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Introduction

In the context of different hematological neoplasms, innovative cellular immunotherapies, such as T-cell engaging antibodies, are transforming the treatment landscape (Table 1) [1-9]. Epcoritamab, (Epkinly™ and Tepkinly®) is a subcutaneously administered bispecific antibody which targets both CD3 and CD20 (Fig 1)[10]. Preclinical studies have demonstrated *in*-vitro cytotoxicity of epcoritamab in CD20 expressing malignant-B cells derived from lymph node (LN) or bone marrow (BM) biopsies obtained from patients with diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) [11].

Based on preliminary clinical trial data related to the use of epcoritamab in the treatment of B-cell non-Hodgkin lymphomas (B-NHLs), including DLBCL, the United States Food and Drug Administration (US FDA) granted approval for epcoritamab in May 2023. This approval specifically applies to the treatment of adults with DLBCL that arise from an underlying indolent lymphoma as well as *de novo* DLBCL relapsing after at least two prior lines of systemic therapy [12]. Notably, in September 2023, the European Medicines Agency (EMA) granted a conditional marketing authorization for epcoritamab monotherapy for the treatment of adults with relapsed/refractory (R/R) DLBCL who have undergone at least two prior lines of systemic therapy [13].

The ongoing clinical development of epcoritamab also includes a potential indication for the treatment of FL and chronic lymphocytic leukemia (CLL) [14-15] . In FL epcoritamab treatment may address unmet clinical needs such as early progression of disease at 24 months (POD24). Whilst in CLL the deployment of epcoritamab may be an option for persons who experience disease progression after treatment with both an inhibitor of Brutons Tyrosine Kinase (BTKi) and B-cell lymphoma 2 (BCL-2).

2 - Epcoritamab in DLBCL

The FDA approval of epcoritamab for the treatment of DLBCL was primarily based upon data derived from the EPCORE NHL-1 trial (NCT03625037). This clinical trial enrolled patients with R/R CD20-positive mature B-cell neoplasms. Participants had undergone two or more lines of antineoplastic therapy, including at least one regimen that featured an anti-CD20 monoclonal antibody. Patients previously treated with chimeric antigen receptor T-cell therapy (CAR-T) were also eligible for epcoritamab therapy in the EPCORE study. During the study dose-expansion phase, patients were treated with subcutaneous epcoritamab with a sequential step-up dosing regimen to the recommended dose of 48 mg. Treatment with epcoritamab was then continued until either disease progression or the development of unacceptable treatment-related toxicity [3,16].

The primary end point was overall response rate (ORR) by the independent review committee (IRC) using Lugano criteria [17]. Imaging assessments for efficacy included mandatory fluorodeoxyglucose positron emission tomography. In a comprehensive re-evaluation of the EPCORE NHL-1 trial data,

an updated analysis reveals that, following a median follow-up period of 20 months, epcoritamab therapy demonstrated ORR of 63% in patients diagnosed with DLBCL (n = 157). The complete response (CR) rate was reported at 39%. Remarkably, of 107 minimal residual disease (MRD)-evaluable patients, 49 (45.8%) were MRD-negative. Moreover, the median duration of response (DOR) reached 15.5 months while for individuals with prior exposure to CAR T-cell therapy, the median DOR remained unreached [3,18].
Grade 3 and higher adverse events (AEs) were observed in 61.1% of patients while treatment-related grade 3 and higher AEs were observed in 26.8% of patients.
Cytokine release syndrome (CRS) emerged as the predominant adverse event (49.7%), predominantly manifesting as low-grade symptoms with a predictable onset. CRS primarily manifested after the initial administration of the dose in cycle one, typically around day 15, with a median time to onset of approximately 20 hours following epcoritamab administration. The majority of CRS events were classified as common terminology criteria for adverse events (CTCAE) grade 1 or 2, while grade 3 or higher CRD events (2.5%) were effectively managed using the interleukin-6 blocker, tocilizumab. Most CRS events resolved, with a median time to resolution of two days.

