

2015 Strategic Priorities

NCTN Disease-Specific

and

Symptom Management & Health Related Quality of Life
Steering Committees

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Overview

The NCI National Clinical Trials Network (NCTN) Working Group recommended in their final report to the Clinical Trials and Translational Research Advisory Committee (CTAC), [NCTN Working Group Final Report July 2014](#), that the Scientific Steering Committees (SSCs) increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN Groups, the NCI Community Oncology Research Program (NCORP) Research Bases and the NCI. To that end strategic priorities were formulated by the SSCs over the last year in conjunction with the NCTN disease committee leadership, NCORP representatives and NCI leadership overseeing the NCTN and NCORP programs. The objective was to set strategic priorities for NCTN therapeutic trials and NCORP symptom management and health related quality of life trials with the goal that, in the future, the majority of submitted concepts would align with the established priorities.

The SSCs were asked to develop strategic clinical trial priorities for each disease area covered by the steering committee. The definition of a strategic priority for this activity included:

- Area of unmet clinical need specific to the disease
- Important unanswered clinical question with regard to improving disease treatment
- Potential new approach to disease treatment
- Encompasses a wide range of potential trial concepts

Specific trial ideas, broad goals, trial design priorities, and translational research priorities were not part of the definition of strategic priorities.

The SSCs assessed the clinical trials within their portfolio to identify gaps and provide context for the identification of strategic priorities. The NCTN Groups/NCORP Research Bases presented their priorities to the SSCs emphasizing clinical importance, suitability for a federal clinical trials system, and feasibility. These priorities were discussed within the SSC to look for common themes across priorities, to determine if there were issues with any specific priority, and address any other relevant topics in response to the presented priorities. After the discussion the SSCs selected their top priorities in each disease area. For some SSCs, this was a single organ site (e.g., breast) whereas for others (e.g. GI) there were separate priorities for different organ sites. As a result, some SSCs have more priorities than others.

As we move forward, the NCTN Groups and NCORP Research Bases will be responsible for concept development within the priority areas. The SSCs will continue to evaluate all submitted concepts for scientific and clinical merit. Trial concepts outside the strategic priority areas will still be considered by the SSCs but may require additional justification. The priorities will be reviewed annually and are expected to change and adapt over time as needed in response to scientific advances and new knowledge. Additionally, the strategic priorities listed in this document have not been ranked; the numerical listing is solely for point of reference.

Breast Cancer Steering Committee (BCSC)

The Breast Cancer Steering Committee (BCSC) has developed the following strategic priorities for therapeutic trials* to be conducted in the National Clinical Trials Network (NCTN) based on recommendations from the NCTN WG (<http://deainfo.nci.nih.gov/advisory/ctac/0714/Sledge.pdf>).

The NCTN conducts a late phase clinical trials program. Trials should be innovative, scientifically/molecularly driven trials with clinically meaningful outcomes and should address high priority needs. Trials should be based upon adequate pre-clinical and early clinical data.

1) Decreasing breast cancer mortality

- a. Improve outcome in advanced triple negative breast cancer (TNBC) through elucidation of subtypes and associated molecular targets
 - Specific approaches in triple negative disease with a DNA damage repair deficiency
- b. Improve outcome in ER+ breast cancer
 - Restoration of responsiveness to anti-hormone therapy in advanced disease
 - Augment response to anti-hormonal therapy in adjuvant setting
 - Develop targeted agents against known ER mutations in advanced disease
- c. Improve outcome in advanced disease through immunotherapy
 - Study strategies to reduce the burden/development of metastatic disease

2) Decreasing toxicity/treatment/costs associated with therapy with negligible clinically meaningful benefits

- a. Decrease chemotherapy in some HER2+ patients
- b. Decrease radiation in some breast conserving therapy (BCT)
- c. Decrease surgery in some breast cancer patients with pathological complete response (pCR)

3) Understanding biology and translating biology into diagnostic and therapeutic strategies

- a.** Develop targeted therapies in advanced triple negative disease
- b.** Develop targeted agents against known ER mutations
- c.** Predictors of relapse in ER+ disease
- d.** Use of novel biomarkers to direct therapy or to assess therapeutic response
- e.** Use of novel imaging to direct therapy
- f.** Define novel therapeutics in metastases (e.g., through the use of persistent circulating tumor cells (CTCs))

* The above priorities were identified specifically for therapeutic clinical trials to be reviewed by the BCSC and funded by the Cancer Therapy Evaluation Program in the Division of Cancer Treatment and Diagnosis. Ductal carcinoma in situ (DCIS) is not included in the above priorities since DCIS trials are reviewed and funded through the Division of Cancer Prevention.

Brain Malignancy Steering Committee (BMSC)

The following summary is based upon input from a series of strategic planning activities: 1) a preliminary teleconference on October 9, 2014 dedicated to the Strategic Priorities planning process, which formulated broad features of clinical trials that BMSC views as key priorities for concept development, 2) a face-to-face meeting in conjunction with the Society of Neuro-Oncology meeting on November 14, 2014, and 3) a subsequent conference call on January 9, 2015, which provided additional discussion and feedback. Each of the pediatric and adult cooperative groups and consortia presented their recent and ongoing development plans in the context of these meetings.

Common themes that emerged from these discussions were: 1) That there was a wealth of molecular data driving genomically-targeted therapeutic strategies for newly identified subsets of common tumor types in both pediatric and adult neuro-oncology; 2) The diversity of tumor types and relevant targets in pediatric neuro-oncology, and the recognition of molecularly distinct subsets of adult gliomas necessitates a broad and inclusive approach to prioritization; 3) Implementation of novel modalities (e.g. immunotherapy) should also be prioritized; 4) BMSC should be open to consider the most promising new ideas, based on rapidly evolving genomic and tumor biologic insights, rather than prioritizing particular agents or modalities to the exclusion of others.

