, December 12, 2021.

Disclosures: Study funded by Seagen Inc. All authors are employees of and report equity ownership in Seagen Inc.

Acknowledgements: Medical writing support was provided by Charlie Gray, PhD, and editorial support by Travis Taylor, BA, all of Scion, London, supported by Seagen Inc. Authors would like to acknowledge the contribution of Celine Jacquemont.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from the author of this poster, **David Taft (DTaft@seagen.com).**

Abstract No. 1197
Presented at The 63rd Annual Meeting of the American Society of Hematology (ASH); December 11–14, 2021; Atlanta, Georgia, USA.