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A SITC vision: adapting clinical trials to accelerate drug development in cancer immunotherapy

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ABSTRACT

Clinical trials of cancer immunotherapy (IO) were historically based on a drug development paradigm built for chemotherapies. The remarkable clinical activity of programmed cell death protein 1/programmed death ligand 1 blockade, chimeric antigen receptor-T cells, and T cell engagers yielded new insights into how the mechanistic underpinnings of IO are reflected in the clinic. These insights and the sheer number of novel immunotherapies currently in the pipeline have made it clear that our strategies and tools for IO drug development must adapt. Recent innovations like engineered T cells and tumor-infiltrating lymphocytes demonstrate that immune-based treatments may rely on real-time manufacturing programs rather than off-the-shelf drugs. We now recognize adoptively transferred cells as living drugs. Progression criteria have been redefined due to the unique response patterns of IO. Harnessing the power of both biomarkers and the neoadjuvant setting earlier in drug development is of broad interest. The US Food and Drug Association is increasingly impacting the design of trials with respect to dose optimization and clinical endpoints. The use of novel endpoints such as pathologic complete/major response, treatment-free survival, and minimal residual disease is becoming more common. There is growing acceptance of using patient-reported outcomes as trial endpoints to better measure the true clinical benefit and impact of novel IO agents on quality of life. New opportunities created by modern data science and artificial intelligence to inform and accelerate drug development continue to emerge. The importance of streamlining the clinical research ecosystem and enhancing clinical trial access to facilitate the enrollment of diverse patient populations is broadly recognized. Patient advocacy is critical both to drive the science of IO, and to promote patient satisfaction. To capitalize on these opportunities, the Society for Immunotherapy of Cancer (SITC) has established a goal of at least 100 new, unique IO approvals over the next 10 years. Accordingly, SITC has developed initiatives designed to integrate the viewpoints of diverse stakeholders and galvanize the field in further adapting clinical trials to the unique features of IO, moving us closer to our ultimate goal of using IO to cure and prevent cancer.

INTRODUCTION

Immunotherapy (IO) is now a standard of care for many patients with cancer with early or advanced disease. Years of dedicated work provided initial proof of principle that harnessing the immune system—with cytokines, a vaccine, a cytotoxic T lymphocyte-associated protein 4 (CTLA-4)-specific antibody, or an oncolytic virus—could benefit some patients with cancer. With this foundational clinical evidence in hand, the last decade witnessed a marked acceleration of cancer IO drug approvals by the US Food and Drug Administration (FDA). To date, the most impactful drug platforms are immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR)-T cells, and T-cell engagers (TCEs). These initial cancer immunotherapies transformed cancer care due to their novel mechanisms of action, unique side effect profiles, and delivery of long-term clinical benefits to patients. However, many patients with cancer who appropriately receive IO either have cancers that fail to respond at all (primary resistance), or cancers that progress after initial benefit (secondary resistance).[1] There is clearly significant room for improvement in making treatments accessible and in identifying patients who will benefit from these therapies.

Selected approved agents provide tantalizing hints about how to further accelerate progress (figure 1). Targeting distinct antigens, B cell maturation antigen (BCMA) and G protein-coupled receptor class C group 5 member D (GPRC5D), extended the benefit of CAR-T or TCEs from B-cell cancers to multiple myeloma, a major unmet clinical need.[2–4] The TCE specific for glycoprotein 100/major histocompatibility complex (MHC) (tebentafusp) extended the utility of TCEs from B-cell cancers to solid tumors (uveal melanoma), and from a simple protein

