German Lymphoma Alliance-Registry

Affiliation: German Lymphoma Alliance e. V. (Amtsgericht Göttingen Registernummer: VR 201948)

Short-Title: GLA-R

Protocol-Date: 27.07.2023

Protocol-Version: 1.0

Writing committee

Clinical Part:

- Prof. Dr. Christian Buske, Ulm
- Prof. Dr. Björn Chapuy
- Prof. Dr. Martin Dreyling, München
- Prof. Dr. Marcus Hentrich, München
- Prof. Dr. Georg Heß, Mainz
- Prof. Dr. Kai Hübel, Köln
- Prof. Dr. Gerald Illerhaus, Stuttgart
- Prof. Dr. Christian Scholz, Berlin
- Prof. Dr. Ralf Trappe, Bremen
- Prof. Dr. Lorenz Trümper, Göttingen
- Dr. Thomas Weber, Halle (Saale)

Statistical Advice:

- Prof. Dr. rer. biol. hum. Eva Hoster, München
- Dr. Irene Schmidtmann, Mainz

Biomaterials and correlative sciences:

- Prof. Dr. Björn Chapuy, Berlin
- Prof. Dr. Georg Lenz, Münster

Project coordination on behalf of the GLA:

Prof. Dr. Georg Heß, Dr. Anke Ohler; University Medical Center of the Johannes Gutenberg-University, Department of Internal Medicine III, Langenbeckstr. 1, 55131 Mainz

Project agency

University Medical Center of the Johannes Gutenberg-University Interdisciplinary Center for Clinical Trials (IZKS), Langenbeckstr. 1; 55131 Mainz, Germany

Central Contact of the registry:

E-mail: info@gla-register.de

Document History

Version	Date	Comments/Summary of Changes
1.0	27.07.2023	Original Document

Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned.

Operating institution of Sponsor (German Lymphoma Alliance e. V.)
Prof. Dr. Martin Dreyling (President 2023)

_____

Date, Signature

Registry Delegate of the German Lymphoma Alliance e. V.
Prof. Dr. Georg Heß

_____

Date, Signature

German Lymphoma Alliance e. V., responsible biometrician
Prof. Dr. Eva Hoster

_____

Date, Signature

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

aaIPI	Age-adjusted international prognostic index
ABC	Activated B-cell
ADCs	Antibody-drug conjugates
AIDS	Acquired immune deficiency syndrome
AKdÄ	Drug commission of the German medical profession (Arzneimittelkommission der deutschen Ärzteschaft)
ALK	Anaplastic lymphoma kinase
AMG	German medicinal products act (Arzneimittelgesetz)
ARL	AIDS-related lymphoma
ART	Antiretroviral therapy
BCL2	B-cell leukemia/lymphoma 2 protein
BCL6	B-cell leukemia/lymphoma 6 protein
BfArM	Federal Institute for drugs and medical devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BL	Burkitt lymphoma
BTK	Bruton´s tyrosine kinase
cART	Combination antiretroviral therapy
CAR-T-cell	Chimeric antigen receptor T-cell
CCC	Comprehensive Cancer Center
CDC	Complement dependent cytotoxicity
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
COO	Cell of origin
CR	Complete remission
ctDNA	Circulating tumor deoxyribonucleic acid
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRST	German Registry for Stem Cell Transplantation
GDPR	General data protection regulation
DSHNL	German study group for highly malignant non-hodgkin lymphomas
EBER-ISH	Epstein-Bar Virus encoded RNA in situ hybridization
EBMT	European Group for Blood & Marrow Transplant Research
EBV	Ebstein-Barr Virus
EC	Ethics committee
ECOG	Eastern cooperative oncology group
eCRF	Electronic Case Report Form
EMCL	European mantle cell lymphoma registry
FL	Follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
G-BA	Federal joint committee (Gemeinsamer Bundesausschuss)
GCB	Germinal center B-cell
GLA	German Lymphoma Alliance

GLA-R	German Lymphoma Alliance-Registry
GLSG	German low grade lymphoma study group
HDT	High-dose therapy
HIV	Human immunodeficiency virus
HIV-HL	HIV-associated Hodgkin lymphoma
HL	Hodgkin lymphoma
IC	Informed consent
IMBEI	Institute of Medical Biostatistics, Epidemiology and Informatics
IMiDs	Immunomodulatory imide drugs
IPI	International prognostic index
IPS	International prognostic score
IQWIG	Independent Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
IZKS	Interdisciplinary Center for Clinical Trials
LKR	Landeskrebsregister
MCL	Mantle cell lymphoma
MH	Morbus Hodgkin/Hodgkin´s lymphoma/Hodgkin´s disease
MIPI/MIPI-c	Mantle Cell Lymphoma International Prognostic Index
MM	Multiple Myeloma
moAB	Monoclonal antibody´s
MRD	Minimal residual diseasedisease
mTOR	Mammalian target of rapamycinrapamycin
MYC	MYC proto-oncogene
MZL	Marginal zone lymphomalymphoma
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
PBL	Plasmablastic lymphomalymphoma
PEL	Primary effusion lymphomalymphoma
PD	Progressive disease
PDX	Patient-derived xenograftxenograft
PET	Positron emission tomography
PI3K(i)	Phosphatidylinositol 3-kinase (inhibitor)
PFS	Progression free survival
PLHA	People living with HIV/AIDS
POD12	Progression of disease within 12 month
POD24	Progression of disease within 24 month
PR	Partial response
PTLD	Post-transplant lymphoproliferative disorder
QoL	Quality of life
RKI	Robert Koch Institute
SC	Steering committee
SCT	Hematopoietic stem cell transplantation

SD	Stable disease
SOP	Standard operating procedure
T-NHL	T-cell non-Hodgkin lymphoma
WHO	World health organization
WP	Working Party

1. Overall Background

Real world evidence has become a widely accepted source of information for various cancer entities to add to or partly substitute the result from controlled clinical trials. In detail, real world data collections provide information on therapeutic pathways, use of novel treatments, treatment algorithms and impact of these therapies on the overall/more general patient population (1, 2). Special benefits are the long-term collection of data over the entire disease course and the integration of information of literally all patients without inherent limitations of controlled trials. In addition, long-term collections allow understanding of the change of treatment patterns over time, survival trends in different patient generations, trends in participation in clinical trials and their impact on survival, quality of life (QoL), health care utilization and potentially complications and limitations of multiple treatments (3).

In this intent, the German Lymphoma Alliance will establish a clinical, non-interventional, retro- and prospective clinical registry. All patients with malignant lymphatic malignancies (except chronic lymphocytic leukemia (CLL), morbus hodgkin (MH) and multiple myelom (MM)) and related lymphoproliferative diseases can be included into the registry.

The current lymphoma landscape - the impact of Real World Evidence

Major improvements of biological understanding and classification of malignant lymphomas has been made over the last decades. This has resulted in a continuous fragmentation of disease entities with increasingly smaller samples sizes, which in turn limits the chance to study all entities prospectively in distinct trials.

At the same time, a substantial number of therapeutic improvements were established based on controlled clinical trials. The full impact on routine care, however, can hardly be detected within these studies. In general, this limitation is related to patient selection, limited follow-up and interference with routine treatment strategies. Furthermore, complex and selective inclusion criteria, the overrepresentation of young and fit patients and the underrepresentation of patients treated at private institutions frequently results in inferior outcomes of treatments in routine use—in terms of efficacy and toxicity. In addition, some treatment options were approved on small phase II trials lacking a randomized comparison to standard options, whereas in other controlled trials standard treatments were used, which would no longer be considered the primary choice of treatment. Finally, long-term effects on quality of life and impairment of a variety of dimensions, as well as late toxicities can only be followed in a limited fashion within clinical research projects. All these limitations highlight the importance of real world data, which in part can compensate for the lack of knowledge, which exists if only controlled trials in distinct therapeutic scenarios are considered.

