Iberdomide treatment enhances manufactured CAR T cell expansion and functionality and is immunostimulatory in patients post CAR T cell therapy

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Adolfo Aleman,[1*] Michael Amatangelo,[2*] Leah Grossman,[1] Shriya Desai,[1] Sidorela Reci,[1] Danny Jeyaraju,[2] Anita Gandhi,[2] Samir Parekh[1]

[1]Department of Medicine, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Translational Medicine, Bristol Myers Squibb, Summit, NJ, USA

*These authors contributed equally to this work

Introduction

- Chimeric antigen receptor (CAR) T cell therapies induce high response rates in relapsed/refractory multiple myeloma (RRMM), but many patients lack durable responses due to suboptimal CAR T cell product, limited CAR T cell persistence, and functional immune cell exhaustion[1]
- Novel interventional strategies that may address these limitations include approaches to improve the expansion and functionality of manufactured CAR T cell product, and maintenance treatments that deepen and extend responses
- Iberdomide (IBER) is a CELMoD™ agent currently being investigated in phase 3 studies; as maintenance therapy in newly diagnosed MM (NCT05827016) and as part of triplet therapy in RRMM (NCT04975997)
- IBER modulates the activity of the E3 ligase cereblon to induce degradation of the hematopoietic transcription factors Ikaros and Aiolos, which have been shown to regulate T-cell proliferation, activation, and exhaustion, and may enhance T-cell-redirecting therapies[2-5]

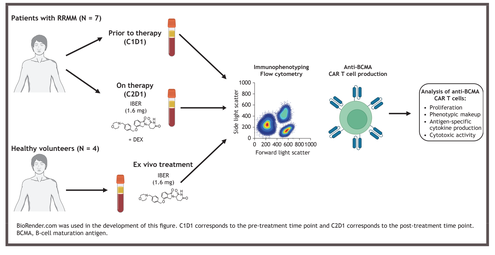
Objective

- To assess whether IBER treatment of patients with RRMM can improve manufactured CAR T cell functionality and stimulate immune responses in patients after CAR T cell therapy

Methods

- Peripheral blood samples were collected from 7 patients receiving IBER (1.6 mg) + dexamethasone (DEX) in the phase 1/2 CC-220-MM-001 study (NCT02773030) prior to treatment initiation (cycle 1 day 1 [C1D1]) and after 1 cycle of treatment (C2D1) (**Figure 1**)
  - Samples were analyzed for T-cell subsets by flow cytometry and prepared for downstream anti-BCMA CAR T cell production

