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Integrated Study Master's Thesis

Real-World Analysis of Bispecific Antibodies in Relapsed or Refractory Non-Hodgkin Lymphoma Patients

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Abbreviations

Abbreviation	Full Term
ABC	Activated B-cell–like
AE / AEs	Adverse Event(s)
AHCT	Allogeneic Hematopoietic Cell Transplantation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ASCT	Autologous Stem Cell Transplantation
BCL	B-cell lymphoma
BiAb / BiAbs	Bispecific Antibody / Bispecific Antibodies
BL	Burkitt Lymphoma
BR	Bendamustine + Rituximab
bsAbs	Bispecific Antibodies
BTK	Bruton Tyrosine Kinase
CAR T-cell / CAR-T	Chimeric Antigen Receptor T-cell Therapy
CD	Cluster of Differentiation
CI	Confidence Interval
CMR	Complete Metabolic Response
CMV	Cytomegalovirus
CNS	Central Nervous System
COO	Cell of Origin
CR	Complete Response
CRR	Complete Response Rate
CRS	Cytokine Release Syndrome
DLBCL	Diffuse Large B-Cell Lymphoma
DH / TH	Double-Hit / Triple-Hit
DOR	Duration of Response
EBV	Epstein-Barr Virus
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FU	Follow-Up
GCB	Germinal Center B-cell–like
GGT	Gamma-Glutamyl Transferase
GemOx	Gemcitabine + Oxaliplatin
HGBCL	High-Grade B-Cell Lymphoma
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
IgG	Immunoglobulin G
IPI	International Prognostic Index
IQR	Interquartile Range
IRC	Independent Review Committee
IV	Intravenous
LBCL	Large B-Cell Lymphoma
MCL	Mantle Cell Lymphoma
mDoCR	Median Duration of Complete Response

mDOR	Median Duration of Response
MIPI	Mantle Cell Lymphoma International Prognostic Index
mo	Months
MRD	Minimal Residual Disease
MYC	Oncogenic transcription factor MYC
NHL / NHLs	Non-Hodgkin Lymphoma(s)
NK	Natural Killer
non-GCB	Non-germinal center B-cell
NT	Neurotoxicity
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
Pola-R-CHP	Polatuzumab Vedotin + Rituximab + Cyclophosphamide + Doxorubicin + Prednisone
Pola-Vedotin	Polatuzumab Vedotin
PR	Partial Response
R^2	Rituximab + Lenalidomide
R-CHOP	Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone
R-CVP	Rituximab + Cyclophosphamide + Vincristine + Prednisone
R-DHAP	Rituximab + Dexamethasone + High-dose Cytarabine + Cisplatin
R-DHAX/C	Rituximab + Dexamethasone + High-Dose Cytarabine + Oxaliplatin / Carboplatin
R-GDP	Rituximab + Gemcitabine + Dexamethasone + Cisplatin
R-ICE	Rituximab + Ifosfamide + Carboplatin + Etoposide
R/R	Relapsed/Refractory
RP2D	Recommended Phase 2 Dose
SC	Subcutaneous
SCT	Stem Cell Transplantation
SD	Standard Deviation
tFL	Transformed Follicular Lymphoma
VR-CAP	Bortezomib + Rituximab + Cyclophosphamide + Doxorubicin + Prednisone
WHO	World Health Organization

Summary

English:

Bispecific antibodies have emerged as a novel therapeutic approach for the treatment of relapsed or refractory B-cell lymphomas, demonstrating promising efficacy in pivotal clinical trials. However, the applicability of these results to routine clinical practice remains uncertain, particularly in heavily pretreated patient populations. Therefore, evaluating the real-world performance of Bispecific Antibodies and comparing these outcomes with existing clinical data is of both scientific and clinical relevance.

The aim of this thesis was to evaluate the efficacy and safety of bispecific antibody therapy in a real-world cohort of patients with relapsed or refractory B-cell lymphomas and to compare these outcomes with results reported in pivotal clinical trials and published real-world studies in order to explore potential limitations and implications for their optimal use. To achieve this aim, patient characteristics and treatment history were assessed, treatment efficacy was determined based on response rates and survival outcomes, and the safety profile was evaluated with a focus on adverse events.

This retrospective observational analysis included twelve patients with relapsed or refractory B-cell lymphoma, of whom seven were treated with Epcoritamab and five with Glofitamab. Clinical data were collected from medical records, and statistical analysis was primarily descriptive due to the small sample size.

The results demonstrated limited efficacy in this real-world cohort. Overall response rates were lower than those reported in clinical trials, with no complete remission observed in patients treated with Epcoritamab and two complete remissions in the Glofitamab subgroup. Median overall survival was approximately eight months after initiation of treatment with bispecific antibodies, reflecting the advanced disease stage and treatment-refractory nature of the cohort. The safety profile was generally consistent with known data, with cytokine release syndrome being the most frequent adverse event. However, a higher incidence of severe adverse events and infections, including sepsis, was observed compared to clinical trial populations.

In conclusion, bispecific antibodies represent a clinically relevant treatment option in patients with limited therapeutic alternatives, but their real-world effectiveness appears reduced compared to clinical trial data. These findings highlight the importance of further research to better define optimal treatment timing, sequencing strategies, and patient selection in order to improve outcomes in routine clinical practice.

Lithuanian:

Bispecifiniai antikūnai tapo nauju terapiniu metodu recidyvavusių arba gydymui atsparių B ląstelių limfomų gydyme pagrindiniuose klinikiniuose tyrimuose rodydami daug žadantį veiksmingumą. Tačiau šių rezultatų pritaikomumas klinikinėje praktikoje išlieka neaiškus, ypač anksčiau intensyviai gydytų pacientų populiacijose. Todėl bispecifinių antikūnų veiksmingumo realiomis klinikinės praktikos sąlygomis vertinimas ir šių rezultatų palyginimas su esamais klinikiniais duomenimis yra svarbūs tiek moksliniu, tiek klinikiniu požiūriu.

Šio baigiamojo darbo tikslas – įvertinti bispecifinių antikūnų terapijos veiksmingumą ir saugumą gydant pacientus, sergančius recidyvavusiomis arba gydymui atspariomis B ląstelių limfomomis bei palyginti rezultatus su klinikinių tyrimų ir gydymo centrųpublikuotais duomenimis, siekiant išnagrinėti terapijos galimus optimalaus skyrimoapribojimus ir reikšmę. Šiam tikslui pasiekti buvo įvertintos pacientų savybės ir gydymo istorija, gydymo veiksmingumas nustatytas remiantis atsako dažniais ir išgyvenamumo rodikliais, o saugumo profilis įvertintas daugiausia dėmesio skiriant nepageidaujamiems reiškiniams.

Į šią retrospektyvinę stebimąją analizę buvo įtraukta dvylika pacientų, sergančių recidyvavusia arba gydymui atsparia B ląstelių limfoma; iš jų septyni buvo gydyti epkoritamabu, o penki – Glofitamabu. Klinikiniai duomenys buvo surinkti iš medicininių įrašų, o statistinė analizė dėl mažos imties buvo aprašomojo pobūdžio.

Rezultatai parodė ribotą veiksmingumą šioje kohortoje. Bendri atsako dažniai buvo mažesni nei klinikiniuose tyrimuose – epkoritamabu gydyti pacientai nepasiekė visiškosremisijos, o Glofitamabo pogrupyje nustatytos dvi visiškos remisijos. Bendro išgyvenamumo mediana po gydymo bispecifiniais antikūnais pradžios buvo maždaug aštuoni mėnesiai, tai atspindi pažengusią ligos stadiją ir gydymui atsparų kohortos pobūdį. Saugumo profilis iš esmės atitiko žinomus duomenis, dažniausias nepageidaujamas reiškinys buvo citokinų išsiskyrimo sindromas. Vis dėlto, palyginus su klinikinių tyrimų populiacijomis, buvo stebėtas didesnis sunkių nepageidaujamų reiškinių ir infekcijų, įskaitant sepsį, dažnis.

Apibendrinant galima teigti, kad bispecifiniai antikūnai yra kliniškai reikšminga gydymo galimybė pacientams, turintiems ribotas terapines alternatyvas, tačiau jų veiksmingumas realiomis klinikinės praktikos sąlygomis atrodo mažesnis nei klinikinių tyrimų duomenyse. Šie rezultatai pabrėžia tolesnių tyrimų svarbą, siekiant geriau nustatytioptimalų gydymo laiką, gydymo sekos strategijas ir pacientų atranką, kad būtų pagerinti gydymo rezultatai įprastinėje klinikinėje praktikoje.

Keywords

Bispecific antibodies, Relapsed/refractory B-cell lymphoma, Real-world data, Treatment sequencing

1. INTRODUCTION

1.1 Overview of Non-Hodgkin Lymphomas

1.1.1 General Overview

Non-Hodgkin lymphomas (NHLs) are defined as a heterogeneous group of monoclonal neoplasms originating from the lymphatic system. Most NHLs arise from precursor or mature B- and T-lymphocytes. Together with Hodgkin lymphomas, they comprise the broader category of malignant lymphomas, of which approximately 75% are non-Hodgkin in nature. Among NHLs, about 85% are B-cell lymphomas and approximately 15% are T-cell lymphomas. NHLs account for around 6% of all malignant diseases. The incidence increases with age.(1)

The etiology of NHLs often remains unclear; however, several risk factors have been identified. These include immunodeficiencies (both congenital and acquired), infections (e.g. Epstein-Barr virus, Helicobacter pylori), exposure to certain chemicals (e.g. pesticides), ionizing radiation, and familial predisposition.

1.1.2 Classification

According to the current World Health Organization (WHO) classification, NHLs are broadly categorized into B-cell, T-cell, and natural killer (NK)-cell lymphomas. Additionally, lymphoproliferative disorders arising in the context of immunosuppression (such as post-transplant lymphoproliferative disorders) and neoplasms of histiocytic or dendritic cell origin are also included under the umbrella of NHLs.(2)

Clinically, a distinction is made between indolent (low-grade) and aggressive (high-grade) NHLs. Indolent lymphomas, often referred to as small-cell lymphomas, account for approximately 85% of cases. These tumours typically originate from mature, differentiated lymphocytes and are characterized by low mitotic activity. In contrast, aggressive NHLs, which comprise roughly 15% of cases, are also known as blastic lymphomas. They arise from immature, rapidly proliferating precursor cells and are associated with a significantly higher growth rate and a more acute clinical course.(1)

A comparative overview of indolent versus aggressive NHL subtypes is presented in the following table.

Table 1: Summary of differences between indolent and aggressive Non-Hodgkin Lymphomas

Indolent NHL	Aggressive NHL
Slow progression	Fast progression and aggressive course of disease
Diagnosis often late, in many cases "watch and wait"-strategy	Responds mostly well to chemoimmunotherapy
Low chance of recovery	Chance of healing around 50%
Follicular Lymphoma, Immunocytoma, MALT-Lymphoma	Diffuse Large B-Cell Lymphoma, Burkitt Lymphoma

In the following sections, the Non-Hodgkin Lymphoma subtypes most relevant to this thesis, namely diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and Burkitt lymphoma (BL), will be discussed in more detail.

A graphic of the cellular origin of the named and relevant NHL types is shown below (see Fig. 1).

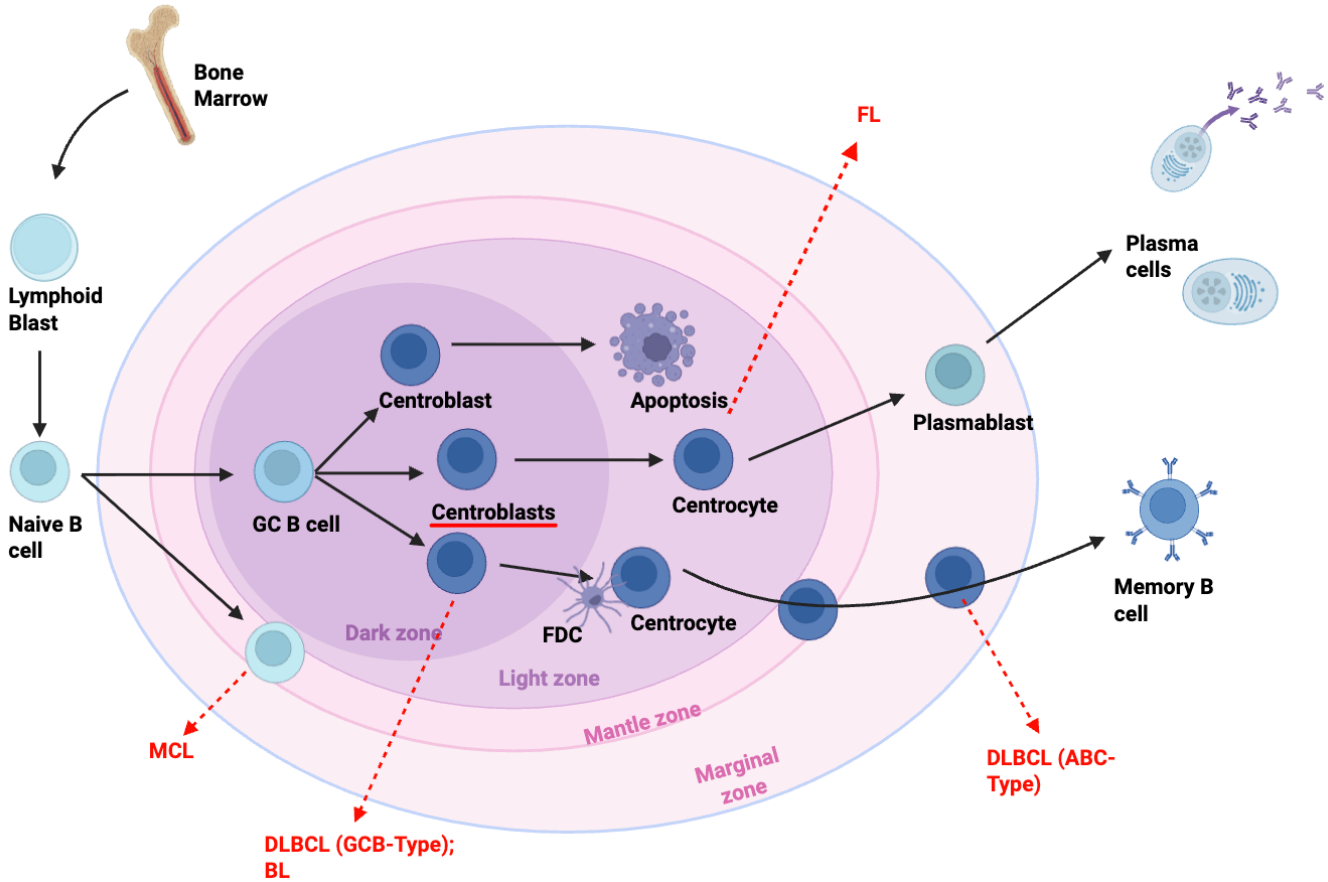

Fig. 1: A lymph follicle and the differentiation of B cells. The malignancies discussed in this work and their location from which they originate are marked in red.; Abbr: MCL – Mantle Cell Lymphoma, FL – Follicular Lymphoma, BL – Burkitt Lymphoma, DLBLC – Diffuse Large B-cell Lymphoma, FDC – Follicular Dentritic Cell, GC – Germinal Center, ABC – Activated B-Cell, GCB – Germinal Center B-Cell; Created with BioRender.

1.1.2.1 Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphomas (DLBCLs) are classified among the high-grade (aggressive) non-Hodgkin lymphomas and, accounting for approximately 30% of all NHL cases, represent the most common subtype. Although DLBCL can occur at any age, the peak incidence is observed around the seventh decade of life. DLBCL arises from mature B cells and is histologically characterized by the presence of large neoplastic B-cell blasts. Several distinct molecular and histological subtypes have been identified. Clinically, DLBCL typically presents with a rapidly enlarging lymph node mass and frequently with so-called "B symptoms", such as fever, night sweats, and unexplained weight loss. In approximately 40% of patients, DLBCL originates at extranodal sites, including the central nervous system (CNS), the gastrointestinal tract, or the lungs. In these cases, the clinical symptoms are primarily determined by the site of involvement.(1)

1.1.2.1.1 Cell of Origin Classification of DLBCL

As shown in Figure 1, diffuse large B-cell lymphoma can be further subdivided based on the cell of origin (COO), reflecting the developmental stage of the malignant B cell at the time of transformation. According to gene expression–based analyses, two major molecular subtypes are distinguished: germinal center B-cell–like (GCB) and activated B-cell–like (ABC) DLBCL, the latter commonly referred to in clinical practice as non-GCB DLBCL.(3) This classification captures fundamental biological differences in B-cell differentiation and transcriptional programs rather than morphological features alone.

The GCB subtype shows gene expression patterns characteristic of normal B cells residing within the germinal center, whereas the non-GCB/ABC subtype resembles B cells that have exited the germinal center and undergone activation during later stages of differentiation. As gene expression profiling is not routinely available in all clinical settings, immunohistochemistry-based algorithms, most commonly the Hans classifier, are frequently applied as surrogate methods to assign COO using marker expression patterns.(4)

The COO classification has become an established framework for molecular stratification of DLBCL and provides a biologically meaningful basis for further investigation of disease behaviour, therapeutic response, and outcome differences, which are discussed in subsequent sections.

