SITC Clinical Immuno-Oncology Network (SCION) commentary on measurement and interpretation of essential biomarkers in early clinical trials

Michael T Lotze, Tricia Cottrell, Carlo Bifulco, Laura Chow, Leslie Cope, Sacha Gnjatic, Holden T Maecker, Joe Yeong Poh Shen

ABSTRACT
Immunotherapy of cancer is now a mainstay of modern oncolgic practise and is being integrated with conventional modalities across clinical settings. The Society for Immunotherapy of Cancer (SITC) has initiated a Clinical Immuno-Oncology Network (SCION), where multidisciplinary teams (including clinical oncologists, scientists/immunologists, biostatisticians, and patient advocates) and early career scholars develop immunotherapy clinical trial protocols during an intensive workshop and Winter School. SCION participants have identified a critical gap in guidance for the prioritization of biomarkers in immunotherapy clinical trials. This commentary proposes an evidence-based consensus review process to generate a prioritized checklist of biomarkers for consideration. We recommend grouping biomarkers into three priority levels based on the strength of evidence, breadth of relevance, and feasibility of testing. Level one biomarkers should have strong evidence to justify inclusion in all immunotherapy trials. Level two biomarkers need early evidence supporting inclusion, dependent on suitable funding and scientific validity. Level three biomarkers are of specific importance for individual trials (eg, evaluating therapeutic targets). We invite feedback from the community on the proposed process and prioritization framework. The SCION faculty will work with the SITC Biomarker and Pathology Committees to publish recommendations emerging from a forthcoming evidence-based consensus review. Leveraging the annual clinical trial workshop, SCION faculty will evaluate emerging data to update recommendations as the field evolves.

PROPOSING A FRAMEWORK FOR PRIORITIZATION OF BIOMARKER STUDIES IN IMMUNOTHERAPY CLINICAL TRIALS
Remarkable advances in cancer immunotherapy as well as sophisticated biospecimen profiling technologies have synergistically transformed clinical trial design. Biomarker studies associated with high-quality clinical data have the potential to drive both scientific and clinical progress by capturing the complexity and evolution of the tumor and the host immune response over space, time, and treatment course. Moreover, these observations will be foundational for the anticipated artificial intelligence (AI) revolution. Members of the Society for Immunotherapy of Cancer (SITC) continue to be at the forefront of this exciting and rapidly evolving field. SITC strives to provide ongoing leadership to support best practises and train the next generation of clinicians and scientists. In 2021, SITC initiated the Clinical Immuno-Oncology Network (SCION) in conjunction with the popular Cancer Immunotherapy Winter School. SCION is an annual 1-week intensive workshop for clinicians and scientists from academia and industry focused on immunotherapy clinical trial protocol development. Each group of six early career scholars is supported by a team that includes a clinical oncologist, a scientist/immunologist, a biostatistician, and a patient advocate. SCION is committed to the principle that the cancer immunotherapy community must learn from every trial, regardless of whether it is successful in establishing a new therapeutic option. Integration of well-chosen correlative biomarkers in trial design is crucial if we are to meet this goal. However, navigating an ever-expanding menu of potential biomarker correlates with limited resources is an ongoing practical challenge. Synthesis of the best available scientific evidence is needed to direct clinical trial biomarker selection, especially for new clinical investigators. With this commentary, and follow-up
Box 1 Proposed immunotherapy biomarker evaluation criteria, process, and deliverables

Biomarker evaluation criteria
⇒ Utility in stratification of patients with treatment response and/or clinical outcomes (clinical relevance).
⇒ Provides biological insights into tumor biology, the tumor microenvironment, and/or the patient’s physiologic or immunologic capacity (biological relevance).
⇒ Relevance across cancer types and stages.
⇒ Standardized assays and analysis approaches.
⇒ Human data prioritized but informed by compelling other sources, including murine and primate models, work with organoids, etc.

Biomarker evaluation process
⇒ Literature review and summary of evidence.
⇒ Consensus/Delphi process to include Society for Immunotherapy of Cancer (SITC) Clinical Immuno-Oncology Network (SCION) faculty and members of the SITC Biomarker and Pathology Committees.

Deliverables (planned publication)
⇒ Checklist of recommended biomarker tests for consideration for all immunotherapy clinical trials, with ranked categorization based on level of evidence and expert consensus (see text box 2).
Future directions
⇒ Annual review and consideration during SCION clinical trials workshop, curated by the current leadership.
⇒ Plan for regular updates/revisions as needed based on evolving data.

Box 2 Proposed framework for immunotherapy biomarker prioritization

Criteria for level one biomarkers: essential
⇒ Strong evidence for association with immunotherapy response and/or patient outcomes.
⇒ Broad relevance across tumor types and treatment approaches.
⇒ High feasibility (standardized testing methods, routine or readily available testing).

