2014 NCCN Policy Summit: Designing Clinical Trials in the Era of Multiple Biomarkers and Targeted Therapies

There are significant challenges faced by clinicians, statisticians, patients, payers, pharmaceutical companies, and regulators in bringing effective oncology therapies to the patients who need them. Clinical trials are increasingly large and expensive, and oncology as a therapeutic category has the lowest proportion of drugs successfully completing development through Phase III. Further, cancers which were once thought to be single diseases based upon histology and tissue origin are now known as heterogeneous collections of diseases when assessed by biomarker expression. Patients with diagnosis assigned by organ or origin and routine histopathologic analysis vary widely in prognosis, treatment responsiveness, and disease progression.

Targeted therapies used to treat disease subsets defined by predictive biomarkers are a step on the road to individualizing treatment for cancer. Targeted therapies can specify treatment according to genetic, proteomic, or epigenetic characteristics of individual tumors. In light of the need to target more than one biological pathway in order to effectively treat a tumor, it will be necessary to generate novel methods to evaluate emerging therapies in clinical trials. There are existing examples of targeted therapies with predictive biomarkers, including such well-defined therapy and biomarker pairs as endocrine therapy and estrogen receptor expression and trastuzumab and HER2 expression or amplification in breast cancer. The extent to which tumor biomarkers will predict clinical benefit from targeted therapies across different tumor types and biomarkers remains generally undefined.

The division of a single disease into many distinct diagnoses, whether or not there are targeted therapies available, results in reducing each tumor type to a collection of rare diseases. This leads to increased difficulties in assessing the value of targeted agents, both as single agents and in combinations, in the resulting small patient populations. Furthermore, additional complications arise as combinations of agents manufactured by more than one pharmaceutical company may be required to achieve effective therapy.

On April 25, 2014, the National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 25 of the world's leading cancer centers dedicated to improving the quality, effectiveness, and efficiency of care provided to patients with cancer, hosted the NCCN Policy Summit, *Designing Clinical Trials in the Era of Multiple Biomarkers and Targeted Therapies*, at the Bethesda Marriott in Bethesda, Maryland to address many of the above concerns. In preparation for the Summit, NCCN convened a Clinical Trials Work Group, chaired by Alan P. Venook, MD, UCSF Helen Diller Family Comprehensive Cancer Center, on March 20, 2014, in Philadelphia, Pennsylvania, to deliberate relevant topics such as adaptive clinical trials design for multiple biomarkers and targeted therapies and disease-specific considerations in biomarker/multi-agent clinical trial design.

The NCCN Clinical Trials Work Group members included: Maria E. Arcila, MD, Memorial Sloan Kettering Cancer Center; Al B. Benson III, MD, FACP, Robert H. Lurie Comprehensive Cancer Center of Northwestern University; Donald A. Berry, PhD, The University of Texas MD Anderson Cancer Center; Marian Birkeland, PhD, NCCN; D. Ross Camidge, MD, PhD, University of Colorado Cancer Center; Robert W. Carlson, MD, NCCN; Toni K. Choueiri, MD, Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center; Valerie Guild, Aim at Melanoma Foundation; Gregory P. Kalemkerian, MD, University of Michigan Comprehensive Cancer Center; Razelle Kurzrock, MD, UC San Diego Moores Cancer Center; Christine M. Lovly, MD, PhD, Vanderbilt-Ingram Cancer Center; Joan S. McClure, MS, NCCN; Amy E. McKee, MD, U.S. Food and Drug Administration (FDA); Robert J. Morgan, Jr., MD, FACP, City of Hope Comprehensive Cancer Center; Anthony J. Olszanski, MD, Fox Chase Cancer Center; Mary W. Redman, PhD, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; Vered Stearns, MD, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; and Dr. Venook.

Robert W. Carlson, MD, Chief Executive Officer of NCCN commenced the Policy Summit by welcoming the attendees and setting the stage for discussion by providing an example from his clinical area of expertise, breast cancer, to show how cancer is becoming more and more stratified. Dr. Carlson explained that, about 10 years ago, it was identified that there were at least four major subtypes of breast cancer that could be defined based upon genetic expression (luminal A-like, luminal B-like, HER2 positive, and triple negative) and the subtypes all differ in natural history and response to therapy. It is now known that triple-negative breast cancers can be further sub-setted into at least six distinct subtypes that likely differ in natural history and response to therapy, he explained.

