Poster Board: #338

Phase 1 Study of Safety and Tolerability of BION-1301 in Patients with Relapsed or Refractory Multiple Myeloma

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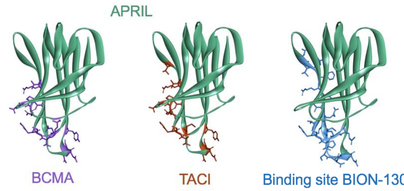
BACKGROUND

- BION-1301 is the first in class humanized monoclonal antibody directed against A PRoliferation-Inducing Ligand (APRIL)
- APRIL secreted by cells in the bone marrow niche binds to BCMA (B-Cell maturation antigen) and TACI (transmembrane activator and CAML interactor) expressed on human multiple myeloma (MM) cells to drive their proliferation and survival[1]
- APRIL induces resistance to dexamethasone, lenalidomide, bortezomib, and other standard-of-care drugs[1] and drives expansion of regulatory T cells and B cells[2]
- In patients with MM, the elevated serum APRIL levels is associated with promotion of malignancy, chemo- and immune-resistance and thus BION-1301 may offer a new therapeutic opportunity in relapsed/refractory MM

Figure 1. BION-1301 Unique Epitope Mapped to Receptor Binding Sites



BION-1301 (blue) shares its APRIL binding site with that of both receptors BCMA (purple) and TACI (orange)

STUDY DESIGN

- This is an open-label, multicenter, first-in-human, Phase 1/2 clinical study (NCT03340883) for subjects with relapsed or refractory MM whose disease has progressed after at least 3 prior systemic therapies
- Objectives
  - Safety and tolerability of BION-1301 when administered as a single-agent
  - Identify the recommended Phase 2 dose (RP2D) and schedule of BION-1301 when administered as a single-agent
  - Characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of BION-1301
- Endpoints
  - Incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), and changes in safety parameters
  - PK parameters based on BION-1301 serum levels following a single dose and after repeated dosing
  - Change from baseline in soluble APRIL levels in serum
  - Relative reduction in serum and urine M-protein levels defined as the maximum percent reduction from baseline

Figure 2. Study Design

Screening Period	Treatment Period (28-day Dosing Cycles)	Follow-Up Period (Q12W)
Confirm eligibility Up to 28 days	*Until disease progression or unacceptable toxicity* BION-1301 (IV infusion)	Safety reporting Subsequent cancer treatment Survival

Study Population & Enrollment Plan:

Adults with Relapsed or Refractory Multiple Myeloma
≥ 3 prior lines of therapy (N ~18-36)

Phase 1
3+3 Design

Dose Escalation	Schedule Exploration
BION-1301 (Q2W) n= 3-6 per cohort ≤ 3-fold dose increase per cohort Starting dose: 50 mg Max dose: 2700 mg	**BION-1301 Q1W* → Q2W** n = 3-6 per cohort Q1W for 2, 4, 6 or 8 weeks followed by Q2W dosing

*** Q1W schedule determined by PK/PD***

RESULTS

- Data cut-off is 17 April 2019
- Results presented for subjects enrolled in the phase 1 dose-escalation study; best available data
- Enrollment in phase 1 dose-escalation study has been completed; doses up to 2700 mg Q2W and 1350 mg Q1W for 8 weeks followed by Q2W dosing were evaluated and no DLTs observed
- Response was assessed by investigators Q4W
- Serum was analyzed for BION-1301 soluble unbound "free APRIL" (fAPRIL) and evaluated by PK-PD modeling. Anti-drug antibodies (ADA) were determined in serum as well.

Table 1. Enrollment by Cohort

Dose/Schedule	Cohort 1 50 mg Q2W	Cohort 2 150 mg Q2W	Cohort 3 450 mg Q2W	Cohort 4 1350 mg Q2W	Cohort 5 2700 mg Q2W	Cohort 6 1350 mg Q1W x 8wks then Q2W
No. Subjects Enrolled/Dosed	4	3	4	4	3	3
No. Subjects On Treatment	0	0	0	0	1	0
No. Subjects in Follow-Up	3	1	4	2	2	3
No. Subjects Deceased	1	2	0	2	0	0

Table 2. Baseline Demographics

Characteristics	All Patients (N=21)	
Median age, years (range)	67	(55-81)
Sex, n (%)		
Male	12	(57)
Female	9	(43)
Race, n (%)		
Caucasian	16	(76)
Black	2	(10)
Not Reported	3	(14)
ECOG, n (%)		
0	6	(29)
Median Prior Systemic Therapies, number (range)	8	(4-17)
Number of Subjects with Prior Transplant, n (%)	1	(5)
Number of Subjects Refractory to Proteosome Inhibitor, n (%)	10	(48)
Number of Subjects Refractory to IMiDS, n (%)	7	(33)
Number of Subjects Refractory to Daratumumab, n (%)	4	(19)

