

## 2015 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. The limitations on biomarkers useful to clinical trial design and endpoint surrogacy places constraints on the portfolio, but also suggests opportunities. 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. Included below, there is 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 developments, select those biomarkers or imaging platforms that should be validated so that they can then 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.

#### ***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.
- 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 a control would allow selection of novel agents most promising for the longer-term goals.

- 3) These goals require that there be 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: those with lowest risk FL have 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 in order 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 be to focus on the groups so molecularly defined.
- 5) Validation of MRD to be used ultimately as an integral marker in studies. This may include the cell free DNA assay as being developed by Sequentia/Adaptive.

### ***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 is the role of autologous transplantation. As active novel therapeutics emerge, the question become ever more relevant. A long-term strategic plan for the MCL will be to answer this question if possible, but to have a number of shorter term strategies that pave the way toward the ultimate goal of answering the transplant question.
- 3) The initial strategy in MCL will be to develop studies that assess the effect of novel therapy on MRD (as compared to 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 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 end of induction, studies will focus on whether there is benefit from additional therapy, and what type of approach is most helpful. This strategy will promote the ability to ultimately 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 for various NHL's. For example, Celgene is conducting a phase 3 of R-CHOP vs lenalidomide-R-CHOP and Pharmacyclics is conducting a phase 3 of R-CHOP vs ibrutinib R-

CHOP in DLBCL. Testing these kinds of combinations is being done increasingly by the 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 rare DLBCL subtypes. The two subgroups designated as “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 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 for 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 the biology will be improved, and forms the critical justification for this strategic priority.

### ***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. Currently the NCTN is leading a phase III trial that was developed in collaboration with the BMTCT; this trial will open later in 2015. This trial will test ibrutinib during transplant and maintenance in ABC DLBCL. No additional transplant studies in DLBCL are planned for now.

In Follicular lymphoma, there is a plan to investigate allogeneic transplant. This is not a high priority for the NCTN, though it may be possible over the next several years to refer patients to BMT CTN clinical trials in this area. If a molecular risk model is ultimately validated for high risk FL, there could be a role for allogeneic transplant earlier in the therapeutic course for patients, and so the NCTN will re-evaluate this issue in the future.