Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende lisocabtagene maraleucel til tredjelinjebehandling af patienter med DLBCL, PMBCL eller FL3B

Patienter med tilbagevendende eller refraktær DLBCL, PMBCL og FL3B efter to eller flere linjer systemisk behandling

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. lisocabtagene maraleucel
2. Forhandlingsnotat fra Amgros vedr. lisocabtagene maraleucel
3. Ansøgers endelige ansøgning vedr. lisocabtagene maraleucel

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Virum, 27.02.2025

Til Medicinrådet

Bristol Myers Squibbs (BMS) tilbagemelding på udkast til vurderingsrapporterne for lisocabtagene maraleucel til 2. og 3. L af patienter med DLBCL, PMBCL eller FL3B.

På trods af 4 måneders forsinkelse i sagsbehandlingen i Medicinrådet, vil vi gerne takke for et rigtig godt samarbejde med sekretariatet.

Vi vil gerne anerkende både sekretariatet og fagudvalget for det gode arbejde, og vi ser frem til Medicinrådets anbefaling på mødet i marts. Der er kun en kommentar fra vores side

Den vedrører antallet af patienter, Medicinrådet mener er kandidater til 3.L behandlingen. I Medicinrådets vurdering af axicabtagene ciloleucel 27.11.2024 vurderes det, at 7 patienter vil være kandidater til behandling med CAR-T i 3.L. For vurderingen af lisocabtagene maraleucel til 3L er antallet af patienter, der er kandidater til 3.L nu faldet til 2-3. Det drastiske fald i antallet af patienter undrer os, da det er mindre end et halvt år siden, den forrige vurdering. Og da flere af patienterne i 3L ikke nødvendigvis har været kandidat til CAR-T i 2.L (tilbagefald >12 måneder) kan dette ikke være svaret.

Hvis det er muligt at uddybe i rapporten, hvordan dette markante fald i egnede patienter til 3L er opstået, vil det hjælpe på forståelsen.

Med venlig hilsen

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05.03.2025
CAF/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.03.2025
Leverandør	Bristol Myers Squibb
Lægemiddel	Breyanzi (lisocabtagene maraleucel)
Ansøgt indikation	Behandling af voksne med diffust storcellet B-celle lymfom (DLBCL), primært mediastinalt storcellet B-celle lymfom (PMBCL) eller follikulært lymfom grad 3B (FL3B), som er recidiveret eller refraktære (R/R) inden for 12 måneder efter gennemførsel af førstelinje kemo-immunterapi.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel, ATMP

Prisinformation

Amgros har forhandlet følgende pris på Breyanzi (lisocabtagene maraleucel) til behandling af patienter i 2. og 3. linje:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Breyanzi	1 stk.	2.570.000	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

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

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, hvis Medicinrådet anbefaler Breyanzi til begge ansøgte indikationer, som behandles på samme møde i Medicinrådet. 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.

[redacted]

Amgros forventer, at aftalen kan starte senest den 01.08.2025 og gælde 4 år frem. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Yescarta (axicabtagene ciloleucel) er anbefalet af Medicinrådet til behandling af patienter med DLBCL i 2. og 3. linje. Nedenstående tabel viser lægemiddeludgiften i forbindelse med engangsbehandling af Yescarta og Breyanzi.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Breyanzi	1 stk.	[redacted]	[redacted]
Yescarta	1 stk.	[redacted]	[redacted]

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
England	Under vurdering	Link til vurdering
Sverige	Under vurdering	Under vurdering

Opsummering

[redacted]

Application for the assessment of lisocabtagene maraleucel (liso-cel) for the treatment of relapsed/refractory large cell B-cell lymphoma

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
	[Definition of color-code]

Contact information

Contact information	
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Abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
2L	Second line	IRRC	Independent Radiological Review Committee
3L	Third line	ISPOR	International Society of Pharmacoeconomic and Outcomes Research
AACR	American Association for Cancer Research	ITC	Indirect treatment comparison
ABC	Activated B-cell	ITT	Intention to treat

AEs	Adverse events	IV	Intravenous
AESI	Adverse events of special interest	IWG	International Working Group
ALC	Absolute lymphocyte count	iwNHL	International Workshop on non-Hodgkin Lymphoma
Allo-HSCT	Allogenic hematologic stem cell transplant	KM	Kaplan-Meier
ALT	Alanine aminotransferase	KOL	Key opinion leaders
ASCO	American Society of Clinical Oncology	LBCL	Large B-cell lymphomas
ASH	American Society of Hematology	LDC	Lymphodepleting chemotherapy
AST	Aspartate aminotransferase	LDH	Lactate dehydrogenase
AUC	Area under the curve	Liso-cel	Lisocabtagene maraleucel
auto-HSCT	Autologous hematopoietic stem cell transplant	LS	Least squares
Axi-cel	Axicabtagene ciloleucel	LTFU	Long-term follow-up
BCL	B-cell lymphoma	LVEF	Left ventricular ejection fraction
BSA	Body surface area	MAIC	Matching adjusted indirect comparison
CADTH	Canadian Agency for Drugs and Technologies in Health	MBD	Missing by design
CAR	Chimeric Antigen Receptor	MCL	Mantle cell lymphoma
CBC	Complete blood count	mCRM	Modified continual reassessment method
CI	Confidence interval	MEDRA	Medical Dictionary for Regulatory Activities
CLL	Chronic lymphocytic leukemia	mEFS	Modified EFS
CNS	Central nervous system	mITT	Modified intention-to-treat
COO	Cell-of-origin	MMRM	Mixed model for repeated measures
COVID 19	Coronavirus disease 2019	MYC	Myelocytomatosis oncogene
CR	Complete response	n	Sample size
CrCl	Creatinine clearance	N	Number of patients
CRP	C-reactive protein	n.a.	Not available
CRR	Complete response rate	NA	Not applicable

CRS	cytokine release syndrome	Nd	Not displayed
CSR	Clinical study report	NHL	Non-Hodgkin lymphoma
CT	Computed tomography	NICE	National Institute for Health and Care Excellence
CTCAE	Common Terminology Criteria for Adverse Events	NOS	Not otherwise specified
DC	Dose-confirmation	NR	Not reported
DCO	Data cut-off	NT	Neurotoxicity
DE	Dose-expansion	NTE	Non-transplant eligible
DF	Dose-finding	OR	Odds ratio
DHL/THL	Double/triple hit lymphoma	ORR	Objective Response Rate
DKK	Danish krona	OS	Overall survival
DL1D	Dose level 1 double-dose schedule	PCR	Polymerase chain reaction
DL1S	Dose level 1 single-dose schedule	PD	Progressive disease
DL2S	Dose level 2 single-dose schedule	PET	Positron emission tomography
DLBCL	Diffuse large B-cell lymphoma	PFS	Progression-free survival
DLG	Danish Lymphoma Group	PICOS	Population, Intervention, Comparator, Outcome, Study
DLTs	Dose Limiting Toxicities	PMBCL	Primary mediastinal large B-cell lymphoma
DoR	Duration of response	PR	Partial response
DRG	Diagnosis-related group	Pri	Primary analysis
EBV	Epstein-Barr virus	PRO	Patient reported outcome
ECG	Electrocardiogram	PRR	Partial response rate
ECHO	Echocardiogram	QALY	Quality-adjusted life year
ECOG	Eastern Cooperative Oncology Group	QoL	Quality of life
ECOG PS	Eastern Cooperative Oncology Group Performance Status	R/R	Relapsed or refractory
EFS	Event-free survival	RCTs	Randomized controlled trials
EGFRt	Truncated epidermal growth factor receptor	RWE	Real-world evidence

EHA	European Hematology Association	SA	Safety analysis
EMA	European Medicines Agency	SA1	Sensitivity analysis 1
EORTC	European Organization for Research and Treatment of Cancer	SA2	Sensitivity analysis 2
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30	sAAIPI	Second-line age adjusted International Prognostic Index
EPAR	European public assessment report	SAEs	Severe adverse events
EQ-5D-5L	Euro-QOL, 5 dimensions, 5 levels	scFv	Single chain variable fraction
ESMO	European Society for Medical Oncology	SD	Standard deviation
ESS	Effective sample size	SDi	Stable disease
EU	European Union	SE	Standard error
EudraCT	Union Drug Regulating Authorities Clinical Trials Database	SLD	Summary-level data
FACT	Functional Assessment of Cancer Therapy Scale	SLL	Small lymphocytic lymphoma
FDA	Food and Drug Administration	SLR	Systematic literature review
FDG	Fluorodeoxyglucose	SMD	Standard mean difference
FISH	Fluorescence in situ hybridization	SmPC	Summary of Product Characteristics
FL	Follicular lymphoma	SoC	Standard of care
FL3B	Follicular lymphoma grade 3B	SOC	System organ class
GCB	Germinal center B-cell-like	SPD	Sum of product diameter
GFR	Glomerular filtration rate	Stat	Statistics
GLM	Generalized linear models	STC	Simulated treatment comparison
HCT-CI	HSCT-specific comorbidity index	TBI	Total body irradation
HDCT	High dose chemotherapy	tCLL	Transformed chronic lymphocytic leukemia
HERC	Health Economics Research Centre	TE	Transplant eligible

HGBCL	High grade B-cell lymphoma	TEAEs	Treatment-emergent Adverse Events
HIV	Human immunodeficiency virus	tFL	Transformed follicular lymphoma
HR	Hazard ratio	THRBCL	T cell/histiocyte-rich large B cell lymphoma
HRQoL	Health-related quality of life	TI	Transplant intended
HRU	Hospital resource utilization	tiNHL	Transformation from indolent lymphoma
HSCT	Hematopoietic stem cell transplant	tiNHLs	Transformed indolent non-Hodgkin lymphoma
HSUVs	Health state utility values	Tisa-cel	Tisagenlecleucel
HTA	Health technology assessment	tMZL	Transformed marginal zone cell
HTAi	Health Technology Assessment International	tPCFCL	Transformed primary cutaneous follicle center lymphoma
IA	Interim analysis	tPCMZL	Transformed primary cutaneous marginal zone B-cell lymphoma
ICER	Incremental cost-effectiveness ratio	TSD	Technical Support Document
ICML	International Conference on Malignant Lymphoma	UK	United Kingdom
ICU	Intensive care unit	US	United States
IFC	Informed consent form	USPI	United States Prescribing Information
IHC	Immunohistochemistry	UTI	Urinary tract infection
INESSS	Institut National d'Excellence en Santé et Services Sociaux	VAS	Visual analog scale
INV	Investigator	VH	Variable heavy chain
IPD	Individual patient data	VL	Variable light chain
IPI	International Prognostic Index	Vs.	Versus
IQR	Interquartile range	WHO	World Health Organization
IRC	Independent review committee		

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Breyanzi
Generic name	lisocabtagene maraleucel (liso-cel)
Therapeutic indication as defined by EMA	Liso-cel is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy [1]. Liso-cel is indicated for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy [1].
Marketing authorization holder in Denmark	Bristol-Myers Squibb
ATC code	L01XL08
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	Liso-cel was approved in Europe on 27 January 2022. Reference Number: EMA/134759/2022 A variation, extension of indication of liso-cel to include treatment of adult patients with second-line (2L) Transplant Intended (TI) LBCL was approved 30 March 2023 Reference Number: EMA/171120/2023
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	EU/3/17/1890 on 17 Jul 2017 in the following condition: Treatment of diffuse large B-cell lymphoma EU/3/18/2018 on 25 May 2018 in the following condition: Treatment of follicular lymphoma EU/3/18/2099 on 19 Nov 2018 in the following condition: Treatment of primary mediastinal large-B-cell lymphoma. Liso-cel was withdrawn from the Community Register of designated orphan medicinal products at the time of the granting of a marketing authorization on 20 February 2022 on request the marketing authorisation holder
Other therapeutic indications approved by EMA	No

Overview of the medicine	
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordiccountries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? Already approved in Sweden.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Liso-cel 1.1-70 × 10^6 CD4+ T cells/mL and 1.1-70 × 10^6 CD8+ cells/mL, dispersion for infusion, intravenous use vial (COC) 4.6 ml per vial 1 to 4 vials of each cell component

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Treatment of adult patients with DLBCL, high grade B cell lymphoma (HGBCL), PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. Treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy.
Dosage regiment and administration	Treatment with liso-cel consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one or more vials. The target dose is 100 × 10^6 CAR-positive viable T cells (consisting of a target 1:1 ratio of CD4+ and CD8+ cell components) within a range of 44-120 × 10^6 CAR-positive viable T cells. Pre-treatment with lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m2/day and fludarabine 30 mg/m2 /day, administered intravenously for three days. Liso-cel is to be administered 2 to 7 days after completion of lymphodepleting chemotherapy. It is recommended that premedication with paracetamol and diphenhydramine (25-50 mg, intravenously or orally) or another H1-antihistamine, be administered 30 to 60 minutes before the infusion of liso-cel to reduce the possibility of an infusion reaction.
Choice of comparator	Yescarta (axi-cel, axicabtagene ciloleucel)
Prognosis with current treatment (comparator)	Large B-cell lymphomas (LBCL) comprise approximately a third of non-Hodgkin lymphomas (NHLs). About 35% of all diffuse LBCL (DLBCL) will experience relapse or be refractory to first-line treatment with current SoC treatments are associated with poor tolerability and side effects, which affect quality of life of treated patients. The incidence of DLBCL and follicular lymphoma (FL) has been increasing in Denmark over time.

Summary	
	The prognosis of DLBCL is relatively good, with a 5-year survival around 65% and with the implementation of CAR-T this is expected to improve. [2, 3]. 30 patients a year will be candidates for CAR-T in 2L treatment [4]. Since CAR-T is a new treatment in Denmark the number of patients with R/R after two or more lines are uncertain. But it is expected to be around 100 where 15 is eligible for CAR-T. In ZUMA-1 the median overall survival (OS) was 25.8 months, and the estimated 5-year OS rate was 42.6% [5].
Type of evidence for the clinical evaluation	The clinical development program for liso-cel in 2L and 3L consist of: • TRANSFORM, (NCT03575351) comparing efficacy of liso-cel to SoC in the 2L treatment of adult patients with LBCL who are refractory to or relapse within 12 months of achieving a complete response (CR) to 1L therapy. • TRANSCEND (017001) (NCT02631044) evaluating liso-cel in patients with R/R LBCL after ≥2 lines of therapy. Liso-cel has not been directly compared to axi-cel in head-to-head clinical trials. Therefore, the relative effectiveness in second- and third line LBCL can only be compared indirectly. The comparative analysis is based on: • An anchored matching adjusted indirect comparison (MAIC) comparing liso-cel (TRANSFORM trial) to axi-cel (ZUMA-7 trial, NCT03391466). • An unanchored MAIC comparing liso-cel (TRANSCEND 017001) to axi-cel (ZUMA-1 study, NCT02348216).
Most important efficacy endpoints (Difference/gain compared to comparator)	**2L (primary MAIC analysis):** Event-free survival: The point estimate between liso-cel and axi-cel favored liso-cel but was not statistically significant [redacted] Progression-free survival: The point estimate between liso-cel and axi-cel favored liso-cel but was not statistically significant [redacted] Overall survival: The point estimate between liso-cel and axi-cel favored liso-cel but was not statistically significant [redacted] Objective response rate: The point estimate of odds of objective response between liso-cel and axi-cel favored liso-cel but were not statistically significant [redacted] Complete response rate: The point estimate of odds of complete response between liso-cel and axi-cel favored axi-cel but were not statistically significant [redacted] **3L (primary MAIC analysis):** Progression-free survival: The HR for liso-cel vs. axi-cel was not statistically significant, albeit in favor of liso-cel [redacted] Overall survival: The HR for liso-cel vs. axi-cel was not statistically significant [redacted]

Summary	
	Overall response rate: the odds of overall response remained similar for liso-cel and axi-cel [redacted] Complete response rate: The comparison showed no significant difference in the odds of response between liso-cel and axi-cel [redacted]
Most important serious adverse events for the intervention and comparator	See section 9 and Appendix E.
Impact on health-related quality of life	Health economic model: NA.
Type of economic analysis that is submitted	Cost-minimization versus axi-cel
Data sources used to model the clinical effects	No clinical effects included in the cost minimization analysis
Data sources used to model the health-related quality of life	No HRQoL included in the model cost minimization analysis
Life years gained	NA
QALYs gained	NA
Incremental costs (Liso-cel vs. axi-cel)	2L: DKK 158,279 3L: DKK 95,724
ICER (DKK/QALY)	NA
Uncertainty associated with the ICER estimate	NA
Number of eligible patients in Denmark	Incidence: 30 patients eligible for CAR T in 2L. 15 patients eligible for CAR-T in 3L.
Budget impact (in year 5)	2L: DKK 2,546,775.4 3L: DKK 997,108.4

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

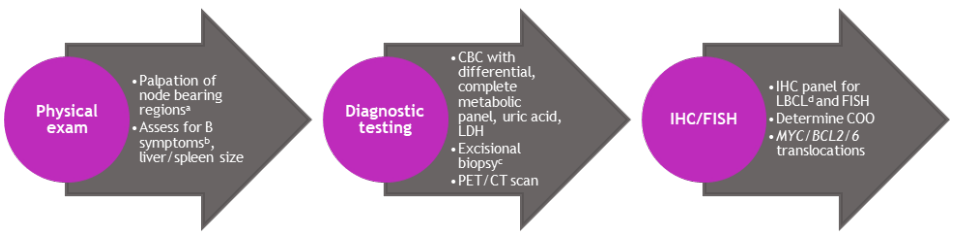
3.1 The medical condition

Large B cell lymphoma (LBCL) refers to several subtypes of non-Hodgkin lymphoma (NHL). More than 60 specific NHL subtypes have been identified, with diffuse large B-cell lymphoma (DLBCL) being the most common subtype (35%)[6]. DLBCL is caused by excessive proliferation and aggressive growth of malignant mature B-cells that lack the typical signals needed to control cell growth and reproduction. These malignant cells impair the normal anatomy of the affected lymph node [6]. High-grade B-cell lymphoma (HGBL) was introduced as a distinct diagnostic category to better classify certain types of B-cell lymphomas that exhibit features of both DLBCL and Burkitt lymphoma (BL) and are characterized by their rapid growth and high proliferation rates [7]. Primary mediastinal large B cell lymphoma (PMBCL), is a rare subtype of aggressive B cell lymphoma that constitutes 2%-3% of all cases of NHL [8]. Follicular lymphoma (FL) is a common type of slow growing (low grade) NHL that includes transformed follicular lymphoma (tFL) and FL grade 3B (FL3B), an infrequent subtype of FL accounting for approximately 5-10% of all FL cases [9]. These subtypes of NHL differ in terms of appearance and genetic features, but are treated similar as DLBCL [10, 11].

Symptoms of DLBCL are variable but often include swollen lymph nodes (with or without pain), lack of energy and "B symptoms", which are systemic symptoms of fever, unexplained weight loss and night sweats commonly associated with lymphomas [2, 3, 12]. The diagnostic process for LBCL is comprised of a series of laboratory tests and a complete physical exam, including screening for B symptoms and assessing the size of the liver and spleen (see Figure 1) [13]. The diagnosis of LBCL is confirmed through an excisional biopsy, if feasible, of an enlarged lymph node with a high index of suspicion based on clinical examination and radiographic imaging [14]. A positron emission tomography and computed tomography (PET/CT) scan may be used to visualize the sites of disease, including extranodal sites, and to determine the preferred site of biopsy [12, 15-17].

Once the biopsy is obtained, cytomorphology and subclassification is ascertained by immunohistochemistry (IHC) and/or flow cytometry [17, 18]. Confirmation of the cell-of-origin (COO) is then assessed to establish a diagnosis of a germinal center B-cell-like (GCB) or non-GCB origin [13, 18, 19]. Cytogenetic fluorescence *in situ* hybridization (FISH) testing may also be carried out to determine the COO molecular classification or to determine whether *MYC*, *BCL2*, and/or *BCL6* rearrangements are present [20, 21].

Figure 1 Diagnostic process for LBCL



[a] Including Waldeyer's ring.

[b] B symptoms include fever, drenching night sweats, and involuntary weight loss [22].[c] In PMBCL, mediastinoscopy, anterior mediastinotomy, or percutaneous CT-guided core needle biopsy are performed as excisional biopsies are not feasible [23]

[d] An IHC panel for LBCL may include CD19, CD20, CD79a, BCL6, CD10, MYC, BCL2, Ki67, IRF4, CyclinD1, CD5, and CD23 [18, 21, 24]

Reference: adapted from [18, 21, 23, 24]

Staging of LBCL is used to define anatomic distribution and extent of disease for the purpose of prognosis and treatment planning [25, 26]. PET/CT is used for pre-treatment staging and for assessment of treatment response [16, 25, 27]. Staging is performed in accordance with the Ann Arbor staging system and stratifies patients into four disease stages (see Table 1) [16].

Table 1 Ann Arbor staging classification

Ann Arbor Stage	Criteria
Stage I	Involvement confined to a single lymph node region or single extranodal site
Stage II	Involvement of more than one lymph node on one side of the diaphragm with or without limited contiguous extranodal involvement
Stage III	Involvement of lymph nodes on both sides of the diaphragm
Stage IV	Diffuse or extensive extranodal involvement, with or without nodal involvement

Reference: El-Galaly et al. (2018) [16].

The prognosis of DLBCL is relatively good, with a 5-year survival around 65%. The risk of developing DLBCL increases with age. Age over 75 years and a performance status greater than 2 are associated with a higher rate of complications and a worse outcome [4, 10]. Although many patients with LBCL may achieve a cure from 1L therapy, 35% of patients exhibit primary refractory disease or relapse [10]. Patients with aggressive LBCLs experience severe physical and psychosocial symptoms, especially after relapse [15, 22, 28, 29]. CAR T-cell therapies offer an effective new treatment option while improving or maintaining HRQOL.

In the assessment report of axi-cel in 2L LBCL, the DMC reference data from the clinical study CORAL, which included HDT-eligible DLBCL patients with R/R disease after 1 line therapy, found a 3-year survival rate of 49%. For non-HDT suitable patients with R/R disease, the prognosis is significantly worse [4].

3.2 Patient population

There are two targeted patient populations for this assessment, adult patients with DLBCL, HGBCL, PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and adult patients with R/R DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy.

Large B cell lymphomas are a heterogeneous group of aggressive NHL characterised by the accumulation of malignant large B-cells in nodal and extranodal tissues. There are 1,650 new cases of lymphoma each year in Denmark, approx. 90% of them are NHLs. There are over 30 subtypes of NHLs, with different courses of disease with DLBCL are the most common (35%) with 500 new cases/year. The incidence of DLBCL has been increasing in Denmark over time [30]. The median age at diagnosis is 67 years. DMC estimates that 30 patients is eligible for CAR-T in 2L [4]. And 15 patients is expected to be eligible for CAR-T in 3.L.

Table 2 Incidence and prevalence in the past 5 years (second and third line)

Year	2019	2020	2021	2022	2023
Incidence in Denmark	500	500	500	500	500
Prevalence in Denmark					NA
Global prevalence*					NA

* For small patient groups, also describe the worldwide prevalence.

Table 3 Estimated number of patients eligible for treatment (second line plus)

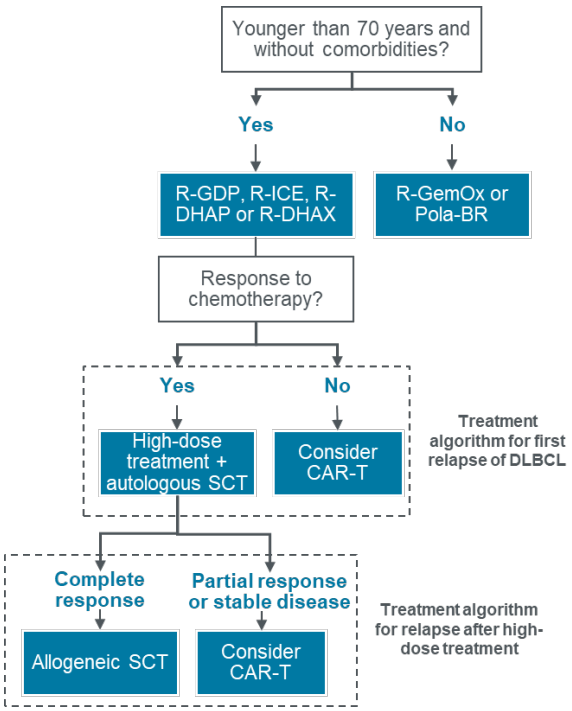
Year	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patients	45	45	45	45	45

3.3 Current treatment options

The Danish Lymphoma Group (DLG) treatment guidelines for DLBCL from 2023 [31] recommend CAR-T treatment to patients under 70 years old and, in good performance, in case of relapse within 12 months from completion of first-line treatment. The alternative option in case of relapse within 12 months from completion of first-line treatment is HDT/ASCT. There is no evidence for one particular regimen as second-line treatment for patients who cannot be offered curative HDT/ASCT or CAR-T.
The DLG guidelines list CAR-T treatment as an option for patients who are refractory to 2L or later lines or that relapse after autologous stem cell transplant [31].

EMA has approved the CAR-T therapies (axi-cel, and liso-cel) [32-34], for the 2L and 3L treatment of R/R LBCL and Kymriah (tisagenlecleucel, tisa-cel) for 3L treatment of R/R LBCL . Axi-cel is recommended and available in Denmark in 2L LBCL and are under re- assessment by DMC for the 3L treatment of R/R LBCL [35, 36].

Figure 2 Treatment algorithm for relapses of DLBCL



3.4 The intervention

Liso-cel is a CAR-T therapy consisting of autologous, individually formulated CD19-directed genetically modified autologous, purified CD8+ and CD4+ T cells in a defined 1:1 composition. After leukapheresis, purified CD8+ and CD4+ T cells are separately transduced *ex-vivo* with a replication-incompetent, lentiviral vector encoding for an scFv-binding domain derived from a murine CD19-specific monoclonal antibody (FMC63), IgG_4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3ζ (zeta) activation domain. CD3ζ signaling is critical for initiating T-cell activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion and persistence of Liso-cel [37].

Transduced CD8+ and CD4+ CAR-T cells are expanded in cell culture, formulated and cryopreserved in separate vials. Together, the CD8+ and CD4+ CAR-T components constitute Liso-cel and are administered in a defined composition to ensure a consistent CD8+ and CD4+ CAR-T cell ratio per dose. The defined composition of Liso-cel results in low variability in the administrated total and CD8+ CAR-T dose [37].

Liso-cel CAR binding to CD19 expressed on the surface of tumor and normal B cells induces activation and proliferation of CAR-T cells, release of pro-inflammatory cytokines and cytotoxic killing of target cells [37].

Table 4 Overview of intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Liso-cel is indicated for the treatment of adult patients with DLBCL, high grade B cell lymphoma (HGBCL), PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy [37]. Liso-cel is also indicated for the treatment of adult patients with relapsed or refractory DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy [37].
Method of administration	Liso-cel must be administered in a qualified treatment center; treatment should be initiated and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for administration of liso-cel and management of treated patients. Two to seven days prior to infusion of liso-cel, lymphodepleting chemotherapy (LDC) is administered to prepare the patient for liso-cel infusion [37]. Prior to administration of liso-cel, it is critical to confirm that at least one dose of tocilizumab and other emergency equipment are available should an AE arise during or after the infusion. To reduce the possibility of infusion reactions, it is recommended that patients receive a premedication 30 to 60 minutes prior to treatment with liso-cel (e.g., paracetamol and diphenhydramine or another H1-antihistamine) [37].
Dosing	Liso-cel is a cell suspension for infusion, with a single dose containing a batch-specific concentration of autologous anti-CD19 CAR-positive viable T cells, with CD8+ and CD4+ CAR-T cells supplied in separate vials. Liso-cel is packaged in one to four vials of each cell component containing a cryopreserved cell suspension of 1.1 to 70 x 10^6 CAR-positive viable T cells/mL in a 4.6 mL volume (5.1 x 10^6 to 322 x 10^6 CAR-positive viable T cells per vial) [37].

Overview of intervention	
	The target dose of liso-cel is 100 x 10^6 CAR-positive viable T cells (consisting of a target 1:1 ratio of CD8+ and CD4+ cell components) within a range of 44 to 120 x 10^6 CAR-positive viable T cells [37]. The infusion volume for each component may differ since it is calculated based on the concentration of the individually cryopreserved CD4+ and CD8+ CAR-T cell components.
Dosing in the health economic model (including relative dose intensity)	Liso-cel was assumed to be given at its target dose.
Should the medicine be administered with other medicines?	Bridging chemotherapy is permitted between apheresis and the start of lymphodepleting chemotherapy with 1 cycle of immunochemotherapy (i.e., rituximab, dexamethasone, cytarabine, and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin, and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]). Local radiation was allowed to a single lesion or subset of lesions if other non-irradiated PET-positive lesions were present and if completed at least 7 days prior to the start of lymphodepleting chemotherapy. Pre-treatment (lymphodepleting chemotherapy): Lymphodepleting chemotherapy consisting of cyclophosphamide 300 mg/m^2/day and fludarabine 30 mg/m^2/day, administered intravenously for three days. Pre-medication: It is recommended that premedication with paracetamol and diphenhydramine (25-50 mg, intravenously or orally) or another H1-antihistamine, be administered 30 to 60 minutes before the infusion of liso-cel to reduce the possibility of an infusion reaction. Source: [43].
Treatment duration / criteria for end of treatment	Treatment consists of a single dose for infusion
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored 2-3 times during the first week following infusion, for signs and symptoms of potential CRS, neurologic events, and other toxicities. Physicians should consider hospitalization at the first signs or symptoms of CRS and/or neurologic events. Frequency of monitoring after the first week should be carried out at the physician's discretion and should be continued for at least 4 weeks after infusion.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Liso-cel 1.1-70 × 10^6 cells/mL/ 1.1-70 × 10^6 cells/mL, dispersion for infusion.

3.4.1 The intervention in relation to Danish clinical practice

The two targeted patient populations are in line with the approved indications of liso-cel by the European Medicines Agency (EMA) in adult patients with diffuse DLBCL, HGBCL, PMBCL and FL3B, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and in adult patients with R/R DLBCL, PMBCL and FL3B, after two or more lines of systemic therapy. In Denmark, these patients are currently recommended treatment with axi-cel if they are fit enough to receive a CAR T. If not received in the 2L, patients may also be eligible for CAR T's in 3L but currently not as SoC.

3.5 Choice of comparator(s)

The relevant comparator to liso-cel in the two targeted patient populations for this assessment is the CAR-T therapy axi-cel. Axi-cel also recommended by DMC and available in Denmark for the 2L indication [36] and under re-assessment by DMC in 3L. The DLG guidelines recommend CAR T treatment for patients that are refractory to 2L or later lines or that relapse after autologous stem cell transplant [31].

Table 5 Overview of comparator

Overview of comparator	
Generic name	axi-cel, axicabtagene ciloleucel
ATC code	L01XL03
Mechanism of action	Axi-cel, an engineered autologous T-cell immunotherapy product, that binds to CD19 expressing cancer cells and normal B-cells. Following anti-CD19 CAR-T cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19-expressing target cells [34].
Method of administration	Axi-cel is intended for autologous use. Axi-cel must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with the medicinal product. On day 3, 4 and 5 prior to infusion of axi-cel, LDC is administered to prepare for axi-cel infusion consisting of cyclophosphamide 500 mg/m^2/day, and fludarabine 30 mg/m^2/day administered intravenously In the event of cytokine release syndrome (CRS), at least 1 dose of tocilizumab, and emergency equipment must be available prior to infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. To reduce the possibility of infusion reactions, it is recommended that patients receive a premedication approximately 1 hour prior to treatment with axi-cel (e.g., paracetamol and diphenhydramine or equivalent medicinal products)

Overview of comparator	
Dosing	Treatment of axi-cel consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one infusion bag. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (within a range of 1×10^6– 2×10^6 cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above.
Dosing in the health economic model (including relative dose intensity)	Axi-cel was assumed to be given at its target dose.
Should the medicine be administered with other medicines?	Pre-treatment (lymphodepleting chemotherapy): A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous must be administered prior to infusing axi-cel. The recommended days are on the 5th, 4th, and 3rd day before infusion of axi-cel. Pre-medication: It is recommended that pre-medication with paracetamol 500-1 000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral, or equivalent medicinal products, be administered approximately 1 hour before the infusion of axi-cel to reduce the possibility of an infusion reaction.
Treatment duration/ criteria for end of treatment	Treatment consists of a single dose for infusion
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Axi-cel 0.4 – 2×10^8 cells dispersion for infusion axicabtagene ciloleucel (CAR+ viable T cells)

3.6 Cost-effectiveness of the comparator(s)

Axi-cel is recommended by the DMC for 2L treatment with DLBCL and HGBL [4].

A reappraisal of axi-cel is ongoing at the DMC for 3L+ [44].

3.7 Relevant efficacy outcomes

3.7.1 Efficacy of liso-cel compared to axi-cel for the treatment of adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

3.7.1.1 Definition of efficacy outcomes included in the application

The efficacy outcome measures relevant for the application in the population in 2L are described in Table 6.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Event-free survival (EFS) [TRANSFORM][a]	DCO May 13, 2022. Median Study Follow-up, months (range): 17.53 (0.9, 37.0)[d]	Time from randomization to (whichever occurs first): death from any cause, progressive disease, start of new antineoplastic therapy due to efficacy concerns, or failure to achieve CR or PR by 9 weeks post-randomization.	IRC-assessed
Event-free survival (EFS) [ZUMA-7][b]	DCO March 18, 2021. Median Study Follow-up, months: 24.9[e]	Time from randomization to (whichever occurs first): death from any cause, progressive disease, or commencement of new lymphoma therapy. The following criteria will be used to further define events and event times: • Subjects with established PR or CR and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the last evaluable disease assessment prior to the new lymphoma therapy. • Subjects with best response of SDi and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the first time SDi was established prior to the new lymphoma therapy. • Subjects who commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of any evaluable disease assessment will have the EFS event date imputed as the randomization date. • Subjects with best response of SDi up to and including Day 150 assessment post randomization will be considered to have an EFS event. For such subjects, the EFS time will be defined as the time from randomization to the first time SDi was established up to and including the Day 150 disease assessment.	IRC-assessed
Progression-free survival (PFS) [TRANSFORM][a]	DCO May 13, 2022. Median Study Follow-up, months (range): 17.53 (0.9, 37.0)[d]	Time from randomization to progressive disease or death from any cause, whichever occurs first.	IRC-assessed

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS) [ZUMA-7][b]	DCO March 18, 2021. Median Study Follow-up, months: 24.9[e]	Time from randomization to disease progression per Lugano Classification [25]or death from any cause.	Assessed by INV
Overall survival (OS) [TRANSFORM]	DCO May 13, 2022. Median Study Follow-up, months (range): 17.53 (0.9, 37.0)[d]	Time from randomization to time of death due to any cause.	
Overall survival (OS) [ZUMA-7]	DCO March 18, 2021. Median Study Follow-up, months: 24.9[e]	Time from randomization to death from any cause.	
Objective Response Rate (ORR) [TRANSFORM][a]	DCO May 13, 2022. Median Study Follow-up, months (range): 17.53 (0.9, 37.0)[d]	Percentage of subjects achieving a PR or better [25].	IRC-assessed
Objective Response Rate (ORR) [ZUMA-7][b]	DCO March 18, 2021. Median Study Follow-up, months: 24.9[e]	The incidence of either a CR or a PR by the Lugano Classification as determined by blinded central review [25].	IRC-assessed
Complete response rate (CRR) [TRANSFORM][a]	DCO May 13, 2022. Median Study Follow-up, months (range): 17.53 (0.9, 37.0)[d]	Percentage of subjects achieving a CR [25].	IRC-assessed
Complete response rate (CRR) [ZUMA-7][b]	DCO March 18, 2021. Median Study Follow-up, months: 24.9[e]	Percentage of subjects achieving a CR[c] [25].	IRC-assessed

[a]For TRANSFORM, all response criteria behind EFS, PFS, ORR, and CRR were based on Lugano Classification [25].
[b]For ZUMA-7, all response criteria behind EFS, PFS, ORR, and CRR were based on Lugano [25].
[c]Reported as part of ORR definition per ZUMA-7 ClinicalTrials.gov record (NCT#03391466) [45].
[d]Follow-up time is reported for TRANSFORM ITT set. Follow-up is reported as time from randomization to last date know alive (months). Last date defined as last valid date of subject assessment prior to or on the data cutoff date in the clinical database [46].
[e]Follow-up time is reported for ZUMA-7 enrolled and randomized set. It was defined as time from randomization to data-cutoff date [47].
This table has been slightly modified to include all data

3.7.2 Efficacy of liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

3.7.2.1 Definition of efficacy outcomes included in the application

The efficacy outcome measures relevant for the application in the population of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy are described in Table 7.

Table 7 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS) [TRANSCEND (017001)]	DCO January 2021. Median study follow-up, months (range): 31.0 (95% CI 28.7, 35.4)[a]	Time from first infusion to the earlier date of disease progression or death due to any cause. Reported based on FDA censoring rules. Patients who proceeded to HSCT were: • censored by IRC • not censored to match to ZUMA-1 INV definition	INV-assessed
Progression-free survival (PFS) [ZUMA-1]	DCO August 2018. Median study follow-up, months (range): 27.1 (IQR 25.7-28.8)[b]	Time from first infusion to progressive disease, based on IWG revised guidelines [48], or death. Reported based on FDA censoring rules. Patients who proceeded to HSCT were: • censored by IRC • not censored by INV	INV-assessed
Overall survival (OS) [TRANSCEND (017001)]	DCO January 2021. Median study follow-up, months (range): 31.0 (95% CI 28.7, 35.4)[a]	Time from infusion to the date of death or data cut-off date for any reason.	
Overall survival (OS) [ZUMA-1]	DCO August 2020. Median study follow-up, months (range): 51.1 (NR)[b]	Time from infusion to the date of death from any cause.	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall Response Rate (ORR) [TRANSCEND (017001)]	DCO January 2021. Median study follow-up, months (range): 31.0 (95% CI 28.7, 35.4)[a]	ORR (CRR + PRR) using Lugano classification [25].	IRC-assessed
Overall Response Rate (ORR) [ZUMA-1]	DCO August 2018. Median study follow-up, months (range): 27.1 (IQR 25.7-28.8)[b]	ORR (CRR + PRR) using IWG revised guidelines [48] with the incorporation of PET scan.	IRC-assessed
Complete response rate (CRR) [TRANSCEND (017001)]	DCO January 2021. Median study follow-up, months (range): 31.0 (95% CI 28.7, 35.4)[a]	Lugano classification [25].	IRC-assessed
Complete response rate (CRR) [ZUMA-1]	DCO August 2018. Median study follow-up, months (range): 27.1 (IQR 25.7-28.8)[b]	IWG revised guidelines [48] with the incorporation of PET scan.	IRC-assessed

[a]The median follow-up time for OS was 31.0 months (95% CI 28.7, 35.4) and is reported in the table. The median follow-up time for PFS was 23.9 months (95% CI 23.6, 24.0). Both were calculated using the reverse Kaplan-Meier method.
[b]Definition not reported.
This table has been slightly modified to include all data

Validity of outcomes

In the DMC assessment of axi-cel for 2L, the DMC stated that EFS, PFS and OS are considered adequate for the evaluation of the treatment effect [36].

The DMC has also assessed axi-cel for the treatment of adult patients with relapsed or refractory DLBCL after several systemic treatments. The protocol defined OS as a critical outcome and PFS and response rates as important outcomes [35].

4. Health economic analysis

Two cost-minimization analyses were performed for this submission.

4.1 Model structure

The cost-minimization analyses compared the costs associated with treatment with liso-cel and axi-cel in patients with relapsed or refractory LBCL (2L and 3L treatment). The following treatment associated costs were included in the analyses:

- Bridging therapy costs
- CAR-T drug acquisition costs (both list and net prices)
- Administration costs
- Costs associated with the inpatient stay after the administration of the CAR-T
- Adverse event costs
- Patient and caregiver costs

All other costs (e.g., leukapheresis costs, lymphodepleting treatment costs, subsequent treatment costs and palliative care costs) were assumed to be equivalent between liso-cel and axi-cel and were therefore not included in the analyses.

The analyses also have the option to only include drug acquisition costs.

4.2 Model features

Table 8 shows the features of the economic model.

Table 8 Features of the economic model

Model features	Description	Justification
Patient population	There are two patient populations for the cost-minimization analyses: adult patients with LBCL, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy and adult patients with R/R LBCL, after two or more lines of systemic therapy.	Same population as described in section 3.2
Perspective	Limited societal perspective.	According to DMC guidelines.
Time horizon	One year.	As both liso-cel and axi-cel are CAR-T treatments, all relevant costs differences are captured within the one-year time horizon.
Cycle length	NA.	NA.
Half-cycle correction	NA.	NA.
Discount rate	No discount rate was applied.	The time horizon is 1 year.
Intervention	Breyanzi® (liso-cel).	NA.

Model features	Description	Justification
Comparator(s)	Yescarta® (axi-cel).	According to the Danish Lymphoma Group (DLG) treatment guidelines [10]. Axi-cel is also recommended by DMC and available in Denmark for the 2L indication.[36], and under re-assessment by DMC in 3L
Outcomes	Total costs and difference in the costs associated with treatment with liso-cel and axi-cel.	These are the standard outcomes in a cost-minimization model.

5. Overview of literature

5.1 Liso-cel compared to axi-cel for the treatment adult patients with LBCL, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

5.1.1 Literature used for the clinical assessment

One of the populations in the application concerns the treatment of adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. The clinical development program for liso-cel in the 2L TE LBCL population is based on (TRANSFORM; NCT03575351).[49] The TRANSFORM study is a global, randomized, multicenter, phase 3 clinical trial designed to compare the efficacy and safety of liso-cel to standard of care (SoC) (ie, salvage therapy followed by HDCT and autologous HSCT [auto-HSCT]) in adult subjects with high-risk, R/R aggressive B-cell NHLs who are eligible for transplant.

Liso-cel has not been directly compared to axi-cel in head-to-head clinical trials for the 2L TE LBCL population. Therefore, the relative effectiveness of liso-cel to axi-cel in this population is currently unclear and can only be compared indirectly using TRANSFORM (liso-cel) and external data sources (axi-cel).

A systematic literature review conducted in July 2020 with an updated SLR in 2023 identified the ZUMA-7 trial as a key data source for evaluating the efficacy and safety of axi-cel for 2L TE LBCL patients [50]. ZUMA-7 (NCT03391466) is an international, randomized, phase 3 clinical trial to compare the efficacy and safety of axi-cel to SoC (ie, 2 to 3 cycles of salvage therapy followed by auto-HSCT) in adult patients with LBCL that was refractory to or had relapsed no more than 12 months after 1L chemoimmunotherapy.

For more information on the SLR please see Appendix H.

An overview of efficacy and safety (the TRANSFORM and ZUMA-7 trials) is presented in Table 9.

Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Abramson, J.S., et al., Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of phase 3 TRANSFORM study. Blood, 2022 [51]. Bristol Myers Squibb, Data on file. BMS-986387: A Global Randomized Multicenter Phase 3 Trial to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult subjects with High-Risk,Transplant-Eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM) (Study JCAR017-BCM-003); Report, Addendum 01. Bristol-Myers Squibb Company; study ongoing. Document Control No. 930193545 [46]. Bristol Myers Squibb, Data on file. LISOCABTAGENE MARALEUCEL Non-interventional Study Technical Report for Study CA082-074 INDIRECT	TRANSFORM	NCT03575351	Study start: 2018-10-23. Study Completion: 2023-10-23. DCO: 13 May 2022.	Liso-cel vs. axi-cel for the treatment of adult patients with Large B-cell lymphoma who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
TREATMENT COMPARISON OF LISOCABTAGENE MARALEUCEL (LISO-CEL) AND AXICABTAGENE CILOLEUCEL (AXI-CEL) FOR SECOND-LINE TREATMENT OF TRANSPLANT INTENDED PATIENTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA. 2023 [52].				
Locke, F.L., et al., Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. New England Journal of Medicine, 2022. 386(7): p. 640-654 [47]. FDA, Yescarta [BLA Clinical Review and Evaluation]. 2022 [53].	ZUMA-7	NCT03391466	Study start: 2018-01-25 Primary Completion: 2023-01-25 Study Completion (estimated): 2035-01 DCO: 18 Mar 2021.	

5.1.2 Literature used for the assessment of health-related quality of life

A SLR was conducted to identify HRQoL evidence in the treatment of R/R large B-cell lymphomas, with a focus on outcomes in 2L. The database searches were restricted to the publication years 01 Jan 2003 to March 1, 2023. An initial search was run on 21 April 2020 and updated searches were run on 08 June 2020, 05 February 2021, 02 May 2022, and March 1, 2023. Conference proceedings from 2018 through to March 2023 were hand searched. The PICOS framework was used to develop the research questions and search strategy for the HRQoL evidence SLR. Consequently, studies were eligible for inclusion based on PICOS criteria established *a priori* [54].

For HRQoL studies, randomized and non-randomized studies and economic evaluations reporting health state utility values or HRQoL measures that can be mapped to health state utility values were eligible. Assessments from HTA agencies with full reviewer's reports available from NICE, CADTH, PBAC, and SMC were also eligible to ensure that the most complete set of analysis results supporting HTA recommendations were captured. Studies were not limited by sample size [54].

In total, 72 records representing 55 unique studies reporting HRQoL outcomes were included in the SLR. Out of the 55 unique studies, 34 reported results for a 3L+ or R/R population only and were not further considered. The remaining studies reported results in a 2L/2L+ population. 14 records representing 10 unique studies reported results in a 2L population. Out of these, three studies reported HRQoL measures for CAR-T cell therapies (TRANSFORM, PILOT and ZUMA-7 studies) [54]. However, the phase 2, single-arm PILOT trial does not include the patient population relevant for this application.

Therefore, the assessment of health-related quality of life (HRQoL) was based on the naïve comparison of the intervention arms (liso-cel and axi-cel) of two head-to-head studies (TRANSFORM and ZUMA-7) with a common comparator arm (salvage chemotherapy followed by high-dose chemotherapy and stem cell transplantation in responsive patients).

An overview of the relevant literature included for the documentation of HRQoL is shown in Table 10.

For more information on the SLR please see Appendix I.

Table 10 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Bristol Myers Squibb, Data on file. Patient-Reported Outcome/Health-Related Quality of Life Report for Study JCAR017-BCM-003. A global, randomized, multicenter Phase 3 trial to compare the efficacy and safety of JCAR017 to standard of care in adult subjects with high risk, transplant-eligible relapsed or refractory aggressive B-cell non-Hodgkin lymphomas (Primary Analysis). 2022 [55]. Bristol Myers Squibb, Data on file. Analysis of Patient-reported Outcome/Quality of Life Data for a Phase III Trial to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects with High-risk, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas (JCAR017-BCM-003 TRANSFORM Study; Topline Results of PRO/HRQoL Endpoints Based on Data with Cut-off Date of 13 May 2022). 2022 [56]. Conor Chandler. Data on file. UK Utility Descriptive Statistics - TRANSFORM Trial. 2024 [57].	NA	Section 10.1

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Elsawy, M., et al., Patient-reported outcomes in ZUMA-7, a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma. Blood, 2022. 140(21): p. 2248-2260 [58].		

5.1.3 Literature used for inputs for the health economic model

A cost-minimization analysis was conducted comparing bridging therapy costs, CAR-T acquisition costs, administration costs, disease management costs (inpatient stay after administration), adverse event costs and patient time costs of liso-cel and axi-cel. These costs were based on publicly available sources relevant for Denmark. Consequently, a systematic literature search was not conducted. Table 11 shows the relevant literature used for input to the cost-minimization analysis.

Table 11 Relevant literature used for input to the cost-minimization analysis

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Publicly available sources/literature	Bridging therapy costs, CAR-T acquisition costs, administration costs, disease management costs (inpatient stay after administration), adverse event costs and patient time costs.	Bridging therapy costs and CAR-T acquisition costs were sourced from medicinpriser.dk. Administration, disease management, and adverse event costs were sourced from Sundhedsdatastyrelsen. Patient costs were derived from Værdisætning af Enhedsomkostninger.	Section 11.

5.2 Liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy

5.2.1 Literature used for the clinical assessment

The application concerns the population of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy.

TRANSCEND (017001) was a single-arm trial and no head-to-head clinical trials comparing liso-cel to current treatment options have been conducted to date in 3L+ R/R LBCL, a comparison of the efficacy and safety of liso-cel to the other treatment options can only be done indirectly using TRANSCEND (017001) and external data sources. ZUMA-1 is the key source of efficacy and safety data for axi-cel, as a 3L+ treatment option for R/R large B-cell NHL.

An overview of the relevant literature included in the assessment of efficacy and safety in this population (the TRANSCEND 017001 and ZUMA-1 trials) is presented in Table 12.

Table 12 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Juno Therapeutics, Data on file. A Phase 1, Multicenter, Open-Label Study of JCAR017, CD19-targeted Chimeric Antigen Receptor (CAR) T Cells, for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL). 2020 [59]. Bristol Myers Squibb, Data on file. LISOCABTAGENE MARALEUCEL INDIRECT TREATMENT COMPARISON OF CAR T-CELL THERAPIES FOR THE THIRD-LINE OR LATER TREATMENT OF RELAPSED OR REFRACTORY LARGE B CELL LYMPHOMA: LISO-CEL DOSE LEVELS DL1S + DL2S + DL1D VERSUS TISAGENLECLEUCEL AND AXICABTAGENE CILOLEUCEL. 21 October 2021 [60].	TRANSCEND (017001)	NCT02631044	Study start date: 2016-01-06 Estimated primary completion date: 2024-05-10 Estimated study completion date: 2024-05-10 DCO 04 Jan 2021.	Liso-cel vs. axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy.
Jacobson C, L.F., Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al.,, Long-Term Survival and Gradual Recovery of B Cells in Patients with Refractory Large B	ZUMA-1	NCT02348216	Study start date: 2015-04-21 Primary completion date: 2020-09-10 Study completion date:	

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Cell Lymphoma Treated with Axicabtagene Ciloleucel (Axi-Cel). Blood, 2020: p. 40-2 [61]. Locke, F.L., et al., Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol, 2019. 20(1): p. 31-42 [62].			2023-07-27 DCO 11 Aug 2018 & 11 Aug 2020.	

5.2.2 Literature used for the assessment of health-related quality of life

The assessment of HRQoL was based on the naïve comparison of the intervention arms (liso-cel and axi-cel of two single-arm studies (TRANSCEND 017001 and ZUMA-1).

An overview of the relevant literature included for the documentation of HRQoL is shown in Table 13.

Table 13 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
BMS, Data on file. STUDY JCAR017-017001. A Phase 1, Multicenter, Open-Label Study of JCAR017, CD19 Targeted Chimeric Antigen Receptor (CAR) T Cells, for Relapsed or Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (NHL) - PATIENT-REPORTED OUTCOMES REPORT. 2021 [63]. Lin VW, J.Y., Chuang LH, Navale L, Cheng P, Purdum A,, P889 Health utilities for patients with relapsed or refractory large B-cell lymphoma (R/R-LBCL): ad hoc analysis from an axicabtagene	NA	Section 10.2

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
ciloleucel (axi-cel) safety management study. Bone Marrow Transplant. 2019. 53: p. 879 [64].		

5.2.3 Literature used for inputs for the health economic model

A cost-minimization analysis was conducted comparing bridging therapy costs, CAR-T acquisition costs, administration costs, disease management costs (inpatient stay after administration), adverse event costs and patient time costs of liso-cel and axi-cel. These costs were based on publicly available sources relevant for Denmark. Consequently, a systematic literature search was not conducted. Table 14 shows the relevant literature used for input to the cost-minimization analysis.

Table 14 Relevant literature used for input to the cost-minimization analysis

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Publicly available sources/literature	Bridging therapy costs, CAR-T acquisition costs, administration costs, disease management costs (inpatient stay after administration), adverse event costs and patient time costs.	Bridging therapy costs and CAR-T acquisition costs were sourced from medicinpriser.dk. Administration, disease management, and adverse event costs were sourced from Sundhedsdatastyrelsen. Patient costs were derived from Værdisætning af Enhedsomkostninger.	Section 11.

6. Efficacy

6.1 Efficacy of liso-cel and axi-cel in adult patients with Large B-cell lymphoma who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

6.1.1 Relevant studies

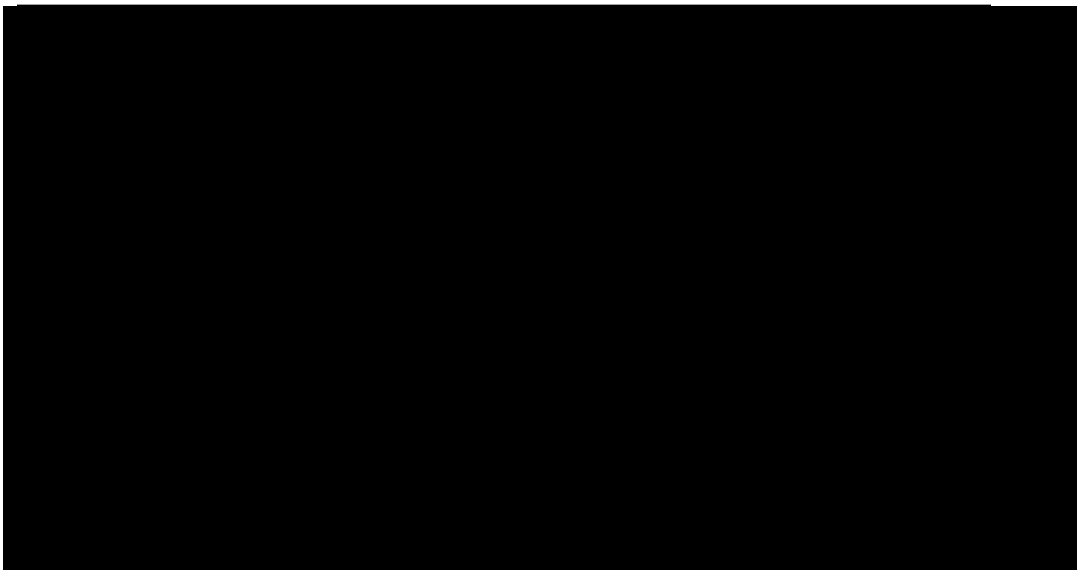
The key clinical trial for efficacy and safety of liso-cel for the second-line treatment of adult patients with LBCL who are refractory to or relapse within 12 months of achieving a complete response (CR) to 1L therapy is the pivotal study TRANSFORM. TRANSFORM (NCT03575351) is a phase 3, randomized, open-label, parallel group, multi-center study. The comparator to liso-cel is standard of care (salvage chemoimmunotherapy followed by high-dose chemotherapy and hematopoietic stem cell transplant in responsive patients).

The key clinical trial for efficacy and safety of axi-cel for the second-line treatment of adult patients with LBCL who are refractory to or relapse within 12 months of achieving a CR to 1L therapy is the pivotal study ZUMA-7. ZUMA-7 (NCT03391466) is a phase 3, randomized, open-label, multi-center study. The comparator to axi-cel in ZUMA-7 is standard of care (salvage chemoimmunotherapy followed by high-dose chemotherapy and autologous stem cell transplant in responsive patients).

The trial design of TRANSFORM and ZUMA-7 is presented in Figure 4 and Figure 5, respectively. The patient disposition is presented in Figure 6 and Figure 7, respectively.

The analysis is based on the 13 May 2022 data cut-off (DCO) of the TRANSFORM study [51], and on the 18 March 2021 DCO of the ZUMA-7 study [47].

Figure 4 TRANSFORM study design



Patients may have received a protocol-defined SoC regimen to stabilize their disease during liso-cel manufacturing.
[b]Only for the 58 (63.0%) patients who received bridging therapy.
[c]Lymphodepletion with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 for 3 days.
[d]SoC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.
[e]EFS is defined as time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first.
Sources: [65]; [66]; [67]; [43]; [51].

Figure 6 Patient disposition in TRANSFORM

[a]During screening, patients were assessed for eligibility for randomization and unstimulated leukapheresis.
[b]Patients randomized to the SoC Arm were to receive 3 cycles of SoC salvage therapy (R-DHAP, R-ICE, or R-GDP) followed by HDCT and HSCT.
[c]Patients randomized to the Breyanzi® (liso-cel) arm were to receive LDC followed by Breyanzi® (liso-cel) infusion; bridging therapy was allowed per protocol.
[d]Patients were approved to crossover by the Medical Monitor after IRC confirmation of a qualifying event. See IA CSR20 for eligibility criteria for patients to cross over from SoC arm to receive LDC followed by Breyanzi® (liso-cel) infusion.
Sources: Bristol [65]; [68]; [51].

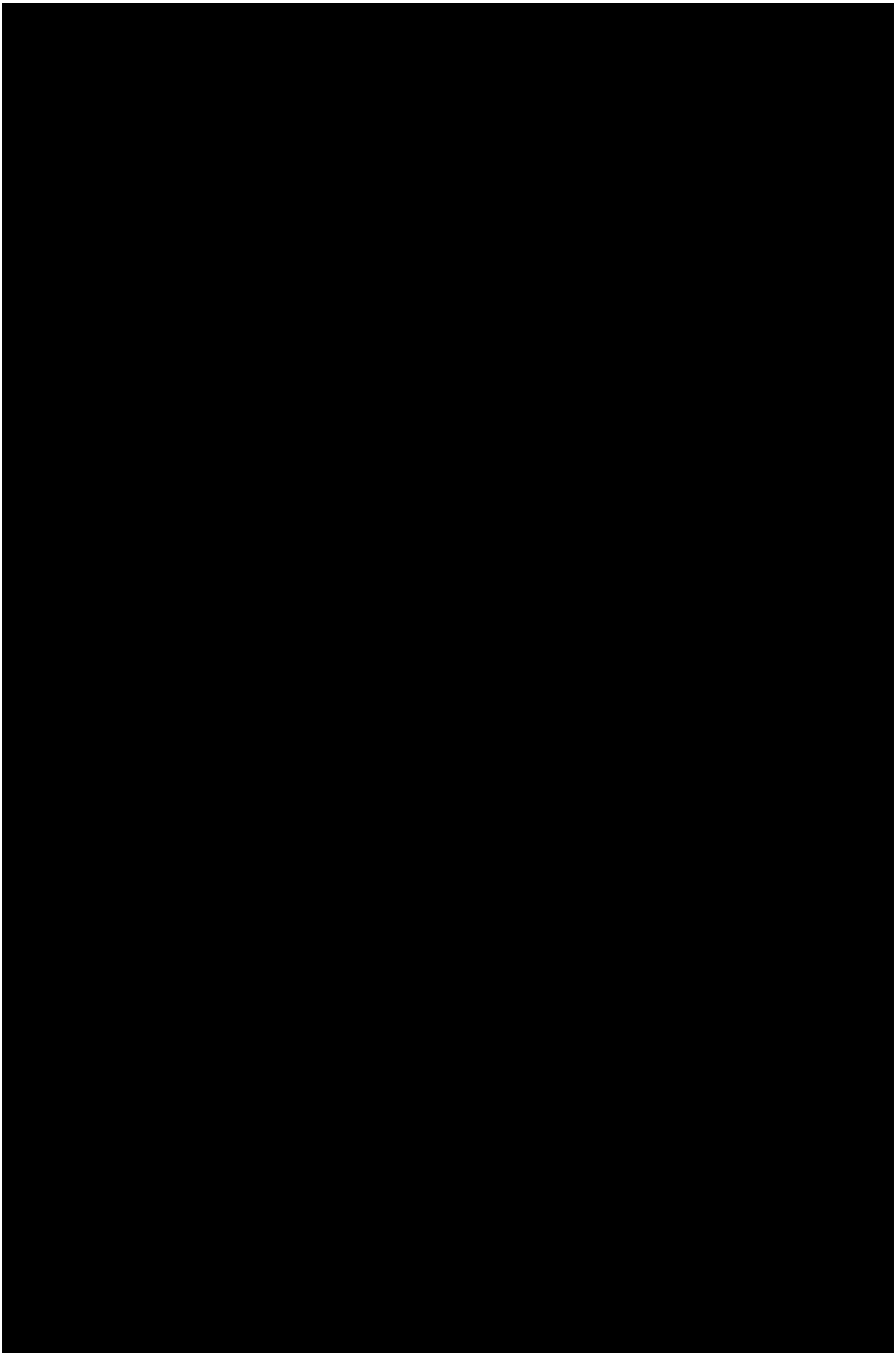


Table 15 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
TRANSFORM, NCT03575351 [51], [46]	Phase 3, randomized, open-label, parallel group, multi-center, global study.	Study start: 2018-10-23 Study Completion: 2023-10-23	Adult patients (aged ≤75 years) with LBCL (defined as DLBCL not otherwise specified [NOS; de novo or transformed indolent NHL], HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology [DHL/THL], PMBCL, T cell/histiocyte-rich large B cell lymphoma (THRBCL), or FL3B according to the World Health Organization (WHO) 2016 classification system) who had primary refractory disease or had relapsed within 12 months of achieving a CR to 1L chemoimmunotherapy and were eligible for HDCT and HSCT. Other key inclusion criteria were an ECOG PS score ≤1 and adequate organ function.	N = 92 All patients randomized to the liso-cel arm received LDC with intravenous (IV) fludarabine (30 mg/m2/day for 3 days) plus cyclophosphamide IV (300 mg/m2/day for 3 days) (flu/cy) concurrently followed at least two days later by liso-cel infusion (100 x 106 CAR+ T cells). Patients in this arm were permitted to receive bridging therapy with one cycle of a SoC regimen to stabilize their disease during liso-cel manufacturing, if deemed necessary by the investigator (i.e, after leukapheresis and prior to LDC).	N = 92 All patients randomized to the SoC arm received three cycles of one of the following SoC salvage regimens: R-DHAP (Rituximab 375 mg/m² on Day 1, dexamethasone 40 mg on Days 1 to 4, cytarabine 2 x 2000 mg/m² on Day 2, and cisplatin 100 mg/m² on Day 1) R-ICE (Rituximab 375 mg/m² on Day 1, ifosfamide 5000 mg/m² on Day 2, etoposide 100 mg/m² on Days 1 to 3, and carboplatin area under the curve [AUC] 5 [maximum dose 800 mg] on Day 2)	<u>Primary efficacy endpoint[a]:</u> • Event free survival (EFS): Time from randomization to death from any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization or start of new antineoplastic therapy due to efficacy concerns, whichever occurred first. Timeframe: up to 3 years post-randomization. <u>Key secondary efficacy endpoints[b]:</u> • Complete response rate (CRR): Percentage of patients who achieved a CR. • Timeframe: up to 3 years post-randomization. • Progression-free survival (PFS): Time from randomization to PD or death from any cause, whichever occurred first. Timeframe: up to 3 years post-randomization. • Overall survival (OS): Time from randomization to time of death due to any cause. Timeframe: up to last patient visit. <u>Secondary efficacy endpoints:</u>

	Investigational therapies were not permitted. Bridging therapy given after randomization must have been stopped at least 7 days prior to LDC. Patients who received bridging chemotherapy were to have a positron emission tomography (PET) scan prior to the start of LDC.	R-GDP (Rituximab 375 mg/m² on Day 1, dexamethasone 40 mg on Days 1 to 4, gemcitabine 1000 mg/m² on Days 1 and 8, and cisplatin 75 mg/m² on Day 1) This was followed by HDCT (BEAM [carmustine (BCNU) 300 mg/m² on Day 1, etoposide 200 mg/m² on Days 2 to 5, cytarabine 200 mg/m² on Days 2 to 5, and melphalan 140 mg/m² on Day 6]) and HSCT in responsive patients. Patients randomized to SoC arm were permitted to cross over to liso-cel if deemed appropriate by the investigator upon central confirmation of one of the following criteria: Failure to achieve CR or PR by nine weeks post-randomization	• Overall response rate (ORR): Percentage of patients who achieved an objective response of PR or better. Timeframe: up to 3 years post-randomization. • Duration of response (DoR): Time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death from any cause. Timeframe: up to 3 years post-randomization. • PFS on next line of treatment (PFS-2): Time from randomization to second objective disease progression or death from any cause, whichever occurred first. Timeframe: up to 3 years post-randomization. • EFS rate: Percentage of patients free of any EFS event at fixed timepoints. Timeframe: at 6, 12, 24, and 36 months post-randomization. • PFS rate: Percentage of patients free of any PFS event at fixed timepoints. Timeframe: at 6, 12, 24, and 36 months post-randomization. • OS rate: Percentage of patients alive at fixed timepoints. • Timeframe: at 6, 12, 24, and 36 months post-randomization. • Clinical, histological, and molecular subgroup analyses: Response rate, EFS, PFS, and OS in clinical, histological and molecular subgroups.

	(ie, after 3 cycles of SoC therapy). Progression at any time. Need to start a new antineoplastic therapy due to efficacy concerns (ie, absence of a CR) after 18 weeks post randomization.	Timeframe: up to 3 years post-randomization. • Rate of HDCT completion: Percentage of patients in the SoC arm completing HDCT. Timeframe: up to 3 years post-randomization. • Rate of HSCT completion: Percentage of patients in the SoC arm completing HSCT. Timeframe: up to 3 years post-randomization. • Response rate post-HSCT: Percentage of patients in response after undergoing HSCT. • Timeframe: at 3 months post-HSCT. • Health-related quality of life (HRQoL): • EORTC QLQ-C30 subscales: • GH/QoL • Fatigue • Physical functioning • Cognitive functioning • FACT-Lym "Additional Concerns" subscale. • Hospital resource utilization (HRU) <u>Secondary outcomes of interest included:</u> • Number of and duration of hospitalizations • Reasons for hospitalization • Unit of admission • ICU and non-ICU inpatient stays • Number of outpatient visits • Exploratory outcomes:

- Pharmacodynamic (Pd; including B-cell aplasia and soluble biomarkers such as chemokines and cytokines) and PK for liso-cel.
- Tumor and tumor microenvironment in mechanisms of response and resistance to liso-cel.
- Safety and efficacy for patients who crossed over to liso-cel.
- Anti liso-cel immune responses
- Other domains/subscales of the EORTC QLQ-C30 not specified as secondary endpoints.
- Health utility and overall health scores assessed using the European Quality of Life – 5 Dimensions Health State Classifier to 5 Levels (EQ-5D-5L) questionnaire.

Safety

- Treatment exposure and duration, cumulative dose, number of days dosed, average daily dose, dose intensity, treatment compliance, relative intensity per treatment arm, per regimen, and per agent when relevant. Dose modifications were also summarized for each treatment arm.
- Type, frequency, and severity of AEs, SAEs, and laboratory abnormalities (overall and in clinical, histological, and molecular subgroups).

ZUMA-7, NCT03391466 [47] [53]	Phase 3, randomized, open-label, multi-center study.	Study start: 2018-01-25 Primary Completion: 2023-01-25 Study Completion (estimated): 2035-01	Adult subjects with r/r LBCL (based on the WHO 2016 lymphoma categorization) after first-line rituximab and anthracycline-based chemotherapy. Refractory disease defined as no complete remission to first-line therapy (subjects who were intolerant to first-line therapy were to be excluded). Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse ≤ 12 months of first-line therapy. Other key inclusion criteria were intent to proceed to HDT and auto-SCT if there was response to second-line chemotherapy and ECOG performance status of 0 or 1.	N = 180 Subjects randomized to the axi-cel arm were to receive a 3-day lymphodepleting chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day on Treatment Days −5 to −3 followed by 2 rest days (before axi-cel infusion on Treatment Day 0) at a target dose of 2 × 10^6 anti CD19 CAR T cells/kg body weight. Subjects were to receive axi-cel in a healthcare facility followed by a minimum 7-day observation period. At the discretion of the investigator, corticosteroid bridging therapy could have been considered for subjects with high disease burden at screening.	N = 179 Subjects randomized to the SoC arm were to receive a second-line (salvage) chemotherapy regimen (R-ICE, R-DHAP, R-ESHAP, or R-GDP) as selected by the treating investigator. Subjects were to receive 2 or 3 cycles of salvage chemotherapy, with each cycle administered every 2 to 3 weeks. Subjects responding to salvage chemotherapy after 2 or 3 cycles were to proceed with HDT and auto-SCT. Subjects who did not respond to salvage chemotherapy could have received additional treatment off protocol.	<u>Primary endpoint:</u> • EFS (with progression events and censoring) per blinded central assessment. <u>Secondary endpoints:</u> *Key secondary endpoints:* • ORR per blinded central assessment. • OS *Additional secondary endpoints:* • EFS (with progression and censoring events) based on investigator disease assessments. • PFS (with progression and censoring events) based on investigator disease assessments. • Duration of response (DOR) by blinded central assessments. • Modified EFS (mEFS). • Incidence of adverse events (AEs) and clinically significant changes in safety laboratory test values, including antibodies to axi-cel. • Changes from screening in the global health status quality of life (QoL) scale and the physical functioning domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30).

		• Changes from screening in the Euro-QOL, 5 dimensions, 5 levels (EQ-5D-5L) index and visual analog scale (VAS) scores. • For a subject who completed the long-term follow-up period, the study was to take approximately 5 or 15 years to complete as determined by randomization to the SoC or axi-cel arms, respectively. Survival status to be ascertained at each clinic visit through Month 9 after which subjects were to be contacted every 3 months through Month 24, then every 6 months until Month 60.

[a]As the primary efficacy endpoint of EFS was met at the time of interim analysis, EFS was not formally re-tested in the primary analysis.
[b]Hypothesis testing on the key secondary endpoint of CRR and subsequently on PFS and OS was performed hierarchically in the primary analysis. The significance threshold to reject the null hypothesis for the key secondary endpoints was $P \leq 0.021$ (adjusted for the actual number of events available for primary analysis and the alpha spent at previous interim analyses).

6.1.2 Comparability of studies

A thorough qualitative comparison of the pivotal trials for liso-cel (TRANSFORM) and axi-cel (ZUMA-7) was conducted to assess the feasibility of an indirect treatment comparison (ITC) in terms of the following components[52]:

- Study design characteristics, including phase, visit schedules, and follow-up time.
- Study eligibility criteria, including clinical and diagnostic definitions, and study treatment protocols (such as use of bridging therapy).
- Baseline characteristics, including availability, definitions, and assessment of imbalance.
- Outcomes, including availability and definitions.

To facilitate the feasibility assessments comparison, individual patient data (IPD) from TRANSFORM and published summary-level data (SLD) from ZUMA-7 were used. Analyses of interest included all patients who were enrolled and randomized for the comparison of efficacy outcomes and all patients who were randomized and received study treatment (i.e., safety analysis set) for the comparison of safety outcomes [52].

The comparison of the study design, eligibility criteria, baseline characteristics, and outcomes of TRANSFORM and ZUMA-7 has shown sufficient similarities between the studies to allow comparison but revealed differences across trials necessitating the conduct of a matching-adjusted indirect comparison (MAIC) to reduce bias when indirectly comparing liso-cel to axi-cel. Large differences in the definitions or categorizations of patient characteristics such as the second-line age adjusted International Prognostic Index (sAAIPI) score, disease histology, tumor burden SPD, and R/R status between trials were identified and required alignment via redefining the variables with TRANSFORM IPD to facilitate a fairer comparison [52].

Investigation of outcome definitions and data availability indicates that MAICs are feasible for all 5 efficacy outcomes of interest (i.e., EFS, PFS, OS, ORR, and CRR) and most key safety outcomes of interest, including CRS and study-defined NT[52].

Two approaches, MAIC and simulated treatment comparison (STC), were considered to minimize bias. The MAIC approach was preferred due to fewer associated assumptions and limitations [69]. A process for identifying and ranking treatment effect modifiers was used to prioritize adjustments, ensuring the most relevant effect modifying factors were considered. Conforming to MAIC standards, the individual patient-level data from TRANSFORM was adjusted to match the clinical factors observed in the ZUMA-7 trial. Clinically significant factors were collectively adjusted in order of their ranked importance [52].

Initially, there were observed imbalances in treatment effect modifiers, with 50.0% showing a standard mean difference (SMD) of less than 0.2 and 7.1% with an SMD less than 0.1. However, following the MAIC, these imbalances were notably improved with 85.7% having an SMD less than 0.2 and 64.3% less than 0.1 [52].

6.1.2.1 Comparability of patients across studies

Definitions and values for the baseline characteristics that were reported in the primary publications from TRANSFORM and ZUMA-7 are reported below (Table 16,Table 17 respectively) [43, 47]. Definitions were compared across trials to determine whether redefinition or recategorization was required using TRANSFORM IPD, to facilitate a fair comparison or use in analysis. The definitions or minimum/maximum threshold differed between the studies for the following 10 patient characteristics: ALC, secondary CNS involvement, disease histology, bridging therapy, race, region, cell of origin (COO), disease stage, tumor burden as measured by sum of the product of perpendicular diameters (SPD), lactate dehydrogenase (LDH), and relapsed or refractory status. The actions needed for definition/categorization alignment in TRANSFORM IPD and the rationale are shown in Table 16.

Baseline patient characteristics reported for TRANSFORM and ZUMA-7 were compared to assess imbalance between the trials (Table 17).

Both studies reported baseline characteristics for patients who were enrolled and randomized (i.e., the ITT set). Some characteristics were similar between TRANSFORM and ZUMA-7. Differences were observed for sex, race, region, disease histology, cell of origin (COO), SPD, sAAIPI score, and secondary CNS involvement. A comparison of lactate dehydrogenase (LDH) was obfuscated by an unclear definition of “elevated” in ZUMA-7. Number of extra-nodal involvement sites, best response to first-line therapy, time from initial diagnosis to randomization, and CD19+ status on immunohistochemical testing were not compared due to lack of data availability in one of the two trials.

Table 16 Comparison of reported baseline characteristics definitions between TRANSFORM and ZUMA-7

Baseline Characteristics	ZUMA-7	TRANSFORM	Action Needed for Definition/Categorization Alignment in TRANSFORM IPD and Rationale
Age	By median (range); In years	By median (range); In years	Estimate mean and standard deviation by quantile estimation method [70]
Sex	Male, Female	Male, Female	None
Race	American Indian or Alaskan native, Black, Asian, Native Hawaiian or other Pacific Islander, White, Other	Black, Asian, White, Other, Not collected or Reported	In TRANSFORM, some patients were categorized under “Not collected or Reported” due to local regulation of sensitive data collection Due to uncertainties in the definition of this category between TRANSFORM and ZUMA-

			7, adjustment on this factor was not feasible
Region	North America, Europe, Israel, Australia	North America, Europe, Japan	TRANSFORM patients from Japan and ZUMA-7 patients from Israel and Australia to be re-categorized as "Other" given they do not no fall into any particular region categories
Disease Histology	• DLBCL NOS (ABC or GCB) • tFL • High grade BCL with or without MYC and BCL2 and/or BCL6 rearrangements (DHL/THL) • THRBCL • Primary cutaneous DLBCL, leg type • EBV+ DLBCL	• DLBCL NOS • tFL • High grade BCL with MYC and BCL2 and/or BCL6 rearrangements (DHL/THL) • PMBCL • THRBCL • FL3B • tiNHL (other than FL)	Remove patients who have FL3B, PMBCL and tiNHL in TRANSFORM to align with ZUMA-7 categorizations Merge THRBCL, Primary cutaneous DLBCL, leg type, and EBV+ DLBCL into the "Other" category[b]
Double or Triple Hit	Double Hit: C-MYC, BCL-2 or BCL-6 genomic alterations by FISH Triple Hit: BCL-2, BCL-6, and C-MYC alterations by FISH	Rearrangement of MYC plus BCL-2, BCL-6, or both genes	None
Other prognostic markers	Double-expressor lymphoma, MYC rearrangement	MYC rearrangement	Do not use as it overlaps with the "Double or Triple Hit" variable
Cells of Origin	GCB, ABC, unclassified, not applicable, missing	GCB, ABC, Unknown	Recategorize cell of origin to GCB, ABC, unknown where patients in ZUMA-7 who had unclassified, not applicable are group into unknown
ECOG PS at Screening	0 or 1	0 or 1[a]	None
ECOG PS at Baseline	0, 1	0, 1, 2[a]	None
sAAIPI	sAAIPI at randomization: 0-1, 2-3	sAAIPI at screening (per IPD): 0-1, 2-3	None

Relapsed or Refractory Status	Refractory disease: PD, SD as best response after at least 4 cycles of first-line therapy or PR as best response after at least 6 cycles of first line therapy Relapsed disease: complete remission to first-line therapy followed by biopsy-proven relapse ≤ 12 months of first-line therapy	Refractory disease: SDi, PD, PR or CR with relapse before 3 months Relapsed disease: (defined as CR with relapse on or after lasting at least 3 months but no more than 12 months), to CD20 antibody and anthracycline containing first-line therapy for disease under study.	Redefine to align with ZUMA-7 definition. TRANSFORM patients who had CR with relapse before 3 months to be reassigned to relapse status per ZUMA-7 definition.
Baseline Disease Stage	I or II, III or IV	I, II, III, IV	Recategorize to ZUMA-7 definition
Tumor Burden as Measured by SPD	Tumor burden determine on the basis of SPD of target lesion according to Cheson 2014 (measured in mm^2) by IRC	Tumor burden determine on the basis of SPD of target lesion according Cheson 2014 (measured in cm^2) by IRC	Unit conversion to mm^2 per ZUMA-7 reporting and estimate mean and SD by quantile estimation method [70]
LDH	Categorized as "Elevated"	≥ 500 units per L	None. Due to the lack of threshold for the "Elevated" category in ZUMA-7, this variable was not feasible to be adjusted
Bone Marrow Involvement	Yes, No, Unknown	Yes, No, Unknown	None
Secondary CNS Involvement	Excluded	Included	Remove patients with secondary CNS involvement
ALC	ALC ≥ 100/uL	No ALC criterion stated in eligibility criteria	Remove patients per ZUMA-7 ALC threshold
Bridging Therapy	Corticosteroid therapy only	R-ICE, R-GDP, R-DHAP	None, cannot be adjusted for due to difference in bridging therapy regimens

[a]ECOG eligibility criteria for both trials was a score of 0 or 1. At baseline (i.e., at randomization, there were 3 patients in TRANSFORM who had a ECOG score of 2 [46]. [b]Subgroup analyses indicated consistent results across various evaluable subgroups including target lymphoma subtypes. In this regard, particularly favourable results were observed in patients with r/r PMBCL (ORR 79% and CRR 50%), with KM-plots showing a high rate of durable responses. Moreover, all patients with r/r FL3B who received JCAR017 across all studies achieved CR with JCAR017, and all patients were alive in ongoing remission at the last data cut-off date (19 Jun 2020), with one response lasting 23 months." There is also a discussion in the EPAR that very few patients have these subtypes.

Table 17 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

Baseline Patient Characteristics	ZUMA-7 (Axi-cel) ITT		TRANSFORM (Liso-cel) ITT	
Treatment Arm	**Axi-cel Arm**	**SoC Arm**	**Liso-cel Arm**	**SoC Arm**
N	180	179	92	92
Age, mean (standard deviation)[a]	53 (11.6)	55.7 (10.8)	58.3 (12.6)	54.2 (13.9)
Age, median	58	60	60.0	58.0
Q1, Q3	NR	NR	53.5, 67.5	42.0, 65.0
Range (Min, Max)	21, 80	26, 81	20, 74	26, 75
Age group (years) – n (%)				
<65	NR	NR	56 (60.9)	67 (72.8)
≥65 - <75	NR	NR	36 (39.1)	23 (25.0)
≥75	NR	NR	0	2 (2.2)
≥65	51 (28.3)	58 (32.4)	36 (39.1) [b]	25 (27.2) [b]
Sex, n (%)				
Female	70 (38.9)	52 (29.1)	48 (52.2)	31 (33.7)
Male	110 (61.1)	127 (70.9)	44 (47.8)	61 (66.3)
Race				
American Indian or Alaska Native	0	1 (0.6)	0	0
Asian	12 (6.7)	10 (5.6)	10 (10.9)	8 (8.7)
Black or African American	11 (6.1)	7 (3.9)	4 (4.3)	3 (3.3)
Native Hawaiian or Other Pacific Islander	2 (1.1)	1 (0.6)	0	0
White	145 (81.0)	152 (84.9)	54 (58.7)	55 (59.8)
Not collected or reported	NR	NR	22 (23.9)	25 (27.2)
Other	10 (5.6)	8 (4.5)	2 (2.2)	1 (1.1)
Hispanic or Latino ethnic group				
Yes	10 (5.6)	8 (4.5)	3 (3.3)	3 (3.3)
No	167 (92.8)	169 (94.4)	65 (70.7)	62 (67.4)
Not reported	3 (1.7)	2 (1.1)	24 (26.1)	26 (28.3)

Unknown	NR	NR	0	1 (1.1)
Region, n (%)[c]				
Europe	34 (18.9)	45 (25.1)	29 (31.5)	31 (33.7)
North America	140 (77.8)	130 (72.6)	58 (63)	57 (62)
Other	6 (3.3)	4 (2.2)	5 (5.4)	4 (4.3)
Histology, n (%)				
DLBCL: NOS	110 (61.1)	116 (64.8)	53 (57.6)	50 (54.3)
DLBCL: Transformed from FL	19 (10.6)	27 (15.1)	5 (5.4)	6 (6.5)
DLBCL: Transformed from Indolent Lymphoma (other than FL)	0	0	2 (2.2)	2 (2.2)
FL3B	0	0	1 (1.1)	0
HGBCL	43 (23.9)	27 (15.1)	22 (23.9)	21 (22.8)
PMBCL	0	0	8 (8.7)	9 (9.8)
THRBCL	5 (2.8)	6 (3.4)	1 (1.1)	4 (4.3)
EBV+ DLBCL	2 (1.1)	0	0	0
Primary cutaneous DLBCL	1 (0.6)	0	0	0
Other	0	3 (1.7)	0	0
Double or Triple Hit, n (%)				
Not Applicable	134 (74.4)	137 (76.5)	70 (76.1)	72(78.3)
Unknown	3 (1.7)	15 (8.4)	0	0
Yes	43 (23.9)	27 (15.1)	22 (24.2)	20 (21.7)
Prognostic marker according to central laboratory — n (%)				
HGBCL, double- or triple-hit	31 (17.2)	25 (14.0)	22 (23.9)	20 (21.7)
Double-expressor lymphoma	57 (31.7)	62 (34.6)	NR	NR
MYC rearrangement	15 (8.3)	7 (3.9)	18 (20.9)	17 (19.5)
Not applicable	74 (41.1)	70 (39.1)	NR	NR
Missing data	3 (1.7)	15 (8.4)	1 (1.1)	2 (2.2)
Cell of Origin, n (%)				
ABC, Non-GCB	16 (8.9)	9 (5)	21 (22.8)	29 (31.5)

GCB	109 (60.6)	99 (55.3)	45 (48.9)	40 (43.5)
Unknown	NR	NR	25 (27.2)	23 (25)
Missing	28 (15.6)	41 (22.9)	1 (1.1)	0
Unclassified	17 (9.4)	14 (7.8)	NR	NR
Not applicable	10 (5.6)	16 (8.9)	NR	NR
ECOG PS at Baseline, n (%)				
0	95 (52.8) [d]	100 (55.9) [d]	46 (50.0)	49 (53.3)
1	85 (47.2)	79 (44.1)	45 (48.9)	41 (44.6)
2	0 [d]	0 [d]	1 (1.1)	2 (2.2)
sAAIPI Score, n (%)				
0 or 1	98 (54.4)	100 (55.9)	56 (60.9)	55 (59.8)
2 or 3	82 (45.6)	79 (44.1)	36 (39.1)	37 (40.2)
Relapse/Refractory Status, n (%)				
Refractory	131 (72.8)	133 (74.3)	67 (72.8)	70 (76.1)
Relapsed	48 (26.7)	47 (26.3)	25 (27.2)	22 (23.9)
Disease Stage, n (%)				
Stage I or II	41 (22.8)	33 (18.4)	24 (26.1)	29 (31.5)
Stage III or IV	139 (77.2)	146 (81.6)	68 (73.9)	63 (68.5)
Number of extranodal involvement sites, median (IQR)	NR	NR	1 (0, 2)	1 (0, 2)
SPD				
mean (standard deviation)[a]	3270 (3839.6)	3100.1 (3434.4)	2336.1 (2638.6)	2517.2 (2927.2)
median (range), mm^2	2123 (181, 22538)	2069 (252, 20117)	NR	NR
median (range), cm^2	NR	NR	11.4 (1, 120)	15.7 (1, 224)
>50 cm^2	NR	NR	10 (10.9)	10 (10.9)
LDH ≥500 units per L	NR	NR	10 (10.9)	11 (12.0)
Elevated LDH, n (%)	101 (56.1)	94 (52.5)	NR	NR

Bone Marrow Involvement, n (%)				
No	163 (90.6)	164 (91.6)	82 (89.1)	77 (83.7)
Unknown	0 (0)	0 (0)	1 (1.1)	2 (2.2)
Yes	17 (9.4)	15 (8.4)	9 (9.8)	13 (14.1)
Secondary CNS lymphoma	0	0	1 (1.1)	3 (3.3)
Never achieved complete response or partial with first-line therapy (chemotherapy refractory)	NR	NR	26 (28.3)	18 (19.6)
Best response to first-line therapy				
Complete response	NR	NR	30 (32.6)	28 (30.4)
Partial response	NR	NR	36 (39.1)	46 (50.0)
Stable disease	NR	NR	7 (7.6)	5 (5.4)
Progressive disease	NR	NR	19 (20.7)	13 (14.1)
Not evaluable	NR	NR	0	0
Time from initial diagnosis to randomization, months (range)	NR	NR	7.57 (2.0, 21.5)	7.72 (2.5, 25.4)
CD19+ status on immunohistochemical testing — n (%)	144 (80.0)	134 (74.9)	NR	NR

[a]The mean and standard deviation were estimate from the reported median and range using methods proposed in the study by McGrath et al. [70].
[b]Values were calculated from the age groups in the above rows.
[c]Region was reported in FDA assessment of ZUMA-7.
[d]Only ECOG PS of 1 was reported in ZUMA-7.20 Hence, ECOG of 0 was calculated based on reported values for ECOG PS of 1. Per the eligibility criteria for ZUMA-7, all patients with ECOG of 0 or 1 were eligible for the trial, no patients would have ECOG PS of 2.
Data source: As reported from ZUMA-7 and TRANSFORM [43, 47]. For ZUMA-7, percentages were reported without decimal place in Locke 2022. Therefore, they may be re-calculated based on reported sample size to report 1 decimal place.

Before MAIC was conducted, baseline characteristic data for TRANSFORM were aligned in definition and categorization to that reported by ZUMA-7 per the actions described in Table 16.

For the MAIC approach, ITCs were formed by “matching” and “adjusting” patients from TRANSFORM to match the eligible patient population and marginal distribution (e.g., mean and variance) of baseline characteristics in patients who received the comparator intervention (axi-cel). Matching consisted of aligning trials on inclusion/exclusion criteria and is required for the positivity assumption of causal inference to be met. Positivity requires that all patients have a non-zero probability of being assigned to either trial, and violations of positivity can bias estimates of treatment effects and their variance [71]. Patients from TRANSFORM were excluded from the IPD set if they would not have satisfied the eligibility criteria used in the ZUMA-7 trial.

After completing the matching phase of the MAIC, patients remaining from TRANSFORM were weighted using a method-of-moments propensity score algorithm [72]. Therefore, adjusting consisted of weighting patients in TRANSFORM so that they represented a population more similar to that of ZUMA-7.

The eligibility criteria and baseline characteristics (together, "clinical factors") that were deemed most likely to be treatment effect modifying were identified and prioritized for the adjustments.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

As described in section 6.1.1, TRANSFORM and ZUMA-7 are phase 3, randomized, open-label, multi-center studies in adult patients with LBCL who were refractory or relapsed within 12 months from first-line therapy. The ITT patient populations in these trials are considered representative of the population eligible for treatment with CAR-T in Denmark. Nonetheless, patients in TRANSFORM and ZUMA-7 were younger (median baseline age 60 and 58 years old in the liso-cel and axi-cel arms, respectively) compared to Danish clinical practice (median age at DLBCL diagnosis is 67 years old) [36].

The model (cost-minimization) baseline inputs related to patient characteristics are body surface area (BSA) and glomerular filtration rate (GFR), used in the calculation of bridging therapy costs before liso-cel administration (Table 18). The BSA was derived from the TRANSFORM study [46], and the GFR was an assumption derived from the National Kidney Foundation [73].

Table 18 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (assumption)	Value used in health economic model
Body surface area (m^2)	1.92	1.92 [46]
Glomerular filtration rate (mL/min/1.73 m^2)	93	93 [73]

6.1.4 Efficacy – results in TRANSFORM and ZUMA-7

The patient disposition in TRANSFORM and ZUMA-7 is presented in Figure 6 and Figure 7, respectively. Key efficacy outcomes examined included EFS, PFS, OS, ORR, and CRR

A summary of the key efficacy findings in both trials is presented below. The data was derived from the 13 May 2022 DCO of the TRANSFORM study [51], and on the 18 March 2021 DCO of the ZUMA-7 study [47]. The median study follow-up time at these DCOs was 17.5 months 24.9 months for TRANSFORM and ZUMA-7, respectively.

6.1.4.1 Event-free Survival (EFS)

Both liso-cel and axi-cel showed longer median EFS and a statistically significantly lower rate of EFS events compared to the SoC arms in their respective trials (HR for liso-cel vs. SoC: 0.37, 95% CI: 0.26, 0.54; HR for axi-cel vs. SoC: 0.40, 95% CI: 0.31, 0.51) (Table 19, Figure 8).

Table 19 Event-free Survival in ZUMA-7 and TRANSFORM

	Axi-cel (ZUMA-7) ITT					Liso-cel (TRANSFORM) ITT				
Treatment Arm	**Axi-cel Arm**		**SoC Arm**		**Axi-cel vs. SoC**	**Liso-cel Arm**		**SoC Arm**		**Liso-cel vs. SoC**
	N	Median, months (95% CI)	N	Median, months (95% CI)	HR (95% CI)	N or ESS	Median, months (95% CI)	N or ESS	Median, months (95% CI)	HR (95% CI)
	180	8.3 (4.5, 15.8)	179	2.0 (1.6, 2.8)	0.40 (0.31, 0.51)	92	not reached (9.53, not reached)	92	2.4 (2.17, 4.93)	0.37 (0.26, 0.54)

[redacted]

6.1.4.2 Progression-free Survival (PFS)

In their respective trial, both liso-cel and axi-cel showed longer median PFS and statistically significantly lower rate of PFS events compared to the respective SoC arms (HR for liso-cel vs. SoC: 0.43, 95% CI: 0.29, 0.64; HR for axi-cel vs. SoC: 0.49, 95% CI: 0.37, 0.65) (Table 20 and Figure 9).

[redacted]

Table 21 Overall survival in ZUMA-7 and TRANSFORM

	Axi-cel (ZUMA-7) ITT					Liso-cel (TRANSFORM) ITT				
Treatment Arm	**Axi-cel Arm**		**SoC Arm**		**Axi-cel vs. SoC**	**Liso-cel Arm**		**SoC Arm**		**Liso-cel vs. SoC**
	N	Median, months (95% CI)	N	Median, months (95% CI)	HR (95% CI)	N or ESS	Median, months (95% CI)	N or ESS	Median, months (95% CI)	HR (95% CI)
	180	Not reached (28.3, not reached)	179	35.1 (18.5, not reached)	0.73 (0.53, 1.01)	92	not reached (29.55, not reached)	92	29.88 (17.88, not reached)	0.66 (0.41, 1.06)

6.1.4.4 Objective Response Rate (ORR)

In the trials, both liso-cel and axi-cel showed significantly greater ORR compared to the respective SoC arms (OR for liso-cel vs. SoC: 6.96, 95% CI: 3.35, 14.47; OR for axi-cel vs. SoC: 4.94, 95% CI: 3.03, 8.07) (Table 22).