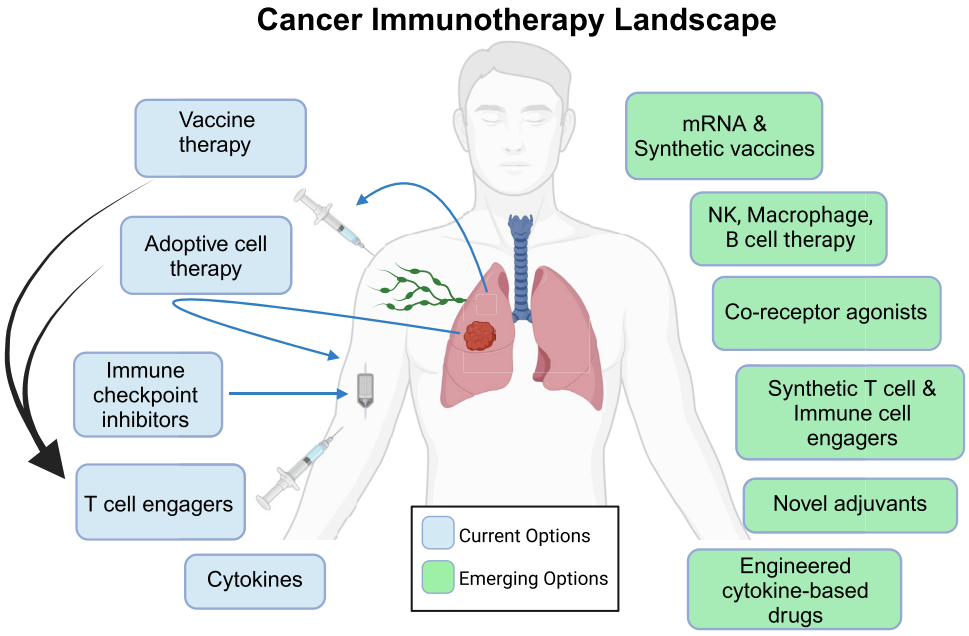

Figure 1 Cancer immunotherapy landscape. The cancer immunotherapy landscape is rapidly evolving. Current FDA-approved options include vaccine therapies, adoptive cell therapy, ICIs, TCEs and cytokines. The deployment of immunotherapies with novel mechanisms of action supported by sophisticated biomarker assessments (figure 4) is expanding the repertoire of treatment options for patients, with the potential for more tailored immunotherapy treatment plans. Created in BioRender. Staff, S. (2025) https://BioRender.com/n80v366. FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; mRNA, messenger RNA; NK, natural killer; TCE, T-cell engager.

to a more complex drug target (antigen to MHC/antigen) on the tumor surface.[5] In 2024, four first-in-class drugs have been FDA-approved. The delta-like ligand 3-specific, half-life extended TCE tarlatamab-dlle was approved for recurrent small cell lung cancer (SCLC).[6] It incorporates a novel antigen target in a less immunogenic solid cancer with significant unmet therapeutic needs. The innovative drug platform of adoptively transferred, autologous tumor-infiltrating lymphocytes (TIL) (lifileucel), was approved for advanced melanoma after programmed cell death protein 1 (PD-1)-based or V-Raf murine sarcoma viral oncogene homolog B (BRAF)-inhibitor-based therapy.[7] This personalized treatment is derived from the patient's own tumor and targets multiple tumor antigens. The interleukin (IL)-15 receptor agonist nogapendekin-alfa inbakicept-pmln (N803) plus bacillus Calmette-Guéri (BCG) was approved for BCG-unresponsive non-muscle-invasive bladder cancer.[8] This molecule has both a unique mechanism of action, and efficacy in a tumor with no good treatment options. Finally, afamitresgene autoleucel is the first approved engineered T-cell receptor (TCR)-T cell therapy, which recognizes the melanoma-associated antigen A4 (MAGE A4) antigen, and is approved for adults with advanced synovial sarcoma previously treated with chemotherapy.[9] This is also the first engineered T-cell therapy approved for a solid tumor.

The rate of clinical progress in IO over the last decade is unprecedented in oncology. Concurrently, the rapid discovery of novel drug targets and the development of new tools for molecular engineering have created a treasure trove of unique molecules currently in advanced preclinical or early clinical studies. These are the agents and drug platforms that will drive the next wave of FDA approvals in cancer IO. However, the field is confronting significant headwinds in the clinical trials and drug delivery ecosystem that will likely hamper our ability to efficiently deliver new IO drugs to patients unless they are addressed. These include excessive regulatory burdens, long delays in trial activation, and the enormous cost of clinical trials that results in a high drug price-point for patients. Compounding these challenges are shortages in both the clinical and research workforce that must be addressed to support continued progress in the field. Although this manuscript is focused on opportunities and challenges in the USA, multiple systemic inefficiencies, some similar and some distinct, also slow drug development in the European Union and beyond.