1.1.2.2 Burkitt Lymphoma

Burkitt lymphoma (BL) is likewise classified among the highly aggressive lymphomas. It is characterized by rapid tumour growth and is frequently associated with Epstein-Barr virus (EBV) infection. Epidemiologically, BL predominantly affects children between the ages of four and seven

years, particularly in regions endemic for malaria. In Western industrialized countries, such as Lithuania, Burkitt lymphoma is considerably rarer, accounting for approximately 1–2% of adult NHL cases. In these settings, it often arises in the context of underlying immunodeficiency. A major risk factor for BL in adults is immunosuppression, particularly that associated with human immunodeficiency virus (HIV) infection. A hallmark of BL is the overexpression of the oncogenic transcription factor c-MYC, resulting from a characteristic chromosomal translocation, most commonly t(8;14)(q24;q32). (5) Clinically, BL is notable for its extraordinarily rapid proliferation, with visible lymphomatous masses increasing in size within days to weeks. The endemic form of BL frequently involves the jaw and other facial bones. In contrast, the sporadic variant presents with extranodal tumour localization in approximately 85% of cases, most commonly within the abdomen. Central nervous system (CNS) involvement is also relatively common and can manifest with neurological symptoms. Additional clinical features may include dysphagia due to tonsillar involvement, bone marrow infiltration, B symptoms (fever, night sweats, weight loss), and general systemic symptoms.(1)

1.1.2.3 Follicular Lymphoma

Follicular lymphoma (FL) is a low-grade (indolent) non-Hodgkin lymphoma and represents the most common subtype among indolent lymphomas. The disease typically affects individuals in the fifth to sixth decade of life, with a slight female predominance reported in epidemiological studies. FL originates from germinal center B cells, specifically centrocytes and centroblasts, within lymphoid follicles. A characteristic molecular feature of FL is the chromosomal translocation t(14;18)(q32;q21), which leads to overexpression of the anti-apoptotic protein BCL2 and is detected in approximately 80–90 % of cases. Clinically, FL often presents with a prolonged indolent course and may remain asymptomatic for an extended period. At diagnosis, patients commonly exhibit painless, slowly progressive lymphadenopathy, most frequently involving cervical and inguinal lymph nodes. Due to the indolent nature of the disease, diagnosis is frequently delayed. Bone marrow involvement is common in advanced stages and may result in cytopenias, particularly anaemia and thrombocytopenia, reflecting impaired haematopoiesis. Despite generally favourable initial responses to therapy, FL is characterized by a pattern of recurrent relapses, and transformation into an aggressive lymphoma can occur over time.(1)

1.1.2.4 Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin lymphoma that is generally classified as an indolent lymphoma but typically follows a more aggressive clinical course than follicular lymphoma. MCL accounts for approximately 5 % of all non-Hodgkin lymphomas and

predominantly affects older adults, with a median age at diagnosis of around 65 years. The disease shows a marked male predominance.

MCL originates from mature B lymphocytes of the mantle zone surrounding germinal centers. A defining molecular hallmark is the chromosomal translocation t(11;14), which results in overexpression of cyclin D1 and promotes dysregulated cell cycle progression.

Clinically, patients frequently present with generalized lymphadenopathy and splenomegaly. Bone marrow involvement is observed in approximately 80–90 % of cases at diagnosis and often contributes to cytopenias. Compared with follicular lymphoma, extranodal manifestations are more common in MCL, with frequent involvement of the gastrointestinal tract, where disease may present as multiple lymphomatous polyposis.

Histopathological examination of affected lymph nodes typically reveals nodular or diffuse infiltrates composed of medium-sized, centrocyte-like lymphoid cells. These cells are characterized by irregular nuclear contours, fine chromatin, and cleaved or indented nuclei, which are considered morphological features characteristic of mantle cell lymphoma.(1)

1.2 Prognostic differences between subtypes

Prognostic stratification plays a central role in the management of aggressive B-cell lymphomas, as it supports risk assessment, therapeutic decision-making, and patient counseling. Given the marked heterogeneity in clinical presentation and disease course, reliable prognostic tools are required to estimate outcomes and to guide treatment intensity. Traditionally, prognosis has been assessed using clinical risk models, most notably the International Prognostic Index (IPI), which integrates readily available patient- and disease-related parameters. However, advances in molecular pathology have demonstrated that biological and genetic factors substantially influence disease behaviour and treatment response beyond clinical risk alone. Consequently, contemporary prognostic assessment increasingly combines established clinical indices with molecular and biological markers, which are summarized in the following sections.

1.2.1 The International Prognostic Index

Prognosis in diffuse large B-cell lymphoma is influenced by multiple clinical and biological factors and varies considerably between individual patients. To account for this heterogeneity, the International Prognostic Index (IPI) was developed as a standardized clinical tool to estimate outcome in patients with aggressive lymphomas. Despite major advances in pathological classification and molecular diagnostics over the past decades, the IPI remains a widely used and clinically relevant prognostic model.

The IPI integrates five readily available clinical parameters: age greater than 60 years, advanced disease stage, involvement of more than one extranodal site, impaired performance status, and elevated serum lactate dehydrogenase levels. Each factor reflects disease burden or patient-related vulnerability and contributes additively to overall risk stratification. Based on the cumulative score, patients are categorized into risk groups associated with distinct survival outcomes. In retrospective analyses, the IPI consistently emerges as an independent predictor of progression-free and overall survival, even when additional biological variables are considered.

Beyond individual risk assessment, the IPI also provides important insight into discrepancies between outcomes observed in clinical trials and those seen in routine clinical care. Patients with high-risk disease are frequently underrepresented in trial populations, which may contribute to more favourable reported outcomes compared to real-world cohorts. Moreover, the IPI enables adjusted analyses that help disentangle the prognostic contribution of emerging molecular and genetic biomarkers.(6)

Although the IPI provides a robust framework for prognostic assessment and treatment planning, it does not capture the full biological diversity of DLBCL. There is increasing evidence that molecular subtypes and genetic alterations influence treatment response, relapse patterns, and survival independently of clinical risk factors. These aspects are addressed in the following section, which focuses on biological subtype–specific prognostic differences and their implications for therapeutic decision-making.

In addition to the IPI, subtype-specific prognostic scores have been developed to improve risk stratification in particular lymphoma entities. These models were conceptually derived from the IPI but adapted to reflect disease-specific clinical characteristics. Two of the most widely used examples are the Mantle Cell Lymphoma International Prognostic Index (MIPI) and the Follicular Lymphoma International Prognostic Index (FLIPI).

The MIPI was specifically designed and validated for mantle cell lymphoma, as the classical IPI was found to provide limited discrimination of survival outcomes in this disease. The score comprises four independent prognostic variables: age, performance status, serum lactate dehydrogenase level, and leukocyte count. It also stratifies patients into distinct risk groups with clearly different survival probabilities.(7) This disease-specific model allows a more accurate identification of low-, intermediate-, and high-risk patients than the IPI in mantle cell lymphoma.(8)

Similarly, the FLIPI was developed for patients with follicular lymphoma and demonstrates improved prognostic discrimination compared with the IPI in this indolent lymphoma subtype. The FLIPI includes five clinical parameters: age, disease stage, serum lactate dehydrogenase level, haemoglobin concentration, and the number of involved nodal regions. In contrast to the IPI, which considers extranodal involvement, focuses more on tumour burden, which is particularly relevant for indolent

lymphomas such as follicular lymphoma. Importantly, the score has remained a valid prognostic tool even after the introduction of rituximab-based immunochemotherapy.(9,10)

1.2.2 Molecular and Biological Prognostic Factors

Prognosis in B-cell non-Hodgkin lymphomas is increasingly shaped by molecular and biological features that reflect the intrinsic behaviour of the malignant clone. These factors complement clinical prognostic indices by capturing differences in proliferation, apoptotic resistance, and cellular differentiation, thereby explaining why patients with comparable clinical characteristics may experience different outcomes, even with the same treatments. Across lymphoma subtypes, alterations involving MYC, BCL2, and BCL6, as well as differences related to cell-of-origin, represent some of the most robust and clinically relevant biological prognostic markers (10).

A central determinant of aggressive disease biology is deregulation of the MYC oncogene. MYC drives cellular proliferation, metabolic reprogramming, and genomic instability, and its aberrant activation is strongly associated with rapid disease progression. When MYC rearrangements occur together with dysregulation of anti-apoptotic pathways, most commonly involving BCL2, tumour cells gain both a proliferative advantage and resistance to programmed cell death. Lymphomas harbouring concurrent MYC and BCL2 rearrangements, termed double-hit lymphomas, consistently show inferior responses to standard immunochemotherapy and a high risk of early relapse.(11) An even more unfavourable biological constellation is observed when rearrangements of MYC, BCL2, and BCL6 coexist (triple-hit lymphomas). In these cases, deregulated proliferation, impaired apoptosis, and disturbed germinal center differentiation converge, resulting in highly aggressive clinical behaviour and poor survival outcomes despite intensified treatment approaches. Recognition of these molecular constellations has therefore become essential for upfront risk stratification and therapeutic planning. Importantly, adverse MYC-driven biology is not limited to chromosomal rearrangements (11). Overexpression of MYC and BCL2 proteins in the absence of detectable gene translocations, commonly referred to as double-expresser lymphomas, is also associated with inferior outcomes compared with biologically low-risk disease. Although the prognosis of these cases is generally intermediate between standard-risk and true double-hit lymphomas, their identification highlights that protein-level dysregulation carries independent prognostic significance (10).

Another major biological determinant of prognosis is the cell-of-origin (COO). Molecular studies have demonstrated that aggressive B-cell lymphomas can be subdivided into tumours resembling germinal center B cells (GCB) and those derived from activated or post-germinal center B cells, commonly grouped as non-GCB. This distinction reflects fundamental differences in oncogenic signalling pathways. In general, GCB-type lymphomas show superior responses to rituximab-based chemotherapy and more favourable survival, whereas non-GCB tumours are associated with chronic

activation of survival pathways and inferior outcomes.(10) Because comprehensive gene expression profiling is not universally available, immunohistochemical algorithms are widely used as surrogate tools to assign COO in routine diagnostics. Despite imperfect concordance with molecular techniques, these approaches reliably identify biologically and prognostically distinct subgroups and remain clinically relevant for risk stratification.

The prognostic relevance of differentiation state is also evident in indolent lymphomas. Recent transcriptomic analyses have identified molecular subtypes resembling normal germinal center B cells and memory B cells, which differ significantly in clinical outcome. Tumours with germinal center–like features tend to show more favourable progression-free survival, whereas memory-like signatures are associated with earlier progression following conventional immunochemotherapy.(12)

In mantle cell lymphoma, molecular heterogeneity further underscores the importance of biological prognostic factors. Beyond cyclin D dysregulation, secondary genetic alterations such as MYC abnormalities, TP53 disruption, and high proliferative activity define high-risk disease with particularly poor outcomes. These molecular features provide prognostic information beyond established clinical indices and contribute to the marked variability in clinical behaviour observed in this entity.(13)

Taken together, molecular prognostic factors in B-cell non-Hodgkin lymphomas act in concert rather than isolation. Alterations affecting proliferation, apoptosis, and cellular differentiation collectively shape disease aggressiveness and treatment sensitivity. The integration of MYC/BCL2 and MYC/BCL2/BCL6 alterations alongside GCB versus non-GCB classification therefore represents a cornerstone of modern prognostication and provides the biological foundation for increasingly individualized therapeutic strategies.(10)

1.3. Current Standard Treatments and Survival Rates

1.3.1 First Line Therapies

First-line treatment strategies for B-cell lymphomas are determined by the biological aggressiveness of the disease, clinical stage, patient fitness, and overall treatment intent, which ranges from curative approaches in aggressive lymphomas to disease control in indolent entities. Despite substantial biological heterogeneity, immunochemotherapy remains the backbone of initial treatment across most B-cell lymphoma subtypes.

DLBCL, the most common aggressive non-Hodgkin lymphoma, is considered a potentially curable disease. Without treatment, it follows a rapidly progressive and often fatal course. Standard first-line treatment consists of rituximab-based immunochemotherapy, most commonly the R-CHOP regimen.

The addition of the anti-CD20 antibody rituximab has significantly improved outcomes across patient subgroups, and six cycles of R-CHOP administered at 21-day intervals are considered the international standard. Treatment adaptations may be applied based on age, risk profile, and interim metabolic response. Although molecular classification into germinal center B-cell–like (GCB) and non-GCB/activated B-cell subtypes provides important biological insight, this distinction currently does not lead to different therapeutic strategies in first-line clinical practice.(14)

In contrast, follicular lymphoma represents a prototypical indolent B-cell lymphoma with a highly variable clinical course. In asymptomatic patients, particularly in advanced stages, an initial watch-and-wait strategy is appropriate, as early treatment has not been shown to improve overall survival.(15) When treatment is required due to symptomatic disease or high tumour burden, first-line therapy also relies on immunochemotherapy combining an anti-CD20 antibody with chemotherapy. Commonly used regimens include R-CHOP, R-bendamustine, and R-CVP, with the choice influenced by patient age, comorbidities, and toxicity considerations.(14) In localized disease, involved-site radiotherapy can achieve long-term disease control and, in some cases, cure.(16)

Mantle cell lymphoma occupies an intermediate position between indolent and aggressive lymphomas, characterized by marked clinical heterogeneity. While some patients with low tumour burden and indolent features may initially be managed with observation, most require systemic therapy.(17) In younger and fit patients, intensive cytarabine-containing immunochemotherapy followed by autologous stem cell transplantation has been shown to improve both progression-free and overall survival. In older or less fit patients, less intensive regimens such as R-bendamustine, VR-CAP, or R-CHOP are commonly employed, reflecting a balance between efficacy and tolerability.(14)

Burkitt lymphoma represents the most aggressive entity among the lymphomas discussed and requires immediate initiation of highly intensive chemotherapy. First-line treatment consists of short, dose-dense multi-agent regimens, frequently combined with rituximab. These approaches achieve high cure rates but are associated with substantial toxicity and therefore require management in experienced centres. Less intensive regimens may be considered in selected patients but are generally associated with inferior disease control in high-risk situations, particularly in the presence of central nervous system involvement.(14)

Across all these entities, first-line treatment strategies reflect shared principles, most notably the central role of anti-CD20–based immunochemotherapy, while differing substantially in intensity, duration, and therapeutic goals. Importantly, despite advances in molecular classification and risk stratification, standard first-line therapy remains largely uniform within each disease entity. Relapse or refractory disease therefore represents a major clinical challenge across lymphoma subtypes and

provides the rationale for the development and implementation of novel immunotherapeutic approaches, including bispecific antibodies, which are addressed in subsequent sections.

1.3.2 Treatment in Relapsed and Refractory Cases

Despite substantial progress in first-line therapy, relapse or refractory disease remains a major clinical challenge across B-cell lymphomas. Treatment strategies in this setting are guided by several overarching factors, including timing of relapse, prior therapies, patient fitness, and treatment intent, rather than by histology alone. In contrast to first-line therapy, management of relapsed or refractory disease is increasingly individualized and often requires sequential use of multiple therapeutic modalities.

Historically, salvage chemotherapy followed by high-dose therapy and autologous stem cell transplantation (ASCT) represented the standard approach for patients with chemosensitive relapse, particularly in aggressive lymphomas. This strategy remains relevant for selected patients with late relapse and sufficient fitness, especially when a considerable response to salvage chemotherapy can be achieved. However, outcomes are generally poor in patients with primary refractory disease or early relapse, as response rates to conventional salvage regimens are limited in this setting. Moreover, increasing patient age, comorbidities, and cumulative toxicity often preclude the use of high-dose therapy, reducing the applicability of ASCT in routine practice.(14)

The development of chimeric antigen receptor (CAR) T-cell therapy has fundamentally altered the treatment landscape of relapsed and refractory B-cell lymphomas. CAR T-cell therapy has demonstrated durable responses in extensively pretreated patients, including those with primary refractory disease or early relapse, and is now established as a standard treatment option in multiple lines of therapy. Importantly, eligibility for CAR T-cell therapy is not strictly limited by chronological age, and real-world data indicate that older patients may derive similar benefit compared with younger cohorts.(18,19) Nevertheless, CAR T-cell therapy is associated with unique acute and long-term toxicities, requires specialized infrastructure, and is not feasible for all patients due to disease kinetics, organ dysfunction, or logistical constraints.(20)

For patients who are not candidates for high-dose therapy or CAR T-cell therapy, alternative systemic approaches have gained increasing importance. These include antibody-based regimens, antibody–drug conjugates, and immunomodulatory combinations, which offer clinically meaningful responses with more favourable tolerability profiles in selected populations. While such therapies may provide effective disease control, their curative potential remains uncertain, and treatment sequencing has become a critical consideration, particularly with respect to preserving future cellular therapy options.