The general Strategic Priorities that arose from these discussions are as follows:

- 1) Biologically or genomically based trial designs**, which take into consideration **molecular subsets of tumors** (e.g., MGMT methylated or unmethylated GBMs, 1p/19q codeleted gliomas, GBMs with molecular alterations that predict potential sensitivity to a novel agent (INSIGHT trial), SHH or beta catenin subsets of medulloblastomas in children and adults, BRAF-targeted therapies for pediatric LGG and HGG), in which case the **biomarkers are integral** to the study design.
- 2) Studies that pair administration of a novel agent (e.g., small molecule) or modality (e.g., immunotherapy), with pharmacodynamic or immunological measures or tissue analyses of the drug target and studies of drug penetration into the tumor**, such that **mechanistic hypotheses** directly relevant to the agent/modality in question can be tested that may form a foundation for subsequent trials.

- 3) Studies that pair novel agents or modalities with **imaging biomarkers or molecular biomarkers** as hypothesis-testing or hypothesis-generating tools.
- 4) Studies that focus on “**process improvement**” approaches that may enhance QOL and/or influence outcome (e.g., whether temozolomide adds benefit post-RT vs. only during RT; use of proton vs. photon irradiation).

Clinical Imaging Steering Committee (CISC)

It is an important mission of the NCI to promote and support clinical trials that incorporate advanced clinical imaging and which result in improved preventative, diagnostic and therapeutic outcomes. To facilitate this mission, the CISC has developed strategic priorities that are aligned with those of the NCTN, NCORP and other NCI-sponsored cancer therapeutics networks and therefore will lead to improved clinical outcomes.

The Clinical Imaging Steering Committee's 2015 Strategic Priorities are:

1) Employment of advanced imaging methods to predict and/or measure therapeutic response

- a. Optimization of techniques and post-processing
- b. Prediction of response to a specific therapy (baseline scans)
- c. Use imaging to select patients likely to respond prior to, during, or at end of therapy
 - (e.g. differentiation of pseudo-progression from true tumor progression)

2) Imaging as an integral *predictive* biomarker

- a. Imaging as a tool to select and stratify patients for precision medicine-based therapies
- b. Imaging as an early biomarker of response and surrogate for established endpoints
- c. Quantitative imaging research investigations
 - MRI and/or PET imaging in measuring therapeutic outcome of novel agent combinations
 - Qualification of imaging biomarkers
 - Standardization of quantitative imaging in large multicenter trials

3) Clinical trials of imaging to inform cancer management

- a. As a means for cancer detection (presence/absence/characterization)
- b. As a surveillance technique to identify cancer recurrence or the transformation of lesions to different biological subtypes.
- c. Incorporation of imaging to guide response adaptive trials

- Trials to alter or adapt patient management can be exploratory or definitive, the latter of which could include a comparator arm not using imaging to inform/adapt therapy. Collection of data on quality of life, resource utilization, quantitative imaging and outcomes is encouraged as a trial component to provide meaningful patient-centered and societal outcomes

4) Refinement of imaging response criteria and promotion of imaging endpoints

- a. Redefine RANO (2.0) (definition of RANO (2.0))
- b. Define response evaluation in bone
- c. Employ volumetric based tumor burden quantitation
- d. Seek automated methods that are accurate and precise and easy to use across commercial scanner platforms
 - Comparison of standard and novel criteria with downstream outcomes

5) Molecular mechanism for quantitative functional imaging

- a. Develop improved physiologic imaging methods
 - Metabolomic, perfusion and diffusion techniques
- b. Seek the biological underpinnings of imaging phenotypes with imaging-pathology correlations
 - Genomic correlates
 - Proteomic correlates
 - Metabolomic correlates

6) Imaging as a tool to measure pharmacokinetics

- a. To reliably determine if and when drug hits a target
- b. To determine blood-brain-barrier integrity

Gastrointestinal Steering Committee (GISC)

Overall goal: To leverage the resources of the NCTN to improve the outcomes of patients with gastrointestinal cancers. This will be accomplished by studies of new agents and modalities, with emphasis on biomarker-driven research that impacts treatment selection and supports scientific discovery.

Colon Cancer

- 1) Adjuvant trial with incorporation of novel biomarkers (e.g., circulating tumor-DNA) as integrated or integral markers for minimal residual disease and treatment response.
- 2) Immunotherapy in a priori immunogenic colorectal cancers (MSI-H) and non-immunogenic cancers by exploring immunomodulatory mechanisms.
- 3) Biomarker-directed treatment approaches in patients with metastatic disease.

Esophagogastric Cancer

- 1) Studies in the locally advanced setting. This includes concepts in the neoadjuvant or high risk adjuvant setting.
- 2) Immunotherapy and molecularly targeted therapies in gastroesophageal malignancies.

Hepatobiliary Cancer

- 1) Hepatocellular Carcinoma
 - a. First line and second line studies of systemic therapy
 - b. HCC locally advanced therapy with TACE- combined with therapies such as immune modulators (PD-L1) or others.
- 2) Biliary Cancer
 - a. Randomized phase II trial in second line therapy after progression on gemcitabine/cisplatin, targeting FGFR and/or IDH1-2 pathways, MEK inhibition
 - b. Phase III randomized adjuvant study evaluating combined modality of radiation plus chemotherapy versus systemic therapy in higher risk extra-hepatic biliary cancer.

Neuroendocrine Tumors

- 1)** Therapy for advanced NET of tubular GI tract
 - a.** Randomized phase II or phase III studies of systemic therapy using targeted agents and immunotherapy approaches
 - b.** Study of regional therapy
- 2)** Therapy for advanced NET of thorax (lung, thymus)
 - a.** Randomized phase II or phase III studies of systemic therapy using targeted agents, immunotherapy approaches, and cytotoxic agents
- 3)** Therapy for advanced NET of pancreas
 - a.** Randomized phase II or phase III studies building upon recent advances, and seeking predictive biomarkers

Pancreas Cancer

- 1)** Late stage pancreas adenocarcinoma
 - a.** Evaluation of novel therapies in second/third-line setting
 - b.** Exploration of immune therapeutic approaches in later stage pancreas adenocarcinoma
- 2)** Borderline resectable (BRPC) and resectable pancreas adenocarcinoma
 - a.** Studies to explore new treatments and define the optimal type and sequencing of systemic therapy in BRPC
 - b.** Studies to determine the contribution of radiation therapy to chemotherapy in disease control. If radiation therapy is of value, what is the optimal dose/method of delivery (IMRT vs. SBRT)?
 - c.** Studies of new neoadjuvant approaches for resectable pancreas adenocarcinoma

Rectal Anal Cancer

- 1)** Investigate the use of total neoadjuvant therapy (TNT), and integration of novel agents and unique approaches in locally advanced rectal cancer.
- 2)** Integrate unique biomarkers (e.g., circulating tumor DNA and use of risk stratification tools) to address patients with a high risk of recurrence for anorectal cancers (T4 and N2/3 disease).