Table 22 Objective Response Rate in ZUMA-7 and TRANSFORM

	Axi-cel (ZUMA-7) ITT					Liso-cel (TRANSFORM) ITT				
Treatment Arm	**Axi-cel Arm**		**SoC Arm**		**Axi-cel vs. SoC**	**Liso-cel Arm**		**SoC Arm**		**Liso-cel vs. SoC**
	N	ORR, %	N	ORR, %	OR (95% CI)	N or ESS	ORR, %	N or ESS	ORR, %	OR (95% CI)
	180	83	179	50	4.94 (3.03, 8.07)	92	87	92	48.9	6.96 (3.35, 14.47)

6.1.4.5 Complete Response Rate

In the trials, both liso-cel and axi-cel showed significantly greater CRR compared to the respective SoC arms (OR for liso-cel vs. SoC: 3.68, 95% CI: 1.98, 6.86); OR for axi-cel vs. SoC: 3.87, 95% CI: 2.50, 6.00) (Table 23).

Table 23 Complete Response Rate in ZUMA-7 and TRANSFORM

	Axi-cel (ZUMA-7) ITT			Liso-cel (TRANSFORM) ITT		
Treatment Arm	**Axi-cel Arm**	**SoC Arm**	**Axi-cel vs. SoC**	**Liso-cel Arm**	**SoC Arm**	**Liso-cel vs. SoC**

	N	CRR, %	N	CRR, %	OR (95% CI)	N or ESS	CRR, %	N or ESS	CRR, %	OR (95% CI)
	180	65	179	32	3.87 (2.50, 6.00)	92	73.9	92	43.5	3.68 (1.98, 6.86)

6.2 Efficacy of liso-cel and axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

6.2.1 Relevant studies

The key clinical trial for efficacy and safety of liso-cel for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy is the TRANSCEND (017001) study. TRANSCEND (017001) (NCT02631044) is a phase 1, open-label, multicenter study.

The key clinical trial for efficacy and safety of axi-cel for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy is the ZUMA-1 study. ZUMA-1 (NCT02348216) is a phase 1/2, single arm, open-label, multicenter study.

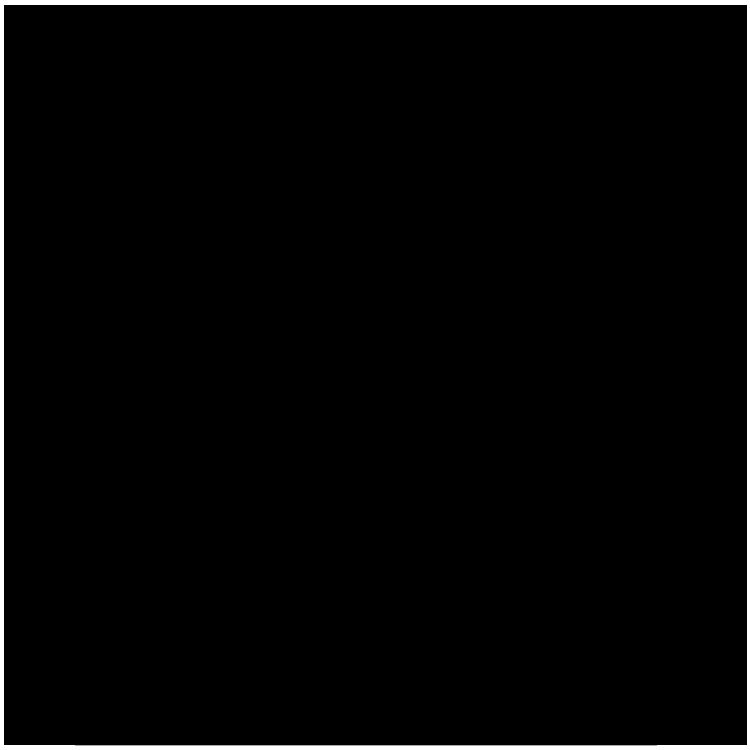
The trial design of TRANSCEND (017001) and ZUMA-1 is presented in

Figure 11 and Figure 12, respectively. The patient disposition is presented in

Figure 13 and Figure 14, respectively.

The analysis is based on the January 2021 DCO of the TRANSCEND (017001) study [59], and on the August 2018 DCO [62], and the August 2020 DCO [61] of the ZUMA-1 study.

[a]Two subjects discontinued from the study prior to leukapheresis: one subject withdrew consent prior to leukapheresis and the other subject died prior to leukapheresis. The third subject had not yet undergone leukapheresis at the time of the data cutoff.
[b]Seven subjects (6 in the DLBCL Cohort and 1 in the MCL Cohort) who underwent leukapheresis were retrospectively determined to have not met inclusion/exclusion criteria.
[e]Includes only subjects who consented during TRANSCEND (017001). Information not available for subjects who consented to LTFU after their final visit in TRANSCEND (017001).
Data as of the 12 Aug 2019 cutoff
Source: [59].



Source: [75]

Table 24 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
TRANSCEND (017001), NCT02631044 [59] [60].	Phase 1, multicenter, open-Label study.	Study start date: 2016-01-06 Estimated primary completion date: 2024-05-10 Estimated study completion date: 2024-05-10	Adult patients with r/r DLBCL, not otherwise specified (NOS; includes transformed DLBCL from indolent histology [transformed iNHL]), HGL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, and FL3B. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have r/r disease after at least 2 lines of therapy or after autologous	N = 344 Following screening and enrollment, subjects underwent leukapheresis to enable generation of liso-cel. If necessary, bridging therapy for disease control was allowed while liso-cel was manufactured. LDC consisting of fludarabine and cyclophosphamide (30 mg/m^2/day and 300 mg/m^2/day, respectively) was administered intravenously for three days, followed by one or two doses (depending on dosing schedule) of liso-cel. In the single-dose schedule, one infusion of liso-cel was	NA.	<u>Primary</u> <u>outcome measures</u> • Treatment-related adverse events (AEs) as assessed by CTCAE v4.03 [Time Frame: Up to 730 days after the final liso-cel infusion]. • Dose-limiting toxicities of liso-cel [Time Frame: 28 days after first (single-dose schedule) or second (2-dose schedule)]. • Objective response rate (ORR) [Time Frame: 24 months]. <u>Secondary outcome measures</u> • Complete response (CR) rate [Time Frame: 24 months]. • Duration of response [Time Frame: 24 months]. • Progression-free survival (PFS) [Time Frame: 24 months]. • Overall survival [Time Frame: Up to 15 years].

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			hematopoietic stem cell transplant (auto-HSCT). Other key inclusion criteria were ECOG performance status of 0 or 1 and adequate organ function.	administered, while in the double-dose schedule, subjects received the first dose as described above, and a second dose of liso-cel 14 days after the first dose (without further LDC between the two doses). The optimal target dose for liso-cel was determined through, dose-finding (DF), dose-expansion (DE), and dose-confirmation (DC) groups and the TRANSCEND (017001) study initially recruited subjects across four dosing regimens: • DL1S: Single dose of 50 × 10^6 CAR+ T cells. • DL2S: Single dose of 100 × 10^6 CAR+ T cells. • DL1D: Two doses of 50 × 10^6 CAR+ T cells. • DL3S: Single dose of 150 × 10^6 CAR+ T cells.		• Health-related quality of life [Time Frame: 24 months]. • Maximum concentration of liso-cel (Cmax) in the peripheral blood [Time Frame: Up to 365 days after the final liso-cel infusion]. • Time to maximum concentration of liso-cel (Tmax) in the peripheral blood [Time Frame: Up to 365 days after the final liso-cel infusion]. • Area-under-the-concentration-vs-time-curve (AUC) in the peripheral blood [Time Frame: Up to 365 days after the final liso-cel infusion]. <u>Exploratory outcomes</u> • Probability of CR. • Anti-therapeutic antibodies to liso-cel. • B-cell, Plasma and TME changes. • Liso-cel product characteristics. • Evaluation of tumor biopsies.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
ZUMA-1, NCT02348216 [61, 62]	Phase 1/2, single arm, open-label, multicenter study.	Study start date: 2015-04-21 Primary completion date: 2020-09-10 Study completion date: 2023-07-27	Adult patients with r/r LBCL, including DLBCL[a] NOS, PMBCL, HGBL, and TFL after 2 or more lines of systemic therapy. Subjects must have received adequate prior therapy including at a minimum anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20-negative and an anthracycline containing chemotherapy regimen. Subjects with transformed FL must have chemo-refractory disease after transformation to DLBCL.	N = 111 3 day lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day on Treatment Days −5 to −3 followed by 2 rest days (before axi-cel IV infusion on Treatment Day 0) at a target dose of 2 × 10^6 anti CD19 CAR T cells/kg body weight.	NA.	<u>Primary outcome measures:</u> • Phase 1 Study: Number of Participants Experiencing Adverse Events (AEs) Defined as Dose Limiting Toxicities (DLTs) [Time Frame: First infusion date of axi-cel up to 30 days]. • Phase 2 Pivotal Study (Cohorts 1 and 2): Overall Response Rate (ORR) as Assessed by Investigator Per Revised International Working Group (IWG) Response Criteria for Malignant Lymphoma [Time Frame: First infusion date of axi-cel to the data cut-off date of 27 January 2017 (maximum: 20 months)]. • Phase 2 Safety Management Study (Cohort 3): Percentage of Participants With Treatment-Emergent Cytokine Release Syndrome (CRS) and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axi-cel to the data cut-off of

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			Other key inclusion criteria were ECOG performance status of 0 or 1 and adequate renal, hepatic, pulmonary and cardiac function.			26 April 2018 (maximum: 35 months)]. • Phase 2 Safety Management Study (Cohort 4): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axi-cel to the data cut-off of 06 May 2019 (maximum: 47.5 months)]. • Phase 2 Safety Management Study (Cohort 5): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axi-cel to the data cut-off of 10 September 2020 (maximum: 64 months)]. • Phase 2 Safety Management Study (Cohort 6): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axi-cel to the data cut-off of

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						16 June 2020 (maximum: 61 months)]. <u>Secondary outcome measures:</u> • Phase 2: Duration of Response (DOR) as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First OR to data cutoff date of 27 Jan 2017, 26 Apr 2018, 6 May 2019, 10 Sep 2010, and 16 Jun 2020 for Cohorts 1 and 2, 3, 4, 5, and 6 respectively (median duration: 5.3, 4.9, 11.1, 5.2, 11.4, and 5.8 months for Cohorts 1, 2, 3, 4, 5, and 6 respectively)]. • Phase 1 Study: ORR as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First infusion date of axi-cell to the data cutoff date of 27 January 2017 (maximum: 20 months)]. • Phase 2 Pivotal Study (Cohorts 1 and 2): ORR Per Independent Radiological Review Committee

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						(IRRC) [Time Frame: First infusion date of axi-cel to the data cutoff date of 27 January 2017 (maximum: 20 months)]. • Phase 2 Safety Management Study (Cohorts 3, 4, 5, and 6): ORR as Assessed by Investigator Per the Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First infusion date of axi-cel to the data cut-off date of 26 Apr 2018, 06 May 2019, 10 Sep 2020, and 16 Jun 2020 for Cohorts 3, 4, 5, and 6 respectively (maximum: 35, 47.5, 64, and 61 months for Cohorts 3, 4, 5, and 6 respectively)]. • Phase 2: Progression-Free Survival (PFS) as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First infusion date to PD or death or data cut-off date 27 Jan 2017, 26 Apr 2018, 06 May 2019, 10 Sep 2020, and 16 Jun 2020 for Cohorts 1 and 2, 3, 4, 5, 6

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						respectively (maximum: 20, 35, 47.5, 64, and 61 months for Cohorts 1 and 2, 3, 4, 5, 6 respectively)]. • Phase 2: Overall Survival (OS) [Time Frame: First infusion date to the death or data cut-off date of 27 Jan 2017, 26 Apr 2018, 6 May 2019, 10 Sep 2020, and 16 Jun 2020 for Cohorts 1 and 2, 3, 4, 5, 6 respectively (maximum: 20, 35, 47.5, 64, and 61 months for Cohorts 1 and 2, 3, 4, 5, 6 respectively)]. • Phase 2 Pivotal Study (Cohorts 1 and 2): Duration of Response (DOR) Using IRRC Per Cheson 2007 [Time Frame: First objective response to the data cut-off date of 27 January 2017 (maximum: 20 months)]. • Phase 2 Pivotal Study (Cohorts 1 and 2): Best Overall Response Using IRRC Per Cheson 2007 [Time Frame: First infusion date of axi-cel to the data cutoff date of 27 January 2017 (maximum: 20 months)].

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						• Phase 2 Pivotal Study (Cohorts 1 and 2): PFS Using IRRC Per Cheson 2007 [Time Frame: First infusion date of axi-cel to the date of disease progression or death from any cause or the data cutoff date of 27 January 2017 (maximum: 20 months)]. • Phase 2 Safety Management Study: Number of Participants With the European Quality of Life Five Dimension Five Level Scale (EQ-5D) Score [Time Frame: Baseline, Week 4, Month 3, and Month 6]. • Phase 2 Safety Management Study: EQ-5D Visual Analogue Scale (VAS) Score [Time Frame: Baseline, Week 4, Month 3, and Month 6]. <u>Other safety outcomes:</u> • Pharmacokinetic and Pharmacodynamic outcomes.

[a]In Cohorts 1 through 3, DLBCL included HGBL which was introduced by the World Health Organization as a distinct category of LBCL in 2016.

6.2.2 Comparability of studies

A thorough qualitative comparison of the pivotal trials of liso-cel (Study 017001) and axi-cel (ZUMA-1) was conducted to assess the feasibility of ITCs in terms of the following factors [76]:

- Study design and eligibility criteria, including clinical and diagnostic definitions for key outcomes of interest, study treatment protocols (such as use of bridging therapy), and median follow-up time.
- Reporting of baseline characteristics, efficacy outcomes, and safety outcomes.
- Clinical definitions of baseline characteristics and reported categorizations of clinical variables.
- Quantitative assessment of the degree of imbalances between studies across baseline clinical factors.

Analyses of interest included all patients who were enrolled and had received CAR T-cell therapy in trials (infused patients) [76].

Comparison of the study design, eligibility criteria, and baseline characteristics of Study 017001, and ZUMA-1 showed sufficient similarities between the studies to allow comparison, but revealed differences across trials necessitating the conduct of an MAIC to reduce bias when indirectly comparing liso-cel to axi-cel [76].

Large differences in the definitions or categorizations of patient characteristics such as IPI score, disease histology, number of prior lines of therapy, and R/R to last therapy between trials were reduced by redefining the variables within the liso-cel IPD to align more closely to those in the comparator study (ZUMA-1) [76].

Investigation of outcome definitions and data availability indicated that MAICs are feasible for all 4 efficacy outcomes of interest (i.e., ORR, CRR, PFS, and OS) in comparisons of liso-cel to axi-cel. For AESI, MAICs are feasible for grade 3 or 4 TEAEs, CRS, study-defined NT, NEs per ND/PD SOC, study-defined NT of encephalopathy, encephalopathy per ND/PD SOC, study-defined NT of aphasia, aphasia per ND/PD SOC, infections, hypogammaglobulinemia, and febrile neutropenia in comparisons of liso-cel to axi-cel. MAICs of grade ≥ 3 and grade 5 TEAEs are also possible for liso-cel versus axi-cel [76].

MAICs were conducted to determine the relative efficacy of liso-cel dose levels DL1S + DL2S + DL1D (from Study 017001) compared to axi-cel (from ZUMA-1) [60].

[redacted]

6.2.2.1 Comparability of patients across studies

Comparison of definitions for baseline characteristics identified some differences between Study 017001 and ZUMA-1 (Table 25). Of the 22 baseline patient characteristics reported in both trials, definitions or minimum/maximum threshold differed between the studies for the following 9 patient characteristics: IPI score, tumor burden, disease histology, number of prior lines of therapy, R/R to last therapy, and CrCl prior to lymphodepleting chemotherapy, LVEF at screening, and absolute lymphocyte count before leukapheresis. The definitions or categorizations for these patient characteristics used in Study 017001 were aligned by either reclassifying or recalculating the corresponding variables within the Study 017001 IPD to match classifications or definitions reported in ZUMA-1 (details presented in Table 25). Definitions and/or categorizations for the remaining patient characteristics were similar between the 2 trials [76].

Table 25 Comparison of Baseline Characteristics Definitions between Study 017001 and ZUMA-1

Baseline Characteristics	Study 017001 (Liso-cel)	ZUMA-1 (Axi-cel)	Action Taken in Study 017001 IPD and Rationale
Age	In years	In years	None
Sex	Male, Female	Male, Female	None
IPI Score	0; 1; 2; 3; 4; 5	0-2; 3-4; 5	Recategorized in Study 017001 to align with ZUMA-1 categorization
ECOG PS at Screening	0; 1; 2	0; 1	None
Disease Stage	I-II; III-IV	I-II; III-IV	None
Tumor Burden	SPD (cm^2) measured at enrollment and before lymphodepleting chemotherapy Assessed by IRC and INV	SPD (cm^2) measured before lymphodepleting chemotherapy Assessed by INV	Considering bridging therapy may have impacted tumor burden[a] for patients in Study 017001, tumor burden SPD from enrollment was used for patients who received bridging therapy, and tumor burden SPD from before lymphodepleting chemotherapy was used for patients who did not receive bridging therapy. INV-assessed SPD was used
Secondary CNS Involvement at Time of Treatment	Allowed	Not allowed (Excluded per protocol)	None
Extranodal Disease	Allowed	Allowed	None

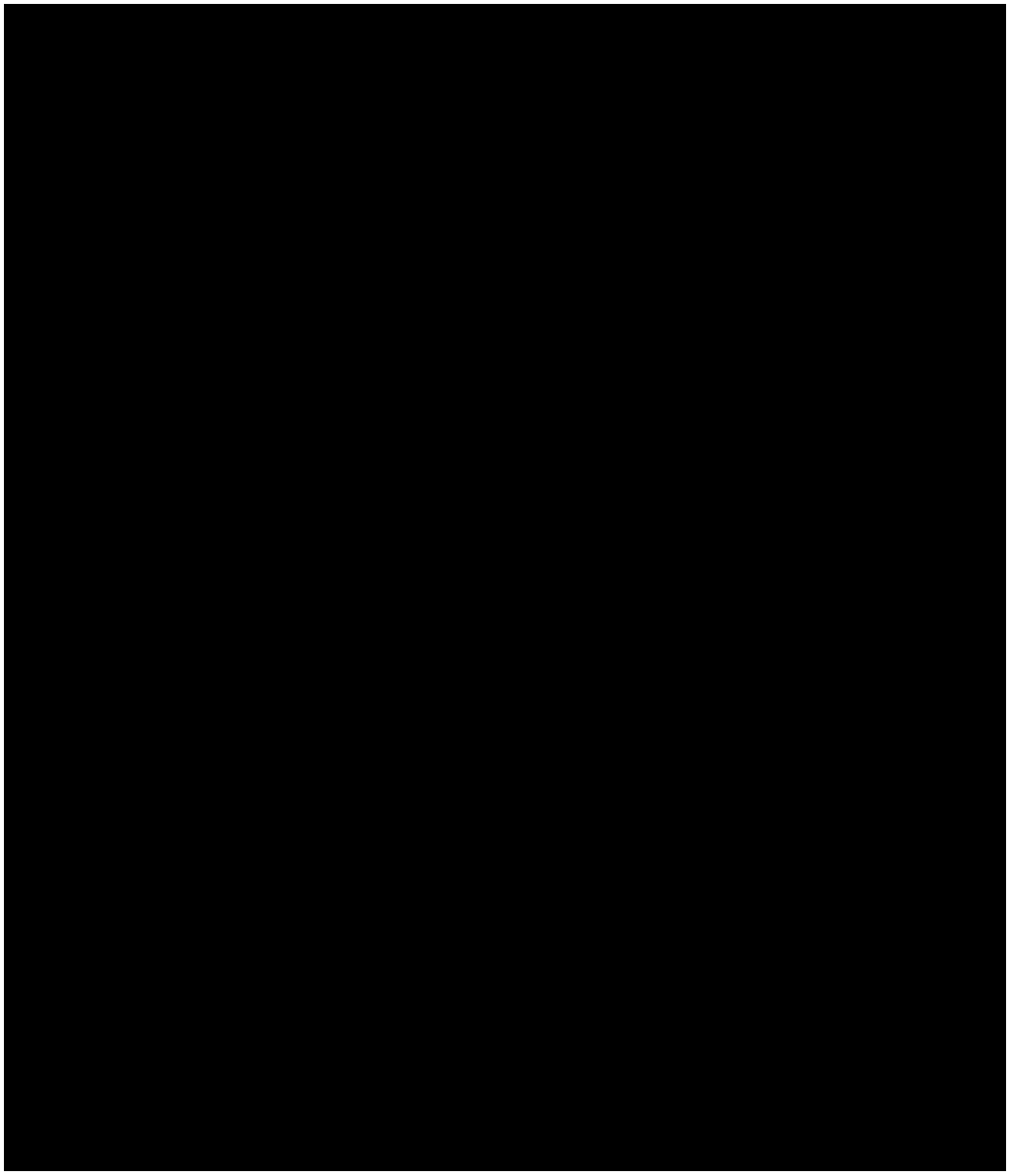
Baseline Characteristics	Study 017001 (Liso-cel)	ZUMA-1 (Axi-cel)	Action Taken in Study 017001 IPD and Rationale
Bulky Disease	Single nodal mass of ≥ 10 cm by CT based on Lugano classification [25]	Single lesion with largest diameter 10 cm or larger or mediastinum wider than 1/3 of the chest on a chest x-ray	None, as definitions were similar between Study 017001 and ZUMA-1
Disease Histology	DLBCL NOS, HGL, tFL, tiNHL, PMBCL, FL3B	DLBCL NOS[b], HGL[c]; PMBCL, tFL	Recategorized Study 017001 to align with ZUMA-1 definition for DLBCL to retain Study 017001 patients. Specifically, DLBCL NOS, HGL, and tiNHL from Study 017001 were grouped together in "DLBCL" for comparison to "DLBCL" category in ZUMA-1
Cell of Origin	GBC; ABC; Unknown	GBC; ABC; Unknown	None
Number of Prior Lines of Therapy	Assessed number of prior systemic lines of therapy, where systemic therapy did not include HSCT, only chemotherapies	Salvage chemotherapy and auto-HSCT were considered separate regimens	Redefined in Study 017001 such that salvage chemotherapy and auto-HSCT were considered as 2 separate lines of therapy to align with ZUMA-1 definition
Prior Allo-HSCT	Allowed	Not allowed (Excluded per protocol)	None
Prior Auto-HSCT	Allowed	Allowed	None
Bridging Therapy	Allowed	Not allowed (Excluded per protocol)	None
R/R to Last Therapy	Refractory: Best response to last therapy as progressive disease, stable disease, or PR Relapsed: Best response to last therapy as CR	Refractory: Best response to last therapy[d] as progressive disease or stable disease Relapsed: best response to last therapy[d] of PR or CR	Redefined in Study 017001 to align with ZUMA-1 definition. Specifically, in Study 017001, % refractory to last therapy was rederived to include progressive disease and stable disease, whereas % relapse was rederived to include PR and CR
CrCl prior to Lymphodepleting Chemotherapy	> 30 mL/min	≥ 60 mL/min	Redefined in Study 017001 to align with ZUMA-1 definition
LVEF at Screening	≥ 40%	≥ 50%	Redefined in Study 017001 to align with ZUMA-1 definition
Pre-leukapheresis Absolute Lymphocyte Count (× 10^9/L)	Adequate bone marrow function, assessed by INV	≥ 0.1	Redefined in Study 017001 to align with ZUMA-1 definition

Baseline Characteristics	Study 017001 (Liso-cel)	ZUMA-1 (Axi-cel)	Action Taken in Study 017001 IPD and Rationale
Double or Triple Hit	Rearrangement of *MYC* plus *BCL-2*, *BCL-6*, or both genes	*MYC+* and *BCL-2+* and/or *BCL-6+* by fluorescence in situ hybridization	None
History of Any Hematologic Comorbidities	Neutropenia, thrombocytopenia, and anemia, assessed at screening, assessed by laboratory values	Neutropenia, thrombocytopenia, and anemia before lymphodepleting chemotherapy, assessed by laboratory values	None

[a]Bridging therapy was not allowed in ZUMA-1. Therefore, using SPD measured prior to lymphodepleting chemotherapy for patients who received bridging therapy in Study 017001 might not best reflect the baseline SPD for these patients. Nonetheless, an analysis of pre- and post-bridging INV-assessed SPD in Study 017001 showed that the difference was minor [38].
[b]ZUMA-1 histology was classified according to WHO 2008 classification. tiNHL was included under DLBCL NOS histology per WHO 2008 [77], and patients with tiNHL were included in ZUMA-1 per study protocol [62].
[c]To clarify, this group was included in the DLBCL histology in axi-cel [75].
[d]ZUMA-1 did not report a definition of "last therapy", thus, was assumed as any therapy received by the patient before entering study.

Baseline characteristics from Study 017001 DLBCL Efficacy Set dose levels DL1S + DL2S + DL1D (04 Jan 2021 data cut) and Axi-cel Phase 2 mITT Set (11 Aug 2020 data cut) are compared in Table 26. Many factors are similar between the dose levels DL1S + DL2S + DL1D from Study 017001 and the infused patients from ZUMA-1. Differences between trials were observed for disease stage, tumor burden, extra-nodal disease, prior allo-HSCT, prior autologous hematopoietic stem cell transplant (auto-HSCT), bridging therapy, R/R to last therapy, and CrCl prior to lymphodepleting chemotherapy [60].

Importantly, these baseline characteristics exhibited sufficient overlap, which allows for additional adjustment to align study populations more closely [60].



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[redacted]

Relevant clinical factors (i.e., study eligibility criteria and baseline characteristics) for matching and adjusting were identified through a targeted literature search of evidence on clinical factors prognostic of outcomes in 3L+ treatment of R/R large B-cell lymphoma, inspection of clinical factors reported in TRANSCEND (017001), and ZUMA-1 trials, and

input from external clinical experts. A final ranked list of clinical factors important for each efficacy outcome and all AESI was derived using an evidence-informed ranking process that considered both ranks by clinical experts and statistical approaches [76].

For each comparison, patients from TRANSCEND (017001) were removed from the IPD set if they did not satisfy the eligibility criteria and treatment protocol of ZUMA-1 (matching phase) [76].

For each comparison, after completing the matching phase of the MAIC, the patients that remained and were included from TRANSCEND (017001) were weighted using a method-of-moments propensity score algorithm [76].

6.2.3 Comparability of the study population(s) with Danish patients eligible for treatment

As described in section 6.2.1, TRANSCEND (017001) and ZUMA-1 are phase 1/2, single arm, open-label, multicenter studies in adult patients with r/r LBCL after at least 2 lines of therapy. The patient populations in these trials are considered representative of the population eligible for treatment with CAR-T in Denmark.

The only model (cost-minimization) baseline input related to patient characteristics was body surface area (BSA), used in the calculation of bridging therapy costs before liso-cel administration (Table 27). The BSA was derived from the TRANSCEND (017001) study [78].

Table 27 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (assumption)	Value used in health economic model
Body surface area (m^2)	1.94	1.94 [78]

6.2.4 Efficacy – results in TRANSCEND (017001) and ZUMA-1

The patient disposition in TRANSCEND (017001) and ZUMA-1 is presented in

Figure 13 and Figure 14, respectively.

Key efficacy outcomes examined included progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and complete response rate (CRR).

A summary of the datasets used for each trial and efficacy outcome is shown in Table 28.

A summary of the key efficacy findings in both trials is presented below.

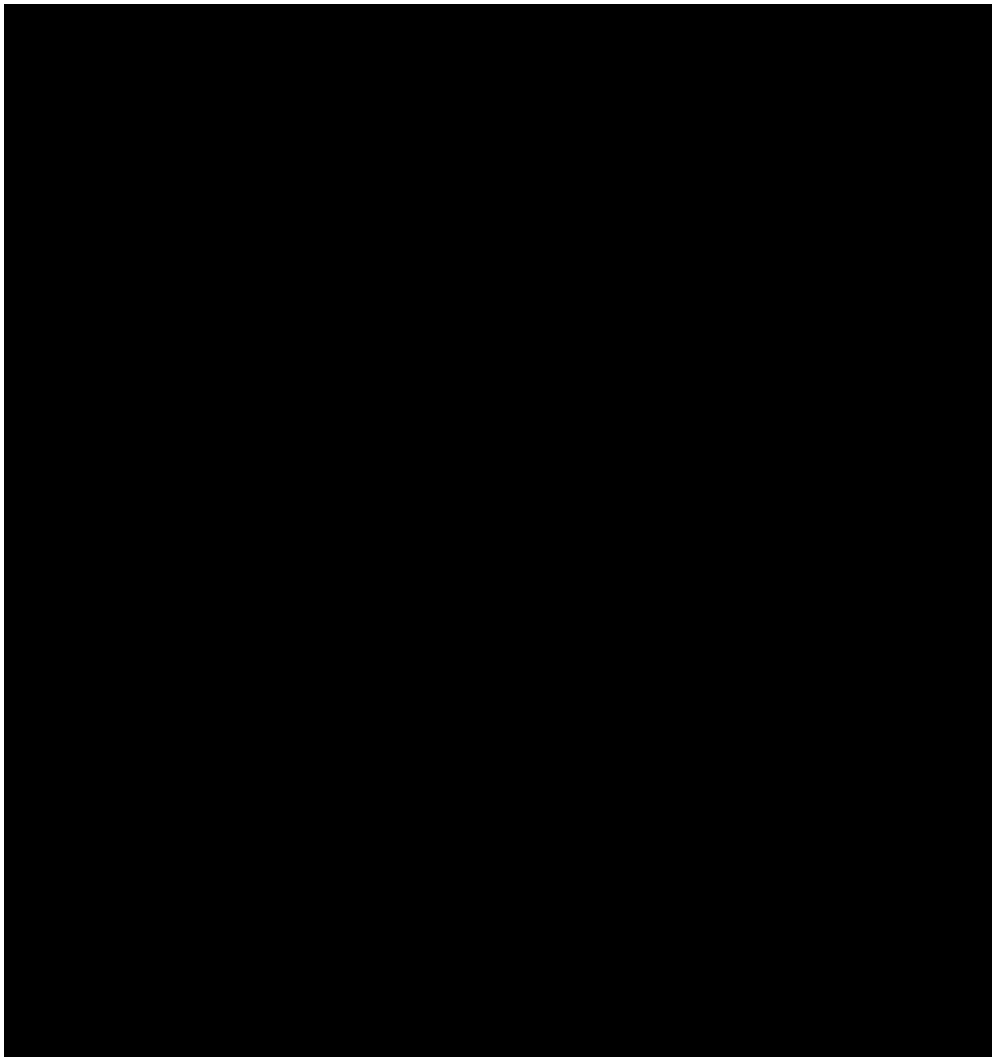
Table 28 Summary of the datasets used for TRANSCEND (017001) and ZUMA-1

Treatment	Trial name	Data cut-off	Primary data source	Median study follow-up, months (range)	Analysis Set	N
Efficacy outcomes						
Liso-cel	TRANSCEND (017001)	January 2021	IPD	31.0 (95% CI 28.7, 35.4)[a]	DLBCL Efficacy Set Dose Levels DL1S + DL2S + DL1D	216
Axi-cel – OS	ZUMA-1	August 2020	[61]	51.1 (NR)[b]	Phase 2 mITT Set	101
Axi-cel – PFS, ORR, CRR	ZUMA-1	August 2018	[62]	27.1 (IQR 25.7-28.8)[b]	Phase 2 mITT Set	101

[a]The median follow-up time for OS was 31.0 months (95% CI 28.7, 35.4) and is reported in the table. The median follow-up time for PFS was 23.9 months (95% CI 23.6, 24.0). Both were calculated using the reverse Kaplan-Meier method.
[b]Definition not reported.
Cut-off date of January 2021 for Study 017001.

6.2.4.1 Progression-free survival (PFS)

[redacted]



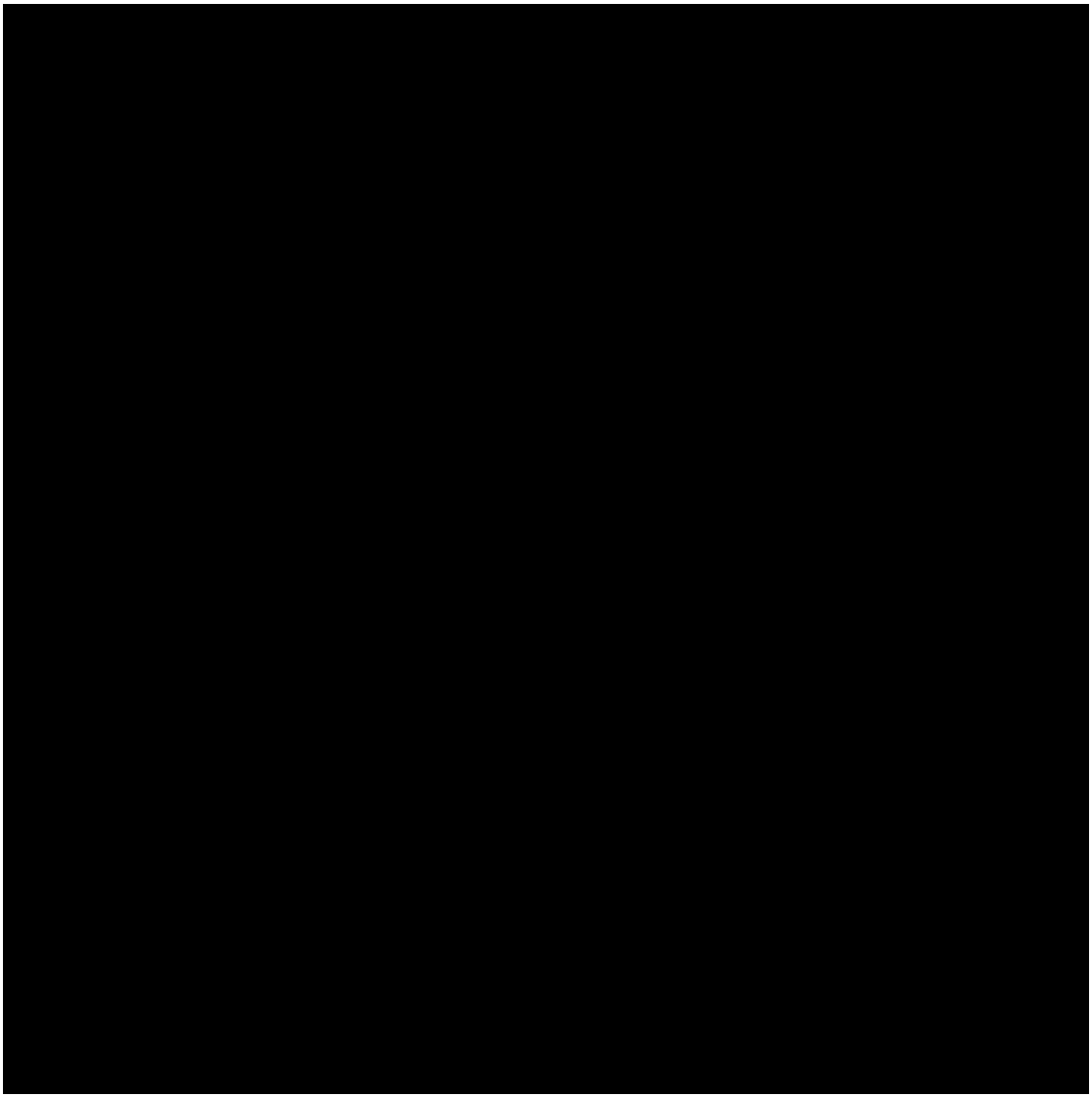
[redacted]

6.2.4.2 Overall survival (OS)

[redacted]

The KM curves demonstrated similar survival for liso-cel and axi-cel for the naïve analysis (Figure 17) [60].

[redacted]



6.2.4.3 Objective response rate (ORR)

[redacted]

6.2.4.4 Complete response rate (CRR)

[redacted]

7. Comparative analyses of efficacy

7.1 Liso-cel compared to axi-cel for the treatment of adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

7.1.1 Differences in definitions of outcomes between studies

Efficacy outcomes evaluated were EFS, PFS, OS, ORR, and CRR. Overall, the definitions were similar between trials (Table 31). Both TRANSFORM and ZUMA-7 used the Lugano classification [25], to define response criteria behind EFS, PFS, ORR and CRR. Both trials reported EFS, ORR, and CRR per IRC assessment. However, while TRANSFORM reported PFS by IRC-assessment, ZUMA-7 reported PFS as assessed by investigator only, which prevented comparison of IRC-assessed PFS [47].

Previous work suggested that the definition of EFS was not aligned between TRANSFORM and ZUMA-7 [79]. Thus, a detailed comparison of each event criteria and censoring rule for EFS was conducted. Notably, in TRANSFORM, patients with best response of SDi by 9 weeks post randomization (after 3 cycles of SoC for SoC Arm and 5 weeks after liso-cel) were considered as having an EFS event. In ZUMA-7, on the other hand, subjects with best response of SDi up to and including Day 150 (i.e., roughly 21.4 weeks) assessment post randomization were considered as having an EFS event. Nonetheless, for these ZUMA-7 patients, EFS time was calculated to the first SDi established, which would likely be earlier than the Day 150 assessment (e.g., Day 50 or Day 100 assessment per ZUMA-7 assessment schedule. Therefore, the difference on response assessment time for patients with best response of SDi should be less pronounced between trials than the initial difference in assessment time points suggest [52].

Additionally, immediate drops were observed in the ZUMA-7 axi-cel and SoC KM curves for EFS (i.e., at time 0, or Day 1, of the KM curves) (Figure 8). The immediate drops may be explained by the EFS event rule “Subjects who commence new lymphoma therapy in the absence of any evaluable disease assessment will have the EFS event date imputed as the randomization date”. Importantly, a larger drop was observed for the SoC arm than for the axi-cel arm. It is perceivable that this criterion of commencing new lymphoma therapy in the absence of any evaluate disease assessment would be more prevalent in the SoC arm and therefore bias the comparison in favor of axi-cel [52]. Indeed, this was observed and expressed as a potential concern by the European Medicines Agency (EMA) in their European public assessment report (EPAR) for axi-cel [75].

In the TRANSFORM trial, patients who received new antineoplastic therapy for reasons other than efficacy concerns were censored instead [46]. This difference is expected to have minimal impact on the comparison between liso-cel and axi-cel if anchoring through respective SoC arms, since within each trial the same approach was taken to the timing of events between randomization and treatment [52].

Table 31 Comparison of Efficacy Outcome Definitions between TRANSFORM and ZUMA-7

Outcome	TRANSFORM (Liso-cel)[a]	ZUMA-7 (Axi-cel)[b]
EFS	Time from randomization to (whichever occurs first): death from any cause, progressive disease, start of new antineoplastic therapy due to efficacy concerns, or failure to achieve CR or PR by 9 weeks post-randomization.	Time from randomization to (whichever occurs first): death from any cause, progressive disease, or commencement of new lymphoma therapy. The following criteria will be used to further define events and event times: • Subjects with established PR or CR and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the last evaluable disease assessment prior to the new lymphoma therapy. • Subjects with best response of SDi and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the first time SDi was established prior to the new lymphoma therapy. • Subjects who commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of any evaluable disease assessment will have the EFS event date imputed as the randomization date. • Subjects with best response of SDi up to and including Day 150 assessment post randomization will be considered to have an EFS event. For such subjects, the EFS time will be defined as the time from randomization to the first time SDi was established up to and including the Day 150 disease assessment.

PFS	Time from randomization to progressive disease or death from any cause, whichever occurs first.	Time from randomization to disease progression per Lugano Classification [25] or death from any cause.
OS	Time from randomization to time of death due to any cause.	Time from randomization to death from any cause.
ORR	Percentage of subjects achieving a PR or better [25].	The incidence of either a CR or a PR by the Lugano Classification as determined by blinded central review [25]
CRR	Percentage of subjects achieving a CR [25].	Percentage of subjects achieving a CR[c] [25]

[a]For TRANSFORM, all response criteria behind EFS, PFS, ORR, and CRR were based on Lugano Classification [25] and were IRC-assessed.
[b]For ZUMA-7, all response criteria behind EFS, PFS, ORR, and CRR were based on Lugano Classification [25]. EFS, ORR, and CRR were IRC-assessed. PFS was assessed by INV.
[c]Reported as part of ORR definition per ZUMA-7 ClinicalTrials.gov record (NCT#03391466) [45].

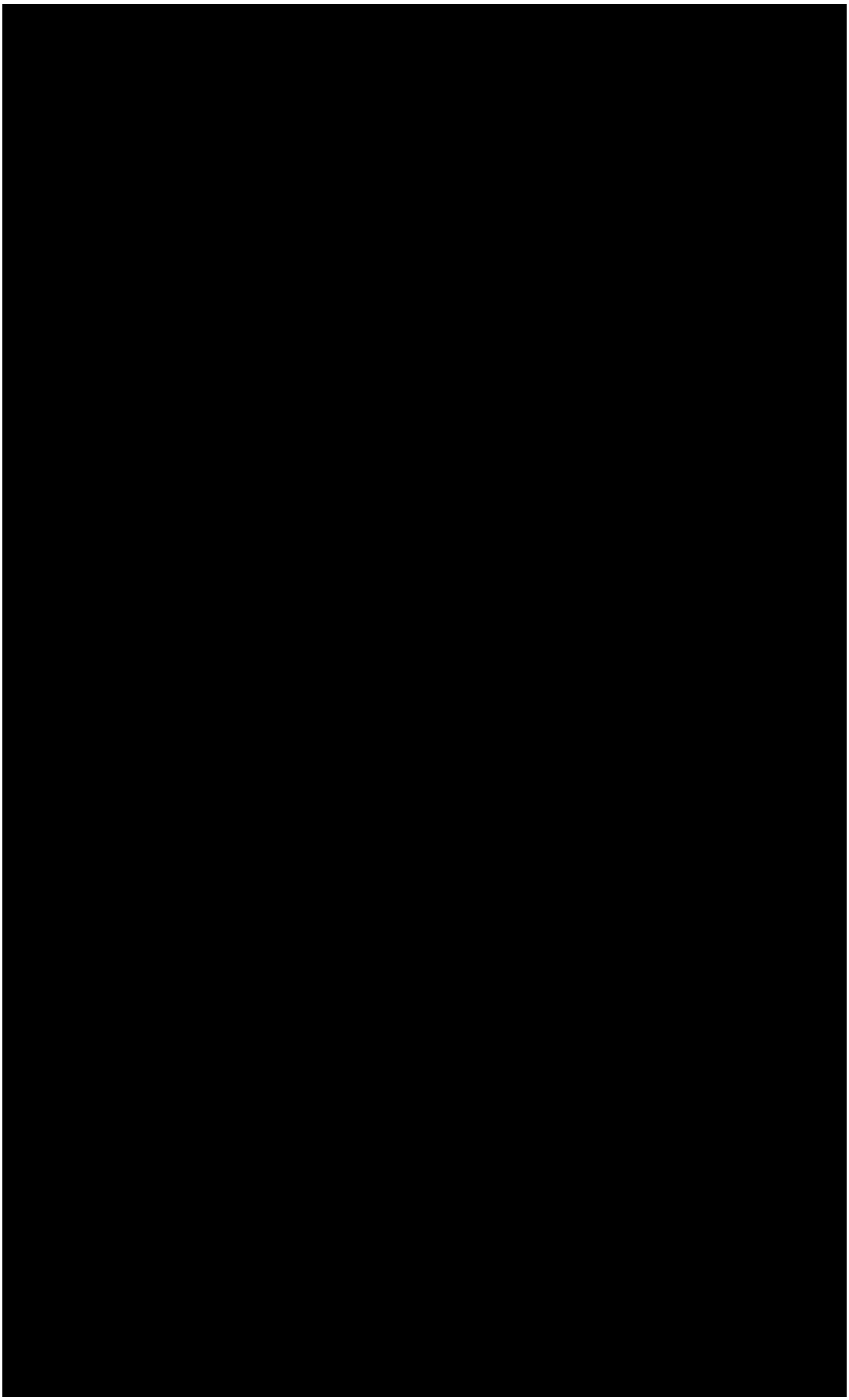
7.1.2 Method of synthesis

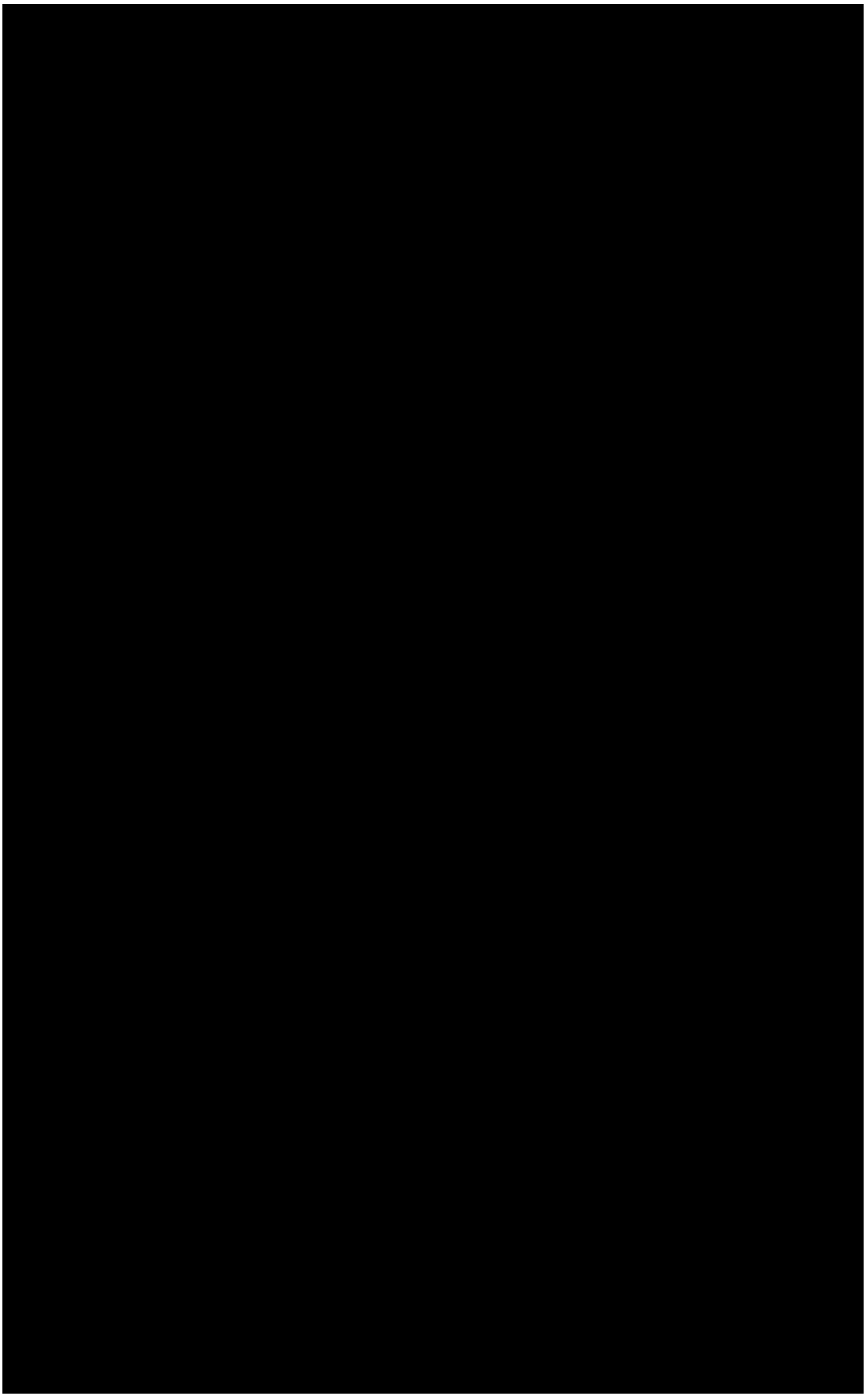
Please see Appendix C.

7.1.3 Results from the comparative analysis

The efficacy results from the comparative analysis (MAIC) of liso-cel vs. axi-cel for the treatment of adult patients with Large B-cell lymphoma who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy are summarized in Table 32. For further information on the efficacy results, see section 7.1.4.

The primary MAIC scenario of efficacy outcomes included 10 highly ranked clinical factors to ensure sufficient effective sample size (ESS) across all efficacy outcome comparisons. Three of the ranked clinical factors (i.e., disease histology, secondary CNS involvement, ALC) related to trial eligibility criteria, and were used as matching criteria (i.e., patients in TRANSFORM who did not satisfy these criteria were excluded). Among the adjusting factors, patient demographic factors (age, sex, region) were prioritized to ensure alignment between the study populations. An additional 5 top-ranked clinical factors (sAAIPI score, SPD at baseline, R/R status, double or triple hit, disease histology) were then adjusted to further reduce residual imbalances between studies. A sensitivity analysis adjusting for all available factors was also performed. The selection of the primary and sensitivity scenarios was made in consultation with clinical experts and diagnostics, aiming to strike a balance between number of factors included, ESS, distribution of patient weights, and SMD values. The resulting ESS in the liso-cel arm for the primary and sensitivity scenarios was 42 and 27, respectively. For more information on the methodology, see Appendix C.





7.1.4 Efficacy – MAIC of liso-cel vs. axi-cel for the treatment of adult patients with Large B-cell lymphoma who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

7.1.4.1 Event-free Survival

[redacted]

[redacted]

For comparison of EFS between liso-cel and axi-cel, the HRs for unmatched and unadjusted comparison, matched and unadjusted comparison, and each adjusted scenario, sequentially and additionally adding in factors one at a time, is presented in Figure 19. Overall, the HR remains consistent as each additional factor was sequentially added (i.e., scenarios A to I)[52].

Visual inspections of the KM curves (Figure 8, Figure 20, Figure 21), and log cumulative hazard plots (Figure 52, Figure 53, Figure 54) of each study showed that the curves were generally parallel across study arms, supportive of the PH (proportional hazards) assumption. Findings for the TRANSFORM study were also consistent after matching and adjusting for prognostic factors and effect modifiers in both the primary and sensitivity scenarios. Additionally, when comparing active (i.e., liso-cel vs axi-cel) or SoC arms between trials, there was some evidence of cross-over in the KM curves at ≥12 months follow-up, though results are subject to increased uncertainty due to the small number of patients remaining at risk of an event at longer-term follow-up. Together, these findings suggest that the proportional hazard assumption was generally appropriate for both studies[52].

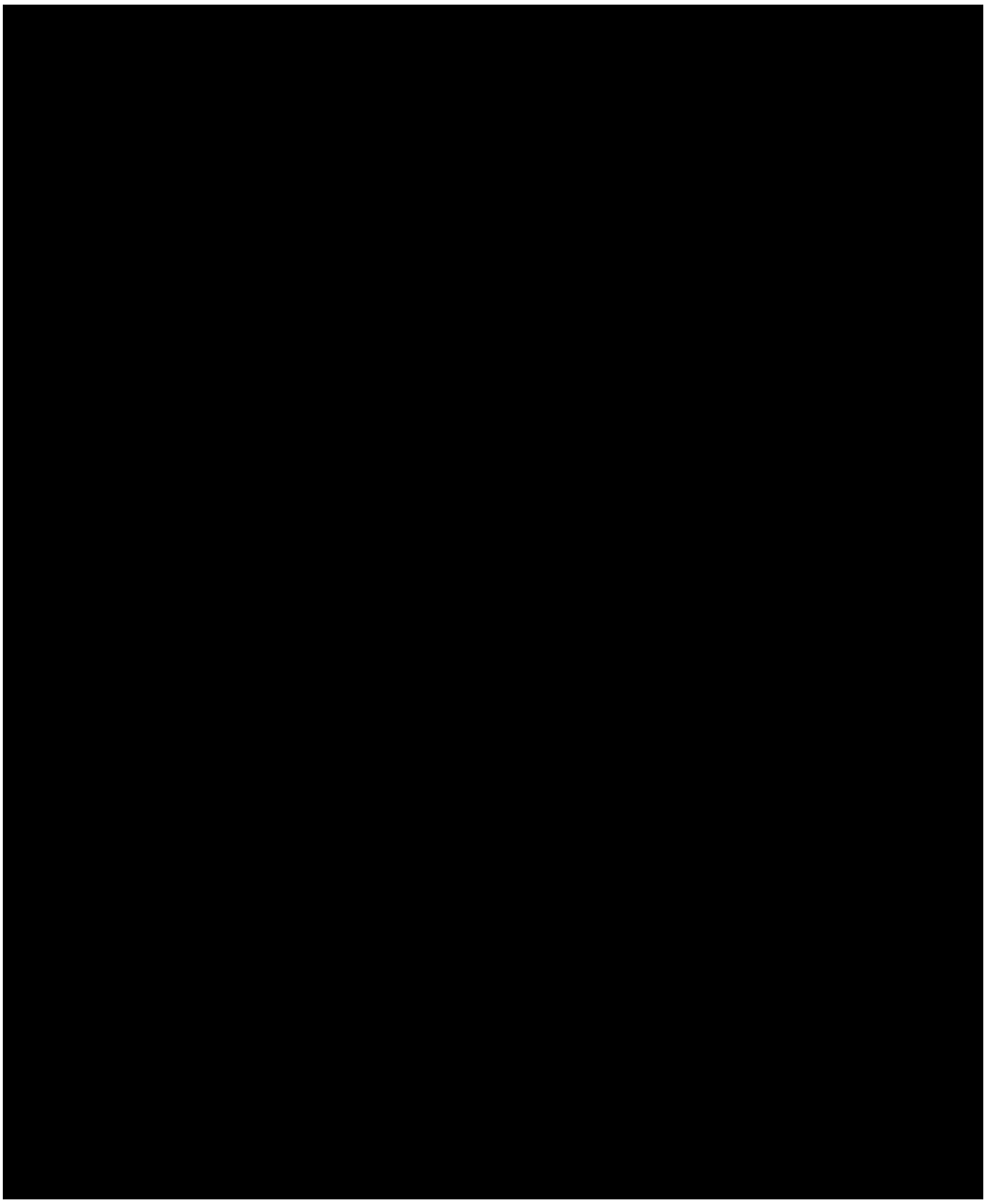
[redacted]

7.1.4.2 Progression-free Survival

[redacted]

Consistent with the above results, KM curves demonstrated similar probability of PFS for liso-cel and axi-cel in the unmatched and unadjusted (Figure 9), primary (Figure 23), and sensitivity analyses (Figure 24)[52].

Visual inspections of the KM curves (Figure 9, Figure 23, Figure 24) and log cumulative hazard plots (Figure 55, Figure 56, Figure 57) for TRANSFORM showed that the curves were generally parallel, supportive of the PH assumption. Findings for TRANSFORM were similar after matching and adjusting in both the primary and sensitivity scenarios. In contrast, for ZUMA-7, there was initial cross-over in the log cumulative hazards reflecting an increase in the hazard of disease progression for the SoC compared to axi-cel over study follow-up, despite no apparent cross-over in the corresponding KM curves[52].



7.1.4.3 Overall survival

Median study follow-up time differed between TRANSFORM (17.5 months) and ZUMA-7 (24.9 months). Due to insufficient number of OS events in both trials (i.e., median OS was not reached for both liso-cel and axi-cel arms), longer follow-up time for either study would improve the ability to compare OS[52].

[redacted]

For comparison of OS between liso-cel and axi-cel, the HRs for unmatched and unadjusted comparison, matched and unadjusted comparison, and each adjusted scenario, sequentially and additionally adding in factors one at a time, is presented in Figure 25. Overall, the HR remains consistent as each additional factor was sequentially added (i.e., scenarios A to I)[52].

Consistent with the above results, KM curves demonstrated similar probability of OS for liso-cel and axi-cel in the unmatched and unadjusted (Figure 10), primary (Figure 26), and sensitivity analyses (Figure 27)[52].

Visual inspections of the KM curves (Figure 10, Figure 26, Figure 27) and log cumulative hazard plots (Figure 58, Figure 59,

Figure 60) for TRANSFORM showed that the curves were generally parallel, supportive of the PH assumption. Findings for TRANSFORM were similar after matching and adjusting in both the primary and sensitivity scenarios. In contrast, for ZUMA-7, there was initial cross-over in the log cumulative hazards reflecting an increase in the hazard

of mortality for the SoC compared to axi-cel over study follow-up, with some initial cross-over in the corresponding KM curves[52].

[redacted]

7.1.4.4 Objective Response Rate

[redacted]

[redacted]

[redacted]

For comparison of ORR between liso-cel and axi-cel, the ORs for unmatched and unadjusted comparison, matched and unadjusted comparison, and each adjusted scenario, sequentially and additionally adding in factors one at a time, is presented in Figure 28. Overall, the ORs remained not statistically significant between liso-cel and axi-cel as each additional factor was sequentially added (i.e., scenarios A to I), despite slight shift of the estimates observed[52].

[redacted]

7.1.4.5 Complete Response Rate

[redacted]

[redacted]

For comparison of CRR between liso-cel and axi-cel, the ORs for unmatched and unadjusted comparison, matched and unadjusted comparison, and each adjusted scenario, sequentially and additionally adding in factors one at a time, is presented in Figure 29. Overall, the ORs remained not statistically significant between liso-cel and axi-cel as each additional factor was sequentially added (i.e., scenarios A to I), despite slight shift of the estimates observed. [redacted]

[redacted]

7.2 Efficacy of liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

7.2.1 Differences in definitions of outcomes between studies

Efficacy outcomes evaluated were ORR, CRR, PFS, and OS. For ORR and CRR assessments, ZUMA-1 used both computed tomography (CT)- and position emission tomography (PET)-based criteria from the revised International Working Group (IWG) criteria [48]. In contrast, the TRANSCEND (017001) study used the more recent PET-based Lugano classification [25] (Table 33). Because PET-based assessment was used in both trials and any uncertain responses would be subject to additional testing, between-trial differences in the assessment criteria for ORR and CRR were anticipated to be minimal. ORR and CRR assessed by IRC were reported in both trials [76].

The definitions for PFS and OS were similar, with both trials capturing INV- and the IRC-assessed PFS. PFS was censored according to FDA censoring rules in both trials. Patients who had not died or experienced disease progression were censored at their last evaluable disease assessment. HSCT after infusion was not censored in INV-assessed PFS in ZUMA-1. Therefore, INV-assessed PFS from TRANSCEND (017001) was re-derived to remove the censoring of patients who had HSCT after infusion [76].

The frequency of PET/CT scans was similar in TRANSCEND (017001) and ZUMA-1 [76].

Table 33 Comparison of Efficacy Outcome Definitions between TRANSCEND (017001) and ZUMA-1

Outcome	TRANSCEND (017001)	ZUMA-1
ORR	ORR (CRR + PRR) using Lugano classification [25]	ORR (CRR + PRR) using IWG revised guidelines [48] with the incorporation of PET scan
CRR	Lugano classification [25]	IWG revised guidelines [48] with the incorporation of PET scan
PFS	Time from first infusion to the earlier date of disease progression or death due to any cause. Reported based on FDA censoring rules. Patients who proceeded to HSCT were: • censored by IRC • not censored to match to ZUMA-1 INV definition	Time from first infusion to progressive disease, based on IWG revised guidelines [48], or death. Reported based on FDA censoring rules. Patients who proceeded to HSCT were: • censored by IRC • not censored by INV
OS	Time from infusion to the date of death or data cut-off date for any reason	Time from infusion to the date of death from any cause

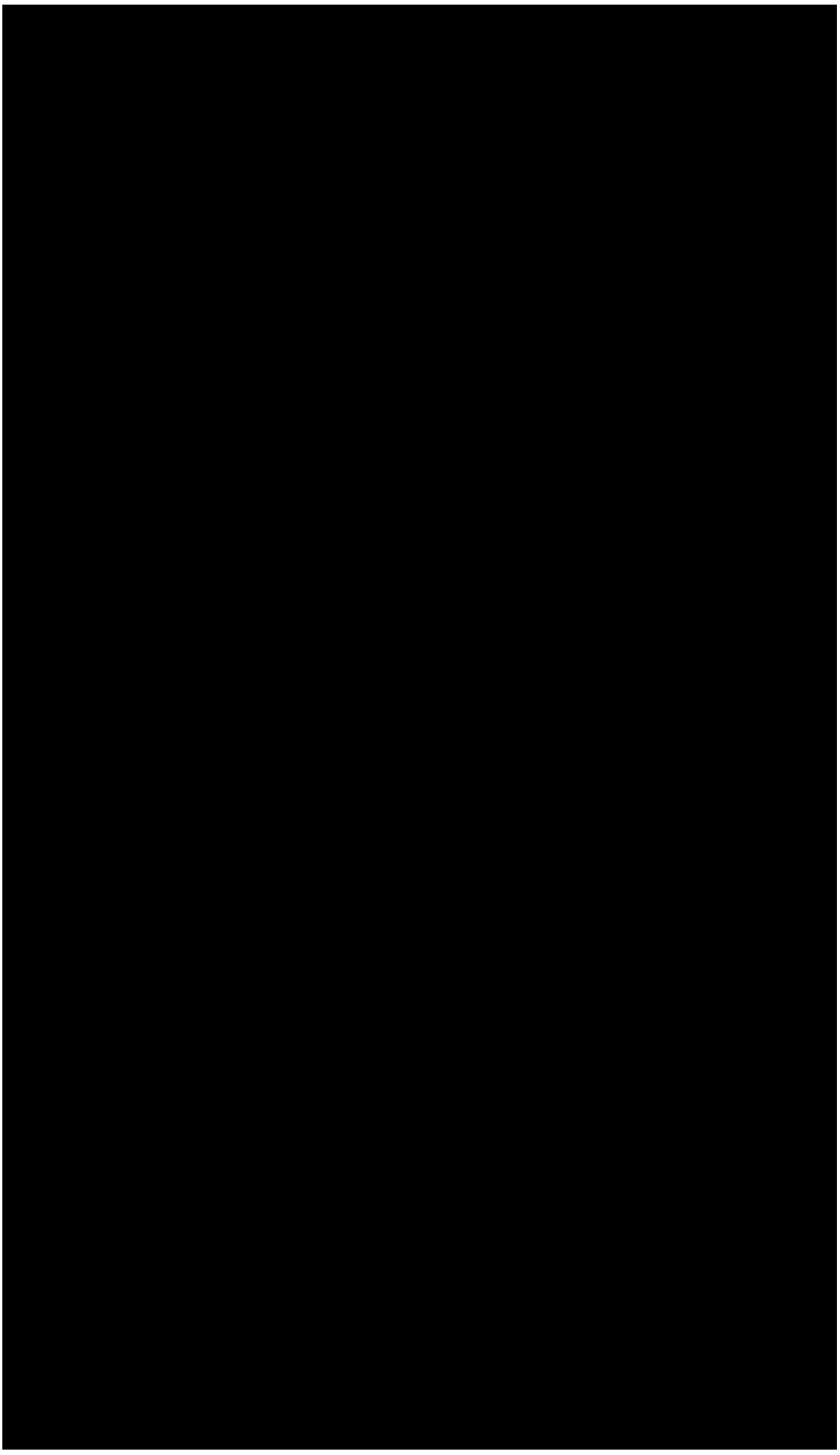
7.2.2 Method of synthesis

Please see Appendix C.2.

7.2.3 Results from the comparative analysis

The efficacy results from the MAIC of liso-cel vs. axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy are summarized in Table 34. For efficacy outcomes, the ranks of clinical factors differed moderately between outcomes based on inputs from 5 clinical experts and literature. The different factors and their weight for each endpoint is listed below in Table 35Three clinical factors, tumor burden, bridging therapy, and R/R to last therapy, were present in the top 5 ranks of all efficacy outcomes, and the top 6 ranked factors were largely consistent across outcomes.

For further information on the efficacy results, see section 7.2.4.



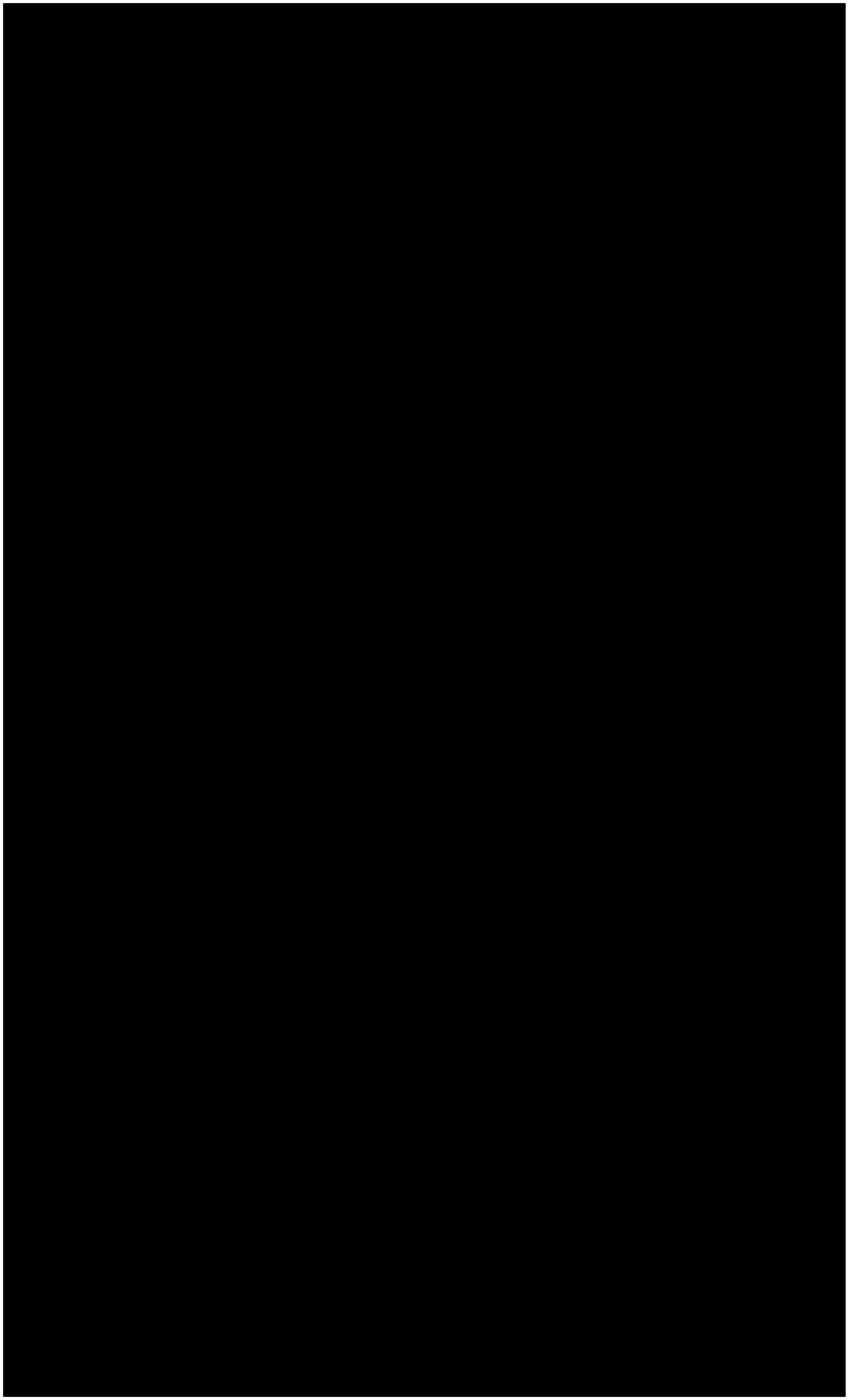


Table 35 Final evidence-informed rankings of clinical factors used to inform the matching and adjusting process for efficacy analyses in the comparison of liso-cel to axi-cel

	Final Ranking[a]			
Clinical Factor[b]	**OS**	**PFS**	**CRR**	**ORR**
Tumor burden - SPD	1	3	1	1
IPI score	2	6	8	14
Bridging therapy	3	5	2	4
Disease histology	4	1	5	8
R/R to last therapy	5	4	3	3
Bulky disease	6	7	7	12
Age	7	11	12	13
Prior auto-HSCT	8	14	4	7
Disease stage	9	13	15	6
Prior allo-HSCT	10	8	10	5

CrCl	11	2	9	2
Extranodal disease	12	12	6	11
Number of prior therapies	13	15	17	17
Sex	14	20	20	19
ECOG PS	15	10	11	10
Absolute lymphocyte count	16	19	18	18
Secondary CNS involvement	17	9	14	9
LVEF	18	18	19	20
Cell of origin[c]	19	16	16	15
Double/Triple Hit or Double Expressor[c]	20	17	13	16

Abbreviations: Allo-HSCT: allogenic hematologic stem cell transplant; Auto-HSCT: autologous hematologic stem cell transplant; Axi-cel: axicabtagene ciloleucel; CNS: central nervous system; CRP: C-reactive protein; CRR: complete response rate; CrCl: creatinine clearance; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LDH: lactate dehydrogenase; Liso-cel: lisocabtagene maraleucel; LVEF: tatus; IPI: International Prognostic Index; LDH: lactate dehydrogenase; Liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; SPD: sum of product of perpendicular diameters.

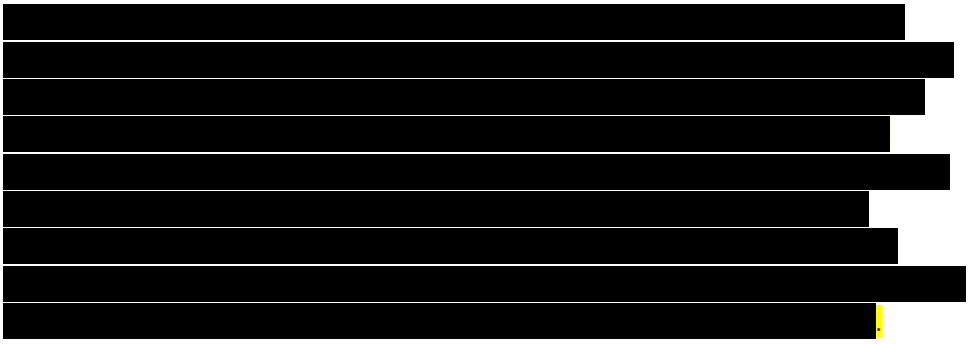
[a]Factors are ranked in order of importance where 1 represent the most important factor and 20 represents the least important factor.

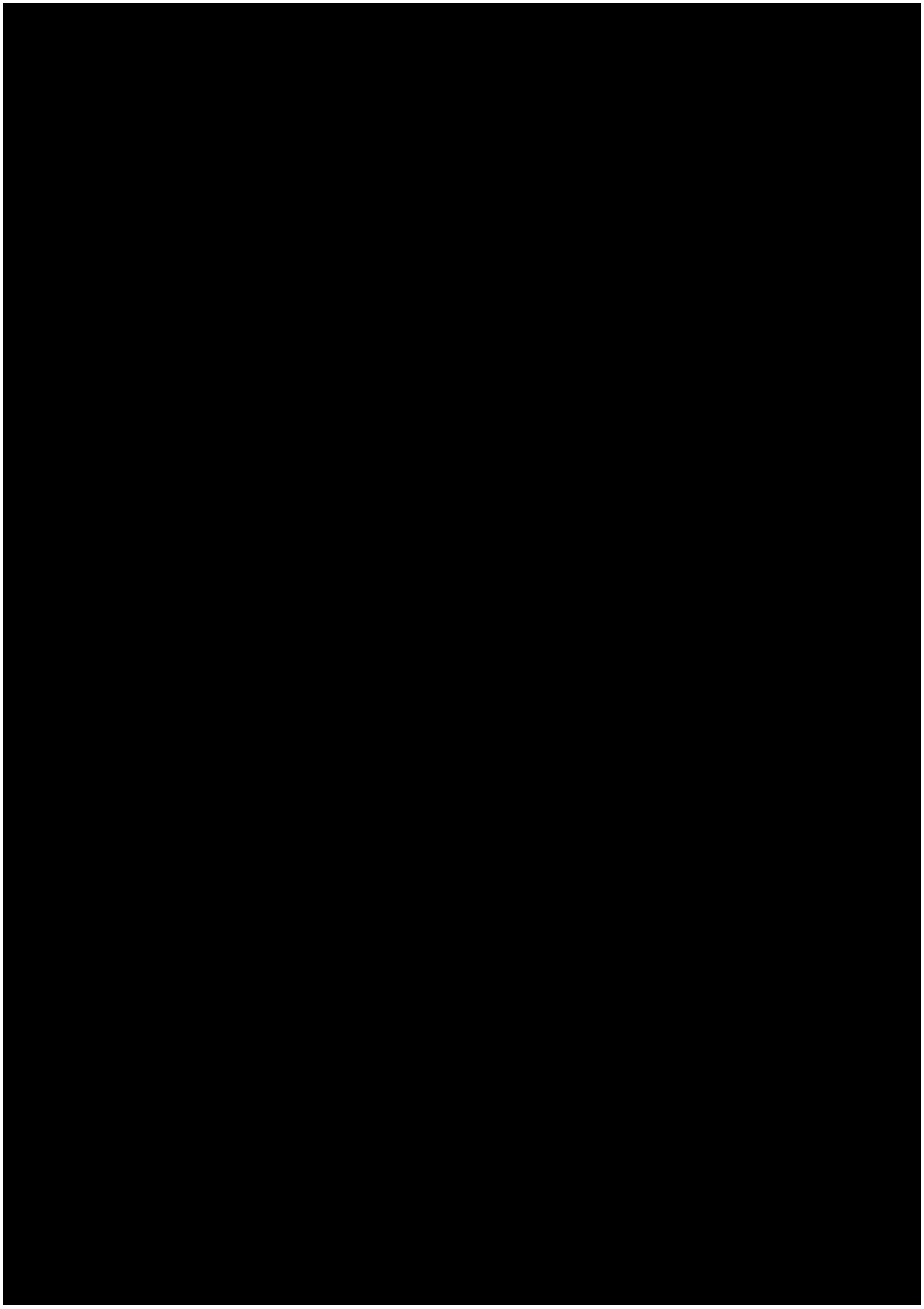
[b]Only 20 of the 24 factors available for analysis in Study 017001 IPD were available for comparison with ZUMA-1 Phase 1+2 Safety Analysis Set. The 4 factors not available (and therefore not ranked on this list) are: tumor burden LDH, CRP, refractory subgroups, and best response to any prior therapy.

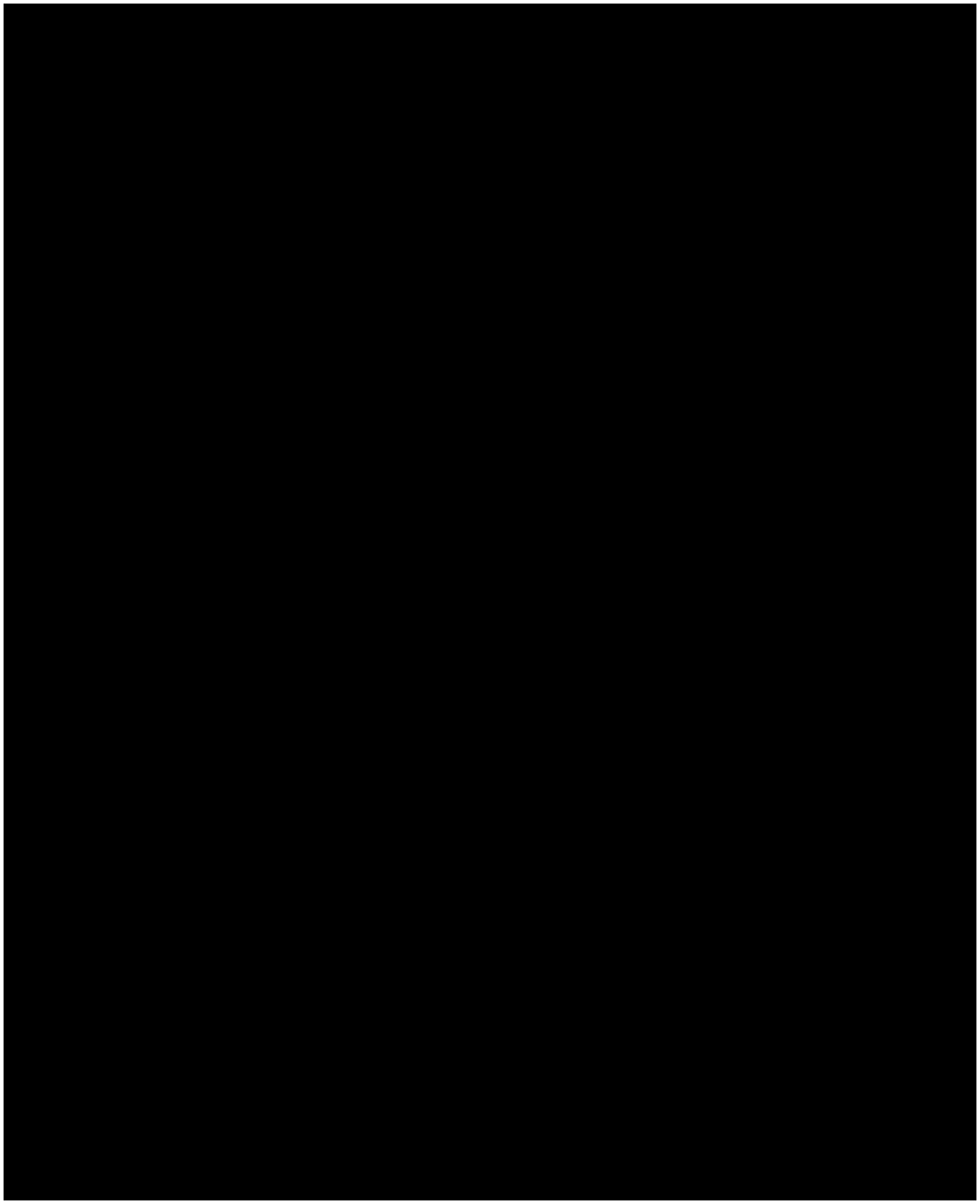
[c] Available for ZUMA-1 Phase 1+2 Safety Analysis Set, but not for ZUMA-1 Phase 2 Efficacy Analysis Set.

7.2.4 Source: [76]Efficacy – MAIC of liso-cel vs. axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

7.2.4.1 Progression-free survival

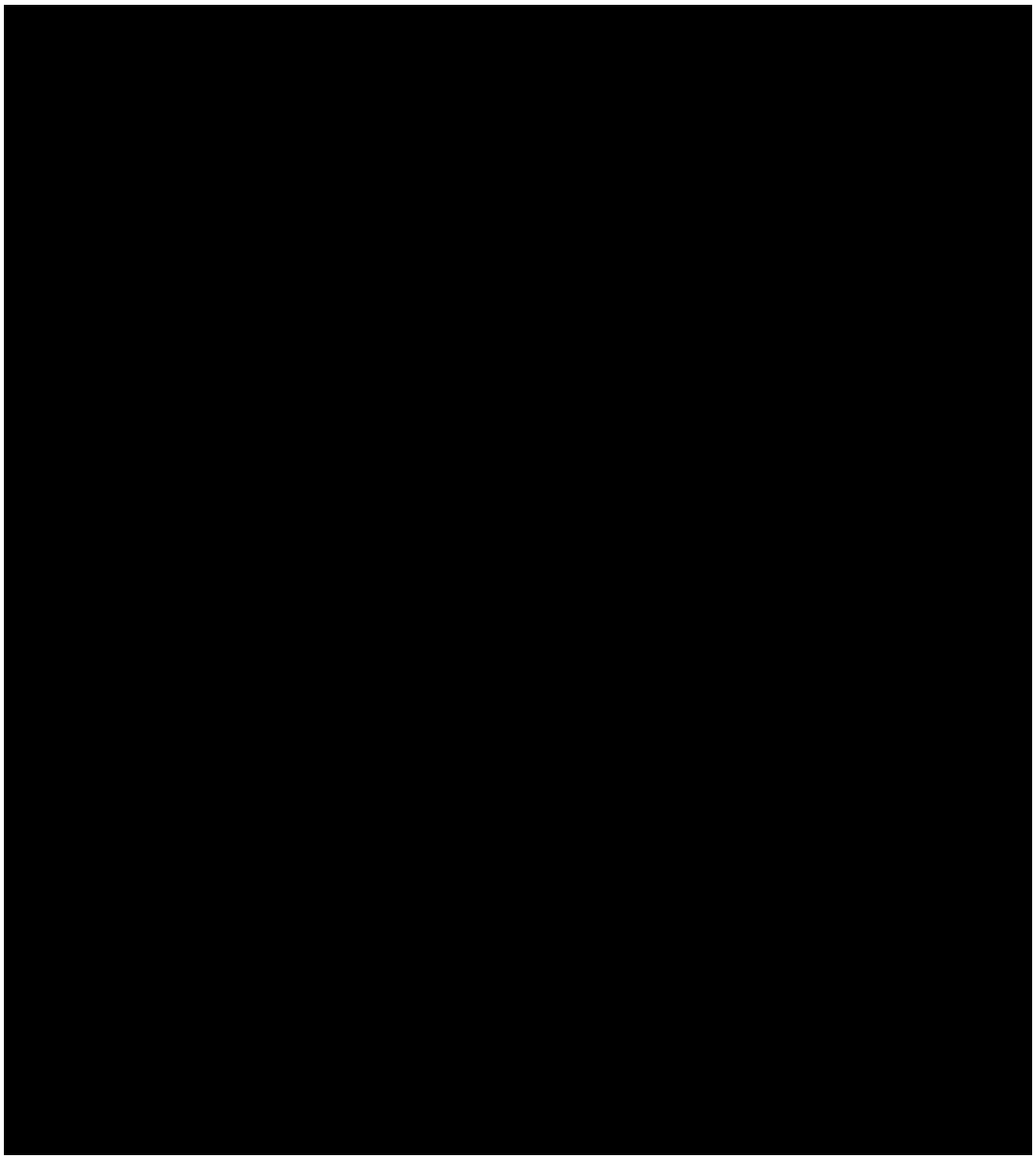


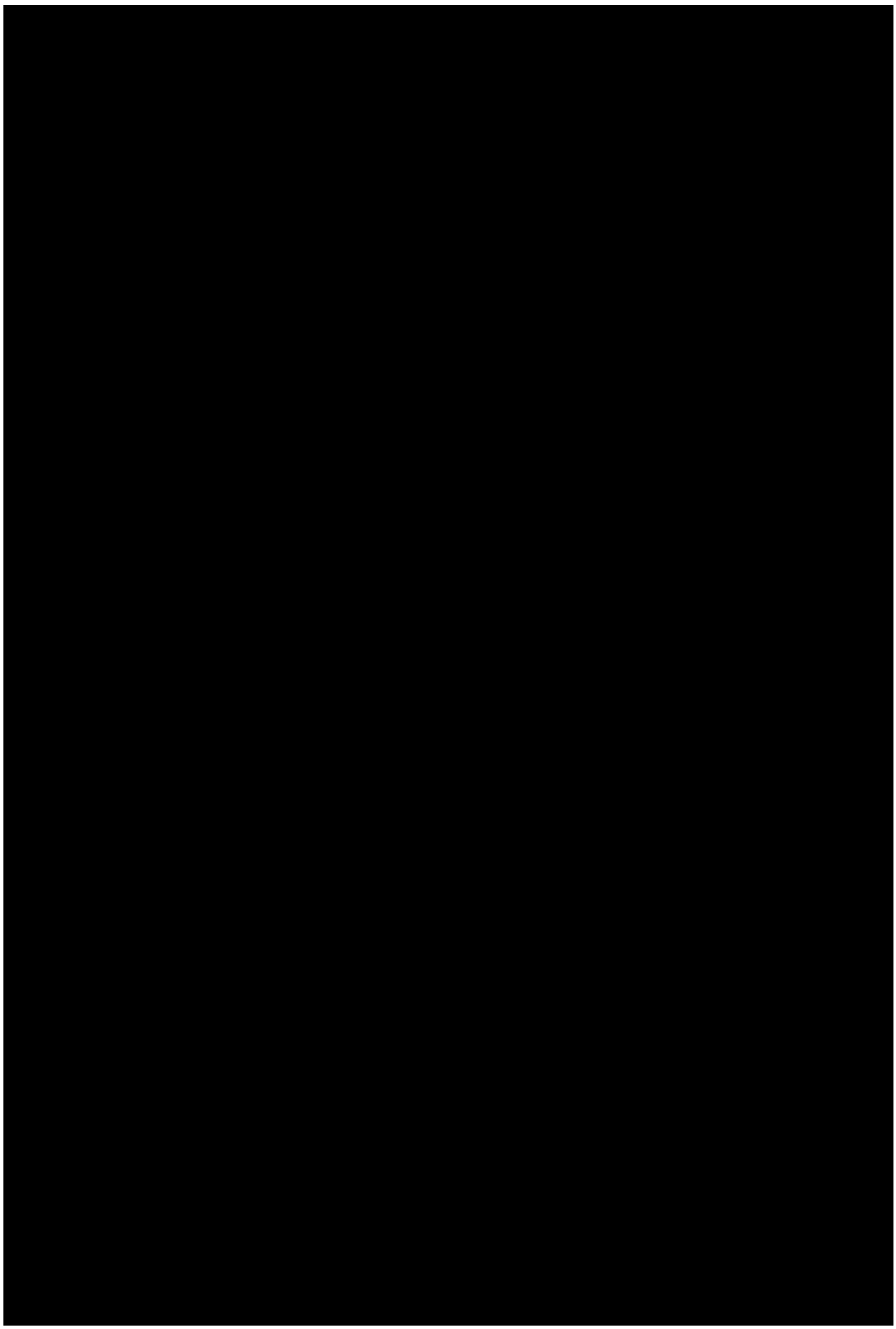


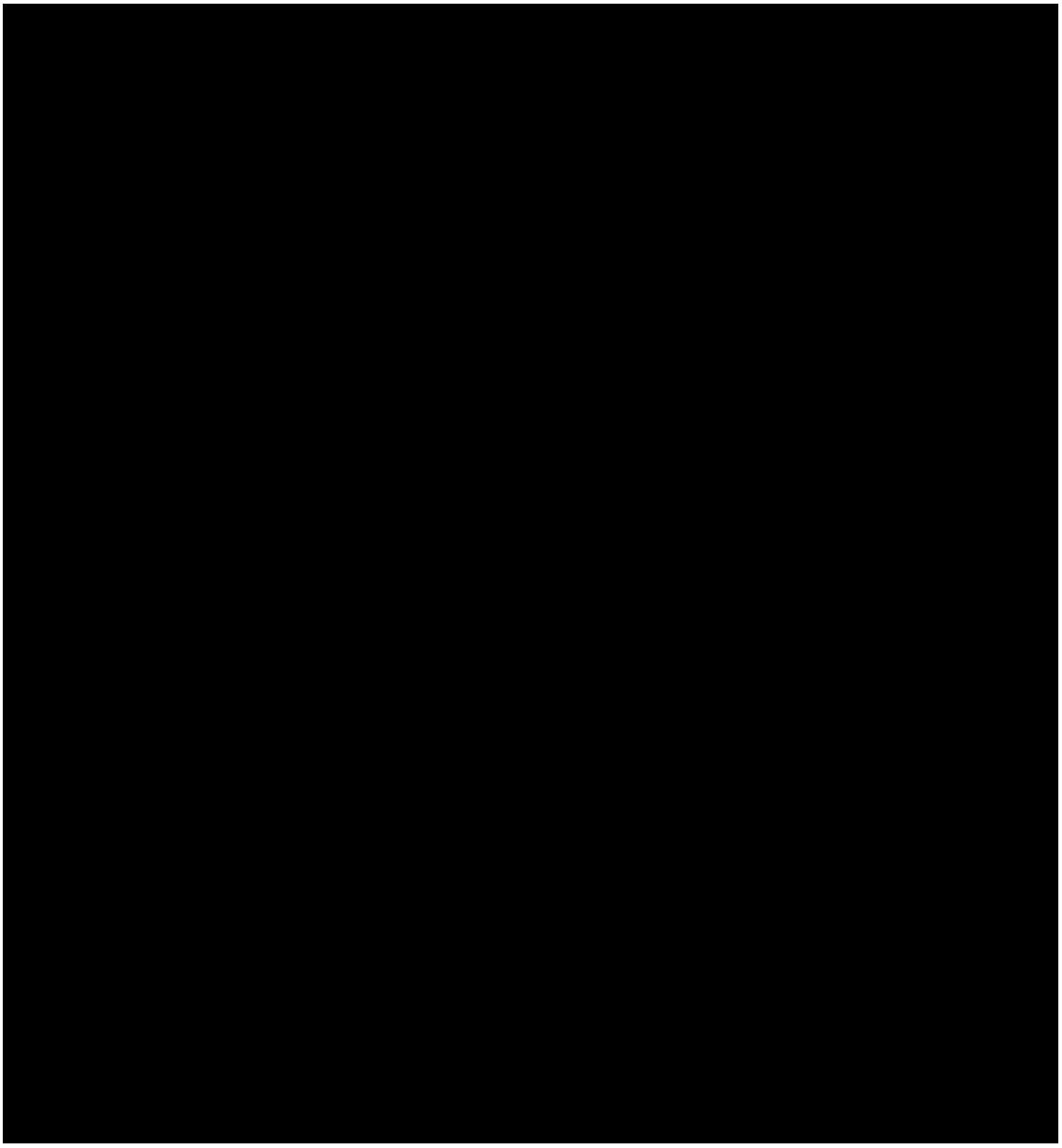


7.2.4.2 Overall survival

[redacted]







7.2.4.3 Overall Response Rate

7.2.4.4 Complete Response Rate

[redacted]

8. Modelling of efficacy in the health economic analysis

Not applicable

9. Safety

9.1 Safety of liso-cel compared to axi-cel for the treatment of adult patients with LBCL who relapsed within 12 months or are refractory to, first-line chemoimmunotherapy

As described in section C.1.2.3, comparisons of safety outcomes used outcome data from the safety analysis sets of both TRANSFORM and ZUMA-7. However, baseline characteristic data for ZUMA-7 was only reported for the ITT population in Locke [47] or very scarcely for a modified safety analysis set in the FDA assessment report [53]. Therefore, for safety outcome comparisons involving adjustment on baseline characteristics, data from the ITT population set was used as if it were the safety analysis set. Given the safety analysis set comprised 94.2% of the ITT population set in ZUMA-7, this was considered a relatively minimal limitation to enable adjustment of baseline factors[52] (Table 38).

Table 38 Summary of the datasets used to inform the safety analyses

Trial Name	Data Cutoff	Median Study Follow-up, months (range)	Analysis Set	Treatment Arm	N
Safety Outcomes					
TRANSFORM (NCT03575351)	May 13, 2022 [46]	17.53 (0.9, 37.0)[a]	Safety analysis set	Liso-cel	92
				SoC	91
ZUMA-7 (NCT03391466)	March 18, 2021 [47, 53]	24.9[b]	ITT (enrolled and randomized) / Safety analysis set	Axi-cel	180/170
				SoC	179/168

[a]Follow-up time is reported for TRANSFORM ITT set. Follow-up is reported as time from randomization to last date know alive (months). Last date defined as last valid date of subject assessment prior to or on the data cutoff date in the clinical database [46].

[b]Follow-up time is reported for ZUMA-7 enrolled and randomized set. It was defined as time from randomization to data-cutoff date [47].

The comparison of safety evaluation criteria and outcome definitions between TRANSFORM and ZUMA-7 is shown in Table 39. The TEAE time window differed between trials in a way where, all else being equal, additional TEAEs may be expected in TRANSFORM than ZUMA-7. The starting time to define a TEAE was from randomization in TRANSFORM but from treatment in ZUMA-7 (i.e., infusion of axi-cel for the axi-cel arm or first dose of chemotherapy for the SoC arm). Therefore, events occurred during

bridging therapy and before treatment would be included as TEAE in TRANSFORM but would not be included in ZUMA-7. The ending time for defining a TEAE was 90 days after treatment in TRANSFORM, whereas ending time details were not reported by ZUMA-7 (albeit AEs in general were captured up to post-treatment Day 150). The comparative analyses of TEAEs may represent a conservative estimate of the relative safety profile of liso-cel versus axi-cel[52].