Integration of registries

Currently, several lymphoma registries are already implemented in Germany focusing on distinct entities (e.g. follicular lymphoma (FL) or mantle cell lymphoma (MCL)), using different documentation formats and platforms, requiring different informed consent forms and have redundant administrative and supportive structures. It is of great importance to secure the data which already have been obtained on the one hand, but develop a common platform, which allows to significantly reduce workload, expanses and required structures. To accomplish this unification (on one platform or an established exchange format) is a central part of the GLA-R.

Further aspects

Ideally, the collection of clinical data will be accompanied by collection or at least registration of a catalog of biological samples for the patients included in the registry, inclusion of prospective patient reported outcomes or theoretically even biometric information as provided by e.g. wearables.

There will be harmonized data sets for all patients with additional entity-specific additions.

In addition, using appropriate statistical instruments like propensity score matching or weighting and regression modelling, valid comparison to data from clinical trials can be made (4). Furthermore, long-term follow-up of clinical trials and further research projects can be managed via registries.

Regulatory considerations

Whereas clinical registries cannot provide the data depth and all quality parameters of controlled clinical trials, it is of great importance to comply with current regulations and suggestions for the conduct of such data collections to standardize results and leverage acceptance of the results obtained (3). Recently, the German Institute for Quality and Efficiency in Health Care (IQWIG) has published a which covers clear instructions for quality measures for research done in clinical registries to comply with requirements for acceptance of respective results (5). To comply with these regulations will be a major effort of the GLA-R to safeguard the future value of the project.

Non-interference with treatment

Within the registry predetermined treatment concepts are not evaluated in terms of indication and appropriateness. Neither is any treatment suggested, nor will any advice be given for the treatment of an individual patient.

2. Aims of the Registry

The following not exclusive aims of the registry have been defined, further aspects may be added at any time:

On an organizational level

- To build an overarching platform for the collection of data of patients with malignant lymphoma
- To integrate currently active registries within the network of the GLA
- To establish appropriate tools for entities not followed currently
- To establish an appropriate structure to conduct projects for:
    - Representation of health care utilization
    - Therapy comparison, Evaluation of Efficacy, and benefit in the routine
    - Analysis of epidemiological differences and correlations
    - Registry based studies
    - Routine Practice Data Collection (e.g. Anwendungsbegleitende Datenerhebungen, AbD)

Establish a platform for linked biologic analyses

- On primary materials and potentially on prospectively sampled materials

To establish a data exchange platform

- With other academic complimentary registries
- To develop a tool to integrate data from clinical trials
- To establish long-term follow-up of clinical trials
- To integrate currently available data from earlier trials as benchmark.

To offer an information resource platform

- For treating physicians, pathologists, researchers
- To support on demand e.g. regulatory bodies
- To interact with patient advocacy groups.

3. Patient selection

All patients with the diagnosis of a malignant lymphoma are eligible in general (exceptions are stated in inclusion criteria chapter 3.1). However, data entry depends on the development status of the registry, e.g. if an appropriate module for the entity already has been activated.

It is especially encouraged, to include patients which would not be eligible to participate in clinical trials due to their age, underlying health conditions or comorbidities, reflecting the daily clinical routine.

Patients can be included regardless of their individual treatment time point during the disease course. If available, all relevant data of the prior disease course will be collected retrospectively.
Application will be made to accept the entry of patients who already have deceased at the time of the initiation of the registry. Restrictions may apply to specific entities, depending on coverage within the registry.

3.1. Inclusion criteria

- Malignant lymphoma (except for Hodgkin's disease (MH) without concomitant HIV infection, multiple myeloma (MM) and chronic lymphocytic leukemia (CLL)) or related lymphoproliferative disease e.g. Castleman's disease
- Informed consent
- ≥ 18 years at the time of consent

There are no exclusion criteria.

4. Objectives

4.1. Overall scientific objectives

It is the purpose to understand efficacy, treatment algorithms, change of treatment patterns, influence of distinct treatment on the subsequent treatment lines, long-term results of clinical research projects, pattern of resistance, quality of life as well as health care utilization. Subgroup analyses will be performed e.g. to understand the influence of specific novel treatment approaches and the fate of distinct risk populations, as defined by clinical, biologic or genetic characteristics.

4.2. Primary Objective

Disease specific: Understand the disease course of different lymphoma entities with the use of different treatment modalities or different treatment sequencing.
Treatment specific: Understand the results and impact of specific treatment methods.

4.3. Secondary Objectives (non-exclusive)

Note: Additional objectives might be added depending on new scientific questions or results

- Understand scope of responses to sequentially applied treatments
- Collect real world data on treatments used
- Collect real world data on progression free survival

- Collect real world data on overall survival
- Collect real world data on healthcare resource utilization (project-specific)
- Develop prediction model for selection of drugs
- Analysis of treatment schedule algorithms
- Long-term follow-up of clinical trials
- Analyze treatment specific adverse events (project-specific)
- Evaluation of prognostic scoring system in the population of subpopulations
- Evaluation of impact of comorbidity scores on outcome
- Evaluation of Quality of Life (project-specific)

Note: QoL analysis are highly relevant and attractive, however cannot be analyzed on a retrospective fashion and therefore will be collected prospectively only from selected patient populations or within distinct research projects.

5. Statistical Analysis

The registry data will be used to evaluate commonly accepted parameters for the description of disease risk, treatments received, response to treatment, pattern of relapse, relapse strategies etc. Non-exclusive parameters are:

Cohort characterization:

- Demographics
- Relevant concomitant diseases
- Disease presentation
- Histology, subtype, clinical and molecular risk factors
- Stage, symptoms, including date of assessment
- Evaluation of risk scores according to current recommendations (adaptive)

Treatment characteristics and outcome:

- Type of treatment in first or subsequent treatment lines: antibody, chemotherapy, HDT, use of novel agents, radiotherapy, use of maintenance, adherence, cellular therapies
- Response to different treatment lines: Quality of remission (CR, PR, SD, PD, n.k.) and the method of detection (clinical, radiographic, PET, MRD etc.)

- Remission duration and survival analysis: DOR, ORR, PFS, OS, cause of death, after first-line treatment and subsequent lines, proportion of early relapses (e.g. POD12, POD24) and impact on results
- Pattern of relapse, method for relapse detection
- Identification of treatment pathways in the entire population and in subgroups (age, risk, growth pattern, period of treatment etc.)
- Reasons for discontinuation of treatment
- Exploratory analysis of above-mentioned parameters in relevant subgroups, e.g. age (discrimination by age itself and fitness for intensive treatment), clinical and genetic risk profile etc.