- 3) Clinical trials of novel approaches utilizing immune modulation for locally advanced and metastatic anal cancer

Genitourinary Cancer Steering Committee (GUSC)

The following summaries are based upon input from a series of strategic planning activities including multiple conference calls and in-person meetings among members of the GUSC and its Task Forces, and NCTN groups' appropriate disease committees, over several months from September 2014 to May 2015. Each of the groups presented their recent and ongoing development plans in the context of these meetings. Common themes that emerged from these discussions are summarized for each one of the Prostate, Bladder and Renal Task Forces.

Prostate Task Force

Prostate cancer is a disease affecting hundreds of thousands of Americans annually with a disease history that frequently traverses many decades and several distinct disease states, while being managed in a very multi-disciplinary fashion. The sheer prevalence of this disease and its long natural history mean that there are huge public health costs and policy implications that can arise from informative trials. The NCI GU Steering Committee, while interested in all aspects of prostate cancer, must of necessity focus on treatment, and within that still broad category, prioritize even further. Surveillance, imaging, and survivorship studies will be addressed elsewhere under the NCI trials structure. Within the treatment domain emphasis will be placed upon trials that aim to sharpen our selectivity for therapy, test the integration of new biologic agents, and improve survival. The two points in the "disease-arc" at which it is felt that an impact can be made and survival benefits felt within a reasonable timeframe are: the castration-sensitive advanced phase (including PSA-only recurrence and oligometastatic disease); and the castration-resistant phase. This is not to say that other points in the disease-arc will not be considered, they will, but they can only be prioritized if there is the potential for substantial practice change.

- 1) Integrate earlier, life-prolonging therapies into castration-sensitive metastatic disease directed toward improvement in survival, including multimodality strategies targeting oligometastatic disease.
- 2) Develop and validate predictive models and biomarkers of outcome for integration into the management of multiple stages of prostate cancer.
- 3) Screen, integrate, and optimize biological therapies in the management of prostate cancer within studies targeting unique high risk populations.
- 4) Develop trials with multimodality approaches or novel mechanistic strategies in castrate-resistant prostate cancer (CRPC).

- 5) Prioritize strategies for randomized or large scale testing studies that can lead to practice change.

Bladder Task Force

Bladder cancer is the most expensive cancer from diagnosis until death and ranks 18th in overall NIH funding representing an enormous unmet need in translational and clinical trials research. There has been no new approved drug in any stage since the approval of Valrubicin for BCG unresponsive CIS in 1998 and the 5-year survival probability for patients with muscle invasive (MI) cancer or visceral metastatic disease has not changed appreciably in the last 3 decades. The publication of specific guidance from the FDA regarding design of registration trials in non-muscle invasive bladder cancer (NMIBC) together with emerging data regarding the potential efficacy of immune based therapies and results from large scale integrative genomic profiling is rapidly accelerating drug development in all stages of bladder cancer. The field is poised to leverage these seminal events to design practice changing therapeutic trials with a rapid expansion of potential therapeutic targets in all phases of the disease. These clinical trials should provide a robust platform for validating predictive and prognostic biomarkers and molecular taxonomy.

- 1) Integrate, evaluate, and optimize molecularly targeted and immune-based therapies into the treatment of NMI and MI bladder cancer and/or other urothelial malignancies.
- 2) Evaluate novel primary treatment approaches alone or in combination with standard of care chemotherapy for high-risk or advanced/metastatic bladder cancer and other urothelial malignancies.
- 3) Identify patients at high risk for recurrence of bladder cancer (and/or other urothelial malignancies) following definitive local or loco-regional therapy, and, in this setting, optimize locoregional management as well as integrate novel treatment approaches (neoadjuvant, concurrent, or adjuvant).
- 4) Evaluate novel treatment interventions for patients suited for bladder-sparing therapy.
- 5) Incorporate and validate pathologic diagnosis and stage, risk stratification, predictive models and biomarkers of outcome into the management of bladder cancer, including integration of surgical innovations and evaluation of patient quality of life.

Renal Task Force

- 1) Evaluate agents and combinations for all clinically relevant histologic subtypes of renal cell carcinoma (RCC), guided by data from TCGA when available. There is a developing trial to evaluate Met inhibitors in papillary RCC.
- 2) Integrate immune-based therapies into the neoadjuvant, adjuvant, and metastatic treatment approaches for renal cell carcinoma. A proposal is in development to evaluate anti-PD-1 monoclonal antibody in the adjuvant and neoadjuvant setting.
- 3) Define mechanisms of resistance to active agents in RCC and identify and test strategies for overcoming this resistance, particularly with respect to anti-VEGF and anti-mTOR agents.
- 4) Develop and validate predictive models and biomarkers of outcome to specific, pathway-directed therapies in RCC. This will be evaluated concurrently with studies developed in priorities 1 and 2.
- 5) Identify biologic characteristics in non-metastatic RCC to guide approaches outlined above in neoadjuvant, adjuvant, and advanced disease settings. This is undergoing evaluation in the ongoing analysis of the intergroup study ECOG-ACRIN 2805.