Fifteen trial patients experienced treatment-emergent adverse events (TEAEs) that proved fatal, with two of these events linked to COVID-19. Other side effects associated with epcoritamab in the EPCORE study included neutropenia (24%), pyrexia (24%), fatigue (23%), nausea (22%), and diarrhea (21%). A small percentage of trial participants encountered immune effector cell–associated neurotoxicity syndrome (ICANS), characterized by symptoms such as aphasia, seizure, headache, and encephalopathy. Importantly, these clinical and neuropsychiatric symptoms were predominantly of CTCAE grade 1 or 2 [3,18].
Notably, patients enrolled in the EPCORE NHL-1 trial exhibited a significant improvement in disease-related symptoms and overall quality of life. These improvements were derived from patient-reported outcomes (PROs), as assessed through qualitative interviews. In these interviews, a majority of patients expressed either 'very satisfied' or 'satisfied' opinions regarding their epcoritamab treatment [19]. These favorable results, indicating both objective responses and enhanced PROs, support the ongoing investigation of epcoritamab.
The combination of epcoritamab and rituximab, cyclophosphamide, doxorubicin, vincristine with prednisone (R-CHOP) was assessed in patients with DLBCL in arm 1 of the phase 1/2 EPCORE NHL-2 trial (NCT04663347). This study focused on high-risk patients, as evidenced by an international prognostic index (IPI) of 3–5, and newly diagnosed with DLBCL. Among patients evaluated for efficacy (n = 31), a 100% ORR was achieved, with 77% achieving a complete metabolic response (CMR). CRS events occurred in 52% of patients, were primarily of low-grade intensity and did not require treatment discontinuation[20].
A phase 3, multicenter, open-label study (NCT05578976) is currently evaluating the effectiveness and safety of epcoritamab combined with R-CHOP in adults with newly diagnosed DLBCL. This trial is set to enroll around 900 patients who will be randomly assigned to receive either epcoritamab and R-CHOP or R-CHOP. The primary efficacy endpoint is progression free survival (PFS) in patients with DLBCL with an IPI of 3–5 The secondary efficacy endpoints are PFS in patients with IPI 2–5, event-free survival (EFS), CMR, overall survival (OS), and negativity for MRD. Safety endpoints include the incidence and severity of treatment-emergent adverse events (AEs), serious AEs, and AEs of special interest (CRS, ICANS, and clinical tumor lysis syndrome) [21].

3 -Epcoritamab in patients with FL

Epcoritamab holds promise in the context of FL, a disease where approximately 20% of patients treated with chemoimmunotherapy experience early progression of disease within 24 months of initial therapy (POD24) with an attendant inferior prognosis. For persons with POD24 FL there is currently no optimal treatment approach [22] . In a cohort of patients with R/R follicular lymphoma (FL) who had received at least two prior lines of therapy in the phase 1/2 EPCORE NHL-1 trial (NCT03625037), epcoritamab therapy was associated with an ORR of 82%. Results from this cohort of 128 R/R FL patients, of whom 70.3% were double refractory to an anti-CD20 monoclonal antibody and an alkylating agent, the observed median DOR was not reached. Additionally, no new safety signals were identified with epcoritamab in the FL population with the most common treatment-emergent adverse event being CRS (66.4% in total, 1.6% at greater than CTCAE grade 2) [23].
In the phase Ib/II EPCORE NHL-2 trial (NCT04663347) 109 R/R FL patients with received 12 cycles of epcoritamab combined with R^2 (rituximab and lenalidomide). The ORR was 97%, with an 86% CR rate and an one-year PFS of 80%. Notably high response rates were seen across all different patient subgroups, including those with POD24 and high-risk follicular lymphoma international prognostic index (FLIPI) scores [22]. These results outperform those obtained with R^2 therapy and epcoritamab as monotherapy [14,24] . However, this patient cohort had received fewer prior treatments (with a median of 1) and had a relatively low percentage of patients who were refractory to previous treatment. Consequently, the added benefit of epcoritamab in combination with R2 remains uncertain [25].
A phase III trial (EPCORE FL-1) is currently underway (NCT05409066) which plans to compare the safety and efficacy of epcoritamab in combination with R^2 to R^2 in subjects with R/R FL [25].

3 - Epcoritamab therapy in R/R CLL and Richter's syndrome

CLL can be distinguished from DLBCL by the presence of elevated circulating tumor cells, T-cell dysfunction, and a characteristic immunophenotype. Such differences make it challenging to extrapolate data from B-NHL to CLL, as they are discrete pathological entities [26]. Nevertheless, CLL cells are sensitivite to T-cell medicated cytotoxicity, as demonstrated by the successful deployment of CAR-T therapy in refractory CLL [27]. Consequently, epcoritamab may be a promising immunotherapeutic candidate for an off-the-shelf approach which harnesses the cytotoxicity of autologous T cells in persons with CLL.