The AE definitions and grading criteria were similar between TRANSFORM and ZUMA-7 for TEAE, treatment-emergent SAE, CRS, severe infections, hypogammaglobulinemia, and other TEAEs, including individual events of CRS and NT, other TEAEs occurring in ≥ 10% of patients, and other SAEs occurring in ≥ 10% of patients [52].

In TRANSFORM, NT was defined as investigator-identified neurological AEs related to liso-cel. In ZUMA-7, NT was defined with a search strategy based on known neurological toxicities associated with anti-CD19 immunotherapy [80]. This difference in approach may be perceived to limit the comparison of study-defined NT. Clinical experts were therefore consulted and advised that the assignment of NT would be expectedly similar across studies. This is because physicians are experienced in identifying and classifying patients as having neurologic symptoms following treatment[52].

Prolonged cytopenia was defined as Grade ≥ 3 decreased hemoglobin, neutrophils, or platelets by central laboratory assessment in TRANSFROM. For ZUMA-7, prolonged cytopenia was defined by standardized MedDRA query in its publication [47] and by laboratory assessment in the FDA assessment of ZUMA-7 data [53]. Therefore, laboratory-assessed prolonged cytopenia from TRANSFORM and FDA-reported ZUMA-7 data will be used for comparison. No outcomes were re-derived from TRANSFORM for alignment with ZUMA-7[52].

Table 39 Comparison of Safety Evaluation Criteria and Outcome Definitions between TRANSFORM and ZUMA-7

	TRANSFORM (Liso-cel)	ZUMA-7 (Axi-cel)
Evaluation Criteria		
TEAE Reporting Window	AEs occurring or worsening on or after the date of randomization and within 90 days after last dose of chemotherapy (Arm A), or within 90 days after the infusion of liso-cel (Arm B or subjects in Arm A crossing over to liso-cel) or start of new antineoplastic therapy, whichever occurs first, as well as those AEs made known to the investigator at any time thereafter that are	Begins at infusion and first dose of chemotherapy for axi-cel and salvage chemotherapy arm respectively End date was not reported[a]

	suspected of being related to study treatment.	
Grading Criteria	CTCAE version 4.03 or higher	CTCAE version 4.03
Definitions		
TEAE	Any investigator assessed TEAE using MedDRA version 23.0	Any investigator assessed TEAE using MedDRA version 23.1
Treatment-emergent SAE	Any AE occurring at any dose that: 1) results in death, 2) is life-threatening (ie, the subject is at immediate risk of death from the AE in the opinion of the investigator), 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions), 5) is a congenital anomaly/birth defect and 6) constitutes an important medical event	Any AE that meets at least 1 of the following serious criteria: 1) fatal, 2) life-threatening (places the subject at immediate risk of death), 3) requires in-patient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) is a congenital anomaly/birth defect and 6) other medical import serious event
AESI		
CRS, Lee 2014 Criteria	Investigator assessed	Investigator assessed
Study defined NT	NT immune effector cell-associated events were provided, where NT immune effector cell-associated events were defined as NT events reported in subjects who received liso-cel only	Neurological events were identified with the use of prespecified search list of preferred terms in the MedDRA version 23.1 on the basis of known neurotoxic effects associated with anti-CD19 immunotherapy, and were specifically identified with the use of methods that were based on the phase 2 study of blinatumomab [80]
Severe Infections	Standardized MedDRA query of SOC Infections and Infestations; Grade ≥ 3	AEs within the SOC of Infections and Infestations that occur on or after Treatment Day 0 (i.e., the

		day that the subject received the first axi-cel infusion)
Hypogammaglobulinemia	Standardized MedDRA query	Identified using a MedDRA search term strategy develop by KITE Inc.
Prolonged cytopenia	Liso-cel arm: Grade ≥ 3 central laboratory results of decreased hemoglobin, neutrophils, or platelets observed at the Study Day 64 visit (35 days after liso-cel infusion) Assessment was based on central laboratory results.	Per FDA's assessment: cytopenias present on or after Day 30 following the axicabtagene ciloleucel infusion on Day 0, based on analysis of the lab dataset
Events of CRS		
Hypotension	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Sinus tachycardia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Hypoxia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Headache	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Chills	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Events of NT		
Tremor	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Confusional state	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Aphasia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1

Encephalopathy	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Paresthesia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Other TEAEs occurred in ≥ 10% of patients from any treatment arm		
Lymphopenia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Febrile neutropenia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1 FDA re-adjudication identified additional subjects with fever that overlapped with grade ≥3 neutropenia in the absence of systemic infection. These were considered as events and agreed by the applicant [53].
Hypophosphatemia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Hypotension	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1
Other SAEs occurred in ≥ 10% of patients from any treatment arm		
Febrile neutropenia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1 Due to re-adjudication, FDA considered the reported serious febrile neutropenia does not represent the true incidence [53]
Pyrexia	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1

Encephalopathy	By preferred term in System Organ Class coded using MedDRA v23.0	By preferred term in System Organ Class coded using MedDRA v23.1

[a]All AEs in ZUMA-7 were reported to the Day 150 post-randomization visit or change in lymphoma therapy, whichever occurs first, but this end time was not explicitly defined for AEs to be treatment-emergent [47].

9.1.1 Safety data from the clinical documentation

Table 40 shows the overview of safety events in TRANSFORM and ZUMA-7.

[redacted]

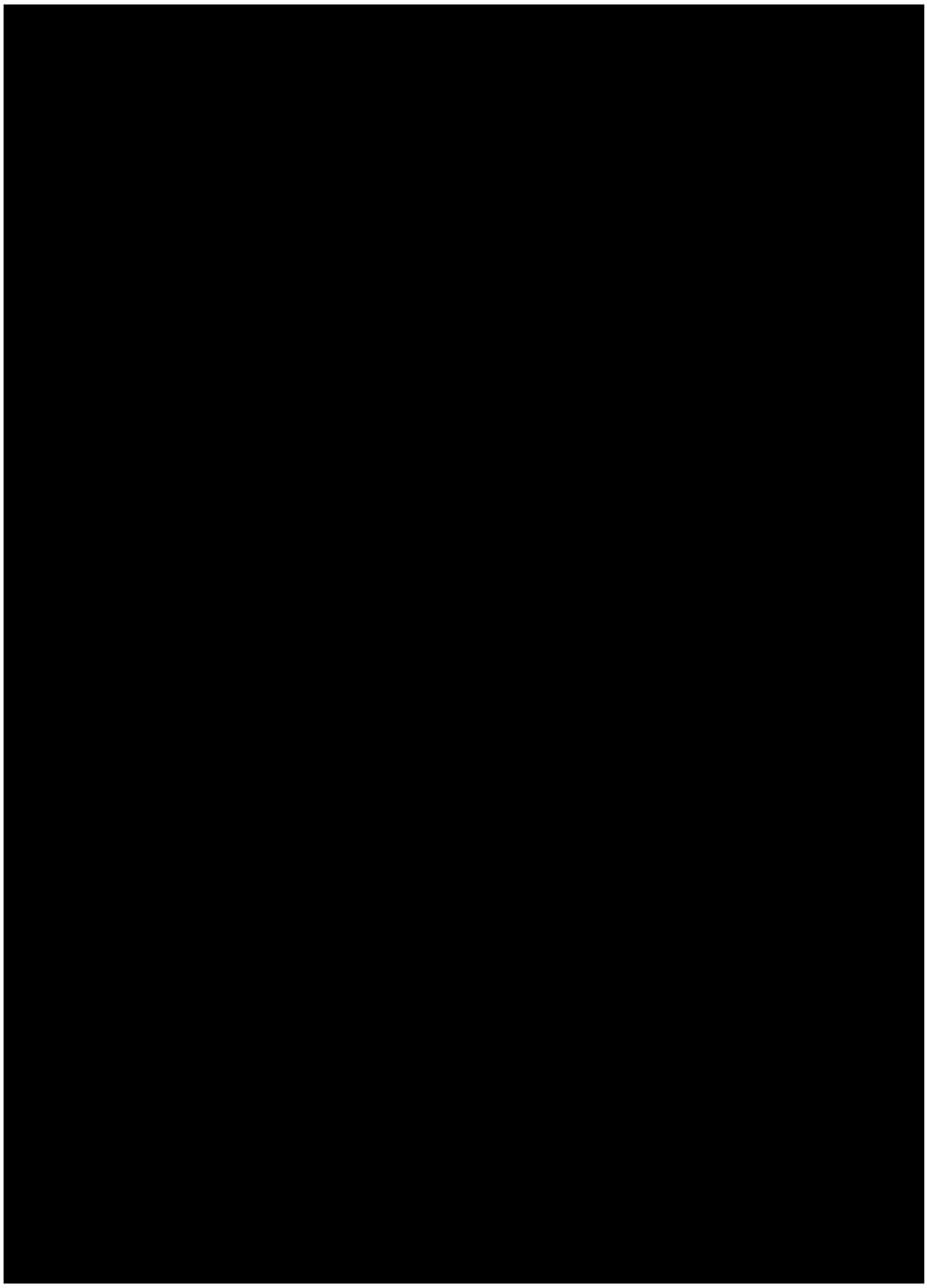


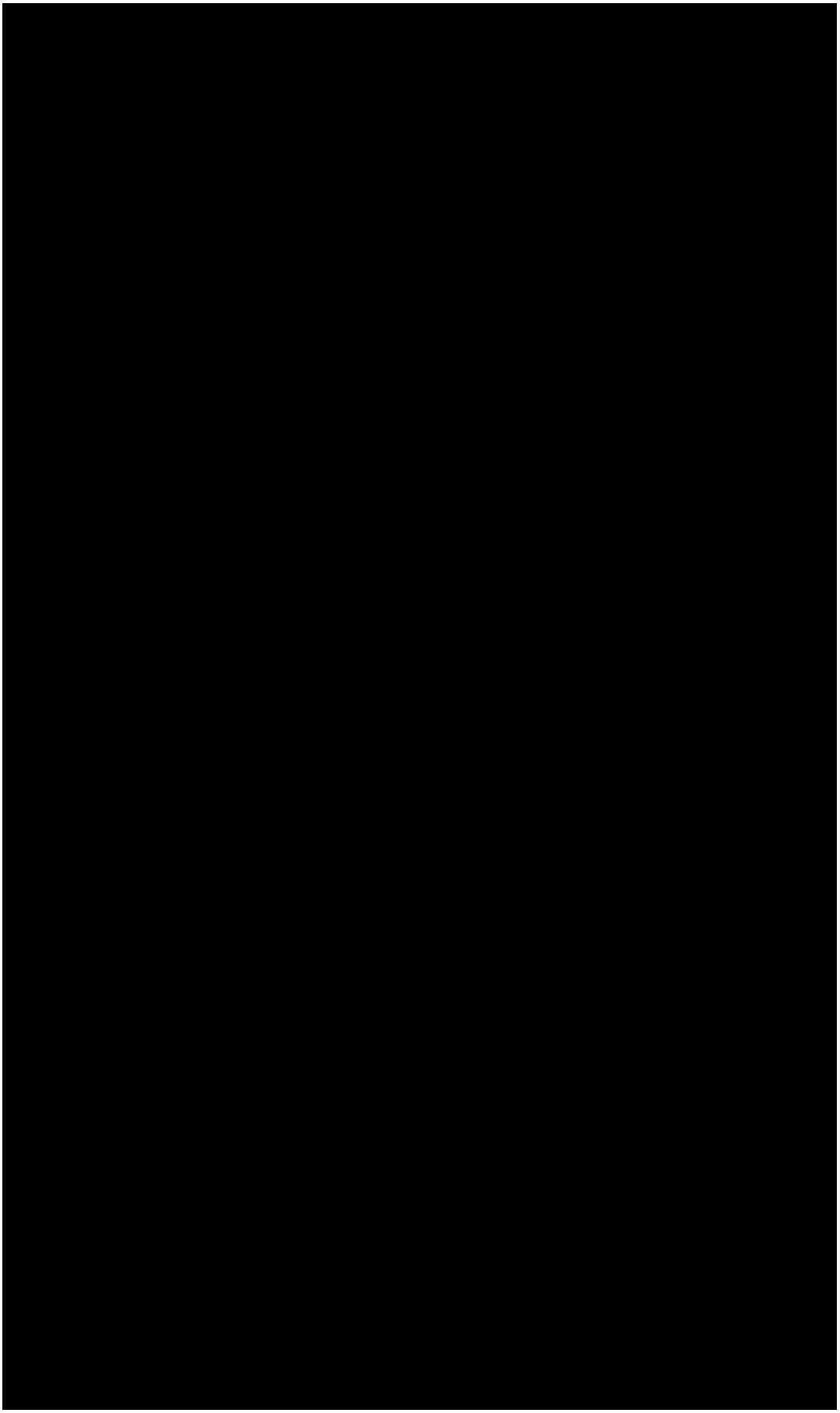
Table 41 and Table 42 show the serious adverse events with frequency of ≥ 5% in any treatment arm recorded in the TRANSFORM and ZUMA-7 trials, respectively.

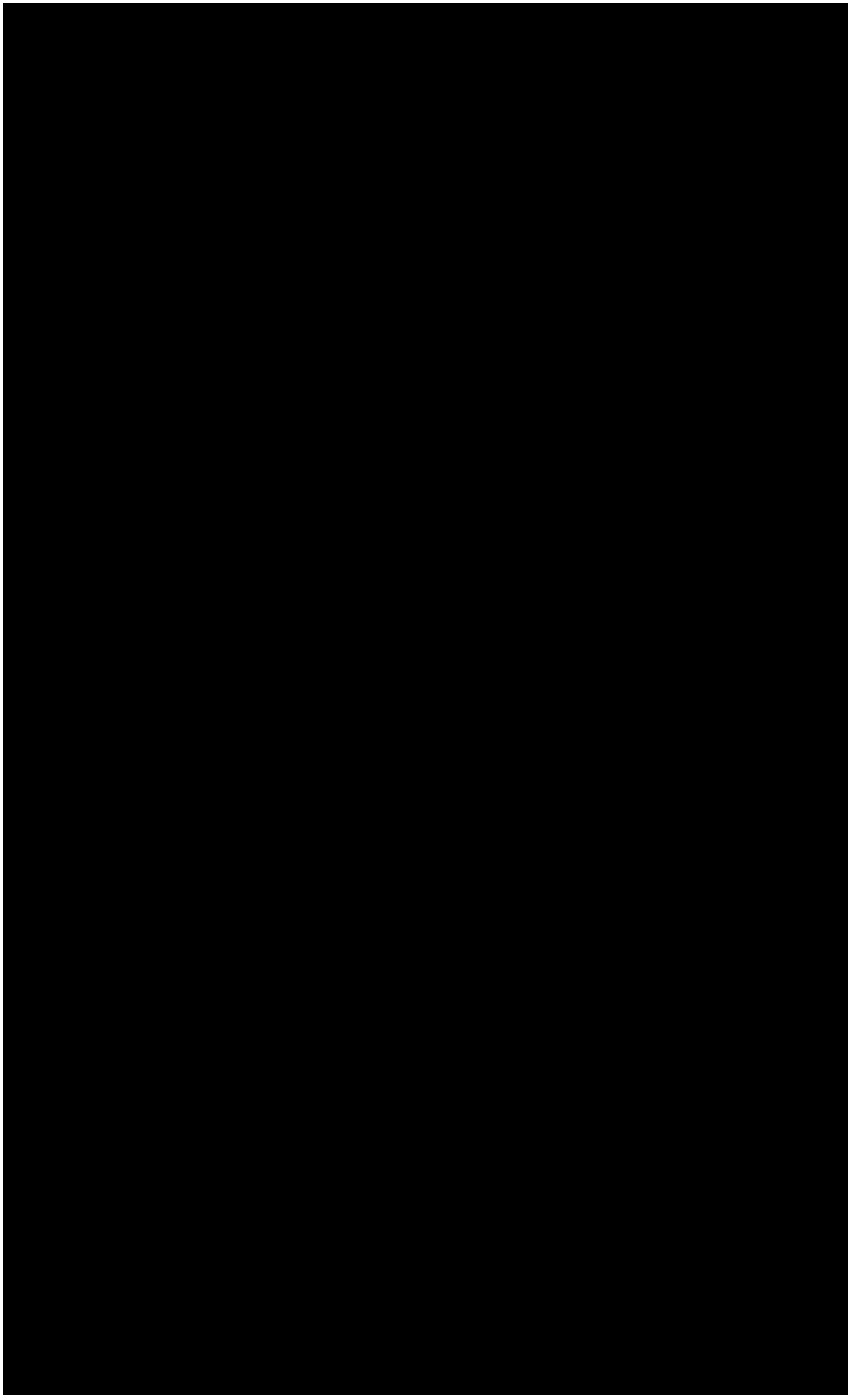
[redacted]

[redacted]

Reported rates of any grades and Grade ≥ 3 AEs for TEAE, treatment-emergent SAE, CRS, and study-defined NT, as well as Grade ≥ 3 infections, any grades hypogammaglobulinemia are presented in Table 43 [52].

[redacted]





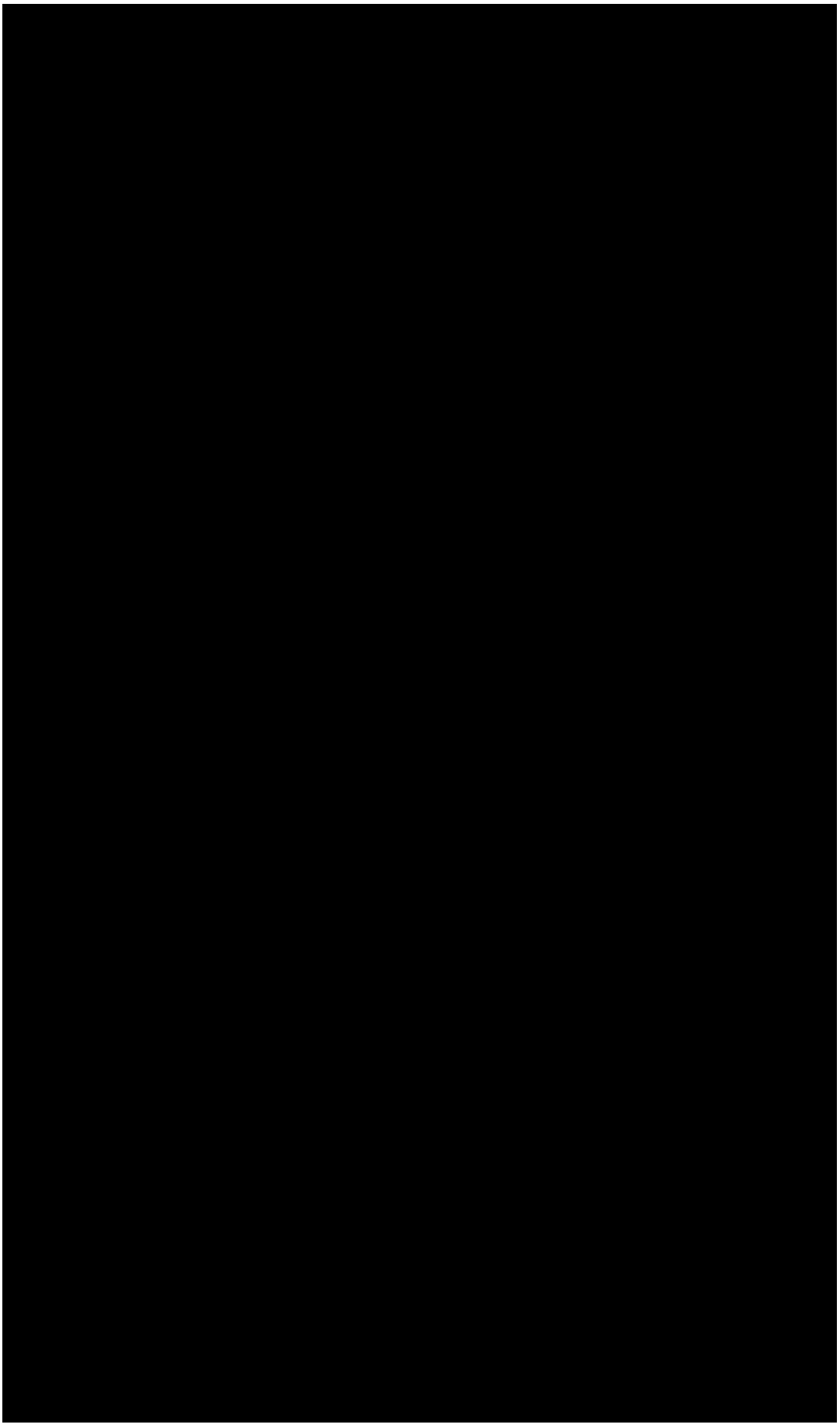
[redacted]

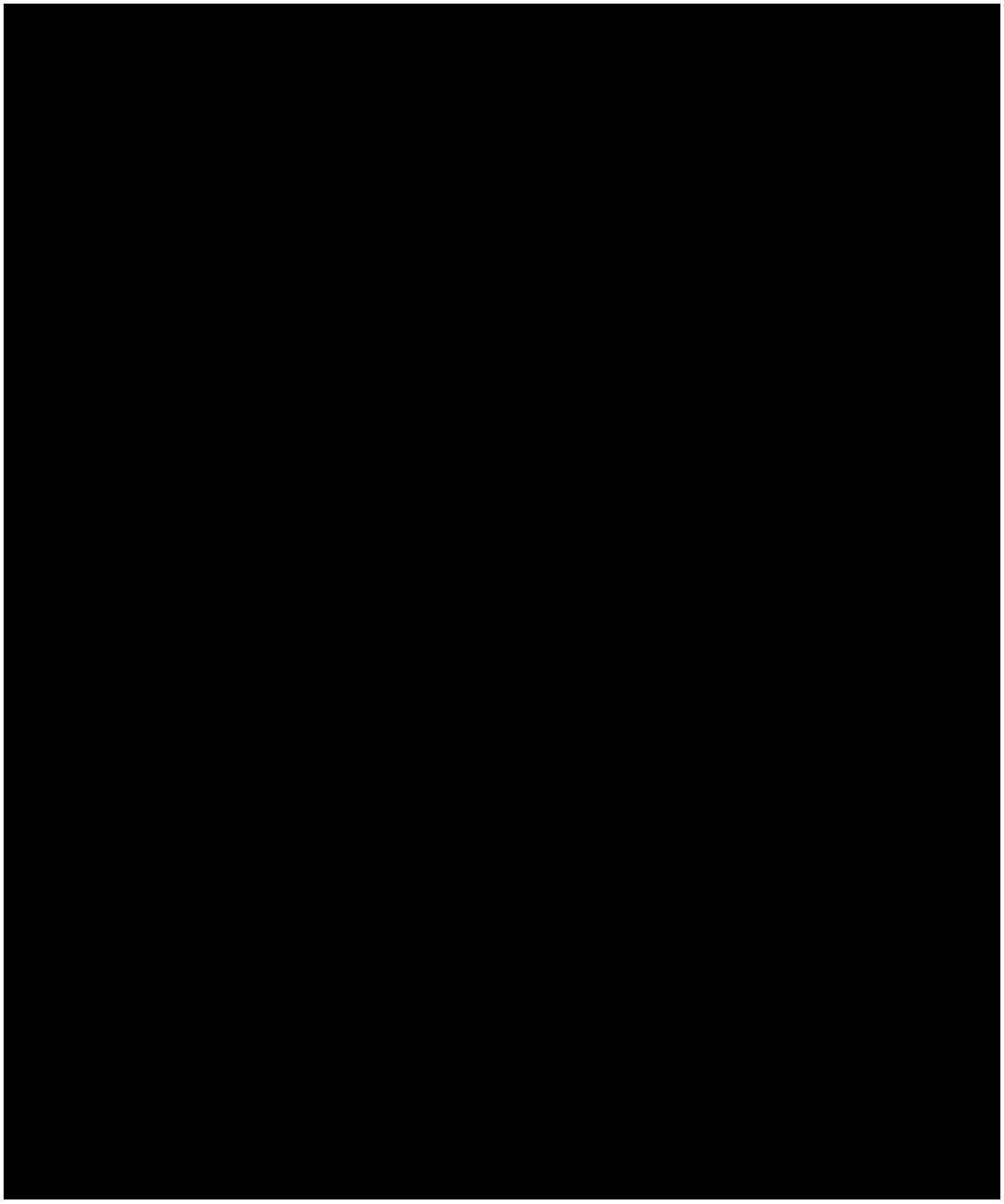
[redacted]

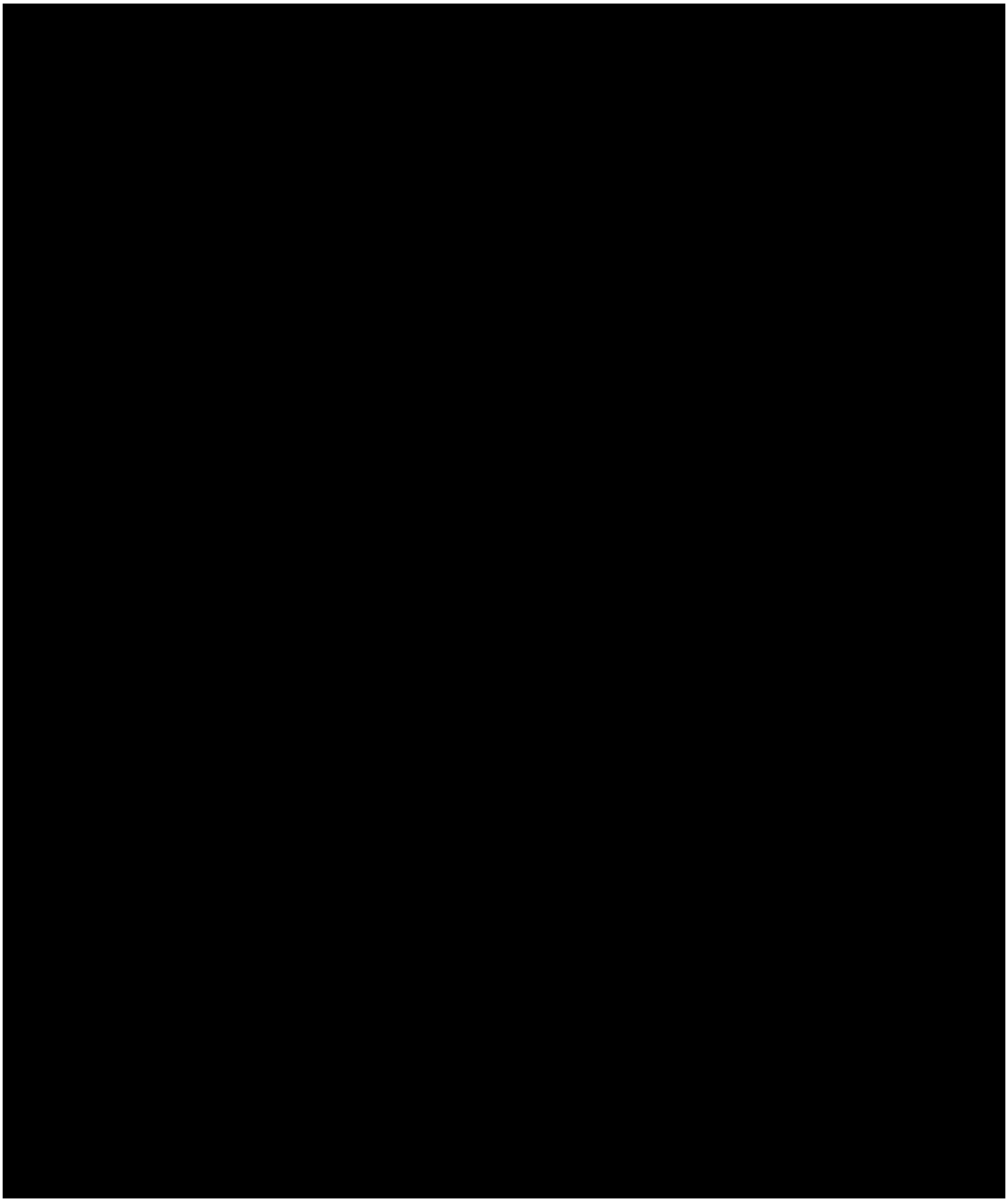
The summary of the MAIC results is presented in Table 44 and

Table 45. Overall, liso-cel showed a more favorable safety profile than axi-cel. Specifically, liso-cel was associated with a significantly lower odds of Grade ≥ 3 treatment-emergent SAE, any grade and Grade ≥ 3 CRS, any grade and Grade ≥ 3 study-defined NT. Odds of any grade and Grade ≥ 3 TEAE, any grade treatment-emergent SAE, Grade ≥ 3 infections, and any grade hypogammaglobulinemia were similar between liso-cel and axi-cel [52].

[redacted]







Most of the AEs will be managed within the hospitalization time after liso-cel/axi-cel administration (see section 11.4). Nonetheless, the cost-minimization analysis includes grade 3 or higher cytokine release syndrome (CRS) and neurotoxicity (NT) AEs.

These were also the AEs costs included by the DMC in their assessment of axi-cel for the 2L treatment of LBCL [36].

The proportion of patients experiencing the selected AEs were sourced from the MAIC between liso-cel (TRANSFORM Safety Analysis Set) and axi-cel (ZUMA-7 Safety Analysis Set) [82].

Table 46 shows the AEs included in the cost-minimization analysis. The costs associated with these AEs are presented in Table 74.

Table 46 Adverse events used in the health economic model (2L cost-minimization analysis)

Adverse events	Liso-cel	Axi-cel		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
CRS (Grade ≥ 3)	0.6%	6.47%	[82] – See Table 44.	See text above.
NT (Grade ≥ 3)	5.30%	21.18%		

9.1.2 Safety data from external literature applied in the health economic model

Not applicable.

9.2 Safety of liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

A summary of the datasets used for the safety analyses is shown in Table 47 [60].

Table 47 Summary of datasets used for the safety analyses

Treatment	Trial Name	Data Cutoff	Primary Data Source	Median Study Follow-up, months (range)	Analysis Set	N
Safety Analysis						
Liso-cel	TRANSCEND (017001)	04 Jan 2021	IPD	31.0 (95% CI: 28.7, 35.4)[a]	DLBCL Treated Set Dose Levels DL1S + DL2S + DL1D	229
Axi-cel	ZUMA-1	11 Aug 2018	Locke, 2019 [62]	27.4 (NA)[b]	Phase 1 + 2 Safety Analysis Set	108

[a]The median follow-up time for OS was 31.0 months (95% CI: 28.7, 35.4) and is reported in the table. The median follow-up time for PFS was 23.9 months (95% CI: 23.6, 24.0). Both were calculated using the reverse KM method.

[b]Definition not reported.

The comparison of AESI evaluation criteria and definitions between TRANSCEND (017001) and ZUMA-1 is shown in Table 48 [76].

Study-defined NT included all TEAEs considered potential manifestations of CAR T cell associated NT. They were evaluated using a study-defined approach and were identified

by trial INVs who were trained in their recognition and management. Therefore, study-defined NT may not be directly comparable due to definition differences among the studies [76].

In the comparison of TRANSCEND (017001) to ZUMA-1, definitions for grade ≥ 3 TEAEs, grade 5 TEAEs, CRS, NEs per ND/PD SOC, encephalopathy per ND/PD SOC, aphasia per ND/PD SOC, infections, hypogammaglobulinemia, prolonged cytopenias as AEs (anemia, neutropenia, and thrombocytopenia), and febrile neutropenia were similar between studies and varied for study-defined NT of encephalopathy, study-defined NT of aphasia, as well as prolonged cytopenia by laboratory assessment. No outcomes were re-derived from TRANSCEND (017001) for alignment with ZUMA-1 [76].

Table 48 Comparison of AESI Evaluation Criteria and Definitions between TRANSCEND (017001) and ZUMA-1

	TRANSCEND (017001) (Liso-cel)	ZUMA-1 (Axi-cel)
Evaluation Criteria		
TEAE Reporting Window	90 days after infusion	92 days after infusion[a]
Grading Criteria	NCI CTCAE v4.03	NCI CTCAE v4.03
Definitions		
Grade ≥ 3 TEAE	Any INV-assessed TEAEs using MedDRA	Any INV-assessed TEAEs using MedDRA
Grade 5 TEAE	Any death due to TEAEs, excluding disease progression	Any death due to TEAEs, excluding disease progression
CRS	INV-assessed TEAEs by Lee 2014 criteria	INV-assessed TEAEs by Lee 2014 criteria
NT per Study Protocol	INV-assessed TEAEs Investigator-identified neurologic events secondary to CAR T cell-associated neurotoxicity and related to liso-cel (prospectively identified)	INV-assessed TEAEs MedDRA-based, sponsor-derived definition (retrospectively identified)[b]
NE per ND/PD SOC	INV-assessed TEAEs All reported TEAEs within ND/PD SOC using MedDRA	INV-assessed TEAEs All reported TEAEs within ND/PD SOC using MedDRA
Encephalopathy per Study Protocol, Grouped Term	As defined for NT per Study Protocol but restricted to encephalopathy events.	As defined for NT per Study Protocol
Encephalopathy per Study Protocol, Preferred term	As defined for NT per Study Protocol, but restricted to Encephalopathy events, and further restricted to those with preferred term Encephalopathy	As defined for NT per Study Protocol
Encephalopathy per ND/PD SOC, Grouped Term	INV-assessed TEAEs	INV-assessed TEAEs

	Grouped per ND/PD SOC using MedDRA	Grouped per ND/PD SOC using MedDRA

	TRANSCEND (017001) (Liso-cel)	ZUMA-1 (Axi-cel)
Aphasia per Study Protocol, Grouped Term	As defined for NT per Study Protocol, but restricted to aphasia events	As defined for NT per Study Protocol
Aphasia per Study Protocol, Preferred term	As defined for NT per Study Protocol, but restricted to aphasia events, and further restricted to those with preferred term Aphasia	As defined for NT per Study Protocol
Aphasia per ND/PD SOC, Grouped term	INV-assessed TEAEs Grouped per ND/PD SOC using MedDRA	INV-assessed TEAEs Grouped per ND/PD SOC using MedDRA
Infections, Any Pathogens, per SOC	INV-assessed TEAEs Grouped per infections and infestations SOC using MedDRA	INV-assessed TEAEs Grouped per infections and infestations SOC using MedDRA
Hypogammaglobulinemia, Grouped term	INV-assessed TEAEs grouped using MedDRA	INV-assessed TEAEs grouped using MedDRA
Prolonged Cytopenia[c] by laboratory assessment	Assessment by laboratory values Grade ≥ 3 not resolved at Day 29 after infusion	Not reported
Prolonged Cytopenias reported as AEs Anemia Neutropenia Thrombocytopenia	INV-assessed TEAEs Grade ≥ 3 not resolved at Day 29 after infusion	INV-assessed TEAEs Grade ≥ 3 not resolved by Day 30 after infusion
Febrile neutropenia	INV-assessed TEAE using MedDRA As a preferred term	INV-assessed TEAE using MedDRA As a preferred term

[a]Also measured until disease progression or 15-year follow-up, whichever comes first. Time window for TEAEs was reported by Locke (2019) [62] to be from lymphodepleting chemotherapy, however not all AESI data points used in ITCs were reported by Locke 2019 [62]. Those reported by documents from EMA and FDA may have reported based on different time windows (eg, from the first infusion).

[b]Neurologic events were identified using a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy [80].

[c]Neutropenia, thrombocytopenia, and anemia by laboratory assessment.

9.2.1 Safety data from the clinical documentation

Table 49 shows the overview of safety events in TRANSCEND (017001) and ZUMA-1.

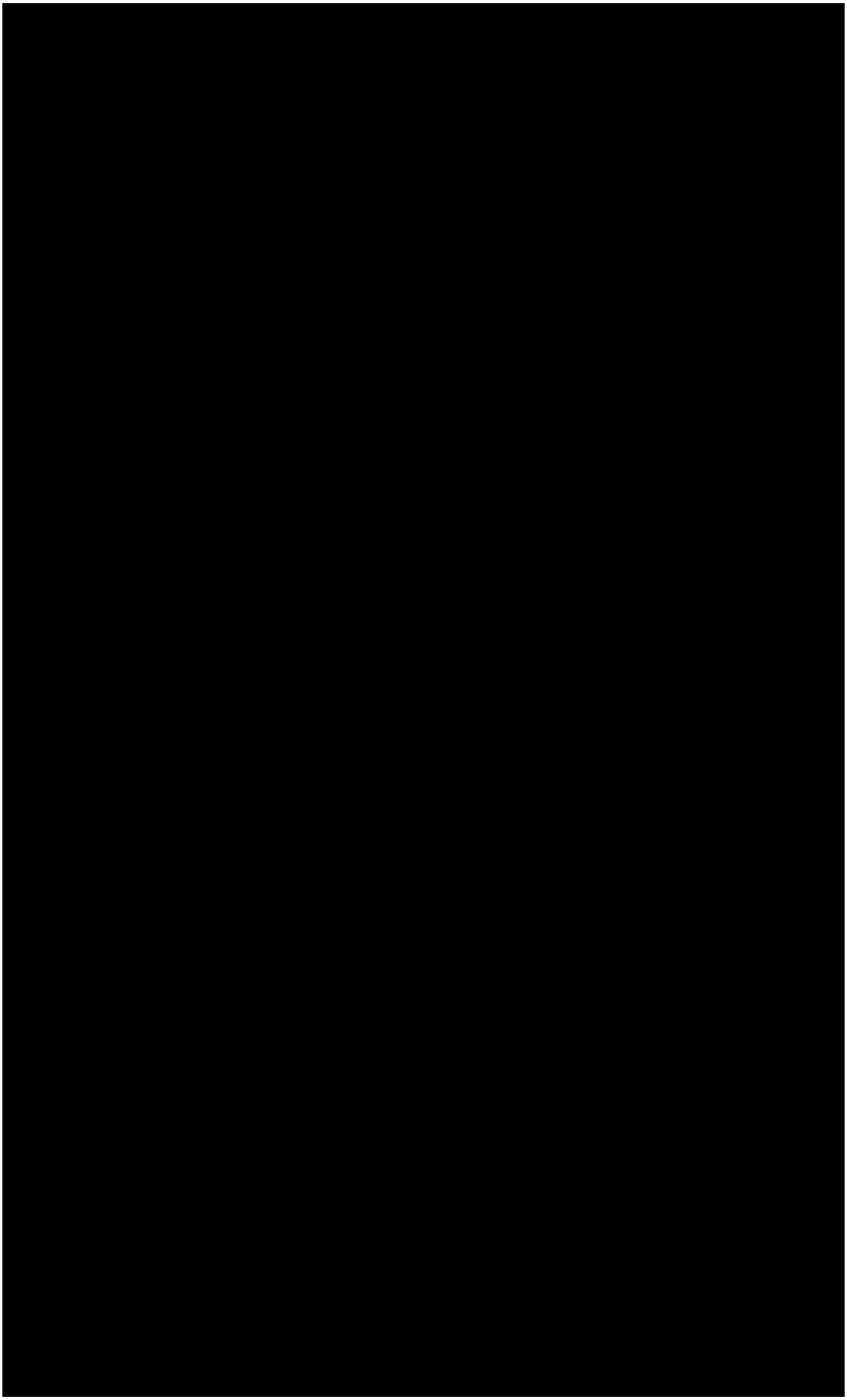
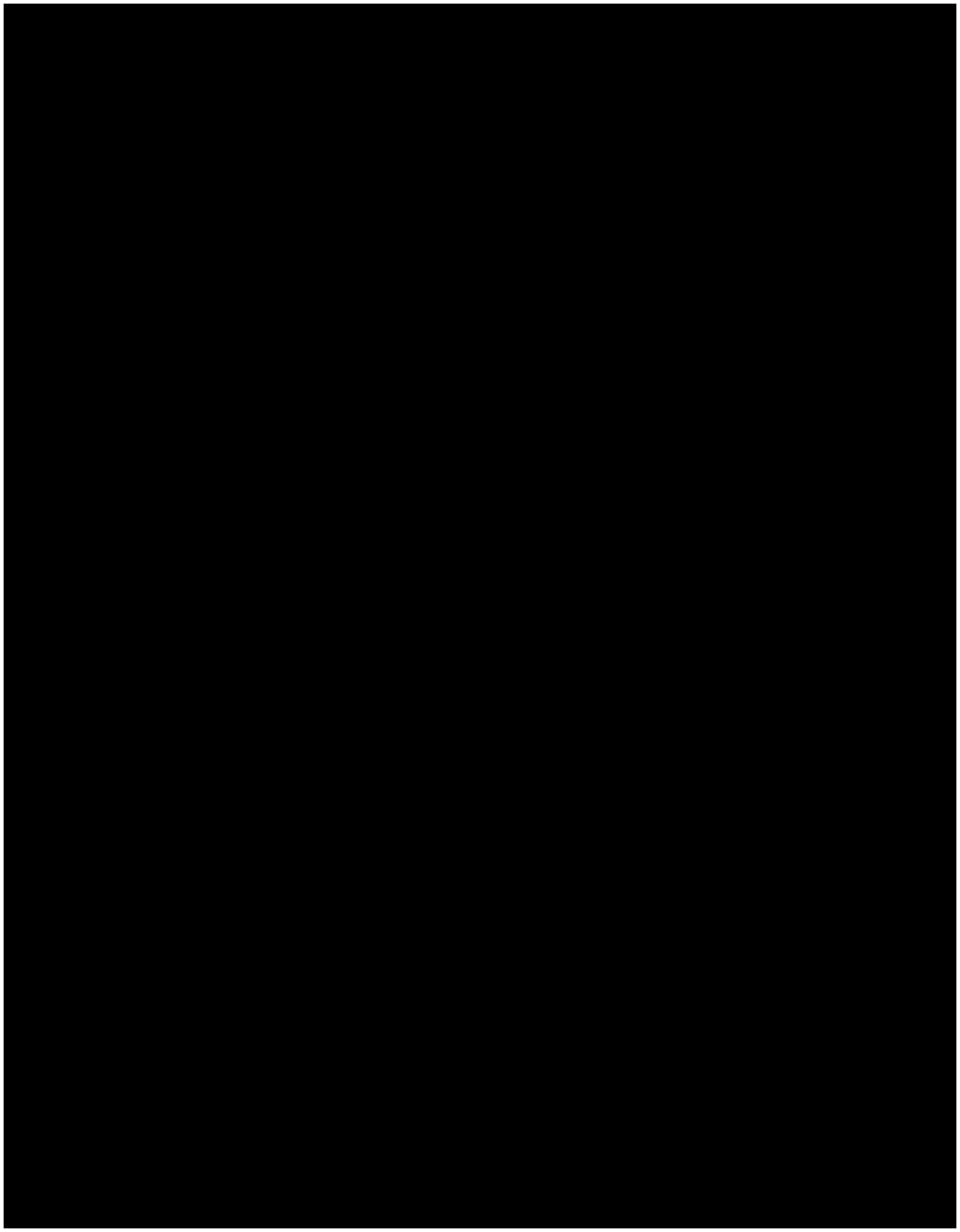
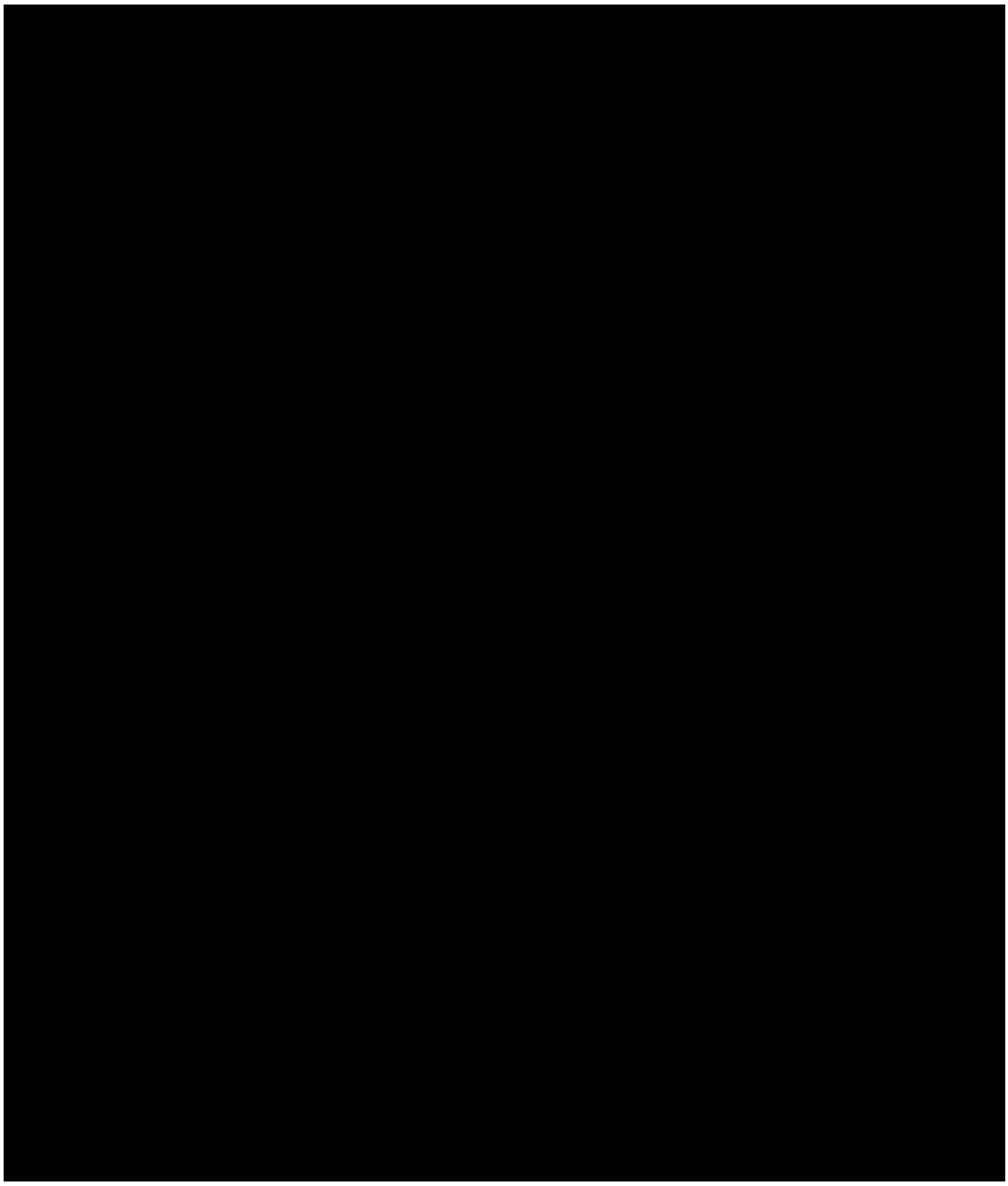
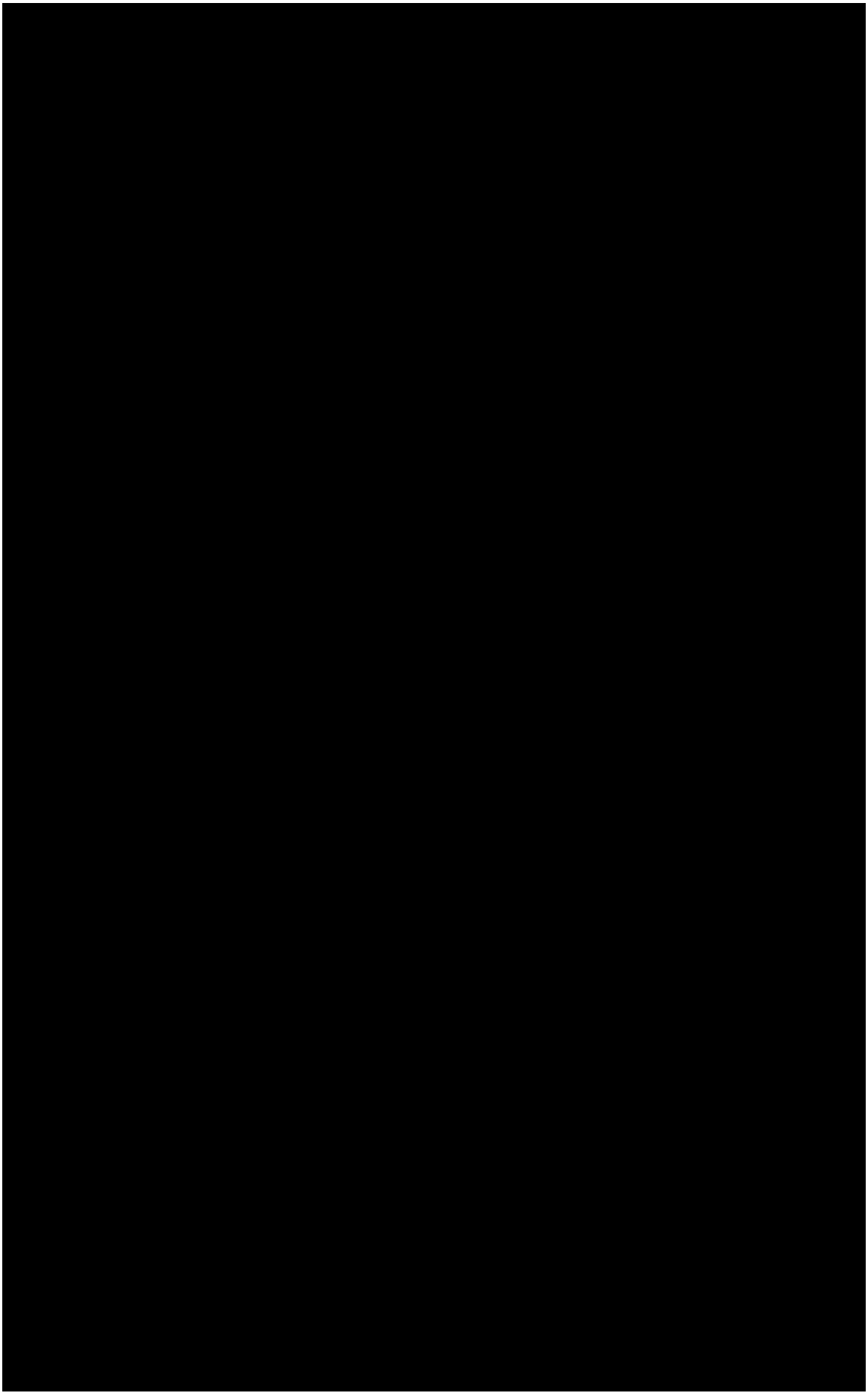


Table 50 shows the serious adverse events with frequency of ≥ 5% in any treatment arm recorded in the TRANSCEND (017001) study. For ZUMA-1, this information is not publicly available.

Rates of all assessed AESI are reported in Table 51 [60].







Most of the AEs will be managed within the hospitalization time after liso-cel/axi-cel administration (see section 11.4). Nonetheless, the cost-minimization analysis includes grade 3 or higher cytokine release syndrome (CRS) and neurotoxicity (NT) AEs.

These were also the AEs costs included by the DMC in their assessment of axi-cel for the 2L treatment of LBCL [36].

The proportion of patients experiencing the selected AEs were sourced from the MAIC between liso-cel (TRANSCEND 017001, DLBCL Treated Set DL1S + DL2S + DL1D) and axi-cel (ZUMA-1, Phase 1+2 Safety Analysis Set) [60].

Table 53 shows the AEs included in the cost-minimization analysis. The costs associated with these AEs are presented in Table 74.

9.2.2 Safety data from external literature applied in the health economic model

Not applicable.

10. Documentation of health-related quality of life (HRQoL)

10.1 Liso-cel compared to axi-cel for the treatment adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

The TRANSFORM and ZUMA-7 trials used the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) and EQ-5D-5L questionnaires to assess HRQoL [55, 56, 58, 65] (Table 54).

Table 54 Overview of included HRQoL instruments (2L)

Measuring instrument	Source	Utilization
EORTC QLQ-C30	TRANSFORM trial. ZUMA-7 trial.	Naïve comparison of HRQoL between liso-cel and axi-cel.
EQ-5D-5L	TRANSFORM trial. ZUMA-7 trial.	Naïve comparison of HRQoL between liso-cel and axi-cel.

10.1.1 Presentation of the health-related quality of life

10.1.1.1 Study design and measuring instrument

QoL was assessed within TRANSFORM and ZUMA-7 using the EORTC QLQ-C30 and the EQ-5D-5L.

The EORTC QLQ-C30 is a self-administered, cancer-specific, 30-item questionnaire with a 1-week recall period. It incorporates 5 2- to 5-item functional scales (physical, role, cognitive, emotional, and social), 3 2- to 3-item symptom scales (fatigue, pain, and nausea and vomiting), a 2-item global health status/QoL scale, and numerous single items that assess additional symptoms commonly reported by patients with cancer (e.g., dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea) and the perceived financial impact of the disease. No items are shared between scales. All scales/items are linearly transformed to a 0 to 100 metric, with high functional scale scores representing high/healthy levels of functioning and high scores for symptom scales/items representing high levels of symptoms/problems [58].

In the TRANSFORM study, the EORTC QLQ C30 GH/QoL, physical functioning, cognitive functioning, fatigue, and pain were selected as the primary domains of interest. These domains were considered the most clinically relevant and important to the target population, as they have been used as the primary HRQoL domains of interest in other published studies [55, 56, 65]. Therefore, these were the EORTC QLQ-C30 domains included in the naïve comparison of HRQoL between liso-cel and axi-cel.

The EQ-5D-5L is a generic and preference-weighted measure for capturing health-related QoL on the assessment day. It is a self-reported instrument that yields a health utility index score. Five domains are evaluated: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is divided into 5 severity levels: “no problem,” “slight problems,” “moderate problems,” “severe problems,” and “extreme problems. The EQ-5D-5L health utility index score summarizes each health status using a single global score (i.e.,utility), anchored at 0 (signifying death) and 1 (signifying perfect health), which reflects preferences from the general population. The ZUMA-7 analysis used the United States time tradeoff value set whereas the TRANSFORM analysis used the UK value set [55, 56, 58, 65]. Danish values are not available so US and UK values are used. This will not affect the result since it is a naïve comparison.

In the TRANSFORM trial, of the 92 patients in the liso-cel arm and 92 patients in the SoC arm (i.e., ITT analysis set):

- 50 (54.3%) and 46 (50.0%) patients, respectively, met the inclusion criteria and were included in the EORTC QLQ-C30 analysis set. The EORTC QLQ-C30 analysis set included ITT patients who completed at least one evaluable assessment at baseline and at least one at a postbaseline visit based on EORTC QLQ-C30. An evaluable EORTC QLQ-C30 assessment was defined as having at least one of the 15 domains nonmissing at a given scheduled assessment visit [55, 56, 65].

- 49 (53.3%) and 44 (47.8%) patients, respectively, were included in the EQ-5D-5L analysis set for health utility. The EQ-5D-5L health utility index analysis set included ITT patients who had at least one evaluable assessment of EQ-5D-5L health utility index at baseline (i.e., at randomization) and at least one evaluable assessment at a postbaseline visit. An evaluable EQ-5D-5L health utility index assessment was defined as having all of the 5 items answered at a scheduled assessment visit [55, 56, 65].

The baseline demographic characteristics, disease characteristics, and diagnosis history of patients in the EORTC QLQ-C30 and EQ-5D analysis set were generally similar to those of the ITT population [55-57]. Most key baseline demographic characteristics were comparable between treatment arms, except that the mean age was higher in the liso-cel arm than in the SoC arm (57.40 vs. 51.37 years and 57.4 vs. 51.8 in the EORTC QLQ-C30 and EQ-5D analysis set, respectively), and the proportion of females was greater in the liso-cel arm than in the SOC arm (56.0% vs 34.8% and 57.1% vs. 35.6% in the EORTC QLQ-C30 and EQ-5D analysis set, respectively) [55-57]. Further, most key baseline disease characteristics in the EORTC QLQ-C30 analysis set were comparable between treatment arms, except that the mean HSCT-specific comorbidity index (HCT-CI) score tended to be lower in the SOC arm than in the liso-cel arm (1.02 vs 1.64). The proportion of patients with a baseline ECOG PS score of 0 was higher in the SOC arm than in the liso-cel arm (60.9% vs 48.0%), as was the proportion of patients with a screening ECOG PS score of 0 (71.7% vs 54.0%) [55, 56, 65, 84].

In the ZUMA-7 trial, The QoL analysis set was defined as patients who had a baseline PRO and at least 1 measure completed at day 50, 100, or 150 from randomization. Measures at baseline and at least 1 follow-up time point were required to compute changes from baseline [58].

In the ZUMA-7 trial, of the 180 patients in the axi-cel arm and 179 patients in the SoC arm (i.e., ITT analysis set):

- 165 patients in the axi-cel arm and 131 patients in the SOC arm met the criteria for the QoL analysis set [58].

Of the 296 patients in the QoL analysis set, 29.7% were 65 years or older and 66.2% were male. The axi-cel cohort had >5% differences compared with SoC in the following baseline characteristics: fewer patients from Europe (axi-cel 18.8% vs SoC 26.0%), more female patients (38.8% vs 27.5%), more patients with Eastern Cooperative Oncology Group performance status 1 (46.1% vs 38.2%), more patients with disease type as HGBL with or without MYC and BCL2 and/or BCL6 rearrangement (22.4% vs 13.0%), more patients with germinal center B-cell–like cell of origin (52.7% vs 42.7%) and fewer not tested (20.6% vs 26.7%), and more patients with status as HGBL double hit (17.6% vs 8.4%), with fewer not tested (17.0% vs 25.2%). No formal statistical testing for differences across treatment arms was undertaken [58].

10.1.1.2 Data collection

In TRANSFORM, PRO/HRQoL, as measured by the EORTC QLQ-C30 and EQ-5D-5L was assessed at the following timepoints [55]:

- At randomization (baseline): Day 1 (+ 3 days).
- During the treatment period: Days 29 (± 7 days), 64 (± 6 days), and 126 (± 7 days).
- During the post-treatment period: Month 6 (± 10 days) and Months 9, 12, 18, 24, and 36 (± 14 days) among subjects who did not receive subsequent antineoplastic treatment.

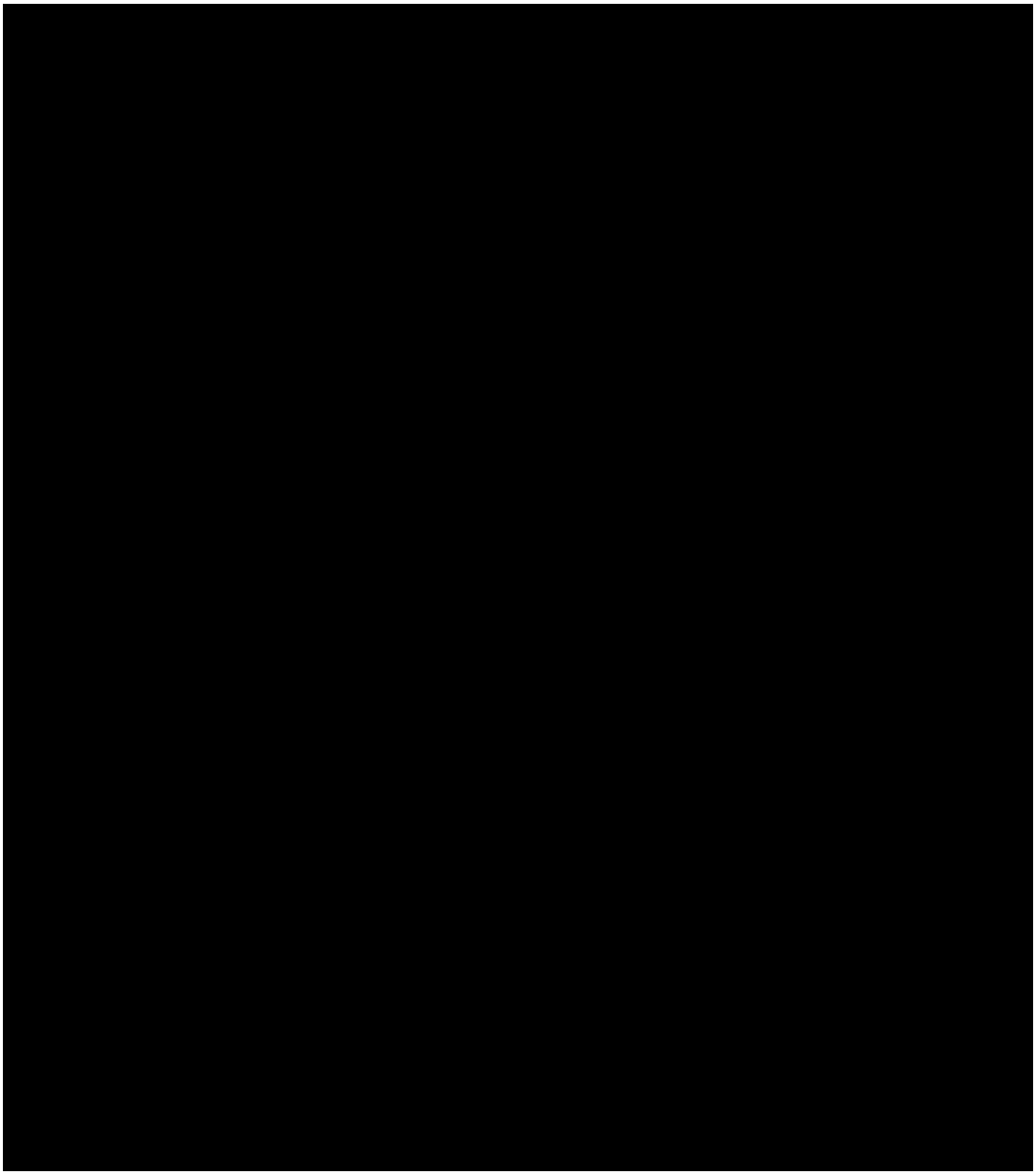
Postbaseline assessment visits could be shifted due to delays in liso-cel infusions or SoC treatment cycles. Additionally, PRO/HRQoL assessments were not performed after subjects switched to liso-cel or received subsequent antineoplastic therapy [55].

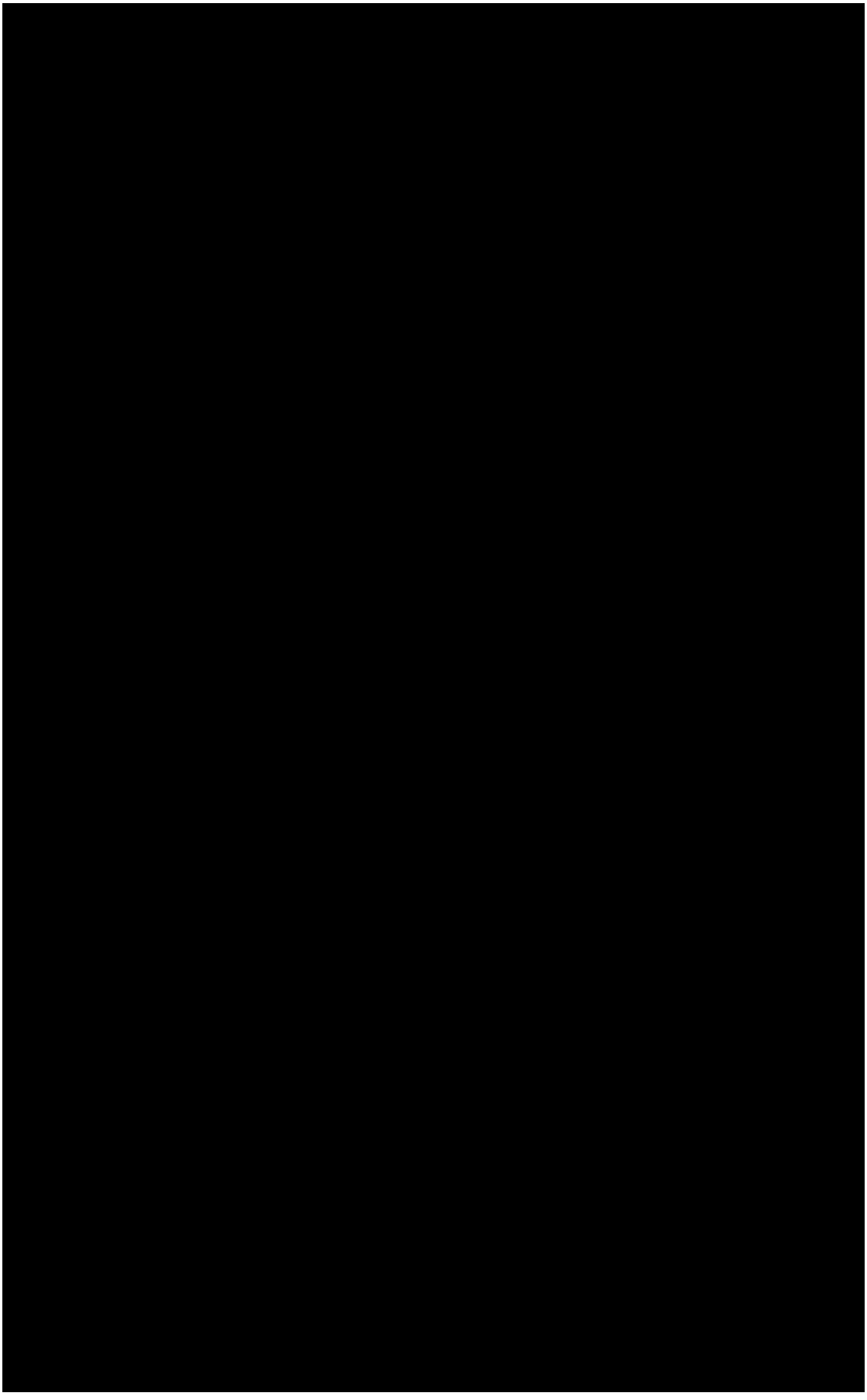
Table 55 and

Table 56 show the pattern of missing data and completion for liso-cel and SoC, respectively (EORTC QLQ-C30; Global Health/Quality of Life domain).

Table 57 and

Table 58 show the pattern of missing data and completion for liso-cel and SoC, respectively (EQ-5D Data Availability).





In ZUMA-7, PRO instruments, including the EORTC QLQ-C30 and the EQ-5D-5L were administered at baseline (prior to treatment with either conditioning or salvage chemotherapy), day 50, day 100, day 150, month 9, and subsequently every 3 months from randomization up to 24 months or time of EFS event. Sites were not required to administer PRO assessments after an EFS event, defined as time from randomization to the earliest date of disease progression per Lugano Classification [25], commencement of new lymphoma therapy, or death from any cause [58].

Table 116 in Appendix F shows the pattern of missing data and completion for axi-cel and SoC.

10.1.1.3 HRQoL results

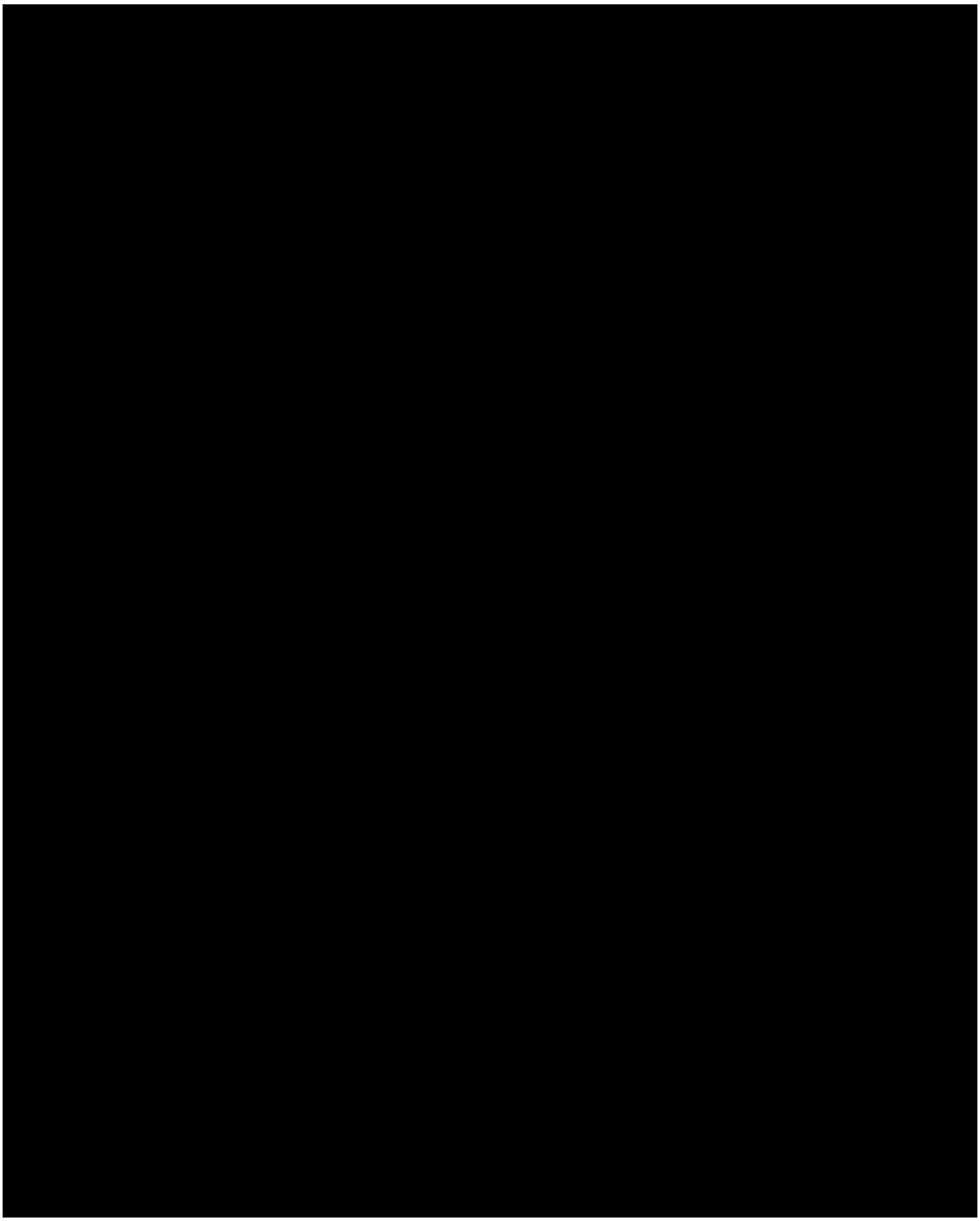
Table 59 summarizes the HRQoL (EORTC QLQ-C30 and EQ-5D-5L) scores at baseline among subjects receiving liso-cel or SoC in TRANSFORM. Figure 40 shows the baseline EORTC QLQ-C30 and EQ-5D-5L scores for patients in the axi-cel and SoC arms in ZUMA-7.

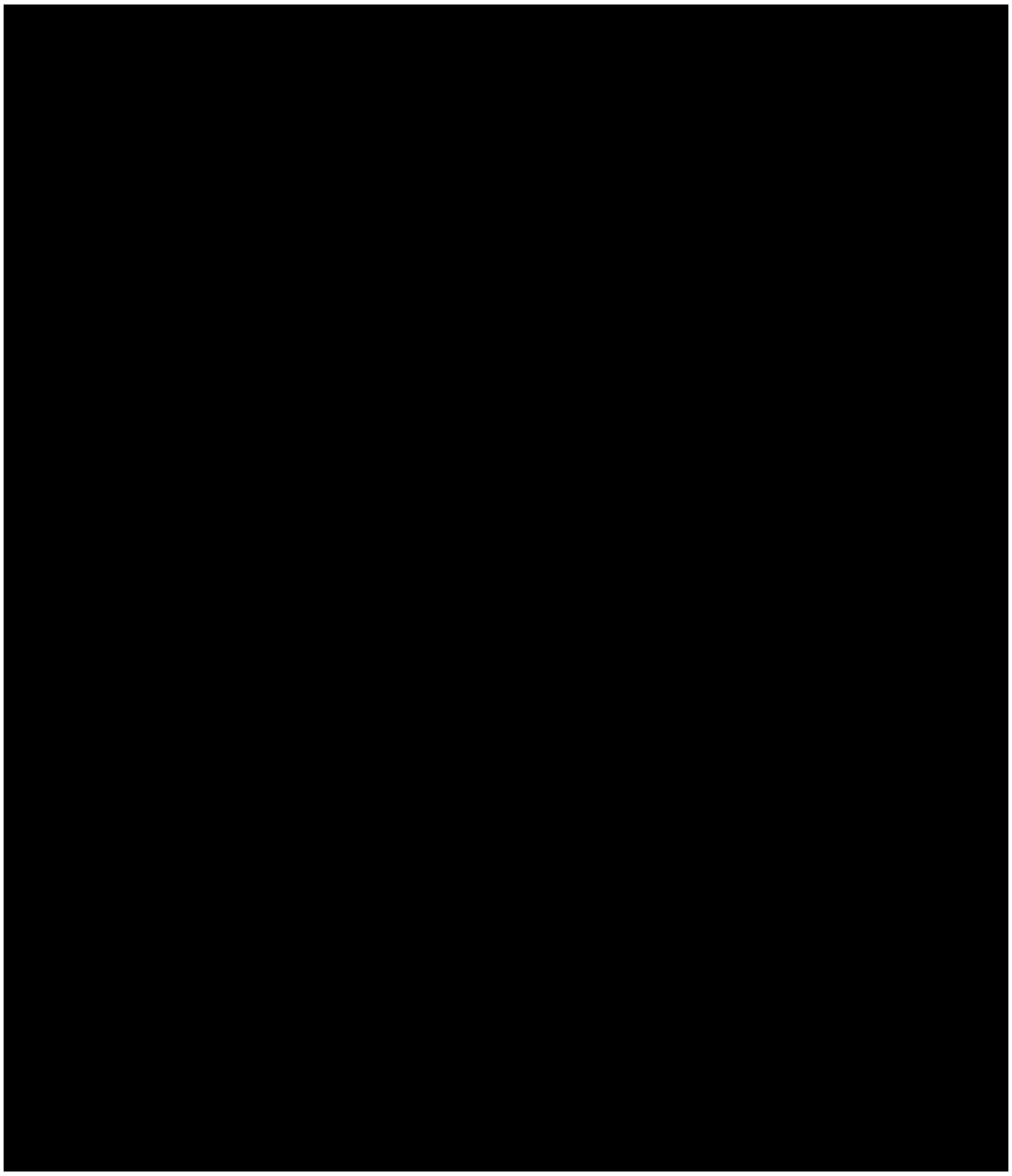
Figure 41 shows the observed mean changes from baseline over time in the liso-cel and SoC arms for the EORTC QLQ-C30 primary domains in the TRANSFORM study. Figure 42 and Figure 43 show the observed mean changes from baseline over time in the liso-cel and SoC arms for the EQ-5D-5L health utility index and EQ-VAS scores respectively in the TRANSFORM study. For more comprehensive data regarding the HRQoL summary statistics at relevant data collection time points see Table 117 HRQoL summary statistics - Observed Scores by Treatment Group (liso-cel and SoC) and Visit – TRANSFORM trial

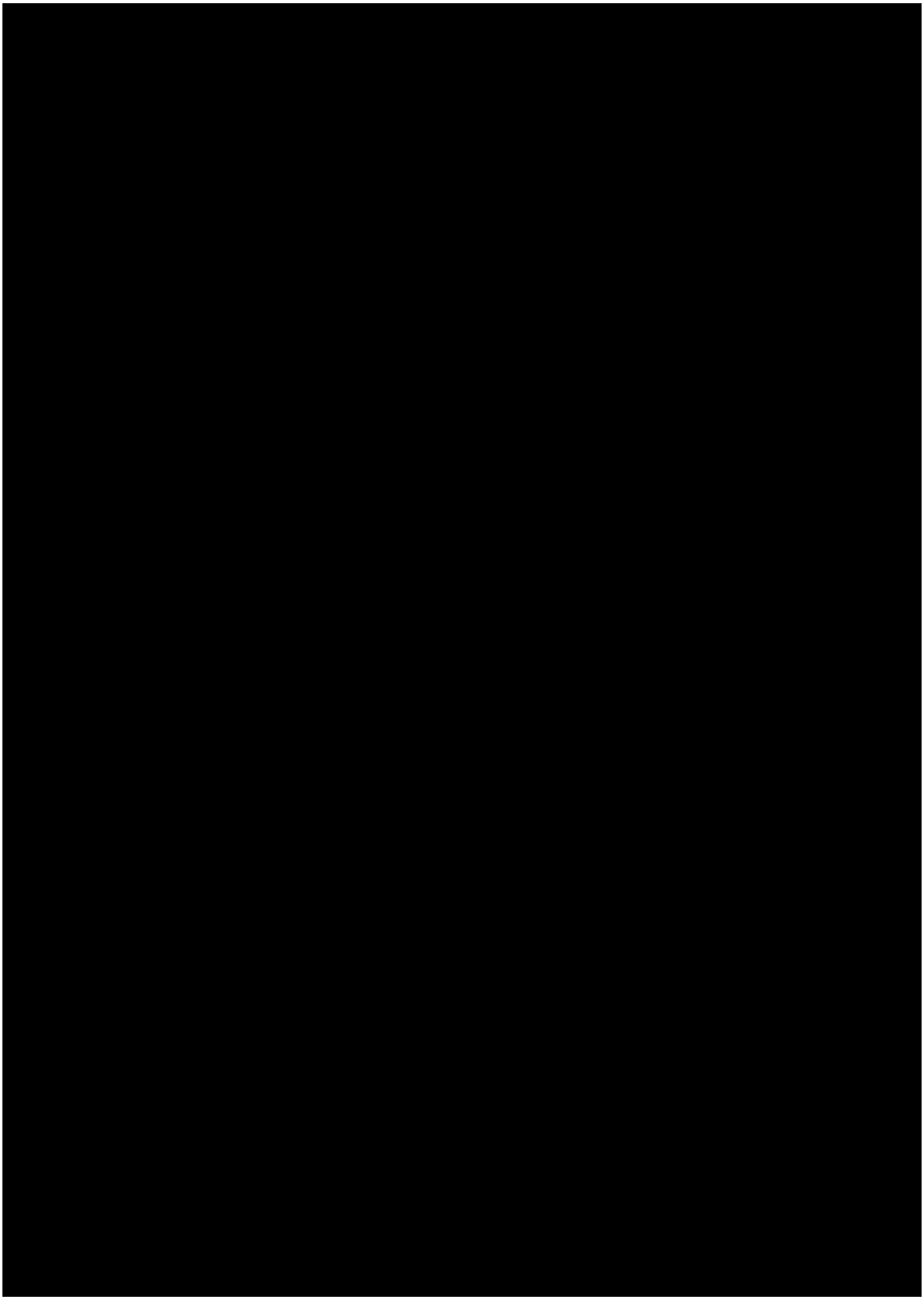
(DCO 13 May 2022). Figure 44 shows EORTC QLQ-C30 and EQ-5D-5L score and score change from baseline for axi-cel and SoC at day 50 in the ZUMA-7 study.

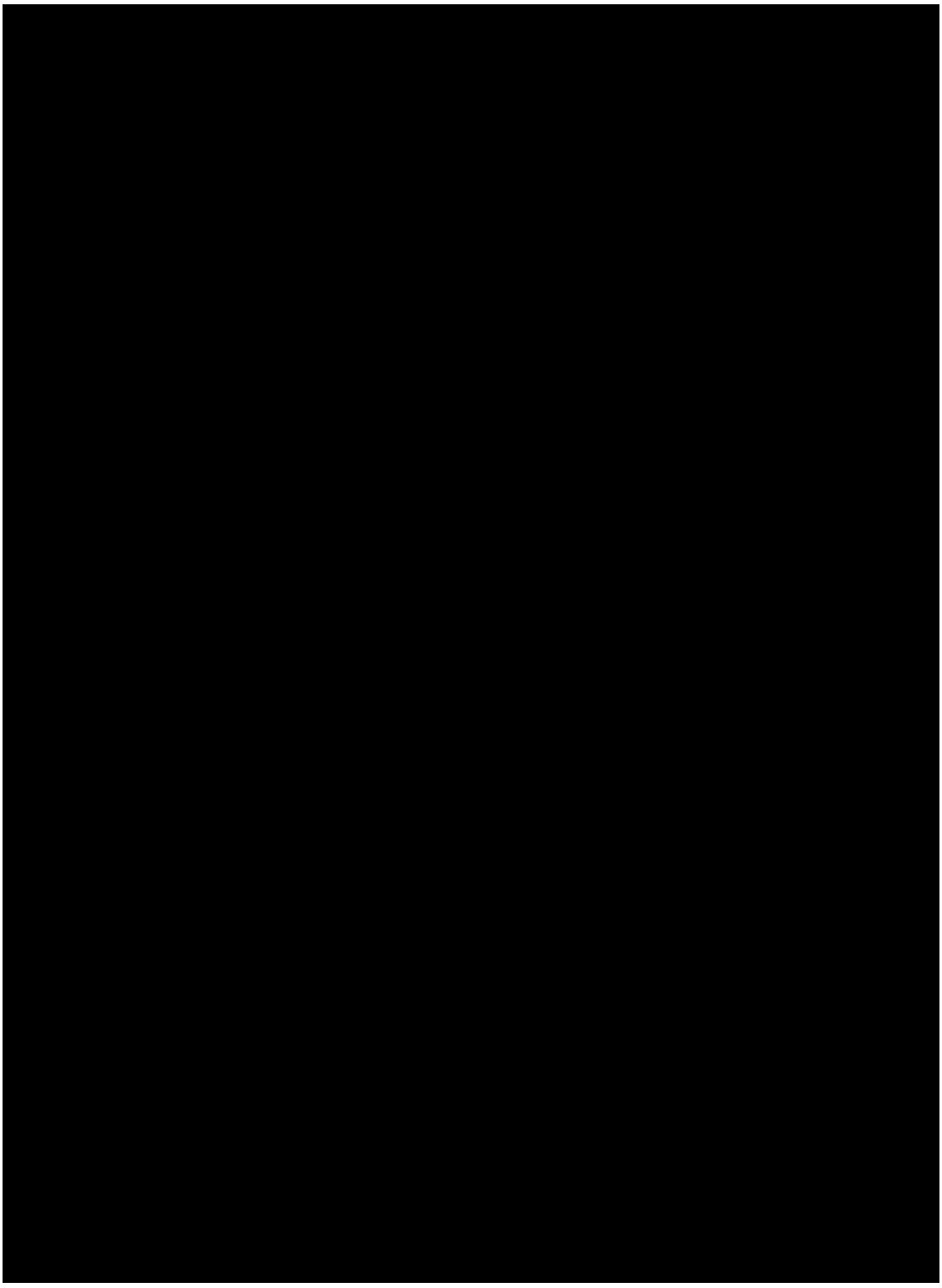
Table 60 summarizes the mixed model for repeated measures (MMRM) overall least squares (LS) mean changes from Baseline to Month 6 (ie, the timepoint at which the model converged) for the TRANSFORM HRQoL Analysis Set.

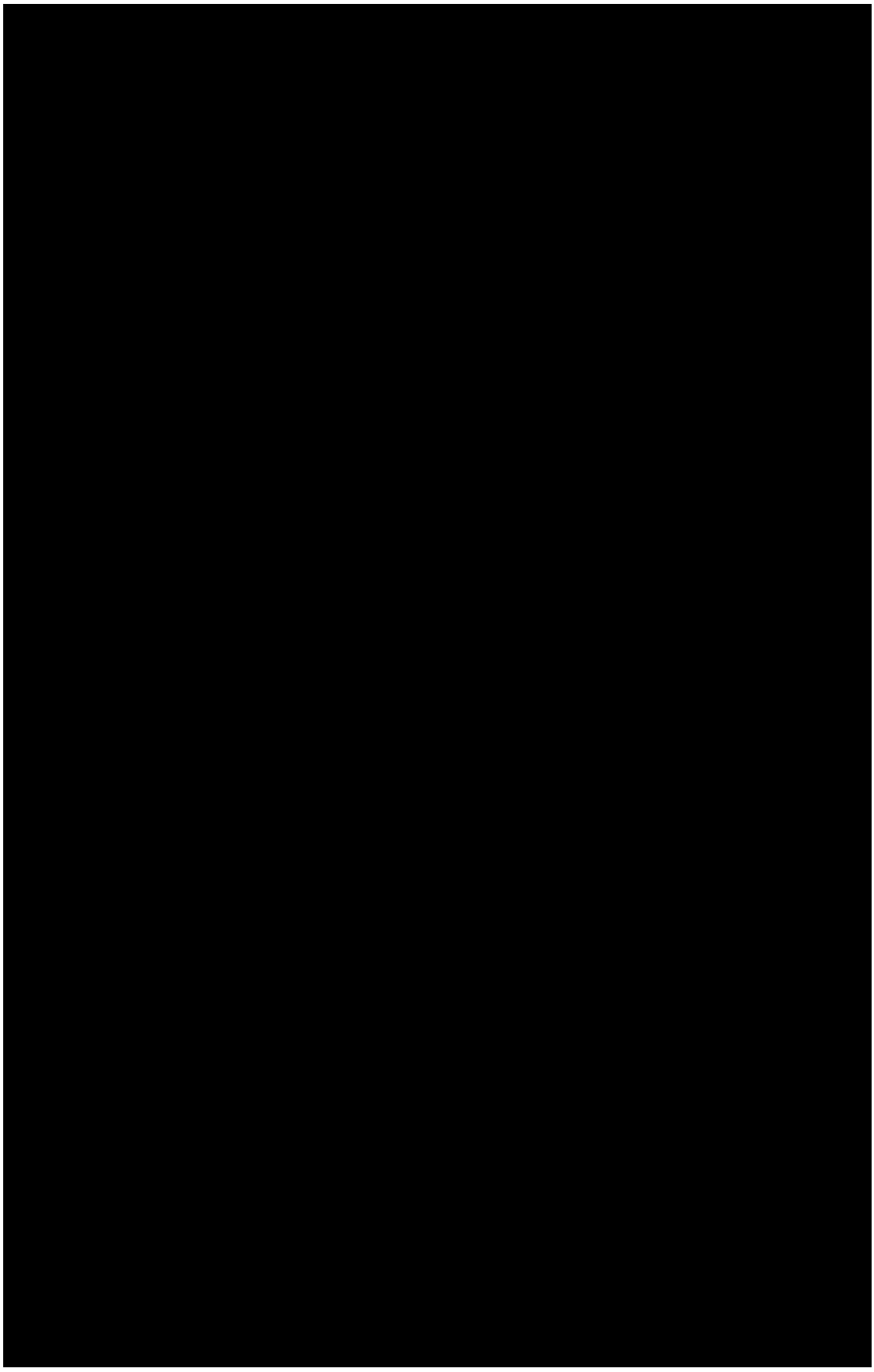
Figure 45 shows the MMRM estimated difference in change from baseline (axi-cel – SoC) for EORTC QLQ-C30 and EQ-5D-5L. Figure 46 shows the MMRM for change from baseline for axi-cel and SoC for EORTC QLQ-C30 and EQ-5D-5L.