Figure 1. Sample analysis scheme



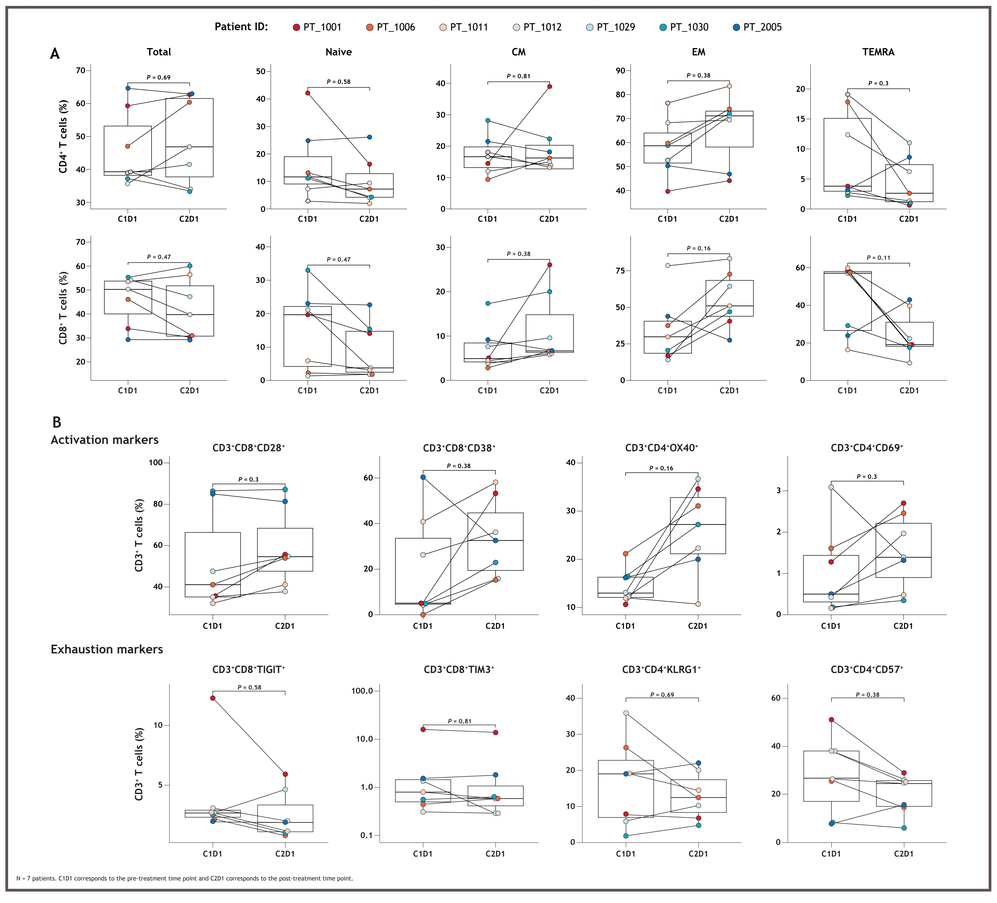
- The effects of IBER + DEX on anti-BCMA CAR T cell product were assessed by comparing CAR T cells produced from samples before and after treatment for proliferation, phenotypic makeup, antigen-specific cytokine production, and cytotoxic activity
  - The effect of IBER treatment on CAR T cell expansion, phenotype, and cytotoxicity was further validated with direct ex vivo treatment of T cells (collected from 4 healthy volunteers) with IBER prior to CAR T cell manufacture
- Immune activation induced by IBER + DEX was also assessed by flow cytometry in 17 patients with RRMM from the CC-220-MM-001 study who were treated previously with CAR T cell therapy

Results

IBER treatment increases activated/memory T cells and decreases exhausted/terminally differentiated effector memory (EM) re-expressing CD45RA (TEMRA) T cells prior to CAR T cell production

- IBER + DEX increased central memory (CM) and EM T cells and T cells expressing activation markers (OX40, CD28, and CD38) in samples collected for CAR T cell production (**Figure 2**)
  - IBER treatment decreased the proportion of TEMRA T cells and T cells expressing exhaustion markers (TIGIT and CD57) (**Figure 2**)

Figure 2. Effect of IBER treatment on T cell subsets prior to CAR T cell production



N = 7 patients. C1D1 corresponds to the pre-treatment time point and C2D1 corresponds to the post-treatment time point.

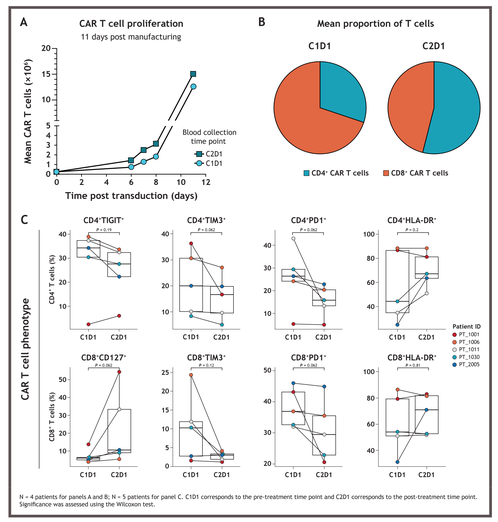
IBER treatment increases manufactured CAR T cell proliferation and activation, and decreases exhaustion ex vivo

- BCMA-targeting CAR T cells manufactured from patients after 1 cycle of IBER + DEX treatment had higher proliferation rates, increased proportions of $CD4^+$ and $HLA\text{-}DR^+$ cells, and decreased proportions of exhausted ($PD1^+$, $TIM3^+$, and $TIGIT^+$) cells compared with CAR T cells manufactured from samples collected before treatment (**Figure 3**)