Findings and Recommendations of NCCN Work Group

Dr. Venook, chairman of the NCCN Clinical Trials Work Group, continued the program by presenting a limited set of the Work Group's findings and recommendations. Dr. Venook started by recalling a study, CALGB80405, that in many ways, is a paradigm for how clinical research has been done historically. The advanced colorectal cancer study started in 2004, took 10 years to complete, and compared chemotherapy plus cetuximab against chemotherapy plus bevacizumab. While the results were worthwhile to obtain having discovered KRAS mutation as a biomarker for lack of response to cetuximab therapy, Dr. Venook explained that the era of doing these types of large, time consuming studies is over. If trials continue to be done via the traditional one drug, one test, one trial paradigm, the practice of oncology will continue to fall far behind the pace of change of the science of oncology, to the detriment of patient care. The science has shown and continues to show that cancer is a diverse genetic disease; defining and using biomarkers in the generation of novel targeted therapies will require more flexibility and use of alternative strategies, he explained.

The current paradigm for targeted drug development necessitates identifying both a driver event and an agent coupled to the activity of that variant. Researchers use biomarker expression to enrich their study population, thus allowing the effect of the targeted therapy to be seen in biomarker-defined populations, an effect that would not be evident across the patient population as a whole. Dr. Venook provided two examples of targeted therapies based on biomarkers. The first was the use of imatinib in gastrointestinal stromal tumors with C-KIT mutations, and the second was the discovery of the ALK translocation in non-small cell lung cancer that could be treated very effectively with crizotinib. Dr. Venook pointed out that the number of targeted therapies has grown extensively over the past few years with the addition of drugs like trastuzumab, dasatinib, erlotinib, vemurafenib, vandetanib, dabrafenib, and ibrutinib.

Dr. Venook reviewed clinical trial designs that were discussed by the Work Group. Common elements exist between all trial types including tumor biomarker evaluation, actionable targets, access to agents for these designated targets, surrogate and intermediate endpoints, and the ability to combine therapeutics. Dr. Venook used the I-SPY 2 TRIAL as an example to describe a platform design that employs an adaptive randomization method where intermediate analysis of tumor responses to therapies are used immediately to inform treatment assignments for subsequent trial participants. The I-SPY 2 TRIAL uses biomarkers from individual patients' tumors to screen promising new treatments,

identifying which treatments are most effective in specific types of patients. The I-SPY 2 TRIAL focuses on treatment in the neoadjuvant therapy setting, in which chemotherapy is given to patients to reduce tumor size before surgery. All patients receive the current standard of care and most participants receive one investigational drug. A distinctive feature of the trial is that it will screen multiple drugs from multiple companies—up to 12 different cancer drugs over the course of the trial. In order to do this, the sponsoring organization received a master Investigational New Drug (IND) approval from the U.S. Food and Drug Administration (FDA), which allows the I-SPY 2 TRIAL team to graduate, drop, and add drugs seamlessly throughout the course of the trial without having to stop the trial to write a whole new protocol. This adaptive platform design will dramatically reduce the time it takes to move from one drug to another in the trial and allow investigators to match drugs with biomarker signatures and more rapidly move effective therapies through clinical development, as well as allow researchers to more easily identify the best candidates for Phase III studies.

The Work Group also looked at bucket and umbrella trial designs. In bucket trials, which are agnostic to histology, a common mutation is identified across cancer types. An example of a mutation found across several different types of cancer is *BRAF*. In such a trial, the role the mutation plays in each cancer type may vary, rendering the targeted agent less active or inactive. Alternatively, in umbrella trials, such as the BATTLE Study for non-small cell lung cancer, patients are tested for biomarkers and then designated for treatment dependent upon the results.