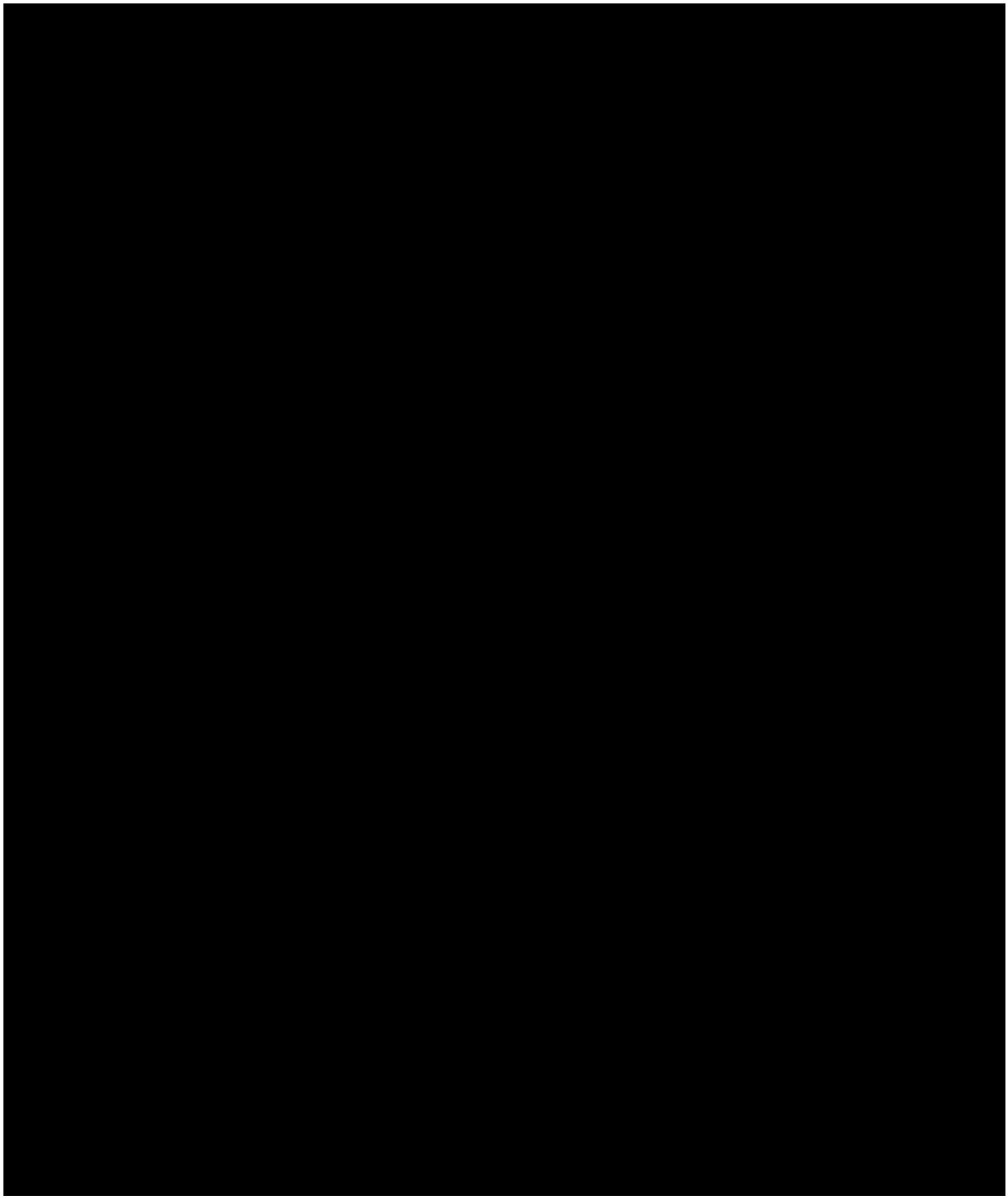


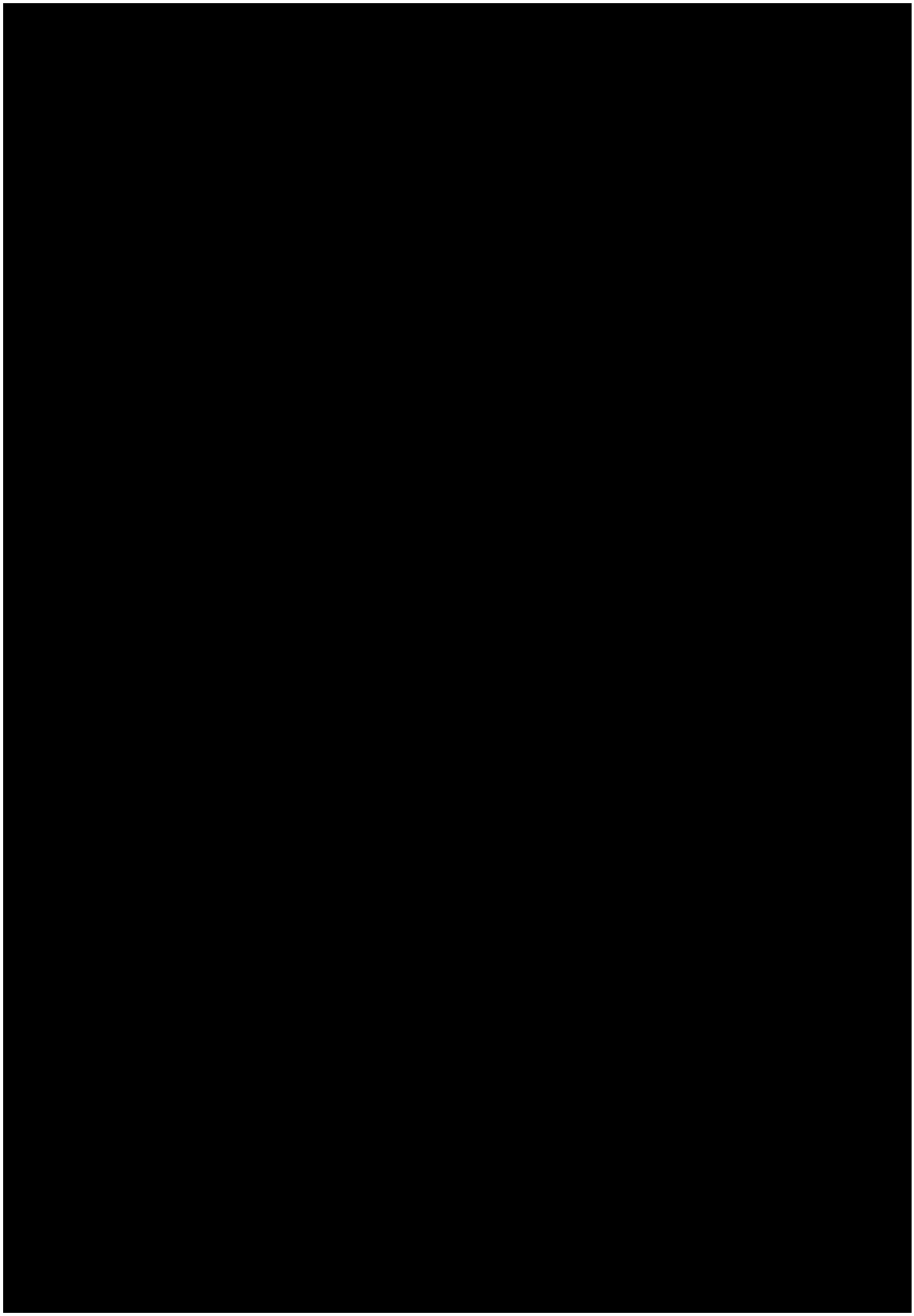


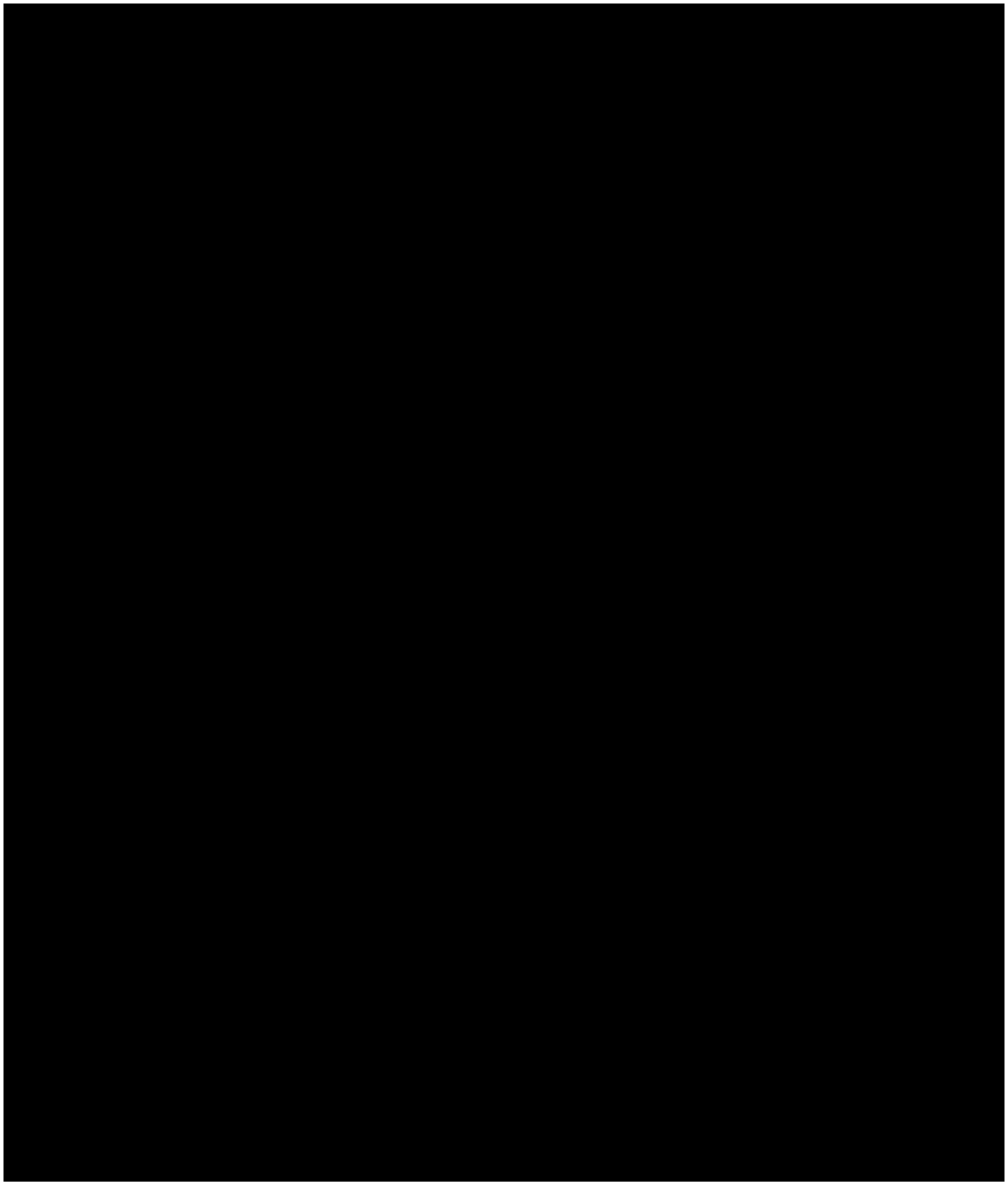


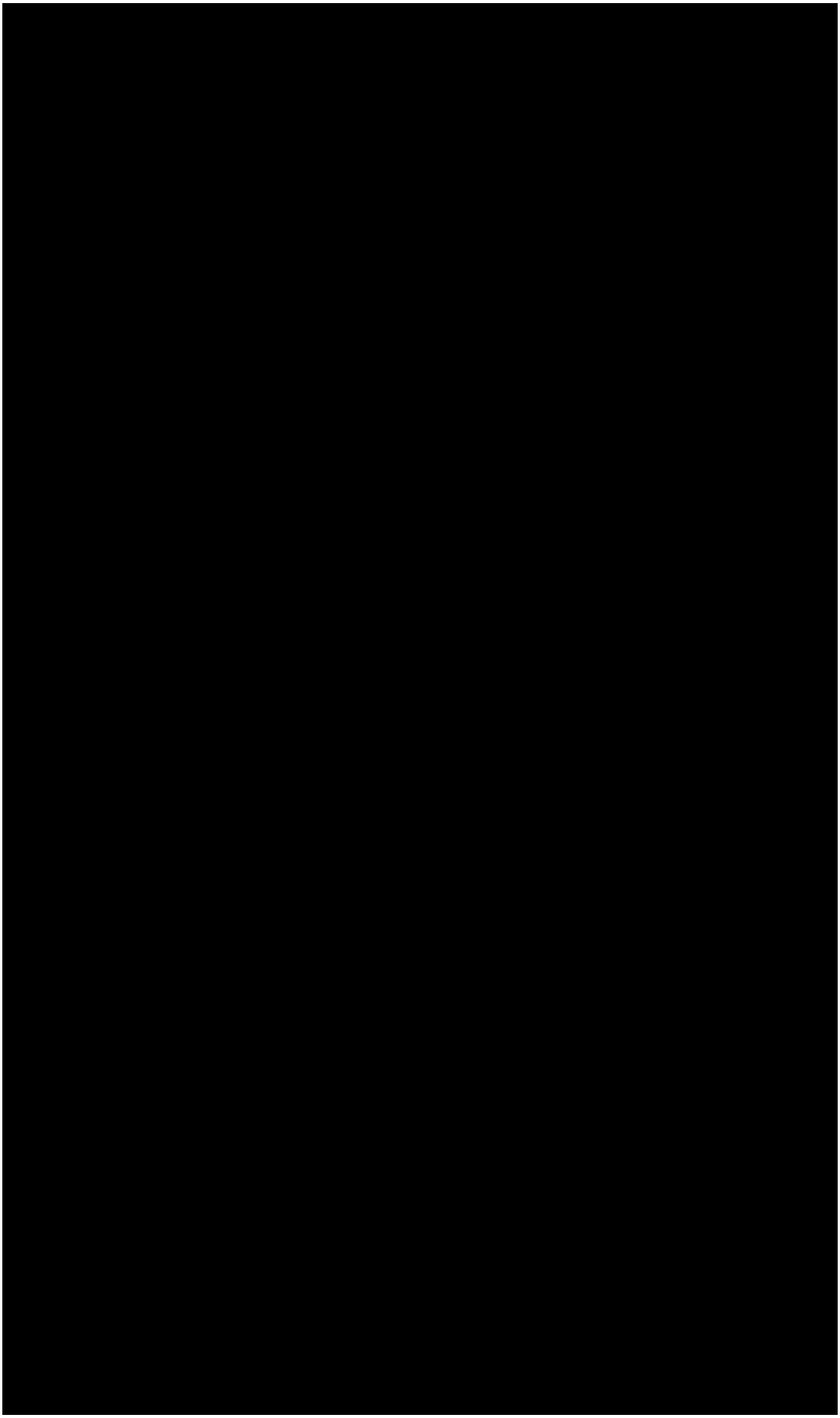


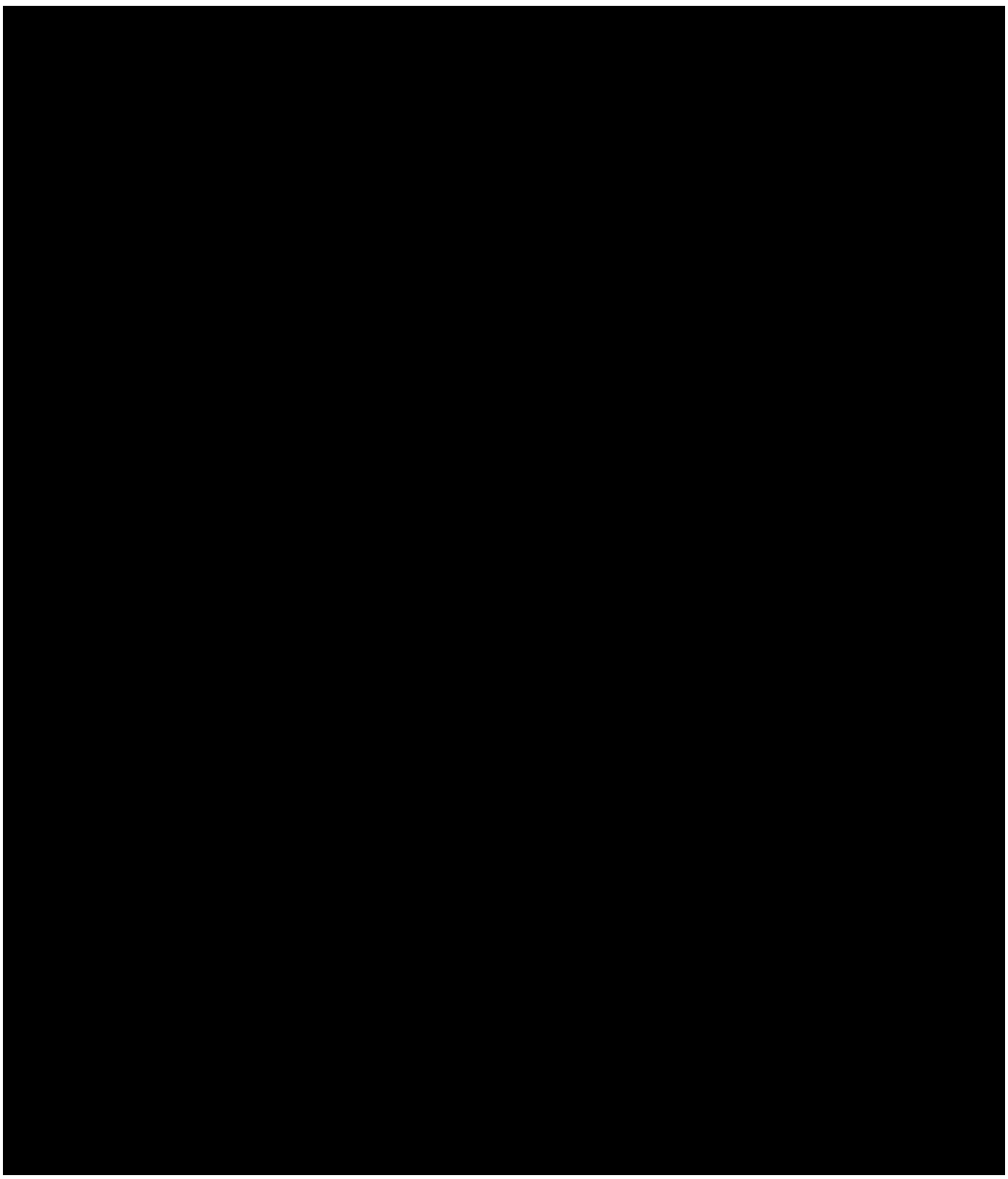


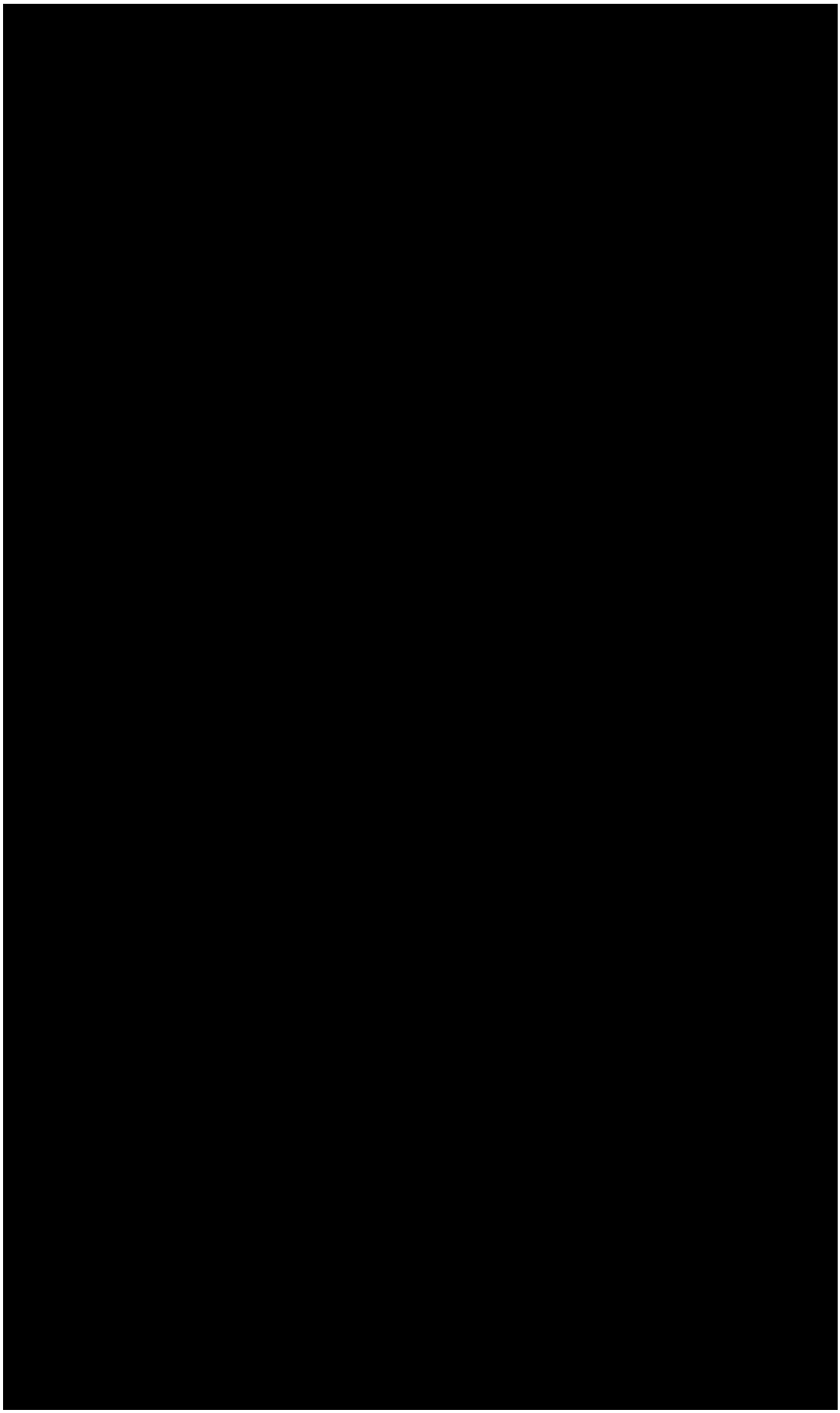


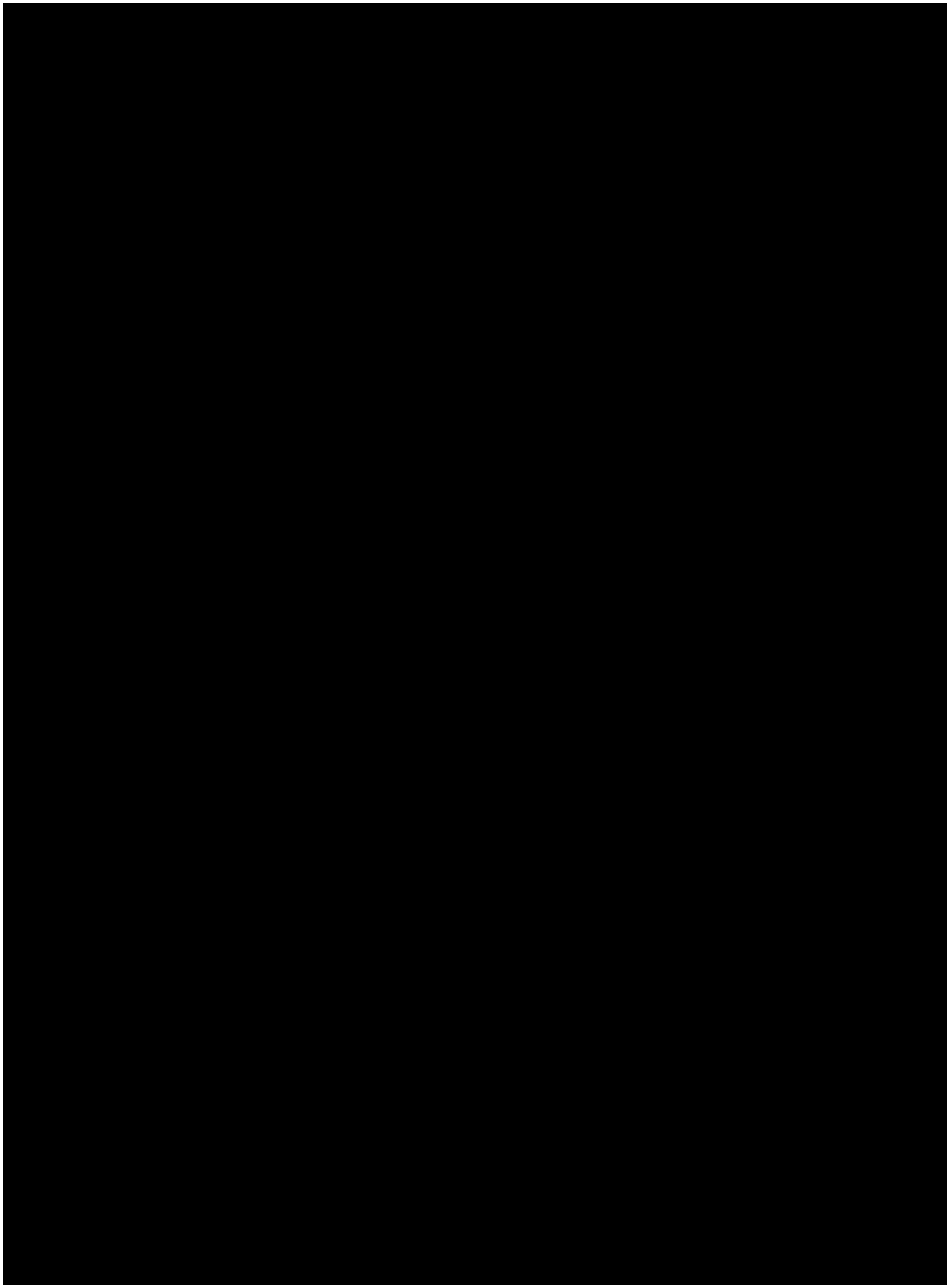












10.1.2 Health state utility values (HSUVs) used in the health economic model

Not applicable.

10.1.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.2 Liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

For axi-cel, only a phase 2 ZUMA-1 safety management study ad hoc analysis investigated the impact of axi-cel treatment on health utility in patients with R/R LBCL in the third-line or later setting, as measured by the EQ-5D-5L [64]. Therefore, only EQ-5D-5L data derived from TRANSCEND (017001) [63] was included in this section to allow for a naïve comparison (Table 61).

Table 61 Overview of included HRQoL instruments (3L)

Measuring instrument	Source	Utilization
EQ-5D-5L	TRANSCEND (017001) trial. ZUMA-1 trial.	Naïve comparison of HRQoL between liso-cel and axi-cel.

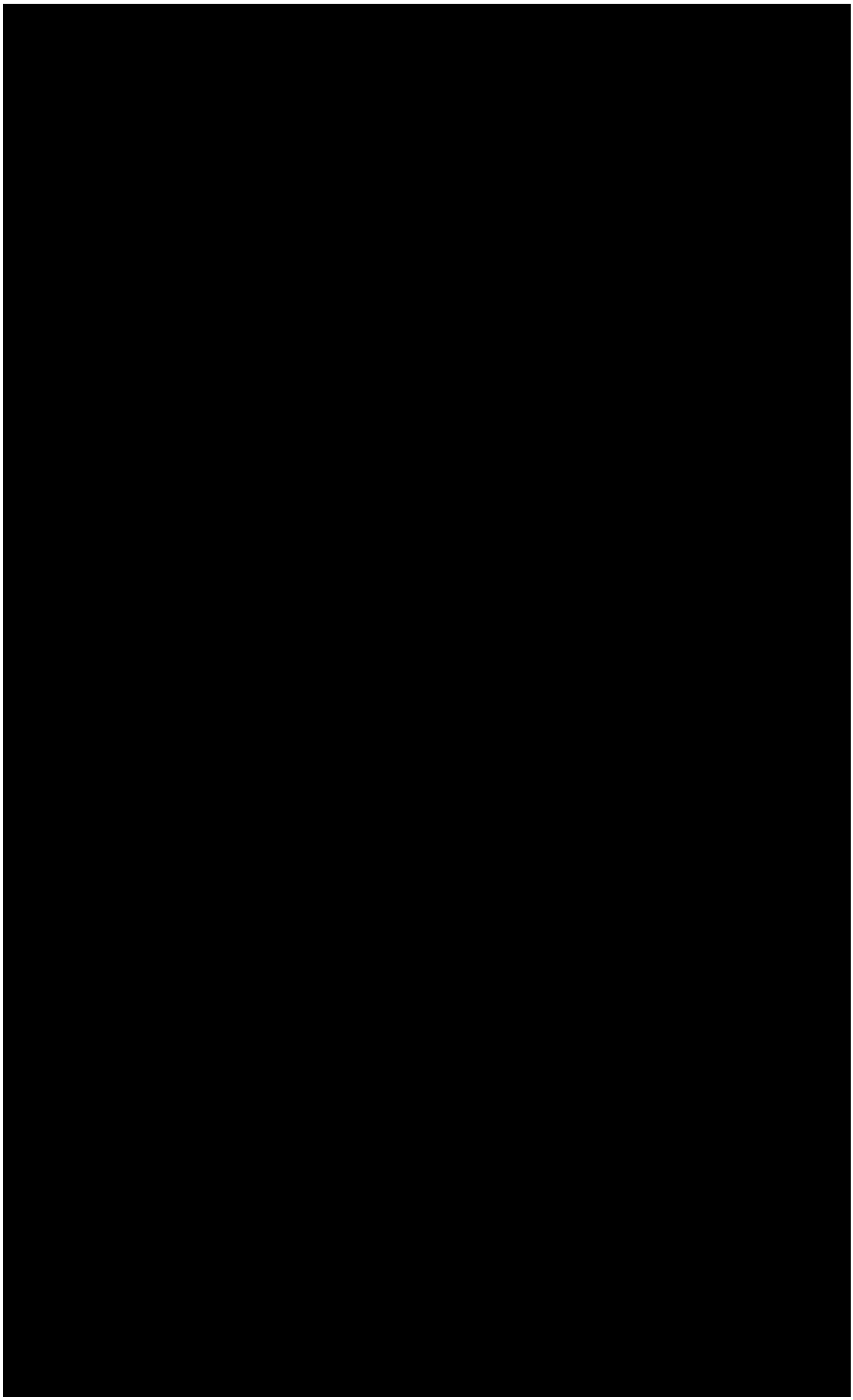
10.2.1 Presentation of the health-related quality of life

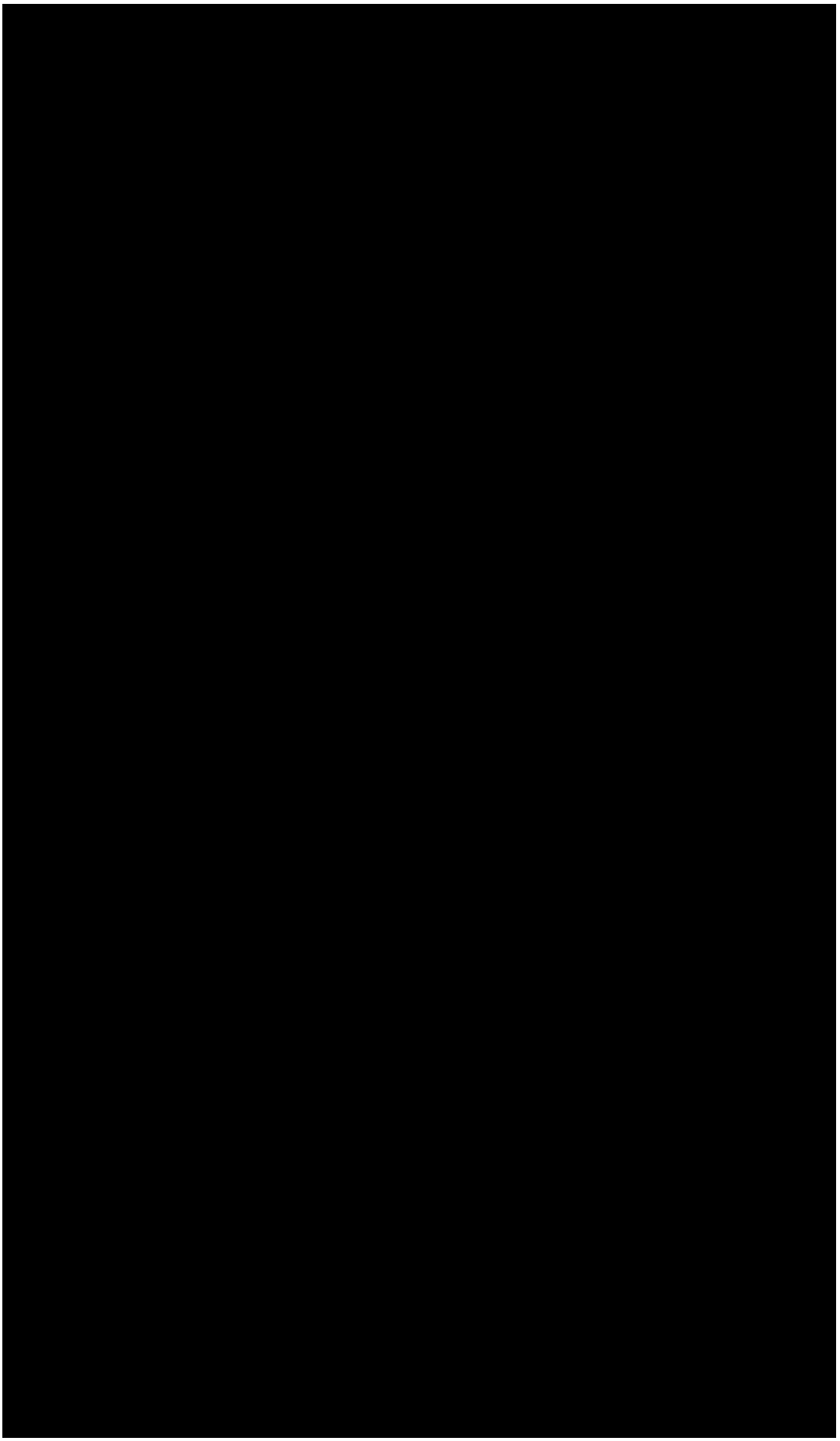
10.2.1.1 Study design and measuring instrument

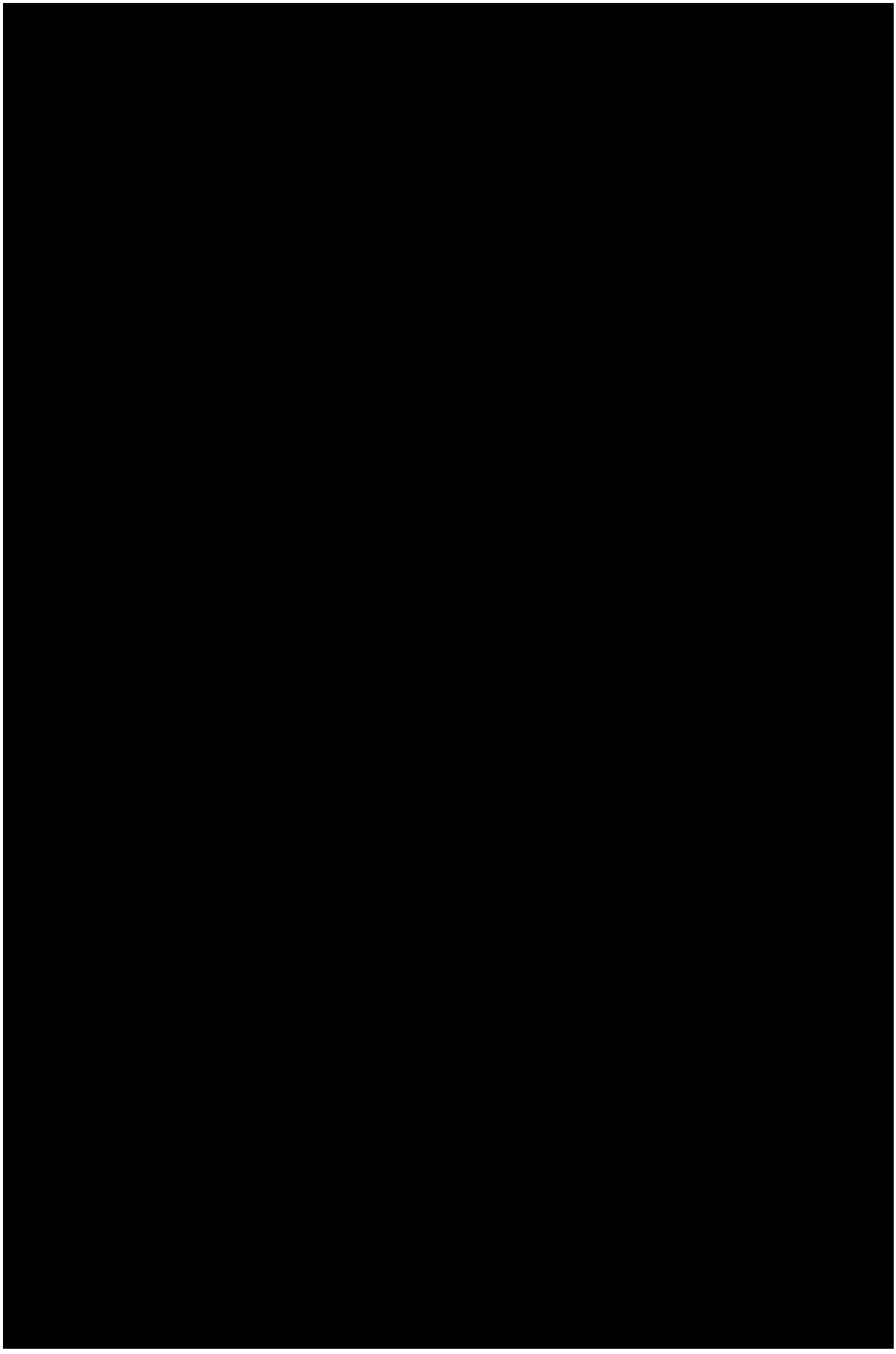
QoL was assessed within TRANSCEND (017001) and ZUMA-1 using the EQ-5D-5L.

The EQ-5D-5L instrument was described in section 10.1.1.1. The ZUMA-1 analysis used the United states value set [64] whereas the TRANSCEND (017001) analysis used the UK value set [63].

[redacted]







In the ZUMA-1 trial, in a total of 34 patients treated with axi-cel, the median (range) age was 51 (21–74) years, 56% were male, 56% had ECOG performance status of 1, and 32% had an International Prognostic Index (IPI) score ≥3. At this ad hoc analysis, EQ-5D-5L were collected from 33, 27, 20, and 7 patients at Screening, Week 4, Month 3 and 6, respectively. The median follow-up (min, max) time among subjects treated was 5.1 (0.3, 9.5) months [64].

10.2.1.2 Data collection

In the TRANSCEND (017001) trial, patients completed PRO assessments at protocol prespecified timepoints. Specifically, at pretreatment (screening), baseline (Day 1), Day 29 (Month 1), 60 (Month 2), 90 (Month 3), 180 (Month 6), 270 (Month 9), 365 (Month 12), 545 (Month 18), 730 (Month 24), or end of study, and at disease progression/relapse. Baseline was defined as the last available assessment on or prior to the administration of the first dose of liso-cel (i.e., the baseline evaluation visit or screening visit if the former was missing). If multiple valid, non-missing observations exist in a window, records were chosen based on the following rules [63]:

- The record closest to the nominal day for that visit was selected.
- If there were two records equidistant from the nominal day, the later record was selected.
- If there were multiple records with the same time or no time recorded on the same day, the value with the highest severity was selected for the EQ 5D 5L.

Table 63 shows the pattern of missing data and completion for liso-cel.

In ZUMA-1, the EQ-5D-5L instrument was administered at Screening, Week 4, and at Month 3 and 6 post-axi-cel infusion. Descriptive analysis was conducted by time of assessment [64].

The pattern of missing data and completion for axi-cel is not available.

10.2.1.3 HRQoL results

Table 64 shows the EQ-5D-5L health utility index score at baseline for the PRO (EQ-5D-5L) evaluable population in TRANSCEND (017001). Table 65 shows the mean EQ-5D-5L index score at screening for patients receiving axi-cel in ZUMA-1.

[redacted]

Table 65 Health Utility Index Score at screening for patients receiving axi-cel in ZUMA-1

	n	Mean	SD
Health utility index score	33	0.80	0.17

Source: [64].

The mean change from baseline for the EQ-5D-5L health utility index score for the PRO (EQ-5D-5L) evaluable population in TRANSCEND (017001) is shown in

Figure 47 and the descriptive summary statistics of EQ-5D-5L utility scores at the data collection time points are shown in

Table 66. The mean change from screening in the EQ-5D-5L Health Utility Index Score for patients receiving axi-cel in ZUMA-1 is shown in

Figure 48 and the descriptive summary statistics of EQ-5D-5L utility scores at the data collection time points are shown in Table 67.

[redacted]

* Indicates data point of a significant change from baseline with unadjusted p-value < 0.05 based on the two-sided Wilcoxon signed rank test. The test was performed only if the sample size at a given assessment visit was at least 10.

Month 0 = Baseline; Month 1 = Day 29

Source: [63].

Source: [64].

Table 67 HRQoL EQ-5D-5L summary statistics for patients receiving axi-cel in ZUMA-1

	Axi-cel	
	N	Mean (SD)
Screening	33	0.80 (0.17)
Week 4	27	0.74 (0.15)
Month 3	20	0.80 (0.13)
Month 6	7	0.82 (0.21)

Source: [64].

10.2.2 Health state utility values (HSUVs) used in the health economic model

Not applicable.

10.2.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

11. Resource use and associated costs

Cost parameters included in the cost-minimization analyses base case were medicine acquisition and administration costs (bridging therapy and CAR-Ts), costs associated with disease management (inpatient stay after CAR-T administration), costs associated with the management of adverse events, and non-medical costs. All costs are reported in DKK.

All other costs (e.g., leukapheresis costs, lymphodepleting treatment costs, subsequent treatment costs and palliative care costs) were assumed to be equivalent between liso-cel and axi-cel and were therefore not included in the analyses.

11.1 Medicine costs - intervention and comparator

The modelled dose, RDI, treatment administration frequency and assumption on vial sharing are presented in Table 68 and Table 69. The acquisition costs are summarized in Table 70 and Table 71.

Total vial sharing (no wastage) was assumed for the drugs composing the bridging therapy regimens.

For the 2L cost minimization analysis, the bridging therapy duration before liso-cel administration was set to 3 weeks based on the TRANSFORM trial protocol [46]. The proportion of patients receiving bridging therapy, as well as the bridging therapy treatment composition and distribution were also based on the TRANSFORM trial [46].

The bridging therapy duration before axi-cel administration was set to 2 days based on the DMC assessment of axi-cel for this patient population [36]. The proportion of patients receiving bridging therapy, as well as the bridging therapy treatment composition and distribution were also based on the DMC assessment [36].

A body surface area (BSA) of 1.92 m^2, derived from TRANSFORM [46], was used to calculate the doses to be administered for the different treatments composing the bridging therapy regimen.

For the 3L cost minimization analysis, the bridging therapy duration before liso-cel administration was also assumed to be 3 weeks. The proportion of patients receiving bridging therapy, as well as the bridging therapy treatment composition and distribution were based on the TRANSCEND (017001) trial [78].

A BSA of 1.94 m^2, derived from TRANSCEND (017001) [78], was used to calculate the doses to be administered for the different treatments composing the bridging therapy regimen.

No bridging therapy costs before axi-cel administration were included as bridging therapy was not allowed in the ZUMA-1 trial [62].

The posology for the included treatments was sourced from key pivotal trials, or corresponding Summary of Product Characteristics (SmPC) or label. A relative dose intensity of 100% was assumed.

Table 68 Medicine costs used in the model (2L cost-minimization analysis)

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Bridging therapy regimen (before liso-cel administration) – 63% of patients				
R-GDP (28%)				

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Gemcitabine (IV)	1,920 mg per administration	100%	Twice every three weeks	Yes
Dexamethasone (Oral)	40 mg per administration	100%	Four times every three weeks	NA
Cisplatin (IV)	144 mg per administration	100%	Once every three weeks	Yes
Rituximab (IV)	720 mg per administration	100%	Once every three weeks	Yes
R-DHAP (22%)				
Dexamethasone (Oral)	40 mg per administration	100%	Four times every three weeks	NA
Cytarabine (IV)	7,680 mg per administration	100%	Once every three weeks	Yes
Cisplatin (IV)	144 mg per administration	100%	Once every three weeks	Yes
Rituximab (IV)	720 mg per administration	100%	Once every three weeks	Yes
R-ICE (50%)				
Carboplatin (IV)	590 mg per administration	100%	Once every three weeks	Yes
Etoposide (IV)	192 mg per administration	100%	Three times every three weeks	Yes
Ifosfamide (IV)	9,600 mg per administration	100%	Once every three weeks	Yes
Rituximab (IV)	720 mg per administration	100%	Once every three weeks	Yes
Liso-cel (IV)	100 x 10^6 CAR-T cells	100%	Administered once	NA
Bridging therapy regimen (before axi-cel administration) – 60% of patients				

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Dexamethasone (oral) – 100%	30 mg per administration	100%	Administered twice in two days	NA
Axi-cel (IV)	2×10^6 anti CD19 CAR-T cells/kg body weight.	100%	Administered once	NA

Table 69 Medicine costs used in the model (3L cost-minimization analysis)

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Bridging therapy regimen (before liso-cel administration) – 64% of patients				
R-GemOx (30%)				
Gemcitabine (IV)	2,332.47 mg per administration	100%	Twice every three weeks	Yes
Oxaliplatin (IV)	233.25 mg per administration	100%	Once every three weeks	Yes
Rituximab (IV)	728.9 mg per administration	100%	Once every three weeks	Yes
GemOx (9%)				
Gemcitabine (IV)	2,332.47 mg per administration	100%	Twice every three weeks	Yes
Oxaliplatin (IV)	233.25 mg per administration	100%	Once every three weeks	Yes
Rituximab monotherapy (14%)				
Rituximab (IV)	728.9 mg per administration	100%	Once every three weeks	Yes
BR (13%)				
Bendamustine (IV)	233.25 mg per administration	100%	Twice every three weeks	Yes
Rituximab (IV)	728.9 mg per administration	100%	Once every three weeks	Yes

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Steroids (20%)				
Prednisolone (oral)	20 mg per administration	100%	Once daily for three weeks	NA
Radiation therapy (14%)	2 Gy	100%	Days 1-5 for 2 weeks	NA
Liso-cel (IV)	DL1S: Single dose of 50 × 10^6 CAR-T cells. DL2S: Single dose of 100 × 10^6 CAR-T cells. DL1D: Two doses of 50 × 10^6 CAR-T cells.	100%	Administered once	NA
Axi-cel (IV)	2 × 10^6 anti CD19 CAR-T cells/kg body weight.	100%	Administered once	NA

Table 70 Medicine costs used in the model (cost information) (2L cost-minimization analysis)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Bridging therapy regimen (before liso-cel administration) – 63% of patients			
Gemcitabine ”Gemkabi” (IV)	38 mg/ml	1,000 mg	162.50
Dexamethasone ”2care4” (Oral)	4 mg	100	588
Cisplatin ”Accord” (IV)	1 mg/ml	50 ml	100
Rituximab ”Mabthera” (IV)	1,400 mg	1	12,689.49
Cytarabine ”Fresenius Kabi” (IV)	100 mg/ml	20 ml	150
Carboplatin ”Accord” (IV)	10 mg/ml	45 ml	226
Etoposide ”Fresenius Kabi” (IV)	20 mg/ml	25 ml	278.72

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Ifosfamide ”Holoxan” (IV)	1,000 mg	1	380
Liso-cel (IV)	NA	1	2,570,000
Bridging therapy regimen (before axi-cel administration) – 60% of patients			
Dexamethasone ”2care4” (Oral)	4 mg	100	588
Axi-cel (IV)	NA	1	2,386,320

Source: Liso-cel costs (BMS), remaining costs (Medicinpriser.dk) – sourced on 22/04/2024 & 23/04/2024 [85].

Table 71 Medicine costs used in the model (cost information) (3L cost-minimization analysis)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Bridging therapy regimen (before liso-cel administration) – 64% of patients			
Gemcitabine ”Gemkabi” (IV)	38 mg/ml	1,000 mg	162.50
Oxaliplatin ”Fresenius Kabi” (IV)	5 mg/ml	40 ml	127.82
Rituximab ”Mabthera” (IV)	1,400 mg	1	12,689.49
Bendamustine ”Fresenius Kabi” (IV)	2.5 mg/ml	200 ml	1,174
Prednisolone ”EQL Pharma” (oral)	25 mg	10	12.72
Radiation therapy	NA	NA	5,475
Liso-cel (IV)	NA	1	2,570,000
Axi-cel (IV)	NA	1	2,386,320

Source: Liso-cel costs (BMS), remaining costs (Medicinpriser.dk) – sourced on 22/04/2024 & 23/04/2024 [85].

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

An administration cost is associated with IV treatments (Table 72). If treatments were administered orally, it was assumed there was no administration cost.

Table 72 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
CAR-T cell therapy administration	Only administered once.	6,723	16PR01 Transfusion af plasma og/eller behandlet blod	Sundhedsdatastyrelsen 2024 [86]
Standard chemotherapy administration	Dependent on the administration frequency of the different medicines (see section 11.1).	1,625	09MA98 "MDC09 1-dagsgruppe, pat. mindst 7 år"	Sundhedsdatastyrelsen 2024 [86]

11.4 Disease management costs

The costs associated with inpatient stay after CAR-T administration were accounted for in the cost-minimization analyses.

[redacted] Patients were assumed to be hospitalized for 18.6 days after axi-cel administration (mean hospitalization time from axi-cel administration in ZUMA-7) [36].

[redacted] It was assumed that patients would also be hospitalized for 18.6 days after axi-cel administration in the 3L treatment (same as in 2L treatment).

Table 73 shows the costs per day of hospitalization.

Table 73 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Day of hospitalization	See description above.	4,834	17MA01 Malign hæmatologisk	Sundhedsdatastyrelsen 2024 [86]

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
			sygdom uden specifik behandling, pat. mindst 18 år	

11.5 Costs associated with management of adverse events

The costs associated with AEs are summarized in Table 74. The respective frequencies for the included AEs are described in Table 46 and Table 53.

AEs are applied as a one-off cost. As described in sections 9.1 and 9.2, only grade 3 or higher cytokine release syndrome (CRS) and neurotoxicity (NT) AEs were included.

Table 74 Cost associated with management of adverse events

	Unit cost [DKK]	DRG code/source
CRS	55,859	Sundhedsdatastyrelsen 2024: 17MA02 - Patienter med hæmatologiske komplikationer [86]
NT	82,186	Sundhedsdatastyrelsen 2024: 26MP23 - Tilstand med allogen knoglemarvstransplantation [86]

11.6 Subsequent treatment costs

Not applicable.

Table 75 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
[Name of subsequent treatment]	[X]	[X]	[X]		
	[X]	[X]	[X]		
[Name of subsequent treatment]	[X]	[X]	[X]		
	[X]	[X]	[X]		

11.7 Patient costs

The analysis adopted a limited societal perspective. This includes non-medical costs due to time spent due to treatment. The costs were based on an hourly wage (DKK 188) taken from Værdisætning af Enhedsomkostninger 2024, by the DMC [89].

The non-medical costs were applied according to the use of time for the disease management (see section 11.4). It was assumed that each hospitalization day was associated with 24 hours of time spent due to treatment. 100% of the patients were assumed to incur in non-medical costs, compared to only 50% of carers (Table 76). Carers are a valuable resource in the healthcare system as it is today. In the report from VIVE 2024 it is concluded that the carers perform a wide range of tasks [90].

In addition, the EPAR states that Liso-cel may have a major influence on the ability to drive and use machines for up to 8 week after infusion.

There is no direct reference for the time used by carers so an assumption of 50 % of the time consumption is used in relation to the number of days the patient is in the hospital.

Transportation costs were not included as they were considered equivalent in both treatment arms.

Table 76 Patient costs used in the model

Activity	Unit cost [DKK]	Time spent [minutes, hours, days]
Patients (hourly rate)	188 [89]	Assumption: 24 hours per hospitalization day. 100% of patients.
Carers (hourly rate)	188 [89]	Assumption: 24 hours per hospitalization day. 50% of carers.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

The base case settings for the cost-minimization analysis of liso-cel and axi-cel are presented in Table 77.

Table 77 Base case overview

Feature	Description
Comparator	Axi-cel.
Perspective	Limited societal.
Type of model	Cost-minimization.
Time horizon	One year.
Treatment line	Second- and third-line treatment of relapsed or refractory LBCL.
Measurement and valuation of health effects	NA.
Costs included	Medicine costs (bridging therapy costs and CAR-T costs). Administration costs. Disease management costs (Inpatient stay after administration). Costs associated with management of adverse events. Patient costs.
Dosage of medicine	Liso-cel and axi-cel are assumed to be given at their target doses.
Average time on treatment	NA.
Parametric function for PFS	NA.
Parametric function for OS	NA.
Inclusion of waste	No.
Average time in model health state Health state 1 Health state 2	NA.

Feature	Description
Health state 3	
Death	

12.1.1 Base case results

Table 78 and Table 79 show the cost-minimization results.

Table 78 Base case results – Liso-cel compared to axi-cel for the treatment adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

	Liso-cel	Axi-cel	Difference
Medicine costs (bridging therapy costs)	DKK 10,703.23	DKK 52.92	DKK 10,650.31
Medicine costs (CAR-T costs)	DKK 2,570,000	DKK 2,386,320	DKK 183,680
Medicine costs – co-administration	NA	NA	NA
Administration (CAR-T)	DKK 6,723	DKK 6,723	DKK 0
Disease management costs (Inpatient stay after administration)	DKK 81,695	DKK 89,912	DKK -8,218
Costs associated with management of adverse events	DKK 4,691.01	DKK 21,018.50	DKK -16,327.49
Subsequent treatment costs	NA	NA	NA
Patient costs	DKK 114,379	DKK 125,885	DKK -11,506
Palliative care costs	NA	NA	NA
Total costs	**DKK 2,788,191**	**DKK 2,629,912**	**DKK 158,279**
Life years gained (health state A)	NA	NA	NA
Life years gained (health state B)	NA	NA	NA

	Liso-cel	Axi-cel	Difference
Total life years	**NA**	**NA**	**NA**
QALYs (state A)	NA	NA	NA
QALYs (state B)	NA	NA	NA
QALYs (adverse reactions)	NA	NA	NA
Total QALYs	**NA**	**NA**	**NA**
Incremental costs per life year gained		**NA**	
Incremental cost per QALY gained (ICER)		**NA**	

Table 79 Base case results – Liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy.

	Liso-cel	Axi-cel	Difference
Medicine costs (bridging therapy costs)	DKK 5,301	DKK 0.00	DKK 5,301
Medicine costs (CAR-T costs)	DKK 2,570,000	DKK 2,386,320	DKK 183,680
Medicine costs – co-administration	NA	NA	NA
Administration (CAR-T)	DKK 6,723	DKK 6,723	DKK 0
Disease management costs (Inpatient stay after administration)	DKK 63,325	DKK 89,912	DKK -26,587
Costs associated with management of adverse events	DKK 3,382.45	DKK 32,828.61	DKK -29,446.17
Subsequent treatment costs	NA	NA	NA
Patient costs	DKK 88,661	DKK 125,885	DKK -37,224
Palliative care costs	NA	NA	NA
Total costs	**DKK 2,737,393**	**DKK 2,641,669**	**DKK 95,724**
Life years gained (health state A)	NA	NA	NA

	Liso-cel	Axi-cel	Difference
Life years gained (health state B)	NA	NA	NA
Total life years	**NA**	**NA**	**NA**
QALYs (state A)	NA	NA	NA
QALYs (state B)	NA	NA	NA
QALYs (adverse reactions)	NA	NA	NA
Total QALYs	**NA**	**NA**	**NA**
Incremental costs per life year gained		**NA**	
Incremental cost per QALY gained (ICER)		**NA**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

12.2.2 Table 80 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA				

12.2.2.1 Scenario analyses

The cost-minimization includes the option to explore a scenario analysis in which only the CAR-T acquisition costs are included. The results of this scenario analysis are presented in Table 81 and Table 82.

Table 81 Scenario analysis result (liso-cel compared to axi-cel for the treatment adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy)

	Liso-cel	Axi-cel	Difference
Medicine costs (CAR-T costs)	DKK 2,570,000	DKK 2,386,320	DKK 183,680

	Liso-cel	Axi-cel	Difference
Total costs	**DKK 2,570,000**	**DKK 2,386,320**	**DKK 183,680**

Table 82 Scenario analysis result (liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy)

	Liso-cel	Axi-cel	Difference
Medicine costs (CAR-T costs)	DKK 2,570,000	DKK 2,386,320	DKK 183,680
Total costs	**DKK 2,570,000**	**DKK 2,386,320**	**DKK 183,680**

12.2.3 Probabilistic sensitivity analyses

Not applicable.

13. Budget impact analysis

13.1 Liso-cel compared to axi-cel for the treatment adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

A budget impact analysis was conducted and incorporated in the cost-minimization analysis. A five-year projection was used in the analysis and costs were estimated for two scenarios. In one scenario, liso-cel is introduced for the 2L treatment of adult patients with r/r LBCL, and in scenario two it is not introduced. Costs were estimated based on the expected number of eligible patients (described in Section 3.2).

The budget impact calculations were based on Pharmacy Purchasing Price of all treatments. The following undiscounted costs (described in Section 11) were included in the analysis:

- Medicine costs (bridging therapy and CAR-T costs).
- Administration costs.
- Disease management costs (inpatient stay after administration costs).
- Management of AE costs.

Number of patients (including assumptions of market share)

Based on the incidence of DLBCL patients presented in Section 3.2, it was assumed that approximately 30 new patients would be eligible for treatment with liso-cel each year. A constant number of eligible patients was assumed over the five-year period. Table 83 presents the estimated patient numbers for both scenarios one and two.

The market share was assumed to be 50% over the five-year period.

Table 83 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) – 2L treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Liso-cel	15	15	15	15	15
Axi-cel	15	15	15	15	15
			Non-recommendation		
Liso-cel	0	0	0	0	0
Axi-cel	30	30	30	30	30

Budget impact

The expected budget impact of introducing liso-cel for the second-line treatment of adult patients with LBCL who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy is presented in Table 84. Liso-cel is expected to have a budget impact of approximately DKK 2.5 million.

Table 84 Expected budget impact of recommending the medicine for the indication – 2L treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	DKK 77,667,580	DKK 77,667,580	DKK 77,667,580	DKK 77,667,580	DKK 77,667,580
The medicine under consideration is NOT recommended	DKK 75,120,805	DKK 75,120,805	DKK 75,120,805	DKK 75,120,805	DKK 75,120,805
Budget impact of the recommendation	DKK 2,546,775	DKK 2,546,775	DKK 2,546,775	DKK 2,546,775	DKK 2,546,775

13.2 Liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

A budget impact analysis was conducted and incorporated in the cost-minimization analysis. A five-year projection was used in the analysis and costs were estimated for two scenarios. In one scenario, liso-cel is introduced for the 3L treatment of adult patients with r/r LBCL, and in scenario two it is not introduced. Costs were estimated based on the expected number of eligible patients (described in Section 3.2).

The budget impact calculations were based on Pharmacy Purchasing Price of all treatments. The following undiscounted costs (described in Section 11) were included in the analysis:

- Medicine costs (bridging therapy and CAR-T costs).
- Administration costs.
- Disease management costs (inpatient stay after administration costs).
- Management of AE costs.

Number of patients (including assumptions of market share)

Based on the incidence of DLBCL patients presented in Section 3.2, it was assumed that approximately 15 new patients would be eligible for treatment with liso-cel each year. A constant number of eligible patients was assumed over the five-year period. Table 85 presents the estimated patient numbers for both scenarios one and two.

The market share was assumed to be 50% over the five-year period.

Table 85 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) – 3L treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Liso-cel	7.5	7.5	7.5	7.5	7.5
Axi-cel	7.5	7.5	7.5	7.5	7.5
			Non-recommendation		
Liso-cel	0	0	0	0	0
Axi-cel	15	15	15	15	15

Budget impact

The expected budget impact of introducing liso-cel for the treatment of adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy is presented in Table 86. Liso-cel is expected to have a budget impact of approximately DKK 1 million.

Table 86 Expected budget impact of recommending the medicine for the indication – 3L treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	DKK 38,733,869	DKK 38,733,869	DKK 38,733,869	DKK 38,733,869	DKK 38,733,869
The medicine under consideration is NOT recommended	DKK 37,736,760	DKK 37,736,760	DKK 37,736,760	DKK 37,736,760	DKK 37,736,760
Budget impact of the recommendation	DKK 997,108	DKK 997,108	DKK 997,108	DKK 997,108	DKK 997,108

14. List of experts

Not applicable.

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Appendix A. Main characteristics of studies included

Table 87 - Table 90 show the main characteristic of the included studies for 2L and 3L respectively.

Table 87 Main characteristic of TRANSFORM (NCT03575351)

Trial name: TRANSFORM	NCT number: NCT03575351
Objective	The objective of the study was to compare safety and efficacy between the standard of care (SoC) strategy versus JCAR017 (lisocabtagene maraleucel or liso-cel) in adult subjects with relapsed or refractory (R/R) aggressive non-Hodgkin lymphoma (NHL).
Publications – title, author, journal, year	Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022 Jun 18;399(10343):2294-2308. doi: 10.1016/S0140-6736(22)00662-6. Erratum in: Lancet. 2022 Jul 16;400(10347):160. PMID: 35717989. Abramson JS et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023 Apr 6;141(14):1675-1684. doi: 10.1182/blood.2022018730. PMID: 36542826; PMCID: PMC10646768.
Study type and design	Global, phase 3 study, conducted in 47 sites in the USA, Europe, and Japan, comparing liso-cel with standard of care as second-line therapy in patients with primary refractory or early (≤12 months) relapsed LBCL. Subjects were randomized to either receive SoC (Arm A) or to receive JCAR017 (Arm B). All subjects randomized to Arm A received Standard of care (SoC) salvage therapy (R-DHAP, RICE or R-GDP) as per physician's choice before proceeding to High dose chemotherapy (HDCT) and Hematopoietic stem cell transplant (HSCT). Subjects from Arm A were allowed to cross over and receive JCAR017 upon confirmation of an EFS event. Subjects randomized to Arm B received Lymphodepleting (LD) chemotherapy followed by JCAR017 infusion.
Sample size (n)	*184 (randomized as 92-92)*
Main inclusion criteria	1. Subject is ≥ 18 years and ≤ 75 years of age at the time of signing the informed consent form (ICF). 2. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. 3. Histologically proven diffuse large B-cell lymphoma (DLBCL) NOS (de novo or transformed indolent NHL), high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma [DHL/THL]), primary mediastinal (thymic) large B-cell lymphoma (PMBCL), T cell/histiocyte-rich large B-cell

Trial name: TRANSFORM	NCT number: NCT03575351
	lymphoma (THRBCL) or follicular lymphoma grade 3B. Enough tumor material must be available for confirmation by central pathology. 4. Refractory or relapsed within 12 months from CD20 antibody and anthracycline containing first line therapy. 5. [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) positive lesion at screening. (Deauville score 4 or 5) 6. Adequate organ function 7. Participants must agree to use effective contraception
Main exclusion criteria	1. Subjects not eligible for hematopoietic stem cell transplantation (HSCT). 2. Subjects planned to undergo allogeneic stem cell transplantation. 3. Subjects with, primary cutaneous large B-cell lymphoma, EBV (Epstein-Barr virus) positive DLBCL, Burkitt lymphoma or transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter transformation). 4. Subjects with prior history of malignancies, other than aggressive R/R NHL, unless the subject has been free of the disease for ≥ 2 years with the exception of the following noninvasive malignancies: o Basal cell carcinoma of the skin o Squamous cell carcinoma of the skin o Carcinoma in situ of the cervix o Carcinoma in situ of the breast o Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative. o Other completely resected stage 1 solid tumor with low risk for recurrence 5. Treatment with any prior gene therapy product. 6. Subjects who have received previous CD19-targeted therapy. 7. Subjects with active hepatitis B, or active hepatitis C are excluded. Subjects with negative polymerase chain reaction (PCR) assay for viral load for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy. Subjects with a history of or active human immunodeficiency virus (HIV) are excluded. 8. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis) despite appropriate antibiotics or other treatment. 9. Active autoimmune disease requiring immunosuppressive therapy. 10. History of any one of the following cardiovascular conditions within the past 6 months prior to signing the ICF: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease. 11. History or presence of clinically relevant central nervous system (CNS) pathology 12. Pregnant or nursing (lactating) women.

Trial name: TRANSFORM	NCT number: NCT03575351
Intervention	Patients in the liso-cel group (n=92) received lymphodepleting chemotherapy (intravenous fludarabine 30 mg/m² and intravenous cyclophosphamide 300 mg/m² daily) for 3 days followed by liso-cel. Patients received liso-cel as two sequential intravenous infusions of CD8+ and CD4+ CAR+ T cells at a total target dose of 100 × 10^6 CAR+ T cells
Comparator(s)	The standard-of-care group (n=92) received three cycles of R-DHAP (intravenous rituximab 375 mg/m² on day 1, dexamethasone 40 mg on days 1–4, two infusions of cytarabine 2000 mg/m² on day 2, and cisplatin 100 mg/ m² on day 1), R-ICE (intravenous rituximab 375 mg/m² on day 1, ifosfamide 5000 mg/m² on day 2, etoposide 100 mg/m² on days 1–3, and carboplatin area under the curve 5 [maximum dose 800 mg] on day 2), or R-GDP (intravenous rituximab 375 mg/m² on day 1, dexamethasone 40 mg on days 1–4, gemcitabine 1000 mg/m² on days 1 and 8, and cisplatin 75 mg/m² on day 1) per investigator choice; responding patients (complete or partial response) were to proceed to one cycle of high-dose chemotherapy (intravenous carmustine 300 mg/m² on day 1, etoposide 200 mg/m² on days 2–5, cytarabine 200 mg/m² on days 2–5, and melphalan 140 mg/m² on day 6) and autologous HSCT. Dose modifications were permitted for adverse events and premedication and were done according to site standards, local label indications, and investigator's decision (protocol; appendix pp 51–230).
Follow-up time	3 years
Is the study used in the health economic model?	No The submission is based on a cost-minimization analysis assuming similar efficacy between the study drug and the comparator.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Other endpoints: NA** **Primary outcome measure:** Event-free survival (EFS) [Time Frame: Approximately 3 years] • Time from randomization to death from any cause, progressive disease (PD), failure to achieve complete response (CR) or partial response (PR), or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first **Secondary outcome measures:** • Complete response rate (CRR) [Time Frame: Approximately 3 years] o Percentage of subjects achieving a complete response (CR)

Trial name: TRANSFORM	NCT number: NCT03575351

- Progression-free survival (PFS) [Time Frame: Approximately 3 years]
    - Time from randomization to PD or death from any cause, whichever occurs first
- Overall survival (OS) [Time Frame: Approximately 4.5 years]
    - Time from randomization to time of death due to any cause
- Overall response rate (ORR) [Time Frame: Approximately 3 years]
    - Percentage of subjects achieving an objective response of partial response (PR) or better according to the Lugano Classification as assessed by IRC review
- Duration of response (DOR) [Time Frame: Approximately 3 years]
    - Time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns or death from any cause
- PFS on next line of treatment (PFS-2) [Time Frame: Approximately 3 years]
    - Time from randomization to second objective disease progression or death from any cause, whichever is first.
- Adverse Events (AEs) [Time Frame: Approximately 3 years]
    - Type, frequency and severity of adverse events (AEs), serious adverse events (SAE), and laboratory abnormalities (overall and in clinical, histological and molecular subgroups)
- HRQoL using European Organisation for Research and Treatment of Cancer - Quality of Life C30 questionnaire (EORTC-QLQ-C30) [Time Frame: Approximately 3 years]
    - European Organisation for Research and Treatment of Cancer - Quality of Life C30 questionnaire: The EORTC QLQ-C30 questionnaire will be used as a measure of health-related quality of life, fatigue, physical and cognitive functions.
- HRQoL parameters assessed by FACT-Lym "Additional concerns" subscale [Time Frame: Approximately 3 years]
    - Functional Assessment of Cancer Therapy-Lymphoma "Additional concerns" subscale: Only the LYM subscale will be administered in this study. This scale

Trial name: TRANSFORM	NCT number: NCT03575351
	addresses symptoms and functional limitations (15 item) that are important to lymphoma patients. • Reasons for hospital resource utilization [Time Frame: Approximately 3 years] o Will be assessed based on reasons for hospitalization • Rate of hematopoietic stem cell transplant (HSCT) [Time Frame: Approximately 3 years] o Rate of completion of HDCT and HSCT • Frequency of hospital resource utilization [Time Frame: Approximately 3 years] o Will be assessed based on frequency of hospitalizations calculated as, inpatient days, intensive care unit (ICU) days, outpatient visits days • Hospital resource utilization (HRU) [Time Frame: Approximately 3 years] o Will be assessed based on frequency of hospitalizations calculated as, inpatient days, intensive care unit (ICU) days, outpatient visits days and reasons for hospitalization
Method of analysis	Efficacy analyses were conducted on the intention-to-treat set, safety analyses in the safety set, and cellular kinetic analyses in the cellular kinetic set.
Subgroup analyses	The following variables (collected at baseline, unless otherwise specified) were considered in subgroup analyses: • Secondary age-adjusted International Prognostic Index status: 0 or 1 versus 2 or 3 • Prior response status: refractory versus relapse to last prior therapy. The status is refractory if a patient achieved progressive disease (PD), stable disease (SDi), partial response, or CR with relapse within 3 months to last prior therapy; otherwise, the status is relapsed • Age: <65, ≥65 to <75, and ≥75 years at the time of randomization • Sex: male versus female • Ethnicity: Hispanic or Latino versus not Hispanic or Latino • Region: Europe, United States, and Japan • Race: White versus other races • Eastern Cooperative Oncology Group performance status at screening: 0 and 1

Trial name: TRANSFORM	NCT number: NCT03575351
	• Sum of the product of perpendicular diameters: >50 cm2 or ≤50 cm2 • Lactate dehydrogenase: <500 unit/L or ≥500 unit/L • Prior chemotherapy response status: chemotherapy refractory versus chemotherapy sensitive to last therapy. The status is chemotherapy refractory if a patient achieved SDi or PD to last chemotherapy-containing regimen; otherwise, the status is chemotherapy sensitive • Central nervous system (CNS) disease status: known CNS disease versus no known CNS disease at the time of randomization • Histological and molecular subtype: o Non-Hodgkin lymphoma (NHL) type: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma grade 3B, high grade B-cell lymphoma with DLBCL histology, primary mediastinal B-cell lymphoma, or T-cell/histiocyte-rich large B-cell lymphoma o DLBCL subtype: DLBCL not otherwise specified de novo or DLBCL from transformed indolent NHL o DLBCL subtype based on cell of origin: germinal center B cell (GCB) or activated B cell, or non-GCB o NHL subtype based on chromosomal translocation: double-hit or triple-hit lymphoma versus non–double-hit or triple-hit lymphoma • Bridging therapy status: impact of bridging therapy treatment effect versus SoC will be evaluated in patients receiving bridging therapy
Other relevant information	-

Table 88 Main characteristic of ZUMA-7

Trial name: ZUMA-7	NCT number: NCT03391466
Objective	To assess whether axicabtagene ciloleucel therapy improves the clinical outcome compared with standard of care second-line therapy in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL).
Publications – title, author, journal, year	Ghobadi A, Munoz J, Westin J, Locke FL, Miklos DB, Rapoport AP, et al. Outcomes of Subsequent Anti-Lymphoma Therapies in Patients (Pts) with Large B-Cell Lymphoma (LBCL) Treated with Axicabtagene Ciloleucel (Axi-Cel) or Standard of Care (SoC) in the Second-Line (2L) ZUMA-7 Study. Blood. 2022;140(Supplement 1):1595-1597.

Trial name: ZUMA-7	NCT number: NCT03391466
	Locke FL, Oluwole OO, Kuruvilla J, Thieblemont C, Morschhauser F, Salles G, et al. Association of Metabolic Tumor Volume (MTV) and Clinical Outcomes in Second-Line (2L) Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL) Following Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care (SoC) Therapy in ZUMA-7. Blood. 2022;140(Supplement 1):638-640. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, Ghobadi A, Rapoport AP, McGuirk J, Pagel JM, Munoz J, Farooq U, van Meerten T, Reagan PM, Sureda A, Flinn IW, Vandenberghe P, Song KW, Dickinson M, Minnema MC, Riedell PA, Leslie LA, Chaganti S, Yang Y, Filosto S, Shah J, Schupp M, To C, Cheng P, Gordon LI, Westin JR; All ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022 Feb 17;386(7):640-654. doi: 10.1056/NEJMoa2116133. Epub 2021 Dec 11. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, Rapoport AP, Sureda A, Jacobson CA, Farooq U, van Meerten T, Ulrickson M, Elsawy M, Leslie LA, Chaganti S, Dickinson M, Dorritie K, Reagan PM, McGuirk J, Song KW, Riedell PA, Minnema MC, Yang Y, Vardhanabhuti S, Filosto S, Cheng P, Shahani SA, Schupp M, To C, Locke FL; ZUMA-7 Investigators; Kite Members. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med. 2023 Jul 13;389(2):148-157. doi: 10.1056/NEJMoa2301665. Epub 2023 Jun 5. PMID: 37272527.
Study type and design	Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus standard of care therapy in participants with relapsed/refractory DLBCL. Adult participants with relapsed/refractory DLBCL after first-line rituximab and anthracycline-based chemotherapy will be randomized in a 1:1 ratio to receive axicabtagene ciloleucel or standard of care second-line therapy.
Sample size (n)	*359*
Main inclusion criteria	• Histologically proven large B-cell lymphoma including the following types defined by World Health Organization (WHO) 2016. o Diffuse large B-cell lymphoma (DLBCL) not otherwise specified activated B-cell/ germinal center B-cell (ABC/GCB). o High-grade B-cell lymphoma (HGBL) with or without myelocytomatosis oncogene (MYC) and B-cell lymphoma (BCL) 2 and/or BCL6 rearrangement. o DLBCL arising from follicular lymphoma (FL). o T-cell/histiocyte rich large B-cell lymphoma. o DLBCL associated with chronic inflammation. o Primary cutaneous DLBCL, leg type.

- Epstein-Barr virus (EBV) + DLBCL.

- Relapsed or refractory disease after first-line chemoimmunotherapy.
  - Refractory disease defined as no complete remission to first-line therapy; individuals who are intolerant to first-line therapy are excluded.
    - Progressive disease (PD) as best response to first-line therapy.
    - Stable disease (SDi) as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP).
    - Partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy.
  - Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven relapse ≤ 12 months of first-line therapy.
- Individuals must have received adequate first-line therapy including at a minimum:
  - Anti-Cluster of Differentiation antigen (CD) 20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and
  - An anthracycline containing chemotherapy regimen.
- No known history or suspicion of central nervous system involvement by lymphoma.
- Eastern cooperative oncology group (ECOG) performance status of 0 or 1.
- Adequate bone marrow function as evidenced by:
  - Absolute neutrophil count (ANC) ≥ 1000/uL
  - Platelet ≥ 75,000/uL
  - Absolute lymphocyte count ≥ 100/uL
- Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by:
  - Creatinine clearance (Cockcroft Gault) ≥ 60 mL/min.
  - Serum Alanine aminotransferase/Aspartate aminotransferase (ALT/AST) ≤ 2.5 Upper limit of normal (ULN).
  - Total bilirubin ≤ 1.5 mg/dl

Trial name: ZUMA-7	NCT number: NCT03391466
	○ Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an Echocardiogram (ECHO), and no clinically significant Electrocardiogram (ECG) findings. ○ No clinically significant pleural effusion. ○ Baseline oxygen saturation > 92% on room air.
Main exclusion criteria	• History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg cervix, bladder, breast) unless disease free for at least 3 years. • Received more than one line of therapy for DLBCL. • History of autologous or allogeneic stem cell transplant. • Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous antimicrobials for management. • Known history of infection with human immunodeficiency virus (HIV) or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). If there is a positive history of treated hepatitis B or hepatitis C, the viral load must be undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing. • Individuals with detectable cerebrospinal fluid malignant cells or known brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases. • History or presence of non-malignant central nervous system (CNS) disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement. • Presence of any indwelling line or drain. Dedicated central venous access catheter such as a Port-a-Cath or Hickman catheter are permitted. • History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac diseases within 12 months of enrollment. • History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment. • History of autoimmune disease, requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years. • History of anti-CD19 or CAR-T therapy or history of prior randomization in ZUMA-7.

Trial name: ZUMA-7	NCT number: NCT03391466
Intervention	**Axicabtagene Ciloleucel**: Participants receivde cyclophosphamide 500 mg/m^2/day intravenously (IV) and fludarabine 30 mg/m^2/day IV conditioning chemotherapy for 3 days followed by axicabtagene ciloleucel administered as a single IV infusion at a target dose of 2 x 10^6 anti-cluster of differentiation antigen (CD) 19 CAR transduced autologous T cells/kg on Day 0. Interventions: Axicabtagene Ciloleucel, Cyclophosphamide, Fludarabine
Comparator(s)	**Standard of Care Therapy**: Participants received 2 or 3 21-day cycles of second-line chemotherapy regimen; R-ICE: rituximab 375 mg/m^2 before chemotherapy,ifosfamide 5 g/m^2 24hour(hr) infusion on Day 2+mesna,carboplatin area under the curve (AUC) 5 on Day 2, maximum dose 800 mg,etoposide 100 mg/ m^2/day on Days 1-3; R-ESHAP: rituximab 375 mg/m^2 Day 1,etoposide 40 mg/m^2/day IV on Days 1-4,methylprednisolone 500 mg/day IV on Days 1-4 or 5,cisplatin at 25 mg/m^2/day Days 1-4,cytarabine 2 g/m^2 on Day 5; R-GDP: rituximab 375 mg/m^2 Day 1(or Day 8),gemcitabine 1g/m^2 on Days 1 and 8,dexamethasone 40 mg on Days 1-4,cisplatin 75mg/m^2 on Day 1 or carboplatin AUC=5; or R-DHAP: Rituximab 375 mg/ m^2 before chemotherapy,dexamethasone 40 mg/day on Days 1-4,highdose cytarabine 2 g/m^2 every 12 hours for 2 doses on Day 2 following/platinum,cisplatin 100 mg/m^2 24hr infusion on Day 1 or oxaliplatin 100 mg/m^2. Participants who will respond will get high dose therapy and autologous stem cell transplant. Interventions: Platinum-containing salvage chemotherapy (eg, R-ICE) followed by high dose therapy (eg, BEAM) and autologous stem cell transplant in responders.
Follow-up time	Median follow-up: 24.9 months
Is the study used in the health economic model?	No. The submission used a cost minimization approach where the efficacy between the intervention and comparator are assumed to be equal or similar.
Primary, secondary and exploratory endpoints	**Endpoints included in this application: NA** **Other endpoints:** **Primary outcome measures:** • Event Free Survival [Time Frame: 3 years] **Secondary outcome measures:** • Objective Response Rate (ORR) Per Blinded Central Assessment [Time Frame: From randomization date up to a median follow-up: 24.9 months] o ORR: Percentage of participants with CR [CMR;CRR] or PR [partial metabolic response (PMR); partial radiologic response (PRR)].CMR: PET 5PS scores of 1

(no uptake above background, 2(uptake≤mediastinum), 3(uptake>mediastinum but≤liver) with/without a residual mass;no new lesions; no evidence of FDG-avid disease in BM. CRR:target nodes/nodal masses regressed to ≤ 1.5 cm in LDi;no extralymphatic sites of disease;absent non-measured lesions (NMLs);organ enlargement regress to normal;no new sites;bone marrow morphology normal. PMR:scores 4 (uptake moderately>liver),5(uptake markedly > liver, new lesions) with reduced uptake compared with baseline and residual mass;no new lesions;responding disease at interim/residual disease at end of treatment (EOT).PRR: ≥50% decrease in sum of the product of perpendicular diameters (SPD) of up to 6 target measurable nodes and extra-nodal sites;absent/normal, regressed, but no increase of NMLs;spleen regressed by >50% in length beyond normal;no new sites.

- Overall Survival (OS) [Time Frame: From randomization date up to a median follow-up: 47.2 months]
    - Overall survival is defined as the time from randomization to death from any cause. Kaplan-Meier (KM) estimates was used for analysis.
- Duration of Response (DOR) Per Blinded Central Assessments [Time Frame: From the date of first confirmed objective response (CR or PR) to disease progression or death regardless of cause (Up to 37.8 months)]
    - DOR is defined only for participants who experience an objective response after axicabtagene ciloleucel infusion and is the time from the first objective response per Lugano classification to disease progression or death from any cause. Objective response is defined in outcome measure 2 and disease progression is defined in outcome measure 1. KM estimates were used for analysis.
- Modified Event Free Survival (mEFS) Per Blinded Central Assessment [Time Frame: From randomization date up to a median follow-up: 24.9 months]
    - Modified event free survival is defined the same way as EFS, except that a best response of SDi up to and including Day 150 assessment post randomization was not considered an event. KM estimates were used for analysis.
- Event Free Survival Per Investigator Disease Assessments [Time Frame: From randomization date up to a median follow-up: 47.2 months]

- EFS was defined as the time from randomization to the earliest date of disease progression per the IWG Lugano Classification, best response of stable disease (SDi) up to and including Day 150, commencement of new lymphoma therapy, or death from any cause. Disease progression is defined in outcome measure 1.

- Progression-Free Survival (PFS) Per Investigator Disease Assessments [Time Frame: From randomization date up to a median follow-up: 47.2 months]
  - PFS is defined as the time from the randomization date to the date of disease progression per Lugano classification or death from any cause. Disease progression is defined in outcome measure 1. KM estimates was used for analysis.

- Modified Event Free Survival (mEFS) Per Investigator Assessment [Time Frame: From randomization date up to a median follow-up: 47.2 months]
  - Modified event free survival is defined the same way as EFS, except that a best response of SDi up to and including Day 150 assessment post randomization was not considered an event. KM estimates were used for analysis.

- Change From Baseline in Global Health Status Scores [Time Frame: Baseline, Days 50, 100, and 150; Months 9, 12, 15, 18, 21 and 24]
  - Global health status was measured using European Organization for Research and Treatment of Cancer (EORTC) Quality Life Questionnaire (QLQ) C-30. This health related quality of life (HRQoL) questionnaire was comprised of 15 questions on functional scales, 13 questions on symptom scales and 2 on global health status scale. Global Health Status used a 7 point Likert-type scale of 1 (Very poor) to 7 (Excellent). All scores were transformed to 0-100. Higher scores for Global Health Status indicated better HRQoL.

- Change From Baseline in EORTC QLQ-C30 Physical Functioning Score [Time Frame: Baseline, Days 50, 100, 150, Months 9, 12, 15, 18, 21 and 24]
  - The EORTC QLQ-C30 is composed of global health status/QoL scale; five functional domains (physical, role, emotional, cognitive, and social); three symptom domains (fatigue, nausea and vomiting, and pain); and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The Physical Functioning domain includes 5 questions in which participants were asked to rate their overall health and overall quality of life as it relates to physical functioning during the past week on a scale from 1 (very poor) to 7 (excellent). The 5 scores were transformed to a scale from 0 to 100, where a high score indicated better QoL. A positive change from baseline indicates better QoL.

- Changes From Baseline in the European Quality of Life Five Dimensions Five Levels Scale (EQ-5D-5L) Index Score [Time Frame: Baseline, Days 50, 100, 150; Months 9, 12, 15, 18, 21 and 24]
    - The Euro-QOL, Five Dimensions, Five Levels (EQ-5D-5L) questionnaire is a generic measure of health status that provides a simple descriptive profile and a single index value. The EQ-5D-5L comprises 2 components: a questionnaire covering 5 dimensions and a tariff of values based upon direct valuations of health states using a visual analog scale (VAS). The total score for EQ-5D-5L index- is presented on a range from 0 to 1 where higher scores indicate better outcome. A positive change from Baseline indicates improvement.
- Change From Baseline in EQ-5D-5L VAS Scale Score [Time Frame: Baseline, Days 50, 100, 150; Months 9, 12, 18, 21 and 24]
    - The EQ-5D-5L VAS is a 20-cm VAS for recording self-rated current HRQoL state and is used to describe the participants' health status on the day of the assessment. The EQ-5D-5L VAS score is recorded by each participant for his or her current HRQoL state and scored 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). The value 100 indicates improvement.
- Number of Participants With Anti-Axicabtagene Ciloleucel Antibodies [Time Frame: From first dose of axicabtagene up to a median follow-up: 24 months]
- Percentage of Participants Experiencing Treatment-emergent Adverse Events [Time Frame: Up to 5 years]
    - A TEAE is defined as any AE that begins on or after the first dose of study treatment (axicabtagene ciloleucel infusion or SoC), excluding bridging therapy. Participant incidence rates of TEAEs, including all, serious, fatal, CTCAE Grade 3 or higher, and treatment related AEs reported will be tabulated by preferred term and system organ class coded with the Medical Dictionary for Regulatory Activities (MedDRA).

Trial name: ZUMA-7	NCT number: NCT03391466
	• Percentage of Participants With Clinically Significant Changes in Laboratory Values Reported as Grade 3 or Higher TEAEs [Time Frame: Up to 5 years] o Grading categories were determined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1: mild, Grade 2: moderate, Grade 3: severe or medically significant, Grade 4: life-threatening.
Method of analysis	The prespecified primary overall survival analysis was to be conducted in the intention-to-treat population after the occurrence of approximately 210 deaths or no later than 5 years after the first patient had undergone randomization. A group sequential testing procedure for overall survival was performed to control the overall one-sided alpha level of 2.5. A log-rank test was used stratified according to randomization factors for the primary comparison of overall survival with an efficacy boundary (two-sided significance level) of 0.0498. In addition to the intention-to-treat analysis, two prespecified sensitivity analyses of overall survival were performed to adjust for the confounding effect of subsequent off-protocol cellular immunotherapy in the standard-care group (defined as treatment switching). Efficacy analyses that were based on the intention-to-treat principle included all the patients who had undergone randomization. Safety analyses included all the patients who had received at least one dose of axi-cel or standard-care treatment according to the protocol.
Subgroup analyses	A subgroup analysis of event-free survival was conducted for prespecified covariates: response to first-line therapy and the second-line age-adjusted International Prognostic Index (IPI) at randomization
Other relevant information	-

Table 89 Main characteristic of TRANSCEND

Trial name: TRANSCEND	NCT number: NCT02631044
Objective	The objective of this study is to determine the safety, pharmacokinetics, and antitumor activity of JCAR017 in adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), follicular lymphoma Grade 3B, and mantle cell lymphoma (MCL).
Publications – title, author, journal, year	Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, Mehta A, Purev E, Maloney DG, Andreadis C, Sehgal A, Solomon SR, Ghosh N, Albertson TM, Garcia J, Kostic A, Mallaney M, Ogasawara K, Newhall K, Kim Y, Li D, Siddiqi T. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020 Sep

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Ogasawara K, Dodds M, Mack T, Lymp J, Dell'Aringa J, Smith J. Population Cellular Kinetics of Lisocabtagene Maraleucel, an Autologous CD19-Directed Chimeric Antigen Receptor T-Cell Product, in Patients with Relapsed/Refractory Large B-Cell Lymphoma. Clin Pharmacokinet. 2021 Dec;60(12):1621-1633. doi: 10.1007/s40262-021-01039-5. Epub 2021 Jun 14. Erratum In: Clin Pharmacokinet. 2021 Jul 3;:

Salles G, Spin P, Liu FF, Garcia J, Kim Y, Hasskarl J. Indirect Treatment Comparison of Liso-Cel vs. Salvage Chemotherapy in Diffuse Large B-Cell

Trial name: TRANSCEND	NCT number: NCT02631044
	Lymphoma: TRANSCEND vs. SCHOLAR-1. Adv Ther. 2021 Jun;38(6):3266-3280. doi: 10.1007/s12325-021-01756-0. Epub 2021 May 10. Patrick DL, Powers A, Jun MP, Kim Y, Garcia J, Dehner C, Maloney DG. Effect of lisocabtagene maraleucel on HRQoL and symptom severity in relapsed/refractory large B-cell lymphoma. Blood Adv. 2021 Apr 27;5(8):2245-2255. doi: 10.1182/bloodadvances.2020003503.
Study type and design	Multicentre, multicohort, phase I, seamless design study at 14 cancer centres in the USA Patients underwent leukapheresis to collect autologous peripheral blood mononuclear cells via venous catheter for manufacture of liso-cel Leukapheresis material was used to immunomagnetically select CD8+ and CD4+ T cells, which were then independently activated, transduced, and expanded. Bridging chemotherapy after leukapheresis was allowed at the discretion of the treating clinician during the liso-cel manufacturing process but required reconfirmation of PET-positive disease before lymphodepleting. Systemic therapy, radiation therapy, or both were allowed for bridging therapy. Lymphodepleting chemotherapy comprising fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) was administered intravenously daily for 3 days once the liso-cel product was available and the patient was confirmed to be eligible for infusion.
Sample size (n)	*387*
Main inclusion criteria	Age ≥18 years 1. Relapsed or refractory B-cell NHL, including a. DLBCL cohort (no longer enrolling): DLBCL, not otherwise specified (NOS; includes transformed DLBCL from indolent histology [tDLBCL]), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (Swerdlow 2016), primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after at least 2 lines of systemic therapy or after auto-HSCT. b. MCL cohort: MCL (diagnosis must be confirmed with cyclin D1 expression or evidence of t(11;14) by cytogenetics, fluorescent in situ hybridization [FISH], or PCR) with relapsed or refractory disease after at least 2 prior lines of systemic MCL therapy. Subjects must have been treated with an alkylating agent, Bruton's tyrosine kinase inhibitor (BTKi), and rituximab (or other CD20-targeted agent).

Trial name: TRANSCEND	NCT number: NCT02631044
	2. PET-positive disease by Lugano classification 3. Archived tumor biopsy tissue available from the last relapse and corresponding pathology report available or, if at least one tumor-involved site is deemed accessible at time of screening, willing to undergo pre-treatment biopsy (excisional when possible) for disease confirmation. If a subject has never had a complete response, a sample from the most recent biopsy is acceptable. 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 5. Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function 6. Adequate vascular access for leukapheresis procedure 7. Participants who have received previous CD19-targeted therapy must have CD19-positive lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy. Participants must agree to use appropriate contraception.
Main exclusion criteria	1. Active central nervous system (CNS)-only involvement by malignancy (note: participants with secondary CNS involvement are allowed on study) 2. History of other primary malignancy not in remission for at least 2 years (The following are exempt from the 2-year limit: nonmelanoma skin cancer, definitively treated stage 1 solid tumor with low risk for recurrence, curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear) 3. Treatment with alemtuzumab within 6 months of leukapheresis or fludarabine or cladribine within 3 months of leukapheresis 4. Active hepatitis B, hepatitis C, or Subjects with a history of or active human immunodeficiency virus (HIV) infectionare excluded. Subjects with active hepatitis B, or active hepatitis C are also excluded. Subjects with a negative PCR assay for viral load for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy 5. Uncontrolled systemic fungal, bacterial, viral, or other infection 6. Presence of graft-vs-host disease (GVHD) 7. History of cardiovascular disease 8. History or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain

injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

9. Pregnant or nursing women
10. Use of the following:
    a. Therapeutic doses of corticosteroids (defined as >20 mg/day prednisone or equivalent) within 7 days of leukapheresis or 72 hours prior to JCAR017 administration. Physiologic replacement, topical, and inhaled steroids are permitted.
    b. Low dose chemotherapy (e.g., vincristine, rituximab, cyclophosphamide ≤300 mg/m2) given after leukapheresis to maintain disease control must be stopped ≥7 days prior to lymphodepleting chemotherapy.
    c. Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (see below) within 1 week of leukapheresis. Oral chemotherapeutic agents, including lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis.
    d. Lymphotoxic chemotherapeutic agents (e.g., cyclophosphamide, ifosfamide, bendamustine) within 2 weeks of leukapheresis.
    e. Experimental agents within 4 weeks of leukapheresis unless no response or disease progression is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
    f. Immunosuppressive therapies within 4 weeks of leukapheresis and JCAR017 administration (e.g., calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolyate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-TNF, anti IL6, or anti-IL6R)
    g. Donor lymphocyte infusions (DLI) within 6 weeks of JCAR017 administration
    h. Radiation within 6 weeks of leukapheresis. Subjects must have progressive disease in irradiated lesions or have additional non-irradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis.
    i. Allo-HSCT within 90 days of leukapheresis

Trial name: TRANSCEND	NCT number: NCT02631044
	11. Prior CAR T-cell or other genetically-modified T-cell therapy, with the exception of prior JCAR017 treatment in this protocol for subjects receiving retreatment 12. Progressive vascular tumor invasion, thrombosis, or embolism 13. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation
Intervention	Experimental arm: JCAR017 1 and 2-dose schedule • Each cycle of JCAR017 (lisocabtagene maraleucel) will be administered as 2 intravenous (IV) injections. 2–7 days after lymphodepleting chemotherapy, liso-cel was administered as two sequential infusions of CD8+ and CD4+ CAR+ T cells, at one of three target dose levels: • 50×10^6 CAR+ T cells (dose level 1), • 100×10^6 CAR+ T cells (dose level 2), and • 150×10^6 CAR+ T cells (dose level 3); • a two-dose schedule at dose level 1 was also investigated (dose level 1D; appendix p 12). TRANSCEND followed the seamless design principle, consisting of dose-finding, dose-expansion, and dose-confirmation phases.
Comparator(s)	-
Follow-up time	From 1 year to 15 years based on outcome measures (ongoing) See below
Is the study used in the health economic model?	No. The submission is based on a cost-minimization analysis assuming similar efficacy between the study drug and the comparator
Primary, secondary and exploratory endpoints	**Endpoints included in this application: NA** **Other endpoints:** **Primary outcome measures:** • Treatment-related adverse events (AEs) as assessed by CTCAE v4.03 [Time Frame: Up to 730 days after the final JCAR017 infusion] o Physiological parameter • Dose-limiting toxicities of JCAR017 [Time Frame: 28 days after first (single-dose schedule) or second (2-dose schedule) JCAR017 infusion] o Physiological parameter

Trial name: TRANSCEND	NCT number: NCT02631044
	• Objective response rate (ORR) [Time Frame: 24 months] o Lugano criteria **Secondary outcome measures:** • Complete response (CR) rate [Time Frame: 24 months] o Lugano criteria • Duration of response [Time Frame: 24 months] o Lugano criteria • Progression-free survival (PFS) [Time Frame: 24 months] o Lugano criteria • Overall survival [Time Frame: Up to 15 years] o Physiological parameter • Health-related quality of life [Time Frame: 24 months] o Questionnaire • Maximum concentration of JCAR017 (Cmax) in the peripheral blood [Time Frame: Up to 365 days after the final JCAR017 infusion] o qPCR • Time to maximum concentration of JCAR017 (Tmax) in the peripheral blood [Time Frame: Up to 365 days after the final JCAR017 infusion] o qPCR • Area-under-the-concentration-vs-time-curve (AUC) in the peripheral blood [Time Frame: Up to 365 days after the final JCAR017 infusion] o qPCR
Method of analysis	DLTs were evaluated in the DLT-evaluable set. Safety was analyzed in the liso-cel–treated set. Efficacy was analyzed in three analysis sets: the liso-cel–treated efficacy-evaluable set, the PAS, and the intent-to-treat analysis set. All three analysis sets were prespecified in the Statistical Analysis Plan of the study. The primary analysis was performed using the PAS, a narrow patient population focused on dose level 2. The reported safety and efficacy data are based on the broader liso-cel–treated and liso-cel–treated efficacy-evaluable sets. The primary analysis was conducted when at least 75 patients in the DC cohort could be evaluated at least 6 months after liso-cel infusion. The efficacy endpoints in the PAS were tested in a sequential order as follows: objective response rate (ORR; null hypothesis of ORR ≤40%), CR rate (null hypothesis of CR rate ≤20%), ORR for chemotherapy refractory group and CR rate for chemotherapy refractory group. Hypothesis testing was performed in the PAS,

Trial name: TRANSCEND	NCT number: NCT02631044
	powered at 98% to reject the null hypothesis of ORR ≤40% assuming an underlying effect size of 25%. Dose escalation was guided by modified Bayesian continuous reassessment methodology. DLT-evaluable set.
Subgroup analyses	Responders (complete + partial response) vs nonresponders Pre-lymphodepleting chemotherapy sum of product diameter (≥50 cm2 vs <50 cm2) Any-grade CRS vs no CRS (cytokine release syndrome) Any grade neurological events vs no NE
Other relevant information	-

Table 90 Main characteristic of ZUMA-1

Trial name: ZUMA-1	NCT number: NCT02348216
Objective	This study will be separated into 3 distinct phases designated as the Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (Cohort 3 and Cohort 4, Cohort 5 and Cohort 6). The primary objectives of this study are: • Phase 1 Study: Evaluate the safety of axicabtagene ciloleucel regimens • Phase 2 Pivotal Study; Evaluate the efficacy of axicabtagene ciloleucel • Phase 2 Safety Management Study: Assess the impact of prophylactic regimens or earlier interventions on the rate and severity of cytokine release syndrome (CRS) and neurologic toxicities
Publications – title, author, journal, year	Topp MS, van Meerten T, Wermke M et al. Preliminary Results of Earlier Steroid Use with Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Large B Cell Lymphoma. Poster presented at the American Society of Presented at: American Society of Clinical Oncology Annual Meeting. May 31-June 4, 2019; Chicago, Illinois; Abstract 7558. Topp, M, van Meerten T, Houot R, et al. (2019). Earlier Steroid Use with Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Large B Cell Lymphoma. Blood (ASH Annual Meeting Abstracts) 134(Suppl 1): 243. Abstract 626. Abstract: Oluwole OO, et al. Prophylactic corticosteroid use with axicabtagene ciloleucel in patients with relapsed/refractory large B-cell lymphoma. Transplantation and Cellular Therapy 2021.

