Immuno-oncology (I-O) Policy Work Group
Recommended Next Steps

Summary:

Immuno-oncology (I-O) has been fueled by numerous clinical trial successes in recent years and has already transformed traditional approaches to cancer treatment. As our understanding advances and I-O therapies are implemented into routine treatment of cancer, many challenges and complexities remain to be addressed. Broadly, outstanding challenges fall into two categories: scientific, related to furthering our understanding of the mechanisms that drive immunotherapy, and systemic, related to ensuring these therapies are appropriately used as single agents or in combination in the clinical setting. At a time when broad adoption of I-O is still taking hold, an opportunity exists to learn from early experiences with I-O in melanoma and lung cancer, and identify and address high priority policy-related issues defined by the emerging science.

Friends of Cancer Research, Pfizer, and EMD Serono, working together with scientific, clinical, patient, policy and industry leaders, aimed to develop an I-O strategic policy plan to accelerate progress across multiple oncology disease states. While many of the challenges, outlined below, will be addressed as our understanding of the mechanisms of action behind immune-oncology develop, there is a role for the multi-stakeholder community to facilitate development of and appropriate access to those scientific discoveries by leveraging and mobilizing our collective knowledge to support innovation in immune-oncology. The identified policy issues may include regulatory, legislative, reimbursement and education/training issues. The output of this effort is informed by recent advancements in research, intended to be outcome-driven, and designed to leverage and complement other ongoing activities in the field.

Strategic Approaches:

The I-O Policy Work Group met in December 2015 to develop a strategic policy plan to accelerate progress for IO in multiple disease types and settings.. In all, ten different constituencies were represented: industry, academia, insurers, advocacy organizations, government, policy makers, patient support networks, research foundations, healthcare networks, and professional societies. The meeting (and one-on-one interviews that preceded it) identified policy issues that may facilitate the development and use of immuno-oncology medicines, including regulatory, legislative, reimbursement and education/training issues.

Meeting participants highlighted a great need to better understand the basic science behind the pathways responsible for immune function; not only is this needed to guide the development of better therapies and biomarkers, but also to guide patient selection, assess meaningful benefit, stimulate the immune system of likely non-responders, improve management of toxicities, and determine appropriate times to stop therapy based on patient response. Participants agreed that engaging the immune system to recognize and kill cancer cells has demonstrated proof of concept for long-term, sustained antitumor activity in solid tumors such as melanoma, which distinguishes I-O from traditional cancer therapies. Indeed immunotherapy has been highly effective for a subset of patients, in various disease settings, but it will likely not be universal in scope. As a result, identifying the most relevant patient cohorts will be an important undertaking both from a scientific and systemic perspective. As the basic research continues to advance, this group intends to work together and in concert with others to focus on the uptake, the appropriate application, use and coverage of I-O therapies and tools.

To begin addressing the most pressing issues in advancing I-O innovation, meeting participants discussed many of the challenges and opportunities highlighted in the table below. Of these, six policy-related focus areas emerged as priorities for the Policy Working Group and the larger community to address in the near term. These included: developing tools that encourage data sharing and banking of bio-specimens to improve biomarker development; collaborating on the

development of combination therapies using novel trial designs; establishing mechanisms to evaluate alternative endpoints that are meaningful to I-O; aligning regulatory review functions for oncology; using patient reported outcomes to learn from broader populations; establishing mechanisms to ensure that provider and patient education keep pace with this evolving field; and identifying where the limitations in knowledge and resource constraints may be in order to mitigate them.

Challenges and Opportunities:

The table below provides examples of the scientific and systemic challenges for the I-O community and potential opportunities to mitigate these challenges.