The Work Group acknowledged certain challenges related to adaptive clinical trial design. Very few cancers are going to be amenable to treatment with a single inhibitor or inhibition of a single pathway, said Dr. Venook. Researchers will want and need to combine agents from competing manufacturers to effectively target multiple mutations with multiple targeted agents. Pharmaceutical companies must find ways to collaborate with each other along with working with the FDA through the regulatory process.

Dr. Venook touched on the elements that must be considered when verifying the presence of a biomarker—samples must be collected, stored, processed, and shipped correctly in order to get accurate and timely results. Dr. Venook provided an example of the complexities of biomarker testing: Clinicians desire a rapid and very reliable method for detection of *BRAF* mutations for treatment and inclusion on clinical trials. Several methods currently exist for detecting a *BRAF* mutation – direct

sequencing, LNA-PNA clamp, MALDI-TOFF, NGS methods, and IHC-mutation specific antibody. Each screening method presents its own merits and disadvantages that must be considered and an oncologist must know which method is best for specific sample or cancer type, or at least communicate effectively with a pathologist that can direct testing.

Dr. Venook discussed the education gap that exists for many practicing oncologists. Community oncologists treat a large majority of the different types of cancer and their breadth of knowledge must include current biomarkers and testing for each type. It seems like an impossible task for many oncologists with the ever-changing landscape of biomarkers, he said. Oncologists, in both community and academic settings, must know what constitutes a mutation, what site to biopsy, what kind of testing should be done, where to send for testing, and how to interpret results.

Dr. Venook expressed his opinion that every patient should have their tumor characterized for mutations when initially diagnosed and biopsied at progression when it is suspected another mutation has occurred and an alternative chemotherapy regimen might be beneficial, and every patient should have insurance coverage for a mandatory consult with an expert that can explain the results to patients. Furthermore, he stated that diagnostic companies should create registries to house all mutation data, stressing that collaboration amongst payers, the FDA, advocacy groups, pharmaceutical and device companies, and cooperative groups is needed to advance the field of study and improve care for patients.

Strategies for Implementation of Clinical Trials in the Era of Small Subsets and Multiple Agents

The first roundtable, *Strategies for Implementation of Clinical Trials in the Era of Small Subsets and Multiple Agents*, moderated by Clifford Goodman, PhD, The Lewin Group, covered many topics including accruing patients for trials, clinical trial endpoints, regulatory requirements, data collection, and costs of conducting clinical trials. Roundtable panelists included David Flockhart, MD, PhD, Indiana University; Ramaswamy Govindan, MD, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; Al Benson III, MD, Robert H. Lurie Comprehensive Cancer Center of Northwestern University; Amy McKee, MD, FDA; Eric Slosberg, PhD, Novartis; and Dr. Venook.

Dr. Goodman opened the roundtable with discussion of how to identify patients for participation in trials for rare diseases. According to the panel, 10 years ago, the mutations being researched could be

found in 40-50% of patients, while today many mutations being studied can be found in only 5% of patients. Much of the low-hanging fruit has been picked and researchers often must find mutations that exist in the tumors of smaller and smaller patient populations. Searching for and enrolling this much smaller subset of patients is time-consuming and expensive. The enrollment in clinical trials has historically been at the 3-5% nationally so in general there is a need to broaden the reach of clinical trials. The National Cancer Institute (NCI) is addressing this problem with the launch of the National Clinical Trials Network. The new system will facilitate the rapid initiation and completion of cancer clinical trials based on improvements in data management infrastructure, the development of a standardized process for prioritization of new studies, consolidation of its component research groups to improve efficiency, and the implementation of a unified system of research subject protection at more than 3,000 clinical trial sites.

Dr. Slosberg explained that accruing patients for pharmaceutical company trials is very challenging. Many more clinical sites must participate, often only contributing one or two patients, in order to capture enough patients with the desired mutation. There is a huge cost burden on the sites, said Dr. Benson, explaining that relying on a central Institutional Review Board (IRB) may reduce the burden on local IRBs in regards to money and resources, and patients could be enrolled more efficiently.

According to Dr. Flockhart, there are distinct differences in conducting clinical trials in the academic setting versus community practice. Community oncologists must find the time to explain a clinical trial to a patient while balancing other responsibilities. Dr. Slosberg highlighted the differences in working with academic institutions and community research centers. The approval process to conduct a clinical trial is much faster in the non-academic setting and the community research centers do not want any intellectual property rights.