Criteria for level two biomarkers: emergent and exploratory
⇒ Emerging evidence for association with immunotherapy response and/or patient outcomes.
⇒ Relevance demonstrated in multiple studies and tumor types.
⇒ Evolving methodology and interpretation standards.

Criteria for level three biomarkers: contextual
⇒ Strong evidence for relevance in the particular tumor type or treatment under investigation.
⇒ Prior data to inform assay methodology and data interpretation.

The current commentary is authored by a team representing SCION faculty as well as leaders of the SITC Pathology and Biomarker Committees. In the context of immunotherapy clinical trial design, we outline the challenges and opportunities of biomarker studies and propose a process and framework for biomarker prioritization (see text boxes 1 and 2). Our goal is to solicit feedback from the SITC and JITC readership community, which will inform the development of recommendations for essential (“Level 1”) biomarker data collection and reporting in immunotherapy clinical trials. Acknowledging the limitations of current data and the rapid evolution of the field, we anticipate iterative revisions of essential biomarker recommendations in response to emerging mechanistic and clinical insights. Please provide your guidance and suggestions directly to SITC staff, Ellie Rickman (erickman@sitcancer.org) and Peter Intile (pintile@sitc.org) who will compile them by the end of the next quarter to be addressed in a full article by SCION faculty.

BIOMARKERS PROVIDE VALUABLE SNAPSHOTS OF THE UNDERLYING BIOLOGY

The Food and Drug Administration (FDA) BEST Resource (https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-S, Biomarkers, Endpoints, and Other Tools) defines a biomarker as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions”, and describes the following categories of biomarkers: (1) a susceptibility/risk biomarker; (2) a diagnostic biomarker; (3) a monitoring biomarker; (4) a prognostic biomarker; (5) a predictive biomarker; (6) a response biomarker; or (7) a safety biomarker (table 1). Biomarkers may include molecular, histologic, radiographic, or physiologic indicators, and some may fall into more than one category (eg, tumor histology can be diagnostic, prognostic, and predictive, as when used for patient selection). With the passage of the 21st Century Cures Act, the FDA has provided additional guidance regarding biomarkers accompanying a therapeutic agent (https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification). They established a three-stage submission process to develop a biomarker for regulatory use. Independent of regulatory requirements, the REMARK initiative (Reporting recommendations for tumor MARKer Prognostic Studies) outlined principles for testing new biomarkers and reporting performance to facilitate evaluation and compare results across studies.1 Despite these thoughtful resources and recommendations, the question of when to use individual biomarkers in research and clinical practice is only settled gradually, through the accumulation of data from research publications and statistical validation across multiple studies.

Immunotherapy clinical trials present unique challenges that beg for a more thoughtful and systematic approach to biomarker testing. A successful antitumor immune response is dependent on the convergence of the immune repertoire, emergent tumor antigens, and the balance of pro-inflammatory and anti-inflammatory signals from the cancer cells, the host cells within the tumor microenvironment, and the patient’s systemic and secondary/tertiary nodal sites. A new paradigm of bedside-to-bench research is quickly emerging as we seek...
to understand antitumor immune responses that are dynamically influenced by interactions among (1) tumor cells (eg, tumor mutational burden, Lactate dehydrogenase (LDH) levels\(^2\)\(^3\); (2) the tumor microenvironment (eg, immune checkpoint molecule expression, lymphocyte count\(^2\)\(^4\); and (3) host factors (eg, patient microbiome) (see table 2). Well-established and emerging biomarkers provide valuable snapshots of these signals. While many of these tests are useful as stand-alone predictive and/or prognostic tests, the lack of standardized data collection and reporting has limited our ability to establish the nuanced integrated interpretations likely required

