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Commentary

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# General Biomarker Recommendations for Lymphoma

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## Abstract

Lymphoid malignancies are a heterogeneous group of tumors that have distinctive clinical and biological behaviors. The increasing prevalence of disease reflects both treatment advances and the fact that some of these tumors are indolent. The ability to determine treatment needs at diagnosis remains problematic for some of the tumors, such as in follicular lymphomas. Major clinical advances will likely depend on precision oncology that will enable identification of specific disease entities, prognostic determination at diagnosis, and identification of precise therapeutic targets and essential pathways. However, refinement in diagnostic evaluation is an evolving science. The ability to determine prognosis at diagnosis is variable, and for many of the lymphoid malignancies prognosis can only be made after initial treatment. Clinical trials that aim to evaluate specific features of these diseases are required in order to advance clinical practice that meaningfully addresses this important public health challenge. Herein, we describe the process and general recommendation from the National Cancer Institute (NCI) clinical trials planning meeting in November 2014 to address clinical trial design and biomarker proposals in the context of NCI-supported lymphoma clinical trials in the National Clinical Trials Network.

Lymphoid malignancies are a heterogeneous group of tumors that have distinctive clinical and biological behaviors. The 1972–2012 SEER data set shows that there has been a steady increase in the age-adjusted incidence, with 11.1 per 100 000 persons in 1976 and 19.7 per 100 000 persons in 2008–2012. In the United States, nearly 72 000 new cases were estimated for 2015, with approximately 20 000 deaths. In 2012, an estimated 549 625 people were living with non-Hodgkin lymphoma in the United States, and another 189 626 were living with Hodgkin lymphoma. Thus, there is continuing need for rapid, impactful, clinical treatment trials in the various subtypes of lymphoma.

In response to the 2010 Institute of Medicine Report and following several years of evaluation, consultation, and coordination among many stakeholders, the National Cancer Institute (NCI) transformed its longstanding cooperative group program into the new NCI National Clinical Trials Network (NCTN). The new program reduced the number of cooperative groups from 10 to five adult groups and one pediatric group. The network groups with a

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major focus in adult lymphoid cancers for the new program included the Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN), and Southwest Oncology Group (SWOG). The NCTN program began March 1, 2014, with an emphasis on a collaboratively networked system to efficiently take advantage of scientific opportunities for precision medicine focused clinical trials. The NCTN included a special funding program for inclusion of correlative studies of biomarkers, imaging, and quality of life that are integrated or integral to the clinical trial. New funding for biospecimen repositories and correlative studies were included in the NCTN program to support these important components of clinical trials.

The NCTN clinical trials portfolio is evaluated and prioritized by disease-specific steering committees. These committees are comprised of academic and community oncology leaders in the specific disease, statisticians recognized in the specific field, diagnostic pathologists, and patient advocates. The NCTN is a networked system, and therefore the NCTN group NRG Oncology has representation on the Lymphoma Steering Committee (LYSC), bringing in additional expertise in radiotherapy. The NCI steering committees have been asked to prioritize those studies that leverage scientific opportunity by utilizing the assets unique to the NCTN. The NCI has set forth a goal of advancing more precise cancer therapeutics and conducting late-phase clinical trials that provide clear evidence of clinical benefit to patients. In order to align the NCTN lymphoid malignancies portfolio with the focus of the new NCTN program, the LYSC began organizing a Clinical Trials Planning Meeting (CTPM) shortly after the NCTN was initiated.

The LYSC formed an executive planning committee (EPC) for the CTPM that was responsible for organizing the overall effort. The EPC was comprised of eight members, including the NCTN group lymphoma chairs, representation from the Leukemia and Lymphoma Society, the Lymphoma Research Foundation, patient advocacy, and NCI senior staff. The EPC established ambitious goals for the CTPM, which included setting priorities for the national lymphoid malignancies portfolio based on biologically based clinical trials with potential to change practice. In order to examine the scientific opportunities and the public health impact of possible clinical trials, the EPC formed subcommittees to focus on specific lymphoid cancer types: diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, Hodgkin lymphoma, and T-cell lymphoma. Two additional subcommittees, biomarkers and statistics, were formed to provide core support functions to the disease-specific subcommittees.