Dr. Govindan drew attention to the amount of paperwork an oncologist must complete when enrolling a patient in a clinical trial. He questioned the need to collect every data point and would prefer to collect only critical data. The rationale for data collection, said Dr. McKee, is that, oftentimes, there has been accelerated development of an agent and insufficient safety data has been collected to confidently establish the safety profile of the drug. The data collected in a registration trial can be used in this situation. Not all data that may be collected is for regulatory use – patient-reported data can be used by

oncologists, patients, and drug developers, while exploratory endpoint data is scientifically important to researchers and pharmaceutical companies, said Dr. McKee.

Dr. Venook pointed out the value in collecting large amounts of data and tumor samples in that it is better to have the information than to need it further down the line, but not have it. The panelists agreed on the concept that, while it is beneficial to collect large amounts of data, simplification is needed in the interpretation and output process.

The panel discussed how to ensure patients have access to clinical trials. Dr. Venook highlighted the value of Clinicaltrials.gov and the internet in advertising available clinical trials. Still, only 3-5% of patients are enrolled in clinical trials, noted the panel, agreeing that physicians are the limiting factor in patient enrollment. A comment from the audience highlighted that it is the rare and sophisticated patient who self-refers to a trial. The question was raised as to how to incentivize the community oncologist to refer patients when it often results in loss of patients both physically and financially.

Jennifer Malin, MD, PhD, Medical Director for Oncology, Wellpoint, questioned the panelists about the suggestion that every single patient should have their tumor sequenced and the resulting cost to payers for such an idea. Dr. Venook explained that with our current capacity to examine and analyze data we may be able to identify subsets of patients that would benefit from a particular therapy along with identifying patients that should not be treated with therapy. He added that there would be a large investment upfront with unknown benefit. Dr. Slosberg also suggested that panel screening can actually be cheaper and quicker than sequential screening for different mutations. Dr. McKee was supportive of widespread tumor sequencing due to its ability to advance more elegant design of subsequent clinical trials.

Dr. Goodman questioned Dr. McKee about how to best work with the FDA. She explained it is best to communicate with the FDA early and often, adding that, in the past two years, the FDA has aimed to be more proactive in fostering new trial designs and using different statistical techniques. Dr. McKee suggested there will be some future workshops to address these issues.

According to the panel, several factors affect how physicians use biomarkers in making treatment decisions for their patients, including, but not limited to their personal knowledge of biomarkers, their

availability to consult with patients, and their friendliness. Dr. Govindan suggested that oncologists need to understand the practical implications of biomarkers and not necessarily the complex biological background. Dr. Venook identified language barriers as a hurdle for many physicians and patients. He also suggested a role for NCCN due to the widespread use of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). A possible solution, he said, would be to break out NCCN Guidelines by mutation. Dr. Flockhart reminded the audience of the need and the benefit of educating nurses and other health care professionals that spend more time with patients than many physicians.

Dr. Goodman ended the discussion with a final question —"It's 2025 and we have a seamless national collaborative system where clinical trials are routinely implemented for rare conditions and the education gap is closed. What happened to get us there?" Answers ranged from having a full understanding of the science to a nationally actionable database to having invested our financial resources for integration and centralization of data. In the end, the panelists agreed steps must be taken to ensure greater enrollment in clinical trials to optimize the value and potential of biomarkers and in turn, improve patient care.

Identifying and Defining Standards of Care for Cancer Subtypes

The day concluded with a second roundtable, titled *Identifying and Defining Standards of Care for Cancer Subtypes*, featuring panelists Michael Deininger, MD, Huntsman Cancer Institute at the University of Utah; Dr. Flockhart; Dr. Govindan; Rosemarie Hakim, PhD, Centers for Medicare and Medicaid Services; Jennifer Malin, MD, PhD, WellPoint; Lisa McShane, PhD, NCI; and Asif Velani, MBA, Genentech. Topics for discussion included coverage and reimbursement of biomarker testing, value of biomarkers, and inclusion of biomarkers in guidelines.