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<thead>
<tr>
<th>Table 1</th>
<th>Biomarker goals in immuno-oncology</th>
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<tr>
<td><strong>Biomarker goal</strong></td>
<td><strong>Definition</strong></td>
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<tr>
<td>Risk determination</td>
<td>Measuring risk or susceptibility for a particular disease.</td>
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<tr>
<td>Disease diagnosis</td>
<td>Determining whether a patient has a specific disease or disease subset.</td>
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<td>Patient selection</td>
<td>Selecting patients that are more likely to benefit from a given therapy.</td>
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<tr>
<td>Prognosis</td>
<td>Assessing outcome from baseline or early treatment samples independent of therapy.</td>
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<tr>
<td>Prediction</td>
<td>Assessing outcome from baseline or early treatment samples to a specific therapeutic intervention.</td>
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<tr>
<td>Monitoring</td>
<td>Following tumor burden or therapeutic progress over time.</td>
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<tr>
<td>Response</td>
<td>Verifying or correlating with a clinical response.</td>
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<tr>
<td>Safety</td>
<td>Alerting to a potential adverse event.</td>
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<tr>
<td>Mechanistic</td>
<td>Defining pathways associated with therapeutic mechanism of action or therapeutic resistance.</td>
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<th>Table 2</th>
<th>Examples of biomarkers that detect features of cancer cells, the tumor immune microenvironment, and systemic factors impacting immunotherapy response</th>
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<td><strong>Tumor tissue biomarkers</strong></td>
<td><strong>Tumor immune microenvironment</strong></td>
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<tr>
<td><strong>Cancer cells</strong></td>
<td>Pathology (eg, histology, grade)(^9)</td>
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<tr>
<td></td>
<td>Targetable driver mutations (eg, Her2/Neu, EGFR)</td>
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<tr>
<td></td>
<td>Tumor mutational burden,(^11)(^13) Microsatellite Instability, MSI status</td>
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<tr>
<td></td>
<td>Serum tumor markers (eg, CA19-9, CEA, CA-125, Prostate Specific Antigen, PSA)(^15)</td>
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<td></td>
<td>Circulating tumor DNA(^17)</td>
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<tr>
<td></td>
<td>Targetable antigen expression (eg, CD19, CD20, mesothelin, Prostate specific membrane antigen, PSMA)</td>
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<td></td>
<td>Stool microbiome 12</td>
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</tbody>
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BRCA, BReast CAnce; CA, cancer; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; Her/Neu, human epidermal growth factor receptor 2/Neu protooncogene; LAG3, lymphocyte activation gene 3; LDH, Lactate dehydrogenase; MSI, Microsatellite instability; PD-1, Programmed Death 1; PD-L1, Programmed Death-Ligand 1; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen; scRNA-seq, single cell ribonucleic acid sequencing.
to optimize cancer therapy (eg, through meta-analyses and AI). Given the burden biospecimen collection places on our patients, physicians, and staff, biomarker studies must be prioritized based on the anticipated value of the resulting data. Recommendations to guide uniform strategies for specimen collection, biomarker prioritization, and data reporting can address these challenges from a scientific perspective.

THE ROLE OF BIOMARKERS IN AN EVOLVING REGULATORY ENVIRONMENT FOR IMMUNOTHERAPY CLINICAL TRIALS

The US FDA has recently launched two major initiatives to guide the design of clinical trials. Project Pragmatica (https://www.fda.gov/about-fda/ oncology-center-excellence/project-pragmatica) seeks to improve the operational efficiency and patient centricity of clinical trials by enhancing the flexibility of trial design and aligning trials more closely with standards of routine clinical practice. In the face of efforts to simplify clinical trials, requirements for biospecimen collection and biomarker testing must be clear and well-justified. Project Optimus (https://www.fda.gov/about-fda/ oncology-center-excellence/project-optimus) focuses on modernizing practices for optimal dosing of novel therapies based on consideration of biological efficacy as well as safety and tolerability. This represents a major paradigm shift from the focus on the maximum tolerated dose that dominated oncology practice for the development of cytotoxic and molecular targeting therapies. Recent studies suggest that the most biologically active dose of immunotherapy agents can be much lower than the maximum tolerated dose. Biological activity can be estimated from pharmacokinetic and pharmacodynamic biomarkers that measure the presence/persistence and activity of immunotherapeutic agents in tumor tissue. The routine incorporation of these studies into early immunotherapy clinical trials is essential for successful therapeutic development.

PRIORITIZING CORRELATIVE BIOMARKERS FOR CLINICAL TRIALS

We propose grouping biomarkers into three priority levels based on the strength of evidence, breadth of relevance, and feasibility of testing. **Level one biomarkers** should be highly informative about a fundamental question of cancer immunology, with a well-validated assay, to justify inclusion in all immunotherapy trials (eg, established biomarkers). One would have to justify *not* including a Level one marker in a trial. **Level two biomarkers** will have early evidence that supports inclusion dependent on suitable funding and scientific validity (eg, emerging biomarkers). **Level three biomarkers** are of specific importance for individual trials.

A CALL TO ACTION: LEARNING SOMETHING FROM EVERY IMMUNOTHERAPY CLINICAL TRIAL

It is imperative that we learn something from every immunotherapy clinical trial. Enthusiasm for rapidly advancing novel agents must be balanced with humility and caution as we perturb a complex and powerful immune system that can cure cancer as well as mediate life-threatening autoimmunity. The design of highly impactful clinical trials is a science, an art, and a moving target. As a community, we can offer leadership by developing an evidence-based resource to guide biomarker incorporation into immunotherapy clinical trials. In this document, we have outlined an approach to prioritization. We invite feedback from the SITC and JITC readership community as we seek to bring the highest-value biomarkers into focus.

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