6. Organizational Structure of the Registry

This pan-lymphoma registry represents a core scientific project of the German Lymphoma Alliance e. V. This implies that all key decisions in respect to the registry are to be discussed and decided within the assembly of the Alliance. For practical reasons, however, a steering committee (SC) and a GLA-R Delegate will be assigned to develop or continue the project for the Alliance in liaison with the board of the GLA, e.g. as responsible person for submission to ethics committee and other relevant regulatory bodies, if required.
The following regulations apply:

6.1. Governance

Contracting for funding (either public or with e.g. companies) is awarded by the GLA or a “for profit” branch of the “e. V.”, whatever is appropriate. The GLA will mandate the conduct of the registry to an appropriate partner (Interdisciplinary Center Clinical Trials (IZKS) and Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI)), which is responsible for technical facilitation, data hosting and quality management, regulatory, and biometry but does not work scientifically on its own intent on the data. However, analysis on demand can be mandated by the GLA, if required. The GLA establishes a steering committee, which consists of the WP registry, members of disease specific WP and qualified researchers, and supervises the GLA-R and advises on the specific projects. Importantly, the steering board will work to established rules for the conduct of registry studies within the GLA-R, e.g. how to evaluate scientific projects, whom to grant access, publication of results, cooperation with non-academic institutions etc. The following diagram summarizes this structure.

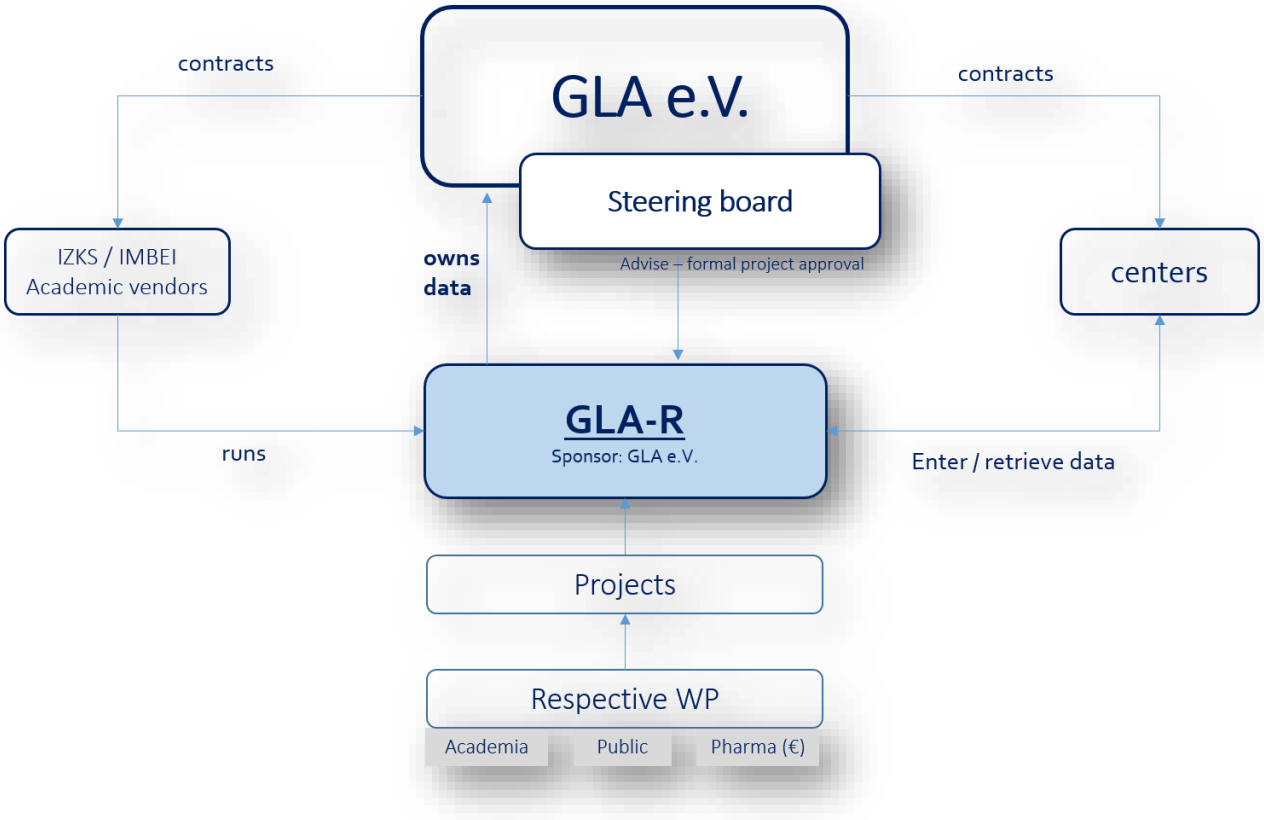

Figure 1: Organizational structure of the registry

6.1.1. Composition of the Steering committee

The following representatives are involved

- Organization/Speaker of the Board: GLA-R Delegate (G. Heß, 2023)
- Further members:
  - Registry Delegate of the GLA
  - Delegate of WP Biometry and Bioinformatics
  - Delegate of WP Diagnostics and Biology
  - Lead of current GLA-registries (MZL/FL, T-NHL, MCL)
  - Delegate of central services (IMBEI/IZKS)
  - Up to 3 Delegates of the group with expertise in the field
- Ombudsman
  - President of the GLA (or President elect as deputy)

6.1.2. Meeting of the Steering committee

The SC will meet once a year in a personal meeting, in which the speaker of the board will present the current status of the entire project.
Up to four virtual meetings will be scheduled to discuss specific projects or actual questions.

6.2. Data Ownership

The database will be owned by the GLA. The transfer of rights to the GLA will be regulated by the informed consent; each patient has to sign prior to participation. For pre-existing data bases migration to the GLA-R is preferred with privileges (e.g. right to veto of data usage, (co-)authorship) for founding institutions for a distinct period (e.g. 10 years in general) or individual regulations, which may apply. Appropriate regulations for the transfer of data from existing registries and former clinical trials into the GLA-R will be made in accordance with applicable law.
Alternatively, and especially during set-up of the registry, data sharing with existing registries might optionally be used for scientific exchange and might be the preferred option prior to final transfer of registry data.

6.3. Data Sources

The GLA-R integrates available data from various sources. Non-exclusive examples are

- Data entered from GLA partner sites upon informed consent of patients with lymphoma in GLA-R (retrospective and prospective).
    - data from patients which have deceased can be entered depending on the specific regulations at the distinct participating sites -depending on EC-approval at the respective sites
- Data from already existing lymphoma specific registries, e.g. MZL-registry, FL-registry, T-NHL-registry, (E)MCL-registry and all others should finally be migrated into the GLA-R.
- Data from former clinical research projects of GLSG, DSHNHL and other preceding trial groups after regulatory clearance.
    - For the transfer of data from ancient trials of precursor trial groups (e.g. GLSG, DSHNL) specific regulations will be defined by the WP Biometry.
- Data transferred from other non-lymphoma specific registries as procedure related registries (e.g. DRST, EBMT), national cancer registries or clinical cancer registries of Comprehensive Cancer Center (CCC) or equivalent.

- Data of upcoming GLA-trials, which mandatory should be transferred in a suitable form into the registry.

The migration of data will be dependent on regulations which will be defined to respect current legal or data protection regulations.

6.3.1. Bidirectional data exchange with existing national registries (LKR or equivalent)

A variety of registries exists, which aim to collect data on the disease course of cancer patients. Namely the registries on country basis (Landeskrebsregister) or clinical cancer registries of CCC's. For reporting institutions, it is tiresome to re-enter data on multiple platforms. Therefore, the GLA aims to establish an exchange strategy with the respective registries. Importantly, LKR's could serve to access all lymphoma patients diagnosed in Germany. The GLA-R could then approach individual sites to collect additional information on all patients or groups of special interest.

