Lymphoma Steering Committee
Clinical Trials Planning Meeting
November 21-22, 2014

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Introduction: The National Cancer Institute (NCI) Lymphoma Steering Committee (LYSC) convened a Clinical Trials Planning Meeting (CTPM) on November 21-22 at the Porter Neuroscience Center on the NIH Campus. Meeting attendees (approximately 75) included LYSC members, Lymphoma clinicians, biostatisticians, pathologists and biomarker experts, patient advocates and NCI staff. The meeting focused on broad issues of critical significance in the five major subtypes of Lymphoma—Diffuse Large B Cell, Follicular, Hodgkin, Mantle Cell and Peripheral T-cell. Issues considered included determining the highest priority patient populations for study, the current standard(s) of care appropriate to serve as a control in a clinical trial, which primary endpoints are sufficiently robust , which biomarkers are currently available or worthy of further development for incorporation into clinical trials, and the most promising novel agent(s) for study. Subcommittees for each Lymphoma subtype were convened six months prior to the CTPM to investigate the critical issues for their subtype, achieve a consensus via teleconferences, and develop their reports to be presented at the CTPM. Members of the Biomarker and Trial Design subcommittees served in advisory roles in these discussions as well as developing their own reports for presentation at the CTPM.

Goals of meeting: The meeting was designed to develop a consensus on the most important therapeutic challenges in each lymphoma subtype and a general strategy for developing new trials to change practice in Lymphoma. The emphasis was on studies uniquely suited to the NCTN that seek to advance therapeutics guided by public health principles and precision medicine. Major issues addressed included trial design questions, including appropriate controls and endpoints. Validation and incorporation of biomarkers into trials were also discussed extensively, with the ultimate goal of mechanistically-based treatments for Lymphoma.

Recommendations: Chairs of each of the seven subcommittees reported on the investigations and discussions of their group. This was followed by an open discussion involving all meeting participants and, finally, a member of the LYSC provided a ‘steering committee perspective’ on the presentation.

Lymphoma Biomarkers: A table of biomarkers relevant to the various Lymphoma subtypes was presented, with each biomarker characterized extensively with respect to its level of validation and clinical utility. Future trials will need to include biopsies at diagnosis to gain further insights on disease mechanisms and ideally at relapse to understand the biology of progression. Although there are many candidate biomarkers, few are fully validated and discussion focused on how to obtain the data necessary for advancing biomarkers to integral status. Next generation DNA and RNA sequencing may be informative, and a unified effort with a standardized and limited set of platforms applied broadly will be critical.

Trial Design: Recommendations are that future trials in Lymphoma should be randomized with defined control arms. Phase II/III designs could increase efficiency but it is important to ensure that the decision to advance to phase III is based on rigorous data, and these phase III trials must have the ability to document clinical benefit. Clinical benefit can be determined by overall survival (or a valid surrogate for survival) or by health related quality of life. There was considerable discussion of ‘master protocols’ regarding appropriate controls for targeted agents, the need for balanced randomization and feasibility for Lymphoma. In general, incorporation of rigorous statistical designs will ensure the validity of trial results.

Diffuse Large B Cell Lymphoma: Molecular heterogeneity of the disease has been described extensively, particularly with respect to cell of origin as ABC or GCB. This underscores the importance of

tissue collection and analysis in DLBCL on a routine basis. MYC/BCL2 double hit/double expressers are the highest risk groups and hence represent an opportunity to test new treatments, but there is no consensus on a standard of care for either of these. One general item of discussion was timing of introduction of targeted therapy given the delay introduced by screening protocols. The consensus was that treatments should be introduced during the first cycle and that patients should be either selected or stratified up front. Furthermore, a reliable method for assigning risk needs to be developed, as the currently available approaches are inadequate. There is also a pressing need to develop reliable surrogate markers, as PFS is problematic in many trial designs. PET scanning is promising and some current trials may provide further validation. Analysis of circulating tumor DNA is a novel technology but largely exploratory at this time.

In the relapsed setting survival is poor and there are no prognostic biomarkers so it is more difficult to assess effects of treatments on defined subgroups. It is unclear if there is any mechanistic difference between relapsed and refractory patients, and collection of samples after relapse is essential to begin to address this question.

Follicular Lymphoma: Steve Ansell stated that curing FL is the ultimate goal, although this may take several rounds of new trials. Initial focus should be on the high risk population, defined by a lack of CR to initial treatment and requirement for new treatments within 30 months. However, it will be essential to define and validate underlying genetic and molecular features that determine this clinically high risk group in order to make the advances set forth in this goal for cure. Recommendation is for a national phase II trial and PET- CR following induction or a continuous CR for 30 months might be valid endpoints. However it was pointed out that this endpoint would require validation in the setting of novel therapeutics. Treatments could include chemotherapy, but not maintenance Rituximab due to the curative intent. Initial studies would be in relapsed high risk patients with effective treatments moved to the front line when appropriate. There are no currently no biomarkers to define the high risk population at diagnosis. This was regarded as a significant unmet need and several possible strategies for addressing this gap were discussed, along with the associated requirement for obtaining biopsies from all FL patients at diagnosis and ideally at relapse. Identification and development of these biomarkers could help to understand the biology of high vs. low risk FL. There was extensive discussion of appropriate control(s) for this trial without arriving at a consensus. Final questions focused on the definition of a cure and how long treatment would be continued to achieve this goal. Biomarkers are necessary to determine risk at diagnosis and samples from prior trials like RESORT or PRIMA might be available for some initial investigations.