The EPCORE CLL-1 trial (NCT04623541) is an open-label, multicenter, phase 1b/2 trial that assessed the safety and effectiveness of epcoritamab at the recommended phase 2 dose of 48 mg in R/R CLL or Richter's syndrome (RS). Among the six RS patients who received epcoritamab as a first-line therapy, an early antitumor, nodal response was observed, with the majority of responses seen at the first assessment at week 6. The ORR was 60%, and the CR rate was 50% [28].
In the dose expansion cohort of EPCORE CLL-1 trial (N = 23) the majority of CLL patients treated exhibited *TP53* aberrations (65%) and were heavily treated (median number of previous therapies, 4; range, 2 to 10). All patients had received BTKi (mainly ibrutinib), with 74% discontinuing BTKi therapy due to disease progression. Additionally, 83% had been treated with a BCL-2 inhibitor, and 4% had undergone CAR-T therapy. The ORR was 82% with a CR rate of 33%, and, the estimated, PFS and OS at 9 months were 67%, and 81%, respectively. Most TEAEs were graded as 1 or 2, with only

two TEAEs leading to treatment discontinuation. Three fatal TEAEs were reported, one of which was pneumonia. CRS resolved in all patients who experienced this complication. Importantly, all ICANS events occurred very early in the context of grade 2 CRS toxicity [15].
These promising results have paved the way for new treatment approaches for double-refractory CLL patients. Notably, in vitro studies suggest that the combination of venetoclax with epcoritamab induced superior killing of CLL cells than either agent alone. Furthermore, the effects of venetoclax in combination with epcoritamab on immune function in patients with CLL appear particularly promising [29]. EPCORE CLL-1 is enrolling patients with R/R CLL/small lymphocytic lymphoma (SLL) or RS (NCT04623541). In this trial, epcoritamab is combined with venetoclax for R/R CLL/SLL and lenalidomide with R-CHOP for RS.

4 - Expert opinion

While the treatment of DLBCL with epcoritamab has shown promising outcomes, questions persist regarding the optimal sequencing and utilization of this agent [3]. In comparing efficacy with CAR-T therapy, epcoritamab demonstrates a comparable CR rate of 38.9% versus 36.5%, based on a juxtaposition of individual patient data from the EPCORE™ NHL-1 trial (NCT03625037) and information from various US academic and community clinical practices. Notably, this comparison is subject to limitations inherent in analyses conducted outside a randomized clinical trial [30].

Findings from the EPCORE NHL-1 trial indicate that prior exposure to CAR-T does not significantly impact the likelihood of DLBCL patients responding to epcoritamab. However, the reverse relationship remains unclear [3].

In considering safety profiles, the side-effect profile of epcoritamab closely resembles that observed with CAR-T therapy. Notably, CRS events associated with epcoritamab therapy tend to occur earlier and have shorter durations, with infrequent instances of grade 3 or 4 CRS events. This suggests that epcoritamab may be safely managed by community physicians, even in settings without immediate access to an intensive care unit [31].

Infectious complications remain a significant threat to morbidity and mortality during epcoritamab therapy. Neutropenia, immune paralysis due to cytokine release during CRS, T-cell exhaustion, and hypogammaglobulinemia all contribute to such increased risk.
While opportunistic infections are a concern, common pathogens such as respiratory viruses and bacteria emerge as the primary culprits. Recent recommendations advocate for several key measures, including immunizations, immunoglobulin substitution, and G-CSF support. Additionally, consideration should be given to prophylaxis against herpes simplex virus and/or varicella-zoster virus, as well as prophylaxis against Pneumocystis jirovecii throughout treatment until total lymphocyte and CD4 counts normalize [32]. By implementing these advices, clinicians can significantly mitigate the risk of infectious complications, contributing to improved patient outcomes during epcoritamab therapy.

Recent investigations indicate that glofitamab, a CD20×CD3 bispecific monoclonal antibody, demonstrates clinical efficacy in high-risk R/R DLBCL comparable to that observed with epcoritamab

[33]. Distinctions in logistical considerations, such as the route of administration, frequency, and duration of treatment, should inform the selection between these bispecific antibodies. The necessity to administer obinutuzumab before glofitamab introduces complexity to the treatment, while the fixed treatment duration of glofitamab presents a compelling argument in its favor. Ultimately, the choice between epcoritamab and glofitamab should be personalized for each patient, with careful consideration given to individual patient preferences regarding the duration of therapy—whether it is time-limited or indefinite [34].

While indefinite treatment poses a potential limitation in epcoritamab therapy, certain critical questions require urgent attention. Currently, there is a lack of data to ascertain whether individuals heavily pretreated would derive benefits from epcoritamab treatment until disease progression, or if a predefined therapy duration would be adequate. Exploring the administration of continuous subcutaneous epcoritamab at reduced frequency post-initial treatment could enhance the likelihood of durable remissions.

In conclusion, promising results observed in DLBCL, R/R FL, CLL and RS indicate that epcoritamab has the potential to become a core therapy for many patients suffering from B-cell malignancies. Ongoing research and clinical real-world experience will continue in refining the optimal use of this treatment and exploring potential combinations with other agents.

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Declaration of interest
Stefano Molica, Marco Rossi, and David Allsup have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Legend Fig.1

Epcoritamab T cell–engagement with the CD3 receptor on T cells and the CD20 receptor on the surface of lymphoma cells. The action releases cytokines and induces B-cell lysis.

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