7. Research Projects within the Registry

7.1. Studies of Members of the GLA

In general, sites can retrieve the information about own patients entered into the registry in a condensed and automatized fashion. If further data/analysis are needed, each member of the GLA has the option to develop a distinct study to be conducted within the registry. An informal inquiry on a limited number of information, e.g. number of available patients and potential costs can be addressed to the managing group of the registry.

An appropriate study application should contain the scientific background, aims and endpoints of the research. All partners involved need to be declared as well as the role of a potential funding source. The application should name the responsible researchers, including the statistician, and describe the required data, the analysis plan and the intended use. The application template provided on the download section of the GLA-R homepage must be used. The application will undergo a central review process to address novelty, soundness and feasibility of the project as well as personal qualification

- The primary review will be performed by the respective working party, e.g. WP indolent lymphoma, aggressive lymphoma or biometry
  - The WP will judge the above-mentioned criteria
  - Will make a general recommendation and
  - Will recommend whether a project should centrally be funded by the GLA

- The secondary review will be performed by the steering committee (SC) of the registry. This review will focus on
  - Feasibility, financing and time lines and availability of resources
  - If there are several projects with WP approval the SC will prioritize work order and central funding of the projects
  - In addition, the steering committee will oversee the selection of authors to safeguard a fair distribution of authorships based on contribution to the respective work.

If there is a positive vote, the researcher may receive data sets for further analysis or a complete analysis as defined in the protocol of his project. Notwithstanding, approval of the project may not cover the costs of the project, however, the GLA can grant the conduct on excellent projects.

7.2. Collaboration with other study groups, legal institutions and commercial entities

Analyses of data within other scientific collaborators will always be an important way to fully exploit the data set obtained in the registry. This might occur in form of collaboration with other academic institution or groups or with commercial entities. Whatsoever, external partners must name a partner within the GLA, who will act as bailsman and will sponsor the project within the GLA.

7.2.1. Academic co-operations

The GLA-registry is open to share its data to the network of national and international academic databases. Whenever necessary, shared data analysis in order to address specific questions or to increase the power of distinct analysis will be performed. Data might be pooled in aggregated form or if necessary, on a patient level. In the latter case, data will be shared in an anonymized fashion, or (double) pseudonymized if indispensable for the work performed.

All these cooperative analyses will need approval of the WP/GLA-R steering committee, as described under 7.1. A contract or appropriate agreement needs to be signed by the involved project partners.

7.2.2. Cooperation with other partners, e.g. commercial entities

Besides the academic project collaborators, commercial entities (e.g. pharmaceutical companies) may ask to partner specific projects. This might be of benefit for patients, if the results can stimulate clinical projects or preclinical research to identify suitable treatment targets or access to treatment can be deemed, based on registry studies. Therefore, in general the GLA accepts to perform shared analysis with non-academic partners if the following criteria are fulfilled:

- The project is scientifically sound and contributes to the research field, assessed by the GLA-R-steering committee.
- The respective GLA-R-steering committee agrees upon the concept (during board meeting, or electronic communication). One member of the working party needs to act as bailsman of the project.
- The raw data remain within the academic network and no retraceable patient information will be provided to the cooperation partners.
- The research is sufficiently funded by the requesting entity and based on a formal agreement, which gives detailed information about scope, data usage, funding and presentation of the data.
- If presentations or publications raise from such co-operations, the GLA is represented adequately based on the relative distribution.

All these cooperative analyses will need approval of the WP/GLA-R-steering committee, as described under 7.1. A contract or appropriate agreement needs to be signed by the involved project partners.

7.2.3. Cooperation with legal entities

The GLA and the associated steering committee of the registry are open to cooperate with legal entities e.g. approval authorities or other relevant legal bodies, e.g. payers. For cooperation a regulatory framework will be used, to share data in an appropriate fashion as requested. However, the GLA reserves at any time the right to deny on the provision of data. If required, adoptions to the data base can be made to serve special requirements of distinct projects, if the costs of such are covered by the project costs.

All these cooperative analyses will need approval of the WP/GLA-R steering committee, as described under 7.1. A contract or appropriate agreement needs to be signed by the involved project partners.

7.3. Data Handling in projects

Aggregated data analysis is the preferred method of collaboration, exemptions can only be made upon presentation of sufficiently justifying reasons.

Patient level data will be provided only if indispensable for the project (double pseudonymized, e.g. Mainzel-Liste, or appropriate tools.) and covered by respective informed consent and approval by relevant authorities.

In the case of cooperation with pharmaceutical companies a neutral third- party data provider must be involved for analysis, in case if single data sets are used for analysis.

8. Methods of the registry

8.1. Type of Investigation

Observational, non-interventional, pro- and retrospective patient registry.

8.1.1. Statement on investigational medical products

There will be no investigational medical products within the registry.

Neither is any treatment included into this protocol, nor will any advice be given for the treatment of an individual patient, based on data of the registry.

8.2. Database

The GLA-R will be implemented as a remote data entry system using an eCRF (electronic Case Report Form). After full implementation the entry portal, the eCRF will be the same for all centers and all lymphoma entities, with a harmonized data set used for all entities and additional specific data sets required for different lymphoma subtypes. Already actively recruiting registries (e.g. MCL, FL, MZL, T-NHL) will - in a first step - be co-affiliated with the GLA-R until integration into the GLA-R, established platform is feasible.

The database will allow to repeatedly access individual patient cases to expand the information available. After registering a patient, centers will receive regular reminders to fill in the appropriate information at least once yearly. Upon registration of a patient, data will be pseudonymized. If all data for an individual patient are entered (entry closed), data will be transferred to an anonymized mode. An appropriate tool will be used to identify potential double entries to avoid duplicates in the registry.

8.3. Data collection time points

In brief, data at baseline, at every treatment initiation, at the end of treatment and subsequent relapse and last follow-up (remission, death, reason for death) will be collected repeatedly.

Time points for the collection of data will be on the one hand event driven e.g. at the date of primary diagnosis, at any new therapy and in the case of death.

On the other hand, the clinical course of the patients will be followed for at least once a year. Centers will receive an annual reminder to fill the appropriate information in a time interval of max. 12 months.

8.4. Sample Size

There is no upper number of patients which can be included into the registry.

8.5. Data Collection (basic data set)

Information will be retrospectively collected during treatment until the moment of entry into the registry and prospectively thereafter. If acceptable by local and national regulations, the registry is open to integrate historical patient data, especially to provide a reasonable historical control.

Non-exclusive parameters are:

- Patient demographics, as age, sex, ethnicity
- Patient characteristics, as relevant concomitant diseases
- General performance parameters (e.g. ECOG)
- Disease characteristics, as histology, subtype, clinical and molecular risk factors
- Stage, subgroup-symptoms, risk group, including date of assessment
- Treatment characteristics, as e.g. Type of primary treatment: antibody, chemotherapy, HDT, use of novel agents, radiotherapy, use of maintenance, adherence
- Response to treatment: type of remission, DOR, PFS, OS after first-line treatment and subsequent lines, proportion of early relapses
- Method of disease evaluation
- Reasons for discontinuation of treatment
- MRD information if available and method of detection
- Pattern of relapse
- Type of subsequent treatment lines in the same way as for primary treatment
- Health care utilization, as hospital stays, use of certain drugs and methods (project-specific)
- Quality of life and late sequalae of treatment (project-specific)

The actual list of items collected are accessible in the internal section of the website of the GLA-R. Due to the nature of this registry, adoption of items will be required over time. In general, suggestions for revision submitted until 31.12. of each business year, will undergo review until 31.03. of the subsequent business year and if accepted will be integrated into the data base until 30.06. of the same year. The revised item list is published at the same time on the GLA-R website for reference. Dedicated questions for the conduct of scientific projects can be posed to the coordinating team of the GLA-R at any time.