Each subcommittee was comprised of six to 10 members, who were vetted by the EPC to ensure that the subcommittees were comprised of senior experts whose primary scientific expertise was compatible with the assigned subcommittee. Nominees could be any senior authority regardless of affiliation, other than industry. Each of the three adult network groups with lymphoma committees had a representative on each subcommittee. The remaining five to seven members of each subcommittee represented the NCI Comprehensive Cancer Centers, international study groups, community oncology, patient advocacy, and translational science in the NCI Specialized Program of Research Excellence (SPORE), P01, and R01 research communities and NCI itself. Additionally, each subcommittee identified accomplished junior faculty to participate in the CTPM in order to promote mentoring and career development. Over the six-month period leading up to the face-to-face meeting, the subcommittees held teleconference and web-based meetings and the EPC held interim teleconferences with each subcommittee to oversee their work. Through this effort, the collaborative evaluation and planning for the national lymphoid malignancies clinical trials portfolio was established for the next five years and beyond.

The subcommittees were asked to examine and report on the state of the science for each lymphoma subtype. In particular, the subcommittees were responsible for identifying and evaluating ongoing phase II and III trials and placing them into a programmatic perspective in order to identify unmet needs and valuable scientific opportunities. Consistent with the NCTN's mission to conduct high-impact late-phase clinical trials uniquely suited to its publically funded mission, a central theme established for the CTPM was to identify clinical questions important to lymphoma therapeutics that would not be addressed outside of a publically funded research effort. The subcommittees were also directed to specify critical elements to include in clinical trials to ensure that the NCTN goals are met.

Areas of particular interest that the subcommittees were asked to identify included opportunities for trials involving novel drug combinations and inclusion of biomarkers relevant to the study agents and to the specific lymphoma biology. In support of these goals, the NCTN includes substantial funding for integral and integrated studies through the Biomarker, Imaging, and Quality of Life Special Funding Program (BIQSFP). Biomarkers (or imagining or quality of life studies) are defined as integral when they are essential for conducting the study as they define eligibility, stratification, and disease monitoring or study end points. Integrated tests are defined as assays or biomarkers that will receive further validation for use in future trials. In contrast, exploratory biomarkers may not have a rigorous statistical plan, and collection of specimens may be voluntary; in general, the BIQSFP program does not support exploratory biomarkers. The committees were asked to provide blueprints for clinical trials incorporating these elements to promote definitive advances in lymphoma therapeutics. If a stepwise approach was necessary to achieve that goal, the subcommittees were encouraged to provide a focused plan on how best to develop the portfolio in a way that might ultimately lead to a definitive trial.

## General Biomarker Recommendations

A major goal of the CTPM was to outline opportunities for incorporation of integral or integrated biomarkers into clinical trials using efficient statistical designs that permit rapid transition to phase III. The Biomarker and Statistics Subcommittees established general principles in this area for the entire portfolio, in addition to addressing issues specific to each subcommittee.

The Statistics Subcommittee broadly reviewed trial designs for accomplishing these goals but also worked directly with each lymphoma subtype subcommittee to address key issues such as accrual requirements and feasibility relevant to specific areas of investigation. A focus on go/no-go decisions for the phase II–III transition was an important aspect of promoting efficient trial designs. This was highlighted as a means to create a nimbler clinical trials program that recognizes early in the course of the protocol development process when a phase III study is unlikely to be successful so that such studies are not launched. Alternatively, the ability to recognize signals favoring the launch of phase III trials efficiently would be enhanced by this approach. The EPC established early in their planning that trial designs that lacked biomarker-related science would require a specific rationale for their inclusion in the NCTN

lymphoid malignancies portfolio. The overall effort was aimed toward developing a strategic vision so that phase III studies launched by the NCTN would have considerable potential for positive outcomes, and so that the outcome would be clear in defining clinical benefit. Alternatively, if the outcome were negative, the trial should include important biomarker information for subset analysis. This would entail an approach recognizing the importance of close industry collaboration. The goal for phase III studies would be to demonstrate clinical benefit by improvement in health-related quality of life or improved overall survival, or other measures showing benefit in addition to increases in progression-free survival.

