NON-INTERVENTIONAL TRIAL PROTOCOL

An observational retrospective cohort study of systemic therapies for relapsed or refractory diffuse large B cell lymphoma (R/R DLBCL), to compare outcomes to those from Tafasitamab + Lenalidomide in the L-MIND study

Sponsor:	MorphoSys AG
Sponsor's Address:	Semmelweisstrasse 7 D-82152 Planegg GERMANY
Protocol Number:	MOR208C213 (RE-MIND2)
Post Authorization Study	No
Effective Date:	31 March 2020
Version of the Clinical Trial Protocol:	Local Version 2.0 (Germany)
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I have read and understood this observational retrospective study protocol. I agree to conduct this observational retrospective study in accordance with the protocol.

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1 SYNOPSIS

Title of Study	An observational retrospective cohort study of systemic therapies for relapsed or refractory diffuse large B cell lymphoma (R/R DLBCL), to compare outcomes to those from Tafasitamab + Lenalidomide in the L-MIND study
Study Protocol Number	MOR208C213 (RE-MIND2)
Sponsor	MorphoSys AG Semmelweisstr. 7 D-82152 Planegg GERMANY
Study Type	Retrospective observational cohort study
Background / Rationale	The combination of Tafasitamab with Lenalidomide (LEN) has yielded very encouraging results in patients with relapsed or refractory (R/R) DLBCL in the single-arm MOR208C203 trial (L-MIND). This retrospective observational cohort study aims to generate a historical control consisting of R/R DLBCL patients who received currently guideline recommended therapies.
Study cohorts	• **Observational study cohort:** Patients who received any systemic therapy for R/R DLBCL listed in NCCN / ESMO guidelines. Cohorts of patients who received any of the following pre-specified treatments: o Bendamustine + Rituximab (BR) o Rituximab Gemcitabine, Oxaliplatin (R-GemOx) o Rituximab + Lenalidomide (R^2) o CD19 CAR-T Therapies o Polatuzumab vedotin + BR o Pixantrone monotherapy Additional treatment cohorts for analysis can be identified if considered useful and will be specified in the SAP. Data from the L-MIND trial (Morphosys-sponsored, interventional study MOR208C203) database will be used for comparison with the observational cohort of RE-MIND2 as described in this protocol.
Study Objectives	**Primary Objective:** To compare the efficacy outcomes of the L-MIND cohort with the effectiveness in a matched patient population treated with systemic NCCN/ESMO guideline listed regimens administered in routine clinical care **Secondary Objectives:**

	1. To compare the effectiveness of each pre-specified matched treatment cohort, i.e., BR, R-GemOx, R2, CD19 CAR-T, Pola-BR or Pixantrone monotherapy with the efficacy outcomes of the L-MIND cohort 2. To characterize the effectiveness of systemically administered therapies for R/R DLBCL therapy 3. To characterize the tolerability of systemically administered therapies in comparison with the L-MIND cohort by time on therapy and reason for discontinuation
Study Endpoints	**Primary Endpoint:** • Overall Survival (OS) **Secondary Endpoints:** • Overall/Objective Response Rate (ORR) • Complete Response Rate (CR) • Duration of Response (DoR) • Event Free Survival (EFS) • Progression Free Survival (PFS) • Time to next treatment (TTNT) • Treatment discontinuation rate due to adverse events • Duration of treatment exposure
Eligibility/non-Eligibility Criteria for data collection of the observational cohorts	**Eligibility Criteria** 1. Age ≥ 18 years at the initial DLBCL diagnosis. 2. One of the following histologically confirmed diagnosis: DLBCL not otherwise specified (NOS); T-cell/histiocyte rich large B-cell lymphoma (THRLBCL); Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL), Grade 3b Follicular Lymphoma (FL), Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification. Additionally, patients with the evidence of histological transformation to DLBCL from an earlier diagnosis of low grade lymphoma (i.e., an indolent pathology such as FL, marginal zone lymphoma, chronic lymphocytic leukemia) into DLBCL with a subsequent DLBCL relapse are also eligible. 3. Relapsed or refractory DLBCL and received at least 2 systemic regimens for the treatment of DLBCL, including at least 1 anti-CD20 containing therapy. **Non-Eligibility Criteria** 1. Patients with central nervous system (CNS) involvement by lymphoma at initial DLBCL diagnosis. 2. Patients who were treated with CD19-targeted therapy or immunomodulatory drugs (IMiDs) (e.g., thalidomide, LEN) as a frontline DLBCL therapy. 3. Patients who underwent an allogeneic stem cell transplant.

	4. Patients who had a prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥5 years prior to inclusion. Note: Patients with the following malignancies within the 5 years period are still eligible: a. basal cell carcinoma of the skin b. squamous cell carcinoma of the skin c. carcinoma in situ of the cervix d. carcinoma in situ of the breast e. carcinoma in situ of the bladder f. incidental histological finding of prostate cancer (Tumor/Node/Metastasis [TNM] stage of T1a or T1b) 5. Patients who received Tafasitamab.
Design and Methodology	Data will be collected retrospectively from health records of patients in routine clinical care settings. This retrospective observational cohort study is designed as follows: Data from approximately 2000 patients fulfilling the eligibility criteria, who received a systemically administered therapy for R/R DLBCL (NCCN/ESMO guideline listed) will be collected. Interim cohort balancing will be performed for systemically administered regimens to evaluate cohort balance with the L-MIND cohort on the basis of nine covariates (i.e., age, number of prior therapy lines, refractoriness status to the last prior therapy, elevated lactate dehydrogenase (LDH) levels, Ann Arbor stage, history of primary refractoriness, prior ASCT, neutropenia and anemia) at index date (start of R/R DLBCL treatment of 2nd, 3rd or 4th line). This interim cohort balancing will provide information if a sufficient number of patients of each pre-specified regimen was collected for the secondary objectives. No comparative outcome analyses will be done in interim cohort balancing analysis. Thereafter, data collection for patients who received any of the pre-specified regimens (i.e., BR, R-GemOx, R^2, CD19 CAR-T, Pola-BR or Pixantrone monotherapy) may be continued to reach a sufficient number of patients to optimize cohort balance with the L-MIND cohort for conducting comparative efficacy analyses. It is estimated to collect data from approximately additional 800 patients (in addition to the 2000 patients from the first part) fulfilling the eligibility criteria. Eligible patients will be identified from sites selected based on their completeness of data in their patient records and number of available patients. Data will be collected retrospectively from health records of patients. Patient visits or laboratory tests are not required for this non-interventional retrospective study.

Data Sources	The data sources for the observational cohort include patient records from academic institutes, national/international study groups, single centers, health networks and research consortiums, as applicable (henceforth referred to as "sites").
Patient Population	The retrospective observational cohort consists of patients who have received at least 2 systemic regimens for the treatment of DLBCL at time of enrolment
Sample Size	- Data to be collected from approximately 2000 patients for interim cohort balancing. - Data to be collected from an estimated additional 800 patients. The number may change if actual data is available and necessitates adaptation.
Participating Regions/Countries/Center	Approximately 280 sites targeted in Europe and North America. Types of sites: Academic hospitals, Public hospitals, Private practice. Data may also be collected from commercial sources and health networks.
Efficacy Assessments	Data on patient outcomes (investigator-assessments of disease response and progression) and other data (e.g., survival) will be collected to assess the efficacy endpoints.
Safety Assessments	Data on duration and reason for discontinuation of treatments will be collected.
Data Analysis and Statistical Methodology	Propensity score (PS) methodology will be employed to balance L-MIND and observational cohorts. The following baseline covariates will be considered: age, number of prior therapy lines, refractoriness status to the last prior therapy, elevated lactate dehydrogenase (LDH) levels, Ann Arbor stage, history of primary refractoriness, prior ASCT, neutropenia, anemia. Patients who fulfilled eligibility criteria will qualify for matching if they have a sufficient follow-up for a documented response or progression to the respective treatment regimen and data on all baseline covariates are available at the start of the respective treatment. ***Primary objective:*** To compare the efficacy outcomes of the L-MIND cohort with the effectiveness in a matched patient population treated with systemic regimens used in real-world. To achieve this, subgroup strata will be categorized on the basis of number of lines of therapy, i.e., two or three or four therapy lines. 1:N *nearest neighbour matching* without replacement will be performed using the remaining eight baseline covariates per each strata to get each matched population set. The final matched population for analysis is the aggregation of the matched population of each strata. Additional matched cohorts will be created on the basis of the following two subgroups of the L-MIND cohort:

	- one prior line before LEN/tafasitamab - two/three prior lines before LEN/tafasitamab "1:N" denotes the ratio of L-MIND cohort to the observational cohort with a maximum ratio of 1:4. In the interim cohort balancing, prior to the data base lock, *nearest neigbour matching* will be performed stepwise increasing the matching ratio from 1:1 to 1:4 until for one or more baseline covariates a standardized mean difference (SMD) of 0.2 is exceeded. The matched population with SMD ≤0.2 for all baseline characteristics and the highest matching ratio will be selected as the main analysis set for endpoint calculations. ***Secondary objective 1:*** To compare the efficacy outcomes of each pre-specified matched treatment regimen with the L-MIND cohort. To achieve this, 1:N *nearest neighbour matching* for nine baseline characteristics will be employed as described for the primary objective. Data from patients who received pre-specified treatment regimens in different lines of therapy can be utilized in matched population sets under different treatment regimens. **Effectiveness endpoints:** OS serves as the primary endpoint, whereas ORR, CR, DoR, PFS, EFS, and TTNT serve as secondary endpoints. All time to event endpoints will be analysed using standard Kaplan-Meier methodology, log-rank test and hazard ratio will be estimated based on Cox proportional hazard model. ORR and CR will be compared between the cohorts using Fisher exact test, and Odds ratio estimated using logistic regression model. For secondary objectives 2 and 3 descriptive statistics will be presented on various population sets, no hypothethesis testing will be performed.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABC	Activated B-cell
AE	Adverse Event
ASCT	Autologous stem cell transplant
BCL	B cell lymphoma
B-ALL	B-Cell Acute Lymphoblastic Leukemia
BEAM	Carmustine, etoposide, cytarabine and melphalan
BR	Bendamustine + Rituximab
CEOP	Cyclophosphamide, Epirubicin, Oncovin (Vincristine), and Prednisone
CEPP	Cyclophosphamide, Etoposide, Procarbazine, and Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
DA	Dose adjusted
DHAP	Cisplatin, Cytarabine, Dexamethasone
DLBCL	Diffuse large B cell- lymphoma
DoR	Duration of response
e	Electronic
EBV	EpsteinBarr Virus
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event-free survival
E/NE	Eligibility/non-eligibility
ENR	Enrolled Patients Set
EOT	End of treatment
EPOCH	Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
ePS	Estimated propensity score
ESHAP	Etoposide, Methylprednisone, Cytarabine, Cisplatin
ESMO	European Society for Medical Oncology
FAS	Full Analysis Set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
GCP	Good Clinical Practice
GDP	Gemcitabine, Dexamethasone, Cisplatin
GPP	Good Pharmacoepidemiology Practices
GemOx	Gemcitabine, Oxaliplatin
HDC	High dose chemotherapy
HDT	High dose therapy
HR	Hazard ratio
ICE	Ifosfamide, Carboplatin, Etoposide
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors

ICSR	Individual Case Safety Reports
IEC	Independent Ethics Committee
IMiD	Immunomodulatory drug
iNHL	Indolent non-Hodgkin lymphoma
IPI	International prognostic index
IRB	Institutional Review Board
IRC	Independent Radiology/Clinical Review Committee
L	Line
LEN	Lenalidomide
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAS_N	Matched Analysis Set
MI	Multiple imputation
MINE	Mesna, Ifosfamide, Mitoxantrone, Etoposide
mFAS	Modified Full Analysis Set
mMAS_N	Modified Matched Analysis Set
mOb-FAS	Modified Observational Full Analysis Set
MYC	A Proto-Oncogene
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
Ob-ENR	Observational Enrolled Analysis Set
Ob-FAS	Observational Full Analysis Set
ORR	Overall/objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
Pola-BR	Polatuzumab vedotin + Bendamustine + Rituximab
PR	Partial response
R	Rituximab
R/R	Relapsed and/or refractory
R^2	Lenolidamide and Rituximab
REAL	Revised European American Lymphoma
RWE	Real World Evidence
SAP	Statistical analysis plan
SD	Stable disease
SLL	Small lymphocytic lymphoma
SMD	Standardized Mean Difference
THRLBL	T-cell/histiocyte rich large B-cell lymphoma
TNM	Tumor/Node/Metastasis
TTNT	Time to next treatment
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

4 INTRODUCTION

4.1 Background Information

Non-Hodgkin lymphoma (NHL) accounts for approximately 4.3% of all cancers and over 70,000 cases annually in the United States (US) (Chihara et al, 2012; Noone et al, 2015; Siegel et al, 2017). Over 40 major subtypes of the disease exist, the most common of which is diffuse large B-cell lymphoma (DLBCL), representing approximately 30-40% of all NHL cases (Chihara et al, 2015; Martelli et al, 2013; Menon et al, 2012).

Although the development of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and similar regimens has substantially improved overall survival (OS), approximately 40% of patients relapse or develop refractory disease (Nowakowski et al, 2016). Prognosis of these patients is poor (Friedberg, 2011).

4.2 Overview of therapies administered for R/R DLBCL

For patients who are willing and fit enough, regimens such as DHAP (cisplatin, cytarabine, dexamethasone), ICE (ifosfamide, carboplatin, etoposide), GDP (gemcitabine, dexamethasone, cisplatin), GemOx (gemcitabine, oxaliplatin), MINE (mesna, ifosfamide, mitoxantrone, etoposide), or ESHAP (etoposide, methylprednisone, cytarabine, cisplatin) with or without added rituximab followed by high dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) are standard salvage treatments, and remain the preferred treatment course for patients with chemosensitive disease (Robinson et al, 2016; Philip et al, 1995; Zelenetz et al, 2016). However, these salvage therapies are effective only for a small proportion of relapsed or refractory (R/R) patients, and a large majority of these patients relapse again. (Gisselbrecht et al, 2010).

Treatment options are even further limited for those patients who are not eligible for ASCT or who relapse following ASCT. Patients may be considered ineligible for, or be poor candidates for HDC/ASCT due to advanced age, comorbidities, chemorefractory disease, or relapse after a prior ASCT or may not wish to undergo ASCT. Though the aging process is extremely variable, age is associated with impaired hematopoietic reserve capacity and increased toxicity of treatment. Further, older patients are more likely to have comorbidities and higher risks of death (Sarkozy et al, 2013).

Patients with R/R DLBCL who are non-transplant eligible have the option of being treated with single agents (e.g., rituximab, bendamustine, lenalidomide [LEN], brentuximab-vedotin, ibrutinib) or chemotherapy combinations (e.g., CEPP, CEOP, DA-EPOCH, GDP, Gem-Ox or variants thereof) or other combinations (e.g., bendamustine+rituximab [BR]; LEN-rituximab) (National Comprehensive Cancer Network [NCCN] Guidelines 2019 and European Society for Medical Oncology [ESMO] Clinical Practice Guidelines 2015, see Appendix D and E). The choice of regimen depends on patient comorbidities, prior treatments, patient preferences and drug availability. However, patient outcomes observed with these regimens remain largely unsatisfactory (see Table 1).

A median progression free survival (PFS) of 3.6-5 months has been reported with the BR regimen (Vacirca et al, 2014; Sehn et al, 2019), 5 months with R-GemOx (Mounier et al,

2013), and 3.7 months with the R^2 regimen (Wang et al, 2013). Overall survival with these regimens was rather unsatisfactory, with a median ranging from 4.7-11 months.

