Abstract: P2060

Title: MODEL-BASED CYCLE (C) 1 OPTIMIZATION OF STEP-UP DOSE REGIMEN FOR EPCORITAMAB IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

Abstract Type: e-Poster Presentation

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

Background:

Epcoritamab is a CD3xCD20 bispecific antibody targeting the T-cell antigen CD3 and the B-cell antigen CD20, triggering potent T-cell–mediated killing of CD20-expressing cells. EPCORE™ NHL-1 (NCT03625037), an ongoing phase 1/2, global, open-label, single-arm trial of epcoritamab in patients (pts) with previously treated, R/R B-cell non-Hodgkin lymphoma (NHL), has dose-escalation (ESC), expansion (EXP), and C1 optimization (OPT) parts including pts with R/R FL. A 2step step-up dose (SUD) regimen, consisting of priming (0.16 mg) and intermediate (0.8 mg) doses followed by full (48 mg) doses, was used in EXP to reduce CRS incidence and severity. C1 OPT investigated different SUD regimens to further reduce incidence and severity of CRS.

Aims:

To identify potential optimal SUD regimens to be tested in pts with R/R FL in C1 OPT using a model-based approach, and to report pharmacokinetic (PK), exposure–CRS, and pharmacodynamic (PD) analyses based on data from pts with R/R FL in C1 OPT, supporting the model-based 3-step SUD regimen as optimal dosing to reduce CRS incidence and severity.

Methods:

A longitudinal exposure–CRS relationship was adequately described using a repeated time-to-event (RTTE) model based on available data from EPCORE NHL-1 ESC and EXP and the supportive EPCORE NHL-3 trial (phase 1/2 trial of epcoritamab in Japanese pts with R/R B-cell NHL; NCT04542824) across a wide range of combinations of priming and intermediate doses. Simulations were performed using the developed model to identify potential optimal SUD regimens to be evaluated. Data were collected in C1 OPT under the model-proposed alternative SUD regimen. Population PK, PK/PD, and exposure–CRS analyses compared 2- and 3-step SUD regimens. The CRS model was updated and simulations were performed using the updated model.

Results:

RTTE model-based simulations suggested that adding a second intermediate dose may reduce incidence of grade (G) ≥2 CRS events in pts with R/R FL. Thus, an alternative 3-step SUD regimen (with epcoritamab 3 mg on C1D15 followed by full doses on C1D22 and thereafter) was evaluated. PK/PD and exposure–CRS analyses in C1 OPT supported the 3-step SUD regimen along with strong recommendations for adequate hydration and prophylactic dexamethasone as an effective strategy to mitigate CRS risk. Epcoritamab PK and response rates were similar in pts who received the 3step SUD regimen and those who received the 2-step SUD regimen. Notably, low IL-6 levels in C1 and beyond and the substantially lower IL-6 levels following the first full dose were consistent with the lower CRS incidence observed in pts who received the 3step vs 2-step SUD regimen (CRS in FL C1 OPT as of Jan 8, 2024: 49% overall, 40% G1, 9% G2; in EXP as of Apr 21, 2023: 66% overall, 40% G1, 25% G2, 2% G3). No consistent relationship was observed between epcoritamab peak concentrations (Cmax) and peak IL-6 levels or between Cmax and risk of any-grade or G≥2 CRS within each dosing period. In addition, the lower CRS risk observed with the 3-step SUD regimen was consistent with prior and updated model predictions. Furthermore, the updated CRS model was able to dissect the benefit of hydration and prophylactic dexamethasone alongside the switch to the 3step SUD regimen.

Summary/Conclusion:

C1 OPT data showed that the model-identified 3-step SUD regimen (with 3mg second intermediate dose) reduced CRS incidence and severity in pts with R/R FL while providing similar response rates relative to the 2step SUD regimen. This modelbased approach helped accelerate C1 dose OPT, reducing the need for clinically testing numerous cohorts.

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