8.5.1. Data for different lymphoma entities

As not all entities with dedicated data sets can be activated at the same time, the GLA will use a step by step strategy.

- First, in lack of a registry for large B-cell lymphomas this will be the first entity to be served in the upcoming registry.
- Second, stepwise all existing registries will be unified by prospectively collecting data on the respective populations and
- Integration of existing data upon clarification of rights and obligations

8.6. Documentation of adverse events

The registry, in contrast to interventional clinical trials, is not subject to the regulations of the current amendment of the AMG on the obligation to report. In principle, however, physicians in Germany are obliged to report adverse events according to § 6 of the professional code of conduct for physicians working in Germany. Reports are to be addressed alternatively to the Drug Commission of the German Medical Association (AKdÄ), the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), the Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich Institut, PEI) or to the manufacturer by the participating site. Formal reporting to the AKdÄ or federal authorities must be carried out by the participating site and is not within the obligations of the GLA-R.

For the evaluation of applied therapy concepts within the registry, knowledge of serious adverse or unexpected events is useful. Hence, serious or unexpected adverse events should be collected on a project-specific basis. Serious events are events that

- Are fatal or life-threatening
- Require inpatient treatment or prolongation of inpatient treatment
- Result in permanent or serious disability or incapacity.
- Lead to a congenital anomaly or birth defect in a newborn/infant with maternal exposure to drugs.
- Represent—in the physician's opinion—a medically significant event, i.e., it could endanger the patient, require medical intervention or surgical intervention to prevent one of the events mentioned above.

In addition, adverse of special interest may be defined for specific disease situations, where current knowledge is limited and new information contribute to a better understanding of potential adverse events.

8.6.1. Adverse events in defined projects

If the GLA-R is part of a distinct research project of a GLA-member or a partner institution in which separate regulations are made for the documentation of adverse events, these regulations will only be followed for the respective project.

8.7. Duration of data collection

No formal end of the data collection is planned. As novel agents enter the therapeutic arena on a regular basis, and still a substantial number of patients die of lymphoma, the perpetuation of the registry is foreseen to evaluate the impact of novel developments. Therefore, last patient last data collection is not defined at this time point.

If there is no sufficient funding for the active conduct of the registry in the future, the collection of data and maintenance of the database might be paused. In this case, available data, will be anonymized and saved centrally in a GLA-owned storage tool in a format which allows further usage upon approval of the relevant committees. Funding of data migration and storage is guaranteed by the GLA. Until the data are secured by the GLA, the University of Mainz guarantees to securely store the data.

8.8. Registration of biological samples

In a first step, the registry is intended as a collection of clinical data. Whatsoever, sites will have the option to indicate whether biological materials are available for different patients (date, material). This information can be used to identify patients with suitable materials for research projects, after an additional and separate informed consent, independent from the registry.

In addition to this strategy, patients will be asked to donate samples which have been sent to a member of the reference pathology network, to make sparse material available for further usage within the GLA-network and to add results of reference pathology review to the data set of the GLA. If a donation is granted, samples will primarily be stored at the respective reference pathology. For the use of these materials based on a detailed project description, ethics applications and approval of the GLA-WP Biology needs to be obtained. Results need to be either integrated or available to the network after the publication of the data.

8.9. Biometry

In accordance with the underlying aims and questions of the registry, the following statistical analyses are performed on a routine basis.

First, a descriptive analysis of the different histological subtypes is performed. This includes, in addition to the frequency distribution of the subtypes, the distribution of demographic patient data, the diagnostics used in each case, treatment strategies, as well as their possible side effects and therapy results.

Frequency tables and graphical representations (in particular bar charts and box-and-whisker plots) are prepared to present the results. The descriptive analyses are supplemented by inferential statistical analyses. Appropriate statistical significance tests are used to examine whether systematic differences exist between the subtypes. Depending on the level of measurement and distribution of the target variables, appropriate hypothesis tests like Mann-Whitney-U-test, F-tests, Kruskal-Wallis tests, and Chi-squared tests are performed. All applied significance tests are performed at a two-sided significance level of 5 % and interpreted in an exploratory sense. Where appropriate, confidence intervals of important parameters are generated to the 95 % level. Time to event endpoints such as OS, PFS, DOR will be analyzed using the Kaplan-Meier method (and corresponding curves) (6). Where necessary, cumulative incidence—taking into account competing risks—will be obtained using the Aalen-Johansen estimator.

Within the scope of the registry, multivariate analyses, important target variables such as therapy outcome are modeled as a function of possible influencing variables. Logistic regression models are created for binary outcome measures such as the achievement of remission. Possible influencing variables are demographic and epidemiological data as well as the different applied therapy concepts. The strength of the influence of significant prognostic factors is quantified using the odds ratio (incl. 95 % confidence interval). Dependence of time to event endpoints on possible influencing variables will be assessed using the Cox-model regression model and suitable extensions (e.g. incorporating time-dependent covariates, time-varying effects of covariates etc.).

Specific research questions may require more sophisticated methods or even method development. This will be part of research proposals addressing such specific research questions.

8.10. Data Management

The GLA-R is using a certified and validated database. A detailed methodology for the data management in the GLA-R will be documented in a data management plan. The center will receive system documentation, training and support for the use of the eCRF. In case of new staff, the training can be performed by personnel of the center.

All data entries, modifications or deletions will be recorded automatically in an electronic audit trail indicating the individual subject, the original and new values, the reason for and time and date of change, as well as the person executing the change. The system will be secured to prevent unauthorized access to

the data or the system. Only people provided with a user ID and a password will be able to enter or change data.

Checks for plausibility, consistency and completeness of the data will be automatically performed during data entry. Based on these checks, queries will be produced. Centralized monitoring, where missing data or inconsistencies will be reported back to the respective center, complements this approach. Moreover a medical data review at certain intervals will help to identify erroneous and potentially unreliable data.

All data management activities will be done according to the current Standard Operating Procedures (SOPs) of the IZKS.

8.11. Quality and Risk Management

Data quality and risks to ensure data protection and reliability of registry results are continuously managed. The measures used will be proportionate to the inherent risks and the importance of the data collected.

If source data verification should become necessary for individual projects, on-site monitoring can be conducted. Details and the rationale for the chosen monitoring strategy will be specified in the monitoring plan. The center must allow the monitor to check all documents concerning the GLA-R and must provide support at all times to the monitor. Additionally to the on-site monitoring, remote monitoring visits could be conducted by the monitor. At the remote monitoring visits primarily administrative aspects and plausibility could be checked. Source data review and source data verification can only be conducted if the technical prerequisites are given and a valid regulatory approval exists.

9. Informed consent, ethics approval and data protection regulations

9.1. Ethics approval

For the GLA-R ethics approval will be obtained at the relevant committees of the participating centers. The process will be initiated at the site of the GLA-R Delegate.

9.2. Informed consent

Participation in this project is entirely voluntary. There is no direct impact on the treatment of the individual patient. The GLA-R informed consent form will be distributed to patients eligible for this registry and still alive. In addition, patients will receive all relevant information on data protection in its latest version and the potential use of their data for the different analyses, including shared analyses with network partners and commercial cooperators.

Historical patient data will be entered if appropriate consent exists by hospital and/or ethic regulations.