CAR T cells manufactured after IBER treatment have greater functionality

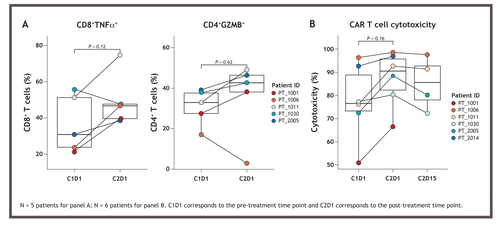
- Stimulation of anti-BCMA CAR T cells produced from patients after IBER + DEX treatment produced greater levels of tumor necrosis factor alpha (TNFα) and granzyme B (GZMB), and these cells were significantly more efficient at killing MM cells compared with CAR T cells manufactured from the same patients prior to treatment (**Figure 4**)

Figure 3. Effect of IBER treatment on manufactured CAR T cell proliferation, activation, and exhaustion ex vivo



N = 4 patients for panels A and B; N = 5 patients for panel C. C1D1 corresponds to the pre-treatment time point and C2D1 corresponds to the post-treatment time point. Significance was assessed using the Wilcoxon test.

Figure 4. Functionality of CAR T cells manufactured after IBER treatment

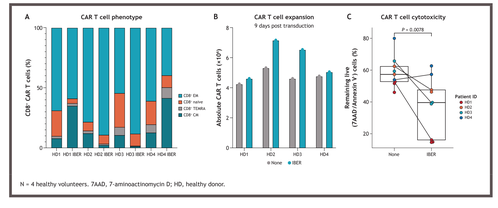


N = 5 patients for panel A; N = 6 patients for panel B. C1D1 corresponds to the pre-treatment time point and C2D1 corresponds to the post-treatment time point..

Ex vivo treatment with IBER increases the proportion of memory CAR T cells, enhances CAR T cell expansion, and increases CAR T cell cytotoxicity

- Ex vivo pre-treatment of healthy volunteers' T cells with IBER alone for 48 hours before CAR T cell manufacture increased the proportion of memory CAR T cells, enhanced CAR T cell expansion, and increased the functionality of BCMA-targeting CAR T cells compared with CAR T cells manufactured without IBER pre-treatment (**Figure 5**)

Figure 5. Impact of ex vivo treatment of T cells with IBER on CAR T cell phenotype, expansion, and cytotoxicity

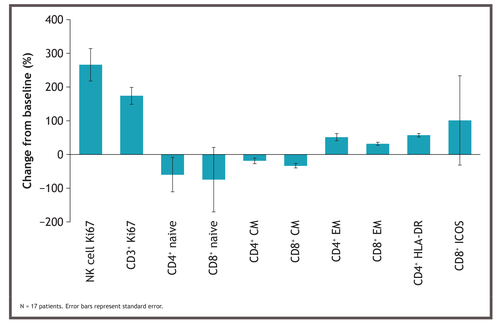


N = 4 healthy volunteers. 7AAD, 7-aminoactinomycin D; HD, healthy donor.

IBER treatment of patients with RRMM exposed to CAR T cell therapies is immunostimulatory

- Treatment of 17 patients with RRMM previously exposed to CAR T cell therapy with IBER + DEX increased T and natural killer (NK) cell proliferation and shifted T cells from a naive to an activated EM phenotype (**Figure 6**)

Figure 6. Effect of IBER on T cell subsets in patients with RRMM exposed to CAR T cell therapy



N = 17 patients. Error bars represent standard error.

Conclusions

- IBER + DEX treatment of patients with RRMM enhanced the proliferation, expansion, and functionality of manufactured anti-BMCA CAR T cells
- These results provide a rationale for IBER as an adjunctive therapy to CAR T cell therapy to improve responses in patients with RRMM
- Our findings suggest that treatment of patients with IBER prior to apheresis may improve T-cell expansion, manufacturing success, and potency of infused CAR T cells
- Moreover, we show that IBER remains immunostimulatory post CAR T cell infusion, suggesting that it may provide benefit as post CAR T cell therapy maintenance, and could help improve product from a second CAR T cell infusion in patients with prior exposure to CAR T cell therapy
- Future studies testing the effects of IBER treatment peri-CAR T cell apheresis and post-CAR T cell infusion are needed to translate these promising results into clinical practice and improve outcomes for patients with MM

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Acknowledgments

- The patients and families who made this study possible
- The clinical study teams who participated
- The study was supported by Celgene, a Bristol-Myers Squibb Company
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Sarah Spaeh, PhD, of Excerpta Medica, funded by Bristol Myers Squibb

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Presented at the 30th European Hematology Association (EHA) Congress; June 12-15, 2025; Milan, Italy.