BIOMARKERS CONSORTIUM

IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

FNIH
Foundation for the National Institutes of Health

Biomarkers Consortium (BC)
Cancer Steering Committee (CSC)
Annual Scientific Symposium
Bethesda North Marriott Hotel, Bethesda, MD
November 5-6, 2018

Executive Summary

The Biomarker Consortium's (BC) Cancer Steering Committee (CSC) held its Annual Scientific Symposium on November 5-6, 2018, in Bethesda, Maryland. Each year, the CSC, led by the Foundation for the National Institutes of Health (FNIH) and its co-chairs Drs. Gary Kelloff (NCI) and Eric Rubin (Merck), brings together experts from academia, pharmaceutical companies, biotechnology companies, not-for-profit organizations, the NIH and the FDA to review advances in the field of biomarker and regulatory science that are relevant to the development of new public-private partnerships for precompetitive biomarkers. The FNIH BC CSC Symposium thus serves as a juncture each year to assess and recalibrate future directions in biomarker discovery and development.

The goals of the meeting this year were to highlight cutting edge science, including projects supported by the FNIH BC to inform the field of the latest developments in critical areas of biomarker science and guide CSC decision making and project planning in the next two to five years. Presentations focused on several priority areas, including analytical validation and clinical utility of liquid biopsy, increasing interest in neoadjuvant therapy, immuno-oncology (IO) biomarkers, biomarker initiatives in the microbiome, novel imaging markers, and minimal residual disease (MRD).

The meeting was headlined by four (4) Keynote presentations from luminaries in the field of oncology and biomarker development. Norman Coleman from NCI opened the meeting with an exposition on the development and status of molecular radiation oncology, and Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER) at FDA, discussed her experience at the forefront of cancer therapeutic development and her expectations for future work and outcomes from ongoing work. Kurt Schalper from Yale provided insights on IO development to start out the second day of the meeting, and Jean Charles Soria, MedImmune, preceded the final session on clinical utility for liquid biopsy with a discussion of new trial design and drug selection inclusive of ctDNA as a useful biomarker.

Session I: State of the Science and Biomarker Development described several ongoing initiatives involving biomarker development including an evaluation of metrics for biological heterogeneity of cancer by D. Lansing Taylor, University of Pittsburgh Medical Center (UPMC), an exploration of the architecture of the tumor microenvironment by Lance Liotta, George Mason University and an overview of proteogenomics in cancer research by Henry Rodriguez of the National Cancer Institute (NCI). The session concluded with Reena Philip's perspective from the FDA and the Center for Devices and Radiological Health (CDRH) on the development and use of complex biomarkers such as those based on next-generation sequencing. Together the

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Session I speakers highlighted major efforts ongoing in biomarker development and set the stage for the two-day Symposium.

Session II: Early Endpoints of Clinical Benefit Part 1 was chaired by Gideon Blumenthal of FDA who introduced the speakers and discussed the key challenges to setting up neoadjuvant trials with early endpoints in multiple cancer types. Tatiana Prowell of FDA further explored current and potential biomarkers to predict clinical benefit and response in the neoadjuvant setting. Mark Kris of Memorial Sloan Kettering Cancer Center (MSKCC) discussed pathological complete response (pCR) and major pathological response in non-small cell lung cancer and Don Berry from MD Anderson followed up with a discussion of the neoadjuvant setting in breast cancer. This discussion of early endpoints was followed by an engaging discussion with attendees who joined the speakers in expressing the need for additional trial level analysis to achieve new endpoint validation.

Session III: Early Endpoints of Clinical Benefit Part 2, chaired by Kim Jessup of Inova, followed with a focus on minimum residual disease (MRD), efforts to validate the marker in clinical studies of multiple myeloma (MM) and correlation with remission or relapse in cancer led by Ken Anderson of the Dana-Farber Cancer Institute. Hartmuth Kolb, Janssen, followed with a discussion of the role of imaging inflammation of the brain as an early prognostic and clinical response marker in glioblastoma and immunotherapy treatment response, and Jane Perlmutter concluded the session with an advocate's perspective on use of early endpoints such as pCR and MRD. The speakers and attendees agreed in the discussion that followed that a patient's perspective, needs and understanding must be incorporated into the development and implementation of these early indicators of clinical outcome.

