2023 Strategic Priorities

Lymphoma Steering Committee (LYSC)

The state of the science in lymphoma biology and biomarkers is inherent to the main therapeutic goals of the NCTN lymphoma portfolio. As genomic assays improve, there is increasing scientific opportunity to incorporate this information into biologically relevant and targeted therapeutics in the NCTN portfolio. A major and essential element of the NCTN lymphoma portfolio in setting forth strategic priorities is to consider potential molecular and imaging modalities that can be used as integral tools in future clinical trials (integral in this sense means that without the tool, the trial could not be conducted). Currently, available integral tools include GEP for DLBCL and FDG-PET for both HL and NHLs, genomic assays, and others.

Included below is a mention of other specific biomarkers slated as priorities to develop and validate for the specific prioritized tumor types. In general, the strategic priority is to either discover or, for those already in development, select those biomarkers or imaging platforms that should be validated to be used as integral tools in later clinical studies. This priority recognizes the requirement that precision medicine cannot be accomplished with the tools currently validated for much of this portfolio.

Evolving therapeutics include cellular and immuno-oncology agents as well as targeted agents. It will be important to leverage these with appropriate clinical trial designs for both phase 2 and phase 3 studies.

The NCTN lymphoma portfolio has a strong presence in Hodgkin lymphoma and primary mediastinal B-cell lymphoma each with a focus on adolescent and young adults. The LYSC conducted working groups to successfully develop several such studies, and this is a model to continue. Additionally, a working group in primary central nervous system lymphoma was established and priorities development of novel agents in the induction space, suited to both younger fit and older patients. The priority is to develop small phase 2 studies and then select the most promising for definitive study but to avoid tying up the NCTN in a large study until compelling data warrants the investment.

As part of the NCI initiative to streamline clinical trials and to use innovative trial designs, the

LYSC proposes that whenever an important scientific opportunity could employ pragmatic designs or otherwise simply trial conduct, this could benefit other priorities such as fostering diversity and inclusion in clinical trials.

Follicular Lymphoma

Developing a cure for FL has been established as the goal for this lymphoma subtype. The strategic plan reflects this goal:

1) The focus will be on high-risk FL. The strategy will be to develop a molecular or other biologically based classifier that establishes prognosis at diagnosis. The importance of having biopsy material for genomic evaluation is stressed, particularly for studies focused on early progression.

2) Because risk categorization is currently clinically based, the strategy will be to initially develop studies that enroll patients who have relapsed within two years after initial therapy. Adaptive trial designs with multiple arms would facilitate selecting the optimal drug combinations as well as obtaining tissue for molecular profiling. For this initial part of the longer-term cure goal, a multi-arm phase II study evaluation of new agents compared to control would allow the selection of novel agents most promising for the longer-term goals.

3) These goals require that there be an improved understanding of the biological and molecular features of FL so that diagnostic material can be used to establish prognosis and clinical trial eligibility. Retrospective analyses of existing trial specimens will be utilized, but there are limitations to the approach (for example, lack of non-tumor tissue). The initial trials will require tumor biopsy so that molecular signatures can be developed and then used as an integral marker in a later trial for previously untreated patients utilizing a multi-arm adaptive phase II/III clinical trial that will validate the high-risk classifier and test the therapeutic effects of novel agents that will be selected based on preclinical or clinical evidence of relevance to the tumor biology. The experimental arms will be randomized against a control arm, selected by consensus of the NCTN Groups.

4) Low Risk Group: Opportunities for low-risk FL are emerging with immunology

approaches that could change the natural history of the disease. This will be an emerging area of opportunity for the lymphoma portfolio. Those with the lowest risk FL have a life expectancy equivalent to the background population. Because it will be essential for assay validation and to further develop predictive (not just prognostic) biomarkers, the strategy will be to include all comers to the later stage studies to validate the biomarkers and to understand characteristics of the patients with a less aggressive presentation that may lead to therapeutic advances for that group as well. Once there is a validated locked-down classifier, the strategy will focus on the groups so molecularly defined. With the increasing availability of novel immunotherapy agents, trials focusing on reducing the need for treatment and prolonged disease remissions are of interest. Opportunities to consider inclusion of HR-QOL in phase 3 trials may help to improve the ability to define clinical benefit when feasibility makes overall survival endpoint out of reach.

5) Validation of MRD to be used ultimately as an integral marker in studies. This may include assays for cell-free DNA or other highly sensitive genomic-based assays.