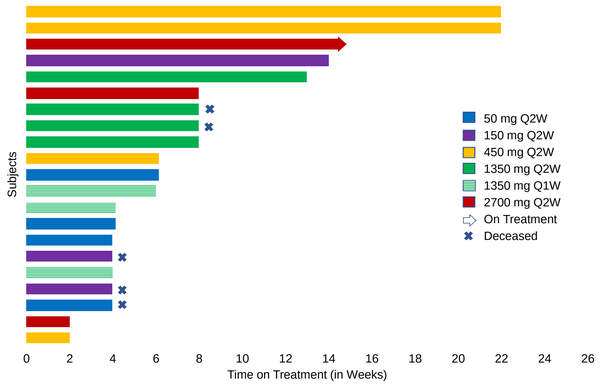
Table 3. Summary of Adverse Events (AE) by Subject

	n (%)	
Number of Subjects Dosed	21	
Number of Subjects with Any AE	18	(76)
Number of Subjects with Any Related AE	8	(38)
Number of Subjects with AE ≥ G3	7	(33)
Number of Subjects with Dose-Limiting Toxicity	0	(0)
Number of Subjects with Any SAE	7	(33)
Number of Subjects with Related SAE	1	(5)*
Number of Subjects with AE Outcome of Death	3	(14)**

*One subject with wheezing and vomiting associated with infusion-related reaction at 4th dose (and outside of DLT period)
**3 subjects with AE outcome of death: (1) Sudden death secondary to relapsed refractory multiple myeloma, secondary to carfilzomib chemotherapy; (1) Febrile neutropenia, (1) Disease progression

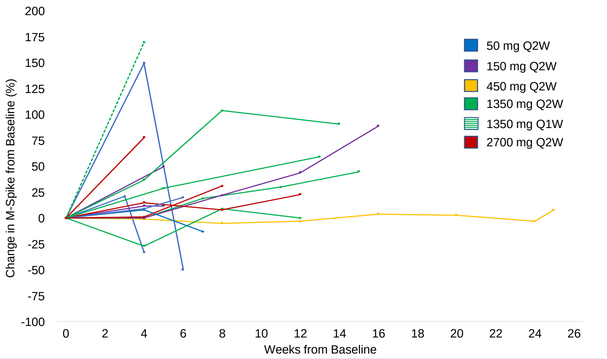
BION-1301 was well tolerated; one subject with wheezing and vomiting associated with infusion-related reaction at 4th dose (and outside of 28-day DLT evaluation period)

Figure 3. Time on BION-1301 Treatment



- One remaining subject receiving BION-1301
- Median time on treatment: 6.1 weeks (range: 2.0-22.0)
- Median number of BION-1301 doses received: 4 (range: 2-12)

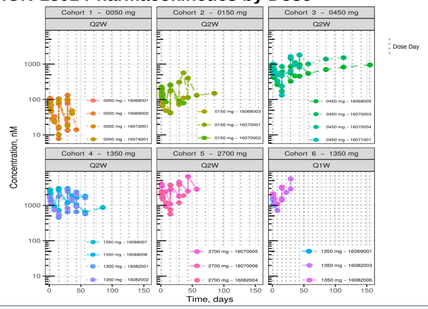
Figure 4. M-Protein Level Normalized to Baseline



- 20/21 evaluable for response*
  - SD: 5/20 (25%)
  - SD (unconfirmed)**: 6/20 (30%)
  - PD: 9/20 (45%)
- 3 subjects with decreases in M-protein (> 25%) all had free light chain disease and had low M-protein levels at baseline

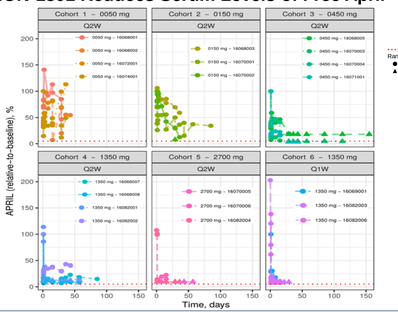
*Response assessment per IMWG criteria (including review of SPEP, UPEP, plasmacytoma, skeletal lesion, bone marrow, calcium, and serum free light chain data)
**Single time point with response = SD

Figure 5. BION-1301 Pharmacokinetics by Dose



BION-1301 exposure in serum increased dose proportionally from 50-2700 mg Q2W. Half-life ($T_{1/2}$) and clearance (CL) did not differ significantly (median $T_{1/2}$ = 7.0 days [range: 3.9-20], median CL = 0.52 L/day [range: 0.32-0.72]) between cohorts 1-5; cohort 6 parameters unreliable because of 1-week follow-up. BION-1301 exposure in bone marrow was similar to serum (data not shown).

Figure 6. BION-1301 Reduces Serum Levels of Free April



- Levels of free APRIL in serum and bone marrow (data not shown) decreased with increasing BION-1301 doses
- At 450 mg, 95% target engagement was achieved around peak exposure levels
- Dosing at 1350 mg Q1W and 2700 mg Q2W results in sustained reduction (>95% relative to baseline) of free APRIL in serum by third week (triangles indicate the lower limit of quantification of values below that limit)
- ADA's were detected in 2/21 pts; 1 of which was neutralizing ADA's

CONCLUSIONS

- BION-1301 was well tolerated (up to 2700 mg dose level)
- BION-1301 exposure in serum increased roughly dose-proportionately from 50-2700 mg Q2W with a corresponding pharmacodynamic reduction in levels of free APRIL; half-life was similar across dose levels with no tendency for lower clearance with dose
- No objective responses observed
- Based on lack of clinical activity and emerging new treatments for multiple myeloma patients, Aduro has decided to discontinue development of BION-1301 in multiple myeloma
  - Additional study results including biomarker data will be published
  - Aduro may consider investigator initiated studies combining BION-1301 with other agents in multiple myeloma
  - Based on the mechanism of action and high unmet need, BION-1301 will be developed for treatment of IgA Nephropathy (IgAN) and possibly other autoimmune diseases

References:
1. Tai *et al.* Blood. 2016.
2. Tai *et al.* Leukemia. 2018.

Acknowledgments:
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