In later treatment lines, allogeneic stem cell transplantation may be considered in highly selected patients who achieve adequate disease control after salvage therapy. This approach offers potential long-term disease control through graft-versus-lymphoma effects but is limited by substantial treatment-related morbidity and mortality and is therefore reserved for exceptional cases.(21)

Across lymphoma subtypes, the need for bridging or salvage therapy prior to definitive treatments such as CAR T-cell therapy is common, particularly in patients with rapidly progressive disease. Bridging strategies aim to stabilize disease and maintain patient fitness while avoiding excessive toxicity that could compromise subsequent cellular therapies. However, evidence guiding the optimal choice and intensity of such approaches remains limited.

Overall, treatment of relapsed and refractory B-cell lymphomas is characterized by increasing therapeutic complexity, limited durability of responses with conventional approaches, and a growing need to balance efficacy, toxicity, and sequencing of available options. These challenges underscore the unmet clinical need for novel, effective, and broadly applicable immunotherapeutic strategies, which will be addressed in the following sections.

1.4. Challenges in Relapsed / Refractory B-Cell Lymphomas

In addressing the complexities and challenges associated with relapsed or refractory B-cell lymphomas, particularly in the European context over the last five years, several key aspects need to be highlighted: the poor prognosis in primary refractory and multiple-relapse patients, the limitations of current therapies including chemotherapy, SCT, and CAR-T therapies, as well as the pressing unmet need for alternative treatment options.

Patients with primary refractory DLBCL exhibit particularly poor survival outcomes: The SCHOLAR-1 study established, that patients with refractory DLBCL had a median overall survival of only 6.3 months and an objective response rate of just 26% (CR rate 7%) to the next line of therapy, with only 20% alive at 2 years.(22) Approximately 35-40% of DLBCL patients relapse or are refractory to first-line R-CHOP, and outcomes deteriorate a lot with each subsequent relapse.(23) Among the transplant-eligible patients, only around half respond to salvage chemotherapy and proceed to autologous stem cell transplantation, yielding an overall cure rate of just 25-35%.(24) Factors contributing to such high rates of resistance include genetic mutations, epigenetic modifications, aberrant signalling pathway activation, drug metabolism alterations, and upregulation of anti-apoptotic proteins, with the tumour microenvironment playing a key mediating role.(25)

Traditional chemotherapy regimens, while pivotal in treating B-cell lymphomas, often yield diminishing efficacy in relapsed patients, leading to high rates of resistance. In cases of relapse or resistance, oftentimes conventional salvage chemotherapy (R-ICE, R-DHAP, R-GDP) can be used. While those regimens have similar efficacy, they are limited by chemoresistance, cumulative toxicity

and inability to produce durable responses in the majority of patients. For chemosensitive relapsed disease cases, ASCT remains the standard consolidate approach. However, only half of patients are eligible due to age, comorbidities, or chemoresistance.(24) Allogeneic hematopoietic cell transplantation (AHCT) offers a graft-versus-lymphoma effect but carries high non-relapse mortality.(26) As another option with transformative efficacy, CAR-T therapy can be used. However, it also faces several critical limitations. Logistic, geographical, and manufacturing constraints mean not all selected patients can receive infusions. Despite that, there can be mechanisms of resistance, such as the CD19 antigen loss.(27) Overall, CAR-T therapy has presented a promising frontier in the treatment of refractory B-cell lymphomas. Nonetheless, toxicity remains a significant barrier, with challenges such as cytokine release syndrome (CRS) and neurotoxicity complicating its administration in certain patients.(28)

Given the limitations of current treatments, there is an urgent need for the development of alternative therapeutic strategies. Research into combination therapies is ongoing, with promising results reported using agents that target mechanisms of resistance. Bispecific antibodies, antibody-drug conjugates, CD22 or CD20-directed CAR-T build a few of several novel approaches, addressing the gaps in relapsed or refractory B-cell lymphomas.(29) Optimal sequencing of those approaches remains undefined, and rational combination strategies guided by molecular subtyping are an area of active investigation.(24)

In summary, the landscape of relapsed or refractory B-cell lymphomas in Europe is marked by significant challenges including poor prognostic outcomes, limitations of existing therapies, and a pressing demand for novel treatment paradigms. A multi-pronged approach focused on understanding the biological mechanisms of resistance and integrating innovative therapeutic strategies will be essential for improving patient outcomes in this patient population.

1.5 Bispecific Antibodies: A Novel Therapeutic Approach

1.5.1 Historical Development

Bispecific antibodies are a relatively new approach and were developed as a response to the need for more targeted immunotherapeutic strategies capable of directly engaging the patient's immune system against malignant cells (30). Unlike conventional monoclonal antibodies, which bind a single antigen, bispecific antibodies are engineered to simultaneously recognize two distinct targets. This dual specificity enables the physical linkage of immune effector cells to tumour cells, thereby facilitating targeted immune-mediated cytotoxicity (31).

Early bispecific antibody constructs were explored several decades ago. However, their clinical application was initially limited by structural instability, short serum half-life, and substantial toxicity

related to excessive immune activation. These limitations hindered sustained therapeutic exposure and restricted early clinical development. Advances in antibody engineering, including the refinement of antibody formats and improved molecular design, have since addressed many of these challenges, enabling the generation of bispecific antibodies with more favourable pharmacokinetic and safety profiles.(31) A major milestone in the clinical development of bispecific antibodies was the introduction of T-cell–engaging constructs targeting CD3 on T cells. These agents demonstrated that effective antitumor activity could be achieved through direct T-cell redirection without the need for antigen presentation via the major histocompatibility complex.(31) The clinical success of early T-cell–engaging bispecific antibodies established proof of concept for this therapeutic strategy and stimulated further development of next-generation molecules.(30) Subsequent efforts focused on optimizing antibody architecture to allow intermittent dosing and improved tolerability, ultimately leading to the development of full-length or modified IgG-based bispecific antibodies.(31) These innovations enabled broader clinical evaluation and paved the way for the introduction of bispecific antibodies targeting CD20 in B-cell malignancies.(30) As a result, bispecific antibodies emerged as a viable therapeutic class within the expanding field of immunotherapy for hematologic cancers. As shown in figure 2, Glofitamab was designed to have bivalent binding valency with CD20, whereas Epcoritamab was designed monovalent.

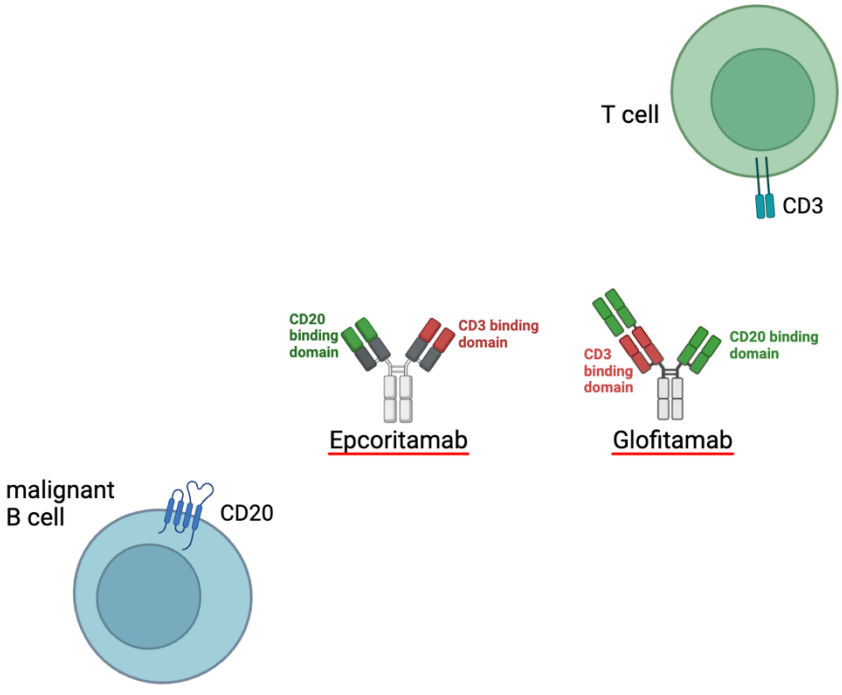

Fig. 2: The structure of the bispecifc antibodies Epcoritamab and Glofitamab. Glofitamab binds to the B-lymphocyte antigen CD20 twice, whereas Epcoritamab binds only once. Created with BioRender.

1.5.2 Clinical Introduction and Current Status

Following advances in antibody engineering and early proof-of-concept studies, bispecific antibodies entered clinical evaluation as a therapeutic option for patients with relapsed or refractory B-cell malignancies. Their clinical development has focused primarily on aggressive lymphomas, where outcomes after standard immunochemotherapy and subsequent treatment lines remain poor. In this context, bispecific antibodies were investigated as an alternative immune-based approach capable of inducing antitumor activity in heavily pretreated patient populations.(30)

Agents such as Glofitamab and Epcoritamab have been evaluated in multicentre clinical trials involving patients with relapsed or refractory large B-cell lymphomas who had received multiple prior lines of therapy. These studies demonstrated clinically meaningful antitumor activity and established the feasibility of bispecific antibody therapy in advanced disease settings.(30) Based on data from phase I and II clinical trials, bispecific antibodies have received regulatory approval for use in later treatment lines of relapsed or refractory large B-cell lymphoma. Phase III trials are expected to run until 2028. The EMA approved both BiAbs in 2023, and the indication for Epcoritamab was expanded in 2024. Their clinical introduction has expanded the therapeutic landscape beyond conventional chemoimmunotherapy and autologous cellular therapies. Importantly, current approvals are largely restricted to patients with limited remaining treatment options, reflecting the populations studied in pivotal trials.(30) Ongoing clinical investigations are exploring the role of bispecific antibodies in additional disease contexts, including earlier lines of therapy, combination regimens, and sequential strategies with other immunotherapies. However, most available evidence to date originates from controlled clinical trial settings with defined inclusion criteria.(30) As a result, the translation of trial findings to broader patient populations treated in routine clinical practice remains an area of active investigation.

1.5.3 Mechanism of Action

Bispecific antibodies exert their antitumor activity by simultaneously binding two distinct antigens, thereby functionally linking immune effector cells to malignant target cells. In the context of B-cell lymphomas, most clinically developed bispecific antibodies are designed to recognize CD20, a surface antigen expressed on mature B cells, and CD3, a component of the T-cell receptor complex present on T lymphocytes. Through this dual binding, bispecific antibodies facilitate direct physical proximity between T cells and tumour cells.(32) Engagement of CD3 by the bispecific antibody leads to T-cell activation, independent of antigen presentation via the major histocompatibility complex. Upon formation of an immunological synapse, activated T cells release cytotoxic effector molecules, including perforin and granzymes, resulting in targeted lysis of the CD20-expressing B cell. This

mechanism allows for efficient tumor cell killing even in the absence of pre-existing tumor-specific T-cell receptors.

Importantly, bispecific antibody–mediated T-cell activation does not require prior sensitization or clonal expansion of T cells. Instead, endogenous T cells present in the patient's immune system are recruited at the tumor site, enabling immediate immune engagement following antibody administration. This feature distinguishes bispecific antibodies from adoptive cellular therapies and underlies their classification as "off-the-shelf" immunotherapeutic agents.(32) The extent of T-cell activation induced by bispecific antibodies is influenced by factors such as antibody format, binding affinity, and dosing strategy. To mitigate excessive immune activation, contemporary bispecific antibody regimens often incorporate step-up dosing schedules, which allow for gradual T-cell engagement while maintaining antitumor efficacy.(31) A schematic overview of the mechanism of action of CD20×CD3 bispecific antibodies is provided in Figure 3, illustrating the simultaneous binding of T cells and malignant B cells and the resulting cytotoxic immune response.

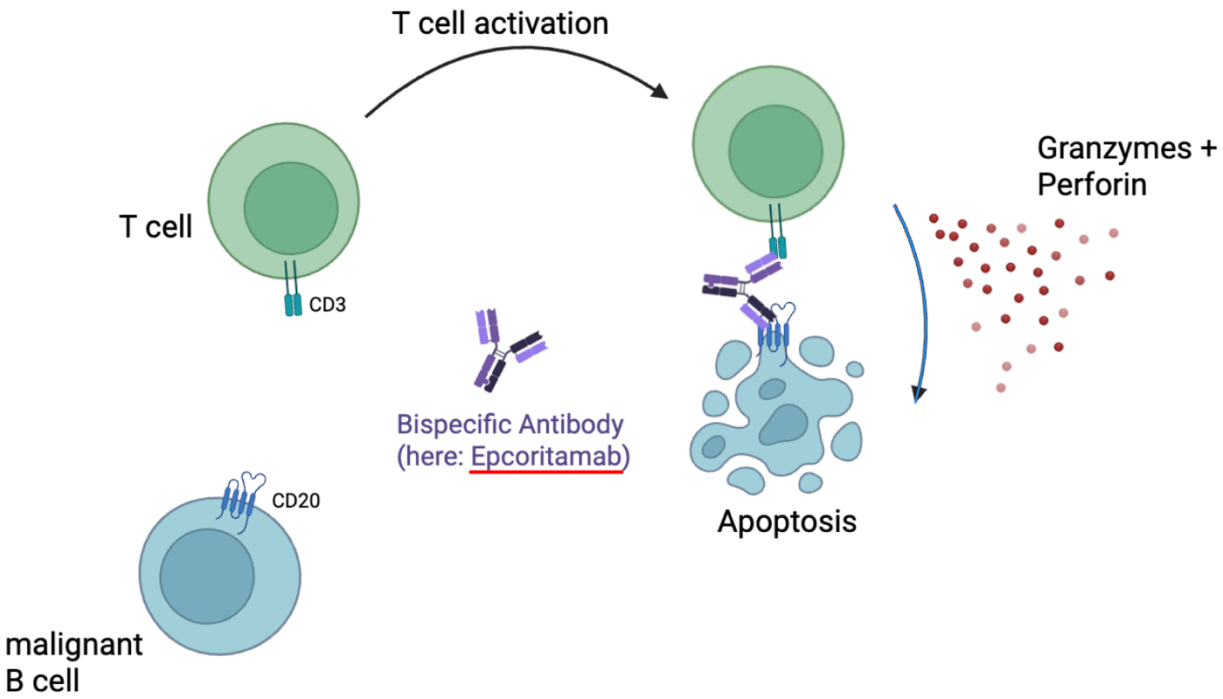

Fig. 3: The mechanism of action of the bispecific antibodies investigated in this thesis. Here the structure shows Epcoritamab. Glofitamab also binds CD20 and CD3, but has a bivalent binding valency towards CD20. Created with BioRender.

1.6 Studio Rationale & Objectives

Bispecific antibodies, such as Glofitamab and Epcoritamab, have emerged as a promising therapeutic option in the treatment of relapsed or refractory B-cell lymphomas, demonstrating substantial efficacy in pivotal clinical trials. However, the transferability of these results to routine clinical practice

remains uncertain, as trial populations are often highly selected and may not fully reflect the characteristics of patients treated in real-world settings

At the same time, real-world data on the use of bispecific antibodies are still limited, and potential differences in efficacy, survival outcomes, and safety profiles compared to clinical trial data have not yet been fully characterized. Therefore, evaluating the performance of BiAbs in routine clinical settings and placing these findings in the context of existing clinical trial evidence is of both scientific and clinical relevance.

The aim of this thesis is to evaluate the efficacy and safety of bispecific antibody therapy in a real-world cohort of patients with relapsed or refractory B-cell lymphomas and to compare these outcomes with results reported in pivotal clinical trials and published real-world data in order to explore potential limitations and implications for their optimal use within current treatment strategies.

To achieve this aim, the clinical characteristics and treatment history of patients receiving bispecific antibody therapy in a real-world setting are evaluated. Furthermore, the efficacy of bispecific antibodies in the analyzed cohort is determined, including response rates and survival outcomes. In addition, the safety profile of bispecific antibody therapy is evaluated, with a focus on adverse events such as cytokine release syndrome and infections. Finally, the observed outcomes are compared with data from pivotal clinical trials and other published real-world studies to identify potential discrepancies, assess limitations of current treatment approaches, and explore implications for treatment sequencing and timing within the therapeutic landscape.

2. LITERATURE REVIEW

Given the recent introduction of bispecific antibodies into clinical practice, the available literature is still limited, particularly with regard to real-world data and long-term outcomes.

The selection of literature primarily focused on pivotal clinical trials investigating the efficacy and safety of Glofitamab and Epcoritamab, as these studies form the basis for their current clinical use. In addition, recently published real-world studies were included where available, in order to provide a broader perspective on treatment outcomes outside controlled trial settings. The majority of the literature considered in this thesis was published within the last five years, with a particular focus on more recent publications reflecting the rapid development of this therapeutic field. All references were published between 2010 and 2026. Relevant sources were identified mainly through PubMed and peer-reviewed oncology journals. Figure 4 shows the used references, sorted according to citation and publication year.

Based on the available literature, it becomes apparent that most of the current evidence is derived from clinical trials conducted in selected patient populations, while data from routine clinical practice remain limited. Furthermore, important clinical questions have not yet been fully resolved. In

particular, the optimal positioning of bispecific antibodies within the treatment algorithm, including their timing in relation to established therapies such as CAR-T cell therapy or stem cell transplantation, remains unclear. Similarly, the extent to which outcomes observed in clinical trials can be transferred to heavily pretreated and high-risk patient populations is not yet well defined.