Gynecologic Cancer Steering Committee (GCSC)

Cancers of the uterine corpus, cervix, and ovary/fallopian tubes constitute a major focus of morbidity and mortality in the US. Ovarian/fallopian tube cancer remains highly lethal with a case:fatality ratio of 0.65 that has not changed significantly in spite of medical advances attributed to, in large part, to the presence of advanced stage at diagnosis. Uterine corpus cancer incidence has increased 50% with a 300% increase in deaths over the last two decades. Over 4000 US women with cervical cancer still die annually from this disease, thus improved treatments for women with advanced and recurrent cervix cancer are still needed. Recent advances in understanding the molecular basis of disease has allowed greater insight into the types and behaviors of these cancers, and is leading to a more focused approach to clinical gynecologic cancer therapeutics. The need for the development of novel trial designs to facilitate the efficient screening of new therapeutic strategies/targeted therapeutic advances within well-defined cancer populations across all gynecologic cancers was recognized. Acquisition of pre- and on-treatment tissue sampling for biomarker development, proof of concept, and to augment knowledge on the disease(s) was stressed. The importance of attending to the inclusion and special needs of diverse populations in clinical trial development and execution was stressed.

Cervical Cancer Strategic Priorities

- 1) Investigation of immunotherapy treatment and predictive biomarkers at all phases of disease life cycle
- 2) Molecular stratification for treatment decisions
- 3) Development of combination (multi-modality) interventions for newly diagnosed and recurrent cervical cancers
- 4) Attention to rare cervical and vulvar tumors
- 5) Application of novel surgical, imaging, and molecular approaches to cervical cancer to optimize therapy

Uterine Corpus Cancer Strategic Priorities

- 1) Identification of molecular and/or clinico-pathologic cancer subsets from which to drive treatment recommendations for all stages of disease.

- 2) Application of novel surgical, imaging, and molecular approaches to uterine corpus cancer to optimize adjuvant treatment decisions.
- 3) Optimization of best first-line treatments and identification of new treatments for recurrent disease for rare uterine subtypes, which may involve treatment of cancers of similar histology that arise from different disease sites.
- 4) Therapeutically target pathways with known association between obesity and endometrial cancer(s).

Ovary/Fallopian Tube Cancers Strategic Priorities

- 1) Biomarker-driven neoadjuvant designs to study novel agents and new chemotherapy approaches with access to pre- and post-therapy biospecimens.
- 2) Identification of molecular and/or clinico-pathologic cancer subsets with which to drive treatment recommendations for all stages of disease.
- 3) Investigation of immunotherapy treatment and predictive biomarkers at all phases of disease life cycle
- 4) Development of combination strategies to enhance synthetic lethality.
- 5) Therapeutic manipulation of the host-tumor microenvironment.

Head and Neck Steering Committee (HNSC)

Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth leading incident cancer worldwide. In the United States, the 2012 disease burden included 52,600 new cases and 11,500 deaths. Despite advances in surgical and radiotherapy techniques, as well as integration of chemotherapy into multimodality treatment paradigms, HNSCC is frequently lethal. Five-year overall survival (OS) is 40-60% and has increased only incrementally since 1990. Improved prognosis is largely attributable to the emerging epidemic of oral human papillomavirus (HPV) infection. An increasing proportion of oropharyngeal HNC is driven by oncogenic HPV, rather than the classic risk factors of tobacco and alcohol. HPV etiology is associated with improved survival after conventional treatments including surgery, cisplatin chemotherapy, and radiation. Although two distinct etiologies for HNSCC exist, environmental carcinogenesis or transformation by HPV oncogenes, in both instances HNSCC is associated with a fundamental failure of immune surveillance, tumor recognition and destruction. HNSCC has long been recognized as an immunosuppressive disease, inducing a permissive cytokine profile, poor antigen-presentation, low absolute lymphocyte counts, and anergy in the major effector cells of innate and adaptive immunity.

Currently available treatment options for HNSCCs consist of surgery, radiation and chemotherapy, administered in single or multi-modality regimens; however, the overall treatment efficacy still needs large improvements. Substantial clinical gains from further intensification or other variations using only these three modalities are unlikely. In addition, recently, immunotherapy has emerged as a highly promising fourth treatment modality in treatment of cancer, and its incorporation into HNSCC treatment can be readily explored now.

Thus, due to unique epidemiologic, anatomic, and clinical characteristics, HNSCC represents an ideal model among epithelial malignancies for studying the clinical trial concepts. These include:

- 1)** HPV-associated oropharyngeal is highly responsive to conventional therapy, presenting the opportunity for reduced intensity treatment, including reduction in dose and schedule of chemo-/radio-therapy or surgery. Current multimodality regimens designed for HPV-negative disease likely represent overtreatment and lead to substantial acute and long-term toxicities. A national priority in HNSCC is the development of rational de-intensification strategies which preserve the high cure rate while sparing late toxicity.
- 2)** HPV-negative HNSCC is a model of a genetically heterogeneous, carcinogen-induced cancer. HPV-negative disease remains associated with a poor prognosis, despite treatment intensification.

The NCTN treatment trials approved by the Head and Neck Steering Committee should reflect the overarching clinical and scientific objectives of improving survival, decreasing morbidity and enhancing quality of life through development and refining of local, regional and systemic therapies for all solid tumors arising about the head and neck.

In the context of the Committee's principal goals, important trial design features may include definition and testing of biomarker-driven treatment algorithms and application of new agents useful in treating all stages of cancers arising about the head and neck. Incorporation of quality of life and patient reported outcome measures into Committee-approved trials is appropriate.

Enumerated without preference, current Strategic Priorities for NCTN treatment trials under the auspices of the Head and Neck Steering Committee are:

- 1)** Facilitate the development and refine the use of systemic therapies for tumors arising in the head and neck and for thyroid cancers (including the testing of immune-modulating and molecularly targeted approaches in appropriately defined populations).
- 2)** Design treatment trials to improve efficacy and survival, decrease morbidity, and increase quality of life.
 - a.** Improve the use and application of focused radiotherapy techniques (such as IMRT, IGRT, SBRT, and particle beam therapy)
 - b.** Improve the use and application of modern surgery (such as natural orifice and minimally invasive approaches)
 - c.** Minimize late treatment-related morbidity by rigorously testing strategies aimed at reducing treatment intensity for patients with good prognosis
- 3)** Develop trials for treatment-resistant head and neck cancers.
- 4)** Pursue trials of rare tumors arising about the head and neck, which can only be undertaken through the NCTN.

