CONCURRENT IBRUTINIB ENHANCES T CELL FUNCTION IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) TREATED WITH LISOCABTAGENE MARALEUCEL (LISO-CEL), A CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY

Jerill Thorpe*, Julie Rytlewski, Heidi Gillenwater, Ken Ogasawara, Yeonhee Kim, Diana Shektor, Eniko Papp, Leanne Peiser. *Bristol Myers Squibb, Seattle, WA, USA*

Background CLL is an incurable hematologic malignancy characterized by progressive accumulation of clonally derived CD19+ B-cell lymphocytes. CAR T cell therapies are promising treatments but inherent T cell dysfunction has limited their development in CLL. Preclinical studies suggest ibrutinib may modulate CAR T cells directly to improve their function independently of antitumor effects. Liso-cel is an autologous, CD19-directed, defined composition, 4-1BB CAR T cell product administered at equal target doses of CD8+ and CD4+ CAR+ T cells. The ongoing TRANSCEND CLL 004 study evaluates the efficacy and safety of liso-cel alone (monotherapy) or with concurrent ibrutinib (combination) in relapsed/refractory (R/R) CLL.¹ We investigated the effect of ibrutinib on post-infusion CAR+ and endogenous T cells relative to monotherapy using a novel cell-sorting, low-input RNA-seq method for analysis of patient cells beyond peak expansion, including 1 and 2 months after liso-cel infusion.

Methods CAR+ and endogenous T cells from patients in TRANSCEND CLL 004 (NCT03331198; monotherapy, n=16; combination, n=19) were isolated from peripheral blood mononuclear cells by fluorescence-activated cell sorting. RNA-seq was performed using cell lysate as input material. CAR+ T cell pharmacokinetics were assessed by flow cytometry. Serum interleukin-6 was measured by electrochemiluminescent multiplex immunoassay. Minimal residual disease (<10⁻⁴) was evaluated by flow cytometry in peripheral blood and next-generation sequencing in bone marrow.

Results Gene set enrichment analyses revealed positive enrichment of cell proliferation-associated gene sets and negative enrichment of inflammation-associated gene sets at peak expansion in CAR+ T cells from combination relative to monotherapy patients. Similar, but less marked, proliferation- and inflammation-associated gene expression changes were also observed in endogenous T cells. Accordingly, increased CAR+ T cell expansion and reduced serum interleukin-6 were observed in combination patients. In addition, an independently derived CLL ibrutinib gene expression score² was increased and sustained in CAR+ and endogenous T cells from combination but not monotherapy patients over time. A higher ibrutinib score trended with a higher rate of undetectable minimal residual disease, longer progression-free survival (PFS), and longer duration of response. Lastly, a T cell exhaustion-related gene signature was significantly reduced in CAR+ but not endogenous T cells with combination treatment, and this reduction was associated with improved PFS.

Conclusions Concurrent ibrutinib treatment in patients with R/R CLL resulted in measurable effects in CAR+ and endogenous T cells, including changes in gene signatures related to proliferation, inflammation, and T cell exhaustion. These changes were associated with enhanced CAR T cell function and efficacy.

Acknowledgements We would like to thank the patients, caregivers, investigators, and study personnel. This study was funded by Juno Therapeutics, a Bristol-Myers Squibb Company. All authors contributed to and approved the abstract;

writing and editorial assistance were provided by Allison Green, PhD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

Trial Registration NCT03331198

REFERENCES

1. Wierda WG, Dorritie KA, Munoz J, et al. TRANSCEND CLL 004: phase 1 cohort of lisocabtagene maraleucel (liso-cel) combined with ibrutinib (IBR) for patients (pts) with R/R CLL/SLL. *Hematol Oncol* 2021;**39**(S2):141–143.
2. Rendeiro AF, Krausgruber T, Fortelny N, et al. Chromatin mapping and single-cell immune profiling define the temporal dynamics of ibrutinib response in CLL. *Nat Commun* 2020;**11**:577.

Ethics Approval This study used patient cells obtained from a clinical trial that was done in accordance with with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, institutional review boards at participating institutions approved the study protocol and amendments, and all patients provided written informed consent.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.449>