Pixantrone is approved for the treatment of R/R DLBCL, however is associated with similar, unsatisfactory outcomes, with a median PFS of 5.3 months and a median OS of 10.2 months. Recently, the antibody-drug conjugate polatuzumab vedotin in combination with BR (median PFS 9.5 months and median OS 12.4 months; Sehn et al, 2019) and the CD-19 CAR-T therapies Axicabtagene Ciloleucel (median PFS 5.9 months, median OS not reached) and Tisagenlecleucel (median OS 12 months) were approved for the treatment of R/R DLBCL. Thus, patients with R/R DLBCL represent a population who are in urgent need of more tolerable and more effective therapeutic alternatives compared to the very limited existing options they currently have.

Real world evidence (RWE) is a rapidly maturing field of increasing importance for researchers, clinicians, and regulators. Comparative effectiveness studies, in particular, have the ability to supplement clinical trials and expand the evidence base to inform clinical and regulatory decision-making (Roche et al, 2014; Schneeweiss et al, 2016; Sherman et al, 2016; Food and Drug Administration (FDA), 2018). A similar approach was applied for the recently approved CAR-T cell therapy Axicabtagene Ciloleucel (Neelapu et al, 2017). Therapies and outcomes in R/R DLBCL patients are summarized in Table 1.

Table 1: Therapies and Outcomes in R/R DLBCL Patients (Selected Publications Based on NCCN/ESMO Guidelines)

Therapy	ORR (n[1])	Median PFS (months)	Median OS (months)	Citations
L-MIND (Tafasitamab+LEN)	60% (n=80)	12.1	Not reached (12-month OS rate= 73.7%)	MorphoSys data on file (CSR Oct2019)
LEN monotherapy	19% (n=26)	4.0	NA	Wiernik et al, 2008
	27.5% (n=51)	3.1	7.1	Czuczman et al, 2017
	28% (n=108)	2.7	NA	Witzig et al, 2011
R-LEN (R[2])	28% (n=32)[2]	2.8	10.2	Wang et al, 2013
	35% (n=23)	NA	NA	Zinzani et al, 2011
BR	45.8% (n=59)	3.6	NA	Vacirca et al, 2014
	62.7% (n=59)	6.7	NA	Ohmachi et al, 2013
	17.5% (n=40)[3]	3.7	4.7	Sehn et al, 2019
R-GemOx	78% (n=32)[4]	NA	NA	Corazzelli et al, 2009
	61% (n=49)	5	11	Mounier et al, 2013
	83% (n=46)[4]	NA	NA	El Gnaoui et al, 2007
R-GDP	53% (n=51)[4]	NA	8.9	Crump et al, 2004
	63% (n=8)	NA	NA	Gopal et al, 2010
R-EPOCH	68% (n=50)[5]	11.8 (EFS)	17.9	Jermann et al, 2004
Ibrutinib	25% (n=80)	1.6	6.4	Wilson et al, 2015
Pixantrone monotherapy	28% (n=70)	5.3	10.2	Pettengell et al, 2012
Tisagenlecleucel (CAR-T)	52% (n=93)	NA	12	Schuster et al, 2019
Axicabtagene ciloleucel (CAR-T)	75% (n=101)	5.9	Not reached	Locke et al, 2018
Pola-BR	40% (n=40)[3]	9.5	12.4	Sehn et al, 2019
SCHOLAR-1 analysis	26% (n=636)	Not reported	6.3	Crump et al, 2017

BR = bendamustine+rituximab; DLBCL = diffuse Large B-Cell Lymphoma; EFS = Event-free survival; EPOCH = Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin; GDP = Gemcitabine, Dexamethasone, Cisplatin; GemOx=Gemcitabine, Oxaliplatin; LEN = lenalidomide; NA = not available; n = number of patients; NCCN = National Comprehensive Cancer Network; ORR = overall/objective response rate; OS = overall survival; Pola-BR= Polatuzumab vedotin + BR, PFS = progression free survival; R = rituximab; R/R = relapsed and/or refractory.

1. Sampe size of the study
2. Includes a subset of patients (13 of 45) with transformed large cell lymphoma or follicular lymphoma
3. EOT IRC-assessed CR rate
4. Includes patients with other B-cell lymphomas
5. Includes a subset of patients (7 of 50) with mantle cell lymphoma

4.3 Tafasitamab-LEN Combination as an Investigational Therapy for R/R DLBCL

4.3.1 CD19 Expression and Biology

CD19 is an important component of B-cell receptor signaling. CD19 is expressed throughout B-cell development up to terminal plasma cell differentiation and is present on the surface of malignant hematopoietic cells, and therefore, represents an important therapeutic target for the treatment of B-Cell malignancies, including DLBCL (Awan et al, 2010; Olejniczack et al, 2006).

4.3.2 Tafasitamab Monotherapy Studies in Lymphoma

Tafasitamab is a humanized, fragment crystallizable (Fc)-engineered monoclonal antibody against the B-cell surface receptor CD19 (Zalevsky et al, 2009, Awan et al, 2010). A phase 1, first in human study of tafasitamab was conducted in patients with R/R chronic lymphocytic leukemia (XmAb®5574-01), and resulted into 12mg/kg as recommended dose for subsequent clinical development for tafasitamab (Woyach et al, 2014). Subsequently, in a phase IIa study of tafasitamab monotherapy (MOR208C201), 92 patients with R/R NHL from various histological subtypes (DLBCL, n=35; follicular lymphoma [FL], n=34; other indolent NHL, n=11 and mantle cell lymphoma, n=12) were treated (Jurczak et al, 2018). Objective responses (complete response [CR] and partial response [PR]) were reported in DLBCL, FL and other indolent NHL (iNHL) cohorts of 26%, 29% and 27%, respectively. The responses were durable, with a median duration of response 20.1 months in the DLBCL cohort. The most common adverse events (any grade) were infusion-related reactions (12%) and neutropenia (12%). Non-hematological toxicities were uncommon, and tafasitamab treatment was well tolerated. Taken together, tafasitamab as single agent is considered an active drug, however, the activity of tafasitamab alone is insufficient as sole treatment of this aggressive disease in R/R DLBCL.

4.3.3 Tafasitamab-LEN Combination Therapy in Study MOR208C203 (L-MIND)

L-MIND is a phase II, single-arm, open-label, multicentre study to evaluate the safety and efficacy of lenalidomide combined with tafasitamab in patients with R/R DLBCL, who are not eligible for an HDC followed by ASCT. Results from the L-MIND study showed encouraging activity of the tafasitamab-LEN combination (n=80) in this difficult to treat patient population. An ORR of 60%, with a CR rate of 42.5% was reported, nased on central independent review. The median PFS was 12.1 months, and majority of the responding patients had durable, ongoing responses. The OS rate at 12 months was 73.7%. The combination was well tolerated and the observed adverse events reflect the established safety profile of LEN. The most common grade ≥3 AEs were neutropenia in 48.1%, thrombocytopenia in 17.3%, anemia in 7.4%, diarrhea in 1.2%, asthenia in 2.5% and pyrexia in 1.2% patients [Salles et al, 2019; MorphoSys data on file (CSR Oct2019)].

4.4 Study Rationale

In DLBCL patients, particularly those who did not achieve cure with the first-line treatment, currently available therapies produce unsatisfactory results. Therefore, novel treatment options are urgently needed.

As Rituximab based regimens have become standard first-line treatment in DLBCL, the efficacy of Rituximab combined with chemotherapy in the second-line setting has decreased and there is a need for new therapies in patients progressing or relapsing after first- or second-line Rituximab-based treatment. It was anticipated that by using tafasitamab instead of Rituximab, it might be possible to partially overcome the Rituximab resistance in R/R NHL, improving ORRs and OS.

The results of the phase 2 L-MIND study [MOR208C203]) in patients with ASCT-ineligible, R/R DLBCL patients are encouraging. The recently conducted, patient-level comparison of the L-MIND cohort with the retrospective cohort of LEN monotherapy patients, demonstrated substantial additional activity of tafasitamab, when added to LEN monotherapy MorphoSys data on file (study MOR208C206 RE-MIND, CSR December 2019). In view of these data, it is important to understand the activity of the tafasitamab+LEN combination in the context of efficacy of various therapies administered for R/R DLBCL in routine clinical care. Therefore, this observational, retrospective study (MOR208C213, RE-MIND2) aims to generate an additional historical control for comparing the results of the L-MIND study with those from the routine clinical care.

