Englumafusp Alfa (CD19-4-1BBL) and Glofitamab Combination In Patients with Relapsed/Refractory Non-Hodgkin Lymphoma (R/R NHL): Biomarker Results From a Phase I Dose-Escalation Trial

Translational

Hematology

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ABSTRACT

Background: Englumafusp alfa is an antibody-like fusion protein that simultaneously targets CD19 on B cells and 4-1BB on T cells and other immune cells. In the presence of a T-cell receptor signal and strictly dependent on CD19 crosslinking, englumafusp alfa co-stimulates T cells via 4-1BB agonism that boosts T-cell effector functions and prevents T-cell anergy. An ongoing Phase I dose-escalation study (NCT04077723) is investigating the safety, efficacy, pharmacokinetics, and pharmacodynamics (PD) of intravenous administration of englumafusp alfa in combination with glofitamab in patients with R/R NHL. We recently presented preliminary clinical data demonstrating promising clinical activity and good tolerability in R/R NHL (Dickinson et al, ICML 2023). Here, we report preliminary peripheral blood (PB) and tissue biomarker analyses to demonstrate mechanisms of action (MoA), dose relationship, and baseline features associated with response.

Methods: Exploratory biomarker analyses included data from 99 patients with R/R indolent or aggressive NHL (aNHL) dosed with 0.36–75mg englumafusp alfa, starting on Cycle 2 Day 8 (C2D8) and followed by combination with the fixed target dose of glofitamab (30mg), once every 3 weeks, from C3D1 for up to 12 cycles. Blood immune profile was analyzed by flow cytometry and plasma cytokines were analyzed by ELLA. On-treatment PD changes during the first five cycles of treatment were evaluated and compared to historical glofitamab monotherapy PD data generated in a phase I/II study (NCT03075696). Circulating tumor DNA (ctDNA) dynamics were evaluated by the Avenio ctDNA assay (Roche) at protocol-specified timepoints in patients with aNHL (n=56). Baseline tumor biopsies were analyzed by immunohistochemistry/immunofluorescence assays (n=62), and RNA-sequencing (n=34).

Results: Englumafusp alfa limited peripheral expansion of fully differentiated and potentially exhausted PD1+ CD8+ effector memory T cells re-expressing CD45RA (Temra), in a dose-dependent manner that was significantly associated with late complete metabolic response (CMR) conversion. Furthermore, the combination also resulted in a significant PB expansion of the activated (HLA-DR+) CD8+ and the ratio of CD8+ effector memory:naïve T cells compared to glofitamab monotherapy that were also more pronounced in responders. Preliminary analysis of ctDNA dynamics showed significant association between ctDNA clearance at C3D1 and CMR (p=0.01), demonstrating deep molecular response in ~50% of CMRs. Moreover, our results indicate patients with larger peripheral expansion of CD8+ Tem cells had greater decrease in plasma ctDNA levels at the end of 12-cycle fixed treatment period (EoT). Finally, we observed ~60% of patients with unfavorable lymphoma biology (TP53 mutant) or "cold tumors" with low CD8+ T-cell infiltration achieved a CMR with englumafusp alfa in a dose-dependent manner.

Conclusions: Here, we demonstrated the MoA of englumafusp alfa in R/R NHL and key PD effects in combination versus glofitamab monotherapy that will support optimal biological dose finding. Furthermore, the preliminary observation linking the expansion of CD8+ Tem cells to deeper ctDNA response at EoT, warrants further investigation between ctDNA dynamics and durability of response. Overall, our PD and biomarker observations so far strengthen the rationale of combining glofitamab with englumafusp alfa to boost immune response and anti-tumor activity in this heavily pre-treated NHL patient population.

SCIENTIFIC IMPACT

This study provides compelling evidence for the first time to support the rationale behind combining costimulatory bispecifics with T-cell engagers in order to further boost and deepen the immune response in patients. The utility of ctDNA monitoring in a phase 1 trial is also demonstrated to be important to further connect the pharmacodynamics with molecular response and will be used to demonstrate the added benefit of combination therapy in terms of durability and depth of response over monotherapy in the next phase of development. Overall, we have utilized and integrated different biomarkers to demonstrate mode of action and identify doses for optimization for a molecule without single agent activity, which will serve as a frontrunner for future molecules of this archetype.

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