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

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 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 reevaluate this issue in the future.

Myeloma Steering Committee (MYSC)

The NCTN Group Myeloma Committee Chairs from Alliance, ECOG, and SWOG and NCIC as well as designated representatives from the BMT CTN, presented their respective strategic plans to the MYSC over several teleconferences. The MYSC then discussed them at a face-to-face meeting. The MYSC has approved the following strategic plan for the NCTN Myeloma portfolio (please note the numerical position does not represent any order of relative hierarchy).

- 1) An important NCTN priority is to design and conduct studies to answer whether early therapy can improve survival or cure myeloma. The thesis here is that by waiting to treat multiple myeloma until after CRAB events occur, the curative potential and other clinical benefit is diminished because the disease burden has become too great, and the tumor biology may have already become more refractory to therapy. In the era of modern myeloma therapeutics, treatment at an early disease stage such as for ultra-high risk smoldering multiple myeloma may provide the opportunity to change the treatment paradigm in plasma cell dyscrasias.
- 2) Another high priority of the NCTN is to generate definitive data addressing whether continuous or intermittent treatment is required for MM. This question is important because the data currently available suggest that continuous maintenance therapy until progression is superior to limited duration of maintenance therapy (data from transplant maintenance trials primarily); however, as additional therapeutic agents become available, it will be increasingly important to understand whether maintenance drugs should be combined, used sequentially, continuously, or stopped and started according to clinical findings such as M protein, or sensitive MRD measurements (see priority 3 below).
- 3) It is not known whether there is clinical benefit in driving myeloma that is already in clinical complete response into MRD negative status. Therefore, an essential priority of the NCTN myeloma portfolio will be to definitively answer whether changing therapy in order to achieve MRD negative status confers meaningful clinical benefit. Given the increasing potency and expanding classes of myeloma therapeutics available (proteasome inhibitors, IMiDs, antibodies/immunotherapy, cellular therapy and transplant), there are many ways to induce MRD negativity. However, the financial cost and the toxicity burden is substantial, and it is not known whether OS or HRQoL is improved by efforts to achieve MRD negativity.

- 4) Validation of MRD assessment and defining its clinical utility are essential strategic priorities for MM, and the other strategic priorities depend on it. Therefore, studies that inform the role of MRD in guiding therapy are an immediate priority. A longer-term priority, and a much more difficult undertaking, is to understand whether MRD might be developed as a valid surrogate marker of clinical benefit (e.g. OS). The strategy will include validation of selected cross-platform MRD assessments. MRD assessment in myeloma is complex and may require more than one platform (e.g. imaging combined with flow cytometry may be required for clinical utility). It is not a priority to confirm, for example, that NGS and flow measure the same thing. One strategic goal of MRD platform combinations is to replace bone marrow biopsy, or at least to reduce the frequency needed in obtaining them. Such an advance would serve both patients and the clinical trials effort well.
- 5) HRQoL studies should be leveraged strategically in the NCTN myeloma portfolio as an integral component when more traditional study endpoints such as EFS, PFS, and OS are not feasible or may not be definitive. In such cases, HRQoL would be of high scientific rigor and would be essential to inform the primary study outcome objective.
- 6) The MYSC invited the Grant PI of the BMT CTN and her designees (beyond those who are MYSC members representing BMT CTN) to present their plans, which were in large part a product of a meeting they held in early 2015 on the state of the science in transplant. Several themes emerged regarding myeloma, including the need to understand the optimal timing of autologous transplantation (i.e. are outcomes better if the transplant is delayed and novel therapeutics are used early in the disease course?), revisiting the role of allogeneic transplant in myeloma, incorporating novel therapies as maintenance in an effort to allow GVMM to develop as the effector of alloimmunity. The MYSC regarded these as areas of potential cooperation, provided that the design and long-term endpoints were informative and definitive. Short-term PFS, for example, would rarely be useful for an allogeneic transplant question with an objective therapeutic question rather than transplant question per se.

Pediatric and Adolescent Solid Tumor Steering Committee (PASTSC)

The overall goal of the NCTN is to perform definitive phase 3 trials. Phase 3 trials are difficult to do therefore proposals for studying agents in the phase 3 setting should be based on agents that are active in the phase 2 setting or in model systems or there is compelling basic and translational science to support a strong rationale in the targeted disease.

Bone Tumors (Osteosarcoma and Ewing Sarcoma)

- 1) Evaluate new agents through a series of phase 2 trials, including when feasible randomized phase 2 trials, in the relapsed or high-risk (e.g. metastatic) settings to identify agents of interest to test in the phase 3 setting. Agents and combinations will be selected based on mechanism of action or compelling basic and translational science studies suggesting a strong rationale, evidence from model systems, and available clinical data. Agents with novel mechanisms (as compared to standard therapy) are a priority in investigations.
- 2) Evaluate the integration of promising new agents with activity against osteosarcoma and Ewing sarcoma into a multi-modal backbone to improve outcome in each of the diseases.
- 3) Evaluate surgical approaches and outcomes for local control of metastatic disease.
- 4) Evaluate biomarkers and interventions for patients predicted to have a poor outcome at diagnosis or high risk of recurrence. Continued tissue collection is essential to advance biomarker determinations for osteosarcoma and Ewing sarcoma and focused new tissue collection may be warranted to access unique tumor (such as metastatic and/or relapsed lesions)

Neuroblastoma

- 1) Evaluate the integration and optimization of clinically rational targeted therapies (e.g. MIBG, immunotherapy, ALK inhibitors) into a multi-modal backbone to improve outcome for high-risk neuroblastoma.
- 2) Identify biomarkers and evaluate novel interventions for patients predicted to have a poor response to treatment or disease progression.