5 STUDY DESIGN

5.1 Overall Study Design and Investigational Plan

This observational retrospective cohort study is designed to characterize the effectiveness of systemically administered therapies in the treatment of R/R DLBCL patients. Eligible patients will be identified from patient health records from academic hospitals, public hospitals and private practices (henceforth referred to as “sites”). Sites will be selected based on completeness of data and number of available patients in their health records.

Data such as baseline characteristics, effectiveness outcomes and treatment termination/drop-out due to adverse events will be collected from existing health records including paper or electronic records of patients treated for R/R DLBCL.

Since this is an observational retrospective study, no patient visits or laboratory tests will be required for the purpose of this study. Only data which have been collected previously within routine clinical care will be in scope.

5.2 Index Date

Patients will be assigned an index date based on the first documented treatment record of the systemically administered therapy for R/R DLBCL under consideration. The pre-index period for each patient will be defined as the time between first documented DLBCL diagnosis, or history of cancer other than DLBCL, and the index date (=start of R/R DLBCL treatment of 2nd, 3rd or 4th line). If a patient has received more than one treatment regimen (therapy lines)

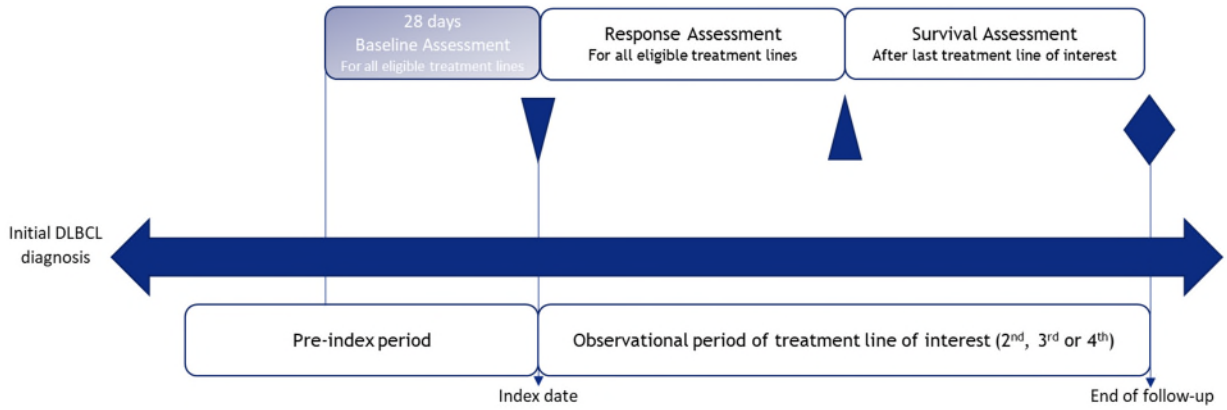
for R/R DLBCL, such a patient will be assigned an index date for each applicable therapy line. This is illustrated as an example in the table below (Table 2):

Table 2: Example of treatment lines of one patient (e.g., Patient #1)

Therapy Line	Treatment regimen	Duration	Index Date Assignment
Frontline therapy after DLBCL diagnosis	R-CHOP	01-JAN-2010 to 30-APR-2010	None
Second line (2L) therapy for relapsed or refractory DLBCL	R-ICE followed by ASCT	R-ICE: 01-JAN-2012 to 29-FEB-2012 ASCT 01-APR-2012	Index Date 2L 01-JAN-2012
Third line (3L) therapy for relapsed or refractory DLBCL	B-R	01-JAN-2013 to 30-APR-2013	Index Date 3L 01-JAN-2013
Fourth line (4L) therapy for relapsed or refractory DLBCL	R-GemOx	01-JAN-2014 to 31-MAR-2014	Index Date 4L 01-JAN-2014
Fifth line therapy for relapsed or refractory DLBCL	LEN	01-JAN-2015 to 30-JUN-2015	None

The observation period will be defined as the time between the index date and end of follow-up. End of follow-up is defined as either death or last available medical record for the systemically administered therapy for R/R DLBCL under consideration.

An example of the individual patient data collection is displayed in Figure 1.



Pre-index period:	Time between initial DLBCL diagnosis and index date of treatments (2nd, 3rd or 4th line)
Index date:	Start of R/R DLBCL treatment (2nd, 3rd or 4th line)
Observational period:	Time between index date and end of follow-up including survival assessment
Baseline:	28 days of baseline assessment prior to index date

Figure 1 Data Collection in the Observational Cohort

Following data collection, the effectiveness of systemically administered therapies and treatment regimens will be compared with the L-MIND cohort using a propensity score based methodology (see Section 9 for details).

Patients who received at least two therapy lines for DLBCL will be assigned an index date (index date 2L, 3L or 4L) for each eligible therapy line. The potential scenarios are illustrated as examples (scenarios A, B and C) in the figure below (Figure 2):

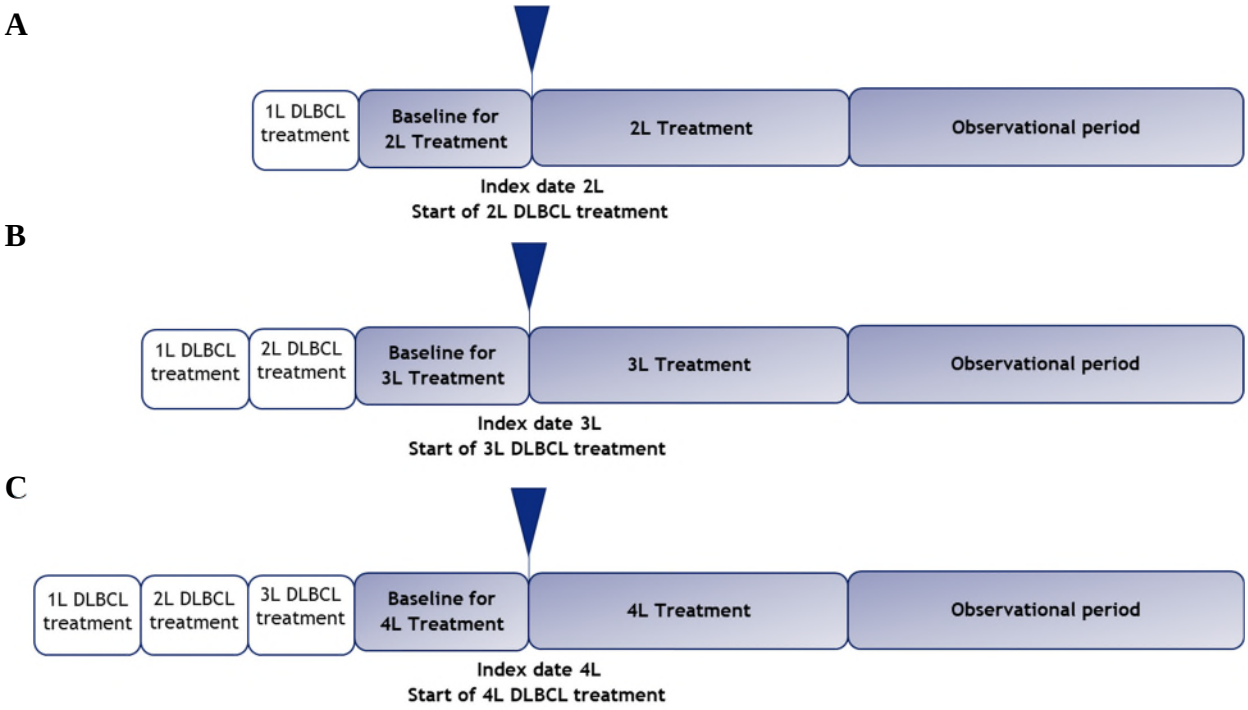


Figure 2 Potential Scenarios for Eligible Lines of Therapy

5.3 Instructions for Counting Lines of Therapies

Recording of prior lines of R/R DLBCL therapy information should be provided on any previous DLBCL-specific therapies since the time point of the first diagnosis of DLBCL. Records including the treatment regimen (e.g., R-CHOP), number of cycles, response assessment, refractoriness status, etc.

