Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende tabelecleucel til behandling af Epstein-Barr-virus-positiv posttransplantations-lymfoproliferativ sygdom (EBV+ PTLD)

Til patienter, som har modtaget mindst én tidligere behandling

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. tabelecleucel
2. Ansøgers endelige ansøgning vedr. tabelecleucel

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31.10.2024
CAF/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.11.2024
Leverandør	Pierre-Fabre
Lægemiddel	Ebvallo (tabelecleucel)
Ansøgt indikation	Tabelecleucel til behandling af Epstein-Barr virus-positiv post-transplantations lymfoproliferativ sygdom (EBV+ PTLD)
Nyt lægemiddel/indikationsudvidelse	Nyt lægemiddel (Advanced Therapy Medicinal Product (ATMP))

Prisinformation

Amgros har forhandlet følgende pris på Ebvallo (tabelecleucel):

Tabel 1: Forhandlingsresultat

Lægemiddel	Behandlinger	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Ebvallo	1 infusion	1 stk.	558.000	[redacted]	[redacted]
Ebvallo	1 behandlings-cyklus består af 3 infusioner	3 stk.	1.674.000	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Hvis Medicinrådet vælger at anbefale Ebvallo til en indsnævret subpopulation, vil prisen stadig være gældende.

Det betyder, at hvis Medicinrådet ikke anbefaler Ebvallo, indkøbes lægemidlet til AIP.

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, hvis Medicinrådet anbefaler Ebvallo til den ansøgte indikation. Aftalen er baseret på Amgros' standardaftale for ATMP'er, der rummer forhold for bl.a. logistik flow, persondata og kvalitet. Aftalen vil gælde hurtigst muligt efter Medicinrådets anbefaling, når disse forhold er forhandlet på plads. Amgros forventer, at aftalen kan starte senest den 01.03.2025 og gælde 4 år frem. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Håndtering af lægemidlet

Ebvallo er den første ATMP under kategorien celleterapi baseret på allogene celler (donor celler). Behandlingen vil altid være donorspecifik, og skal bestilles i et lot/produkt, som passer til patientens HLA-vævstype.

Ebvallo skal gives i behandlingscykler af 3 infusioner over en periode på én måned på hhv. dag 1, 8 og 15 i hver cyklus. Medicinrådet estimerer, at en patient i gennemsnit får 2,56 behandlingscykler, jf. Medicinrådets vurderingsrapport. Dette svarer til et gennemsnitligt antal pakninger på 8. Bestilling af Evballo efter de første 3 infusioner vil ske jf. Medicinrådets vurderingsrapport tabel 1: Behandlingsalgoritme.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence indenfor lægemidler til behandling af Epstein-Barr virus-positiv post-transplantations lymfoproliferativ sygdom (EBV+ PTLD).

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift for en gennemsnitlig behandlings forløb (SAIP, DKK)
Ebvallo	1 stk.	1 hætteglas	[redacted]	[redacted]*

*Jf. Medicinrådets antagelse om at en gennemsnitlig patient skal have 2,56 cykler, svarende til 8 infusioner.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	[redacted]	Link til vurdering
England	Afventer ansøgning	Leverandøren har ikke indsendt en "godkendt" ansøgning. Afventer den endelige ansøgning.	Link

Konklusion

[redacted]

Application for the assessment of Ebvallo® for the treatment of patients with EBV+ PTLD who have received at least one prior therapy. For patients with solid organ transplants, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate.

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Colour scheme for text highlighting	
Colour of highlighted text	**Definition of highlighted text**
Any Colored	**Confidential information**
[other]	**[definition of color-coded]**

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1. Basic information

Contact information	
Name	**Erik Arver**
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Overview of the pharmaceutical	
Proprietary name	Ebvallo®
Generic name	Tabelecleucel
Marketing authorization holder in Denmark	Pierre Fabre
ATC code	L01XL
Pharmacotherapeutic group	Antineoplastic cell and gene therapy
Active substance(s)	An allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy. Each vial contains 1 mL deliverable volume at a concentration of $2.8 \times 10^7 – 7.3 \times 10^7$ viable T cells/mL dispersion for injection. This medicine contains cells of human origin
Pharmaceutical form(s)	Dispersion for injection. A translucent, colorless to slightly yellow cell dispersion.
Mechanism of action	Ebvallo® is an allogeneic, EBV-specific T-cell immunotherapy which targets and eliminates EBV-infected cells in an HLA-restricted manner. Ebvallo® has an equivalent mechanism of action to that demonstrated by endogenous circulating T cells in the donors from which the medicinal product is derived. The T-cell receptor of each clonal population within Ebvallo® recognizes an EBV peptide in complex with a specific HLA molecule on the surface of target cells (the restricting HLA allele) and allows the medicinal product to exert cytotoxic activity against the EBV-infected cells.
Dosage regimen	A single dose of Ebvallo® contains 2×10^6 viable T lymphocytes per kg of body weight. It is administered as an intravenous (IV) injection over 5 to 10 minutes. During each 35-day cycle, patients receive Ebvallo® on Days 1, 8, and 15, followed by observation until Day 35, during which a response is assessed at approximately Day 28. If a patient misses a dose, the missed dose should be given as soon as reasonably possible.

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Ebvallo® is indicated as monotherapy for treatment of adult and pediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV^+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Each carton contains 1 to 6 vials. Each vial contains 1 mL deliverable volume at a concentration of $2.8 \times 10^7 – 7.3 \times 10^7$ viable T cells/mL dispersion for injection.
Orphan drug designation	Yes

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2. Abbreviations

Abbreviation	
AE	Adverse event
AST	American society of transplantation
ATG	Anti-thymocyte globulin
ATMP	Advanced therapy medicinal product
BCSH	British committee for standards in haematology
BLCL	EBV transformed B-lymphoblastoid cell line
BOR	Best overall response
BSC	Best supportive care
BTS	British transplantation society
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CE	Cost effectiveness
CHMP	Committee for medicinal products for human use
CHOP	Cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CTL	Cytotoxic T-lymphocyte
DKK	Danish kronor
DLBCL	Diffuse large B-cell lymphoma
DMCG	Danish multidisciplinary cancer groups
DLI	Donor lymphocyte infusion
DOR	Duration of response
DRR	Durable response rate
EAP	Expanded access programs
EBV	Epstein-Barr virus
ECIL	European conference on infections in leukaemia
ECOG	Eastern cooperative oncology group
EMA	European medicines agency
FACT	Functional assessment of cancer therapy
FAS	Full analysis set
GDP	Cisplatin, dexamethasone, and gemcitabine
GVHD	Graft versus host disease
H0	Null hypothesis
HCT	Haematopoietic cell transplant
HCV	Hepatitis C
HLA	Human leukocyte antigen

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HR	Hazard ratio
HRU	Healthcare resource utilisation
ICU	Intensive care unit
IDCOP	Infectious diseases community of practice
IORA	Independent review
IQR	Intra-quartile range
IR	Indeterminate response
ISS	Integrated summary of safety
ITC	Indirect treatment comparison
IV	Intravenous
LDH	Lactate dehydrogenase
LYRIC	Lymphoma response to immunomodulatory therapy criteria
LYs	Life years
KM	Kaplan-Meier
MRI	Magnetic resonance imaging
NE	Not estimable
NCCN	National comprehensive cancer network
OPTN	Organ procurement and transplantation network
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PP	Per-protocol
PR	Partial response
PRO	Patient reported outcomes
PTLD	Post-transplant lymphoproliferative disease
RCT	Randomized controlled trials
RIS	Reduction of immunosuppression
RKKP	Danish quality program – National clinical registries
RR	Relative risk
R/R	Relapsed or refractory
RTX	Rituximab
RU	Resource use
SD	Stable disease
2L	Second line
SIR	Standardised incidence ratio
SMR	Standardized mortality rate
SMRW	Standardized mortality/morbidity ratio weighting
SOT	Solid organ transplants
SRTR	Scientific registry of transplant recipients
TCR	T-cell receptor

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TEAE	Treatment emergent adverse event
TTBR	Time to best response
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale

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3. Tables and Figures

3.1 List of Tables

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4. Summary

4.1 Population

EVB$^+$ PTLD is a rare and aggressive haematological malignancy that can occur after allogeneic haematopoietic cell transplant (HCT) or solid organ transplant (SOT). The estimated annual incidence of EBV$^+$ PTLD in the European Union (EU) is approximately 125 to 150 patients in the SOT setting and approximately 90 to 140 patients in the HCT setting (EPAR) [1] . Approximately four patients per year are expected to be eligible for treatment with Ebvallo® in Denmark.

The target patient population for this assessment consists of adult and paediatric Danish patients with EBV$^+$ PTLD who are refractory to one line of treatment, in line with the approved indication for Ebvallo®. The current treatment guidelines in Denmark for patients with EBV$^+$ PTLD do not differentiate between HCT and SOT patients, however, HCT patients have a more individualized treatment plan, according to a Danish clinical expert [2]. The first step in treating EBV$^+$ PTLD is to reduce immunosuppression (RIS) followed by rituximab monotherapy [3]. In case of treatment failure (i.e., complete response not achieved) or aggressive disease, the addition of chemotherapy to rituximab should be considered. To reflect the inclusion criteria for the population in ALLELE, the pivotal trial for Ebvallo®, the indication was modified following a request from the Committee for Medicinal Products for Human Use (CHMP), clarifying that for SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate [3]. In Denmark, the most relevant comparator for treatment of EBV$^+$ PTLD patients is best supportive care (BSC) which includes various lymphoma-targeting combinations of chemotherapy with or without rituximab.

4.2 Intervention: Ebvallo®

Ebvallo® is an allogeneic EBV-specific T lymphocyte immunotherapy which targets and eliminates EBV-expressing cells in a human leukocyte antigen (HLA)-restricted manner and is indicated as monotherapy for treatment of adult and paediatric patients, 2 years of age or older with relapsed or refractory EBV$^+$ PTLD who have received at least one prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate. Ebvallo® received a positive opinion from CHMP on 13 October 2022, followed by a European Commission decision on 16 December 2022 and a market authorisation holder transfer from Atara Biotherapeutics, Inc. to Pierre Fabre on 6 February 2023.

4.3 Comparator: Best supportive care

The Danish treatment guidelines for PTLD refer only to patients that has undergone SOT. In the case of relapse or refractory (R/R) EBV$^+$ PTLD, after SOT, the recommendation is to give rituximab with the addition of chemotherapy: R-CHOP, rituximab-cyclophosphamide-doxorubicin-hydrochloride (hydroxydaunorubicin)-vincristine sulfate-prednisone. An alternative to R-CHOP is according to a Danish clinician GDP: cisplatin, dexamethasone, and gemcitabine [2]. No treatment guidelines for EBV$^+$ PTLD for patients that has undergone HCT were identified and it was confirmed with a Danish clinician that they follow the same guidelines, but tend to have a more individualized treatment plan as their condition is worse [2].

4.4 Comparative analysis

The ALLELE study represents the main source informing the effectiveness and safety of Ebvallo®. ALLELE is an ongoing global, multicentre, open-label, single-arm phase III study. All patients had biopsy-proven EBV$^+$ PTLD that was relapsed/refractory to at least one prior therapy that included rituximab. Ebvallo® was partially matched to each patient from an HLA-characterised library using one EBV HLA restriction allele and at least one other matched HLA allele.

The primary efficacy outcome was objective response rate (ORR) following administration of Ebvallo® with up to two different HLA restrictions in the SOT or HCT cohort. The secondary efficacy outcomes included duration of response (DOR) in each cohort, ORR and DOR in the combined cohort, rate of complete response (CR), time to response (TTR), time to best response (TTBR), and overall survival (OS).

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The relative effect of Ebvallo® was estimated using an external comparator arm based on the study ATA129-RS002 (hereafter referred as Study RS002), a retrospective chart review study. This study included patients with biopsy-proven EBV+ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy and were refractory (failed to achieve CR or partial response [PR]) or had relapsed at any point after such therapy.

4.5 Safety

Safety endpoints were included in ALLELE. These included: rates of allograft loss/rejection episodes (for SOT cohort only) defined according to appropriate criteria for the organ transplant, adverse event (AE) of special interest (serious or non-serious), number of patients experiencing AEs, treatment-emergent AE (TEAE), AEs that led to treatment discontinuation. The safety evaluation, as assessed by EMA, was based on all cohorts enrolled in the trial, as well as the integrated summary of safety which includes studies for other EBV-driven diseases.

4.6 Health economic analysis

A cost effectiveness analysis from a Danish limited societal perspective was performed for Ebvallo® compared to BSC. The outcomes from the analysis included total costs as well as benefits measured by life years (LYs) and quality adjusted life years (QALYs) gained. Furthermore, incremental differences were reported and summarized as an incremental cost effectiveness ratio (ICER). The base case analysis predicted that Ebvallo® was associated with 4.14 additional LYs and 2.84 additional QALYs compared to BSC. Treatment with Ebvallo® led to an incremental cost of DKK 3,958,587 and resulted in an ICER of DKK 1,392,909 per QALY gained over a lifetime.

Table 1. Base case results (discounted)

	Increment
Total life years (LYs)	4.14
Total quality adjusted life years (QALYs)	2.84
Total cost (DKK)	3,958,587
ICER (DKK/QALY)	1,392,909

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

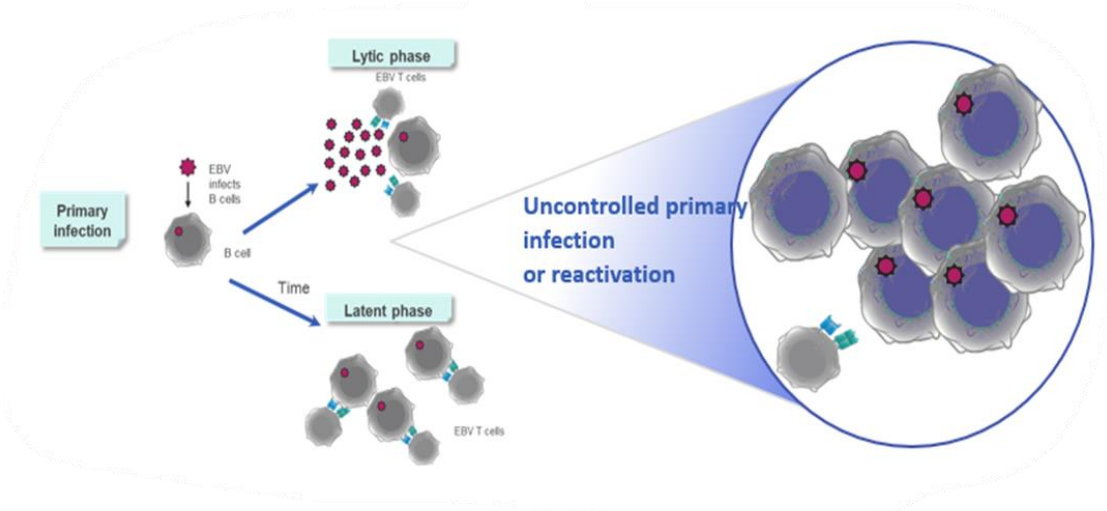
5.1.1 EBV+ PTLD

PTLD is a rare and deadly haematological malignancy that can occur after allogeneic HCT or SOT. This disease is among the most serious and potentially fatal complications of transplantation. It can affect transplant patients of any age and is a consequence of routine immunosuppressant treatment to prevent graft rejection [5, 6].

In most cases, PTLD is associated with EBV infection of B lymphocytes, either because of reactivation of the virus post-transplantation or from primary EBV infection. EBV$^+$ PTLD is the most common cause of PTLD following HCT or SOT, accounting for almost all cases of HCT PTLD and approximately 50% of SOT PTLD [7, 8]. In these immunosuppressed patients, the risk of PTLD is highest in the first year after transplantation [9]. In HCT, most PTLDs are of donor origin, whereas for SOT most PTLDs are of host origin [7, 9, 10]. Given the association between PTLD and EBV in both transplant settings, pathology testing of tumour cells for EBV is standard of care in cases of PTLD [6, 8].

During the treatment with immunosuppressant aimed at preventing graft rejection, transplanted patients will undergo the inhibition of anti EBV-specific T lymphocytes. In this setting, the EBV-infected B lymphocytes may proliferate in an uncontrolled manner (Figure 1) [6]. This proliferation might be especially strong when patients are EBV negative and acquire a primary infection when immunosuppressed, as it might be the case in paediatric patient [9].

Figure 1. Infection of B lymphocytes by Epstein-Barr virus



EBV+ PTLD affects transplanted patients of any age, including children, resulting in a younger population being affected compared to other lymphomas. PTLD disproportionately affects younger patients due to a higher likelihood of EBV negativity in these transplant recipients [11]. At diagnosis, PTLD patients are 25-30 years younger than overall lymphoma patients, with an average age of 34.4 years (HCT) and 38.6 years (SOT).

In both HCT and SOT, PTLD typically occurs early after transplant, usually within the first few months following HCT and in the first 1-2 years following SOT [7, 8, 10, 12-16]. However, there is a distinct incidence pattern in SOT patients with two peaks: one in the first two years post-transplant and one around 7-10 years post-transplant [16-20]. However, the EBV genome is more prevalent in the early onset of PTLD, compared to the later one. The median time to occurrence of EBV$^+$ PTLD was reported to be 10 months after transplantation, compared to 50 months for EBV-negative [21]. HCT and SOT patients are under severe immunosuppression regimens: HCT patients receive immunosuppression before transplantation which may continue in the first year following transplantation to prevent graft versus host disease (GvHD) [22, 23], whereas SOT patients receive immunosuppression before transplantation and may need lifelong immunosuppression after transplantation to prevent organ rejection. In both instances, patients are

immunosuppressed to a greater degree early after the transplantation due to the time required for immune reconstitution (for HCT) or due to higher post-transplant immunosuppression (for SOT). This is why almost all early-onset cases of PTLD are EBV$^+$ for both SOT and HCT [10, 24]. In SOT, patients continue to be at risk of developing PTLD even after 20 to 30 years following transplant due to the long-term use of immunosuppressive anti-organ rejection medications, albeit with a lesser degree of EBV association [16, 17, 25].

Risk factors for developing EBV$^+$ PTLD vary according to the transplanted organ (for SOT patients), as well as pre-transplantation EBV status (of both the recipient and the donor), and the type and duration of the post-transplantation immunosuppressive therapy [6, 7, 16, 26]. EBV status is an important consideration in the evaluation of risk factors after HCT and SOT. Patients who are EBV negative are at an increased risk of PTLD compared to EBV positive, meaning that paediatric patients have an increased risk. This is particularly the case when the donor is EBV$^+$ [7, 27-29], although PTLD can also occur in EBV$^+$ patients. PTLD patients have been reported to be 25-30 years younger than overall lymphoma patients at diagnosis. Various studies have shown that patients who are younger are more likely to be diagnosed with PTLD within the first year after HCT and SOT [12, 30]. As a prevention strategy, since EBV mismatch (i.e., EBV$^-$ recipient and EBV$^+$ donor) is a significant risk factor [14, 31], the Sixth European Conference on Infections in Leukaemia recommended that all HCT patients and donors should be tested for EBV antibodies before transplantation, and the selection of an EBV-matched donor (if possible) might be beneficial [8].

5.1.2 Burden of disease

Patients with EBV$^+$ PTLD who fail initial therapy experience a worsened clinical burden with complications and poor outcomes, high mortality rates and short survival time. Additionally, with the increased morbidity, patients are at risk of graft rejection.

A systematic literature review (SLR) showed, in PTLD patients after HCT (almost all EBV$^+$), a 1-year OS rate of 6.7-20% in untreated patients and 14.6-66.7% in patients who received rituximab or rituximab plus other treatments (concomitant or as later lines of treatment) [32]. Median OS was reported in five studies and ranged from 0.7 months to 2.5 months [34]. However, it is important to note that in the two studies with the lowest OS, a significant number of patients received no treatment at all. In comparison, HCT patients without PTLD have a reported 3-year survival rate of 62% and an estimated mean OS of 25.9 years [24]. Furthermore, the mortality of HCT EBV$^+$ PTLD is similar in adult and paediatric populations [25].

PTLD represents a significant threat also in SOT, with a high mortality rate in comparison to SOT patients without PTLD. The situation is worse in EBV$^+$ patients and for those who are R/R to therapy. In eight prospective and eight retrospective studies of different types of PTLD and at different treatment lines, 3-year OS ranged from 36% to 80% [37], 5-year OS ranged from 21% to 71% [19] and one study estimated the 10-year OS rate to 49.5% [38]. Median survival ranged from 3.3 months to 6.6 years [40]; the 3.3 months estimate being in patients with R/R EBV$^+$ PTLD.

Patients with R/R EBV$^+$ PTLD patients has an increased clinical burden. Half of HCT patients treated with rituximab are found to be unresponsive to the further therapy. In PTLD following HCT, a recent study showed that approximately 50% of patients with EBV$^+$ PTLD fail treatment with rituximab [15]. In SOT, around 33% of patients failed initial rounds of treatment [17, 19]. These are the patients for which Ebvallo® is indicated and the patient population covered in this application.

5.1.3 Epidemiology

The estimated incidence for EBV$^+$ PTLD and the number of patients potentially eligible for treatment with Ebvallo® per year in Denmark are presented in Table 2. It is assumed that there is no prevalent population as patients who fail to respond to treatment are not expected to survive beyond one year (see section 5.1.2). However, if treatment is successful, then cure is expected.

An estimated yearly total of 156 individuals receive allogeneic HCT in Denmark [44]. Danish-specific reported incidence of PTLD is 1-2% for HCT patients [45]. As EBV⁺ PTLD accounts for almost all cases of PTLD in HCT patients, EBV⁺ was assumed for the entire incident population [8]. It was assumed that 50% of HCT patients were R/R [15].

The number of patients receiving SOT (kidney and other organ transplants) in 2021 was collected for Denmark [46]. Based on the available literature, a PTLD incidence of 1 – 3% was assumed for kidney SOT [45]. For other organ transplants, the literature reports PTLD incidence ranging from 0.14% – 3.22% [47]. A total of 50% of PTLD cases post SOT are EBV⁺ [8] and 33% of EBV⁺ PTLD patients post SOT are R/R [17, 19]. The final total incidence is estimated to be four patients, see Table 2. The final number of patients was validated by a Danish clinical expert [2].

Table 2. Incidence of EBV⁺ PTLD and patients eligible for treatment with Ebvallo® in Denmark per year.

	Assumption	Patients (n)
Patients, HCT (allogenic)		156 [44]
With PTLD	1–2% [45]	3
EBV⁺ PTLD	100% [8]	3
Not responding to previous treatment	50% [15]	2
Patients SOT, kidney		252 [46]
With PTLD	1–3% [45]	6
Patients SOT, other organ transplants		100[a] [46]
With PTLD	0.14%–3.22% [47]	2
Total SOT patients with PTLD		8*
EBV⁺ PTLD	50% [8]	4
Not responding to previous treatment	33% [17, 19]	2
Total SOT and HCT patients potentially eligible for treatment		**4**

Note: When a range is stated, the average between the highest and lowest values in the range was used.

a Sum of liver, heart, heart-lung, lung, pancreas and small bowel transplantations.

*The number also corresponds to the approximation of patient numbers mentioned in the national treatment guidelines of patients with PTLD, after SOT being between 5-10.

Table 3 Estimated number of patients eligible for treatment with Ebvallo®

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years (HCT and SOT)	4	4	4	4	4

Note: The calculated value for 2023 was assumed to be valid for the coming 4 years. The 2023 value was validated by a clinical expert [2].

5.1.4 Patient populations relevant for this application

The target population in this assessment consists of adult and paediatric Danish patients with EBV⁺ PTLD, who have received at least one prior line of therapy. This will position Ebvallo® as second line (2L) treatment. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate. The relevant patient population in Denmark is also aligned with the approved indication for Ebvallo® and the population in ALLELE. This was validated by a clinical expert in Denmark [2]. The clinician stated a different distribution for the proportions of transplants received by SOT patients [2]. These were tested in a scenario analysis (Table 47).

In ALLELE, EBV+ PTLD included both HCT and SOT patients who were R/R to first-line treatment [3]. Efficacy data from ALLELE considered relevant for this assessment include a pooled analysis set of patients who received SOT or HCT. Table 4 gives an overview of the baseline characteristics for the pooled analysis which is representative for the Danish population.

Table 4. Baseline characteristics: ALLELE

Characteristic	ALLELE (N=39)
Age at index date†, years, median (Q1, Q3)	42.1 (21.1, 63.9)
Female, n (%)	17 (43.6)
Extranodal sites of PTLD, n (%)	28 (71.8)
Early PTLD onset‡, n (%)	17 (43.6)
Response to initial rituximab treatment, n (%)	
Responders (CR, PR)	14 (35.9)
Non-responders (SD, PD)	25 (64.1)
CD 20 marker at diagnosis, n (%)	
Positive	23 (59.0)
Negative	8 (20.5)
Unknown	8 (20.5)
Number of prior therapies, n (%)	
1	22 (56.4)
≥2	17 (43.6)
Transplant type	
HCT	20 (51.3)
SOT	19 (48.7)
Transplant organ type (SOT only)	
Kidney	7 (36.8)
Liver	0
Lung	1 (5.3)
Heart	7 (36.8)

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Other	0
Multiorgan†	4 (21.1)
Time from transplant to date of PTLD diagnosis, months, median (Q1, Q3)	6.7 (3.7, 63.7)
Time from PTLD diagnosis to R/R date, months, median (Q1, Q3)	1.9 (0.9, 6.6)

† Multiorgan transplant: in ALLELE, 2 kidney/pancreas transplants,1 kidney/pancreas/colon/stomach transplant, and 1 bilateral/lung/liver transplant.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The Danish treatment guidelines, published by the Danish Multidisciplinary Cancer Groups (DMCG) and the Danish Clinical Quality Program– National Clinical Registries (RKKP) in 2019 only present recommendations for SOT. They recommend starting with RIS. For patients who do not achieve a complete response to RIS, rituximab monotherapy is recommended (375 mg/m^2) on days 1, 8, 15 and 22. In case of disease progression, it is advised to add CHOP to rituximab. The addition of antiviral therapy with valaciclovir (1g x 3 daily) is also recommended [48]. A Danish clinical expert confirmed that the same treatment algorithm would also be used for EBV+ PTLD following HCT [2] with the addition of GDP (cisplatin, dexamethasone, and gemcitabine) without rituximab as a possible treatment. The clinician also specified that HCT patients received a highly individualized treatment plan [2]. Table 5 summarises the recommended treatments in Denmark for adult EBV$^+$ PTLD patients.

Table 5. Summary of treatment recommendations for EBV$^+$ PTLD patients in Denmark

Treatment recommendations in Denmark		Source
Adults		
RIS		[2, 48]
Rituximab	+ Valaciclovir	
R-CHOP		
GDP		

Abbreviations: RIS: reduction of immunosuppression, R-CHOP: Rituximab-cyclophosphamide-doxorubicin-hydrochloride (hydroxydaunorubicin)-vincristine sulfate-prednisone, GDP: cisplatin, dexamethasone, and gemcitabine

5.2.2 Choice of comparator(s)

The most relevant comparator to Ebvallo® for the treatment for EBV$^+$ PTLD patients in 2L in Denmark is rituximab with chemotherapy (R-CHOP) or chemotherapy (GDP), referred to as BSC.

5.2.3 Description of the comparator(s)

BSC consists of R-CHOP or GDP. Each regimen is assumed to be used in an equal share and treatment to progression was assumed. The posology and administration for each regimen were sourced from Danish treatment guidelines for R-CHOP [48] and from the Swedish guidelines for GDP (cisplatin, dexamethasone, and gemcitabine) [49], as they were not available in the Danish treatment guidelines and it was assumed they are transferable to the Danish practice.

Table 6. Description of regimens included in BSC and their components

Drug	Pharmaceutical form	ATC Code	Posology	Source

	& method for admin			
R-CHOP				
Rituximab	IV	L01FA02	375 mg/m^2 once every 21 days	[48, 50]
Cyclophosphamide	IV	L01AA01	750 mg/m^2 once every 21 days	[48, 50]
Doxorubicin	IV	L01DB01	50 mg/m^2 once every 21 days	[48, 50]
Vincristine	IV	L01CA02	1.4 mg/m^2 once every 21 days	[48, 50]
Prednisone	Oral	H02AB07	50 mg/m^2 on days 1-5 every 21 days	[48, 50]
GDP				
Cisplatin	IV	L01XA01	75 mg/m^2 once every 21 days	[49]
Dexamethasone	Oral	H02AB02	40 mg 4 times every 21 days	[49]
Gemcitabine	IV	L01BC05	1,000 mg/m^2 twice every 21 days	[49]

Abbreviations: R-CHOP, GDP

5.3 The intervention

Mode of action: Ebvallo® is an allogeneic, EBV-specific T-cell immunotherapy which targets and eliminates EBV infected cells in an HLA-restricted manner. Ebvallo® has an equivalent mechanism of action to that demonstrated by endogenous circulating T cells in the donors from which the medicinal product is derived. The T-cell receptor of each clonal population within Ebvallo® recognises an EBV peptide in complex with a specific HLA molecule on the surface of target cells (the restricting HLA allele) and allows the medicinal product to exert cytotoxic activity against the EBV-infected cells [3] .

Pharmaceutical form: Dispersion for injection.

Posology: Treatment consists of multiple doses for injection containing a dispersion of viable T cells in one or more vials (i.e., up to six). The recommended dose of Ebvallo® contains 2 × 10^6 viable T cells per kg of the patient's body weight, and is calculated as:

- Patient weight (kg) × target dose (2 × 10^6 viable T cells/kg) = Total viable T cells to be administered
- Total viable T cells to be administered ÷ Actual concentration (viable T cells/mL) per the Lot Information Sheet (LIS) and carton = Volume of thawed cell dispersion required (mL)

Ebvallo® is administered over multiple 35-day cycles, during which patients receive Ebvallo® on days 1, 8 and 15, followed by observation through day 35 (see Figure 2). A response is assessed at approximately day 28. If a patient misses a dose, the missed dose should be given as soon as reasonably possible [3].

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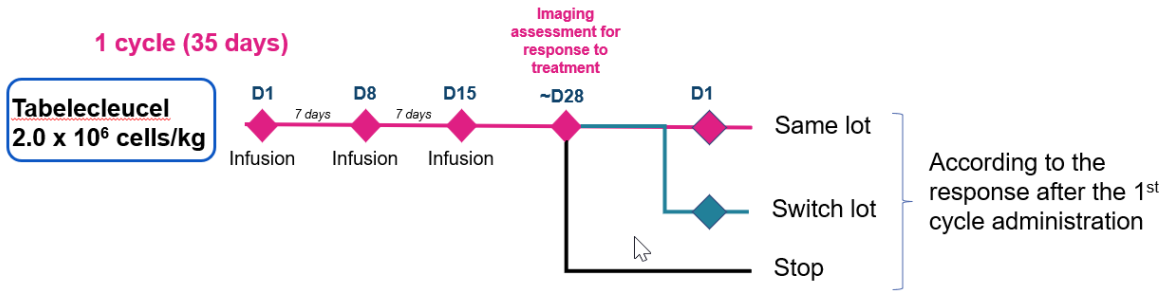
Figure 2. Ebvallo® treatment scheme



Source: [4]

Method of administration: Ebvallo® should be administered as a single dose intravenous (IV) injection over 5 to 10 minutes.

Should the pharmaceutical be administered with other medicines? N/A

Treatment duration / Criteria for end of treatment: The number of cycles of the medicinal product to be administered is determined by the response to treatment as shown in Table 7. If a complete or partial response is not obtained, patients may be switched to an Ebvallo® lot with a different HLA restriction (up to four different restrictions) selected from the existing product inventory.

Table 7. Treatment algorithm

Response observed[a]	Action
Complete response (CR)	Administer another cycle of Ebvallo® with the same HLA restriction. If the patient achieves 2 consecutive CRs (maximal response), no further treatment with Ebvallo® is recommended.
Partial response (PR)	Administer another cycle of Ebvallo® with the same HLA restriction. If the patient achieves 3 consecutive PRs (maximal response), no further treatment with Ebvallo® is recommended.
Stable disease (SD)	Administer another cycle of Ebvallo® with the same HLA restriction. If the subsequent cycle results in a second SD, administer Ebvallo® with a different HLA restriction.
Progressive disease (PD)	Administer another cycle Ebvallo® with a different HLA restriction.
Indeterminate response (IR)	Administer another cycle of Ebvallo® with the same HLA restriction. If the subsequent cycle results in a second IR, administer Ebvallo® with a different HLA restriction.

[a] Complete response at the end of a cycle followed by partial response or other response at any subsequent cycle is considered progressive disease.

Necessary monitoring, both during administration and during the treatment period: It is recommended to monitor vital signs immediately prior to each Ebvallo® injection, within 10 minutes following the conclusion of the injection and 1 hour after the initiation of the injection.

Need for diagnostic or another test: No

In summary, Ebvallo® is an efficacious therapy for patients with EBV+ PTLD after first line treatment. Currently, in Denmark for patients who do not respond to RIS, rituximab with or without chemotherapy are the treatment options available. EBV+ PTLD patients that relapse or are refractory to first-line therapy experiences a high clinical burden with complications and poor outcomes, high mortality rates and short survival time. Ebvallo®, an EBV-specific cytotoxic T-lymphocytes intervention, is the first and only approved treatment by EMA specifically for the treatment of EBV+ PTLD for patients who fail first-line treatments. Results from ALLELE, showed that Ebvallo® is an efficacious treatment to treat EBV+ PTLD patients following HCT or SOT in patients who are R/R to rituximab or rituximab in combination with chemotherapy. See section 5.2.1 for current treatment options.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Using the findings from the clinical SLR, the feasibility assessment for an indirect comparison (ITC) of Ebvallo® versus standard of care/BSC for the treatment of EBV+ PTLD after failure or relapsed from first-line treatment, led to the identification of two studies, Dharnidharka 2021 and Sanz 2021, assessing BSC, for performing an ITC [20, 41]. These two studies come from the non-interventional retrospective chart review study ATA129-RS002, which collected data to create a control arm for the single-arm pivotal study ALLELE assessing Ebvallo®[51].

The basis for the efficacy of Ebvallo® for the treatment of patients with EBV+ PTLD who have received at least one prior therapy, in this assessment is from the pivotal phase III trial, ALLELE (ATA129-EBV-302). In addition, the clinical development program for Ebvallo® for the treatment of patients with EBV+ PTLD who have received at least one prior therapy also includes the following ongoing or planned trials (see overview section 3.3):

- Three phase I and/or II supportive studies (EBV-CTL-201; 11-130; 95-024) and their pooled data (Integrated Summary of Efficacy [ISE]
- Three expanded access programs (EAPs) (ATA129-EAP-901; ATA129-EAP-902; ATA-129-SPU).
- An Integrated Summary of Safety (ISS), including the totality of evidence across the pivotal study (ALLELE) and the 3 supportive studies (EBV-CTL-201; 11-130; 95-024), as well as the EAPs (ATA129-EAP-901; ATA-129-SPU). All patients treated with Ebvallo® regardless of their EBV-driven disease were included.

All four clinical studies (ALLELE, EBV-CTL-201, 11-130, and 95-024) have a single arm, open-label design, which was accepted by EMA given the claimed indication of an ultra-rare condition (EBV+ PTLD) and the lack of an appropriate comparator. A post-authorization safety study (PASS) is also in development following the EMA approval. This would be an observational study to describe the safety, effectiveness, patient population, and treatment patterns in patients with EBV+ PTLD, in Europe.

The basis for the efficacy of the comparator, BSC was study ATA129-RS002 (hereafter referred as Study RS002) was a large, descriptive, multinational, multicenter non-interventional retrospective chart review study. This study included patients with biopsy-proven EBV+ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory (failed to achieve CR or PR) or had relapsed at any point after such therapy. The study aimed to assess the treatment landscape for this population which has not changed significantly over the last 20 years.

The study population included the one indicated for Ebvallo® (i.e., as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received at least one prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate) and was consistent with recommendations in current treatment guidelines.

Data were collected from 29 centres located in Europe (specifically Austria, Belgium, France, Germany, Italy, Spain, and Sweden) and North America (Canada and the United States). The database was locked on 26 January 2021. The conduct

of the study was standardized, with processes similar to those for clinical trials. RS002 study demonstrated very poor OS for patients following HCT and SOT who failed rituximab +/- chemotherapy. A vast majority of the patients ultimately died (91% of HCT patients and 73% of SOT patients after failure of rituximab + chemotherapy); deaths were mostly related to PTLD in each cohort.
Furthermore, RS002 study confirmed the high unmet need in the EBV⁺ PTLD population who failed initial treatment, especially among HCT patients who failed rituximab and SOT patients who failed rituximab plus chemotherapy [20, 34, 41, 42, 52, 53].

6.2 List of relevant studies

The selection of the relevant studies for the comparison between patients treated with Ebvallo® with patients treated with BSC included the single-arm Phase 3 pivotal study ALLELE (ATA129-EBV-302), and an external control arm, using the non-interventional retrospective chart review study RS002 (ATA129-RS002). Data for Ebvallo® was informed by the pivotal trial ALLELE, whereas data for the comparator (i.e., the RS002 study) was identified via a global SLR, followed by a feasibility assessment.

Table 8 includes the relevant studies used for ITC of Ebvallo® vs BSC for EBV+ PTLD patients post HCT or SOT who relapse or are refractory to at least one prior therapy, for SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.
Detailed information about the included studies is presented in Appendix B Main characteristics of included studies.

Table 8. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Use of the study in the application
Multicentre, Open-Label, Phase 3 Study of Ebvallo® for Solid Organ or Allogeneic Hematopoietic Cell Transplant Patients with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy, Pierre Fabre, Data on file 2023	ALLELE	NCT03394365	Ongoing Initiated in 2018 Data are reported to the cut-off date of 29 July 2022.	Main results regarding efficacy and safety of the intervention
A descriptive, multinational, multicenter non-interventional retrospective chart review study of patients with biopsy-proven EBV+ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory or had relapsed after such therapy, Pierre Fabre, Data on file, 2022	ATA129 -RS002	N/A	Ongoing Data are reported to the cut-off date of 26 January 2021	The HR for the comparator arm
Multicenter,single-arm,open-label expanded access study for treatment of EBV-associated viremia or malignancies for whom there are no appropriate alternative therapies.	EBV-CTL-201	NCT02822495	Completed in 2020 Initiated in 2016	Included in the ISS

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Use of the study in the application
Single-centre, open-label study for treatment of EBV+PTLD and other EBV-associated lymphoproliferative diseases or malignancies	11-130	NCT01498484	Completed in 2018 Initiated in 2011	Included in the ISS
Single-centre, open-label study for treatment of EBV+PTLD and other EBV-associated lymphoproliferative diseases or malignancies, Atara Biotherapeutics	95-024	NCT00002663	Completed in 2018 Initiated in 1995	Included in the ISS
Multicenter, multicohort, open label, single-arm, Phase 2 study to assess the efficacy and safety of tabelecleucel for the treatment of EBV-associated diseases in participants who are newly diagnosed or relapsed/refractory to prior treatment, Atara Biotherapeutics	ATA129-EBV-205	NCT04554914	Ongoing Initiated in 2021	Not used
Multicenter, open-label, single-arm Phase 1B/2 study to assess the safety and efficacy of tabelecleucel in combination with pembrolizumab for the treatment of subjects with platinum-pretreated, recurrent/metastatic EBV+ NPC, Atara Biotherapeutics	ATA129-NPC-202	NCT03769467	Completed in 2021 Initiated in 2019	Not used
A protocol to provide expanded access to tabelecleucel to participants with Epstein-Barr virus-associated diseases and malignancies for whom there are no other appropriate therapeutic options, and who are not eligible to enroll in clinical studies designed to support the development and registration of tabelecleucel, Atara Biotherapeutics	ATA129-EAP-901	NCT02822495	Terminated Initiated in 2016	Not used
A Phase 1/2, Two-part, Open-label Dose-escalation and Double-blind, Placebo-controlled Dose-expansion Study With an Open-label Extension to Evaluate the Safety and Efficacy of ATA188 in Subjects With Progressive Multiple Sclerosis, Atara Biotherapeutics	ATA188-MS-101	NCT03283826	Ongoing Initiated in 2017	Not used

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Use of the study in the application
An open-label, single-arm, Phase II Study of Carboplatin and Docetaxel Followed by Epstein-Barr Virus Cytotoxic T Lymphocytes in Patients With Refractory/Relapsed EBV-positive Nasopharyngeal Carcinoma(CADEN), Baylor College of Medicine	25145-CADEN	NCT00953420	Completed in 2015 Initiated in 2009	Not used
A multi-center open-label, non-randomized phase I/II intervention study in which three consecutive doses of donor-derived EBV Tscm-CTLs will be administered to 10 patients with treatment-refractory EBV lymphoma, diseases or PTLDs. EBV Tscm-CTLs will derive from hematopoietic cell transplant (HCT) or third-party donors.	2022-01210; am22Khanna	NCT05688241	Not yet recruiting	Not used
An open-label, single-arm, Phase II, pilot study in the Treatment of Refractory Epstein-Barr Virus (EBV) Infection With Related Donor EBV Cytotoxic T-Lymphocytes in Children, Adolescents and Young Adult Recipients, New York Medical College	NYMC 581	NCT03266653	Ongoing Initiated in 2020	Not used
An open label, non-randomised, multicentre Phase I to determine the safety of tacrolimus-resistant autologous EBV-specific cytotoxic T-cells (EBV CTL) and compare their expansion/persistence with control EBV CTL in solid organ transplant patients with post-transplant lymphoproliferative disease (PTLD). Each patient will receive an infusion of two ATIMPs - autologous EBV CTL retrovirally transduced with (a) a calcineurin mutant (CNA12) that confers resistance to tacrolimus and (b) a control calcineurin mutant (CNA8), University College, London	UCL/16/0529	NCT03131934	Ongoing Initiated in 2019	Not used
ADVERSE EVENTS AND CLINICAL BURDEN ASSOCIATED WITH CHEMOTHERAPY IN… by Heiner	N/A	N/A	N/A	Informing the comparator – RS002

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Use of the study in the application
Zimmermann [Internet]. Inc MG. [cité 16 sept 2022]. Disponible sur: ht tps://library.ehaweb.org/eha/2020/eha25th/293756/heiner.zimmermann.adverse.events.and.clinical.burden.associated.with.html				
Clinical Outcomes of EBV⁺ PTLD Patients Following HCT Who Fail Rituximab: A Retrospective Chart Review Study from France. Socié G, Pigneux A, Herbaux C, Chauvet P, Xu H, Thirumalai D, et al. :1.	N/A	N/A	N/A	Informing the comparator – RS002
Clinical outcomes of solid organ transplant patients with EBV+PTLD who fail first-line rituximab or rituximab plus chemotherapy: an analysis of German PTLD registry:PF19, Zimmermann H, Xu H, Barlev A, Feng A, Li X, Navarro W, et al. HemaSphere. 2019	N/A	N/A	N/A	Informing the comparator – RS002
Burden of Hospitalizations Due to Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disorder (EBV+PTLD) in Patients Who Failed First Line Rituximab or Rituximab Plus Chemotherapy Following Solid Organ Transplant (Post-SOT): A Retrospective Chart Review Study of German PTLD Registry. Zimmermann H, Xu H, Barlev A, Zhang Y, Thirumalai D, Watson C, et al. Blood. 2019	N/A	N/A	N/A	Informing the comparator – RS002
Clinical Outcomes of Solid Organ Transplant Patients with Epstein-Barr Virus-Driven (EBV +) Post-Transplant Lymphoproliferative Disorder (PTLD) Who Fail Rituximab Plus Chemotherapy: A Multinational, Retrospective Chart Review Study. Dharnidharka V, Thirumalai D, Jaeger U, Zhao W, Dierickx D, Xun P, et al. Blood. 2021.	N/A	N/A	N/A	Informing the comparator – RS002

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Use of the study in the application
Clinical Outcomes of Patients with Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disease Following Hematopoietic Stem Cell Transplantation Who Fail Rituximab: A Multinational, Retrospective Chart Review Study. Sanz J, Storek J, Socié G, Thirumalai D, Guzman-Becerra N, Xun P, et al. Blood. 2021.	N/A	N/A	N/A	Informing the comparator – RS002

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7. Efficacy and safety

7.1 Efficacy and safety of Ebvallo® compared to BSC for the treatment of patients with EBV+ PTLD who have received at least one prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate.

7.1.1 Relevant studies

7.1.1.1 ALLELE

7.1.1.1.1 Study design

This pivotal Phase III study, ALLELE (ATA129-EBV-302 study) is an ongoing global, multicenter, open-label, single-arm phase III study. ALLELE was conducted to determine the clinical benefit of Ebvallo® and to characterize the safety profile in patients with EBV+ PTLD following SOT after failure of rituximab or rituximab plus chemotherapy or allogenic HCT after failure of rituximab.

All patients had biopsy-proven EBV+ PTLD that was relapsed/refractory to at least one prior therapy that included rituximab. Enrollment was preceded by the confirmation of availability of partially human leukocyte antigen (HLA)-matched and restricted Ebvallo® for the patient. Ebvallo® was partially matched to each patient from an HLA-characterised library using 1 EBV HLA restriction allele and at least 1 other matched HLA allele. Patients were assigned to prespecified cohorts based on transplant type and treatment failure to the prior therapy regimen (Figure 3).

- SOT cohort, consisting of SOT patients with EBV+ PTLD who had failed rituximab alone (***C-SOT-R***) which is not included in the EMA approved indication, and SOT patients who had failed both rituximab and chemotherapy (***C-SOT-R+C***) for the treatment of PTLD.
- HCT cohort, consisting of HCT patients with EBV+ PTLD who had failed rituximab for the treatment of PTLD.

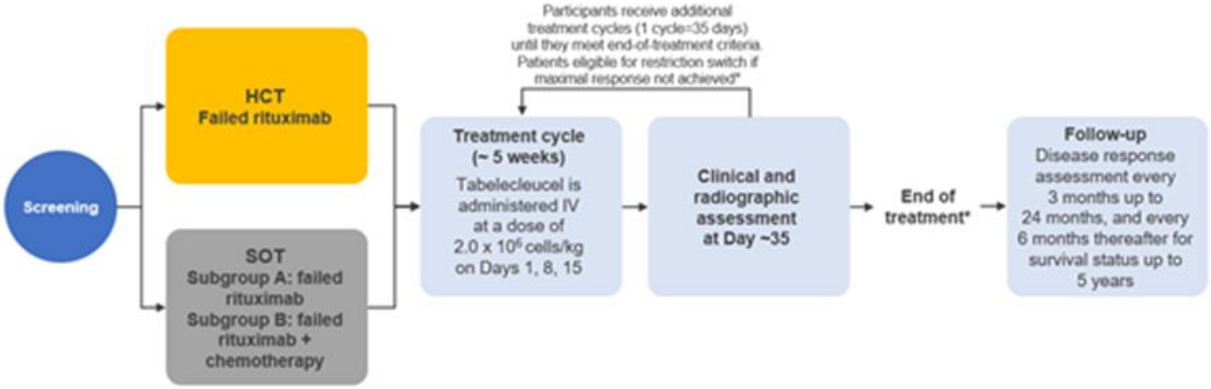
Ebvallo® was administered in cycles lasting 5 weeks (35 days). At the end of each cycle, each patient's response was assessed clinically and radiographically by the investigator and subsequent independent review by IORA, using the Lugano classification response criteria [54] with the LYRIC modification [55].

The investigator assessments were used for making clinical decisions, and the overall response and progression/relapse for efficacy assessment were determined by IORA. Treatment continued until maximal response, unacceptable toxicity, initiation of non-protocol therapy, or failure of the maximum allowable HLA restrictions, with up to 2 different HLA restrictions (SOT patients) or up to 4 different HLA restrictions (HCT patients), if available.

Maximal response was reached when the patient received 3 consecutive PR assessments, or 2 consecutive CR assessments as assessed by the investigator using Lugano classification response criteria with LYRIC modification. In instances where the patient's PTLD rapidly progressed during the first cycle, the patient had documented radiographic or clinical progressive disease (PD) any time after the third Ebvallo® dose (cycle 1 day 15), and the medical monitor had been consulted and approved, restriction switch (ie, treatment with Ebvallo® with a different HLA restriction) could be initiated before the 35 days of cycle 1 was complete. The first dose of Ebvallo® after the restriction switch would constitute cycle 2 day 1.

After treatment was completed or discontinued, patients were assessed for disease response every 3 months, up to 24 months from cycle 1 day 1, and every 6 months thereafter up to 5 years from cycle 1 day 1 for survival status.

Figure 3. Study design



Abbreviations: DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic stem cell transplant; HLA, human leukocyte antigen; IV, intravenously; ORR, objective response rate; OS, overall survival; SOT, solid organ transplant; TTR, time to response

*Treatment ends with any of the following: maximal response achieved, unacceptable toxicity, initiation of non-protocol therapy, failure of up to 4 Ebvallo® with different HLA (HCT) or 2 Ebvallo® with different HLA restrictions (SOT).

†Evaluated by independent review (IORA).

Ebvallo® was selected for each patient from the existing product inventory based on appropriate HLA restriction. In each cohort, Ebvallo® was administered by intravenous (IV) infusion in cycles lasting 5 weeks (35 days). During each cycle, patients received 3 doses of Ebvallo® (2×10^6 cells/kg of recipient body weight measured at baseline[1]) administered on day 1, day 8, and day 15, followed by observation until day 35.

The number of cycles of Ebvallo® to be administered was determined by the response to treatment algorithm presented in Table 9. Each patient's response was assessed clinically and radiographically after each treatment cycle. If a complete or partial response is not obtained, patients could be switched to a Ebvallo® lot with a different HLA restriction selected from the existing product inventory.

Table 9. Actions following response assessed clinically and radiographically (ALLELE)

Response Observed	Action	Comments
Complete Response (CR)	Administer another cycle of Ebvallo® with same HLA restriction	If 2 consecutive CRs, patient had achieved maximum response and proceeded to follow-up
Partial Response (PR)	Administer another cycle of Ebvallo® with same HLA restriction	If 3 consecutive PRs, patient had achieved maximum response and proceeded to follow-up
Stable Disease (SD)	If SD was the first cycle response, administer Ebvallo® with same HLA restriction for the next cycle; if this SD was the second cycle response, administer Ebvallo® with different HLA restriction (restriction switch) for the next cycle	If 2 consecutive SDs with Ebvallo® with same HLA restriction, then Ebvallo® with different HLA restriction (restriction switch) could have been administered. Note: The patient could have received a maximum of Ebvallo® with 2 different HLA restrictions (SOT cohort); or Ebvallo® with 4 different HLA restrictions (HCT cohort)

[1] There was no dose adjustment for obesity or for weight changes after baseline.

Indeterminate Response (IR): sponsor's medical monitor consultation required before selecting this response	Administer another cycle of Ebvallo® with same HLA restriction	IR could have been selected as the assessment after cycle 1 only when there was no clinical deterioration, but radiographic assessment showed one of the following: IR1: increase in overall Tumour burden by SPD of ≥50% of up to 6 measurable lesions within the first 12 weeks of therapy initiation OR IR2: Appearance of new lesions or growth of one or more existing lesion(s) ≥50% at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall Tumour burden, as measured by SPD of up to 6 lesions at any time during the treatment OR IR3: Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number [55]
Progressive Disease (PD)	Subsequent cycles with Ebvallo® with different HLA restriction (restriction switch)	If restriction switch resulted in PD, Ebvallo® with different HLA restriction (second restriction switch) If restriction switch resulted in CR/PR/SD, continue with subsequent cycles defined in this table. Note: The patient could have received a maximum of 2 Ebvallo® with different HLA restrictions (SOT cohort); or 4 Ebvallo® with different HLA restrictions (HCT cohort)

Abbreviations: CR, complete response; FDG, ^{18}F-deoxyglucose; HCT, haematopoietic cell transplant; HLA, human leukocyte antigen; IR, indeterminate response; PD, progressive disease; PR, partial response; SD, stable disease; SOT, solid organ transplant; SPD, sum of the product of the diameters

Note: During the 35-day observation period of cycle 1 (at least 1 week after the third dose), if the patient had confirmed PD and the medical monitor had been consulted, restriction switch (i.e., treatment with Ebvallo® with a different HLA restriction) may have been initiated before completion of the observation period for cycle 1

[a] If Ebvallo® was not available with the same restriction, Ebvallo® with a different but appropriate HLA restriction may have been substituted

7.1.1.1.2 Inclusion and Exclusion criteria

The key inclusion and exclusion criteria are shown in Table 10 below.

Table 10. Key inclusion and exclusion criteria for study participation (ALLELE)

Key Inclusion criteria	Key Exclusion criteria
• Prior SOT of kidney, liver, heart, lung, pancreas, small bowel, or any combination of these (SOT cohort); or prior allogeneic HCT (HCT cohort). • Biopsy-proven EBV+ PTLD. • Availability of appropriate partially HLA-matched and restricted tebelecleucel confirmed by the sponsor. • Measurable 18F-deoxyglucose-avid (Deauville score ≥3) systemic disease using Lugano classification response criteria [54]. • Treatment failure of rituximab or interchangeable commercially available biosimilar monotherapy (C-SOT-R or C-HCT cohorts) or rituximab plus any concurrent or sequentially administered chemotherapy regimen (C-SOT-R+C) for treatment of PTLD. • Males and females of any age.	• Burkitt lymphoma, classical Hodgkin lymphoma, or any T-cell lymphoma. • Daily steroids of >0.5 mg/kg prednisone or glucocorticoid equivalent, ongoing methotrexate, or extracorporeal photopheresis. • Untreated CNS PTLD or CNS PTLD for which the patient was actively receiving CNS-directed chemotherapy (systemic or intrathecal) or radiotherapy at enrolment. • Suspected or confirmed grade ≥2 GvHD. • Ongoing or recent use of a checkpoint inhibitor agent • For HCT cohort only: active adenovirus viremia. • Need for vasopressor or ventilatory support. • Antithymocyte globulin or similar anti-T-cell antibody therapy ≤ 4 weeks prior to enrolment. • Treatment with EBV-CTLs or chimeric antigen receptor T cells directed against B cells within 8 weeks of enrolment (SOT or

- Eastern Cooperative Oncology Group (ECOG) performance status ≤3 for patients aged ≥16 years; Lansky score ≥20 for patients <16 years.
- For HCT cohort only: if allogeneic HCT was performed as treatment for an acute lymphoid or myeloid malignancy, the underlying primary disease for which the patient underwent transplant must have been in morphologic remission.
- Adequate organ function.
- Patient or patient's representative was willing and able to provide written informed consent.

HCT cohorts) or unselected donor lymphocyte infusion within 8 weeks of enrolment (HCT cohort only).

- Female who was breastfeeding or pregnant, or female of childbearing potential, or male with a female partner of childbearing potential unwilling to use a highly effective method of contraception.
- Inability to comply with study-related procedures.

7.1.1.2 RS002

Observational real-world data were collected (Study RS002) to create a control arm for the single arm study ALLELE. The data were collected retrospectively in the time span of over 20 years. The objective of this analysis was to compare OS in patients treated with Ebvallo® in the study ALLELE with the control arm of subjects who received standard of care treatment for EBV+ PTLD.

7.1.1.2.1 Study design

This study is a large, descriptive, multinational, multicentre, non-interventional retrospective chart review of two patient cohorts: post-allogeneic HCT and post-SOT patients with biopsy-proven EBV⁺ PTLD. This study is still ongoing. Analysis was conducted separately for post-HCT and post-SOT cohorts. Data were collected for patients with biopsy-proven EBV⁺ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018. The study sites for this study span across 9 countries and 29 centres in North America (6 in the USA, 3 in Canada) and Europe (6 in France and 6 in Spain, 4 in Italy, 1 in Austria, 1 in Belgium, 1 in Germany, and 1 in Sweden) [33].

The database was locked on 26 January 2021, which is the data cut-off of the results presented in this application. The conduct of the study was standardised, with processes similar to those for clinical trials.

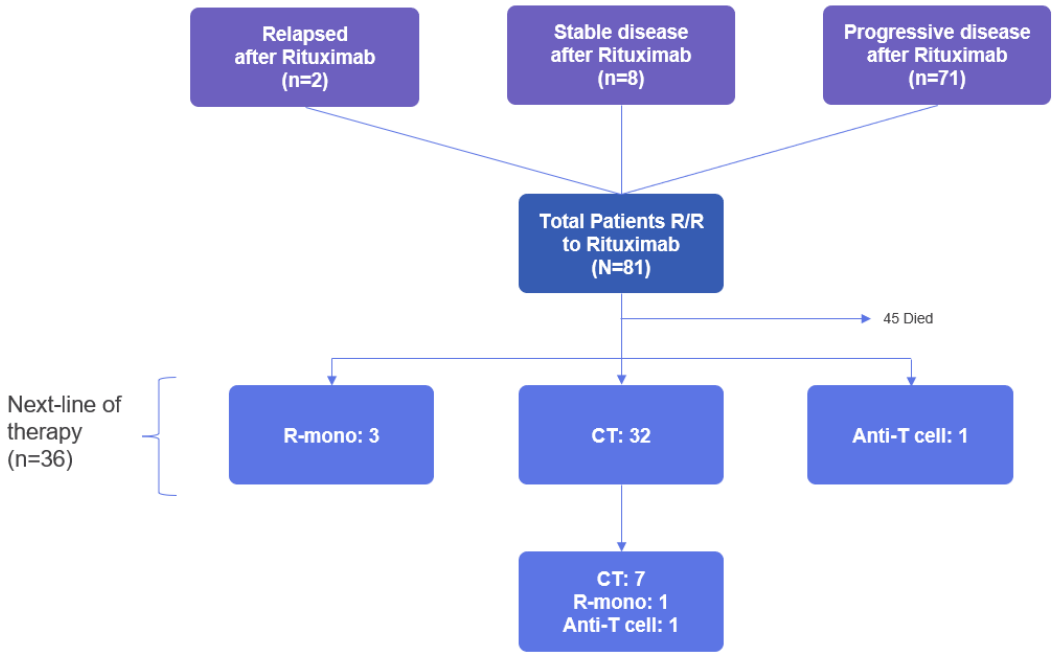
The endpoint of the RS002 study was OS. OS was measured from the date of PTLD diagnosis, the date patients relapsed and/or were refractory to first-line treatment (rituximab +/- chemotherapy), and the date of initiation of next-line therapy to death from any cause. In contrast to other endpoints, OS can be accurately assessed in a real-world setting.