To galvanize the field and capitalize on the enormous progress we have made, the Society for Immunotherapy of Cancer (SITC) has established a goal of 100 new approvals of unique cancer immunotherapies over the next decade. Supporting this goal, SITC developed a series of manuscripts that identify areas of challenge and opportunity, the first of which provided a broad, high-level overview.[10] This manuscript, which is focused on adapting clinical trials to the unique features of IO drugs, is one of three others that focus on IO mechanisms of antitumor immunity, toxicity, and resistance, novel IO constructs, host and environmental factors that impact immunity, and premalignant immunity. As described in this overview focused on clinical trials, SITC aims to engage diverse stakeholders to deploy innovations in clinical trial design,

novel biomarkers for patient selection/stratification and clinical trial endpoints, employ new tools in data science to accelerate clinical development, generate advances in regulatory science, streamline the clinical trials ecosystem, and expand the translational and clinical workforce to accelerate the delivery of novel cancer immunotherapies to patients for cancer treatment, interception, and ultimately prevention.

CLINICAL TRIAL DESIGN AND ENDPOINT OPPORTUNITIES

The mechanisms of action of cancer immunotherapies are distinct from conventional oncology agents. Thus, traditional oncology clinical trial methodology often falls short, especially with respect to development strategy and measurement of effect. Cancer drugs have historically been developed by initially looking for activity in heavily treated patients, then advancing the investigations to earlier lines of therapy. Patients with advanced cancer are known to be relatively immunosuppressed due both to cancer burden and prior treatments. They thus may have a greater number of active immune resistance pathways than patients with early-stage malignancies. Additionally, early-phase trials studying a new IO in a late-stage cancer population may not provide a robust assessment of either acute-term or long-term toxicity, particularly for the new agent combined with an approved IO agent. This is because patients participating in such earlier phase trials are typically selected for those who did not experience substantial toxicity to the approved IO agent previously, and thus may not be representative of a more general population. These observations call for innovative trial designs that rapidly evaluate the safety and clinical activity of novel IO agents alone and combined with approved immunotherapies in both early-stage and late-stage diseases at the earliest stages of drug development. Increasing the use of such an integrated approach should accelerate IO drug development in both early and late disease settings by creating opportunities for potential cross-fertilization of knowledge, and by optimizing fiscal, temporal, and patient resources.

There was an initial lack of confidence within the oncology community surrounding the CTLA-4-specific antibody ipilimumab, the first-in-class ICI approved. In early clinical trials, the response rate and progression-free survival (PFS) as assessed by traditional response criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO), were modest; yet, overall survival (OS) improvement was achieved in the pivotal phase 3 trial.[11] Investigators managed unfamiliar patterns of clinical response such as pseudoprogression and minor tumor regression, coded as progressive or stable disease by traditional response criteria, respectively. These atypical responses were counterintuitively often associated with durable clinical benefits from IO. Thus, unique response patterns combined with new, class-specific immune-related side effects initially complicated the development of anti-CTLA-4 treatment. After we learned how to manage the unique features of anti-CTLA-4 therapy, the greater clinical activity and lower toxicity of anti-PD-1/programmed cell death ligand 1 (PD-(L)1) agents mitigated the concerns around response assessment and toxicity during anti-PD-(L)1 development, and protocols began to allow treatment beyond disease progression.

The adoptive transfer of CAR-T cells, TCR-transduced T cells and TIL face additional novel complexities in clinical development relative to historical chemotherapy approaches. CAR-T therapies have had profound impacts on hematologic cancers, yet difficulties in developing clinically and commercially successful products remain. Some of these include prolonged manufacturing times, the tremendous financial capital required to run both early phase and randomized confirmatory studies, and access to study subjects for clinical trials of iterative cell engineering procedures. Cell therapy for solid tumors is also on the verge of having a transformational impact, bringing additional complexity. Screening solid tumor patients who are reasonable candidates for tumor resection and systemic conditioning, have the appropriate human leukocyte antigen (HLA) background for TCR therapy, or express the target tumor antigen for CAR-T cell or TCR-T cell therapy is both resource-intensive and time-intensive. The use of comprehensive next-generation sequencing (NGS) technology will streamline, simplify, and personalize screening for clinical trials and approved IO therapies in the clinic.