Dr. Goodman started the discussion with a question about what constitutes enough evidence to get a biomarker test included in the NCCN Guidelines for a particular cancer type. Dr. Govindan explained that biomarkers must have therapeutic significance and an associated agent to be included in NCCN Guidelines. Dr. Deininger expounded on several factors that influence incorporation of a biomarker test – patient population, quality of clinical studies, and clinical judgment of panelists.

Discussion turned to the coverage and reimbursement of biomarker tests. While guidelines were not initially developed for coverage decisions, an evolution has occurred where many payers utilize the

NCCN Guidelines for coverage decision-making. A dichotomy exists between the flexibility and opportunity for clinical judgment within NCCN Guidelines and the payers' need for clear direction on appropriate care. Dr. Hakim explained that Medicare looks beyond the data provided to the FDA for approval, requiring that the test have an impact on patient outcomes in order to pay for it. Dr. Malin further detailed what WellPoint is looking for: they will not cover investigational or experimental tests and tests must have not only reliability and validity, but also clinical utility.

Dr. Goodman then asked the panelists to discuss the coverage of biomarker tests within clinical trials. While the Affordable Care Act (ACA) did expand coverage of clinical trials, experimental tests generally are not covered. Dr. Hakim covered the concept of Coverage with Evidence Development (CED) and the possibility of using CED for coverage of experimental biomarker tests in Medicare patients.

The panel debated the issue of who should pay for sequencing a tumor genome and the value it would provide. Traditionally, public and private payers cover and reimburse interventions that are medically necessary and sequencing of the whole tumor genome is not considered medically necessary. Dr. Malin calculated for WellPoint's cancer population it would cost about $350 million a year and increase premiums by about $10 a year per member. Dr. Malin questioned whether payers should be the ones to make the investment and what value they would receive. Dr. Govindan highlighted a potential benefit – preventing patients from receiving ineffective therapies and the resulting cost savings.

Dr. Govindan pointed out that cancer is a very complex genomic disease and is often predicated on several mutations that may be on genes that are not known to be related to one another. Clinicians and researchers are now realizing that chemotherapy alone does not cure many cancers and that they have the tools and technology to start looking at the entire picture, he said, adding that society would be remiss to miss that opportunity. It is possible that in 10 years we will wish we had sequenced all tumor genomes at the time of their diagnosis. Will sequencing now save money later? If we don't take the opportunity now will we lose out in the future? These are all questions no panel member could definitively answer.

Dr. Flockhart raised the point of whether the value of tumor genome sequencing is in the whole or in the individual tests. He hypothesized the value must be in the whole if we are going to spend millions of dollars to do sequencing for all diagnosed cancers. Dr. Razelle Kurzrock, UC San Diego Moores Cancer

Center, questioned the panel as to whether physicians and payers should treat genomic screening any differently than other diagnostic tests for establishing a diagnosis. This information can tell physicians both what the patient has as well as what they do not have. Dr. Kurzrock stressed that this is the first step in the delivery of the standard of care.

Dr. Goodman returned to the cost of tumor sequencing and who should be responsible. Payers need sufficient evidence to cover such testing and current regulations preclude Medicare from paying for services that are not deemed medically necessary. An audience question from a payer raised the point that if clinicians want payers to cover tumor genomic screening, they will need to cut costs elsewhere. Where can costs be better controlled in order to free up dollars for widespread tumor genomic screening? Dr. Govindan suggested two areas – imaging and end-of-life care.

Dr. Goodman finished the session with a question for the panelists – "By 2020 will we have a system in place that all patients receive tumor genome sequencing and research, regulation, and reimbursement are aligned and capable of handling all the information?" The overall consensus was yes, that point will be reached, but perhaps not by 2020. According to the panelists, the science will continue to evolve and big data management will be key. The largest unknown is how society will pay for it.

Ultimately, the panel struggled to resolve the divide that currently exists between the science of biomarkers and the coverage and reimbursement of biomarker testing. The panel debated the value of tumor genome sequencing and who should be responsible financially, but was unable to reach a consensus.