Assessment of pharmacodynamic efficacy biomarkers from a phase 1, first-in-human study of arlocabtagene autoleucel in relapsed and refractory multiple myeloma

Safiyyah Ziyad, PhD[1]; Kristina M. Jordahl, PhD[1]; Hongxiang Hu, PhD[1]; Ethan Thompson, PhD[1]; Susan Bal, MD[2]; Myo Htut, MD[3]; Larry D. Anderson, Jr, MD, PhD[4]; Tara Gregory, MD[5]; Luciano J. Costa, MD[2]; Omar Nadeem, MD[6]; Naomey Sarkis, PharmD, RPh[1]; Ziyan Guo, PhD[1]; Wei-Ming Kao, MD, PhD[1]; Allison J. Kaeding, MD[1]; Shari Kaiser, PhD[1]; Michael R. Burgess, MD, PhD[1]; Jesús G. Berdeja, MD[7]

[1]Bristol Myers Squibb, Princeton, NJ, USA; [2]University of Alabama at Birmingham, Birmingham, AL, USA; [3]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [4]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [5]Colorado Blood Cancer Institute, Sarah Cannon Cancer Network, Denver, CO, USA; [6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [7]Greco-Hainsworth Tennessee Oncology Centers for Research, Nashville, TN, USA

Background

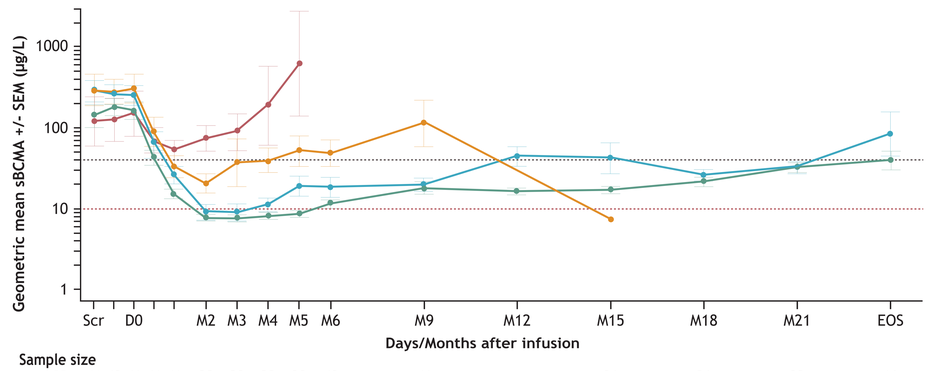
- Arlocabtagene autoleucel (arlo-cel) is a chimeric antigen receptor (CAR) T-cell therapy that targets G protein-coupled receptor class C group 5 member D (GPRC5D), which is a validated target in relapsed/refractory multiple myeloma (RRMM), and demonstrates first-in-class potential[1-3]
- Arlo-cel was evaluated in a first-in-human, phase 1, multicohort, dose escalation and expansion study (NCT04674813) in patients with RRMM
  - A one-time infusion of arlo-cel demonstrated deep and durable responses in patients with RRMM in 1-3 prior lines of therapy (1-3 pLoT) and ≥ 3 prior lines of therapy (≥ 3 pLoT)[4-5]
  - Among efficacy-evaluable (E-E) patients in the ≥ 3 pLoT cohort (n = 79), after a median of 23.8 months follow-up (range, 3.8-39.7 months), the median progression-free survival (PFS) (95% CI) was 18.3 months (11.8-21.9), and the overall response rate (ORR) was 85.7%, with a complete response (CR) achieved in 53.6% of patients[4]
  - Among all treated patients in the 1-3 pLoT cohort (n = 31), after a median of 18.2 months follow-up (range, 3.8-24.3 months), the ORR was 94%, with CR achieved in 71% of patients; the 12-month PFS rate was 75.6% (95% CI, 55.4-87.5)[5]
- Here we report a pharmacodynamic (PD) analysis of this phase 1 study to further evaluate arlo-cel efficacy using soluble B-cell maturation antigen (sBCMA) and minimal residual disease (MRD) as exploratory biomarkers of patient response with prognostic value
  - sBCMA is a measure of tumor burden that can be assessed frequently in the serum and tracked as a response biomarker
  - MRD is a measure of deep clinical response that is assessed less frequently in the bone marrow