The informed consent to participate in the registry may be withdrawn by the patient verbally or in written form at any time during the trial. The patient must not entail any disadvantage therefor or be coerced or unduly influenced to continue to participate. Furthermore, the patient is not obligated to disclose reasons for the withdrawal of the consent.

9.3. Data protection

Within the registry, the applicable data protection is respected. The EU Regulation 2016/679 of the European Parliament and the Council GDPR, which has been in force in Germany since May 2018, defines various legal aspects of data protection. According to Article 6(1) (a), the processing of personal data is permitted if "the data subject has given his or her consent to the processing of personal data for one or more purposes". Article 5(1) (b) also states that "personal data may be used only for specified, explicit and legitimate purposes and may not be used for other purposes not agreed upon; the further use of data intended for archives in the public interest, for scientific or historical research projects or for statistical purposes is not incompatible with the original purposes pursuant to Article 89(1)". Article 7(1) further states that "if the use of the data is based on consent, the person responsible must prove that the individual concerned has given consent to the use of personal data".

In order to comply with the provisions of the GDPR, the collection of data in the registry is only possible if written consent has been obtained from the patient, if not addressed in special regulations (e.g. deceased patients).

If consent is given, the collected data are entered into an access-protected database. This database does not contain any information that allows clinical data to be assigned to an individual person. Instead, all data are assigned to a clearly defined alphanumeric pseudonym that contains neither parts of the name nor the date of birth.

9.4. Data Protection regulations

Data protection regulations in their latest version will be followed at any time, including withdrawal and consent and the right of deletion of data.

The patient is entitled to withdraw his informed consent to the collection, storage and transfer of his patient data at any time. Depending on the patient's declaration, the data collected so far can either be corrected, updated or made anonymous. A withdrawal of the informed consent does not affect the lawfulness of the data processing carried out until the withdrawal (Article 7 paragraph 3 GDPR).

9.5. Trusted third party

Patient identifying data (e.g. surname, first name, date of birth and address) will be collected and stored separated of the medical data in the trusted third part in safe custody. There will be an organizational separation from other registry operations. Only trained and authorized personnel will have access to the personal identifying data. The disclosure to any third party is excluded.

10. Data reports

A summary report of the clinical data of the registry is prepared annually. The following analysis will be performed by the institution to which the conduct of the registry will be delegated on behalf of the GLA.

- Number of patients included into the registry and in the different lymphoma subtypes
- Patient characteristics
- Cumulative entity overall survival, depending on age, sex

Each center has the option to receive the data of their own patients entered on a per center analysis (with and without benchmark data). All members of the registry have access to e.g. the annual analyses and other appropriate materials. If used, the GLA-R needs to be referenced.

Note: As of 2023 IZKS/IMBEI Mainz are responsible for the provision of the annual analysis.

For each lymphoma entity-specific data points or research questions may be predefined which will be specific to the respective part of the GLA-registry. The basis for these data points will be revised annually by the speakers of the respective working parties to keep the data base updated for the most recent development. Changes to the item list will be reported on the website of the society. Reminders will be sent by the project coordination in summer of the preceding year, to be discussed at the annual meeting and then to be integrated into a regular database release in Q1 or Q2 of the subsequent year.

Primary data analyses will be provided in Q2 to the WP for discussion and distribution, in general for presentation at the annual meeting.

11. Role of funding sources

There is no single funding source to cover the costs of the registry. For the start of the project the GLA e. V. provides funding to establish the data base and facilitate registry coordination and management. In addition, cooperation projects with industrial partners have been defined to cover remaining project costs. As of Q1 2023 funding for the first 3 years is covered.

The GLA is planning to conduct the registry as a long-term project. Therefore, during the set-up phase of the registry additional applications for future funding (2026 - 2030) will be made from a variety of funding sources such as:

- GLA funding
- Public funding (German Cancer Aid, foundations, payers such as GBA, IQWIG
- Restricted funding for defined research projects (industrial partners)
- Individual grants for studies within the registry (GLA-members)

12. Disease specific Registries

12.1. Registry for large B-cell lymphomas

12.1.1. 2023 Project lead:

Prof. Dr. B. Chapuy, Berlin

12.1.2. Scientific rationale

Aggressive Lymphomas are the most frequent lymphomas in the Western world and lymphoma is still the leading reason for death in patients affected, which underlines the continuously existing medical need.

In recent years the classification of large B-cell lymphoma has experienced major changes, with latest changes made in the 2022 WHO-classification (7, 8).

According to the latest WHO-classification, the following subgroups can be entered in the registry:

- Large B-cell lymphomas, diffuse large B-cell lymphoma, NOS
- T-cell/histiocyte-rich large B-cell lymphoma
- Diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements
- ALK-positive large B-cell lymphoma
- Large B-cell lymphoma with IRF4 rearrangement; High-grade B-cell lymphoma with 11q aberrations; Lymphomatoid granulomatosis
- EBV-positive diffuse large B-cell lymphoma
- Diffuse large B-cell lymphoma associated with chronic inflammation
- Fibrin-associated large B-cell lymphoma
- Fluid overload-associated large B-cell lymphoma
- Plasmablastic lymphoma
- Primary large B-cell lymphoma of immune-privileged sites
- Primary cutaneous diffuse large B-cell lymphoma, leg type; Intravascular large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma; Mediastinal gray zone lymphoma
- High-grade B-cell lymphoma, NOS
- Burkitt lymphoma
- Primary effusion lymphoma
- KSHV/HHV8-positive diffuse large B-cell lymphoma
- KSHV/HHV8-positive germinotropic lymphoproliferative disorder

Several important treatment options have been introduced over recent years. However, frequently the full impact of novel treatments is not fully understood and especially the impact of treatment sequencing and algorithms never have been studied in a prospective fashion.

Therefore, clinical and molecular diversity and the enlarging therapeutic armamentarium require a wide data set for comprehensive analysis.

Whereas basic analysis for patients with aggressive lymphomas will be built on the general data set, the following additional information will be collected in addition.

Specific information obtained in addition

The following additional information will be requested upon registration of a patient with aggressive lymphoma in the GLA-R:

Specific characteristics

- Classification interchangeability
- The most actual version of the WHO-classification will be used. However, to keep data sets interchangeable, prior WHO-classifications will be either be documented, or remain in the data base when the diagnosis is updated to the most recent classification
- Genetic information
- COO: ABC vs. GCB vs. unclassified, Methodology of analysis
- MYC, BCL2, BCL6
- EBER-ISH
- Cytogenetic findings, e.g. 11q-
- Diagnostic findings
- PET-result
- Risk scores
- IPI, aaIPI, CNS-IPI
- Treatment
- Use of CNS prophylaxis, type
- Use of moAB's, chemotherapy
- Use of immunconjugates
- Use of HDT
- Use of allogeneic SCT

- Use of CAR-T-cells and toxicities
- Use of bispecific antibodies
- Targeted agents, e.g. PI3K, BTK, BCL2 inhibitors and others as appropriate

12.1.3. Associated scientific program

While the primary data points of the registry are clinically, the collection of blood and tissue sampling will be encouraged for translational research at sites with active bio-banking programs and respective informed consents.

At this time, the GLA-R will not run a physical bio-banking itself but will do so *in silico*. This means, that the availability of any biological sample can be indicated in the database, which will allow researchers to identify suitable patients for distinct projects with sufficient clinical data and available biomaterials. This research project, however, will be independently performed and regulatory preparations are up the researcher, who is conducting the work.