The ALLELE cohort of patients with EBV⁺ PTLD following SOT who relapsed and/or are refractory to rituximab only does not illustrate the SOT population under Ebvallo® indication for which 'chemotherapy is considered inappropriate'; this was not a pre-defined criterion of the ALLELE trial for this cohort; this cohort was hence not considered for the European Medicine Agency positive benefit-risk assessment conclusion leading to the approved indication for Ebvallo®.

In this context, it was not possible to use data from the RS002 study for SOT patients for which chemotherapy is considered inappropriate and to compare it with ALLELE; this patient population not being appropriately available in the ALLELE trial. For this reason, results presented for the RS002 study will focus on patients included in the indirect comparison between ALLELE and RS002 studies: HCT patients who had failed rituximab; and SOT patients who had failed rituximab plus chemotherapy, with an index date between 2010 and 2018.

The descriptions of each subgroup (C-HCT and C-SOT-R+C) are presented in Figure 4-Figure 5 and Figure 6-Figure 7, respectively.

Figure 4. C-HCT subgroup treatment description 2000-2018*



*2 patients were removed from the ITC after achieving partial response following rituximab + chemotherapy, and chemotherapy followed by rituximab respectively.

Figure 5. C-HCT subgroup treatment description 2010-2018

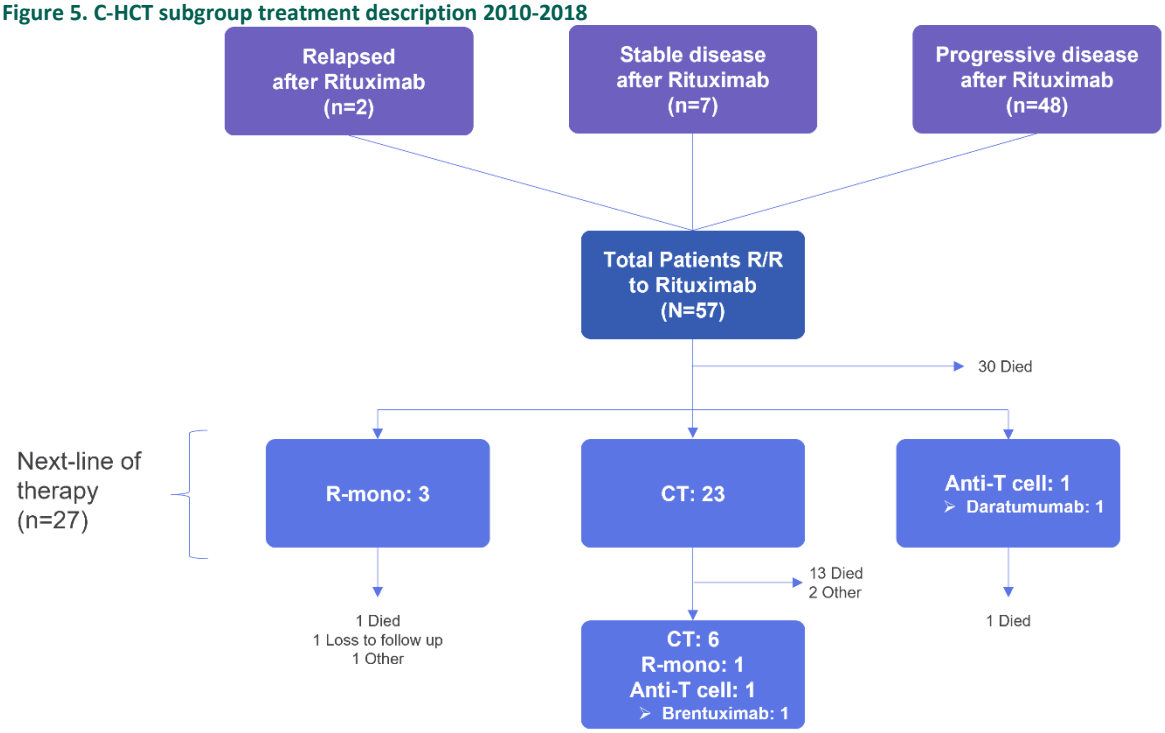
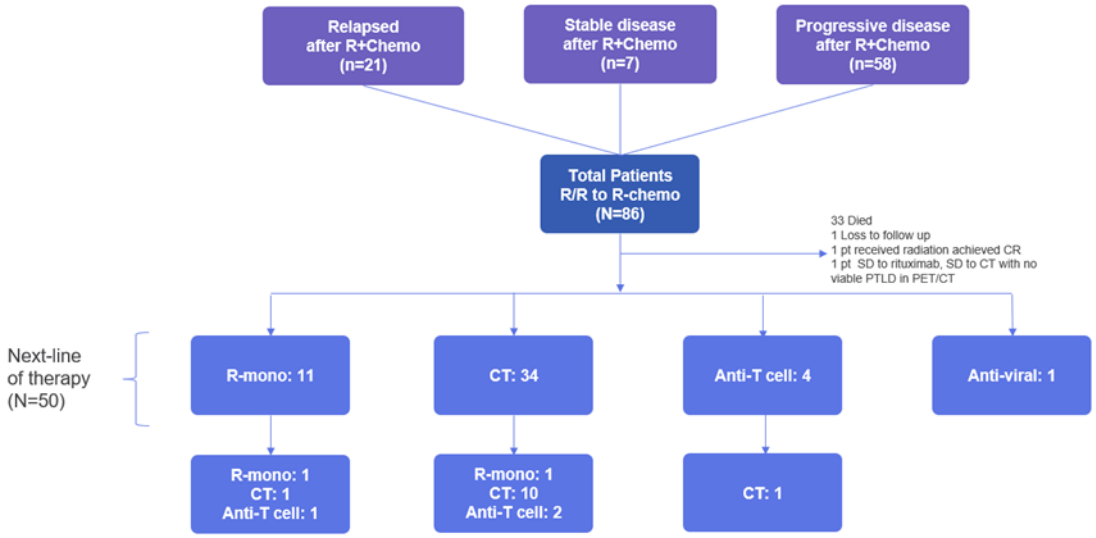
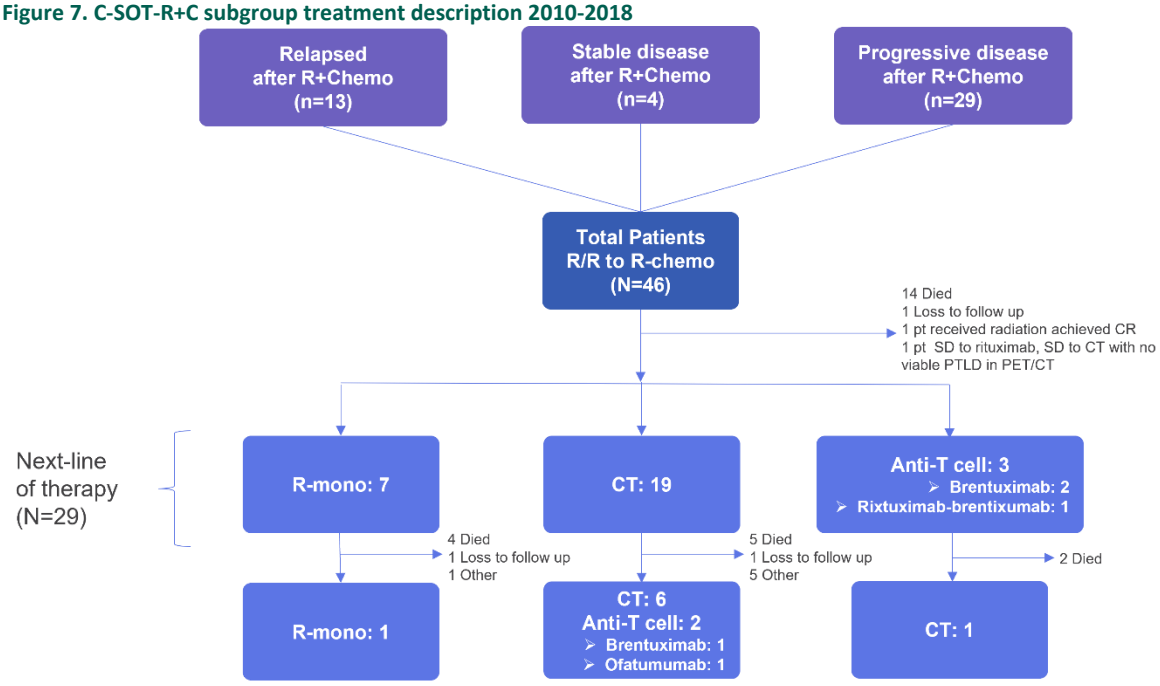


Figure 6. C-SOT-R+C subgroup treatment description 2000-2018*



*2 patients were removed from the ITC after achieving partial response following rituximab + chemotherapy, and chemotherapy followed by rituximab respectively.

Figure 7. C-SOT-R+C subgroup treatment description 2010-2018



7.1.1.2.2 Inclusion and exclusion criteria

Clinical data from any male or female patient of any age diagnosed with EBV+ PTLD after allogeneic HCT (C-HCT) or SOT (C-SOT), including SOT subjects who had failed rituximab and chemotherapy (C-SOT-R+C), were recruited into the study from 01 January 2000 and 31 December 2018. More specific patient selection criteria were applied to define key patient population for each objective. Notably, the key exclusion criteria were aligned with the ALLELE study.

7.1.2 Efficacy and safety – results per study

7.1.2.1 Results from ALLELE

Ebvallo® is indicated for the treatment of patients above 2 years old with EBV+ PTLD who have received at least one prior therapy. For SOT patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate. The two cohorts of ALLELE – HCT cohort after patients are relapsed and/or refractory to rituximab, and SOT cohort after patients are relapsed and/or refractory to rituximab and chemotherapy – informed the efficacy of Ebvallo® when assessed by the EMA, were the ones allowing a positive benefit-risk assessment conclusion from the EMA, and hence correspond to the indication of Ebvallo®. The SOT cohort after patients are relapsed and/or refractory to rituximab only does not correspond to a population of patients for which chemotherapy is considered inappropriate; this is not a pre-defined criterion of ALLELE. Even though the SOT-R cohort does not correspond to the indication for Ebvallo® and efficacy results from this cohort should not be considered, safety results from this cohort are part of the safety data package for Ebvallo®.

Efficacy results are presented for the latest data cut-off of 29 July 2022 with focus on the following subject cohorts that corresponds to the indication of Ebvallo® and are the focus in this assessment:

- C-HCT: patients with EBV+ PTLD following HCT (relapsed and/or refractory to rituximab).
- C-SOT-R+C: patients with EBV+ PTLD following SOT (relapsed and/or refractory to rituximab and chemotherapy).

The EMA assessment is based on the data cut-off from November 2021, for which results are presented in Appendix K Results from the November 2021 data cut-off.
All enrolled patients had received at least one dose of Ebvallo® and were included in the FAS (i.e., FAS population); therefore, the number of patients in the FAS is the same for the all-enrolled analysis set (which is also known as the intent-to-treat population). As the overall population includes the cohort excluded by EMA for the efficacy evaluation, it is not considered for this evaluation.

Table 11. Analysis sets (cut-off 29 July 2022)

	C-SOT-R	C-SOT-R+C	Total C-SOT	C-HCT	Overall Total [C-PTLD]
All Enrolled Analysis Set	14	19	33	20	53
Full Analysis Set	14	19	33	20	53
Evaluable Analysis Set	13	19	32	20	52

Abbreviations: C-HCT, patients with EBV$^+$ PTLD following HCT; C-SOT, patients with EBV$^+$ PTLD following SOT; C-SOT-R, patients with EBV$^+$ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV$^+$ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; HCT, haematopoietic cell transplant; SOT, solid organ transplant
All Enrolled Analysis Set included patients whose study eligibility was confirmed and who were enrolled into the study
Full Analysis Set consists of all patients who received at least one dose of Ebvallo®
Evaluable Analysis Set consists of all patients who received >1 dose of Ebvallo® and had >1 evaluable post-baseline disease assessment per IORA, or discontinued the study, or received non-protocol anti-PTLD therapy

Efficacy results in the upcoming sections are presented per IORA. The results are for the latest data cut-off, 29 July 2022 and presented for the FAS for all cohorts. The cohorts of interest (i.e., C-SOT-R+C, C-HCT) are emphasized.

7.1.2.1.1 Demographic and Baseline characteristics

The main demographics and baseline characteristics for the FAS are shown in Table 12. The At the time of the data cut-off, 29 July 2022, the median age overall was 44.4 years, and was lower in C-SOT-R+C patients (37.2 years), but higher in the C-HCT patients (49.3 years). The majority of patients (86.8%) were adults ≥18 years of age. Both sexes were well represented (39.6% females and 60.4% males) and there were no important differences between groups in terms of race or ethnicity

Table 12. Demographics and Baseline characteristics (FAS) (cut-off 29 July 2022)

	C-SOT-R (N = 14)	C-SOT-R+C (N = 19)	Total C-SOT (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Sex, n (%)					
Male	10 (71.4)	9 (47.4)	19 (57.6)	13 (65.0)	32 (60.4)
Female	4 (28.6)	10 (52.6)	14 (42.4)	7 (35.0)	21 (39.6)
Race, n (%)					
Asian	0	1 (5.3)	1 (3.0)	1 (5.0)	2 (3.8)
Black or African American	1 (7.1)	0	1 (3.0)	0	1 (1.9)
Native Hawaiian/ Other Pacific Islander	0	1 (5.3)	1 (3.0)	0	1 (1.9)
White	11 (78.6)	17 (89.5)	28 (84.8)	18 (90.0)	46 (86.8)
Other	2 (14.3)	0	2 (6.1)	1 (5.0)	3 (5.7)
Ethnicity - n (%)					
Hispanic/Latino	3 (21.4)	1 (5.3)	4 (12.1)	4 (20.0)	8 (15.1)
Not Hispanic/Not Latino	11 (78.6)	17 (89.5)	28 (84.8)	16 (80.0)	44 (83.0)
Unknown	0	1 (5.3)	1 (3.0)	0	1 (1.9)
Age (years), median (min, max)	52.9 (6.1, 75.7)	37.2 (12.9, 81.5)	42.8 (6.1, 81.5)	49.3 (3.2, 73.2)	44.4 (3.2, 81.5)
Age Category, n (%)					
<17 years	2 (14.3)	2 (10.5)	4 (12.1)	1 (5.0)	5 (9.4)
≥17 years	12 (85.7)	17 (89.5)	29 (87.9)	19 (95.0)	48 (90.6)
<18 years	3 (21.4)	3 (15.8)	6 (18.2)	1 (5.0)	7 (13.2)
≥18 years	11 (78.6)	16 (84.2)	27 (81.8)	19 (95.0)	46 (86.8)
Extranodal disease at screening					
Yes	11 (78.6)	15 (78.9)	26 (78.8)	13 (65.0)	39 (73.6)
No	3 (21.4)	4 (21.1)	7 (21.2)	7 (35.0)	14 (26.4)
Number of lines of prior systemic therapies, median (min, max)	1 (1, 2)	2 (1, 5)	1 (1, 5)	1 (1, 4)	1 (1, 5)

Patient who discontinued treatment					
Disease progression	8 (57.1)	12 (63.2)	20 (60.6)	11 (55.0)	31 (58.5)
Death	4 (28.6)	5 (26.3)	9 (27.3)	6 (30.0)	15 (28.3)
Adverse event	1 (7.1)	3 (15.8)	4 (12.1)	1 (5.0)	5 (9.4)
Additional matched product not available	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Initiation of subsequent non-protocol treatment	1 (7.1)	1 (5.3)	2 (6.1)	0	2 (3.8)
Other[a]	0	1 (5.3)	1 (3.0)	1 (5.0)	2 (3.8)
Withdrawal by patient	1 (7.1)	0	1 (3.0)	1 (5.0)	2 (3.8)

Abbreviations: Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy. Patients with AE preferred term disease progression leading to study treatment discontinuation were considered as discontinuing study treatment due to disease progression [a] The treating physician started non-protocol treatment for small intestinal obstruction

7.1.2.1.2 Objective response rate

The primary efficacy endpoint is ORR following SOT and HCT and is summarised in Table 13 for the latest 29 July 2022 cut-off date for all subjects along with the best overall response (BOR). In the C- PTLD, the ORR rate was 50.9% (95% CI: 36.8, 64.9) per IORA assessment. The BOR per IORA among patients in the C-PTLD was CR for 15 (28.3%, 95% CI 16.8, 42.3) patients and PR for 12 (22.6%, 95% CI 12.3, 36.2) patients.

- In the C-HCT, the ORR rate was 55.0% (95% CI: 31.5, 76.9) per IORA assessment. In the C-HCT (N=20), the BOR was CR for 8 (40.0%, 95% CI 19.1, 63.9) patients and PR for 3 (15.0%, 95% CI 3.2, 37.9) patients

- In the C-SOT R+C, the ORR rate was 47.4% (95% CI: 24.4, 71.1) per IORA assessments. In the C-SOT-R+C (N=19), the BOR was CR for 5 (26.3%, 95% CI 9.1, 51.2) patients and PR for 4 (21.1%, 95% CI 6.1, 45.6) patients

Table 13. Summary of objective response rate (FAS) (cut-off 29 July 2022)

Per IORA	C-SOT-R (N = 14)	C-SOT-R+C (N = 19)	Total C-SOT (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Responders–n (%)	7 (50.0)	9 (47.4)	16 (48.5)	11 (55.0)	27 (50.9)
95% CI	23.0, 77.0	24.4, 71.1	30.8, 66.5	31.5, 76.9	36.8, 64.9
Best Overall Response, n (%)					
CR	2 (14.3)	5 (26.3)	7 (21.2)	8 (40.0)	15 (28.3)
95% CI	1.8, 42.8	9.1, 51.2	9.0, 38.9	19.1, 63.9	16.8, 42.3
PR	5 (35.7)	4 (21.1)	9 (27.3)	3 (15.0)	12 (22.6)
95% CI	12.8, 64.9	6.1, 45.6	13.3, 45.5	3.2, 37.9	12.3, 36.2

SD	2 (14.3)	0	2 (6.1)	3 (15.0)	5 (9.4)
PD	3 (21.4)	8 (42.1)	11 (33.3)	4 (20.0)	15 (28.3)
NE	2 (14.3)	2 (10.5)	4 (12.1)	2 (10.0)	6 (11.3)
p-value (H0: ORR ≤ 20%)[a]	0.0116	0.0067	0.0002	0.0006	<0.0001

Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-SOT, patients with EBV+ PTLD following SOT; C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; CR, complete response; H0, null hypothesis; IORA, independent oncologic response adjudication; NE, includes not evaluable, missing, and indeterminate response (for patients still on study); ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

[a] The p-value is nominal

In the pre-specified subgroups of age (<18 vs ≥18 years, <16 vs ≥16 years), gender (male, female), race (white vs other), ethnicity (Hispanic vs non-Hispanic), and region (North America, Asia Pacific vs Europe), the interpretation of ORR results was limited to the uneven distribution of patients and small samples subgroup sizes. In the sex subgroup, however, males and females were well represented and showed similar ORRs.

7.1.2.1.3 Duration of response

DoR for responders (i.e., those who achieved a CR or PR) per IORA is summarized in Appendix D Efficacy and safety results per study. At the 29 July 2022 cut-off date, the ORR rate was 50.9% (95% CI: 36.8, 64.9) per IORA assessment in the C-PTLD, with a complete response (CR) for 28.3% (95% CI 16.8, 42.3) of patients and partial response (PR) for 22.6% (95% CI 12.3, 36.2) of patients. Median duration of response for responders (i.e., those who achieved a CR or PR) per IORA was 23.0 (95% CI: 3.8, NE) in C-PTLD.

- In the C-HCT, median DOR was 23.0 (95% CI: 1.7, NE) per IORA assessment
- In the C-SOT R+C, median DOR was NE (95% CI: 0.8, NE) per IORA assessments

7.1.2.1.4 Time to treatment and Time to best response

At the 29 July 2022 cut-off date, median TTR was 1.0 month (0.6, 4.7) and median TTBR was 1.1 month (0.6, 9.0) per IORA in the C-PTLD (Table 14).

- In the C-HCT, for the 11 responders, median TTR was 1.0 month (0.6, 4.7) and median TTBR was 1.0 month (0.6, 9.0).
- In the C-SOT-R+C, for the 9 responders, median TTR was 1.1 months (0.7, 4.1) and median TTBR was 1.1 months (0.7, 4.4).

Table 14. Summary of TTR and TTBR – responders only per IORA (FAS) (cut-off 29 July 2022)

	C-SOT-R (N = 7)	C-SOT-R+C (N = 9)	Total C-SOT (N = 16)	C-HCT (N = 11)	Overall Total [C-PTLD] (N = 27)
TTR (months)					
Median (min, max)	2.1 (1.0, 3.0)	1.1 (0.7, 4.1)	1.6 (0.7, 4.1)	1.0 (0.6, 4.7)	1.0 (0.6, 4.7)
TTBR (months)					
Median (min, max)	2.4 (1.0, 7.3)	1.1 (0.7, 4.4)	1.6 (0.7, 7.3)	1.0 (0.6, 9.0)	1.1 (0.6, 9.0)

Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-SOT, patients with EBV+ PTLD following SOT; C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; IORA, independent oncologic response adjudication; TTBR, Time to best response; TTR, time to response

7.1.2.1.5 Overall survival

At the 29 July 2022 cut-off date, median OS was 18.6 months (95% CI: 9.0, NE), with a 1-year survival rate at 60.6% (95% CI: 45.1, 73.0) in the C-PTLD (Table 15).

- In the C-HCT, 35.0% (7/20) of patients died. The median OS was not estimable, with a 1-year survival rate at 66.0% (95% CI: 38.5, 83.5).
- In the C-SOT-R+C, 47.4% (9/19) of patients died. The median OS was 16.4 months (95% CI: 3.5, NE), with a 1-year survival rate at 62.7**%** (95% CI: 37.2, 80.2).

Table 15. Summary of overall survival (FAS) (cut-off 29 July 2022)

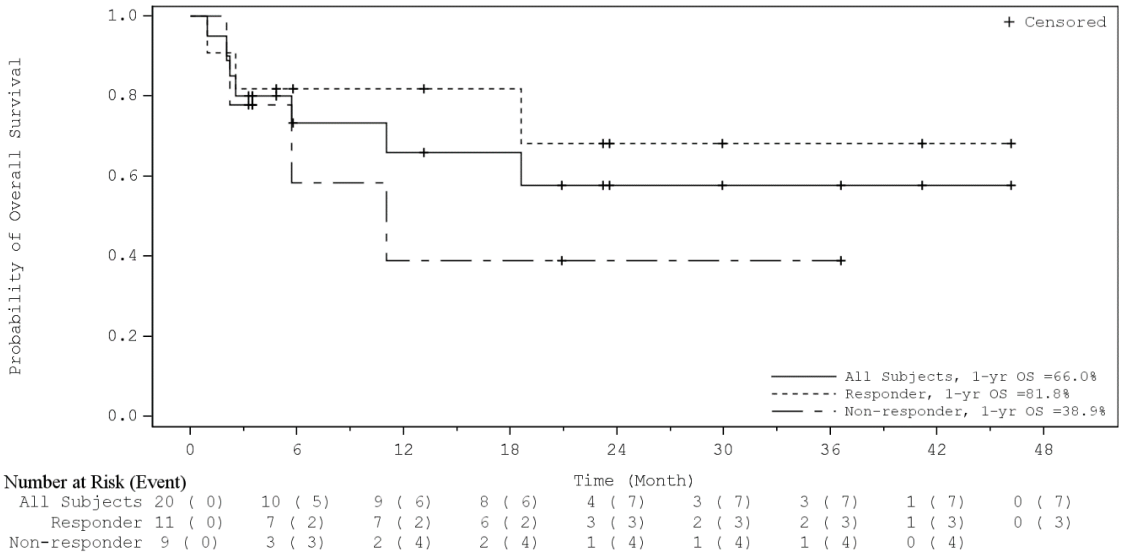
	C-SOT-R (N = 14)	C-SOT-R+C (N = 19)	Total C-SOT (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Status, n (%)					
Death	7 (50.0)	9 (47.4)	16 (48.5)	7 (35.0)	23 (43.4)
Censored	7 (50.0)	10 (52.6)	17 (51.5)	13 (65.0)	30 (56.6)
Follow-up time (months) n					
Median (min, max)	8.4 (0.5, 42.2)	5.9 (0.4, 30.6)	7.8 (0.4, 42.2)	8.4 (1.0, 46.2)	7.8 (0.4, 46.2)
OS estimate (K-M) (months) Median (95% CI)	18.4 (1.8, NE)	16.4 (3.5, NE)	16.4 (5.0, NE)	NE (5.7, NE)	18.6 (9.0, NE)
OS rate (95% CI) (K-M), %					
At 6 months	69.2 (37.3, 87.2)	62.7 (37.2, 80.2)	65.4 (46.2, 79.2)	73.3 (46.8, 88.1)	68.1 (53.1, 79.1)
At 12 months	52.7 (23.4, 75.5)	62.7 (37.2, 80.2)	57.9 (38.5, 73.1)	66.0 (38.5, 83.5)	60.6 (45.1, 73.0)
At 24 months	39.6 (11.9, 66.8)	43.0 (16.6, 67.3)	41.6 (21.6, 60.5)	57.8 (29.8, 78.0)	47.6 (31.3, 62.3)

Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-PTLD, total EBV+ patients enrolled and treated; C-SOT, patients with EBV+ PTLD following SOT; C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; FAS, full analysis set; K-M, Kaplan-Meier; NE, not estimable OS, overall survival

Full Analysis Set consists of all patients who received at least one dose of Ebvallo®; CI was calculated using log-log transformation method

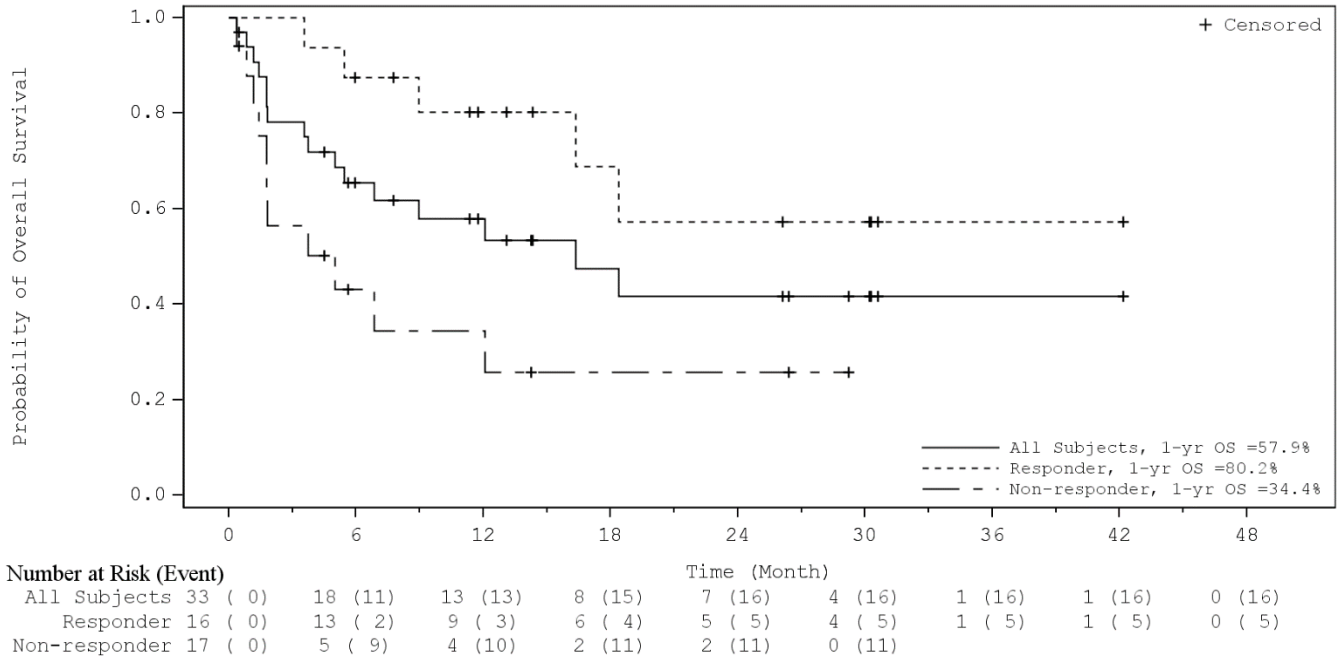
For OS, interpretation by subgroup (ie, by sex, race, ethnicity, age group, and region) is limited due to an uneven distribution of patients and small sample sizes among subgroups; however, OS rates at 1 year were generally similar among subgroups.

Figure 8: Kaplan-Meier plot of overall survival in the C-HCT – responders vs non-responders per IORA (FAS) (cut-off 29 July 2022)



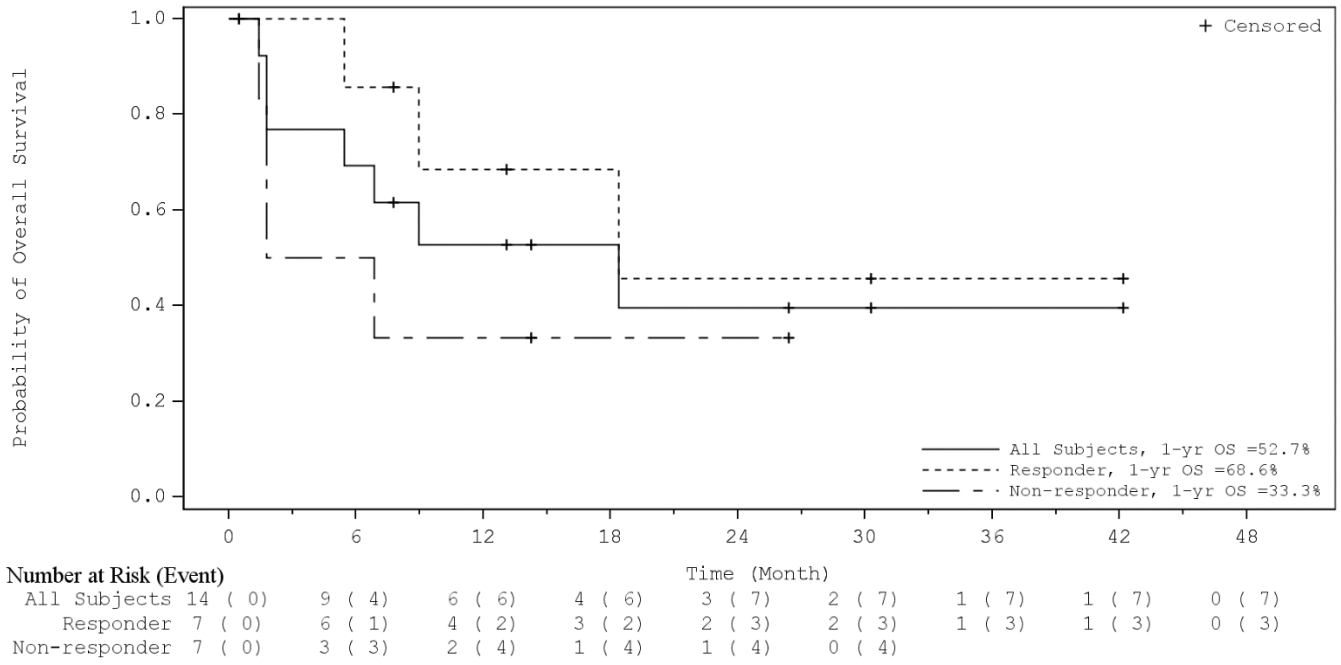
Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; FAS, full analysis set; OS, overall survival
Full Analysis Set consists of all patients who received at least one dose of Tab-cel

Figure 9: Kaplan-Meier plot of overall survival in the C-SOT-Total – responders vs non-responders per IORA (FAS) (cut-off 29 July 2022)



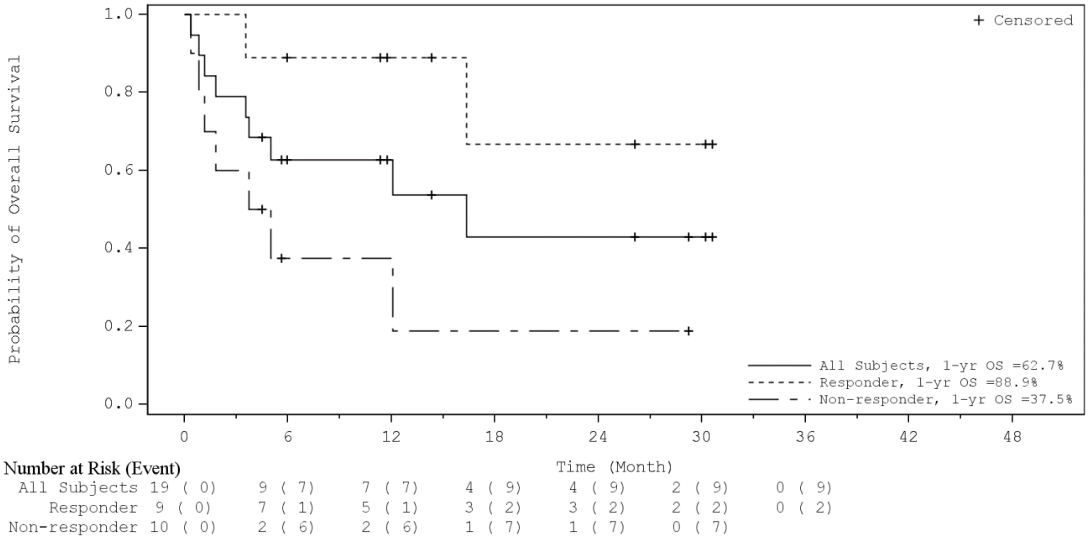
Abbreviations: C-SOT, patients with EBV+ PTLD following SOT; FAS, full analysis set; OS, overall survival
Full Analysis Set consists of all patients who received at least one dose of Tab-cel

Figure 10: Kaplan-Meier plot of overall survival in the C-SOT-R – responders vs non-responders per IORA (FAS) (cut-off 29 July 2022)



Abbreviations: C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; FAS, full analysis set; OS, overall survival
Full Analysis Set consists of all patients who received at least one dose of Tab-cel

Figure 11: Kaplan-Meier plot of overall survival in the C-SOT-R+C – responders vs non-responders per IORA (FAS) (cut-off 29 July 2022)



Abbreviations: C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; FAS, full analysis set; OS, overall survival
Full Analysis Set consists of all patients who received at least one dose of Tab-cel

7.1.2.1.6 Progression-free survival

At the 29 July 2022 cut-off date, 60.4% (32/53) of patients had PFS events in the C-PTLD. The median PFS was 2.7 months (95% CI: 1.4, 16.9) (Table 16).

- In the C-HCT, 55.0% (11/20) of patients had PFS events. The median PFS was 5.8 (95% CI: 1.2, NE).
- In the C-SOT-R+C, 68.4% (13/19) of patients had PFS events. The median PFS was 1.9 months (95% CI: 1.0, NE).

Table 16. Summary of progression-free survival (FAS) (cut-off 29 July 2022)

	C-SOT-R (N = 14)	C-SOTR+C (N = 19)	Total C-SOT (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Status, n (%)					
Events	8 (57.1)	13 (68.4)	21 (63.6)	11 (55.0)	32 (60.4)
Deaths	2 (14.3)	2 (10.5)	4 (12.1)	4 (20.0)	8 (15.1)
Progression	6 (42.9)	11 (57.9)	17 (51.5)	7 (35.0)	24 (45.3)
Censored	6 (42.9)	6 (31.6)	12 (36.4)	9 (45.0)	21 (39.6)
Follow-up time (months) – n					
Median (min, max)	2.5 (0.03, 26.1)	1.9 (0.4, 27.8)	2.1 (0.03, 27.8)	2.9 (0.03, 24.2)	2.3 (0.03, 27.8)
PFS estimate (K-M) (months)					
Median (95% CI)	3.3 (0.9, NE)	1.9 (1.0, NE)	2.4 (1.0, 7.7)	5.8 (1.2, NE)	2.7 (1.4, 16.9)
PFS rate (95% CI) (K-M)					
At 6 months	35.2 (11.2, 60.7)	36.8 (16.5, 57.5)	36.1 (19.8, 52.7)	48.6 (24.1, 69.3)	40.7 (26.8, 54.2)
At 12 months	35.2 (11.2, 60.7)	27.6 (8.8, 50.6)	31.0 (15.1, 48.3)	48.6 (24.1, 69.3)	37.6 (23.7, 51.4)
At 24 months	35.2 (11.2, 60.7)	27.6 (8.8, 50.6)	31.0 (15.1, 48.3)	19.4 (1.5, 52.6)	26.7 (12.1, 43.9)

Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-PTLD, total EBV+ patients enrolled and treated; C-SOT, patients with EBV+ PTLD following SOT; C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; FAS, full analysis set; IORA, independent oncologic response adjudication; K-M, Kaplan-Meier; PD, progressive disease; PFS, progression-free survival. Full Analysis Set consists of all patients who received at least one dose of Ebvallo®; CI was calculated using log-log transformation method.

7.1.2.1.7 Patient reported outcomes

PROs were measured using two instruments: EQ-5D-5L and Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym). For the EQ-5D-5L, visual analog scale (VAS) and utility index values were reported. Summary statistics were provided for actual values and the change from baseline for each of the scores at each time point for FAS patients ≥16 years of age. The same summary of the utility index was also provided for responders (CR or PR) and non-responders per IORA assessment. For the FACT-Lym, the scores for the 5 subscales of the FACT-Lym (physical well-being, social/family well-being, emotional well-being, functional well-being, lymphoma-specific subscale), the FACT-G Total Score, the FACT-Lym Total Score, and the FACT-Lym Trial Outcome Index were calculated per the instrument scoring instruction. Summary statistics were provided for actual values and change from baseline for each of the scores at each time point for FAS patients ≥ 18 years of age. PROs were administered at Day 1 and Day 15 of the first cycle, at Day 1 of each subsequent cycle, at safety follow-up 30 days after last dose, at safety follow-up 180 days after last dose, and at two-year study visit.

Completion rates for EQ-5D-5L VAS and utility scores, and for each subscale of FACT-Lym are presented in Appendix D Efficacy and safety results per study. Numbers are presented by subgroups in the text below the table, while in the table they are presented for the entire cohort.
At baseline, 27/30 (90%) SOT and 18/19 (95%) HCT patients answered the EQ-5D-5L VAS and utility index questionnaires. At baseline, mean scores were similar between SOT and HCT patients. Mean changes from baseline were negative for SOT (indicating a deterioration of quality of life) and positive for HCT patients (indicating an improvement of quality of life) at cycles 2 and 3. At cycle 4, only 10/49 (20%) overall patients answered the questionnaires. At safety follow-ups 30 and 180 days after last dose, mean changes from baseline were always positive for both SOT and HCT patients. Only 9 patients answered the questionnaires at 2-year study visit.
Mean score plots per cycle are represented in Appendix D Efficacy and safety results per study.
At baseline, 26/27 (96%) SOT and 18/19 (95%) HCT patients answered the FACT-Lym questionnaires. At safety follow-up 30 days after last dose, mean changes from baseline were always positive for both SOT and HCT patients and for each subscale. Only 9 patients answered the questionnaires at 2-year study visit. Mean score plot for FACT-LYM total scores is represented in Appendix D Efficacy and safety results per study . Overall, mean changes across time were positive for the HCT cohort, and negative for SOT patients. For the health economic analysis relevant to the submission, only baseline values were considered.

7.1.2.2 Safety results

For the safety analysis of Ebvallo®, EMA considered both the safety results from ALLELE, and the integrated summary of safety (ISS). ISS contains data for subjects with EBV-driven diseases including the supportive clinical studies and all subjects in the Expanded Access Programs (EAPs). Both of these are presented in this document, starting with results from the pivotal trial, ALLELE's latest data cut-off (i.e., 29 July, 2022) and following with the ISS (data cut-off November 2021). The complete EMA report on safety can be found in the European public assessment report (EPAR) [1, 55]. Furthermore, for the safety evaluation, EMA considered the results from all cohorts in ALLELE.

7.1.2.2.1.1 Overview of AEs

Nearly all patients (90.6%) from the study (C-PTLD) experienced treatment-emergent adverse events AEs (87.9% in the C-SOT, 95.0% in the C-HCT). Grade 3+ AEs rates were at 73.6% in the overall population (C-PTLD) and were consistent between C-SOT and C-HCT cohorts (75.8% vs. 70.0%). SAEs rates were at 58.5% in the overall population (C-PTLD) and were consistent between C-SOT and C-HCT cohorts (57.6 vs. 60.0%). On-treatment patient deaths rates were at 15.1% in the overall population while 34.0% of patients experienced AEs leading to treatment discontinuation (Table 17). AEs were considered related to treatment (per investigator assessment) for 37.7% of patients in the overall population (C-PTLD). Among them, 8 patients (15.1%) experienced a grade 3+ AE. There is no treatment-related AE which was fatal or led to treatment discontinuation (Table 17).

Table 17. Summary of patient incidence of treatment-emergent adverse events (FAS) from ALLELE, data cut-off 29 July 2022

Number (%) of patients with	C-SOT-R (N = 14)	C-SOTR+C (N = 19)	Total (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Any AE	11 (78.6)	18 (94.7)	29 (87.9)	19 (95.0)	48 (90.6)
Worst grade ≥3	10 (71.4)	15 (78.9)	25 (75.8)	14 (70.0)	39 (73.6)
Serious	8 (57.1)	11 (57.9)	19 (57.6)	12 (60.0)	31 (58.5)
Fatal	1 (7.1)	4 (21.1)	5 (15.2)	3 (15.0)	8 (15.1)
Leading to study treatment discontinuation	5 (35.7)	6 (31.6)	11 (33.3)	7 (35.0)	18 (34.0)
Leading to study treatment withheld	6 (42.9)	2 (10.5)	8 (24.2)	3 (15.0)	11 (20.8)

Leading to interruption of study treatment injection	0	0	0	0	0
Any AE related to study treatment	6 (42.9)	8 (42.1)	14 (42.4)	6 (30.0)	20 (37.7)
Worst grade ≥3	4 (28.6)	3 (15.8)	7 (21.2)	1 (5.0)	8 (15.1)
Serious	2 (14.3)	2 (10.5)	4 (12.1)	1 (5.0)	5 (9.4)
Fatal	0	0	0	0	0
Leading to study treatment discontinuation	0	0	0	0	0
Leading to study treatment withheld	1 (7.1)	0	1 (3.0)	0	1 (1.9)
Leading to interruption of study treatment injection	0	0	0	0	0

Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-SOT, patients with EBV+ PTLD following SOT; C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; AE, treatment-emergent adverse event

Note: Treatment-emergent adverse events include any AE that occurred on or after first dose date of Ebvallo® through 30 days after last dose of Ebvallo® or any related AE with date of onset on or after first dose date of Ebvallo®.

7.1.2.2.1.2 Treatment-emergent adverse events

TEAEs that occurred in more than 5% of patients in ALLELE, by preferred term, are presented in Appendix D Efficacy and safety results per study.

7.1.2.2.1.3 Severity of adverse events

In the 29 July 2022 data cut-off, in the overall population (C-PTLD) 73.6% of patients experienced a grade 3+ AE. This result was consistent between C-SOT and C-HCT cohorts (75.8% vs. 70.0%). Patient distributions among grades were as follow with 41.5% of patients experiencing a grade 3 AE, 17.0% a grade 4 AE and 15.1% a grade 5 AE (Appendix D Efficacy and safety results per study).

7.1.2.2.1.4 Adverse events of special interest

Tumor flare reaction and GvHD are important identified risks, while infusion-related reaction, cytokine release syndrome, transmission of infectious agents, marrow or organ rejection, immune effector cell-associated neurotoxicity syndrome (ICANS), immunogenicity, and decrease in cell viability due to inappropriate handling of the product are important potential risks. At the 29 July 2022 cut-off date, in the C-PTLD, 5 patients (9.4%) experienced AEs of potential risks. These included two AE of organ rejection in the C-SOT and three AE of GvHD (1 acute, 1 chronic, 1 unknown) in the C-HCT. No patients experienced identified risk of tumour flare reactions or potential risks of infusion-related reactions, cytokine release syndrome, marrow rejection, transmission of infectious disease including CMV.

7.1.2.2.1.5 Fatal adverse events

In total, there were 8 (15.1%) patients who experienced fatal AEs in the latest data cut-off (i.e., 29 July 2022). More specifically, there was 1 (7.1%) patient in the C-SOT, 4 (21.1%) patients in the C-SOT-R+C, and 3 (15.0%) patients in the C-HCT who experienced fatal AEs. According to the Medical Dictionary for Regulatory Activities preferred term, fatal AEs included disease progression for 4 patients (7.5%), and COVID-19, multiple organ dysfunction syndrome, respiratory

failure, and shock for 1 patient each (1.9%) in the overall population (C-PTLD). None of the fatal AEs were considered by the investigator as related to treatment [4].

7.1.2.3 Integrated summary of safety

As part of the EMA assessment, safety was evaluated based on data for all subjects in the pivotal study and an integrated summary of safety (ISS) for subjects with EBV-driven diseases including the supportive clinical studies and all subjects in the Expanded Access Programs (EAPs). In the ISS, data were pooled across all clinical studies for all disease cohorts (EBV$^+$ PTLD and non-PTLD combined), all EBV$^+$ PTLD cohorts, and all non-PTLD disease cohorts. The full report can be found in the EPAR [1]. The data cut-off for the ALLELE study included in the ISS is November 2021.

While the pivotal study is limited to the proposed indication of EBV$^+$ PTLD, the supportive clinical studies and the Expanded Access Programs also contain patients with other EBV driven diseases. The ISS included 340 patients, of which 202 were recruited in clinical studies and 138 exposed to Ebvallo® through EAPs. This included 52 elderly patients (36 from clinical studies and 16 in EAPs), and 86 paediatric and adolescent patients (45 from clinical studies and 41 in EAPs).

The median dose of Ebvallo® in the ISS was 2×10^6 cells/kg (range: 0.8-3.3) The median number of cycles was 2.0 (range: 1-14) over a median of 1.7 months (range: 0.03-52.5) of treatment. In the total PTLD cohort population (N = 183) across all clinical studies and EAPs, the median dose of Ebvallo® was 2×10^6 cells/kg (range: 0.8-2.4). The median number of cycles was 2.0 (range:1-9) over a median of 1.8 months (range: 0.03-18.5) of treatment.

The demographic characteristics were similar across the studies. About half subjects were females (46.5%). Most subjects were White/Caucasian (64.1%), not Hispanic/Latino (56.5%) with a mean age of 37.8 years (range of 1-84 years, the majority of subjects (80.0%) were ≥ 16 years of age), about 15% were elderly (≥ 65 years). In general, all age groups were represented across EBV$^+$ PTLD and non-PTLD populations except for the children < 2 years of age who were only represented in the non-PTLD population.

7.1.2.3.1 Treatment-emergent adverse events

TEAE 11-130 and 95-024 (i.e., the 2 EAPs). Because EBV-CTL-201 included other patients than C-PTLD patients, a special category “non-PTLD” has been included and corresponds to all patients having EBV+ disease (i.e., C-PTLD, C-AID, C-PID, C-VIR, C-LMS, C-LYM, C-NCP, C-OST). Nearly all subjects in Studies ATA129-EBV-302 (ALLELE) and EBV-CTL-201 experienced TEAEs: (96.1%). Most frequently reported TEAEs by preferred term were disease progression, pyrexia, and diarrhoea, followed by fatigue, cough, nausea, and vomiting. TEAEs had a maximum severity of grade 3 for 37 (35.9%) subjects, grade 4 for 17 (16.5%) subjects, and grade 5 for 15 (14.6%) subjects. Treatment-emergent adverse event with a maximum severity of grade 4 that occurred in > 1 subject were neutrophil count decreased (reported for 5 subjects [4.9%]), white blood cell count decreased and sepsis (reported for 4 subjects [3.9%] each), lymphocyte count decreased (reported for 2 subjects [1.9%]). Treatment emergent adverse events with a maximum severity of grade 5 that occurred in > 1 subject included disease progression (8 subjects [7.8%]) and multiple organ dysfunction syndrome (reported in 2 subjects [1.9%]).

Treatment-related TEAEs (based on investigator assessment) for ALLELE, and EBV-CTL-201 were reported for 39.8% of subjects. Treatment-related TEAEs with the highest subject number by preferred term were pyrexia, fatigue, hypotension and nausea followed by neutrophil count decreased and diarrhoea. 16.5% of subjects had grade ≥ 3 TEAEs. No fatal treatment related TEAEs were reported. One subject (1.0%) had a treatment related TEAE that led to study discontinuation.

7.1.2.3.2 Severity of AEs

In the ISS population, 57.9% of subjects were reported as having any TESAEs. The most frequently reported system organ classes for those patients were Infections and Infestations (27.4%), General disorders and administration site conditions (24.1%), Respiratory, thoracic and mediastinal disorders (13.2%) and Gastrointestinal disorders (10.9%). The most frequently reported PTs were disease progression (10.9%), pneumonia (10.3%), pyrexia (7.6%), sepsis (4.7%), febrile neutropenia (4.1%), respiratory failure (4.1%), death (3.8%), acute kidney injury (2.9%), and device related infection (2.9%).

7.1.2.3.3 Deaths

In the pivotal study ALLELE, a total of 18 subjects (41.9%) died; 5 subjects (11.6%) had a fatal TESAE, and 13 subjects (30.2%) died due to other causes. By PT, fatal TESAEs included disease progression (3 subjects [7.7%]), multiple organ dysfunction syndrome (1 subject [2.6%]), and respiratory failure (1 subject [2.6%]). None of the fatal TESAEs were considered by the investigator as related to treatment.

Across all 4 clinical studies and Expanded Access Programs, 71 fatal TESAEs were reported (20.0%). The most frequent fatal TESAEs were disease progression and death, in all cohorts, followed by pneumonia and pneumonia adenoviral. None of the fatal TESAEs were considered related to treatment except one subject in the Expanded Access Programme (C-HCT cohort) had 2 grade 5 TESAEs (Enterococcal infection and Citrobacter bacteraemia) that were considered possibly related to Ebvallo® by the investigator.

7.1.2.4 Results from RS002

RS002 collected data primarily on the efficacy of available treatments for EBV+ PTLD patients, with either SOT following treatment with rituximab and chemotherapy and HCT patients. No safety data was collected. The safety data used in the model is described in section 8.2.2.5.

7.1.2.4.1 Demographic and baseline characteristics

Demographic and baseline characteristics are summarized for the two comparator arms in Table 18. The characteristics for patients in RS002 are presented for those included in the timeframe 2010 to 2018. At the index date, patients in the pivotal study ALLELE had a median age of 42.4 years and 17 of 39 (43.6%) were female. For patients selected for the external control arm (Study RS002), the median age at the time of PTLD diagnostic was 44.1 years and 22 of 55 (40.0%) were female.

The onset of PTLD occurred early (≤ 100 days from the time of HCT or ≤ 2 years from the time of SOT) for 43.6% of patients in the pivotal study ALLELE and for 47.3% of patients in Study RS002; the PTLD had spread to extranodal sites for 71.8% of patients in the pivotal study ALLELE and 61.8% of patients in Study RS002. Rituximab or rituximab plus chemotherapy was the only prior PTLD therapy for 56.4% of patients in the pivotal study ALLELE and 69.1% of patients in Study RS002; two or more prior therapies were reported for 43.6% of patients in the pivotal study ALLELE and 30.9% of patients in Study RS002.

Table 18: Characteristics of the study populations at PTLD diagnostic

Characteristics	RS002 (N=55*)	ALLELE (N=39)
Age at index date		
Median (Q1, Q3)	44.1 (32.6, 60.1)	42.4 (24.0, 65.1)
Min, Max	3.3, 73.6	3.2, 81.5
Female, n (%)	22 (40.0)	17 (43.6)
Extra nodal sites of PTLD, n (%)	34 (61.8)	28 (71.8)
Early PTLD onset, n (%) †	26 (47.3)	17 (43.6)
Response to initial RTX treatment, n (%)		
Responders (CR+PR),	17 (30.9)	14 (35.9)
Non-responders (SD+PD)	38 (69.1)	25 (64.1)
No. of prior therapies, n (%)		
1	38 (69.1)	22 (56.4)
≥2	17 (30.9)	17 (43.6)

† Defined according to time from transplant to PTLD diagnosis: early onset (late onset) was defined as ≤100 (>100) days for HCT patients, and ≤ 2 (>2) years for SOT patients. *One patient from the SOT-R+C cohort from RS002 was not included in the ITC because this patient achieved partial response following rituximab + chemotherapy.

7.1.2.4.2 Transplant characteristics

Transplant characteristics, for the cohort of interest to this application of patients registered from 2010 to 2018, are summarized for the two comparator arms in Table 19. In the pivotal study ALLELE, EBV+ PTLD was following haematopoietic cell transplant (HCT) for 51.3% patients and following solid organ transplant (SOT) for 48.7% patients. For SOT patients, the most frequent organ was kidney (36.8%).

In Study RS002, EBV+ PTLD was following haematopoietic cell transplant (HCT) for 49.1% patients and following solid organ transplant (SOT) for 50.9% patients. For SOT patients, the most frequent organ was kidney (20.0%).

Table 19. Transplant characteristics

Characteristics	RS002 (N=55**)	ALLELE (N=39)
Transplant type		
HCT	27 (49.1)	20 (51.3)
SOT	28 (50.9)	19 (48.7)
Transplant organ type*		
Kidney	11 (20.0)	7 (36.8)
Liver	5 (9.1)	0 (0)
Lung	7 (12.1)	1 (5.3)
Heart	3 (5.5)	7 (36.8)
Other	1 (1.8)	0 (0)
Multiorgan†	1 (1.8)	4 (21.1)

* Only for solid organ transplant and “other” is for other single-organ in addition to liver, kidney, lung and heart

† Multiorgan transplant: in RS002, 1 liver/lung; in ALLELE, 2 kidney/pancreas transplants,1 kidney/pancreas/colon/stomach transplant, and 1 bilateral/lung/liver transplant.

*One patient from the SOT-R+C cohort from RS002 was not included in the ITC because this patient achieved partial response following rituximab + chemotherapy.

7.1.2.4.3 Time-related variables

Several time-related variables related to the diagnosis and treatment for both arms are summarized in Table 20. The median time from transplant to PTLD diagnosis was 6.7 months for patients in the pivotal study ALLELE and 6.5 months for patients in Study RS002. The median time from diagnosis to next line of therapy was 3.7 months for patients in the pivotal study ALLELE and 3.8 months for patients in Study RS002.

Table 20: Time-related variables

Variables	RS002 (N=55**)	ALLELE (N=39)
Transplant to PTLD dx, months		
Median (Q1, Q3)	6.5 (3.0, 100.8)	6.7 (3.7, 63.7)

Min, Max	0.9, 334.5	0.6, 282.5
PTLD diagnosis to the index date (next line of therapy), months		
Median (Q1, Q3)	3.8 (1.0, 12.5)	3.7 (1.8, 13.0)
Min. Max	0.1, 77.4	0.7, 190.5

*a prior initiation of rituximab in HCT setting before PTLD diagnosis by biopsy **One patient from the SOT-R+C cohort from RS002 was not included in the ITC because this patient achieved partial response following rituximab + chemotherapy.

7.1.2.4.4 Efficacy results RS002

PTLD was the main cause of death in each cohort:

- In C-HCT, 50 patients (88%) died at the time of data collection, with PTLD accounting for 62% of all deaths.
- In C-SOT-R+C, 30 patients (65%) died at the time of data collection, with PTLD accounting for 67% of all deaths.

7.1.2.4.4.1 Overall survival in C-HCT

In C-HCT, median OS was 2.1, 0.9 and 2.1 months from PTLD diagnosis date, refractory/relapsed date to rituximab, or start date of next line of therapy, respectively (Table 21).

Table 21. OS in C-HCT

	OS – Index Date		
	PTLD diagnosis date (N=57)	R/R date to any rituximab containing therapy (N=57)	Start date of next line of therapy (N=27)
Follow up time (months), median (Range)	2.1 (0.03-107.6)	0.9 (0.03-107.1)	2.1 (0.1-107.1)
KM median OS (months) (95% CI)	2.1 (1.6, 2.6)	0.9 (0.4, 1.7)	2.1 (1.4, 14.5)
KM OS Rate, % (95% CI)			
At 3 months	31.6 (21.6, 46.3)	24.6 (15.6, 38.7)	40.7 (25.9, 64.2)
At 6 months	21.1 (12.7, 34.8)	17.5 (10.0, 30.8)	29.6 (16.6, 53.0)
At 12 months	15.8 (8.7, 28.8)	15.6 (8.5, 28.7)	29.6 (16.6, 53.0)
At 24 months	12.0 (5.9, 24.5)	11.7 (5.7, 24.2)	25.4 (13.2, 48.9)

Less than 12% of patients were alive at 24 months post rituximab failure (Figure 12).

