## Abstract: P825

# Title: SOLUBLE FACTORS CORRELATED WITH CYTOKINE RELEASE SYNDROME (CRS) WITH IV VS SUBCUTANEOUS (SC) ALNUCTAMAB (ALNUC; BMS-986349; CC-93269) IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

**Abstract Type: Poster Presentation**

**Session Title: Myeloma and other monoclonal gammopathies - Biology & Translational Research**

**Background:**

SC and IV administration of ALNUC, a 2+1 BCMA x CD3 T-cell engager (TCE), have been investigated in an open-label, phase 1 study in patients (pts) with RRMM (NCT03486067). IV ALNUC showed promising activity but elicited CRS in 76% of pts. ALNUC recruits T cells to BCMA-expressing myeloma target cells, leading to T-cell cytotoxic activity and cytokine release. Measuring T-cell activating factors and cytokine secretion in peripheral blood (PB) is a useful marker of ALNUC pharmacodynamic activity and risk of CRS.

**Aims:**

To investigate whether ALNUC treatment promotes T-cell activity and the release of cytokines directly correlated with CRS grade (G), and if SC dosing reduces cytokine release compared with IV dosing, improving ALNUC tolerability.

**Methods:**

IV and SC ALNUC used step-up dosing (IV: 3 mg starting dose, weekly step-up dosing to 6 mg, final target dose 10 mg; SC: 3 mg starting dose at cycle 1 d 1 [C1D1], 3-d step-up dosing to 6 mg [C1D4], final target doses 10, 15, 30, or 60 mg from C1D8). Flat doses were also explored with IV ALNUC (0.15–10 mg). PB was collected pre- and post-treatment (6, 12, 24, and 48 h post doses 1, 2, and 3 in C1). Plasma analytes were measured using Luminex® 17-plex and 8-plex human cytokine arrays.

**Results:**

IV ALNUC led to transient release of T-cell specific and pro-/anti-inflammatory cytokines (**Table**). CRS frequency was highest after the 1st dose (71%; 50 events/70 doses) vs subsequent doses (2nd dose: 22%, 14 events/63 doses; 3rd dose: 13%, 8 events/61 doses) in line with prior observations of blunted cytokine release with subsequent infusions of TCEs. G ≥3 CRS was rare in the 70 treated pts but occurred with 3-mg (n=4) and 6-mg (n=1) starting doses. G ≥2 CRS was more common at 6- or 10-mg (6/12 pts [50%]) vs 3-mg starting dose (17/55 pts [31%]), suggesting that higher early exposure is a driving component of CRS in many pts.

Univariate analyses identified treatment-induced soluble factors correlated with G ≥3 CRS after the 3-mg IV dose, including proinflammatory cytokines (IL-10, IL-6, MIP-1α) and factors related to T-cell activity (IL-2, granzyme B, TNFα), highlighting the close relationship between T-cell antitumor activity and CRS. In pts receiving 3 mg SC ALNUC, induction of many factors was delayed and reduced (**Table**). Peak ALNUC serum concentration ($C_{max}$) was delayed and reduced with 3 mg SC vs IV starting dose, suggesting that changes in the SC pharmacokinetic profile contributed to delayed effects on soluble factors. All-G/G ≥3 CRS was reduced with SC (56%/0%, all regimens [n=73]) vs IV ALNUC (76%/7%, all regimens [n=70]).

Despite lower $C_{max}$ with SC vs IV 3-mg starting dose, ALNUC concentrations at the 30-mg target dose exceeded the predicted >90% maximal effective concentration by C2D1 and were comparable to the $C_{max}$ of the IV ALNUC 10-mg target dose. Higher SC target doses did not increase CRS severity; all-G/G1/G2 CRS occurred in 52%/41%/11% of 27 pts who received 3/6/30 mg SC vs 72%/64%/8% of 25 pts who received 3/6/10 mg SC (Nov 9, 2022 datacut).

**Summary/Conclusion:**

IV ALNUC in C1 induced transient and dose-dependent secretion of soluble factors and cytokines associated with T-cell antitumor activity and CRS. SC dosing reduced and delayed the secretion of factors correlated with G ≥3 CRS. Plasma exposure to initial SC doses was lower than IV ALNUC; however, the target dose of 30 mg achieved predicted optimal exposure for efficacy. This suggests that SC delivery widens the therapeutic index of ALNUC, enabling higher target doses to be tested to increase efficacy while reducing proinflammatory cytokine release and CRS-related toxicity.

**Table.** Transient induction of the 10 soluble factors most strongly correlated with high-grade CRS (IV delivery) in C1 after 3 mg IV or SC ALNUC starting dose. Mixed-model coefficients, reflective of fold change, are shown for each visit. Pts included in the analysis: 4, 13, and 38 pts with grade 3, 2, and 1/0 CRS, respectively, and dosed IV; 31 pts with grade 1/0 CRS and dosed SC.

| | IV delivery soluble factor induction | | | SC delivery soluble factor induction | | | |
|---|---|---|---|---|---|---|---|
| | C1D1 | C1D2 | C1D3 | C1D1 | C1D1 | C1D2 | C1D3 |
| Factor | 6 hrs | 24 hrs | 48 hrs | 6 hrs | 12 hrs | 24 hrs | 48 hrs |
| IL-10 | 5.46 | 3.47 | 1.27 | 1.82 | 1.51 | 1.95 | 2.37 |
| MIP-1α | 1.38 | 0.47 | 0.11 | 0.12 | 0.21 | 0.84 | 1.01 |
| IL-2 | 3.36 | 0.69 | 0.04 | 0.31 | 0.22 | 0.81 | 0.51 |
| Granzyme B | 3.88 | 2.97 | 1.47 | 0.38 | 0.29 | 0.97 | 1.36 |
| CD137 | 1.62 | 0.94 | 0.50 | -0.23 | -0.23 | 0.17 | 0.65 |
| TNF-α | 2.46 | 1.23 | 0.66 | -0.12 | 0.11 | 0.94 | 1.28 |
| Perforin | 1.53 | 1.04 | 0.52 | -0.05 | -0.17 | -0.16 | 0.48 |
| IL-8 | 4.09 | 1.63 | 0.82 | 0.36 | 0.64 | 0.39 | 0.75 |
| IL-6 | 3.35 | 3.08 | 2.45 | -0.08 | -0.12 | 1.36 | 2.20 |
| IL-2Rα (sCD25) | 0.85 | 1.65 | 1.36 | 0.09 | 0.18 | 0.49 | 0.69 |

Fold change from baseline: Reduced induction — High induction

C, cycle; CRS, cytokine release syndrome; D, day; IV, intravenous; pts, patients; SC, subcutaneous.

**Keywords:** B-cell maturation antigen, Cytokine release syndrome, Bispecific, Multiple myeloma