

The Search for Surrogate Endpoints in Trials in Diffuse Large B-Cell Lymphoma: The Surrogate Endpoints for Aggressive Lymphoma Project

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Traditional study endpoints, such as overall survival (OS), are widely accepted in current clinical studies as valid outcomes for new drug approval. However, these established primary endpoints for oncology clinical studies often require many years to attain sufficiently mature data to provide necessary power for demonstration of a clinical benefit, especially when studying novel agents. Thus, identification of potential surrogates to accompany or replace these endpoints is important for accelerating cancer treatment development. The most common and accepted methods for surrogate endpoint evaluation require individual patient data (IPD) from multiple clinical trials. Beside surrogacy evaluation studies, other evidence-based research also recognizes the limitations of data from a single clinical trial. For example, one-trial data commonly cannot provide sufficient sample size to address a research question targeting rare populations or events. Combining information from several individual studies may answer questions that a single trial cannot. This type of data sharing at the patient level from individual clinical trials, and subsequent integration into a comprehensive meta-analytic database, can provide the necessary information to support goals of identifying and evaluating potential surrogate endpoints, enhancing recognition of optimal therapies, and evaluating prognostic features in rare but important populations. Such collaborations create significant challenges because they may require cooperation across international borders and data-sharing agreements between companies, academic institutions, or both. However, multiple meta-database collaborations (as described below, Adjuvant Colon Cancer End Points [ACCENT], Analysis and Research in Cancers of the Digestive System [ARCAD], and Follicular Lymphoma Analysis of Surrogacy Hypothesis [FLASH]) have demonstrated that these research initiatives can be successfully performed. These meta-database groups established the statistical methods of

retrospectively combining and analyzing data from large collections of previously completed studies to provide evidence for supporting evidence-based research.

The ACCENT group validated 3-year disease-free survival as a surrogate endpoint of 5-year OS for 20,898 patients from 18 studies of adjuvant treatment in colorectal cancer (CRC) [1]. The database answered significant and important questions about early stage colon cancer, including the use of adjuvant chemotherapy in elderly patients, evidence for cure by adjuvant therapy, and factors influencing survival following recurrence [2, 3]. Similarly, the ARCAD group analyzed data from 16,762 patients with metastatic CRC who received a variety of frontline therapies in the modern era. A moderate correlation between long-term OS and early progression or death was identified at both patient and trial levels [4]. This analysis provided an updated surrogacy evaluation of progression-free survival (PFS) for examining newer, novel treatments.

Similar analyses have occurred in patients with follicular lymphoma. The FLASH group analyzed data from patients who had received multiple types of frontline therapy and identified a robust association between complete response (CR) at 30 months and PFS in phase III trials [5]. These data provide a significantly shorter time to recognize a clinical benefit with newer therapy, whereas a much longer follow-up time (over twice as long) is generally required to observe a median PFS in patients with follicular lymphoma. These studies have demonstrated a viable and reproducible path for evaluating surrogate endpoints that may provide an earlier indication of clinical benefit and facilitate the new drug approval process.

Establishing surrogate endpoints is especially critical in patients with more aggressive disease, such as diffuse large B-cell lymphoma (DLBCL). As the most common aggressive form of non-Hodgkin lymphoma (NHL), comprising ~30% of all types

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Table 1. Clinical trials in patients with diffuse large B-cell lymphoma incorporated or planned for inclusion in the Surrogate Endpoints for Aggressive Lymphoma database