The Biomarker Subcommittee focused on issues related to tissue and imaging biomarkers and included pathologists, medical oncologists, translational scientists, radiologists, and biostatisticians. The committee addressed general principles of tissue usage and imaging that should be common to all types of lymphoma clinical trials and then provided more detailed recommendations for each specific disease. For example, the discussions included strategies to utilize biomarkers for intermediate end points, such as fluorodeoxyglucose-positron emission tomography (FDG-PET) and minimal residual disease (MRD), which could be used as go/no-go phase II–phase III end points. Biomarker validation through incorporation of integrated assays in clinical trials was promoted to generate markers that could subsequently be used as integral markers in future trials. Specific tissue biomarkers will be discussed in the disease-focused reviews arising from the Lymphoma CTPM; a brief summary of the consensus imaging recommendations is included with this overview.

The first recommendation was that minimal tissue requirements should be specified and adhered to for each trial. Diagnostic confirmation and use of the tissue for biomarker analyses should be planned carefully so that the residual sample can be banked for future studies. The committee emphasized the absolute requirement of a pretreatment tissue sample as either an excisional biopsy or multiple core biopsies with the necessary immunophenotyping and molecular genetic analysis to arrive at an accurate World Health Organization diagnosis using 2016 nomenclature when that is released (1). Because lymphoma can occur in difficult-to-biopsy locations, utilization of fine needle aspirates and small biopsy samples often pose diagnostic challenges. Although expedient in the short term, enrolling patients with inadequate tissue samples and therefore incomplete classification ultimately undermines the quality of information revealed by the clinical trial. The subcommittee therefore strongly recommended that minimal tissue requirements be set and adhered to for each trial.

A second recommendation was that diagnostic materials should be reviewed by a centrally designated expert hematopathologist with recognized expertise in the field and particular disease subtype under study. Due to the extreme complexity of lymphoma diagnosis, expert review is a critical quality assurance step to ensure that the resulting data from an expensive and time-consuming clinical trial are accurate. Two recent studies describe up to a 30% change in diagnosis after expert hematopathology review (2–4). If local institutional regulations prohibit release of diagnostic material, whole-slide scanned images of hematoxylin and eosin and immunostained sections acquired on readily available platforms such as Aperio can be used. In addition, 10 unstained sections or formalin-fixed and paraffin-embedded tissue (FFPE) blocks should be submitted for any diagnostic studies required. Along with slides, blocks, or images, the accompanying immunophenotypic (immunohistochemistry or flow cytometry), genetic (cytogenetic or fluorescence in situ hybridization), and molecular (polymerase chain reaction [PCR], reverse transcription PCR, DNA sequencing, etc.) reports from the originating sites should be included. Adequate personnel and funding for the accrual sites and NCTN biospecimen banks need to be assigned to these tasks. Whenever there are integral or integrated biomarkers included in the study, ongoing assessment to ensure the tissue is sufficient and properly prepared for subsequent analytic procedures is essential.

The third recommendation focused on the importance of tissue analysis in understanding mechanisms of resistance to treatment. Collection of specimens from patients with refractory disease (de novo resistance) or at time of relapse (acquired resistance) should be encouraged. In trials of novel therapy, a plan should be developed to obtain specimens for banking with a clear plan for subsequent analysis aimed at investigating mechanisms of resistance. These tissues should undergo expert pathology review similar to the original diagnostic specimens to ensure diagnostic accuracy and provide tissue to study mechanisms of treatment resistance. Biopsies should be gathered from all relapsed patients on clinical trials in order to maximize understanding of clinical behavior and disease biology. Biopsies from negative trials, in particular, can provide valuable insight to guide further investigation.

The committee's fourth recommendation indicated that specimens should be collected and prepared in formats to permit their efficient use and maximize their utility. In order to spare tissue, tissue microarrays (TMAs) should be constructed whenever possible from each trial as it is completed and reviewed. This will allow parsimonious use of materials for future correlative studies. TMAs would ideally include two 1 mm cores per case and should be made in duplicate, including as many cases as possible in the second TMA so to avoid depleting the tissue. The NCTN banks have protocols to perform this service on site with tumor blocks that are rapidly returned if requested.

Due to the rapidly evolving technology, the fifth general recommendation for molecular testing that will be performed on diagnostic tissues after the trial is completed focused primarily on collecting appropriate materials for a broad variety of purposes, without commitment to particular techniques. In contrast, integral biomarkers require locked-down methods and analytics in order to be included in a study.