- 3) Evaluate the addition of molecularly and cellularly targeted therapy for relapsed neuroblastoma that ultimately can be applied to newly diagnosed patients.
- 4) Evaluate treatment approaches associated with a reduction or elimination of therapy that will improve safety yet maintain efficacy for patients with biologically favorable neuroblastoma.
- 5) Optimize biologic specimen collection as a key aspect in determining biomarkers and targets in neuroblastoma.

Soft Tissue Sarcomas

- 1) Evaluate new agents through a series of phase 2 trials, including when feasible randomized phase 2 trials, in the relapsed or high-risk (e.g. metastatic) settings to identify agents of interest to test in the phase 3 setting. Agents will be selected based on mechanism of action, evidence from model systems, and available clinical data.
- 2) Validate functional and molecular markers (e.g., circulating tumor DNA) that may be associated with outcome or risk classification. Tissue collection is essential to achieve these goals in soft tissue sarcomas.
- 3) Collaborate with other NCTN groups to identify soft tissue sarcoma subgroups of interest to evaluate new treatment approaches.

Pediatric Leukemia and Lymphoma Steering Committee (PLLSC)

The overall goal of the NCTN is to perform definitive phase 3 trials. Pediatric phase 3 trials are inherently limited in number due to the thankfully small numbers of patients with specific cancer types. Hence it is essential that questions of therapy for pediatric phase 3 trials for childhood leukemias and lymphomas be thoughtfully prioritized based on compelling basic and translational science and based on clinical experience documenting the activity and the feasibility of the planned therapeutic intervention.

Acute Lymphoblastic Leukemia (ALL)

- 1) Evaluate novel immunotherapy approaches for selected patient populations.
- 2) Evaluate the addition of targeted therapies to standard chemotherapy for patient populations whose leukemia cells have activating mutations in targetable kinases, or actionable aberrancies in other pathways.
- 3) Evaluate treatment approaches that minimize long-term morbidity such as osteonecrosis, neurocognitive deficits, and second cancers; or that would be potentially more effective and carry less adverse side effects than allogeneic hematopoietic stem cell transplantation.
- 4) Optimize pharmacologically rational approaches to further improve outcomes for average and high-risk patient populations.
- 5) Collaborate with other NCTN groups to identify acute lymphoblastic leukemia subgroups of interest to evaluate new treatment approaches.

Myeloid Leukemia

- 1) Evaluate the addition of targeted therapies to standard chemotherapy for genomically-defined patient populations whose leukemia cells have potentially targetable mutations including, but not limited to, mutations that occur at substantial rates in both the pediatric and adult age range.
- 2) Evaluate treatment approaches that reduce the acute and long-term morbidity of therapy for children with AML while maintaining or improving overall outcome.

- 3) Evaluate novel immunotherapy and other approaches for high-risk patient populations that may be more effective and carry less adverse side effects than allogeneic hematopoietic stem cell transplantation.
- 4) Evaluate special myeloid leukemia subgroups (e.g., APL, Down syndrome AML, and JMML) for which there are research opportunities and clinical needs.
- 5) Collaborate with other NCTN groups to identify myeloid leukemia subgroups of interest to evaluate new treatment approaches.

Symptom Management & Quality of Life Steering Committee (SxQOL SC)

In 1983, the National Cancer Institute created the Community Clinical Oncology Program Network (CCOP) to: **1)** efficiently conduct cancer clinical trials, **2)** engage community oncologists in the conduct of clinical trials, **3)** extend access to clinical trials to cancer patients treated in the community, and **4)** expedite the dissemination of empirical findings into community-based oncology practices. In 2014, the CCOP was transformed into the National Cancer Institute Clinical Oncology Research Program (NCORP). NCORP provides the opportunity for world-renown oncology professionals and scientists to design and conduct cancer screening, prevention, treatment, control and care delivery research in a community setting.

A priority in NCORP is to increase the knowledge base for effective symptom management through the conduct of research as part of cancer control clinical trials focusing on: 1) identifying effective treatments to ameliorate and/or prevent toxicities, side effects and symptoms arising from cancer and its treatments, 2) elucidating biopsychosocial pathways through which symptoms, toxicities and side effects arise, 3) discovering mechanisms of action whereby interventions are effectively treating or preventing symptoms, toxicities and side-effects, and 4) developing novel biomarkers to predict risk for symptoms, toxicities and side effects, as well as individual patient response to available interventions. This is especially true in cancer control studies that test novel approaches to treating symptoms, toxicities and side effects stemming from cancer and its treatments rather than preventing or treating the actual disease. This area of cancer control research is also often referred to in oncology as symptom science. In support of this mission, the SXQOL Steering Committee is leading strategic planning efforts to maximally utilize NCORP resources to conduct rigorous cancer control research in a cost-effective and efficient manner that will have the greatest chance of rapidly, significantly and positively affecting cancer care in the United States and globally. This prioritization document addresses the “symptom” half of the Symptom Management and Quality of Life Steering Committee charge, which is to promote the best symptom science possible with available resources.

The process for research strategic planning followed the procedures outlined in the SXQOL Steering Committee Plan for Research Priority Setting (Version October 30, 2014). In turn, this research strategic plan document was prepared with input from stakeholders including: 1) members of the NCORP SXQOL Steering Committee, 2) NCI staff in the Divisions of Cancer Prevention and Cancer Control and Population Sciences, 3) Cancer Patient and Lay Caregiver Advocates, 4) Principal Investigators of NCORP Research Bases, 5) Principal Investigators and Administrators of NCORP Community Partners and 6) Participants in NCI Clinical Trials Planning Meetings. The SXQOL Steering Committee and its stakeholders also considered information from several sources, including

several national and international groups comprised of eminent scientists, clinicians and patient advocates that identified critical knowledge gaps in cancer control research and symptom science. The committee reviewed findings and suggestions from the:

- 1) 2009 NCI CIPN Clinical Trials Planning Meeting Working Group,*
- 2) 2010 NCI CCOP Strategic Planning Committee*
- 3) 2010 NCI CRF Clinical Trials Planning Meeting Working Group,*
- 4) 2011-2013 NCI SxQOL SC Cancer-Related Fatigue Working Group,*
- 5) 2012-2014 NCI NCTN Working Group,*
- 6) 2014 NCI SxQOL SC,*
- 7) 2014 NCI SxQOL SC Translational Research Working Group*
- 8) 2012-2014 MASCC International Fatigue Study Group, and*
- 9) 2012-2014 MASCC International Fatigue and Biomarkers Working Group.*

Toxicities, side effects and symptoms are expected but unwanted sequelae of a cancer diagnosis and its treatments. Some toxicities, side effects and symptoms occur in the acute setting immediately before or after diagnosis and during treatment. While some of these acute sequelae may subside and return to pre-diagnosis or pre-treatment levels, many will never return to baseline levels and become chronic persisting long after definitive treatments end. Some of these chronic toxicities, side effects and symptoms will also continue to escalate and worsen for months or years after treatments are complete. Moreover, cancer and its treatments also portend late effects that arise for the first time months or years after treatments are finished. These toxicities, side effects and symptoms encompass a wide variety of physiological, psychological and sociological problems and can involve intricate interactions among numerous biopsychosocial and cultural systems.

Despite advances in the treatment of cancer and improvements in the length of survival, these toxicities, side effects and symptoms interfere with the completion of cancer treatments, negatively affect prognosis, increase the chances of recurrence, increase the occurrence of second cancers, result in multiple co-morbidities, increase healthcare costs and increase mortality. In turn, patients experience impairments in a wide variety of quality of life domains. Therefore, it is critical to identify the most clinically noxious toxicities, side effects and symptoms and to develop effective treatments to prevent and manage them in order to also improve the quality of life experienced by survivors. This is a critically important public health imperative across a broad landscape. Although all toxicities, side effects and symptoms experienced by patients are important, identification and prioritization of a specific set of high priority areas where focused research efforts in NCORP can rapidly, significantly and positively affect cancer care in the United States and globally is essential.

NCORP SXQOL Overarching High Priority Strategic Research Foci

The SXQOL and its stakeholders identified overarching guidelines for high priority research foci including:

- 1)** Studies that are particularly suited for the NCORP mechanism and support through public funding agencies rather than studies that would be supported by private industry
- 2)** Studies that address toxicities, side effects and symptoms with a high level of clinical relevance
- 3)** Studies that address toxicities, side effects and symptoms with high levels of prevalence, incidence, severity, morbidity and/or mortality
- 4)** Studies that are feasible and practical to conduct using the NCORP mechanism and in the community oncology environment
- 5)** Studies that do not create excessive patient or provider burden
- 6)** Studies across all types of cancer
- 7)** Studies across all types of cancer treatments for the disease
- 8)** Studies investigating all types of treatments for toxicities, side effects and symptoms, such as behavioral, integrative, nutraceutical, pharmaceutical and others.
- 9)** Studies that test supportive care treatments that will be well-suited for broad dissemination in the community oncology environment
- 10)** Studies that address needs across all adolescent, young adult and adult populations affected by cancer and its treatments (e.g., patients, survivors, providers and caregivers)
- 11)** Studies that address the needs of underserved and underrepresented populations (e.g., geriatric patients, caregivers, lesbian, gay, bisexual and transgender patients, ethnic, racial, rural, low socio-economic status)
- 12)** Studies across the entire cancer trajectory from pre-treatment through long-term survivorship and palliative care
- 13)** Studies that utilize a clearly articulated and plausible theoretical framework
- 14)** Studies that include clearly articulated and testable biopsychosocial mechanistic hypotheses
- 15)** Studies that utilize rigorous research designs including single and multi-arm, as well as, randomized and non-randomized clinical trials
- 16)** Studies that utilize valid and reliable objective (e.g. clinical, biomarker), and subjective (e.g. patient-reported, proxy and provider), biopsychosocial endpoints
- 17)** Studies that include a strong cadre of multidisciplinary research teams

- 18) Studies that are supported by rigorous and compelling preliminary pre-clinical and clinical research
- 19) Studies that address translational science across the entire spectrum from T1 through T4 (e.g., bench to bedside to community dissemination/implementation)

NCORP SXQOL High Priority Areas for research

Importantly, one of the *major strengths* of research in the SXQOL portfolio is that it addresses a wide variety of toxicities, side effects and symptoms across all cancers, all populations affected by cancer, all types of cancer treatments, and all phases of the cancer trajectory from pre-treatment through long-term survival and palliative care. Unlike other NCTN disease site steering committees, the mission and purpose of the research supported through the SXQOL is broad and all-encompassing stemming from the necessity to address a myriad of challenges experienced by patients and clinicians. In an effort to preserve this strength of the SXQOL portfolio as cited in the NCTN working group review report of July, 2014, we will continue to focus on a wide variety of toxicities, side effects and symptoms. As such, the committee will accept concepts and approve studies related to any toxicities, side effects or symptoms for which there is high clinical need, defined mechanistic hypotheses, sufficient preliminary data and high probability of practical success in completing the study within the NCORP network.

With this in mind, the SXQOL steering committee and its stakeholders have identified the following areas as toxicities, side effects and symptoms where there is a particularly high clinical need, emerging knowledge regarding potential biopsychosocial mechanistic pathways, and strong preliminary data to warrant larger longitudinal, prospective, cohort studies and large phase II and phase III randomized clinical trials. The SXQOL steering committee, its stakeholders and participants in NCI Clinical Trials Planning Meetings believe that focused research in these areas has the greatest potential to rapidly, significantly and positively affect cancer care in the United States and globally in the next few years. These areas include:

NCORP SxQOL First Tier High Priority Areas for Research

- 1) Cognitive Impairment
- 2) Neurotoxicity
- 3) Cardiovascular Toxicity
- 4) Fatigue
- 5) Cancer Specific Pain

NCORP SxQOL Second Tier High Priority Areas For Research

- 6) Sleep Disorders
- 7) Bone Health Toxicity
- 8) Metabolic Toxicity
- 9) Psychological Distress

In summary, the SxQOL SC along with its stakeholders have identified a clear and present need for more research in the field of symptom science where some, but not necessarily all, of the greatest opportunities for significant growth in the field of symptom science is through increasing the scientific foci on these high priority areas as part of cancer control clinical trials conducted via NCORP. Leveraging the NCORP network as a premier venue to test important hypotheses related to symptom science in these high-priority areas is not just a good option, it is absolutely the optimal option, because no other NIH or NCI network or program has the equivalent expertise, experience or infrastructure to do this type of cancer control science as rigorously, quickly, cost-effectively or efficiently in the United States or internationally.