Figure 12. OS from R/R date to rituximab in C-HCT

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

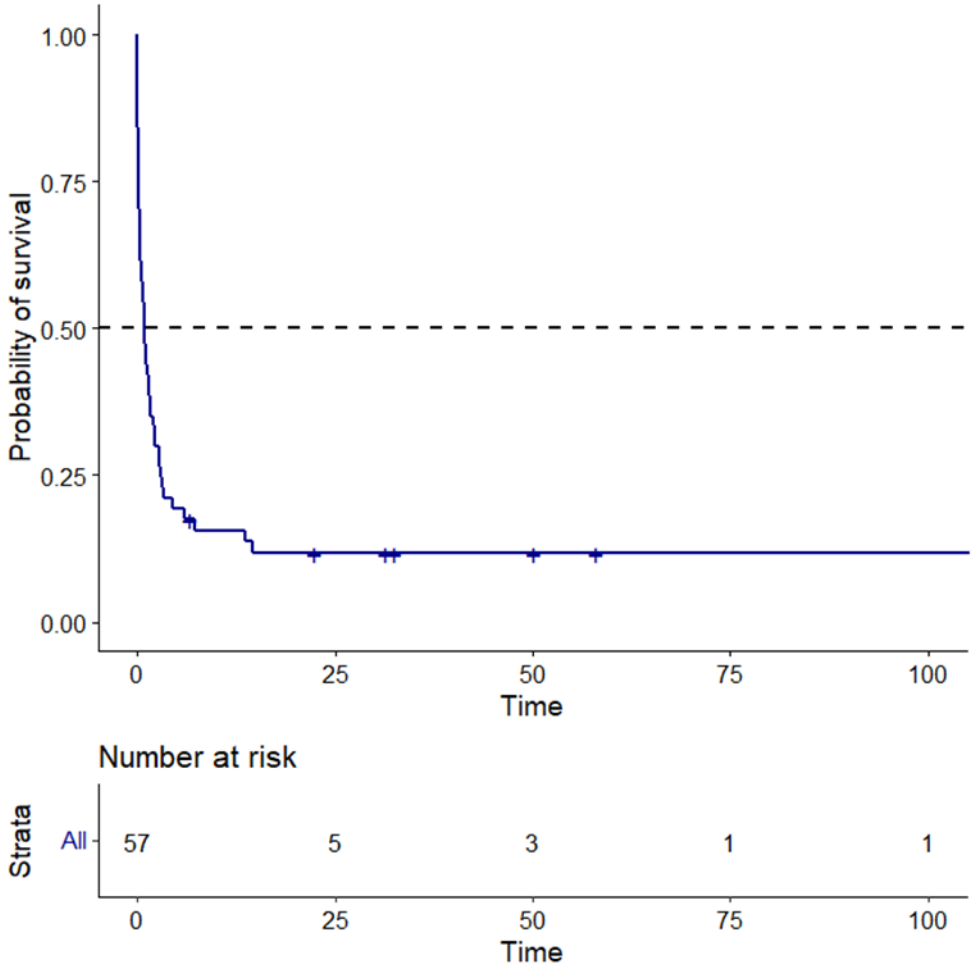


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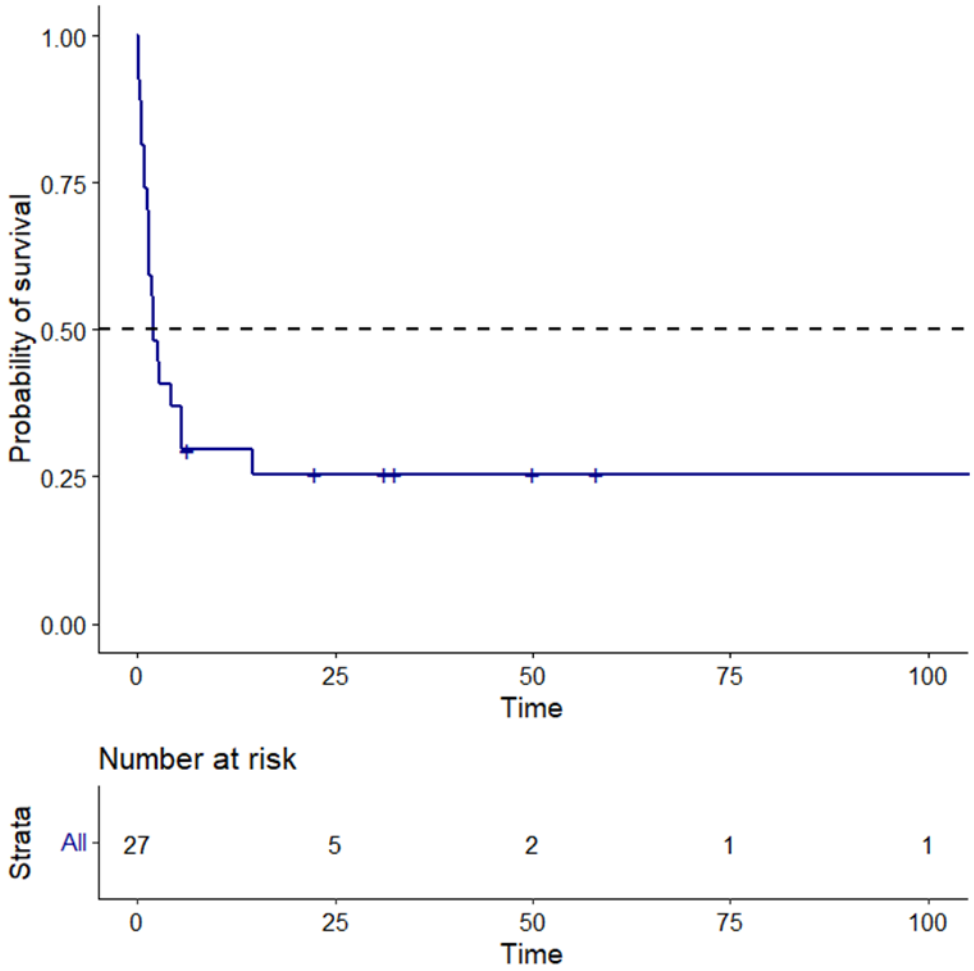
Figure 13. OS from start date of next line of therapy in C-HCT



7.1.2.4.4.2 Overall survival in C-SOT-R+C

In C-SOT-R+C, median OS was 15.9, 4.1 and 19.4 months from PTLD diagnosis date, refractory/relapsed date to rituximab, or start date of next line of therapy, respectively (Table 22).

Table 22. OS in C-SOT-R+C

	OS – Index Date		
	PTLD diagnosis date (N=46)	R/R with R-chemo as systemic treatment and were R/R to any line of R-chemo (N=46)	Start date of next line of therapy (N=29)
Follow up time in months, Median (Range)	13.5 (0.8-116.3)	3.7 (0.03-92.9)	6.9 (0.5, 91.6)
KM Median OS (months) (95% CI)	15.9 (8.7, 62.4)	4.1 (2.3, NA)	19.4 (3.3, NA)
KM OS Rate (95% CI)			
At 3 months	91.3 (83.5, 99.8)	56.2 (43.5, 72.7)	72.1 (57.4, 90.6)
At 6 months	73.6 (61.8,87.6)	44.9 (32.4, 62.0)	60.7 (45.0, 81.9)

At 12 months	59.8 (47.0, 76.1)	39.3 (27.0, 57.0)	52.0 (36.0, 75.2)
At 24 months	34.9 (23.0, 52.9)	36.0 (23.9, 54.3)	46.8 (30.7, 71.5)

Post rituximab and chemotherapy, 36.0% of patients were alive at 24 months (Figure 14).

Figure 14. OS from R/R date to rituximab in C-SOT-R+C

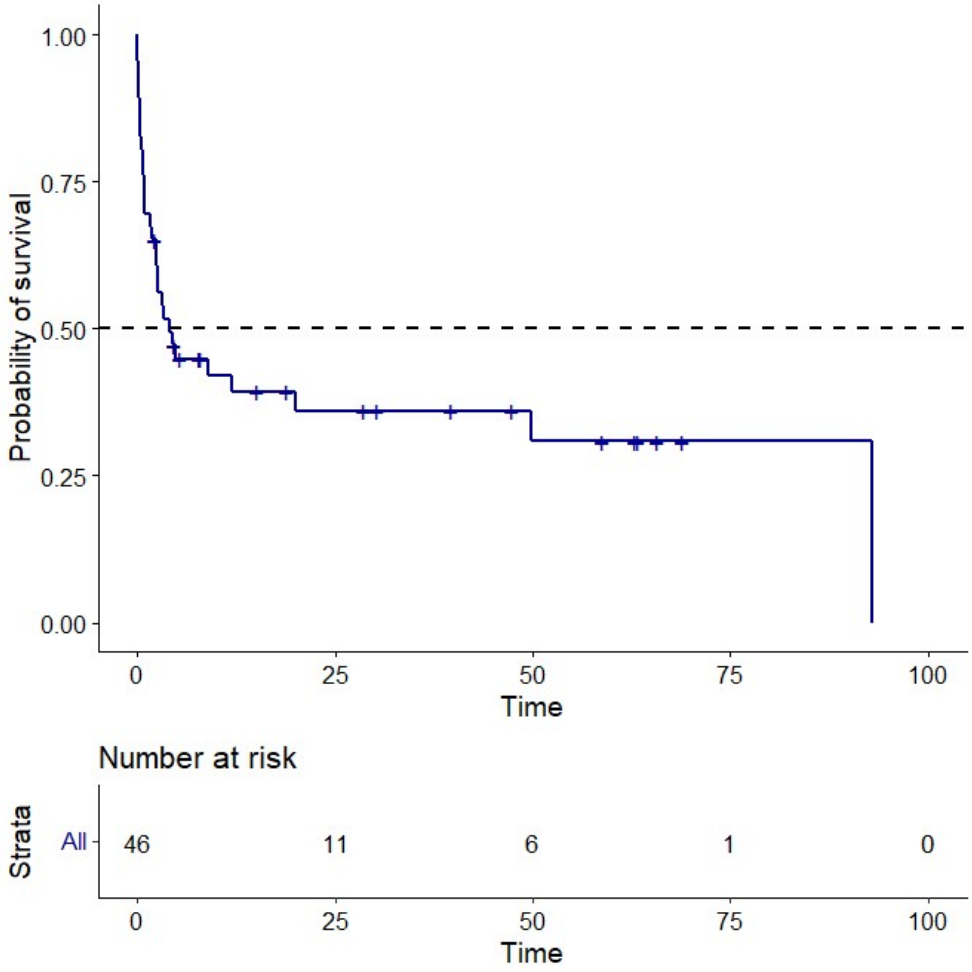
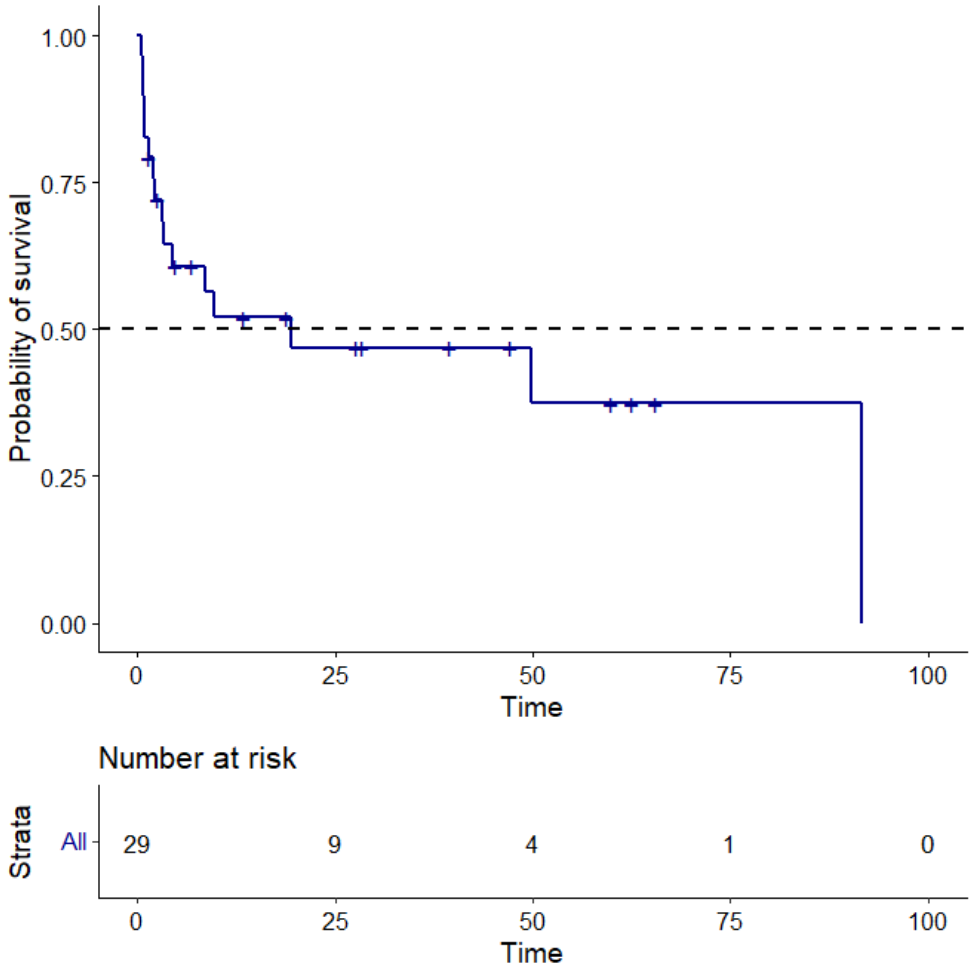


Figure 15. OS from start of next line of therapy in C-SOT-R+C



7.1.3 Comparative analyses of efficacy and safety

7.1.3.1 Method of synthesis

The comparative external control arm for the pivotal study ALLELE was created from the Study RS002 population of patients for whom data were collected through chart review. Baseline characteristics of these patients were compared with those of patients under Ebvallo®'s indication enrolled in the pivotal study ALLELE. To substantially improve the balance of potential confounders between the treatment (Ebvallo®; ALLELE) and control (standard of care; RS002) arms, propensity score (PS)-based standardized mortality/morbidity ratio weighting (SMRW) method was utilized.

A total of 39 patients from the pivotal study ALLELE (with a data cut-off date of 29 July 2022) were included in this analysis (C-SOT-R+C and C-HCT). The 39 patients consisted of 20 patients (51.3%) with EBV⁺ PTLD following HCT who had relapsed or were refractory (R/R) to rituximab prior to study entry and 19 patients (48.7%) with EBV⁺ PTLD following SOT and R/R to rituximab plus chemotherapy prior to study entry. The patients correspond to the marketing authorization patient population.

For the external control arm (Study RS002), a total of 55 patients were included in the analysis, (one patient from the SOT-R+C cohort from RS002 was not included in the ITC because this patient achieved partial response following rituximab + chemotherapy), diagnosed between 2010 and 2018, consisting of 27 patients (49.1%) with EBV⁺ PTLD

following HCT and R/R to rituximab and 28 patients (50.9%) with EBV+ PTLD following SOT and R/R to rituximab plus chemotherapy.
The full methodology of the ITC is described in Appendix F Comparative analysis of efficacy and safety.

Characteristics of study participants at the time of PTLD diagnosis, transplant characteristic, time-related variables and disease risk factors were collected. All continuous variables were summarized using a valid measurement (n), median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. All categorical variables were summarized using frequencies and percentages.

PS-SMRW method was used as follows:

1/ PS was defined as the conditional probability of being treated with Ebvallo® based on prespecified confounders including individual baseline demographic factors and prognostic factors. As compared with an ad hoc randomization in randomized controlled trials (RCTs), PS is a post hoc randomization technique to mimic what happens in RCT situation by balancing covariates at "randomization" point, and thus can substantially reduce the selection bias in observational studies.

Based on a review of the literature, the following prognostic factors were associated with OS and were considered to estimate the probability for patients to "receive" treatment with Ebvallo®, i.e., propensity score:

- Age at diagnosis
- Gender
- Response to Rituximab, initial treatment
- Multi-site bone marrow involvement
- LDH
- Organ type
- PTLD stage
- CNS involvement
- Performance status
- Time from transplant to PTLD
- Reduction of immunosuppression at PTLD diagnosis
- Co-morbidities
- ATG treatment/Anti-IL2 antibody
- Race
- Serum albumin, creatinine, blood counts
- EBV positive
- Transplant/PTLD Era

The final variables were determined based on the literature, data availability (for example, in a real-world setting, ECOG is not assessed on a regular basis, thus, it could not be included), and clinical relevance. These variables were included in a logistic regression model to estimate PS:

- Age
- Gender
- LDH risk
- Onset of PTLD
- Transplant type (HCT vs. SOT)
- Extra nodal sites of PTLD
- No. of lines of prior therapies
- Time from PTLD diagnosis to relapse/refractory date.

2/ PS-based weighting: To make full use of all observations for better precision in the estimation of potential OS benefit of Ebvallo® and to better represent the real-world population with a larger sample size, a PS-based weighting strategy was used instead of PS-based matching (3): Treated patients were given a weight of 1, and control patients were given

a weight of PS/(1-PS). The SMRW method reweights the control patients to be representative of the treated patients, which results in an estimate of the average treatment effect among the treated population (3).

3/ The balance of baseline characteristics was assessed following PS-based weighting. The standardized difference before and after PS-based weighting was assessed for each covariate. As a rule of thumb, a standardized mean difference < 0.1 indicates a good balance. A graphical assessment of the difference in each covariate as well as the PS distribution was also conducted.

7.1.3.2 Propensity score distribution

For further evaluation of baseline comparability, PS was estimated, then PS-based weights were defined, and the covariate balance between patients in the pivotal study ALLELE and Study RS002 was assessed before and after PS adjustment.

The distribution of PS estimated from the logistic regression model showed sufficient agreement between the external control arm (Study RS002; median = 0.432; Q1, Q3: 0.326, 0.474) and the treatment arm (pivotal study ALLELE; median = 0.465; Q1, Q3: 0.379, 0.537) (see Table 81 and Figure 16). The PS overlapped for the majority of total subjects included in the analysis (i.e., 87/94 patients [92.6%] from both pivotal study ALLELE and RS002). The propensity score distribution between the pivotal study ALLELE and Study RS002 is acceptable.

The PS procedure resulted in similar overlap between the Study RS002 and the pivotal study ALLELE populations, with the base case analysis (92.6 vs. 91.9%), the analytical methods were identical to the base case analysis.

Table 23: Estimated conditional probability of receiving treatment

Analysis Variable: p1_PS Estimated Probability							
Treatment	N	Mean	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
RS002	55*	0.393	0.432	0.326	0.474	0.130	0.573
ALLELE	39	0.462	0.465	0.379	0.537	0.164	0.705

*One patient from the SOT-R+C cohort from RS002 was not included in the ITC because this patient achieved partial response following rituximab + chemotherapy.

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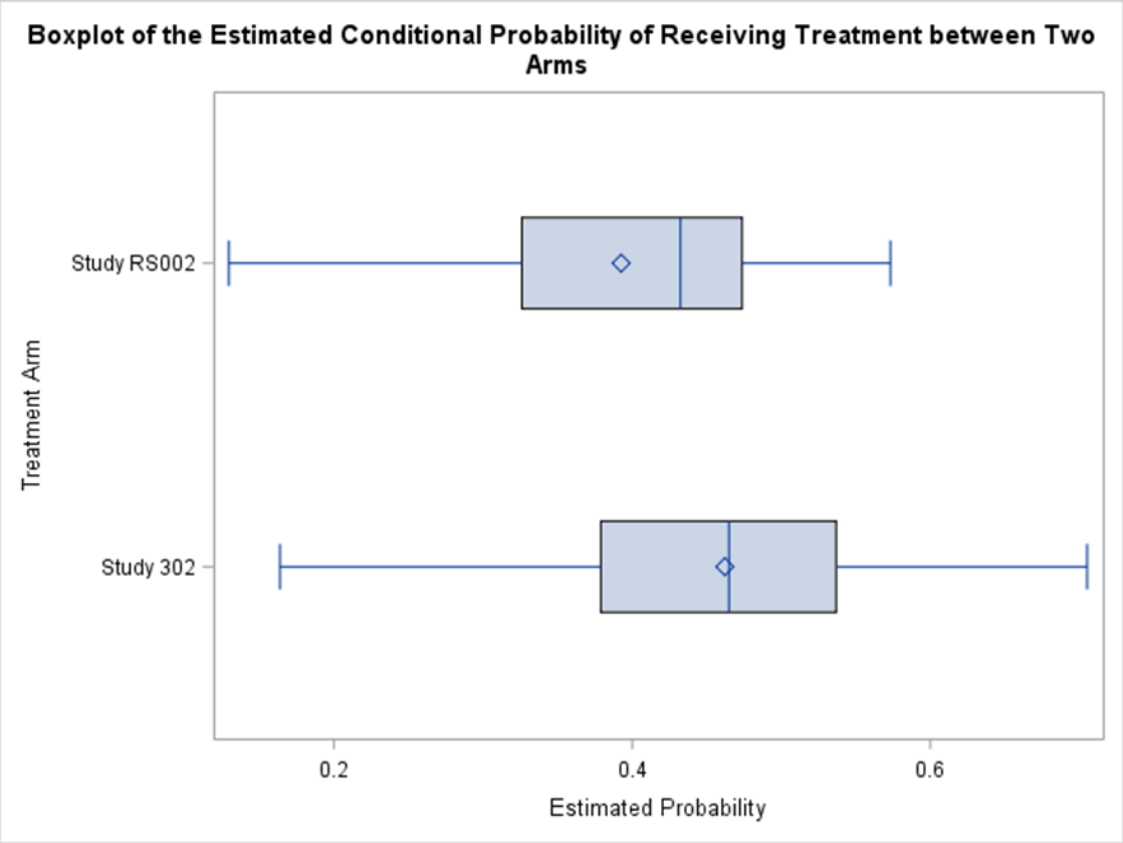
Figure 16: Boxplot of the estimated conditional probability of receiving treatment between the treatment arm and the external control arm. ALLELE = Study 302



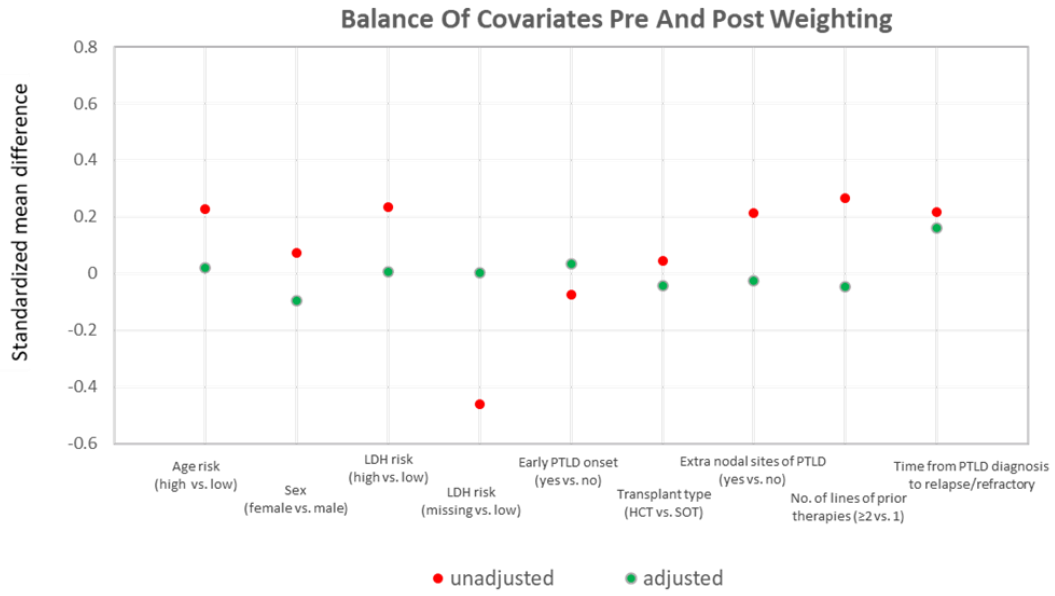
The PSs were then used to estimate weights; the balance of each covariate was evaluated in both pre- and post-weighting scenarios. a standardized mean difference < 0.1 indicates a good balance. Based on the standardized mean difference, the post weighting balance for the baseline covariates was achieved (Table 82 and Figure 40).

Table 24: Comparison of baseline covariates before and after weighting

Covariates	Comparison	Standardized Mean Difference	
		Unadjusted	Adjusted
Age risk	High vs. low	0.228	0.022
Gender	Female vs. male	0.073	-0.095
LDH risk	High vs. low	0.233	0.005
	Missing vs. low	-0.460	0.003
Early onset of PTLD	Early vs. late	-0.074	0.036
Transplant type	HCT vs. SOT	0.044	-0.044
Extra nodal sites of PTLD	Yes vs. no	0.213	-0.024
No. of lines of prior therapies	≥ 2 vs. 1	0.265	-0.046

Time from PTLD diagnosis to R/R	–	0.218	0.160

Figure 17: Comparison of baseline covariates before and after weighting



7.1.3.2.1 Overall survival (OS)

In study RS002, 19 patients out of 55 (34.6%) were censored in study RS002 vs. 23 patients out of 39 (59.0%) in ALLELE. In total, 42 patients (44.7%) were censored. The median OS was estimated to be 4.5 months in the external control arm (95% CI: 2.1, 19.4) and not estimable (95% CI: 5.68, NE) in the treatment arm (see Table 25).

Table 25: Median OS estimated in the treatment arm and the external control arm

Summary of the median survival			
Treatment	**Total**	**Median OS (month)**	**95% CI**
RS002	55**	4.5	2.1, 19.4
ALLELE	39	NE*	5.68, NE
Total	94	11.0	4.3, 36.0

* NE: not estimable, **One patient from the SOT-R+C cohort from RS002 was not included in the ITC because this patient achieved partial response following rituximab + chemotherapy.

Kaplan-Meier analysis showed significantly lower mortality in the patients treated with Ebvallo® compared with patients receiving standard of care in the control arm (see Figure 18). This result was supported by analysis using SMRW method (see Figure 19).

Figure 18: Kaplan-Meier survival estimates between the treatment arm and the external control arm (PS unadjusted). ALLELE = Study 302

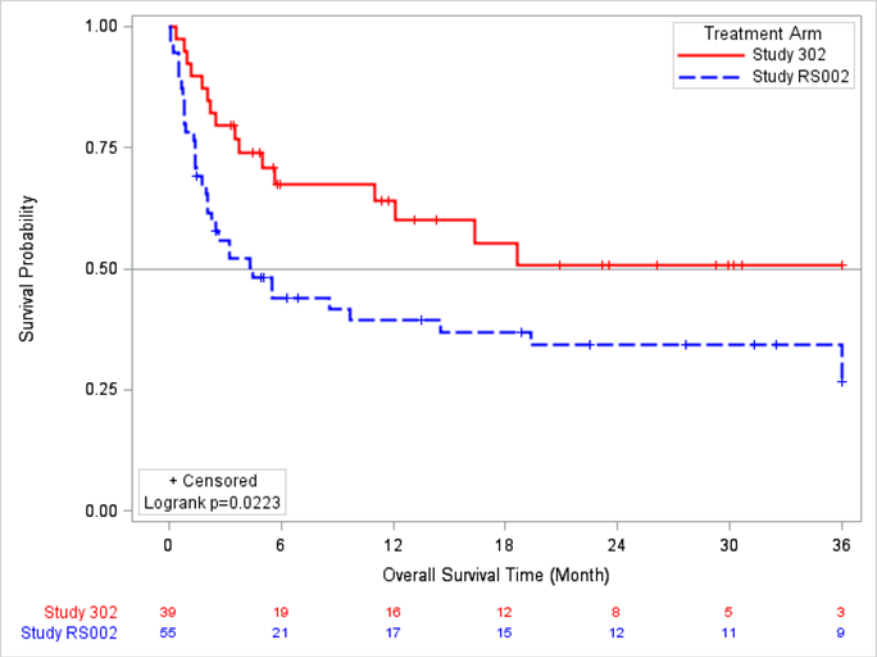
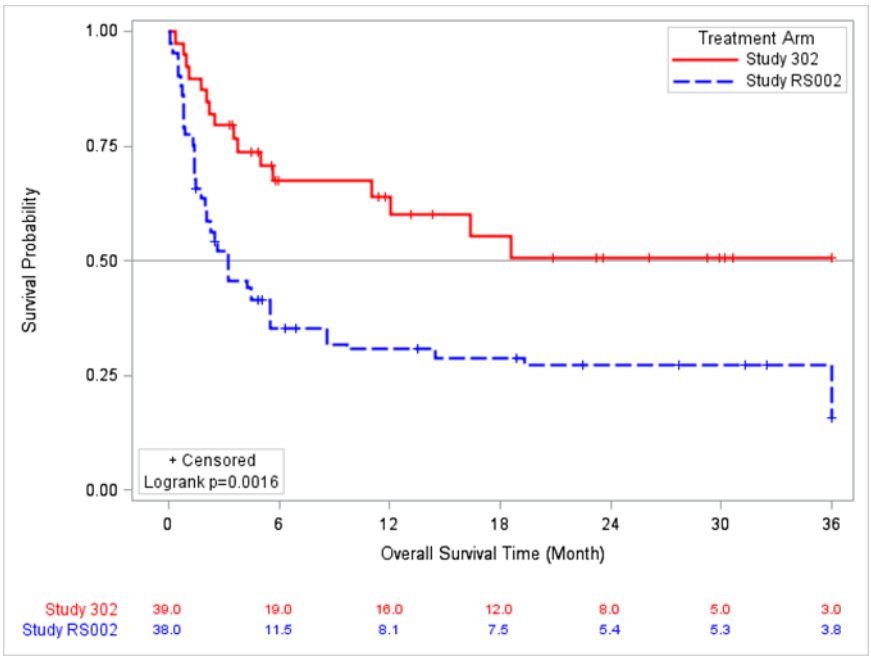


Figure 19: Kaplan-Meier survival estimates between the treatment arm and the external control arm (PS adjusted by SMRW). ALLELE = Study 302



In this analysis of patients treated between 2010 and 2018 in Study RS002, Ebvallo® demonstrates significant OS benefit compared to BSC with an unadjusted HR of 0.51 (95% CI: 0.29, 0.90) (see Table 26). This association was strengthened after adjustment (HR = 0.41; 95% CI: 0.23, 0.72). The results of both unadjusted and adjusted models were consistent and robust.

Table 26: Overall Survival benefit of Ebvallo® compared to Standard of Care

	N_T vs. N_C (39 vs. 55*)	
	HR (95% CI)	P-value
Unadjusted	0.51 (0.29, 0.90)	0.020
Adjusted	0.41 (0.23, 0.72)	0.020

*One patient from the SOT-R+C cohort from RS002 was not included in the ITC because this patient achieved partial response following rituximab + chemotherapy.

As previously discussed, due to the small sample size of each cohort in ALLELE (HCT and SOT), no robust evaluation per cohort can be provided. Similarly, due to the small sample size of each type of standard of care treatment, no robust evaluation per type of standard of care treatment can be provided for meaningful interpretation.

7.1.3.2.2 Discussion and Conclusion

Ebvallo® demonstrated a significant OS benefit compared to BSC with an unadjusted HR of 0.51 (95% CI: 0.29, 0.90) and an adjusted HR of 0.41 (95% CI: 0.23, 0.72). An appropriate method to adjust for differences in important prognostic factors was applied to attain covariate balance between the treatment and control arms. Use of observational data is indeed often associated with various biases such as selection bias, immortal bias, survival bias, and confounding bias. To address those biases, careful consideration was given to selection of the identification of the important prognostic factors, and minimization of missing data. In addition, while descriptive analysis suggests a numeric OS benefit in the HCT and SOT subgroups, the sample size in these subgroups is too small for meaningful interpretation.
Despite all the measures implemented to overcome biases, some associated with observational data may remain (e.g., bias due to unmeasured confounders).

Overall, these results support the contextualization of Ebvallo® efficacy results from the pivotal ALLELE study, compared to standard of care in real-life from study RS002.

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8. Health economic analysis

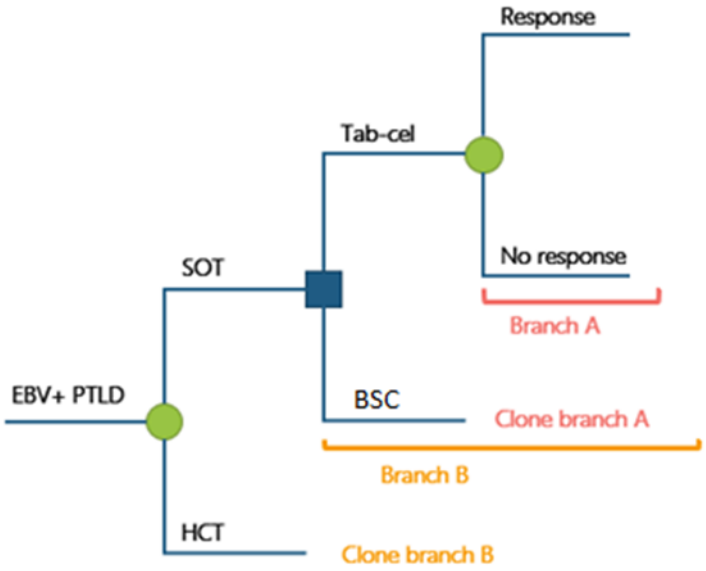
A cost-utility analysis was conducted to estimate the costs and outcomes of treating patients with EBV+ PTLD with Ebvallo® compared to BSC in Denmark. The analysis covered a lifetime horizon and was conducted in accordance with the guidelines published by the Danish Medicines Council (DMC) [56]

8.1 Model

A cost-effectiveness model (CEM) was previously developed in Microsoft Excel® and adapted to fit the Danish setting. The model follows a partitioned survival (PSM) structure with a defined cure point, with patients stratified by transplant type and response status (responder or non-responder). This structure was deemed the most appropriate based on the data available and the widely accepted suitability of the PSM approach in oncology [57].

An overview of the model subgroups is provided below.

Figure 20. Overview of model subgroups



Abbreviations: EBV, Epstein–Barr virus; HCT, haematopoietic stem cell transplantation; PTLD, post-transplant lymphoproliferative disorder; BSC, best supportive care; SOT, solid organ transplantation.

Circles represent chance nodes; squares represent decision nodes.

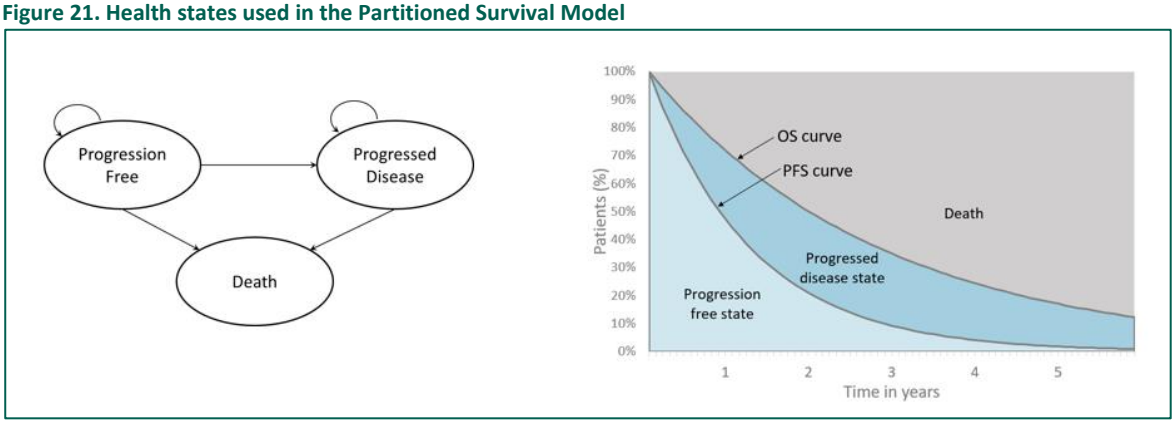
The PSM uses overall survival (OS) and progression-free survival (PFS) data from ALLELE and the hazard ratios from the ITC versus RS002 (for BSC). ALLELE is the pivotal clinical trial for Ebvallo® and RS002 was a descriptive, multinational, multicentre, non-interventional, retrospective chart review study of patients with biopsy-proven EBV+ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory (failed to achieve complete response [CR] or partial response [PR]) or had relapsed at any point after such therapy. Please see prior sections for more detailed information.

The PSM is informed by OS and PFS data stratified by response status (response versus non-response). The decision was made to stratify by response status to give weight to the primary endpoint of ALLELE (ORR). The ALLELE trial reported response status in greater detail than “responder” versus “non-responder” (i.e., complete response, partial response, stable disease and progression), but analysis at this level of granularity resulted in extremely small patient numbers, which limited the feasibility of statistical analysis. Patients were therefore grouped into responders and non-responders. Similarly, separate analysis of HCT and SOT patients resulted in extremely low patient numbers (in many cases $n \leq 5$) for the fitting of parametric models, and some models (e.g., generalised gamma) did not converge. To maximise the data

available for the fitting of parametric survival models, efficacy outcomes (OS and PFS) for HCT and SOT patients were therefore pooled by response status.

In each model cycle, patients are allocated to one of three health states: progression-free (PF), progressed disease (PD), or death. PFS is used to directly inform the occupation of the PF state, whereas health state occupancy for the PD state is determined by subtracting the proportion of patients in the PF state from the proportion of patients alive (informed by OS). The health states used in the model are shown in Figure 21.

Figure 21. Health states used in the Partitioned Survival Model



Abbreviations: OS, overall survival; PFS, progression-free survival.

In the base case analysis, health state occupancy is derived directly from Kaplan–Meier data sourced from the ALLELE study. The model also includes correction based on general population mortality to ensure that the probability of death does not fall below the mortality rate of the general population.

The model considers patients in the progression-free health state beyond a defined time period to be functionally cured of PTLD. Mortality for SOT patients are then modelled using data from Graham et al, 2022 [58] a publication reporting long-term survival for transplant patients, while HCT patients then move onto general population mortality adjusted by a standardized mortality ratio (SMR) [59]. The SMR is estimated based on the mortality of patients that receive a HCT (overall population value) in Martin et al, 2010 [59]. Both sources were validated by a Danish clinical expert [2]. Costs and utility weights are assigned to each health state and multiplied by the time spent alive for each health state to calculate overall outcomes.

8.1.1 Time horizon

A lifetime time horizon was used in accordance with the DMC HTA guidelines [56] as treatment with Ebvallo® is believed to extend survival. Consequently, a time horizon of 50 years was chosen for the analysis based on the starting age (42.3 years) to capture all costs and benefits associated with the treatment over a lifetime horizon.

8.1.2 Discounting

Discounting was applied to both costs and outcomes with current rates from the Danish Ministry of finance [56].

Table 27. Discount rates

Years	Rate
1 – 35	3.5%
36 – 70	2.5%
≥70	1.5%

Source: [56]

8.1.3 Half cycle correction

A half-cycle correction is applied, an average transition of halfway through a cycle (i.e., not at the beginning or end of a cycle).

8.1.4 Model Validation

8.1.4.1 Internal Validation

The model was subjected to an internal validation process in line with ISPOR best practices guidance [60] In addition, the validation an adapted form of the TECH-VER internal validity checklist [61].

8.1.4.2 External Validation

A health economic expert was consulted to assist in the conceptualisation of the economic model. An additional pragmatic validation was conducted by a different external health economic consultant [62].

8.1.5 Key model assumptions

Table 28 below provides an overview of the key assumption made in the development of the model.

Table 28. Overview of key model assumptions

Assumption	Justification
BSC is assumed to comprise of R-CHOP and GDP in equal share.	Treatment options selected in line with Danish clinician feedback and representing potential EBV+ PTLD treatment options of varying intensity [2].
Patients are considered functionally cured if still progression-free at the defined cure points of the analysis	In line with clinician input and ALLELE data [2]. Patients would ultimately be managed according to their transplant type without additional PTLD-related management.
Patients on BSC are assumed to remain on treatment as long as they remain in the progression-free health state or reach the defined cure point in the analysis.	It is reasonable to assume that patients who are progression-free would remain on treatment until reaching the structural cure point or death
Patients on Ebvallo® incur all treatment costs instantaneously on model entry rather than spreading the costs over several weeks as would happen in reality.	This assumption was made to limit the complexity of the model engines – the implication of this assumption is that some Ebvallo® cycles may not be discounted appropriately, leading to a slight overestimation in the costs of Ebvallo®.
Patients cannot move from the progressed disease state back to the progression-free state.	This is in line with the natural history of EBV+ PTLD and is a structural assumption implemented in the model.
HCT and SOT patients experience similar outcomes (response, OS, PFS and DoR) when treated with Ebvallo®	This assumption was made due to data limitations preventing a robust analysis of HCT and SOT patients separately. Differences in long-term outcomes are considered.
Health state resource use is assumed to be in line with those for patients with B-cell lymphoma.	B-cell lymphoma believed to be a suitable proxy for PTLD in the absence of PTLD-specific data which was confirmed by a Danish clinical expert [2].
Subsequent treatment is assumed to be the same as BSC.	This assumption was made due to limited data regarding the choice of subsequent treatment and highly individualized treatment plans. All patients are assumed to receive active treatment, in line with clinician input [2].
Proportional hazards assumed between Ebvallo® and BSC.	This is aligned with diagnostic plots and residuals test.

Average number of cycles is used to capture cycles regardless of HLA restrictions change	In the clinical trial, patients who did not had a response could change to another HLA restriction. To simplify and capture it in the model, the average numbers of cycles across all patients was used.

Abbreviations: BSC, best supportive care; EBV, Epstein-Barr virus; GDP, gemcitabine-dexamethasone-cisplatin; HCT, hematopoietic stem cell transplantation; OS, overall survival; PFS, progression-free survival; PTLD, post-transplant lymphoproliferative disorder; R-CHOP, rituximab-cyclophosphamide, doxorubicin, oncovin, prednisolone; SOT, solid organ transplantation.

8.1.6 Limitations

The model and analysis are associated with certain limitations. Firstly, proxy data was used in certain cases to inform model inputs due to limited data available for EBV$^+$ PTLD and the small number of participants enrolled in the pivotal clinical trial ALLELE. The use of proxy data may increase the uncertainty on how representative the model and analysis are for EBV$^+$ PTLD. Additionally, data needed to be pooled in some cases, such as outcomes for HCT and SOT patients from ALLELE, due to small patient numbers.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The input data regarding clinical effectiveness, adverse reactions and quality of life inputs used for the base case analysis were derived primarily from the pivotal clinical trial ALLELE [63], study RS002 [3] and other literature sources. A clinical expert from Denmark provided validation on the representativeness of ALLELE to the Danish setting [2].

A summary of included clinical inputs is presented in Table 29 below.

Table 29. Summary of clinical inputs included in the model

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	Source
Baseline characteristics			
Age, median (years)	42.30	42.30	[63]
Proportion male (%)	56.40	56.40	[63]
Proportion SOT (%)	48.72	48.72	[63]
Proportion HCT (%)	51.28	51.28	[63]
Health state utility values			
Progression-free health state	0.83	0.83	[64]
Progressed-disease Health state	0.71	0.71	[63]
Adverse events – Ebvallo®			
Anemia	7.55%	7.55%	[63]

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Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	Source
Neutrophil count decrease	15.09%	15.09%	[63]
Fatigue	5.66%	5.66%	[63]
Vomiting	7.55%	7.55%	[63]
Febrile neutropenia	7.55%	7.55%	[63]
Acute kidney injury	7.55%	7.55%	[63]
Sepsis	9.43%	9.43%	[63]
Hypertension	5.66%	5.66%	[63]
Pneumonia	5.66%	5.66%	[63]
Respiratory failure	5.66%	5.66%	[63]
Hypotension	5.66%	5.66%	[63]
Adverse events – BSC			
Anemia	7.54%	7.54%	[65]
Neutropenia	38.12%	38.12%	[65]
Infection	6.86%	6.86%	[66]
Thrombosis	5.88%	5.88%	[66]
Fatigue	9.80%	9.80%	[66]
Vomiting	7.19%	7.19%	[66]
Febrile neutropenia	15.22%	15.22%	[65]
Pneumonia	4.98%	4.98%	[65]
Respiratory failure	2.86%	2.86%	[66]
Leukopenia	10.10%	10.10%	[65]
Hypotension	2.29%	2.29%	[66]
Clinical Effect (outcomes)			
Ebvallo®			
OS	Median: 18.6 months	Median: 18.6 months	[63]
PFS	Median: 2.7 months	Median: 2.7 months	[63]
HR (for survival benefit of Ebvallo®	0.41	0.41	ITC

Abbreviations: OS – Overall Survival, PFS – Progression-free survival

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

8.2.2.1.1 The Danish patient population:

The patient population eligible for treatment with Ebvallo® in Denmark are individuals with EBV+ PTLD following HCT after failure of rituximab or following SOT after failure of rituximab plus chemotherapy. This patient population is in line with the indication for Ebvallo®. The relevant patient population in Denmark was validated by a Danish clinical expert [2]. Additionally, the median age at diagnosis of EBV+ PTLD patients is 42.3 years as verified by the Danish KOL.

8.2.2.1.2 Patient population in the clinical documentation submitted:

The patient population in ALLELE comprised individuals with a median age of 42.3 years, with EBV+ PTLD following SOT after failure of rituximab or rituximab plus chemotherapy, or HCT after failure of rituximab. The proportion of males was 56.40%.

Study RS002 (which informed inputs for the comparator, BSC) comprised a patient population of individuals diagnosed with EBV+ PTLD after HCT after failure with rituximab or SOT after failure of rituximab or rituximab plus chemotherapy.

8.2.2.1.3 Patient population in the health economic analysis submitted:

The patient population included in the health economic analysis were individuals with EBV+ PTLD following HCT after failure of rituximab and SOT following failure of rituximab plus chemotherapy. The starting age was set at 42.30 years and the proportion males was 56.40%.

Table 30. Overview of patient population characteristics

Patient population Important characteristics Baseline	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice
Age, median	42.30 [63]	42.30 [63]	42.30 [2]
Proportion male (%)	56.40 [63]	56.40 [63]	56.40 [2]
Height, mean (cm)	168.86 [63]	168.86 [63]	168.86 [2]
Weight, mean (kg)	65.03 [63]	65.03 [63]	65.03 [2]
BSA, mean (m^2)	1.73 [63]	1.73 [63]	1.73 [2]
Proportion SOT (%)	48.70 [63]	48.70 [63]	48.70 [2]
Heart transplant	52.30 [63]	52.30 [63]	52.30 [2]
Kidney transplant	7.70 [63]	7.70 [63]	7.70 [2]
Liver transplant	30.80 [63]	30.80 [63]	30.80 [2]
Lung transplant	19.20 [63]	19.20 [63]	19.20 [2]
Proportion HCT (%)	51.39 [63]	51.39 [63]	51.39 [2]

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8.2.2.2 Intervention

8.2.2.2.1 Danish clinical practice

The intervention, Ebvallo® (previously described in section 5.3) is expected to be used according to the approved indication and in the relevant population described above, i.e., EBV+ PTLD patients following HCT or SOT who are relapsed/refractory to prior therapy. For SOT patients, prior therapy must include chemotherapy unless chemotherapy is considered inappropriate.

8.2.2.2.2 Clinical documentation submitted

The key clinical documentation for the intervention is based on the pivotal clinical trial ALLELE [63]. Please see section 7.1.1.1 for more detailed information on efficacy and safety.

8.2.2.2.3 Health economic analysis

Inputs relating to the intervention (Ebvallo®) used in the model were primarily informed by the pivotal clinical trial, ALLELE [63]. In the model, treatment with Ebvallo® was implemented based on the ALLELE trial according to the recommended dosage of 2 x 10^6 viable T lymphocytes per kg of body weight, administered as an intravenous injection on days 1, 8 and 15. This is in line with the expected use of Ebvallo® in Denmark. A summary of the intervention is provided in Table 32 below.

In the economic model, the mean number of cycles (each cycle including 3 doses) of treatment as administered in ALLELE are used. The mean number of Ebvallo® treatment cycles stratified by category of response are shown below inTable 31. The average number of treatment cycles for all patients (i.e., 2.56) is used in calculating the cost of treatment for Ebvallo®. The Ebvallo® treatment cycles will serve to inform the relevant treatment costs.

Table 31. Ebvallo® treatment cycles received by response status

Response status	Ebvallo® treatment cycles, mean (SD)		Reference
	C-SOT-R+C	C-HCT	
Responders	3.67 (1.41)	3.00 (1.26)	Post-hoc analysis of ALLELE July 2022 data
Non-responders	1.20 (0.42)	2.44 (1.42)	

Abbreviations: C-HCT, cohort of HCT patients; C-SOT-R+C, cohort of SOT patients who were R/R to rituximab + chemotherapy; SD, standard deviation.

Table 32. Overview of intervention

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	2 x 10^6 viable T lymphocytes per kg of body weight administered as an intravenous injection [63]	2 x 10^6 viable T lymphocytes per kg of body weight administered as an intravenous injection [63]	2 x 10^6 viable T lymphocytes per kg of body weight administered as an intravenous injection.
Length of treatment (time on treatment) (mean/median)*	2.56 cycles [63]	2.56 cycles	2.56 cycles
Criteria for discontinuation	• Any grade GvHD (SOT cohort) or grade ≥ 3 GvHD (HCT cohort) • Grade 3 or greater CRS	Progression or death	Lack of response or toxicity

	• Any grade 4 non-hematologic AE • Pregnancy • Death • Lost to follow-up • Additional Matched Product Not Available • Study terminated by sponsor • Withdrawal of consent • Other Source: [63].		
The pharmaceutical's position in Danish clinical practice	Second line of therapy for HCT patients and third line of therapy for SOT patients.	Second line of therapy for HCT patients and third line of therapy for SOT patients.	Second line of therapy for HCT patients and third line of therapy for SOT patients, as per EMA indication.

*Only 1 patient (2.6%) was still receiving treatment at the end of study follow-up, so average number of doses and cycles can be considered representative.
Abbreviations: C-HCT – Hematopoietic Cell Transplantation cohort, C-SOT-R+C – Solid Organ transplant Rituximab + Chemotherapy cohort, HCT-Hematopoietic Cell Transplantation, SOT – Solid Organ Transplantation.

8.2.2.3 Comparators

8.2.2.3.1 Danish clinical practice

Current clinical practice for the patient population outlined in this dossier includes treatment with rituximab as a monotherapy or a combination of rituximab and chemotherapy. The chemotherapy regimen recommended in published treatment guidelines [56] is CHOP, which comprises cyclophosphamide, doxorubicin, vincristine and prednisone. Additional validation on standard of care in Denmark was received from a Danish clinical expert [2]. The clinical expert validated that additional chemotherapy regimens may be used in Danish clinical practice, namely GDP (cisplatin, gemcitabine, dexamethasone) [2]. More detailed information is presented in section 5.2.2.

8.2.2.3.2 Clinical documentation

The pivotal clinical trial for Ebvallo® was a phase-3, single-arm study [63]. As such, study RS002 (a large, descriptive, multinational, multicenter non-interventional retrospective chart review study of patients with biopsy-proven EBV$^+$ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy) informed the clinical documentation for the comparator (see section 7.1.1.2 for more detailed information) [51].

8.2.2.3.3 Health economic analysis

The comparator in the health economic analysis was validated by a Danish clinical expert [2]. BSC was deemed the most appropriate comparator to Ebvallo® and consists of two chemotherapy regimens: R-CHOP and GDP.

Table 33. Overview of comparator (clinical documentation, Danish clinical practice and health economic analysis)

Drug	Mode of administration	Recommended dose	Frequency during drug cycle	Duration of drug cycle
R-CHOP				
Rituximab	IV	375 mg/m^2	1.00	21 days
Cyclophosphamide	IV	750 mg/m^2	1.00	21 days

Doxorubicin	IV	50 mg/m^2	1.00	21 days
Vincristine	IV	1.4 mg/m^2	1.00	21 days
Prednisone	Oral	50 mg/m^2	5.00	21 days
GDP				
Cisplatin	IV	75 mg/m^2	1.00	21 days
Dexamethasone	Oral	40 mg	4.00	21 days
Gemcitabine	IV	1,000 mg/m^2	1.00	21 days

Source: R-CHOP [48], GDP [49].

The chemotherapy regimens that make up BSC differs slightly between what is presented in the clinical documentation and what is used in Danish clinical practice as well as in the health economic analysis. This difference arose as a result of input and validation from the previously mentioned Danish clinical expert [2]. The clinical expert stated that the chemotherapy regimens used in Danish clinical practice were R-CHOP and GDP [2]. As such, these were included in the model and allocated equally (i.e., 50% each). Additionally, the Danish treatment guidelines recommend only R-CHOP as the chemotherapy regimen to administer, which differed from the input from the clinical expert who suggested additional regimens are used. This is because the treatment guidelines do not make recommendations past 2nd line of treatment.

8.2.2.4 Relative efficacy outcomes

8.2.2.4.1 Clinical documentation

The relative efficacy outcomes used to compare Ebvallo® with BSC were response rates (RR), overall survival (OS), progression-free survival (PFS) and duration of response (DoR). Relative efficacy outcomes were based on an indirect treatment comparison (ITC) between Ebvallo® (ALLELE) and BSC (RS002).

8.2.2.4.2 Danish clinical practice

The efficacy outcomes included in ALLELE and RS002 are reflective of the goals of treatment of patients with EBV$^+$ PTLD and are considered to reflect Danish clinical practice.

8.2.2.4.3 Health economic analysis

The health economic model was populated with key outcomes from the ALLELE clinical trial and RS002 studies [51, 63]. Table 34 presents an overview of the relative efficacy outcomes from the clinical documentation and the health economic analysis.

Table 34. Overview of relative efficacy outcomes

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Overall survival (OS)	Median: 18.6 months	Median: 18.6 months
Progression-free survival (PFS)	Median: 2.7 months	Median: 2.7 months

Source: [51, 63].

8.2.2.5 Adverse events

8.2.2.5.1 Clinical documentation

For the Ebvallo® arm, AE rates were sourced directly from the ALLELE trial [63]. Data were pooled across the HCT and SOT populations, including the C-SOT-R patients, due to limited patient numbers. As disease progression was captured separately, it is not included as an adverse event in the model.

For the BSC arm, AE rates were not collected in RS002, and thus were sourced from the literature, with sources identified via a targeted search (see appendix A for more detail on the literature search). Table 35 below presents the AEs (from both the clinical documentation and used in the model) with their respective rates and source. AEs, for the intervention, are described and discussed in greater detail in section 7.1.2.2 and Appendix E Safety data for intervention and comparator(s).

8.2.2.5.2 Health economic analysis

Due to the paucity of available data, the same rates of AEs were applied across both the HCT and SOT patient populations in the model. In both treatment arms, AEs disutilities were assumed to apply for the first model cycle only. Aes were included in the analysis if they met the inclusion criteria of occurring in ≥5% of patients in any treatment arm and having a severity of grade 3 or greater.

Table 35. Overview of adverse events

Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)
Ebvallo® arm		
Acute kidney injury	7.5% [63]	7.5% [63]
Anemia	7.5% [63]	7.5% [63]
Fatigue	5.7% [63]	5.7% [63]
Febrile neutropenia	7.5% [63]	7.5% [63]
Hypertension	5.7% [63]	5.7% [63]
Hypotension	5.7% [63]	5.7% [63]
Neutrophil count decreased	15.1% [63]	15.1% [63]
Pneumonia	5.7% [63]	5.7% [63]
Respiratory failure	5.7% [63]	5.7% [63]
Sepsis	9.4% [63]	9.4% [63]
Vomiting	7.5% [63]	7.5% [63]
BSC arm		
Anemia	7.5% [65]	7.5% [65]
Neutropenia	38.1% [65]	38.1% [65]
Infection	6.9% [66]	6.9% [66]
Thrombosis	5.9% [66]	5.9% [66]
Fatigue	9.8% [66]	9.8% [66]
Vomiting	7.2% [66]	7.2% [66]
Febrile neutropenia	15.2% [65]	15.2% [65]
Pneumonia	4.9% [65]	4.9% [65]
Respiratory failure	2.9% [66]	2.9% [66]

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Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)
Leukopenia	10.1% [65]	10.1% [65]
Hypotension	2.3% [66]	2.3% [66]

8.3 Extrapolation of relative efficacy

The survival outcomes modelled are OS, and PFS. The base case modelling followed a piecewise approach, in which Kaplan-Meier data was used to model the short-term survival without any extrapolation, and long-term survival data was informed by external sources. As the estimation of survival parameters requires enough data to produce robust results, this was considered the best approach, given the sparsity of the available data, and the low number of patients by response category from the pivotal clinical trial ALLELE. Standard parametric extrapolations were explored in the scenario analysis to address potential uncertainties associated with the piecewise approach, paired with a hybrid model combining both Kaplan-Meier data and standard parametric distributions.

The switch between short-term and long-term survival is defined by the cure point informed by clinical experts [2]. Patients remaining in PFS after a specified number of years are considered to be functionally cured and moved onto long-term survival functions for their respective type of transplant. For HCT, this is defined as general population mortality (as determined by Danish life tables) adjusted via an SMR [59]. The SMR was sourced and estimated for a population of HCT patients. The Danish clinical expert estimated that a 1-year cure point is appropriate for Danish patients, but the SMR of 4.5 times is too high. He stated that a more realistic SMR is between 3 to 3.5 times higher than the general population [2]. These values were tested in a scenario analysis.

For SOT patients, long-term survival data from Graham et al 2022 are used [58]. As only OS data are available from the Graham publication and population life tables, the same hazards were applied to the OS and PFS curves in the model. The general approach to modelling survival is summarized in Table 36 below.