Oluwole OO, Bouabdallah K, Munoz J, De Guibert S, Vose JM, Bartlett NL, Lin Y, Deol A, McSweeney PA, Goy AH, Kersten MJ, Jacobson CA, Farooq U, Minnema MC, Thieblemont C, Timmerman JM, Stiff P, Avivi I, Tzachanis D, Kim JJ, Bashir Z, McLeroy J, Zheng Y, Rossi JM, Johnson L, Goyal L, van Meerten T. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021 Aug;194(4):690-700. doi: 10.1111/bjh.17527. Epub 2021 Jul 22.

Santa Monica, Calif. New Four-Year Data Show Long-Term Survival in Patients With Large B-Cell Lymphoma Treated With Yescarta® in ZUMA-1 Trial. Data presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition. December 5, 2020; Abstract 1187

Max S. Topp, Tom van Meerten, Martin Wermke, Pieternella J. Lugtenburg, Monique C. Minnema, Kevin W. Song, Catherine Thieblemont, Yizhou Jiang, Vicki Plaks, Anne Kerber, Marie José Kersten. Preliminary Results of Earlier Steroid Use With Axicabtagene Ciloleucel in Patients With Relapsed/ Refractory Large B Cell Lymphoma. Poster presented at ASCO 2019 Annual Meeting. June 3, 2019; Abstract 7558

Sattva S. Neelapu, Caron A. Jacobson, Olalekan O. Oluwole, Javier Munoz, Abhinav Deol, David B. Miklos, Nancy L. Bartlett, Ira Braunschweig, Yizhou Jiang, Jenny J. Kim, Lianqing Zheng, John M. Rossi, Frederick L. Locke. Axicabtagene Ciloleucel (Axi-Cel) In Refractory Large B Cell Lymphoma: Outcomes in Patients ≥ or < 65 Years of Age in the Pivotal Phase 1/2 ZUMA-1 Study. Poster presented at EHA 2019. June 15, 2019; Abstract 1066

Max S. Topp, Tom van Meerten, Martin Wermke, Pieternella J. Lugtenburg, Monique C. Minnema, Kevin W. Song, Catherine Thieblemont, Yizhou Jiang, Vicki Plaks, Anne Kerber, Marie José Kersten. Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Large B Cell Lymphoma: Preliminary Results of Earlier Steroid Use. Poster presented at EHA 2019. June 15, 2019; Abstract 1067

Sattva S. Neelapu, John M. Rossi, Caron A. Jacobson, Frederick L. Locke, David B. Miklos, Patrick M. Reagan, Scott Rodig, Lazaros J. Lekakis, Ian W. Flinn, Lianqing Zheng, Francesca Milletti, Edmund Chang, Allen Xue, Vicki Plaks, Jenny J. Kim, Adrian Bot. CD19-Loss With Preservation of Other B Cell Lineage Features in Patients With Large B Cell Lymphoma Who Relapsed Post-Axi-Cel. Blood (ASH Annual Meeting Abstracts) 134(Suppl 1): 203. Abstract 704.

Sattva S. Neelapu, Frederick L. Locke, Nancy L. Bartlett, Lazaros J. Lekakis, Patrick Reagan, David B. Miklos, Caron A. Jacobson, Ira Braunschweig, Olalekan Oluwole, Tanya Siddiqi, Yi Lin, Michael Crump, John Kuruvilla, Eric Van Den Neste, Umar Farooq, Lynn Navale, Venita DePuy, Jenny J. Kim, Christian Gisselbrecht. A Comparison of Two-Year Outcomes in ZUMA-1 (Axicabtagene Ciloleucel) and SCHOLAR-1 in Patients With Refractory Large B Cell Lymphoma. Blood (ASH Annual Meeting Abstracts) 134(Suppl 1): 4095. Abstract 626.

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Trial name: ZUMA-1	NCT number: NCT02348216
Study type and design	Phase 1/2, multicenter, interventional, pivotal, open label study
Sample size (n)	*307*
Main inclusion criteria	1. Histologically confirmed: o Diffuse Large B Cell Lymphoma (DLBCL) o Primary Mediastinal Large B Cell Lymphoma (PMBCL) o Transformation Follicular Lymphoma (TFL) o High grade B-cell lymphoma (HGBCL) 2. Chemotherapy-refractory disease, defined as one of more of the following: o No response to last line of therapy i. Progressive disease (PD) as best response to most recent therapy regimen ii. Stable disease (SDi) as best response to most recent therapy with duration no longer than 6 month from last dose of therapy OR o Refractory post-autologous stem cell transplant (ASCT) i. Disease progression or relapsed less than or equal to 12 months of ASCT (must have biopsy proven recurrence in relapsed individuals) ii. If salvage therapy is given post-ASCT, the individual must have had no response to or relapsed after the last line of therapy 3. Individuals must have received adequate prior therapy including at a minimum: o anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20-negative and o an anthracycline containing chemotherapy regimen o for individual with transformed FL must have chemorefractory disease after transformation to DLBCL. 4. At least one measurable lesion per revised IWG Response Criteria 5. Eastern cooperative oncology group (ECOG) performance status of 0 or 1 6. Absolute neutrophil count (ANC) ≥ 1000/uL 7. Absolute lymphocyte count ≥ 100/uL 8. Platelet count ≥ 75,000/uL 9. Adequate renal, hepatic, pulmonary and cardiac function defined as:

Trial name: ZUMA-1	NCT number: NCT02348216
	○ Creatinine clearance (as estimated by Cockcroft Gault) > 60 mL/min ○ Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) < 2.5 upper limit of normal (ULN) ○ Total bilirubin < 1.5 mg/dL, except in individuals with Gilbert's syndrome ○ Cardiac ejection fraction >50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant pleural effusion ○ Baseline oxygen saturation >92% on room air 10. All individuals or legally appointed representatives/caregivers, must personally sign and date the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved consent form before initiating any study specific procedures or activities. 11. Relapsed or refractory large B-cell lymphoma including DLBCL, PMBCL, TFL, and HGBCL after two systemic lines of therapy
Main exclusion criteria	1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years 2. History of allogeneic stem cell transplantation 3. Prior CAR therapy or other genetically modified T cell therapy 4. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment 5. History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection. Individuals with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America (IDSA) guidelines 6. Individuals with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of central nervous system (CNS) lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases 7. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement Note: Other protocol defined Inclusion/Exclusion criteria may apply.

Trial name: ZUMA-1	NCT number: NCT02348216
Intervention	• Biological: Axicabtagene Ciloleucel (Yescarta®) o A single infusion of chimeric antigen receptor (CAR)-transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. • Drug: Fludarabine o Administered according to package insert • Drug: Cyclophosphamide o Administered according to package insert
Comparator(s)	NA
Follow-up time	median follow-up of 15.4 months, maximum 20 months
Is the study used in the health economic model?	No. The submission used a cost minimization approach where the efficacy between the intervention and comparator are assumed to be equal or similar.
Primary, secondary and exploratory endpoints	**Endpoints included in this application: NA** **Other endpoints:** **Primary outcome measures:** • Phase 1 Study: Number of Participants Experiencing Adverse Events (AEs) Defined as Dose Limiting Toxicities (DLTs) [Time Frame: First infusion date of axicabtagene ciloleucel up to 30 days] o DLT was defined as axicabtagene ciloleucel-related events with onset within first 30 days following infusion: ▪ Grade (GR) 4 neutropenia lasting > 21 days and GR 4 thrombocytopenia lasting > 35 days from day of cell transfer; ▪ Any axicabtagene ciloleucel-related AE requiring intubation; ▪ All other GR 3 toxicities lasting > 3 days and all GR 4 toxicities, with exception of following conditions which were not considered DLTs: aphasia/dysphasia or confusion/cognitive disturbance which resolved to GR ≤ 1 within 2 weeks and to baseline within 4 weeks; fever GR 3; myelosuppression defined as lymphopenia, decreased hemoglobin, neutropenia and thrombocytopenia unless neutropenia and

thrombocytopenia met DLT definition described above; immediate hypersensitivity reactions occurring within 2 hours of cell infusion that were reversible to a ≤ GR 2 within 24 hours of cell administration with standard therapy; hypogammaglobulinemia GR 3 or 4.

- Phase 2 Pivotal Study (Cohorts 1 and 2): Overall Response Rate (ORR) as Assessed by Investigator Per Revised International Working Group (IWG) Response Criteria for Malignant Lymphoma [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff date of 27 January 2017 (maximum: 20 months)]
    - ORR was defined as the percentage of participants achieving either a complete response (CR) or a partial response (PR), as assessed by the study investigators using revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007). CR: complete disappearance of all detectable clinical evidence of disease and disease-related symptoms; all lymph nodes and nodal masses must have regressed to normal size; spleen and/or liver must be normal size, not be palpable, and no nodules; bone marrow aspirate and biopsy must show no evidence of disease. PR: a ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses; no increase in size of nodes, liver or spleen and no new sites of disease; multiple splenic and hepatic nodules (if present) must regress by ≥ 50% in the SPD; > 50% decrease in the greatest transverse diameter for single nodules. 95% confidence interval (CI) was calculated by Clopper-Pearson method.
- Phase 2 Safety Management Study (Cohort 3): Percentage of Participants With Treatment-Emergent Cytokine Release Syndrome (CRS) and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff of 26 April 2018 (maximum: 35 months)]
    - TEAE was defined as any AE with onset on or after the start of treatment. CRS events were graded by Lee et al 2014. Grade 1 : No life threatening symptoms and require symptomatic treatment only; Grade 2: Symptoms require and respond to moderate intervention; Grade 3: Symptoms require and respond to aggressive intervention; Grade 4: Life-threatening symptoms and requirements for ventilator support or continuous venovenous hemodialysis (CVVHD), and Grade 5: Death. Neurologic toxicities were graded by Common Terminology Criteria for Adverse Events (CTCAE)

version 4.03. Grade 1: Mild, asymptomatic or mild symptoms and intervention not indicated; Grade 2: Moderate and minimal, local or noninvasive intervention indicated; Grade 3: Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; Grade 4: Life-threatening and urgent intervention indicated; Grade 5: Death related to AE.

- Phase 2 Safety Management Study (Cohort 4): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff of 06 May 2019 (maximum: 47.5 months)]
    - TEAE was defined as any AE with onset on or after the start of treatment. CRS events were graded by Lee et al 2014. Grade 1 : No life threatening symptoms and require symptomatic treatment only; Grade 2: Symptoms require and respond to moderate intervention; Grade 3: Symptoms require and respond to aggressive intervention; Grade 4: Life-threatening symptoms and requirements for ventilator support or CVVHD, and Grade 5: Death. Neurologic toxicities were graded by CTCAE version 4.03. Grade 1: Mild, asymptomatic or mild symptoms and intervention not indicated; Grade 2: Moderate and minimal, local or noninvasive intervention indicated; Grade 3: Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; Grade 4: Life-threatening and urgent intervention indicated; Grade 5: Death related to AE.
- Phase 2 Safety Management Study (Cohort 5): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff of 10 September 2020 (maximum: 64 months)]
    - TEAE was defined as any AE with onset on or after the start of treatment. CRS events were graded by Lee et al 2014. Grade 1 : No life threatening symptoms and require symptomatic treatment only; Grade 2: Symptoms require and respond to moderate intervention; Grade 3: Symptoms require and respond to aggressive intervention; Grade 4: Life-threatening symptoms and requirements for ventilator support or CVVHD, and Grade 5: Death. Neurologic toxicities were graded by CTCAE version 4.03. Grade 1: Mild, asymptomatic or mild symptoms and intervention not indicated; Grade 2: Moderate and minimal, local or noninvasive intervention indicated; Grade 3: Severe or medically significant

but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; Grade 4: Life-threatening and urgent intervention indicated; Grade 5: Death related to AE.

- Phase 2 Safety Management Study (Cohort 6): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff of 16 June 2020 (maximum: 61 months)]
    - TEAE was defined as any AE with onset on or after the start of treatment. CRS events were graded by Lee et al 2014. Grade 1 : No life threatening symptoms and require symptomatic treatment only; Grade 2: Symptoms require and respond to moderate intervention; Grade 3: Symptoms require and respond to aggressive intervention; Grade 4: Life-threatening symptoms and requirements for ventilator support or CVVHD, and Grade 5: Death. Neurologic toxicities were graded by CTCAE version 4.03. Grade 1: Mild, asymptomatic or mild symptoms and intervention not indicated; Grade 2: Moderate and minimal, local or noninvasive intervention indicated; Grade 3: Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated; Grade 4: Life-threatening and urgent intervention indicated; Grade 5: Death related to AE.

Secondary outcome measures:

- Phase 2: Duration of Response (DOR) as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First OR to data cutoff date of 27 Jan 2017, 26 Apr 2018, 6 May 2019, 10 Sep 2010, and 16 Jun 2020 for Cohorts 1 and 2, 3, 4, 5, and 6 respectively (median duration: 5.3, 4.9, 11.1, 5.2, 11.4, and 5.8 months for Cohorts 1, 2, 3, 4, 5, and 6 respectively)]
- Phase 1 Study: ORR as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff date of 27 January 2017 (maximum: 20 months)]
- Phase 2 Pivotal Study (Cohorts 1 and 2): ORR Per Independent Radiological Review Committee (IRRC) [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff date of 27 January 2017 (maximum: 20 months)]
- Phase 2 Safety Management Study (Cohorts 3, 4, 5, and 6): ORR as Assessed by Investigator Per the Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff date of 26 Apr 2018, 06 May 2019, 10 Sep 2020, and 16 Jun 2020 for

Cohorts 3, 4, 5, and 6 respectively (maximum: 35, 47.5, 64, and 61 months for Cohorts 3, 4, 5, and 6 respectively)]

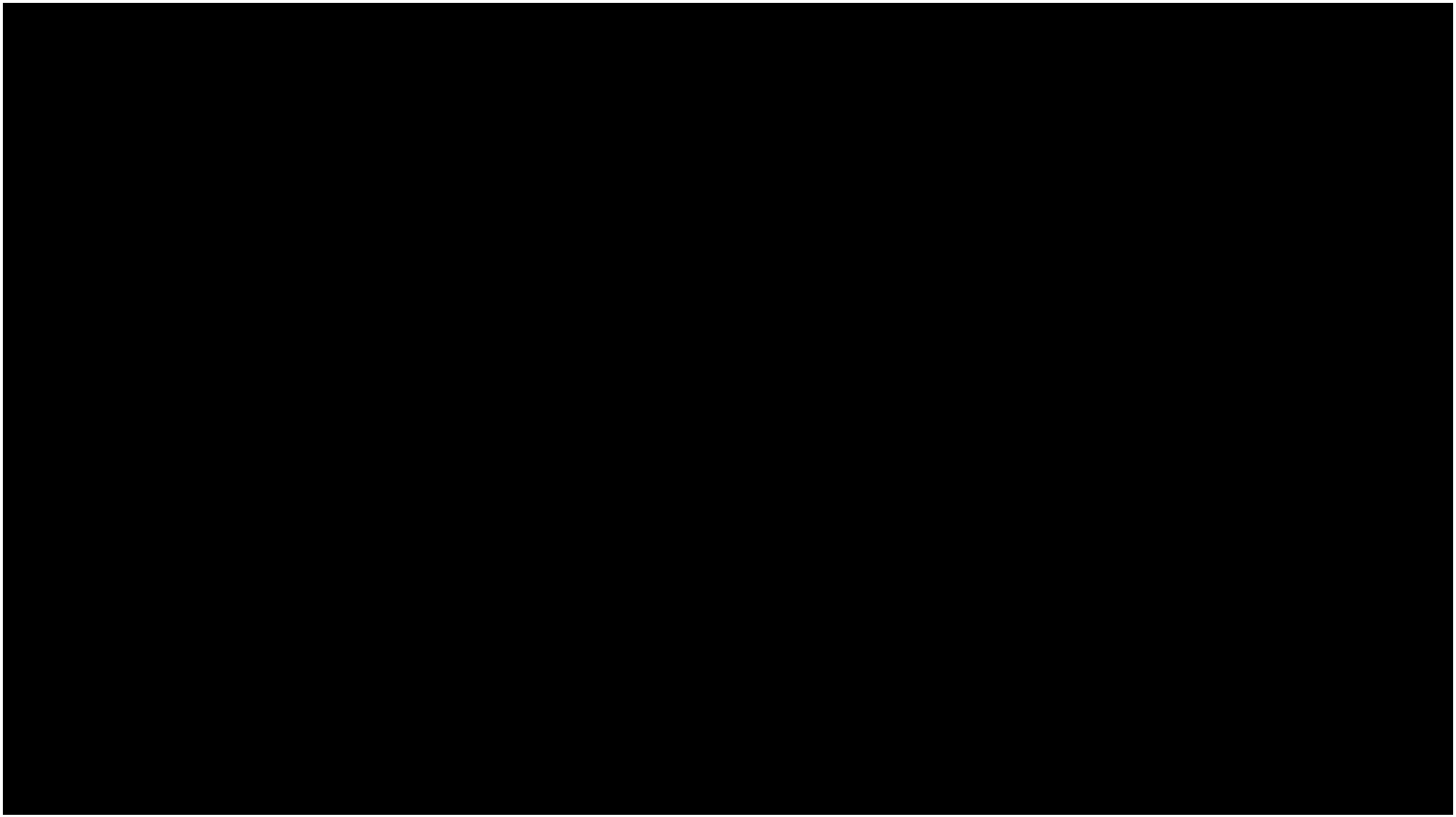
- Phase 2: Progression-Free Survival (PFS) as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma [Time Frame: First infusion date to PD or death or data cutoff date 27 Jan 2017, 26 Apr 2018, 06 May 2019, 10 Sep 2020, and 16 Jun 2020 for Cohorts 1 and 2, 3, 4, 5, 6 respectively (maximum: 20, 35, 47.5, 64, and 61 months for Cohorts 1 and 2, 3, 4, 5, 6 respectively)]
- Phase 2: Overall Survival (OS) [Time Frame: First infusion date to the death or data cutoff date of 27 Jan 2017, 26 Apr 2018, 6 May 2019, 10 Sep 2020, and 16 Jun 2020 for Cohorts 1 and 2, 3, 4, 5, 6 respectively (maximum: 20, 35, 47.5, 64, and 61 months for Cohorts 1 and 2, 3, 4, 5, 6 respectively)]
- Phase 2 Pivotal Study (Cohorts 1 and 2): Duration of Response (DOR) Using IRRC Per Cheson 2007 [Time Frame: First objective response to the data cutoff date of 27 January 2017 (maximum: 20 months)]
- Phase 2 Pivotal Study (Cohorts 1 and 2): Best Overall Response Using IRRC Per Cheson 2007 [Time Frame: First infusion date of axicabtagene ciloleucel to the data cutoff date of 27 January 2017 (maximum: 20 months)]
- Phase 2 Pivotal Study (Cohorts 1 and 2): PFS Using IRRC Per Cheson 2007 [Time Frame: First infusion date of axicabtagene ciloleucel to the date of disease progression or death from any cause or the data cutoff date of 27 January 2017 (maximum: 20 months)]
- Percentage of Participants Experiencing Treatment-Emergent Adverse Events (TEAEs) [Time Frame: First infusion date to data cutoff 27 Jan 2017 (Phase 1,Cohorts 1,2), 26 Apr 2018, 6 May 2019, 10 Sep 2020, 16 Jun 2020 for Cohorts 3,4,5,6 respectively (maximum: 20 months for Phase 1,Cohorts 1,2; 35, 47.5, 64, 61 months for Cohorts 3,4,5,6 respectively)]
- Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 4 and Grade 3 or Higher Resulting From Increased Parameter Value [Time Frame: First infusion date to data cutoff 27 Jan 2017 (Phase 1,Cohorts 1,2), 26 Apr 2018, 6 May 2019, 10 Sep 2020, 16 Jun 2020 for Cohorts 3,4,5,6 respectively (maximum: 20 months for Phase 1,Cohorts 1,2; 35, 47.5, 64, 61 months for Cohorts 3,4,5,6 respectively)]
- Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 4 and Grade 3 or Higher Resulting From Decreased Parameter Value [Time Frame: First infusion date to data cutoff 27 Jan 2017 (Phase 1,Cohorts 1,2), 26 Apr 2018, 6 May 2019, 10 Sep 2020, 16 Jun 2020 for Cohorts 3,4,5,6 respectively (maximum: 20 months for Phase 1,Cohorts 1,2; 35, 47.5, 64, 61 months for Cohorts 3,4,5,6 respectively)]

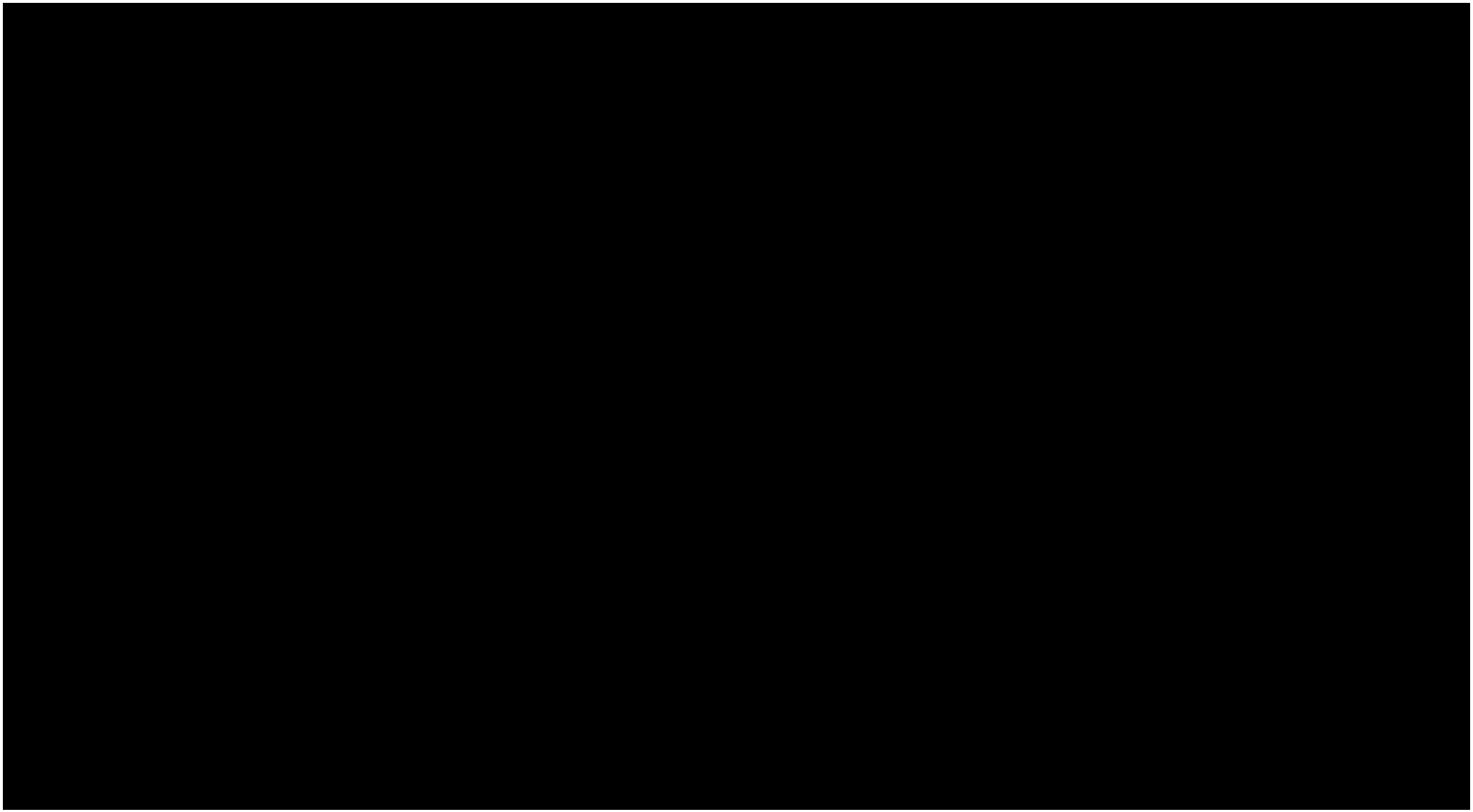
Trial name: ZUMA-1	NCT number: NCT02348216
	• Percentage of Participants With Anti-Axicabtagene Ciloleucel Antibodies [Time Frame: First infusion date to data cutoff 27 Jan 2017 (Phase 1,Cohorts 1,2), 26 Apr 2018, 6 May 2019, 10 Sep 2020, 16 Jun 2020 for Cohorts 3,4,5,6 respectively (maximum: 20 months for Phase 1,Cohorts 1,2; 35, 47.5, 64, 61 months for Cohorts 3,4,5,6 respectively)] • Pharmacokinetics: Peak Level of Anti-CD19 CAR T Cells in Blood [Time Frame: Enrollment up to Month 6] • Pharmacodynamics: Peak Level of Cytokines in Serum (Phase 1 and Phase 2 Cohorts 1, 2, and 3) [Time Frame: Enrollment up to Week 4] • Pharmacodynamics: Peak Level of Cytokines (IP-10, Granzyme B, IFN-gamma, IL-1 RA, IL-10, IL-15, IL-2, IL-6, IL-7, IL-8, TNF Alpha, and GM-CSF) in Serum (Phase 2 Cohorts 4, 5, and 6) [Time Frame: Enrollment up to Week 4] • Pharmacodynamics: Peak Level of Cytokines (Ferritin, ICAM-1, IL-2 R, Perforin, and VCAM-1) in Serum (Phase 2 Cohorts 4, 5, and 6) [Time Frame: Enrollment up to Week 4] • Pharmacodynamics: Peak Level of Cytokine (CRP) in Serum [Time Frame: Enrollment up to Week 4] • Pharmacodynamics: Peak Level of Cytokine (Ferritin) in Serum (Phase 1 and Phase 2 Cohorts 1 and 2) [Time Frame: Enrollment up to Week 4] • Pharmacodynamics: Peak Level of Cytokine (Ferritin) in Serum (Phase 2 Cohort 3) [Time Frame: Enrollment up to Week 4] • Percentage of Participants With Positive Replication Competent Retrovirus (RCR) [Time Frame: Day 0 (pre-infusion) to data cutoff 27 Jan 2017 (Phase 1,Cohorts 1,2), 26 Apr 2018, 6 May 2019, 10 Sep 2020, 16 Jun 2020 for Cohorts 3,4,5,6 respectively (maximum:20 months for Phase 1,Cohorts 1,2; 35, 47.5, 64, 61 months for Cohorts 3,4,5,6 respectively)] • Phase 2 Safety Management Study: Number of Participants With the European Quality of Life Five Dimension Five Level Scale (EQ-5D) Score [Time Frame: Baseline, Week 4, Month 3, and Month 6] • Phase 2 Safety Management Study: EQ-5D Visual Analogue Scale (VAS) Score [Time Frame: Baseline, Week 4, Month 3, and Month 6]
Method of analysis	The primary analysis was conducted at the point when 92 patients could be evaluated 6 months after the axi-cel infusion. Efficacy and safety analyses were reported in the modified intention-to-treat population of all the patients who had received axi-cel.

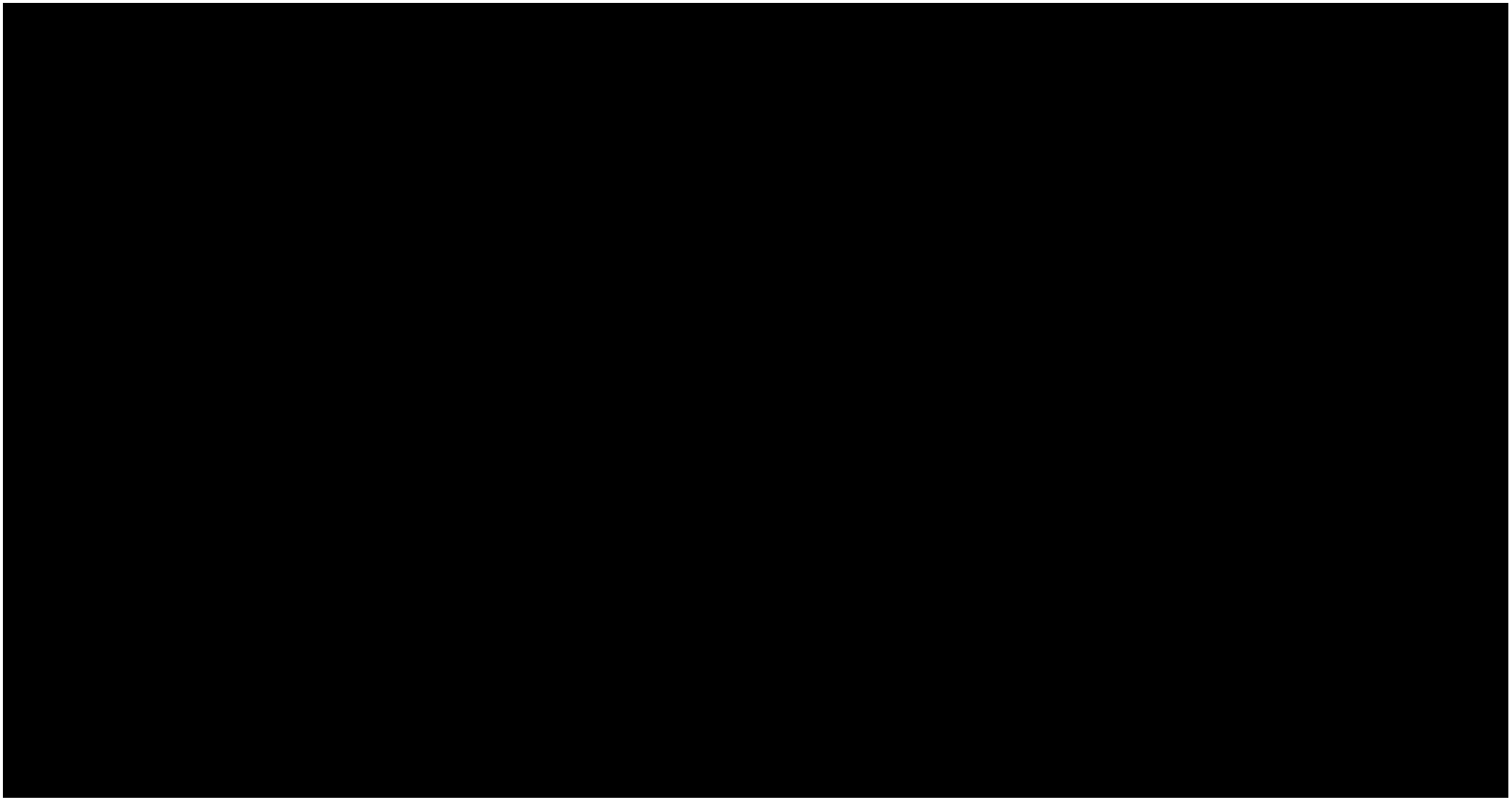
Trial name: ZUMA-1	NCT number: NCT02348216
Subgroup analyses	
Other relevant information	

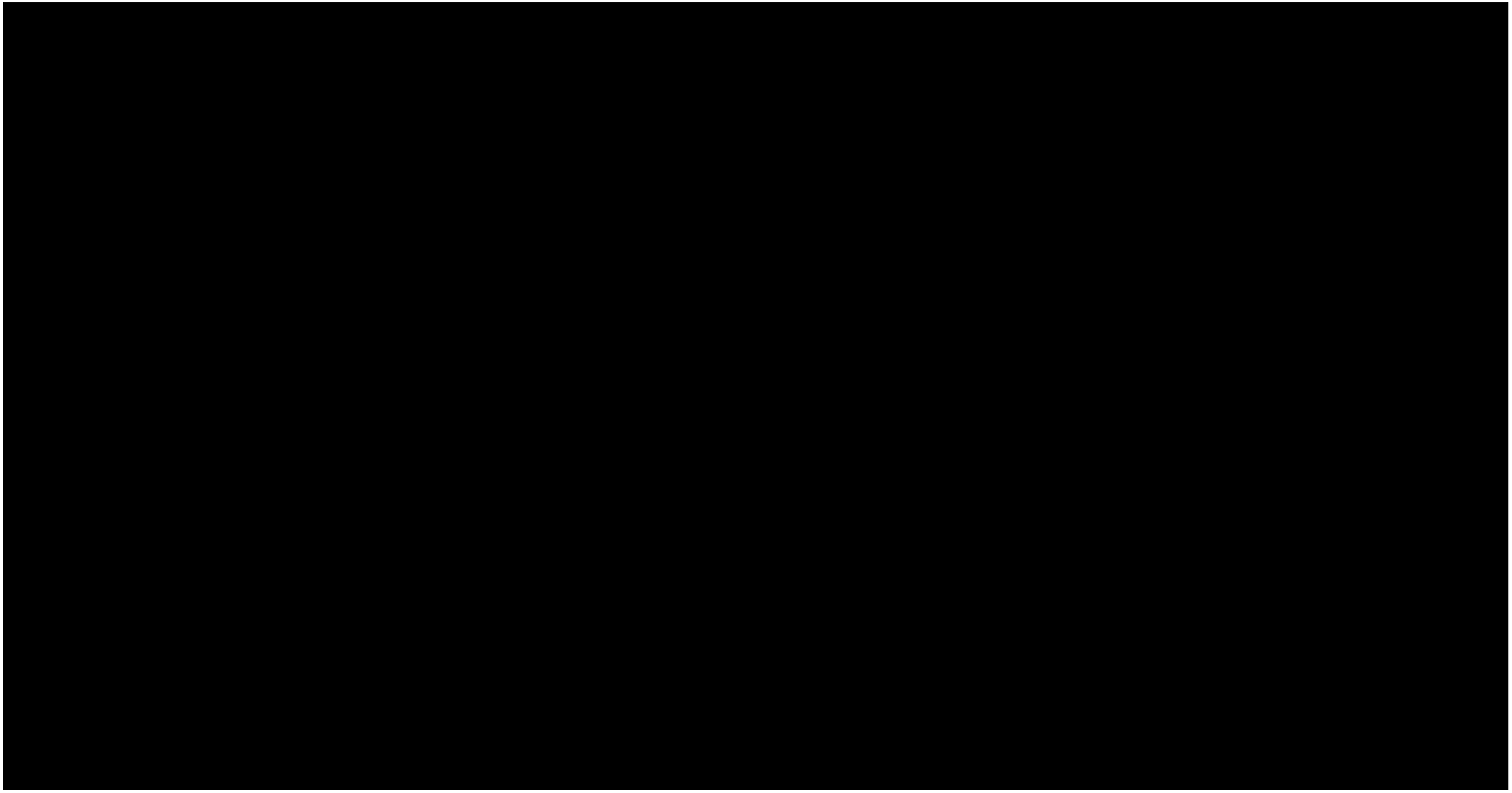
Appendix B. Efficacy results per study

Results per study









Appendix C. Comparative analysis of efficacy

C.1 Efficacy of liso-cel compared to axi-cel for the treatment of transplant eligible, adult patients with Large B-cell lymphoma who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy

C.1.1 Rationale for Matching Adjusted Indirect Comparisons (MAIC)

In networks with many pairwise comparisons between treatments it can sometimes be possible to adequately address these differences via meta-regression. Comparisons of liso-cel and axi-cel were informed by single study connections, making meta-regression impossible. To adjust for the differences between trials, individual patient data (IPD) from one trial is required. Anchored MAIC analysis is one option to derive indirect comparisons when IPD is available, in the presence of common treatment arms or anchors (e.g., placebo, standard of care). Compared to unanchored MAICs, wherein the comparisons of interest do not share an anchor, an anchored MAIC is considered more robust. This is because it is innately protected against both observed and unobserved differences in prognostic factors and is thus able to focus on adjusting for cross-trial differences in only treatment effect modifiers [52].

An alternative population-adjustment ITC approach to MAIC is simulated treatment comparisons (STC). The MAIC approach was preferred over STC for this analysis due to likely more severe assumptions and limitations associated with the latter [52].

C.1.2 Statistical analysis

C.1.2.1 Overview of Statistical Analysis

For the MAIC approach, ITCs were formed by “matching” and “adjusting” patients from TRANSFORM to match the eligible patient population and marginal distribution (e.g., mean and variance) of baseline characteristics in patients who received the comparator intervention (axi-cel). Matching consisted of aligning trials on inclusion/exclusion criteria and is required for the positivity assumption of causal inference to be met. Positivity requires that all patients have a non-zero probability of being assigned to either trial, and violations of positivity can bias estimates of treatment effects and their variance. Adjusting consisted of weighting patients in TRANSFORM so that they represent a population more similar to that of ZUMA-7 [52].

As recommended by NICE TSD 18 [95], given there is a common comparator arm between TRANSFORM and ZUMA-7 (the SoC arm), anchored MAICs were conducted for the efficacy analyses and, by leveraging the common comparator, represent an ideal form of indirect comparison. For the safety outcomes, unanchored MAICs were used to

compare liso-cel and axi-cel arms for two reasons. First, SoC arm data was not available or very limited for several safety outcomes. For example, CRS is a CAR T-specific outcome and was not recorded or reported for either trial in the SoC arm. Several Grade ≥ 3 AEs also had 0 events in the SoC arm, technically limiting the ability to conduct anchored comparisons. Second, it may not be clinically valid to use the SoC arm as the common comparator due to the fundamental differences in treatment modalities and toxicity profile between CAR-T cell and chemotherapies [53].

Patients in the TRANSFORM IPD were matched and adjusted to ZUMA-7. The following sections describe the MAIC methods in more detail[52].

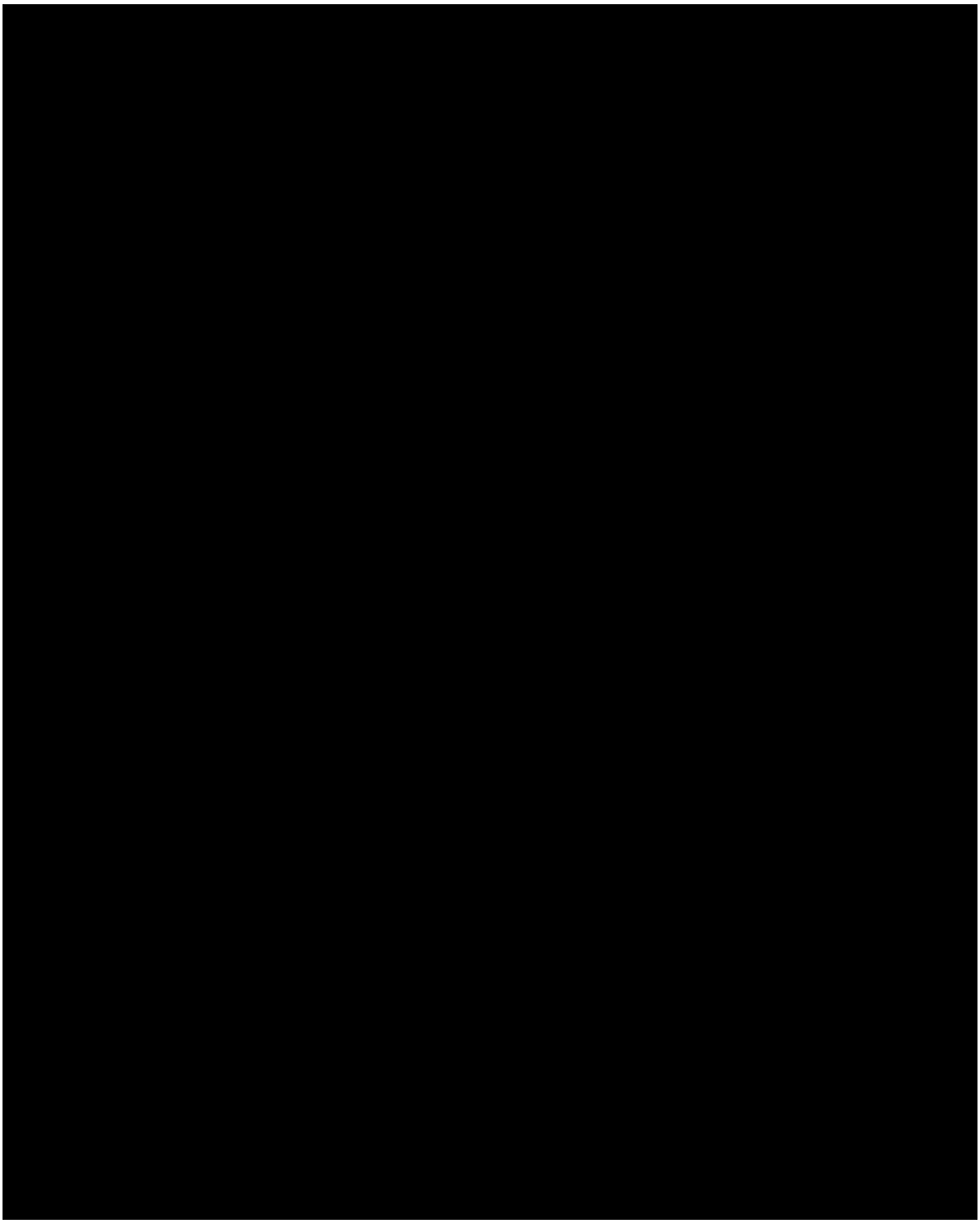
C.1.2.2 Identification and Ranking of Clinical Factors used for Matching and Adjusting

For the anchored comparison of efficacy outcomes, eligibility criteria and baseline characteristics (together, "clinical factors") that were deemed most likely to be treatment effect modifying were identified and prioritized[52].

Clinical factors for adjustment in MAIC were identified based on variables available in both studies (TRANSFORM and ZUMA-7) and a prior ranking exercise for CAR T-cell therapies (i.e., in the third-line or later (3L+) R/R LBCL MAICs of liso-cel to axi-cel [93] and tisagenlecleucel [96]). Briefly, data-driven ranking for each outcome was initially performed using the Bayesian Additive Regression Trees (BART) method using TRANSFORM IPD. The clinical factors were ranked by assessing the interaction effect between treatment (i.e., liso-cel vs. SoC) and the clinical factors in predicting the efficacy outcomes in a statistical model[52].

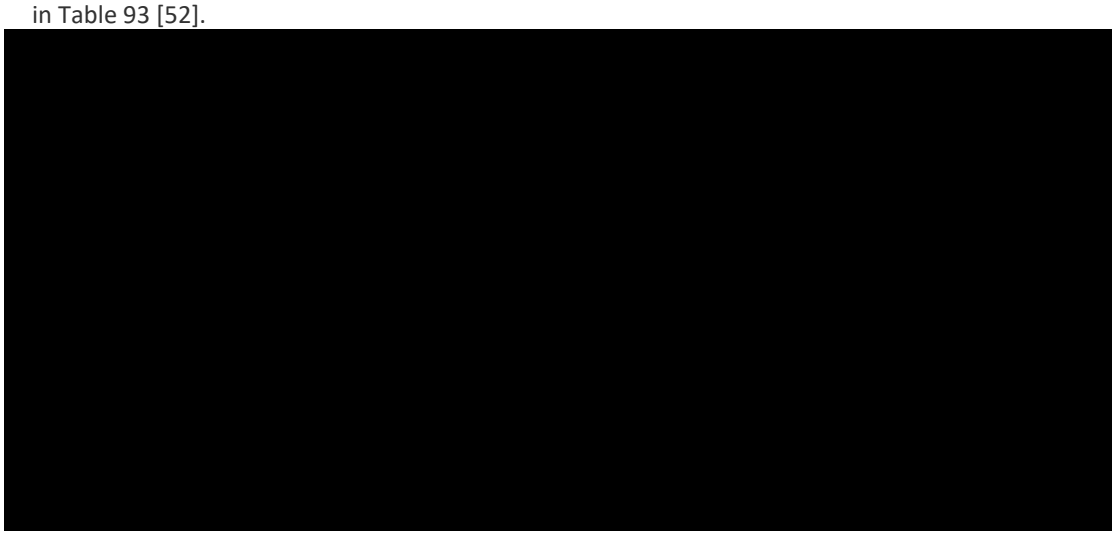
The rankings were then reviewed and revised by a panel of 3 external clinicals experts to create the final ranking of clinical factors to be considered for analysis. The clinical experts oversaw the identification and ranking of clinical factors as well as the selection of analysis scenarios. For anchored comparisons of efficacy outcomes, the panel of experts engaged in several rounds of interviews to ensure all relevant factors were considered for analyses. Clinical factors were evaluated for all efficacy outcomes[52].

The ranking of clinical factors used to inform the matching and adjusting process for efficacy analyses in the comparison of Liso-cel to Axi-cel is shown in Table 92 [52].



A different approach was taken to identify and rank-order the most relevant factors for safety outcomes. Clinical factors used for matching and adjustment for safety outcome comparisons were identified from a previously conducted targeted literature review of prognostic factors in R/R LBCL (i.e, 2L+) and ranked based on ranks determined for efficacy outcome comparisons. Specifically, if a factor identified from the literature was associated with at least one key safety outcome of interest, it was flagged for possible matching and adjustment for all key safety outcomes of interest, to be all-inclusive initially. Among the 17 identified factors, 2 factors (prior HSCT and number of prior lines of therapy) were excluded since they were not relevant to the 2L indication. Six

additional factors (bulky disease, metabolic tumor volume, serum albumin, interleukin-6, fibrinogen level, and CRP) were not considered due to lack of reporting in ZUMA-7. LDH at baseline and bridging therapy were also excluded due to differences in definitions between TRANSFORM and ZUMA-7 (Table 16). For the remaining 7 factors, bilirubin and LVEF were eligibility criteria and therefore were considered as matching factors. Rank-order for the 5 adjustment factors was borrowed from the rank-order established for the efficacy analyses and was validated by clinical experts. The final rankings are presented in Table 93 [52].



C.1.2.3 Data Used for Analyses

Comparisons of efficacy outcomes used the outcome and baseline characteristic data from the ITT population set of both TRANSFORM and ZUMA-7. Comparisons of safety outcomes used outcome data from the safety analysis sets of both TRANSFORM and ZUMA-7. However, baseline characteristic data for ZUMA-7 was only reported for the ITT population in Locke 2021 [47] or very scarcely for a modified safety analysis set in the FDA assessment report [53]. Therefore, for safety outcome comparisons involving adjustment on baseline characteristics, data from the ITT population set was used as if it were the safety analysis set. Given the safety analysis set comprised 94.2% of the ITT population set in ZUMA-7, this was considered a relatively minimal limitation to enable adjustment of baseline factors[52].

Before MAIC was conducted, baseline characteristic data for TRANSFORM were aligned in definition and categorization to that reported by ZUMA-7 per the actions prescribed in Table 16.

C.1.2.4 Matching Criteria

Patients from TRANSFORM were excluded from the IPD set if they would not have satisfied the eligibility criteria used in the ZUMA-7 trial. Note that the matching phase of the MAIC requires that TRANSFORM has a broader patient population than the comparator study[52].

C.1.2.5 Adjusting Patients

After completing the matching phase of the MAIC, patients remaining from TRANSFORM were weighted using a method-of-moments propensity score algorithm [72]. Method-of-moments is typically chosen both due to only having SLD for comparator trials and because it seeks an exact balancing of covariates between comparison trials of interest. That is, after reweighting patients, the means (or proportions) and standard deviations of covariates from TRANSFORM should be almost exactly equal to those published in the comparator study (ZUMA-7) [72, 97]. For anchored analyses, patients from TRANSFORM were weighted so they matched the marginal distribution of baseline characteristics from the combined population of axi-cel and SoC arms from ZUMA-7. For unanchored analyses, patients from TRANSFORM's liso-cel arm were weighted so they matched the marginal distribution of baseline characteristics from the axi-cel arm from ZUMA-7[52].

C.1.2.6 Estimating Indirect Treatment Effects

Estimates of the comparative efficacy of liso-cel versus axi-cel was derived as the difference between (a) an estimate of the outcome of interest for liso-cel based on matched and adjusted IPD from TRANSFORM (to align with patients in ZUMA-7), and (b) the estimated outcome for axi-cel based on published SLD from ZUMA-7. The steps for deriving the ITC were as follows, depending on the outcome type[52]:

Time-to-event efficacy outcomes: For the anchored analysis of EFS, PFS, and OS, a weighted log HR of liso-cel vs. SoC was estimated in TRANSFORM by fitting a weighted, unstratified Cox PH model with binary treatment covariate and MAIC adjustment weights [98]. Robust standard errors (SEs) were estimated using the R package 'survival' [99]. An estimate of the log HR for liso-cel vs. axi-cel was derived by taking the difference between this weighted log HR and the estimated log HR for axi-cel vs. SoC from the published ZUMA-7 data. The variance of the log HR of liso-cel vs. axi-cel was estimated as the sum of the variance of these two log HRs. The Cox PH model assumes the relative hazard function between treatments is constant over time. This assumption was validated for the analyses through visual inspections of the Kaplan-Meier (KM) curves, plots of log cumulative hazards, and Grambsch-Therneau test on the slope of the Schoenfeld residuals [100].

Binary efficacy outcomes: For the anchored analysis of ORR and CRR, a weighted log odds ratio (OR) of liso-cel vs. SoC was estimated in TRANSFORM by fitting a logistic regression model with binary treatment covariate and MAIC adjustment weights. Robust SEs were estimated using the sandwich estimator via the R package 'sandwich' [101, 102]. An estimate of the log OR for liso-cel vs. axi-cel was derived as the difference between this weighted log OR for liso-cel vs SoC and the estimated log OR for axi-cel vs. SoC based on SLD from the published ZUMA-7 data. The variance of the log OR of liso-cel vs. axi-cel was estimated as the sum of the variance of these two log ORs.

Binary safety outcomes: For the unanchored analysis of safety outcomes, weighted log odds for liso-cel were estimated in TRANSFORM by fitting an intercept-only logistic regression model with MAIC adjustment weights. Robust SEs were estimated using the sandwich estimator via the R package 'sandwich' [101, 102]. An estimate of the log OR for liso-cel vs. axi-cel was derived as the difference between this weighted log odds for liso-cel and the estimated log odds for axi-cel based on SLD from the published ZUMA-7

data. The variance of the log OR of liso-cel vs. axi-cel was estimated as the sum of the variance of these two log odds.

Point estimates (HR, OR) and 95% CI were reported for each analysis.

C.1.2.7 Performance Assessment and Model Selection

For a given set of ranked clinical factors, separate MAICs were conducted sequentially, adjusting for 1 additional variable at a time in order of ranked importance. After fitting each model, the performance and suitability of each MAIC model was assessed based on the following criteria[52]:

- Effective sample size (ESS); as calculated by ESS = $(\sum w_i)^2/(\sum w_i^2)$, where w_i, i=1,…N, are the patients weights estimated by the propensity score model. A low ESS compared to the original sample size N indicates large differences in patient weights due to large imbalances in patient populations prior to reweighting. The ESS is interpreted as the number of independent, non-weighted individuals needed to obtain an equally precise estimate compared to that calculated from the weighted sample [72, 103]. That is, it may be interpreted as the number of patients in a sample after weighting in the context of the current MAIC.

- Distribution of patient weights. Extreme patient weights can indicate uncertainty in the resulting relative treatment effect.

- Summary statistics (e.g., means, proportions) for each clinical factor before and after matching and adjusting steps were assessed to evaluate the improvement in balance between trial populations. Balance was assessed using the absolute value of the standardized mean difference (SMD) for each covariate. An SMD ≥ 0.10 or 0.20 was considered indicative of potentially important imbalances between comparisons [104]. For a given covariate, a reduction in the SMD after matching and adjusting signifies a reduction in imbalance between studies.

- For OS and PFS, the assumption of PH underlying Cox PH models was assessed by examining cross-over in KM curves and applying the Grambsch- Grambsch statistical test for proportional hazards [100].

The primary analysis of the MAIC model was chosen based on achieving a balance between these criteria, while also considering the number of clinical factors included.

C.1.2.8 Assessment of Proportional Hazards Assumption

The fundamental assumption in the Cox PH model is that relative hazards between interventions (e.g., liso-cel and axi-cel) remains constant over time. The appropriateness of this PH assumption was assessed based on visual inspection of the KM curves and visual inspection of log-cumulative hazard plots [96].

A visual assessment was conducted to carefully assess the shape of the curves over time. For example, as the number of patients declines, survival estimates become less certain, and it is difficult to determine if the PH assumption is truly violated, or due to chance. If there was clear evidence that the PH assumption was violated, alternative methods to account for time-varying hazards were considered, such as comparison of restricted mean survival time [105]. For all analyses, the number of patients at risk over time was presented and uncertainty in the survival curves inspected[52].

C.1.2.9 Analysis Scenarios for Efficacy Outcomes

The primary MAIC scenario of efficacy outcomes included 10 highly ranked clinical factors to ensure sufficient ESS across all efficacy outcome comparisons (Table 94). As 3 of the ranked clinical factors (i.e., disease histology, secondary CNS involvement, ALC) related to trial eligibility criteria, these factors were used first as matching criteria in MAICs (i.e., patients in TRANSFORM who did not satisfy these criteria were excluded). The primary MAIC scenario was determined based on clinical key opinion leaders (KOLs) consultation to ensure an appropriate number of clinical differences were accounted for and ESS to select a scenario with a robust enough sample size. Among the adjusting factors, patient demographic factors (age, sex, region) were prioritized to ensure alignment between the study populations. An additional 5 top-ranked clinical factors (sAAIPI score, SPD at baseline, R/R status, double or triple hit, disease histology [remaining imbalances after matching]) were then adjusted to further reduce residual imbalances between studies. sAAIPI score was identified as a key clinical factor by clinical experts as it is a composite score comprising several important patient and disease characteristics (e.g., ECOG PS, LDH, disease stage). A sensitivity analysis adjusting for all available factors was also performed to validate the primary analysis results. The selection of the primary and sensitivity scenarios was made as described in section C.1.2.7[52].

Table 94 Clinical Factors Included in Efficacy Analyses comparing Liso-cel to Axi-cel

Clinical Factor	Efficacy Analyses	
	Primary	**SA**
Factors that were matched on	Disease histology	Disease histology
	Secondary CNS involvement	Secondary CNS involvement
	ALC	ALC
Factors that were adjusted for	Age, sex, and region	Age, sex, and region
	sAAIPI	sAAIPI
	SPD at baseline	SPD at baseline

	R/R status	R/R status
	Double or Triple Hit	Double or Triple Hit
	Disease histology	Disease histology
	-	Baseline cell of origin
	-	Bone marrow involvement
	-	ECOG score at baseline
	-	Baseline Ann Arbor Stage

C.1.2.10 Analysis Scenarios for Safety Outcomes

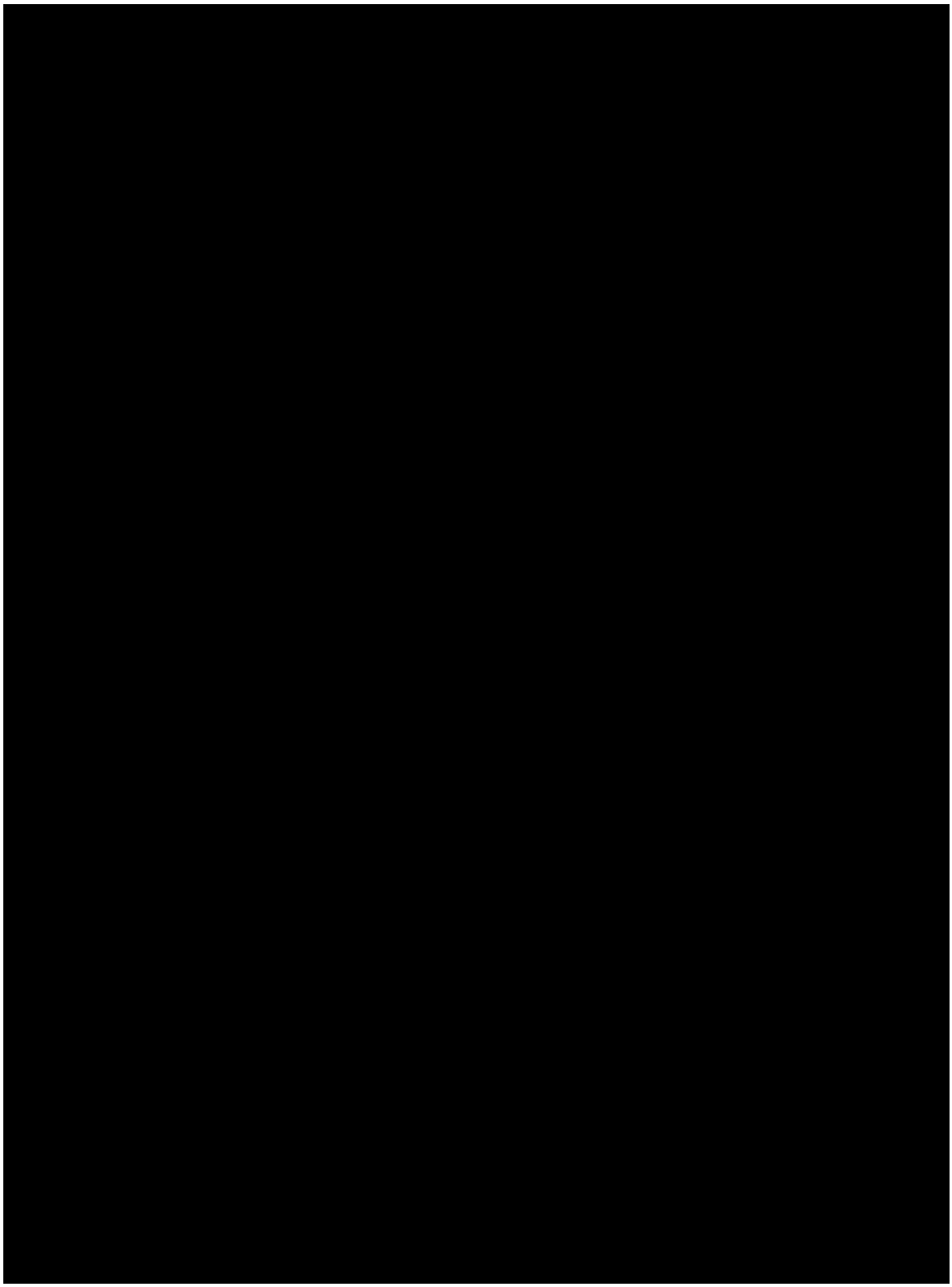
Detailed description of clinical factor identification and ranking for safety analyses are presented in section C.1.2.2. Safety analyses was conducted through an unanchored MAIC approach comparing the liso-cel arm from TRANSFORM to the axi-cel arm from ZUMA-7. Therefore, there was less sample size available for safety outcome MAICs to adjust for factors compared to what was available for efficacy outcome MAICs. In total, the safety MAIC analyses included 4 highly ranked safety clinical factors to ensure sufficient ESS (Table 95). As 2 of the clinical factors (i.e., LVEF at screening and bilirubin at screening) related to trial eligibility criteria, these factors were used first as matching criteria in MAICs (i.e., patients in TRANSFORM who did not satisfy these criteria were excluded). Among the adjusting factors, patient demographic factors (age) still ranked important for safety outcomes and was prioritized to ensure alignment between the study populations. An additional top-ranked clinical factor, sAAIPI score, was then adjusted to further reduce residual imbalances between studies. Selection was made in consultation with clinical experts and aimed to strike a balance between number of factors included, ESS, distribution of patient weights, and SMD values[52].

Table 95 Clinical Factors Included in Safety Analyses comparing Liso-cel to Axi-cel

Clinical Factor	Safety Analyses
	MAIC
Factors that were matched on	LVEF at screening
	Bilirubin at screening
Factors that were adjusted for	Age
	sAAIPI

C.1.2.11 Comparison of Clinical Factors at Baseline after Alignment of Definition and Categorization (Efficacy Analyses)

The baseline values after redefinition or recategorization are summarized in Table 96 [52].



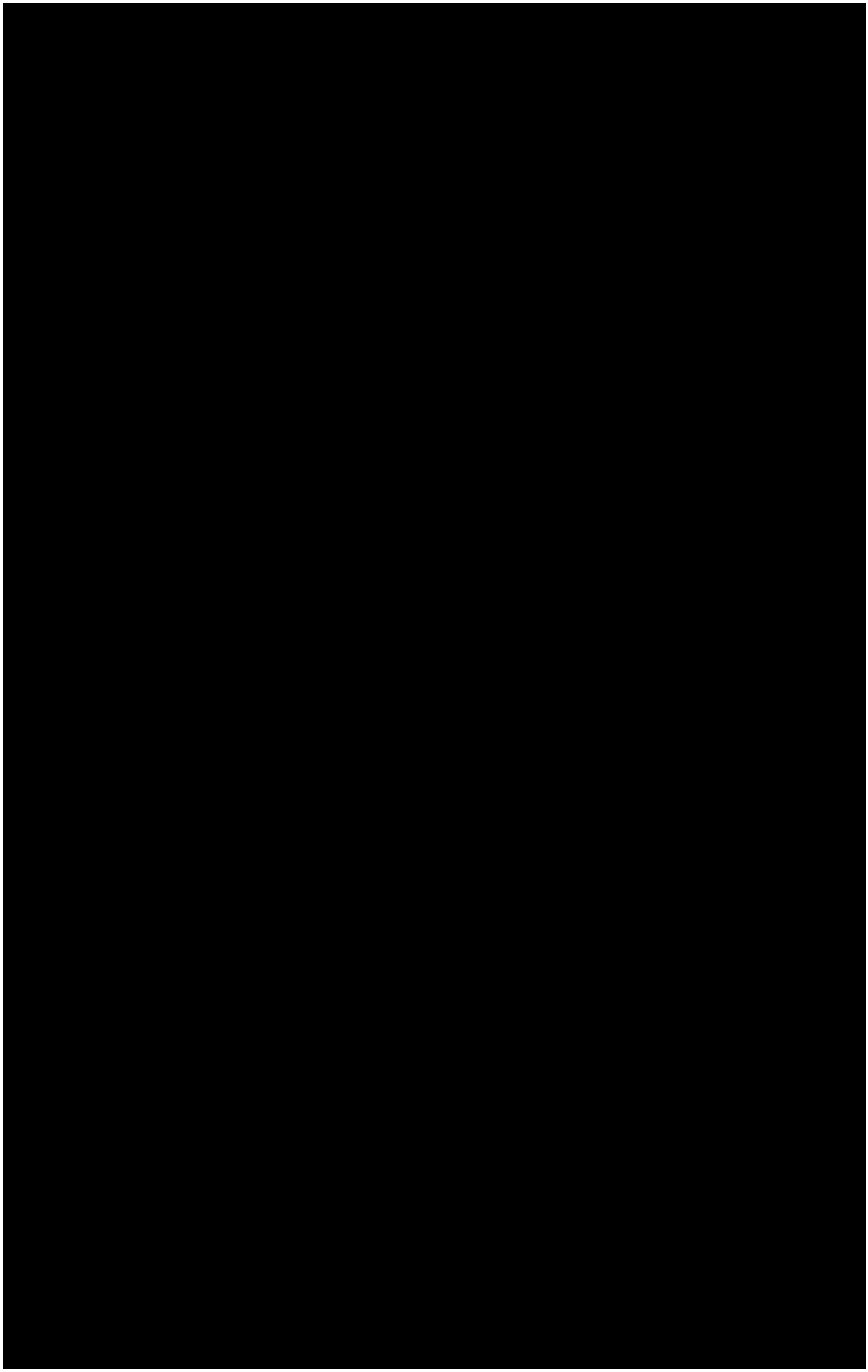
DLBCL: Transformed from Indolent Lymphoma (other than FL)	0	0	0	0
Other[c]	8 (4.4)	9 (5)	12 (13)	15 (16.3)
Cell of Origin, n (%)				
ABC, Non-GCB	16 (8.9)	9 (5)	21 (22.8)	29 (31.5)
GCB	109 (60.6)	99 (55.3)	45 (48.9)	40 (43.5)
Unknown	55 (30.6)	71 (39.7)	26 (28.3)	23 (25)
Bone Marrow Involvement, n (%)				
No	163 (90.6)	164 (91.6)	82 (89.1)	77 (83.7)
Unknown	0 (0)	0 (0)	1 (1.1)	2 (2.2)
Yes	17 (9.4)	15 (8.4)	9 (9.8)	13 (14.1)
ECOG PS at Baseline, n (%)				
0	95 (52.8)	100 (55.9)	46 (50)	49 (53.3)
1	85 (47.2)	79 (44.1)	45 (48.9)	41 (44.6)
2	0 (0)	0 (0)	1 (1.1)	2 (2.2)
Disease Stage, n (%)				
Stage I or II	41 (22.8)	33 (18.4)	24 (26.1)	29 (31.5)
Stage III or IV	139 (77.2)	146 (81.6)	68 (73.9)	63 (68.5)
ALC, n (%)				
< 100/uL	0	0	1 (1.1)	0 (0)
Secondary CNS lymphoma, n (%)	0	0	1 (1.1)	3 (3.3)

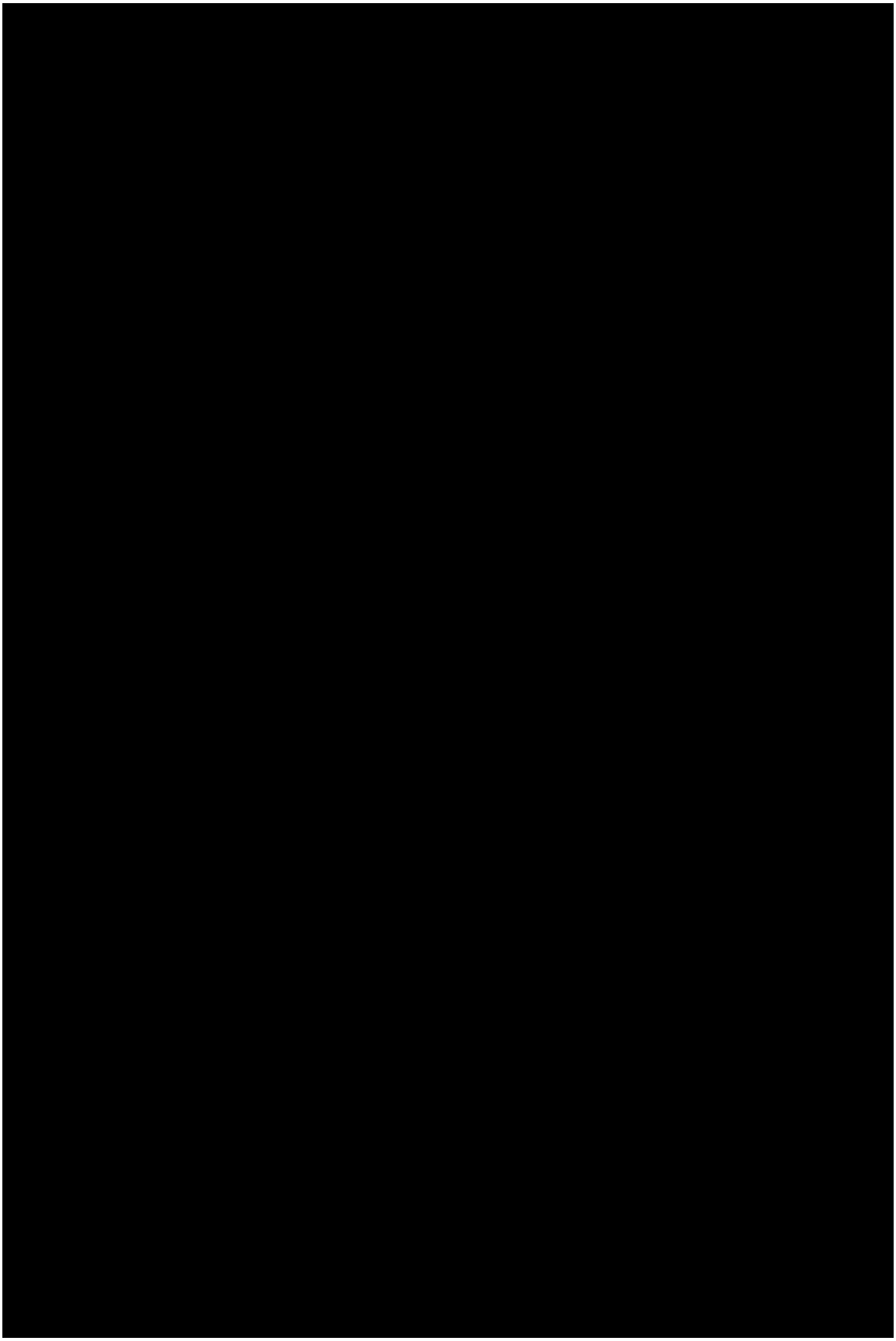
[a]The mean and SD were estimated from the reported median and range using methods proposed in the study by McGrath et al [70].

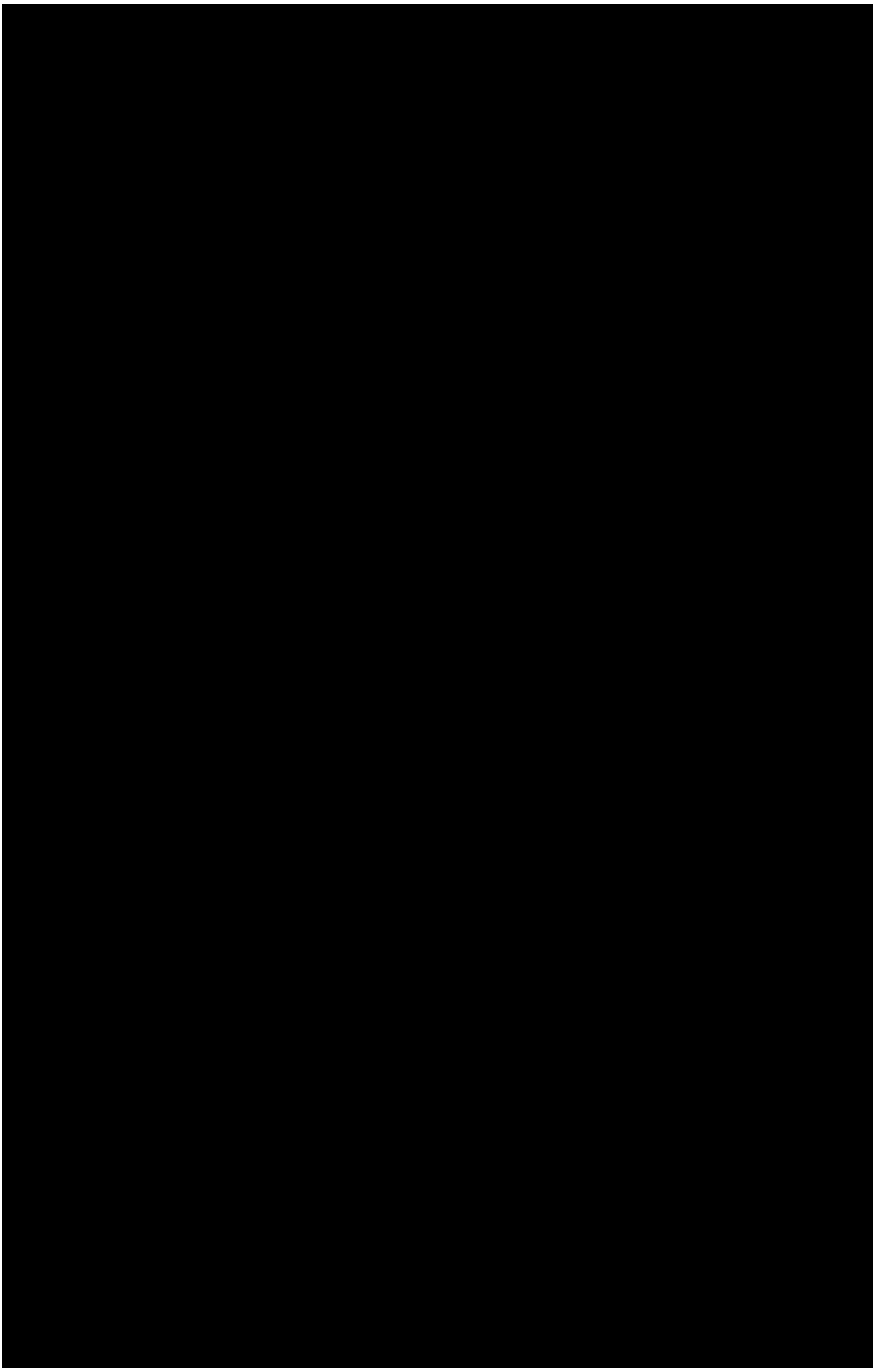
[b]Region was reported in FDA assessment of ZUMA-7 [53].

[c]The category included THRBCL, EBV+ DLBCL, primary cutaneous DLBCL – leg type.

C.1.2.12 Comparison of Clinical Factors Before and After MAIC (Efficacy Analyses)







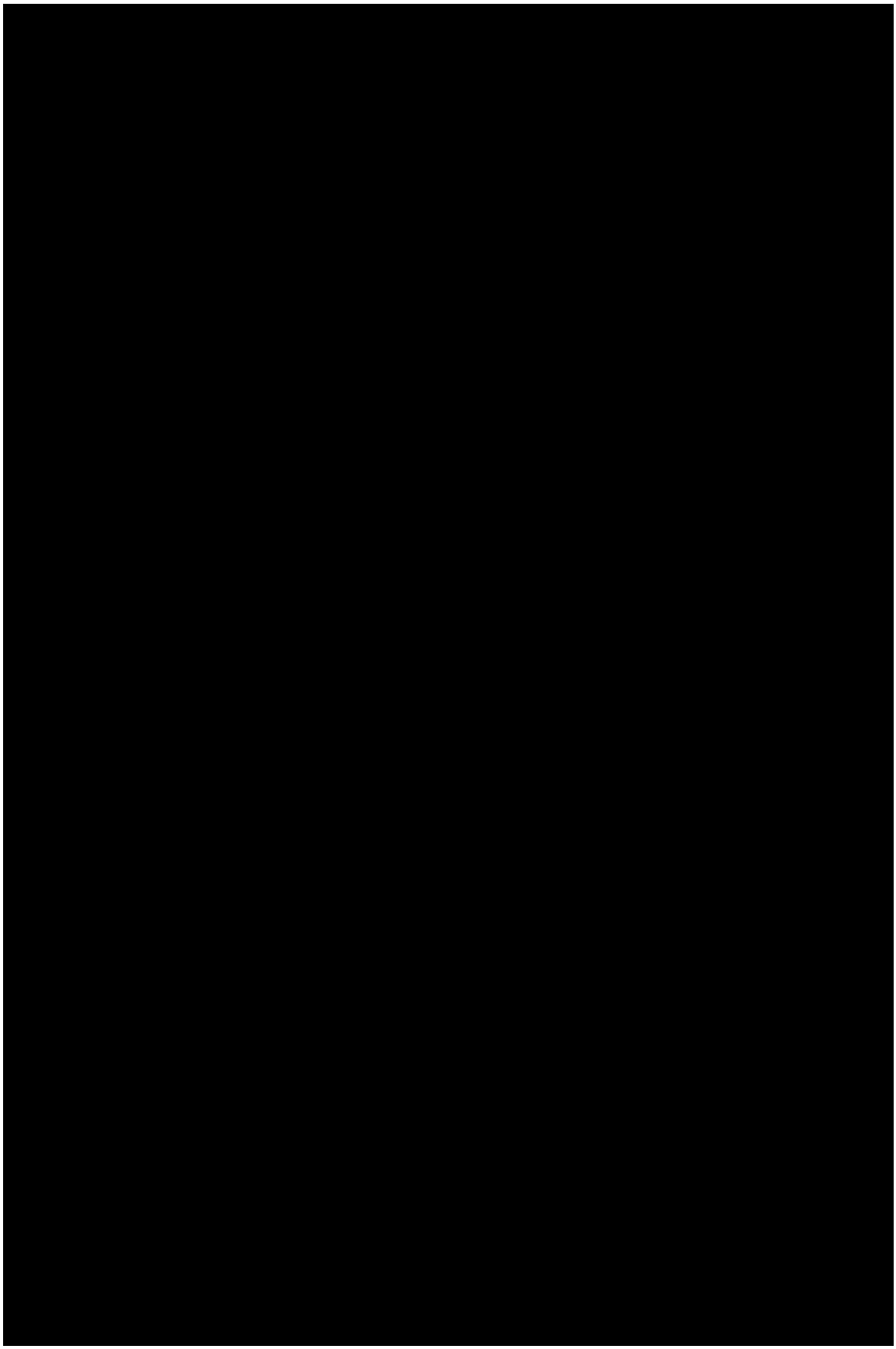
[redacted]

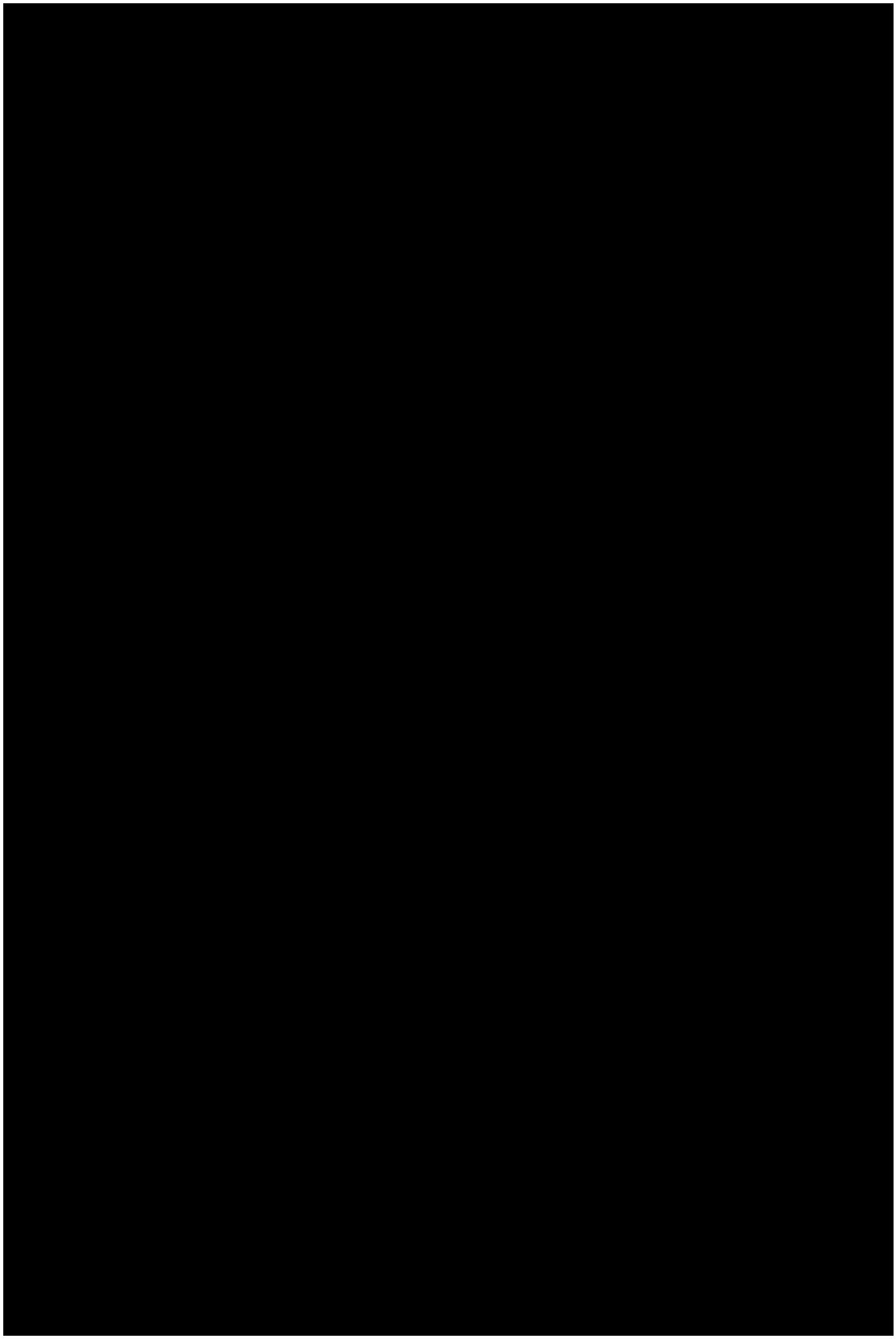
C.1.2.13 Comparison of Clinical Factors at Baseline after Alignment of Definition and Categorization (Safety Analyses)

Clinical factors from the safety analysis set in TRANSFORM and the ITT set in ZUMA-7 were used to inform the safety analyses [52].

The definitions and categorizations of these factors were first aligned based on the actions specified in Table 16. The baseline values after alignment were summarized in Table 99 [52].

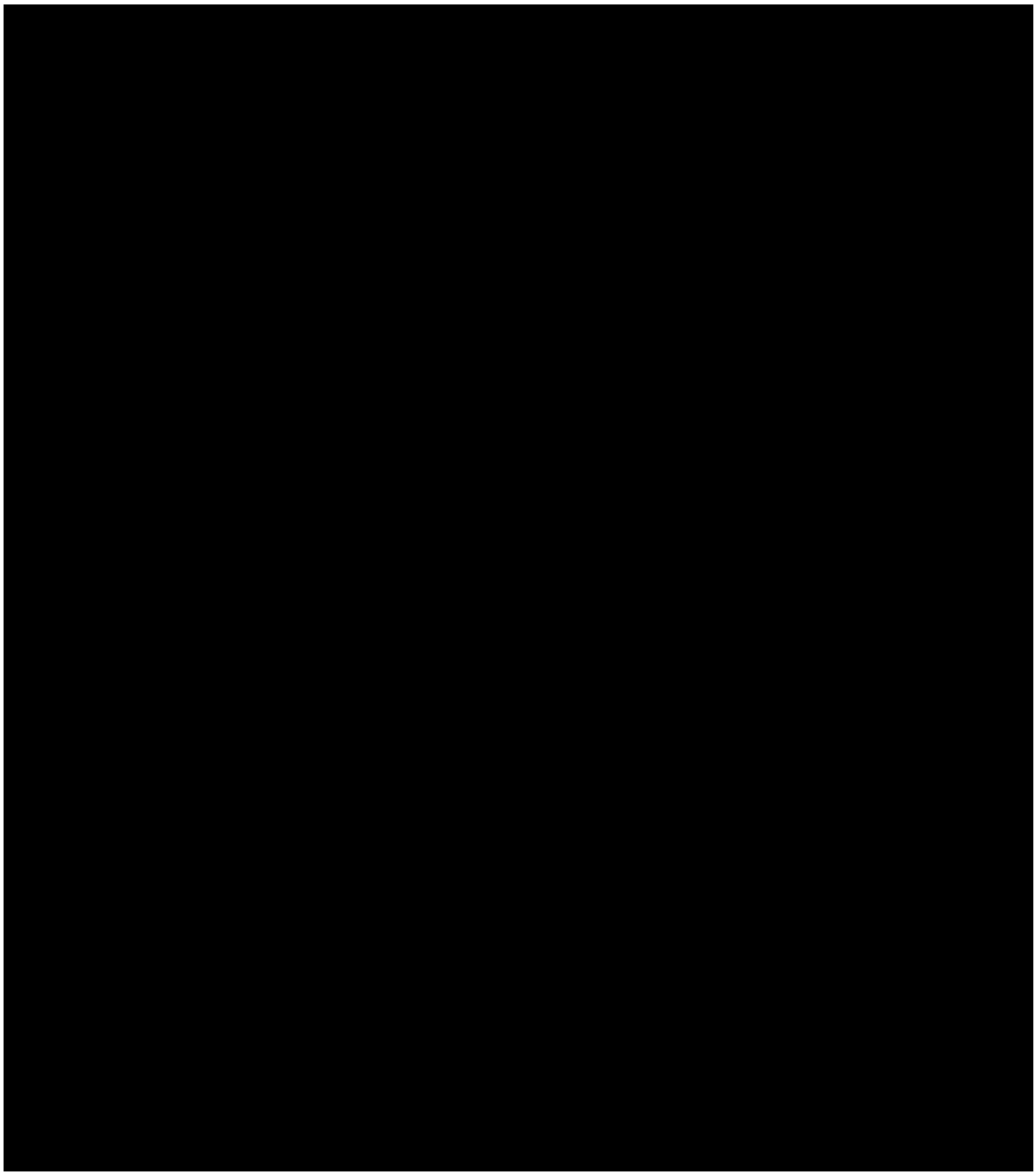
[redacted]





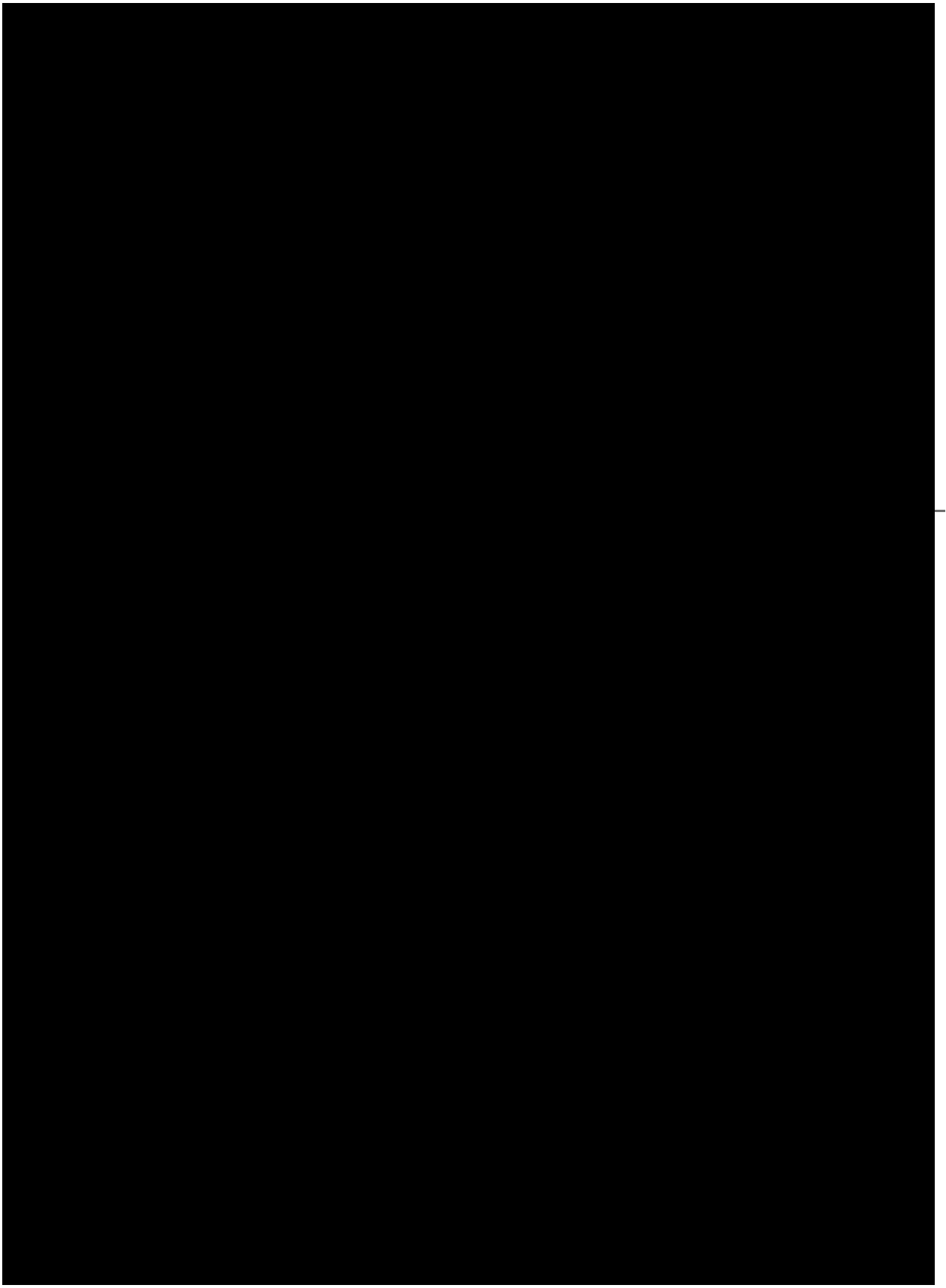
C.1.2.15 Distribution of patient weights in TRANSFORM for efficacy Comparisons between Liso-cel and Axi-cel

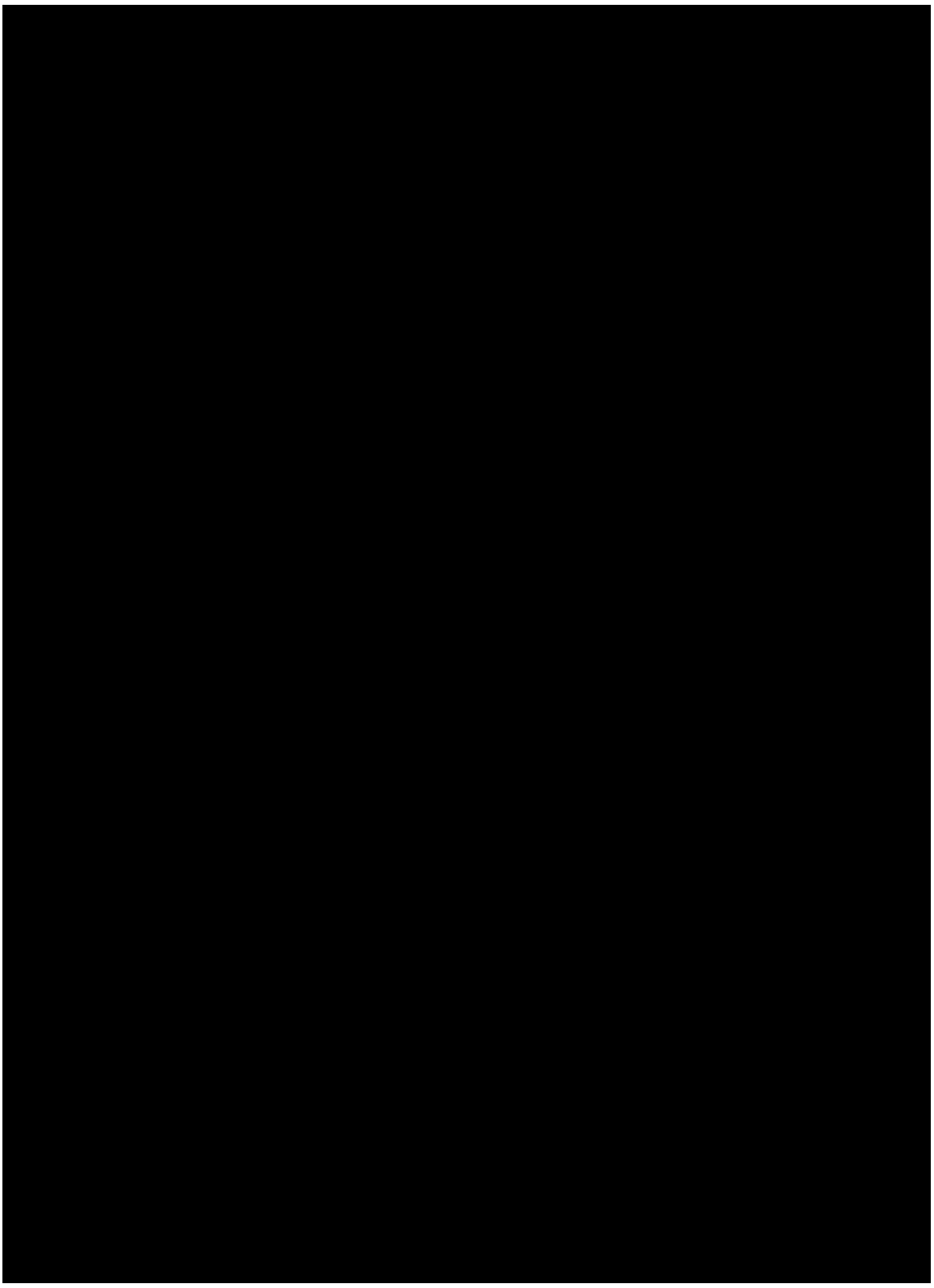
Patient weights distribution after MAIC are presented in Figure 49 and Figure 50[52].