SCIENTIFIC		
Area	**Challenges**	**Opportunities**
Predictive markers	• Dynamic nature of immune system and the advantage of obtaining pretreatment samples • Markers can take a variety of forms and are often not binary in immunology • Need to further develop insights into the mechanism of action for immune response and resistance	• Develop a national bio-banking system that captures relevant patient data (i.e., number of specimens, clinical annotation) to facilitate patient selection and long-term follow-up • Identify alternative biomarker models to facilitate patient access (i.e., mutation burden, immune signatures)
Measurement of immune response	• Multitude of technologies with inconsistencies in assay protocols & data reporting • No tests exist to predict immune system's ability to cause tumor regression	• Define a multi-dimensional basic science initiative to ID responders vs non-responders to specific IO agents and/or combination regimens • Incentivize broader use of Phase 0 trials
Development of IO-appropriate tumor response and progression endpoints	• The confounding effects of pseudoprogression and delayed response to therapy • Disease specific vs. generalizable endpoints • OS and PFS are problematic due to prolonged delay in read-out and progression before response, respectively • Defining curative therapy vs. durability of response vs. treatment free intervals	• Develop an aggregated control arm or determine best practices for use of historical comparator data to minimize need for randomization • Establish "safe-haven" for public data-sharing to facilitate evaluation of alternative endpoints (i.e., landmark survival, ir-RECIST, PRO, etc.) • Establish consensus definitions for clinical outcomes (i.e., cure, durable response, etc.)
Optimizing treatment and developing novel combinations	• Concurrent vs. sequential treatment • Dose optimization and timing and treatment vacations • Managing toxicities and long-term follow-up	• Establish centralized, master protocol, clinical trial to facilitate patient selection and testing of therapeutic combinations and dosing schedules and stopping points

	• Intellectual Property issues (when agents from multiple sponsors are used in a single regimen) • Novel drug combinations with approved drugs (i.e., TKIs and I-O) • Combinations in the adjuvant and neo-adjuvant setting	
Pre-clinical Development	• Improved models of disease • Identifying novel combination therapies and elucidating MOAs	• Incentivize development of improved pre-clinical models and the identification of drug combinations in the pre-clinical setting
SYSTEMIC		
Regulatory oversight	• Variable approaches and requirements, e.g., CDER guidance applicability to CBER • Multiple IND submissions for each indication • Approval of combo therapies that span multiple centers, i.e., checkpoint inhibitor + cell based therapy or vaccine • Production challenges with I-O based on regulatory requirements (GMP, etc.)	• Establish multi-disciplinary, cross-institute mechanisms to streamline regulatory review of combination therapies • Define novel statistical approaches for clinical trial endpoints • Provide guidance to industry relating to combination therapies approvals; intermediate endpoints; evidentiary standards for 2nd-, 3rd-line approvals; optimizing manufacturing
Reimbursement	• Determine strategies to evaluate payment structures that support shorter term therapies with longer term benefits; manage delayed side effects;	• Evaluate options for alternate reimbursement approaches that consider the unique attributes of I-O therapies.
Patient access and engagement	• Clinical trial access and efficient enrollment for real world patient groups (i.e., increased inclusion of prior immunotherapy)	• Establish broader, scientifically driven clinical trial eligibility criteria, e.g., inclusion of patients who receive prior immunotherapy into trials and have other previously excluded conditions
Implementation in the community setting	• Rapidly evolving concept of standards of care (new I-O agents in the clinic; I-O moving from metastatic to primary setting) • Lack of standardized guidelines and practices • Clinical training for new/combination agents, including managing toxicities • Long term patient follow-up	• Identify adjuvant and neo-adjuvant opportunities for I-O • Identify mechanisms to expand therapy management education in the community setting (i.e., established qualified centers for I-O delivery)
Education and training	• Frequently outdated with rapidly evolving science and ideas of value, in terms of time, cost, etc. • Identifying focused training needs for: clinical staff, patients, and policy makers	• Identify mechanisms to improve ensure healthcare provider/patient education on the unique patterns of treatment response

Collaborative development	• Leveraging lessons from other fields (e.g., HIV) • Streamlining disparate efforts (e.g., precision medicine, diagnostic development; bone marrow transplantation) and ensuring collaborative approaches	• Incentivize industry and other third party collaboration for development of combination therapies
Resources	• Managing scarce resources to drive development (including patients, regulatory, basic research, other)	• Identify focused funding needs (basic and translational) in the I-O space to address outstanding questions • Introduce trial efficiencies into clinical trials to maximize patient resources (i.e., centralized control arms)

