2015 Strategic Priorities

Leukemia Steering Committee (LKSC)

The LKSC recognizes the need to streamline a method for laboratory analysis of newly diagnosed patients with leukemia in order to select patients for specific trials or arms of trials so that the field can be advanced toward precision medicine. The LKSC consensus is that the goal is to develop and utilize assay systems with turnaround times of 5 days or less.

Acute Lymphoblastic Leukemia (ALL)

1) Standardization of MRD and development of various platforms to understand which perform best for a given use (e.g. prognosis, stratification, surrogate marker etc.). The ultimate goal would be multiplex categorization: MRD + genetic abnormalities and eventual development of up front molecular screening to classify ALL subtypes.

2) A high priority is to focus on the BCR-ABL-1 like phenotype. Identification would be through molecular screening at diagnosis and patients would be allocated to matched therapy selections and/or allogeneic transplant.

3) Optimizing the "backbone" therapy in Adult ALL remains important, so the strategic priority will be to combine age-appropriate backbone therapeutics with novel therapy, in particular immunotherapy:

- **a.** Conjugated antibodies
- **b.** Bi-Specific antibodies
- **c.** CAR-T cell therapy

The priority is not dependent on the actual immunotherapy bulleted above, but rather to test whether the likelihood of a cure can be increased by incorporating them, and to determine if it is possible to de-intensify backbone therapy consequent to novel therapy (such as immunotherapy) while maintaining or even improving the cure rate.

4) An important question for Ph+ adult ALL is the relative role of TKI therapy and conventional chemotherapy, and whether allogeneic transplantation is necessary following induction to a MRD negative status. This is a critical question to answer and is a top strategic priority for the portfolio.

Acute Myeloid Leukemia (AML)

1) A critical strategic priority is to improve therapy for older patients with AML. This requires development and validation of tools to identify patients unlikely to benefit from standard therapy, and development of clinical studies aimed at improving the outcome for this population.

2) Validate gene expression and clinical assays for patient selection on clinical trials.

3) Progress beyond the multitude of AML genotypic prognostic markers to predictive markers and incorporate them into clinical trials involving targeted therapies appropriate to the markers.

4) Utilize adaptive clinical trials designs to rapidly close/open arms or alternatively proceed to phase III.

5) Develop randomized phase II / phase III studies to evaluate addition of novel agents to less intensive therapy in those unlikely to benefit from intensive therapy.

Myelodysplastic Syndrome

Incorporate the mutational spectrum and epigenetic findings of MDS biology into the clinical trial designs:

1) Utilize novel agents biologically relevant to the disease based on the identified mutations (and pathways) and epigenetics

2) Test whether these agents can augment the action of hypomethylating agents

3) Adaptive clinical trial designs with multiple arms that can close early for futility or rapidly inform the subsequent phase III trial

4) Include in the trial designs specific arms where there are predictive marker mutations and an available targeted agent specific for the MDS risk features to improve efficiency and more rapidly advance the field.

CLL

CLL therapeutics are rapidly advancing and the NCTN currently has two phase III trials for previously untreated CLL using ibrutinib (one trial is for younger fit, the other for older patients. These trials have the potential to change the treatment paradigm for CLL. If this turns out to be the case, then there will be important initiatives informed by these trials:

1) Ibrutinib failure may comprise a substantial population of patients over time. The strategic plan will be to address therapeutics to prevent and treat ibrutinib resistance.

CML

The tremendous success of tyrosine kinase inhibitors has made the initiation of phase III trials for chronic phase CML rather difficult. Further discussions regarding potential large trials will be informed by the results several smaller trials being carried on by pharmaceutical sponsors as well as institutions across the NCTN network groups. The next NCTN trials will revolve around the issue of TKI discontinuation, and the treatment of relapsed and progressive disease.

BMT-CTN Collaboration

The Grant PI of the BMT CTN and her designees (beyond those who are LKSC members representing the BMT CTN) were invited to participate and to explain their priorities. These were accepted by the LKSC:

1) Post-transplant maintenance to prevent relapse.

2) Comparative evaluation of transplantation as a consolidation strategy in older AML.