Meeting Summary with Interim Recommendations

NCI National Clinical Trials Network Working Group (NCTN WG)

December 16-17, 2012

On December 16-17, 2012, the NCI National Clinical Trials Network (NCTN) Working Group (WG) held the second of four meetings to review the active phase 3 and large phase 2 (>100 patient) therapeutic clinical trials conducted by the NCTN Program. The NCTN WG has been charged with assessing the strength and balance of the NCTN Program trial portfolio both within and across diseases and recommending new strategic priorities and directions. The December meeting refined the process of conducting clinical trials portfolio analysis and developing recommendations by assessing five disease-specific portfolios.

This summary synthesizes key conclusions and recommendations that emerged from the presentations, discussion, and rating of trial concepts approved by the Disease-Specific Scientific Steering Committees (DS SSCs) for five disease sites: breast, leukemia, gastrointestinal (GI), lymphoma, and genitourinary (GU). Cross-disease and disease-specific comments and recommendations aimed at improving the portfolio are summarized.

Cross-disease comments and recommendations highlight that some disease portfolios have more scientific opportunities than do others resulting in more highly rated clinical trials. However, despite these differences, some common concerns emerged including:

- A tension between selection of more nimble, biology-driven, randomized phase 2 trials versus larger, more resource-intensive phase 3 trials
- Lack of drug availability due to pharma/biotech unwillingness to collaborate in certain areas; and
- Difficulties of predicting accrual feasibility in advance.

Recommendations focused on how to best advance cutting-edge science in the genomics era in a time of fiscal constraint. In particular, the NCTN WG recommended improving the integration of genomics and biomarkers in study design across the portfolios. The WG concluded that the NCTN Program's strength in the future may reside in conducting trials with more correlative science, such as molecular characterization and biomarker tests, which can be attractive to industry collaborators. This should also serve to distinguish NCI's NCTN Program in the global research arena from its European competitors whose medical systems facilitate better accrual in some diseases. These future directions will require adequate funding, appropriate infrastructure for biomarker validation, and strategic planning and guidance by the DS SSCs and the NCTN Groups to support and incentivize the most scientifically and clinically important studies.

Interim Cross-Disease Recommendations

- NCI should conduct an analysis of resource allocation across diseases, taking into account current survival rates and likely cost/benefit from additional advances
- NCTN Groups and DS SSCs should work together to achieve the appropriate balance of innovative, randomized phase 2 trials and larger more resource intensive phase 3 trials in each disease portfolio
- NCTN Groups and DS SSCs should emphasize biology-driven (e.g., molecularly-driven, pathway-driven) trials that advance the science by incorporating genomics, biomarker tests and correlative science into study designs
- To empower innovative, biology-driven trials, additional NCI funding should be provided for correlative science studies, biomarker validation and the development of molecular classification algorithms
- Accrual challenges should be taken more seriously in proposing and approving trial concepts, balancing the importance of the clinical question with the perceived difficulty of accrual
- More consideration should be given to competing European and industry trials in proposing and approving trial concepts as well as to the potential for collaboration with European and industry partners
- DS SSCs should increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN Groups
- DS SSCs should develop standardized guidelines for the level and types of preliminary data required for trial concepts
- DS SSCs should optimize their use of Task Forces (TFs), Working Groups (WGs) and Clinical Trial Planning Meetings (CTPMs)
- Greater emphasis should be placed on sharing strategic and tactical best practices across diseases in terms of trial design, accrual, preliminary data requirements, etc

The breast cancer portfolio was assessed as strong in that it addressed several key clinically important questions. Studies are multidisciplinary and the portfolio has a good balance of systemic and local-regional trials.

Key recommendations to enhance the breast portfolio include incorporating smaller, more nimble randomized phase II trials of newer approaches to balance large adjuvant studies, as they may provide unique opportunities for translational science. Special priority should be given to molecularly-driven trials, marker validation, correlative science, and studies on limiting toxicity, improving quality of life (QOL), and assessing survivorship. The breast cancer SSC (BCSC) can facilitate these changes by providing strategic guidance for concept selection, developing standards to improve trial design, and optimizing the use of TFs, WGs, and CTPMs.

The leukemia portfolio includes many innovative, biologically-based, and scientifically and clinically important trials. Chronic Lymphocytic Leukemia (CLL) trials in older adults are noted strengths.

Recommendations to improve the portfolio include integrating more correlative science, prioritizing biospecimen collection, support of molecular classification algorithms for patient stratification, and using more biomarker and imaging technologies. Additional priorities include more molecularly-driven Acute Lymphocytic Leukemia (ALL) and Acute Myeloid Leukemia (AML) trials and studies for relapsed disease. The Leukemia SSC (LKSC) should build on its strengths in strategic planning, collaboration, and refining trial ideas by working collaboratively with the NCTN Groups to make these improvements and work to enhance accrual.

The GI portfolio was felt to be moving in the right direction and **s**trengths of the portfolio include addressing clinically important questions and questions industry would be unlikely to support as well as rare cancers.

Recommendations include placing greater focus on scientific innovation, biology, and genomics by promoting studies that incorporate pathways, biomarker screening, targeted therapy and the use of molecular classification for treatment selection. Future priorities should also include incorporating surgical and imaging studies into the portfolio. The GI SSC (GISC) should leverage its strengths in organization, efficiency, use of TFs and intergroup and global collaboration to work collaboratively with the NCTN Groups to make these recommended improvements. The GISC should also develop guidelines regarding the requirements for preclinical data in concepts and improve its process for assessing accrual feasibility.

The lymphoma portfolio only recently began to be prioritized by the Lymphoma SSC (LYSC) and some significant challenges were discussed. There was special concern that competition from industry and Europe has resulted in the best new agents in lymphoma not being developed through the NCTN.

Recommendations to improve the portfolio include focusing on innovative, correlative and translational science, and incorporating integral biomarkers and molecular characterization into trial concepts. There should be an effort to collaborate rather than compete with Europe and industry. In addition, the lymphoma SSC (LYSC) should continue its strategic planning and guidance of early concept development and work with the NCTN Groups to promote development of phase II trials that inform or lead to phase III trials, develop a niche in applying molecular science to trials, work on data standardization and address accrual issues.

The GU portfolio was judged to likely provide only moderate scientific and clinical benefit although it does address questions industry would be unlikely to support.

Recommendations include investing in diseases with poorer outcomes, focusing on scientifically important, molecularly-driven, multidisciplinary trials with greater clinical impact, leveraging new drugs, and moving toward smaller phase II studies. Additional opportunities include

incorporating more molecular correlates and biomarkers, technology assessment, QOL and patient reported outcomes into trial designs. To enhance the portfolio, the GU SSC (GUSC) and the NCTN Groups should develop a strategic plan to guide concept development and decision-making processes, and balance prostate and large phase III trials with other diseases and trial types.

In conclusion, fruitful discussion at the December 2012 NCTN WG meeting allowed for a comprehensive and critical review of five disease-specific clinical trial portfolios. The process of disease-specific review allowed for a critical assessment of the strengths and weaknesses of the portfolios presented which led to the development of interim recommendations to improve clinical cancer research portfolios supported by the NCI. These recommendations will be further refined and perhaps expanded based on the review of trial portfolios for the remaining diseases in NCTN WG meetings to be held during the spring and summer of 2013.