To become eligible for this MOR208C213 (RE-MIND2) study, the patients must have received at least 2 systemic regimens for the treatment of DLBCL, including at least 1 anti-CD20 containing therapy (e.g., Rituximab).

Changing to a different systemic chemotherapy regimen is regarded as a separate line of therapy. If the treatment is changed to a different systemic chemotherapy caused by toxicity of the employed regimen, the new regimen is regarded a separate line. If the dose of a treatment is changed, the treatment will not be regarded a separate line.

Radiotherapy of the involved site (limited field radiotherapy) or pre-planned radiation or CNS prophylaxis will not be considered a separate prior line of therapy. Surgical interventions are also not considered a line of therapy.

The administration of a mAb monotherapy (e.g., Rituximab-monotherapy) counts as a separate line of therapy. On the other hand mAb maintenance treatment subsequent to a chemotherapy/chemoimmunotherapy regimen is considered to be part of this treatment line, provided that the mAb was part of the initially planned treatment regimen.

As for the ASCT, the induction (salvage chemoimmunotherapy, e.g., R-ICE), stem cell collection, high dose preparative regimen [(e.g., carmustine, etoposide, cytarabine and

melphalan (BEAM)], and stem cell reinfusion, will be considered a single line of therapy. This applies also for pre-planned consolidation of responding patients, where the ASCT is regarded together as a part of the systemic therapy line. The same applies for CAR-T cell therapies which are usually preceded by lymphodepleting chemotherapy.

5.4 Risks and Benefits to Patients

As this study is observational and retrospective in nature, there are no safety risks to patients.

Patients will receive no intervention if they participate in this study. Their participation in the study will not have any influence on the current or future medical care provided by the physician to treat their disease. The data for the observational cohort (systemically administered therapies) will be collected from the existing health records of the patients. Therefore, no tests will be performed on the patients and patients are not required to attend any site visits for participation in the study.

The data generated in this observational study will help develop future treatment options for patients suffering from R/R DLBCL.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Objectives

Primary Objective:

To compare the efficacy outcomes of the L-MIND cohort with the effectiveness in a matched patient population treated with systemic NCCN/ESMO guideline listed regimens administered in routine clinical care

Secondary Objectives:

1. To compare the effectiveness of each pre-specified matched treatment cohort, i.e., BR, R-GemOx, R2, CD19 CAR-T, Pola-BR or Pixantrone monotherapy with the efficacy outcomes of the L-MIND cohort

2. To characterize the effectiveness of systemically administered therapies for R/R DLBCL therapy

3. To characterize the tolerability of systemically administered therapies in comparison with the L-MIND cohort by time on therapy and reason for discontinuation

6.2 Endpoints

Primary Endpoint

- Overall Survival (OS)

Secondary Endpoints

- Overall/Objective Response Rate (ORR)

- Complete Response Rate (CR)
- Duration of Response (DoR)
- Event Free Survival (EFS)
- Progression Free Survival (PFS)
- Time to next treatment (TTNT)
- Treatment discontinuation rate due to adverse events
- Duration of treatment exposure

7 SELECTION OF PATIENTS

7.1 Geographic Distribution of Sites

Approximately 280 study sites will be selected in Europe and North America.

7.2 Eligibility Criteria For Patient Enrolment

The eligibility criteria are based on the patient population enrolled in the L-MIND study. Data for patients in the observational cohort will be collected using the following eligibility criteria.

7.2.1 Eligibility criteria

1. Age ≥ 18 years at the initial DLBCL diagnosis.
2. One of the following histologically confirmed diagnosis: DLBCL not otherwise specified (NOS); T-cell/histiocyte rich large B-cell lymphoma (THRLBCL); Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL), Grade 3b Follicular Lymphoma (FL), Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification. Additionally, patients with the evidence of histological transformation to DLBCL from an earlier diagnosis of low grade lymphoma (i.e., an indolent pathology such as FL, marginal zone lymphoma, chronic lymphocytic leukemia) into DLBCL with a subsequent DLBCL relapse are also eligible.
3. Relapsed or refractory DLBCL and received at least 2 systemic regimens for the treatment of DLBCL, including at least 1 anti-CD20 containing therapy.

7.2.2 Non-Eligibility Criteria

1. Patients with central nervous system (CNS) involvement by lymphoma at initial DLBCL diagnosis.
2. Patients who were treated with CD19-targeted therapy or immunomodulatory drugs (IMiDs) (e.g., thalidomide, LEN) as a frontline DLBCL therapy.
3. Patients who underwent an allogeneic stem cell transplant.

4. Patients who had a prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥5 years prior to inclusion.

Note: Patients with the following malignancies within the 5 years period are still eligible:

   a. basal cell carcinoma of the skin
   b. squamous cell carcinoma of the skin
   c. carcinoma in situ of the cervix
   d. carcinoma in situ of the breast
   e. carcinoma in situ of the bladder
   f. incidental histological finding of prostate cancer (Tumor/Node/Metastasis [TNM] stage of T1a or T1b)

5. Patients who received tafasitamab.

7.3 Patient Withdrawal and Replacement

Patients will be included in the study until the sample size specified in Section 9.4 has been reached. Patients may withdraw from the observational cohort at any time and for any reason.

In all cases, the reason(s) for withdrawal must be recorded. Withdrawn patients will be replaced unless the necessary sample size for cohort balancing has been reached.

7.4 Medical Review

The Sponsor or representative will perform medical review of all data recorded for verification of patient eligibility, data accuracy and medical plausibility. Patients who do not fulfill eligibility criteria after medical review will be excluded from analyses, and the reason for exclusion will be documented.

7.5 Study Variables

The variables for this study (see Table 3) are composed of patient characteristics, clinical measures, medications, clinical encounters outcomes and other data relevant in the care of DLBCL patients. For each treatment line the variables covering the pre-index, baseline, treatment and follow up periods will be collected.

Table 3: Study Variables to be collected*

	Pre-Index period	During Treatment	After Treatment
Informed Consent, if applicable, to be collected prior to any data collection in the eCRF.			
Eligibility criteria (will be checked prior to any data collection in the eCRF)	X		
Demographics (year of birth, race, gender)[1]	X		
Date and histological subtype of initial DLBCL diagnosis[1]	X		
History of cancers other than DLBCL	X	X	X
Reasons why patient was not considered a candidate for ASCT at the time of start of treatment[2]	X		
Baseline covariates[3]	X		
ECOG performance status if available	X		
Therapies administered for DLBCL[4]	X	X	X
Treatment details including start date, stop date or discontinuation (including reason for the same, e.g. AE)		X	
Efficacy outcomes recorded for DLBCL therapies[5]	X	X	X
Bone marrow[6]	X	X	X
Tumor biopsies[7]	X	X	X
Patient survival information (date and cause of death and date of last contact to patient)		X	X
Response assessment criteria used (e.g., Cheson 1999, Cheson 2007, Cheson 2014)	X	X	X

ASCT = autologous stem cell transplant; BCL = B-cell lymphoma; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HDT = high dose therapy; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LEN = lenalidomide; PET = positron emission tomography; PR = partial response; Pre-index date = initial DLBCL diagnosis; Index date = start of R/R DLBCL treatment (2nd, 3rd or 4th line); baseline (28 days of baseline assessment prior to index date); Pre-Index period = Time between pre-index date and index data

* These variables will be collected for each of the 2nd, 3rd and 4th line of DLBCL treatment.