Table 36. Summary of the general modelling approach used in the base case analysis

Transplant type	Cure point, years	Short-term (prior to cure) survival data source	Long-term (following cure) survival data source
HCT	1	ALLELE and RS002 [51, 63], capped* by SMR applied to Danish life tables.	Danish life tables with SMR from Martin et al, 2010 [59].
SOT (heart)	3	ALLELE and RS002 [51, 63], capped* by flexible spline model or Danish life tables.	Flexible spline model for heart transplant, from Graham et al, 2022 [58] capped* by Danish life tables.
SOT (kidney)	3	ALLELE and RS002 [51, 63] capped* by flexible spline model or Danish life tables.	Flexible spline model for kidney transplant, from Graham et al, 2022 [58] capped* by Danish life tables.
SOT (liver)	3	ALLELE and RS002 [51, 63] capped* by flexible spline model or Danish life tables.	Flexible spline model for liver transplant, from Graham et al, 2022 [58] capped* by Danish life tables.
SOT (lung)	3	ALLELE and RS002 [51, 63] capped* by flexible spline model or Danish life tables.	Flexible spline model for lung transplant, from Graham et al, 2022 [58] capped* by Danish life tables.

Abbreviations: HCT, haematopoetic stem cell transplant; SMR, standardised mortality ratio; SOT, solid organ transplant. *Mortality risk may not be lower than the cap.

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8.3.1 Time to event data – summarized:

8.3.1.1 Clinical outcomes for the Ebvallo® arm

Outcomes were stratified by response status as it is a clinically meaningful prognostic factor, and responders and non-responders to treatment can be expected to achieve different outcomes.
The patient population of ALLELE was limited in number (*n*=53). After removal of the prior rituximab monotherapy SOT patients (*n*=14), only 39 patients remained; 4 of these patients did not have an evaluable response, leaving an evaluable population of 35 patients. When patients were split into categories of response based on transplant type, the low numbers of patients in each subcategory meant that it was not feasible to calculate survival outcomes in a reliable manner. This is illustrated in Table 37.

Table 37. Number of patients by response category stratified by transplant type from ALLELE.

Response category	Number of patients (%)	
	C-HCT	C-SOT-R+C
CR	8 (40.0)	5 (26.3)
PR	3 (15.0)	4 (21.1)
SD	3 (15.0)	0
PD	4 (20.0)	8 (42.1)
NE	2 (10.0)	2 (10.5)
All patients	20	19
Evaluable patients	20	19
Source	Table 2.1.1-1.1, ALLELE July 2022 data cut [67]	

Abbreviations: C-HCT, cohort of HCT patients; CR, complete response; C-SOT-R+C, cohort of SOT patients who were R/R to rituximab + chemotherapy; HCT, hematopoietic stem cell transplant; NE, not evaluable; PD, progressed disease; PR, partial response; SD, stable disease; SOT, solid organ transplant.

Patients were grouped into responders versus non-responders to increase the number of patients in each response category. The categories of response were pooled as shown in Table 38. This approach is aligned with the responder/non-responder categorisation pre-specified in the protocol for the ALLELE trial [68]. Different OS and PFS projections were applied for responders and non-responders in the PSM.

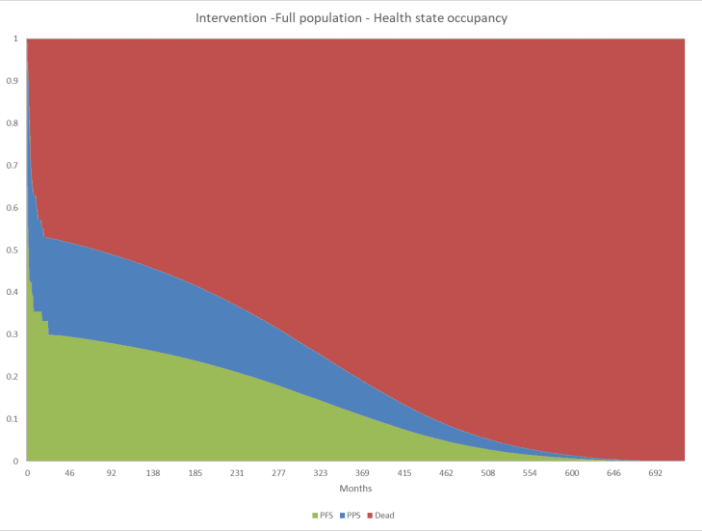
Table 38. Response category groupings and model inputs

ALLELE response	Response status categorisation	C-HCT	C-SOT-R+C
CR	Responder	55.00%	47.37%
PR			
SD	Non-responder	45.00%	52.63%
PD			
NE			

Abbreviations: CR, complete response; N/A, not applicable; NE, not evaluable; PD, progressed disease; PR, partial response; SD, stable disease.

To address the limitation presented by the data, health states transition for the patients were modelled combining the Kaplan-Meier curves from ALLELE and the long-term survival beyond cure point using external data, which was validated by a Danish clinician. Due to the low number of patients in ALLELE, the Kaplan-Meier curves do not reach the cure points. Therefore, it was assumed that the during the interval between the last data point from the trial and the cure time, the survival was constant. The health states transition for the Ebvallo® arm for the full population are shown in Figure 22. The full population was obtained by weighting the relevant PFS and OS data from SOT and HCT patients and the share of responder and non-responders.

Figure 22. Health states occupancy – full population, Ebvallo® arm



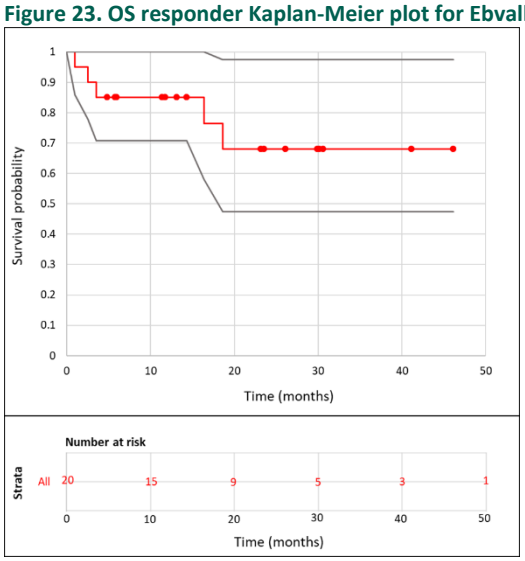
Abbreviations: PFS, progress-free survival, PPS, progressed survival

8.3.1.1.1 Overall Survival

8.3.1.1.1.1 Short-term survival: prior to the cure point – Kaplan Meier

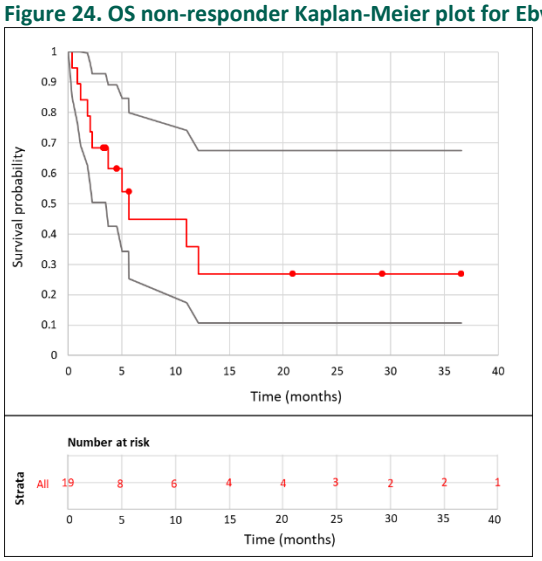
Fitting a parametric distribution to Kaplan-Meier data requires the generation of parameters, which is associated with high uncertainty when the sample size is small. To limit this uncertainty, Kaplan-Meier data from ALLELE Ebvallo® arm were used directly. Standard parametric distributions, together with a hybrid approach, were tested in scenario analysis and are described in Appendix G – Extrapolation. Patients were stratified by response status (responders or non-responders). Kaplan–Meier data for OS by response status are presented below in Figure 23 and Figure 24.

Figure 23. OS responder Kaplan-Meier plot for Ebvallo®



Abbreviations: OS, overall survival. Legend: Red curve = Kaplan-Meier plot, Grey curves = upper confidence-interval and lower-confidence interval

Figure 24. OS non-responder Kaplan-Meier plot for Ebvallo®



Abbreviations: OS, overall survival. Legend: red curve = Kaplan-Meier plot, grey curves = upper confidence-interval and lower-confidence interval

8.3.1.1.1.2 Long term survival: following the cure point - SOT flexible spline models

If SOT patients were still in the progression-free health state following the cure point of 3 years applied in the base case, mortality rate data were applied from an analysis of SOT registry data [58] specifically the US-based Scientific Registry of Transplant Recipients (SRTR) and the UK Transplant Registry (UKTR). According to the Danish clinician data from these registries, especially the UK registry, can be transferable to the Danish setting based on treatment similarities [2]. The cubic spline models from the Graham 2022 publication, which used data from the SRTR and UKTR, were used to calculate per-cycle death rates based on the type of SOT received (kidney, liver, heart or lung). The SRTR is a US-based data system which includes detailed patient and graft survival data for all SOT in the US from 1990 to 2018. The UKTR contains UK-specific patient and graft survival data for all SOTs in the UK from 1995 to 2017. As the publication only examined OS data, the same calculated hazards were also assumed to apply to PFS.

Within the Graham 2022 publication, the three-knot splines were the best-fitting for all long-term organ transplants.

The parameters for the flexible spline models are shown below in Table 39. In the base case, the three-knot models were used.

Table 39. Parameters for flexible spline models used for long-term survival

Model		Parameter	Coefficient	Lambda	Ln(knot)	Knot time (days)
2-knot model	**kidney**	gamma0	-7.8531	1.0000	0.0000	1
		gamma1	0.8786	0.3474	5.9006	365.25
		gamma2	0.1637	0.2707	6.5937	730.5
		gamma3	-0.1968	0.0000	9.0416	8447
3-knot model	**kidney**	gamma0	-7.8079	1.0000	0.0000	1
		gamma1	0.8636	0.3474	5.9006	365.25
		gamma2	0.1459	0.2707	6.5937	730.5
		gamma3	-0.1652	0.0726	8.3855	4383
		gamma4	-0.0365	0.0000	9.0416	8447

2-knot model	**liver**	gamma0	-5.4333	1.0000	0.0000	1
		gamma1	0.6976	0.3481	5.9006	365.25
		gamma2	0.1516	0.2715	6.5937	730.5
		gamma3	-0.1792	0.0000	9.0510	8527
3-knot model	**liver**	gamma0	-5.3569	1.0000	0.0000	1
		gamma1	0.6704	0.3481	5.9006	365.25
		gamma2	0.1024	0.2715	6.5937	730.5
		gamma3	-0.0853	0.0016	9.0361	8400.75
		gamma4	-5.4291	0.0000	9.0510	8527
2-knot model	**heart**	gamma0	-4.1752	1.0000	0.0000	1
		gamma1	0.5090	0.2706	6.5937	730.5
		gamma2	0.3517	0.2257	6.9992	1095.75
		gamma3	-0.4104	0.0000	9.0394	8429
3-knot model	**heart**	gamma0	-4.1369	1.0000	0.0000	1
		gamma1	0.4998	0.2706	6.5937	730.5
		gamma2	0.2507	0.2257	6.9992	1095.75
		gamma3	-0.2405	0.0275	8.7910	6574.5
		gamma4	-0.4097	0.0000	9.0394	8429
2-knot model	**lung**	gamma0	-4.7943	1.0000	0.0000	1
		gamma1	0.5606	0.1898	7.2869	1461
		gamma2	0.1361	0.0879	8.2032	3652.5
		gamma3	-0.2964	0.0000	8.9936	8051
3-knot model	**lung**	gamma0	-4.8160	1.0000	0.0000	1
		gamma1	0.5700	0.1898	7.2869	1461
		gamma2	0.1811	0.0879	8.2032	3652.5
		gamma3	-0.9378	0.0356	8.6732	5844
		gamma4	1.3466	0.0000	8.9936	8051

8.3.1.1.1.3 Long term survival: following the cure point – HCT adjusted life tables

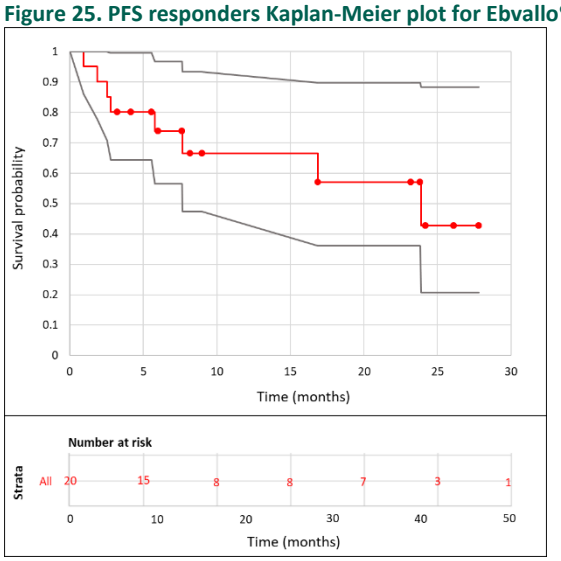
For patients who received HCT, National Life Tables for Denmark were used to calculate survival probabilities after the HCT-specific cure point [69]. The lifetables were adjusted via application of a standardised mortality ratio (SMR) of 4.5 sourced from Martin et al (2010) [59]. The Danish clinician considered an increased in the mortality of 4.5 times was too high for these patients and suggested the SMR should fall between 3 and 3.5. These values were tested in scenario analyses. As with the short-term pre-cure point, the survival of a patient is estimated by taking the maximum value between the mortality rate used in the general population life tables (for HCT patients this includes when the SMR has been applied) and the OS data sourced from ALLELE. The mortality rate is then applied to the OS from the previous model cycle to estimate the OS value for the current model cycle.

8.3.1.1.2 Progression-free survival

8.3.1.1.2.1 Short-term survival: prior to the cure point – Kaplan-Meier data

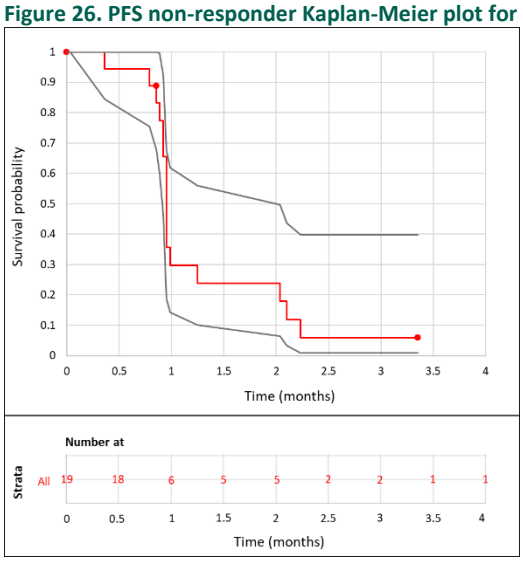
Progression-free survival data were obtained directly from the ALLELE study. Patients were stratified by response status as previously described. Kaplan-Meier data for PFS in responders and non-responders are presented below in Figure 25 and Figure 26.

Figure 25. PFS responders Kaplan-Meier plot for Ebvallo®



Abbreviations: PFS, progression-free survival. Legend: Red curve = Kaplan-Meier plot, Grey curves = upper confidence-interval and lower-confidence interval

Figure 26. PFS non-responder Kaplan-Meier plot for Ebvallo®



Abbreviations: PFS, progression-free survival. Legend: Red curve = Kaplan-Meier plot, Grey curves = upper confidence-interval and lower-confidence interval

8.3.1.1.2.2 Long term survival: following the cure point – SOT flexible spline models

The spline models following the cure point for PFS were identical to those specified for OS, described in section 8.3.1.1.1.2 The same spline models were applied to the OS and PFS curves, effectively meaning that the PFS curves following the cure point are a set ratio of the OS curves.

8.3.1.1.2.3 Long term survival: following the cure point – HCT adjusted life tables

Life tables were applied to the probability of progression for PFS in the same manner as was done for OS, described in section 8.3.1.1.1.3.

8.3.1.2 Clinical outcomes for the BSC arm

8.3.1.2.1 Response rates

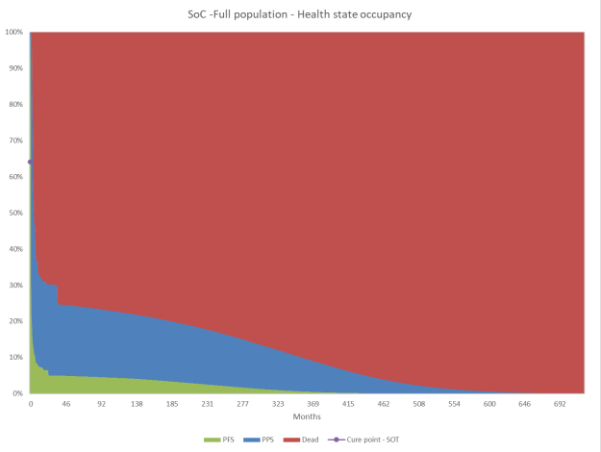
In the analysis patients are pooled by response status. Response rates for the BSC arm are displayed in Table 40 and are sourced from the RS002 study [51]. The health state occupancy for the full population is shown in Figure 27. This has been calculated following the same rationale for the Ebvallo® arm, as explained in section 8.3.1.1 and weighting for the HCT and SOT, responder and non-responder status.

Table 40. BSC response rate

Response status categorisation	C-HCT	C-SOT-R+C
Responder	21.00%	24.40%
Non-responder	79.00%	75.60%

Abbreviations: BSC – best supportive care.

Figure 27. Health states occupancy – full population, BSC arm



Abbreviations, BSC, best supportive care, PFS, progression-free survival, PPS, progressed survival.

8.3.1.2.2 Overall survival

8.3.1.2.2.1 ITC hazard ratios

An ITC was performed to generate estimates of relative efficacy for Ebvallo® versus BSC. The objective of the analysis was to compare the overall survival in patients treated with Ebvallo® in ALLELE with patients treated with BSC in an external control arm, the non-interventional retrospective chart review study RS002.

The standardized mortality/morbidity ratio weighting (SMRW) is an appropriate method to adjust the patients baseline characteristics between two arms when the sample size is small.

Data from RS002 were collected for patients diagnosed with PTLD from 2000 to 2018. To be more closely aligned with current clinical practices, an analysis using data from 2010 to 2018 was conducted. Ebvallo® demonstrated significant OS benefit compared to BSC with an adjusted HR of 0.41 (0.23-0.72). Using data from 2000 to 2018 produced similar results (HR of 0.44, 95% CI 0.25-0.76). Section 7.1.3 describes the ITC in detail.

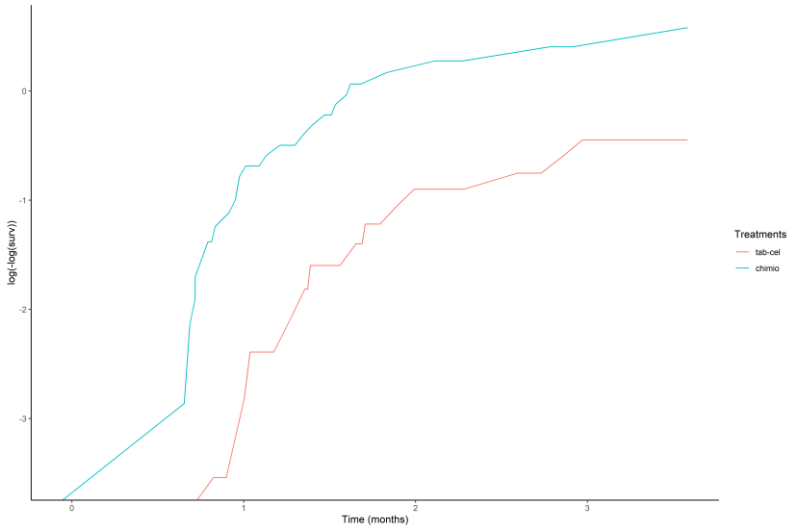
Table 41. HRs from the ITC of ALLELE vs RS002 – overall survival benefit of Ebvallo® compared with best supportive care

Analysis		OS HR (95% CrI)
Base case	SMRW adjustment (patients in the RS002 dataset diagnosed between 2010-2018)	0.41 (0.18, 0.53)

Abbreviations: CrI, credible interval; HR, hazard ratio; OS, overall survival; SMRW, standardised mortality ratio weighting.

The use of HR is dependent on the proportional hazard assumption. This was assessed through complementary log-log plot and Schoenfeld residuals test, as recommended by NICE DSU TSD14 [70]. The parallel curves (Figure 28) and the non-significant p-value of the Schoenfeld residuals test (p-value = 0.0933) indicated that the proportional hazard assumption could be considered valid.

Figure 28. Complementary log-log plots



Source: [67, 70]

8.3.1.2.3 Progression-free survival

PFS of BSC was not collected in RS002. To estimate PFS of BSC in the model, the OS HR used to estimate BSC OS was applied to Ebvallo® PFS. It assumes that treatment effect between Ebvallo® and BSC on OS is the same on PFS.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

EQ-5D-5L data were captured as part of the ALLELE study. EQ-5D-5L utility scores were available for 45/49 patients who were aged ≥16 years at baseline. Subsequent EQ-5D-5L data were captured for each following treatment cycle, but there were a high number of missing values, and low numbers of patients overall. Further to this, utility values were not calculable by disease progression status, which was required so that health state utility values could be generated; results were only presented on a temporal basis, i.e., at given treatment cycles, 30-day safety follow-up (n=20), and 180

days following the last dose (n=13). Subgroup specific utility values are described in Appendix M – Baseline utilities values per subgroups.

It was assumed that the baseline utility value in ALLELE was equivalent to the utility value for the "progressed disease" health state; however, clinical expert opinion indicates that this is likely to be an overestimate of the true utility value for progressed disease. Given the low number of patients for the follow-up time points and the absence of EQ-5D-5L data stratified by progression status, literature sources were consulted to inform other health state values. The systematic literature review did not identify any publications which reported utility values for EBV^+ PTLD. As part of early model development, a grey literature search was therefore conducted to identify utility values within the broader lymphoma indication and for patients who had received SOT.

The "multiplicative method", as recommended by NICE DSU TSD 12 [71] was used to generate different utility values for patients who were either progression-free or had progressed disease and had received a given organ transplant [72].

Table 42 presents the HSUV used in the model with their corresponding sources.

Table 42. Utility values used in the model

Health state	Mean utility	SE	Source	Population
Health state				
Progression-free	0.83	0.17	Cost-effectiveness study of chemotherapy with stem cell support for non-Hodgkin's lymphoma, Fagnoni *et al,* 2009 [64] Mean age and male (%) estimated as a weighted average from the data reported in the study.	Patients who are in complete remission following acute treatment, before a relapse or death
Progressed-disease	0.71	0.05*	Table 2.12.1-1.1, ALLELE July 2022 data cut [63] with Danish weights.	All patients at baseline
Transplant-specific utilities				
HCT	0.84	0.17	Cost-effectiveness model for the treatment of chronic GvHD treated with HCT, Crespo *et al,* 2012 [73] Baseline characteristics were not reported in this study, so as a placeholder the ALLELE trial median age and male (%) have been used as a substitute.	Patients with a complete response to HCT treatment
SOT: Kidney	0.81	0.16	Meta-analysis of 5 studies reporting quality of life for renal replacement patients, Liem *et al,* 2008 [74] Mean age and male (%) represent the values reported from Liem et al	Patients with a renal transplant

			(sourced from Polsky et al 2001)).	
SOT: Liver	0.84	0.17	Cost-effectiveness analysis for the treatment of acute hepatitis C, Bethea *et al,* 2018 (Page 16, Table 1) [75]. Mean age and male (%) represent the values reported from Chong et al (2003) [76].	Post-liver transplant patients
SOT: Heart	0.83	0.17	Cost-effectiveness analysis of left-ventricular assist devices for advanced heart failure patients, Clarke *et al,* 2014 (Page 341, Table 2) [77]. Mean age and male (%) represent the values reported from Gohler et al (2015). Note the disutility is assumed equal to 0, because the general population utility exceeds the mean utility.	Post-heart transplant patients
SOT: Lung	0.83	0.17	Paper evaluating quality of life among lung transplantation patients, Anyanwu *et al,* 2001 (Page 221, Table 5) [78]. Mean utility score for bilateral lung transplant patients 7-18 months after transplantation. Mean age reported from study. Male (%) was not reported in the study and so an assumption of a 50%/50% male/female split has been made.	Bilateral lung transplant patients 7-18 months after transplantation

*Calculated as SE=SD/√n

8.4.2 Age adjustment

An age adjustment for health state utility values (HSUV) was applied according to the Danish guidelines and implemented as the base case analysis. The multiplicative method was used to calculate the health state utility values (HSUV) over time, where the original value for the HSUV is multiplied by an adjustment index and gives an age adjusted HSUV relevant for the local Danish setting. This was done using the Danish general population utilities stratified by age groups to calculate the age-dependent multipliers. The age-dependent multipliers were then used to adjust the individual's undiscounted utility levels each cycle according to their age.

8.4.3 Disutilities due to adverse events

A grey literature search was conducted to identify disutilities for each adverse event included in the analysis. Where possible, the disutilities were sourced from studies which examined the broader lymphoma indication due to a lack of data specific to PTLD.

Searches were performed using the terms “lymphoma”, “adverse events” and “health state utilities”. Five possible papers were identified from this search. One was a systematic review of health state utility values in metastatic non-small cell lung cancer (Paracha 2018)[79]. The majority of the remaining identified papers were cost-effectiveness analyses for the treatment of other oncology indications, including multiple myeloma (Jakubowiak 2016),[80] relapsed lymphoma (Zhang 2020),[81] mantle cell lymphoma (Petersohn 2022)[82] and non-small cell lung cancer (Lemmon 2022)[83] .

One publication referenced was a cost-effectiveness analysis in idiopathic pulmonary fibrosis (Rinciog 2020).[84] This paper was used to derive a disutility value for bowel perforation and cardiovascular-related events).
If the standard error and duration of events were identified, these were also reported. Where multiple papers reported a different value for the same adverse event, the disutility from the paper with the largest sample size was used in the model.

The papers identified in the grey literature search did not report disutilities for cytopenia, thrombosis, syncope, peripheral sensory neuropathy, constipation or alopecia. To provide these values, a search of adverse event disutilities in previous NICE submissions for lymphoma was performed. An appraisal for the treatment of follicular lymphoma (TA627, 2020),[85] provided values for all remaining events except cytopenia. In the absence of other information, the disutility of cytopenia was assumed to be equal to that of thrombocytopenia.

An overview of the disutilities associated with each adverse event is presented in Table 43 below.

Table 43. Disutilities per adverse event used in the model

Adverse event	Disutility	Duration (days)	QALY loss	Source
Anaemia	0.12	14.00	-0.0046	Petersohn S, et al 2022. Supplementary material, Table 4[82]
Neutropenia	0.09	47.00	-0.0116	Petersohn S, et al 2022. Supplementary material, Table 5[82, 86]
Neutrophil count decrease	0.15	17.00	-0.0070	Petersohn S, et al 2022. Supplementary material, Table 5[82, 86]
Infection	0.20	34.00	-0.0182	Tolley K, et al 2013. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. European Journal of Health Economics. 14(5): 749-759[87]
Thrombosis	0.06	21.00	-0.0036	Jakubowiak A, et al (2016). Cost-effectiveness of adding carfilzomib to lenlidomide and dexamethasone in relapsed multiple myeloma from a US perspective. Journal of Medical Economics. 19(110): 1061-1074[80]
Fatigue	0.07	31.50	-0.0063	Nafees B, et al (2008). Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes. 6(84): 1-15[88]

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Vomiting	0.05	6.00	-0.0008	Nafees B, et al (2008). Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes. 6(84): 1-17[88]
Febrile neutropenia	0.15	7.14	-0.0029	Nafees B, et al (2008). Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes. 6(84): 1-18[88]
Acute kidney injury	0.15	7.00	-0.0029	Petersohn S, et al 2022. Supplementary material, Table 9[82, 86]
Sepsis	0.15	7.00	-0.0029	Petersohn S, et al 2022. Supplementary material, Table 10[82, 86]
Hypertension	0.15	5.00	-0.0021	Petersohn S, et al 2022. Supplementary material, Table 10[82, 86]
Pneumonia	0.15	7.00	-0.0029	Petersohn S, et al 2022. Supplementary material, Table 10[82, 86]
Respiratory failure	0.15	7.00	-0.0029	Petersohn S, et al 2022. Supplementary material, Table 10[82, 86]
Leukopenia	0.15	21.00	-0.0086	Petersohn S, et al 2022. Supplementary material, Table 10[82, 86]
Hypotension	0.15	5.00	-0.0021	Petersohn S, et al 2022. Supplementary material, Table 10[82, 86]

8.5 Resource use and costs

Costs considered in the analysis include drug acquisition cost, drug administration costs, co-medication cost, subsequent treatment, routine follow-up and monitoring cost, cost of managing AEs, end of life costs and non-medical cost including patient time and travel cost. All costs are reported in DKK and were sourced from the latest available public price list from 2023 [89]. The resource use frequencies were validated by a Danish clinical expert [2]. Treatment costs (BSC) were sourced from the "Medicinpriser" database from Laegemiddelstyrelsen [90]. All the relevant inputs related to the costs are listed in Appendix N – Unit costs.

8.6 Results

8.6.1 Base case overview

Table 44 presents the base case settings.

Table 44 Base case overview

Comparator	Best supportive care
Type of model	Partitioned survival model with a cure point
Time horizon	50 years (life-time)
Treatment line	2nd line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in ALLELE, for non-responders, and Fagnoni et al for responders [64]. Danish

	population weights were used to estimate health-state utility values.
Included costs	Pharmaceutical costs Hospital costs Costs of adverse events Patient costs
Dosage of pharmaceutical	Based on weight
Average time on treatment	Intervention: SOT responders: 4.22 months, SOT non-responders: 1.38 months HCT responders: 3.45 months, HCT non-responders: 2.80 months Comparator: 8.4 months

8.6.2 Base case results

Table 45 presents the discounted results for the base case.

Table 45 Base case results (discounted)

Item	Ebvallo®	BSC	Incremental
Life years			
PFS			
Responder	4.65	0.72	3.92
Non-responder	0.49	0.06	0.43
Total	5.14	0.79	4.35
PPS			
Responder	1.39	0.23	1.16
Non-responder	1.92	3.30	-1.37
Total	3.31	3.52	-0.21
Overall	8.45	4.31	4.14
QALYs			
PFS			
Responder	3.17	0.49	2.67
Non-responder	0.33	0.04	0.30
Total	3.50	0.53	2.97
PPS			
Responder	0.81	0.13	0.68

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Item	Ebvallo®	BSC	Incremental
Non-responder	1.12	1.92	-0.80
Total	1.92	2.05	-0.13
Overall	5.42	2.58	2.84
Treatment costs (DKK)			
Responder	2,834,258 kr	210,303 kr	2,623,955 kr
Non-responder	1,457,652 kr	26,413 kr	1,431,240 kr
Total	4,291,910 kr	236,716 kr	4,055,195 kr
Admin costs (DKK)			
Responder	0 kr	25,577 kr	-25,577 kr
Non-responder	0 kr	3,212 kr	-3,212 kr
Total	0 kr	28,789 kr	-28,789 kr
PFS health state costs (DKK)			
Responder	465,942 kr	120,820 kr	345,122 kr
Non-responder	77,659 kr	32,818 kr	44,840 kr
Total	543,601 kr	153,638 kr	389,963 kr
PPS health state costs (DKK)			
Responder	1,698,419 kr	235,343 kr	1,463,076 kr
Non-responder	2,368,154 kr	4,244,592 kr	-1,876,437 kr
Total	4,066,573 kr	4,479,934 kr	-413,361 kr
Terminal care costs (DKK)			
Responder	19,411 kr	11,952 kr	7,459 kr
Non-responder	24,952 kr	40,592 kr	-15,639 kr
Total	44,364 kr	52,543 kr	-8,180 kr
AE costs (DKK)			
Responder	8,447 kr	6,028 kr	2,419 kr
Non-responder	8,025 kr	20,579 kr	-12,554 kr
Total	16,472 kr	26,607 kr	-10,135 kr
Subsequent therapy costs (DKK)			
Responder	10,550 kr	4,917 kr	5,633 kr

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Item	Ebvallo®	BSC	Incremental
Non-responder	22,537 kr	54,276 kr	-31,739 kr
Total	33,087 kr	59,194 kr	-26,106 kr
Total costs	8,996,007 kr	5,037,420 kr	3,958,587 kr
ICER			**1,392,909 kr**

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

A one-way deterministic sensitivity analysis (OWSA) was conducted. Input values were varied using the upper and lower limits of their 95% confidence intervals. When the standard errors were unknow the confidence intervals were estimated using a 10% deviation from the mean. Table 46 shows the results of the OWSA including the 10 values which had the largest impact on the ICER when being varied. The Tornado diagram in Figure 29 shows the ten most sensitive values. The number of treatment cycles for SOT responder had the largest impact on the ICER, followed by number of treatment cycles for HCT responders and non-responders.

Table 46 One-way sensitivity analyses results

Parameter	Upper	Lower
% SOT	1,492,607	1,304,955
Number of treatment cycles_SOT_Responder	1,492,080	1,375,137
Number of treatment cycles__HCT_Responder	1,491,988	1,375,155
Number of treatment cycles__HCT_Non-responder	1,459,307	1,381,560
Number of treatment cycles_SOT_Non-responder	1,429,822	1,387,339
Inpatient days___RU	1,411,290	1,390,971
Inpatient days___unit costs	1,410,623	1,392,764
Hazard ratio - ITC	1,410,568	1,392,853
% males	1,402,919	1,385,263
Progressed ___utilities	1,399,456	1,383,673

RU: Resource use, SOT: solid organ transplant, HCT: Haematopoietic cell transplant

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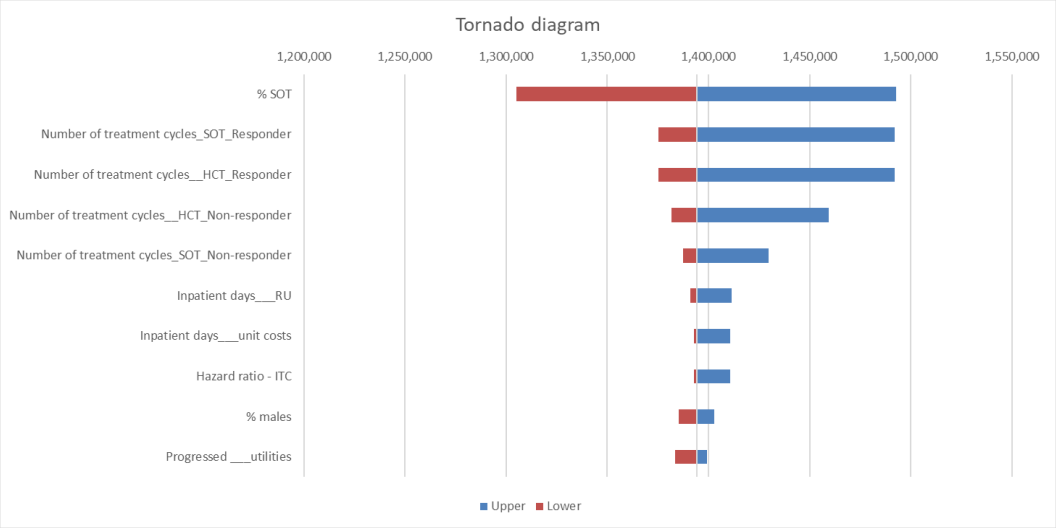
Figure 29. Tornado diagram



8.7.2 Scenario analyses

Table 47 presents the results of the scenario analyses.

Table 47 Scenario analyses

Parameter	Base case value	Scenario value/s	Scenario results				Difference in ICER vs base case
			Costs (DKK)	Life Years gained	QALYs	ICER (DKK)	
Discount rate costs and effects	3.5%, 3.5%	0%, 0%	3,688,233	6	4	862,061	-530,849
		5%, 5%	4,024,243	4	2	1,637,137	244,228
Time horizon	50	5	4,271,684	1	1	5,579,492	4,186,582
		10	4,210,922	2	1	2,937,960	1,545,050
		15	4,153,596	3	2	2,156,828	763,918
		20	4,094,812	3	2	1,796,618	403,709
		30	3,997,341	4	3	1,494,540	101,630
Half cycle correction	Yes	No	3,968,447	4	3	1,395,467	2,557
BSC: OS and PFS estimation method	Survival parameters: OS, HR: PFS	HR: OS and PFS	6,218,947	6	4	1,589,747	196,838
		HR: OS Ratio: PFS	6,498,327	6	4	1,674,409	281,499
		Survival parameters: OS, Ratio: PFS	4,438,330	4	3	1,596,266	203,357
Cost perspective	Limited societal	Payer	3,962,541	4	3	1,394,301	1,392

Cure point: SOT responders and non-responders	3	1	3,447,192	4	3	1,204,440	-188,469
Cure point: SOT responders and non-responders	3	5	4,035,815	4	3	1,417,226	24,317
Cure point: HCT responders and non-responders	1	3	5,363,432	4	3	1,931,871	538,962
Cure point: HCT responders and non-responders	1	5	5,505,030	4	3	1,981,411	588,502
Median age of population at baseline	42.3	60	4,064,607	3	2	2,039,465	646,556
Mean utility: responder	0.83	0.5	3,958,587	4	2	2,378,623	985,714
Mean utility: non-responder	0.71	0.2	3,958,587	4	3	1,349,920	-42,990
Short term parametrization SOT and HCT, responder and non-responder, OS and PFS based on lowest AIC/BIC	KM	Hybrid model: Parametrisation based on lowest AIC/BIC	3,958,587	4	3	1,392,909	0
Age adjustment	Yes	No	3,958,587	4	3	1,373,852	-19,057
Transplant proportion: liver, kidney, heart, lung,	42%, 70%, 30%, 20%	50%, 25%, 15%, 10%	3,989,912	4	3	1,361,772	-31,137
SMR	4.5	3	3,958,587	4	3	1,392,909	0
		3.5	3,940,386	4	3	1,339,975	-52,935
Patient population	All	SOT	4,471,452	3	2	2,063,389	670,479
		HCT	3,471,364	5	3	996,624	-396,285
Index date	Start of subsequent treatment	Refractory to rituximab	4,445,433	5	3	1,433,477	40,568

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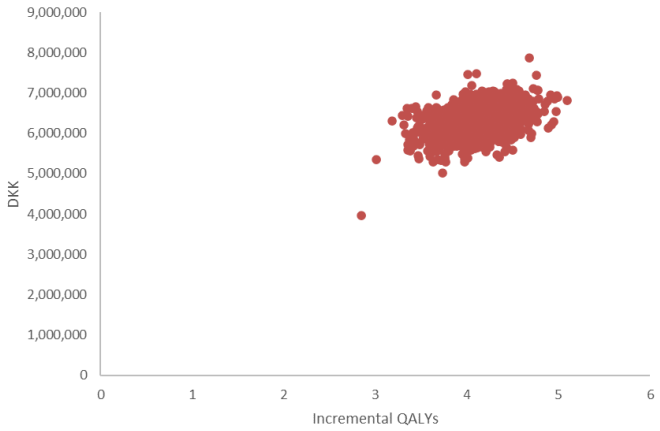
8.7.3 Probabilistic sensitivity analyses

To evaluate uncertainty associated with parameter precision, probabilistic sensitivity analyses were conducted to establish the impact of such uncertainty. A second-order Monte Carlo simulation was run for 1,000 iterations including the simultaneous variation of all parameters. Multiple sets of parameter values were sampled from predefined probability distributions to characterize the uncertainty associated with the precision of mean parameter values. Figure 30 presents the cost-effectiveness plane, which showed that most of the 1,000 iterations were in the north-east quadrant indicating that Ebvallo® resulted in more QALYs and higher costs compared to physician's choice.

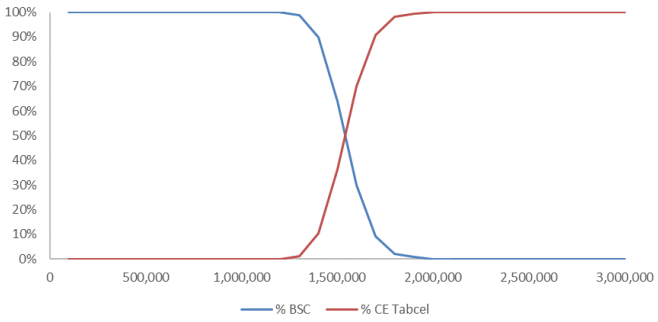
Figure 30. Cost-effectiveness plane



Abbreviations: QALYs – quality adjusted life years.

Figure 31 presents the cost-effectiveness acceptability curve (CEAC). The CEAC showed that Ebvallo's® probability of being cost-effective is 50% at a willing-to-pay of approximately DKK 1,600,000.

Figure 31. Cost-effectiveness acceptability curve



9. Budget impact analysis

A budget impact analysis was conducted and incorporated in the CEM. A five-year projection was used in the analysis as per Danish guidelines [97]. Costs for two scenarios were estimated. In one scenario Ebvallo® is introduced as a standard treatment for EBV⁺ PTLD, and in scenario two it is not introduced. Costs were estimated based on the expected number of eligible patients.

The budget impact calculations are based on Pharmacy Purchasing Price (PPP) of all treatments.

The following costs were included in the analysis:

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- Drug costs
- Administration costs
- Follow-up costs
- Adverse events costs
- Subsequent treatment costs
- End-of-life costs

The results of the budget impact analysis are presented below. An estimated DKK 16.2 million in additional cost at year five is projected after introduction of Ebvallo® as a treatment for EBV+ PTLD.

Number of patients

Based on the prevalence and incidence of patients with EBV+ PTLD, following at least one line of treatment, Pierre Fabre is assuming 1 patient to be treated with Ebvallo® in the first year after the therapy is introduced, followed by 4 patients in the years after. A constant prevalence and incidence rate was assumed over the five-year period. Table 48 below presents the estimated patient numbers for scenario one and Table 49 scenario two, respectively. These values were validated by a Danish clinician [2].

Table 48. Number of patients expected to be treated over the next five-year period – if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Ebvallo®	1	3.6	3.8	3.8	3.8
BSC	3	0.4	0.2	0.2	0.2
Total number of patients	4	4	4	4	4

Table 49. Number of patients expected to be treated over the next five-year period – if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Ebvallo®	0	0	0	0	0
BSC	4	4	4	4	4
Total number of patients	4	4	4	4	4

Expenditure per patient

Table 50 and Table 51 present the drug expenditure, per patient per year, for both scenario one and two respectively. The cost includes PFS and PPS cost for Ebvallo® and BSC respectively. For full details and cost break down please see model sheet BIM in the cost-effectiveness model.

Table 50. Costs per patient per year – if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Ebvallo®	9,886,069	651,917	610,435	448,305	442,281
BSC	1,423,944	601,666	571,919	476,191	467,868

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Table 51. Costs per patient per year – if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Ebvallo®	0	0	0	0	0
BSC	1,423,944	601,666	571,919	476,191	467,868

Budget impact

Table 52 below presents the expected budget impact of introducing the pharmaceutical at the current indication. At year five Ebvallo® is expected to have a budget impact of approximately DKK 16.2 million.

Table 52. Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 1					
Treatment costs	4,463,266	15,501,569	16,339,046	16,340,159	16,341,758
Admin costs	21,826	9,717	7,371	7,507	7,701
PFS health state costs	654,500	1,376,833	1,737,423	1,926,536	1,939,814
PPS health state costs	1,492,468	2,098,333	2,969,873	3,768,248	4,645,744
Terminal care costs	148,830	115,420	124,709	127,469	125,308
AE costs	96,292	69,941	67,914	67,914	67,914
Subsequent therapy costs	201,768	136,358	136,469	138,507	138,642
Total	7,078,950	19,308,171	21,382,806	22,376,339	23,266,881
Scenario 2					
Treatment costs	239,290	313,910	368,823	422,872	475,508
Admin costs	29,102	38,177	44,855	51,429	57,830
PFS health state costs	440,380	523,489	560,335	560,335	560,335
PPS health state costs	1,638,797	2,665,268	3,701,593	4,586,523	5,462,263
Terminal care costs	164,998	171,042	178,116	184,832	185,689
AE costs	106,427	106,427	106,427	106,427	106,427
Subsequent therapy costs	228,894	232,908	234,910	235,022	235,122

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	Year 1	Year 2	Year 3	Year 4	Year 5
Total	2,847,888	4,051,221	5,195,059	6,147,441	7,083,176
Budget impact of the recommendation	4,231,062	15,256,950	16,187,746	16,228,899	16,183,705

10. Discussion on the submitted documentation

The objective of this analysis was to evaluate the cost-effectiveness of Ebvallo® compared to BSC for the treatment of children and adults with EBV⁺ PTLD, after one line of treatment from a Danish limited societal perspective. For SOT patients, previous treatment includes chemotherapy unless deemed inappropriate.

Ebvallo® compared to BSC was associated with higher costs and gains in QALYs with a cost per additional QALY gained of DKK 1,392,909 over a lifetime time horizon (50 years).

In conclusion, from a Danish limited societal perspective, the use of Ebvallo® predicts more QALYs at a higher cost compared to BSC.

11. List of experts

Peter Brown – Clinical Associate Professor, Department of Internal Medicine: Haematology [2].

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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are rare lymphomas that can develop following solid organ transplant (SOT) or allogenic (donor) haematopoietic stem cell transplants (HCTs). Most cases of PTLD are associated with Epstein-Barr virus (EBV) infection [98]. Current treatment is mostly rituximab with or without chemotherapy but despite treatment, prognosis is very poor and the 3 year overall survival (OS) of patients with PTLD is 20–47% and 49–62% for HCT and SOT, respectively [99]. Tabelecleucel (Ebvallo®) is a first-in-class, allogeneic T-cell immunotherapy developed for EBV-positive PTLD. Ebvallo® is indicated for the treatment of patients with EBV$^+$ PTLD who have received at least one prior therapy (for SOT patients, prior therapy includes chemotherapy unless chemotherapy was considered inappropriate). An Ebvallo® Phase 3 clinical trial is still ongoing for the treatment of EBV-positive PTLD following SOT after the failure of rituximab or rituximab and chemotherapy, and for the treatment of EBV-positive PTLD following allogeneic HCT after the failure of rituximab (ALLELE study) [55].

Objective of the literature search

To understand the current state of knowledge on the treatment of PTLD and identify the burden and unmet treatment needs that demonstrate the value of Ebvallo®, a systematic literature review (SLR) on the clinical efficacy and safety, for PTLD following HCT or SOT were conducted.

The priority population and subgroups of interest were that for which Ebvallo® is indicated, i.e., EBV$^+$ PTLD following HCT or SOT patients who have received at least one prior therapy (for SOT patients, prior therapy includes chemotherapy unless chemotherapy was considered inappropriate). This is also taking into account in the design of the ALLELE study [55] where Ebvallo® was assessed in patients with EBV-positive PTLD who had failed rituximab for SOT and HCT subpopulations, or who had failed rituximab plus chemotherapy for the SOT subpopulation. The use of rituximab and chemotherapy could be in combination or in sequence.

Methods

As part of the current review, the following sources were searched to identify potentially relevant publications for all SLRs (unless stated otherwise):

- Electronic databases (Table 53)
- Reference lists of eligible studies
- Global Health Technology Assessment (HTA) bodies
- Conference proceedings (Table 55)
- Clinical trial registries (Table 54)
- Additional databases/websites (non-clinical).

Embase, MEDLINE, EBM reviews and EconLit were searched in February 2022 for studies of patients with PTLD following SOT or allogenic HCT (Table 53).

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For the clinical SLR assessing the efficacy and safety of available treatment options, this included randomised controlled trials (RCTs), clinical studies and observational studies investigating pharmacological interventions that reported outcomes including overall response rate (ORR) and OS.

Two independent reviewers screened the records, one performed data extraction and quality assessment, whilst a second checked.

Databases

Table 53 – Table 55 summarise the information on the databases used in this SLR.

Table 53. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	1974 to present	07.02.2022
Medline	Ovid	1946 to present	04.02.2022
EBM Reviews[a]	Ovid	NA	07.02.2022
Econlit[b]	Ovid	1886 to present	07.02.2022

[a]Including: ACP Journal Club; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews; Cochrane Clinical Answers; Cochrane Methodology Register; Database of Abstracts of Reviews of Effects (DARE); HTA database; National Health Service Economic Evaluation Database (NHS EED). [b]Cost and economic evaluation SLRs only. Abbreviations: NA, Not applicable.

Table 54. Registers included in the search

Database	Platform	Date of search
US NIH registry & results database	https://clinicaltrials.gov	07.02.2022
WHO ICTRP registry	https://apps.who.int/trialsearch/	07.02.2022

Abbreviations: US NIH, United States National Institutes of Health; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Table 55.Conference material included in the literature search

Conference	Source of abstracts	Search strategy
American Society of Hematology (ASH)	https://www.hematology.org/	Manual search on the last 3 years
American Society of Clinical Oncology (ASCO)	https://www.asco.org/	Manual search on the last 3 years
European Haematology Association (EHA)	https://ehaweb.org/	Manual search on the last 3 years
European Society for Medical Oncology (ESMO)	https://www.esmo.org/	Manual search on the last 3 years

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Conference	Source of abstracts	Search strategy
Transplantation and Cellular Therapy (TCT)	https://www.astctjournal.org/	Manual search on the last 3 years
European Society for Blood and Marrow Transplantation (EBMT)	https://www.ebmt.org/	Manual search on the last 3 years
American Association for Cancer Research (AACR)	https://www.aacr.org/	Manual search on the last 3 years
American Transplant Congress (ATC)	https://atcmeeting.org/	Manual search on the last 3 years
International Conference on Malignant Lymphoma (ICML)	https://www.aacr.org/meeting/international-conference-on-malignant-lymphoma-icml/	Manual search on the last 3 years

Additional sources

The following HTA websites were searched to identify relevant previous HTA submissions (08.02.2022):

- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/
- Scottish Medicines Consortium (SMC): https://www.scottishmedicines.org.uk/
- Canadian Agency for Drugs and Technologies in Health (CADTH), including the pan-Canadian Oncology Drugs Review (pCODR): https://www.cadth.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC): https://www.pbs.gov.au/pbs/home
- Agencia Española de Medicamentos y Productos Sanitarios (AEMPS): https://www.aemps.gob.es/
- Agenzia Italiana del Farmaco (AIFA): https://www.aifa.gov.it/
- Haute Autorité de Santé (HAS): https://www.has-sante.fr/
- Institute for Quality and Efficiency in Health Care (IQWiG): https://www.iqwig.de/
- Institute for Clinical and Economic Review (ICER): https://icer-review.org/
- US Food and Drug Administration: https://www.fda.gov/
- European Medicines Agency: https://www.ema.europa.eu/en.

The following additional databases/websites were also searched (08.02.2022):

- EuroQoL website: https://euroqol.org/ (HRQoL SLR only)
- University of Sheffield's ScHARRHUD database: https://www.scharrhud.org/ (HRQoL, cost/resource use, economic evaluation SLRs)
- CEA Registry: http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx (Economic evaluations SLR)
- RePEc website (EconPapers): https://econpapers.repec.org/ (HRQoL, cost/resource use, economic evaluation SLRs)
- International Network of Agencies for Health Technology Assessment (INAHTA): https://database.inahta.org/
- National Institute for Health Research (NIHR): https://www.nihr.ac.uk/.

Search strategy

Eligibility criteria

Table 56 summarizes the eligibility criteria used in the Clinical SLR.

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Table 56. Eligibility criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients of any age with PTLD following SOT or allogeneic HCT	
Intervention and comparators	Pharmacological treatments given to treat PTLD	Immunosuppression treatments not for PTLD Unclear treatments
Outcomes	Clinical review: Median/mean overall survival (time to death) Survival rates (yearly) (n/N %) Mortality rates (n/N %) Progression free survival (time to progression) Response rates (overall response rate; objective response rate, complete response; partial response; progressive disease; stable disease; relapse) (n/N %) TTR DOR All AE, all TR AE (n/N %) All SAE, all TR SAE (n/N %) AE leading to mortality or discontinuation (n/N %) Specified AE: Neutropenia (all types) (n/N %) Anaemia (n/N %) Leukopenia (n/N %) Infection (n/N %) Nausea/vomiting (n/N %) Thrombocytopenia (n/N %) Peripheral neuropathy (n/N %)	Clinical review: Individual AE unless specified
Study design	Clinical review: Randomised controlled trials Prospective non-randomised trials Prospective/retrospective cohort observational studies Cross sectional studies Cost/resource use studies: Prospective/retrospective cohort studies observational studies Cross sectional studies Budget impact model SLRs†	Clinical review: Qualitative studies PTLD samples size <10 Case studies
Subgroups of interest	Patients who do not respond to first line rituximab Patients who do not respond to first line chemotherapy Patients who do not respond to first line rituximab and chemotherapy Patients with PTLD associated with Epstein Barr Virus	
Geography	No restriction	
Publication date	Clinical review:	

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	Any
Language	No restriction

Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; DOR, duration of response; HRQoL, health related quality of life; HCT, hematopoietic stem cell transplant; HSUV, health state utility value; LYG, life year gained; NMB, net monetary benefit; PTLD, post-transplant lymphoproliferative disease; QALY, quality-adjusted life year; SAE, serious adverse event; SG, standard gamble; SLR, systematic literature review; SOT, solid organ transplant; TTO, time trade off; TR, treatment related; TTR, time to response; VAS, visual analog scale.
†These publications were not included in the review but identified for reference checking and if appropriate summarised in the qualitative report.

Search strings for the clinical SLR

Trials Filter based on: Technical Supplement to Chapter 4. Box 3.e Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase: (2018 revision); Ovid format (Glanville et al 2019b). (Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from: www.training.cochrane.org/handbook.)

Observational study filter based on: Scottish Intercollegiate Guidelines Network study design filter: https://www.sign.ac.uk/what-we-do/methodology/search-filters/

Table 57 – Table 60 summarize the search strings used, per database.

Table 57. Embase (Ovid): 1974 to 2022 February 04: searched 7.2.2022

#	Searches	Results
1	posttransplant lymphoproliferative disease/	3299
2	((post transplant$ or posttransplant$) adj2 lymphoma$).ti,ab.	490
3	((post transplant$ or posttransplant$) adj2 lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	5942
4	PTLD.ti,ab.	4967
5	or/1-4	8349
6	lymphoproliferative disease/	20275
7	(lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	23675
8	6 or 7	31519
9	transplantation/ or exp organ transplantation/	536272
10	(transplant$ or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT).ti,ab.	899466
11	9 or 10	1002025
12	8 and 11	10486

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13	5 or 12	12791
14	Randomized controlled trial/	694049
15	Controlled clinical study/	464932
16	random$.ti,ab.	1751446
17	randomization/	92888
18	intermethod comparison/	279499
19	placebo.ti,ab.	335955
20	(compare or compared or comparison).ti.	556431
21	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	2439813
22	(open adj label).ti,ab.	94288
23	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	252953
24	double blind procedure/	191942
25	parallel group$1.ti,ab.	28822
26	(crossover or cross over).ti,ab.	114639
27	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	372122
28	(assigned or allocated).ti,ab.	438313
29	(controlled adj7 (study or design or trial)).ti,ab.	398752
30	(volunteer or volunteers).ti,ab.	264478
31	human experiment/	564249
32	trial.ti.	349795
33	or/14-32	5652598
34	Clinical study/	157200
35	Case control study/	183619
36	Family study/	25379
37	Longitudinal study/	167253

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38	Retrospective study/	1196334
39	Prospective study/	742964
40	Randomized controlled trials/	219619
41	39 not 40	734407
42	Cohort analysis/	802260
43	(Cohort adj (study or studies)).mp.	385403
44	(Case control adj (study or studies)).tw.	150979
45	(follow up adj (study or studies)).tw.	68293
46	(observational adj (study or studies)).tw.	208767
47	(epidemiologic$ adj (study or studies)).tw.	114383
48	(cross sectional adj (study or studies)).tw.	276672
49	or/34-38,41-48	3309180
50	33 or 49	7906510
51	13 and 50	3660

Table 58. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 04, 2022

#	Searches	Results
1	((post transplant$ or posttransplant$) adj2 lymphoma$).ti,ab.	330
2	((post transplant$ or posttransplant$) adj2 lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	3737
3	PTLD.ti,ab.	2265
4	or/1-3	4145
5	Lymphoproliferative Disorders/	8803
6	(lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	15965
7	5 or 6	19184
8	exp Transplants/	29132

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9	(transplant$ or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT).ti,ab.	602864
10	8 or 9	618115
11	7 and 10	5531
12	4 or 11	6096
13	randomized controlled trial.pt. or “randomized controlled trials as topic”/	704834
14	controlled clinical trial.pt.	94683
15	random$.ti,ot.	267321
16	placebo.ab.	225379
17	drug therapy.fs.	2439416
18	random$.ab.	1252110
19	trial.ab.	586400
20	groups.ab.	2307416
21	or/13-20	5543792
22	Epidemiologic studies/	8989
23	exp case control studies/	1281535
24	exp cohort studies/	2292165
25	Case control.tw.	140533
26	(cohort adj (study or studies)).tw.	261373
27	Cohort analy$.tw.	9944
28	(Follow up adj (study or studies)).tw.	52887
29	(observational adj (study or studies)).tw.	134599
30	Longitudinal.tw.	284540
31	Retrospective.tw.	640630
32	Cross sectional.tw.	433652
33	Cross-sectional studies/	410498
34	or/22-33	3444583

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35	21 or 34	7850577
36	12 and 35	2539

Table 59. EBM Reviews (Ovid): Cochrane Methodology Register 3rd Quarter 2012, Database of Abstracts of Reviews of Effects 1st Quarter 2016, Health Technology Assessment 4th Quarter 2016, NHS Economic Evaluation Database 1st Quarter 2016, Journal Club 1991 to November 2021, Cochrane Clinical Answers November 2021, Cochrane Central Register of Controlled Trials January 2022, Cochrane Database of Systematic Reviews 2005 to December 02, 2021: searched 7.2.22

#	Searches	Results
1	((post transplant$ or posttransplant$) adj2 lymphoma$).ti,ab.	6
2	((post transplant$ or posttransplant$) adj2 lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	148
3	PTLD.ti,ab.	156
4	or/1-3	232
5	Lymphoproliferative Disorders/	85
6	(lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	342
7	5 or 6	390
8	exp Transplants/	544
9	(transplant$ or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT).ti,ab.	49148
10	8 or 9	49346
11	7 and 10	225
12	4 or 11	303

DARE=2, NHS EED=1, CENTRAL=294, CDSR=6.