As the sixth tissue biomarker recommendation, the committee endorsed collections of plasma and serum as simple noninvasive samples that can be gathered with regular blood draws. These samples should be collected and handled according the best practices (NCTN banks may be consulted for such practices) and divided into smaller aliquots before storage so that they can be used for various future studies, avoiding multiple freeze-thaw cycles. In particular, when MRD is being studied, the committee recommended evaluation of blood samples at pre- and post-treatment time points. MRD can be monitored in the blood by PCR analysis of the immunoglobulin heavy chain or T-cell receptor for B-cell and T-cell malignancies, respectively, or tumor-specific mutations. The pretreatment time point is important to establish the marker that will be followed in subsequent studies. The post-treatment sample is important to determine whether MRD is present and to correlate it as a possible surrogate marker to imaging study results.

In addition, as a seventh recommendation, when germline DNA is required, a buccal swab was recommended as a source of germline DNA. As lymphoid tumors or circulating cell free tumor DNA may sometimes involve the patient's blood, collection of buccal swabs is considered a preferred sample for germline studies.

The committee then had an eighth recommendation for routine extraction of nucleic acids, DNA/RNA/microRNA from unstained sections, tissue cores (which can be obtained at the time of cores taken for TMAs), or scrolls from the FFPE tissue block collected for the diagnostic review. These materials can then be banked for future studies such as gene expression profiling, whole-transcriptome RNA sequencing, or targeted resequencing of important mutations. As methodologies and information on genetic alterations and expression patterns continue to evolve, the highest priority at this time is robust tissue collection with banking in a manner suitable for future study. Resources for this activity should be applied whenever possible.

The Biomarker Committee's ninth recommendation was for standardization of imaging protocols with anatomic imaging to assess tumor size at baseline and end of therapy, as well as FDG-metabolic imaging to assess tumor metabolic change at baseline and during or at end of therapy. For clinical trials designed to determine independent predictors of response or survival using functional imaging studies, both qualitative and quantitative image metrics are challenged by variability in methodology. Therefore, harmonization of imaging protocols including patient preparation, dosage adjusted for patient weight and the scanner type, acquisition and reconstruction settings, data analysis, and quality control are necessary to increase the power of the study (5–7). It is probably not feasible to control the entire scope of the variables involved in image data characteristics, but this can be achieved to a large extent by maintaining a quality control program involving proper scanner calibration, cross-calibration of the position emission tomography/computer-aided tomography (PET/CT) systems with the dose calibrators and across various scanners that will be used for the trial. "Phantom" studies across participating centers will aid in minimizing differences in image quality and quantification and make a posteriori image processing and analysis possible (5,6,8). This may be an arduous task, but at a minimum imaging centers should have fulfilled an accreditation process and the modality-specific program requirements of a reliable accreditation organization such as the American College of Radiology prior to participation in the trial (http://www.acr.org/quality-safety/accreditation/nuclear-med-pet). In addition to standardization of image protocols, maintenance of the same scanner and acquisition settings for sequential imaging studies will increase the reliability and quality of data.

The 10th recommendation regarded qualitative PET/CT interpretation criteria, endorsing that an a priori set of standardized interpretation criteria should be used by the participating sites if local reads are used for trial end points. In this context, the Deauville five-point scoring system (D 5PS) has recently been approved and recommended by the International Conference on Malignant Lymphomas Imaging Working Group both at midtreatment and end of therapy in most lymphoma subtypes (9,10). These harmonization approaches will ensure that comparable data will be obtained for imaging end point analyses in multicenter clinical trials.

These biomarker and imaging recommendations provide a general blueprint for the major NCTN studies to be launched and conducted over the next five or more years and represent input from a wide array of stakeholders in the public system. Disease-specific biomarker considerations will focus on priorities established by the clinical trials planning meeting, capitalizing on scientific opportunities to address public health needs by mounting specific national clinical trials. The subsequent five disease-specific reviews arising from the clinical trials planning meeting (11–15) will incorporate the themes discussed in this introduction and include greater detail on the scientific and clinical features relevant to the proposed trials.

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## Notes

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