1. These data will be collected only once.
2. The following potential reasons may apply and need to be captured as applicable:
   Age >70 years; Diffusion lung capacity for carbon monoxide <50% by pulmonary function test; Left ventricular ejection fraction <50% by multiple gated acquisition echocardiogram; Other organ dysfunction or comorbidities precluding the use of HDT/ASCT on the basis of unacceptable risk of treatment; If other organ dysfunction, please specify; Failure to achieve PR or CR with salvage therapy; Patient refusal of HDT/ASCT; Other reasons.
3. The following data on baseline covariates will be collected: Age, refractoriness status to last therapy line, number of previous lines of therapy, elevated lactate dehydrogenase (LDH) levels, history of primary refractoriness, prior ASCT, neutropenia, anemia, Arbor stage at initial DLBCL diagnosis and within 28 days prior to each index date. Multiple sets of baseline covariates will need to be captured pertaining to each of the therapies administered for R/R DLBCL.
4. All systemically administered anti-DLBCL therapies will be captured. Type, start and end date for each therapy line including immunochemotherapy (e.g., use of rituximab with or without chemotherapy), for DLBCL, ASCT and experimental therapies will be captured. In addition, details on radiotherapy, surgery, pre-phase or CNS prophylaxis will be captured. See chapter 5.3.

5. Type and date of response recorded and date of disease progression/relapse for each DLBCL therapy. Response assessments recorded at index date until one of the following timepoints (whichever occured first): Lost to follow up: the patient has 12 consecutive months without clinical data for response assessments (end of observation period is defined as the last day of the 12th month); Initiation of a new anti-cancer treatment (end of observational period is defined as the date of its initiation); Discontinuation of treatment (end of observational period is defined as the last documented treatment intervention); Disease progression; Death due to any cause. The type of scan performed (with or without PET) and the criteria that were used for response assessment (e.g., Cheson et al, 2007) shall be captured.
6. Bone marrow involvement (yes or no) will be captured at initial diagnosis, within 56 days prior to index date and during or after index date.
7. Tumor biopsies from initial DLBCL diagnosis until next treatment after index date will be captured including information on type of tissue and lymphoma infiltration. FISH results for MYC, BCL2 and BCL6 and cell of origin will also be collected.

8 DATA MANAGEMENT

8.1 Source Documents

Source documents will consist of the patient's electronic or paper health records (including scans). Depending on the type of record maintained at sites, data will be collected either via an electronic case report form (eCRF) or via electronic data extraction.

8.2 Data Collection

8.2.1 Data Collection Through Electronic Case Report Form (eCRF)

For sites using eCRF [within the electronic data capture (EDC) system], data will be entered by trained physicians or his/her staff in accordance with the eCRF completion guidelines.

The physician or his/her staff will be given password-protected access to the eCRF system for data entry.

Data collected should accurately reflect the source documents. All data requested on the eCRF must be recorded, if available.

Any queries on the data will be raised within the eCRF and should be resolved by the physician or his/her staff. The audit trail of the eCRF will record all changes made, including the date and time of the correction and the person correcting the error.

Confirmation on the accuracy of data collected will be provided by the physician through electronic signature in the eCRF.

8.2.2 Data Collection Through Electronic Extraction

For sites applying electronic data extraction, the data required by the protocol will be extracted from patient health records and then organized in an electronic file within a secure and validated system of the site. The data will be transferred in accordance to the established and approved data transfer plan for cleaning and processing.

8.2.3 Identification of Duplicate Records

Data will be collected from patient health records from a mix of academic hospitals, public hospitals and private practices. It is theoretically possible that 2 or more sources may contain the same patient health record.

For the identification of potential duplicate patient health records, a de-duplication algorithm will be applied to de-identified (i.e., coded) patient data, prior to statistical analysis as defined in the Patient De-duplication Plan.

8.3 Data Processing

The Sponsor (or representative) will be responsible for the processing and quality control of the data within the validated system. The handling of data, including data quality control, will comply with applicable regulatory guidelines.

9 DATA ANALYSIS

Full details of all analyses will be described in the statistical analysis plan (SAP).

9.1 General Statistical Methodology

Demographic and other baseline characteristics of patients in the analysis populations, the reasons for exclusion, and completeness of data points will be summarized by cohort and overall. Summary statistics for continuous variables will include number of patients, mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be provided. When required for the statistical analysis of a particular variable, the baseline value will be the last recorded value prior to the index date. All CIs will be constructed at the 2-sided 95% CIs.

9.2 General Aspects of Cohort Balancing

Comparable patient populations from the observational cohort and the L-MIND cohort in respect to the following baseline covariates will be created:

- age (as categorical variable with subgroups <70 vs. ≥70 years of age)
- refractoriness status to last therapy line (Yes vs. No)
- number of previous lines of therapy (1 vs. 2/3)
- elevated lactate dehydrogenase (LDH) levels (>upper limit of normal [ULN]) (Yes vs. No)
- Ann Arbor Stage (I/II vs. III/IV) (see Appendix B)
- history of primary refractoriness (Yes vs. No)
- prior ASCT (Yes vs. No)
- neutropenia (cut-off <1.5 x 109/L) (Yes vs. No)
- anemia [cut-off <10 g/dL (= 6.21 mmol/L)[1]] (Yes vs. No)

1. conversion formula (g/dL x 0.621 = mmol/L)

In this study, multiple sets of baseline covariates will be collected for each therapy line (2nd, 3rd and 4th) administered and used for cohort balancing utilizing estimated propensity scores (ePS). Propensity scores will be estimated for patients with complete information on all baseline covariates (complete case analysis).

1:N *nearest neighbour matching* without replacement will be performed in which each L-MIND cohort patient is randomly selected for matching with N observational cohort patient that are nearest neighbours arithmetically on the ePS (Rosenbaum et al, 1983). "1:N" denotes the ratio of L-MIND cohort to the observational cohort with a maximum ratio of 1:4. In interim cohort balancing, prior to the data base lock, *nearest neigbour matching* will be performed stepwise increasing the matching ratio from 1:1 to 1:4 until for one or more baseline covariates a standardized mean difference (SMD) of 0.2 is exceeded.

The matched population with SMD ≤0.2 for all baseline characteristics and the highest matching ratio will be selected as the main analysis set for endpoint calculations.

For balancing the L-MIND cohort versus systemically administered therapies, a subgroup strata ePS approach will be utilized to achieve perfect balance for number of therapy lines, i.e. separately for patients with two, three and four therapy lines. Separate ePS will be generated and matched population will be created within each subgroup of different number of therapy lines. The matched populations of each subgroup will be aggregated to the overall matched population for analysis.

Additional matched cohorts will be created on the basis of the following *subgroup analysis*:

- 1:N nearest neighbour matching without replacement for patients in 2nd therapy line from L-MIND
- 1:N nearest neighbour matching without replacement for patients in 3rd/4th therapy line from L-MIND

For balancing the L-MIND cohort versus pre-specified treatment regimens, 1:N nearest neighbour matching for nine baseline characteristics will be performed. Patients with different treatment regimens as specified in section 6.1 can be utilized in matched population sets under different treatment regimens. Comparative analysis with L-MIND cohort may be performed only if a certain balance of baseline characteristics is achieved (SMD <0.2 for all covariates).

9.3 Analysis populations

The Enrolled Patients Set (ENR) includes all patients in the observational study and in the L-MIND study who received at least one dose of any study drug along with the complete date of the first dose of the study drug.

The Observational Enrolled Analysis Set (Ob-ENR) includes all patients enrolled in the observational study for whom any data was collected during this study.

The Observational Full Analysis Set (Ob-FAS) includes all patients in Ob-ENR with a minimum of 6 months of follow-up and who met the E/NE criteria as described in Section 7 and received at least one dose of any study drug along with the complete date of the first dose of the study drug.

A minimum of 6 months of follow-up time is met if:

- a patient responded (CR or PR) or progressed or died within 6 months from index date of the utilized therapy line (from study day 1 to 183),

OR

- a responding patient (CR or PR as best response in the study within the analysis window) has a baseline tumor assessment and at least one post-baseline response assessment available at 6 months or later (on or after study day 184)

OR

- a patient has at least one disease response assessment with stable disease (SD), "indeterminate", "not evaluable" or "other" within 6 months from index date of the utilized therapy line (from study day 1 to 183) with at least one assessment or death at 6 months or later (on or after study day 184)

Patients do not fulfill the minimum of 6 months of follow-up time if they are non-responding (e.g., SD or progressive disease [PD] as best response) with a first tumor response assessment beyond 6 months.