Given these limitations, the focus of this thesis was placed on the comparison of outcomes from pivotal clinical trials with data obtained from a real-world patient cohort. This approach allows for the identification of potential differences between controlled study conditions and routine clinical practice. The results of this comparison are further interpreted in the discussion section in the context of recently published studies, including additional real-world data, in order to assess current limitations and to explore implications for future research, particularly with regard to treatment sequencing and clinical applicability.

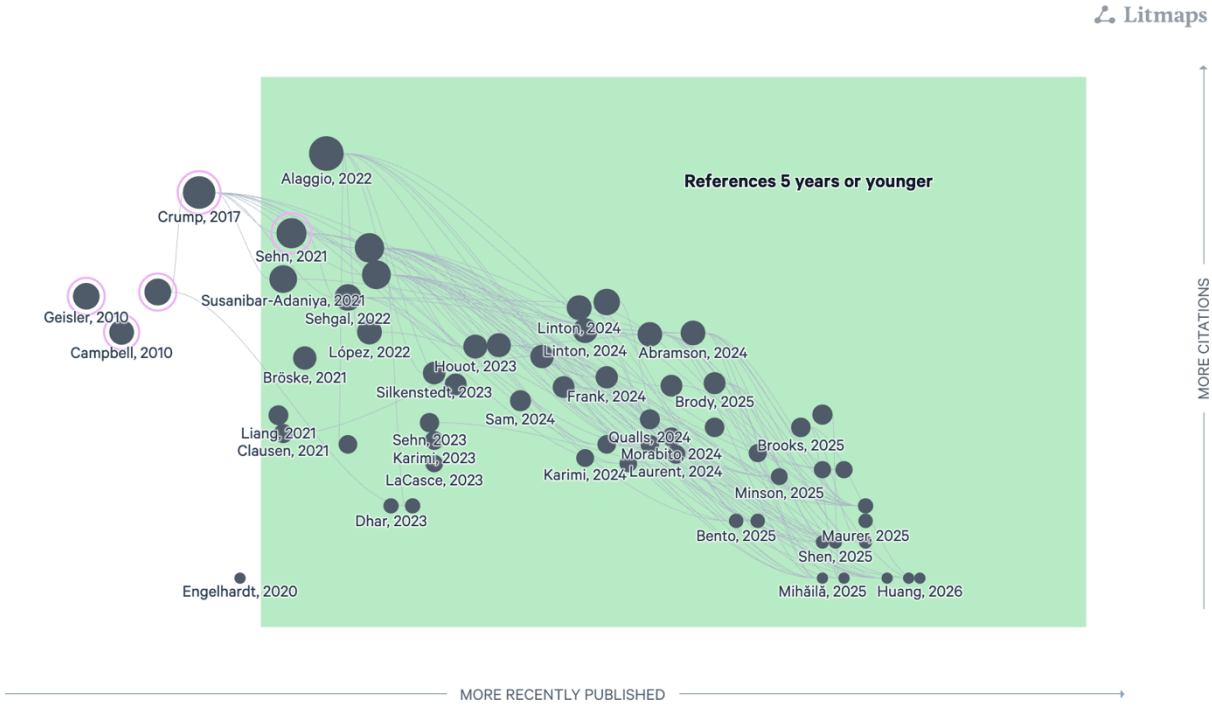

Fig. 4: The used references for discussion. In the green box all references published in the last 5 years are marked, highlighting the choice of up-to-date references. Created with Litmaps.

3. METHODS

3.1 Study Design and Patient Population

This retrospective observational analysis included a cohort of twelve patients diagnosed with diffuse large B-cell lymphoma and related subtypes, as well as follicular lymphoma and mantle cell lymphoma. All patients were treated at Vilnius University Hospital Santaros Clinics and had received at least two prior lines of systemic therapy before initiation of BiAb treatment.

Eligible patients had documented disease progression or refractory status to previous therapies. The majority presented with aggressive histological variants, including non-germinal center B-cell (non-GCB) and double- or triple-hit lymphoma subtypes, which can be categorised as high-risk population. Patients received treatment with either Glofitamab or Epcoritamab according to institutional or manufacturer-recommended protocols. Clinical data were collected from medical records and laboratory documentation, including demographic characteristics, treatment history, disease subtype, BiAb regimen, treatment response, adverse events, and survival outcomes. This analysis was conducted in accordance with the principles of the Declaration of Helsinki and local data protection regulations. All patient data were pseudonymized before analysis to protect confidentiality.

3.2 Statistical Analysis

Given the small sample size and disease heterogeneity, the statistical approach was primarily descriptive. Continuous variables, such as age and number of treatment cycles, were summarized using median and interquartile range (IQR), while categorical variables, such as sex, disease type, and response category, were presented as absolute counts and percentages.

Where appropriate, Fisher's exact test was used to compare categorical outcomes, as this test is suitable for small datasets. Overall survival (OS) was calculated from the date of treatment initiation to the date of death. Survival probabilities were estimated using the Kaplan–Meier method, and median survival as well as 6- and 12-month survival rates were reported.

Due to the limited number of events, Cox proportional hazards models were not applied. All statistical analyses were performed using R and RStudio, utilizing packages including dplyr, ggplot2, survival, and survminer for data manipulation, statistical analysis, and visualization. Graphs were generated in RStudio and exported for inclusion in this thesis; selected schematic figures were created using BioRender.

4. RESULTS

4.1 Patient Characteristics

A total of 12 patients treated with bispecific antibodies were included in the analysis. The cohort comprised predominantly male patients with a median age of 53 years (range: 38–64). The predominant underlying histologies were diffuse large B-cell lymphoma (DLBCL) subtypes, including non-germinal center B-cell (non-GCB) and GCB variants, but also follicular lymphoma (FL) and mantle cell lymphoma (MCL). Multiple patients presented with double- or triple-hit features

(MYC/BCL2 or MYC/BCL2/BCL6 rearrangements), reflecting the biologically aggressive disease profile. A summary of patients' characteristics can be found in table 2.

Table 2: A summary of important patient characteristics of the analysed group.

			Glofitamab (n=5)	Epcortamab (n=7)	Total Cohort (Glofitamab + Epcoritamab; n=12)
Age			median 51 (34-64)	median 54 (38-61)	median 53 (34-64)
Sex	Male		100% (n=5)	57.14% (n=4)	75% (n=9)
	Female		0% (n=0)	42.86% (n=3)	25% (n=3)
Diagnosis	DLBCL	GCB	0% (n=0)	14.29% (n=1)	8.33% (n=1)
		Non-GCB	20% (n=1)	42.86% (n=3)	33.33% (n=4)
		DH	0% (n=0)	14.29% (n=1)	8.33% (n=1)
		TH	20% (n=1)	0% (n=0)	8.33% (n=1)
	FL		0% (n=0)	28.57% (n=2)	16.67% (n=2)
	BL		20% (n=1)	0% (n=0)	8.33% (n=1)
	MCL		40% (n=2)	0% (n=0)	16.67% (n=2)
Number of prior therapy lines			Mean 3.2 (2-4)	Mean 2.57 (2-4)	Mean 2.83 (2-4)
Refractory to first-line therapy			60% (n=3)	57.14% (n=4)	58.33% (n=7)
Refractory to last-line therapy			100% (n=5)	100% (n=7)	100% (n=12)
Monotherapy			80% (n=4)	100% (n=7)	91.67% (n=11)
BiAb combinations			20% (n=1) (Glofitamab + Polatuzumab)	0% (n=0)	8.33% (n=1)
Treatment prior to BiAbs	CAR-T		40% (n=2)	0% (n=0)	16.67% (n=2)
	SCT		40% (n=2)	0% (n=0)	16.67% (n=2)
Treatment after BiAbs	CAR-T		40% (n=2)	42.86% (n=3)	41.66% (n=5)
	SCT		60% (n=3)	14.29% (n=1)	33.33% (n=4)

All patients had received at least two prior lines of therapy, with a median of three (range 2–4). The majority were refractory to both first- and last-line therapy (n=7), emphasizing the limited responsiveness to previous treatments. Only a minority had undergone autologous or allogeneic stem cell transplantation (SCT) or CAR-T therapy prior to BiAb initiation, while a small subset received such treatments after BiAb failure.

To evaluate the balance of the study group, an unpaired t-test was performed. There was no significant difference of age within the male and female groups (p=0.9). The sample groups both passed the Shapiro-Wilk normality test (male p=0.29; female p=0.38). Levene test of equal variances proved that the standard deviations are not significantly different (p=0.61). It can be concluded that the age distribution within the two groups was balanced.

The treatment in our cohort consisted of Glofitamab or Epcoritamab, administered according to the respective protocols. The number of treatment cycles is illustrated in Figure 5. Most patients completed between one and three cycles. One patient finished the standardized twelve cycles of treatment with Glofitamab. This patient also reached complete remission. The reasons for the low number of cycles are discussed later in this section, with disease progression identified as the most frequent cause for treatment discontinuation.

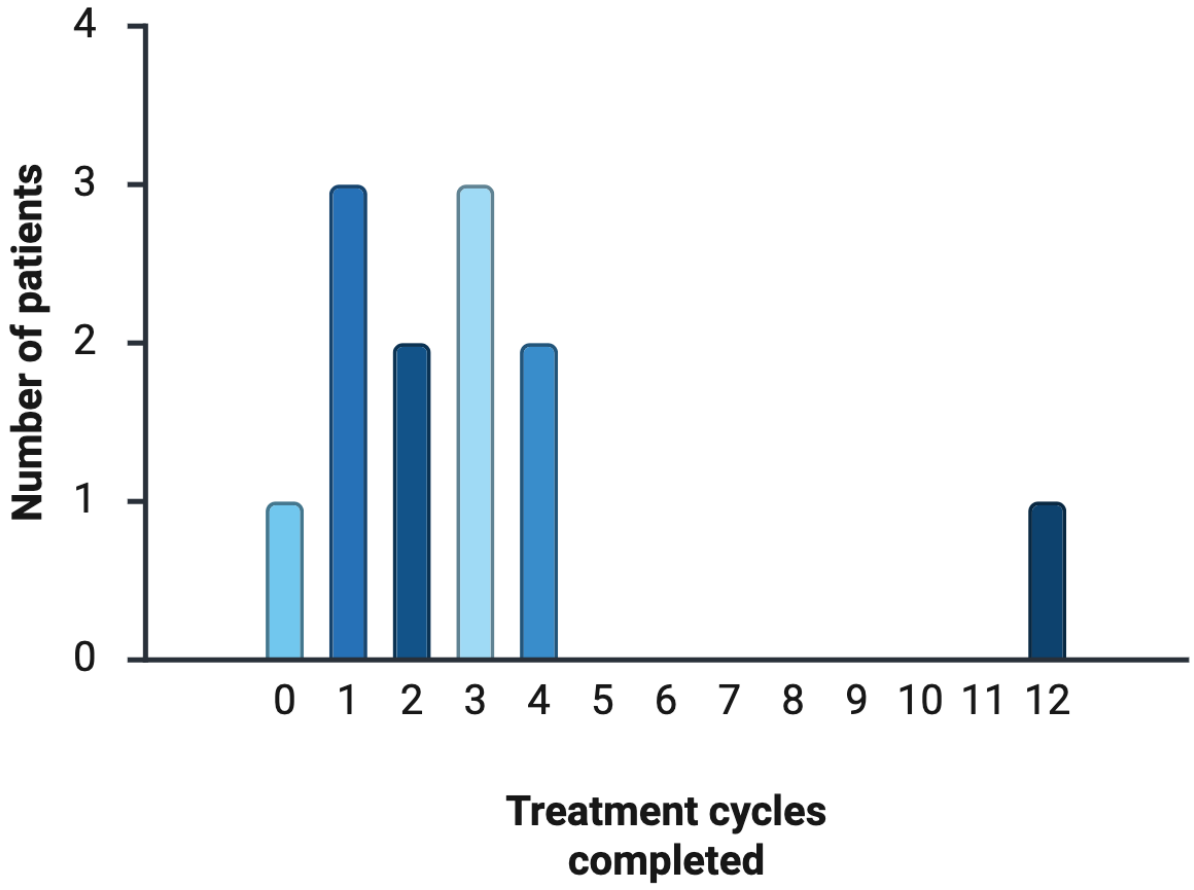

Fig 5: Distribution of treatment cycles

It can be concluded that the overall clinical composition of the cohort represents a high-risk, treatment-refractory population with limited therapeutic options at baseline.

4.2 Efficacy

4.2.1 Response per BiAb Type

The overall response rate (ORR) in the total cohort was 25.0% with 16.7% complete responses (CR). In the Ecoritamab and Glofitamab groups, the ORR was 14.3% (0.0% CR) and 40.0% (40.0% CR), respectively (Figure 6). According to Fisher's exact test, no statistically significant difference in response distribution between the two agents was detected ($p = 0.52$ for ORR, $p=0.15$ for CR). Although trends suggested a numerically higher rate of complete responses among patients treated with Glofitamab, with two patients getting into complete remission, a superiority of Glofitamab cannot be concluded due to limited number of patients.

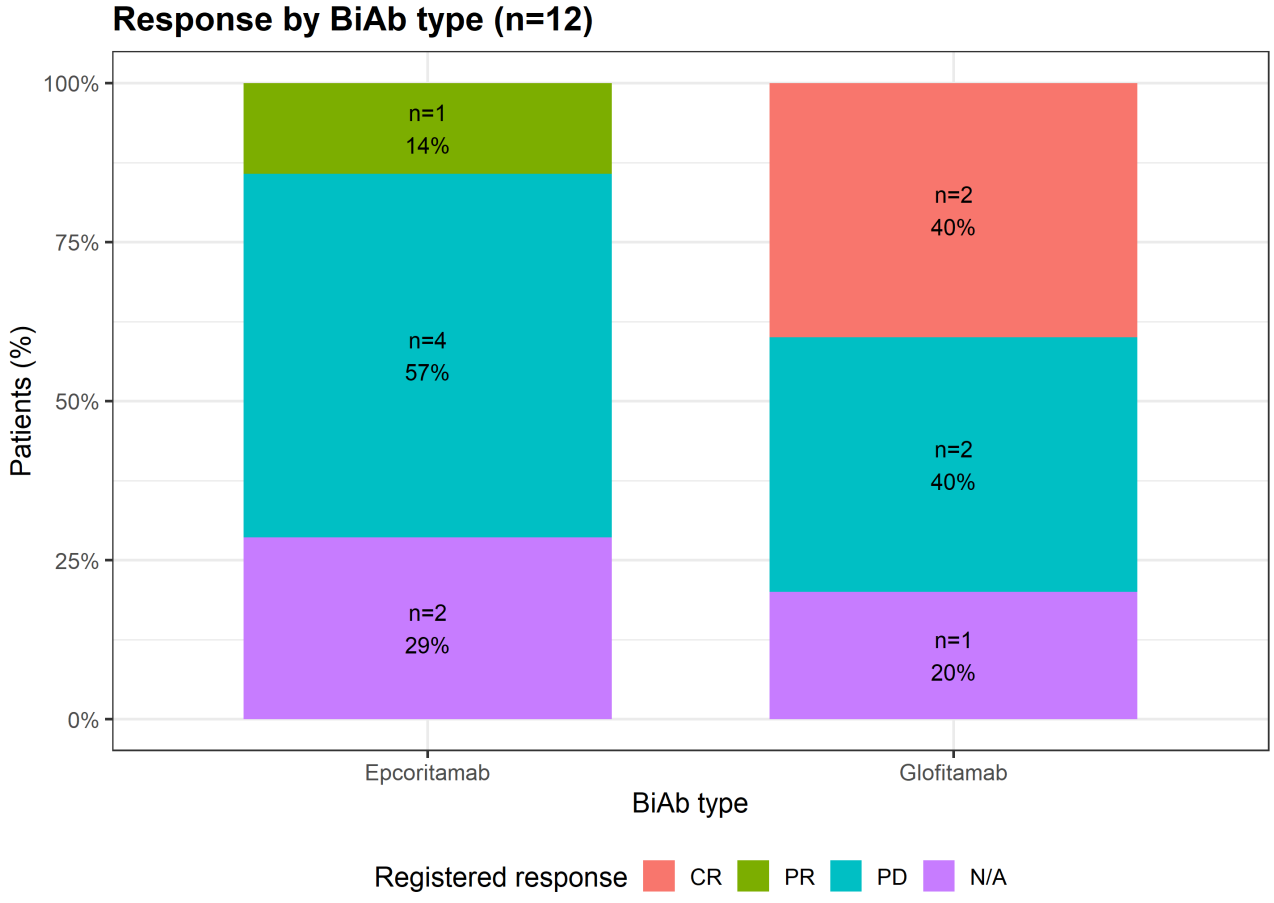

Fig. 6: Response distribution by BiAb type within the cohort

4.2.2 Response by Disease Type

Response outcomes stratified by lymphoma subtype are shown in figure 7. The analysis revealed heterogeneous activity of BiAb therapy across histologic entities. Complete responses were observed

in isolated cases of Burkitts and mantle cell lymphoma, while progressive disease remained the predominant outcome in most patients.