Table 60. CRD HTA: https://www.crd.york.ac.uk/CRDWeb/: searched 8.2.22

#	Searches	Results
1	(((post transplant* or posttransplant*) NEAR2 lymphoma*)) OR (((post transplant* or posttransplant*) NEAR2 lymphoprolif* NEAR2 (disease* or disorder*))) OR (PTLD) IN HTA FROM 2016 TO 2022	0
2	MeSH DESCRIPTOR Lymphoproliferative Disorders EXPLODE ALL TREES	673

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3	* IN HTA FROM 2016 TO 2022	1,323
4	#2 AND #3	58
5	((lymphoprolif* NEAR2 (disease* or disorder*))) IN HTA FROM 2016 TO 2022	2
6	MeSH DESCRIPTOR transplants EXPLODE 1 IN HTA	8
7	((transplant* or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT)) IN HTA FROM 2016 TO 2022	61
8	#4 OR #5	58
9	#6 OR #7	64
10	#8 AND #9	6

Systematic selection of studies

Figure 32 shows the PRISMA diagram for the SLR.

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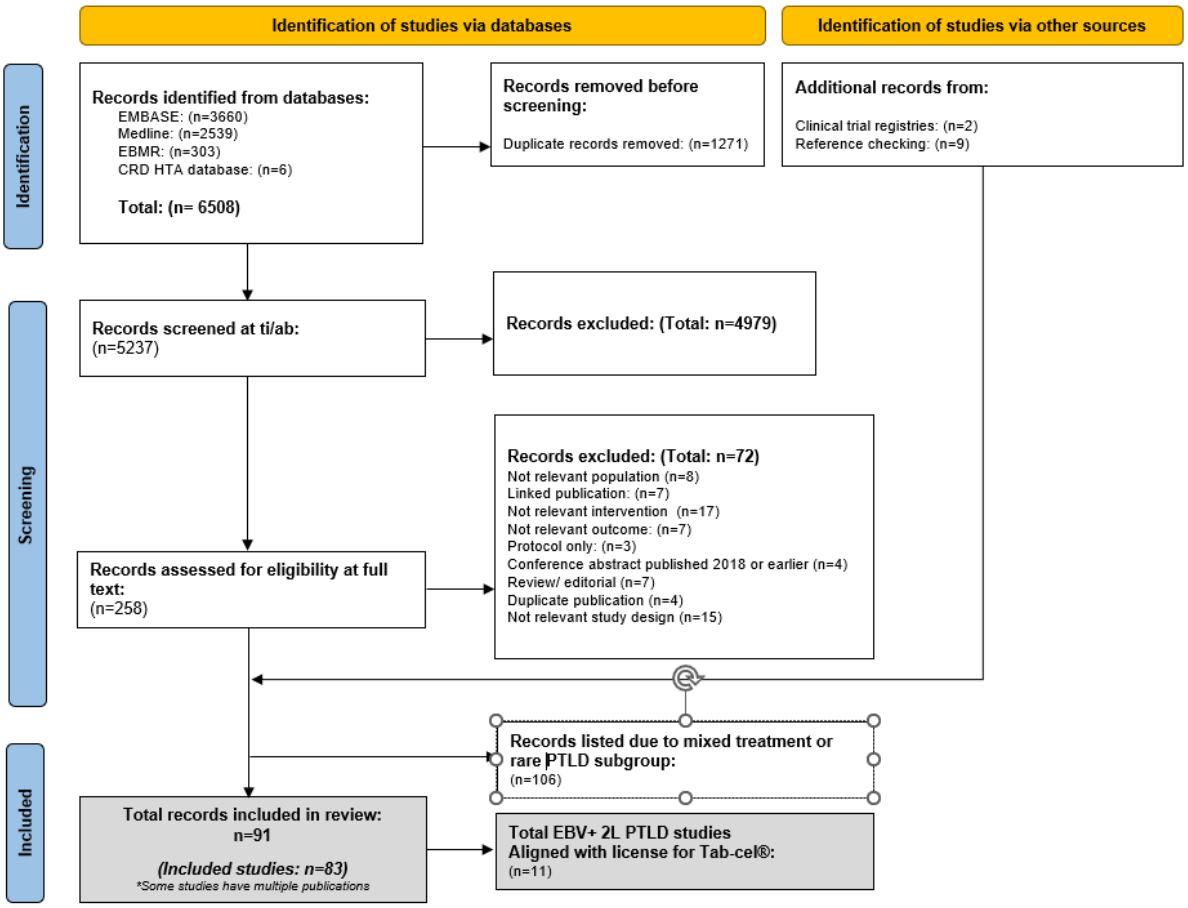
Figure 32. PRISMA study flow diagram



Abbreviations: 2L, second line; CRD, Centre for Reviews and Dissemination; EMBR, Evidence Based Medicine Reviews; EBV, Epstein-Barr virus, HTA, heath technology assessment; n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PTLD, post-transplant lymphoproliferative disorder.

Table 61. The total EBV+ 2L PTLD studies aligned with license for Ebvallo®

Study	Study size	Population age	Transplant type	1st line treatment	2nd line Treatment	ORR	OS			Other outcomes reported
							Median, months 95% (CI)	Definition Of follow-up	KM	
ClinicalTrials.gov (2021) [100] • **Prospective clinical trial, USA**	18	Mixed	SOT	Rituximab	Rituximab Rituximab and allogeneic LMP1/LMP2-	NR	NR	NR	NR	Mortality, AEs, SAEs

					Specific Cytotoxic T-Lymphocytes					
Dharnidharka 2021 [101] • **Retrospective cohort study, USA and Canada**	86	Mixed	SOT	R±CT	Standard care (unknown)	NR	15.5 (8.3-22.9) [f.up 12.9]	From PTLD diagnosis	NR	Mortality
							4.1 (1.9–8.5) [f.up NR]	From when patients became R/R to R+CT.	✓	
Doubrovina 2012 [102] • **Prospective clinical study, USA**	19	Adult	HCT	Rituximab (n=13)	HLA-disparate EBV-specific T cells	68% [80 months f.up]	NR	NR	NR	CR, mortality
	30	Adult	HCT	Rituximab (n=9)	HLA-compatible donor leukocyte infusions	73% [80 months f.up]	NR	NR	NR	CR, mortality
Garcia-Cadenas 2019 [103] ** **Retrospective cohort study, Spain**	9	Mixed	HCT	Rituximab	T cell therapy: HLA-matched third-party EBV-CTLs (n=5); unselected DLI (n=1), donor derived EBV specific CTL (n=3)	40% [f.up NR]	NR	NR	NR	ORR, OS (for 1st line)
	27	Mixed	HCT	Rituximab	Chemotherapy (CHOP in most cases)	37% [f.up NR]	NR	NR	NR	
Luo 2020 [104] •	8	Mixed	HCT	Rituximab	DLI	NR	25%	NR	NR	PTLD-related

Retrospective cohort study **China**							[Median f.up 365 days]			mortality, response to treatment, relapse
	8	Mixed	HCT	Rituximab	EBV-specific CTL	NR	37.5% [Median f.up 365 days]	NR	NR	PTLD-related mortality, response to treatment, relapse
	1	Mixed	HCT	Rituximab	Chemotherapy	NR	100% [Median f.up 365 days]	NR	NR	PTLD-related mortality, response to treatment, relapse
Sanz 2021 [33] • **Retrospective cohort study** **North America and Europe**	81	Adult	HCT	R±CT	Standard care (unknown)	NR	1.7 (1.1-2.3) [f.up 1.7]	From PTLD diagnosis	✓	Mortality
Styczynski 2013 [105] • **Retrospective cohort study** **Europe**	31	Mixed	HCT	Rituximab± RI	Chemotherapy	NR	Alive from PTLD: 16 (51.6%)	NR	NR	PTLD related mortality, OS (KM) presented for whole population (R±RI±CT)
	31	Mixed	HCT	Rituximab± RI	Chemotherapy	NR	Alive total: 11 (35.5%)	NR	NR	
Kazi 2019 [106] • **Retrospective cohort study** **UK and others**	59	Mixed	SOT and HCT	R±CT	T cell therapy: Viral-specific cytotoxic lymphocytes	59% [f.up NR]	NR	NR	NR	CR, PR, SD
	28	Mixed	HCT	R±CT	T cell therapy: Viral-specific cytotoxic lymphocytes	46% [f.up NR]	0.1 years (0.05-0.15) [6 years f.up]	NR	✓	CR, PR, mortality

	20	Mixed	SOT	R±CT	T cell therapy: Viral-specific cytotoxic lymphocytes	75% [f.up NR]	3.87 years (0.00-8.66) [6 years f.up]	NR	✓	CR, PR, mortality
Prockop 2020 [107] • **Prospective clinical trial** **USA**	38	Mixed	SOT and HCT	R±CT	T cell therapy (Ebvallo®)	50% (95% CI 33.4-66.6) [6 months f.up]	18.4 (6.9 - NR) [median 9.4 months f.up]	NR	✓	
	33	Mixed	HCT	R±CT	T cell therapy (Ebvallo®)	68% [f.up NR]	Probability of survival 57% [f.up 2 years]	NR	✓	CR, PR, SD, POD, AE
	13	Mixed	SOT	R±CT	T cell therapy (Ebvallo®)	54% [f.up NR]	54%	NR	✓	CR, PR, SD, POD, AE
Prockop 2021 [108] • **Prospective clinical trial** **Multinational**	14	Mixed	HCT	R±CT	T cell therapy (Ebvallo®)	50% (95% CI 23-77) [6 months f.up]	Median OS not reached [median 10.6 months f.up]	NR	✓	OS, mortality, discontinuation, progression of disease, CR, PD, SD, objective response rate, SAE's, fatal AE's
	24	Mixed	SOT	R±CT	T cell therapy (Tab-cel®)	50% (95% CI 29.1-70.9) [6 months f.up]	16.4 (3.5, NE) [median 8 months f.up]	NR	✓	OS, mortality, discontinuation, progression of disease, CR, PD, SD, objective response rate, SAE's, fatal AE's

Prockop 2020 [109] • **Expanded access program** **USA**	14	Mixed	HCT	R±CT	T cell therapy (Ebvallo®)	50% [f.up 2 years]	Probability of survival 60% [median 3 month f.up]	NR	NR	AE
	12	Mixed	SOT	R±CT	T cell therapy (Ebvallo®)	83% [f.up 2 years]	Probability of survival 83% [median 15 month f.up]	12	Mixed	SOT

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List of included studies

Table 62 – Table 65 summarize the included studies.

Table 62. Summary of included clinical study characteristics (SOT)

Study	NCT Number	Trial name	Associated publication(s)	Publication type	Experimental or observational	Study design	Single arm or comparative	Sample size	Type of PTLD	Line of treatment	Interventions
Ashrafi 2015 [110]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	13	PTLD	First, second, third	Rituximab added to low-dose cyclophosphamide and prednisone
Ashrafi 2021[111]	NR	NR	NA	Journal Article	Observational	Retrospective case series	Single arm	20	PTLD	NR	Rapamycin, rituximab, chemotherapy, R-CHOP
Aversa 2008 [112]	NR	NR	NA	Journal Article	Observational	Prospective cohort study	Single arm	30	PTLD	First	Single-agent rituximab
Bakker 2005 [113]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	1560	PTLD	First	Rituximab monotherapy, CHOP, chemoimmunotherapy, reduction in immunosuppression, R-CHOP, rituximab combined with high-dose chemotherapy including high-dose MTX and Ara-C (Burkimab

											regimen [17]) (n=3), and R-EPOCH (n=1)
Blaes 2005 [114]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Single arm	11	PTLD	First	Rituximab, other therapy
Boyle 2020[115]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative ; single	91	mPLTD: DLBCL	First, second	Rituximab monotherapy, Rituximab and chemotherapy
Buell 2005 [116]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	193	PTLD	First	CHOP, promace, multidrug, single-agent chemotherapy
Burns 2020 [117]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	101	PTLD	First	Rituximab; R-CHOP
Chaganti 2021[118]	NR	TIDal	NA	Conference abstract	Experimental	Prospective clinical trial	Single arm	39	PTLD	First	Rituximab, ibrutinib, chemotherapy
Chan 2012[119]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	19	PTLD	First	Rituximab with or without chemotherapy
Chiou 2018 [120]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	11	PTLD	Second	Rituximab, reduction of immunosuppression (RIS), Epstein-Barr virus-specific cytotoxic T-lymphocyte therapy

Chong 2021[76]	NR	NR	NA	Conference abstract	Observational	Retrospective case series	Comparative	117	PTLD	First	RI plus rituximab ; RI plus chemotherapy
Choquet 2007[121]	NR	NR	Choquet 2006[122]	Journal Article	Experimental	Prospective cohort study	Single arm	63	PTLD	First	Rituximab (4 weekly doses of 375 mg/m^2)
Choquet 2007[123]	NR	NR	NA	Letter	Observational	Retrospective cohort study	Single arm	26	PTLD	Second	CHOP-21
ClinicalTrials.gov (2021) [100]	NCT02900976	NR	NA	Trial record	Experimental	Prospective clinical trial	Comparative	18	PTLD	First and second	Rituximab and and Allogeneic LMP1/LMP2-Specific Cytotoxic T-Lymphocytes, Rituximab
Dharnidharka 2021[101]	NCT03394365	NR	Non-interventional retrospective chart review study conducted by Atara	Conference abstract	Observational	Retrospective cohort study	Single arm	86	PTLD	Second	Standard care (details not reported)
Elstrom 2006 [124]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	35	PTLD	First	Rituximab, Rituximab + adoptive cellular immunotherapy
Evens 2010 [125]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	80	PTLD	First	Cyclophosphamide (600 mg/m^2 intravenous for 1 day) and prednisone (2

											mg/kg orally for 5 days)
Eyre 2021[126]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	21	PTLD	NR	autoSCT
Fararjeh 2018[127]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	45	PTLD	NR	RI plus rituximab; RI plus rituximab and chemotherapy; RI plus rituximab and CTL; RI plus and chemotherapy; RI plus and CTL
Fohrer 2006 [128]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	33	PTLD	First	Rituximab and reduction in immunosuppression (47/51) de-escalation of immunosuppression no additional therapy (3/51) DLI (1/51)
Gallego 2010 [129]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	457	PTLD	Unclear	Rituximab, chemotherapy
Ghobrial 2005 [130]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	30	PTLD	Second	Rituximab, non-rituximab
Gonzalez-Barca 2021[131]	NR	NR	Gonzalez-Barca 2007 [132]	Journal Article	Experimental	1) Prospective clinical trial 2) Real world study	Comparative	38	mPTLD: B cell	First	Rituximab, chemotherapy, immunosuppression reduction, R-chemotherapy

Gross 2002 [133]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Single arm	39	PTLD	Unclear	Low dose chemotherapy regimen
Gross 2005 [134]	NR	NR	NA	Journal Article	Experimental	Prospective cohort study	Single arm	36	PTLD	Mixed	Cyclophosphamide and prednisone, Standard regimens (chemotherapy)
Gross 2012 [135]	NCT00066469	NR	NCT00066469 [136]	Journal Article	Experimental	Prospective clinical trial	Single arm	54	PTLD	Unclear	Cyclophosphamide, prednisone, rituximab
Gupta 2010 [137]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	30	PTLD	First	Rituximab and reduced dose of chemotherapy (R/C), RI, interferon-alpha or rituximab/prednisone or radiotherapy, other chemotherapy agents
Haddad 2001 [138]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Single arm	12	B PTLD	First	Rituximab
Hayashi 2001[139]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	10	PTLD	First	RI plus chemotherapy
Jain 2005 [140]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	17	PTLD	Mixed	Rituximab
Jain 2020[141]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	168	mPTLD: B cell	First	R-primary and R-CHOP, Rituximab

											and R-chemotherapy
Jeong 2017 [142]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	18	PTLD	Second	CHOP + rituximab, MTX-based chemotherapy
Kinch 2014 [143]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	115	PTLD	First	Any initial therapy (115): reduction in immunosuppression alone (21), Rituximab monotherapy (2) rituxiamb combinations (19), Chemotherapy alone (34) chemotherapy combinations (39), Radiotherapy (18), Surgery (27) Antiviral therapy (34)
Knight 2009 [144]	NR	NR	NA	Full paper	Observational	Retrospective analysis	Comparative	78	PTLD	First	Chemotherapy, Rituximab plus chemotherapy, Rituximab monotherapy
Liu 2021[145]	NR	NR	NA	Conference abstract	Observational	Retrospective analysis	Single arm	20	PTLD	Second	CD19 CAR-T
Lopes 2019 [146]	NR	NR	NA	Conference abstract	Observational	Retrospective cohort study	Single arm	3878	PTLD	Unclear	Rituximab

Mamzer-Bruneel 2000 [147]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	16	PTLD	First	Chemotherapy, CHOP
Martinez-Calle 2017 [148]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	1335	PTLD	First	CHOP
Mumtaz 2015 [149]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	1372	PTLD	First	Rituximab, Rituximab + CHOP
Oertel 2005 [150]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Single arm	17	PTLD	First	Reduced immunosuppression, Antiviral agents, Anti-CD20 moAbs, Surgical excision, Radiotherapy, Anthracycline-based chemotherapy
Orjuela 2011 [151]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	45	PTLD	First	Chemotherapy with and without rituximab
Porcu 2002 [152]	NR	NR	NA	Journal Article	Experimental	Prospective cohort study	Single arm	11	PTLD	First	Acyclovir and immunosuppression reduction, Rituximab
Ready 2018 [153]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative ; single	37	pPTLD; DLBCL	First	Rituximab, rituximab + chemotherapy
Sakhuja 2013 [154]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	2000	PTLD	First	Rituximab, rituximab and

											chemotherapy, chemotherapy
Swinnen 2008 [155]	NR	NR	NA	Journal Article	Experimental	Prospective cohort study	Single arm	17	PTLD	NR	Interferon therapy and chemotherapy
Taylor 2006 [156]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	18	PTLD	First	Various first-line treatments
Taylor 2015[157]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	24	PTLD	First	Chemotherapy plus low dose immunosuppression
Trappe 2007 [158]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	11	PTLD	Second	CHOP
Trappe 2009 [159]	NR	PT-LPD-1, PTLD-1, PTLD registry, PTLD D2006–2012	NA	Journal Article	1) Two clinical trials 2) Observational study	1) Pooled data from two prospective trials 2) Registry	Comparative	58	PTLD	First	Rituximab and CHOP
Trappe 2012 [160]	NR	NR	Trappe 2015 [161]; Zimmermann 2018 [162]; Trappe 2017 [163]	Journal Article	Experimental	Prospective cohort study	Comparative	70	mPTLD: B cell	First	Rituximab and CHOP in sequence
Voorhees 2019 [164]	NR	NR	NA	Conference abstract	Observational	Retrospective cohort study	Single arm	29	mPTLD	First	Rituximab monotherapy, Rituximab + chemoimmunotherapy

Wilsdorf 2013 [165]	NR	NR	NA	Journal Article	Experimental	Prospective cohort study	Comparative	16	PTLD	NR	Rituximab, chemotherapy (vincristine, cyclophosphamide, prednisone, methotrexate)
Zimmermann 2019 [166]	NR	NR	NA	Conference abstract	Observational	Retrospective registry review	Comparative	36	PTLD	NR	Rituximab
Zimmermann 2020 [167]	NR	NR	Zimmermann 2019 [168]	Conference abstract	Observational	Retrospective cohort study	Single arm	51	PTLD	First	Rituximab, rituximab plus chemotherapy
Zimmermann 2021[169]	NCT02042391	PTLD-2	NA	Conference abstract	Experimental	Prospective clinical trial	Single arm	60	PTLD	First	Rituximab SC monotherapy, RSC-CHOP-21 and modified RSC-DHAOx, RSC-CHOP-21 chemotherapy

Abbreviations: CAR-T, chimeric antigen receptor T cell; DLBCL, diffuse large B cell lymphoma; DLI, donor leukocyte infusion; NA, not applicable; NR, not reported; PTLD, post-transplant lymphoproliferative disorder; RI, reduced immunosuppression; SCT, stem cell transplant; SOT, solid organ transplant.

Table 63. Summary of included clinical study characteristics (HCT)

Study	NCT Number	Trial name	Associated publication(s)	Publication type	Experimental or observational	Study design	Single arm or comparative	Sample size	Type of PTLD	Line of treatment	Interventions
Doubrovina 2012[102]	NR	NR	NA	Journal Article	Experimental	Prospective cohort study	Comparative	49	PTLD	Mixed	Adoptive immunotherapy with third-party donor-derived EBV-CTLs

Faye 2001 [170]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	12	mPTLD: B cell	First	Rituximab
Fox 2014 [171]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	62	PTLD	First	Rituximab, reduction in immunosuppression, chemotherapy, radiotherapy
Garcia-Cadenas 2019[103]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	102	PTLD	Mixed	RI and rituximab; chemotherapy; T cell therapy
Heslop 2010 [172]	NCT00058812	NR	NA	Journal Article	Observational	Prospective cohort study	Single arm	114	PTLD	Unclear	EBV-specific cytotoxic T lymphocytes (CTLs)
Jiang 2016 [173]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Comparative	84	PTLD	First	Rituximab based, non-rituximab based
Kalra 2018[174]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	43	PTLD	First	Rituximab
Luo 2020 [104]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	70	PTLD	First, second	Single-agent rituximab (375 mg/m^2/week); EBV-CTL; DLI; chemotherapy
Montanari 2019 [175]	NR	NR	NA	Conference abstract	Observational	Retrospective cohort study	Comparative, single arm	49	mPLTD: DLBCL	First	R-EPOCH and R-CHOP
Sanz 2021 [33]	NCT03394436	NR	Non-interventional retrospective chart review study conducted by Atara	Conference abstract	Observational	Retrospective analysis	Single arm	81	PTLD	Second plus	Rituximab monotherapy, Rituximab plus chemotherapy
Styczynski 2013 [105]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	144	PTLD	First and second	Rituximab, reduction on immunotherapy (RI) and R-CHOP

Uhlin 2014 [176]	NR	NR	NR	Journal Article	Observational	Retrospective cohort study	Comparative	40	PTLD	Mixed	Rituximab, rituximab and chemotherapy/donor lymphocyte infusion/virus-specific CTL
Xu 2012[177]	NR	NR	NA	Journal Article	Observational	Retrospective analysis	Single arm	11	PTLD	First	Rituximab (375mg/m^2/week)
Xu 2015 [178]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	45	PTLD	First	Mixed treatments; Rituximab
Zhu 2019 [179]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	27	PTLD	First	Rituximab based Chemo based non-rituximab (other)

Abbreviations: DLI, donor leukocyte indusion; EBV-CTL, Epstein-Barr virus-specific T cells; HCT, haematopoietic stem cell transplant; NA, not applicable; NR, not reported; PTLD, post-transplant lymphoproliferative disorder; RI, reduced immunosuppression.

Table 64. Summary of included clinical study characteristics (Mixed)

Study	NCT Number	Trial name	Associated publication(s)	Publication type	Experimental or observational	Study design	Single arm or comparative	Sample size	Type of PTLD	Line of treatment	Interventions
Bishnoi 2017[180]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Comparative	141	PTLD	NR	Rituximab (+/- IS), Rituximab plus chemotherapy (+/- IS)
Haque 2007[181]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Single arm	33	PTLD	Mixed	EBV-CTLs
Messahel 2006 [182]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	22	PTLD	Mixed	Rituximab
Montanari 2015 [183]	NR	NR	NA	Journal Article	Observational	Retrospective analysis	Comparative	120	PTLD	First	Rituximab and chemotherapy, Non-rituximab containing

											chemotherapy, Rituximab monotherapy
Pearse 2020 [184]	NR	NR	NA	Conference abstract	Observational	Retrospective analysis	Single arm	56	PTLD	First	Rituximab (NR)
Vickers 2014 [185]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Single arm	9	PTLD	NR	EBV-specific cytotoxic T lymphocytes

Abbreviations: EBV-CTL, Epstein-Barr virus-specific T-cell; IS, immunosuppression; NA, not applicable; NR, not reported; PTLD, post-transplant lymphoproliferative disorder.

Table 65. Summary of included clinical study characteristics (Both – separately)

Study	NCT Number	Trial name	Associated publication(s)	Publication type	Experimental or observational	Study design	Single arm or comparative	Sample size	Type of PTLD	Line of treatment	Interventions
Fischer 1991[186]	NR	NR	NA	Journal Article	Experimental	Prospective clinical trial	Single arm	18	mPTLD: B cell	NR	Anti-B cell antibodies
Kazi 2019 [106]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	59	PTLD	Second	CTL
Milpied 2000 [187]	NR	NR	NA	Journal Article	Observational	Retrospective cohort study	Single arm	32	B PTLD	First	Rituximab, Rituximab + CHOP
Prockop 2020 [107]	NCT01498484, NCT00002663	NR	NA	Journal article	Experimental	Prospective clinical trial	Single arm	46	PTLD	Second	T cell immunotherapy (Tab-cel®)
Prockop 2021 [108]	NCT03394365	ALLELE	NA	Conference abstract	Experimental	Prospective clinical trial	Single arm	38	PTLD	Second	T cell immunotherapy (Tab-cel®)
Prockop 2020 [109]	NCT02822495	EBV-CTL-201	Prockop 2019 [188]	Conference abstract	Experimental	Expanded access program	Single arm	26	PTLD	Second	T cell immunotherapy (Tab-cel®)

Abbreviations: CTL, cytotoxic T-cell lymphocyte; NA, not applicable; NR, not reported; PTLD, post-transplant lymphoproliferative disorder.

List of excluded studies

Table 66 summarizes the excluded studies in the clinical SLR.

Table 66. Summary of studies in the clinical SLR excluded at full publication review

Author	Title	Journal	Year	Citation
Not relevant population (n=8)				
Pearse, W. B.	A phase I/II trial of brentuximab vedotin plus rituximab as frontline therapy for patients with immunosuppression-associated CD30+ and/or EBV + lymphomas	Leukemia and Lymphoma	2021	62(14):3493-3500.
Shimony, S.	Late onset neutropenia after rituximab and obinutuzumab treatment-characteristics of a class-effect toxicity	Leukemia and Lymphoma	2021	62(12):2921-2927.
Awada, H.	Long-Term Experience with Large Granular Lymphocytic Leukemia Evolving after Solid Organ and Hematopoietic Stem Cell Transplantation	Blood	2019	134(Supplement 1):1226.
Pearse	A Phase I/II Trial of Brentuximab Vedotin (BV) Plus Rituximab (R) As Frontline Therapy for Patients with Immunosuppression-Associated CD30+ and/or EBV+ Lymphomas	Blood	2019	134(Supplement 1):351.
Savoldo, B.	Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs)	Blood	2006	108(9):2942-9.
Nehring, A. K.	Epstein-Barr virus T-cell immunity despite rituximab	British Journal of Haematology	2007	136(4):628-32.
Posey, L. A.	Posttransplantation lymphoproliferative disease in children: otolaryngologic manifestations and management	Southern Medical Journal	1999	92(11):1079-82.
Sica, S.	Autologous transplantation of peripheral blood progenitor cells mobilized by chemotherapy with or without G-CSF (filgrastim) in resistant lymphoproliferative diseases: enhanced hemopoietic recovery with filgrastim primed progenitors	Haematologica	1993	78(6):383-8.
Linked publication (n=7)				

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Trappe, R. U.	Treatment stratification in B-cell PTLD after solid organ transplantation (SOT) by international prognostic index (IPI) and response to rituximab: Interim results from the PTLD-2 trial	Journal of Clinical Oncology. Conference	2020	38(15).
Worel, N.	29P ALLELE study: A multicenter, open label, phase III study of tabelecleucel for solid organ or allogeneic hematopoietic cell transplant subjects with Epstein-Barr virus-driven post-transplant lymphoproliferative disease (EBV+ PTLD) after failure of rituximab or rituximab and chemotherapy	Annals of Oncology	2020	31(Supplement 7):S1426-S1427.
Eyre, T.	Autologous stem cell transplantation in post-transplant lymphoproliferative disorders: A retrospective analysis from the lymphoma working party of the EBMT	HemaSphere	2020	4(Supplement 1):662-663.
Zimmermann, H.	Treatment stratification in B-cell ptld after solid organ transplantation by transplanted organ, international prognostic index (IPI) and response to rituximab: Interim results from the PTLD-2 trial	HemaSphere	2020	4(Supplement 1):567.
McDonald, L.	Post-transplant lymphoproliferative disorder post solid organ transplant-a heterogenous, aggressive disorder: A multicentre report	HemaSphere	2020	4(Supplement 1):603-604.
Prockop, S. E.	A Multicenter, Open Label, Phase 3 Study of Tabelecleucel for Solid Organ Transplant Subjects with Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disorder (EBV+PTLD) after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE)	Biology of Blood and Marrow Transplantation	2020	26(3 Supplement):S274.
Prockop, S.	A Multicenter, Open Label, Phase 3 Study of Tabelecleucel for Solid Organ Transplant Subjects with Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disease (EBV+PTLD) after Failure of Rituximab or Rituximab and Chemotherapy	Blood	2019	134(Supplement 1):5326.
Not relevant intervention (n=17)				
Darema	Post-transplant lymphoproliferative disease in kidney transplant recipients: A singlecenter study	Transplant International	2021	34(SUPPL 1):167.

Zierhut, H.	Course of renal allograft function after diagnosis and treatment of post-transplant lymphoproliferative disorders in pediatric kidney transplant recipients	Pediatric Transplantation	2021	25(6) (no pagination)(e14042).
Seki, J.	Outcomes of EBV viremia and PTLD after rituximab: A phamraco-cost analysis	Bone Marrow Transplantation	2020	55:772.
Socie	Clinical outcomes of EBV+ ptld patients following hct who fail rituximab: A retrospective chart review study from France	Bone Marrow Transplantation	2020	55:515-516.
Fujimoto, A.	Low incidence of posttransplant lymphoproliferative disorder after allogeneic stem cell transplantation in patients with lymphoma treated with rituximab	Hematological Oncology	2020	38(2):146-152.
Fareen, M.	Alemtuzumab containing renal transplant protocols are associated with late onset EBV+ PTLD, with poorer overall survival	British Journal of Haematology	2020	189(Supplement 1):179-180.
Naik, S.	Survival outcomes of allogeneic hematopoietic cell transplants with EBV-positive or EBV-negative post-transplant lymphoproliferative disorder, A CIBMTR study	Transplant Infectious Disease	2019	21(5) (no pagination)(e13145).
Caillard, S.	A French cohort study of kidney retransplantation after post-transplant lymphoproliferative disorders	Clinical Journal of the American Society of Nephrology	2017	12(10):1663-1670.
Hayes, D.	Posttransplant lymphoproliferative disease and survival in adult heart transplant recipients	Journal of Cardiology	2017	69(1):144-148.
Akbas, A.	Post-transplant lymphoproliferative disorders with naso- and oropharyngeal manifestation	Transplant International	2015	28(11):1299-1307.
Aliakbarian, M.	Prevention of posttransplant lymphoproliferative disorder in pediatric patients with a liver transplant	Experimental and Clinical Transplantation	2015	13(5):426-429.
Dayton, J. D.	Role of immunosuppression regimen in post-transplant lymphoproliferative disorder in pediatric heart transplant patients	Journal of Heart and Lung Transplantation	2011	30(4):420-425.
Saadat	Posttransplantation lymphoproliferative disorders in renal transplant recipients: report of over 20 years of experience	Transplant Proc	2007	39(4):1071-3.

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Boyle	Posttransplantation lymphoproliferative disorders in pediatric thoracic organ recipients	Journal of Pediatrics	1997	131(2):309-13.
Tsai	Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients	Transplantation	2001	71(8):1076-88.
Miller	Posttransplantation lymphoproliferative disorder: changing manifestations of disease in a renal transplant population	Critical Reviews in Diagnostic Imaging	1997	38(6):569-85.
Purighalla	Acute renal allograft rejection in patients with Epstein-Barr virus associated post-transplant lymphoproliferative disorder	Clinical Transplantation	1997	11(6):574-6.
Not relevant outcome (n=7)				
Coelho, I.	Post-transplant lymphoproliferative disorder (PTLD): Single institutional experience of two decades	Nephrology Dialysis Transplantation	2020	35(SUPPL 3):iii2002.
Kizilbash, S.	Long-term outcomes and the feasibility of kidney retransplantation in pediatric survivors of post-transplant lymphoproliferative disease	American Journal of Transplantation	2019	19(Supplement 3):977-978.
Van Der Velden, W. J. F. M.	Reduced PTLD-related mortality in patients experiencing EBV infection following allo-SCT after the introduction of a protocol incorporating pre-emptive rituximab	Bone Marrow Transplantation	2013	48(11):1465-1471.
Worth, A.	Pre-emptive rituximab based on viraemia and T cell reconstitution: A highly effective strategy for the prevention of Epstein-Barr virus-associated lymphoproliferative disease following stem cell transplantation	British Journal of Haematology	2011	155(3):377-385.
Birkeland	Long-term follow-up of kidney transplant patients with posttransplant lymphoproliferative disorder: duration of posttransplant lymphoproliferative disorder-induced operational graft tolerance, interleukin-18 course, and results of retransplantation	Transplantation	2003	76(1):153-8.
Zimmermann	Burden of Hospitalizations Due to Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disorder (EBV+PTLD) in Patients Who Failed First	Blood	2019	134(Supplement 1):65.

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	Line Rituximab or Rituximab Plus Chemotherapy Following Solid Organ Transplant (Post-SOT): A Retrospective Chart Review Study of German PTLD Registry			
Yu	Post-transplant lymphoproliferative disorder-related admissions in the United States	Journal of Clinical Oncology. Conference	2019	37(Supplement 15).
Protocol only (n=3)				
Worel, N.	Allele study: A multicenter, open label, phase 3 study of tabelecleucel for solid organ or allogeneic hematopoietic cell transplant subjects with epsteinbarr virus-driven post-transplant lymphoproliferative disease (EBV+ PTLD) after failure of rituximab or rituximab and chemotherapy	Transplant International	2021	34(SUPPL 3):25.
Isrctn	A study using a response-based combination therapy of rituximab and ibrutinib in patients with post-transplant lymphoproliferative disorder (PTLD)	https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN32667607.	2016	
Worel, N.	ALLELE Study: A multicenter, open label, phase 3 study of tabelecleucel for solid organ or allogeneic hematopoietic cell transplant subjects with EBV+ PTLD after failure of rituximab or rituximab and chemotherapy	Oncology Research and Treatment	2021	44(SUPPL 2):193-194.
Conference abstract published 2018 or earlier (n=4)				
Prockop, S.	Adoptive therapy with EBV-specific T cells for treatment of CNS EBV post-transplant lymphoproliferative disease arising after hematopoietic stem cell transplant or solid organ transplant	Blood. Conference: 60th Annual Meeting of the American Society of Hematology, ASH	2018	132(Suppl. 1).
Van Keerberghen, C.	Role of interim and end of treatment PET/CT for response assessment and prediction of relapse in post-transplant lymphoproliferative disorder	European Journal of Nuclear Medicine and Molecular Imaging	2018	45(Supplement 1):S440-S441.
Prockop, S.	Long term outcomes of tabelecleucel (allogeneic third-party ebv-targeted cytotoxic t lymphocytes) for rituximab-refractory post-transplant EBV+ lymphomas: A single center experience	HemaSphere	2018	2(Supplement 2):155.

Prockop, S. E.	Efficacy and safety of ATA129, partially matched allogeneic third-party Epstein-barr virus-targeted cytotoxic T lymphocytes in a multicenter study for post-transplant lymphoproliferative disorder	Biology of Blood and Marrow Transplantation	2018	24(3 Supplement 1):S41-S42.
Review/ editorial (n=7)				
Montanari, F.	Joining Efforts for PTLD: Lessons Learned from Comparing the Approach and Treatment Strategies Across the Pediatric and Adult Age Spectra	Current Hematologic Malignancy Reports	2021	16(1):52-60.
Lee, J. J.	Role of chemotherapy and rituximab for treatment of posttransplant lymphoproliferative disorder in solid organ transplantation	Annals of Pharmacotherapy	2007	41(10):1648-1659.
Sprangers, B.	Posttransplant Lymphoproliferative Disorder Following Kidney Transplantation: A Review	American Journal of Kidney Diseases	2021	78(2):272-281.
Ma, H.	A peripheral T-cell lymphoma (PTCL) arising as a post-transplant lymphoproliferative disorder: efficacy of pralatrexate in primary refractory disease and review of the literature	Leuk Lymphoma	2019	60(13):3300-3303
Bollard, C. M.	T-cell therapy in the treatment of post-transplant lymphoproliferative disease	Nature Reviews Clinical Oncology	2012	9(9):510-9.
Svoboda, J.	Management of patients with post-transplant lymphoproliferative disorder: the role of rituximab	Transplant International	2006	19(4):259-69.
Raj, R.	Lung retransplantation after posttransplantation lymphoproliferative disorder (PTLD): a single-center experience and review of literature of PTLD in lung transplant recipients	Journal of Heart & Lung Transplantation	2005	24(6):671-9.
Duplicate publication (n=4)				
Chong, E. A.	Post-transplant lymphoproliferative disorder in kidney transplant patients: A multicenter report	Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO	2021	39(15 SUPPL).
Watson	Qualitative Findings on the Impact of Disease in Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disease Patients, as Measured by EQ-5D, SF-36, and the FACT-LYM	Oncology and Therapy	2020	8(2):299-310.
Xu, L. P.	[The efficacy and safety of rituximab in treatment of Epstein-Barr virus disease post allogeneic	Zhonghua nei ke za zhi [Chinese journal of internal medicine]	2012	51(12):966-970.

	hematopoietic stem-cell transplantation]. [Chinese]			
Nct	Reduced Immunosuppressive Therapy With or Without Donor White Blood Cells in Treating Patients With Lymphoproliferative Disease After Organ Transplantation	https://clinicaltrials.gov/show/NCT00033475	2002	
Not relevant study design (n=15)				
Liu, Y.	Post-transplant lymphoproliferative disorder after paediatric liver transplantation	International Journal of Clinical Practice	2021	75(4) (no pagination)(e13843).
Shimizu, D.	Post-Transplant Lymphoproliferative Disorder in Lung Transplantation: A Single-Center Experience in Japan	Journal of Heart and Lung Transplantation	2021	40(4 Supplement):S312.
Wang, X.	Efficacy of donor and 'third party' derived EBV-specific cytotoxic t cells for treatment of rituximab-refractory EBV-PTLD after allo-HSCT in pediatric patients	HemaSphere	2020	4(Supplement 1):662.
Raberahona, M.	Dynamics of Epstein-Barr viral load after hematopoietic stem cell transplantation and effect of preemptive rituximab therapy	Transplant Infectious Disease	2016	18(6):889-895.
Hart, M.	EBV-positive mucocutaneous ulcer in organ transplant recipients: a localized indolent posttransplant lymphoproliferative disorder	The American journal of surgical pathology	2014	38(11):1522-1529.
Zimmermann, H.	Plasmablastic posttransplant lymphoma: Cytogenetic aberrations and lack of Epstein-Barr virus association linked with poor outcome in the prospective german posttransplant lymphoproliferative disorder registry	Transplantation	2012	93(5):543-550.
Orjuela, M.	A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation	Clinical Cancer Research	2003	9(10 II):3945s-3952s.
Choi, S.	Stage IV Classical Hodgkin Lymphoma-type Posttransplant Lymphoproliferative Disorder in a Pediatric Liver Transplant Patient: A Case Report and Review of the Literature	Journal of Pediatric Hematology/Oncology	2021	43(7):e1015-e1019.
Feng, G.	Safety and Efficacy of Anti-CD19-Chimeric Antigen Receptor T Cell Combined With	Frontiers in Oncology	2021	11:726134.

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	Programmed Cell Death 1 Inhibitor Therapy in a Patient With Refractory Post-Transplant Lymphoproliferative Disease: Case Report and Literature Review			
Nabors, L. B.	Isolated central nervous system posttransplant lymphoproliferative disorder treated with high-dose intravenous methotrexate	American Journal of Transplantation	2009	9(5):1243-8.
Oertel, S. H.	Salvage chemotherapy for refractory or relapsed post-transplant lymphoproliferative disorder in patients after solid organ transplantation with a combination of carboplatin and etoposide	British Journal of Haematology	2003	123(5):830-5.
Yedibela, S.	Anti-CD20 monoclonal antibody treatment of Epstein-Barr virus-induced intrahepatic lymphoproliferative disorder following liver transplantation	Transplant International	2003	16(3):197-201.
Smets, F.	Indications and results of chemotherapy in children with posttransplant lymphoproliferative disease after liver transplantation	Transplantation	2000	69(5):982-4.
Sculerati, N.	Otolaryngologic management of posttransplant lymphoproliferative disease in children	Annals of Otology, Rhinology & Laryngology	1990	99(6 Pt 1):445-50.
Lindsay, J.	Epstein-Barr virus posttransplant lymphoproliferative disorder: update on management and outcomes	Current Opinion in Infectious Diseases	2021	34(6):635-645.

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Results of clinical review

The clinical SLR identified 91 publications that reported on 83 studies eligible for the clinical SLR. Of these, 11 studies [33, 100-109] were assessing populations aligned with the Ebvallo® indication, i.e., EBV⁺ PTLD following HCT or SOT patients who have received at least one prior therapy (for SOT patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate). This is also taking into account the design of the ALLELE study assessing Ebvallo® in patients with EBV-positive PTLD who had failed rituximab for SOT and HCT subpopulations, or who had failed rituximab plus chemotherapy for the SOT subpopulation [189]. The use of rituximab and chemotherapy could be in combination or in sequence.

Conclusions

There were limited high quality studies that were well reported and investigated the pharmacological treatment of PTLD. The majority were small, retrospective, and observational and many did not clearly report line of treatment or EBV status. Ebvallo® represents an additional treatment option for EBV⁺ PTLD following HCT or SOT patients who have received at least one prior therapy (for SOT patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate).
Patients who develop PTLD following SOT or HCT represent a substantial cost burden, even when only direct medical costs are considered. Patients with PTLD also require a number of healthcare interventions, with most patients utilising inpatient and outpatient services in the year following their diagnosis.

Please refer to the following sections in the document linked below:

- chapter 3 for the methodology of the clinical SLR,
- chapter 4 for the identified studies,
- chapter 8.1.1 for a summary of the results.

Comparator – adverse events

BSC adverse event rates were not collected in RS002, therefore were sourced from the literature, with sources identified via a targeted search. A rapid targeted literature review was performed to identify adverse event rates for BSC treatments: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP), and gemcitabine-dexamethasone-cisplatin (GDP). Search strings were developed to find adverse event rates for each treatment in PTLD and analogous disease areas.

Initially, search strings for each treatment contained the terms “lymphoma”, “adverse event” and the treatment name. Further searches were performed with variations on search terms for the disease area, such “Epstein–Barr virus” instead of “lymphoma”. Finally, variations were performed on the terms used for the treatment name, such as using combinations of brand and generic names for the drug components. The search strings that produced the papers used in the model are reported in Table 67.

These searches were restricted to studies published within the past 10 years. They were also run without restrictions. The number of hits per search string was recorded for each treatment and the returning titles and abstracts were screened. Papers that were not of interest were excluded. For example, papers that did not report adverse events for all drug components of a treatment were excluded. The remaining titles were catalogued, and the full papers were reviewed. Data were extracted on the reported adverse event rates, as well as the respective sample sizes.

Table 67: Comparator adverse events search string results

Treatment	R-CHOP	GDP
Search string	(Lymphoma) AND (Adverse events) AND (R-CHOP)	(lymphoma) AND (safety) AND (GDP OR (Gemcitabine AND Dexamethasone AND Cisplatin)
Papers returned	207	99
Papers excluded	201	83
Papers remaining	6	10

Abbreviations: GDP, gemcitabine, dexamethasone, cisplatin; N/A, not applicable; R-CHOP, rituximab, cyclophosphamide, doxorubicin, oncovin, prednisolone.

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Appendix B Main characteristics of included studies

ALLELE

Table 68. Main characteristics of ALLELE

ALLELE NCT03394365	Multicentre, Open-Label, Phase 3 Study of Ebvallo® for Solid Organ or Allogeneic Hematopoietic Cell Transplant Patients with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study), Atara Biotherapeutics, 2022 [190]
Objective	The objective of the study was to evaluate the response to Ebvallo® in patients following solid organ or allogeneic hematopoietic cell transplant patients with Epstein Barr virus-associated posttransplant lymphoproliferative disease after failure of rituximab or rituximab and chemotherapy.
Publications – title, author, journal, year	No manuscript to date
Study type and design	A Phase 3, multicentre, open-label, non-randomised, single-arm trial at 23 study sites in US, Canada, Australia and Europe
Sample size (n)	Total C-PTLD n= 53 C-SOT n= 33 (C-SOT-R n=14 and C-SOT-R+C n=19) C-HCT n=20 This application focuses on the cohort C-SOT-R+C and HCT, as per EMA indication.

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ALLELE NCT03394365	Multicentre, Open-Label, Phase 3 Study of Ebvallo® for Solid Organ or Allogeneic Hematopoietic Cell Transplant Patients with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study), Atara Biotherapeutics, 2022 [190]
Main inclusion and exclusion criteria	Inclusion criteria: • Prior SOT of kidney, liver, heart, lung, pancreas, small bowel, or any combination of these (SOT cohort); or prior allogeneic HCT (HCT cohort). • Biopsy-proven EBV^{+} PTLD. • Availability of appropriate partially HLA-matched and restricted Ebvallo® confirmed by the sponsor. • Measurable 18F-deoxyglucose-avid (Deauville score ≥3) systemic disease using Lugano classification response criteria [54]. • Treatment failure of rituximab or interchangeable commercially available biosimilar monotherapy (C-SOT-R or C-HCT cohorts) or rituximab plus any concurrent or sequentially administered chemotherapy regimen (C-SOT-R+C) for treatment of PTLD. • Males and females of any age. • Eastern Cooperative Oncology Group (ECOG) performance status ≤3 for patients aged ≥16 years; Lansky score ≥20 for patients <16 years. • For HCT cohort only: if allogeneic HCT was performed as treatment for an acute lymphoid or myeloid malignancy, the underlying primary disease for which the patient underwent transplant must have been in morphologic remission. • Adequate organ function. Patient or patient's representative was willing and able to provide written informed consent. Exclusion criteria: • Burkitt lymphoma, classical Hodgkin lymphoma, or any T-cell lymphoma. • Daily steroids of >0.5 mg/kg prednisone or glucocorticoid equivalent, ongoing methotrexate, or extracorporeal photopheresis. • Untreated CNS PTLD or CNS PTLD for which the patient was actively receiving CNS-directed chemotherapy (systemic or intrathecal) or radiotherapy at enrolment. • Suspected or confirmed grade ≥2 GvHD. • Ongoing or recent use of a checkpoint inhibitor agent • For HCT cohort only: active adenovirus viremia. • Need for vasopressor or ventilatory support. • Antithymocyte globulin or similar anti-T-cell antibody therapy ≤ 4 weeks prior to enrolment. • Treatment with EBV-CTLs or chimeric antigen receptor T cells directed against B cells within 8 weeks of enrolment (SOT or HCT cohorts) or unselected donor lymphocyte infusion within 8 weeks of enrolment (HCT cohort only). • Female who was breastfeeding or pregnant, or female of childbearing potential, or male with a female partner of childbearing potential unwilling to use a highly effective method of contraception. • Inability to comply
Intervention	Ebvallo® (tabelecleucel)
Comparator(s)	N/A single arm
Follow-up time	Follow up period of 5 years, however not yet complete. Median 18.9 months at the November 2021 data cut
Is the study used in the health economic model?	Yes

ALLELE NCT03394365	Multicentre, Open-Label, Phase 3 Study of Ebvallo® for Solid Organ or Allogeneic Hematopoietic Cell Transplant Patients with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study), Atara Biotherapeutics, 2022 [190]
Primary, secondary and exploratory endpoints	The secondary efficacy endpoints were as follows: • DOR (defined as the time from the date of initial response until either progression after the last response or death due to any cause) in SOT and HCT cohorts separately. • ORR and DOR in SOT and HCT cohorts combined. • Rate of CR (defined as the proportion of subjects who achieved best overall response of CR) and PR (defined as the proportion of subjects who achieved best overall response of PR). • TTR (defined as the time from the date of first dose of Ebvallo® to the date of first response, either CR or PR, whichever occurred first) and TTBR (defined as the time from first dose of Ebvallo® to the date of achieving the first best overall response). • OS (defined as the time from first dose of Ebvallo® to the date of death from any cause). The exploratory endpoints were as follows: • PFS (defined as the time from first dose of Ebvallo® to either progression after last response to Ebvallo® or death due to any cause, whichever occurred first). • DRR (defined as CR + PR, lasting > 6 months). • TTP (defined as the time from first dose of Ebvallo® to progression after last response). • Efficacy endpoints (including disease assessment-related endpoints and OS) in each of the 2 SOT subgroups. • PROs: EQ-5D-5L (Age >= 16 years) and FACT-Lym (Age >= 18 years) scores over time. • The association of EBV-CTL precursor (EBV-CTLp) with efficacy. • The association of EBV-CTLp with safety. • Subject, Ebvallo®, and disease factors that may predict clinical benefit. • The association of cytokine profile with clinical activity and efficacy.
Method of analysis	In total, 3 efficacy analyses were planned based on the SOT cohort, with 2 interim analyses (at N=15 and 21 patients) and 1 final analysis. At the first interim analysis (N = 15), a futility analysis was also performed. An O'Brien Fleming spending function was used for the interim efficacy analyses with 1 sided alpha being 0.0009, 0.0047 and 0.0234 at the 2 interim analyses and the final analysis, respectively. If the timing of an interim analysis deviated from the schedule, the alpha level was kept the same as prespecified. For the futility analysis at N=15 patients, the conditional power approach was used. More specifically, if the conditional power under the average of observed data and alternative hypothesis was less than 10%, the futility boundary was considered to be met. At the interim analyses, the totality of data was also considered in addition to the statistical boundary for formal decision making. While no formal interim analysis was planned for the HCT cohort, it was analyzed in addition to the SOT cohort. Further statistical analysis methods are presented in Appendix 3: ALLELE study (supportive items) (which include endpoints methodology and sample size calculation).

ALLELE NCT03394365	Multicentre, Open-Label, Phase 3 Study of Ebvallo® for Solid Organ or Allogeneic Hematopoietic Cell Transplant Patients with Epstein Barr Virus-Associated Posttransplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE Study), Atara Biotherapeutics, 2022 [190]
Subgroup analyses	Subgroup analysis were to be performed for ORR, as well as OS and PFS (considering PD after last response). The following subgroups were prespecified in the Statistical Analysis Plan: • Age (<18 vs ≥18 years, <16 vs ≥16 years) • Gender (male, female) • Race (White vs other) • Ethnicity (Hispanic vs non-Hispanic) • Region (North America, Asia Pacific vs Europe).
Other relevant information	N/A

RS002

Table 69. Main characteristics of RS002

ATA129-RS002	RS002 Study: A descriptive, multinational, multicenter non-interventional retrospective chart review study of patients with biopsy-proven EBV$^+$ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory or had relapsed after such therapy, Pierre Fabre, 2022 [191]
Objective	Main objectives of the study were to evaluate the efficacy of standard of care in patients with EBV$^+$ PTLD after allogeneic HCT or SOT following treatment with rituximab or rituximab plus chemotherapy, as measured by the overall survival (OS); to describe the natural history and patient characteristics of EBV$^+$ PTLD post HCT or post SOT; and to use these data for an indirect comparative analysis with the pivotal study ALLELE assessing Ebvallo®.

ATA129-RS002	RS002 Study: A descriptive, multinational, multicenter non-interventional retrospective chart review study of patients with biopsy-proven EBV+ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory or had relapsed after such therapy, Pierre Fabre, 2022 [191]
Publications – title, author, journal, year	1. Zimmermann H, Xu H, Barlev A, Feng A, Li X, Navarro W, et al. CLINICAL OUTCOMES OF SOLID ORGAN TRANSPLANT PATIENTS WITH EBV+PTLD WHO FAIL FIRST-LINE RITUXIMAB OR RITUXIMAB PLUS CHEMOTHERAPY: AN ANALYSIS OF GERMAN PTLD REGISTRY: PF719. HemaSphere. 1 juin 2019 ;3 :314. [42] 2. Zimmermann H, Xu H, Barlev A, Zhang Y, Thirumalai D, Watson C, et al. Burden of Hospitalizations Due to Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disorder (EBV+PTLD) in Patients Who Failed First Line Rituximab or Rituximab Plus Chemotherapy Following Solid Organ Transplant (Post-SOT): A Retrospective Chart Review Study of German PTLD Registry. Blood. 13 nov 2019;134(Supplement_1):65. [52] 3. Inc MG. ADVERSE EVENTS AND CLINICAL BURDEN ASSOCIATED WITH CHEMOTHERAPY IN… by Heiner Zimmermann [Internet]. [cité 16 sept 2022]. Disponible sur: ht tps://library.ehaweb.org/eha/2020/eha25th/293756/heiner.zimmermann.adverse.events.and.clinical.burden.associated.with.html [53] 4. Socié G, Pigneux A, Herbaux C, Chauvet P, Xu H, Thirumalai D, et al. Clinical Outcomes of EBV+ PTLD Patients Following HCT Who Fail Rituximab: A Retrospective Chart Review Study from France. :1. [34] 5. Dharnidharka V, Thirumalai D, Jaeger U, Zhao W, Dierickx D, Xun P, et al. Clinical Outcomes of Solid Organ Transplant Patients with Epstein-Barr Virus-Driven (EBV +) Post-Transplant Lymphoproliferative Disorder (PTLD) Who Fail Rituximab Plus Chemotherapy: A Multinational, Retrospective Chart Review Study. Blood. 5 nov 2021;138(Supplement 1):2528. [20] 6. Sanz J, Storek J, Socié G, Thirumalai D, Guzman-Becerra N, Xun P, et al. Clinical Outcomes of Patients with Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disease Following Hematopoietic Stem Cell Transplantation Who Fail Rituximab: A Multinational, Retrospective Chart Review Study. Blood. 23 nov 2021;138:1454.[33]
Study type and design	This study is a large, descriptive, multinational, multicenter non-interventional retrospective chart review (ongoing study).
Sample size (n)	The study sites for this study span across 9 countries and 29 centers in North America (6 in the USA, 3 in Canada) and Europe (6 in France and 6 in Spain, 4 in Italy, 1 in Austria, 1 in Belgium, 1 in Germany, and 1 in Sweden).

ATA129-RS002	RS002 Study: A descriptive, multinational, multicenter non-interventional retrospective chart review study of patients with biopsy-proven EBV+ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory or had relapsed after such therapy, Pierre Fabre, 2022 [191]
Main inclusion and exclusion criteria	Inclusion criteria: • Patient of any age diagnosed with EBV+ PTLD after allogeneic HCT or SOT • Patient receiving rituximab or rituximab plus chemotherapy for PTLD between 01 January 2000 and 31 December 2018 • Patient who relapsed or failed to respond to rituximab or rituximab plus chemotherapy • Data records available Exclusion criteria: • Patients diagnosed with EBV-negative PTLD • Patients who received investigational EBV cytotoxic T lymphocytes (EBV-CTL) based therapy at any time • Patients who received donor lymphocyte infusion (DLI) after the diagnosis of PTLD • Primary central nervous system (CNS) patients • Patients with Hodgkin lymphoma, peripheral T-cell lymphoma and Burkitt lymphoma
Intervention	Current standard treatment (see Figure 4 and Figure 6 for detailed overview of intervention)
Comparator(s)	Not applicable
Follow-up time	The database was locked on 26 January 2021.
Is the study used in the health economic model?	*Yes*
Primary, secondary and exploratory endpoints	OS Median OS in C-HCT cohort was: • 1.7 months from PTLD diagnosis date • 0.7 months refractory/relapsed date to rituximab • 2.0 months start date of next line of therapy Median OS in the C-SOT-R+C was: • 15.5 months from PTLD diagnosis date • 4.1 months refractory/relapsed date to rituximab • 9.7 months start date of next line of therapy

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ATA129-RS002	RS002 Study: A descriptive, multinational, multicenter non-interventional retrospective chart review study of patients with biopsy-proven EBV+ PTLD following HCT or SOT who received rituximab or rituximab plus chemotherapy between January 2000 and December 2018 and were refractory or had relapsed after such therapy, Pierre Fabre, 2022 [191]
Method of analysis	Continuous variables were summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum and maximum. Categorical variables were summarized by the number and proportion in each category. OS was summarized using the Kaplan-Meier method. Efficacy endpoints that are defined as proportions were summarized using two-sided exact binomial 95% CI.
Subgroup analyses	No planned subgroup analyses
Other relevant information	N/A

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Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 70 presents patient and PTLD specific characteristics of those enrolled in the RS002 study, for the cohort 2000-2018.