Recommended Areas of Focus:

This group will work over the coming months to identify policy levers, ongoing or novel, that will elaborate and operationalize these focus areas to advance the I-O community:

- **Aligning oncology review functions within the FDA** – Moving away from functional centers and toward a single functional unit to enable consistent evaluation of cancer drugs, biologics and devices is needed to reflect 21st century science. Oncology could be a pilot for other disease areas and could be spurred forward based on the specific issues, with I-O providing an important test case for coordinated regulatory review raised in the I-O space (e.g., drugs, biologics and diagnostics are all highly relevant in I-O for monotherapy and especially combinations). Within oncology, streamlined review through a single clinical review would incorporate input from clinicians, statisticians, safety and clinical pharmacology.
    - **Next steps**: With increased support from Vice President Biden's National Cancer Moonshot, Friends is working to advance the implementation of this initiative while soliciting feedback and support from the I-O Policy Working Group, among other stakeholders, on effective implementation strategies for this initiative.

Develop consensus around I-O specific alternative endpoints and definitions that are appropriate to I-O and have sufficient rigor to be acceptable to regulatory agencies –A recognized phenomenon with immunotherapies is the potential for delayed treatment effect due to the fact that immunotherapies act on a prolonged timescale. In some cases tumor regression may only appear after apparent tumor progression ("pseudoprogression" or tumor flare) that occurs due to the presence of immune cell infiltrates and inflammation at tumor sites. In addition, although immunotherapies have demonstrated significant improvements in overall survival, survival curves may separate late leading to an incorrect determination of futility at an interim analysis. Delayed separation of survival curves may also result in reduced statistical power to assess the overall survival benefit after trial completion, necessitating alternative statistical approaches that can account for non-proportional hazards. Because of these issues, immunotherapy trials historically have not compared favorably on traditional interim endpoints that might be used as surrogates for overall survival, such as imaging-based endpoints, including response rate (RR) and progression-free survival (PFS), which are based on criteria developed for chemotherapeutic agents. Endpoints that reflect the biology of immunotherapies are needed. Alternative, immune-related endpoints (such as ir-RR and ir-PFS, clinical benefit rate, landmark survival, treatment free survival) and alternative statistical modeling approaches have been proposed based on preliminary phase two data-sets; however, determination of how these endpoints relate to long-term outcomes that are meaningful and relevant to patients such as improved survival or long-term disease stabilization, is needed in order to use such endpoints to support approval.

- **Next steps**: While initiatives are underway to examine modifications to tumor response and progression (RECIST) criteria (e.g., the VOL-PACT initiative led by the FNIH focused on volumetric versus conventional RECIST-based endpoints), these could be enhanced with an I-O specific focus on landmark survival, control for censoring and cross-over, and engagement of additional companies. The I-O PWG recommends that a subgroup composed of FNIH leadership, VOL-PACT study team, clinicians and industry leaders with expertise in trials of I-O agents, and experts from FDA, convene to determine: 1) how to incorporate analyses of landmark survival and PFS into the existing effort, 2) the availability of existing randomized data of checkpoint inhibitors that could be included in this study to retrospectively evaluate proposed new measures of efficacy, and 3) early endpoints that accurately identify patients who derive long-term benefit from I-O and would be sufficiently rigorous to serve as the basis for regulatory approval. This information could build upon previous publications on this topic. [1,2,3]