Hodgkin Lymphoma: In general cure rates are impressive with current treatments, but there are concerns about quality of life issues and long term effects, particularly with radiotherapy. Additionally, prognostic biomarkers and surrogates for late effects would be invaluable resources for informing treatment decisions. Randy Gascoyne has made considerable progress with a GEP that appears to define the high risk population (about 30% of the total). Recommendation therefore is sample collection from all HL patients, but the trial design in which this might be accomplished is uncertain; samples from previous studies might be available. Support is accumulating for PET scanning as a surrogate marker but it is not yet fully validated. The long-term goal would be a phase III PET-directed trial in bulky HL, but these patients can be difficult to accrue. Other possible designs were discussed extensively, including transplantation and immunotherapy. HL subcommittee members previously assigned priorities to the many possibilities for trials but failed to reach a consensus. HL involves about 10K patients per year with 1K deaths but there are many long-term survivors. Many of these are over 65 and could manifest late effects of treatment. These patients are typically seen in the community and might therefore be appropriate subjects for NCTN-based studies, which could help develop surrogate markers for late effects and provide some epidemiologic information. There was extensive discussion of the rationale for studying the impact of treatment reductions in HL and prioritization of NCTN resources given the high cure rates in HL and the extremely long follow up times to assess late effects of treatment. An important contribution NCTN could make is biomarker identification at diagnosis of those unlikely to be cured with standard therapy and to target these patients for experimental therapeutics. Alternatives include second line/relapsed, a transplant up front or secondary biologic studies in up front studies with mandatory tissue collection. The transplant study could be an upfront question and could be practice changing. Carla

Casulo did some modeling that suggested feasibility, although the difficulties in randomizing between transplant and observation were noted.

Mantle Cell Lymphoma: MCL is a rare disease with few prognostic markers or surrogate endpoints. There have been many phase II studies but few phase IIIs, and one clear result is that intense treatment prolongs PFS. However, those with best performance status and thus better prognosis may skew these findings and intensive treatment cannot be given to all patients. Possible trial designs discussed included a low-intensity treatment in low risk young and older patients. However, endpoint(s) are uncertain as neither PET nor MRD have been validated in MCL. The role and value of transplantation is also an important question but it would likely be difficult to accrue patients to the 'non-transplant' arm. There was interest in the relapse situation and a trial of intensive treatment in younger 'fit' patients. Participants engaged in considerable debate on the value of maintenance therapy, to the extent that an ad hoc survey of meeting participants indicated that half would include maintenance treatment for MCL and half would not. Clearly further investigation of the role of maintenance is warranted. Possible inclusion of overall survival, quality of life and other assessments as endpoints were discussed, and the value of proliferative index (Ki67) was noted, as it may help to define levels of risk. Some sort of GEP analysis could be informative in combination with other genomic information like copy number. There was an extensive discussion of appropriate control arms for an MCL trial with no real consensus. Overall, if drivers and appropriate targeted agents in MCL could be identified, the disease might be managed by some sort of long-term maintenance, as with imatinib in CML.

T-Cell Lymphoma: TCL is essentially an orphan disease with poor prognosis and few effective treatments. There is very little understanding of the biological mechanisms involved, but there appear to be many molecular subtypes. The ALK+ group has reasonably good prognosis but the others progress rapidly. CHOP might be the only option available currently, so it would be logical to try some novel agents in combination with this backbone. There are many candidates, but it's not clear if any would be effective. Given the heterogeneity of TCL, some sort of adaptive design could be entertained, such as a two stage design with a biomarker targeted agent at the second stage. The goal would be to move effective treatments from second line to upfront; there was some discussion on appropriate controls and how much evidence might be necessary for this transition. TCL might be an appropriate candidate for the NCI MATCH trial and the logistical challenges of leveraging that possibility were noted. Alternatively, doublets might be of interest because they could include some FDA-approved agents. The consensus was that some sort of adaptive design with a variety of doublets would be the first choice, with MATCH as an alternative should the doublets fail. In either scenario the necessity for rapid treatment should be recognized, as TCL typically progresses rapidly. As there is little understanding of disease biology samples should be obtained from all patients and next-gen sequencing analysis might be the initial approach to identify driver mutations.

Meeting Consensus: Efforts in DLBCL, Mantle Cell and Follicular Lymphoma should build on currently available results to eventually transition to practice-changing phase III studies. In general, future trials in Lymphoma should incorporate the critical elements discussed during this CTPM, including statements and testing of specific hypotheses, clear evidence of clinical benefit, attention to Quality of Life issues, and routine collection of biopsies. Development and validation of biomarkers (imaging and molecular) to be used as research tools is essential. These include those markers that can be used as early surrogate endpoints for use in go/no-go decisions in randomized phase II/III trial. A longer-term goal would be to develop surrogate markers for survival in indolent Lymphoma subtypes so that the clinical trials can provide early reliable information on clinical benefit. Extensive discussion of appropriate standards of care resulted in a tentative consensus that one to three control arms could be acceptable. Although this would likely increase the statistical complexity of the trials, it would also increase their acceptability in the community and thereby enhance accrual.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research