



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

651. MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Modakafusp Alfa Demonstrates Type I Interferon-Mediated Innate and Adaptive Immune Enhancement in a Phase 1/2 Study in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

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Modakafusp alfa (moda), a novel immunocytokine, is an innate immunity enhancer comprising two attenuated interferon (IFN) α 2b molecules fused to an anti-CD38 IgG4 monoclonal antibody backbone, driving preferential IFN α signalling in CD38-expressing innate and adaptive immune cells as well as myeloma cells. Here, we present pharmacodynamic (PD) data from the first-in-human Phase 1/2 study of moda as a monotherapy in patients with RRMM (iinnovate-1; NCT03215030).

A total of 37 patients treated with moda at 1.5 or 3 mg/kg every 4 weeks were included in the analysis. Peripheral blood (PB) and bone marrow (BM) samples were collected during screening or pre-dose on cycle 1 day 1 (C1D1) and at multiple timepoints after treatment. BM and PB samples were evaluated by cytometry time of flight (CyTOF) and bulk RNA sequencing (RNAseq) to assess pharmacodynamic changes in immune cell populations, cell activation, and gene expression.

Administration of moda led to enhanced innate immune cell activation and cytotoxic function as demonstrated by increased proportions of CD69+ and granzyme B+ in peripheral NK cells analyzed by CyTOF. This was accompanied by a decrease in the proportion of TIGIT+ NK cells, indicating reduced inhibitory signaling. Furthermore, enhanced proliferation (%Ki67+) of NK cells was observed in both BM and PB. Moda also impacted myeloid cell populations in BM and PB. Dendritic cells (DCs) and monocytes in PB showed increased surface expression of the co-stimulatory molecule CD86, suggesting a potential for enhanced antigen presentation and co-stimulation ability. Increased proliferation (%Ki67) of DCs and monocytes was detected in both PB and BM, accompanied by a decrease in numbers of peripheral DCs which may indicate recruitment or homing to secondary lymphoid organs. Additionally, RNAseq analysis revealed that treatment with moda led to upregulation of CD68 expression in both PB and BM, indicating a proinflammatory M1 macrophage type response. Finally, CyTOF analysis also indicated that moda significantly impacted adaptive immunity. We observed enhanced activation (%CD69, %PD1 and %CD40L) and cytotoxic function (%granzyme B) of peripheral CD8 T cells, and increased CD8 T cell proliferation (%Ki67 CD8) in both PB and BM samples. Enhanced activation of peripheral CD4 T cells (%CD69, %CD40L) was also detected. Consistent with activation of the adaptive immune system, there was a reduction in naïve CD8 T cells accompanied by an increase in CD8 T effector memory cells in PB. Analysis of exhaustion markers (TIGIT, PD-1) in cycle 1 (C1D8, C1D15, and C2D1 predose) showed that moda did not induce CD8 T cell exhaustion in either PB or BM, and there was no change in FoxP3+ Treg cells. Moda-induced innate and adaptive immune cell phenotypic changes were evaluated for correlation with clinical response at timepoints with sufficient number of evaluable samples. While none of the associations were statistically significant after correcting for multiplicity testing (using the false discovery rate method), we observed trends warranting further investigation. There was a greater increase of CD40L+ NK cells and PD1+ CD8 cells in responders vs. non-responders at C1D2. Additionally, at C1D15 responders showed a lower increase in proliferation (%Ki67+) of classical monocytes, NK cells, and myeloid DCs in PB as compared to non-responders. A similar trend was also observed in the BM classical monocytes. Even though the peak of Ki67 expression was observed at C1D8, diminished increases of proliferating cells at C1D15 in responders was a surprising observation that needs further consideration.

The PD biomarker data from this first-in-human clinical trial demonstrated that treatment with moda enhances both innate and adaptive immune cell activation in PB and BM. Importantly, moda-mediated immune activation did not result in T cell exhaustion during cycle 1, as evaluated in both PB and BM. We have observed interesting trends of immune phenotypic changes that may correlate with response. Follow-up analyses of the correlation of biomarkers with clinical response are in progress and will be presented. Further clinical trials are underway (iinnovate-2, NCT05556616; iinnovate-3, NCT05590377) to evaluate moda's novel immune activating mechanism in combination with standard of care anti-multiple myeloma therapies.

Disclosures Saggiu: *Takeda*: Current Employment. **Lee:** *Takeda*: Current Employment, Current equity holder in publicly-traded company. **Dunbar:** *Takeda*: Current Employment, Current equity holder in publicly-traded company; *AbbVie*: Ended employment in the past 24 months. **Singh:** *Takeda*: Current Employment. **Sachsenmeier:** *Takeda*: Current Employment. **Vogl:** *Active Biotech*: Research Funding; *Sanofi*: Consultancy; *Genentech*: Consultancy; *Takeda*: Consultancy, Research Funding; *GSK*: Consultancy; *Karyopharm*: Consultancy. **Holstein:** *BMS/Celgene*: Research Funding; *AbbVie*: Consultancy; *Genentech*: Consultancy; *GSK*: Consultancy; *Janssen*: Consultancy; *Oncopptides*: Consultancy, Research Funding; *Sorrento*: Consultancy; *Takeda*: Consultancy. **Nadeem:** *Takeda*: Membership on an entity's Board of Directors or advisory committees, Research Funding; *BMS*: Membership on an entity's Board of Directors or advisory committees; *Sanofi*: Membership on an entity's Board of Directors or advisory committees; *GPCR Therapeutics*: Membership on an entity's Board of Directors or advisory committees; *GSK*: Membership on an entity's Board of Directors or advisory committees; *Janssen*: Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Kaufman:** *Incyte*: Consultancy; *Sanofi*: Consultancy; *BMS*: Consultancy; *AbbVie*: Consultancy. **Joshi:** *Takeda Pharmaceuticals*: Current Employment, Current equity holder in publicly-traded company. **Suryanarayan:** *Takeda*: Current Employment, Current equity holder in publicly-traded company. **Collins:** *Takeda Development Center Americas*: Current Employment, Current equity holder in publicly-traded company.

OffLabel Disclosure: This abstract contains information about investigational use of modakafusp alfa in patients with relapsed/refractory multiple myeloma. Safety and efficacy have not been determined.

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