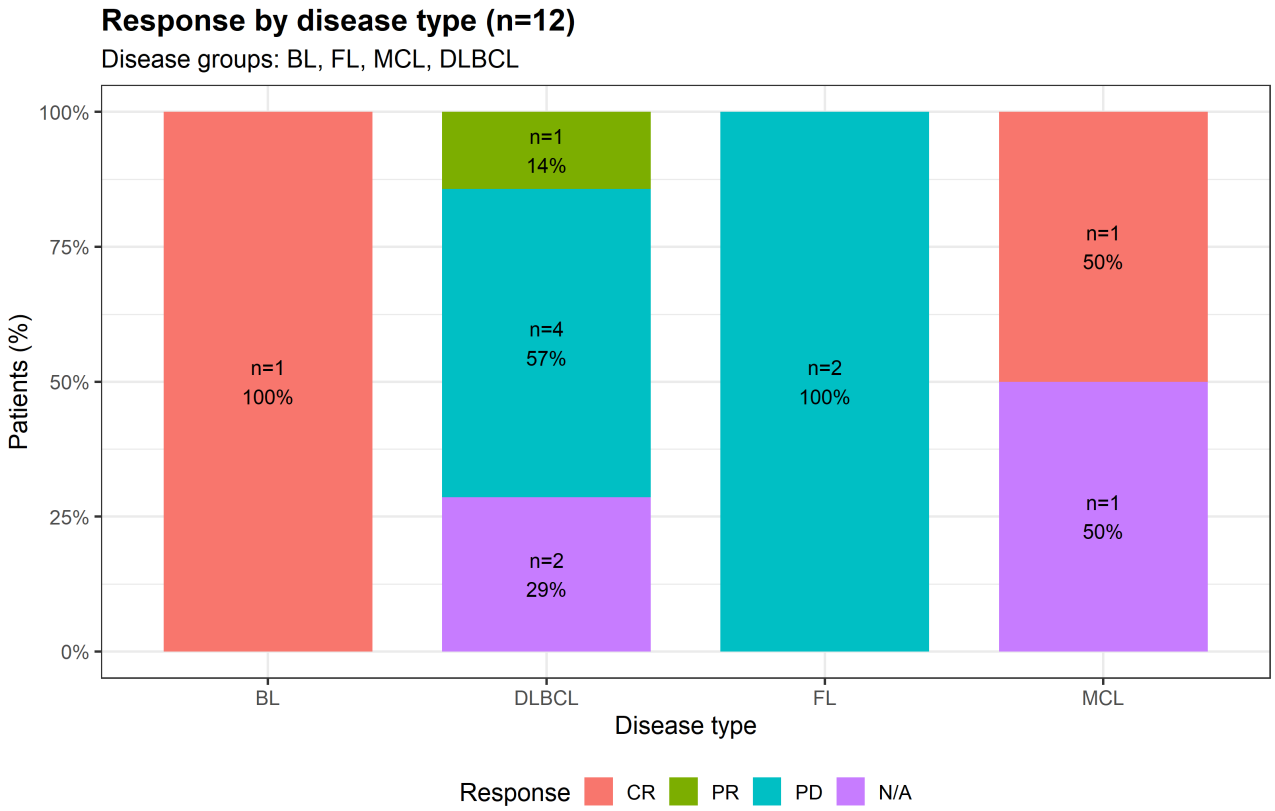

Fig. 7: Distribution of responses by disease type. Patients with complete remission had Burkitt Lymphma (n=1) and Mantle Cell Lymphoma (n=1). Most patients presented with progressive disease.

Although Fisher's exact test did not reach statistical significance (p = 0.24), descriptive patterns indicate that aggressive histologies responded less favorably, possibly reflecting prior therapy burden and disease kinetics. The cohort was too small to show significant differences.

4.2.3 Survival Analysis

Median progression-free survival (PFS) was 1.9 months (95% confidence interval [CI], 1.1 months to not reached), and median overall survival (OS) was 8.1 months (95% CI, 3.0 months to not reached) from the estimated date of BiAb treatment start. The 6-month PFS rate was 8.3% (95% CI, 1.3–54.4%), and the 6-month OS rate was 50.0%, visible in Figure 8 and 9 (95% CI, 28.4–88.0%).

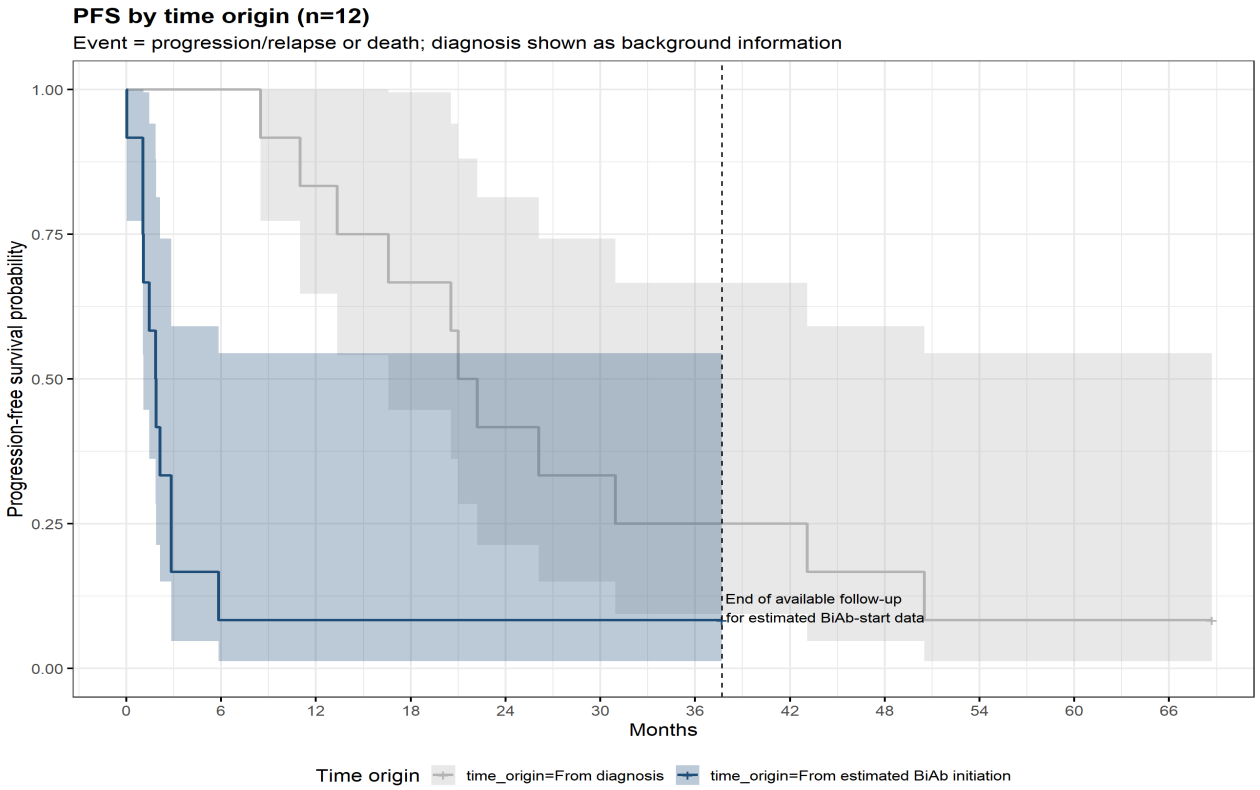

Fig. 8: Kaplan-Meier median progression free survival

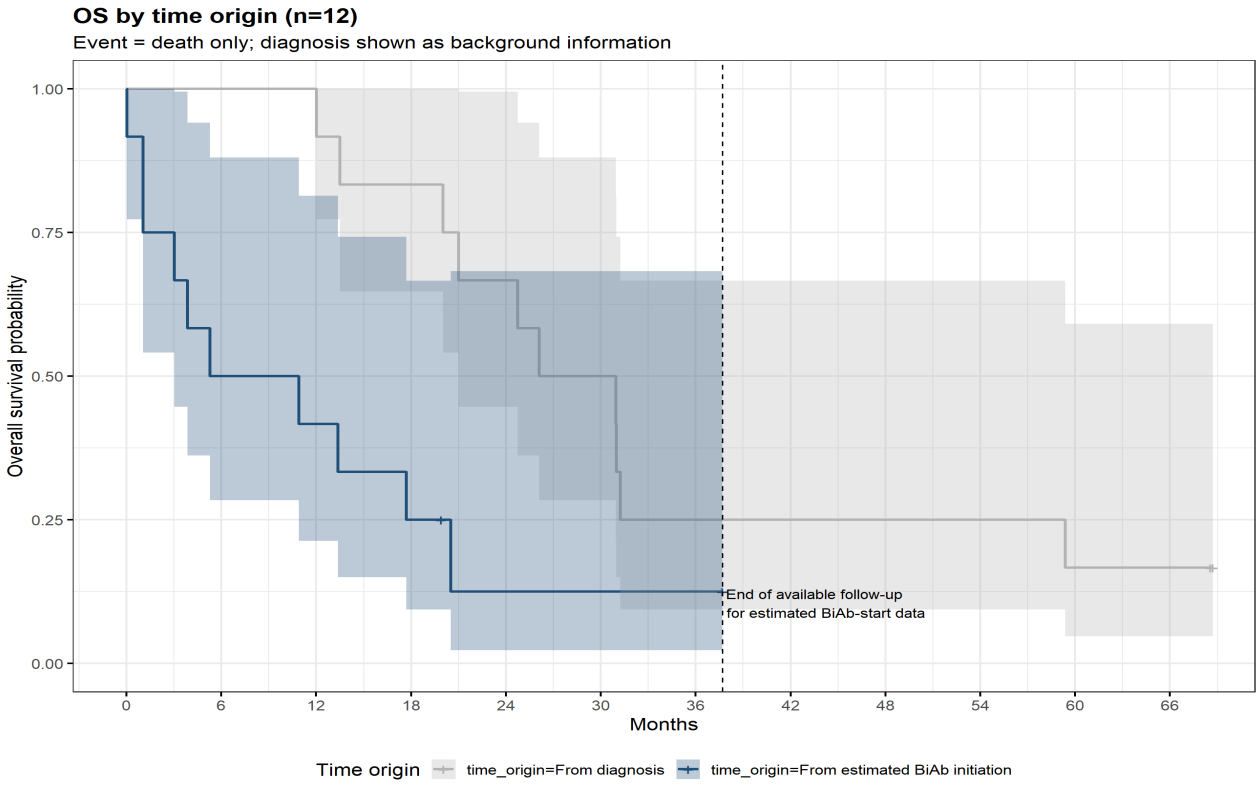

Fig 9: Kaplan Meier median overall survival

Due to the small sample size, Cox regression and subgroup comparisons were not statistically meaningful.

4.2.4 Influence of other Therapies

Exploratory analyses were conducted to assess associations between CAR-T exposure, SCT exposure, number of prior therapy lines, and treatment response. A statistically significant association with ORR was observed for CAR-T exposure before BiAb therapy (Fisher's exact test, p=0.045) and SCT before BiAb therapy (p=0.045), whereas no statistically significant association was observed for CAR-T exposure after BiAb therapy (p=1.000) or SCT after BiAb therapy (p=0.236). The association between the number of prior therapy lines and ORR was also not statistically significant in exploratory logistic regression (p=0.679). Given the small cohort size, these analyses should be interpreted descriptively. Response rates decreased with increasing prior lines of therapy, supporting the assumption that cumulative treatment resistance impacts BiAb efficacy. These associations are visualized in figure 10.

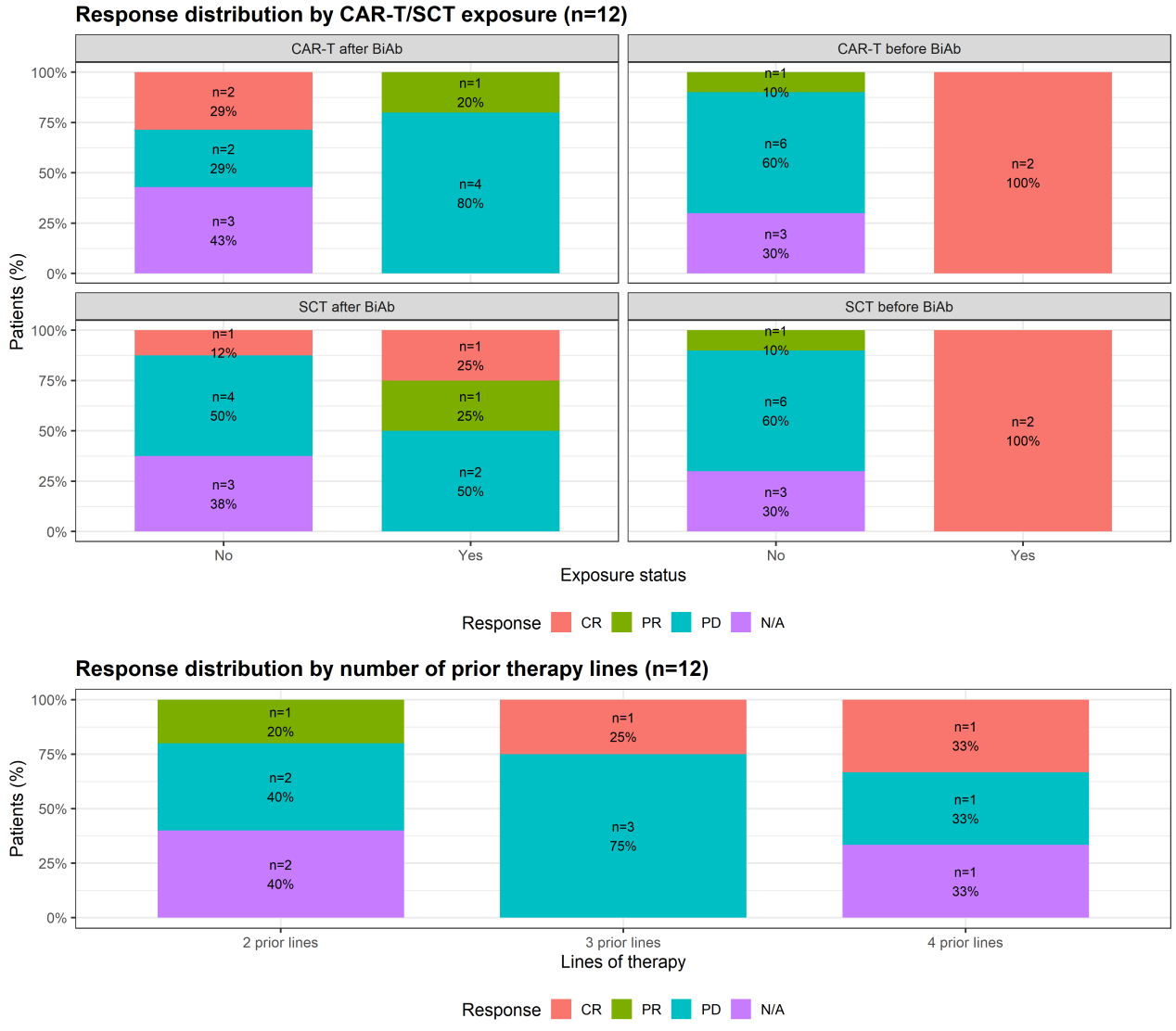

Fig. 10: Response distribution by other treatments

4.3. Safety and Adverse Events

All patients experienced at least one adverse event (AE) during BiAb treatment. The most common AEs were cytokine release syndrome (CRS), hypogammaglobulinemia, hematologic toxicity such as anemia, neutropenia, and thrombocytopenia, as well as infections including sepsis and lung infections. The summary of all observed AEs is presented in table 3.

Table 3: Summarized adverse events of patients within the cohort

AE	Patients (n=12)	%
CRS	8	66.7%
Hypogammaglobulinemia	6	50.0%
Neutropenia	4	33.3%
Anemia	4	33.3%
Thrombocytopenia	3	25.0%
Sepsis	3	25.0%
Ascites	2	16.7%
Lung infection	2	16.7%
Atrial fibrillation	2	16.7%
Adrenal insufficiency	2	16.7%
Single-occurrence AEs: Edema limbs, Lower GI hemorrhage, Pleural effusion, Edema face, Thromboembolic event, Hypercalcemia, Blood bilirubin increased, ICANS, CMV reactivation, AST increased, ALT increased, GGT increased, Secondary leukemia	1	8.3% each

4.3.1 CRS and ICANS

CRS occurred in the majority of patients, with grades ranging from G1 to G5. High-grade (≥ G3) CRS was rare but clinically relevant, often requiring dose adjustments or temporary treatment interruption. There was one fatal CRS G5 within the cohort. Immune effector cell–associated neurotoxicity syndrome (ICANS) was observed only one time. The distribution of CRS grades is shown in figure 11.