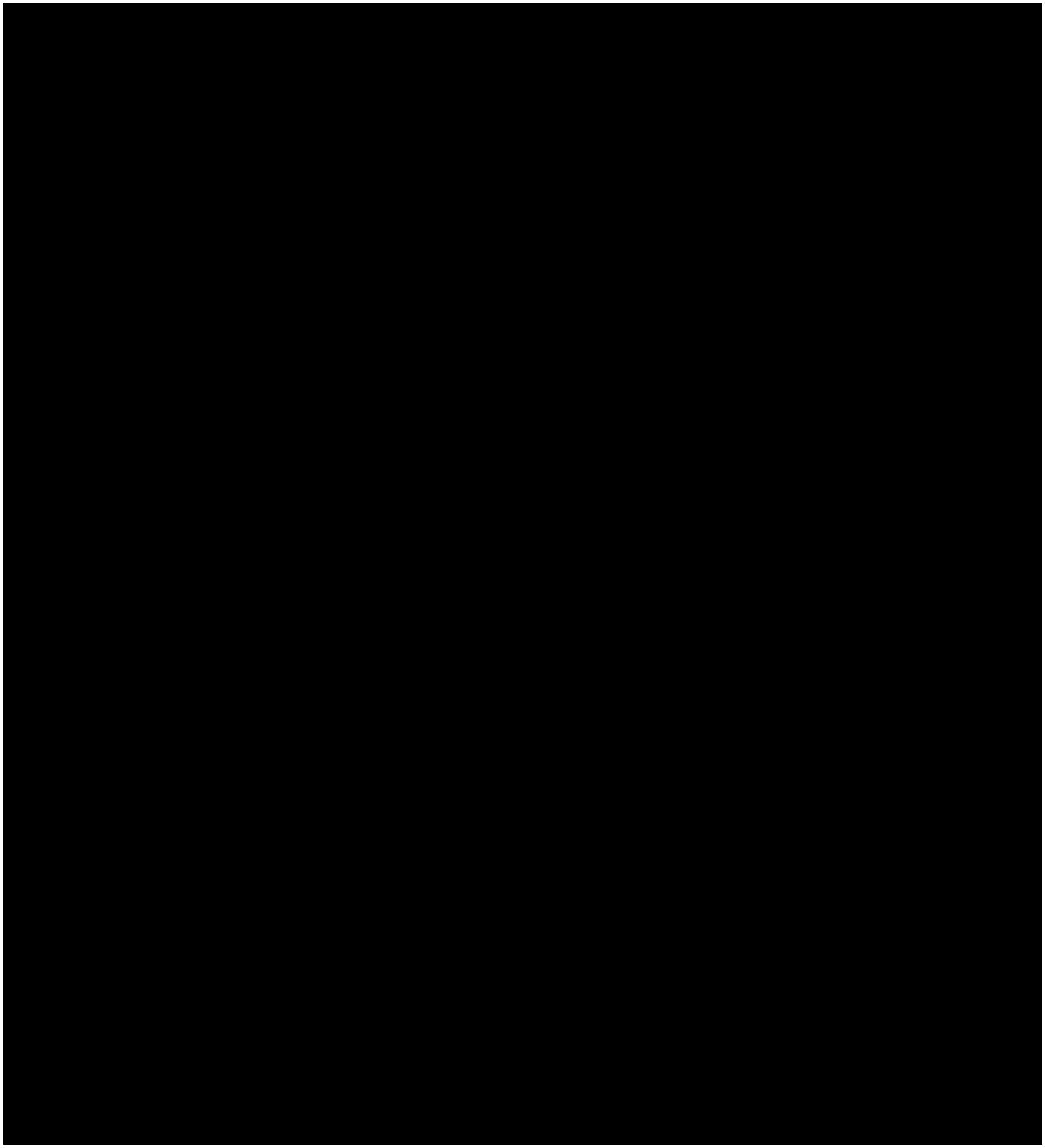


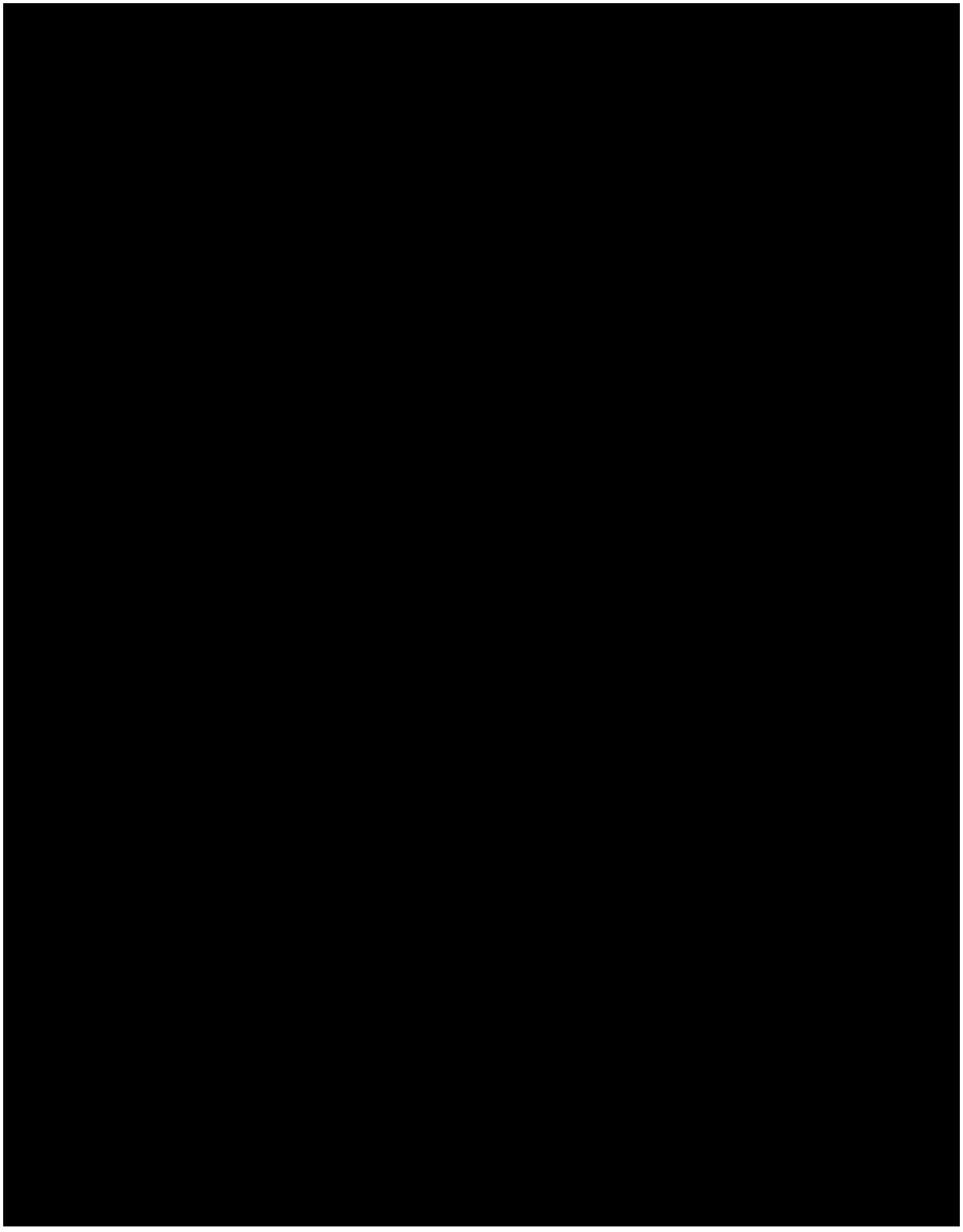
C.1.2.16 Distribution of Patient Weights in the Liso-cel Arm of TRANSFORM for Safety Comparisons between Liso-cel and Axi-cel

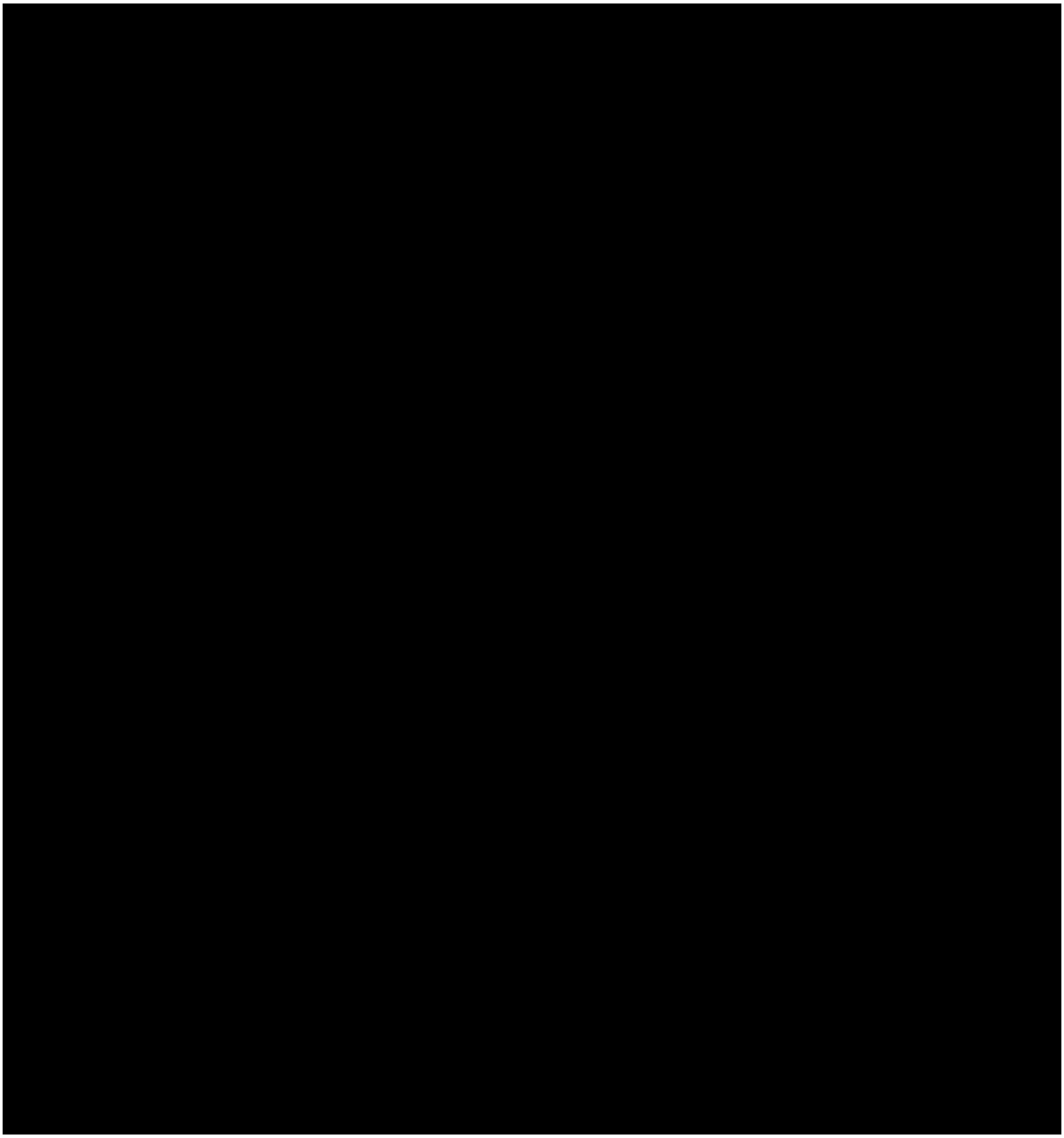
Patient weights distribution after MAIC is presented in Figure 51 [52].











C.2 Efficacy of liso-cel compared to axi-cel for the treatment of adult patients with relapsed or refractory Large B-cell lymphoma after two or more lines of systemic therapy

C.2.1 Rationale for Matching Adjusted Indirect Comparisons

Naïve comparisons of efficacy outcomes between trials typically introduce bias because of differences (unmatched and unadjusted) in baseline demographic and clinical characteristics, which are either prognostic or treatment-effect modifiers. When there are considerable differences in patient and study characteristics, analysis using IPD may

be required. In these situations, MAICs are commonly used to derive relative treatment effects [76].

In open-label, single-arm clinical trials (i.e., in the absence of a common comparator), unanchored MAICs can be conducted. The validity of inferences drawn from such comparisons is based on the assumption that all relevant prognostic factors have been incorporated in the MAIC [72]. Although it is virtually impossible to adjust for all possible factors that may differ between trials, adjustment for most known, clinically relevant prognostic factors can help alleviate the risk of bias associated with relative treatment effects obtained via unanchored MAIC [76].

C.2.2 Statistical Methods

C.2.2.1 Overview of Statistical Analysis

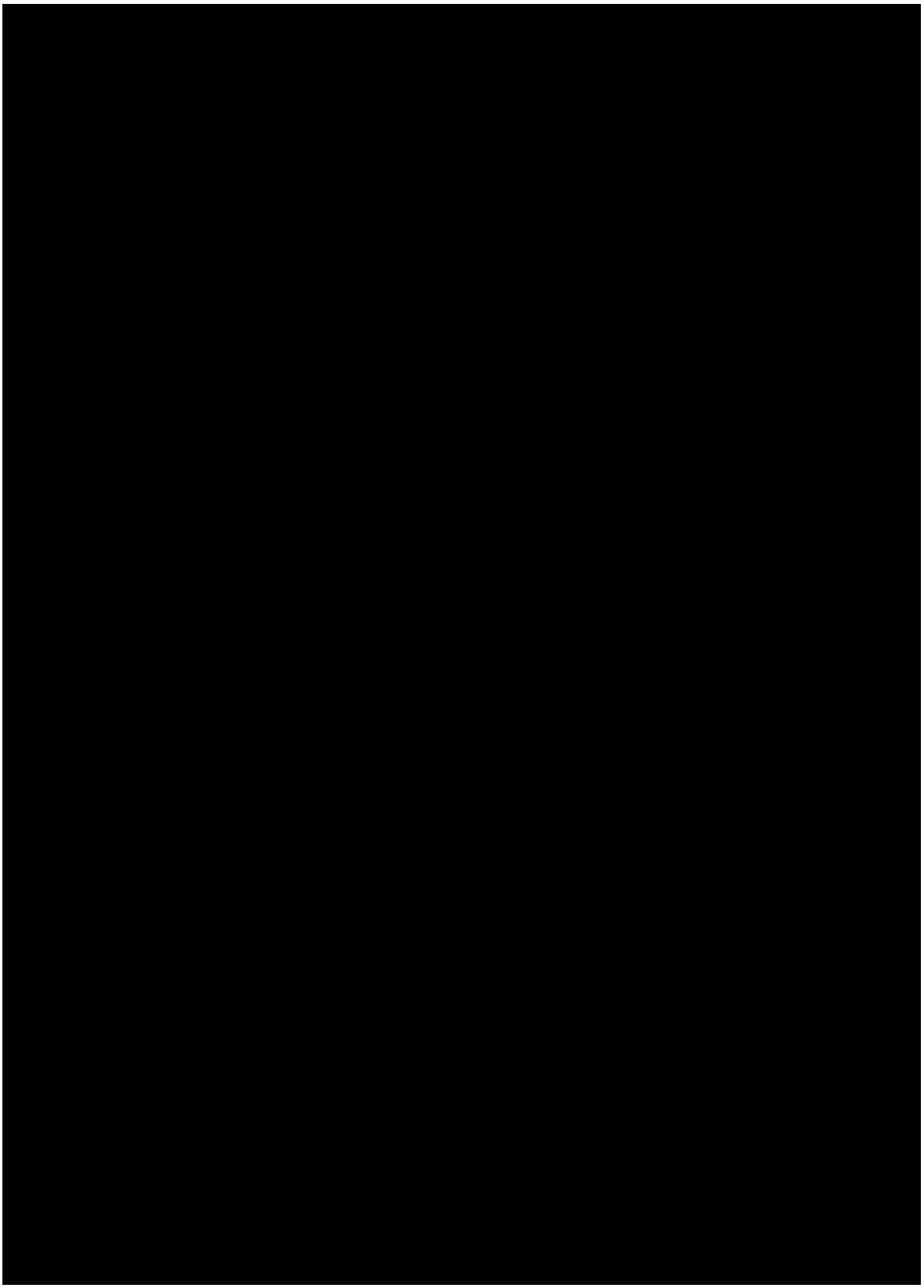
Unanchored MAICs were conducted to determine the relative efficacy of liso-cel dose levels DL1S + DL2S + DL1D (from TRANSCEND) compared to axi-cel (from ZUMA-1). Efficacy outcomes of interest were ORR, CRR, PFS, and OS. AESI for MAIC were grade ≥ 3 TEAEs, grade 3 4 TEAEs, grade 5 TEAEs, CRS, study-defined NTs, NEs per ND/PD SOC, study-defined NT of encephalopathy, encephalopathy per ND/PD SOC, study-defined NT of aphasia, aphasia per ND/PD SOC, infections, hypogammaglobulinemia, prolonged cytopenia by laboratory assessment, prolonged cytopenia reported as an AE, and febrile neutropenia. Relative efficacy and safety were assessed in infused patients. Generalized linear models (GLM) for binary outcomes (i.e., ORR, CRR, AESI) were used to estimate odds ratios (ORs). Cox proportional hazards models for time-to-event outcomes (i.e., OS, PFS) were used to estimate HRs [76].

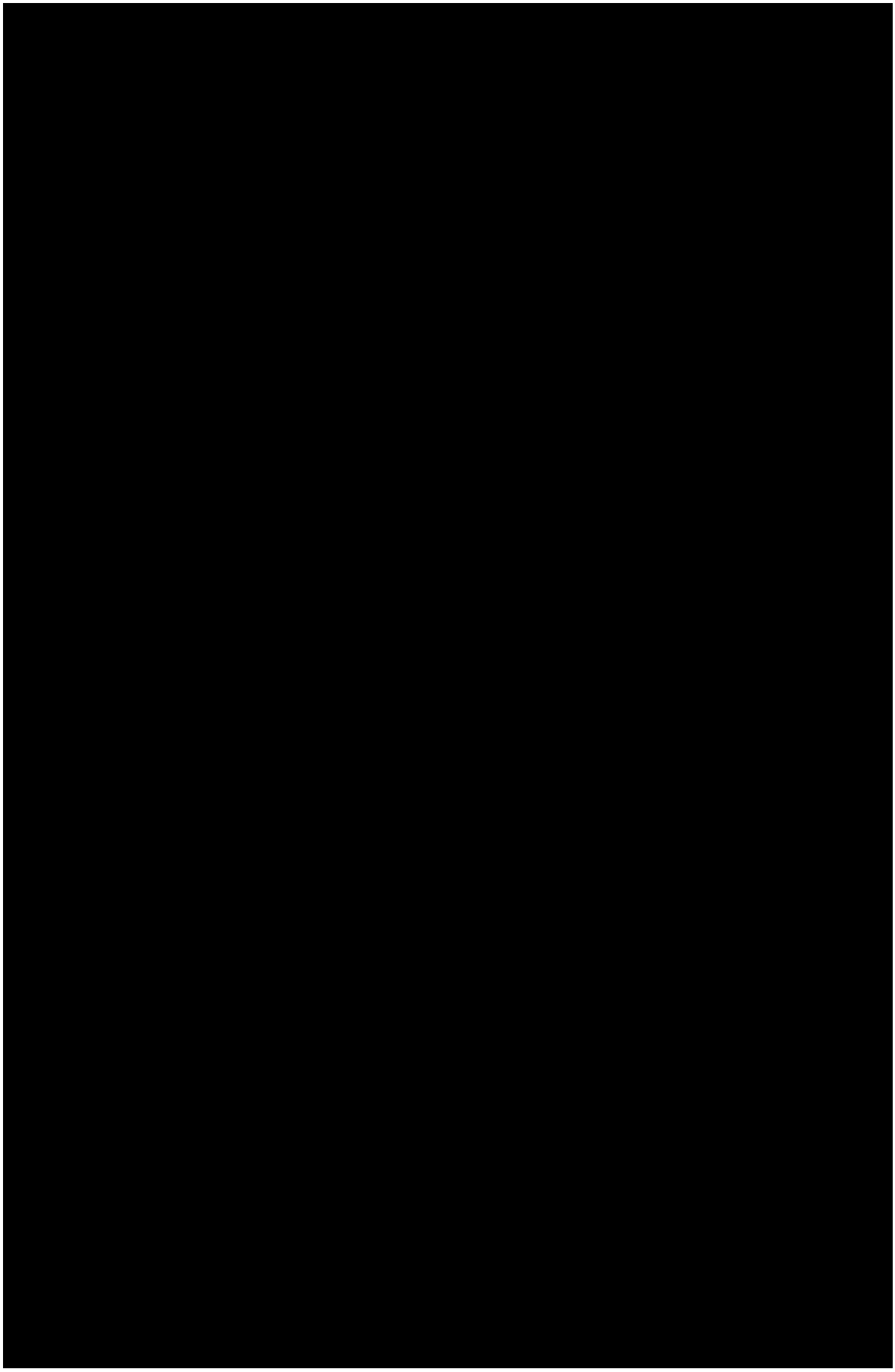
All analyses were conducted using R (R Core Team), based on code outlined in the NICE Evidence Synthesis Technical Support Document (TSD) Series MAIC [106].

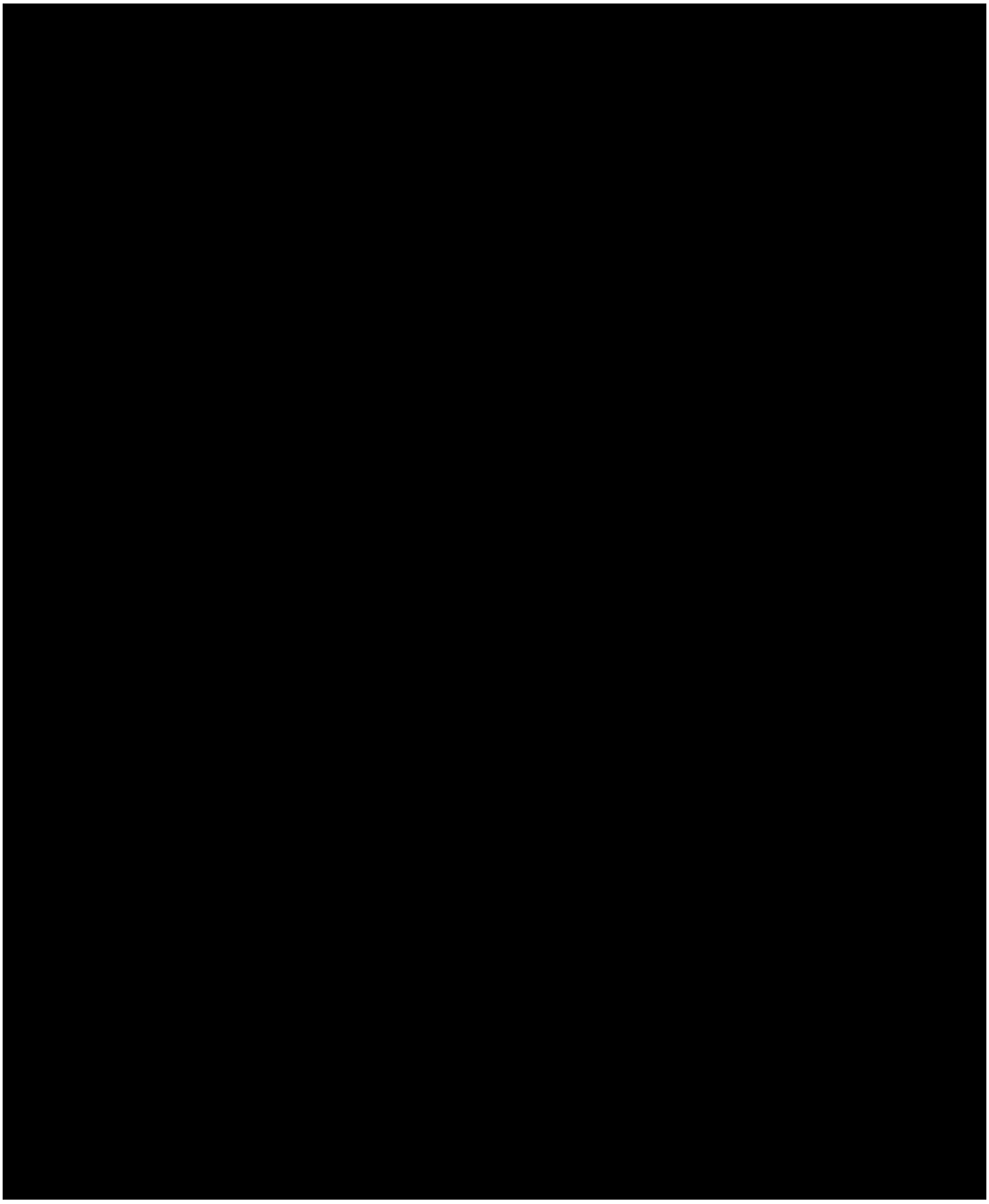
C.2.2.2 Clinical Factors used for Matching and Adjusting

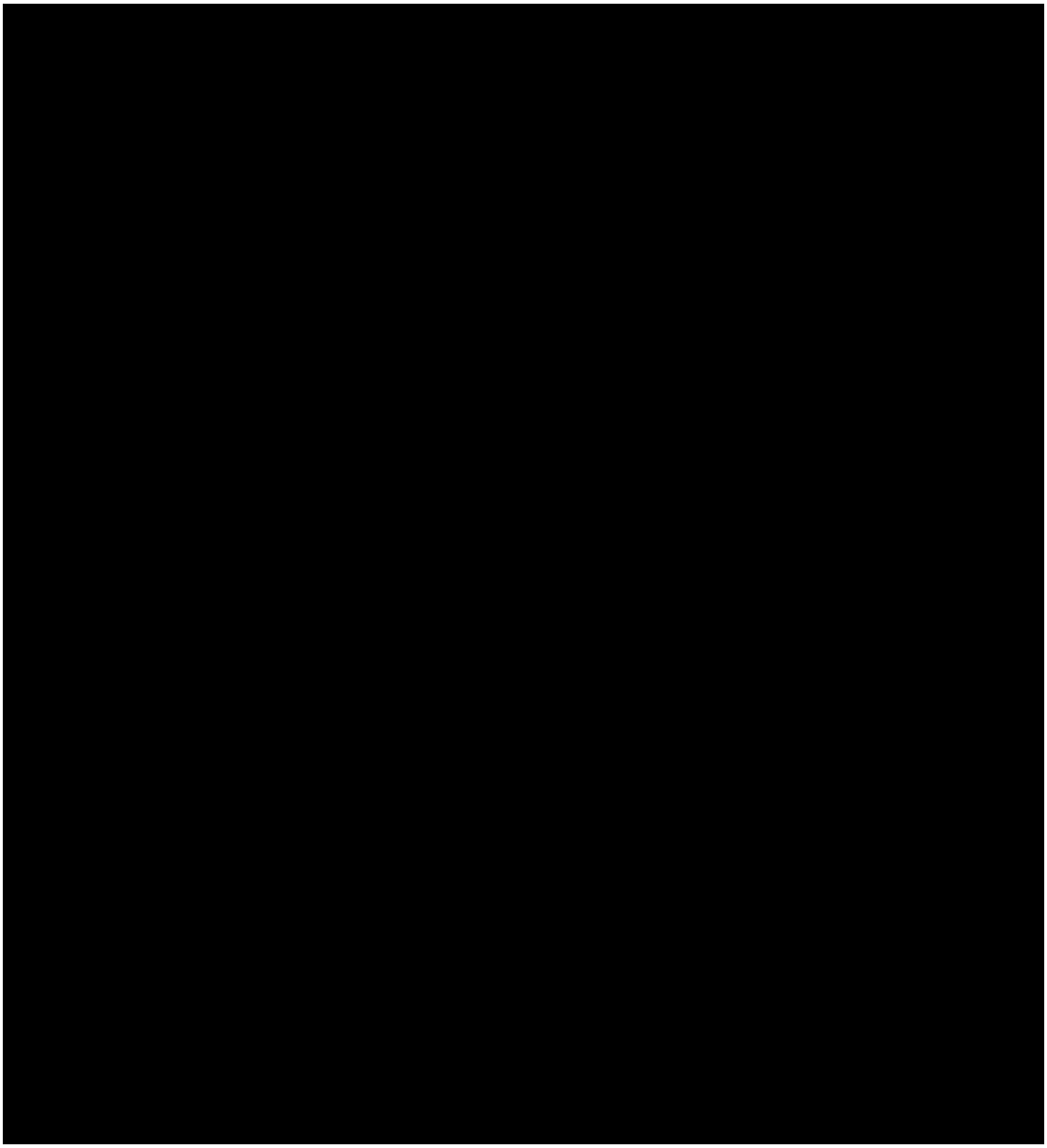
Study eligibility criteria and baseline characteristics were considered as clinical factors. Relevant clinical factors for matching and adjusting were identified through a targeted literature search of evidence on clinical factors prognostic of outcomes in 3L+ treatment of R/R large B-cell lymphoma, inspection of clinical factors reported in the TRANSCEND and ZUMA-1 trials, and input from external clinical experts. A panel of 5 external clinical experts from various countries (Canada, France, Germany, the UK, and the US) was established to oversee the identification and rank-order of clinical factors. This was done based on relative importance as prognostic factors or treatment effect modifiers relative to the outcomes of interest. Leveraging their diverse, multi-national expertise, the panel of experts engaged in several rounds of interviews to ensure as many relevant factors were considered for analyses. Clinical factors were evaluated for each efficacy outcome (i.e., 4 lists of factors, 1 for each efficacy outcome), and for all AESI (i.e., 1 list of factors for all AESI). A final ranked list of clinical factors important for each efficacy outcome and all AESI was derived using an evidence-informed ranking process that considered both ranks by clinical experts and statistical approaches (Table 101 -

Table 105) [76].





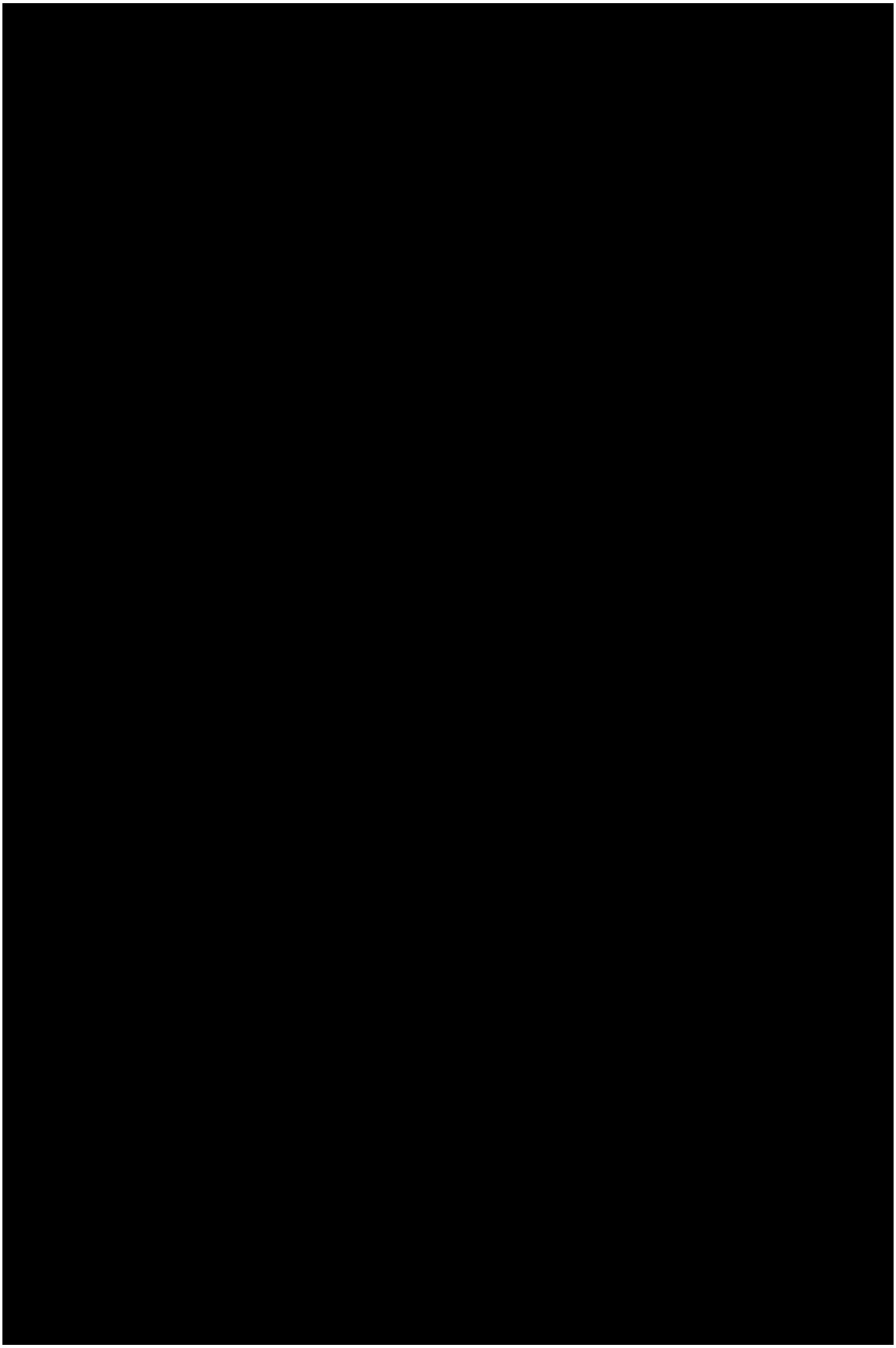




[a]Factor not considered for comparison with axi-cel due to lack of reporting for ZUMA-1.

[b]Factor not considered for comparison with axi-cel due to redundancy with R/R to last therapy factor.

Not ranked means that the clinical expert did not rank the factor due to it being not important; at least less important than any other factor they rank-ordered.



C.2.2.3 Matching Criteria

Patients from TRANSCEND were removed from the IPD set if they did not satisfy the eligibility criteria and treatment protocol of ZUMA-1. The factors that were matched in the comparison of liso-cel and axi-cel are shown in Table 106 [76].

C.2.2.3.1 Matching on the Bridging Therapy Factor

A key factor that differed between the trials was allowance of bridging therapy. Bridging therapy is often used to prevent disease progression in patients awaiting treatment. However, patients who have received bridging therapy in real-world settings often have poorer prognosis than those who do not receive bridging therapy [107].

The TRANSCEND study permitted bridging therapy as needed to patients awaiting CAR T-cell infusion. In contrast, ZUMA-1 did not permit bridging therapy [62].

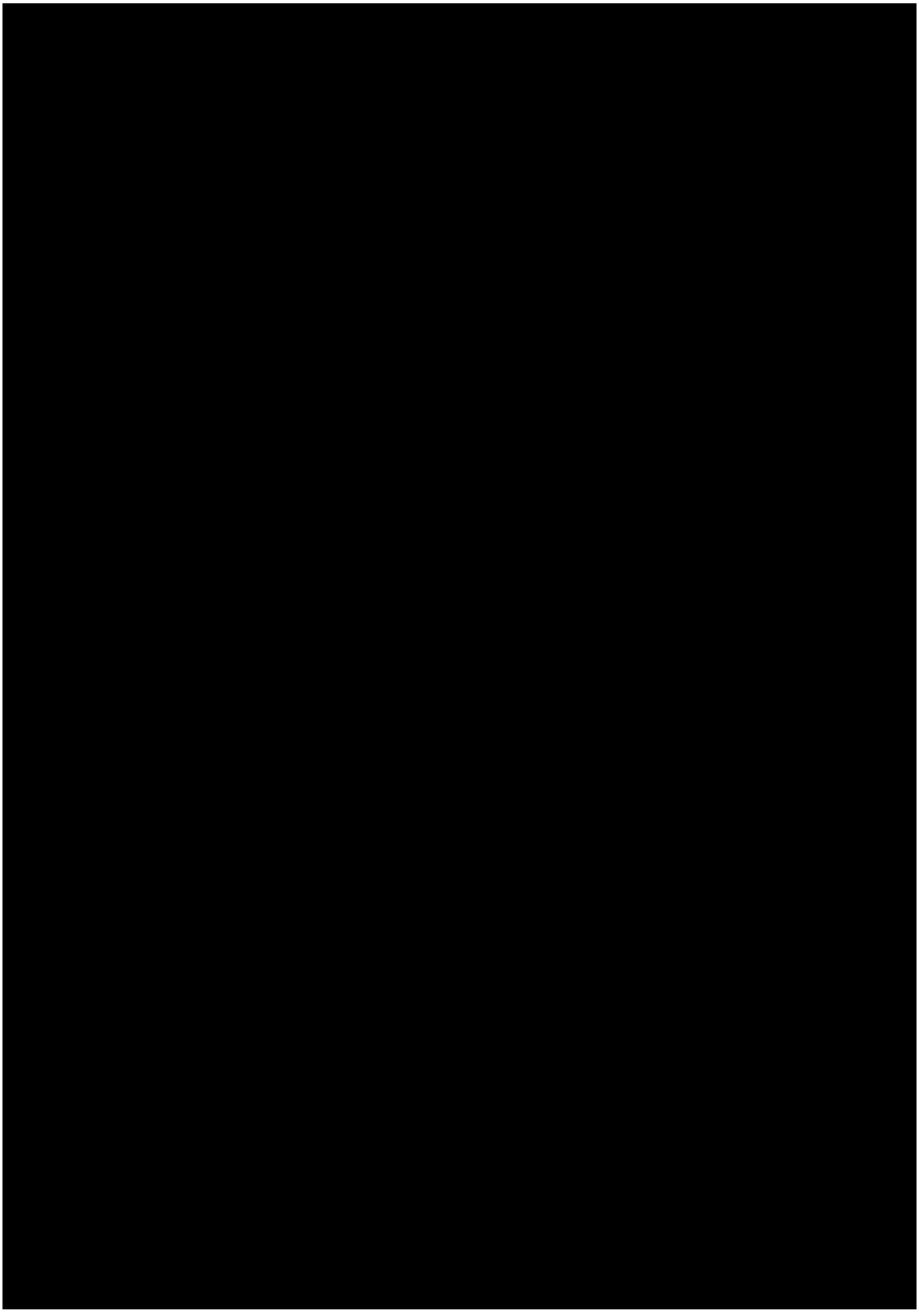
Bridging therapy was included in the clinical factor ranking process and was ranked highly for the TRANSCEND vs. ZUMA-1 comparisons. However, there was no clear consensus among clinicians on whether to match on this factor. This was mainly due to the relationship between the decision to provide bridging therapy and patient enrollment, manufacturing time, and treatment protocol [76].

Finally, given that patients in ZUMA-1 were not permitted to receive bridging therapy, analyses of liso-cel (from TRANSCEND) versus axi-cel (from ZUMA-1) removed patients from TRANSCEND who received bridging therapy (i.e., matching on bridging therapy). Sensitivity analyses not matching on the use of bridging therapy were also conducted [76].

C.2.2.4 Adjusting Patients

After completing the matching phase of the MAIC, the patients that remained and were included from TRANSCEND were weighted using a method-of-moments propensity score algorithm. Method-of-moments was chosen because only SLD were available from ZUMA-1 and it guarantees an exact balancing of clinical factors between comparison

trials of interest. That is, after weighting patients, the means (or proportions) and standard deviations of clinical factors from TRANSCEND should be almost exactly equal to those published in ZUMA-1 [72, 97]. Factors that were adjusted for efficacy outcomes are listed in Table 107. Table 107 also shows the matched factors for efficacy outcomes [76].



For analyses of AESI 9 clinical factors were included. Four of the clinical factors (i.e., secondary CNS involvement, bridging therapy, ECOG status, and prior allo-HSCT) were related to trial eligibility criteria and treatment protocol. Therefore, TRANSCEND IPD was first matched to the ZUMA-1 trial for these factors across all AESI (i.e., patients in TRANSCEND who would not be eligible for ZUMA-1). Five additional clinical factors were then adjusted to minimize differences between studies in the remaining patients according to the final rank-order for all AESI (

Table 105). Bone marrow involvement was excluded from MAIC analyses [76].

C.2.2.5 Estimating Indirect Treatment Effects

Estimates of the comparative efficacy of liso-cel versus axi-cel were derived as the difference between (a) an estimate of the outcome of interest for liso-cel based on adjusted IPD from TRANSCEND (to align with patients in ZUMA-1), and (b) the estimated outcome for axi-cel based on published SLD from ZUMA-1 [76].

The steps for deriving the ITC were as follows [76]:

- Binary endpoints: After matching patients from TRANSCEND to patients from ZUMA-1, a weighted estimate of the liso-cel outcome was derived using MAIC adjustment weights. For binary endpoints (e.g., ORR, CRR, AESI), estimates were derived from an intercept only logistic regression model with MAIC adjustment weights. The intercept represents a prediction of the log odds of the outcome of interest if a typical patient from ZUMA-1 had received liso-cel. Robust standard errors were estimated using the sandwich estimator via the R package 'sandwich'. An estimate of the log OR for liso-cel versus axi-cel was derived as the difference between the predicted log odds for liso-cel and the estimated log odds based on SLD from ZUMA-1. The variance of the log OR between liso-cel

versus axi-cel was estimated as the sum of the variances of the log odds for liso-cel and axi-cel.

- Time to event endpoints: For PFS and OS, weighted IPD from TRANSCEND were combined with pseudo-IPD (setting weights for pseudo-observations equal to 1) representing patients from ZUMA-1. This dataset was then used to fit a weighted Cox proportional hazards model with a binary treatment indicator (i.e., liso-cel versus axi-cel). The estimated regression coefficient for the treatment indicator was used to represent the log HR for liso-cel versus axi-cel. Pseudo-IPD for PFS and OS from ZUMA-1 was generated by first digitizing KM survival curves and then using the Guyot 2012 approach to derive time to event data for both outcomes [108]. "Log transformation" (the default option in R) was used to estimate confidence intervals of the median time to event.

Test-wise P-values are presented and multiplicity of testing was not considered.

C.2.2.6 Performance Assessment and Model Selection

For a given set of ranked clinical factors, separate MAICs were conducted sequentially, adjusting for 1 additional variable at a time in order of ranked importance. After fitting each model, the performance and suitability of each MAIC model was assessed based on the following criteria [76]:

- Effective sample size (ESS); as calculated by ESS = $(\sum w_i)\ ^2/(\sum w_i^2)$, where w_i, i=1,…N, are the patient weights estimated by the propensity score model. A low ESS compared to the original sample size N indicates large differences in patient weights due to large imbalances in patient populations prior to reweighting. The ESS is interpreted as the number of independent, non-weighted individuals needed to obtain an equally precise estimate compared to that calculated from the weighted sample [72]. That is, it may be interpreted as the number of patients in a sample after weighting in the context of the current MAIC.

- Distribution of patient weights. Extreme patient weights can indicate uncertainty in the resulting relative treatment effect.
- Summary statistics (e.g., means, proportions) for each clinical factor before and after the matching and adjusting steps were assessed to evaluate the improvement in balance between trial populations. Balance was assessed using the absolute value of the SMD for each covariate. An SMD ≥ 0.10 is considered indicative of potentially important imbalances between comparisons [104]. For a given covariate, a reduction in the SMD after matching and adjusting signifies a reduction in imbalance between studies.

- For OS and PFS, the assumption of proportional hazards underlying Cox proportional hazards models was assessed by examining cross-over in KM curves and applying the Grambsch- Grambsch Therneau statistical test for proportional hazards [100].

The primary analysis of the MAIC model was chosen based on achieving a balance between these criteria, while also considering the number of clinical factors included. Sensitivity analysis was chosen by incorporating the additional clinical factors for each outcome [76].

C.2.3 Analysis Selection for MAIC

C.2.3.1 Efficacy outcomes

Primary analyses of efficacy outcomes were conducted for patients who did not receive bridging therapy (i.e., bridging therapy factor included). In total, 10 clinical factors were included (Table 107) in this analysis. As 5 of the clinical factors (i.e., bridging therapy, disease histology, ECOG PS, secondary CNS involvement, prior allo-HSCT) related to trial eligibility criteria and treatment protocol, these factors were used first as matching criteria in MAICs. An additional 5 clinical factors (e.g., tumor burden, IPI score, R/R to last therapy, bulky disease, and age for comparison of OS) were then adjusted to reduce residual imbalances between studies among matched patients. These 5 factors varied across outcomes based on evidence-informed clinical rankings [76].

The following sensitivity analyses were also performed [76]:

- Sensitivity 1: A repeat of the primary analysis but removing bridging therapy as a matching factor (Table 107). This was conducted to help assess the effect of bridging therapy on results, recognizing that the receipt of bridging therapy could be related to other factors associated with aggressive disease.

- Sensitivity 2: A repeat of the primary analyses but removing bridging therapy as a matching factor and adjusting for additional factors (Table 107). This was conducted to assess the effect of balancing more factors after gaining ESS upon excluding bridging therapy.

C.2.3.2 Safety outcomes

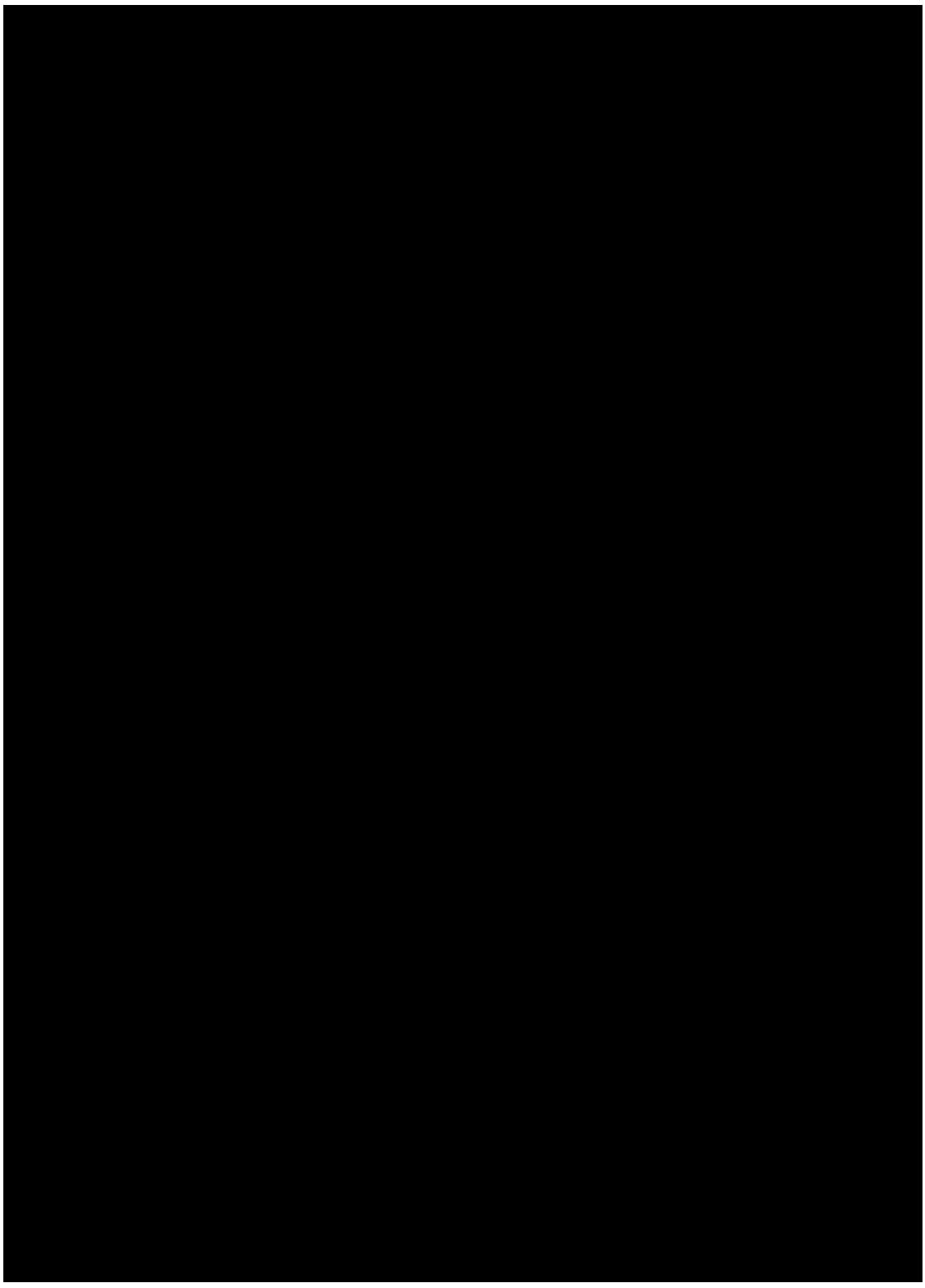
See section C.2.2.4

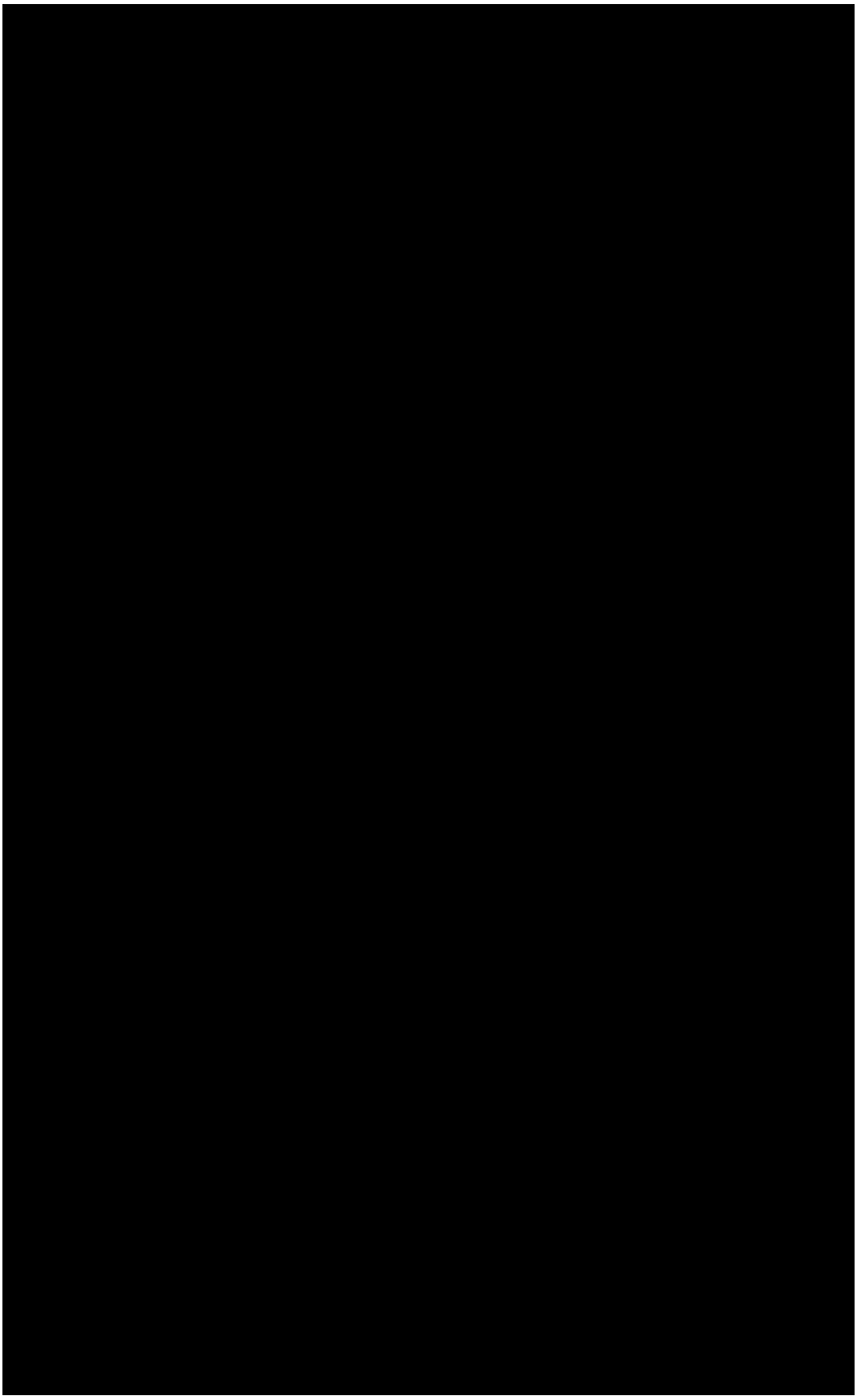
C.2.4 Comparison of Clinical Factors Before and After MAIC (Efficacy analyses)

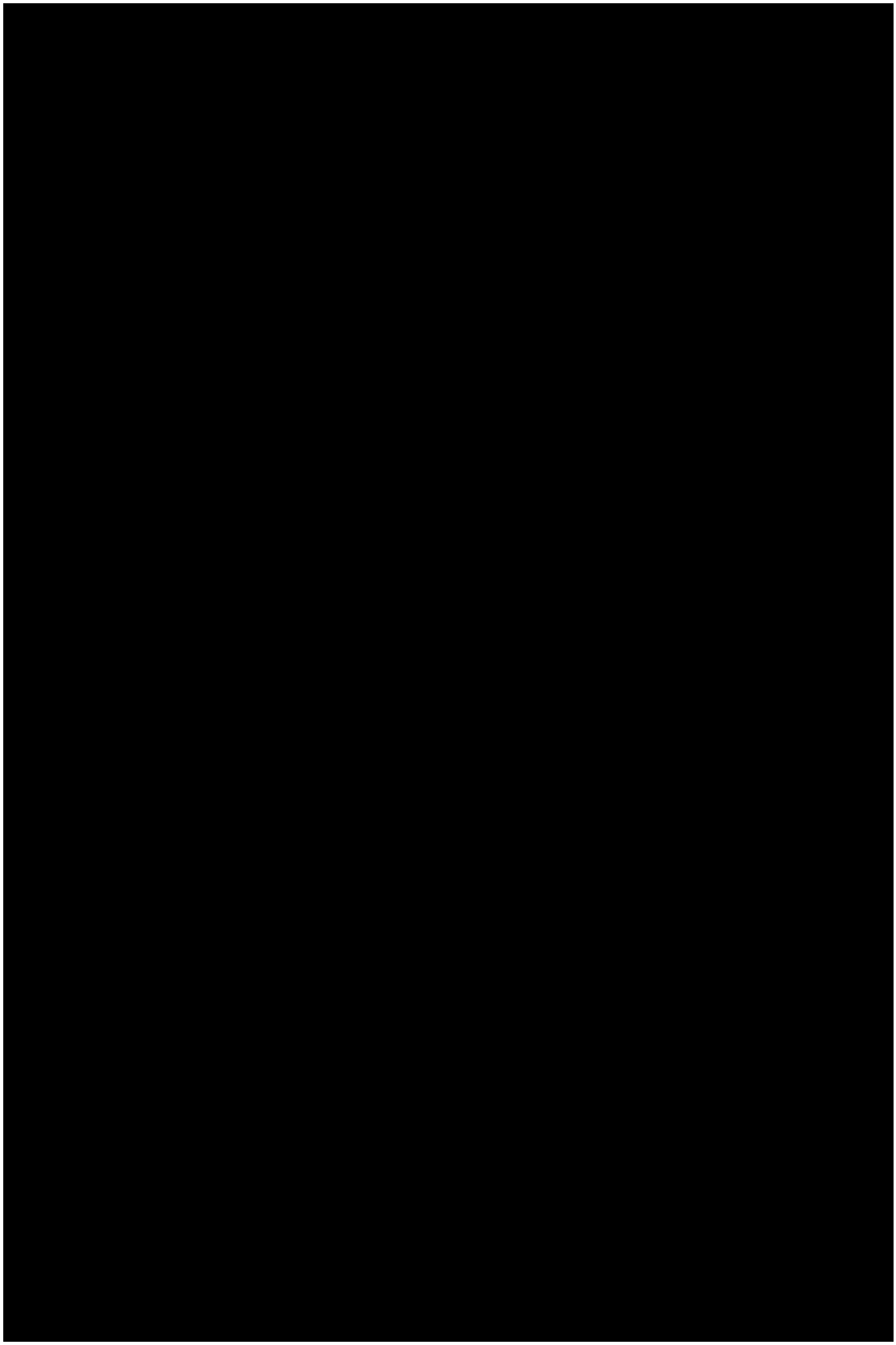
[redacted]

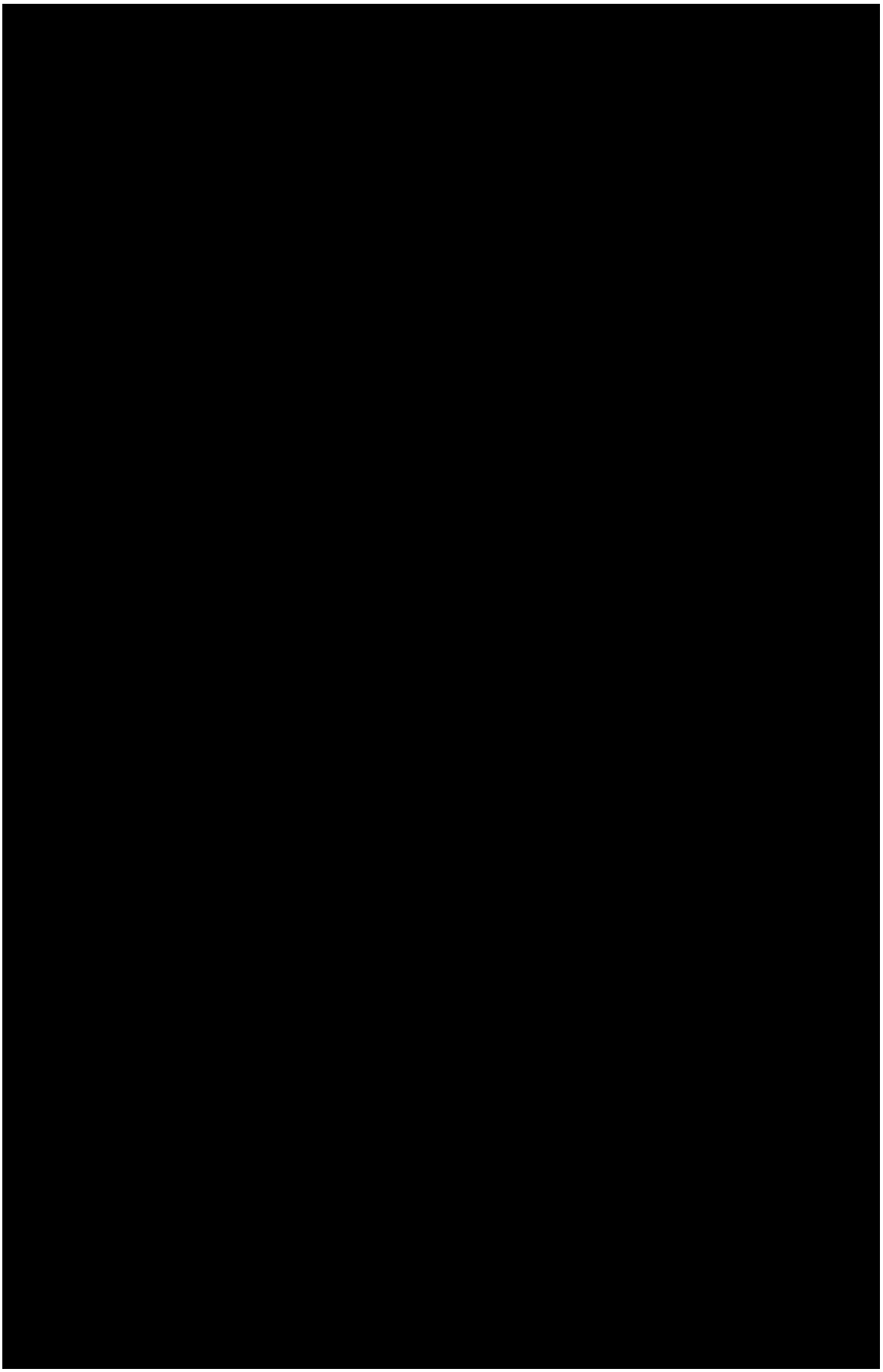
A detailed assessment of clinical factors for each MAIC is presented in Table 109 - Table 112 [60].

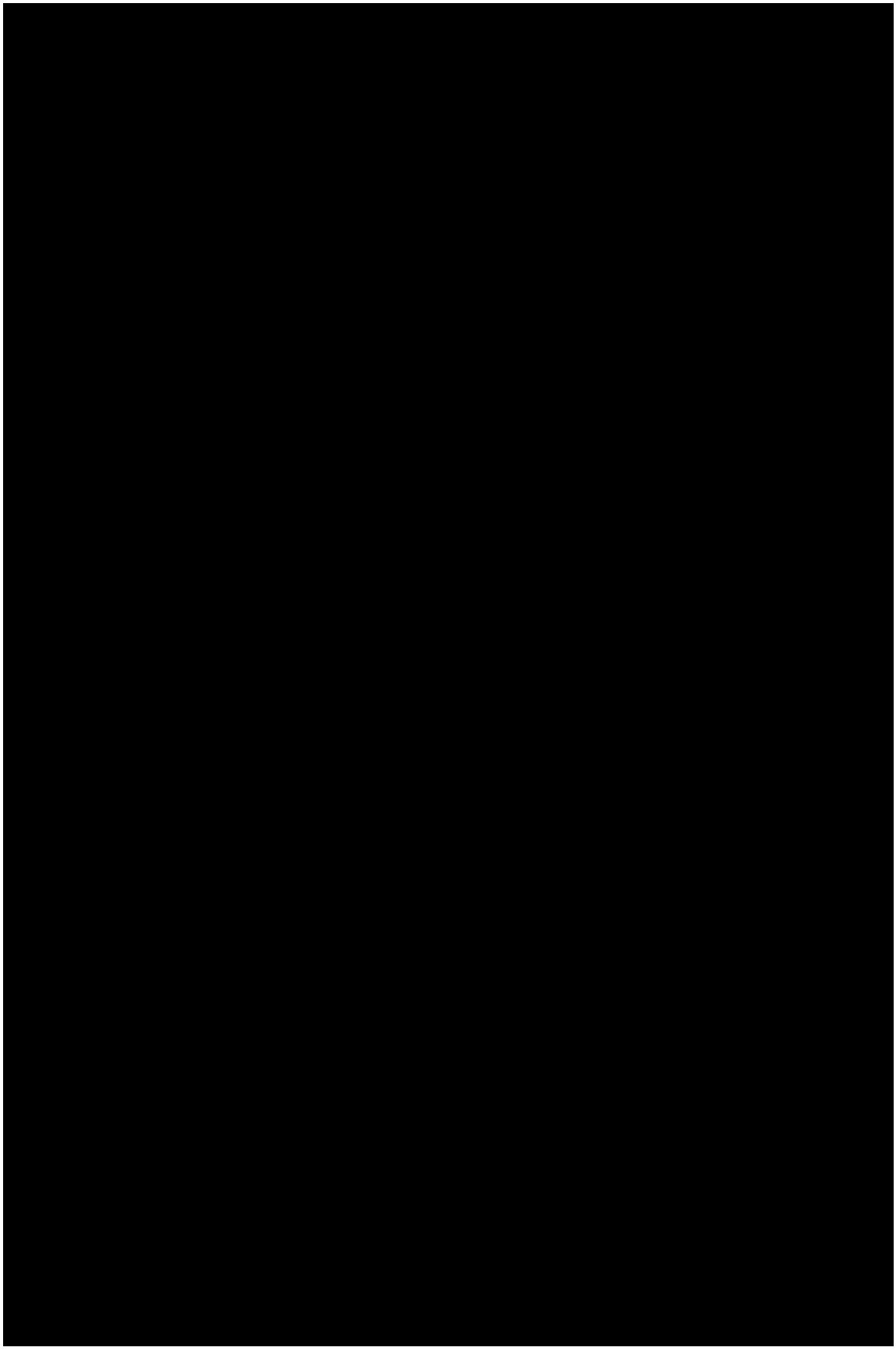
[redacted]