Table 70. Patient and PTLD baseline characteristics from RS002

Characteristics	C-HCT (N=81)	C-SOT-R+C (N=86)
Country of origin, n (%)		
Austria	1 (1.2)	7 (8.14)
Belgium	5 (6.2)	7 (8.14)
Canada	19 (23.4)	3 (3.5)
France	21 (25.9)	9 (10.5)
Germany	3 (3.7)	17 (19.8)
Italy	3 (3.7)	10 (11.6)
Spain	20 (24.7)	7 (8.1)
Sweden	4 (4.9)	0
USA	5 (6.2)	26 (30.2)
Early PTLD onset[a], n (%)	44 (54.3)	44 (51.2)
Age at transplant (years), median (range)	48.7 (2-75)	35 (0.20-74)
Age at PTLD diagnosis (years), median (range)	49 (2-75)	43 (1-78)
Time to PTLD from transplant (months), median (range)	3 (0.8-100.8)	20.3 (1.6, 334.5)
Male, n (%)	49 (60.5)	58 (67.4)
SOT transplant type[b], n (%)		
Kidney	-	27 (31.4)
Liver	-	22 (25.6)
Lung	-	23 (26.7)
Heart	-	17 (19.8)
PTLD histology type, n (%)		
Early lesions	2 (2.5)	2 (2.3)

Polymorphic	18 (22.2)	18 (20.9)
Monomorphic	52 (64.2)	66 (76.7)
Diffuse large B-cell lymphoma (DLBCL)	46 (56.8)	58 (67.4)
Missing	9 (11.1)	0 (0.0)
CD 20 marker at diagnosis, n (%)		
Positive	52 (64.2)	73 (84.9)
Negative	15 (18.5)	8 (9.3)
Unknown	14 (17.3)	5 (5.8)
Extra nodal sites of PTLD, n (%)	56 (69.1)	65 (75.6)
PTLD stage at initial diagnosis, n (%)		
Stage I	4 (4.9)	21 (24.4)
Stage II	4 (4.9)	21 (24.4)
Stage III	17 (21/0)	18 (20.9)
Stage IV	46 (56.8)	42 (48.8)
Unknown	10 (12.3)	5 (5.9)
Secondary CNS PTLD, n (%)	7 (8.6)	-

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; PTLD, post-transplant lymphoproliferative disease; Q, quartile; R/R, relapse/refractory; SD, stable disease

[a] Defined according to the time from transplant to PTLD diagnosis: early onset (late onset) was defined as ≤100 (>100) days for HCT patients and ≤2 (>2) years for SOT patients

[b] Not mutually exclusive

Below table present baseline characteristics for patients in RS002 corresponding to the period 2010-2018.

Table 71. Patient and PTLD baseline characteristics from RS002

Characteristics	C-HCT (N=57)	C-SOT-R+C (N=46)
Country of origin, n (%)		
Austria	1 (1.8)	2 (4.4)
Belgium	4(7.0)	2 (4.4)
Canada	14 (24.6)	3 (6.5)
France	17 (29.8)	3 (6.5)
Germany	2 (3.5)	7 (15.2)
Italy	2 (3.5)	7 (15.2)

Spain	15 (26.3)	3 (6.5)
USA	2 (3.5)	19 (41.3)
Early PTLD onset[a], n (%)	32 (56.1)	20 (43.8)
Age at transplant (years), median (range)	49.9 (1.6-74.9)	36.4 (0.4-73.6)
Age at PTLD diagnosis (years), median (range)	51 (2-75)	44.0 (1.0-75.0)
Time to PTLD from transplant (months), median (range)	3.0 (0.8-100.8)	45.5 (1.6, 334.5)
Male, n (%)	33 (57.9)	26 (56.5)
SOT transplant type[b], n (%)		
Kidney	-	17 (37.0)
Liver	-	9 (19.6)
Lung	-	13 (28.3)
Heart	-	9 (19.6)
PTLD histology type, n (%)		
Early lesions	2 (3.5)	1 (2.2)
Polymorphic	10 (17.5)	10 (21.7)
Monomorphic	39 (68.4)	35 (76.1)
Diffuse large B-cell lymphoma (DLBCL)	34 (59.6)	31 (67.4)
Missing	6 (10.5)	0 (0.0)
CD 20 marker at diagnosis, n (%)		
Positive	36 (63.2)	40 (87.0)
Negative	12 (21.1)	2 (4.4)
Unknown	9 (15.8)	4 (8.7)
Extra nodal sites of PTLD, n (%)	42 (73.7)	32 (69.6)
PTLD stage at initial diagnosis, n (%)		
Stage I	2 (3.5)	5 (10.9)
Stage II	2 (3.5)	4 (8.7)
Stage III	11 (19.3)	12 (26.1)
Stage IV	34 (59.6)	21 (45.7)
Unknown	8 (14.0)	1 (2.2)
Secondary CNS PTLD, n (%)	5 (8.8)	5 (10.9)

The table below presents some of the disease characteristics of the patients in ALLELE and RS002 respectively, that was included for the comparative analysis of efficacy and safety.

Table 72. Baseline and disease characteristics of patients in studies included for the comparative analysis of efficacy and safety

	RS002		ALLELE				
	C-HCT (N=27)	C-SOT-R+C (N=28)	C-SOT-R (N = 14)	C-SOT-R+C (N = 19)	Total C-SOT (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Sex Male n (%)	16 (59.3)	17 (60.7)	10 (71.4)	9 (47.4)	19 (57.6)	13 (65.0)	32 (60.4)
Age (years), median (min, max)	44.0 (10-66)	44.0 (3-73)	52.9 (6.1-75.7)	52.9 (6.1-75.7)	42.8 (6.1-81.5)	49.3 (3.2-73.2)	44.4 (3.2-81.5)
Extra nodal sites of PTLD, n (%)	18 (66.7)	16 (57.1)	11 (78.6)	15 (78.9)	26 (78.8)	13 (65.0)	39 (73.6)
Time to PTLD from transplant (months), median (range)	3.0 (0.9-100.8)	66.0 (2.1, 334.5)	-	-	-	-	-
Time from transplant to diagnosis of EBV⁺ PTLD (years)	-	-	1.0 (0.4, 26.2)	1.4 (0.3, 23.2)	1.1 (0.3, 26.2)	4.2 (0.6, 66.0)	-
Rituximab monotherapy – n (%)	-	-		11 (57.9)		20 (100)	45 (84.9)
SOT transplant type n (%)							
Kidney	-	11 (39.3)	4 (28.6)	7 (36.8)	11 (33.3)	-	-
Liver	-	5 (17.9)	2 (14.3)	0	2 (6.1)	-	-
Lung	-	7 (25.0)	4 (28.6)	1 (5.3)	5 (15.2)	-	-
Heart	-	3 (10.7)	1 (7.1)	7 (36.8)	8 (24.2)	-	-

Comparability of patients across studies

Demographic and baseline characteristics are summarized for the two arms in the analysis from the respective study. As previously have been described, an external control arm for ALLELE was constituted from RS002. These patients were matched based on characteristics in the ITC. Further the analysis in the ITC captures patients diagnosed between 2010-2018 considered to be aligned with current clinical practice.

Comparability of the study populations with Danish patients eligible for treatment

The ALLELE study population is assessed to be comparable with the Danish patients eligible for treatment. The target patient population for this assessment consist of patients with EBV^{+} PTLD following HCT after failure of rituximab or following SOT, after failure of rituximab plus chemotherapy. Key patient characteristics and efficacy was based on ALLELE, the pivotal clinical trial, which correspond well to Danish patients.

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Primary efficacy endpoint			
Overall response rate (ORR)	Complete response or partial response obtained following administration of Ebvallo® with up to two different HLA restrictions.	Lugano classification criteria with LYRIC modification*	Relevant
Secondary efficacy endpooints			
Duration of response (DoR)	The time from the date of initial response until either progression after the last response or death due to any cause in, SOT and HCT cohorts separately.	Lugano classification criteria with LYRIC modification*	Relevant
ORR combined with DoR	In the SOT and HCT cohorts combined.	Lugano classification criteria with LYRIC modification*	Relevant
Rate of CR	The proportion of subjects who achieved best overall response of CR..	Lugano classification criteria with LYRIC modification*	Relevant
Rate of PR	The proportion of subjects who achieved best overall response of PR.	Lugano classification criteria with LYRIC modification*	Relevant
Time to Treatment Response (TTR)	The time from the date of first dose of Ebvallo® to the date of first response, either CR or PR, whichever occurred first.	Lugano classification criteria with LYRIC modification*	Relevant

Outcome measure	Definition	Validity	Clinical relevance
Time to Best Response (TTBR)	The time from first dose of Ebvallo® to the date of achieving the first best overall response.	Lugano classification criteria with LYRIC modification*	Relevant
OS	The time from first dose of Ebvallo® to the date of death from any cause.	Lugano classification criteria with LYRIC modification*	Relevant
Rates of allograft loss/rejection episodes (SOT cohort only)	Loss is defined as allograft removal, resumption of renal replacement therapy (kidney), initiation of a ventricular assist device (heart), need for mechanical ventilation or extracorporeal membrane oxygenation (lung), re-transplant (any), or placement on a SOT list (any); rejection episodes will be defined according to appropriate criteria for the particular organ transplant.	Lugano classification criteria with LYRIC modification*	Relevant
PTLD PFS	The time from first dose of Ebvallo® to either progression after last response to Ebvallo® or death due to any cause, whichever occurred first.	Lugano classification criteria with LYRIC modification*	Relevant
Durable response rate	CR + PR, lasting > 6 months	Lugano classification criteria with LYRIC modification*	Relevant
Time to progression	The time from first dose of Ebvallo® to progression after last response	Lugano classification criteria with LYRIC modification*	Relevant
Other efficacy endpoints (including disease assessment-related endpoints and			

Outcome measure	Definition	Validity	Clinical relevance
OS for both SOT subgroups)			
PROs scores over time: - **EQ5D (age ≥16 years)** - **FACT-Lym (age ≥ 18 years)**		EQ-5D and FACT-Lym instruments**	Relevant
The association of EBV-CTL precursor (EBV-CTLp) with efficacy		Lugano classification criteria with LYRIC modification*	Relevant
Subject, Ebvallo®, and disease factors that may predict clinical benefit		Lugano classification criteria with LYRIC modification	Relevant
The association of cytokine profile with clinical activity and efficacy		Lugano classification criteria with LYRIC modification	Relevant

*Sources: [54, 55] **Sources: [56, 192]

Results per study

Table A3a Results of ALLELE (NCT03394365) Data cut off: 29 July 2022 (FAS)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study cohort**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ORR	C-HCT	20	55%	NA	31.5,76.9	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	14	50%	NA	23.0,77.0	NA	NA	NA	NA		
	C-SOT-R+C	19	47.4%	NA	24.4, 71.1	NA	NA	NA	NA		
DoR	C-HCT	11	23 months	NA	1.7, NE	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	7	NE	NA	0.6, NE	NA	NA	NA	NA		
	C-SOT-R+C	9	NE	NA	0.8, NE	NA	NA	NA	NA		
ORR and DOR in C-SOT and C-HCT combined (C-PTLD)	C-PTLD – responders (DOR, months)		23.0	NA	3.8, NE	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.* [54, 55]	
	C-PTLD – (ORR)		50.9%	NA	36.8,64.9	NA	NA	NA	NA		
	C-PTLD – CR (ORR)		28.3%	NA	16.8, 42.3	NA	NA	NA	NA		
	C-PTLD – PR (ORR)		22.6%	NA	12.3,36.2	NA	NA	NA	NA		

Rates of CR	C-HCT	20	40.0% (n= 8)	NA	19.1, 63.9	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	14	14.3%	NA	1.8, 42.8	NA	NA	NA	NA		
	C-SOT-R+C	19	26.3%	NA	9.1, 51.2	NA	NA	NA	NA		
Rate of PR	C-HCT	11	1 month	NA	0.6, 9.0	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	7	2.4 months	NA	1.0, 7.3	NA	NA	NA	NA		
	C-SOT-R+C	9	1.1 months	NA	0.7, 4.4	NA	NA	NA	NA		
TTR	C-HCT	11	1 month	NA	0.6, 4.7	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	7	2.1 months	NA	1.0, 3.0	NA	NA	NA	NA		
	C-SOT-R+C	9	1.1 months	NA	0.7, 4.4	NA	NA	NA	NA		
TTBR	C-HCT	11	1.0 month	NA	0.6, 9.0	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	7	2.4 moths	NA	1.0, 7.3	NA	NA	NA	NA		
	C-SOT-R+C	9	1.1 months	NA	0.7, 4.4	NA	NA	NA	NA		
OS	C-HCT	20	NE (1 year survival rate at 66%)	NA	38.5, 83.5	NA	NA	NA	NA	Kaplan-Meier method	[56]
	C-SOT-R	14	18.4 months (1 year survival rate at 52.7%)	NA	1.8, NE	NA	NA	NA	NA		

	C-SOT-R+C	19	16.4 months (1 year survival rate at 62.7%)	NA	3.5, NE	NA	NA	NA	NA		
PFS	C-HCT	20	5.8 months (55% of patients had PFS events)	NA	1.3, NE	NA	NA	NA	NA	Kaplan-Meier method	[56]
	C-SOT-R	14	3.3 months (57.1% of patients had PFS events)	NA	0.9, NE	NA	NA	NA	NA		
	C-SOT-R+C	19	1.9 months (68.4% of patients had PFS events)	NA	1.0, NE	NA	NA	NA	NA		
DRR	C-HCT	20	30.0%	NA	11.9, 54.3	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	14	14.3%	NA	1.8, 42.8	NA	NA	NA	NA		
	C-SOT-R+C	19	26.3%	NA	9.1, 51.2	NA	NA	NA	NA		
TTP	C-HCT	20	16.9 months (50% of patients progressed)	NA	1.3, NE	NA	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	14	3.3 months (42.9% of	NA	0.9, NE	NA	NA	NA	NA	NA		

			patients progressed)								
	C-SOT-R+C	19	1.9 months (68.4% of patients progressed)	NA	1.0, NE	NA	NA	NA	NA	NA	
Patient reported outcomes: EQ-5D	At baseline, 27/30 (90%) SOT and 18/19 (95%) HCT patients answered the EQ-5D-5L VAS and utility index questionnaires. At baseline, mean scores were similar between SOT and HCT patients. Mean changes from baseline were negative for SOT (indicating a deterioration of quality of life) and positive for HCT patients (indicating an improvement of quality of life) at cycles 2 and 3. At cycle 4, only 10/40 (20%) overall patients answered the questionnaires. At safety follow-ups 30 and 180 days after last dose, mean changes from baseline were always positive for both SOT and HCT patients. Only 9 patients answered the questionnaires at 2-year study visit.									EQ-5D-5L instrument	[192] [56]
Patient reported outcomes: FACT-Lym	At baseline, 26/27 (96%) SOT and 18/19 (95%) HCT patients answered the FACT-Lym questionnaires. At safety follow-up 30 days after last dose, mean changes from baseline were always positive for both SOT and HCT patients and for each subscale. Only 9 patients answered the questionnaires at 2-year study visit.									Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) instrument	[193]
CBR	C-HCT	20	70.0%	NA	45.7, 88.1	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	14	64.3%	NA	35.1, 87.2	NA	NA	NA	NA		
	C-SOT-R+C	19	47.4%	NA	24.4, 71.1	NA	NA	NA	NA		
Objective response rate	C-HCT	20	50.0%	NA	27.2, 72.8	NA	NA	NA	NA	*Lugano classification response criteria with LYRIC modification.*	[54, 55]
	C-SOT-R	14	50.0%	NA	23.0, 77.0	NA	NA	NA	NA		

(including response data before first restriction switch)	C-SOT-R+C	19	31.6%	NA	12.6, 56.6	NA	NA	NA	NA		
Sensitivity analysis for progression free survival	A sensitivity analysis was performed on the FAS that defined PFS as the time from the first dose of Ebvallo® to either of the following events, whichever occurred first, (1) the first progression or (2) death due to any cause. The results of this analysis were identical to the results of the primary analysis per IORA.									Per IORA assessment	NA
Post Hoc analysis: HLA restriction	18 (34.0%) patients in the FAS required treatment with a Ebvallo® lot that had a different HLA restriction from the first lot (restriction switch). Of these 18 patients, 15 received 1 restriction switch, 3 received 2 restriction switches.									Per IORA assessment	NA

Abbreviations: C-HCT – Cohort Hematopoietic Cell Transplant, C-SOT-R – Cohort Solid Organ Transplant Rituximab, ORR – overall response rate, DoR – duration of response, CR – Complete response, PR – Partial response, TTR – Time to treatment response, TTBR – time to best treatment response, OS – Overall survival, PFS – progression free survival, DRR – Durable response rate, TTP – Time to response, CBR – Clinical benefit rate.

Source: [63]

Table 73. Results on the duration of response – responders only per IORA (FAS) (cut-off 29 July 2022)

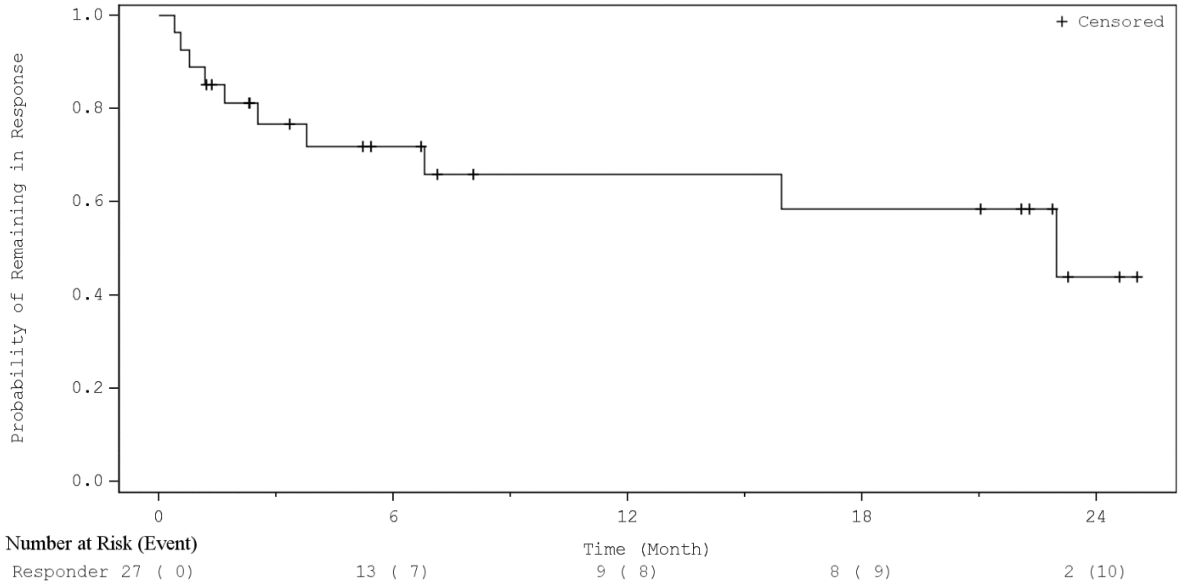
Per IORA	C-SOT-R (N = 7)	C-SOT-R+C (N = 9)	Total C-SOT (N = 16)	C-HCT (N = 11)	Overall Total [C-PTLD] (N = 27)
DOR status, n (%)					
Events	2 (28.6)	3 (33.3)	5 (31.3)	5 (45.5)	10 (37.0)
Deaths	1 (14.3)	0	1 (6.3)	2 (18.2)	3 (11.1)

Progression	1 (14.3)	3 (33.3)	4 (25.0)	3 (27.3)	7 (25.9)
Censored	5 (71.4)	6 (66.7)	11 (68.8)	6 (54.5)	17 (63.0)
Follow-up time after achieving first response (months) – n					
Median (min, max)	5.2 (0.6, 25.0)	6.7 (0.8, 24.6)	5.3 (0.6, 25.0)	8.0 (0.4, 23.3)	5.4 (0.4, 25.0)
DOR estimate (K-M) (months)					
Median (95% CI)	NE (2.5, NE)	NE (0.8, NE)	NE (2.5, NE)	23.0 (1.7, NE)	23.0 (3.8, NE)

Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-SOT, patients with EBV+ PTLD following SOT; C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; DOR, duration of response; IORA, independent oncologic response adjudication; K-M, Kaplan-Meier; NE: not estimable

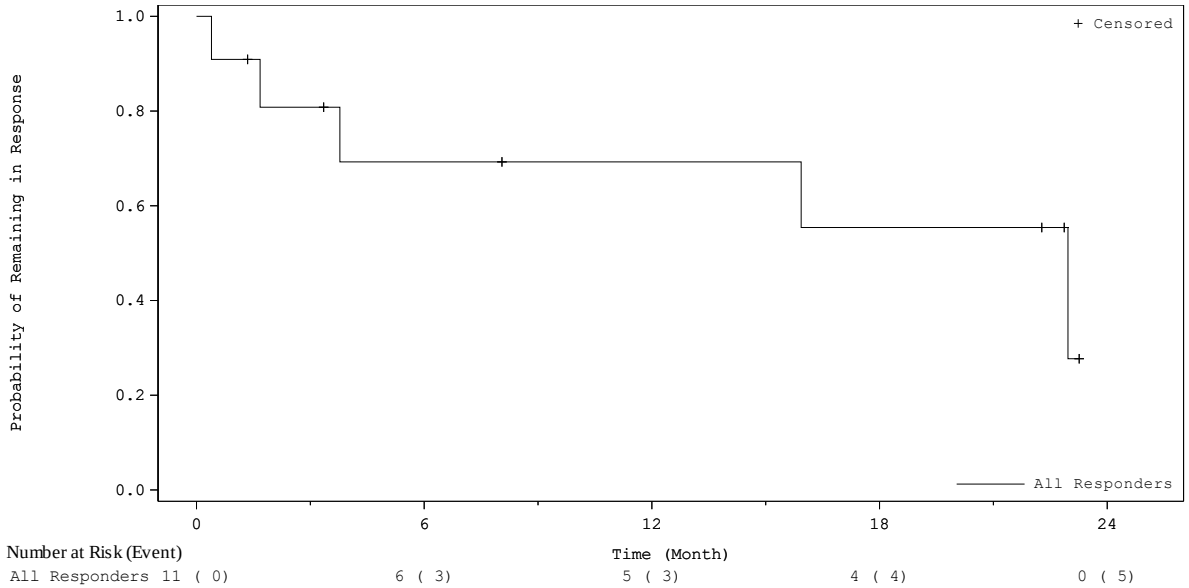
Evaluable Analysis Set consists of all patients who received ≥1 dose of Ebvallo® and had ≥1 evaluable post-baseline disease assessment per IORA, or discontinued study, or received non-protocol anti-PTLD therapy. A patient was considered as a responder if the best overall response was either complete response or partial response; CI was calculated using log-log transformation method

Figure 33. Kaplan-Meier plot of duration of response (DOR) in the C-PTLD – responders per IORA (FAS) (cut-off 29 July 2022)



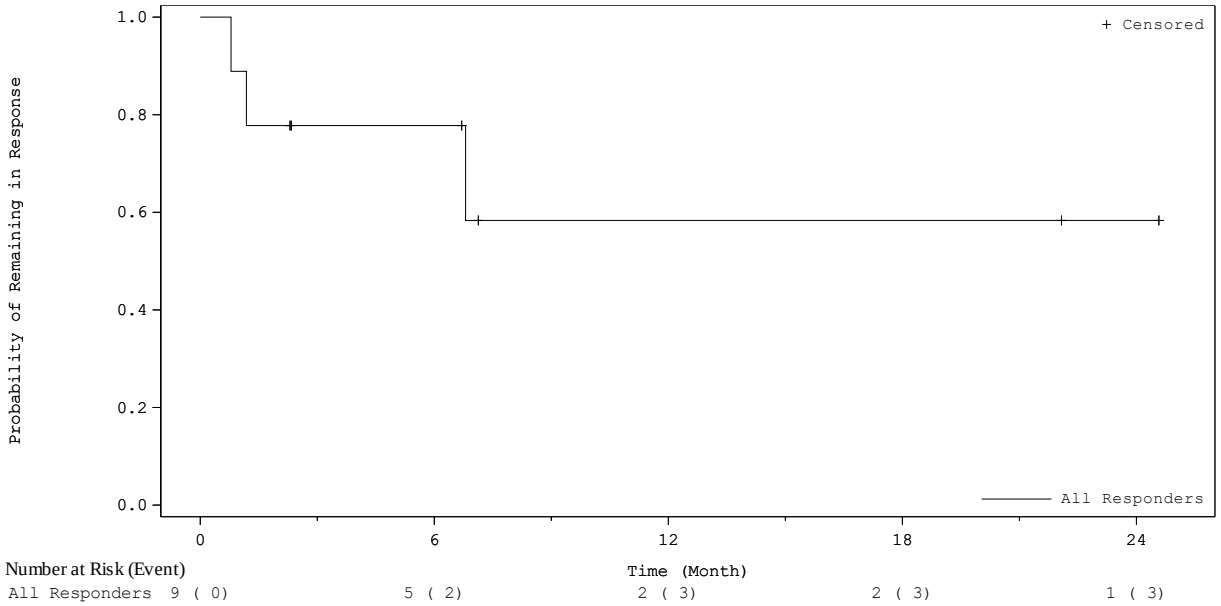
Abbreviations: C-PTLD, total EBV+ patients enrolled and treated; FAS, full analysis set; IORA, independent oncologic response adjudication. A patient was considered as a responder if the best ORR was either CR or PR.

Figure 34. Kaplan-Meier plot of duration of response (DOR) in the HCT – responders per IORA (FAS) (29 July 2022 cut-off)



Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; IORA, independent oncologic response adjudication; A patient was considered as a responder if the best ORR was either CR or PR.

Figure 35. Kaplan-Meier plot of duration of response (DOR) in the C-SOT-R+C – responders per IORA (FAS) (cut-off 29 July 2022)



Abbreviations: C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; FAS, full analysis set; IORA, independent oncologic response adjudication; A patient was considered as a responder if the best ORR was either CR or PR.

Table A3a Results of Study RS002

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study cohort**	**N**	**Result (96% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**	**-**	**-**

OS	C-HCT	27	2.1 months (1.4, 14.5)	NA	NA	NA	NA	NA	NA	-	-
	C-SOT-R+C	29	19.4 months (3.3, NA)								

Abbreviations: OS – Overall survival, C-HCT – Cohort Hematopoietic Cell Transplant, C-SOT-R – Cohort Solid Organ Transplant Rituximab+Chemotherapy

Source: [51]

Table 74. PRO completion rates in C-PTLD (FAS) (cut-off 29 July 2022)

	EQ-5D-5L (N=49)	FACT-Lym (N=46)
Baseline	45/49 (92%)	44/46 (96%)
Cycle 1 Day 15	20/49 (41%)	20/46 (43%)
Cycle 2 Day 1	32/49 (65%)[a]	29/46 (63%)
Cycle 3 Day 1	22/49 (45%)	22/46 (48%)
Cycle 4 Day 1	10/4920%)	10/46 (22%)
Cycle 5 Day 1	5/49 (10%)	5/46 (11%)
Cycle 6 Day 1	1/49 (2%)	1/46 (2%)
30 days after last dose	20/49 (41%)	20/46 (43%)
180 days after last dose	13/49 (27%)	13/46 (28%)

2-year study visit	9/49 (18%)	9/46 (20%)

[a] 31 (63%) for utility scores, Results are descriptive only. Due to the modest number of patients, they must be interpreted with caution.

Figure 36. Mean score plot of EQ-5D-5L Visual Analogue Scores (VAS) (Age >= 16 years old) per cycle (FAS) (cut-off 29 July 2022

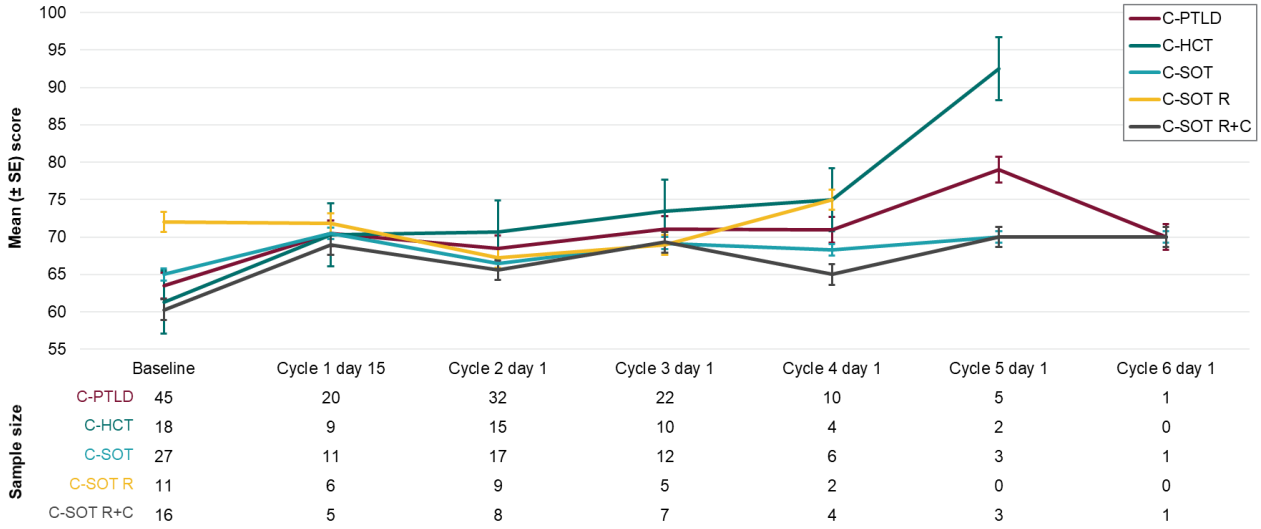
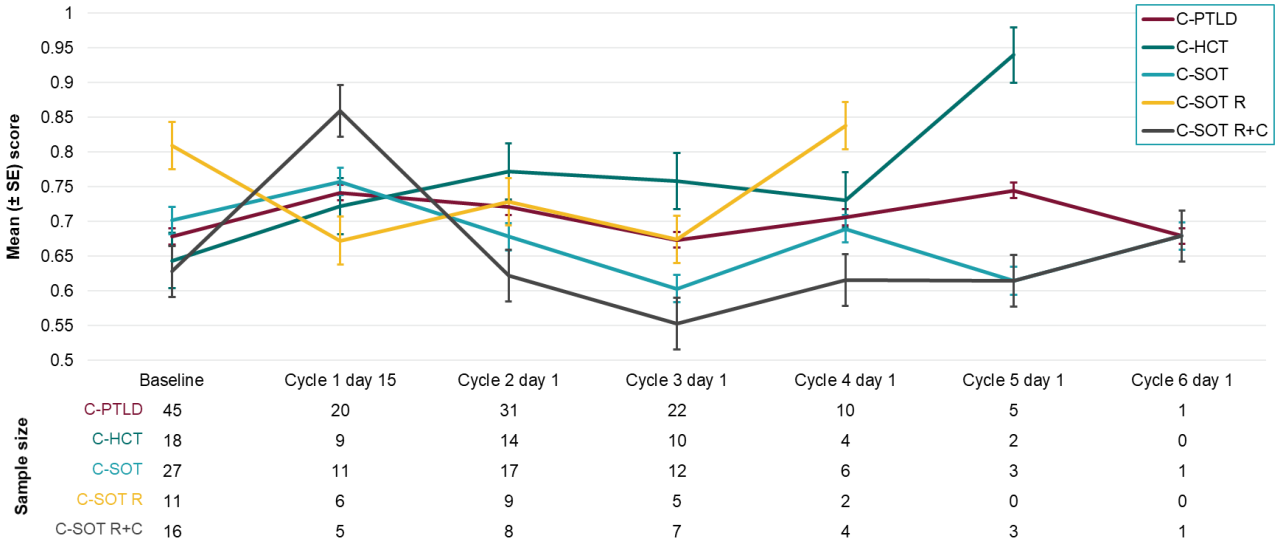


Figure 37. Mean score plot of EQ-5D-5L utilities (Age >= 16 years old) per cycle (FAS) (cut-off 29 July 2022)



Sample size	Baseline	Cycle 1 day 15	Cycle 2 day 1	Cycle 3 day 1	Cycle 4 day 1	Cycle 5 day 1	Cycle 6 day 1
C-PTLD	45	20	31	22	10	5	1
C-HCT	18	9	14	10	4	2	0
C-SOT	27	11	17	12	6	3	1
C-SOT R	11	6	9	5	2	0	0
C-SOT R+C	16	5	8	7	4	3	1

Figure 38. Mean score plot of FACT-Lym total scores (Age >= 18 years old) per cycle (FAS) (cut-off 29 July 2022) [i]

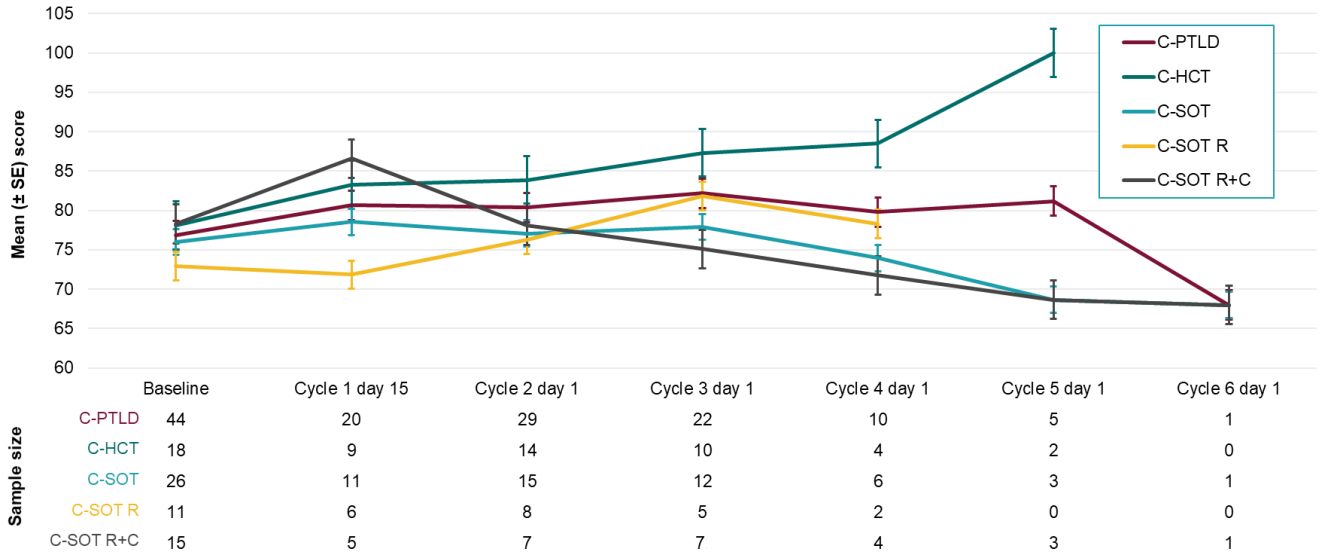


Table 75. Treatment-emergent adverse events reported for patient (≥5%) in ALLELE, by preferred term (FAS)

	C-SOT-R (N = 14)	C-SOTR+C (N = 19)	Total C-SOT (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Patients reporting any TEAEs, n (%)	**11 (78.6)**	**18 (94.7)**	**29 (87.9)**	**19 (95.0)**	**48 (90.6)**
Disease progression	8 (57.1)	11 (57.9)	19 (57.6)	7 (35.0)	26 (49.1)
Pyrexia	4 (28.6)	6 (31.6)	10 (30.3)	6 (30.0)	16 (30.2)
Diarrhoea	4 (28.6)	4 (21.1)	8 (24.2)	4 (20.0)	12 (22.6)

Fatigue	4 (28.6)	2 (10.5)	6 (18.2)	6 (30.0)	12 (22.6)
Nausea	3 (21.4)	2 (10.5)	5 (15.2)	4 (20.0)	9 (17.0)
Neutrophil count decreased	1 (7.1)	3 (15.8)	4 (12.1)	5 (25.0)	9 (17.0)
Vomiting	4 (28.6)	2 (10.5)	6 (18.2)	3 (15.0)	9 (17.0)
Hypokalaemia	1 (7.1)	3 (15.8)	4 (12.1)	4 (20.0)	8 (15.1)
Constipation	3 (21.4)	2 (10.5)	5 (15.2)	2 (10.0)	7 (13.2)
Hypotension	3 (21.4)	3 (15.8)	6 (18.2)	1 (5.0)	7 (13.2)
Acute kidney injury	2 (14.3)	4 (21.1)	6 (18.2)	0	6 (11.3)
Anaemia	1 (7.1)	3 (15.8)	4 (12.1)	2 (10.0)	6 (11.3)
Cough	1 (7.1)	2 (10.5)	3 (9.1)	3 (15.0)	6 (11.3)
Decreased appetite	1 (7.1)	2 (10.5)	3 (9.1)	3 (15.0)	6 (11.3)
Dizziness	2 (14.3)	1 (5.3)	3 (9.1)	3 (15.0)	6 (11.3)
Dyspnoea	1 (7.1)	2 (10.5)	3 (9.1)	3 (15.0)	6 (11.3)
Hypomagnesaemia	2 (14.3)	2 (10.5)	4 (12.1)	2 (10.0)	6 (11.3)
Abdominal pain	0	3 (15.8)	3 (9.1)	2 (10.0)	5 (9.4)
Dehydration	1 (7.1)	1 (5.3)	2 (6.1)	3 (15.0)	5 (9.4)
Febrile neutropenia	2 (14.3)	2 (10.5)	4 (12.1)	1 (5.0)	5 (9.4)
Pruritus	0	2 (10.5)	2 (6.1)	3 (15.0)	5 (9.4)

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Rash maculo-papular	1 (7.1)	0	1 (3.0)	4 (20.0)	5 (9.4)
Sepsis	2 (14.3)	0	2 (6.1)	3 (15.0)	5 (9.4)
Blood creatinine increased	3 (21.4)	1 (5.3)	4 (12.1)	0	4 (7.5)
COVID-19	1 (7.1)	1 (5.3)	2 (6.1)	2 (10.0)	4 (7.5)
Chills	1 (7.1)	2 (10.5)	3 (9.1)	1 (5.0)	4 (7.5)
Fall	2 (14.3)	0	2 (6.1)	2 (10.0)	4 (7.5)
Headache	3 (21.4)	1 (5.3)	4 (12.1)	0	4 (7.5)
Hypertension	0	2 (10.5)	2 (6.1)	2 (10.0)	4 (7.5)
Hyponatraemia	2 (14.3)	1 (5.3)	3 (9.1)	1 (5.0)	4 (7.5)
Hypophosphataemia	0	0	0	4 (20.0)	4 (7.5)
Hypoxia	2 (14.3)	0	2 (6.1)	2 (10.0)	4 (7.5)
Oedema peripheral	3 (21.4)	0	3 (9.1)	1 (5.0)	4 (7.5)
Pain in extremity	0	2 (10.5)	2 (6.1)	2 (10.0)	4 (7.5)
Pleural effusion	1 (7.1)	2 (10.5)	3 (9.1)	1 (5.0)	4 (7.5)
Pneumonia	1 (7.1)	1 (5.3)	2 (6.1)	2 (10.0)	4 (7.5)
Rash	2 (14.3)	2 (10.5)	4 (12.1)	0	4 (7.5)
Thrombocytopenia	2 (14.3)	2 (10.5)	4 (12.1)	0	4 (7.5)
White blood cell count decreased	1 (7.1)	2 (10.5)	3 (9.1)	1 (5.0)	4 (7.5)

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Anxiety	0	2 (10.5)	2 (6.1)	1 (5.0)	3 (5.7)
Arthralgia	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Back pain	1 (7.1)	2 (10.5)	3 (9.1)	0	3 (5.7)
Blood alkaline phosphatase increased	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Hyperhidrosis	2 (14.3)	0	2 (6.1)	1 (5.0)	3 (5.7)
Hyperkalaemia	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Hypoglycaemia	0	2 (10.5)	2 (6.1)	1 (5.0)	3 (5.7)
Influenza	0	2 (10.5)	2 (6.1)	1 (5.0)	3 (5.7)
Muscular weakness	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Nasal congestion	3 (21.4)	0	3 (9.1)	0	3 (5.7)
Pain	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Respiratory failure	2 (14.3)	1 (5.3)	3 (9.1)	0	3 (5.7)
Tachycardia	1 (7.1)	2 (10.5)	3 (9.1)	0	3 (5.7)
Urinary tract infection	0	3 (15.8)	3 (9.1)	0	3 (5.7)
Weight increased	0	1 (5.3)	1 (3.0)	2 (10.0)	3 (5.7)
Wheezing	2 (14.3)	1 (5.3)	3 (9.1)	0	3 (5.7)

Abbreviation: C-HCT, patients with EBV$^+$ PTLD following HCT; C-SOT, patients with EBV$^+$ PTLD following SOT; C-SOT-R+C, patients with EBV$^+$ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; AE, treatment-emergent adverse event.

Note: Treatment-emergent adverse events include any AE that occurred on or after first dose date of Ebvallo® through 30 days after last dose of Ebvallo® or any related AE with date of onset on or after first dose date of Ebvallo®.

Table 76. Summary of the number (%) of subjects with Treatment-emergent Adverse Events by Maximum Severity in ALLELE (FAS) (cut-off 29 July 2022)

	C-SOT-R (N = 14)	C-SOTR+C (N = 19)	Total (N = 33)	C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
Patients reporting any AEs, n (%)	**11 (78.6)**	**18 (94.7)**	**29 (87.9)**	**19 (95.0)**	**48 (90.6)**
Grade 1	0	0	0	2 (10.0)	2 (3.8)
Grade 2	1 (7.1)	3 (15.8)	4 (12.1)	3 (15.0)	7 (13.2)
Grade 3	8 (57.1)	8 (42.1)	16 (48.5)	6 (30.0)	22 (41.5)
Grade 4	1 (7.1)	3 (15.8)	4 (12.1)	5 (25.0)	9 (17.0)
Grade 5	1 (7.1)	4 (21.1)	5 (15.2)	3 (15.0)	8 (15.1)
Grade ≥ 3	10 (71.4)	15 (78.9)	25 (75.8)	14 (70.0)	39 (73.6)

Table 77. Treatment-emergent Adverse Events (AEs) with a grade 3+ severity (>10% in C-PTLD), by Preferred Term (FAS) (cut-off 29 July 2022).

	C-SOT			C-HCT (N=20)	Overall Total [C-PTLD] (N=53)
	C-SOT-R (N= 14)	C-SOTR+C (N=19)	Total (N=33)		
AE with Grade ≥3, n (%)	**10 (71.4)**	**15 (78.9)**	**25 (75.8)**	**14 (70.0)**	**39 (73.6)**
Disease progression	5 (35.7)	8 (42.1)	13 (39.4)	7 (35.0)	20 (37.7)
Neutrophil count decreased	1 (7.1)	3 (15.8)	4 (12.1)	4 (20.0)	8 (15.1)

Abbreviations: C-HCT, subjects with EBV+ PTLD following HCT; C-SOT, subjects with EBV+ PTLD following SOT; C-SOT-R, subjects with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, subjects with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; AE, treatment-emergent adverse event. Treatment-emergent adverse events include any AE that occurred on or after first dose date of tabelecleucel through 30 days after last dose of tabelecleucel or any related AE with date of onset on or after first dose date of tabelecleucel. Each subject is counted once for each preferred term reported. Sorted by the descending order in the overall total column.

Table 78. Treatment-related AEs with a grade 3+ severity, by Preferred Term (FAS) (cut-off 29 July 2022).

	C-SOT				
	C-SOT-R (N=14)	C-SOTR+ C (N=19)	Total (N=33)	C-HCT (N=20)	Overall Total [C-PLTD] (N=53)
Treatment-related AE with Grade ≥3, n (%)	**4 (30.8)**	**3 (18.8)**	**7 (24.1)**	**1 (7.1)**	**8 (18.6)**
Neutrophil count decreased	0	2 (10.5)	2 (6.1)	1 (5.0)	3 (5.7)
Fatigue	1 (7.1)	0	1 (3.0)	0	1 (1.9)
Hypotension	1 (7.1)	0	1 (3.0)	0	1 (1.9)
Blood fibrinogen decreased	0	1 (5.3)	1 (3.0)	0	1 (1.9)
Hypoxia	1 (7.1)	0	1 (3.0)	0	1 (1.9)
Lymphocyte count decreased	0	1 (5.3)	1 (3.0)	0	1 (1.9)
Rash erythematous	1 (7.1)	0	1 (3.0)	0	1 (1.9)
Upper respiratory tract infection	1 (7.1)	0	1 (3.0)	0	1 (1.9)
White blood cell count decreased	0	1 (5.3)	1 (3.0)	0	1 (1.9)

Abbreviation: C-HCT, subjects with EBV+ PTLD following HCT; C-SOT, subjects with EBV+ PTLD following SOT; C-SOT-R, subjects with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, subjects with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; AE, treatment-emergent adverse event. Treatment-emergent adverse events include any AE that occurred on or after first dose date of

tabelecleucel through 30 days after last dose of tabelecleucel or any related AE with date of onset on or after first dose date of tabelecleucel. Each subject is counted once for each preferred term reported. Sorted by the descending order in the overall total column.

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Appendix E Safety data for intervention and comparator(s)

Intervention

The following data was considered by the EMA when assessing the safety profile of tabelecleucel and it is part of the integrated summary of safety.

Treatment emergent adverse events

Nearly all subjects in Studies ATA129-EBV-302 (ALLELE) and EBV-CTL-201 experienced TEAEs: (96.1%). Most frequently reported TEAEs by preferred term were disease progression, pyrexia, and diarrhoea, followed by fatigue, cough, nausea, and vomiting. TEAEs had a maximum severity of grade 3 for 37 (35.9%) subjects, grade 4 for 17 (16.5%) subjects, and grade 5 for 15 (14.6%) subjects. Treatment-emergent adverse event with a maximum severity of grade 4 that occurred in > 1 subject were neutrophil count decreased (reported for 5 subjects [4.9%]), white blood cell count decreased and sepsis (reported for 4 subjects [3.9%] each), lymphocyte count decreased (reported for 2 subjects [1.9%]). Treatment emergent adverse events with a maximum severity of grade 5 that occurred in > 1 subject included disease progression (8 subjects [7.8%]) and multiple organ dysfunction syndrome (reported in 2 subjects [1.9%]).

Treatment-related TEAEs (based on investigator assessment) for ALLELE, and EBV-CTL-201 were reported for 39.8% of subjects. Treatment-related TEAEs with the highest subject number by preferred term were pyrexia, fatigue, hypotension and nausea followed by neutrophil count decreased and diarrhoea. 16.5% of subjects had grade ≥ 3 TEAEs. No fatal treatment-related TEAEs were reported. One subject (1.0%) had a treatment-related TEAE that led to study discontinuation.

Severity of AEs

In the ISS population, 57.9% of subjects were reported as having any TESAEs. The most frequently reported system organ classes for those patients were Infections and Infestations (27.4%), General disorders and administration site conditions (24.1%), Respiratory, thoracic and mediastinal disorders (13.2%) and Gastrointestinal disorders (10.9%). The most frequently reported PTs were disease progression (10.9%), pneumonia (10.3%), pyrexia (7.6%), sepsis (4.7%), febrile neutropenia (4.1%), respiratory failure (4.1%), death (3.8%), acute kidney injury (2.9%), and device related infection (2.9%).

Deaths

In the pivotal study ATA129-EBV-302 (ALLELE), a total of 18 subjects (41.9%) died; 5 subjects (11.6%) had a fatal TESAE, and 13 subjects (30.2%) died due to other causes. By PT, fatal TESAEs included disease progression (3 subjects [7.7%]), multiple organ dysfunction syndrome (1 subject [2.6%]), and respiratory failure (1 subject [2.6%]). None of the fatal TESAEs were considered by the investigator as related to treatment.

Across all 4 clinical studies and Expanded Access Programs, 71 fatal TESAEs were reported (20.0%). The most frequent fatal TESAEs were disease progression and death, in all cohorts, followed by pneumonia and pneumonia adenoviral. None of the fatal TESAEs were considered related to treatment except one subject in the Expanded Access Programme (C-HCT cohort) had 2 grade 5 TESAEs (Enterococcal infection and Citrobacter bacteraemia) that were considered possibly related to Ebvallo® by the investigator.

Comparator

The chosen papers from the targeted literature review as described in Comparator – adverse events, are presented in Table 79, alongside their reported adverse event rates. Adverse event rates were not identified among these BSC treatments for all adverse events associated with Ebvallo®. However, these papers reported the largest sample size, so were deemed appropriate to source adverse event rates for the model. Given the limited published data available on the rates of adverse events in patients with lymphoma, it was expected that leveraging AE data from studies of lymphoma populations may underestimate the rates or severity of AEs in a PTLD population. In order to address this issue, the decision was therefore made to cross-reference the AE rates across the identified papers and use the highest rate of the four regimens in the model.

This approach is unlikely to be reflective of clinical practice as clinical experts indicate that selection of chemotherapy regimen is based on differences in their toxicity profiles.[194-197] In particular, palliative chemotherapy regimens are associated with less toxicity and are therefore used in patients who are not expected to be able to tolerate the toxicity of intensive curative chemotherapy regimens. However, this approach was considered to be the only feasible option given the data limitations.

Adverse event rates for acute kidney injury, sepsis, pneumonia, and bowel perforation were sourced from a separate study by Evens *et al,* 2010,[125] which reported adverse events among SOT patients receiving first-line chemotherapy (with or without rituximab) for the treatment of PTLD. Finally, the probability of a cardiovascular event was sourced from a systematic review and meta-analysis of cardiovascular events in patients with non-Hodgkin lymphoma treated with first-line CHOP or R-CHOP (Linschoten *et al,* 2020).[198]

Table 79. Adverse event rates for the BSC treatments in the HCT and SOT populations

Adverse event, n (%)	R-CHOP (N=703)		Pola-BR (N=35)		GDP (N=306)		Oral DECC (N=38)		Selected rate
	n	%	n	%	n	%	n	%	%
Anaemia	53	7.54%	13	37.14%					37.14%
Neutropenia	268	38.12%	11	31.43%	18	5.88%			38.12%
Thrombocytopenia			7	20.00%					20.00%
Platelet count decrease			7	20.00%					20.00%
Neutrophil count decrease			7	20.00%					20.00%
White blood cell count decrease			8	22.86%					22.86%
Cytopenia							5	13.16%	13.16%
Infection			6	17.14%	21	6.86%	1	2.63%	17.14%
Thrombosis					18	5.88%			5.88%
Fatigue					30	9.80%			9.80%
Vomiting					22	7.19%			7.19%
Febrile neutropenia	107	15.22%			28	9.15%			15.22%
Acute kidney injury									22.22%†
Sepsis									17.78%†
Hypertension (included in Ebvallo® arm)									0.00%

Hypotension					7	2.29%		2.29%
Pneumonia	35	4.98%						11.11%†
Respiratory failure			1	2.86%				2.86%
Leukopenia	71	10.10%						10.10%
Bowel perforation								11.11%†
Cardiovascular-related								2.35%
Reported adverse events	Grade 3-5 adverse events reported by ≥5% of patients in either group		Grade 3-4 AEs in ≥10% of patients		Grade 3-4 AEs in ≥5% of patients		Not specified (conference abstract)	
Source	Vitolo et al 2017[65]		Terui et al 2021[199]		Crump et al 2014[66]		Shrubsole and Osborne 2018[200]	

Appendix F Comparative analysis of efficacy and safety

Method of comparative analysis

Objective

The objective of the comparative analysis was to evaluate the overall survival (OS) in relapsed or refractory EBV+ PTLD patients treated with Ebvallo® in the single-arm Phase 3 pivotal study ALLELE (ATA129-EBV-302) compared with real-world patients treated with standard of care in the non-interventional retrospective chart review Study RS002. To conduct this analysis, the following steps were undertaken: first, was ensured that the inclusion and exclusion criteria from the pivotal study ALLELE were well applied to subjects from Study RS002 to create an external control arm (the RS002 study having been pre-defined for an indirect comparison with ALLELE, with its design aligning inclusion and exclusion criteria with ALLELE); second, analytic techniques were applied to achieve the best balance between the treatment arm and the control arm; and third, OS between the 2 arms was compared.

Endpoint

Overall survival was chosen as the endpoint for the comparative analysis as it can be assessed accurately in a real-world setting and represents the most clinically relevant endpoint in this context.

Although the response rate was the primary efficacy endpoint of the pivotal study ALLELE, response rate data obtained in a real-world setting are associated with important limitations, and this particularly when data are collected retrospectively as in study RS002. These limitations include no standardized modalities and timepoints for evaluating response to treatment, temporal changes in treatment and technology, variable evaluation frequencies, and variability in physicians' practices. These factors are supporting overall survival (OS) as the endpoint of relevance for a robust indirect comparative analysis.

Study population

The study population for this comparative analysis is aligned with the indication for Ebvallo® (i.e., patients with EBV+ PTLD following HCT after failure of rituximab or following SOT after failure of rituximab plus chemotherapy) and is consistent with recommendations in current treatment guidelines. Ebvallo® is also indicated for EBV+ PTLD following SOT after failure of rituximab alone, only when chemotherapy is inappropriate and not possible to be given to the patient. However, the ALLELE study assessing Ebvallo® did not pre-defined this criterion of ineligibility to chemotherapy and hence data on this population is not available from the ALLELE trial. SOT patients of the ALLELE trial having received rituximab alone before Ebvallo® were generally appropriate candidates to chemotherapy.

A total of 84 EBV+ PTLD patients were identified from Study RS002 having relapsed/were refractory to rituximab +/- chemotherapy: 36 HCT patients relapsed/ were refractory to rituximab, and 48 SOT patients relapsed/ were refractory to rituximab plus chemotherapy. These 84 patients, selected with inclusion and exclusion criteria aligned with ALLELE, were identified to constitute the external control arm assessing standard of care in a real-world setting for the indirect treatment comparison (ITC) versus Ebvallo®.

The treatment arm assessing Ebvallo® consisted of 39 patients from the pivotal study ALLELE (data cutoff date of 29 July 2022), including 20 HCT patients who failed rituximab and 19 SOT patients who failed rituximab plus chemotherapy. As previously explained, was excluded the SOT subgroup of ALLELE having failed rituximab alone, these patients not representing the population indicated for Ebvallo®.

All these patients with prior HCT who failed rituximab and patients with prior SOT who failed rituximab plus chemotherapy from the pivotal study ALLELE (treatment) and matched patients from Study RS002 (control) were included in the comparative analysis. Considering the very low number of patients per subgroup from ALLELE (20 HCT and 19 SOT), the ITC was conducted pooling HCT and SOT subgroups for allowing an appropriate robustness and appropriate estimation precision, an increased power, and for accounting for the important variability in prognostic factors for this heterogeneous population. This is not possible to have a robust analysis not pooling the HCT and SOT cohorts from ALLELE.

Included patients in Study RS002 were PTLD diagnosed between 2000 and 2018; 63 (38.2%) from 2000-2009 and 102 (61.8%) from 2010-2018. The base case analysis considered patients diagnosed between 2010 and 2018, while a scenario analysis considered all patients PTLD diagnosed.

Index date

The choice of an appropriate index date (time zero; randomization point), in the absence of ad hoc randomization, was carefully considered for Study RS002, in order to illustrate effect estimation between comparison arms as it should be anticipated in real-life setting with the availability of Ebvallo®.

The index date was defined as the time of initiation of next treatment. This is in principle acceptable as it is a clear definition, however, it is not fully clear whether this choice is optimal. Obviously, untreated patients are excluded from the analysis by this definition, and it could be argued that this selection may even be conservative. However, one needs to assume that the decision to initiate a new therapy followed the same standards in the historical data and in the trial. This may not be true, and historically, patients may have received treatment later, for example due to less precise diagnostic methods. Physicians strongly expressed the intention to prescribe Ebvallo® to their patients immediately at confirmation of relapse/refractory to rituximab +/- chemotherapy. The allogenic profile of Ebvallo® allows it; the intervention being developed from healthy donors and being ready for use.
For that reason, to assess the extent of the uncertainty of the incremental benefit of Ebvallo® versus current clinical practice, the scenario using as index date in Study RS002 the date of relapse/refractory to rituximab or rituximab plus chemotherapy, time from which Ebvallo® can be initiated at the earlies is an important scenario.

Statistical methods and analysis

The comparative external control arm for the pivotal study ALLELE was created from the Study RS002 population of patients for whom data were collected through chart review (refer to the section describing Study RS002). Baseline characteristics of these patients were compared with those of patients under Ebvallo®'s indication enrolled in the pivotal study ALLELE. To substantially improve the balance of potential confounders between the treatment (Ebvallo®; ALLELE) and control (standard of care; RS002) arms, propensity score (PS)-based standardized mortality/morbidity ratio weighting (SMRW) method was utilized.

Creation of an External Control Arm

Inclusion and exclusion criteria from the pivotal study ALLELE were pre-defined and applied to the patients for whom data were collected during the chart review Study RS002. The external control arm for indirect comparison was then created. Characteristics of study participants at the time of PTLD diagnosis, transplant characteristic, time-related variables and disease risk factors were collected. All continuous variables were summarized using a valid measurement (n), median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. All categorical variables were summarized using frequencies and percentages.

