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POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Mitigating the Risk of Cytokine Release Syndrome (CRS): Preliminary Results from a DLBCL Cohort of Epcore NHL-1

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Background: Epcoritamab SC, a CD3xCD20 T-cell-engaging bispecific antibody, has recently been approved by the US FDA for the treatment of adults with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after ≥2 lines of systemic therapy. As a single agent, epcoritamab SC has demonstrated deep, durable responses with a manageable safety profile in patients with R/R large B-cell lymphoma in the expansion portion of the phase 1/2 EPCORE ™ NHL-1 trial (NCT03625037). Cytokine release syndrome (CRS) events in the dose expansion part of the trial were primarily low grade (49.7% overall; 31.8% grade [G] 1, 15.3% G2, 2.5% G3); timing was predictable, and the majority of events occurred following the first full dose at cycle 1 day 15 (C1D15). To mitigate CRS in dose expansion, subcutaneous administration, step-up dosing, and premedication, including prednisolone, were used. Here, we present preliminary results from a DLBCL optimization cohort of the EPCORE NHL-1 trial that further investigates mitigating the risk of CRS in patients treated with epcoritamab SC monotherapy.
Methods: Adult patients with R/R CD20 $^{+}$ DLBCL (previously treated with ≥2 lines of systemic therapy) were enrolled to receive epcoritamab SC in 28-d cycles as follows: weekly, C1-3; every 2 weeks, C4-9; every 4 weeks, C≥10 until progressive disease or unacceptable toxicity. Patients received 2 step-up doses (step-up dose 1, 0.16 mg, and step-up dose 2, 0.8 mg) followed by 48-mg full doses. To further mitigate CRS, C1 of the optimization cohort included mandatory administration of dexamethasone 15 mg as premedication on D1, D8, D15, and D22 and as prophylaxis on D2-4, D9-11, D16-18, and D23-25, and diphenhydramine and acetaminophen as premedication on D1, D8, D15, and D22 with each dose. In C1, it was strongly recommended that patients be well hydrated and that antihypertensive medications be held for 24 h prior to epcoritamab SC administration. Patients were also encouraged to monitor their temperatures following the first 4 doses. Hospitalization

and inpatient observation were optional. The primary endpoint was rate of G2 or higher CRS and all CRS events. Secondary pharmacokinetic/pharmacodynamic (PK/PD) analyses were performed.

Results: As of April 21, 2023, 24 patients (median age, 65 y) had been treated in this DLBCL optimization cohort. The median number of prior lines of treatment was 3 (range, 2-10), 75% of patients were primary refractory, 71% had stage IV disease, and 58% had prior CAR T. With a median follow-up of 1.3 mo, 18 patients (75%) remained on treatment. The most common treatment-emergent AEs (TEAEs) of any grade were infections (38%; COVID-19, 8%), fatigue (21%), CRS (17%), headache (17%), anemia (13%), constipation (13%), decreased platelet count (13%), dyspnea (13%), hyponatremia (13%), insomnia (13%), and neutropenia (13%; febrile neutropenia, 4%). All CRS events were G1; 1 patient was treated with anticytokine therapy (tocilizumab); there were no treatment discontinuations due to CRS. The most commonly observed CRS symptom was fever (100%). Most CRS events (3/5 events) occurred following the first full dose on C1D15. The median time to CRS resolution was 3.5 d (range, 1-25) and all events resolved. Compared with the DLBCL expansion cohort, circulating interleukin 6 (IL-6) levels were decreased 24 h after the first full dose (C1D15) of epcoritamab SC (**Figure**). The median circulating IL-6 level at C1D16 was lower in the dose optimization cohort at 6.92 pg/mL (2.97 pg/mL at C1D1 predose), compared with 21.24 pg/mL (2.45 pg/mL at C1D1 predose) in the DLBCL expansion cohort. The addition of dexamethasone and fluids in optimization did not appear to interfere with T-cell margination or T-cell activation, given that the fold-change values of T-cell absolute counts and percentage of activated T cells were similar between DLBCL optimization and expansion cohorts at C1D16. No patients experienced ICANS, clinical tumor lysis syndrome, or fatal TEAEs.