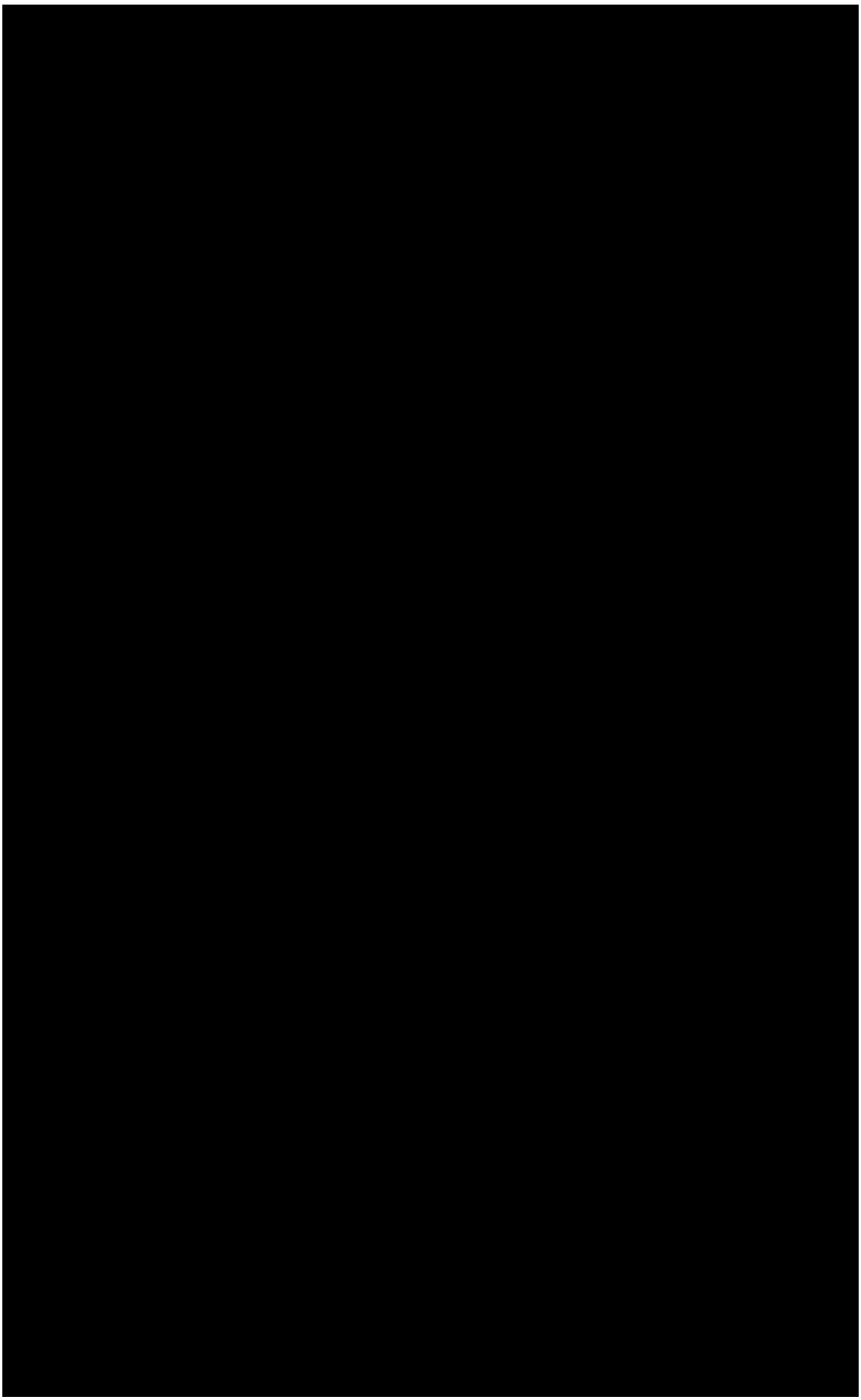


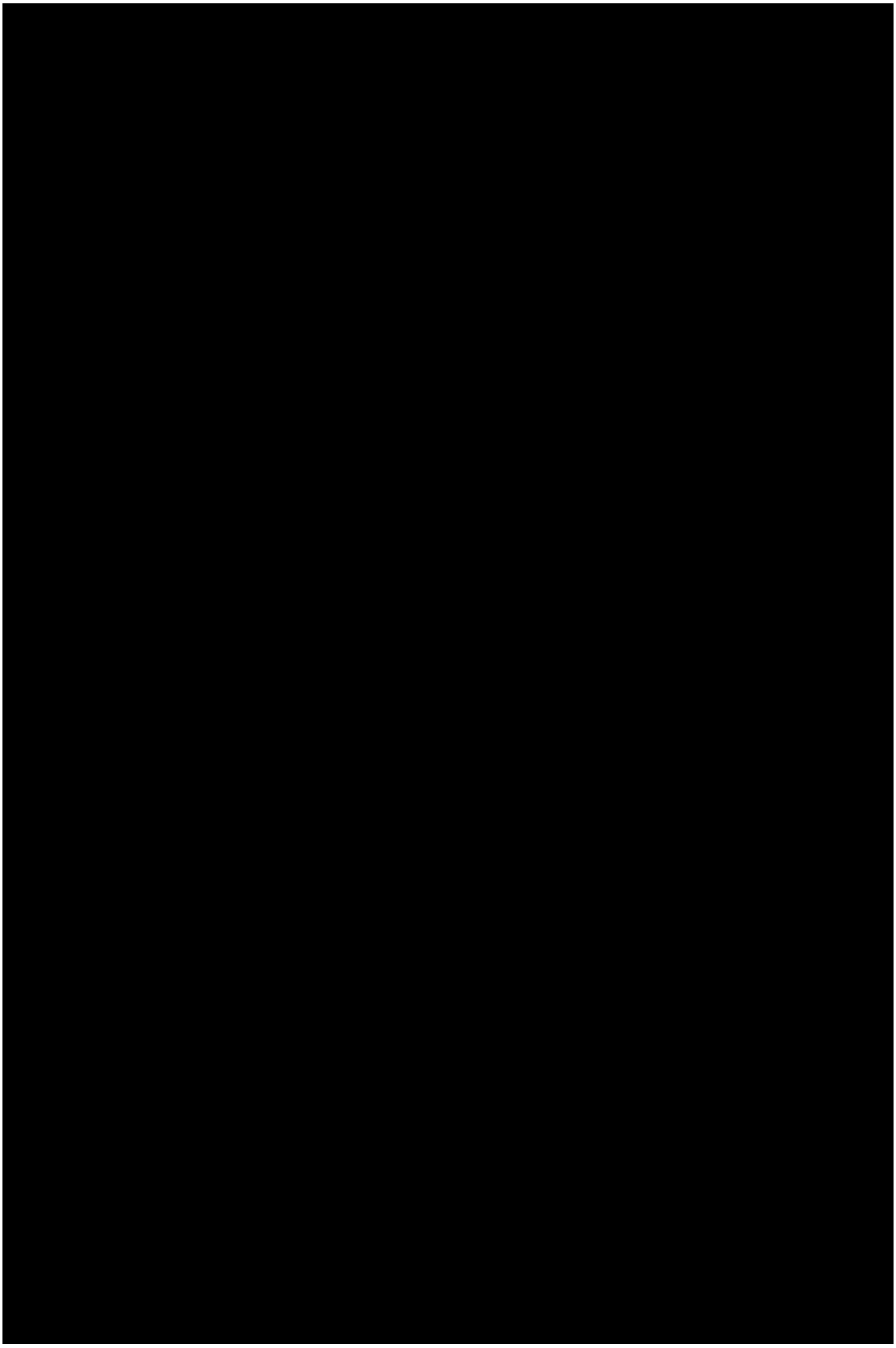


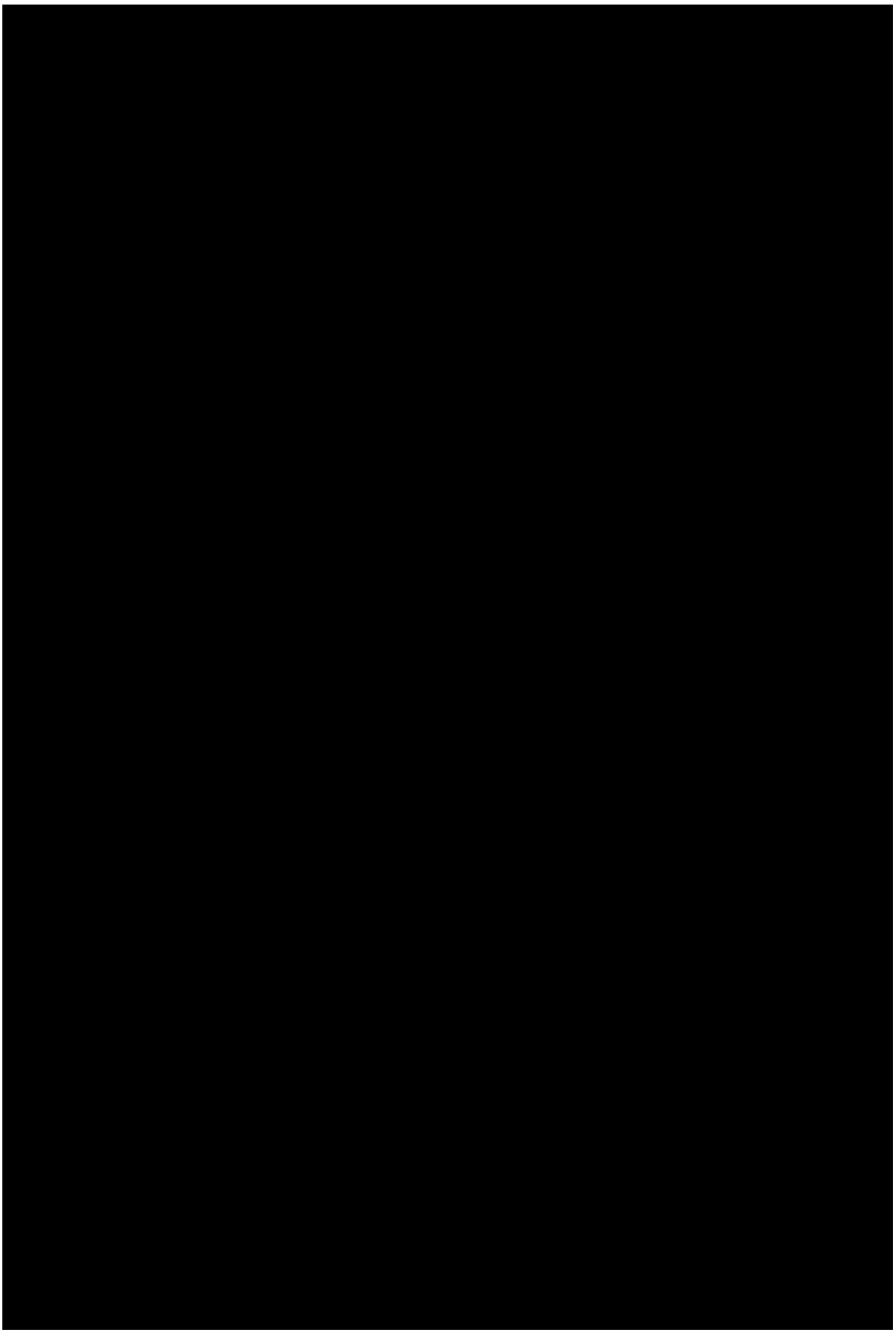


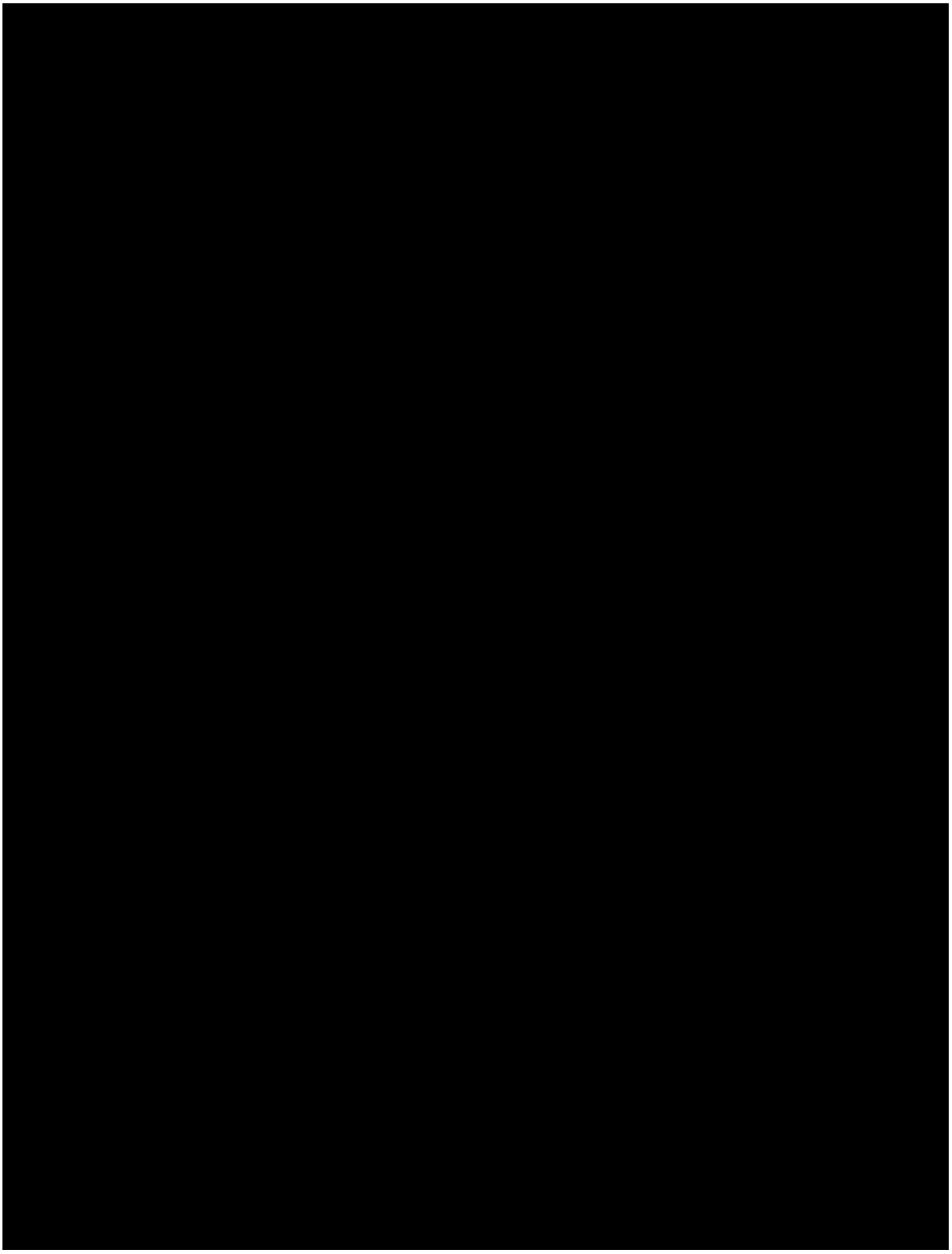


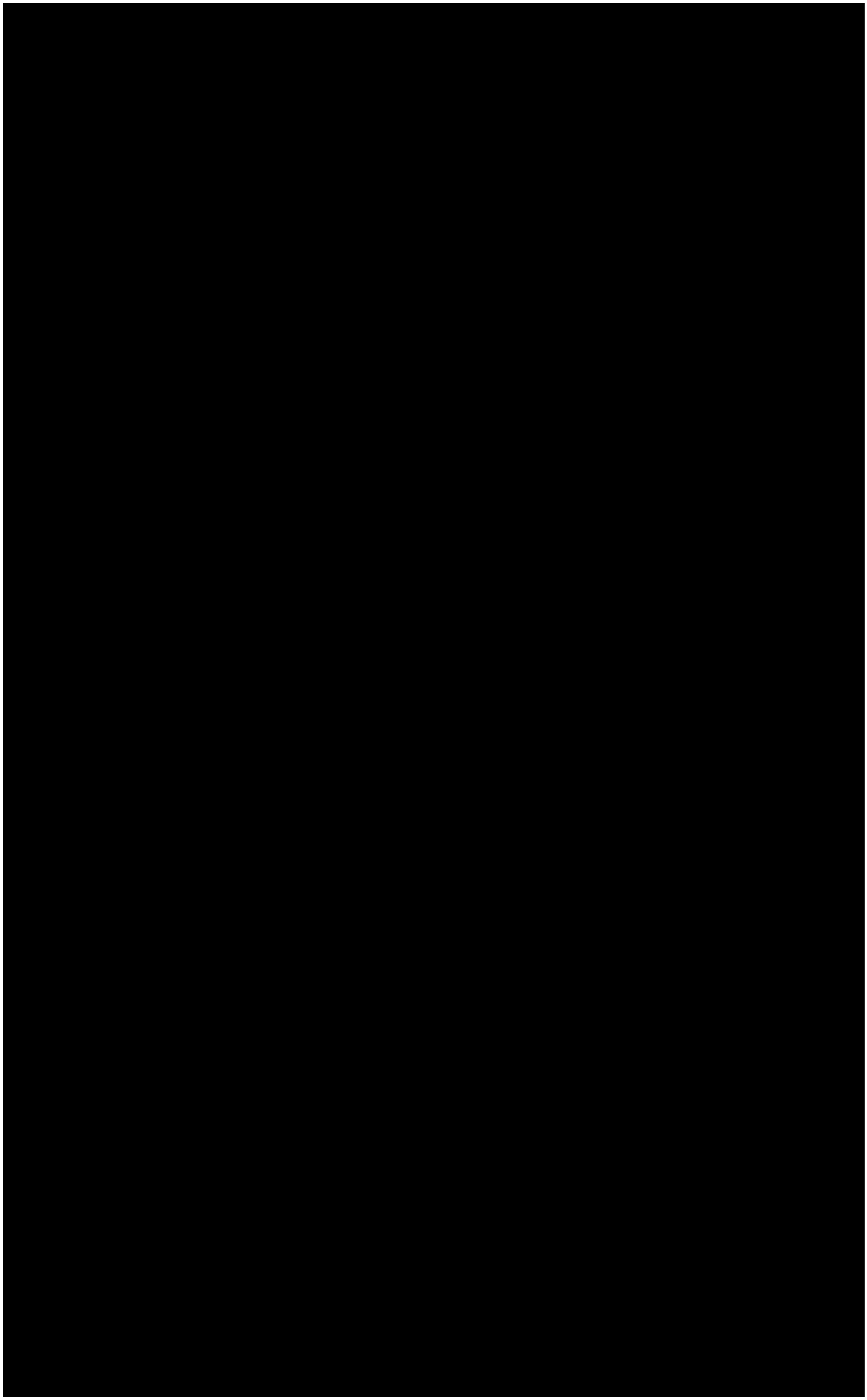


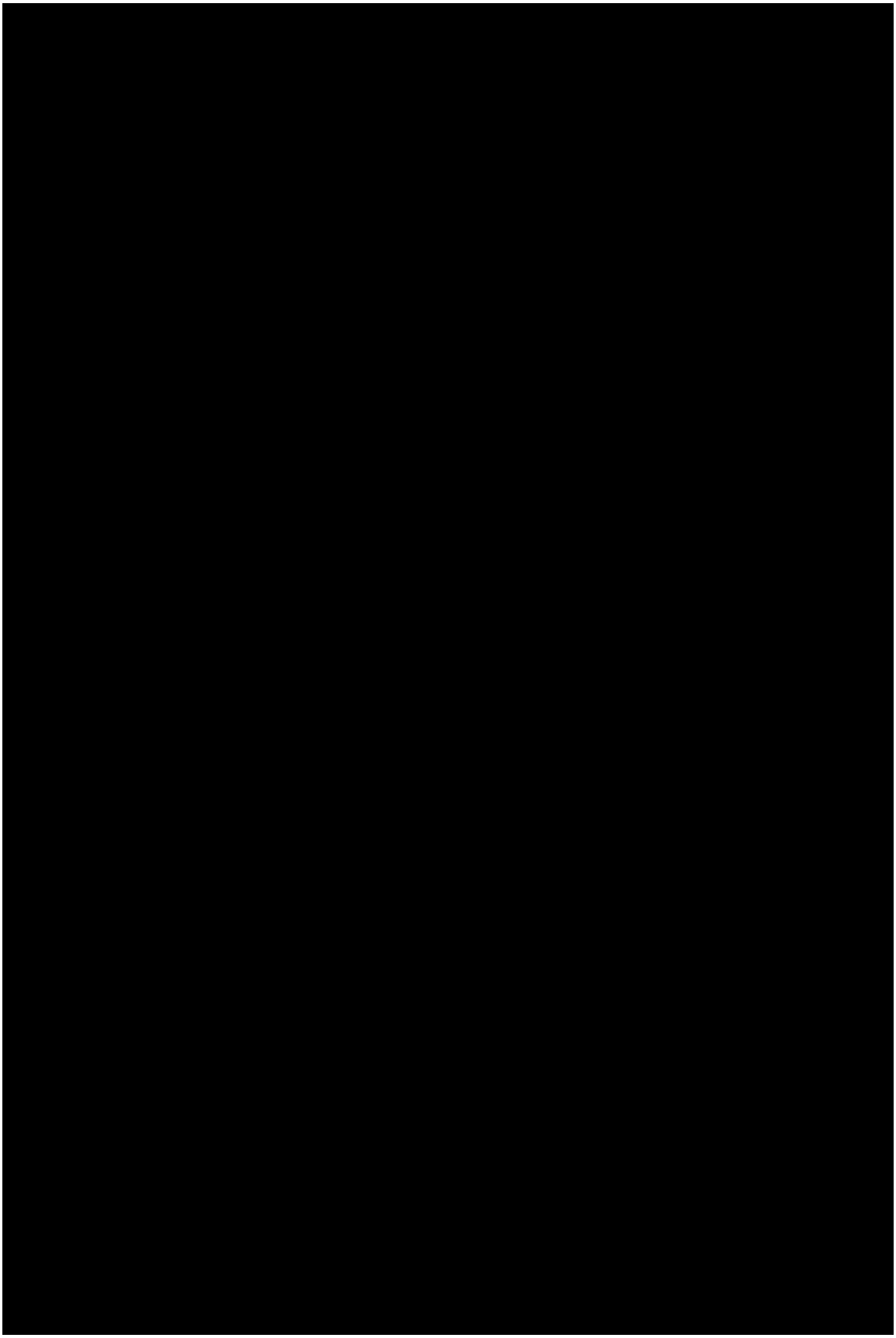


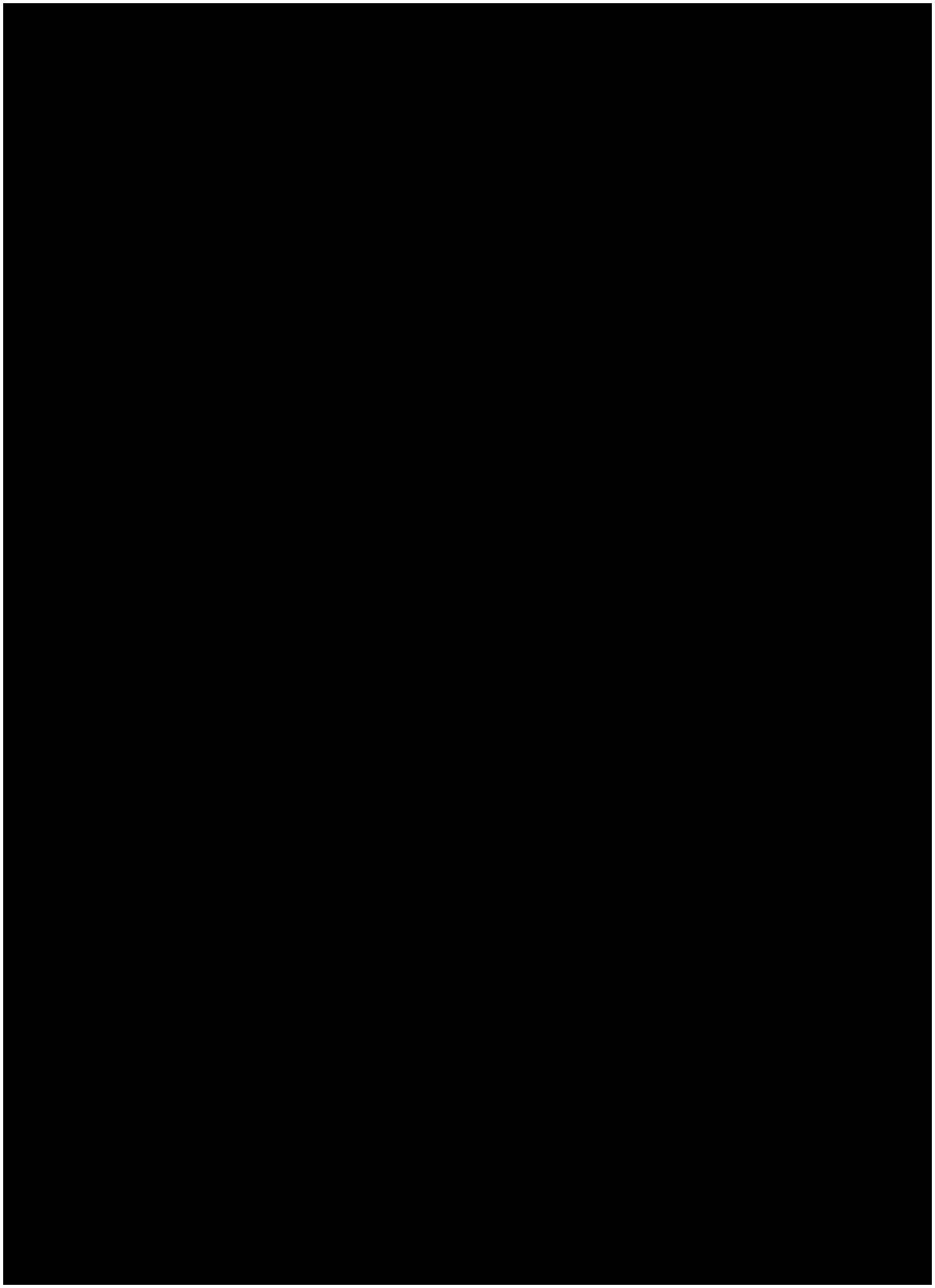


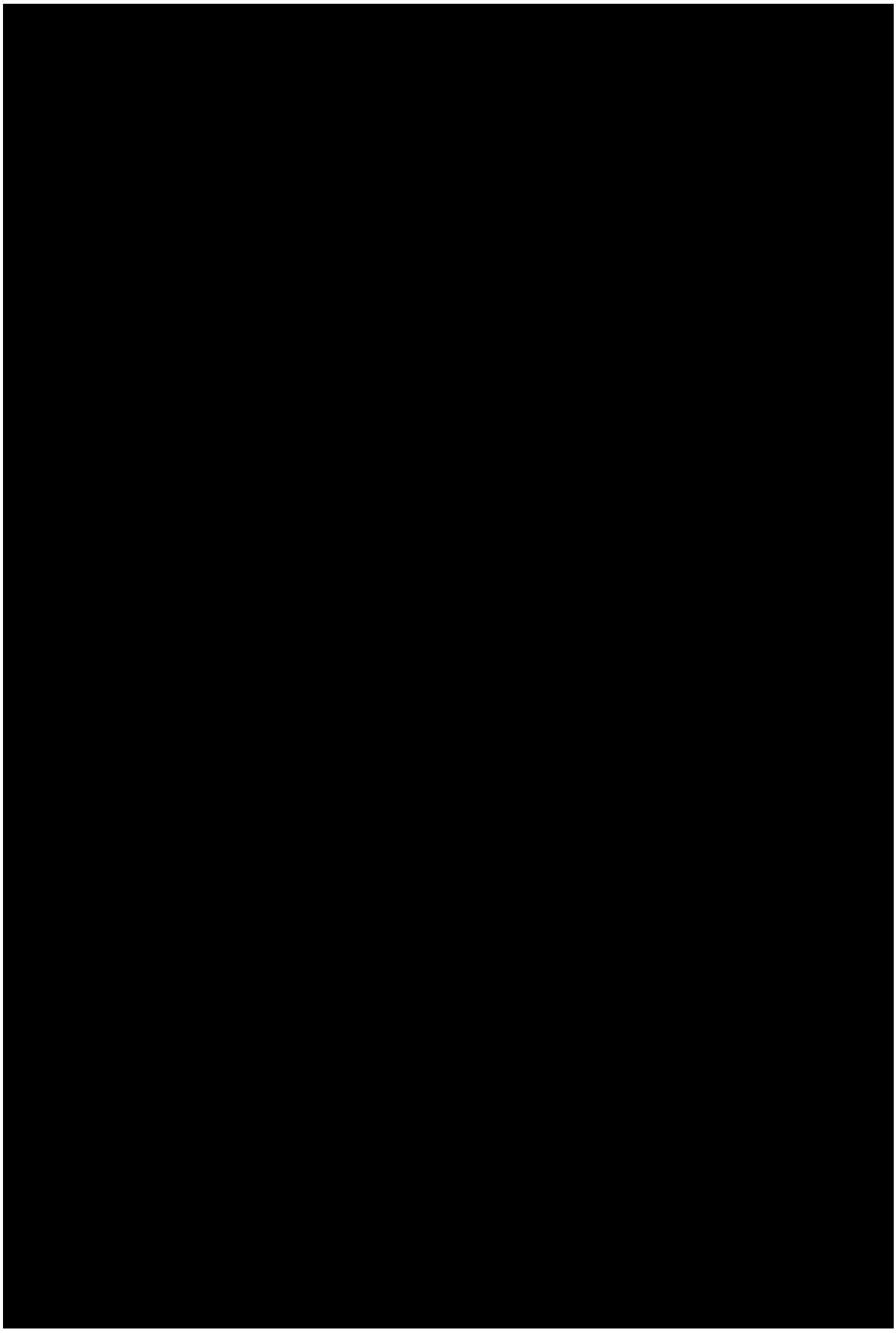


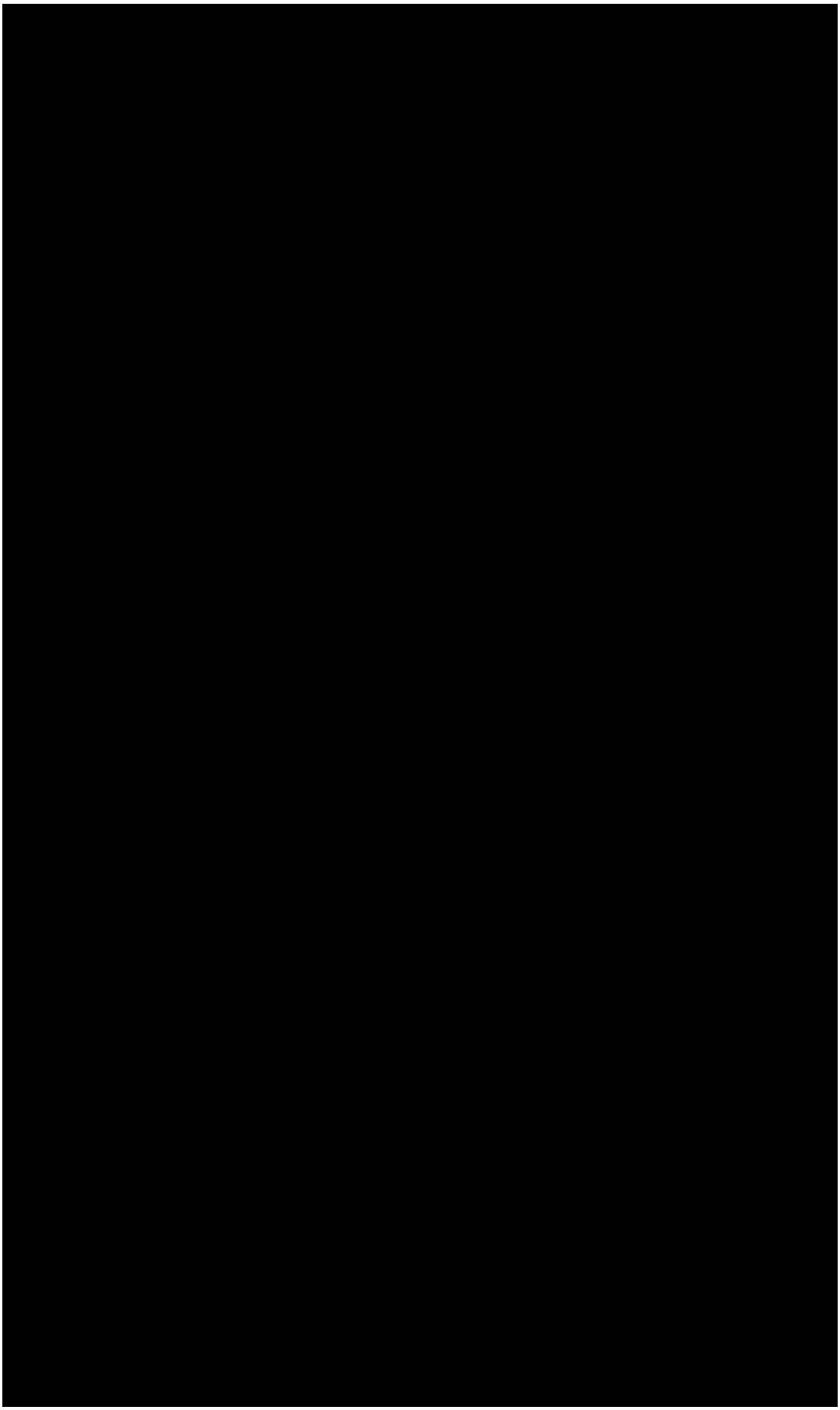


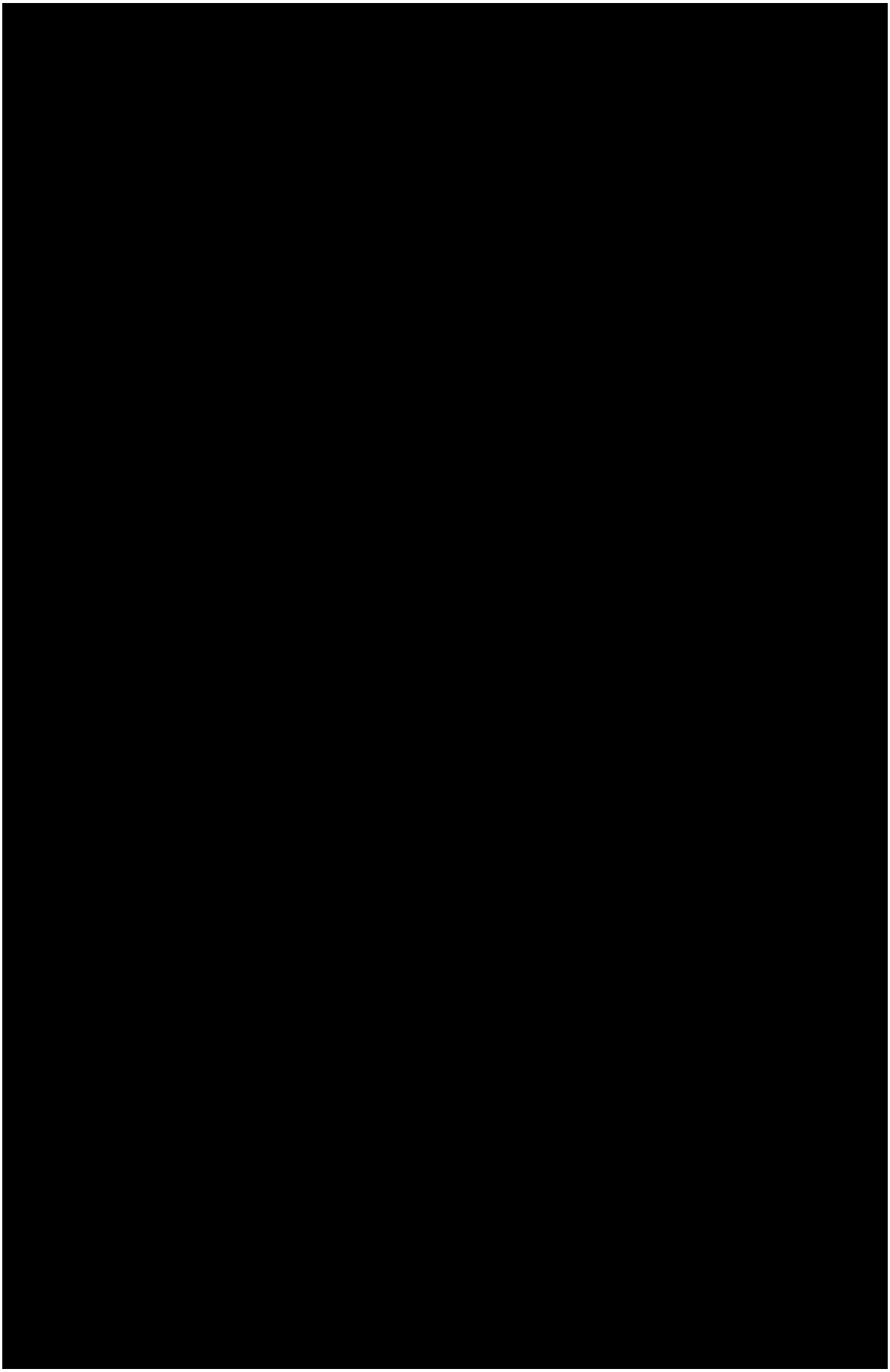




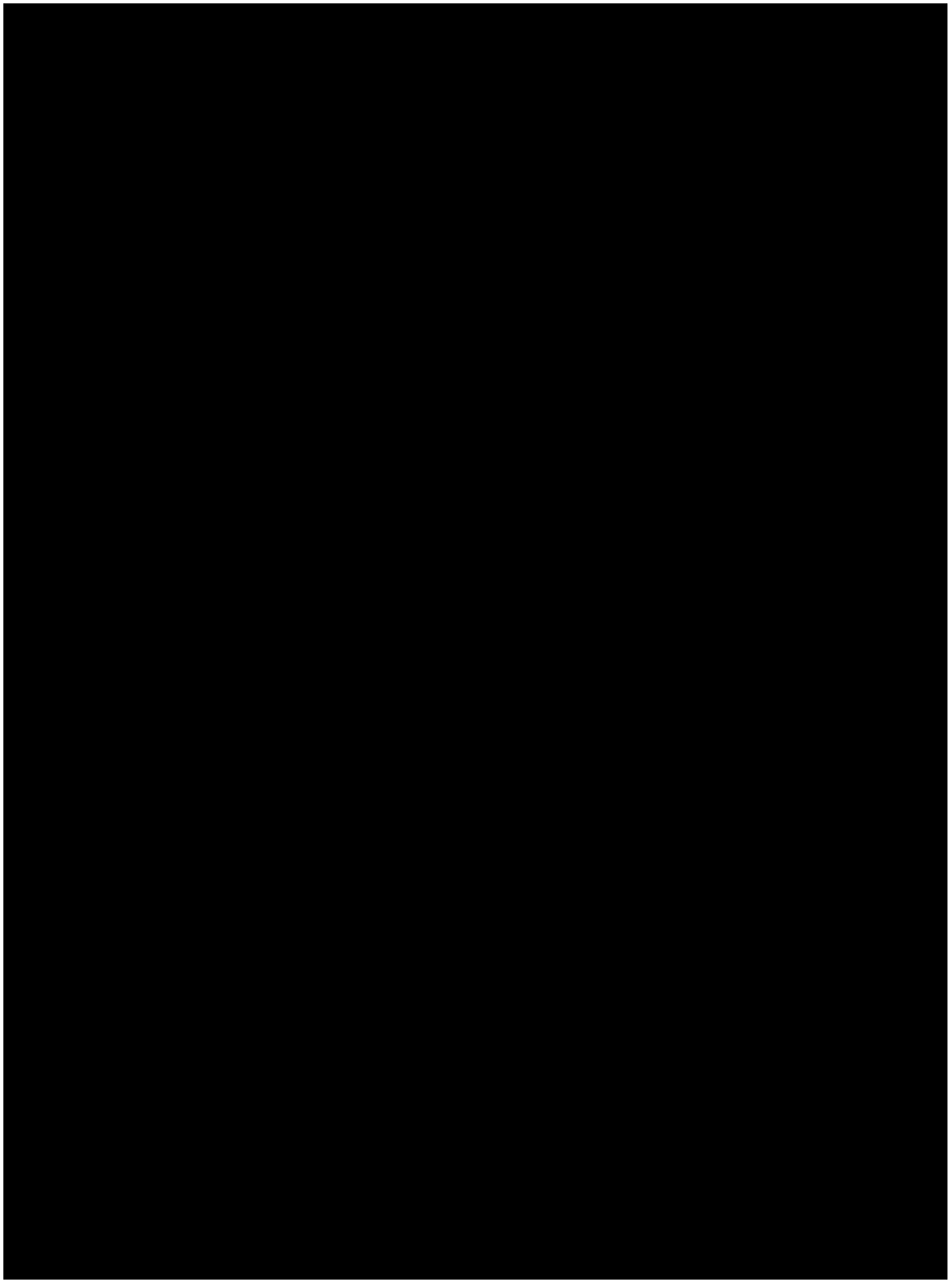


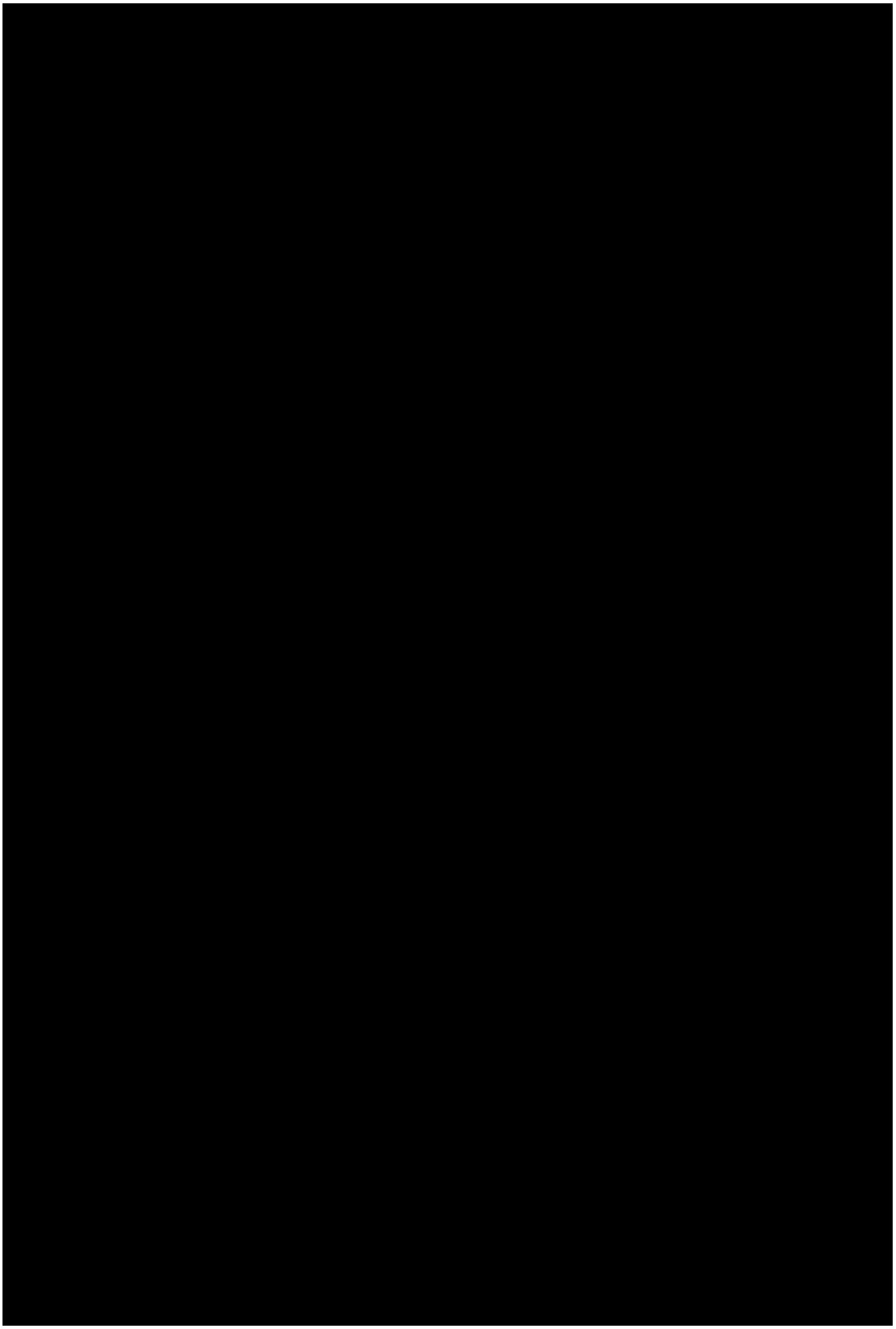


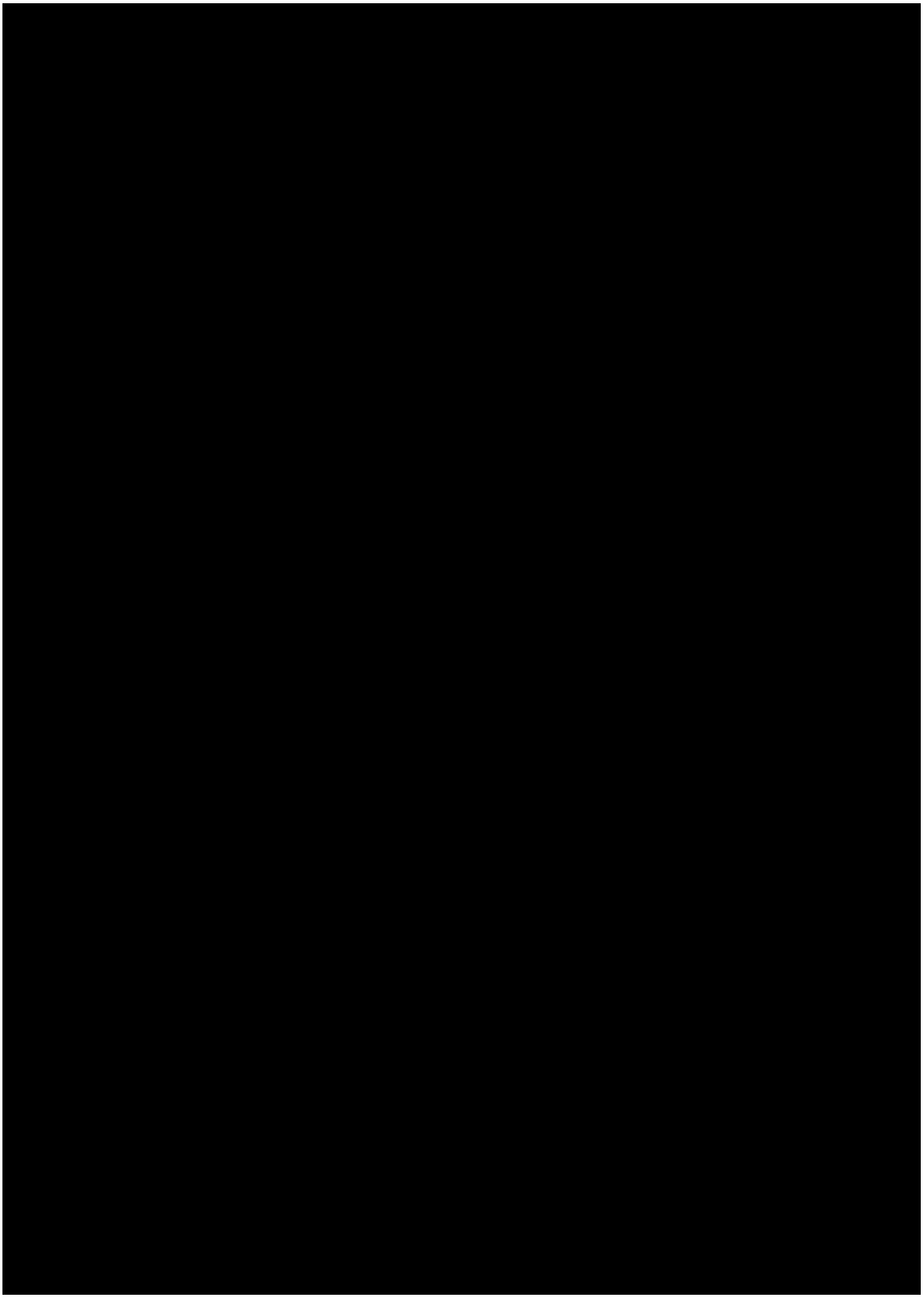


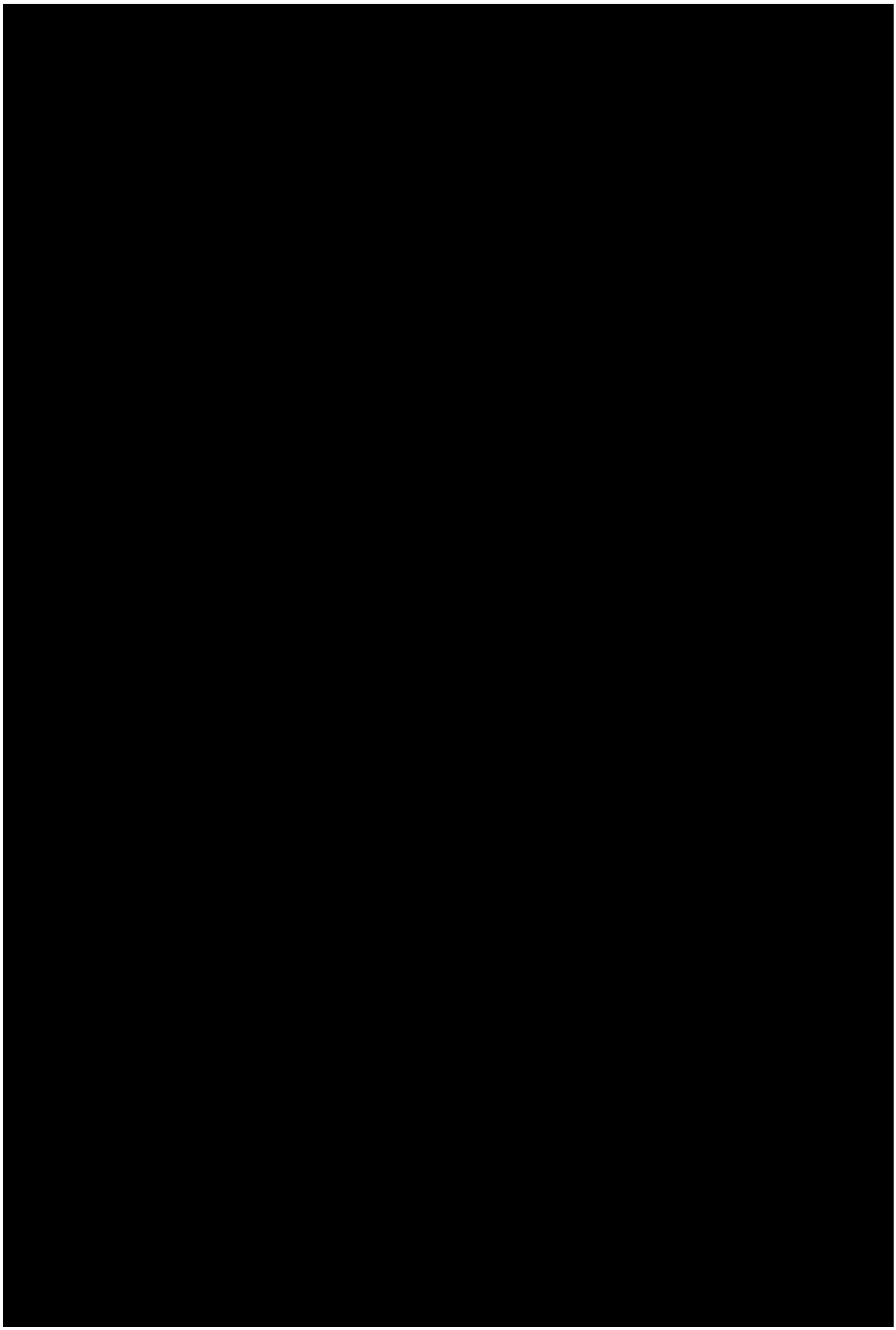


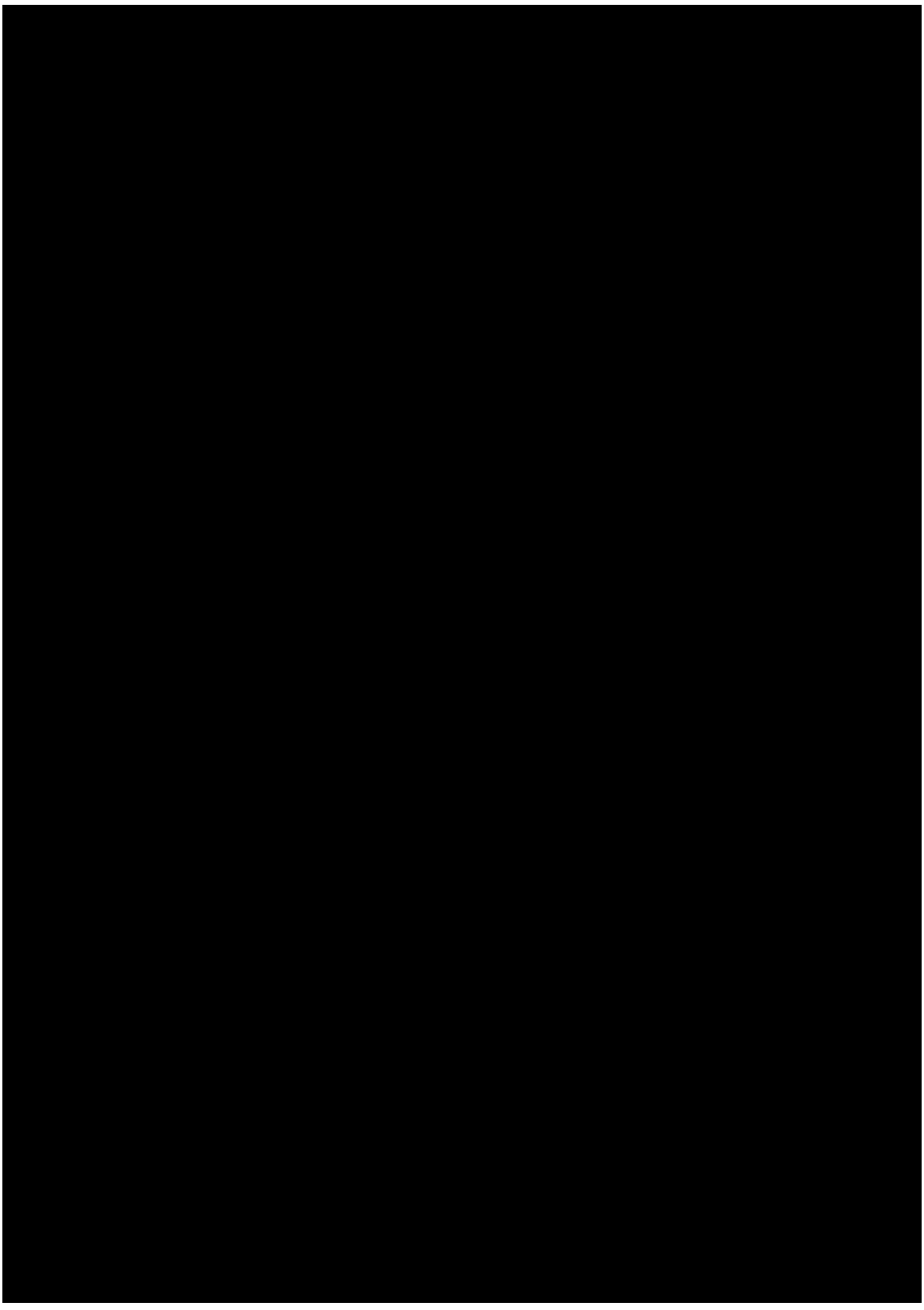
C.2.6 Distribution of Patient Weights in Liso-cel after MAICs (Efficacy analyses)

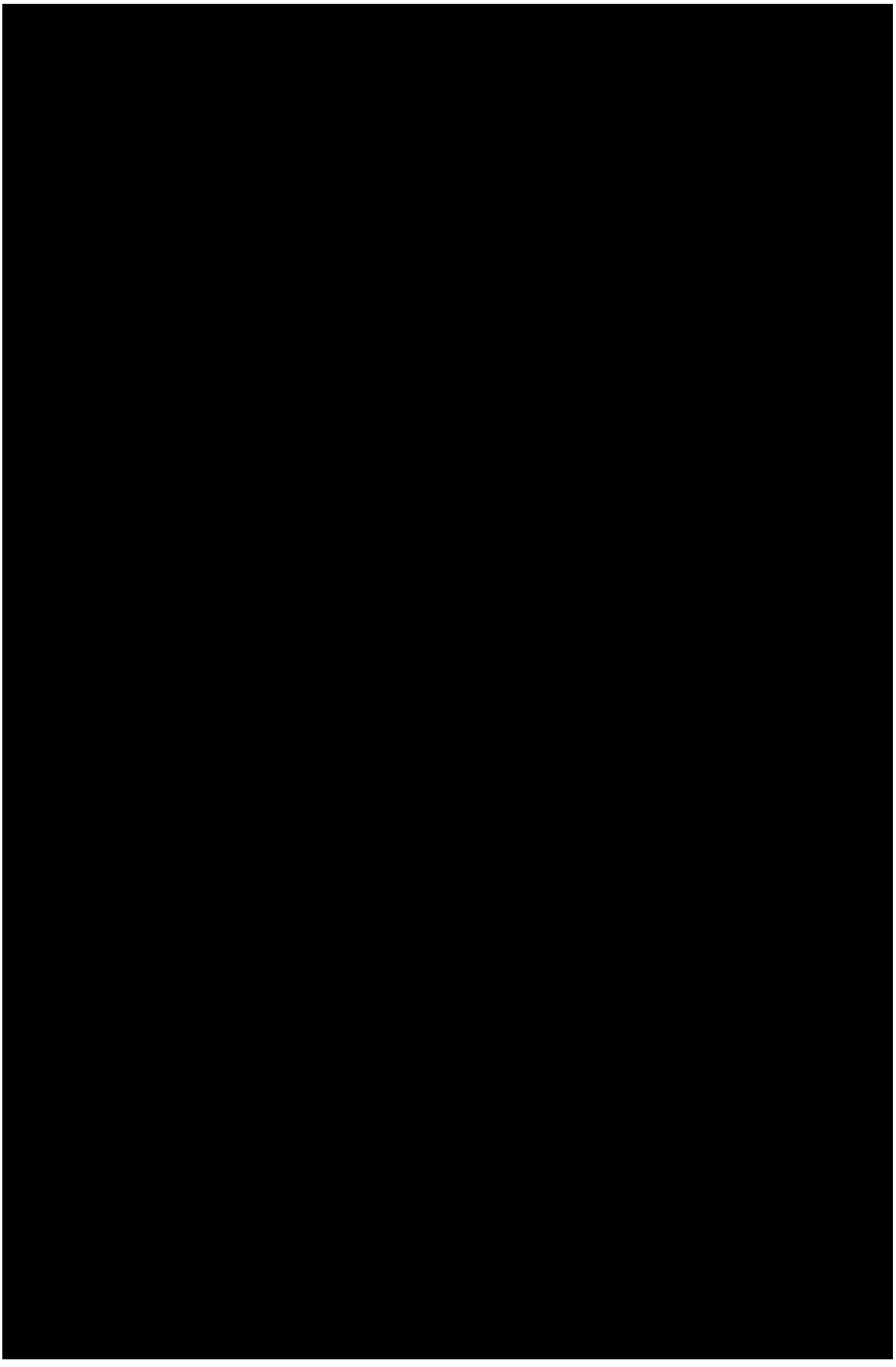


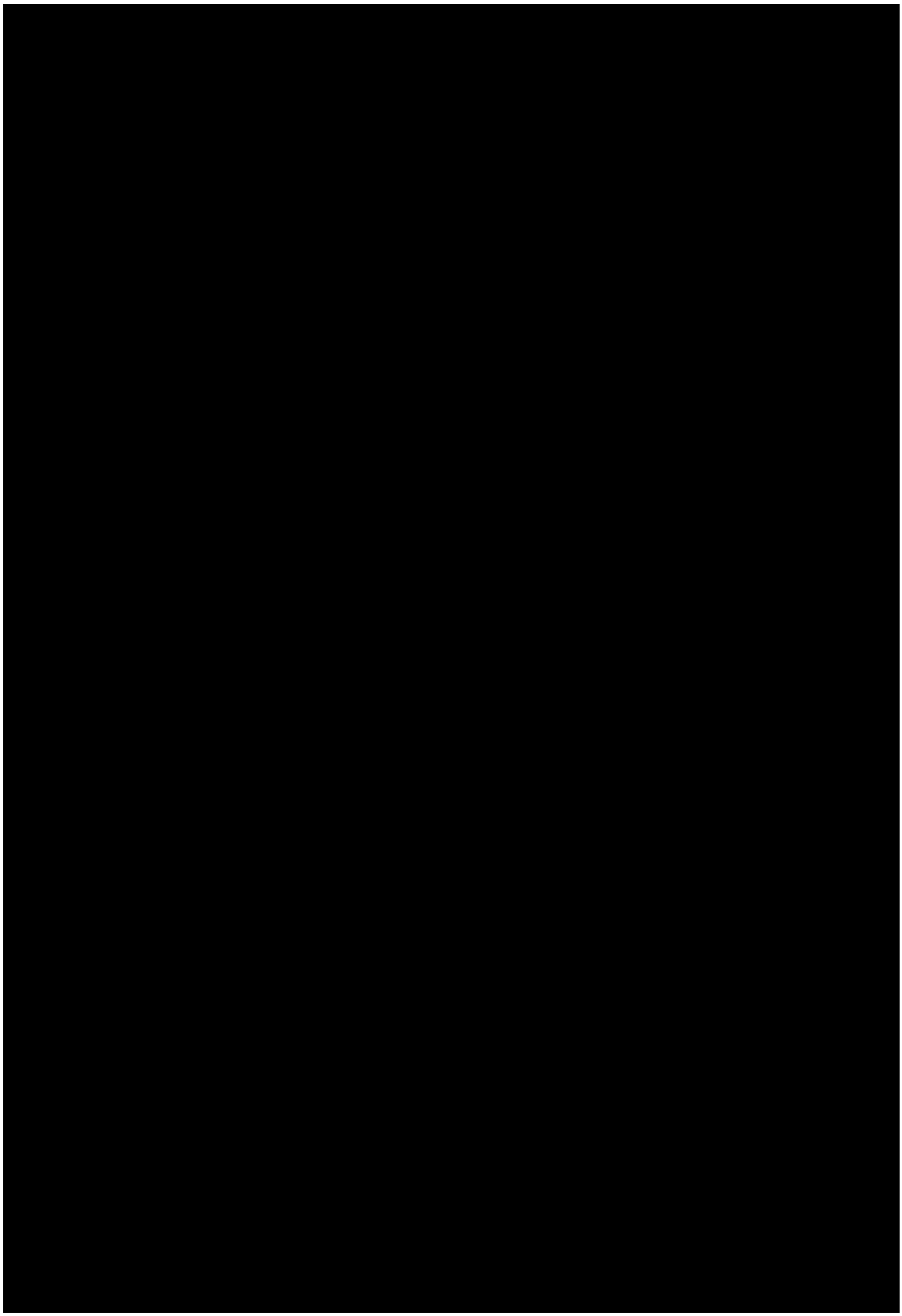


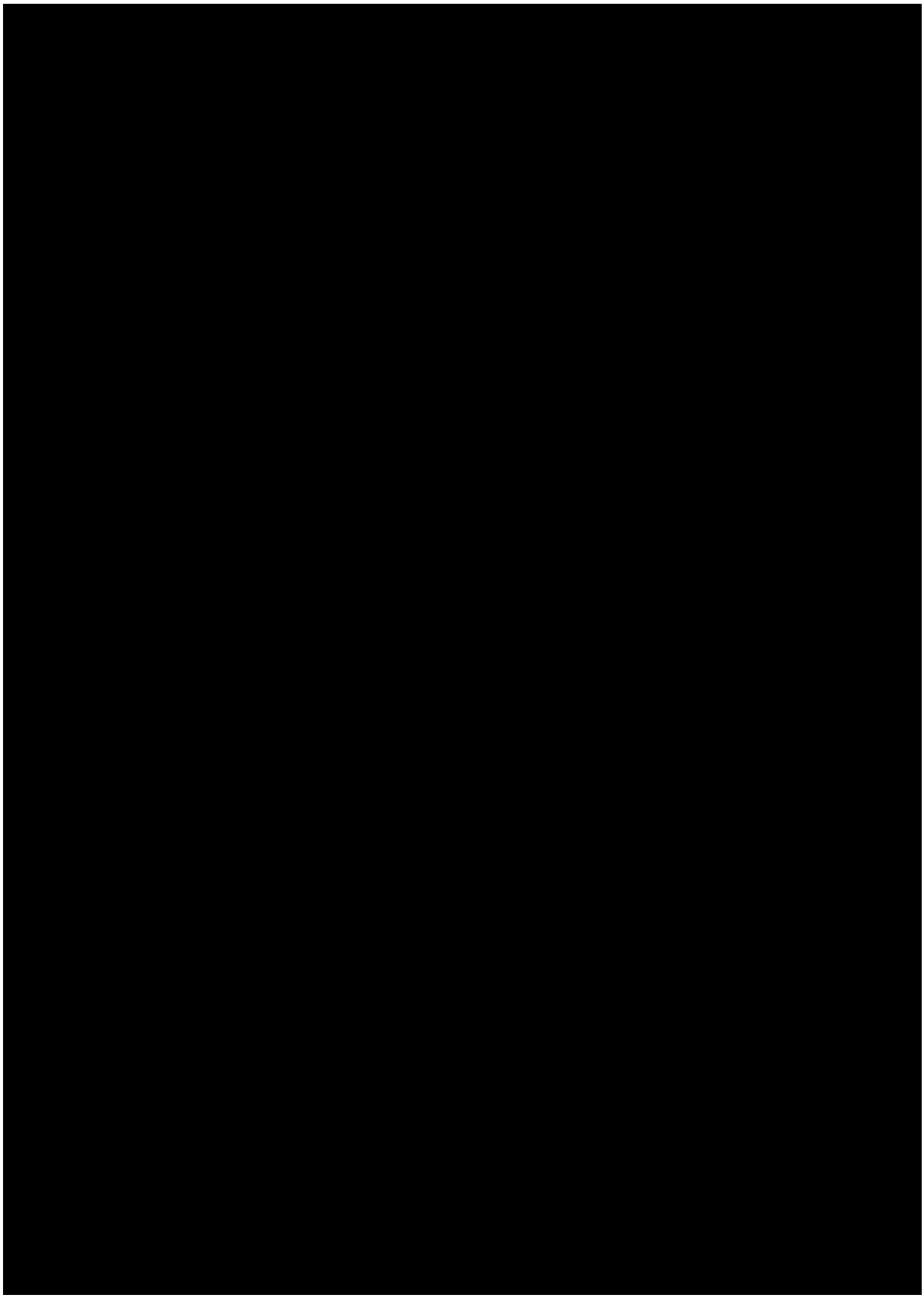












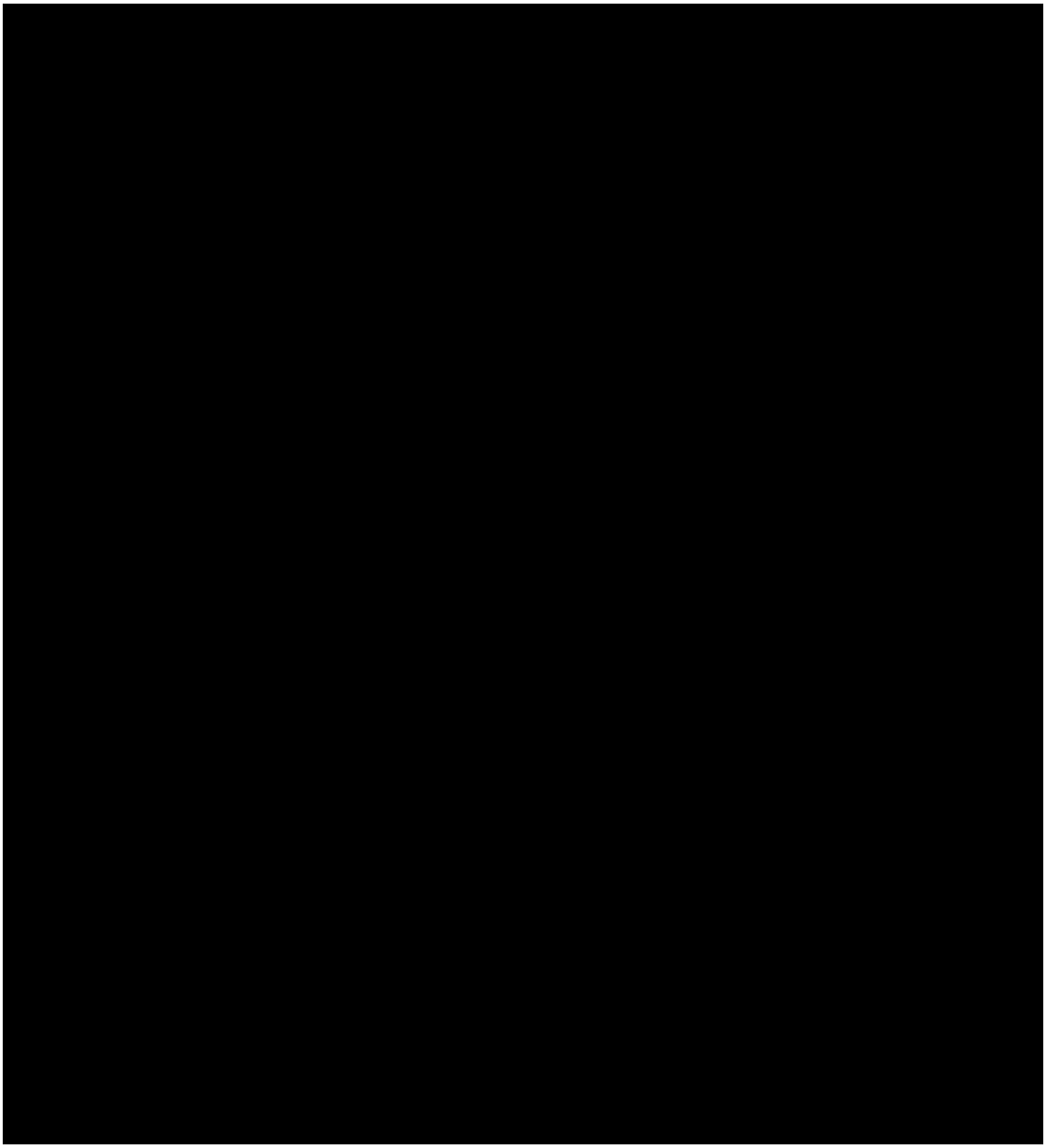
Appendix D. Extrapolation

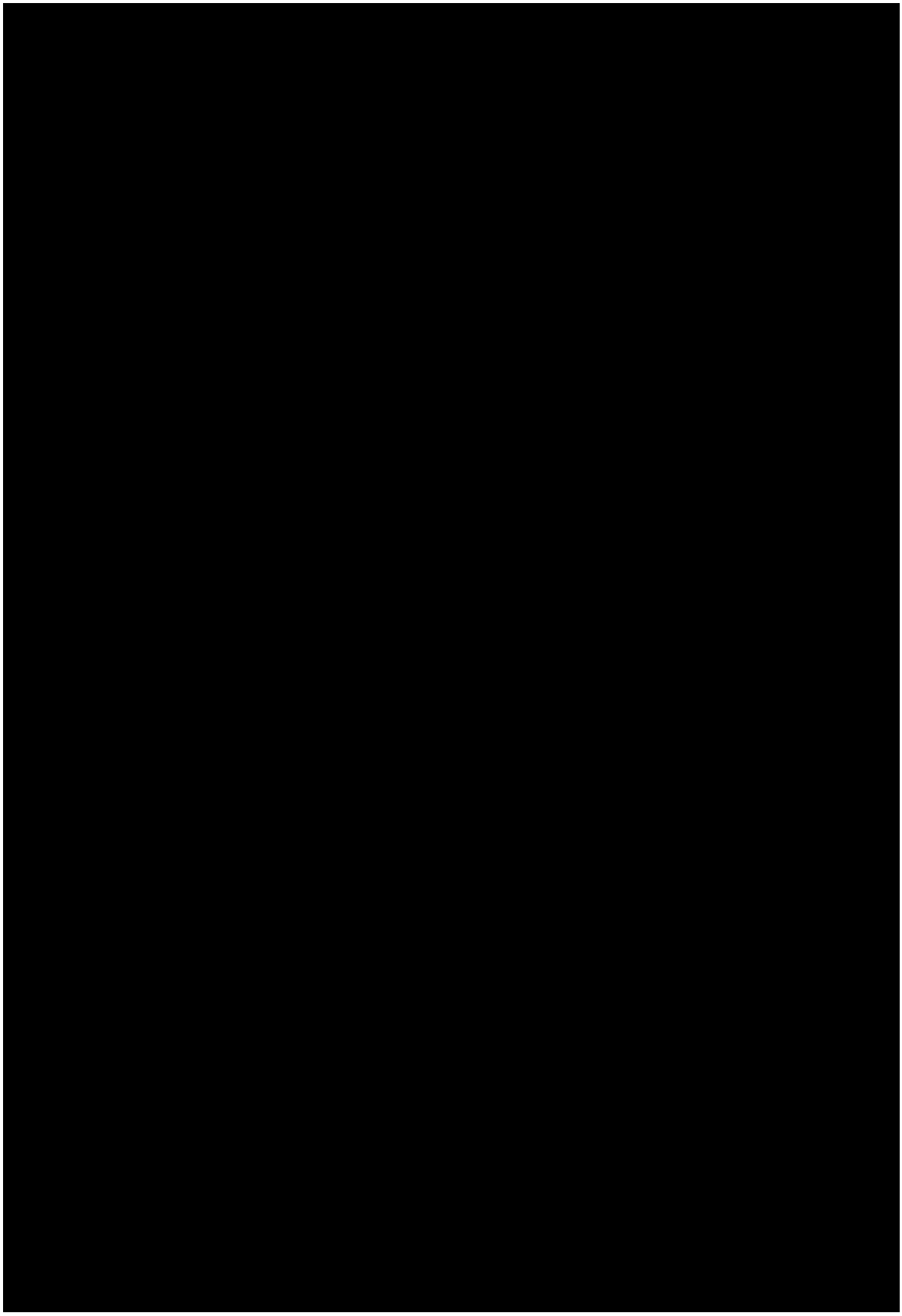
Not applicable.

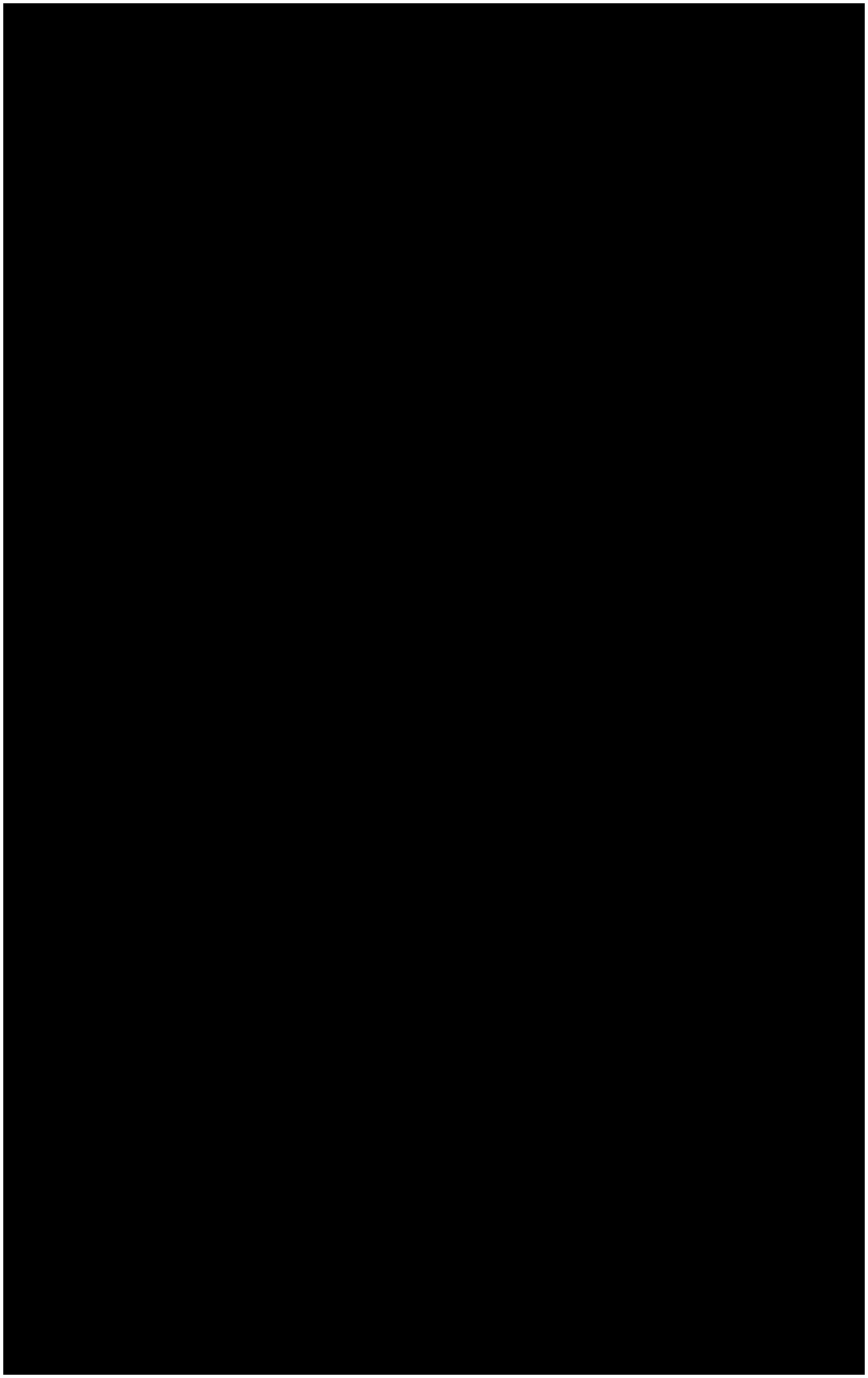
Appendix E. Serious Adverse Events

Figure 74 shows the serious treatment-emergent adverse events in TRANSFORM [46]. The full list of serious adverse events in ZUMA-7 is not publicly available. Figure 75 shows the list of serious adverse events occurring in at least three patients in the safety analysis set [47].

Figure 76 shows the serious treatment-emergent adverse events in TRANSCEND (017001) [109]. The full list of serious adverse events in ZUMA-1 is not publicly available.







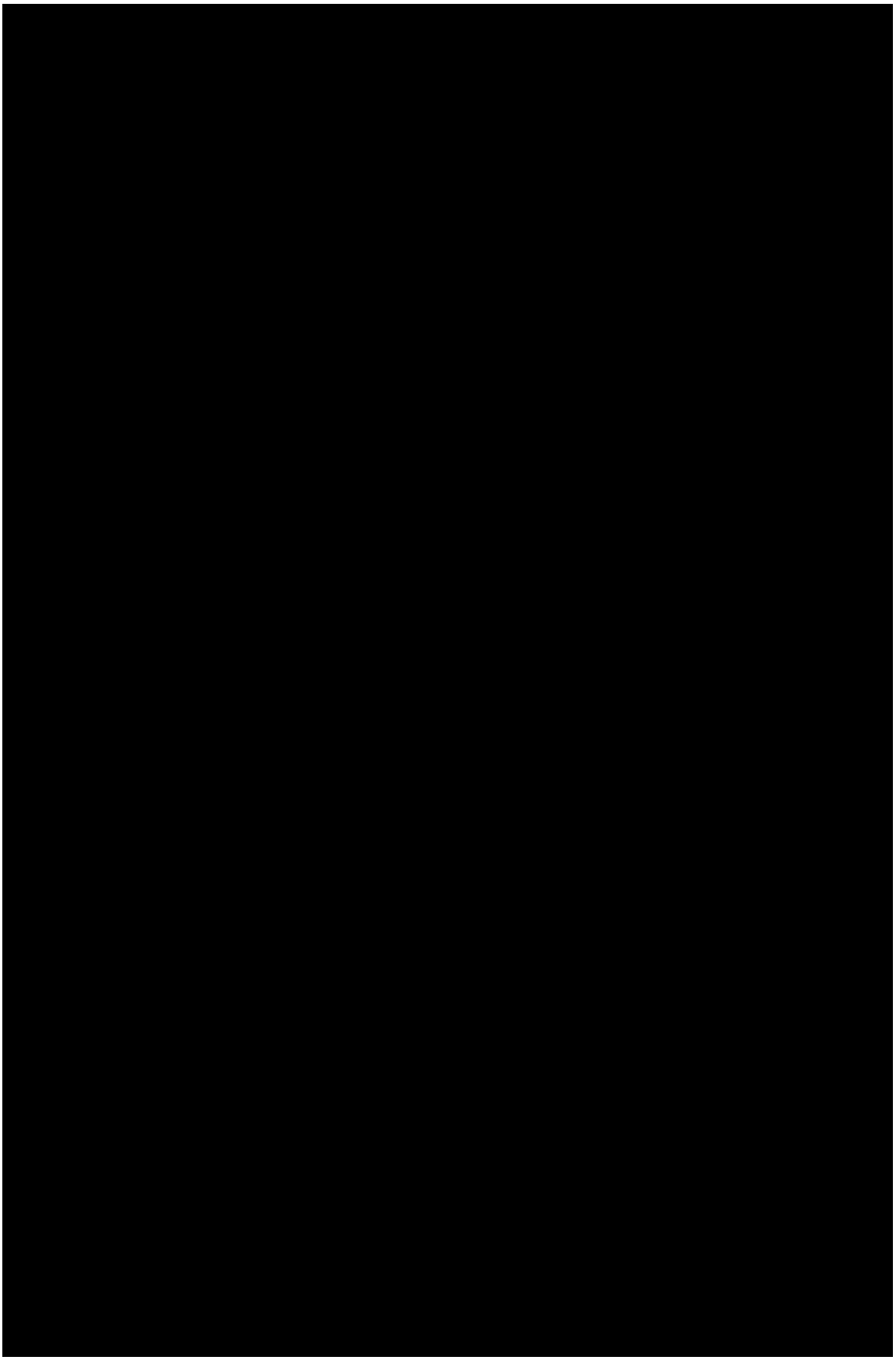
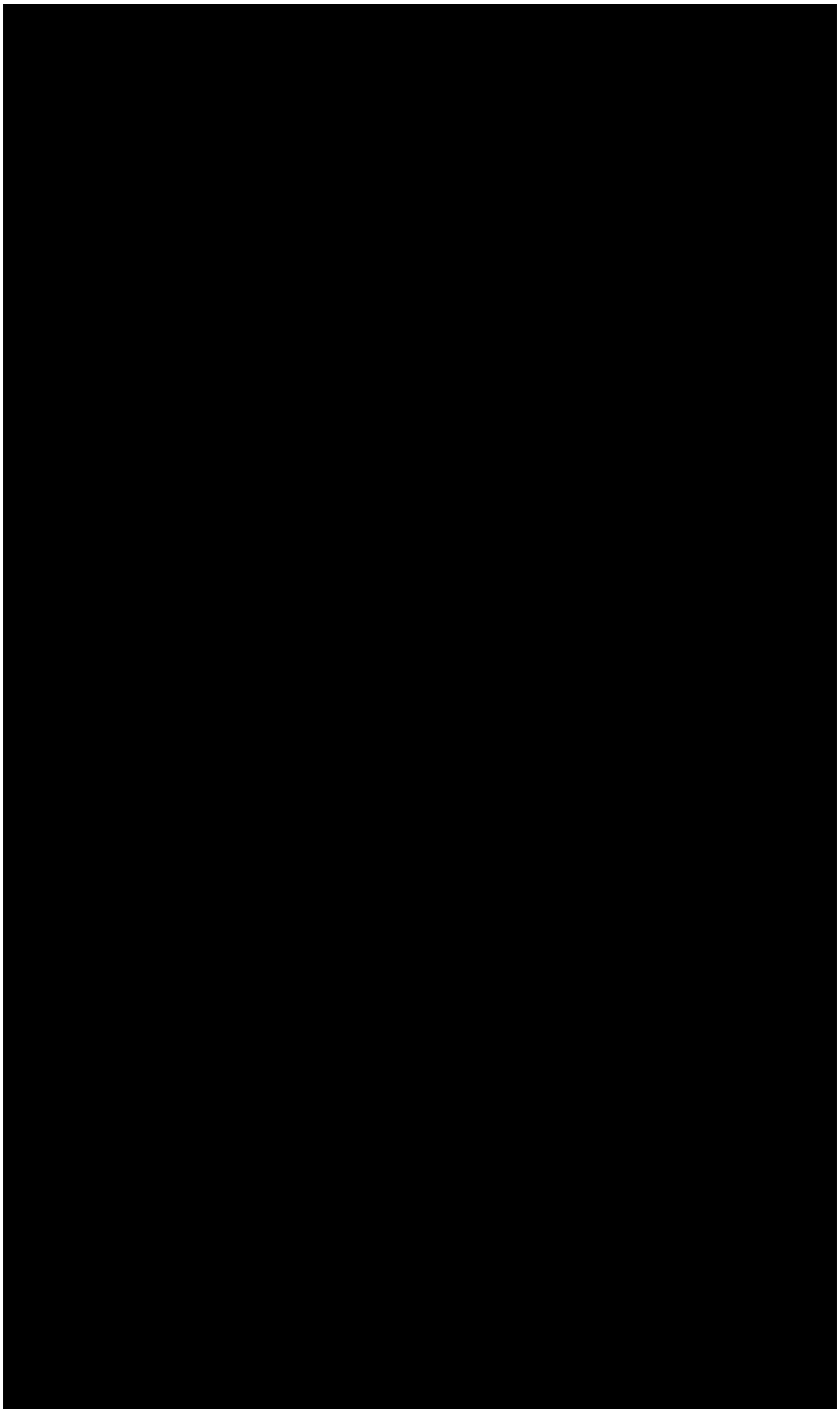


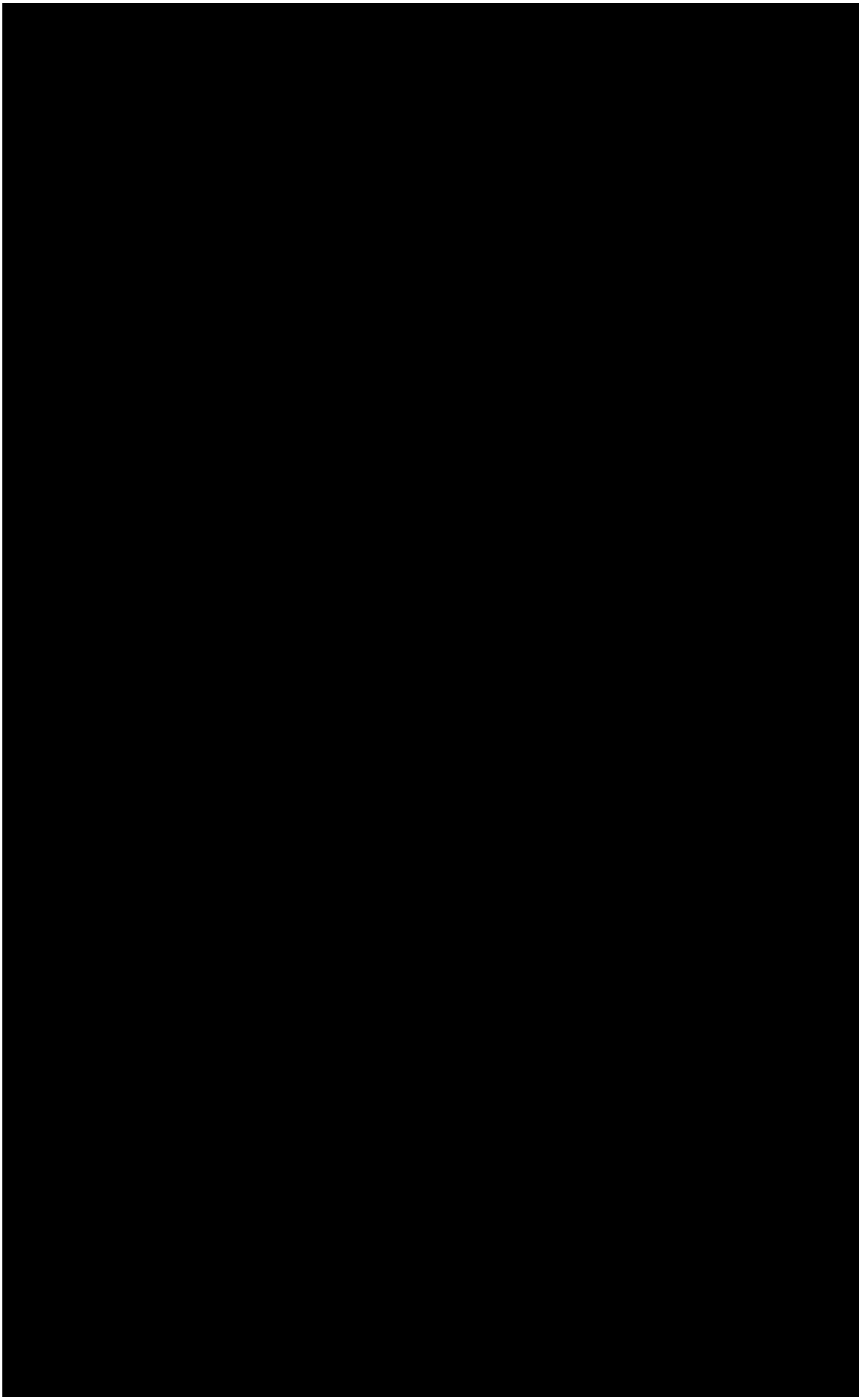
Figure 75 Serious Adverse Events Occurring in at Least Three Patients in the safety analysis set - ZUMA-7 trial.

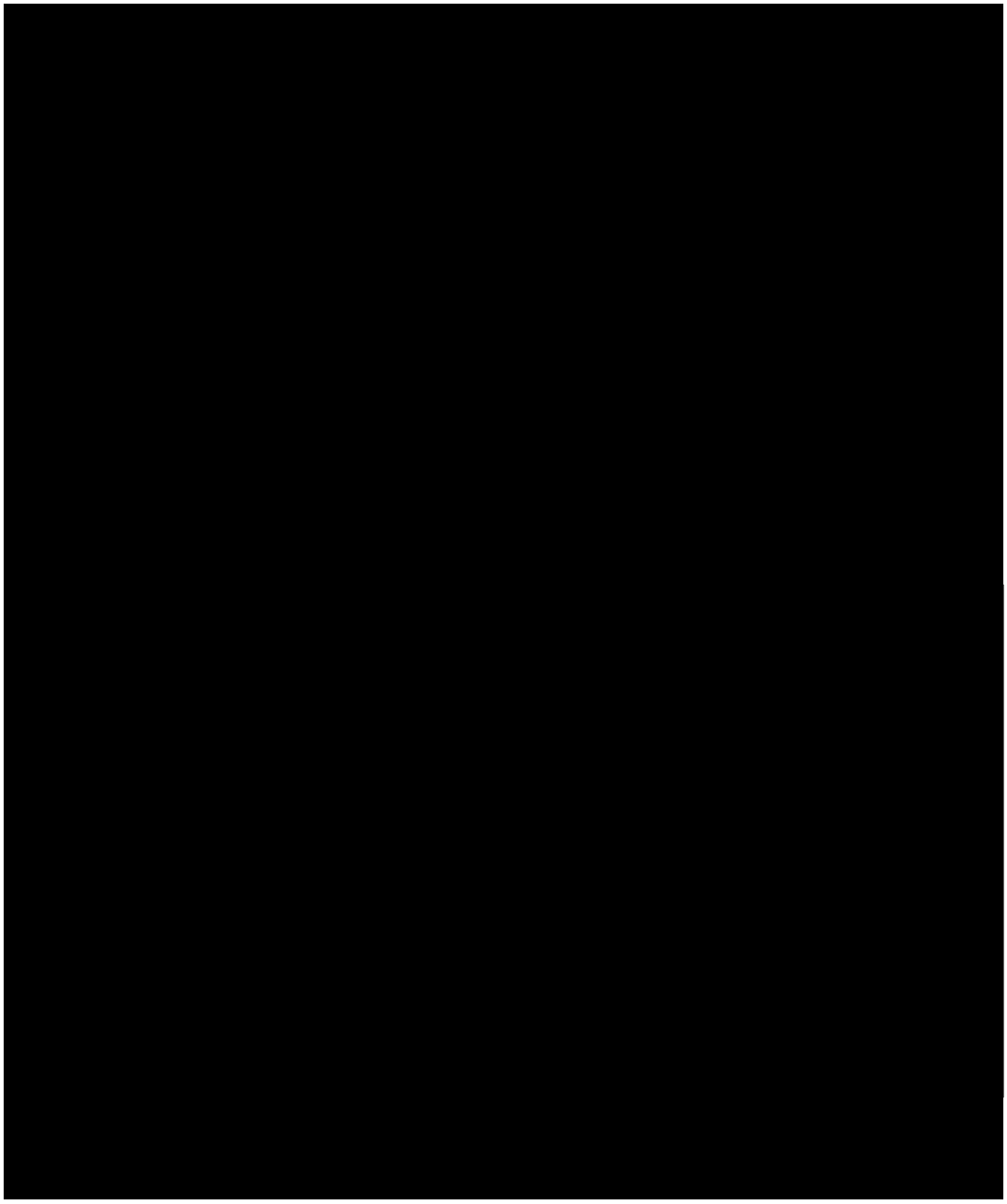
	Axi-cel N=170		SOC N=168	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any serious adverse event	85 (50)	72 (42)	77 (46)	67 (40)
Pyrexia	27 (16)	1 (1)	8 (5)	0 (0)
Encephalopathy	17 (10)	15 (9)	1 (1)	0 (0)
Hypotension	15 (9)	7 (4)	3 (2)	3 (2)
Pneumonia	8 (5)	6 (4)	4 (2)	3 (2)
Aphasia	9 (5)	8 (5)	0 (0)	0 (0)
B-cell lymphoma	7 (4)	7 (4)	5 (3)	5 (3)
Confusional state	6 (4)	4 (2)	0 (0)	0 (0)
Neutropenia*	6 (4)	5 (3)	4 (2)	4 (2)
Somnolence	5 (3)	3 (2)	0 (0)	0 (0)
Tremor	5 (3)	1 (1)	0 (0)	0 (0)
Acute kidney injury	3 (2)	2 (1)	8 (5)	4 (2)
Atrial fibrillation	4 (2)	3 (2)	2 (1)	0 (0)
Febrile neutropenia	4 (2)	4 (2)	22 (13)	22 (13)
Abdominal pain	3 (2)	2 (1)	2 (1)	1 (1)
Hypoxia	3 (2)	1 (1)	2 (1)	2 (1)
Dyspnea	3 (2)	3 (2)	1 (1)	1 (1)
Headache	4 (2)	3 (2)	0 (0)	0 (0)
Fatigue	3 (2)	2 (1)	0 (0)	0 (0)

COVID-19	3 (2)	3 (2)	0 (0)	0 (0)
Muscular weakness	3 (2)	2 (1)	0 (0)	0 (0)
Anemia	1 (1)	1 (1)	3 (2)	3 (2)
Decreased appetite	1 (1)	1 (1)	3 (2)	3 (2)
Hyponatremia	2 (1)	2 (1)	1 (1)	1 (1)
Malaise	2 (1)	0 (0)	1 (1)	0 (0)
Sinus tachycardia	2 (1)	1 (1)	2 (1)	1 (1)
Syncope	1 (1)	1 (1)	3 (2)	3 (2)
Back pain	1 (1)	0 (0)	2 (1)	2 (1)
Sepsis	2 (1)	2 (1)	4 (2)	4 (2)
Nausea	1 (1)	0 (0)	2 (1)	2 (1)
Dehydration	0 (0)	0 (0)	3 (2)	3 (2)
Thrombocytopenia†	0 (0)	0 (0)	6 (4)	6 (4)

*Combined Medical Dictionary for Regulatory Activities preferred terms of neutropenia and neutrophil count decreased. †Combined Medical Dictionary for Regulatory Activities preferred terms of thrombocytopenia and platelet count decreased. Axi-cel, axicabtagene ciloleucel; SOC, standard of care.







Appendix F. Health-related quality of life

The pattern of missing data and completion for axi-cel and SoC is shown in Table 116.

Table 116 Pattern of missing data and completion for axi-cel and SoC

Variable	Category	Overall, n (%) (N = 296)	Axicabtagene ciloleucel, n (%) (n = 165)	Standard-of-care therapy, n (%) (n = 131)
EORTC QLQ-C30 Global Health Status/QoL				
Screening				
PRO data category at Screening	2: Expected to complete	296 (100.0)	165 (100.0)	131 (100.0)
Expected to complete subcategory at Screening	3: Expected: Not completed	1 (0.3)	0 (0.0)	1 (0.8)
	4: Expected: Completed	295 (99.7)	165 (100.0)	130 (99.2)
Completion rate (denominator: all patients) at Screening	-	295 (99.7)	165 (100.0)	130 (99.2)
Compliance rate (denominator: expected to complete) at Screening	-	295 (99.7)	165 (100.0)	130 (99.2)
Day 50				
PRO data category at day 50	1: MBD	1 (0.3)	0 (0.0)	1 (0.8)
	2: Expected to complete	295 (99.7)	165 (100.0)	130 (99.2)
MBD subcategory at day 50	1: MBD: Post-event	1 (100.0)	0 (0.0)	1 (100.0)
Expected to complete subcategory at day 50	3: Expected: Not completed	7 (2.4)	2 (1.2)	5 (3.8)
	4: Expected: Completed	288 (97.6)	163 (98.8)	125 (96.2)
Completion rate (denominator: all patients) at day 50	-	288 (97.3)	163 (98.8)	125 (95.4)
Compliance rate (denominator: expected to complete) at day 50	-	288 (97.6)	163 (98.8)	125 (96.2)
Day 100				
PRO data category at day 100	1: MBD	73 (24.7)	16 (9.7)	57 (43.5)
	2: Expected to complete	223 (75.3)	149 (90.3)	74 (56.5)
MBD subcategory at day 100	1: MBD: Post-event	72 (98.6)	16 (100.0)	56 (98.2)
	2: MBD: Exit from trial	1 (1.4)	0 (0.0)	1 (1.8)
Expected to complete subcategory at day 100	3: Expected: Not completed	15 (6.7)	3 (2.0)	12 (16.2)
	4: Expected: Completed	208 (93.3)	146 (98.0)	62 (83.8)
Completion rate (denominator: all patients) at day 100	-	208 (70.3)	146 (88.5)	62 (47.3)
Compliance rate (denominator: expected to complete) at day 100	-	208 (93.3)	146 (98.0)	62 (83.8)
Day 150				
PRO data category at day 150	1: MBD	126 (42.6)	53 (32.1)	73 (55.7)
	2: Expected to complete	170 (57.4)	112 (67.9)	58 (44.3)

Variable	Category	Overall, n (%) (N = 296)	Axicabtagene ciloleucel, n (%) (n = 165)	Standard-of-care therapy, n (%) (n = 131)
MBD subcategory at day 150	1: MBD: Post-event	125 (99.2)	53 (100.0)	72 (98.6)
	2: MBD: Exit from trial	1 (0.8)	0 (0.0)	1 (1.4)
Expected to complete subcategory at day 150	3: Expected: Not completed	4 (2.4)	2 (1.8)	2 (3.4)
	4: Expected: Completed	166 (97.6)	110 (98.2)	56 (96.6)
Completion rate (denominator: all patients) at day 150	-	166 (56.1)	110 (66.7)	56 (42.7)
Compliance rate (denominator: expected to complete) at day 150	-	166 (97.6)	110 (98.2)	56 (96.6)
Month 9				
PRO data category at month 9	1: MBD	159 (53.7)	70 (42.4)	89 (67.9)
	2: Expected to complete	137 (46.3)	95 (57.6)	42 (32.1)
MBD subcategory at month 9	1: MBD: Post-event	158 (99.4)	70 (100.0)	88 (98.9)
	2: MBD: Exit from trial	1 (0.6)	0 (0.0)	1 (1.1)
Expected to complete subcategory at month 9	3: Expected: Not completed	9 (6.6)	7 (7.4)	2 (4.8)
	4: Expected: Completed	128 (93.4)	88 (92.6)	40 (95.2)
Completion rate (denominator: all patients) at month 9	-	128 (43.2)	88 (53.3)	40 (30.5)
Compliance rate (denominator: expected to complete) at month 9	-	128 (93.4)	88 (92.6)	40 (95.2)
Month 12				
PRO data category at month 12	1: MBD	173 (58.4)	77 (46.7)	96 (73.3)
	2: Expected to complete	123 (41.6)	88 (53.3)	35 (26.7)
MBD subcategory at month 12	1: MBD: Post-event	173 (100.0)	77 (100.0)	96 (100.0)
Expected to complete subcategory at month 12	3: Expected: Not completed	11 (8.9)	9 (10.2)	2 (5.7)
	4: Expected: Completed	112 (91.1)	79 (89.8)	33 (94.3)
Completion rate (denominator: all patients) at month 12	-	112 (37.8)	79 (47.9)	33 (25.2)
Compliance rate (denominator: expected to complete) at month 12	-	112 (91.1)	79 (89.8)	33 (94.3)
Month 15				
PRO data category at month 15	1: MBD	185 (62.5)	85 (51.5)	100 (76.3)
	2: Expected to complete	111 (37.5)	80 (48.5)	31 (23.7)
MBD subcategory at month 15	1: MBD: Post-event	185 (100.0)	85 (100.0)	100 (100.0)
Expected to complete subcategory at month 15	3: Expected: Not completed	18 (16.2)	13 (16.3)	5 (16.1)

Variable	Category	Overall, n (%) (N = 296)	Axicabtagene ciloleucel, n (%) (n = 165)	Standard-of-care therapy, n (%) (n = 131)
	4: Expected: Completed	93 (83.8)	67 (83.8)	26 (83.9)
Completion rate (denominator: all patients) at month 15	-	93 (31.4)	67 (40.6)	26 (19.8)
Compliance rate (denominator: expected to complete) at month 15	-	93 (83.8)	67 (83.8)	26 (83.9)
Month 18				
PRO data category at month 18	1: MBD	193 (65.2)	89 (53.9)	104 (79.4)
	2: Expected to complete	103 (34.8)	76 (46.1)	27 (20.6)
MBD subcategory at month 18	1: MBD: Post-event	193 (100.0)	89 (100.0)	104 (100.0)
Expected to complete subcategory at month 18	3: Expected: Not completed	9 (8.7)	5 (6.6)	4 (14.8)
	4: Expected: Completed	94 (91.3)	71 (93.4)	23 (85.2)
Completion rate (denominator: all patients) at month 18	-	94 (31.8)	71 (43.0)	23 (17.6)
Compliance rate (denominator: expected to complete) at month 18	-	94 (91.3)	71 (93.4)	23 (85.2)
Month 21				
PRO data category at month 21	1: MBD	220 (74.3)	112 (67.9)	108 (82.4)
	2: Expected to complete	76 (25.7)	53 (32.1)	23 (17.6)
MBD subcategory at month 21	1: MBD: Post-event	220 (100.0)	112 (100.0)	108 (100.0)
Expected to complete subcategory at month 21	3: Expected: Not completed	11 (14.5)	8 (15.1)	3 (13.0)
	4: Expected: Completed	65 (85.5)	45 (84.9)	20 (87.0)
Completion rate (denominator: all patients) at month 21	-	65 (22.0)	45 (27.3)	20 (15.3)
Compliance rate (denominator: expected to complete) at month 21	-	65 (85.5)	45 (84.9)	20 (87.0)
Month 24				
PRO data category at month 24	1: MBD	247 (83.4)	129 (78.2)	118 (90.1)
	2: Expected to complete	49 (16.6)	36 (21.8)	13 (9.9)
MBD subcategory at month 24	1: MBD: Post-event	247 (100.0)	129 (100.0)	118 (100.0)
Expected to complete subcategory at month 24	3: Expected: Not completed	5 (10.2)	4 (11.1)	1 (7.7)
	4: Expected: Completed	44 (89.8)	32 (88.9)	12 (92.3)
Completion rate (denominator: all patients) at month 24	-	44 (14.9)	32 (19.4)	12 (9.2)
Compliance rate (denominator: expected to complete) at month 24	-	44 (89.8)	32 (88.9)	12 (92.3)
EORTC QLQ-C30 Physical Functioning				

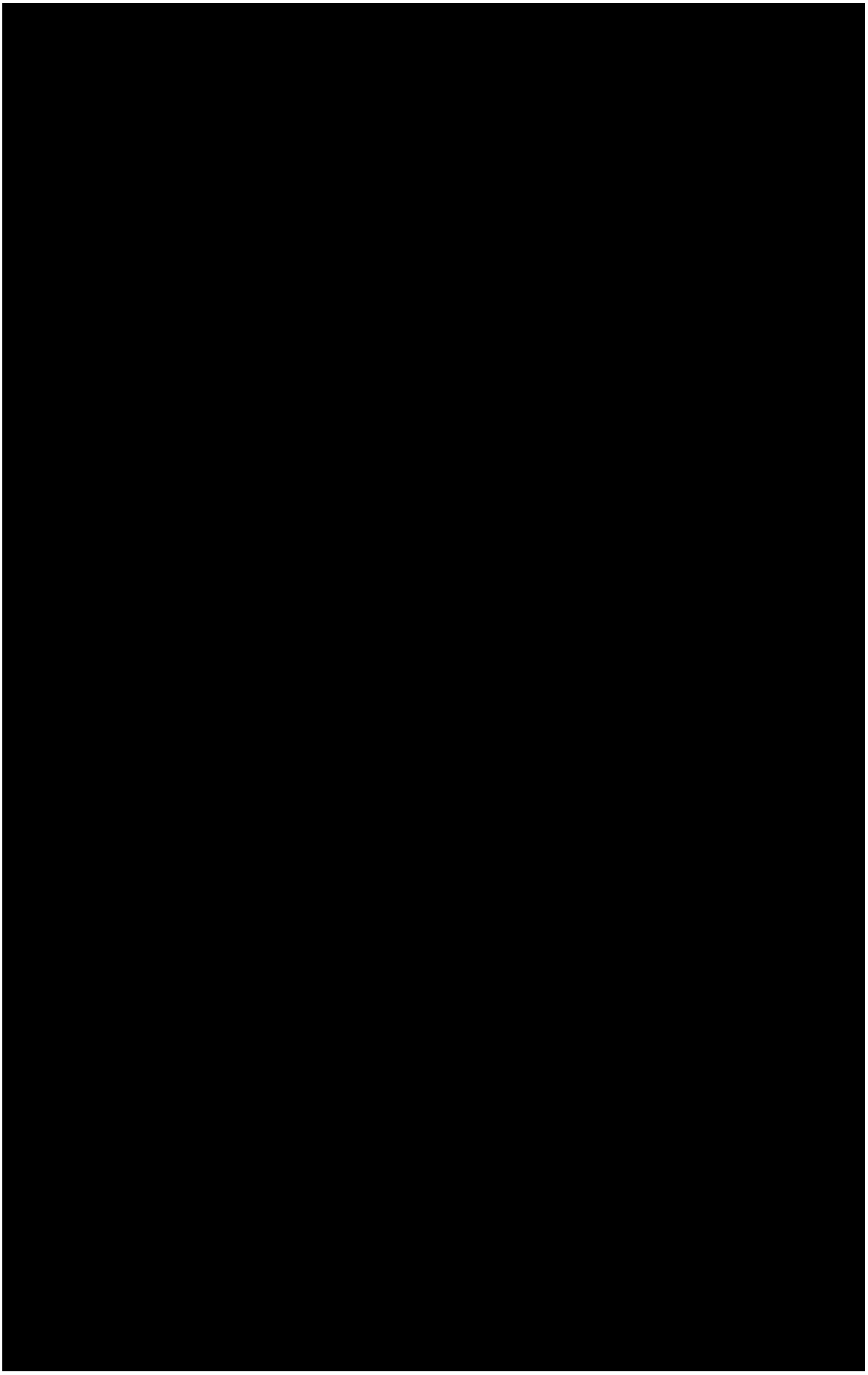
Variable	Category	Overall, n (%) (N = 296)	Axicabtagene ciloleucel, n (%) (n = 165)	Standard-of-care therapy, n (%) (n = 131)
Screening				
PRO data category at Screening	2: Expected to complete	296 (100.0)	165 (100.0)	131 (100.0)
Expected to complete subcategory at Screening	3: Expected: Not completed	1 (0.3)	1 (0.6)	0 (0.0)
	4: Expected: Completed	295 (99.7)	164 (99.4)	131 (100.0)
Completion rate (denominator: all patients) at Screening	-	295 (99.7)	164 (99.4)	131 (100.0)
Compliance rate (denominator: expected to complete) at Screening	-	295 (99.7)	164 (99.4)	131 (100.0)
Day 50				
PRO data category at day 50	1: MBD	1 (0.3)	0 (0.0)	1 (0.8)
	2: Expected to complete	295 (99.7)	165 (100.0)	130 (99.2)
MBD subcategory at day 50	1: MBD: Post-event	1 (100.0)	0 (0.0)	1 (100.0)
Expected to complete subcategory at day 50	3: Expected: Not completed	6 (2.0)	2 (1.2)	4 (3.1)
	4: Expected: Completed	289 (98.0)	163 (98.8)	126 (96.9)
Completion rate (denominator: all patients) at day 50	-	289 (97.6)	163 (98.8)	126 (96.2)
Compliance rate (denominator: expected to complete) at day 50	-	289 (98.0)	163 (98.8)	126 (96.9)
Day 100				
PRO data category at day 100	1: MBD	73 (24.7)	16 (9.7)	57 (43.5)
	2: Expected to complete	223 (75.3)	149 (90.3)	74 (56.5)
MBD subcategory at day 100	1: MBD: Post-event	72 (98.6)	16 (100.0)	56 (98.2)
	2: MBD: Exit from trial	1 (1.4)	0 (0.0)	1 (1.8)
Expected to complete subcategory at day 100	3: Expected: Not completed	13 (5.8)	3 (2.0)	10 (13.5)
	4: Expected: Completed	210 (94.2)	146 (98.0)	64 (86.5)
Completion rate (denominator: all patients) at day 100	-	210 (70.9)	146 (88.5)	64 (48.9)
Compliance rate (denominator: expected to complete) at day 100	-	210 (94.2)	146 (98.0)	64 (86.5)
Day 150				
PRO data category at day 150	1: MBD	127 (42.9)	54 (32.7)	73 (55.7)
	2: Expected to complete	169 (57.1)	111 (67.3)	58 (44.3)
MBD subcategory at day 150	1: MBD: Post-event	126 (99.2)	54 (100.0)	72 (98.6)
	2: MBD: Exit from trial	1 (0.8)	0 (0.0)	1 (1.4)

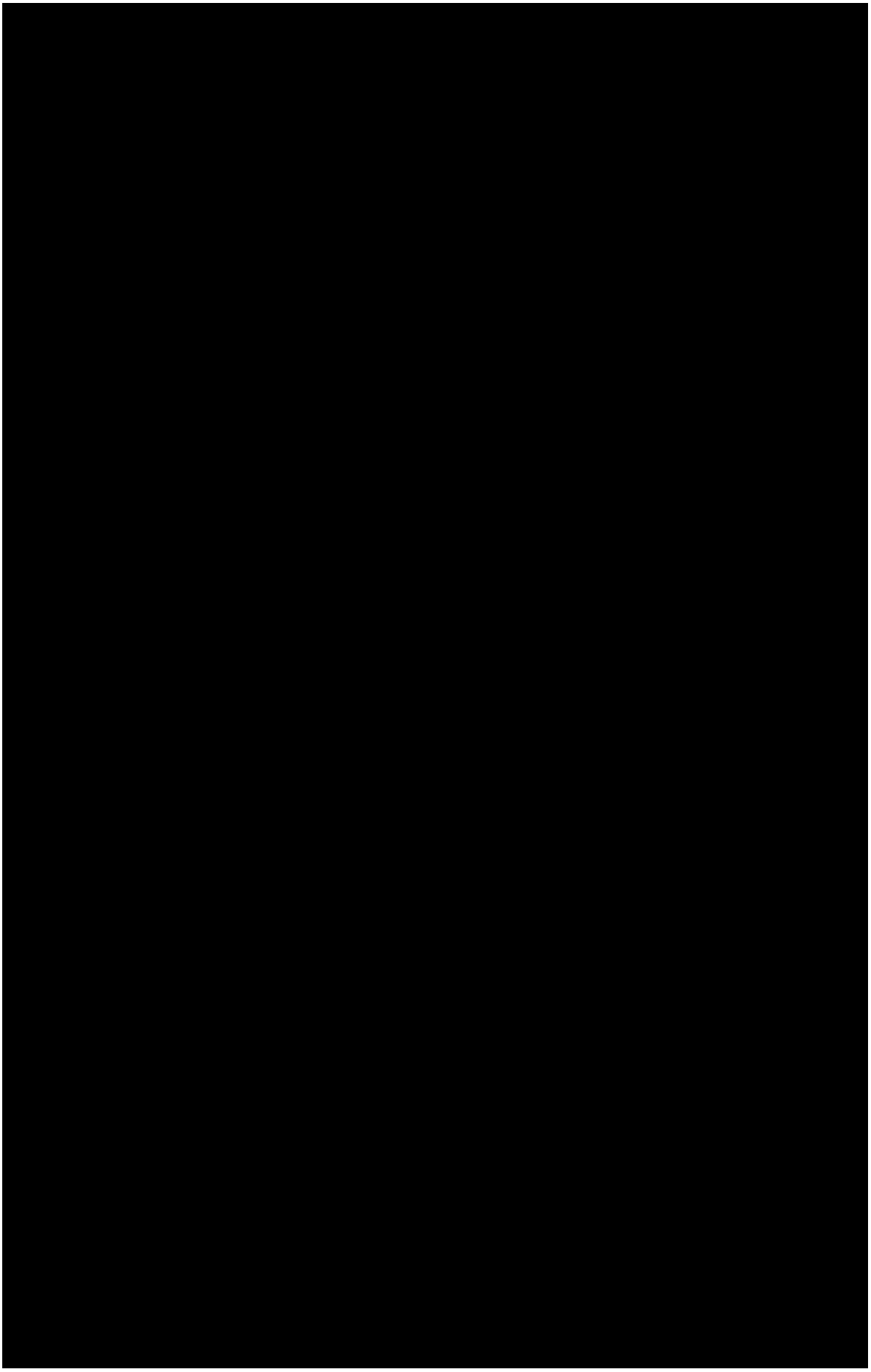
Variable	Category	Overall, n (%) (N = 296)	Axicabtagene ciloleucel, n (%) (n = 165)	Standard-of-care therapy, n (%) (n = 131)
Expected to complete subcategory at day 150	3: Expected: Not completed	4 (2.4)	2 (1.8)	2 (3.4)
	4: Expected: Completed	165 (97.6)	109 (98.2)	56 (96.6)
Completion rate (denominator: all patients) at day 150	-	165 (55.7)	109 (66.1)	56 (42.7)
Compliance rate (denominator: expected to complete) at day 150	-	165 (97.6)	109 (98.2)	56 (96.6)
Month 9				
PRO data category at month 9	1: MBD	159 (53.7)	70 (42.4)	89 (67.9)
	2: Expected to complete	137 (46.3)	95 (57.6)	42 (32.1)
MBD subcategory at month 9	1: MBD: Post-event	158 (99.4)	70 (100.0)	88 (98.9)
	2: MBD: Exit from trial	1 (0.6)	0 (0.0)	1 (1.1)
Expected to complete subcategory at month 9	3: Expected: Not completed	9 (6.6)	7 (7.4)	2 (4.8)
	4: Expected: Completed	128 (93.4)	88 (92.6)	40 (95.2)
Completion rate (denominator: all patients) at month 9	-	128 (43.2)	88 (53.3)	40 (30.5)
Compliance rate (denominator: expected to complete) at month 9	-	128 (93.4)	88 (92.6)	40 (95.2)
Month 12				
PRO data category at month 12	1: MBD	173 (58.4)	77 (46.7)	96 (73.3)
	2: Expected to complete	123 (41.6)	88 (53.3)	35 (26.7)
MBD subcategory at month 12	1: MBD: Post-event	173 (100.0)	77 (100.0)	96 (100.0)
Expected to complete subcategory at month 12	3: Expected: Not completed	11 (8.9)	9 (10.2)	2 (5.7)
	4: Expected: Completed	112 (91.1)	79 (89.8)	33 (94.3)
Completion rate (denominator: all patients) at month 12	-	112 (37.8)	79 (47.9)	33 (25.2)
Compliance rate (denominator: expected to complete) at month 12	-	112 (91.1)	79 (89.8)	33 (94.3)
Month 15				
PRO data category at month 15	1: MBD	185 (62.5)	85 (51.5)	100 (76.3)
	2: Expected to complete	111 (37.5)	80 (48.5)	31 (23.7)
MBD subcategory at month 15	1: MBD: Post-event	185 (100.0)	85 (100.0)	100 (100.0)
Expected to complete subcategory at month 15	3: Expected: Not completed	18 (16.2)	13 (16.3)	5 (16.1)
	4: Expected: Completed	93 (83.8)	67 (83.8)	26 (83.9)
Completion rate (denominator: all patients) at month 15	-	93 (31.4)	67 (40.6)	26 (19.8)