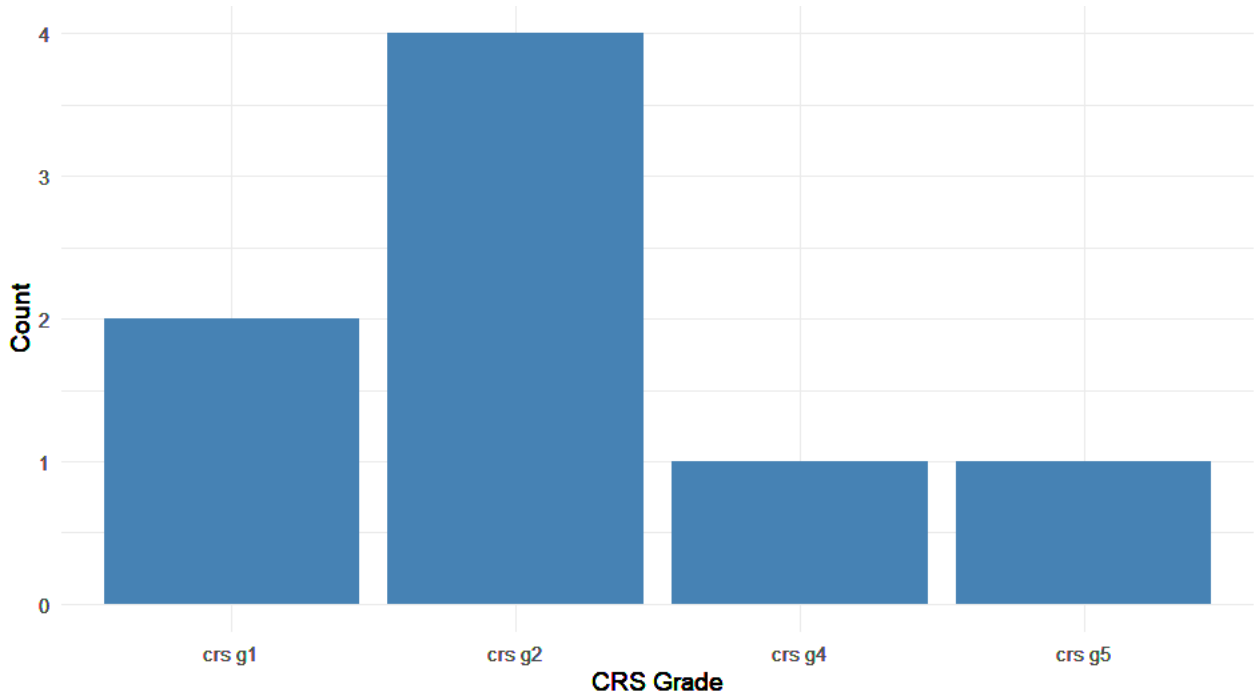

Fig. 11: CRS events by Grade

4.3.1.1 AE Distribution by BiAb Type

When stratified by BiAb type, no clear difference in the incidence of severe (grade ≥ 3) AEs was observed.

Epcoritamab-treated patients experienced slightly more hematologic toxicity, while Glofitamab was more frequently associated with cytokine-related and infectious events. Given the small sample size, these findings should be interpreted descriptively. A detailed summary of the adverse events within the patients treated with Glofitamab or Epcoritamab can be found in Table 4 and 5.

Table 4: AEs of all Epcoritamab patients together

AE	Patients (n=7)	%
Hypogammaglobulinemia	5	71.4%
CRS	4	57.1%
Neutropenia	4	57.1%
Anemia	4	57.1%
Thrombocytopenia	3	42.9%
Sepsis	3	42.9%
Ascites	2	28.6%

Lung infection	2	28.6%
Atrial fibrillation	2	28.6%
Adrenal insufficiency	2	28.6%
Single-occurrence AEs (14.3% each): Edema limbs, Lower GI hemorrhage, Pleural effusion, Edema face, Thromboembolic event, Hypercalcemia, Blood bilirubin increased, ICANS, CMV reactivation	1	14.3% each

Table 5: AEs of all Glofitamab patients together

AE	Patients (n=5)	%
CRS	4	80.0%
Hypogammaglobulinemia	1	20.0%
AST increased	1	20.0%
ALT increased	1	20.0%
GGT increased	1	20.0%
Secondary leukemia	1	20.0%

4.4 Discontinuation and Outcome

Treatment discontinuation and outcome are summarized in figure 12. Treatment discontinuation was most commonly related to disease progression, whereas a smaller proportion of patients discontinued treatment because of toxicity or treatment-related complications (see figure 13). One patient discontinued treatment after achieving complete remission, completing the full protocol-defined course of Glofitamab. Patients who discontinued because of disease progression almost uniformly had progressive disease as best registered response, whereas patients discontinuing for other reasons included patients with partial or complete responses. The swimmer plot further illustrates the heterogeneity of treatment duration, response, subsequent therapy, and final outcome across individual patients.

At the time of data cut-off, 10 of 12 patients had died (83.3%), while 2 patients were alive (16.7%). The most common cause of death was disease progression, accounting for 7 of 10 deaths (70.0%; 58.3% of the total cohort). Other causes of death included septic shock in 2 patients (20.0% of deaths; 16.7% of the total cohort) and cytokine release syndrome in 1 patient (10.0% of deaths; 8.3% of the total cohort). The predominance of disease progression as cause of death may reflect the advanced disease stage and late initiation of BiAb therapy in this heavily pretreated cohort. Among the two surviving patients, one patient was alive after receiving CAR-T therapy following BiAb treatment, and one patient remained in complete remission after combination treatment with Glofitamab and Polatuzumab.

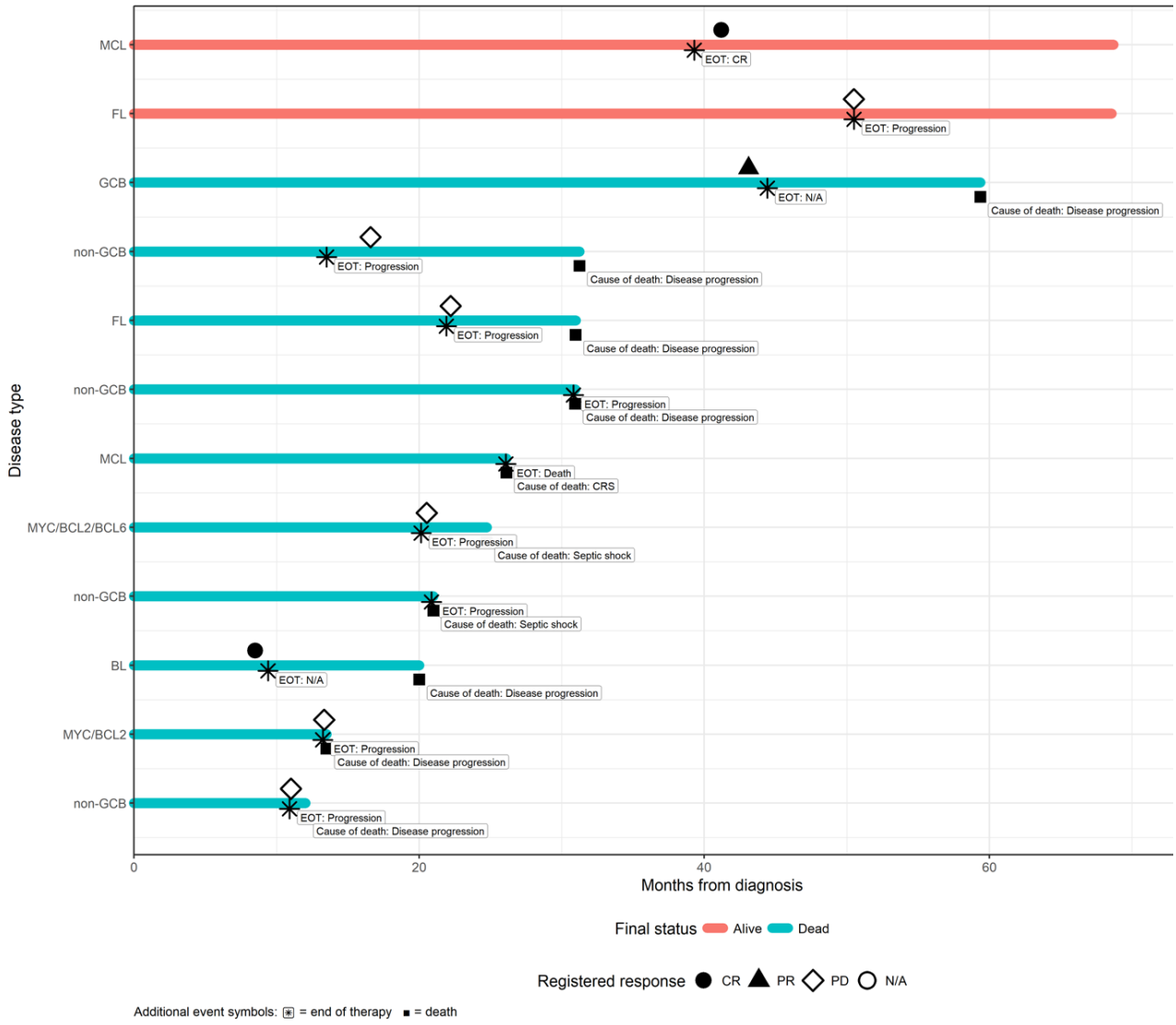

Fig. 12: Swimmer plot of all patients in the cohort

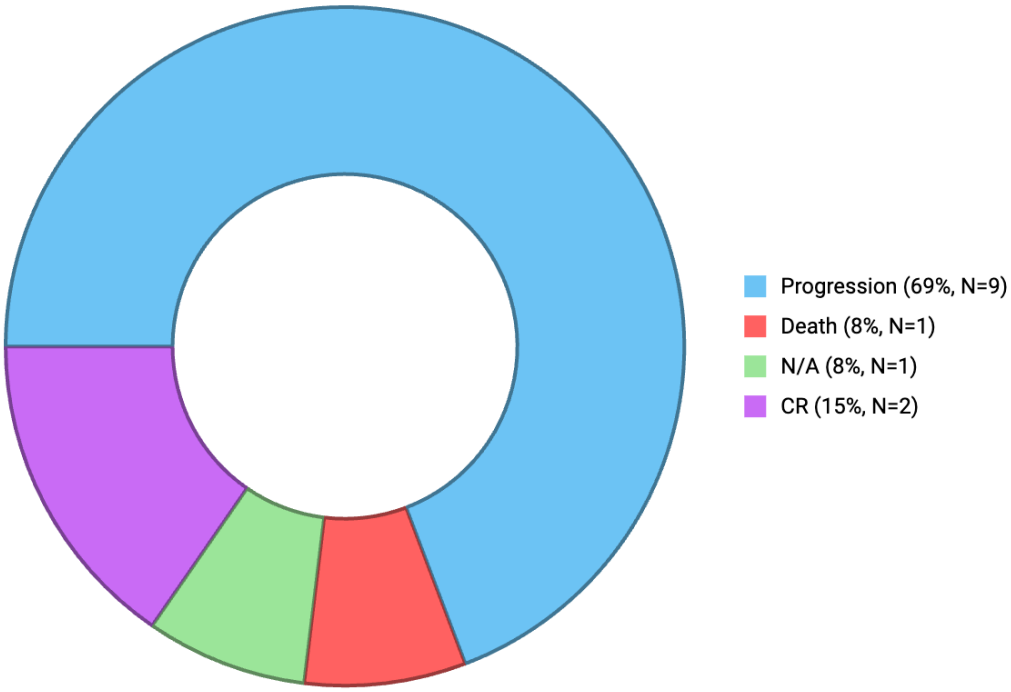

Fig. 13: Cause of treatment discontinuation within the cohort

5. DISCUSSION

5.1 Efficacy and (survival) outcomes

Efficacy and survival outcomes data were gathered from different pivotal and follow up studies, as well as real world data. A summary of the gathered data is provided in Annex 1 and 2.

5.1.1 Response Rates

Both Glofitamab and Epcoritamab monotherapy achieve clinically meaningful response rates in relapsed/refractory Diffuse large B-cell lymphoma, with complete response (CR) rates of approximately 39–40% and overall response rates (ORR) of 52–63% across pivotal trials (23,41). Importantly, a substantial proportion of patients achieving CR experience durable remissions, with many remaining progression-free beyond two years.

For Glofitamab, the NP30179 study demonstrated an ORR of 52% with a CR rate of 39%, while approximately 35% of patients had progressive disease as their best response. Median progression-free survival (PFS) was 4.9 months, with a 12-month PFS rate of 37%, indicating that disease progression can be effectively halted in roughly one-third of patients at one year. Among complete

responders, 78% remained in remission at 12 months, with a median duration of CR of 34.2 months, supporting the potential for long-term disease control in a subset of patients. (23)

Similarly, Epcoritamab demonstrated robust efficacy in the EPCORE NHL-1 trial, with ORR of 63% and CR rates of 39–40% (41,42). At extended follow-up, 24-month PFS was 27.8% and overall survival (OS) was 44.6% (41). Among patients achieving CR, 64.2% remained in remission at 24 months, and the median duration of CR had not been reached at over 31 months of follow-up (37,42). Median OS was 18.5 months, with approximately 58% of patients alive at 12 months (43). Additionally, minimal residual disease (MRD) negativity was observed in 45.4% of evaluable patients and was associated with improved survival outcomes (41).

However, real-world data demonstrate consistently inferior outcomes compared with clinical trials, highlighting the impact of broader and more heavily pretreated patient populations. In a multicenter cohort (N=245), ORR was comparable at approximately 51–53%, but CR rates were lower at 23–30%, and median PFS was only 2.6 months, with a 6-month PFS of 36%. Median overall survival was 7.8 months, reflecting the limited durability of response in routine clinical practice. (44)

Findings from the present cohort, although limited by small sample size (N=12), are directionally consistent with these observations. Among patients treated with Epcoritamab (n=7), no complete responses were observed and only a single partial response was documented (ORR 14%, CR 0%), with the majority of patients experiencing early disease progression. In contrast, Glofitamab-treated patients (n=5) achieved two complete responses (ORR 40%, CR 40%), while the remaining patients had progressive disease or early death (see table 6).

Given the small and heterogeneous cohort, these results cannot be interpreted definitively. However, they suggest a trend toward reduced efficacy compared with clinical trial populations, particularly for Epcoritamab, and align more closely with the lower response rates and limited PFS observed in real-world studies.

Overall, while bispecific antibodies can induce deep and durable remissions in a subset of patients, the likelihood of sustained disease control in routine practice remains modest, underscoring the need for improved patient selection and combination strategies.

Table 6: Response Rates of Glofitamab and Epcoritamab in the pivotal studies vs our cohort

Parameter	Glofitamab (NP30179)	Epcoritamab (EPCORE NHL-1)	Our Cohort
N	155	157	12
Median prior lines	3	3	3
Prior CAR-T	33%	39%	16.7%
ORR	52%	63%	25%
CR rate	39%	39–40%	16.7%
PR rate	13%	~23%	8.3%
Median OS	11.5 mo	18.5 mo	5.3 mo

5.1.2 Differences in Efficacy and Survival Outcomes between Epcoritamab and Glofitamab

To date, no randomized head-to-head trial directly compares Epcoritamab and Glofitamab, and cross-trial comparisons must therefore be interpreted with caution. Overall, the available data suggest broadly comparable efficacy, with some numerical differences that are difficult to interpret due to variations in study populations and treatment design. Most notably, CR rates are highly consistent between the two agents, at approximately 39–40% across pivotal trials (23,41). This is particularly relevant, as CR represents the most clinically meaningful endpoint, given that patients achieving complete remission derive the greatest likelihood of long-term disease control with both therapies.

In contrast, ORR appear numerically higher with Epcoritamab (63% vs. 52%), largely driven by a higher proportion of partial responses (23,42). However, this difference must be interpreted cautiously, as the Epcoritamab study population included a higher proportion of patients with prior CAR-T exposure (39% vs. 33%), potentially confounding direct comparisons.

With regard to survival outcomes, median overall survival (OS) appears longer with Epcoritamab (18.5 vs. 11.5 months) (23,37). However, this observation is likely influenced by multiple factors, including differences in patient selection, access to subsequent therapies, and treatment strategy. Notably, Epcoritamab is administered continuously until disease progression, whereas Glofitamab follows a fixed-duration approach (12 cycles), which may impact both response kinetics and survival estimates.

Importantly, the durability of response among complete responders is comparable between agents. Glofitamab demonstrates a median duration of CR of 34.2 months in its supporting cohort despite fixed-duration therapy, while for Epcoritamab the median duration of CR has not yet been reached at over 31 months of follow-up (23,37). These findings suggest that, once a CR is achieved, both agents are capable of inducing sustained, multi-year remissions.

Finally, real-world data do not indicate a meaningful difference between the two therapies. In a multicenter cohort, ORR was similar (51% for Epcoritamab vs. 53% for Glofitamab), with CR rates of 23% and 30%, respectively (44). These results further support the interpretation that the two agents have broadly comparable effectiveness in routine clinical practice.