Methods

- This was an open-label, phase 1, dose-escalation, dose-expansion study in patients with RRMM
  - Patients ≥ 18 years of age with 1-3 or ≥ 3 prior anti-MM regimens were eligible to enroll; prior anti-MM regimens in the ≥ 3 pLoT cohort included a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 therapy
  - Prior BCMA-directed therapies, including CAR T cells, were allowed
- After screening and leukapheresis (and optional bridging therapy), patients received lymphodepleting chemotherapy followed by a one-time infusion of arlo-cel
- The primary objective was to determine the safety of this therapy; secondary objectives included determining the clinical activity of this therapy per International Myeloma Working Group (IMWG) Uniform Response Criteria and its pharmacokinetics
- The exploratory objectives included assessments of the PD biomarkers sBCMA and MRD
  - sBCMA concentration was measured from serum at baseline and longitudinally until disease progression
  - Baseline sBCMA was defined as the concentration measured closest but prior to the time of infusion
  - sBCMA nadir was defined as the lowest concentration measured for each patient following arlo-cel treatment
  - A threshold of 10 µg/L was used to define deep sBCMA clearance, which approximately corresponds to the third quartile of sBCMA nadir concentration in all patients with complete response or better (≥ CR)
  - MRD was assessed via next-generation sequencing of bone marrow aspirate in responders at pre-specified time points, with MRD-negative status defined at a depth of 10^{-5}
- PFS was defined as time from arlo-cel infusion to the first documentation of progressive disease, or death from any cause, whichever occurs first; landmark PFS began at the 5-month landmark
- Cox proportional hazards models and Wilcoxon and Kruskal-Wallis tests were used to assess statistical significance where appropriate
- *P* values less than 0.1 were considered statistically significant
- The data cutoff date for this analysis was June 2025

Greater sBCMA clearance was associated with depth of clinical response following arlo-cel treatment in the ≥ 3 cohort

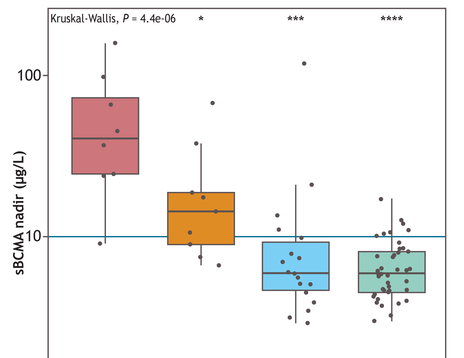
Figure 1A. Longitudinal sBCMA profiles by best overall response (BOR) in the ≥ 3 pLoT cohort



Sample size

	Scr	D0	M2	M3	M4	M5	M6	M9	M12	M15	M18	M21	EOS
≥ CR	41	40	41	41	41	38	38	39	38	40	41	35	31	26	22	16
VGPR	17	17	17	17	17	17	16	16	14	14	12	11	8	5	4	5
PR	9	9	9	8	8	9	7	7	6	5	2		1			
NR	8	8	7	8	8	7	7	4	2							

Figure 1B. Nadir levels of sBCMA by BOR in the ≥ 3 pLoT cohort



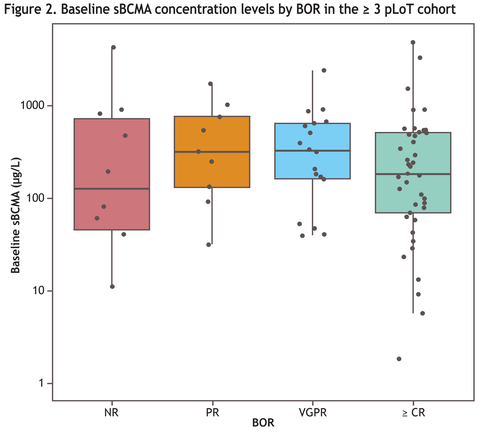
Note: the black dotted line is the line corresponding to the normal healthy donor levels of sBCMA, while the red dotted line is the threshold for deep clearance.
D, day; EOS, end of study; M, month; NR, no response; PR, partial response; Scr, screening.

Results

Pharmacodynamic biomarkers of arlo-cel efficacy

- In the ≥ 3 pLoT cohort, greater sBCMA clearance was associated with deeper and more durable responses (**Figure 1A**)
  - After month 1, the geometric means of very good partial response (VGPR) and ≥ CR patients generally remained below or near the concentration of sBCMA seen in normal healthy donors
- Greater sBCMA clearance was associated with depth of clinical response following arlo-cel treatment, with the lowest median sBCMA nadir levels observed in patients achieving VGPR and ≥ CR in the ≥ 3 pLoT cohort (**Figure 1B**)
- Baseline sBCMA concentrations were not associated with BOR, given a similar distribution observed in patients achieving no response (NR: stable disease and minimal response), PR, VGPR, and ≥ CR in the ≥ 3 pLoT cohort (**Figure 2**); similar findings were observed in the 1-3 pLoT cohort
- In the ≥ 3 pLoT cohort, pre-infusion (screening or pre-treatment) levels of beta-2 microglobulin and bone marrow biopsy (BMB) plasma cell percentage (**Figure 3**) were not associated with BOR
- In the ≥ 3 pLoT cohort, baseline sBCMA was not associated with PFS (*P* = 0.13), though continued monitoring is warranted in larger datasets from ongoing phase 2 and phase 3 trials; the 1-3 pLoT cohort was not evaluated for association with PFS due to limited sample size
- Median time to sBCMA nadir was 2.2 months (interquartile range, 1.9-3.1 months) post-infusion, with 69% (53/77) of patients in the ≥ 3 pLoT cohort reaching nadir levels below the clearance threshold