First author, year (study name, group) [reference]	Study identifier	Treatment (control vs. experimental)	Start of accrual	Sample size, n	DLBCL stage	Primary endpoint
Merli et al., 2012 (ANZINTER3, FIL) [13]	NCT01148446	R-CHOP21 vs. R-miniCEOP	2003	224	II–IV	EFS
Habermann et al., 2006 (ECOG E4494/CALGB 9793) [14]	NCT00003150	Induction CHOP21 vs. R-CHOP21 Maintenance (CR/PR) Observation vs. rituximab	1998	546 352	I–IV	FFS
Ketterer et al., 2013 (LNH031B, LYSARC) [15]	NCT00140595	ACVBP vs. R-ACVBP	2003	223	I–II	EFS
Recher et al., 2011 (LNH032B, LYSARC) [16]	NCT00140595	R-CHOP21 vs. R-ACVBP	2003	380	I–IV	EFS
Delarue et al., 2013 (LNH036B, LYSARC) [17]	NCT00144755	R-CHOP21 vs. R-CHOP14	2003	602	I–IV	EFS
Haioun et al., 2009 (LNH98-3, LYSARC) [18]	NCT00169169	Induction (responders to HDT/ASCT) ACVBP vs. ACE Maintenance (CR/CRu/PR) Observation vs. rituximab	1999	476 269	I–IV	EFS
Coiffier et al., 2002 (LNH98-5, LYSARC) [19]	LYSARC	CHOP21 vs. R-CHOP21	1998	399	I–IV	EFS
Seymour et al., 2014 (MAIN, Roche) [20]	NCT00486759	R-CHOP (14/21) vs. RA-CHOP (14/21)	2007	787	NS	Safety
Schmitz et al., 2012 (MEGACHOE, DSHNHL/Deutsche Krebshilfe) [21]	NCT00129090	R-CHOEP14 vs. R-MegaCHOEP	2003	262	I–IV	EFS
Pfreundschuh et al., 2006 (MINT, DSHNHL/Roche) [22]	NCT00064116	CHOP-like vs. R-CHOP-like	2000	824	I–IV	EFS
Jaeger et al., 2015 (NHL13, AGMT) [23]	NCT00400478 EUDRACT #2005-005187-90	Maintenance (CR/CRu) Observation vs. rituximab	2004	683	DLBCL, FL3b	EFS
Herbrecht et al., 2013 (PIX203, CTI) [24]	NCT00268853	R-CHOP21 vs. R-CPOP	2005	124	II–IV	CR/CRu
Pfreundschuh et al., 2008 (RICOVER-60, DSHNHL) [25]	NCT00052936	6 vs. 8 cycles of CHOP14 ± R	2000	1,222	I–IV	EFS
Cunningham et al., 2013 (RCHOP14v21) [26]	ISCRTN 16017947	R-CHOP21 vs. R-CHOP14	2005	1,080	IA–IV	OS

Abbreviations: ACE, doxorubicin, cyclophosphamide, and etoposide; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; AGMT, Arbeitsgemeinschaft Medikamentöse Tumortherapie; CEOP, cyclophosphamide, epirubicin, vinblastine, and prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CPOP, cyclophosphamide, pixantrone, vincristine, and prednisone; CR, complete response; CRu, CR unconfirmed; CTI, Cell Therapeutics, Inc.; DLBCL, diffuse large B-cell lymphoma; DSHNHL, German NHL study group; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FFS, failure-free survival; FIL, Fondazione Italiana Linfomi; FL3b, follicular lymphoma grade 3b; HDT/ASCT, high-dose therapy and autologous stem cell transplantation; LYSARC, Lymphoma Academic Research Organisation; MINT, MabThera International Trial; NHL, non-Hodgkin lymphoma; NS, not stated; OS, overall survival; PFS, progression-free survival; PR, partial response; R, rituximab; RA, rituximab, bevacizumab; RICOVER-60, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab for patients older than 60 years; UCL, University College London.

of NHL [6–8], there remains a large unmet need to identify more effective therapies for patients with DLBCL. In particular, DLBCL patients who experience early relapse or primary treatment failure following standard therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) experience poor outcomes [9, 10]. In initial studies, PFS at 24 months has been reported to be a robust endpoint for disease-related outcome in DLBCL [11, 12]. Studies to identify surrogate endpoints for survival are needed to more rapidly identify frontline regimens that can improve outcomes for patients who are at a high risk of relapse or progression. Thus, the Surrogate Endpoints for Aggressive Lymphoma (SEAL) collaboration was established to (a) construct a meta-database integrating IPD from randomized clinical trials in DLBCL, (b)

evaluate potential surrogate endpoints for OS in DLBCL trials, and (c) support continuous translational research such as prognostic analyses, risk classifications, subgroup analyses, etc.

Here we describe the progress of the SEAL clinical trials program to date and invite colleagues to collaborate in sharing data to continue building a large meta-database of individual patient data from multiple clinical trials. The SEAL group comprises hematologists/oncologists, scientists, and statisticians, as well as partners from Celgene who provided support for the efforts of data collection and analyses. Core team members meet on a regular basis to discuss compilation database integration and analyses of proposed projects and data access to external nonmembers, and ensure appropriate ongoing management of the information. The overall goal of SEAL is to

compile a large meta-database providing adequate source information for proposing, endorsing, analyzing, reviewing, and publishing research initiatives.