Despite these challenges, IO has clearly transformed the oncology landscape. Table 1 outlines common IO trial designs. Initially, trial designs focused on treatment-refractory, but IO-naive patients (figure 2), with substantial success observed across many tumor types. In fact, the treatment of relatively modest numbers of patients led to regulatory approval and evaluation in earlier lines of therapy. Two of the most dramatic examples of this were single-arm phase 2 trials examining the genomic biomarkers of microsatellite instability (MSI) and high tumor mutational burden (TMB), which facilitated the approval of pan-tumor indications.[12 13]

Paradoxically, success with single-arm trials in heavily treated patients, which often lacked stringent biomarker stratification, set the stage for a period of malaise in drug development. Anti-PD-(L)1 agents combined with conventional drugs received accelerated approval in settings where a clinical signal was detected, but the long-term benefit was not definitively established as required by the FDA. As a result, several accelerated approvals have subsequently been retracted by trial sponsors.[14] This reality, despite a robust pipeline of innovative, promising IO drugs with diverse mechanisms of action, shaped the perception by some that IO may currently overpromise and underdeliver. This perception has inevitably led to difficulty raising funds to support novel IO drug development in the biotech space, resulting in the failure of multiple biotech companies. As these discovery-oriented biotech companies ultimately feed the large pharma

Table 1 Common immunotherapy trial designs and phases

Phase	Description	Intent	Example
Phase 0 / window of opportunity	Pre-surgical	Biomarker/translational	Liakou *et al*[74]
Phase 1	First-in-subjects with cancer	Safety determination	Brahmer *et al*[75]
Phase 1 expansion	Refractory cohorts of specific cancers	Preliminary signal seeking	Kang *et al*[27]
Phase 2	Single-arm	Efficacy description and safety	Chen *et al*[76]
	Randomized	Enhanced efficacy and safety description	Cho *et al*[77]
Phase 3	Randomized	Efficacy confirmation	Mirza *et al*[78]
Adjuvant (Phase 3)	Randomized	Efficacy	Choueiri *et al*[79]
Neoadjuvant (Phase 2)	Single-arm or randomized	Biomarker/translational Safety Prelim efficacy	Amaria *et al*[80] Patel *et al*[81]
Neoadjuvant (Phase 3)	Randomized	Efficacy	Wakelee *et al*[82]
Phase 4	Randomized	Therapy refinement	Baetz *et al*[83]

drug pipeline, this dynamic puts the entire IO ecosystem at risk. These diverse factors highlight the complexity of host antitumor immunity, the impact of the lack of effective patient selection for IO trials, and the shortcomings of the ecosystem that develops IO agents that harness the antitumor immune response for therapeutic benefit.

After preliminary safety assessment in advanced disease, many trial sponsors now position investigational drugs in earlier lines of therapy for safety and efficacy assessment in less heavily treated patients. This strategy reflects more classic drug development paradigms in randomized and/or biomarker-informed phase 2 studies in anti-PD-(L)1-treatment-naïve populations. Additionally, opportunity spaces are emerging to investigate novel agents in the neoadjuvant setting. This strategy has yielded new biological insights that support evaluating promising neoadjuvant observations in definitive phase 3 trials.[15 16] Neoadjuvant, perioperative, and adjuvant trial spaces are currently the areas of highest interest for anti-PD-(L)1 agents. It is likely that most patients who receive

