Abstract: P2059

Title: MINIMAL RESIDUAL DISEASE (MRD), PHARMACOKINETIC (PK), AND PHARMACODYNAMIC (PD) ASSESSMENT OF EPCORITAMAB 2- VS 3-STEP STEP-UP DOSING IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA (R/R FL)

Abstract Type: e-Poster Presentation

Topic: Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

Background:

In the pivotal EPCORE™ NHL1 trial (phase 1/2; NCT03625037), epcoritamab treatment (tx) with a 2-step step-up dose (SUD) regimen led to high overall and complete response rates of 82% and 63%, respectively, in patients with R/R FL. Safety was manageable, with CRS events being primarily low grade. However, further mitigation of CRS may enhance the accessibility of epcoritamab for the tx of R/R FL.

Aims:

To assess MRD, PK, and PD of a 2-step SUD regimen in cycle (C) 1 in comparison with a 3-step optimization regimen in C1 (C1 OPT) in patients with R/R FL.

Methods:

Patients with CD20+ R/R FL (grade 1–3A) with ≥2 prior tx lines received subcutaneous epcoritamab in 2-step (0.16 and 0.8 mg) or 3-step (0.16, 0.8, and 3 mg) SUD regimens in C1, followed by 48-mg full doses in 28-day (d) Cs (QW, C1–3; Q2W, C4–9; Q4W, C≥10) until disease progression. The C1 OPT cohort received recommendations for adequate hydration and dexamethasone as the preferred steroid for CRS prophylaxis. Hospitalization for monitoring was based on investigator discretion. T-cell phenotypes were assessed by validated flow cytometry assays and cytokines were tested with the Meso Scale Discovery platform. MRD analysis was performed on peripheral blood mononuclear cells collected at prespecified time points (clonoSEQ® assay, Adaptive Biotechnologies). Screening tumor biopsies were used to identify trackable tumor clones; samples were quantified as tumor clones detected per 1 million nucleated cells. Overall response and progression-free survival (PFS) were assessed by Lugano criteria per investigator assessment.

Results:

PK was comparable between 2-step SUD and C1 OPT cohorts except for transient, lower epcoritamab trough concentrations, as expected, after SUD 3 (3 mg) on C1D15 in the C1 OPT cohort compared with the 2-step SUD cohort, which received the full dose (48 mg) on C1D15. The 2-step SUD cohort showed a marked increase in median IL-6 levels 24 h after the first full dose on C1D15, whereas the C1 OPT cohort showed low median IL6 levels in C1 and beyond, supporting the reduction of CRS in the C1 OPT cohort. Rapid, sustained depletion of circulating CD3−CD19+ peripheral B cells was observed by C1D15 in both groups. In addition, in both groups, T-cell margination was observed in C1, followed by recovery to baseline levels by C2D1 and modest Tcell expansion for subsequent doses. Frequency of proliferating Ki67+ and activated PD1+ CD4+ and CD8+ T cells increased after each dose in C1 in both groups. T-cell proliferation and activation were prolonged to C2 in the C1 OPT cohort. From C3 onward, the frequency of proliferating and activated T cells returned to near-baseline levels and was similar in both groups. MRD negativity was observed in 61 (67%) of 91 evaluable patients in the 2-step SUD cohort and 28 (64%) of 44 patients in the C1 OPT cohort (**Table**). In the majority of durable responders in both groups, epcoritamab induced MRD negativity by C3D1. In both groups, patients who lost MRD-negative status also lost their response, and the majority of nonresponders never became MRD negative. Median PFS was not reached in MRD-negative patients; for both dosing regimens, median PFS was around 4 mo for responders who were not MRD negative.

Summary/Conclusion:

MRD-negativity rate and kinetics, PK, longitudinal peripheral Bcell depletion, and T-cell counts were similar between groups and consistent with comparable clinical efficacy reported for the C1 OPT and 2-step SUD regimens. In contrast, IL-6 levels were substantially reduced for C1 OPT vs the 2-step SUD regimen.

Table. MRD-negativity rates in 2- and 3-step SUD cohorts

FL grade 1–3A cohort	MRD-negative patients[a] n	MRD-evaluable patients[a] n	MRD-negativity rate[b] % (95% CI)
2-step SUD	61	91	67.0 (56.4–76.5)
C1 OPT	28	44	63.6 (47.8–77.6)

[a]Based on the clonoSEQ® assay, using peripheral blood mononuclear cells as an analyte at a 10^{-6} cutoff.
[b]Percentages are based on the number of MRD-evaluable patients (those with ≥1 baseline or on-treatment MRD result and not MRD negative at baseline), and 95% CIs are based on the Clopper–Pearson method. C, cycle; FL, follicular lymphoma; MRD, minimal residual disease; OPT, optimization; SUD, step-up dose.

Keywords: Bispecific, Hematological malignancy, Non-Hodgkin’s lymphoma, Follicular lymphoma