OM336, a B cell maturation antigen (BCMA) targeting T cell engager antibody, demonstrates initial safety and efficacy in the treatment of relapsed/refractory multiple myeloma (R/R MM)

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Background

- Chimeric antigen receptor T cell therapies (CAR T) targeting B cell antigens (e.g. CD19, BCMA) have demonstrated compelling efficacy for the treatment of B cell-related malignancies, but present logistical and technical challenges for drug production and administration.
- T cell engagers (TCEs) can achieve potent depletion of B cell lineage populations and offer the opportunity for a favorable profile vs. CAR T, without the need for leukapheresis and preconditioning, as well as off-the-shelf convenience.
- OM336, a novel BCMAxCD3 TCE, is being investigated in patients with heavily pre-treated R/R MM and in patients with refractory autoimmune cytopenias, including autoimmune hemolytic anemia (AIHA).
- Prior case studies with a BCMA-targeting TCE have resulted in treatment-free remissions across various autoimmune indications, with comparable immunophenotypic changes as observed following CAR T treatment[3,4], suggesting the potential for an "immune reset."

OM336 is a novel BCMA TCE

- OM336 is an investigational, novel, 1+1 BCMAxCD3 TCE with an IgG4 backbone (**Figure 1**).
- The binding affinity of OM336 for CD3 has been de-tuned, in order to mitigate the risk of excessive cytokine release from T cells.
- OM336 has been formulated for subcutaneous (SC) injection in clinical development, highlighting the opportunity for a more optimized route of administration, with improved drug PK properties.

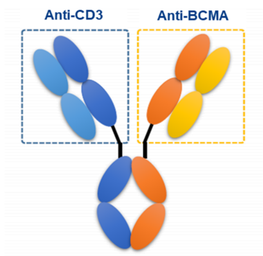

Figure 1. OM336 structure.
Bispecific 1+1 TCE with IgG4 backbone.

Favorable potency & cytokine release vs. BCMAxCD3 comparator *in vitro*

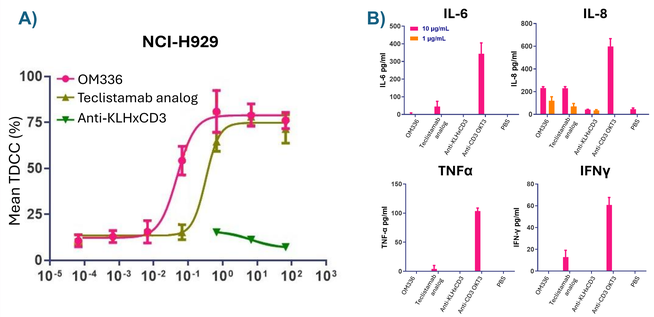

Figure 2. OM336 mediated T cell-dependent cellular cytotoxicity (TDCC) of BCMA+ cells with a detuned cytokine release profile *in vitro*. **(A)** OM336 induces T cell activation and cytotoxicity toward BCMA+ cells (NCI-H929 cell lines shown) with increased potency (EC_{50}=0.048nM) vs. a teclistamab analogue (EC_{50}=0.325nM). **(B)** Cytokine release by human peripheral blood mononuclear cells (PBMCs) with 10 or 1 ug/mL of OM336 is the same or less than that induced by the comparator (teclistamab analog) at the same concentrations.
Anti-KLHxCD3 = isotype control, anti-CD3 OKT3 = positive control; PBS = phosphate buffered saline (negative control)

Ongoing Ph1/2 Study in Patients with R/R MM

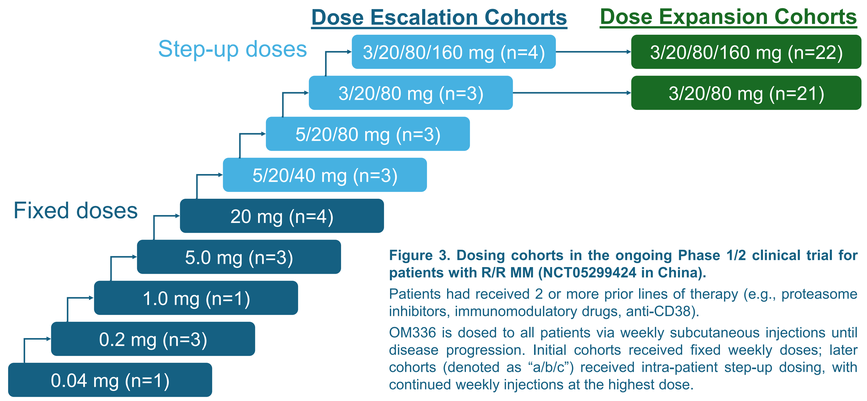

Figure 3. Dosing cohorts in the ongoing Phase 1/2 clinical trial for patients with R/R MM (NCT05299424 in China).
Patients had received 2 or more prior lines of therapy (e.g., proteasome inhibitors, immunomodulatory drugs, anti-CD38).
OM336 is dosed to all patients via weekly subcutaneous injections until disease progression. Initial cohorts received fixed weekly doses; later cohorts (denoted as "a/b/c") received intra-patient step-up dosing, with continued weekly injections at the highest dose.