The **modified Ob-FAS (mOb-FAS)** consists of patients in Ob-ENR who met the E/NE criteria, but without consideration of the 6 month follow-up rule.

The **Full Analysis Set (FAS)** includes

- patients from the observational cohort who meet the E/NE criteria of the observational study and a minimum of 6 months of follow-up time

AND

- patients from the L-MIND cohort who belong to the L-MIND primary analysis set with a minimum of 6 months of follow-up time. Of note: the E/NE criteria described in Section 7 of this protocol will also be applied to the L-MIND patients prior to their inclusion in the primary analysis set.

The **Modified Full Analysis Set (mFAS)** includes

- patients from the Ob-ENR who met the E/NE criteria described in Section 7

AND

- patients from the L-MIND study who belong to the L-MIND primary analysis set . The E/NE criteria described in Section 7 will also be applied to the L-MIND patients prior to their inclusion in the the primary analysis set

For the mFAS, the 6-month follow-up rule is not applied.

The **Matched Analysis Set (MAS_N)** is a subset of the FAS and includes 1:N matched patients from the L-MIND study and the observational cohort using baseline covariates as explained in Section 9.2 (complete case analysis). This will be performed respectively for the systemically administered therapies and pre-specified treatment regimens. The MAS_N will be the primary analysis population.

The **Modified Matched Analysis Set (mMAS_N)** is a subset of the mFAS and includes 1:N matched patients from the L-MIND study and the observational cohort using baseline covariates as explained in Section 9.2 (complete case analysis), without considering the 6 month follow-up rule. This will be performed respectively for the systemically administered therapies and pre-specified treatment regimens.

For patients in the observational cohort, the above mentioned population sets will be categorized in the datasets on the basis of systemically administered therapies and each pre-specified treatment cohort. Details will be provided in the SAP.

Additional analysis sets may be considered for sensitivity analyses. If applicable, these will be defined in the SAP.

9.4 Sample Size Justification

Interim cohort balancing will be performed based on the nine baseline covariates as described above. Interim analysis will be conducted in order to evaluate the quality of balance, to determine the ratio for *1:N nearest neigbour matching* and the potential need to augment the systemically administered therapies and pre-specified treatment regimens with additional patients. No comparative efficacy analyses will be done in this interim analysis.

In general, inclusion of approximately 2800 patients with any systemic therapies as per NCCN/ESMO guidelines administered is expected to be necessary to complete a successful cohort balancing before conducting comparative efficacy outcome analyses.

As the L-MIND primary analysis set consisted of n=80 patients, the ePS-based 1:N matching will result in a maximal sample size of n=400 in the MAS_4, with a matching ratio of 1:4.

In the table below (Table 4) statistical power and the minimal detectable hazard ratio for different scenarios based on different matching ratios and different number of total OS events for a range of true but unknown HR is provided. A power of 81% would be achieved if more than 91 OS events are observed (e.g. in MAS_1, 37 events in L-MIND cohort versus 53 events in comparator observational for a two-sided logrank test with alpha = level of 0.05c), assuming a true HR of 0.572.

Table 4. Estimated OS events, Hazard ratio and Power

Match ratio	Sum of Estimated OS Events in MAS_N	Estimated OS Events in L-MIND cohort in MAS_N	Estimated OS Events in Observational cohort in MAS_N	True Hazard Ratio	Detectable minimum Hazard Ratio	Power
1:1 NN matching	90	37	53	0.572	0.662	0.76
	91	37	54	0.552	0.663	0.81
1:2 NN matching	137	37	100	0.633	0.701	0.71
	138	37	101	0.622	0.702	0.75
	139	37	102	0.612	0.703	0.78
	140	37	103	0.602	0.704	0.81
1:3 NN matching	184	37	147	0.655	0.716	0.70
	185	37	148	0.647	0.717	0.73
	186	37	149	0.640	0.718	0.75
	187	37	150	0.633	0.718	0.77
	188	37	151	0.626	0.719	0.79
	189	37	152	0.619	0.719	0.82
1:4 NN matching	231	37	194	0.666	0.724	0.70
	232	37	195	0.660	0.725	0.71
	233	37	196	0.655	0.725	0.73
	234	37	197	0.649	0.726	0.75
	235	37	198	0.644	0.726	0.77
	236	37	199	0.638	0.727	0.79
	237	37	200	0.628	0.727	0.80

9.5 Comparative Efficacy Outcome Analysis

For binary endpoints like ORR, CR rate and DoR, Fisher's exact tests will be performed and p-values will be reported. Treatment effect will be estimated in terms of Odd's Ratio using logistic regression model. Difference in the proportions and the ratio of the proportions along with 95% CI will be estimated. More details on analysis methods are provided in the SAP.

For time to event endpoints like OS, PFS, TTNT, DoR and EFS, log-rank test will be performed and p-values will be reported. Hazard ratio (HR) along with 95% CI will be estimated using Cox PH model. More details on analysis methods are provided in the SAP.

9.6 Sensitivity Analyses of Efficacy Endpoints

The following Sensitivity analysis will be performed:

- *1:N nearest neigbour matching* with a *caliper* and *Balancing with Overlap Weights* (Austin, 2011; Li et al, 2018).
- Multiple imputation (MI) technique for missing data in baseline covariates will be applied in the FAS before cohort balancing.
- Potential unmeasured confounding will be assessed (Rosenbaum and Rubin, 1983; Rosenbaum, 1995).

Additional sensitivity analyses may be considered and defined in the SAP.

9.7 Analyses of Tolerability

Treatment discontinuation rates per cohort due to adverse event and duration of exposure to study treatment will be analysed via descriptive statistics.

9.8 Measures to Avoid Bias

The Sponsor takes the following measures to avoid important sources of potential bias.

1) Site selection

The following criteria are taken into account for selection of possible sites for participation in the observational retrospective study:

- Data will be collected from patient health records from a mix of academic hospitals, public hospitals and private practices. It is theoretically possible that 2 or more sources may contain the same patient health record.
- For the identification of potential duplicate patient health records, a de-duplication algorithm will be applied to de-identified (i.e., coded) patient data, prior to statistical analysis as defined in the Patient De-duplication Plan.

2) Patient selection

Patients included in this observational cohort study will be selected to closely resemble characteristics of the patients treated in the L-MIND study (Salles et al, 2019). As such, several key eligibility criteria identical to those employed in the L-MIND study will be used to identify patients for the observational RE-MIND2 cohort. These measures minimize the likelihood of including patients in the observational cohort, who are not comparable to the L-MIND patients.

3) Bias due to systematically missing data

All studies are subject to missing data. Missing data may bias estimation if it is systematically missing. The L-MIND cohort data are subject to monitoring as specified in the L-MIND study protocol. The observational RE-MIND2 cohort data will be monitored for excessive and unexpected missingness, particularly data for the baseline covariates used to balance cohorts. Only complete cases regarding pre-specified covariates will be considered for ePS estimation. However, multiple imputation (MI) for missing data will be performed as a sensitivity analysis.

4) Confounding bias

Cohort balancing will be conducted to address potential confounding from measured baseline covariates. The potential effect of unmeasured confounding factors will be evaluated through sensitivity analyses.

5) Cohort balancing and endpoint analyses

Cohort balancing will be performed following the methods pre-specified in the protocol and Statistical Analysis Plan, which will be finalized prior to Data Base Lock. The choice of baseline covariates to be used for matching and definition of analysis sets and collection period of patient data will also be pre-specified in these documents.

6) Bias due to different follow-up periods

The required minimum follow-up of 6 months for the comparative analysis prevents a bias in favor of the L-MIND cohort due to the following reasons.

a) For patients treated in daily practice a short lasting response may be missed because the schedule of assessments per local practice may be less frequent or be influenced by external factors such as scan availability etc. In such cases only a progression event might be recorded.

b) Patients treated in daily practice may have a lower chance to have an objective response recorded to a particular treatment due to an early discontinuation without adequate assessment of tumor progression. To control such bias, censoring rules for time to event endpoints will be depicted in SAP.