- **Opportunities to collect relevant data, including patient reported outcomes (PROs) such as symptom and quality of life information, from real-world experience** – Several areas fall under this umbrella: 1) relaxing restrictions on eligibility criteria of trial participants to more closely reflect the real-world population so as to enable important questions to be asked in clinical trials of I-O therapies, such as the extent to which an agent improves patient symptoms; 2) developing a more standardized approach to collecting real-world data post-approval that could advance our understanding in this arena; and 3) determine extent and how best I-O-specific PRO data can inform clinical decision making.
  - **Next steps**: A Friends/FDA/ASCO workshop on May 12th, 2016 will address broad issues around eligibility criteria in clinical trials as well as delve into specific eligibility criteria that are commonly used (such as inclusion of pediatric populations, organ dysfunction, HIV status and the presence of brain metastases). Recommendations from this workshop will address potential trial designs that can incorporate broader patient populations while allowing efficacy analyses in more traditional clinical trial populations. Such designs could include subset analyses of a more homogenous population within a broader trial, or expansion cohorts of specific sets of patients that typically are not included in cancer clinical trials. Additionally, consideration of I-O related issues in expanding trial eligibility criteria (including performance status and prior treatment), gathering real-world data, and determining appropriate context for use of this data (such as developing a case study for implementation) would contribute to efforts stemming from this workshop and may inform future FDA guidance development.

- **Promote novel trial designs in I-O, such as basket-type studies** – Incentivize industry collaboration and clarify opportunities for regulatory flexibility for studies aimed at improved understanding for how best to use I-O drugs. Examples include developing biomarkers within and across tumor types, evaluating sequencing among therapies and/or most appropriate combinations, identifying optimal stopping rules/intermittent dosing schedules, and developing window trials to test potentially curative immunotherapies in disease settings where alternative treatment options exist.
  - **Next steps**: Convene members of the I-O policy working group to prioritize opportunities for consensus and progress, develop best practices for any of the above types of clinical trials, and potentially launch a collaborative effort to design a trial, such as a window trial, for implementation.

- **Promote virtual bio-bank/common data platform** – Improve study designs and gain biological insights through sharing of I-O patient data (including samples, clinical information, imaging data, AEs). Develop a focused set of tangible questions, data points necessary to address these questions, and rules

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[1] Tai-Tsang Chen. 2015. **Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors.** *JNCI J Natl Cancer Inst* (2015) 107(9): djv156

[2] Conference on Clinical Cancer Research–Issue Brief. November 2013. **Facilitating the Development of Immunotherapies: Intermediate Endpoints for Immune Checkpoint Modulators**. Accessible at: http://www.focr.org/sites/default/files/Immunotx%20%20final%2011%204.pdf

[3] Conference on Clinical Cancer Research-Issue Brief November 2015. **Modernizing Measurement of Tumor Response to Therapy: Application to Immunotherapeutics**. Accessible at: http://www.focr.org/sites/default/files/FINAL%20RECIST%20pre-conference%20draft.pdf

for data use (e.g. what drives exceptional response, non-response, and/or resistance). Requires industry, institution, and cooperative group engagement and support.

- **Next steps**: Efforts such as the Oncology Research Information Exchange Network (ORIEN) precision cancer research collaboration, ASCO's CancerLinQ, Project Data Sphere, and others are developing mechanisms to share and learn from patient data. Members of the I-O policy working group will convene a sub-group to identify important questions related to what data elements need to be collected, while learning from existing efforts and methods to remove existing barriers. The output of this effort could inform larger collaborative efforts, including Vice President Biden's National Cancer Moonshot.

- **Develop an education initiative for the full-spectrum of care providers in a patient's care team within the community setting** – Use a systems approach to standardize and manage education of I-O therapies in the clinic. The development of broad standards for educating patients and medical teams (including oncologists, radiologists, nurses, pharmacists, ER, social workers, genetic counselors, administrative staff, etc.) could be used as part of an accreditation system particularly for advanced therapies like CAR-T or combination therapies, similar to the bone marrow transplant model.
  - **Next steps**: Convene a sub-group to identify education elements that need standardization and determine best steps forward to implement them. This group could also consider models of community education in order to reach all providers prescribing immunotherapies with treatment management information.

Disclaimer: The views presented in this document are intended to summarize the views of the individual work group participants and do not necessarily reflect the views or policies of any of the supporting organizations.