Promising initial efficacy and manageable safety profile observed in R/R MM including depletion of CD19+ B cells

	Dose escalation cohorts (n=25)		Dose expansion cohorts (n=43)		Total (n=68)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cytokine release syndrome*	17 (68%)	1 (4%)	30 (70%)	0 (0%)	47 (69%)	1 (1%)
Lymphopenia	16 (64%)	14 (56%)	26 (60%)	23 (53%)	42 (62%)	37 (54%)
Anemia	18 (72%)	10 (40%)	24 (56%)	9 (21%)	42 (62%)	19 (28%)
Neutropenia	16 (64%)	13 (52%)	20 (47%)	13 (30%)	36 (53%)	26 (38%)
Leukopenia	12 (48%)	5 (20%)	23 (53%)	9 (21%)	35 (51%)	14 (21%)
Pneumonia	13 (52%)	9 (36%)	16 (37%)	10 (23%)	29 (43%)	19 (28%)
Hypokalemia	10 (40%)	2 (8%)	19 (44%)	4 (9%)	29 (43%)	6 (9%)
Pyrexia	11 (44%)	1 (4%)	17 (40%)	0 (0%)	28 (41%)	1 (1%)
Thrombocytopenia	9 (36%)	3 (12%)	17 (40%)	4 (9%)	26 (38%)	7 (10%)
Upper respiratory tract infection	11 (44%)	2 (8%)	12 (28%)	2 (5%)	23 (34%)	4 (6%)

Figure 4. TEAEs occurring in ≥30% of patients treated with OM336 in the ongoing Ph1/2 study. *A single event of Grade 3 CRS occurred after a 5 mg injection in one patient (5/20/80 mg cohort). In the 3/20/80 + 3/20/80/160 mg cohorts (n=50), Grade 1 CRS was 64%, Grade 2 CRS was 8% and there were no cases of ≥Grade 3 CRS. No ICANS of any grade occurred in any cohort.

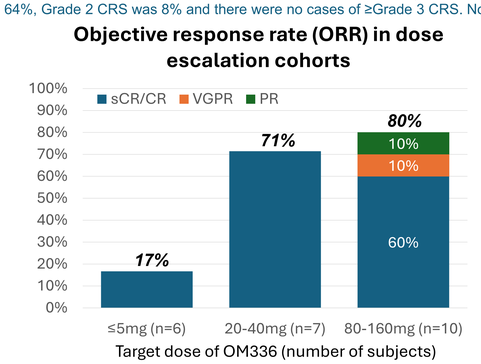

Figure 5. ORR by target dose (dose escalation cohorts).
Median follow-up = 12.1 months; median time to sCR/CR: 4.0 months. sCR/CR, stringent complete response/complete response; VGPR, very good partial response; PR, partial response.
Median follow-up of dose expansion cohorts currently = 2.8 months, ORR not shown.

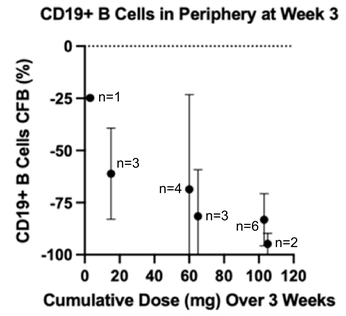

Figure 6. Mean change from baseline (CFB) in CD19+ B cells (dose escalation cohorts). Administration of OM336 to patients with R/R MM results in dose-dependent depletion of CD19+ B cells in the peripheral blood.
Data cut as of: 15 November 2024

Compelling mechanism of action for autoimmune cytopenias with initial clinical validation under compassionate use

- It was hypothesized that OM336 could induce "immune reset" in autoantibody-driven diseases by depleting both the antibody-producing cells and the B cell memory compartment (**Figure 7**).

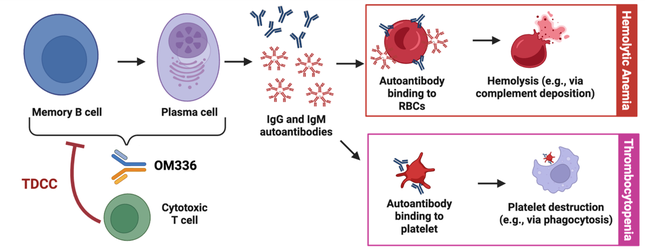

Figure 7. Mechanism of action of OM336 in autoimmune cytopenias. OM336 has been shown to deplete both plasma cells and early lineage B cells in R/R MM, and thus has the potential to induce "immune reset" in antibody-mediated diseases, including autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP).

- Two patients with autoimmune hemolytic anemia (AIHA) that was relapsed/refractory to multiple drugs, including autologous CD19 CAR T therapy, were treated with OM336 in a compassionate use trial[5] (**Figure 8**).
- OM336 was administered in a fractionated fashion over 5-6 injections and then discontinued.
- Rapid clinical activity (including hemoglobin normalization within 3 weeks) was observed, with durable, treatment-free remissions ongoing at 6 months without blood transfusions.
- There have been no events of CRS, ICANS or infections.
- **An Ouro-sponsored Ph1b study for refractory autoimmune cytopenias is planned for 2025**

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Zhang et al

Figure 8. Correspondence regarding the administration of OM336 to patients with relapsed/refractory AIHA.

Summary

- OM336 is a potent, subcutaneously-administered, BCMA-targeting TCE with clinical validation in both R/R MM and AIHA. These trials are ongoing, and data continue to be collected.
- A Ph2 study for patients with immune thrombocytopenia (ITP) has been initiated in China (NCT06799611), and a multi-national, Ph1b study for OM336 in patients with refractory autoimmune cytopenias is planned to begin in 2025.
- These studies will investigate the safety and efficacy of a single dose of OM336, administered in a fractionated fashion, as well as the potential for drug-free remissions.

Acknowledgements

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References

References: 1) Müller F, et al. NEJM 390.8 (2024): 687-700; 2) Qin C, et al. PNAS 121.6 (2024): e2315990121; 3) Alexander T, et al. NEJM 391.9 (2024): 864-866; 4) Hagen M, et al NEJM (2024) 391:867-869; Mechanism of action image made in BioRender