10 QUALITY CONTROL & QUALITY ASSURANCE

Sponsor or representative will check data quality by reviewing the data collected from the different sources for completeness and accuracy, and in accordance with the data management and medical review plans.

For each patient in the study, source documents which entail the data collected must be retained. All collected information must be traceable to these source documents.

Sponsor or representative must be given access to all relevant source documents to confirm their consistency with the database entries, and if required, for audit purposes.

Site monitoring will be performed by the Sponsor or representative as required to review the progress of the study and to ensure compliance with the protocol, standard operating procedures and guidelines.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

For this retrospective non-interventional cohort study with secondary use of previously collected data in patient medical records (including follow-up data from health care professionals), a submission of suspected adverse reactions in the form of Individual Case Safety Reports (ICSR) is not required. The adverse events/reactions collected as reasons for treatment discontinuation will be recorded and summarized within the final study report.

12 PROTECTION OF HUMAN SUBJECTS

12.1 Protection of Personal Data

Every patient will be assigned a unique identification number and all collected study information will be coded with this number. The identification record that allows linking the patient number to her/his identifiable information will only be kept at the site for monitoring and audit purposes and may not be disclosed.

Patient's personal information will be accessible only to the following authorized representatives or agencies who are obligated to maintain confidentiality by the nature of their work, or are bound by confidentiality agreements: physician as well as his/her staff and entitled representatives, national and foreign health authority inspectors, Sponsor and their authorized representatives.

The Sponsor will assess its representative(s) responsible for data capturing, processing and statistical analysis to ensure that necessary data protection level is guaranteed.

12.2 Regulatory and Ethical Compliance

Compliance with the Sponsor and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in this study are protected (consistent with the principles that have their origin in the Declaration of Helsinki), and that the study data are credible and responsibly reported.

This study is designed and shall be implemented and reported in accordance with Guidelines for Good Pharmacoepidemiology Practices (GPP), section 4.9.5 of the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and with the ethical principles laid down in the Declaration of Helsinki.

Prior to study start, the responsible physician is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with the protocol and to give access to all relevant data and records to Sponsor or representative, and regulatory authorities as required. If a regulatory authority requests an inspection , the physician must immediately inform the Sponsor.

12.3 Records Retention

Since the data from this study will be used to support marketing authorization of tafasitamab, study documents including patient health records will have to be retained per the ICH GCP requirements until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (tafasitamab). These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the sites as to when these documents will no longer need to be retained.

12.4 Informed Consent

Where required by law or regulation, informed consent (approved by IEC/IRB) will be obtained from patients before the start of data collection, or if incapable of doing so, such consent will be provided by a legally acceptable representative of the patient.

It will also be explained to the patients that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to current or future treatment. Patient's willingness to participate in the study will be documented in a signed and dated informed consent form (ICF). The physician will keep the original informed consent and a copy will be given to the patient.

For deceased or otherwise unreachable patients, in line with European Regulation n. 2016/679 and with related national legislations, no informed consent will be collected for the study, provided that the competent IEC/IRB has provided favorable opinion and that any other local regulatory requirements on this matter is met.

An unreachable patient refers to a patient that cannot be reached by the physician or his/her staff after diligent effort has been made to obtain the informed consent.

Appropriate and specific measures will be taken to safeguard the interests of the patient such as the pseudonymization of personal data and the encryption of personal data.

12.5 Protocol Approval and Amendment

Where required per local regulatory requirements, the Sponsor or representative will submit the protocol and any amendments to an IEC/IRB and/or regulatory authority for approval of the study conduct. The decision of the IEC/IRB and/or regulatory authority concerning the conduct of the study will be made in writing to the Sponsor or representative. No data collection will commence prior to all required written approvals are obtained.

12.6 Study Termination

The Sponsor may terminate the study at any time and for any reason.

13 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study may be submitted for publication and/or posted in a public database. Publications will comply with internal standards of the Sponsor and the International Committee of Medical Journal Editors (ICMJE) guidelines.

14 REFERENCES

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15 APPENDICES

15.1 Appendix A: International Prognostic Index

International Prognostic Index (IPI):

Source: International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993.

- age older than 60
- lactate dehydrogenase level higher than normal
- Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or greater (see Appendix C: ECOG)
- stage III or IV disease
- more than 1 involved extranodal disease site

The International Prognostic Index (IPI) gives 1 point for each of the above characteristics, for a total score ranging from 0 to 5 correlating with the following risk groups:

- low risk: 0–1 points
- low-intermediate risk: 2 points
- high-intermediate risk: 3 points
- high risk: 4–5 points

15.2 Appendix B: Ann Arbor Staging

Ann Arbor Staging* - Cotswolds Recommendations**

Sources: *Carbone et al, 1971 **Lister et al, 1989

Stage I: involvement of a single lymphatic region (I), or localised involvement of a single extralymphatic organ or site (IE).

Stage II: involvement of 2 or more lymphatic regions on the same side of diaphragm (II) or localised involvement of an extralymphatic organ or site and 1 or more lymph node regions the same side of diaphragm (IIE).

Stage III: involvement of 2 or more lymphatic regions on both sides of diaphragm (III) which may also be accompanied either by localised involvement of an extralymphatic organ or site (IIIE), or by involvement of the spleen (IIIS).

Stage IV: Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissue, with or without associated lymph node involvement. Bone marrow or liver involvement will always be considered as stage IV.

Criteria for B-symptoms

The presence of: (a) unintentional weight loss of more than 10% within the previous 6 months and/or (b) fevers of greater than 100.5° F or 38.0° C for at least 3 consecutive days without other evidence of infection and/or (c) drenching night sweats without evidence of infection, is denoted by the suffix letter ‘B’. ‘A’ indicates the absence of these symptoms.

15.3 Appendix C: ECOG Performance Status

Grade	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al, 1982

Credit: the Eastern Cooperative Oncology Group (ECOG), Robert Comis M.D., Group Chair.

15.4 Appendix D: Recommended Therapies for R/R DLBCL - NCCN Guidelines Version 6.2019

https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

Suggested Treatment Regimens for Second-line and Subsequent Therapy (intention to proceed to transplant)

DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab

DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab

GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab

GemOx (gemcitabine, oxaliplatin) ± rituximab

ICE (ifosfamide, cisplatin, etoposide) ± rituximab

MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Suggested Treatment Regimens for Second-line and Subsequent Therapy (non-candidates for transplant)

Bendamustine ± rituximab

Bendamustine, rituximab and polatuzumab vedotin-piiq (after ≥2 prior therapies)

Brentuximab vedotin for CD30+ disease

CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab

CEOP (cyclophosphamide, etoposide, vincristine, procarbazine) ± rituximab

DA-EPOCH ± rituximab

GDP ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab

GemOx ± rituximab

Gencitabine, vinorelbine ± rituximab

Ibrutinib (non-GCB DLBCL)

Lenalidomide ± rituximab (non-GCB DLBCL)

Rituximab

CAR-T Cell Therapy after two or more lines of systemic therapy

Axicabtagene ciloclecucel
Tisagenlecleucel

15.5 Appendix E: Recommended Therapies for R/R DLBCL – ESMO Guidelines 2015

First Relapse / Progress	
Eligible for Transplant	Not eligible for Transplant
Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, R-GDP) as salvage treatment For chemosensitive patients: R-HDCT with ASCT as remission consolidation Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse	Platinum- and/or gemcitabine-based regimens Clinical trials with novel drugs
>2 Relapse / Progress	
Eligible for Transplant	Not eligible for Transplant
Allogeneic transplantation Clinical trials with novel drugs	Same salvage regimens as in patients eligible for transplant Clinical trials with novel drugs R-GEMOX (rituximab, gemcitabine, oxaliplatin) Pixantrone

Source:
Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
H. Tilly, M. Gomes da Silva, U. Vitolo, A. Jack, M. Meignan, A. Lopez-Guillermo et al, Annals of Oncology 26 (Supplement 5): v116–v125, 2015.