Eric Rubin from Merck chaired *Session IV: Immuno-Oncology Biomarkers*, in which the speakers delved into immune response to IO therapy. Suzanne Topalian from Johns Hopkins University described the identification and development of biomarkers in immune checkpoint blockade and provided an overview of drug development to date. Josh LaBaer of Arizona State University provided an overview of his team's efforts to profile the immune response through evaluation of full length human proteins, and Elad Sharon from NCI discussed autoimmune toxicity associated with dysregulation of normal immune functions caused by immunotherapies. Tobias Janowitz, Cold Spring Harbor Laboratory, concluded the session with an exploration of mechanisms of action (MOAs) and targets for immunotherapy and their connection to metabolic and immunological response. The speakers shared common ground in their assertion that evaluation of the tumor immune environment (TME), and the influence of the gut microbiome on the TME, will inform future IO therapy development, patient response and treatment of adverse events.

Breakout Sessions on Day 2 of the meeting provided an opportunity for investigators to present their work to attendees and receive feedback on progress and ideas for further exploration. These *Project Development Sessions* featured speakers representing academic and industry research efforts, who provided perspective and commentary on emerging techniques and technologies for the development of new project concepts.

The first breakout session included presentations on radiomic imaging analysis and the use of artificial intelligence (AI) to develop new biomarkers, validation of molecular blood assays for broadened clinical utility, including two cases studies in real world implementation from different hospital systems, and industry efforts to develop tools to assess and augment the effects of the microbiome on treatment and patient response. The second breakout session included presentations on development and utility of a pharmacodynamics assay network and a rapid-fire roundtable of new topics for the CSC, including neuroimaging probes, nanotechnology, pediatric cancer biomarkers, and utilization of big data.

The CSC will continue to discuss these concepts in subsequent meetings in consideration of the Committee's priorities for future project development. Several concepts will be brought before Working Groups to assess funding interest and potential for consortium building. The CSC also intends to develop new Working Groups in additional topic areas that were discussed including a Radiomics specific group and a cross sector collaboration within the FNIH to develop a project on the Microbiome.

Session V: Liquid Biopsy: Beyond DNA, Clinical Utility and Challenges for Development was chaired by Bob McCormack, who leads the FNIH ctDNA Quality Control standards project. He asked Geoff Oxnard of Dana-Farber Cancer Institute to provide his thoughts on establishing "truth" for liquid biopsies through tissue comparison, and implications for clinical utility. Jon Chung from Foundation Medicine introduced the group to his organization's work with hybrid capture genomic profiling next-generation sequencing (NGS) using a 60-gene panel to evaluate ctDNA in blood and Dana Tsui, MSKCC, described efforts to develop and implement an NGS-based circulating free and ctDNA test at her institution. These assays can be used for both diagnosis and longitudinal follow-up of patients. Carl Barrett, AstraZeneca, provided a comparison of ctDNA assays among several labs and an expose of how such tests perform in real life testing. He showed that work has yet to be done to provide reliable, comparable utility between laboratories and assays for liquid biopsy. Howard Scher, MSKCC, closed the session with an update from the Blood Profiling Atlas in Cancer (BloodPAC) group, which is working on standards development with labs across the country.

Overall, the CSC's Annual Scientific Symposium successfully helped to define critical next steps in biomarker project development in the focus areas of the CSC. Next steps for the FNIH and the BC CSC include establishing working groups to identify and define potential public-private partnerships that could be developed to address these needs, and further discussing identified topics of study in sub-committee for subsequent review by the full Steering Committee.