The translational research program in conjunction with the GLA-R

To gain insights into molecular signatures that predict response and resistance to front line and/or salvage treatment, an extensive correlative science program will be initiated that includes assessment of the molecular composition of the tumor itself (genome, transcriptome, proteome) its interaction to the tumor microenvironment, the immune fitness and functional phenotypes (apoptotic thresholds, ex vivo drug treatment, PDX models). As it is increasingly clear that dynamic changes to the tumor under therapy are an additional important response criterion, circulating tumor DNA (ctDNA) as a minimal residual disease (MRD) marker with and without correlation to clinical and imaging-based response assessment will be evaluated.

Essential will be also to gain insight into the molecular make-up of the tumors that do not respond to the treatment prompting us to encourage biopsies at relapse (complete excised lymph node or alternatively core biopsies). Serial or longitudinal collection of blood and plasma samples will be helpful for analysis in conjunction with the clinical data of the registry.

Importantly, projects approved for cooperation will be required to make results obtained (raw data) available in an appropriate data format within the registry.

12.1.4. Project phases

The registry on large B-cell lymphomas will be the first to be realized within the registry project. From 2023-2025 the first project phase will be started with the following assumptions:

- Realization of the database
- Programming, testing of the database (2023)
- Approval of the protocol and the informed consent (2023)
- Selection of active sites in Germany (2023)
- First patient in (2023)
- Completion of the first cohort of patients (see below) (2023–2025)
- First data snapshot 2023
- First data analysis 2024
- Clinical
- Molecular, if available

12.1.5. Expected patient number

DLBCL is the most frequent nodal lymphoma in Western countries. In Germany approximately 9000 (RKI, 2018, > 18 y) new cases are diagnosed each year. The GLA-registry aims to document at least 10% of the patients diagnosed each year.

In the initial project phase a number of 500 patients entering the registry/year is expected for the first 3 years with an incremental number/year over time.

12.2. Registry for Mantle Cell Lymphoma

12.2.1. 2023 Project lead:

Prof. Dr. Georg Heß, Mainz

Currently the European Mantle cell lymphoma network, led by the German chapter, runs a European MCL-registry. Until Q1/2023 approx. 1400 patients have been enrolled. In the future, German patient data will be integrated into the GLA-R, after all necessary technical and administrative preparations have been completed.

12.2.2. Scientific rationale

Mantle cell lymphoma is a rare subtype of malignant B-cell-lymphomas with a generally aggressive disease course and poor prognosis. In recent years biological understanding of the pathophysiology of the disease has markedly increased and thereby prognostic stratification could be established. The improved understanding led to the identification variety of potential molecular treatment targets and development of specific drugs, which have improved current treatment results. Still, most patients continue to develop refractory disease and die due to the underlying lymphoma. Therefore, there is still a high need for improved understanding and better treatments.

Due to the nature of clinical research in phase I–III, most trials focus on the results of specific treatment lines and cannot provide an overview of the entire disease course, which is necessary to answer many unsolved questions as described above. To overcome the issue of lacking data from prospective data on the entire disease course of patients, only data from a registry are able to provide the information needed and close the current gap in knowledge. Furthermore, in contrast to data available from prospective clinical trials, the collection of data over the entire disease course helps to understand the change of treatment patterns, complications of the disease and multiple treatments and allows for the comparison of survival of different patient generations.

Non-exclusive examples of specific questions to be addressed from registry data are: fate of indolent NHL, course of primarily extranodal MCL, impact of high risk characteristics and influence of treatment selection on the results of the following treatment line.

12.2.3. Specific information obtained

The following additional information will be requested upon registration of a patient with Mantle Cell Lymphoma in the GLA-R:

- Disease characteristics
- Subtype, classical, blastoid
- Pathologic, genetic findings
- Cyclin D1-expresion, p53 (methodology)
- Specific disease presentations
- Extranodal
- Risk scores
- MIPI, MIPI-c
- Treatment (non-exclusive)
- Use of moAB's, chemotherapy
- Use of targeted agents, BTK-inhibitors, Venetoclax, Lenalidomid, mTOR's
- Use of HDT
- Use of allogeneic SCT
- Use of CAR-T-cells
- Use of bispecific antibodies

12.2.4. Associated scientific program

Special emphasis will be made on the understanding of therapeutic pathways and their impact on results. Currently, the availability of different therapeutic options results in a variety of individual treatment pathways. Therefore, a therapeutic modeling will be performed to separate e.g. the early vs. the late use of distinct treatment options. If therapeutic meaningful differences are identified, e.g. sequence of special treatments may impact on ORR, PFS or survival, another cohort will serve as a control group. Sample size will be matched and adapted in respect to statistical requirements.

Another core project of the registry will be the analysis of patients failing BTK-inhibitor-treatment.

Third, if available sequential analysis of biological samples shall explore the genetic development during the disease course and especially if distinct treatments induce a shift of the mutation profile.

12.3. Registry for HIV-associated lymphomas

12.3.1. 2023 Project lead:

Marcus Hentrich, München & Kai Hübel, Köln (& Christian Hoffmann)

Between January 2005 and April 2018 more than 550 patients with HIV-related lymphomas from 33 participating institutions were included in the prospective German HIV-related lymphoma cohort study. Multiple analyses resulted in several scientific publications. However, the study terminated in 2018 for organizational reasons and due to regulatory issues.

It would be helpful if a new prospective registry for HIV-associated lymphomas could be activated building upon the network of the former HV-related lymphoma cohort study.

12.3.2. Scientific rationale

Aggressive B-cell Non-Hodgkin lymphomas (NHL) are AIDS-defining and the second most common malignancy in people living with HIV/AIDS (PLHA). The incidence of AIDS-related lymphoma (ARL) has declined since the introduction of combination antiretroviral therapy (cART). However, the risk is still increased by 10–37-fold compared to the general population. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL subtype, followed by Burkitt lymphoma (BL) and plasmablastic lymphoma (PBL). Among AIDS-related causes of death NHL are most frequent. Compared with the general population, the incidence of HIV-associated Hodgkin Lymphoma (HIV-HL) is increased by approximately 10 to15-fold with about 45-55 new cases per 100.00 person-years among HIV-infected persons.

The prognosis of ARL has markedly improved since the introduction of cART. In the German HIV-lymphoma cohort study the 2-year-overall survival (OS) of patients with BL and DLBCL was reported to be 69 % and 62 %, respectively (7). Although this represents an improved outcome compared to data from pre-cART-era, survival outcomes are still inferior to that in HIV-negative individuals with DLBCL or BL. The prognosis of patients with HIV-related CD20-negative lymphoma such as PBL is particularly unfavorable with a median survival of 10 months and a 43% 2-year-survival rate. Poor outcomes have also been reported for patients with primary effusion lymphoma (PEL) with a median survival of 10–12 months. Thus, there is still a high need for improved understanding of disease characteristics and better treatments.

The outcome of patients with HIV-HL has considerably improved during the last two decades. However, many questions remain unanswered, e.g. the role of more intensive first-line therapies such as BEACOPP escalated or the role of brentuximab vedotin and checkpoint inhibitors in relapsed/refractory HIV-HL.

Follicular lymphoma

12.3.3. Associated scientific program

Regarding different lymphoma subtypes special emphasis will be made on the understanding of therapeutic approaches and their impact on remission rates and survival. Further, the impact of modern antiretroviral therapies (ART) on outcomes and the course of HIV infection will be studied. Data may be compared with historical controls or data from the literature to evaluate possible changes over time. Findings from the registry may serve as a basis for future prospective trials addressing special lymphoma entities.