Thoracic Malignancy Steering Committee (TMSC)

Lung cancer remains the deadliest cancer in the world despite the progress that has been made with the approval of targeted and immunotherapies. With 5-year survival at a dismal 17% across all stages, there is dire need to conduct clinical research via innovative trial designs that are biomarker driven with clinically meaningful endpoints for this patient population.

The Thoracic Malignancy Steering Committee (TMSC) has been in existence for 5 years and has reviewed a robust portfolio of clinical trials in lung cancer. Most notably has been the initiation of two novel paradigm-shifting trials in biomarker-driven molecularly targeted therapies that were a direct result of the Joint FDA-NCI Clinical Trials Planning Meeting in February 2012. These trials, ALCHEMIST (randomized phase III adjuvant therapy) and LungMAP (A stepwise rapid evaluation of potential novel agents in stage IV non-small cell lung cancer (NSCLC)) are directing lung cancer care into an era of personalized medicine. These trials are based on platforms of tissue acquisition with molecular testing.

At the recent face-to-face meeting in Santa Monica in February 2015, the steering committee highlighted accomplishments and set goals for the next several years; notably to increase awareness of trial development in mesothelioma, small cell lung cancer (SCLC) and thymoma, as well as focusing on enhanced integration of the SPORE and PO1 investigators on the committee into clinical trial design. In fact, there have been two recent meetings concerning the “State of the Science” for investigations into novel therapies for SCLC. Moreover, the TMSC is in the process of forming a working group of experts in mesothelioma, an unmet need in the community that is unlikely to be filled by industry. Below are a summary of the directions the TMSC plans to emphasize over the next few years.

1) Innovative clinical trials that facilitate rapid development of immunotherapies and novel targeted agents for newly defined subsets in thoracic malignancies.

Immunotherapy has become another pillar in treatment of advanced malignancy in addition to chemotherapy and radiation and may have a role in earlier stages of disease, either alone or in combination with existing treatments. Unfortunately, existing biomarker selection has been only minimally successful in identifying patients most likely to benefit from these agents, leaving an opportunity to use the strength in collaboration between basic/translational scientists and lung cancer clinicians from the TMSC to develop a new series of trials:

- a. Examine potential synergies between various immunotherapy agents in patients with advanced NSCLC.
- b. Evaluate tumor tissue for development of new biomarkers of agent activity and tumor response.
- c. Examine any role for these agents in the NSCLC adjuvant setting in resectable disease and as part of multimodality therapy for stage III disease as well as in other thoracic malignancies (mesothelioma, SCLC).

2) The rapid testing of new agents and strategies for the treatment of small cell lung cancer (SCLC) through innovative, real world trial designs that recognize the aggressive and widely metastatic nature of the disease and consequent patient disability.

Little change has occurred in the treatment of SCLC over the past 25 years. Advances in genomic/genetic profiling have identified potential targets for therapy in significant subsets of patients. A concerted effort of the TMSC is focused on SCLC, with development of a structure for rapid evaluation of these targeted therapies. A SCLC workshop was conducted at Memorial Sloan Kettering in April 2015 followed by a meeting at the NCI in May 2015. The focus of these meetings was on ways to understand the biology of SCLC with an emphasis on developing the best preclinical models and innovative trial designs.

It was noted that the trials conducted so far in extensive disease with add-ons to the standard cisplatin/etoposide regimen have not yielded positive results. Investigators familiar with the disease feel that a major impediment to progress is the clinical reality that these patients frequently present with severely compromised performance status and need to be treated quickly. As such, they are frequently excluded from trials despite the fact that SCLC responds well to the initial chemo/radiotherapy, usually accompanied by marked improvements in performance status followed within months by rapid disease progression. Alternative trial designs, such as the use of maintenance therapy with eligibility criteria based upon clinical condition after initial chemotherapy, are considered to be of high priority for trial design. A potential approach would have multiple arms with various agents, including immunotherapy, with an option to add on arms when new drugs become available.

3) Exploration of neoadjuvant therapy for localized, resectable NSCLC, both as a method to potentially improve outcome as well as a way to evaluate the biological efficacy of new therapies.

The use of short duration induction trials in patients with resectable NSCLC creates an opportunity to obtain pre-therapy and post-therapy tumor tissue for the rapid development/assessment of potential

activity of new agents as well as the evaluation of potential biomarkers of clinical response for a variety of targeted therapies or immunotherapy agents. This paradigm was also a priority of the 2012 FDA-NCI meeting.

4) Rapid testing to determine the optimal role in terms of both efficacy and toxicity of new radiation approaches including protons, image-guided radiation therapy, stereotactic body radiation therapy (SBRT), etc.

There are now subsets of patients with NSCLC who are observed to have an extensive survival after first and second line therapy. SBRT is a safe and effective local control modality that needs to be examined for its potential in controlling these metastatic lesions in patient with stage IV lung cancer and possibly prolonging survival or even offering a curative local approach with minimal morbidity. It will be critical to define the number and extent of oligometastatic lesions in order to identify a true subset of patients most likely to benefit. Prospective randomized trials will be required to test the incremental value of local therapy added to systemic therapy, in order to overcome the inherent selection bias of such trials enrolling a patient population especially likely to do well independent of interventions pursued. In addition, trials are being developed to examine the efficacy of novel radiation techniques such as proton beam therapy. For both SBRT and proton beam therapy trials, overall survival should be the primary endpoint of choice, in light of the potential for post-treatment scarring to render the area around the treated lesion(s) uninterpretable.