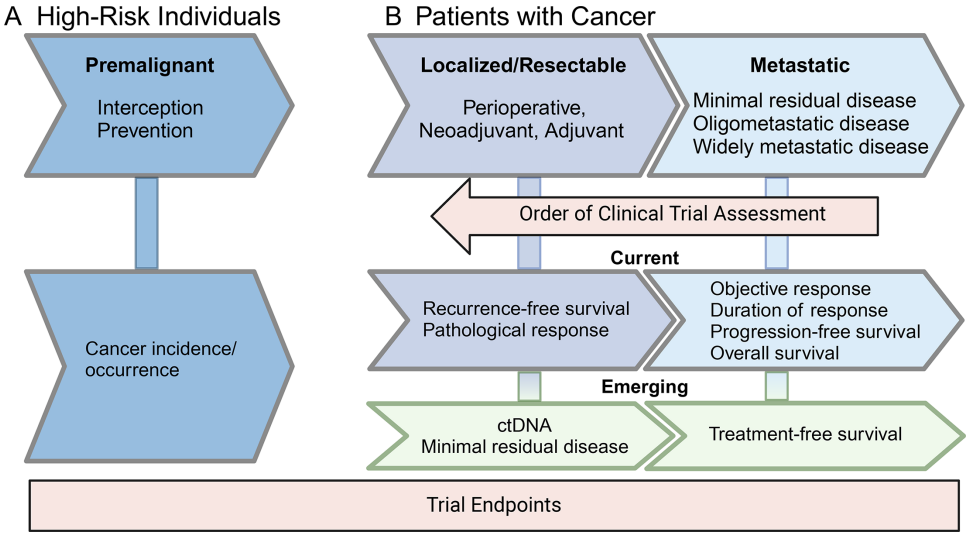

Figure 2 Current clinical development paradigms. (A) There is increasing interest in identifying individuals at high risk for cancer development who are healthy, or who have premalignant lesions likely to progress to frank malignancy. Here, clinical trials aim to either prevent cancer outright, or to intercept the progression of high-risk precancerous lesions to overt malignancy. The endpoints for clinical trials of immune interception or prevention strategies include the incidence or (re-)occurrence of high-risk premalignancy or overt cancer. (B) Historically, immunotherapies have first been tested in patients with metastatic disease. Recently, clinical trials have increasingly focused on testing immunotherapies in early-stage disease, particularly the neoadjuvant setting. Here, immunotherapies may have the greatest clinical impact, as disease burdens and tumor-associated immune suppression are lower, and patients have been exposed to fewer drugs that may adversely impact host immunity. Thoughtful drug development strategies are required to safely and effectively flip the script of drug development for cancer immunotherapies. To this end, emerging surrogate clinical endpoints that are both patient-centric and reflect survival benefits should both modernize and accelerate the development of effective immunotherapies for patients. Created in BioRender. Staff, S. (2025) https://BioRender.com/f08g904. ctDNA, circulating tumor DNA.

anti-PD-(L)1 in the future will receive these agents prior to the development of metastatic disease, which may impact the risk/benefit profile of newer IO drugs tested in advanced disease. Moreover, the risk/benefit trade-off is different in patients with early-stage cancers for which non-IO treatment options with curative potential are frequently available. For early-stage disease, it is important to determine how much IO exposure is required to maximize benefits and minimize toxicity. This also highlights the need for intense initial then sustained long-term monitoring and reporting of adverse events given the lifelong impact of some immune-related adverse events.

The development of CAR-T cell therapy in hematologic cancers followed the traditional paradigm of initial testing in treatment-refractory disease and then in earlier lines of therapy; whether this approach will be feasible in solid tumors is unknown. Major issues include defining appropriate control arms for randomized studies, and effectively evaluating the contribution of components for cell therapies incorporating lymphodepleting chemotherapy and/or IL-2. Only one study of TIL therapy in solid tumors has been randomized;[17] other studies are ongoing or planned.[18] Given the increasing use of ICI in the neoadjuvant, perioperative, and adjuvant settings, many patients who develop metastatic disease will be ICI-experienced or refractory. Thus, early identification of appropriate candidates for adoptive cellular therapy will be critical, and considerations for patient stratification may be complicated.

Phase 3 or 4 trials can be used to refine dose intensity, length of treatment, toxicity risks, and other considerations unique to specific subpopulations of patients. For example, in the perioperative setting, robust debate about the need for three-arm or four-arm trials prior to approval to identify whether treatment pre-surgery, post-surgery, or both are required for optimal patient benefit is ongoing.[19] Beyond these questions, IO strategies for cancer interception or prevention are receiving increasing interest, with early data supporting IO to interrupt cancer development.[20]

It is critical to rigorously evaluate the mechanism of action of any emerging IO in early-phase trials. New agents with monotherapy activity in treatment-refractory patients can be rapidly evaluated in earlier disease settings. Immunotherapies with modest monotherapy activity or activity within a biomarker-selected population are more challenging to evaluate. Here, the patient population, trial design, and primary clinical endpoints must be very carefully chosen. Traditional endpoints such as objective response rate (ORR), PFS, event-free survival (EFS), and OS may poorly describe the potential impact of a new therapy. Instead, detailed pharmacodynamic analysis, rigorous assessment of the extent of tumor shrinkage, determining the disease control rate (DCR) at a fixed point in time, and measuring novel dynamic biomarkers, such as circulating tumor DNA (ctDNA), may help identify an agent with clinical activity. For example, the ORR underestimates the clinical benefit of tebentafusp, and ctDNA monitoring can more effectively guide patient care. Building on these observations, ctDNA monitoring has been used to evaluate continuing treatment with pembrolizumab or treatment intensification in non-SCLC (NSCLC).[21 22] Thus, ctDNA evaluation in adaptive clinical trials can guide continuing open-ended treatment, treatment intensification, or treatment de-escalation. Underlying such an adaptive therapeutic strategy is the observation that long-term disease control represents a hallmark of successful IO. Finally, when multiple immune agents are tested in a regimen, appropriately sequencing them may be important.