Additional information obtained

The following information will be requested of a patient with HIV-related malignant lymphoma

Diagnosis

- Lymphoma subtype
- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Primary CNS lymphoma
- Hodgkin lymphoma
- Other subtypes
- HIV infection
- Date of HIV-diagnosis | CDC stage
- Prior AIDS-defining illness
- History of and current antiretroviral therapy (ART)
- Risk scores
- IPI, ARL-IPI, IPS (for HL)
- Treatment (non-exclusive)
- Use of rituximab
- Use and type of chemotherapy
- Use of high-dose chemotherapy with autologous SCT
- Use of allogeneic SCT
- Use of immune checkpoint inhibitors
- Use of CAR-T-cells
- Use of antiretroviral therapies

12.4. T-cell-lymphoma registry

12.4.1. 2023 Project lead

Thomas Weber, Halle (Saale)

Since 2021, clinical data and biological specimens for mature T-cell lymphoma (MTCL or T-NHL) have been collected through the National T-NHL Registry and Biobank by the GLA and the East German Hematology and Oncology Study Group (OSHO). Q2/2023, the T-NHL Registry has over 25 active centers that have enrolled nearly 300 patients with T-NHL. The registry is coordinated at the University Hospital Halle (Saale), but defines itself as part of the GLA-R.

12.4.2. Scientific rationale

T-NHL are a rare group of non-Hodgkin lymphomas with a mostly aggressive course of disease. T-NHLs are highly heterogeneous with many subtypes differing in clinical presentation and molecular background. This diversity of T-NHL and the small number of patients compared to other lymphomas makes it difficult to perform controlled clinical trials. This means that aspects of the therapy of T-NHL are carried out in analogy to the therapy of B-cell lymphomas. In addition, it makes it difficult to dissect the impact of different treatments on outcome parameters in individual subtypes. Little is known about the treatment practice of T-NHL in Germany. In recent years, based on a better understanding of molecular mechanisms of T-NHL, many new therapeutic concepts have been developed. Due to the before mentioned heterogeneity and rarity of T-NHL, implementation in controlled clinical trials worldwide has been slow. The collection of "real-word data" is therefore of great importance in order to reflect the treatment practice in Germany, to generate evidence for new treatment concepts and in rare T-NHL subtypes, and to provide a basis for future clinical studies. To achieve these goals, the T-NHL Registry aims to document the epidemiological and clinical data of patients with T-NHL in all participating centers in Germany on a pro- and retrospective basis. In addition, biological materials are collected in a biobank to link clinical and molecular data in future analyses.

Specific information obtained

The following additional information will be requested upon registration of a patient with T-NHL in the registry:

- Ethnicity
- Disease subtype according to WHO-classification
- Reference pathological evaluation
- LMP-IHC, EBER-ISH

- Immune phenotype including ALK- and CD30-expression
- Genetic findings including e.g. DUSP22-rearrangements
- Risk score variables to calculate risk scores as e.g. IPI, PIT, PINK
- Disease characteristics
- Disease manifestations
- Comorbidities
- Treatment (non-exclusive)
- Use of chemotherapy
- Use of targeted agents, ADC (brentuximab vedotin), IMIDs (Lenalidomid) epigenetic modifiers (HDACi, 5-Azacytidin), PI3Ki, etc.
- Use of HDT
- Use of allogeneic SCT
- Use of radiotherapy
- Quality of life outcome measures

12.4.3. Associated scientific program

One focus will be the analysis of optimal treatment modalities of not particularly in T-NHL evaluated treatments as e.g. radiotherapy. Second, comparative analyses of different treatment modalities will be conducted, with respect to treatment efficacy endpoints, sometimes in collaboration with other registries, such as the use of brentuximab vedotin in the first-line treatment of non-ALCL PTCL. Third, distinct pathological and molecular characteristics will be correlated with outcome parameters of different treatment regimen. Fourth, serial analyses of biological samples during treatment will reveal the molecular evolution of T-NHL subtypes under common therapies.

12.5. Follicular Lymphoma

12.5.1. 2023 Project lead:

Prof. Dr. Christian Buske

12.5.2. Scientific rationale

The aim of this national registry for FL is to understand the treatment landscape of this second most frequent B-cell lymphoma in Germany and to collect biomaterial for future translational research projects. FL belongs to the group of indolent lymphomas, for which no established curative treatment is available. Based on this and on the chronic course of the disease multiple treatment regimens are used and particularly in the relapsed setting no clearly defined standard treatment exists. Due to this, treatment approaches are very heterogeneous ranging from single agent rituximab to dose intense chemotherapies or stem cell transplantation. In addition, new treatments have emerged such as bispecific antibodies or CAR-T cells, which in part are already approved for the treatment of relapsed FL. Taken together, we are facing a highly heterogeneous and rapidly moving treatment landscape in FL. In order to understand how patients are currently treated, how treatment is evolving and which treatment outcomes are associated with the distinct treatment concepts in a real world setting, a prospective registry is required. The FL-registry comprises 83 active centers in Germany, was started in 5/2020 and has since then included 950 patients. It is coordinated at the University Hospital Ulm, but defines itself as part of the GLA-R. Inclusion criteria are an age of 18 years or higher and the need of a reference pathology. The latter one assures high quality of diagnostics and at the same time allows to build up a biobank of tumor biopsies associated with the registry and with this all clinical data collected. Collection of data occurs via eCRF; data are validated by “remote monitoring” performed by the study team in Ulm.

Specific information obtained

The following additional information will be requested upon registration of a patient with FL in the registry:

- Disease characteristics
- Among others grading, stage, extranodal
- Pathologic, genetic findings
- Among others BCL-2 expression, t(14;18) translocation
- Risk scores
- FLIPI
- Treatment (non-exclusive)

- Use of moAB's, chemotherapy
- Use of immunomodulatory imide drugs (IMIDS), i.e. Lenalidomid, Lenalidomid/Rituximab
- Use of PI3K inhibitors
- Use of HDT
- Use of allogeneic SCT
- Use of CAR-T-cells
- Use of bispecific antibodies

12.5.3. Associated scientific program

The associated scientific program deals with specific clinical questions, e.g. the treatment of late relapses in the real world setting or translational questions, correlating distinct molecular characteristics with clinical data of the registry. Different projects are currently running in this setting.

12.6. Further entities

The criteria for the following registries have to be defined in a subsequent project phase

- Marginal Zone Lymphoma
- Waldenströms disease
- Primary CNS lymphoma
- PTLD
- Other projects to be defined at any time

13. References

1. Booth CM, Karim S, Mackillop WJ. Real-world data: towards achieving the achievable in cancer care. Nat Rev Clin Oncol. 2019;16(5):312-25.
2. Prang KH, Karanatsios B, Verbunt E, Wong HL, Yeung J, Kelaher M, et al. Clinical registries data quality attributes to support registry-based randomised controlled trials: A scoping review. Contemp Clin Trials. 2022;119:106843.
3. Franklin JM, Liaw KL, Iyasu S, Critchlow CW, Dreyer NA. Real-world evidence to support regulatory decision making: New or expanded medical product indications. Pharmacoepidemiol Drug Saf. 2021;30(6):685-93.
4. Nowakowski G, Maurer MJ, Cerhan JR, Dey D, Sehn LH. Utilization of real-world data in assessing treatment effectiveness for diffuse large B-cell lymphoma. Am J Hematol. 2023;98(1):180-92.
5. IQWiG. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V. 2020.
6. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association. 1958;53(282):457-81.
7. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBdO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-48.
8. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229-53.