Figure 2. Baseline sBCMA concentration levels by BOR in the ≥ 3 pLoT cohort



- PFS after 5-month landmark was significantly longer in patients with sBCMA below vs above the deep clearance threshold (*P* = 0.04)
  - As there were a limited number of patients without deep sBCMA clearance in the 1-3 pLoT cohort, relationships with landmark PFS were not assessed
- In both the 1-3 pLoT and ≥ 3 pLoT cohorts, median overall survival (OS) was not reached; therefore, the relationship between sBCMA or MRD and OS could not be evaluated
- Among ≥ 3 pLoT E-E responders with available MRD data, MRD-negative rates at 10^{-5} depth at months 3, 6, and 12 ranged from 76%-83% (**Table 1**)

Figure 3. Pre-infusion visit %CD138+ in the BMB by BOR in the ≥ 3 pLoT cohort

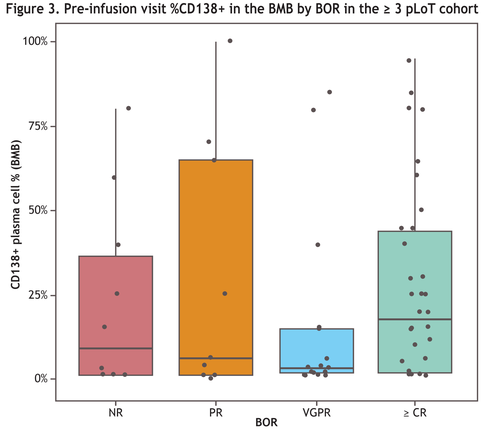


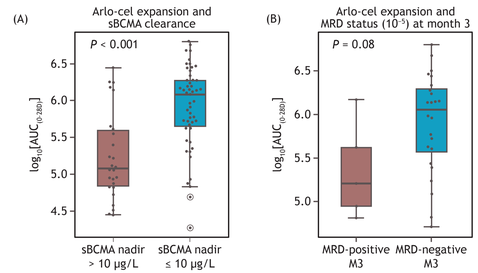
Table 1. 10^{-5} depth MRD negativity rates at months 3, 6, and 12 in the ≥ 3 pLoT cohort

	MRD negativity rate 10^{-5} (≥ 3 pLoT cohort)
Month 3	24/29 = 83%
Month 6	26/32 = 81%
Month 12	16/21 = 76%

Note: assessed in the MRD-evaluable patients among the E-E population.

- E-E responders who were MRD-negative at 10^{-5} depth had a significantly longer time from MRD assessment to progression event at months 3 (*P* = 0.003) and 6 (*P* < 0.0001) compared with MRD-positive patients, while those who were MRD-negative at month 12 had not yet reached a median time
- In the ≥ 3 pLoT cohort, higher arlo-cel expansion was associated with lower sBCMA nadir levels and MRD-negative status (10^{-5}) at month 3 (**Figure 4**)

Figure 4. Relationship between arlo-cel expansion and sBCMA clearance or MRD status (10^{-5}) at month 3 in the ≥ 3 pLoT cohort



P value calculated from Wilcoxon test.
AUC, area under the curve.

Conclusions

- Efficacy and PD data from this small, first-in-human, phase 1 study support that a one-time administration of arlo-cel led to deep and durable responses in RRMM, including in patients with high baseline tumor burden
- sBCMA is a surrogate measure of tumor burden and an exploratory PD biomarker of response. Using pre-infusion sBCMA and CD138% in BMB, no relationship was found between tumor burden and best overall response in this study
- Greater sBCMA clearance following arlo-cel treatment was associated with deeper clinical response; sBCMA nadir level and MRD negativity were prognostic of longer responses in the ≥ 3 pLoT cohort
- The relationship of robust CAR T-cell expansion with greater sBCMA clearance and negative MRD status at month 3 demonstrates that arlo-cel drives deep therapeutic responses
- These preliminary findings, based on time points as early as 2-3 months post-infusion, demonstrate the potential use of sBCMA and MRD as prognostic PD biomarkers of arlo-cel treatment efficacy, with continued monitoring in the ongoing phase 2 (QUINTESSENTIAL; NCT06297226) and phase 3 (QUINTESSENTIAL-2; NCT06615479) studies

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Contact: www.globalbmsmedinfo.com