5.1.3 Differences in response by disease type

Differences in efficacy between Epcoritamab and Glofitamab may become more apparent when outcomes are considered by disease subtype, although available data remain limited and are often based on small subgroup numbers (see table 7). In DLBCL of standard risk, both agents appear broadly comparable, with complete response (CR) rates of approximately 39–40% across pivotal studies (23,42,43). In this setting, the most relevant distinctions are therefore not clearly efficacy-

related, but rather practical differences such as treatment duration and route of administration, with Glofitamab given as a fixed-duration intravenous regimen and Epcoritamab as a continuous subcutaneous therapy.

The most notable potential difference emerges in high-risk aggressive disease, particularly high-grade B-cell lymphoma (HGBCL) and double-hit/triple-hit lymphoma. In the Glofitamab monotherapy dataset, no complete responses were observed among 11 patients with HGBCL, with only 2 partial responses reported, suggesting limited single-agent activity in this subgroup (44). In contrast, Epcoritamab appeared to show more consistent activity across high-risk subgroups, including patients with IPI ≥3, in whom the CR rate was 37%, as well as patients with double-hit/triple-hit rearrangements, although these analyses were also based on small patient numbers (9 HGBCL and 13 DH/TH cases) (37). Taken together, these findings suggest a possible advantage for Epcoritamab in biologically high-risk disease, although the available evidence remains insufficient for firm conclusions.

In follicular lymphoma, Epcoritamab currently has the more mature evidence base. In a pivotal phase 2 cohort of 128 patients, Epcoritamab achieved an ORR of 82% and a CR rate of 62.5%, supporting its regulatory approval in this indication (39). Glofitamab has also shown promising activity in follicular lymphoma, with early-phase data in approximately 24 patients demonstrating an ORR of 79% and a CR rate of 71%, but these data remain less mature and have not resulted in the same regulatory positioning (45). Thus, while both agents appear highly active in FL, Epcoritamab currently has the stronger clinical footing.

In mantle cell lymphoma, the situation is reversed. Glofitamab has the more substantial supporting dataset, with a dedicated cohort of 60 patients showing an ORR of 85% and a CR rate of 78%, including a CR rate of 71% in patients previously exposed to BTK inhibitors (33). By comparison, Epcoritamab data in mantle cell lymphoma remain extremely limited, with only 4 patients reported in dose-escalation cohorts and an ORR of 50% (45). At present, this suggests a more clearly established role for Glofitamab in this disease type.

For Burkitt lymphoma, clinical evidence remains essentially absent. No prospective trial data are available for either agent, and the published literature is limited to a single case report describing a favorable response to Glofitamab combined with a BTK inhibitor in CNS-involved relapsed/refractory Burkitt lymphoma (46). Neither Epcoritamab nor Glofitamab is currently approved or guideline-recommended for this indication.

This point is particularly relevant in the context of the present cohort, in which Burkitt lymphoma was represented, thereby extending beyond the disease entities more commonly included in published bispecific antibody trials. However, because of the small cohort size and marked heterogeneity of histologies, these observations cannot be interpreted as evidence of disease-specific efficacy. Rather,

they highlight an important real-world issue: bispecific antibodies may increasingly be used in aggressive B-cell lymphomas outside the core trial populations, but for rare entities such as Burkitt lymphoma, the evidence base remains extremely limited. As such, any apparent signals from small real-world series should be viewed as hypothesis-generating only.

Overall, the currently available data suggest that standard-risk DLBCL outcomes are broadly similar between agents, that Epcoritamab may have relatively more consistent activity in high-risk HGBCL/DH/TH disease, that Epcoritamab has the strongest evidence in follicular lymphoma, and that Glofitamab is currently better supported in mantle cell lymphoma. For rarer entities such as Burkitt lymphoma, including those represented in our cohort, meaningful conclusions are not yet possible.

Table 7: Efficacy of Treatment in Different Tumour Types

Disease Type	Agent	Trial	N	ORR	CR	PR	References
DLBCL (all)	Glofitamab	NP30179	155	52%	39%	13%	(23)
DLBCL (all)	Epcoritamab	EPCORE NHL-1	157	63%	40%	~23%	(41)
HGBCL / DH-TH	Glofitamab	NP30179	11	18%	0%	18%	(23)
HGBCL / DH-TH	Epcoritamab	EPCORE NHL-1	9 (HGBCL); 13 (DH/TH by FISH)	~consistent with overall	~37% (IPI≥3 subgroup)	—	(41)
FL (grade 1–3A)	Epcoritamab	EPCORE NHL-1	128	82%	62.5%	19.5%	(39)
FL	Glofitamab	NP30179 (phase 1/2)	~24 (indolent NHL)	79%	71%	~8%	(23)
MCL	Glofitamab	NP30179	60	85%	78%	7%	(33)
MCL	Epcoritamab	Phase 1 dose-escalation	4	50%	25%	25%	(41)
Burkitt lymphoma	Either	—	—	No clinical trial data	—	—	

5.1.4 Monotherapy vs Combination Treatment

In our cohort, the only patient who remained alive in complete remission received combination treatment with Glofitamab plus Polatuzumab and completed all 12 planned cycles. Although this represents only a single patient and therefore cannot be interpreted as evidence of superiority, this observation is consistent with emerging clinical data suggesting that BiAb-based combination strategies may increase response depth compared with monotherapy in similar lymphoma entities.

For relapsed/refractory large B-cell lymphoma, Glofitamab monotherapy in the pivotal NP30179 DLBCL cohort achieved an ORR of 52% and a CR rate of 39%. In comparison, the combination of Glofitamab plus Polatuzumab in relapsed/refractory LBCL showed numerically higher activity, with an ORR of 78% and a CR rate of 60%.(23,35) Similarly, in the phase III STARGLO trial, Glofitamab in combination with gemcitabine and oxaliplatin demonstrated improved efficacy compared with R-GemOx, with a CR rate of 59% versus 19%.(34) These data suggest that in LBCL, Glofitamab-based combinations may achieve deeper responses than monotherapy alone.

A comparable pattern is seen with Epcoritamab in large B-cell lymphoma. In the pivotal EPCORE NHL-1 LBCL cohort, Epcoritamab monotherapy achieved an ORR of 59% and a CR rate of 41%. In contrast, Epcoritamab-based combinations in relapsed/refractory DLBCL reported higher response rates, including ORR 85% and CR 61% with Epcoritamab plus GemOx, and ORR 79% and CR 69% with Epcoritamab plus R-DHAX/C in transplant-eligible patients. These findings support the hypothesis that combination approaches may improve response quality in comparable aggressive B-cell lymphoma populations.(34,40,41)

For follicular lymphoma, Epcoritamab monotherapy achieved an ORR of 82% and CR rate of 63% in relapsed/refractory FL. Combination treatment with Epcoritamab plus R^2 showed higher activity, with an ORR of 96% and CR rate of 88% in EPCORE NHL-2, and the phase III EPCORE FL-1 study also demonstrated improved response rates for Epcoritamab plus R^2 compared with R^2 alone.(39) This further supports the concept that BiAbs may be particularly effective when integrated into rational combination regimens.

Overall, while BiAb monotherapy has demonstrated substantial activity across relapsed/refractory B-cell lymphomas, the available suggest that combination strategies may increase ORR and CR rates. Prospective studies are needed to determine whether BiAb combinations can improve outcomes, particularly in heavily pretreated patients and in those receiving BiAbs late in the disease course.

5.2 Safety Profile

5.2.1 Adverse Events

Even though the common side effects of Glofitamab and Epcoritamab are quite similar, as is the mechanims of action, the adverse event profile differs somewhat by indication and whether used as monotherapy or in combination.

In the pivotal NP30179 study (N=155) for Glofitamab, the most common adverse reactions (≥20%) were CRS (63–70%), musculoskeletal pain (21%), rash (20%), and fatigue (20%). The most common grade 3–4 adverse events were neutropenia (27%), thrombocytopenia (8%), and anaemia (6%).

Infections occurred in 38% of patients (grade ≥3 in 15%), with COVID-19 and sepsis being the most frequent serious infections. Tumour flare (grade 2 or higher in 7%) and hepatic enzyme elevations (grade ≥2 in 7%) were registered as well.(23) Comparable to that in the EPCORE NHL-1, N=157) trial for Epcoritamab, the most common adverse reactions (≥20%) were CRS (51%), pyrexia (24.8), fatigue (24.2%), neutropenia (23.6%), nausea (21.7%), anaemia (21%), diarrhea (21%). A unique feature of Epcoritamab is the high rate of injection site reactions (given its subcutaneous route), which is not seen with IV Glofitamab(41). In this small real-world cohort, the overall safety profile of Epcoritamab and Glofitamab was broadly consistent with findings from the pivotal NP30179 and EPCORE NHL-1 trials. The incidence of cytokine release syndrome (CRS) was comparable across datasets, occurring in 66.7% of our patients overall, with slightly higher rates observed in the Glofitamab subgroup and similar rates for Epcoritamab relative to published data. Hematologic toxicities, however, appeared more pronounced in our cohort, particularly among patients receiving Epcoritamab, where rates of neutropenia, anaemia, and thrombocytopenia exceeded those reported in clinical trials. In contrast, these adverse events were not observed in the small Glofitamab subgroup, likely reflecting a sampling artifact (limited sample size). Infectious complications occurred at frequencies comparable to trial data, although the observed rate of severe infections, especially sepsis, was numerically higher and may represent a clinically relevant signal in a real-world setting. In our Epcoritamab cohort groups sepsis occurred in 42.9% (N=3), whereas in the EPCORE NHL-1 trial, this complication was only reported in 3.2% (N=5). Because of the substantial difference in sample size, these findings must be interpreted with caution. However, they may suggest a signal that sepsis warrants particularly close monitoring in routine clinical practice, as its incidence could be higher than reported in clinical trials and may require targeted preventive and management strategies. Notably as well, hypogammaglobulinemia was frequently documented, particularly in the Epcoritamab group, despite not being prominently reported in the pivotal trials, suggesting a potentially underrecognized toxicity with implications for infection risk and long-term management. Conversely, common low-grade adverse events described in trials, such as fatigue, gastrointestinal symptoms, and rash, were not captured in this cohort, likely due to the retrospective nature of data collection and underreporting of non-severe symptoms. As cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) represent adverse events of special interest, they are addressed in a dedicated section and will be discussed in detail separately.

5.2.1.1 CRS and ICANS

The incidence of CRS in our cohort (66.7%) was consistent with rates reported in pivotal trials for both Glofitamab (63–70%) and Epcoritamab (51%). When considering treatment subgroups, CRS appeared numerically more frequent in patients receiving Glofitamab compared to Epcoritamab.

However, these differences are difficult to interpret given the very small subgroup sizes and the resulting susceptibility to random variation. For this reason, we primarily report pooled data across both treatments, while referencing drug-specific trial results for contextual comparison (see table 9). In contrast to overall CRS rates, the frequency of severe CRS (grade ≥3) was notably higher in our cohort (16.7%) compared to published data (3–4% for Glofitamab and approximately 2.5% for Epcoritamab). Similarly, one case of fatal CRS (8.3%) was observed, whereas no fatal events were reported in the respective monotherapy trial populations. While these findings may suggest a higher burden of severe CRS in real-world settings, they must be interpreted with caution given the limited sample size. Nevertheless, they may indicate a potential signal that severe CRS requires particularly vigilant monitoring in routine clinical practice, as an increased incidence compared to trial populations cannot be excluded and may warrant optimized management strategies.

As shown in table 8, with regard to immune effector cell-associated neurotoxicity syndrome (ICANS), the overall incidence in our cohort (8.3%) was comparable to trial data (8% for Glofitamab and 6% for Epcoritamab). No cases of severe (grade ≥3) or fatal ICANS were observed, whereas low rates have been reported in clinical trials. Similar to CRS, minor numerical differences between treatment subgroups were observed but are not considered meaningful in this context.

Table 8: Comparison of CRS and ICANS

Parameter	Glofitamab	Epcoritamab	Our cohort
CRS any grade	63–70% (monotherapy)	51% (LBCL mono)	66.7%
CRS grade ≥3	3–4% (grade 3: 2.8–3%; grade 4: 1.4%)	2.5% (LBCL mono, grade 3 only)	16.7%
Fatal CRS	0%	0% (monotherapy)	8.3%
ICANS any grade	8% (monotherapy)	6% (phase 1/2)	8.3%
ICANS grade ≥3	3% (monotherapy)	3% (phase 1/2); rare in later studies	0%
Fatal ICANS	0%	0.6% (LBCL label)	0%

In summary, one can say that CRS and ICANS remain a side effect that should not be ignored due to the potential danger. Nevertheless, both the real word data and the approval studies show that a certain CRS effect is normal and that serious complications from CRS and ICANS occur comparatively rarely.

5.2.2 Differences in AEs by tumor type

Both agents are approved for B-cell lymphomas, but the AE profile varies between DLBCL and FL. Exemplary, the FDA label for FL monotherapy reports permanent discontinuation due to AEs in 19% and fatal AEs in 9%, substantially higher than in LBCL, driven primarily by infections (COVID-19, pneumonia) and second primary malignancies. Most likely cause is that the longer treatment duration in FL (continuous until progression) leads to higher cumulative infection rates and more treatment-emergent adverse events overall.

For further comparions, especially focusing on Glofitamab, there is not enough data yet. Our cohort does now allow to interpret differences in AEs by tumour type. As there is strong evidence from EPCORE NHL-1 trial, that adverse events can differ significantly, depending on the tumour type, further data should be collected with focus on this topic.

5.2.3 Treatment Discontinuation

Glofitamab's fixed 12-cycle design means that treatment completion is a defined endpoint, but in the R/R DLBCL setting, the majority of patients (70%) discontinue before completing all cycles, predominantly due to progressive disease. In the pivotal NP30179 monotherapy study, at the data cutoff, 70% (108/154) of patients had discontinued treatment, while only 22% (34/154) completed the planned full 12-cycle course and 8% were still on treatment. Epcoritamab's treat-until-progression design means that "completion" is not a predefined concept in LBCL monotherapy; instead, patients accumulate longer exposure, leading to higher cumulative AE-related discontinuation (especially infections) but also longer treatment durations in responders. In the pivotal EPCORE NHL-1 LBCL monotherapy cohort (N=157), at the 3-year update (median follow-up 37.1 months), treatment was ongoing in a diminishing fraction of patients. At the ~20-month follow-up, 36/157 (23%) remained on treatment. Permanent discontinuation due to AEs was only 3.8%, but overall discontinuation was driven primarily by progressive disease, given that Epcoritamab is administered until progression or unacceptable toxicity. The pivotal studies data match quite well with our observed data: main discontinuation cause was progressive disease as well (69%). It is important to mention that few discontinuations happen due to side effects. This suggests that the treatment is well tolerated

5.3 Comparison of Stem Cell Transplantation, CAR-T therapy and BiAbs

Glofitamab and Epcoritamab, have emerged as an important therapeutic modality in relapsed and refractory B-cell lymphomas, offering a distinct set of advantages and limitations when compared with stem cell transplantation (SCT) and CAR-T cell therapy.

A major advantage of BiAbs lies in their immediate availability as “off-the-shelf” therapies, eliminating the need for leukapheresis, ex vivo manufacturing, and lymphodepletion. This contrasts sharply with CAR-T therapy, where the median vein-to-vein time is approximately 35–43 days, potentially delaying treatment in patients with rapidly progressive disease (47,48). Similarly, autologous SCT requires prior demonstration of chemosensitivity and patient eligibility for conditioning, further limiting rapid deployment. In this context, BiAbs provide a critical option for patients requiring urgent therapy.

In addition, BiAbs offer superior accessibility and ease of administration. Following initial step-up dosing, they can generally be delivered in outpatient or community settings, unlike CAR-T therapy, which is restricted to specialized centers, or SCT, which requires transplant-capable infrastructure (48,49). The subcutaneous formulation of Epcoritamab further enhances convenience and may improve patient experience.

From a safety standpoint, BiAbs demonstrate a more favorable toxicity profile. Rates of severe cytokine release syndrome (CRS grade ≥3) are low (2%) compared with 8% for CAR-T therapy, and severe neurotoxicity/ICANS occurs in approximately 1% versus 11%, respectively (50). In contrast, ASCT carries a one-year non-relapse mortality of approximately 9% (51). BiAbs are also associated with fewer prolonged cytopenias and reduced need for intensive care support, reinforcing their tolerability in a broader patient population.

Importantly, BiAbs retain clinically meaningful activity in the post–CAR-T setting, where treatment options are otherwise limited. Meta-analytic data further support their efficacy, demonstrating pooled overall response rates of 54.5% and CR rates of 35.6% with monotherapy, increasing to ORR 70% and CR 44.2% in combination regimens (52). Their combinability with agents such as GemOx chemotherapy and Polatuzumab vedotin further enhances their therapeutic potential, with CR rates reaching 55–61% in combination settings (40,34,35).

Additional practical advantages include the fixed-duration treatment approach of Glofitamab, which is administered over 12 cycles and provides a defined endpoint, potentially reducing long-term treatment burden (23). Furthermore, BiAbs are substantially less costly than CAR-T therapy, making them suitable for financially more limited healthcare systems (48).