Conclusions: Encouraging preliminary data from this DLBCL CRS optimization cohort, which incorporates prophylactic dexamethasone and hydration of patients during cycle 1, indicate that this approach is effective in decreasing rates and severity of CRS. Data with additional patients and follow-up will be presented.

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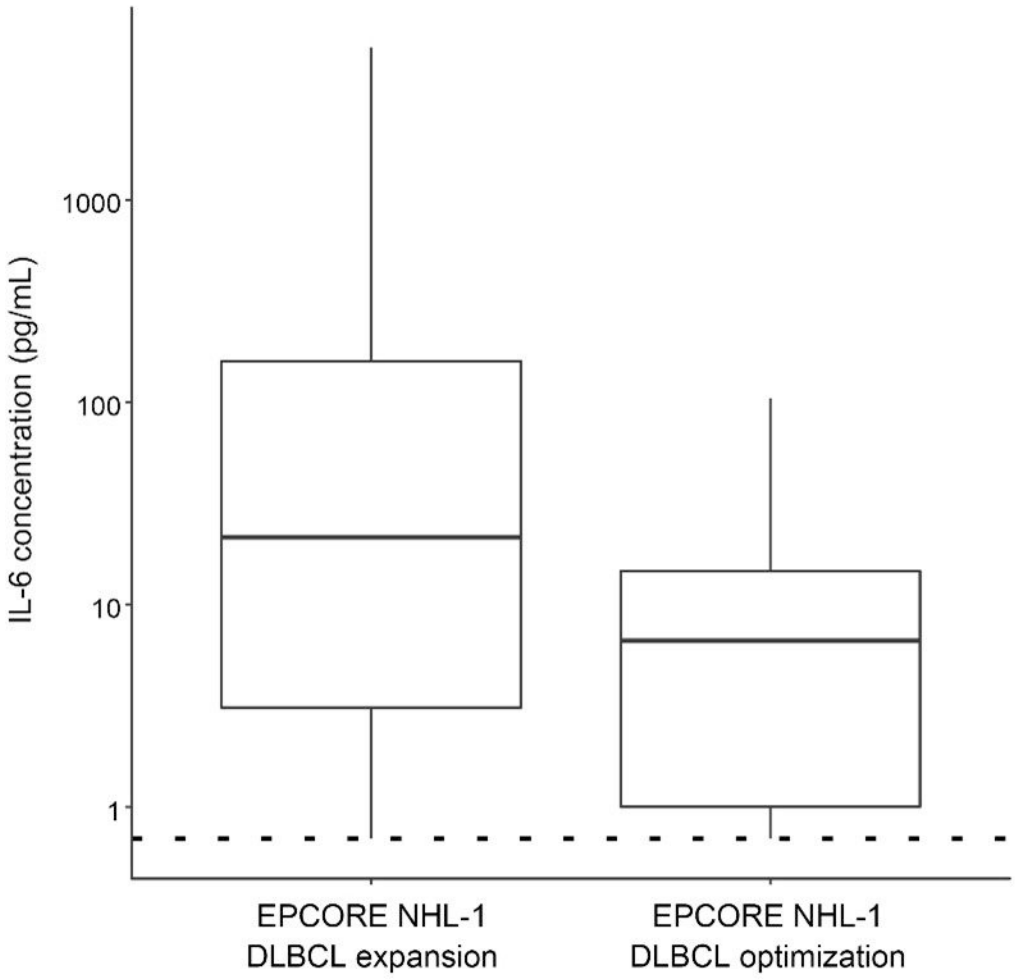
Figure. IL-6 concentration 24 h after first full dose on C1D15



The horizontal dashed line indicates the lower limit of quantification (0.695 pg/mL) of the IL-6 assay.
DLBCL, diffuse large B-cell lymphoma; IL-6, interleukin 6.

Figure 1

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