Propensity score-based Standardized mortality/morbidity ratio weighting (SMRW) method was used as follows:

1/ Propensity score (PS) was defined as the conditional probability of being treated with Ebvallo® based on prespecified confounders including individual baseline demographic factors and

prognostic factors. As compared with an ad hoc randomization in randomized controlled trials (RCTs), PS is a post hoc randomization technique to mimic what happens in RCT situation by balancing covariates at "randomization" point, and thus can substantially reduce the selection bias in observational studies.

Based on a review of the literature, the following prognostic factors were associated with OS and were considered to estimate the probability for patients to "receive" treatment with Ebvallo®, i.e., propensity score:

- Age at diagnosis
- Gender
- Response to Rituximab, initial treatment
- Multi-site bone marrow involvement
- LDH
- Organ type
- PTLD stage
- CNS involvement
- Performance status
- Time from transplant to PTLD
- Reduction of immunosuppression at PTLD diagnosis
- Co-morbidities
- ATG treatment/Anti-IL2 antibody
- Race
- Serum albumin, creatinine, blood counts
- EBV positive
- Transplant/PTLD Era

The final variables were determined based on the literature, data availability (for example, in a real-world setting, ECOG is not assessed on a regular basis, thus, it could not be included), and clinical relevance. These variables were included in a logistic regression model to estimate PS:

- Age
- Gender
- LDH risk
- Onset of PTLD
- Transplant type (HCT vs. SOT)
- Extra nodal sites of PTLD
- No. of lines of prior therapies
- Time from PTLD diagnosis to relapse/refractory date.

2/ PS-based weighting: To make full use of all observations for better precision in the estimation of potential OS benefit of Ebvallo® and to better represent the real-world population with a larger sample size, a PS-based weighting strategy was used instead of PS-based matching (3): Treated patients were given a weight of 1, and control patients were given a weight of PS/(1-PS). The SMRW method reweights the control patients to be representative of the treated patients, which results in an estimate of the average treatment effect among the treated population (3).

3/ The balance of baseline characteristics was assessed following PS-based weighting. The standardized difference before and after PS-based weighting was assessed for each covariate. As a rule of thumb, a standardized mean difference < 0.1 indicates a good balance. A graphical assessment of the difference in each covariate as well as the PS distribution was also conducted.

Endpoint analysis

Overall survival was defined from the date of next line of therapy (i.e., the date of the first dose of Tabcel in the pivotal study ALLELE and the date of next line therapy for patients in Study RS002) to death, lost to follow-up, or the end of follow-up (or cutoff date), whichever came first. The distribution of the time-to-event endpoint (i.e., OS) was summarized using Kaplan-Meier estimator along with their corresponding 95% confidence interval (CI). Unweighted as well as weighted Kaplan-Meier curves are presented. The difference in OS was compared between the external control arm (patients from Study RS002) and the treatment arm (patients from the pivotal study ALLELE) by using unweighted or weighted log-rank tests. The OS benefit of Tab-cel®

compared to standard of care was quantified as the hazard ratio with 95% CI by using unweighted or weighted Cox proportional hazards regression models with a robust "sandwich" variance estimate (4). In the survival analysis, survival time was truncated in the control arm to match the follow up time in the pivotal study ALLELE.Result from the comparative analysis

Components of PTLD adapted prognostic index

The components of the PTLD prognostic index are summarized in Table 80. The proportion of patients with ECOG /Karnofsky (Lansky) score ≥ 2 was 33.3% in the pivotal study ALLELE and 27.3% in Study RS002. In a real-world setting ECOG is not assessed on a regular basis (50.9% of missing data in Study RS002), thus it was not included in the final logistic regression model to estimate prospensity score. The proportion of patients with elevated LDH was 74.4% in the pivotal study ALLELE and 63.6% in Study RS002. There was 20.0% of missing data in Study RS002 compared to 5.1% in the pivotal study ALLELE.

Considering that the same inclusion and exclusion criteria were applied to the two studies and the compared population characteristics, populations from RS002 and ALLELE were judged to be sufficiently comparable for being compared by indirect comparison.

Table 80: Components of PTLD Adapted Prognostic Index

Risk components	RS002 (N=55)	ALLELE (N=39)
1) Age risk, n (%)		
< 60 (low risk)	41 (74.5)	25 (64.1)
≥ 60 (high risk)	14 (24.5)	14 (35.9)
2) ECOG /Karnofsky (Lansky) score, n (%)		
< 2/≥70% (low risk)	12 (21.8)	26 (66.7)
≥ 2/<70% (high risk)	15 (27.3)	13 (33.3)
Missing	28 (50.9)	0 (0)
3) Serum LDH, n (%)		
Normal (low risk)	9 (16.4)	8 (20.5)
Elevated (high risk)	35 (63.6)	29 (74.4)
Missing	11 (20.0)	2 (5.1)

Propensity score distribution

For further evaluation of baseline comparability, PS was estimated, then PS-based weights were defined, and the covariate balance between patients in the pivotal study ALLELE and Study RS002 was assessed before and after PS adjustment.

The distribution of PS estimated from the logistic regression model showed sufficient agreement between the external control arm (Study RS002; median = 0.432; Q1, Q3: 0.326, 0.474) and the treatment arm (pivotal study ALLELE; median = 0.465; Q1, Q3: 0.379, 0.537) (see Table 81 and Figure 39). The PS overlapped for the majority of total subjects included in the analysis (i.e., 87/94 patients [92.6%] from both pivotal study ALLELE and RS002). The propensity score distribution between the pivotal study ALLELE and Study RS002 is acceptable.
The PS procedure resulted in similar overlap between the Study RS002 and the pivotal study ALLELE populations, with the base case analysis (92.6 vs. 91.9%), the analytical methods were identical to the base case analysis.

Table 81: Estimated conditional probability of receiving treatment

Analysis Variable: p1_PS Estimated Probability							
Treatment	N	Mean	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
RS002	55*	0.393	0.432	0.326	0.474	0.130	0.573
ALLELE	39	0.462	0.465	0.379	0.537	0.164	0.705

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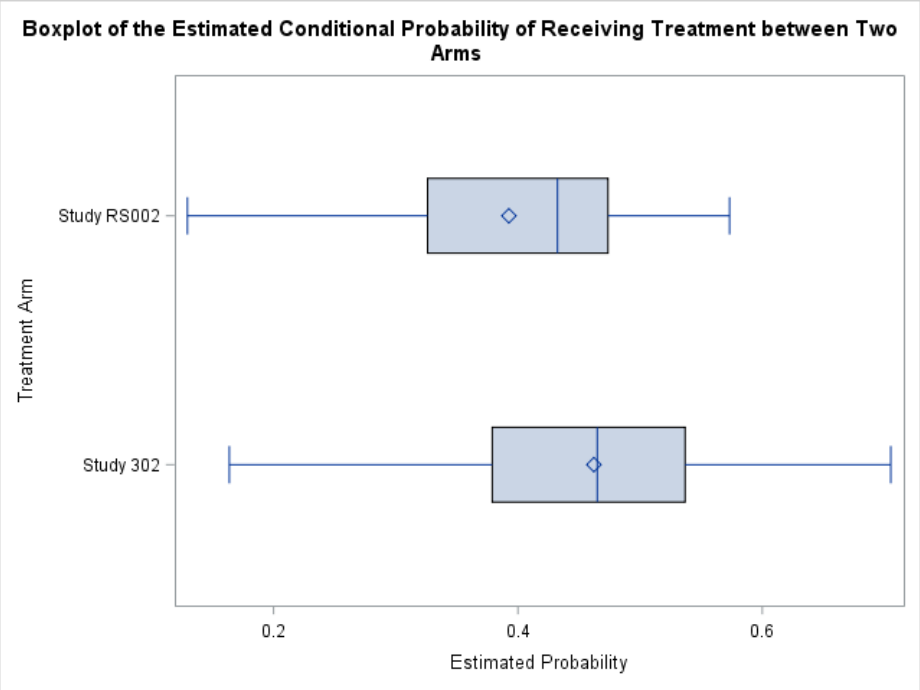
Figure 39: Boxplot of the estimated conditional probability of receiving treatment between the treatment arm and the external control arm. ALLELE = Study 302

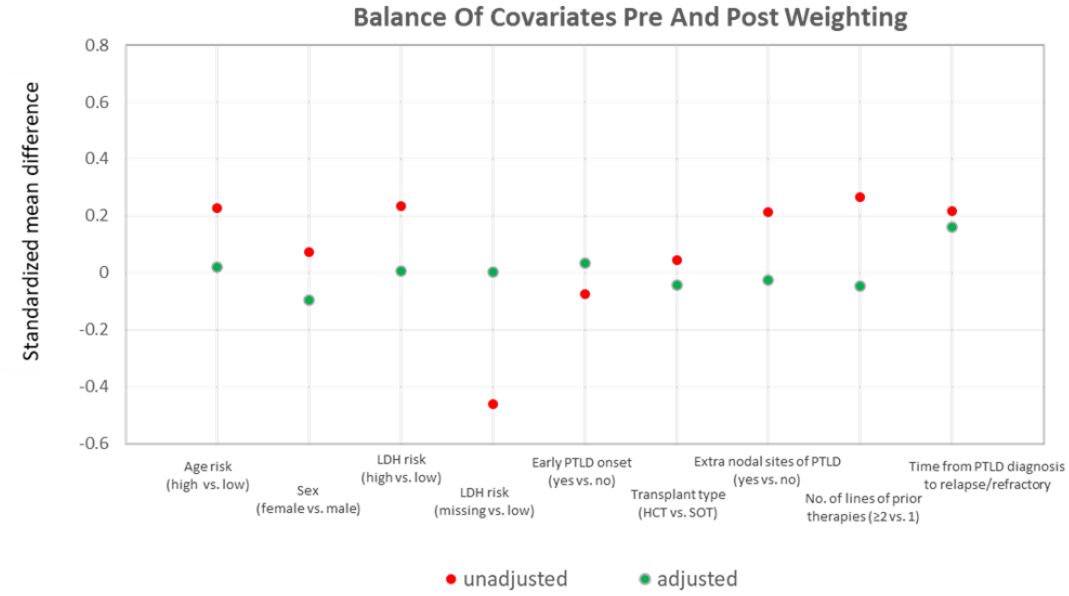


The PSs were then used to estimate weights; the balance of each covariate was evaluated in both pre- and post-weighting scenarios. a standardized mean difference < 0.1 indicates a good balance. Based on the standardized mean difference, the post weighting balance for the baseline covariates was achieved (Table 82 and Figure 40).

Table 82: Comparison of baseline covariates before and after weighting

Covariates	Comparison	Standardized Mean Difference	
		Unadjusted	Adjusted
Age risk	High vs. low	0.228	0.022
Gender	Female vs. male	0.073	-0.095
LDH risk	High vs. low	0.233	0.005
	Missing vs. low	-0.460	0.003
Early onset of PTLD	Early vs. late	-0.074	0.036
Transplant type	HCT vs. SOT	0.044	-0.044
Extra nodal sites of PTLD	Yes vs. no	0.213	-0.024
No. of lines of prior therapies	≥ 2 vs. 1	0.265	-0.046
Time from PTLD diagnosis to R/R	—	0.218	0.160

Figure 40: Comparison of baseline covariates before and after weighting



Appendix G – Extrapolation

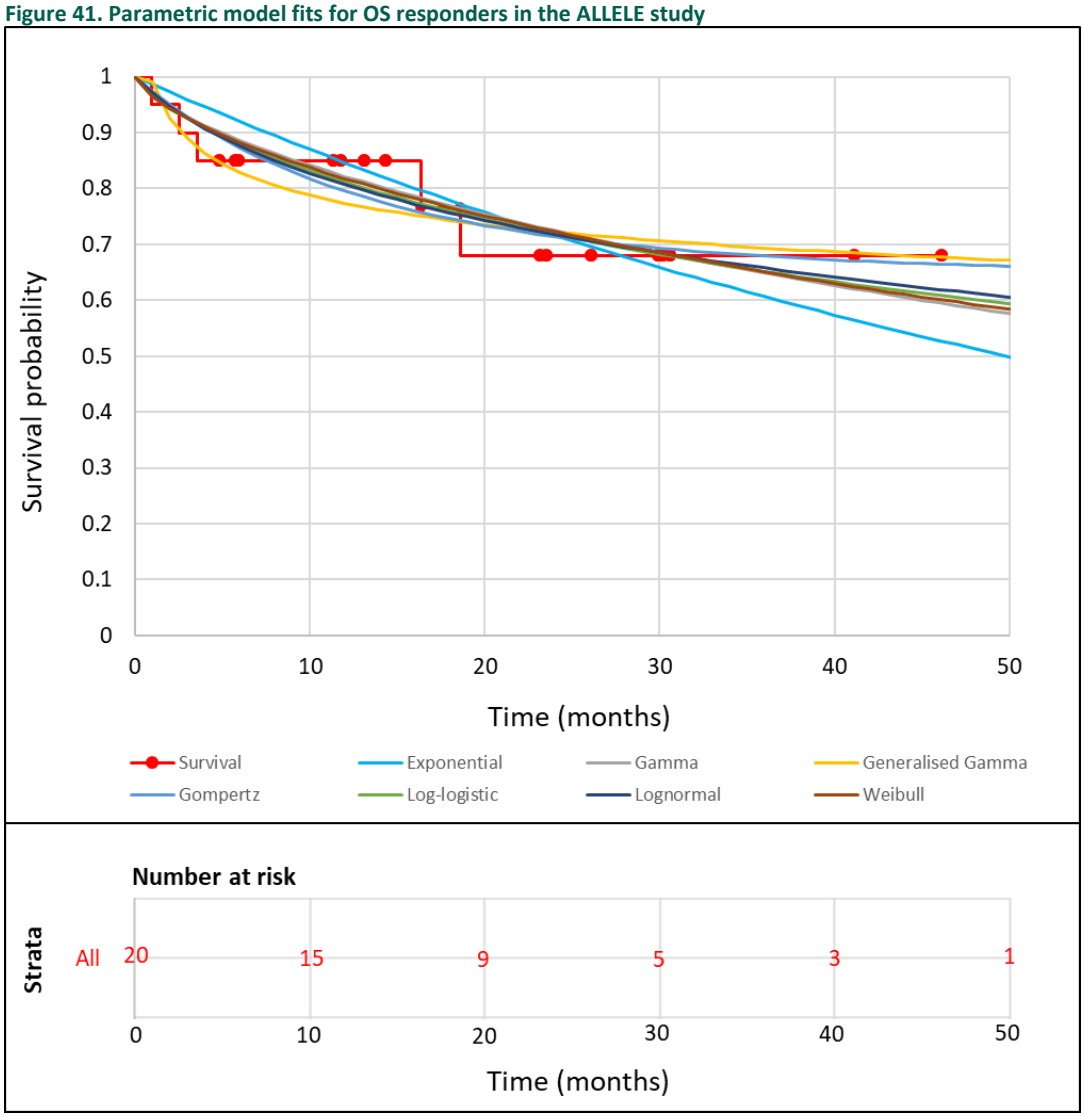
Short-term survival: prior to the cure point – parametric and hybrid model

To address potential uncertainties associated with the piecewise approach, standard parametric extrapolations were explored in the scenario analysis. Ebvallo® Kaplan-Meier data were used to generate parametric models of OS using the following standard parametric distributions:

- Exponential
- Gamma
- Generalised gamma
- Gompertz
- Log-logistic
- Lognormal
- Weibull

The fits of the parametric models versus the observed Kaplan-Meier data are shown below in Figure 41 for responders and Figure 43 for non-responders. The model coefficients are presented in Table 83. NICE DSU TSD 14 was used to guide the model selection process [70].

Figure 41. Parametric model fits for OS responders in the ALLELE study



Abbreviations: OS, overall survival.

Figure 42. Parametric model fits for OS responders in the model – Ebvallo® arm, entire time horizon

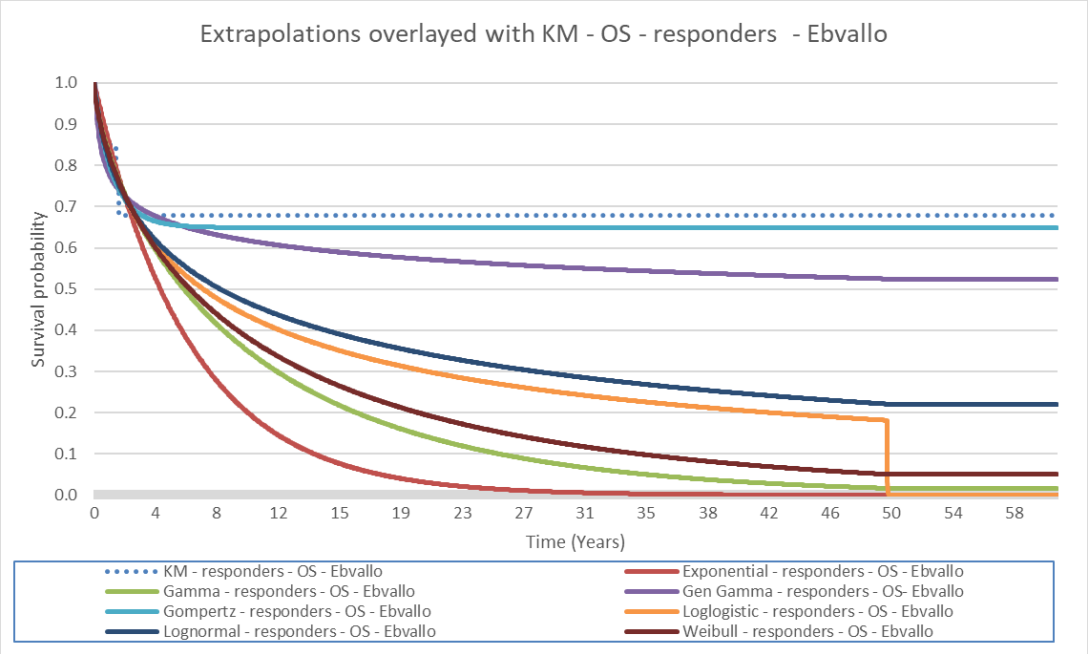
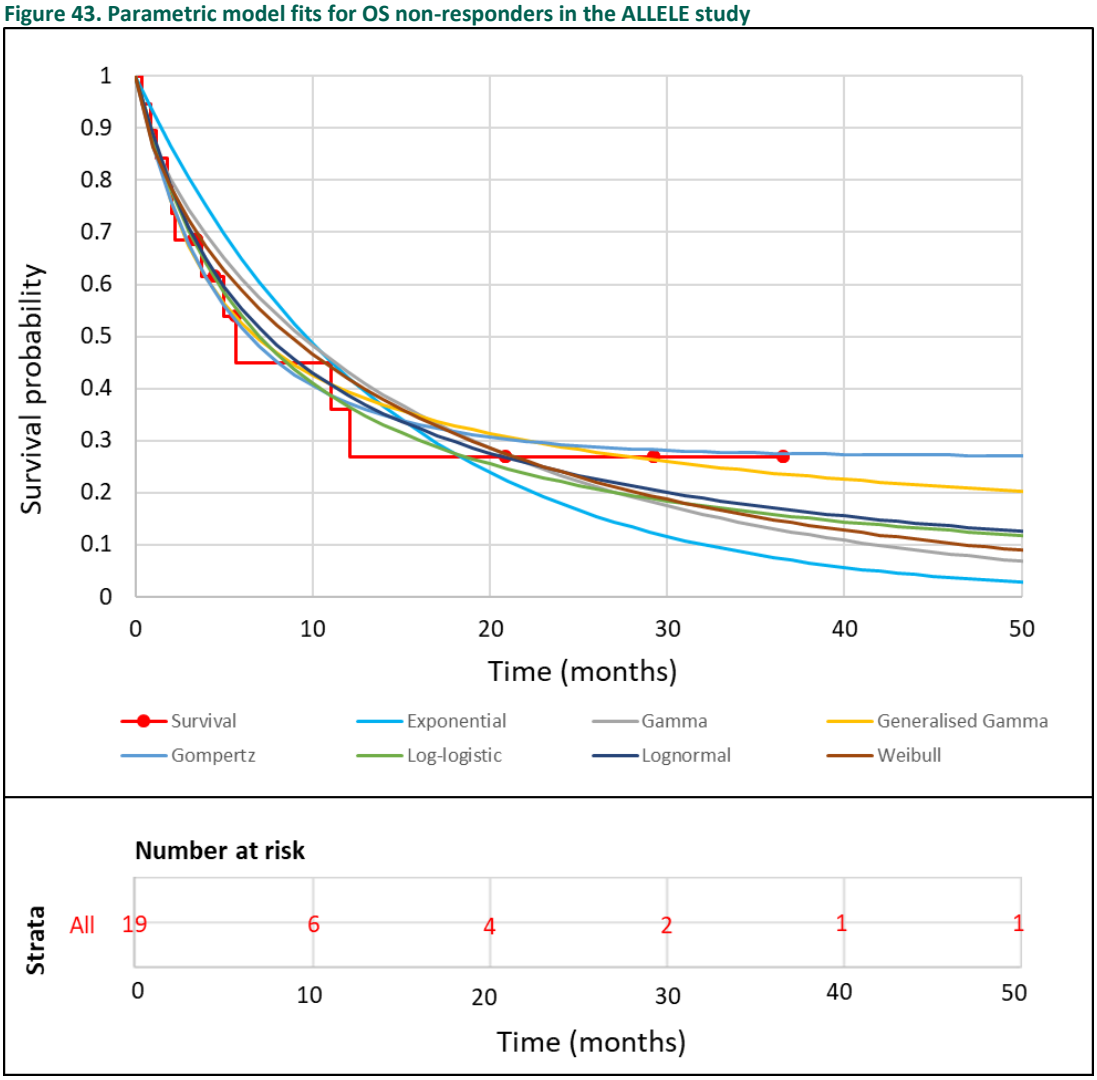


Figure 43. Parametric model fits for OS non-responders in the ALLELE study



Abbreviations: OS, overall survival.

Figure 44. Parametric model fits for OS non-responders in the model – Ebvallo® arm, entire time horizon

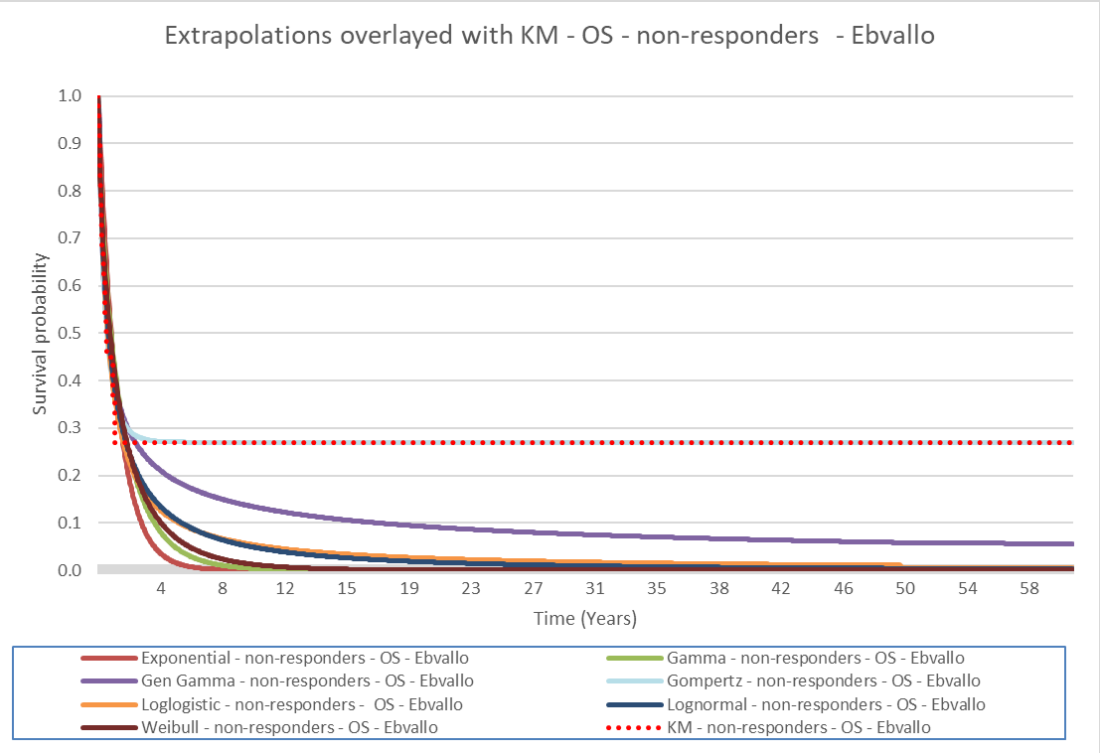


Table 83. Ebvallo® OS parametric model parameters

Distribution	Parameter	Responder coefficient value (July 2022)	Non-responder coefficient value (July 2022)
Exponential	Intercept	-4.276894	-2.6332
Gamma	Shape	-0.4094886	-0.3908047
	Rate	-5.1979234	-3.1926937
Generalised gamma	Mu	-1.07979192	1.1841035
	Sigma	-0.01332644	0.4884683
	Q	-29.55322732	-1.1906
Gompertz	Shape	-0.06281137	-0.1168751
	Rate	-3.60642472	-1.8772676
Log-logistic	Shape	-0.2753973	0.02464217
	Scale	4.4089939	1.94844724
Lognormal	Meanlog	4.555382	2.0134985

	Sdlog	0.8710947	0.5006497
Weibull	Shape	-0.3705284	-0.3331957
	Scale	4.8087572	2.6806064

Abbreviations: OS, Overall survival.

Goodness-of-fit criteria AIC and BIC are presented in Table 84.

Table 84. AIC and BIC for parametric models fitted to Ebvallo® OS data

Parametric model	OS			
	Responders		Non-responders	
	AIC	BIC	AIC	BIC
Exponential	**54.77**	**55.76**	81.93	82.87
Gamma	55.87	57.86	82.40	84.29
Generalised gamma	55.23	58.22	79.81	82.64
Gompertz	55.34	57.33	**78.05**	**79.94**
Log-logistic	55.61	57.60	79.43	81.32
Lognormal	55.21	57.20	78.95	80.84
Weibull	55.77	57.76	81.62	83.51

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

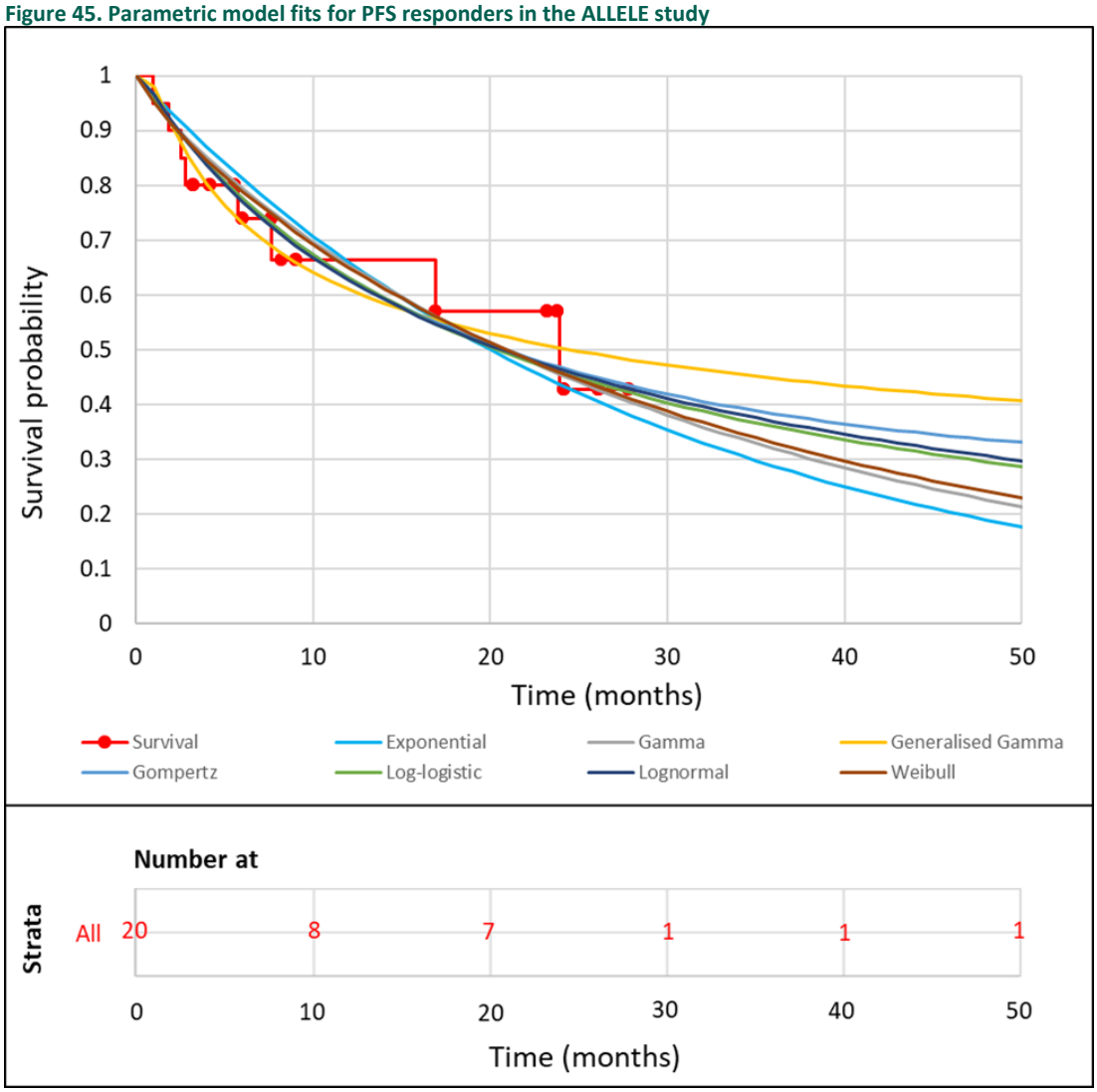
Because long-term survival is modelled with external data, short-term survival should mostly be driven by the best fit to observed Kaplan-Meier data. For the responders, the exponential distribution was associated with the lowest AIC/BIC, even though it may underestimate Ebvallo® survival according to visual fit. For the non-responders, the Gompertz distribution provided the best fit according to AIC/BIC criteria. These distributions were used in scenario analysis. The parametric functions are fitted beyond the Kaplan-Meier data, until the cure point is reached.

Furthermore, another scenario available in the model is a hybrid approach. Within this setting, the Kaplan-Meier curves are used until the last data point. Thereafter, parametric distributions are fitted to the data using the best fit for responders and non-responders for the short term. This interval is used to model the period in between the latest available Kaplan-Meier observation and the cure point. Both scenarios are explored in section 8.7.2.

Short-term survival : prior to the cure point – parametric models

For the purpose of scenario analysis, Kaplan-Meier data were used to generate parametric models of PFS using the same methods as for OS described above. PFS parametric models are shown below in Figure 45. Parametric model fits for PFS responders in the ALLELE study and Figure 47. Parametric models parameters and goodness of fit statistics are reported in Table 85 and Table 86 respectively. Furthermore, a hybrid approach is also explored in the scenario, in which Kaplan-Meier curves are used, followed by parametric extrapolations in between the latest observation and the cure point (described above).

Figure 45. Parametric model fits for PFS responders in the ALLELE study



Abbreviations: PFS, progression-free survival

Figure 46. Parametric model fits for PFS responders in the model – Ebvallo® arm, entire time horizon

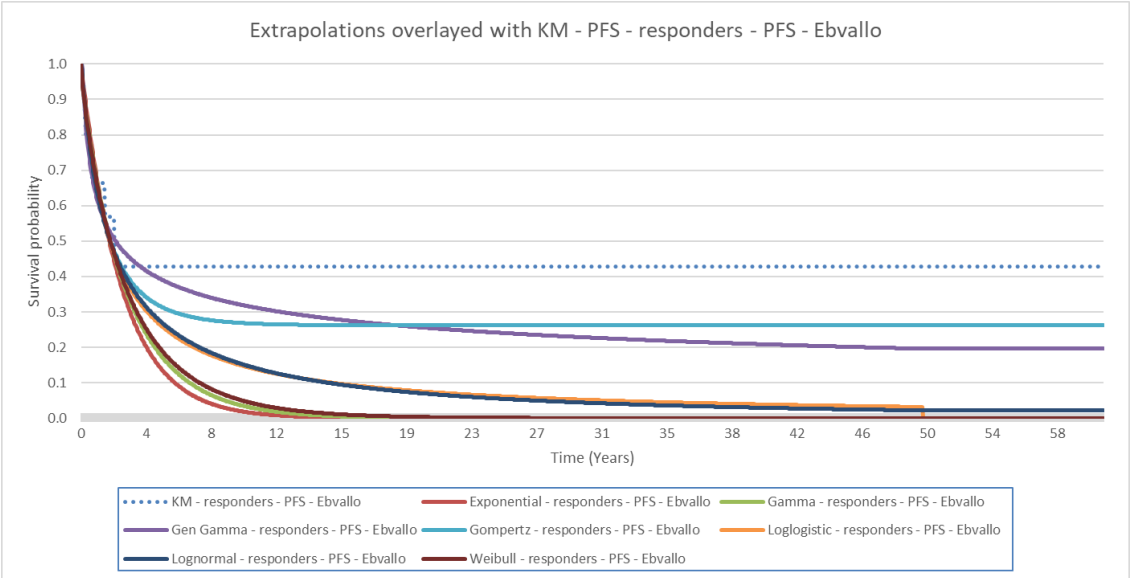
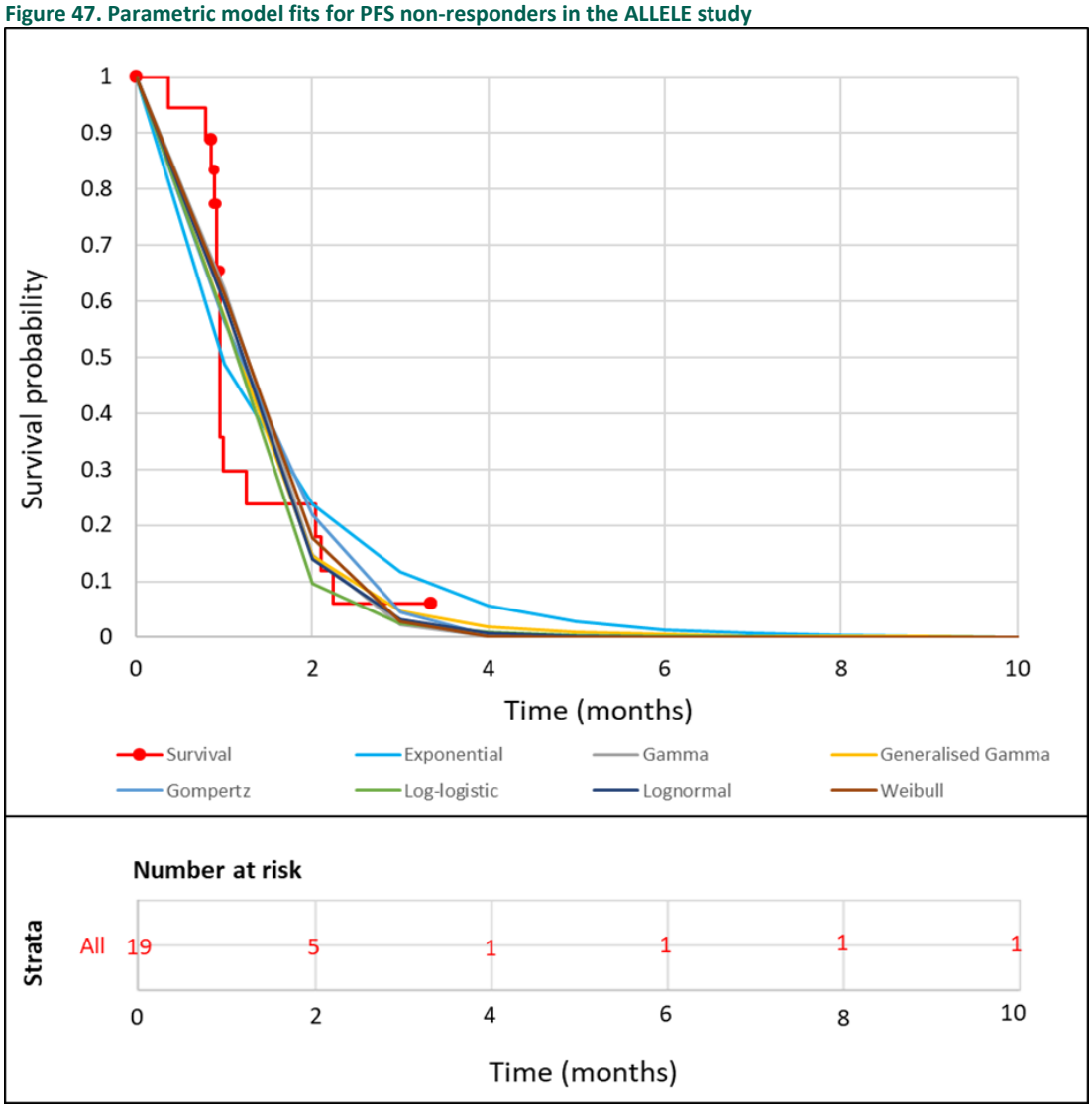


Figure 47. Parametric model fits for PFS non-responders in the ALLELE study



Abbreviations: PFS, progression-free survival

Table 85. Ebvallo® PFS parametric model parameters

Distribution	Parameter	Responder coefficient value (July 2022)	Non-responder coefficient value (July 2022)
Exponential	Intercept	-3.364	-0.334
Gamma	Shape	-0.161	1.308
	Rate	-3.632	1.042
Generalised gamma	Mu	0.533	-0.684
	Sigma	1.731	0.011
	Q	-1.983	-0.472
Gompertz	Shape	-0.035	0.503

	Rate	-3.062	-0.818
Log-logistic	Shape	0.014	1.289
	Scale	3.017	0.077
Lognormal	Meanlog	3.028	0.128
	Sdlog	0.512	-0.652
Weibull	Shape	-0.149	0.596
	Scale	3.465	0.393

Table 86. Goodness-of-fit statistics for parametric models fitted to Ebvallo® PFS data

Parametric model	PFS			
	Responders		Non-responders	
	AIC	BIC	AIC	BIC
Exponential	**71.82**	**72.82**	44.68	45.63
Gamma	73.64	75.63	35.91	37.79
Generalised gamma	73.98	76.97	34.56	37.40
Gompertz	73.35	75.34	43.98	45.86
Log-logistic	73.25	75.24	**32.03**	**33.92**
Lognormal	72.61	74.60	33.41	35.30
Weibull	73.56	75.55	38.90	40.79

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Parametric model fits for the comparator arm

Below are the parametric fits overlayed with the Kaplan-Meier for the comparator arm, over the entire time horizon.

Overall survival

Figure 48. Parametric model fits for OS responders in the model – comparator arm, entire time horizon

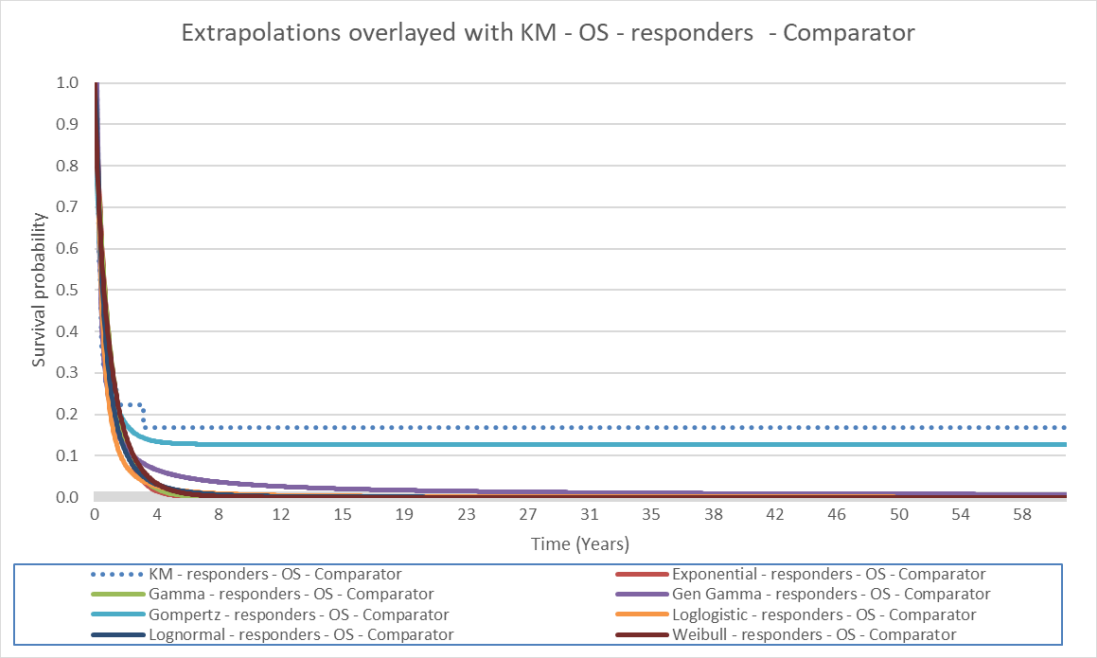
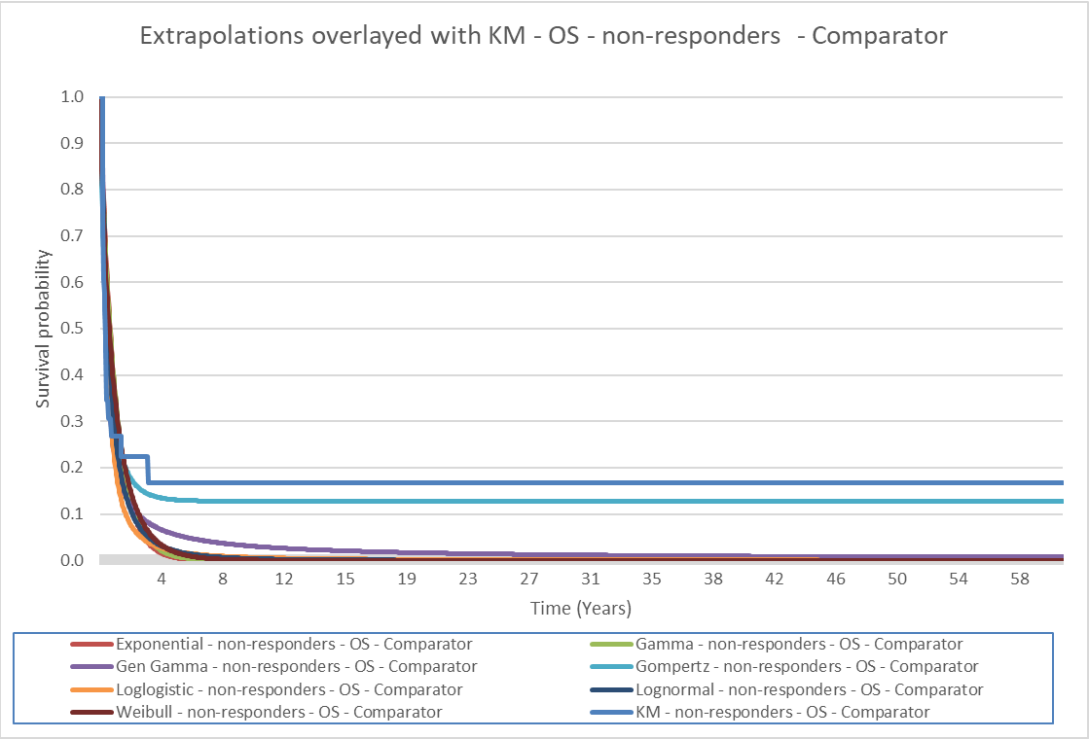


Figure 49. Parametric model fits for OS non- responders in the model – comparator arm, entire time horizon



Progression-free survival

Figure 50. Parametric model fits for PFS responders in the model – comparator arm, entire time horizon

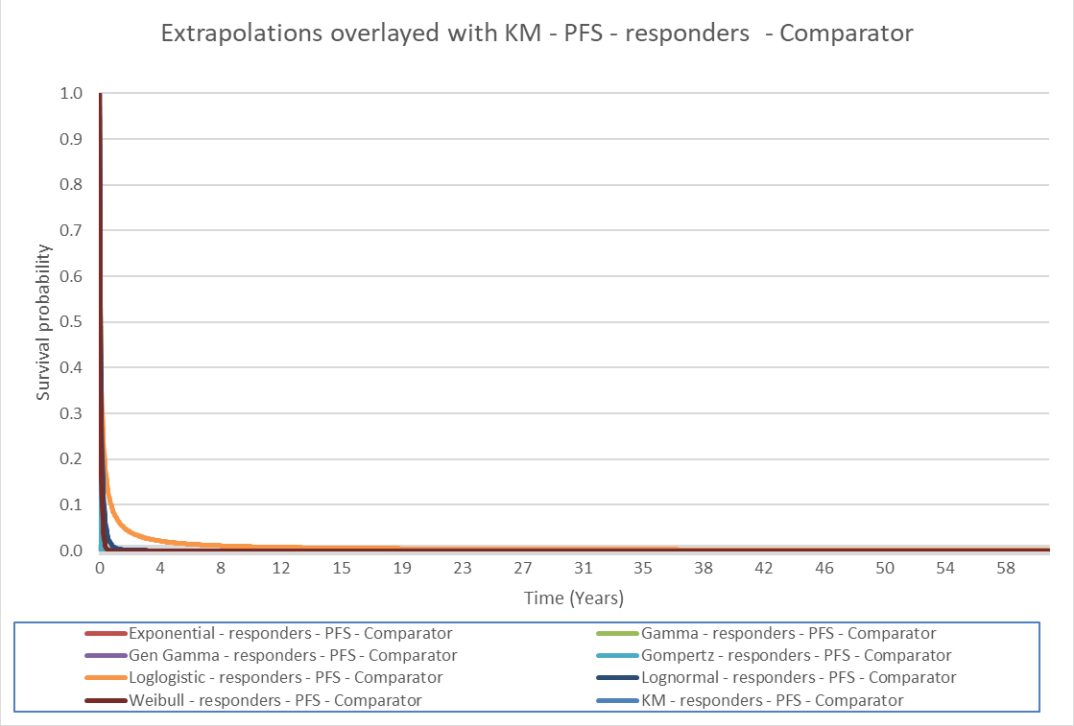
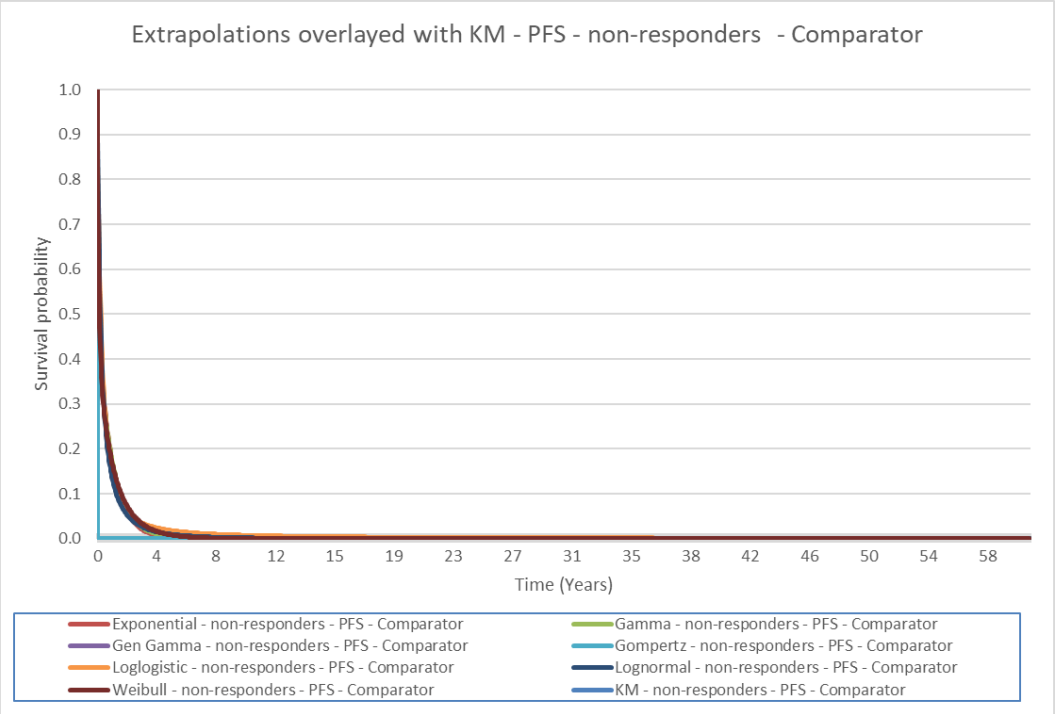


Figure 51. Parametric model fits for PFS non- responders in the model – comparator arm, entire time horizon



Appendix H – Literature search for HRQoL data

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are rare lymphomas that can develop following solid organ transplant (SOT) or allogenic (donor) haematopoietic stem cell transplants (HCTs). Most

cases of PTLD are associated with Epstein-Barr virus (EBV) infection [98]. Current treatment is mostly rituximab with or without chemotherapy but despite treatment, prognosis is very poor and the 3 year overall survival (OS) of patients with PTLD is 20–47% and 49–62% for HCT and SOT, respectively [99]. Tabelecleucel (Ebvallo®) is a first-in-class, allogeneic T-cell immunotherapy developed for EBV-positive PTLD. Ebvallo® is indicated for the treatment of patients with EBV$^+$ PTLD who have received at least one prior therapy (for SOT patients, prior therapy includes chemotherapy unless chemotherapy was considered inappropriate). An Ebvallo® Phase 3 clinical trial is still ongoing for the treatment of EBV-positive PTLD following SOT after the failure of rituximab or rituximab and chemotherapy, and for the treatment of EBV-positive PTLD following allogeneic HCT after the failure of rituximab (ALLELE study) [55].

Objective of the literature search

To understand the current state of knowledge on the treatment of PTLD and identify the burden and unmet treatment needs that demonstrate the value of Ebvallo®, a systematic literature review on the health-related quality of life was conducted.

The priority population and subgroups of interest were that for which Ebvallo® is indicated, i.e., EBV$^+$ PTLD following HCT or SOT patients who have received at least one prior therapy (for SOT patients, prior therapy includes chemotherapy unless chemotherapy was considered inappropriate). This is also taking into account in the design of the ALLELE study [55] where Ebvallo® was assessed in patients with EBV-positive PTLD who had failed rituximab for SOT and HCT subpopulations, or who had failed rituximab plus chemotherapy for the SOT subpopulation. The use of rituximab and chemotherapy could be in combination or in sequence.

Methods

Please refer to the subsection Methods in Appendix A Literature search for efficacy and safety of intervention and comparator(s).

Databases

Please refer to the subsection Databases in Appendix A Literature search for efficacy and safety of intervention and comparator(s).

Search strategy

Eligibility criteria

Table 87 summarises the eligibility criteria in the HRQoL SLR.

Table 87. Eligibility criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients of any age with PTLD following SOT or allogeneic HCT	
Intervention and comparators	Pharmacological treatments given to treat PTLD Note: the HRQoL and cost/resource use reviews were not restricted by intervention	Immunosuppression treatments not for PTLD Unclear treatments

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Outcomes	HRQoL/HSUV review: Disease specific tools HSUVs (and disutilities for relevant health states) derived using the following techniques: Generic, preference-based instruments (e.g. EQ-5D, SF-6D) Direct methods (e.g. TTO, SG, VAS) Mapping algorithms allowing data from disease-specific/generic measures to be mapped to preference-based HSUVs Cost/resource use studies: Total costs (direct + indirect) Direct costs (medical and non-medical) Indirect costs, including but not limited to: Work/opportunity loss Travel time to appointments Absenteeism/presenteeism Healthcare resource utilisation	None
Study design	HRQoL review: Randomised controlled trials Prospective non-randomised trials Prospective/retrospective cohort observational studies Cross sectional studies Cost/resource use studies: Prospective/retrospective cohort studies observational studies Cross sectional studies Budget impact model SLRs†	None
Subgroups of interest	Patients who do not respond to first line rituximab Patients who do not respond to first line chemotherapy Patients who do not respond to first line rituximab and chemotherapy Patients with PTLD associated with Epstein Barr Virus	
Geography	No restriction	
Publication date	HRQoL review: 2010 to present (Conference abstracts limited to 2019 onwards; systematic reviews limited to the past 5 years)	
Language	No restriction	

Abbreviations: AE, adverse event; CEA, cost-effectiveness analysis; DOR, duration of response; HRQoL, health related quality of life; HCT, hematopoietic stem cell transplant; HSUV, health state utility value; LYG, life year gained; NMB, net monetary benefit; PTLD, post-transplant lymphoproliferative disease; QALY, quality-adjusted life year; SAE, serious adverse event; SG, standard gamble; SLR, systematic literature review; SOT, solid organ transplant; TTO, time trade off; TR, treatment related; TTR, time to response; VAS, visual analog scale.

†These publications were not included in the review but identified for reference checking and if appropriate summarised in the qualitative report.

Search strings

Table 88 - Table 92 summarize the search strings used in the HRQoL SLR.