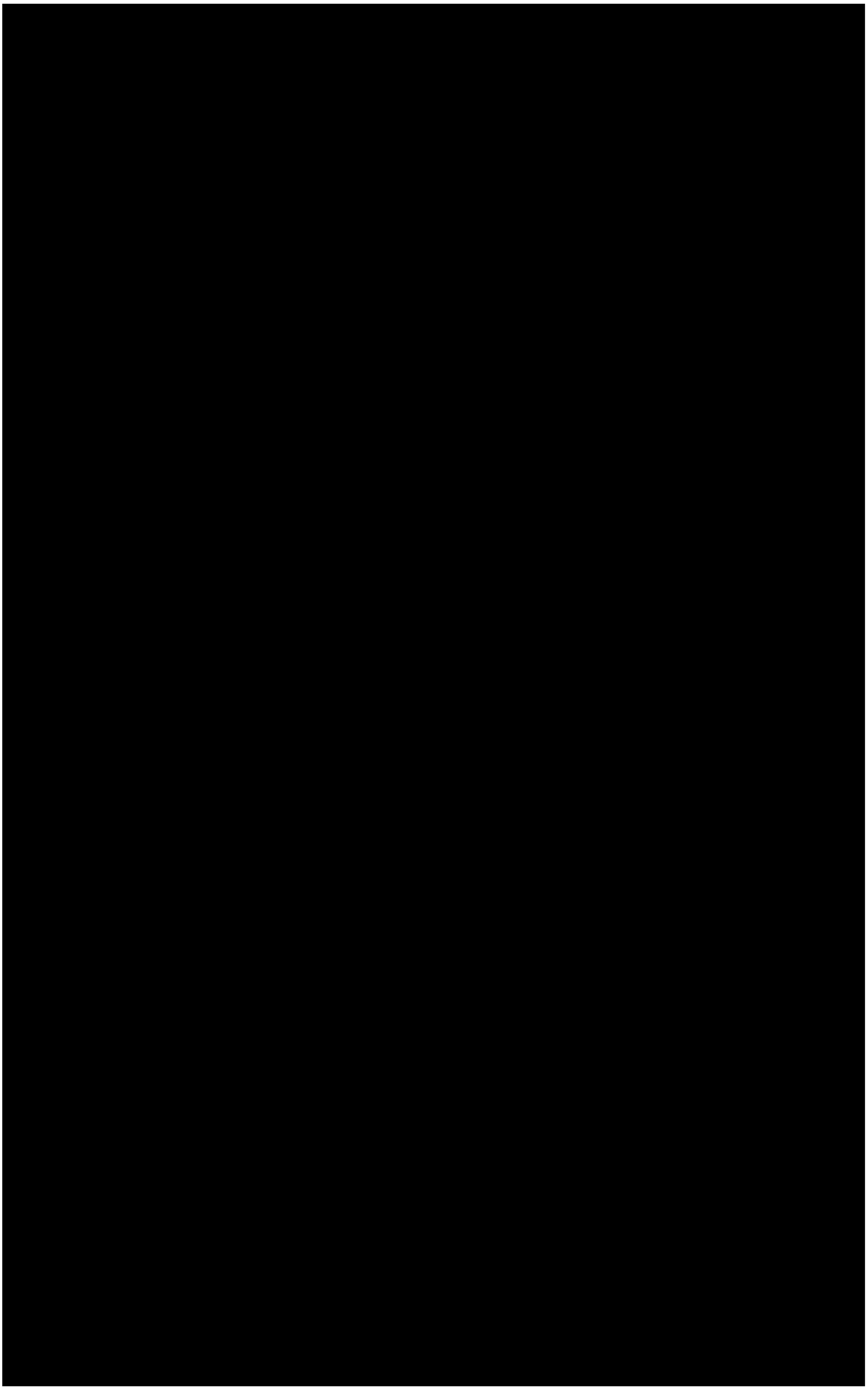
Variable	Category	Overall, n (%) (N = 296)	Axicabtagene ciloleucel, n (%) (n = 165)	Standard-of-care therapy, n (%) (n = 131)
Compliance rate (denominator: expected to complete) at month 15	-	93 (83.8)	67 (83.8)	26 (83.9)
Month 18				
PRO data category at month 18	1: MBD	193 (65.2)	89 (53.9)	104 (79.4)
	2: Expected to complete	103 (34.8)	76 (46.1)	27 (20.6)
MBD subcategory at month 18	1: MBD: Post-event	193 (100.0)	89 (100.0)	104 (100.0)
Expected to complete subcategory at month 18	3: Expected: Not completed	9 (8.7)	5 (6.6)	4 (14.8)
	4: Expected: Completed	94 (91.3)	71 (93.4)	23 (85.2)
Completion rate (denominator: all patients) at month 18	-	94 (31.8)	71 (43.0)	23 (17.6)
Compliance rate (denominator: expected to complete) at month 18	-	94 (91.3)	71 (93.4)	23 (85.2)
Month 21				
PRO data category at month 21	1: MBD	220 (74.3)	112 (67.9)	108 (82.4)
	2: Expected to complete	76 (25.7)	53 (32.1)	23 (17.6)
MBD subcategory at month 21	1: MBD: Post-event	220 (100.0)	112 (100.0)	108 (100.0)
Expected to complete subcategory at month 21	3: Expected: Not completed	11 (14.5)	8 (15.1)	3 (13.0)
	4: Expected: Completed	65 (85.5)	45 (84.9)	20 (87.0)
Completion rate (denominator: all patients) at month 21	-	65 (22.0)	45 (27.3)	20 (15.3)
Compliance rate (denominator: expected to complete) at month 21	-	65 (85.5)	45 (84.9)	20 (87.0)
Month 24				
PRO data category at month 24	1: MBD	247 (83.4)	129 (78.2)	118 (90.1)
	2: Expected to complete	49 (16.6)	36 (21.8)	13 (9.9)
MBD subcategory at month 24	1: MBD: Post-event	247 (100.0)	129 (100.0)	118 (100.0)
Expected to complete subcategory at month 24	3: Expected: Not completed	5 (10.2)	4 (11.1)	1 (7.7)
	4: Expected: Completed	44 (89.8)	32 (88.9)	12 (92.3)
Completion rate (denominator: all patients) at month 24	-	44 (14.9)	32 (19.4)	12 (9.2)
Compliance rate (denominator: expected to complete) at month 24	-	44 (89.8)	32 (88.9)	12 (92.3)

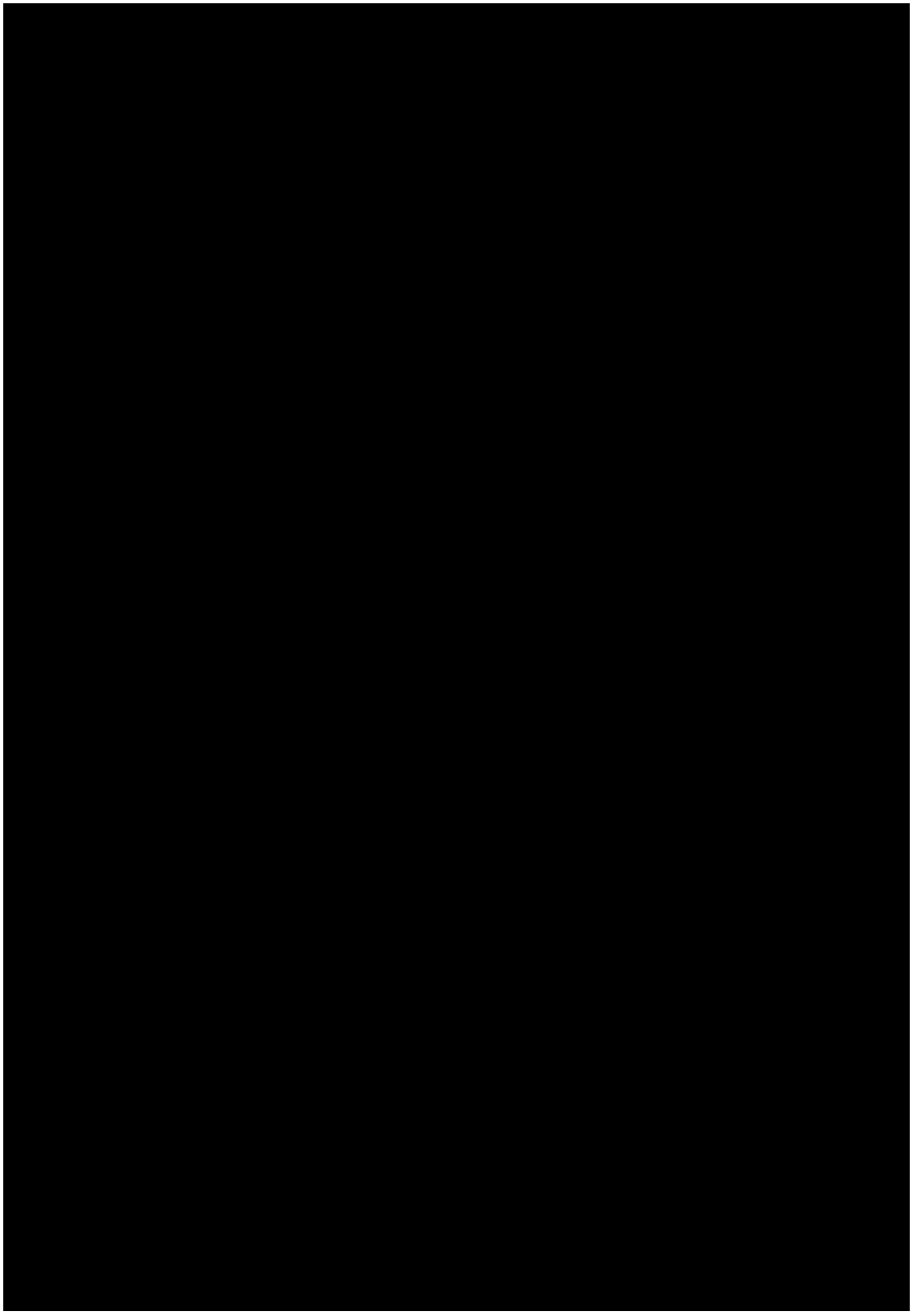
	Completion			Compliance		
	Overall, n (%)	Axi-cel, n (%)	SOC, n (%)	Overall, n (%)	Axi-cel, n (%)	SOC, n (%)
Screening						
Role Functioning	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Emotional Functioning	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Cognitive Functioning	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Social Functioning	295 (99.7)	165 (100.0)	130 (99.2)	295 (99.7)	165 (100.0)	130 (99.2)
Fatigue	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Nausea and Vomiting	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Pain	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Dyspnea	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Insomnia	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Appetite Loss	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Constipation	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Diarrhea	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Financial Difficulties	294 (99.3)	164 (99.4)	130 (99.2)	294 (99.3)	164 (99.4)	130 (99.2)
EQ-5D-5L Index	296 (100.0)	165 (100.0)	131 (100.0)	296 (100.0)	165 (100.0)	131 (100.0)
Day 50						
Role Functioning	289 (97.6)	163 (98.8)	126 (96.2)	289 (98.0)	163 (98.8)	126 (96.9)
Emotional Functioning	288 (97.3)	163 (98.8)	125 (95.4)	288 (97.6)	163 (98.8)	125 (96.2)
Cognitive Functioning	288 (97.3)	163 (98.8)	125 (95.4)	288 (97.6)	163 (98.8)	125 (96.2)
Social Functioning	288 (97.3)	163 (98.8)	125 (95.4)	288 (97.6)	163 (98.8)	125 (96.2)
Fatigue	289 (97.6)	163 (98.8)	126 (96.2)	289 (98.0)	163 (98.8)	126 (96.9)
Nausea and Vomiting	289 (97.6)	163 (98.8)	126 (96.2)	289 (98.0)	163 (98.8)	126 (96.9)
Pain	289 (97.6)	163 (98.8)	126 (96.2)	289 (98.0)	163 (98.8)	126 (96.9)
Dyspnea	288 (97.3)	163 (98.8)	125 (95.4)	288 (98.0)	163 (98.8)	125 (96.9)
Insomnia	288 (97.3)	163 (98.8)	125 (95.4)	288 (97.6)	163 (98.8)	125 (96.2)
Appetite Loss	289 (97.6)	163 (98.8)	126 (96.2)	289 (98.0)	163 (98.8)	126 (96.9)
Constipation	289 (97.6)	163 (98.8)	126 (96.2)	289 (98.0)	163 (98.8)	126 (96.9)
Diarrhea	287 (97.0)	163 (98.8)	124 (94.7)	287 (97.3)	163 (98.8)	124 (95.4)
Financial Difficulties	288 (97.3)	163 (98.8)	125 (95.4)	288 (97.6)	163 (98.8)	125 (96.2)
EQ-5D-5L Index	286 (96.6)	163 (98.8)	123 (93.9)	286 (96.9)	163 (98.8)	123 (94.6)
Day 100						
Role Functioning	210 (70.9)	146 (88.5)	64 (48.9)	210 (94.2)	146 (98.0)	64 (86.5)
Emotional Functioning	209 (70.6)	146 (88.5)	63 (48.1)	209 (93.7)	146 (98.0)	63 (85.1)
Cognitive Functioning	209 (70.6)	146 (88.5)	63 (48.1)	209 (93.7)	146 (98.0)	63 (85.1)
Social Functioning	209 (70.6)	146 (88.5)	63 (48.1)	209 (93.7)	146 (98.0)	63 (85.1)
Fatigue	210 (70.9)	146 (88.5)	64 (48.9)	210 (94.2)	146 (98.0)	64 (86.5)
Nausea and Vomiting	210 (70.9)	146 (88.5)	64 (48.9)	210 (94.2)	146 (98.0)	64 (86.5)
Pain	210 (70.9)	146 (88.5)	64 (48.9)	210 (94.2)	146 (98.0)	64 (86.5)
Dyspnea	209 (70.6)	145 (87.9)	64 (48.9)	209 (94.1)	145 (98.0)	64 (86.5)
Insomnia	210 (70.9)	146 (88.5)	64 (48.9)	210 (94.2)	146 (98.0)	64 (86.5)
Appetite Loss	209 (70.6)	146 (88.5)	63 (48.1)	209 (93.7)	146 (98.0)	63 (85.1)
Constipation	209 (70.6)	146 (88.5)	63 (48.1)	209 (93.7)	146 (98.0)	63 (85.1)
Diarrhea	209 (70.6)	146 (88.5)	63 (48.1)	209 (93.7)	146 (98.0)	63 (85.1)
Financial Difficulties	209 (70.6)	146 (88.5)	63 (48.1)	209 (93.7)	146 (98.0)	63 (85.1)
EQ-5D-5L Index	211 (71.3)	146 (88.5)	65 (49.6)	211 (94.6)	146 (98.0)	65 (87.8)
Day 150						
Role Functioning	166 (56.1)	110 (66.7)	56 (42.7)	166 (97.6)	110 (98.2)	56 (96.6)
Emotional Functioning	166 (56.1)	110 (66.7)	56 (42.7)	166 (97.6)	110 (98.2)	56 (96.6)
Cognitive Functioning	166 (56.1)	110 (66.7)	56 (42.7)	166 (97.6)	110 (98.2)	56 (96.6)
Social Functioning	166 (56.1)	110 (66.7)	56 (42.7)	166 (97.6)	110 (98.2)	56 (96.6)

Fatigue	165 (55.7)	109 (66.1)	56 (42.7)	165 (97.6)	109 (98.2)	56 (96.6)
Nausea and Vomiting	165 (55.7)	109 (66.1)	56 (42.7)	165 (97.6)	109 (98.2)	56 (96.6)
Pain	166 (56.1)	110 (66.7)	56 (42.7)	166 (97.6)	110 (98.2)	56 (96.6)
Dyspnea	165 (55.7)	109 (66.1)	56 (42.7)	165 (97.6)	109 (98.2)	56 (96.6)
Insomnia	165 (55.7)	109 (66.1)	56 (42.7)	165 (97.6)	109 (98.2)	56 (96.6)
Appetite Loss	165 (55.7)	109 (66.1)	56 (42.7)	165 (97.6)	109 (98.2)	56 (96.6)
Constipation	165 (55.7)	109 (66.1)	56 (42.7)	165 (97.6)	109 (98.2)	56 (96.6)
Diarrhea	166 (56.1)	110 (66.7)	56 (42.7)	166 (97.6)	110 (98.2)	56 (96.6)
Financial Difficulties	166 (56.1)	110 (66.7)	56 (42.7)	166 (97.6)	110 (98.2)	56 (96.6)
EQ-5D-5L Index	165 (55.7)	109 (66.1)	56 (42.7)	165 (97.1)	109 (97.3)	56 (96.6)
Month 9						
Role Functioning	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Emotional Functioning	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Cognitive Functioning	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Social Functioning	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Fatigue	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Nausea and Vomiting	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Pain	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Dyspnea	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Insomnia	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Appetite Loss	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Constipation	127 (42.9)	87 (52.7)	40 (30.5)	127 (92.7)	87 (91.6)	40 (95.2)
Diarrhea	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
Financial Difficulties	128 (43.2)	88 (53.3)	40 (30.5)	128 (93.4)	88 (92.6)	40 (95.2)
EQ-5D-5L Index	127 (42.9)	88 (53.3)	39 (29.8)	127 (92.7)	88 (92.6)	39 (92.9)
Month 12						
Role Functioning	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Emotional Functioning	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Cognitive Functioning	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Social Functioning	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Fatigue	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Nausea and Vomiting	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Pain	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Dyspnea	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Insomnia	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Appetite Loss	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Constipation	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Diarrhea	112 (37.8)	79 (47.9)	33 (25.2)	112 (91.1)	79 (89.8)	33 (94.3)
Financial Difficulties	111 (37.5)	78 (47.3)	33 (25.2)	111 (90.2)	78 (88.6)	33 (94.3)
EQ-5D-5L Index	111 (37.5)	79 (47.9)	32 (24.4)	111 (90.2)	79 (89.8)	32 (91.4)
Month 15						
Role Functioning	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Emotional Functioning	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Cognitive Functioning	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Social Functioning	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Fatigue	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Nausea and Vomiting	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Pain	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Dyspnea	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Insomnia	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Appetite Loss	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Constipation	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Diarrhea	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
Financial Difficulties	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)
EQ-5D-5L Index	93 (31.4)	67 (40.6)	26 (19.8)	93 (83.8)	67 (83.8)	26 (83.9)









Appendix G. Probabilistic sensitivity analyses

Not applicable.

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s) in 2L R/R LBCL

To understand the efficacy and safety of current therapies used in the treatment of R/R LBCL an original systematic literature review (SLR) was previously conducted in October 2017 and updated in April 2019. The search was subsequently updated specifically for the 2L population in July 2020. In subsequent searches conducted in June 2021, December 2021, and March 2023 (present update), the research objective was to characterize unmet medical needs specifically for the treatment of patients with 2L transplant eligible (TE) LBCL. This SLR has been adapted to the current application for Liso-cel in Denmark and is described below.

The SLR was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in alignment with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) guidelines [110, 111].

The following databases and websites of conferences were searched, MEDLINE, Embase, Cochrane CENTRAL (Table 118).

Table 118 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Cochrane CENTRAL	EBM Reviews - Cochrane Central Register of Controlled Trials and EBM Reviews - Cochrane Database of Systematic Reviews	January 2023, 2005 to 28 February 2023	01.03.2023
Embase	Embase	1974 to 27 February 2023	01.03.2023
MEDLINE	Ovid MEDLINE Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily	1946 to 27 February 2023	01.03.2023

In addition, searches at American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Hematology Association (EHA), American

Society of Hematology (ASH), International Conference on Malignant Lymphoma (ICML), American Association for Cancer Research (AACR), European Organisation for Research and Treatment of Cancer (EORTC), and the International Workshop on non-Hodgkin Lymphoma (iwNHL) was done (Table 119). For 2023 update, conference proceedings from 2017 through to present were hand-searched. Grey literature searches were conducted from 2008 onwards. Additionally, bibliographies of on-topic SLRs published from 2015 onwards were reviewed for relevant studies.

Also, grey literature searches were conducted using ClinicalTrials.gov, WHO clinical trials registry, FDA United States Prescribing Information (USPI), EMA EPAR, the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), and bibliographic handsearching of published SLRs.

Table 119 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinical trials.gov	www.clinicaltrials.gov	Grey search	01.03.2023
World Health Organization (WHO)	NA	Grey search in clinical trials registry	01.03.2023
FDA United States	NA	Grey search of Prescribing Information (USPI)	01.03.2023
EMA	www.ema.com	European Public Assessment Reports (EPAR)	01.03.2023
European Union Drug Regulating Authorities	NA	Clinical Trials Database (EudraCT)	01.03.2023

Table 120 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical Oncology (ASCO)	Conference website	Manual hand search	NA	01.03.2023
European Society for Medical	Conference website	Manual hand search	NA	01.03.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Oncology (ESMO)				
European Hematology Association (EHA)	Conference website	Manual hand search	NA	01.03.2023
American Society of Hematology (ASH)	Conference website	Manual hand search	NA	01.03.2023
International Conference on Malignant Lymphoma (ICML)	Conference website	Manual hand search	NA	01.03.2023
American Association for Cancer Research (AACR)	Conference website	Manual hand search	NA	01.03.2023
European Organisation for Research and Treatment of Cancer (EORTC)	Conference website	Manual hand search	NA	01.03.2023
International Workshop on non-Hodgkin Lymphoma (iwNHL)	Conference website	Manual hand search	NA	01.03.2023

H.1.1 Search strategies

The SLR contains reviews conducted from six sequential searches: (1) the original R/R LBCL review in October 2017, (2) an update in April 2019, (3) a 2L-specific update on July 17, 2020, (4) a 2L TE-specific update conducted on June 30, 2021, (5) a 2L TE-specific update conducted on December 1, 2021, and (6) the current 2L TE-specific update conducted on March 1, 2023. The current update conducted in March 2023 was focused on 2L patients who are TE.

The PICOS framework was used to develop research questions and search strategy. The 2L-specific search strategy focused on identifying randomized and non-

randomized/observational clinical evidence pertaining to patients with 2L DLBCL, HGBCL, FL3B, PMBCL, DLBCL transformed from indolent NHL, and R/R DLBCL with secondary CNS lymphoma. Patients of interest were those who had failed 1L therapy and were being treated in 2L. The eligible histologies and treatment line were designed to align with the patients investigated in JCAR017-BCM-003 (TRANSFORM study; NCT03575351). In the most recent updates (March 2023), the geographic scope of the search was not limited by country.

Table 121 Search strategy table for Database(s): Embase, Cochrane CENTRAL and MEDLINE: RCT, Observational Studies, and Reviews, March 2023

No.	Query	Results
1	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf. [DIFFUSE LARGE B-CELL LYMPHOMA]	84463
2	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. [DLBCL-SCNSL-FL3B-HIGH GRADE-PMBCL]	20997
3	1 or 2	97916
4	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. [RELAPSE/REFRACTORY]	6191846
5	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf.	6087
6	(3 and 4) or 5	30945

7	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. [RICHTER-MZL-PCMZL/PCFCL-HAIRY CELL-WM-LOW GRADE]	70472
8	Cell Transformation, Neoplastic/ or transform$.tw,kf. [TRANSFORMATION]	1334260
9	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf.	147577
10	(1 or 9) and 7 and 8	4016
11	6 or 10 [R/R DLBCL OR TRANSFORMED SUBTYPES]	33570
12	randomized controlled trials as topic/ or clinical trials as topic/ or exp randomized controlled trial/ or clinical trial/ or random allocation/ or double blind method/ or single blind method/ or controlled clinical trial/ or cross-over studies/ or placebos/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kf. [RCTs]	7576302
13	11 and 12	9340
14	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ or Non-Randomized Controlled Trials as Topic/ or Controlled Before-After Studies/ or Interrupted Time Series Analysis/ or Historically Controlled Study/ or Control Groups/ or trial.ti. or controlled clinical trial.pt. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT?) or (control$ adj3 ("before and after" or "before after")) or time series or (pre-adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kf. [NON-RANDOMIZED STUDIES]	4927903

15	11 and 14	3099
16	Observational study/ or exp Cohort Studies/ or Retrospective Studies/ or Case-Control Studies/ or Cross-Sectional Studies/ or Registries/ or Comparative Study/ or (cohort? or (longitudinal or prospective or retrospective or Cross-Sectional) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison or noncomparative or non-comparative) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or "single arm" or "real world" or registr$).tw,kf. [OBSERVATIONAL]	1237742 2
17	11 and 16	12382
18	13 or 15 or 17	17478
19	18 use ppez [Medline results]	4337
20	exp Animals/ not (exp Animals/ and Humans/)	1674361 3
21	19 not 20 [ANIMALS-ONLY REMOVED]	4307
22	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	3293280
23	21 not 22 [UNDER 18 REMOVED]	4279
24	(comment or editorial or news or newspaper article or historical article or (letter not (letter and randomized controlled trial))).pt.	4770401
25	23 not 24 [OPINION PIECES REMOVED]	4203
26	limit 25 to dt="20211201-20230131" [Medline results for period 01 Dec 2021 - Current]	464
27	exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	85719
28	(follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or	21419

	primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	
29	27 or 28	99455
30	cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	6131800
31	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	6083
32	(29 and 30) or 31	31747
33	marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	70361
34	cell transformation/ or transform$.tw,kw.	1305215
35	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	146009
36	(27 or 35) and 33 and 34	3941
37	32 or 36	34292
38	clinical trial/ or randomized controlled trial/ or controlled clinical trial/ or clinical trial/ or exp randomization/ or single	8357221

	blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or triple blind procedure/ or prospective study/ or "randomized controlled trial (topic)"/ or "clinical trial (topic)"/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kw.	
39	37 and 38	10241
40	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/ or time series analysis/ or pretest posttest control group design/ or controlled study/ or control group/ or trial.ti. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT$1) or (control$ adj3 ("before and after" or "before after")) or "time series" or (pre- adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kw. [NON-RANDOMISED RCTs]	1372031 1
41	37 and 40	10541
42	cohort analysis/ or retrospective study/ or longitudinal study/ or prospective study/ or follow up/ or family study/ or observational study/ or population research/ or exp comparative study/ or exp case control study/ or cross-sectional study/ or register/ or (cohort? or (longitudinal or prospective or retrospective) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or (cross-section$ or crosssection$) or "single arm" or "real world" or registr$).tw,kw. [OBSERVATIONAL]	1389475 3
43	37 and 42	15536
44	39 or 41 or 43	21728
45	44 use oemezd [Embase results]	16572
46	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	5812271 5
47	exp human/ or exp human experimentation/ or exp human experiment/	4699456 4
48	45 not (2 not 3) [ANIMALS-ONLY REMOVED]	16572

49	(exp adolescent/ not (exp adult/ and exp adolescent/)) or (((exp child/ not (exp adult/ and exp child/)) or fetus/) not (exp adult/ and fetus/))	4343570
50	48 not 49 [UNDER 18 REMOVED]	16299
51	(editorial or note).pt. or (letter.pt. not (randomized controlled trial/ and letter.pt.))	4847217
52	50 not 51 [OPINION PIECES REMOVED]	16053
53	limit 52 to dc="20211201-20230131" [Embase results for period 01 Dec 2021 - Current]	2648
54	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	83910
55	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	20836
56	54 or 55	97359
57	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	6163091
58	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	6083
59	(56 and 57) or 58	30837
60	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-	69970

	associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	
61	Cell Transformation, Neoplastic/ or transform$.tw,kw.	1325819
62	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	146009
63	(54 or 62) and 60 and 61	3965
64	59 or 63	33424
65	exp Animals/ not (exp Animals/ and Humans/)	16743613
66	64 not 65 [ANIMALS-ONLY REMOVED]	27121
67	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	3293280
68	66 not 67 [UNDER 18 REMOVED]	26832
69	68 use cctr [CENTRAL RECORDS]	1376
70	("202111*" or "202112*" or "2022*" or "2023*").up.	40473196
71	69 and 70 [CENTRAL results for period 01 Nov 2021 - Current]	1376
72	26 or 53 or 71 [MEDLINE, Embase and CENTRAL results - Update Period]	4488
73	limit 72 to yr="2021-current" [Limit all results to 2021 - Current publication date]	3215
74	**remove duplicates from 73 [RCTs and Observational Studies - results]**	**2343**

75	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf. [DIFFUSE LARGE B-CELL LYMPHOMA]	84463
76	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. [DLBCL-SCNSL-FL3B-HIGH GRADE-PMBCL]	20997
77	75 or 76	97916
78	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. [RELAPSE/REFRACTORY]	6191846
79	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf.	6087
80	(77 and 78) or 79	30945
81	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or	70472

	"transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. [RICHTER-MZL-PCMZL/PCFCL-HAIRY CELL-WM-LOW GRADE]	
82	Cell Transformation, Neoplastic/ or transform$.tw,kf. [TRANSFORMATION]	1334260
83	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf.	147577
84	(75 or 83) and 81 and 82	4016
85	80 or 84 [R/R DLBCL OR TRANSFORMED SUBTYPES]	33570
86	exp systematic reviews as topic/ or exp meta-analysis as topic/ or exp Technology assessment, biomedical/ or (systematic review or meta analysis).pt. or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy$ or metanaly$ or metaanaly$ or met analy$ or integrative research or integrative review$ or integrative overview$ or research integration or research overview$ or collaborative review$ or (systematic review$ or systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence adj3 (review$ or overview$)) or meta-review$ or meta-overview$ or meta-synthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs) or (network adj (meta-analy$ or metanaly$ or metaanaly$ or met analy$)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kf. [SRs/NMAs/MAs]	1242929
87	85 and 86	565
88	87 use ppez [Medline results]	175
89	exp Animals/ not (exp Animals/ and Humans/)	16743613
90	88 not 89 [ANIMALS-ONLY REMOVED]	175
91	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	3293280
92	90 not 91 [UNDER 18 REMOVED]	174
93	(comment or editorial or news or newspaper article or historical article or (letter not (letter and randomized controlled trial))).pt.	4770401

94	92 not 93 [OPINION PIECES REMOVED]	172
95	limit 94 to dt="20211201-20230131" [Medline results for period 01 Dec 2021 - Current]	42
96	exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	85719
97	(follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	21419
98	96 or 97	99455
99	cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	6131800
100	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	6083
101	(98 and 99) or 100	31747
102	marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or	70361

	((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	
103	cell transformation/ or transform$.tw,kw.	1305215
104	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	146009
105	(96 or 104) and 102 and 103	3941
106	101 or 105	34292
107	systematic review/ or "systematic review (topic)"/ or meta analysis/ or "meta analysis (topic)"/ or biomedical technology assessment/ or network meta-analysis/ or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy$ or metanaly$ or metaanaly$ or met analy$ or integrative research or integrative review$ or integrative overview$ or research integration or research overview$ or collaborative review$ or (systematic review$ or systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence adj3 (review$ or overview$)) or meta-review$ or meta-overview$ or meta-synthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs) or (network adj (meta-analy$ or metanaly$ or metaanaly$ or met analy$)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kw. [SRs/NMAs/MAs]	1366307
108	106 and 107	734
109	108 use oemezd [Embase results]	546
110	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	58122715
111	exp human/ or exp human experimentation/ or exp human experiment/	46994564
112	109 not (110 not 111) [ANIMALS-ONLY REMOVED]	542

113	(exp adolescent/ not (exp adult/ and exp adolescent/)) or (((exp child/ not (exp adult/ and exp child/)) or fetus/) not (exp adult/ and fetus/))	4343570
114	112 not 113 [UNDER 18 REMOVED]	538
115	(editorial or note).pt. or (letter.pt. not (randomized controlled trial/ and letter.pt.))	4847217
116	114 not 115 [OPINION PIECES REMOVED]	532
117	limit 116 to dc="20211201-20230131" [Embase results for period 01 Dec 2021 - Current]	128
118	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	83910
119	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	20836
120	118 or 119	97359
121	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (secondline$ or second-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	6163091
122	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	6083
123	(120 and 121) or 122	30837
124	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-	69970

	associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	
125	Cell Transformation, Neoplastic/ or transform$.tw,kw.	1325819
126	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	146009
127	(118 or 126) and 124 and 125	3965
128	123 or 127	33424
129	exp Animals/ not (exp Animals/ and Humans/)	16743613
130	128 not 129 [ANIMALS-ONLY REMOVED]	27121
131	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	3293280
132	130 not 131 [UNDER 18 REMOVED]	26832
133	132 use coch [Cochrane CDSR results]	4
134	("202111*" or "202112*" or "2022*" or "2023*").up.	40473196
135	133 and 134 [Cochrane CDSR results for period 01 Nov 2021-Current]	2
136	95 or 117 or 135 [Medline, Embase and Cochrane CDSR results for period]	172
137	limit 136 to yr="2021-current" [Limit all results to 2021 - Current publication date]	167
138	**remove duplicates from 137 [Reviews - All results]**	**123**

139	**74 or 138 [All results]**	**2369**
140	**remove duplicates from 139**	**2368**

H.1.2 Systematic selection of studies

Data extraction was performed using a standardized form implemented in Microsoft Excel. For each study, one reviewer extracted all information required for the review and a second researcher performed independent verification of this information. The data gathered included information regarding the following:

- Publication characteristics (including citation data, trial identifying information, year, study sponsor, objective)
- Study setting (including countries, centers/hospitals)
- Study methods (including design, duration, follow-up length, patient enrollment criteria, interventions administered, randomization details, blinding details, concomitant therapies allowed, outcomes assessed, approach to statistical analysis)
- Study participants (including participant flow information and important demographics such as time from diagnosis, prior lines of therapy, age, sex, DLBCL histology, disease stage at baseline [e.g., Ann Arbor status])
- Study findings (including OS, PFS, event-free survival [EFS], treatment response, and safety outcomes)

The quality of published trials was assessed using the checklist recommended by the National Institute for Health and Care Excellence (NICE) [112]. For single-arm trials and observational studies, the Downs and Black checklist was used [113].

Studies were screened based on PICOS criteria established *a priori* (Table 122) and were assessed by two independent reviewers; conflicts were resolved by consensus and/or a third reviewer.

Study screening of the database search was conducted in two stages in DistillerSR Inc: (1) review of titles and abstracts, and (2) review of full-text articles. Exclusion reasons were recorded in detail during the full-text screening stage. Searches for grey literature including conference abstracts, and hand-searches of bibliographies of published SLR were conducted by a single reviewer and verified by a second reviewer.

Randomized and non-randomized studies, including retrospective studies, were eligible if they included 2L TE patients with DLBCL, HGBCL, FL3B, PMBCL, DLBCL transformed from indolent NHL, and/or R/R DLBCL with secondary CNS lymphoma. The minimum population size was ≥25 patients by treatment arm (or ≥50 patients per study). Studies that did not report any 2L-specific outcomes or had <25 patients in 2L were excluded in the 2020 search; however, the 2021 searches applied a new criterion that mixed-line studies (ie, 2L+) could be included if the median number of prior treatment lines was one, regardless of whether there were 2L-specific subgroup results. Finally, only English-language studies were eligible for inclusion.

Table 122 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients Relapsed or refractory Second line ('2L') Secondary CNS lymphoma Eligible for HSCT One of the following NHL subtypes: • DLBCL NOS, or • DLBCL tFL, or • DLBCL tiNHLs, or • FL3B, or • HGL, with MYC and BCL2 and/or BCL6 translocations with DLBCL histology, or • PMBCL, or • THRBCL	Patients aged <18 years Any line of therapy not inclusive of second line All other lymphoma types Primary CNS lymphoma Ineligible for HSCT
Intervention	Therapies: • Single-agent or multiagent chemotherapy • Chemoimmunotherapy • Single-agent or multiagent immunotherapy • CAR T-cell therapies • Allo-HSCT • Auto-HSCT Treatment concepts: • Salvage therapy • Best supportive care • Placebo • No comparator	Those not listed
Comparators	Therapies: • Single-agent or multiagent chemotherapy • Chemoimmunotherapy	Those not listed

	• Single-agent or multiagent immunotherapy • CAR T-cell therapies • Allo-HSCT • Auto-HSCT Treatment concepts: • Salvage therapy • Best supportive care • Placebo No comparator	
Outcomes	Response endpoints: ORR, CR, PR, SDi, PD, DOR Survival endpoints: OS, PFS, EFS AEs: withdrawals (e.g., withdrawals, withdrawals due to AEs, withdrawals due to death and withdrawals due to lack of efficacy), neurotoxicity, CRS, hematologic events (e.g., neutropenia, lymphopenia, leukopenia, thrombocytopenia, anemia, pancytopenia, febrile neutropenia), infections, treatment-related deaths, TLS	None
Study design/publication type	RCTs Non-randomized studies, observational studies (e.g., RWE, registry, retrospective cohort study, cross-sectional, case-control, single-arm studies) Minimum sample size by treatment arm: ≥25 patients (or ≥50 patients per study) Studies published in 2003 or later Conference abstracts (2017 onwards)	Animal studies, *in vitro* studies, case reports, expert opinion articles, commentaries, letters Articles published prior to 2003 Conference abstracts published prior to 2017
Language restrictions	English	All other language

The searches conducted on October 2017 and April 2019, respectively, included R/R LBCL patients regardless of treatment line. As of the April 2019 update, the database search identified 9,144 records, plus an additional four records identified through searches of ASCO, EHA, and ASH conference websites. After removing duplicates, 8,683 records were

screened at the title and abstract stage and of these, 8,056 records were excluded. Full texts of the remaining 627 records were obtained and assessed for eligibility. Five additional records were identified through reviews of reference lists and supplementary searches. Finally, a total of 104 records describing 78 unique studies were included as of the April 2019 update.

The search update performed on July 17, 2020 narrowed the target population to 2L patients. This search identified an additional 3,521 records for screening. Of these, 3,012 were excluded at the title and abstract phase. The full texts of the remaining 509 records were obtained and assessed for eligibility. Additionally, the 104 records included in the April 2019 search were re-screened at the full-text level for eligibility in the 2L-specific update. Additional records were identified through a hand search of bibliographies of existing systematic reviews (n = 2), as well as clinical guidelines (n = 5), and grey literature including conference abstracts and trial registries (n = 597). In total, 68 records were identified as eligible, representing 55 unique studies. Of the 55 studies, 39 were in the TE population.

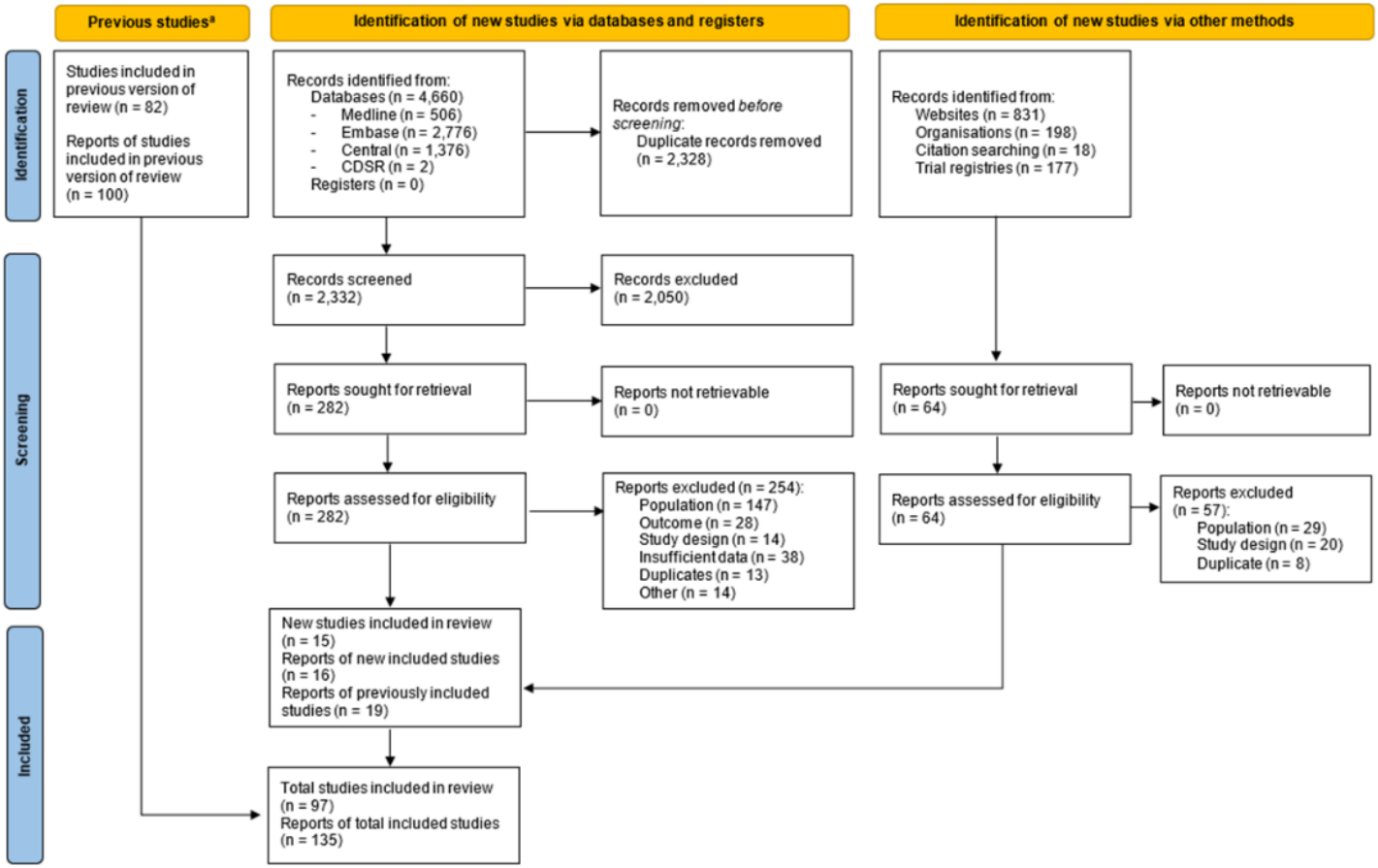
The search update performed on June 30, 2021 further narrowed the target population to 2L TE patients, and identified an additional 2,143 records for screening. Of these, 1,796 were excluded at the title and abstract phase, 347 were assessed at the full-text level, and 13 were ultimately included. Additionally, 17 studies (21 records) were identified for inclusion through re-screening the studies excluded at the full-text level during the 2017 and 2019 searches. A hand-search of bibliographies of existing systematic reviews identified one record representing one study, and a search of conference abstracts and trial registries identified a further seven records representing four studies for inclusion. Forty-two new records were identified for inclusion, of which 36 reported on 32 new unique studies, and 6 reported on previously included studies. A total of 87 records representing 71 unique studies were included as of the June 30, 2021 update.

The search update performed on December 1, 2021 identified an additional 936 records for screening. Of these, 784 were excluded at the title and abstract phase and two were not available for retrieval. One-hundred and fifty records were assessed at the full-text level and six were ultimately included. A hand-search of bibliographies of recent systematic reviews and a search of conference abstracts and trial registries identified seven additional records for inclusion. Thirteen new records were included, representing 11 new studies. A total of 100 records representing 82 unique studies were included as of the December 1, 2021 update.

The present search update was performed on March 1, 2023. An additional 2,332 records from the database search were identified for screening. Of these, 2,050 were excluded at the title and abstract phase, 282 were assessed at the full-text level, 253 were excluded and 29 were ultimately included.

A hand-search of bibliographies of recent systematic reviews and a search of conference abstracts and trial registries identified 7 additional records for inclusion. Thirty-five new records were included, representing 15 new studies. Overall, a total of 135 records representing 97 unique studies are included in this SLR (Figure 78).

Figure 77 PRISMA Flow diagram



Of the 97 unique studies identified, 25 were clinical trials (eight were RCTs, two were non-randomized controlled trials with two treatment arms, 14 were single-arm trials, and one was a post-hoc analysis of two RCTs), and 72 were observational studies (7 prospective, 63 retrospective, 2 unspecified).

Three studies investigated CAR T-cell therapies and 21 studies investigated SoC.

The focus in this assessment is the investigated CAR T-cell therapies [114-116] (Table 123). As the relevant comparator to liso-cel in Denmark is axi-cel, the SLR identifed TRANSFORM and ZUMA-7 as a key data source for evaluating the efficacy and safety of 2L TE LBCL patients. An indirect treatment comparison (ITC) was performed to assess the relative efficacy of liso-cel (TRANSFORM) and axi-cel (ZUMA-7) (see further section 7.1).

Table 123 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
TRANSFORM NCT03575351	Compare safety and efficacy between the SoC followed by autologous stem cell transplantation strategy versus liso-cel	RCT, open-labela, multicenter	Adult subjects with R/R LBCL	Liso-cel (n=92) and SoC (R-DHAP, R-ICE, or R-GDP + HDT + Auto-HSCT (n=92)) Total n=184	EFS (17.53 months)	OS, PFS, PFS2, ORR, CRR, DOR, AEs, HRQoL (17.53 months)
ZUMA-7 NCT03391466	Assess whether axi-cel therapy improves the clinical outcome compared with standard of care	RCT, multicenter	Second-line therapy in patients with R/R DLBCL	Axi-cel (n=180) and SoC (R-GDP, R-DHAP, R-ICE or R-ESHAP + HDT + Auto-HSCT (n=179)) Total n= 359	EFS (24.9 months)	OS, PFS ORR, DOR, HRQoL, AEs (24.9 months)

H.1.3 Excluded fulltext references

Studies Excluded at the Full-Text Review Stage. Of the 359 studies reviewed at the full-text stage, 311 studies were excluded for the following reasons: Population: n = 176, Outcome: n = 28, Study design: n = 34, Incomplete data: n = 38, Duplicate citation: n = 21, Other: n = 14.

Excluded due to population (n = 176)

Phase 2 Study of Plamotamab Combined With Tafasitamab Plus Lenalidomide Versus Tafasitamab Plus Lenalidomide in R/R DLBCL. A Phase 2 Randomized, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of XmAb13676 (Plamotamab) Combined With Tafasitamab Plus Lenalidomide Versus Tafasitamab Plus Lenalidomide in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. 2022. #volume#:#pages#

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H.1.4 Quality assessment

The conduct of this review was based on best practices, including the use of the PICOS question design, a comprehensive database literature search as well as supplementary searches of bibliographies and grey literature, a standardized approach to study selection and data extraction, and a rigorous quality assessment process.

The quality of the published CAR-T trials was assessed using the checklist recommended by the National Institute for Health and Care Excellence (NICE) [112]. Quality assessments were conducted by a single reviewer and validated by a second reviewer. Conflicts were resolved by a third reviewer when the two reviewers did not reach an agreement. BELINDA and ZUMA-7 provided clear evidence of appropriate randomization and evidence of selective outcome reporting was found. In all the three CAR-T trials, imbalances in dropouts between groups were apparent and all full-text RCTs was conducted an intention-to-treat analysis. [49, 114-116]

H.1.5 Unpublished data

NA

H.2 Efficacy and safety of the intervention and comparator(s) in 3L+ R/R LBCL

The objective of the SLR was to characterize the clinical evidence for the treatment of patients with R/R LBCL after at least two prior lines of therapy through a qualitative synthesis of studies investigating therapies used in the third or later line of therapy (3L+) R/R LBCL setting.

A global literature search was performed to identify randomized controlled trials (RCTs) and non-randomized studies published between 01 Jan 2003 and 08 February 2021. This SLR has been adapted to the current application and is described below.

The SLR was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in alignment with the PRISMA guidelines.

The following databases and websites of conferences were searched, MEDLINE, Embase, Cochrane CENTRAL (Table 124).

Table 124 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Cochrane CENTRAL	EBM Reviews - Cochrane Central Register of Controlled Trials and	December 2020	08.02.2021
Embase	Embase	1974 to 04 February 2021	08.02.2021
MEDLINE	Ovid MEDLINE Epub Ahead of Print, In-Process, In-Data-Review & Other Non-	1946 to 04 February 2021	08.02.2021

Indexed Citations and Daily

In addition, searches at ASCO, ESMO, EHA, ASH, ICML, AACR, EORTC and the iwNHL was done The Conference proceedings from 2016 through to 2020 were hand searched, including the ASH annual conferences held on 07-10 December 2019 and 05-08 December 2020, the AACR annual conference held on 24-29 April 2020, the ASCO annual conference held on 29-31 May 2020, and the EHA annual conference held on 10-21 June 2020 (Table 125).

Also, grey literature searches were conducted using ClinicalTrials.gov, WHO clinical trials registry, FDA USPI, EMA EPAR, EudraCT, and bibliographic handsearching of published SLRs (Table 126).

Table 125 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinical trials.gov	www.clinicaltrials.gov	Grey search	08.02.2021
World Health Organization (WHO)	NA	Grey search in clinical trials registry	08.02.2021
FDA United States	NA	Grey search of Prescribing Information (USPI)	08.02.2021
EMA	www.ema.com	European Public Assessment Reports (EPAR)	08.02.2021
European Union Drug Regulating Authorities	NA	Clinical Trials Database (EudraCT)	08.02.2021

Table 126 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical	Conference website	Manual search according to PICO	NA	08.02.2021

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Oncology (ASCO)		inclusion and exclusion criteria		
European Society for Medical Oncology (ESMO)	Conference website	Manual search according to PICO inclusion and exclusion criteria	NA	08.02.2021
European Hematology Association (EHA)	Conference website	Manual search according to PICO inclusion and exclusion criteria	NA	08.02.2021
American Society of Hematology (ASH)	Conference website	Manual search according to PICO inclusion and exclusion criteria	NA	08.02.2021
International Conference on Malignant Lymphoma (ICML)	Conference website	Manual search according to PICO inclusion and exclusion criteria	NA	08.02.2021
American Association for Cancer Research (AACR)	Conference website	Manual search according to PICO inclusion and exclusion criteria	NA	08.02.2021
European Organisation for Research and Treatment of Cancer (EORTC)	Conference website	Manual search according to PICO inclusion and exclusion criteria	NA	08.02.2021
International Workshop on non-Hodgkin Lymphoma (iwNHL)	Conference website	Manual search according to PICO inclusion and exclusion criteria	NA	08.02.2021

H.2.1 Search strategies

The review was conducted in two stages: (1) an original review in Apr 2019, and (2) updates covering the period between April 2019 and 08 February 2021; with an initial update search run in December 2019, and subsequent updates run in June 2020 and

February 2021. In the 08 February 2021 update of the review, the scope of the search was narrowed and included 3L+ R/R patients only, where the original review also included 2L patients.

The Population, Intervention, Comparator, Outcome, Study (PICOS) framework was used to develop the research questions and search strategy. The search strategy focused on identifying randomized and non- randomized/observational clinical evidence within the 3L+ R/R DLBCL, FL3B, PMBCL, DLBCL transformed from indolent NHL (ie, originated from FL, MZL, CLL, primary cutaneous follicle center lymphoma [PCFCL], primary cutaneous marginal zone lymphoma [PCMZL], hairy cell leukemia, WM), and R/R DLBCL with secondary CNS lymphoma patient populations. These patient populations are consistent with the patients investigated in TRANSCEND. Patients of interest were those who had failed two or more prior therapies.

The geographic scope of this review focused on regions with a large research presence and where BMS is planning to submit to local health technology assessment (HTA) agencies for reimbursement: Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, The Netherlands, Norway, Spain, Sweden, Switzerland, the United Kingdom (UK), and the US.

Table 127 Search strategy table for Database(s): Embase, Cochrane CENTRAL and MEDLINE: RCTs, non-RCTs, Observational, February 2021

No.	Query	Results
1	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf. [DIFFUSE LARGE B-CELL LYMPHOMA]	68307
2	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. [DLBCL-SCNSL-FL3B-HIGH GRADE-PMBCL]	17252
3	1 or 2	79895

4	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. [RELAPSE/REFRACTORY]	5549830
5	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf.	3879
6	(3 and 4) or 5	23522
7	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. [RICHTER-MZL-PCMZL/PCFCL-HAIRY CELL-WM-LOW GRADE]	62677
8	Cell Transformation, Neoplastic/ or transform$.tw,kf. [TRANSFORMATION]	1162387
9	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf.	123241
10	(1 or 9) and 7 and 8	3150
11	6 or 10 [R/R DLBCL OR TRANSFORMED SUBTYPES]	25698

12	randomized controlled trials as topic/ or clinical trials as topic/ or exp randomized controlled trial/ or clinical trial/ or random allocation/ or double blind method/ or single blind method/ or controlled clinical trial/ or cross-over studies/ or placebos/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kf. [RCTs]	6679126
13	11 and 12	6772
14	Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ or Non-Randomized Controlled Trials as Topic/ or Controlled Before-After Studies/ or Interrupted Time Series Analysis/ or Historically Controlled Study/ or Control Groups/ or trial.ti. or controlled clinical trial.pt. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT?) or (control$ adj3 ("before and after" or "before after")) or time series or (pre- adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kf. [NON-RANDOMIZED STUDIES]	4534015
15	11 and 14	2576
16	Observational study/ or exp Cohort Studies/ or Retrospective Studies/ or Case-Control Studies/ or Cross-Sectional Studies/ or Registries/ or Comparative Study/ or (cohort? or (longitudinal or prospective or retrospective or Cross-Sectional) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison or noncomparative or non-comparative) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or "single arm" or "real world" or registr$).tw,kf. [OBSERVATIONAL]	10438101
17	11 and 16	8576
18	13 or 15 or 17	12535
19	exp Animals/ not (exp Animals/ and Humans/)	18013750
20	18 not 19 [ANIMALS-ONLY REMOVED]	8806

21	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	2950668
22	20 not 21 [UNDER 18 REMOVED]	8740
23	(comment or editorial or news or newspaper article or historical article or (letter not (letter and randomized controlled trial))).pt.	4322183
24	22 not 23 [OPINION PIECES REMOVED]	8659
25	24 use ppez [Medline results]	3396
26	limit 25 to dt="20200609-20211231"	194
27	**limit 26 to yr="2020 -Current" [Medline results for period 09 June 2020 - Current]**	**191**
28	exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	70174
29	(follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	17912
30	28 or 29	82085
31	cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$")	5543399

	or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	
32	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	3880
33	(30 and 31) or 32	24357
34	marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	63407
35	cell transformation/ or transform$.tw,kw.	1137177
36	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	123805
37	(28 or 36) and 34 and 35	3140
38	33 or 37	26503
39	clinical trial/ or randomized controlled trial/ or controlled clinical trial/ or clinical trial/ or exp randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or triple blind procedure/ or prospective study/ or "randomized controlled trial (topic)"/ or "clinical trial (topic)"/ or trial.ti. or (randomi#ed or randomi#ation? or randomly or RCT or placebo$ or "crossover procedure" or double-blind$ or "prospective study" or ((controlled or clinical) adj3 (trial? or stud$)) or	7333903

	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dumm$))).tw,kw.	
40	38 and 39	7589
41	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/ or time series analysis/ or pretest posttest control group design/ or controlled study/ or control group/ or trial.ti. or ((control$ adj2 trial$) or (nonrandom$ or non-random$ or quasi-random$ or quasi-experiment$) or (nRCT or nRCTs or non-RCT$1) or (control$ adj3 ("before and after" or "before after")) or "time series" or (pre- adj3 post-) or (pretest adj3 posttest) or (control$ adj2 stud$3) or (control$ adj2 group$1)).tw,kw. [NON-RANDOMISED - NCTs]	11612315
42	38 and 41	6952
43	cohort analysis/ or retrospective study/ or longitudinal study/ or prospective study/ or follow up/ or family study/ or observational study/ or population research/ or exp comparative study/ or exp case control study/ or cross-sectional study/ or register/ or (cohort? or (longitudinal or prospective or retrospective) or ((followup or follow-up) adj (study or studies)) or (observation$2 adj (study or studies)) or ((population or population-based) adj (study or studies or analys#s)) or ((multidimensional or multi-dimensional) adj (study or studies)) or ((comparative or comparison) adj (study or studies)) or ((case-control$ or case-based or case-comparison) adj (study or studies)) or (cross-section$ or crosssection$) or "single arm" or "real world" or registr$).tw,kw. [OBSERVATIONAL]	11807289
44	38 and 43	11030
45	40 or 42 or 44	15869
46	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	51932847
47	exp human/ or exp human experimentation/ or exp human experiment/	41589256
48	45 not (2 not 3) [ANIMALS-ONLY REMOVED]	15869
49	(exp adolescent/ not (exp adult/ and exp adolescent/)) or (((exp child/ not (exp adult/ and exp child/)) or fetus/) not (exp adult/ and fetus/))	3893974

50	48 not 49 [UNDER 18 REMOVED]	15573
51	(editorial or note).pt. or (letter.pt. not (randomized controlled trial/ and letter.pt.))	4362234
52	50 not 51 [OPINION PIECES REMOVED]	15390
53	52 use oemezd [Embase results]	10945
54	limit 53 to dc="20200609-20211231"	855
55	**limit 54 to yr="2020 -Current" [Embase results for period 09 June 2020 - Current]**	**770**
56	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	68494
57	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	17306
58	56 or 57	80082
59	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	5576251

60	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	3880
61	(58 and 59) or 60	23590
62	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	62966
63	Cell Transformation, Neoplastic/ or transform$.tw,kw.	1168855
64	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	123805
65	(56 or 64) and 62 and 63	3175
66	61 or 65	25788
67	exp Animals/ not (exp Animals/ and Humans/)	18013750
68	66 not 67 [ANIMALS-ONLY REMOVED]	18034
69	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	2950668
70	68 not 69 [UNDER 18 REMOVED]	17837
71	70 use cctr	1595
72	(("202006*" not ("20200601" or "20200602" or "20200603" or "20200604" or "20200605" or "20200606"	4604793

	or "20200607" or "20200608")) or 202007* or 202008* or 202009* or 202010* or 202011* or 202012* or 2021*).up.	
73	**71 and 72 [Central results for period 09 June 2020 - Current]**	**147**
74	**27 or 55 or 73 [Medline, Embase and Central results for period 09 June 2020 - Current]**	**1108**

Table 128 Search strategy table for Database(s): Embase, Cochrane CENTRAL and MEDLINE: Reviews, February 2021

No.	Query	Results
1	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf. [DIFFUSE LARGE B-CELL LYMPHOMA]	66488
2	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf. [DLBCL-SCNSL-FL3B-HIGH GRADE-PMBCL]	16470
3	1 or 2	77568
4	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf. [RELAPSE/REFRACTORY]	5129169

5	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf.	3502
6	(3 and 4) or 5	21968
7	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf. [RICHTER-MZL-PCMZL/PCFCL-HAIRY CELL-WM-LOW GRADE]	61254
8	Cell Transformation, Neoplastic/ or transform$.tw,kf. [TRANSFORMATION]	1153740
9	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf.	119526
10	(1 or 9) and 7 and 8	3048
11	6 or 10 [R/R DLBCL OR TRANSFORMED SUBTYPES]	24121
12	exp systematic reviews as topic/ or exp meta-analysis as topic/ or exp Technology assessment, biomedical/ or (systematic review or meta analysis).pt. or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy$ or metanaly$ or metaanaly$ or met analy$ or integrative research or integrative review$ or integrative overview$ or research integration or research overview$ or collaborative review$ or (systematic review$ or systematic overview$ or evidence-based review$ or evidence-based overview$ or	931878

	(evidence adj3 (review$ or overview$)) or meta-review$ or meta-overview$ or meta-synthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs) or (network adj (meta-analy$ or metanaly$ or metaanaly$ or met analy$)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kf. [SRs/NMAs/MAs]	
13	11 and 12	325
14	exp Animals/ not (exp Animals/ and Humans/)	18066804
15	13 not 14 [ANIMALS-ONLY REMOVED]	219
16	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	2914095
17	15 not 16 [UNDER 18 REMOVED]	219
18	(comment or editorial or news or newspaper article or historical article or (letter not (letter and randomized controlled trial))).pt.	4317835
19	17 not 18 [OPINION PIECES REMOVED]	218
20	19 use ppez [Medline results]	104
21	limit 20 to dt="20200609-20211231" [Limit not valid in CDSR,Embase; records were retained]	10
22	limit 21 to yr="2020 -Current" [Medline results for period 09 June 2020 - Current]	10
23	exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	68355
24	(follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or	17132

	NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	
25	23 or 24	79761
26	cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	5113621
27	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	3503
28	(25 and 26) or 27	22790
29	marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	61968
30	cell transformation/ or transform$.tw,kw.	1127716

31	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	119959
32	(23 or 31) and 29 and 30	3037
33	28 or 32	24912
34	systematic review/ or "systematic review (topic)"/ or meta analysis/ or "meta analysis (topic)"/ or biomedical technology assessment/ or network meta-analysis/ or (cochrane or health technology assessment or evidence report or systematic reviews).jw. or (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review* or (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or umbrella review? or technology assessment* or HTA or HTAs) or (network adj (meta-analy* or metanaly* or metaanaly* or met analy*)) or (network adj (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs) or indirect* compar* or (indirect treatment* adj1 compar*) or (mixed treatment* adj1 compar*) or (multiple treatment* adj1 compar*) or (multi-treatment* adj1 compar*) or simultaneous* compar* or mixed comparison?).tw,kw. [SRs/NMAs/MAs]	1018435
35	33 and 34	432
36	exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/	51342612
37	exp human/ or exp human experimentation/ or exp human experiment/	40995314
38	35 not (2 not 3) [ANIMALS-ONLY REMOVED]	432
39	(exp adolescent/ not (exp adult/ and exp adolescent/)) or (((exp child/ not (exp adult/ and exp child/)) or fetus/) not (exp adult/ and fetus/))	3849754
40	38 not 39 [UNDER 18 REMOVED]	430
41	(editorial or note).pt. or (letter.pt. not (randomized controlled trial/ and letter.pt.))	4355502

42	40 not 41 [OPINION PIECES REMOVED]	426
43	42 use oemezd [Embase results]	322
44	limit 43 to dc="20200609-20211231" [Limit not valid in CDSR; records were retained]	39
45	limit 44 to yr="2020-Current" [Embase results for period 09 June 2020 - Current]	37
46	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	66657
47	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	16524
48	46 or 47	77741
49	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	5145848
50	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	3503
51	(48 and 49) or 50	22016

52	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	61515
53	Cell Transformation, Neoplastic/ or transform$.tw,kw.	1159333
54	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	119959
55	(46 or 54) and 52 and 53	3072
56	51 or 55	24191
57	exp Animals/ not (exp Animals/ and Humans/)	18066804
58	56 not 57 [ANIMALS-ONLY REMOVED]	16403
59	((exp Child/ not (exp Adult/ or Adolescent/)) or exp Infant/) not (exp Adult/ or Adolescent/)	2914095
60	58 not 59 [UNDER 18 REMOVED]	16212
61	60 use coch [Cochrane SLR results]	4
62	61 and (("202006*" not ("20200601" or "20200602" or "20200603" or "20200604" or "20200605" or "20200606" or "20200607" or "20200608")) or 202007* or 202008* or 202009* or 202010* or 202011* or 202012* or 2021*).up.	0
63	limit 62 to yr="2020-Current" [Cochrane SLR results for period 09 June 2020 - Current]	0

64	22 or 45 or 63 [Medline, Embase and Cochrane SLR results 47 for period 09 June 2020 - Current]

H.2.2 Systematic selection of studies

Data extraction for each study was performed using a standardized form implemented in Microsoft Excel. For each study, one reviewer extracted all information required for the review and a second reviewer performed independent verification of this information. The data gathered included information regarding the following:

- Publication characteristics (citation data, trial identifying information, year, study sponsor, objective)
- Study setting (countries, centers/hospitals)
- Study methods (design, duration, follow-up length, patient enrollment criteria, interventions administered, randomization details, blinding details, concomitant therapies allowed, outcomes assessed, approach to statistical analysis)
- Study participants (including participant flow information and important demographics such as time from diagnosis, prior lines of therapy, age, sex, DLBCL histology, baseline Ann Arbor status)
- Study findings (including OS, PFS, EFS, treatment response, safety outcomes, and QoL)

DigitizeIt digiting software was used to gather information reported only within the figures of a study publication, where possible. One reviewer extracted the data from the publications and a second reviewer independently reviewed extracted data for accuracy and completeness.

Study screening was conducted in two stages in DistillerSR. In the first stage, titles/abstracts retrieved from the electronic literature search were screened to identify potentially relevant citations according to the a priori eligibility criteria. In the second stage, the full-text articles of the citations deemed potentially eligible were acquired for further review against the study selection criteria to confirm the final set of included studies. Reasons for exclusion of publications were recorded. Potentially eligible studies were screened by two independent reviewers. Conflicts were resolved by consensus through discussion or a third reviewer.

Studies were eligible for inclusion based on PICOS criteria established *a priori* (Table 129). These inclusion criteria were designed to match the TRANSCEND clinical trial population as closely as possible and align with the target population for lisocabtagene maraleucel.

Randomized and non-randomized studies, including retrospective studies, were eligible if they included patients with 3L+ R/R DLBCL, FL3B, PMBCL, DLBCL transformed from indolent NHL (i.e., originated from FL, MZL, CLL, PCFCL, PCMZL, hairy cell leukemia, WM), and R/R DLBCL with secondary CNS lymphoma who were pretreated with both an anthracycline-containing regimen and a rituximab (or other CD20-targeted agent)-

containing regimen, or with autologous hematopoietic stem-cell transplant (auto-HSCT) in any previous line of therapy. Studies had to have ≥25 patients by treatment arm (or ≥50 patients per study). Studies including second-line populations were included if a subgroup of patients with 3L+ LBCL was identified, or at least 65% of the study population had 3L+ disease.

Searches for grey literature and conference abstracts and hand searches of published SLRs were conducted by a single reviewer and verified by a second reviewer. Conflicts were resolved by a third reviewer when the two reviewers did not reach an agreement.

Table 129 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients Relapsed or refractory Third and later line ('3L+') Secondary CNS lymphoma One of the following NHL subtypes: • DLBCL NOS, or • DLBCL tFL, or • DLBCL tiNHLs, including o tCLL (Richter's syndrome/transformation) tMZL, tPCMZL, tPCFCL • Hairy cell leukemia • Waldenström Macroglobulinemia • Other low grade/indolent lymphomas • FL3B, or • HGL, with MYC and BCL2 and/or BCL6 translocations with DLBCL histology, or • PMBCL, Patients treated with both an anthracycline-containing regimen and rituximab (or other CD20-targeted agent)-containing regimen or with auto-HSCT in any previous line of therapy.	Patients aged <18 years old All other lymphoma types Second-line patients (TE and NTE) Patients not previously treated with rituximab (or other CD20-targeted agent)-containing regimens in previous lines of therapy Primary CNS lymphoma
Intervention	Therapies: • Single-agent or multiagent chemotherapy	Those not listed

	• Chemoimmunotherapy • Single-agent or multiagent immunotherapy • CAR T-cell therapies • Allo-HSCT • Auto-HSCT Treatment concepts: • Salvage therapy • Best supportive care • Placebo • No comparator	
Comparators	Therapies: • Single-agent or multiagent chemotherapy • Chemoimmunotherapy • Single-agent or multiagent immunotherapy • CAR T-cell therapies • Allo-HSCT • Auto-HSCT Treatment concepts: • Salvage therapy • Best supportive care • Placebo No comparator	Those not listed
Outcomes	Response endpoints (ORR, CR, PR, SDi, PD, DOR) Survival endpoints (OS, PFS, EFS) Subsequent HSCT after treatment AEs (withdrawals [eg, withdrawals, withdrawals due to AEs, withdrawals due to death and withdrawals due to lack of efficacy], neurotoxicity (for any therapy), CRS, hematologic events [eg, neutropenia, lymphopenia, leukopenia, thrombocytopenia, anemia, pancytopenia, febrile neutropenia], infections, treatment-related deaths)	None

	Patient-reported outcomes & QoL/utilities	
Study Design	RCTs, non-randomized studies, (eg, RWE, registry, retrospective cohort study, cross-sectional, case-control, single-arm studies) Minimum sample size by treatment arm: ≥25 patients (or ≥50 patients per study) Studies published in 2003 to 08 February 2021* Studies conducted in one or more of the following countries: Belgium, the Netherlands, Switzerland, Denmark, Finland, Norway, Sweden, Germany, France, Italy, Spain, the UK, the US, Japan, Australia, and Canada Conference abstracts (2016 onwards)	Animal studies, *in vitro* studies, case reports, expert opinion articles, commentaries, letters Articles published prior to 2003
Language	Articles in English, French, German, Italian, Spanish, Japanese, Danish, Finnish, Norwegian, or Swedish language articles	All other

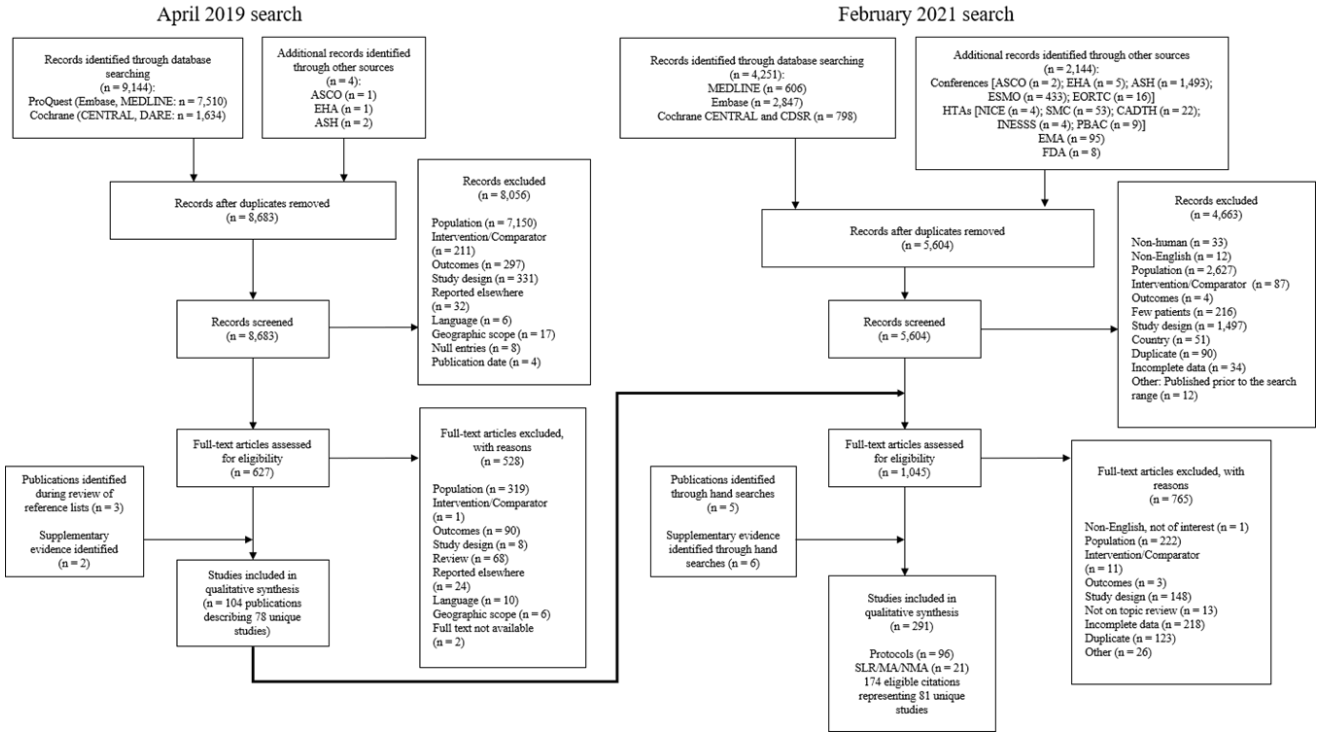
*Original search Apr 2019, with updates run in December 2019, June 2020, and February 2021.

The April 2019 database search covering the period from 2003 to April 2019 identified 9,144 records with an additional 4 records identified through searches of ASCO, EHA, and ASH conference websites. After removing duplicates, 8,683 records were screened at the title and abstract stage and of these, 8056 records were excluded. Full texts of the remaining 627 references were obtained and assessed for eligibility. Five additional references were identified through reviews of reference lists and supplementary searches. Finally, a total of 104 publication describing 78 unique studies were included in the April 2019 search.

The search update performed in February 2021 covering the period between April 2019 to February 2021 identified an additional 5604 deduplicated articles for screening. Of these, 4663 were excluded at the title and abstract phase. The full texts of the remaining 941 articles were obtained and assessed for eligibility. Additionally, the 104 publications eligible from the April 2019 database search were re-screened at the full-text level for eligibility in the current SLR. Thus, a total of 1045 articles were reviewed at the full-text level. Eleven additional references were identified through a hand search of bibliographies of included studies, existing systematic reviews and guidelines, and grey literature.

Across the entire database search covering the period from 2003 to February 2021, a total of 291 eligible publications were identified, of which 174 references representing 81 unique studies were included (Figure 73).

Figure 78 PRISMA Flow diagram



Of the 291 citations identified in this SLR, 174 eligible citations representing 81 unique studies were eligible for this SLR. These citations represented a total of 5 RCTs, 32 single-arm trials (Phase 1 or 2), and 44 observational studies.

A total of 5 RCTs, 32 single-arm trials (Phase 1 or 2), and 44 observational studies (4 prospective, 40 retrospective) were identified in the literature search. Twenty-six studies investigated CAR T-cell therapies.

The focus in this assessment is the investigated CAR T-cell therapies, and as the relevant comparator to liso-cel in Denmark is axi-cel, the SLR identifed TRANSCEND and ZUMA-1 as a key data source for evaluating the efficacy and safety of 3L LBCL patients (Table 110). An indirect treatment comparison (ITC) was performed to assess the relative efficacy of liso-cel (TRANSCEND) and axi-cel (ZUMA-1) (see further section 7.2).

Table 130 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
TRANSCEND (NCT02631044)	Investigate the efficacy and safety of liso-cel as a 3L+ treatment in patients with R/R large B-cell lymphoma	Phase 1 Multicenter, open label, single arm	Adult patients with relapsed or refractory B-cell NHL	Lisocabtagene maraleuce (mITT n=269 (infused)	AEs (19.1 months) and ORR (NA)	CRR, DOR, OS, PFS (NA)
ZUMA-1 NCT02348216	Evaluating the safety and efficacy of axi-cel in refractory aggressive NHL	Phase 1/2 Multicenter, open label, single arm	Adults with refractory aggressive NHL	Axicabtagene ciloleucel (mITT n=101 infused)	ORR (27.1 months)	OS, DOR, PFS (27.1 months) AEs (27.4 months)

H.2.3 Quality assessment

Separate quality assessments were performed for clinical trials and for observational studies in this SLR. Assessment for RCTs was completed for each unique trial using the criteria for assessment of risk of bias in RCTs as outlined by the York Centre for Reviews and Dissemination [112] and recommended by NICE. These criteria include questions on randomization scheme, allocation concealment, balance of prognostic factors, blinding

of patients, care providers, and outcome assessors, imbalances in dropouts between groups, selective outcome reporting, and intention to treat analysis/handling of missing data.

Quality assessment for single-arm clinical trials and observational studies, including those presented as abstracts, was completed for each unique study using the modified Downs and Black checklist [117-119].

Quality assessments were conducted by a single reviewer and validated by a second reviewer. Conflicts were resolved by a third reviewer when the two reviewers did not reach an agreement.

H.2.4 Unpublished data

NA

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The objective the SLR was to understand the breadth of economic and HRQoL evidence and identify health state utility values associated with treatments in R/R large B-cell lymphomas, with a focus on outcomes in 2L.

The current application for liso-cel in Denmark is based on a cost minimization analysis between liso-cel and axicel and QoL data is not used for the health economic analysis. The SLR performed are described below.

The SLR is in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in alignment with the PRISMA guidelines. The PICOS framework was used to develop the research questions and search strategy for the HRQoL evidence SLR. In earlier versions of this SLR, the PubMed database was searched as part of the database search. In the May 2022 update, PubMed was not searched due to equivalency in coverage between Ovid MEDLINE and PubMed. PubMed was not included in the current March 2023 update.

Single searches of conferences and grey literature sources common to both searches were conducted and results separated into the economic SLR and HRQoL SLR. Bibliographic handsearching of published systematic literature reviews was also conducted; results were separated into the economic SLR and HRQoL SLR. As part of the hand search, economic evaluations and HTA reports identified in the economic SLR were reviewed for inclusion in the HRQoL SLR.

The database searches were restricted to the publication years 01 Jan 2003 to Match 1, 2023. Conference proceedings from 2018 through to March 2023 were hand searched (Table 133). In addition, grey literature searches were conducted (Table 132).

Table 131 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE	Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily	1946 to 27 February, 2023	01.03.2023

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase	1974 to 27 February, 2023	01.03.2023
Cochrane	EBM Reviews Cochrane Database of Systematic Reviews	2005 to 28 February, 2023	01.03.2023
NHS EED	EBM Reviews NHS EED	1st Quarter 2016	01.03.2023

Table 132 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	www.clinicaltrials.gov	Grey search	01.03.2023
WHO clinical trials registry	NA	Grey search	01.03.2023
FDA	NA	Grey search	01.03.2023
EMA	NA	Grey search	01.03.2023
EUDRA-CT	NA	Grey search	01.03.2023
CADTH	NA	Grey search	01.03.2023
INESSS	NA	Grey search	01.03.2023
SMC	NA	Grey search	01.03.2023
NICE	NA	Grey search	01.03.2023
PBAC	NA	Grey search	01.03.2023
EQ-5D Publications Database	NA	Grey search	01.03.2023

Table 133 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	Conference website	Manual hand search	NA	01.03.2023
ESMO	Conference website	Manual hand search	NA	01.03.2023
EHA	Conference website	Manual hand search	NA	01.03.2023
ASH	Conference website	Manual hand search	NA	01.03.2023
AACR	Conference website	Manual hand search	NA	01.03.2023
ISPOR	Conference website	Manual hand search	NA	01.03.2023
HTAi	Conference website	Manual hand search	NA	01.03.2023

I.1.1 Search strategies

A database search strategy were developed and independently conducted to identify HRQoL evidence (see Table 114) below. The search strategies focused on identifying published, peer-reviewed studies, systematic reviews and meta-analyses, and assessments from HTA agencies within R/R LBCL, including DLBCL, FL3B, PMBCL, DLBCL transformed from indolent NHL (ie, originated from FL, or MZL), and high-grade B-cell lymphomas with double- or triple-hit gene rearrangements in MYC and BCL2, BCL6, or both. These histology subtypes are similar to those investigated in the TRANSFORM study.

An initial search was run on 21 April 2020 and updated searches were run on 08 June 2020, 05 February 2021, 02 May 2022, and March 1, 2023 (the current search strategy, see table Table 114).

Table 134 Search strategy for

No.	Query	Results
1	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf.	82495

2	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf.	20141
3	1 or 2	95380
4	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf.	5938942
5	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf.	5656
6	(3 and 4) or 5	29535
7	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf.	69007
8	Cell Transformation, Neoplastic/ or transform$.tw,kf.	1324676
9	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf.	143771
10	(1 or 9) and 7 and 8	3893
11	6 or 10	32137

12	Economics/ or exp "Costs and Cost Analysis"/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/ or exp models, economic/ or markov chains/ or monte carlo method/ or exp Decision Theory/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or markov or monte carlo or budget$ or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kf.	2278653
13	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	892230
14	12 or 13	2589587
15	11 and 14	896
16	(cost$ or cost benefit analys$ or health care costs).mp.	2193546
17	exp "costs and cost analysis"/ or costs.tw. or cost effective$.tw.	1351619
18	11 and 16	923
19	11 and 17	507
20	15 or 18 or 19	1282
21	exp Animals/ not (exp Animals/ and Humans/) [ANIMAL STUDIES ONLY - REMOVE - MEDLINE]	16740966
22	(address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. [Opinion publications - Remove -MEDLINE]	4848125
23	20 not (21 or 22) [ANIMAL STUDIES and OPINION PUBLICATIONS - REMOVED - MEDLINE]	1147
24	23 use ppez [MEDLINE results]	175
25	exp diffuse large B cell lymphoma/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or	83730

	NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kw.	
26	(follicular lymphoma/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kw.	20563
27	25 or 26	96900
28	cancer recurrence/ or tumor recurrence/ or cancer resistance/ or relapse/ or exp treatment failure/ or salvage therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kw.	5867696
29	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kw.	5652
30	(27 and 28) or 29	30310
31	marginal zone lymphoma/ or hairy cell leukemia/ or waldenstrom macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kw.	68880
32	cell transformation/ or transform$.tw,kw.	1294609
33	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kw.	142073
34	(25 or 33) and 31 and 32	3816

35	30 or 34	32831
36	Economics/ or Cost/ or exp Health Economics/ or Budget/ or Statistical Model/ or Probability/ or monte carlo method/ or Decision Theory/ or Decision Tree/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or budget$ or markov or monte carlo or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kw.	3960813
37	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	892230
38	36 or 37	4247214
39	(cost or costs).tw.	1643988
40	35 and 38	1249
41	35 and 39	671
42	40 or 41	1411
43	(exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE]	12303951
44	(editorial or letter or note or short survey or tombstone).pt. [OPINION PIECES REMOVE - Embase]	5207117
45	42 not (43 or 44) [ANIMAL STUDIES and OPINION PUBLICATIONS - REMOVED - Embase]	1381
46	conference abstract.pt.	4688629
47	45 and 46 [CONFERENCE ABSTRACTS ONLY]	742
48	limit 47 to yr="2021 -Current"	221
49	45 not 46 [CONFERENCE ABSTRACTS REMOVED]	639
50	48 or 49 [LAST 2 YRS OF ABSTRACTS RETAINED]	860
51	50 use oemezd	611

52	Lymphoma, Large B-Cell, Diffuse/ or (((large or diffuse?) adj2 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)) or ((diffuse? large or large diffuse?) adj3 (lymphoma$ or NHL)) or (histiocytic$ adj2 (lymphoma$ or NHL)) or "T rex lymphoma" or TINHL or tiNHL or (T-immunoblastic adj NHL) or DLBCL).tw,kf.	82495
53	(Lymphoma, Follicular/ and (3B or IIIB or three-B or grade 3?).tw,kf.) or ((second$ adj2 (central nervous system or CNS) adj2 (lymphoma$ or NHL or involvement or relaps$)) or (SCNSL or SCNS) or (((follicul$ adj2 (lymphoma$ or NHL)) or FL) adj2 (3B or IIIB or three-B or grade 3?)) or (FL3B or 3BFL) or (("high grade" or HG or HGL) adj3 (lymphoma$ or NHL)) or (double hit adj (lymphoma$ or NHL)) or (MYC adj3 (BCL2 or BCL-2 or BCL6 or BCL-6) adj7 (lymphoma$ or NHL)) or ((primary mediastin$ or primary media-stin$) adj4 (lymphoma$ or NHL)) or ((mediastin$ or media-stin$ or thymic$) adj2 (b-cell$ or bcell$ or cell b) adj2 (lymphoma$ or NHL)) or tFL or "transformed follicular lymphoma" or PMBCL).tw,kf.	20141
54	52 or 53	95380
55	Neoplasm Recurrence, Local/ or Drug Resistance, Neoplasm/ or Recurrence/ or Treatment Failure/ or Salvage Therapy/ or (recurren$ or resistan$ or refract$ or relaps$ or "refractory/relapsed" or recrudescen$ or (thirdline$ or third-line$) or (fail$ adj2 (treatment or therap$)) or ((fail$ or lack) adj2 respon$) or (nonrespon$ or non-respon$ or unrespon$ or unrespon$ or no respon$ or "not respon$") or (reappear$ or re-appear$ or reoccur$ or re-occur$) or (salvage adj2 (therap$ or treatment$ or regime$))).tw,kf.	5938942
56	((refract$ or relaps$) adj3 (b-cell$ or bcell$ or cell b) adj3 (lymphoma$ or NHL)).tw,kf.	5656
57	(54 and 55) or 56	29535
58	Lymphoma, B-Cell, Marginal Zone/ or Leukemia, Hairy Cell/ or Waldenstrom Macroglobulinemia/ or ((richter$ adj2 (transform$ or syndrome$)) or ((marginal zone? or mucosa-associated or MALT) adj3 (lymphoma$ or NHL)) or maltoma? or MZL or (primary cutaneous adj3 (lymphoma$ or NHL)) or (PCFCL? or PCMZL? or PCFCCL? or PCLBCL? or PCBCL?) or Hairy cell$ or (leuk?emi$ adj2 (reticuloendothelios#s or reticulo-endothelios#s or tricholeukocytary)) or histiolymphocytos#s or (macroglobulin?emia or macro-globulin?emia or macroglobin?emia or macro-globin?emia) or ((lymphoplasmacytic or "lympho-plasmacytic" or plasmacytoid) adj2 (lymphoma$ or NHL)) or (waldenstrom$ adj2 (macroglobulin$ or macro-globulin$ or macroglobin$)) or ((low-grade or slow$ or indolent) adj3 (lymphoma$ or NHL)) or tCLL or "transformed chronic lymphocytic leukaemia" or "transformed chronic lymphocytic leukemia" or tMZL or "transformed MZL" or tPCMZL or "transformed PCMZL" or tPCFCL or "transformed PCFCL").tw,kf.	69007
59	Cell Transformation, Neoplastic/ or transform$.tw,kf.	1324676

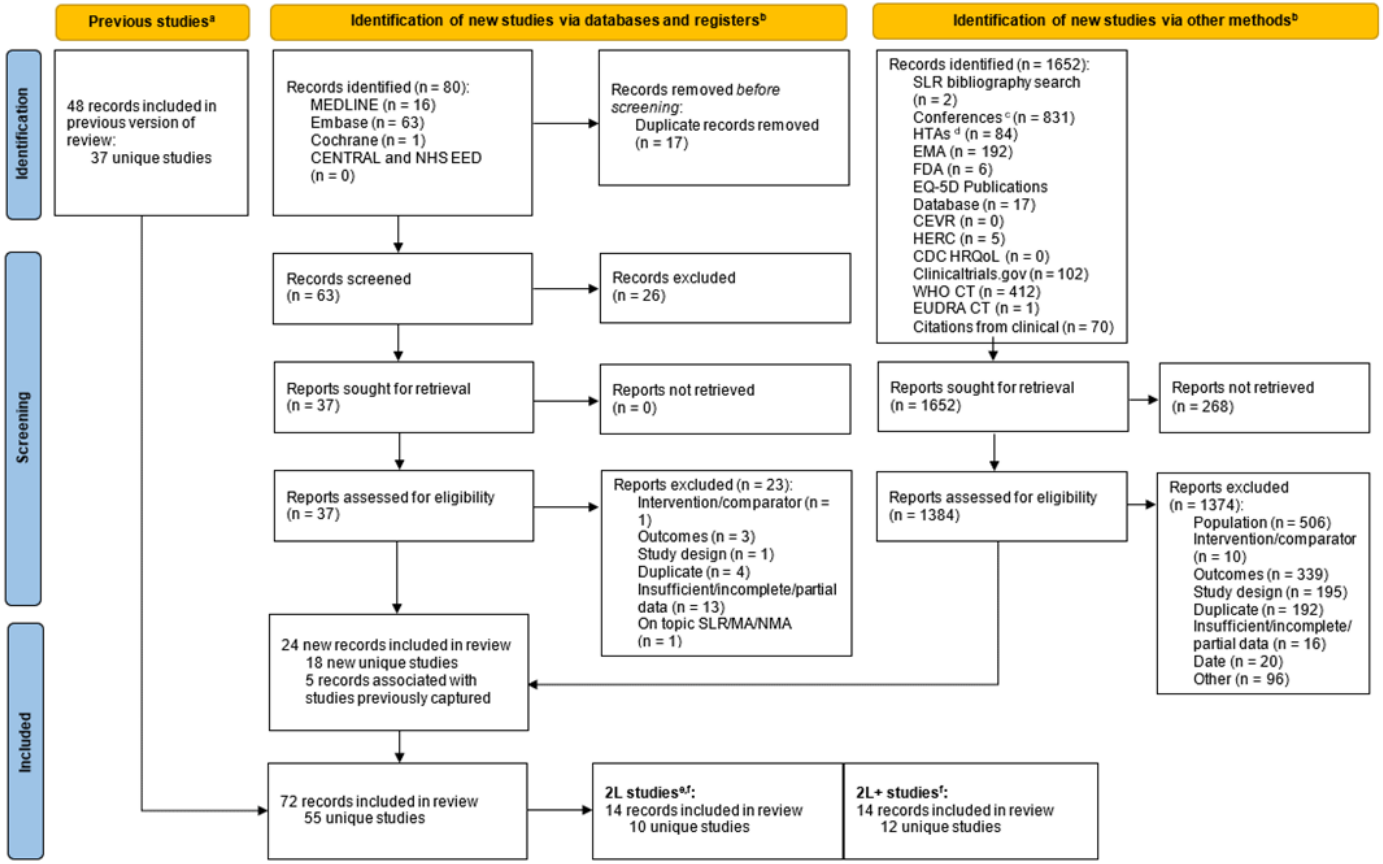
60	(((bcell or b-cell or cell b) adj3 lymphoma$) or ((high grade or aggressive or fast$) adj3 (lymphoma$ or NHL)) or ((refract$ or relaps$) adj3 lymphoma$)).tw,kf.	143771
61	(52 or 60) and 58 and 59	3893
62	57 or 61	32137
63	Economics/ or exp "Costs and Cost Analysis"/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/ or exp Economics, Hospital/ or Economics, Dental/ or exp "Fees and Charges"/ or exp Budgets/ or exp models, economic/ or markov chains/ or monte carlo method/ or exp Decision Theory/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. or ((cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)) or economic model$).ab,kw. or ((value adj2 (money or monetary)) or markov or monte carlo or budget$ or (decision$ adj2 (tree$ or analy$ or model$))).ti,ab,kf.	2278653
64	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	892230
65	63 or 64	2589587
66	62 and 65	896
67	(cost$ or cost benefit analys$ or health care costs).mp.	2193546
68	exp "costs and cost analysis"/ or costs.tw. or cost effective$.tw.	1351619
69	62 and 67	923
70	62 and 68	507
71	66 or 69 or 70	1282
72	71 use coch	1
73	71 use clhta,cleed	7
74	limit 24 to dt="20220401-20231231" [Limit not valid in CDSR,CLHTA,CLEED,Embase; records were retained]	31
75	limit 74 to yr="2022 -Current" [Medline results for period Apr 2022 - Current]	31
76	limit 51 to dc="20220401-20231231" [Limit not valid in CDSR,CLHTA,CLEED; records were retained]	149

77	limit 76 to yr="2022 -Current" [Embase results for period Apr 2022 - Current]	137
78	72 and ((2022* not (202201* or 202202* or 202203*)) or 2023*).up. [Cochrane SRD results for period Apr 2022 - Current]	1
79	73 and ((2022* not (202201* or 202202* or 202203*)) or 2023*).up. [HTA, EED results for period Apr 2022 - Current]	0
80	75 or 77 or 78 or 79 [Results for period Apr 2022 - Current]	169
81	remove duplicates from 80	140

The database search performed on 01 March 2023 identified 80 records (Figure 79). After removal of duplicates, 63 records were screened. Of these, 37 records were included for full-text review. Twenty-three records were excluded with reasons at full-text screening. Additionally, a grey literature search identified 1,652 records, all of which were retrieved and assessed for eligibility. Twenty-four new records, representing 18 new unique studies and 6 records associated with studies previously captured, were included in the qualitative synthesis.

In total, with these results added to those from the previously run searches 72 records representing 55 unique studies reporting HRQoL outcomes were included in the qualitative synthesis. Eight studies (6 clinical trials, 1 point-in-time survey, and 1 utility study) were identified that assessed and reported health state utility values (HSUV) (n = 4) and/or disease-specific health-related quality of life (HRQoL) measures (n = 6) in a 2L/2L+ population.

Figure 79 PRISMA Flow Diagram for the HRQoL SLR



Note: a “Previous studies” refers to the studies identified in the 21 April 2020, 08 June 2020, 05 February 2021, 02 May 2022 searches.

b “Identification of new studies” refers to the present search conducted on March 1, 2023.

c Conferences searched included: American Association for Cancer Research (n=85), American Society of Hematology (n=691), European Organisation for Research and Treatment of Cancer (n=12), International Society of Pharmacoeconomic and Outcomes Research (n=19), International Workshop on non-Hodgkin Lymphoma (n=24).

d Sources of HTAs searched included: Canadian Agency for Drugs and Technologies in Health (n=27), Institut National d’Excellence en Santé et Services Sociaux (n=9), National Institute for Health and Care Excellence (n=14), Pharmaceutical Benefits Advisory Committee (n=25), and Scottish Medicines Consortium (n=9).

e Includes one utility study that reported outcomes for both a 2L and 3L+ subgroup

f Includes one point in time survey that reported outcomes for both a 2L subgroup and an overall 2L+ population.

Three studies were reporting QoL for CAR T-cell therapies in 2L LBCL. TRANSFORM, the PILOT trial, and ZUMA-7 trial. The two studies relevant for this assessment in Denmark are TRANSFORM and ZUMA-7 trial (results of from these studies with regards to QoL are presented in section 10).

Literature search results included in the model/analysis: NA

I.1.2 Quality assessment and generalizability of estimates

NA

I.1.3 Unpublished data

NA

Appendix J. Literature searches for input to the health economic model

Not applicable.

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