Despite these advantages, BiAbs are associated with several important limitations. Most notably, they demonstrate inferior depth and durability of response as monotherapy compared with CAR-T therapy. In the third-line and later setting, pooled CR rates are approximately 36% for BiAbs versus 51% for CAR-T ($p<0.01$), with corresponding 1-year PFS rates of 32% versus 44% ($p<0.01$) (50).

Related to this is the issue of uncertain long-term curative potential. CAR-T therapy exhibits a plateau in progression-free survival curves at approximately 40%, consistent with durable remission or cure in a subset of patients. In contrast, BiAb monotherapy has not yet demonstrated a comparable plateau

(53). For example, Epcoritamab achieves a 24-month PFS of 27.8% in clinical trials, while real-world data report a median PFS of only 2.6 months, raising concerns about the durability of responses outside controlled study settings (41,44).

Indeed, real-world outcomes with BiAbs appear significantly inferior to clinical trial results. While ORR remains similar at 51-53%, CR rates decline to 23–30% compared with approximately 40% in trials, and median PFS decreases from around 5 months to 2.6 months (44). This discrepancy likely reflects the broader and more heavily pretreated patient populations encountered in routine clinical practice.

A key biological limitation is the reliance of BiAbs on sustained CD20 antigen expression. Real-world analyses show that up to 88% of patients may lose CD20 expression following BiAb therapy based on paired biopsies (44). Mechanisms include MS4A1 mutations, alternative splicing, and epigenetic silencing, all of which contribute to resistance (54). Accordingly, clinical guidelines note that CD3×CD20 BiAbs have limited efficacy in CD20-negative disease.

Treatment burden also remains a consideration, particularly for Epcoritamab, which requires continuous administration until disease progression, in contrast to the fixed-duration approach of Glofitamab or the single-infusion paradigm of CAR-T therapy. This may increase cumulative toxicity, infection risk, and overall cost over time.

Mechanistically, BiAbs are further constrained by their dependence on endogenous T-cell fitness and the tumor microenvironment. Their efficacy is closely linked to the presence of functional, non-exhausted T cells, and integrative genomic analyses suggest that the host immune milieu has a greater impact on outcomes with BiAbs than with CAR-T therapy (55). As a result, patients with “cold” tumors or T-cell exhaustion, common after multiple prior therapies or CAR-T exposure, may experience worse responses (54,55).

Another important limitation is the lack of randomized head-to-head comparisons with CAR-T therapy. Although indirect analyses using inverse probability of treatment weighting (IPTW) suggest no statistically significant differences in some settings, such findings are inherently limited by confounding and differences in patient selection (56).

Finally, treatment sequencing remains an area of active investigation. Prior CAR-T therapy may reduce subsequent BiAb efficacy, as suggested by meta-analytic data, whereas the use of BiAbs earlier in the treatment course or as bridging therapy may enhance subsequent CAR-T outcomes (49). These findings underscore the importance of optimizing therapeutic sequencing to maximize patient benefit (see table 9).

Table 9: Summary of Efficacy and Safety profile of CAR-T cell therapy, BiAbs, and autologous SCT (19,23,41,41,49,51,56,56–58)

Feature	CAR-T Cell Therapy	Glofitamab	Epcoritamab	Autologous SCT
EFFICACY				
CR rate (pivotal trials)	40–65% (3L: 40–58%; 2L: 65%)	39% (3L mono); 50% (2L+ combo)	40% (3L mono); 61% (2L+ combo)	48–60% (pre-ASCT salvage response)
ORR (pivotal trials)	52–83%	52% (mono); 78–85% (combo)	63% (mono); 85% (combo)	~50% to salvage chemotherapy
Median PFS (pivotal)	14.7 mo (2L); 5.9–11.1 mo (3L+)	4.9 mo (mono); 13.8 mo (combo)	~5 mo (mono); NR (combo)	~2.7 yr (if transplanted)
24-month PFS	28–42% (3L); 42% (2L)	Under investigation	27.8% (mono)	~51% (6-year)
Median OS	NR (2L, 4-yr: 54.6%); 12–24 mo (3L)	50% at 12 mo (mono); 25.5 mo (combo)	44.6% at 24 mo (mono); 21.6 mo (combo)	~63% (6-year)
SAFETY PROFILE				
Grade ≥3 CRS	4–8%	2–3%	2.5%	N/A
Grade ≥3 neurotoxicity/ICANS	7–21%	~1%	1%	N/A
Grade ≥3 infections	11–17%	Lower than CAR-T	Lower than CAR-T	Variable
Non-relapse mortality	Low	Very low	Very low	~9% at 1 year

5.4 Positioning in treatment landscape

As of right now, in the third-line and beyond setting, both Glofitamab and Epcoritamab are positioned as bispecific antibody options for relapsed/refractory DLBCL, including in patients with disease progression after transplant or CAR T-cell therapy. In the second-line setting, the therapeutic landscape has evolved significantly following results from the STARGLO trial. The combination of Glofitamab plus GemOx demonstrated a significant overall survival benefit compared with rituximab-GemOx (median 25.5 months vs. 12.9 months; HR 0.62) in transplant-ineligible patients with relapsed/refractory DLBCL after at least one prior line of therapy. This represents a meaningful advance for a population with historically limited treatment options and has the potential to influence clinical practice across Europe.(41)

A critical emerging question is the optimal sequencing of bispecific antibodies relative to CAR T-cell therapy. A recent systematic review and meta-analysis by Sorin et al. in The Lancet Haematology (2026), encompassing 2,122 patients across 30 studies, found that the complete response rate for CAR T after prior bispecific antibody exposure was 53.7%, compared with 29.4% for bispecific antibodies after prior CAR T (p=0.0008). Furthermore, bispecific antibody combination therapy after CAR T yielded a higher pooled CR of 46.4% compared with bispecific monotherapy

after CAR T (29.4%, p=0.0005).(49) A comparison of results with different sequences is shown in table 10.

Table 10: CAR-T therapy and BiAbs sequencing data for DLBCL by Sorin et al. in The Lancet Haematology(49)

	Complete Remission Rates	CRS with sequencing
BsAb → CAR-T	CR 53.7% (improved vs CAR-T alone; RR 1.62, p=0.0004)	79% any-grade (CAR-T after BsAb)
CAR-T → BsAb	CR 29.4% (inferior to BsAb alone)	36% any-grade (BsAb after CAR-T)

5.4.1 Future Directions

The clinical trajectory of bispecific antibodies such as Glofitamab and Epcoritamab is clearly shifting toward earlier lines of therapy and increasingly sophisticated combination strategies, with the potential to further reshape the treatment paradigm in Diffuse large B-cell lymphoma.

A major focus of ongoing research is their integration into the frontline setting. The phase 3 EPCORE DLBCL-2 trial (NCT05578976) is evaluating Epcoritamab in combination with R-CHOP versus standard R-CHOP in newly diagnosed high-risk patients (IPI ≥2), building on early-phase data demonstrating an overall response rate (ORR) of 100% and complete metabolic response (CMR) of 76% in this population (38). Similarly, the phase 1b COALITION study investigating Glofitamab in combination with Pola-R-CHP or R-CHOP in younger high-risk patients has reported a complete response (CR) rate of 98% and an estimated 2-year progression-free survival (PFS) of 86% (36). Overall, at least 15 randomized frontline trials in large B-cell lymphoma are currently underway, underscoring the rapid expansion of this therapeutic class into earlier disease settings (59).

In parallel, combination strategies are being explored actively to enhance efficacy and overcome resistance. Both Glofitamab and Epcoritamab are being studied in combination with chemotherapy backbones, antibody-drug conjugates such as Polatuzumab vedotin, immunomodulatory agents like lenalidomide, and immune checkpoint inhibitors. Preclinical data further support combinations with

novel co-stimulatory approaches, including CD19-targeted 4-1BBL and CD28 agonists, as well as checkpoint blockade targeting PD-1 and LAG-3 pathways, highlighting the potential to augment T-cell activation and persistence (60,61).

Another emerging priority is the identification of optimal treatment sequencing strategies. A meta-analysis by Sorin et al. has proposed a randomized trial design comparing Glofitamab plus GemOx in the second-line setting followed by CAR T-cell therapy at relapse, versus the reverse sequence of second-line CAR T-cell therapy followed by Glofitamab-based therapy upon progression. Importantly, such a design emphasizes progression-free and overall survival measured from the point of randomization, reflecting a growing recognition that treatment sequence, rather than individual modality alone, may be a critical determinant of long-term outcomes (49,53).

Finally, a deeper understanding of resistance mechanisms is essential for the next phase of development. Loss of CD20 antigen expression is emerging as a key mechanism of resistance to CD20-directed bispecific antibodies, reinforcing the importance of confirmatory biopsy prior to therapy initiation. This challenge is driving the development of alternative-target bispecific constructs, including CD19×CD3 agents such as Surovatamig, which may help overcome antigen escape and expand therapeutic options (44,62).

6. CONCLUSION AND PRACTICAL RECOMMENDATIONS

This retrospective analysis of a small real-world cohort provides insight into the performance of bispecific antibodies, specifically Glofitamab and Epcoritamab, in heavily pretreated patients with relapsed or refractory B-cell lymphomas. When interpreted in the context of existing clinical trial data, the findings highlight a clear discrepancy between controlled study outcomes and routine clinical practice.

While pivotal trials report overall response rates of approximately 52–63% and complete response rates around 39–40%, the cohort analysed here demonstrated markedly reduced efficacy. These findings are consistent with other real-world analyses, which similarly report lower complete remissions rates and shorter progression-free survival, indicating that trial populations may not fully reflect the complexity of patients treated in routine practice.

The discrepancy between clinical trial and real-world outcomes is likely driven by differences in patient characteristics, particularly advanced disease stage, aggressive biology, and extensive prior treatment exposure. The observed decline in response rates with increasing prior lines of therapy supports the interpretation that cumulative treatment resistance is a major determinant of limited bispecific antibodies efficacy. In this context, the findings highlight the importance of treatment sequencing as a critical factor influencing outcomes. Although this analysis does not allow for definitive conclusions, the results support ongoing investigation into the optimal positioning of

bispecific antibodies within the treatment algorithm, particularly in relation to CAR-T cell therapy. Emerging literature suggesting improved outcomes when bispecific antibodies are used prior to CAR-T or together with other immune- and chemotherapies further reinforces this as a priority area for prospective research.

Survival outcomes in this cohort were poor, with a median overall survival of approximately eight months after start of bispecific antibodies treatment, substantially shorter than the 11.5 to 18.5 months reported in pivotal trials. This again aligns more closely with real-world data and emphasizes that, in late-line settings, bispecific antibodies provide clinical benefit for a subset of patients but do not overcome the overall poor prognosis of advanced, treatment-refractory disease. These findings support the need to better define the timing of bispecific antibodies therapy, as the reduced efficacy observed in heavily pretreated patients suggests that earlier integration may be beneficial, although this cannot be concluded from the present data alone and requires prospective validation.

The safety profile observed was broadly consistent with known class effects, particularly the high incidence of cytokine release syndrome. However, the numerically higher rates of severe Cytokine Release Syndrome and infectious complications, especially sepsis, suggest that toxicity may be more pronounced in real-world populations than in clinical trials. While limited by sample size, this finding highlights a clinically relevant signal and supports the need for careful monitoring in routine practice, particularly regarding early recognition and management of Cytokine Release Syndrome and infectious complications.

No meaningful conclusions could be drawn regarding differences between Glofitamab and Epcoritamab or the impact of prior CAR-T therapy or stem cell transplantation, reflecting the small cohort size and heterogeneity of the population. These aspects remain important areas for further investigation.

Taken together, this analysis confirms that bispecific antibodies represent a relevant therapeutic option in patients with limited alternatives, but their real-world effectiveness appears restricted. Their current clinical value lies primarily in providing an additional treatment modality rather than consistently achieving durable disease control.

From a practical perspective, the findings of this analysis primarily inform future research directions rather than immediate changes in clinical practice. First, the consistent observation of reduced efficacy in heavily pretreated patients highlights the need to further investigate earlier use of bispecific antibodies within treatment algorithms. Second, the potential impact of treatment sequencing, particularly in relation to CAR-T cell therapy, emerges as a key area requiring prospective evaluation, as current evidence suggests that sequence may influence treatment outcomes. Additional data are required to better define the role of bispecific antibodies in combination regimens together with CAR-T cell therapy or other treatment modalities. Third, the observed discrepancy

between clinical trial and real-world toxicity profiles supports the importance of vigilant clinical monitoring in routine practice, particularly for severe Cytokine Release Syndrome and infectious complications. Finally, the limitations of this small and heterogeneous cohort underline the necessity for larger real-world datasets and prospective studies to better define predictors of response, optimize treatment strategies, and improve patient outcomes.

In conclusion, bispecific antibodies hold significant therapeutic potential, but their optimal clinical use remains incompletely defined. Future progress will depend on integrating real-world evidence with prospective clinical data to refine treatment sequencing, improve patient selection, and enhance the durability of responses and management of associated toxicities, particularly infections.

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8. ANNEXES

Annex 1: Analysed Glofitamab Clinical Studies and Data

Study	Phase	Disease	Regimen	N	ORR	CR Rate	CRS (any/≥G3)	Refs
NP30179 (dose escalation)	I	R/R B-NHL (DLBCL, FL, MCL, tFL)	Glofitamab mono (IV), step-up dosing ± obinutuzumab pretreatment	171	54% (66% at RP2D)	37% (57% at RP2D)	50% / 4%	(23)
NP30179 (pivotal Ph II, DLBCL)	I/II	R/R DLBCL (≥2L)	Glofitamab mono (12 cycles, fixed duration)	155	52%	39%	63% / 4%	(23)
NP30179 (MCL cohort)	I/II	R/R MCL (≥1L)	Glofitamab mono (12 cycles)	60	85%	78%	70% / varies by Gpt dose	(33)
NP30179 (retreatment)	I/II	R/R NHL (DLBCL, FL, MCL, tFL)	Glofitamab mono retreatment after prior response	13	69%	39%	54% / 0%	(23)
STARGLO (NCT04408638)	III	R/R DLBCL (≥1L, ASCT-ineligible)	Glofit-GemOx vs R-GemOx	274 (2:1)	79% vs 42% (CR)	59% vs 19%	44% / low	(34)
Glofit + Polatuzumab vedotin (NCT03533283)	Ib/II	R/R LBCL incl. HGBCL (≥1L)	Glofitamab + pola-vedotin	129	78%	60%	43% / ~1%	(35)
COALITION	II	1L high-risk LBCL (≤65 y)	Glofit + Pola-R-CHP or Glofit + R-CHOP	80	100%	98%	21% / 0%	(36)

Annex 2: Analysed Epcoritamab Clinical Studies and Data

Study	Phase	Disease	Regimen	N	ORR	CR Rate	Key Survival Data	CRS (any/≥G3)	Refs
EPCORE NHL-1 (dose escalation)	I/II	R/R B-NHL (DLBCL, FL, others)	Epcoritamab mono (SC), dose escalation 0.0128–60 mg	68	68% (DLBCL); 90% (FL)	45% (DLBCL); 50% (FL)	—	59% / 0%	(37)
EPCORE NHL-1 (pivotal LBCL, 3-yr update)	I/II	R/R LBCL (≥2L)	Epcoritamab mono 48 mg SC (continuous)	157	59%	41%	mDoCR 36.1 mo; mOS 18.5 mo; mPFS	51% / 3%	(37)

Study	Phase	Disease	Regimen	N	ORR	CR Rate	Key Survival Data	CRS (any/≥G3)	Refs
							37.3 mo (CRs)		
EPCORE NHL-1 (pivotal FL)	II	R/R FL (≥2L)	Epcoritamab mono 48 mg SC	128	82%	63%	mPFS 17.4 mo FU; high MRD negativity	65% / 2%	(37)
EPCORE NHL-2 Arm 1 (1L DLBCL)	Ib/2	1L high-risk DLBCL (IPI ≥3)	Epcoritamab + R-CHOP	47	100%	76% CMR	mDOR, PFS, OS NR	60% / 2%	(38)
EPCORE NHL-2 Arm 2 (R/R FL)	Ib/2	R/R FL	Epcoritamab + R² (fixed duration, up to 2 yr)	108	96%	88%	2-yr PFS 76%; 2-yr OS 90%	51% / 2%	(39)
EPCORE NHL-2 Arm 3 (R/R DLBCL + GemOx)	Ib/2	R/R DLBCL (ASCT-ineligible)	Epcoritamab + GemOx	103	85%	61%	mDoCR 23.6 mo; mOS 21.6 mo	52% / 1%	(40)
EPCORE NHL-2 Arm 4 (R/R DLBCL + R-DHAX/C)	Ib/2	R/R DLBCL (transplant-eligible)	Epcoritamab + R-DHAX/C	29	79%	69%	3-yr PFS 59%; 3-yr OS 76%; 55% proceeded to ASCT	45% / 0%	(40)
EPCORE FL-1 (NCT05409066)	III	R/R FL (≥1L chemoimmunotherapy)	Epcoritamab + R² vs R²	488	95% vs 79%	83% vs 50%	PFS significantly improved (HR favoring Epcoritamab + R²)	CRS manageable	(39)