106 TREATMENT WITH CC-99282 ENHANCES ANTITUMOR FUNCTION OF THE ANTI-CD19 CAR T CELL THERAPY LISOCABTAGENE MARALEUCEL (LISO-CEL)

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Background Liso-cel, an autologous, CD19-directed, defined composition, 4-1BB CAR T cell product administered at equal target doses of CD8+ and CD4+ CAR+ T cells, has demonstrated efficacy and a favorable safety profile in adult patients with third-line or later large B-cell lymphoma. Clinically, disease relapse or progression may be due partly to CAR T cell exhaustion. Combination therapies promoting sustained CAR T cell pharmacologic function may increase the rate, depth, and durability of responses. CC-99282 is a novel cereblon E3 ligase modulator (CELMoD®) compound capable of co-opting cereblon to induce the recruitment and subsequent ubiquitin-mediated degradation of Ikaros/Aiolos, resulting in therapeutic effects, including enhanced antitumor activity and augmentation of T cell function.We examined CC-99282 in combination with liso-cel in acute activation and chronic stimulation assays to assess the effect of CC-99282 on liso-cel activation, exhaustion onset, and exhaustion rescue.

Methods Liso-cel produced from healthy donor T cells was subjected to acute activation (up to 72 hours) or chronic stimulation (6–7 days) to recapitulate CAR T cell exhaustion and assess effects of CC-99282 on liso-cel in a concurrent or rescue setting after CAR T cells achieved a hypofunctional exhausted state. Functional activity was measured by proliferation, cytolysis, effector cytokine production, and gene signature analyses after further culture of liso-cel with CD19+ non-Hodgkin lymphoma (NHL) cells or tumor spheroids.

Results In acute activation assays, CC-99282 degraded Ikaros/Aiolos in liso-cel after 24 hours and uncoupled liso-cel proliferation from cytokine production after 72 hours, demonstrated by a simultaneous increase in interferon-gamma and slowed proliferation. Concurrent incubation of liso-cel with low concentrations (nM) of CC-99282 during chronic stimulation limited liso-cel exhaustion onset with increased cytokine production and cytolysis against CD19+ NHL spheroids. Furthermore, incubation of CC-99282 with exhausted liso-cel in the rescue setting resulted in enhanced cytokine production and cytolysis compared with control. Gene expression analysis by RNA-seq confirmed that CC-99282 modulated gene signatures associated with liso-cel hypofunctionality. Interestingly, transient dosing with higher CC-99282 concentrations further alleviated T cell exhaustion, enhancing liso-cel–mediated cytolysis against CD19+ NHL cells and preserving a less differentiated CAR T cell memory phenotype.

Conclusions At clinically relevant concentrations, CC-99282 enhanced liso-cel antitumor activity and reduced liso-cel exhaustion in in vitro CD19+ NHL models. The combination may improve efficacy of liso-cel, including response duration, in the treatment of CD19+ NHL. Additionally, CC-99282 substrate potency may support an intermittent dosing regimen for CC-99282 and liso-cel combination treatment, which could potentially improve tolerability.

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Ethics Approval The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration. Written informed consent was obtained from the healthy donor subjects.

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