Table 88. Embase (Ovid): 1974 to 2022 February 07: searched 8.2.22

#	Searches	Results

1	posttransplant lymphoproliferative disease/	3301
2	((post transplant$ or posttransplant$) adj2 lymphoma$).ti,ab.	490
3	((post transplant$ or posttransplant$) adj2 lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	5943
4	PTLD.ti,ab.	4969
5	or/1-4	8351
6	lymphoproliferative disease/	20280
7	(lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	23682
8	6 or 7	31527
9	transplantation/ or exp organ transplantation/	536420
10	(transplant$ or allogenic or allograft or autologous or SOT or HCT or SCT).ti,ab.	898264
11	9 or 10	1000907
12	8 and 11	10466
13	5 or 12	12773
14	socioeconomics/	150604
15	exp Quality of Life/	566307
16	quality of life.ti,kw.	153654
17	((instrument or instruments) adj3 quality of life).ab.	5060
18	Quality-Adjusted Life Year/	30789
19	quality adjusted life.ti,ab,kw.	22998
20	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.	38569
21	disability adjusted life.ti,ab,kw.	5045
22	daly*.ti,ab,kw.	4970
23	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	45946
24	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.	2666
25	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.	938
26	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.	10886
27	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	63
28	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.	486
29	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.	33719
30	(hye or hyes).ti,ab,kw.	151
31	(health* adj2 year* adj2 equivalent*).ti,ab,kw.	52
32	(pqol or qls).ti,ab,kw.	690
33	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.	805
34	nottingham health profile*.ti,ab,kw.	1609
35	nottingham health profile/	574
36	sickness impact profile.ti,ab,kw.	1267
37	sickness impact profile/	2360

38	health status indicator/	3292
39	(health adj3 (utilit* or status)).ti,ab,kw.	105046
40	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.	22526
41	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.	16575
42	disutilit*.ti,ab,kw.	1067
43	rosser.ti,ab,kw.	134
44	willingness to pay.ti,ab,kw.	10938
45	standard gamble*.ti,ab,kw.	1171
46	(time trade off or time tradeoff).ti,ab,kw.	2192
47	tto.ti,ab,kw.	1941
48	(hui or hui1 or hui2 or hui3).ti,ab,kw.	2713
49	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.	32316
50	duke health profile.ti,ab,kw.	115
51	functional status questionnaire.ti,ab,kw.	163
52	dartmouth coop functional health assessment*.ti,ab,kw.	13
53	or/14-52	874593
54	13 and 53	370
55	limit 54 to yr="2010 -Current"	248

Table 89. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R): 1946 to February 07, 2022: searched 8.2.22

#	Searches	Results
1	((post transplant$ or posttransplant$) adj2 lymphoma$).ti,ab.	330
2	((post transplant$ or posttransplant$) adj2 lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	3737
3	PTLD.ti,ab.	2265
4	or/1-3	4145
5	Lymphoproliferative Disorders/	8805
6	(lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	15972
7	5 or 6	19192
8	exp Transplants/	29137
9	(transplant$ or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT).ti,ab.	603075
10	8 or 9	618329
11	7 and 10	5531
12	4 or 11	6096
13	"Value of Life"/	5780
14	Quality of Life/	232893
15	quality of life.ti,kf.	101158
16	((instrument or instruments) adj3 quality of life).ab.	3676
17	Quality-Adjusted Life Years/	14349
18	quality adjusted life.ti,ab,kf.	15345
19	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	24535

20	disability adjusted life.ti,ab,kf.	4289
21	daly*.ti,ab,kf.	3866
22	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	28419
23	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	2398
24	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	573
25	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	6818
26	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	36
27	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	432
28	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	20934
29	(hye or hyes).ti,ab,kf.	75
30	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	48
31	(pqol or qls).ti,ab,kf.	421
32	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	649
33	nottingham health profile*.ti,ab,kf.	1203
34	sickness impact profile.ti,ab,kf.	1083
35	exp health status indicators/	333957
36	(health adj3 (utilit* or status)).ti,ab,kf.	82538
37	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	14157
38	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	12707
39	disutilit*.ti,ab,kf.	540
40	rosser.ti,ab,kf.	105
41	willingness to pay.ti,ab,kf.	7200
42	standard gamble*.ti,ab,kf.	892
43	(time trade off or time tradeoff).ti,ab,kf.	1534
44	tto.ti,ab,kf.	1235
45	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1772
46	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	19331
47	duke health profile.ti,ab,kf.	90
48	functional status questionnaire.ti,ab,kf.	126
49	dartmouth coop functional health assessment*.ti,ab,kf.	13
50	or/13-49	688276
51	12 and 50	110
52	limit 51 to yr="2010 -Current"	55

Table 90. EBM Reviews (Ovid): Cochrane Methodology Register 3rd Quarter 2012, Database of Abstracts of Reviews of Effects 1st Quarter 2016, Health Technology Assessment 4th Quarter 2016, NHS Economic

Evaluation Database 1st Quarter 2016, Journal Club 1991 to November 2021, Cochrane Clinical Answers November 2021, Cochrane Central Register of Controlled Trials January 2022, Cochrane Database of Systematic Reviews 2005 to December 02, 2021: searched 8.2.22

#	Searches	Results
1	((post transplant$ or posttransplant$) adj2 lymphoma$).ti,ab.	6
2	((post transplant$ or posttransplant$) adj2 lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	148
3	PTLD.ti,ab.	156
4	or/1-3	232
5	Lymphoproliferative Disorders/	85
6	(lymphoprolif$ adj2 (disease$ or disorder$)).ti,ab.	343
7	5 or 6	391
8	exp Transplants/	551
9	(transplant$ or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT).ti,ab.	49324
10	8 or 9	49525
11	7 and 10	225
12	4 or 11	303
13	"Value of Life"/	148
14	Quality of Life/	28465
15	quality of life.ti,kf.	22360
16	((instrument or instruments) adj3 quality of life).ab.	1008
17	Quality-Adjusted Life Years/	4687
18	quality adjusted life.ti,ab,kf.	5080
19	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	6678
20	disability adjusted life.ti,ab,kf.	286
21	daly*.ti,ab,kf.	242
22	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	14335
23	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	245
24	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	251
25	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	3014
26	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	19
27	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	90
28	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	6837
29	(hye or hyes).ti,ab,kf.	13
30	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	2
31	(pqol or qls).ti,ab,kf.	155
32	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	602
33	nottingham health profile*.ti,ab,kf.	387

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34	sickness impact profile.ti,ab,kf.	299
35	exp health status indicators/	23367
36	(health adj3 (utilit* or status)).ti,ab,kf.	13333
37	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	3886
38	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	2383
39	disutilit*.ti,ab,kf.	90
40	rosser.ti,ab,kf.	13
41	willingness to pay.ti,ab,kf.	1722
42	standard gamble*.ti,ab,kf.	112
43	(time trade off or time tradeoff).ti,ab,kf.	241
44	tto.ti,ab,kf.	196
45	(hui or hui1 or hui2 or hui3).ti,ab,kf.	306
46	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	11649
47	duke health profile.ti,ab,kf.	9
48	functional status questionnaire.ti,ab,kf.	41
49	dartmouth coop functional health assessment*.ti,ab,kf.	0
50	or/13-49	106502
51	12 and 50	6
52	limit 51 to yr="2010 -Current" [Limit not valid in DARE; records were retained]	2

Table 91. EBM Reviews (Ovid): Health Technology Assessment 4th Quarter 2016, NHS Economic Evaluation Database 1st Quarter 2016: searched 7.2.22

#	Searches	Results
1	((post transplant$ or posttransplant$) adj2 lymphoma$).af.	0
2	((post transplant$ or posttransplant$) adj2 lymphoprolif$ adj2 (disease$ or disorder$)).af.	3
3	PTLD.af.	1
4	or/1-3	3
5	Lymphoproliferative Disorders/	3
6	(lymphoprolif$ adj2 (disease$ or disorder$)).af.	9
7	5 or 6	9
8	exp Transplants/	6
9	(transplant$ or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT).af.	1349
10	8 or 9	1349
11	7 and 10	6
12	4 or 11	6
13	limit 12 to yr="2010 -Current"	2

Table 92. CRD HTA, https://www.crd.york.ac.uk/CRDWeb/: searched 8.2.22

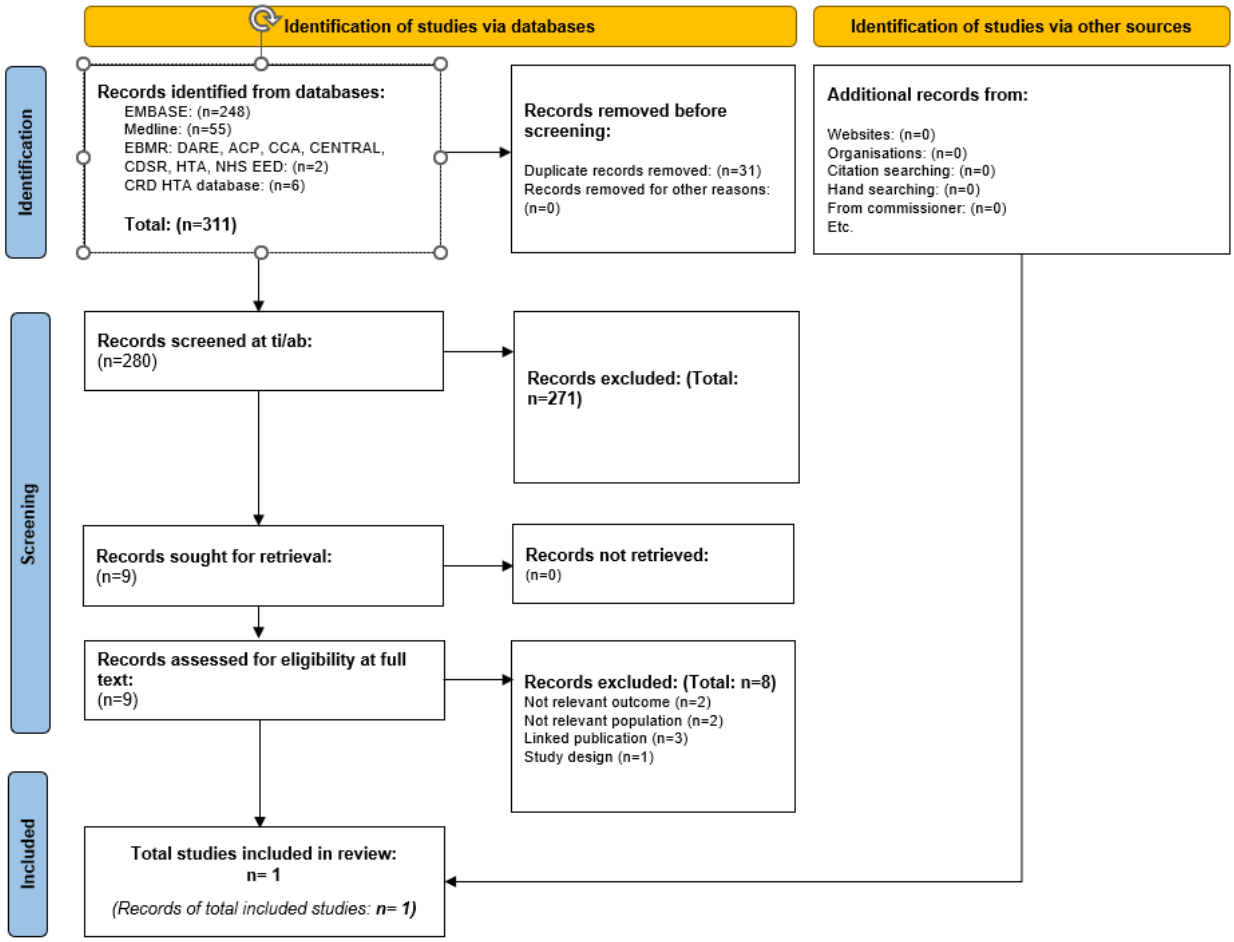
#	Searches	Results

1	(((post transplant* or posttransplant*) NEAR2 lymphoma*)) OR (((post transplant* or posttransplant*) NEAR2 lymphoprolif* NEAR2 (disease* or disorder*))) OR (PTLD) IN HTA FROM 2016 TO 2022	0
2	MeSH DESCRIPTOR Lymphoproliferative Disorders EXPLODE ALL TREES	673
3	* IN HTA FROM 2016 TO 2022	1,323
4	#2 AND #3	58
5	((lymphoprolif* NEAR2 (disease* or disorder*))) IN HTA FROM 2016 TO 2022	2
6	MeSH DESCRIPTOR transplants EXPLODE 1 IN HTA	8
7	((transplant* or allogenic or allograft or autologous or SOT or HCT or SCT or HSCT)) IN HTA FROM 2016 TO 2022	61
8	#4 OR #5	58
9	#6 OR #7	64
10	#8 AND #9	6

Systematic selection of studies

Please refer to Figure 32 for the PRISMA diagram for the SLR.

Figure 52. PRISMA study flow diagram



Abbreviations: ACP, American College of Physicians; CCA, Cochrane Clinical Answers; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; EBMR, Evidence Based Medicine Reviews; HTA, health technology assessment; NHS EED, NHS Economic Evaluation Database.

List of included studies

Table 93 summarizes the included studies in the HRQoL SLR

Table 93. Summary of studies included in the quality-of-life SLR

Study ID	Publication Type	Other linked publications	Country	# centres	Study Design	Sample Size
Watson (2020) [201]	Full publication	Watson 2019 [202] Trivedi 2019 [203]	USA	NR	Cross-sectional study	6

Abbreviations: NA, not applicable; NR, not reported; SLR, systematic literature review; USA, United States of America.

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List of excluded studies

Table 94 summarizes the excluded studies excluded in the HRQoL SLR.

Table 94. Summary of studies in the HRQoL SLR excluded at full publication review

Endnote	Author	Title	Citation	DOI
Not relevant population (n=2)				
6119	Ng, V. L.	Health status of children alive 10 years after pediatric liver transplantation performed in the US and Canada: report of the studies of pediatric liver transplantation experience	160(5):820-6.e3.	https://dx.doi.org/10.1016/j.jpeds.2011.10.038
5982	Valkova, V.	The quality of life following allogeneic hematopoietic stem cell transplantation - a multicenter retrospective study	63(5):743-51.	https://dx.doi.org/10.4149/neo_2016_511
Linked publication (n=3)				
5986	Watson, C.	Pro145 the Humanistic Burden of Short-Term Adverse Events Associated with the Chop Chemotherapy Regimen in Patients with Lymphoproliferative Disorders in European Countries: A Comprehensive Literature Review	22(Supplement 3):S868.	http://dx.doi.org/10.1016/j.jval.2019.09.2474
6012	Watson, C.	Pcn480 Relevance of Selected Patient-Reported Outcome (Pro) Measures in Epstein-Barr Virus Associated (Ebv+) Post-Transplant Lymphoproliferative Disease (Ptld) Patients	22(Supplement 3):S530.	http://dx.doi.org/10.1016/j.jval.2019.09.672
6104	Trivedi, B.	Impact of disease on patient functioning in Epstein-Barr virus associated (EBV1) post-transplant lymphoproliferative disease (PTLD) Patients	28(SUPPL 1):S87.	https://dx.doi.org/10.1007/s11136-019-02257-y
Not relevant outcome (n=2)				

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5989	Summers, J.	Primary CNS posttransplant lymphoproliferative disease (PCNS-PTLD): Diagnosis, minimal treatment toxicity, and surveillance in renal transplant patients	92(15 Supplement 1).	-
6063	Jacob, S.	Long term follow-up of liver transplant recipients: Considerations for non-transplant specialists	30(2):283-290.	http://dx.doi.org/10.15403/jgld-3616

Abbreviations: HSUV, health state utility value; SLR, systematic literature review.

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Results of the quality-of-life review

One publication identified by the database search was eligible for inclusion in the quality of life review [11]. In the cross-sectional study based in the USA, Watson et al (2020) evaluated the applicability of general and lymphoma-specific PROs (EQ-5D, SF-36v2, and FACT-LYM) from the perspective of patients with EBV and PTLD (N=6). Participants reported the impact of their EBV and PTLD on their quality of life. Focus groups were held to discuss the relevance of patient reported outcome (PRO) instruments for PTLD populations. The EQ-5D was reported as relevant for the pain/discomfort and anxiety/depression domains; most SF-36v2 domains were relevant, with the exception of the general health perception domain, which was not applicable; all domains in the FACT-LYM were relevant. No utility values were reported for the study population.

Conclusions

There were limited high quality studies that were well reported and investigated the pharmacological treatment of PTLD. The majority were small, retrospective, and observational and many did not clearly report line of treatment or EBV status. Ebvallo® represents an additional treatment option for EBV^+ PTLD following HCT or SOT patients who have received at least one prior therapy (for SOT patients, prior therapy includes chemotherapy unless chemotherapy is considered inappropriate).
Very limited data and no utilities values were identified on quality of life in PTLD patients representing a substantial evidence gap.

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Appendix I Mapping of HRQoL data

Not applicable

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Appendix J Probabilistic sensitivity analyses

The following table presents the items varied in the probabilistic sensitivity analysis, alongside the value that the item takes, the standard error, the distribution used to vary the item, as well as the 95% confidence interval, i.e., the highest and lowest value of the interval.

	Expected value	Standard error	Probability distribution	Parameter distribution (High)	Parameter distribution (Low)
Anaemia	4,210	420.966667	Gamma	5073.86694	3425.152818
Neutropenia	38,209	3820.9	Gamma	46052.9056	31088.36742
Thrombocytopenia	38,209	3820.9	Gamma	46052.9056	31088.36742
Platelet count decrease	2,005	200.5	Gamma	2416.6054	1631.348025
Neutrophil count decrease	2,002	200.2	Gamma	2412.98953	1628.907105
White blood cell count decrease	2,005	200.5	Gamma	2416.6054	1631.348025
Cytopenia	2,005	200.5	Gamma	2416.6054	1631.348025
Infection	41,862	4186.2	Gamma	50455.8281	34060.59402
Thrombosis	30,716	3071.6	Gamma	37021.6716	24991.76355
Fatigue	4,728	472.8	Gamma	5698.60865	3846.889506
Vomiting	3,425	342.5	Gamma	4128.11646	2786.7167
Febrile neutropenia	19,631	1963.1	Gamma	23661.0377	15972.56512
Acute kidney injury	45,038	4503.8	Gamma	54283.8275	36644.71438
Sepsis	46,987	4698.7	Gamma	56632.9367	38230.49857
Hypertension	17,304	1730.4	Gamma	20856.3291	14079.22505
Pneumonia	33,134	3313.4	Gamma	39936.0615	26959.14486
Respiratory failure	38,476	3847.6	Gamma	46374.7179	31305.60927
Leukopenia	2,005	200.5	Gamma	2416.6054	1631.348025
Bowel perforation	135,507	13550.7	Gamma	163325.161	110253.9036
Cardiovascular-related	24,817	2481.7	Gamma	29911.669	20192.10171
Hypotension	17,304	1730.4	Gamma	20856.3291	14079.22505
R-CHOP	1	0	Dirichlet	0.5	0.5
GDP	1	0	Dirichlet	0.5	0.5
Median age of population at baseline	42	4.23	Normal	50.5906477	34.00935235
% males	1	0.0564	Beta	0.65928325	0.466290944
Mean height, cm	169	16.886	Normal	201.955952	135.7640482
Mean weight, kg	65	6.503	Normal	77.7756458	52.28435421
Mean BSA, m2	2	0.173	Normal	2.06907377	1.390926231
% SOT	0	0.04871795	Beta	0.58471257	0.390172618
Cure point (years) (SOT)	3	0.3	Normal	3.5879892	2.412010805
Cure point (years) (SOT)	3	0.3	Normal	3.5879892	2.412010805
Number of treatment cycles	4	0.367	Normal	4.38930678	2.950693218
Number of treatment cycles	1	0.12	Normal	1.43519568	0.964804322
Ebvallo® response status (%)	1	0	Beta	0.64586338	0.452241421
Cure point (years) (HCT)	1	0.2	Normal	2.3919928	1.608007203
Cure point (years) (HCT)	1	0.2	Normal	2.3919928	1.608007203
Number of treatment cycles	3	0.3	Normal	3.5879892	2.412010805

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Number of treatment cycles	2	0.244	Normal	2.91823121	1.961768788
SMR	5	0.45	Lognormal	10.8705923	1.862823977
Oncologist	1	0.1	Normal	1.1959964	0.804003602
Radiologist	1	0.066	Normal	0.78935762	0.530642377
Nurse	1	0.066	Normal	0.78935762	0.530642377
Specialist nurse	1	0.066	Normal	0.78935762	0.530642377
PET scan	1	0.066	Normal	0.78935762	0.530642377
Full blood counts	1	0.1	Normal	1.1959964	0.804003602
LDH	1	0.1	Normal	1.1959964	0.804003602
Liver function	1	0.1	Normal	1.1959964	0.804003602
Renal function	1	0.1	Normal	1.1959964	0.804003602
Immunoglobulin	1	0.1	Normal	1.1959964	0.804003602
Calcium phosphate	1	0.1	Normal	1.1959964	0.804003602
Inpatient days	2	0.2	Normal	2.3919928	1.608007203
Oncologist	3	0.3	Normal	3.5879892	2.412010805
Palliative care team	4	0.4	Normal	4.78398559	3.216014406
Specialist nurse	4	0.4	Normal	4.78398559	3.216014406
PET scan	4	0.4	Normal	4.78398559	3.216014406
Full blood counts	3	0.3	Normal	3.5879892	2.412010805
LDH	3	0.3	Normal	3.5879892	2.412010805
Liver function	3	0.3	Normal	3.5879892	2.412010805
Renal function	3	0.3	Normal	3.5879892	2.412010805
Immunoglobulin	3	0.3	Normal	3.5879892	2.412010805
Calcium phosphate	3	0.3	Normal	3.5879892	2.412010805
Hospice	1	0.094	Normal	1.12423661	0.755763385
End of life cost	1	0.1	Normal	1.1959964	0.804003602
Oncologist	1	0.1	Normal	1.1959964	0.804003602
Full blood counts	1	0.1	Normal	1.1959964	0.804003602
LDH	1	0.1	Normal	1.1959964	0.804003602
Liver function	1	0.1	Normal	1.1959964	0.804003602
Renal function	1	0.1	Normal	1.1959964	0.804003602
Immunoglobulin	1	0.1	Normal	1.1959964	0.804003602
Calcium phosphate	1	0.1	Normal	1.1959964	0.804003602
Hospice	0	0.00157692	Normal	0.01885994	0.012678518
Inpatient days	1	0.1	Normal	1.1959964	0.804003602
Oncologist	2	0.2	Normal	2.3919928	1.608007203
Palliative care team	2	0.2	Normal	2.3919928	1.608007203
Specialist nurse	2	0.2	Normal	2.3919928	1.608007203
PET scan	2	0.2	Normal	2.3919928	1.608007203
Full blood counts	2	0.2	Normal	2.3919928	1.608007203
LDH	2	0.2	Normal	2.3919928	1.608007203
Liver function	2	0.2	Normal	2.3919928	1.608007203
Renal function	2	0.2	Normal	2.3919928	1.608007203
Immunoglobulin	2	0.2	Normal	2.3919928	1.608007203
Calcium phosphate	2	0.2	Normal	2.3919928	1.608007203

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Oncologist	1,066	106.6	Gamma	1284.83858	867.3401467
Radiologist	1,066	106.6	Gamma	1284.83858	867.3401467
Transplant physician	1,066	106.6	Gamma	1284.83858	867.3401467
PET scan	2,023	202.3	Gamma	2438.30061	1645.993543
Full blood counts	22	2.163	Gamma	26.0704114	17.59903131
LDH	14	1.4	Gamma	16.8740527	11.39095878
Liver function	68	6.8	Gamma	81.9596845	55.32751405
Renal function	72	7.209	Gamma	86.8893184	58.65530129
Immunoglobulin	47	4.7	Gamma	56.6486054	38.24107589
Calcium phosphate	13	1.3	Gamma	15.6687632	10.57731886
Inpatient days	18,627	1862.7	Gamma	22450.9271	15155.67065
Health care visits	140	14	Gamma	168.740527	113.9095878
End of life cost	60,330	6033	Gamma	72715.1142	49086.89592
Drug administration	2,005	200.5	Gamma	2416.6054	1631.348025
Progression-free	0.83	0	Beta	0.89666668	0.750853659
Progressed	0.71	0	Beta	0.76732172	0.585858389
HCT	0.84	0	Beta	0.90470591	0.762439718
SOT: Kidney	0.81	0	Beta	0.88031565	0.727955782
SOT: Liver	0.84	0	Beta	0.90470591	0.762439718
SOT: Heart	0.83	0	Beta	0.89666668	0.750853659
SOT: Lung	0.83	0	Beta	0.89666668	0.750853659

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Appendix K Results from the November 2021 data cut-off

Efficacy results

Efficacy results are presented per IORA.

ORR by cohorts

Table 95 presents results for the previous data cut-off for the primary efficacy endpoint ORR, all per IORA assessments. In the C-HCT, the ORR rate was 50.0% (95% CI: 23.0, 77.0). In the C-SOT, the ORR rate was 51.7% (95% CI: 32.5, 70.6). More specifically, in the C-SOT-R+C the ORR rate was 56.3% (95% CI: 29.9, 80.2).

Table 95. Summary of objective response rate (FAS)

Per IORA	C-SOT			C-HCT (N = 14)	Overall Total [C-PTLD] (N = 43)
	C-SOT-R (N = 13)	C-SOT-R+C (N = 16)	Total (N = 29)		
Responders–n (%)	6 (46.2)	9 (56.3)	15 (51.7)	7 (50.0)	22 (51.2)
95% CI	19.2, 74.9	29.9, 80.2	32.5, 70.6	23.0, 77.0	35.5, 66.7
Best Overall Response, n (%)					
CR	1 (7.7)	5 (31.3)	6 (20.7)	6 (42.9)	12 (27.9)
95% CI	0.2, 36.0	11.0, 58.7	8.0, 39.7	17.7, 71.1	15.3, 43.7
PR	5 (38.5)	4 (25.0)	9 (31.0)	1 (7.1)	10 (23.3)
95% CI	13.9, 68.4	7.3, 52.4	15.3, 50.8	0.2, 33.9	11.8, 38.6
SD	2 (15.4)	0	2 (6.9)	3 (21.4)	5 (11.6)
PD	3 (23.1)	4 (25.0)	7 (24.1)	2 (14.3)	9 (20.9)
NE	2 (15.4)	3 (18.8)	5 (17.2)	2 (14.3)	7 (16.3)
p-value (H0: ORR ≤ 20%)[a]	0.0300	0.0015	0.0001	0.0116	<0.0001

Abbreviations: CI, confidence interval; HCT, hematopoietic cell transplant; IORA, independent oncologic response adjudication; ORR, objective response rate; N, number of subjects; SOT, solid organ transplant.

Secondary efficacy endpoints

The results for the secondary efficacy endpoints from the 5 November 2021 data cut-off are presented in Table 96.

Table 96. Summary results for main secondary endpoints

Per IORA	C-SOT			C-HCT (N = 7)	Overall Total [C-PTLD] (N = 22)
	C-SOT-R (N = 6)	C-SOT-R+C (N = 9)	Total (N = 15)		

DOR status, n (%)					
Events	2 (33.3)	4 (44.4)	6 (40.0)	2 (28.6)	8 (36.4)
Deaths	1 (16.7)	0	1 (6.7)	0	1 (4.5)
Progression	1 (16.7)	4 (44.4)	5 (33.3)	2 (28.6)	7 (31.8)
Censored	4 (66.7)	5 (55.6)	9 (60.0)	5 (71.4)	14 (63.6)
Follow-up time after achieving first response (months) – n					
Median (min, max)	2.4 (0.6, 21.0)	2.3 (0.8, 15.2)	2.3 (0.6, 21.0)	15.9 (1.3, 23.3)	7.0 (0.6, 23.3)
DOR estimate (K-M) (months)					
Median (95% CI)	NE (0.6, NE)	15.2 (0.8, 15.2)	15.2 (1.2, NE)	23.0 (15.9, NE)	23.0 (6.8, NE)
TTR and TTBR					
TTR (months)					
Median (min, max)	1.6 (1.0, 3.0)	1.1 (0.7, 4.1)	1.6 (1.0, 3.0)	1.0 (1.0, 4.7)	1.6 (1.0, 3.0)
TTBR (months)					
Median (min, max)	1.6 (1.0, 3.3)	1.1 (0.7, 4.4)	1.6 (1.0, 3.3)	1.0 (1.0, 4.7)	1.6 (1.0, 3.3)
OS					
Status, n (%)					
Death	7 (53.8)	7 (43.8)	14 (48.3)	4 (28.6)	18 (41.9)
Censored	6 (46.2)	9 (56.3)	15 (51.7)	10 (71.4)	25 (58.1)
Follow-up time (months) n					
Median (min, max)	6.9 (0.1, 35.4)	5.5 (0.4, 25.3)	6.0 (0.1, 35.4)	14.1 (2.0, 35.4)	11.0 (0.1, 35.4)

OS estimate (K-M) (months)	9.0 (1.8, NE)	16.4 (3.5, NE)	16.4 (5.0, NE)	NE (5.7, NE)	18.4 (6.9, NE)
Median (95% CI)					
OS rate (95% CI) (K-M), %					
At 6 months	66.7 (33.7, 86.0)	64.3 (33.8, 83.5)	65.6 (44.1, 80.5)	77.9 (45.9, 92.3)	69.8 (52.9, 81.6)
At 12 months	47.6 (18.2, 72.4)	64.3 (33.8, 83.5)	56.2 (34.6, 73.2)	70.1 (38.5, 87.6)	61.1 (43.7, 74.5)
At 24 months	35.7 (9.8, 63.3)	44.1 (15.8, 69.5)	40.1 (19.7, 59.7)	70.1 (38.5, 87.6)	49.5 (31.3, 65.3)
PFS					
Status, n (%)					
Events	8 (61.5)	10 (62.5)	18 (62.1)	6 (42.9)	24 (55.8)
Deaths	2 (15.4)	2 (12.5)	4 (13.8)	2 (14.3)	6 (14.0)
Progression	6 (46.2)	8 (50.0)	14 (48.3)	4 (28.6)	18 (41.9)
Censored	5 (38.5)	6 (37.5)	11 (37.9)	8 (57.1)	19 (44.2)
Follow-up time (months) – n					
Median (min, max)	2.3 (0.03, 23.1)	2.2 (0.03, 18.9)	2.3 (0.03, 23.1)	4.7 (0.03, 24.2)	2.5 (0.03, 24.2)
PFS estimate (K-M) (months)					
Median (95% CI)	2.7 (0.9, NE)	2.8 (0.9, 18.4)	2.8 (1.0, 18.4)	20.4 (1.0, NE)	5.5 (1.5, 23.9)
PFS rate (95% CI) (K-M)					
At 6 months	25.9 (4.8, 54.8)	45.7 (20.1, 68.3)	37.0 (18.4, 55.8)	66.7 (33.7, 86.0)	47.1 (30.5, 62.1)
At 12 months	25.9 (4.8, 54.8)	34.3 (10.5, 60.2)	30.8 (13.2, 50.5)	66.7 (33.7, 86.0)	43.2 (26.5, 58.8)

At 24 months	NA	NA	NA	25.0 (1.4, 63.5)	16.2 (1.6, 44.8)

Safety

Nearly all patients (93.0%) from the study (C-PTLD) experienced treatment-emergent adverse events AEs (89.7% in the C-SOT, 100% in the C-HCT). Grade 3+ AEs rates were at 69.8% in the overall population (C-PTLD) and were consistent between C-SOT and C-HCT cohorts (69.0% vs. 71.4%). SAEs rates were at 53.5% in the overall population (C-PTLD) and were consistent between C-SOT and C-HCT cohorts (51.7 vs. 57.1%). On-treatment patient deaths rates were at 11.6% in the overall population while 32.6% of patients experienced AEs leading to treatment discontinuation. AEs were considered related to treatment (per investigator assessment) for 37.2% of patients in the overall population (C-PTLD). Among them, 8 patients (18.6%) experienced a grade 3+ AE. There is no treatment-related AE which was fatal or led to treatment discontinuation (Table 97).

Table 97. Summary of patient incidence of treatment-emergent adverse events (FAS)

Number (%) of patients with	C-SOT			C-HCT (N=14)	Overall Total [C-PTLD] (N = 43)
	C-SOT-R (N=13)	C-SOT-R+C (N=16)	Total (N =29)		
Any AE	**11 (84.6)**	**15 (93.8)**	**26 (89.7)**	**14 (100)**	**40 (93.0)**
Worst grade ≥3	9 (69.2)	11 (68.8)	20 (69.0)	10 (71.4)	30 (69.8)
Serious	7 (53.8)	8 (50.0)	15 (51.7)	8 (57.1)	23 (53.5)
Fatal	1 (7.7)	3 (18.8)	4 (13.8)	1 (7.1)	5 (11.6)
Leading to study treatment discontinuation	5 (38.5)	3 (18.8)	8 (27.6)	6 (42.9)	14 (32.6)
Leading to study treatment withheld	5 (38.5)	1 (6.3)	6 (20.7)	3 (21.4)	9 (20.9)
Leading to interruption of study treatment injection	0	0	0	0	0
Any AE related to study treatment	**6 (46.2)**	**7 (43.8)**	**13 (44.8)**	**3 (21.4)**	**16 (37.2)**
Worst grade ≥3	4 (30.8)	3 (18.8)	7 (24.1)	1 (7.1)	8 (18.6)
Serious	2 (15.4)	2 (12.5)	4 (13.8)	0	4 (9.3)
Fatal	0	0	0	0	0
Leading to study treatment discontinuation	0	0	0	0	0
Leading to study treatment withheld	1 (7.7)	0	1 (3.4)	0	1 (2.3)
Leading to interruption of study treatment injection	0	0	0	0	0

Abbreviations: C-HCT, patients with EBV+ PTLD following HCT; C-SOT, patients with EBV+ PTLD following SOT; C-SOT-R, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab; C-SOT-R+C, patients with EBV+ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; AE, treatment-emergent adverse event Note: Treatment-emergent adverse events include any AE that occurred on or after first dose date of Ebvallo® through 30 days after last dose of Ebvallo® or any related AE with date of onset on or after first dose date of Ebvallo®.

Treatment-emergent AEs

The treatment-emergent adverse events that occurred in more than 5% of patients in ALLELE, by preferred term, are presented in Table 98.

Table 98. Treatment-emergent adverse events reported for patient (≥5%), by preferred term (FAS)

	C-SOT			C-HCT (N = 20)	Overall Total [C-PTLD] (N = 53)
	C-SOT-R (N = 14)	C-SOTR+C (N = 19)	Total (N = 33)		
Patients reporting any AEs, n (%)	**11 (78.6)**	**18 (94.7)**	**29 (87.9)**	**19 (95.0)**	**48 (90.6)**
Disease progression	8 (57.1)	11 (57.9)	19 (57.6)	7 (35.0)	26 (49.1)
Pyrexia	4 (28.6)	6 (31.6)	10 (30.3)	6 (30.0)	16 (30.2)
Diarrhea	4 (28.6)	4 (21.1)	8 (24.2)	4 (20.0)	12 (22.6)
Fatigue	4 (28.6)	2 (10.5)	6 (18.2)	6 (30.0)	12 (22.6)
Nausea	3 (21.4)	2 (10.5)	5 (15.2)	4 (20.0)	9 (17.0)
Neutrophil count decreased	1 (7.1)	3 (15.8)	4 (12.1)	5 (25.0)	9 (17.0)
Vomiting	4 (28.6)	2 (10.5)	6 (18.2)	3 (15.0)	9 (17.0)
Hypokalaemia	1 (7.1)	3 (15.8)	4 (12.1)	4 (20.0)	8 (15.1)
Constipation	3 (21.4)	2 (10.5)	5 (15.2)	2 (10.0)	7 (13.2)
Hypotension	3 (21.4)	3 (15.8)	6 (18.2)	1 (5.0)	7 (13.2)
Acute kidney injury	2 (14.3)	4 (21.1)	6 (18.2)	0	6 (11.3)
Anaemia	1 (7.1)	3 (15.8)	4 (12.1)	2 (10.0)	6 (11.3)
Cough	1 (7.1)	2 (10.5)	3 (9.1)	3 (15.0)	6 (11.3)
Decreased appetite	1 (7.1)	2 (10.5)	3 (9.1)	3 (15.0)	6 (11.3)
Dizziness	2 (14.3)	1 (5.3)	3 (9.1)	3 (15.0)	6 (11.3)
Dyspnoea	1 (7.1)	2 (10.5)	3 (9.1)	3 (15.0)	6 (11.3)
Hypomagnesaemia	2 (14.3)	2 (10.5)	4 (12.1)	2 (10.0)	6 (11.3)

Abdominal pain	0	3 (15.8)	3 (9.1)	2 (10.0)	5 (9.4)
Dehydration	1 (7.1)	1 (5.3)	2 (6.1)	3 (15.0)	5 (9.4)
Febrile neutropenia	2 (14.3)	2 (10.5)	4 (12.1)	1 (5.0)	5 (9.4)
Pruritus	0	2 (10.5)	2 (6.1)	3 (15.0)	5 (9.4)
Rash maculo-papular	1 (7.1)	0	1 (3.0)	4 (20.0)	5 (9.4)
Sepsis	2 (14.3)	0	2 (6.1)	3 (15.0)	5 (9.4)
Blood creatinine increased	3 (21.4)	1 (5.3)	4 (12.1)	0	4 (7.5)
COVID-19	1 (7.1)	1 (5.3)	2 (6.1)	2 (10.0)	4 (7.5)
Chills	1 (7.1)	2 (10.5)	3 (9.1)	1 (5.0)	4 (7.5)
Fall	2 (14.3)	0	2 (6.1)	2 (10.0)	4 (7.5)
Headache	3 (21.4)	1 (5.3)	4 (12.1)	0	4 (7.5)
Hypertension	0	2 (10.5)	2 (6.1)	2 (10.0)	4 (7.5)
Hyponatraemia	2 (14.3)	1 (5.3)	3 (9.1)	1 (5.0)	4 (7.5)
Hypophosphataemia	0	0	0	4 (20.0)	4 (7.5)
Hypoxia	2 (14.3)	0	2 (6.1)	2 (10.0)	4 (7.5)
Oedema peripheral	3 (21.4)	0	3 (9.1)	1 (5.0)	4 (7.5)
Pain in extremity	0	2 (10.5)	2 (6.1)	2 (10.0)	4 (7.5)
Pleural effusion	1 (7.1)	2 (10.5)	3 (9.1)	1 (5.0)	4 (7.5)
Pneumonia	1 (7.1)	1 (5.3)	2 (6.1)	2 (10.0)	4 (7.5)
Rash	2 (14.3)	2 (10.5)	4 (12.1)	0	4 (7.5)
Thrombocytopenia	2 (14.3)	2 (10.5)	4 (12.1)	0	4 (7.5)
White blood cell count decreased	1 (7.1)	2 (10.5)	3 (9.1)	1 (5.0)	4 (7.5)
Anxiety	0	2 (10.5)	2 (6.1)	1 (5.0)	3 (5.7)
Arthralgia	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Back pain	1 (7.1)	2 (10.5)	3 (9.1)	0	3 (5.7)
Blood alkaline phosphatase increased	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Hyperhidrosis	2 (14.3)	0	2 (6.1)	1 (5.0)	3 (5.7)

Hyperkalaemia	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Hypoglycaemia	0	2 (10.5)	2 (6.1)	1 (5.0)	3 (5.7)
Influenza	0	2 (10.5)	2 (6.1)	1 (5.0)	3 (5.7)
Muscular weakness	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Nasal congestion	3 (21.4)	0	3 (9.1)	0	3 (5.7)
Pain	1 (7.1)	1 (5.3)	2 (6.1)	1 (5.0)	3 (5.7)
Respiratory failure	2 (14.3)	1 (5.3)	3 (9.1)	0	3 (5.7)
Tachycardia	1 (7.1)	2 (10.5)	3 (9.1)	0	3 (5.7)
Urinary tract infection	0	3 (15.8)	3 (9.1)	0	3 (5.7)
Weight increased	0	1 (5.3)	1 (3.0)	2 (10.0)	3 (5.7)
Wheezing	2 (14.3)	1 (5.3)	3 (9.1)	0	3 (5.7)

Abbreviation: C-HCT, patients with EBV$^+$ PTLD following HCT; C-SOT, patients with EBV$^+$ PTLD following SOT; C-SOT-R+C, patients with EBV$^+$ PTLD following SOT and relapsed/refractory to rituximab plus chemotherapy; AE, treatment-emergent adverse event.
Note: Treatment-emergent adverse events include any AE that occurred on or after first dose date of Ebvallo® through 30 days after last dose of Ebvallo® or any related AE with date of onset on or after first dose date of Ebvallo®.

Appendix L – Life tables

Table 99 presents the life tables used in the cost effectiveness model.

Table 99. Life tables

Age	Males	Females	Males	Females	Males	Females	Males	Females
x	q_x	q_x	l_x	l_x	d_x	d_x	e_x	e_x
0	0.00349	0.00295	100000	100000	349	295	79.37	83.25
1	0.0002	0.00017	99651	99705	20	17	78.65	82.5
2	0.00016	0.00007	99631	99688	16	7	77.66	81.51
3	0.00008	0.00005	99615	99681	7	6	76.68	80.52
4	0.00007	0.00007	99608	99675	7	7	75.68	79.52
5	0.00006	0.00008	99601	99668	7	8	74.69	78.53
6	0.00008	0.00005	99594	99660	8	4	73.69	77.54
7	0.00006	0.00008	99586	99656	6	8	72.7	76.54
8	0.00009	0.00004	99580	99648	9	4	71.7	75.55
9	0.00005	0.00003	99571	99644	4	3	70.71	74.55
10	0.00008	0.00004	99567	99641	9	3	69.71	73.55
11	0.00007	0.00006	99558	99638	7	7	68.72	72.55
12	0.00008	0.00006	99551	99631	8	6	67.72	71.56
13	0.00007	0.00004	99543	99625	7	4	66.73	70.56
14	0.00011	0.00006	99536	99621	11	6	65.73	69.57
15	0.00015	0.00013	99525	99615	15	13	64.74	68.57
16	0.00017	0.0001	99510	99602	17	10	63.75	67.58
17	0.00023	0.0001	99493	99592	23	10	62.76	66.58
18	0.00032	0.00012	99470	99582	32	12	61.78	65.59
19	0.00037	0.00019	99438	99570	37	18	60.8	64.6
20	0.00037	0.00019	99401	99552	36	19	59.82	63.61
21	0.00039	0.00016	99365	99533	39	16	58.84	62.62
22	0.00037	0.00018	99326	99517	37	18	57.86	61.63
23	0.0005	0.00016	99289	99499	49	15	56.88	60.64
24	0.00043	0.00015	99240	99484	43	16	55.91	59.65
25	0.00041	0.00021	99197	99468	40	21	54.94	58.66
26	0.00042	0.00019	99157	99447	41	19	53.96	57.67
27	0.00045	0.00019	99116	99428	45	19	52.98	56.69
28	0.0005	0.00025	99071	99409	49	24	52	55.7
29	0.00052	0.00025	99022	99385	52	26	51.03	54.71
30	0.00046	0.00027	98970	99359	46	26	50.06	53.72
31	0.0006	0.00033	98924	99333	59	33	49.08	52.74
32	0.00051	0.00027	98865	99300	50	28	48.11	51.76
33	0.00057	0.00033	98815	99272	57	32	47.13	50.77
34	0.00062	0.00034	98758	99240	61	34	46.16	49.79
35	0.00079	0.00038	98697	99206	78	38	45.19	48.8
36	0.00077	0.0004	98619	99168	76	39	44.22	47.82
37	0.00075	0.00038	98543	99129	75	38	43.26	46.84

38	0.0009	0.00067	98468	99091	88	66	42.29	45.86
39	0.00098	0.00052	98380	99025	96	51	41.33	44.89
40	0.0009	0.00072	98284	98974	89	71	40.37	43.91
41	0.00115	0.00065	98195	98903	112	64	39.4	42.94
42	0.00118	0.00073	98083	98839	116	72	38.45	41.97
43	0.00133	0.00071	97967	98767	130	71	37.49	41
44	0.00139	0.00088	97837	98696	136	86	36.54	40.03
45	0.0016	0.00105	97701	98610	157	104	35.59	39.06
46	0.0018	0.00096	97544	98506	176	94	34.65	38.1
47	0.00199	0.00122	97368	98412	194	120	33.71	37.14
48	0.0024	0.00133	97174	98292	233	131	32.78	36.19
49	0.00249	0.00147	96941	98161	242	144	31.85	35.23
50	0.00286	0.00178	96699	98017	277	174	30.93	34.28
51	0.00313	0.00184	96422	97843	301	180	30.02	33.34
52	0.00334	0.00225	96121	97663	321	220	29.11	32.4
53	0.00366	0.0025	95800	97443	351	244	28.21	31.48
54	0.00422	0.0027	95449	97199	403	262	27.31	30.55
55	0.00465	0.00292	95046	96937	442	283	26.42	29.64
56	0.00519	0.00317	94604	96654	491	306	25.54	28.72
57	0.00597	0.00396	94113	96348	562	382	24.67	27.81
58	0.00659	0.00411	93551	95966	617	394	23.82	26.92
59	0.00762	0.00481	92934	95572	708	460	22.97	26.03
60	0.00815	0.00512	92226	95112	751	487	22.15	25.15
61	0.00922	0.0059	91475	94625	844	558	21.32	24.28
62	0.01037	0.00633	90631	94067	940	596	20.52	23.42
63	0.01133	0.00696	89691	93471	1016	650	19.73	22.57
64	0.0123	0.00759	88675	92821	1091	705	18.95	21.72
65	0.01359	0.00878	87584	92116	1190	808	18.18	20.88
66	0.0151	0.00997	86394	91308	1305	911	17.42	20.06
67	0.01617	0.01061	85089	90397	1376	959	16.68	19.26
68	0.01788	0.01115	83713	89438	1497	998	15.95	18.46
69	0.01963	0.01176	82216	88440	1614	1040	15.23	17.66
70	0.02135	0.01299	80602	87400	1721	1136	14.52	16.87
71	0.02164	0.01437	78881	86264	1707	1240	13.83	16.08
72	0.02346	0.0159	77174	85024	1810	1352	13.12	15.31
73	0.02707	0.01771	75364	83672	2040	1482	12.43	14.55
74	0.03024	0.01922	73324	82190	2218	1580	11.76	13.8
75	0.03327	0.02248	71106	80610	2366	1811	11.11	13.06
76	0.03635	0.02472	68740	78799	2499	1949	10.47	12.35
77	0.04088	0.02764	66241	76850	2708	2123	9.85	11.65
78	0.04286	0.03035	63533	74727	2723	2268	9.25	10.97
79	0.04916	0.03367	60810	72459	2989	2440	8.64	10.3
80	0.05497	0.0392	57821	70019	3179	2745	8.06	9.64
81	0.0625	0.04341	54642	67274	3415	2920	7.5	9.01
82	0.07082	0.04998	51227	64354	3628	3216	6.97	8.39
83	0.07959	0.05714	47599	61138	3789	3493	6.46	7.81
84	0.08857	0.0655	43810	57645	3880	3776	5.98	7.25

85	0.1017	0.07284	39930	53869	4060	3924	5.51	6.73
86	0.11532	0.08589	35870	49945	4137	4290	5.08	6.22
87	0.132	0.09731	31733	45655	4189	4443	4.67	5.75
88	0.14653	0.11095	27544	41212	4036	4572	4.31	5.32
89	0.16565	0.12079	23508	36640	3894	4426	3.96	4.92
90	0.18898	0.13782	19614	32214	3706	4440	3.65	4.52
91	0.20066	0.15289	15908	27774	3192	4246	3.38	4.17
92	0.22074	0.17112	12716	23528	2807	4026	3.11	3.83
93	0.24515	0.18841	9909	19502	2429	3675	2.85	3.52
94	0.27364	0.21735	7480	15827	2047	3440	2.62	3.23
95	0.29409	0.23816	5433	12387	1598	2950	2.42	2.99
96	0.3193	0.25512	3835	9437	1224	2407	2.24	2.77
97	0.3495	0.27581	2611	7030	913	1939	2.06	2.56
98	0.38084	0.30688	1698	5091	647	1562	1.9	2.35
99	0.42041	0.31859	1051	3529	1051	3529	1.79	2.17

Appendix M – Baseline utilities values per subgroups

Table 100. Summary of EQ-5D-5L Utility Score (Age>=16 Years), Full Analysis Set

	Ebvallo® SOT EBV⁺ PTLD			Ebvallo® HCT EBV⁺ PTLD	Overall Ttoal
Baseline	**R/R Rituximab (N=12)**	**R/R Rituximab + Chemo (N=18)**	**Total (N=30)**	**R/R Rituximab (N=19)**	**(N=49)**
n	11	16	27	18	45
Mean	0.8088	0.6279	0.7016	0.6438	0.6785
SD	0.13851	0.31604	0.27056	0.32830	0.29278
Median	0.8140	0.7085	0.7430	0.6985	0.7350
Q1,Q3	0.7430,0.8790	0.4190,0.8715	0.5920,0. 8790	0. 4050,0.8790	0.5160,0.8790
Min, Max	0.516,1.000	0.026,1.000	0.026,1.000	-0.142,1.000	-0.142,1.000

Abbreviations: HCT: hematopoietic cell transplant; SOT: solid organ transplant; EBV: Epstein-Barr Virus; PTLD: post-transplant lymphoproliferative disease; R/R: relapsed/refractory; Chemo: chemotherapy. Full analysis set consists of all subjects who received at least one dose of tabelecleucel. Utility index values are calculated using UK crosswalk value set. Source: [191]

Appendix N – Unit costs

Treatment costs

Treatment specific costs were sourced and included in the cost-effectiveness analysis to reflect the Danish setting. Cost items included drug acquisition costs for Ebvallo®, comparator treatments, subsequent treatments, and drug administration.

Ebvallo®

Conditioning chemotherapy costs

The cost of conditioning chemotherapy is assumed to be represented in the average per patient Ebvallo® cost input.

Preparation costs for leukapheresis and HLA typing

Preparation costs for leukapheresis and HLA typing are assumed to be represented in the average per patient Ebvallo® cost input.

Acquisition cost

Patients on Ebvallo® were given 3 administrations on days 1, 8, and 15 followed by observation through day 35. It is recommended to monitor vital signs immediately prior to each Ebvallo® injection, within 10 minutes following the conclusion of the injection and 1 hour after the initiation of the injection. The cost of administration and preparation is assumed to be part of the list price. The drug cost is DKK 558,000 per package, corresponding to one injection. See Table 101 for price per cycle (i.e., 3 injections), and price per patient assuming an average number of cycles per patient of 2.56. Only 1 patient (2.6%) was still receiving treatment at the July 2022 data cutoff (38 of 39 patients had either discontinued or completed treatment), the average number of doses and cycles can thus be considered representative.

Table 101. Drug acquisition costs for the intervention

	Administration type	Pack size	List price (DKK)	Price per cycle (DKK)	Price per patient (DKK)	Reference
Ebvallo®	IV	1 (1 – 6 vials)	558,000	1,647,000	4,291,910.27	Pierre Fabre

Abbreviations: IV = intravenous.

Best supportive care

BSC was assumed to be made up of a mix of chemotherapy regimens, with the composition validated by a Danish clinical expert [2]. Drug acquisition costs were based on pharmacy purchasing prices (PPP) listed in the ”Medicinpriser” database [90]. When multiple pack sizes were available, the lowest price per milligram was used in the cost calculation.

Relative dose intensity was assumed 100% for all drugs.

Table 102. Drug acquisition unit costs for best supportive care mix

Regimen	Administration type	Strength	Pack size	PPP per pack (DKK)	Source
R-CHOP: Cyclophosphamide	IV	1000	1	330	Medicinpriser [90]
R-CHOP: Doxorubicin	IV	2	100	350	Medicinpriser [90]
R-CHOP: Rituximab	IV	1400	1	12,378	Medicinpriser [90]
R-CHOP: Vincristine	IV	1	1	390	Medicinpriser [90]
R-CHOP: Prednisolone	Oral	5	100	35	Medicinpriser [90]
GDP: Cisplatin	IV	1	50	100	Medicinpriser [90]
GDP: Dexamethasone	Oral	4	100	386	Medicinpriser [90]
GDP: Gemcitabine	IV	10	4	420	Medicinpriser [90]

Abbreviations: IV= intravenous; PPP=pharmacy purchasing price

Wastage

For the intervention an assumption of no vial sharing was made. This assumption was based on the rationale that, given the rarity of the disease and small patient numbers as a result as well as the fact that patients are matched based on the human leucocyte antigen (HLA) restriction, the opportunity for vial sharing would be unlikely in clinical practice. Wastage was also included for the comparator treatments in BSC.

Administration costs

The costs for drug administrations were sourced from the interactive DRG list provided by Sundhedsdatastyrelsn [91]. The same cost was assumed for the first and subsequent treatment cycles. Table 103 summarises the drug administration costs included in the model.

Table 103. Drug administration costs

Mode of Administration	Value (DKK)	Comment	Reference
Cost per IV administration	2,005.00	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	DRG takster 2023 [92]
Cost per oral drug initiation	0	Assumption	N/A

Abbreviations: IV = intravenous.

Subsequent treatment costs

Subsequent treatment is assumed to be the same regimen mix as for the BSC comparator in both arms (see Table 104). Subsequent treatment impacts costs but not explicitly survival outcomes in the model. The cost of subsequent treatment is captured in the progressed health state and applied as a one-off cost at disease progression to all patients. It is costed for a median treatment duration of 4 cycles, based on the average treatment duration of GDP regimen in patients with relapsed/refractory peripheral T-cell lymphoma [93]. The use of the comparator mix for subsequent treatment was confirmed by a Danish clinician [2].

Table 104. Subsequent treatment mix

	Ebvallo®	BSC	Reference
% receiving any subsequent treatment	100%	100%	Assumption
Median duration of subsequent treatment (cycles)	4	4	Based on GDP regimen in patients with refractory peripheral T-cell lymphoma [93].
Duration of subsequent treatment in model cycles	6	6	Calculation based on median number of cycles (4) and model cycle length (2 weeks).

Healthcare resource use costs

The model captures visits, tests, and diagnostics as well as hospitalization for the different health state of each of the patient subgroups (i.e., HCT and SOT). As no economic evaluations in EBV$^+$ PTLD were identified in the cost-effectiveness SLR, a grey literature search was undertaken to identify health state resource use in the broader lymphoma indication. The health state resource used in the model were sourced from NICE TA559 (axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies) [94]. The items considered under resource use and their frequencies were validated with a Danish clinician [2]. For progression-free and progressed disease patients, health state costs were applied on a per-cycle basis. No distinction was made between HCT or SOT patients in terms of health state costs. No health state costs are assumed to apply to patients post-cure.

Table 105. Biweekly resource use frequencies

		HCT		SOT	
		(progression free)	(progressed)	(progression free)	(progressed)
Healthcare professionals	Oncologist	1	3	1	2
	Radiologist	0.66	4	0.33	2
	Nurse	0.66	4	0.33	2
	Palliative care team	0.66	4	0.33	2
	Specialist nurse	0.66	4	0.33	2
	PET-CT scan	0.66	4	0.33	2
	Transplant physician	1	3	1	2
Tests and diagnostics	Full blood counts	1	3	1	2
	LDH	1	3	1	2
	Liver function	1	3	1	2
	Renal function	1	3	1	2
	Immunoglobulin	1	3	1	2
	Calcium Phosphate	1	3	1	2
Professional and social services	Hospice	0.04	0.94	0.02	0.47
Hospitalisation	Inpatient days	2	0.2	1	0.2

Abbreviations: HCT – hematopoietic stem cell transplant; SOT – solid organ transplant.

Table 106. Costs for routine follow-up care

Item	Unit cost (DKK)	Comment	Source
Healthcare professionals			
Oncologist	1,066	Ledende overlæger/professorer. Cost assumed to be same as salary per 1 hour.	Source: Medicinrådet. Værdisætning af enhedsomkostninger, version 1.6. 2023.
Radiologist	1,066	Ledende overlæger/professorer. Cost assumed to be same as salary per 1 hour.	Source: Medicinrådet. Værdisætning af
Nurse	453	Sygeplejersker. Cost assumed to be same as salary per 1 hour.	enhedsomkostninger, version 1.6. 2023.
Palliative care team	4,284	26MP45 Specialiseret Palliativ indsats, Stor.	Source: Sundhedsdatastyrelsen. DRG-takster 2023.
Specialist nurse	592	Ledende sygeplejersker. Cost assumed to be same as salary per 1 hour.	Source: Medicinrådet. Værdisætning af

			enhedsomkostninger, version 1.6. 2023.
PET-CT scan	2,023	Assumed same as CT scan. 30PR07 CT-scanning, ukompliceret, el. Osteodensitometri (assumption).	Source: Sundhedsdatastyrelsen. DRG-takster 2023.
Tests and diagnostics			
Full blood counts	22	7110 Blod. Takstkort 29A - Laboratorieundersøgelser.	Source: Laeger.dk. Takstkort. 2022.
LDH	14	NPU19658 Laktatdehydrogenase [LDH];P.	Source: Rigshospitalets Labportal 2022
Liver function	68	NPU19654 Aspartattransaminase [ASAT];P (14kr), NPU19651 Alanintransaminase [ALAT];P (13kr), NPU19673 Albumin;P (13kr), NPU19657 gamma-Glutamyltransferase;P (14kr), NPU19658 Laktatdehydrogenase [LDH];P (14kr).	Source: Rigshospitalets Labportal 2022
Renal function	72	7112 P-kreatinin. Takstkort 29A - Laboratorieundersøgelser.	Source: Laeger.dk. Takstkort. 2022.
Immunoglobulin	47	NPU19813 Csv-Immunglobulin G; massek.	Source: Rigshospitalets Labportal 2022
Calcium phosphate	13	NPU01443 Calcium;P (Assumption).	Source: Rigshospitalets Labportal 2022
Professional and social services			
Hospice	4,284	26MP45 Specialiseret Palliativ indsats, Stor.	Source: Sundhedsdatastyrelsen. DRG-takster 2023.
Hospitalisation			
Inpatient day	18,627	17MA05 Observation pga. mistanke om malign hæmatologisk sygdom, pat. Mindst 18 år.	Source: Sundhedsdatastyrelsen. DRG-takster 2023.

Adverse event costs

Costs of AEs were sourced based on the conversion of the international classification of disease version 10 (ICD-10) codes for the respective co-morbidities to the relevant Danish diagnosis-related group (DRG) codes. The costs of treatment-specific AEs were estimated based on incidence rates for AEs and per-event treatment costs. They are assumed to apply for the first model cycle only.

Table 107. Cost of adverse events

Adverse events	Unit cost (DKK)	Comment	Reference
Anaemia	4,210	16MP06 Mangelanæmier, full cost divided by the number of days (21)	[92]
Neutropenia	38,209	16MA03 Granulo- og trombocytopeni.	[92]
Neutrophil count decrease	2,002	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år.	[92]

Infection	41,862	18MA08 Andre infektioner eller parasitære sygdomme.	[92]
Thrombosis	30,716	01MP12 Trombolysebehandling af akut apopleksi.	[92]
Fatigue	4,728	23MA03, Symptomer og fund, u. kompl. bidiag.	[92]
Vomiting	3,425	06MA17 Observation for sygdom i fordøjelsesorganerne, u. endoskopi.	[92]
Febrile neutropenia	19,631	18MA04 Feber af ukendt årsag, pat. mindst 18 år, uden biopsi og/eller scopi.	[92]
Acute kidney injury	45,038	11MA01 Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese.	[92]
Sepsis	46,987	18MA01 Sepsis.	[92]
Hypertension	17,304	05MA11 Hypertension. Source: Sundhedsdatastyrelsen.	[92]
Pneumonia	33,134	04MA14 Lungebetændelse og pleurit, pat. 18-59 år.	[92]
Respiratory failure	38,476	04MA10 Lungeødem og respirationssvigt.	[92]
Leukopenia	2,005	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år.	[92]
Hypotension	17,304	Assumed same as Hypertension	[92]

Abbreviations: CT= chemotherapy, AE = Adverse event.

End-of-life costs

The analysis included a specific cost to reflect additional resource use associated with the terminal stage of life, which is presented in Table 108.

Table 108. End-of-life costs

Item	Cost (DKK)	Comment	Source
End of life	60,330	15MP01 Død eller overflyttet inden for 1 dag (multiplied by 30 days).	Sundhedsdatastyrelsen. DRG-takster 2023.

Non-medical costs

The analysis includes costs associated with resource use (time spent due to treatment and transportation), incurred by patient. These non-medical costs are included in the base case analysis. Cost for patients was estimated by taking the time spent due to treatment (i.e. medical tests and physician visits) and average income per hour into consideration regardless of employment situation [95]. Patient cost was sourced from Medicinrådet, based on the value of time spent on treatment and was 181 DKK. The transportation cost was also sourced from Medicinrådet on the basis of the cost of transport per a hospital visit and was 140 DKK for a roundtrip Table 109 [96]. Resource use frequencies for test and visits were used to calculate health states-related non-medical costs (for frequencies details see Table 105. Table 110 includes an overview of the average weekly non-medical resource use for the progression-free and progressed health state before cure point. After cure point, it was assumed that resource use was 0.

Table 109. Resource use unit costs

Item	Value	Comment and source

Patient time cost (DKK)	181	Værdisættelse af tid brugt på behandling, kr./timen, Medicinrådet, 2022
Time per visit or drug administration (hour)	4	Assumption
Transportation costs for roundtrip (DKK)	140	Transportomkostninger pr. besøg på sygehus. Medicinrådet, 2022

Table 110. Average biweekly non-medical resource use by health state

	HCT				SOT			
	Progression-free		Progressed		Progression-free		Progressed	
Travel costs	1 h	140 DKK	4 h	560 DKK	1 h	140 DKK	2h	280 DKK
Patient cost (patient time)	4 h	724 DKK	16 h	2,896 DKK	4 h	724 DKK	2h	362 DKK

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