Mantle Cell Lymphoma

1) The strategic effort in MCL will focus on developing therapeutic approaches that adjust therapeutic intensity based on patient characteristics yet optimize the outcome. Development and validation of MRD assessment as part of overall clinical management is essential to the overall strategic plan for MCL.

2) One of the most important clinical questions in MCL has been the role of autologous transplantation, and more recently, cellular therapy/immunooncology approaches have emerged as important scientific opportunities. Despite the findings of the recently reported TRIANGLE study at the annual ASH meeting in 2022, the role of transplant in MCL remains controversial as this study did not uniformly employ rituximab maintenance, and the primary endpoint was PFS, not OS. Therefore, the ongoing EA4151 study evaluating the role of transplant on OS in undetectable patients following transplant retains its importance. As active novel therapeutics emerge, the question becomes ever more relevant, and a valid test of the role of transplant for the larger population (not just the MRD undetectable) remains

undefined. A long-term strategic plan for the MCL will be to answer this question, if possible, but it will be necessary to have a number of shorter-term strategies that pave the way toward the ultimate goal of properly answering the transplant question. In addition, improving the outcomes after cellular therapy using immunooncology approaches and novel therapeutics will be an important area of opportunity. The strategy to develop these therapies successfully may lead to opportunities to reconsider the feasibility and interest of transplant therapy in the future.

3) The initial strategy in MCL will be to develop studies that assess the effect of novel therapy on MRD (as compared to the effects of a control regimen) and to validate that the MRD findings translate into a valid prognostic marker. This strategy is envisioned to promote the development of improved therapeutic regimens for MCL utilizing novel and novel-novel combinations of agents that result in a higher proportion of patients who are MRD negative at the end of induction therapy for MCL.

4) A longer-term strategy will be based on the validation of MRD as a prognostic marker and the ability to achieve the majority MRD negativity with novel induction therapies. The longer-term strategy will be to assess the role of consolidation, maintenance, and or transplant for patients who are MRD-negative following induction (through randomized trials). In addition, for those who are MRD positive at the end of induction, studies will focus on whether there is a benefit from additional therapy and what type of approach is most helpful. This strategy will promote the ability ultimately to better designate the therapeutic approach a given patient will benefit from the most.

DLBCL

1) At present, a number of novel agents are being developed in combination with standard therapy for various NHL's. Agent "X" plus R-CHOP and its variations are probably the dominion of the pharma industry (exemplified by polatuzumab vedotin development), except in unique populations more suited for the NCTN. Testing these kinds of combinations is being done increasingly by drug companies, and unless there is a unique and important opportunity that would not get done otherwise without NCTN support, these kinds of studies will not be part of the NCTN portfolio strategic priorities.

2) A unique scientific opportunity that would require NCTN involvement and support

in DLBCL would be to focus on DLBCL subtypes or molecular clusters. The two subgroups designated a "double-hit" (dual chromosomal rearrangements, specifically of *MYC* and either *BCL2* or, less commonly, BCL6) and those termed "double expresser" (that overexpress Myc or BCL2 protein as assessed by IHC) have a poor prognosis and are a strategic priority for the NCTN. The underlying biology of the "double hit" and the "double expresser" are quite different, and agents that act on both may be possible, but the underlying importance of studying these will be to definitively document whether the double hit translocation is present in every patient entered on the studies. In this way, the ability to understand therapeutic outcome based on biology will be improved and forms the critical justification for this strategic priority.

A high priority for the NCTN could be to leverage resources to facilitate screening and include molecular characterization for cluster designation. Matching patients to clinical trials to define whether targeted therapy relevant to a cluster's biology can improve outcomes would likely be attractive to industry partners and possibly assay companies as well. This effort will require a valid assay to identify molecular features prior to therapy.

Transplant and Collaboration with the BMT CTN

The Grant PI of the BMT CTN and her designees (beyond those on the LYSC who represent the BMT CTN) were invited to participate in the NCTN priority setting. As CAR-T and other approaches are developed, collaboration with this network may yield important opportunities. This has already been the case at the BMT CTN 2022 State of the Science Symposium. For example, S2114, entitled " A Randomized Phase II Trial of Consolidation Therapy Following CD19 CAR T-Cell Treatment For Relapsed/Refractory Diffuse Large B-Cell Lymphoma or Grade IIIB Follicular Lymphoma has been developed testing bi-specific antibodies following CAR-T for follicular lymphoma. Other similar opportunities, for example in Hodgkin lymphoma, have also leveraged the BMT CTN collaboration (EA4211: "A Randomized Phase III Trial of Chemotherapy vs. Pembrolizumab Plus Chemotherapy for Relapsed/Refractory Classical Hodgkin Lymphoma."