The current SEAL objectives are multifold, including the following: (a) determine trial- (primary) and patient-level (secondary) correlations between surrogate endpoint candidates and OS following frontline treatment for DLBCL using well-established statistical methods based on individual patient data from a large collection of completed, multicenter, randomized controlled clinical trials, and (b) investigate potential surrogate endpoint candidates: event-free survival, PFS, CR at 24 months or earlier, and others as they become available. Candidate endpoints that may become available in the future include more sensitive tests for residual disease such as positron emission tomography scan and circulating tumor DNA. Biologically defined DLBCL subtypes such as cell-of-origin may also be evaluated in the future. Detailed definitions of these candidates and evaluation strategies are preplanned before any analyses.

The initial focus of the group will be on analyzing results from clinical trials of induction therapy in patients with DLBCL, with plans to extend the analyses into maintenance therapy upon sufficient collection of data from relevant maintenance trials. These trials should include chemotherapy and an anti-CD20 antibody, as well as biological agents that have been studied in phase III trials, to ensure that surrogate endpoints are applicable to a wide range of agents studied in phase III trials. Potential analyses beyond surrogacy include evaluating prognostic models, performing subgroup analyses, and gaining knowledge about disease processes.

The current SEAL study was initiated with a search of the published literature. Required inclusion criteria are original clinical trials published in English after January 1, 1995, or abstracts published within the last 2 years. Studies must involve randomization of ≥ 100 adult patients with previously untreated DLBCL or aggressive NHL by World Health Organization/Revised European American Lymphoma classification (or any synonymous abbreviation, term, or different spelling of those terms), and at least one treatment arm should include rituximab and have an active comparator. Excluded studies are those in only early-stage (I or II) patients, pediatrics, low-grade or human immunodeficiency virus-related lymphoma, relapsed/refractory disease, salvage treatment, supportive care, growth factor palliative care (as the main topic), quality of life, and health economic trials.

Trials of aggressive NHL required IPD for DLBCL patients. Based on availability of IPD from each included trial, the statistical analysis plan for evaluating potential surrogate endpoints may include more than one endpoint and subpopulation analysis. Selection of potential surrogate endpoints involves teleconferences between SEAL investigators, the SEAL executive committee, and SEAL biostatisticians after review of the literature. Surrogacy evaluation within subpopulations provides insights of consistency or heterogeneity of a particular candidate endpoint.

Table 1 provides an overview of current trials that are or will be incorporated into the SEAL database. Although response rates vary based on the selected treatment regimen and patient characteristics, initial response to chemoimmunotherapy is generally very high, leading to prolonged follow-up and OS. Given the duration of follow-up occurring in these trials, surrogate endpoints could provide meaningful clinical value for

determining the benefits of novel therapy sooner, limiting prolonged exposure to ineffective therapies, and more rapidly identifying patients in need of additional therapy.

We encourage additional collaborators (both academic and industrial) to participate in this initiative to expand the SEAL database and contribute to the knowledge that may be derived from ongoing and future studies. At the present time, access to raw data from each trial is restricted to the SEAL coordinating statistics and data center at the Mayo Clinic because individual trials have not agreed to full public data access. Requests for specific analyses based on the SEAL database will be considered by the SEAL Steering Committee and, if approved, will be conducted by the SEAL statistics and data center in conjunction with the initiating investigator. Individual trial owners will have the ability to allow their data to be included or excluded in each specific SEAL analysis.

The SEAL's success to date provides another example of how patient-level data can be integrated together to answer specific key questions in the field. These types of efforts complement those of larger clinical data-sharing efforts. A major emphasis of the Cancer Moonshot, a U.S. presidential initiative to accelerate cancer research, is to assimilate data from decades of trials and thousands of individual patients across different malignancies and treatments. Publicly accessible databases, such as Project Data Sphere, where researchers can share, analyze, and integrate all available cancer research data, are becoming a critical part of cancer research communities. The goal of these larger all-encompassing repositories is to bring all the information together upfront, which will allow researchers to ask specific questions as they arise. Databases such as SEAL are an important first step in this initiative to bring cancer researchers and their data together to answer disease-level questions. Following the data-sharing integration analysis model developed through the already established international meta-database initiatives (ACCENT, ARCAD, and FLASH), SEAL collaboration can provide new insights to enhance these types of international collaborations.

We encourage you to reach out to collaborate with us on this important initiative. Contact information for inquiries about the SEAL group can be directed to the corresponding author.

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