There is intense interest in the use of novel surrogate clinical endpoints (such as ctDNA) to accelerate the evaluation of new IO agents. Leveraging the durability of response with IO, treatment-free survival (TFS) has gained substantial support as a patient-centric consideration, particularly with ICI-based therapies.[23 24] In addition, composite endpoints including multiple efficacy endpoints (ORR and PFS) or a mix of efficacy endpoints and safety thresholds may also be informative in early phase studies. Additionally, combining an efficacy endpoint such as OR with ctDNA or a pharmacodynamic measure may be relevant, provided the latter is highly validated. One of the most promising surrogate endpoints in oncology has been the complete pathologic response (pCR) to neoadjuvant therapy, which has predicted favorable long-term outcomes at the patient level. For IO, long-term clinical benefit is also associated with major pathologic response (mPR), defined as a residual tumor of 10% or less.[25] The regulatory landscape surrounding the use of pathologic response as a trial endpoint for regulatory approval remains uncertain, as its surrogacy with longer OS has not yet been demonstrated at the trial level. Finally, drug developers should remain cognizant of the power of machine learning and artificial intelligence (AI) for clinical trial analyses. For example, radiomic analysis may soon enable a patient enrichment strategy to detect clinical signals,[26] thus accelerating drug development programs.

As we evolve our clinical trial designs and endpoints, an urgent need to support more effective drug and biomarker development is the generation of preclinical models that more accurately recapitulate human immunobiology. While millions of people worldwide have received immune checkpoint-blocking antibodies, we still do not know how they work in vivo. The heterogeneity of responses observed underscores our lack of understanding of their mechanisms of action and the host factors that underlie response and resistance in patients with cancer. Importantly, we see similar heterogeneity in the efficacy of these immunotherapies in preclinical models. This holds true of a specific cancer type, and in the context of a defined genetic background. This response heterogeneity in both human and preclinical models likely reflects the intrinsic capacity of the immune system to integrate multiple inputs to generate an adaptive response (or not) in the context of microenvironmental

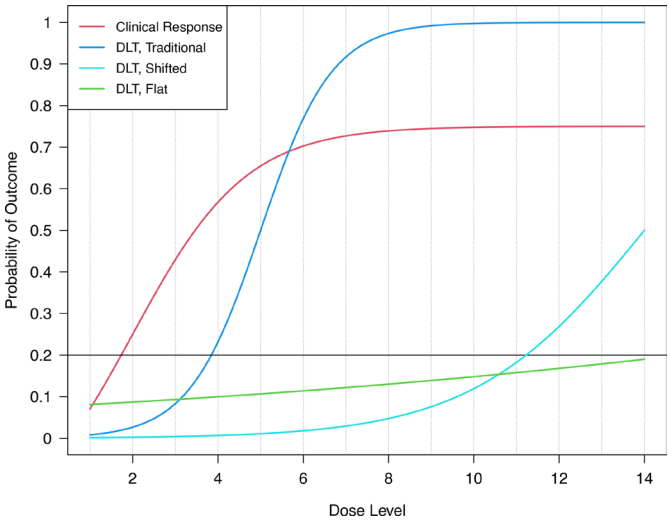

Figure 3 Dose-toxicity relationships. Shown are examples of dose-toxicity relationships for cytotoxic (traditional) anti-cancer agents and other agents that do not require dosing to a toxic level to achieve anti-cancer activity (flat or shifted curves). The horizontal line at 0.20 reflects the acceptable dose-limiting toxicity. DLT, dose-limiting toxicity.

and macroenvironmental signals. This is a critical difference between IO and highly targeted precision medicine therapies. Thus, we need not only more relevant preclinical models, but also more robust data analysis methodologies that better account for the adaptive nature of the immune system.

Dose optimization considerations

The traditional cancer drug development paradigm assumes that the highest tolerable dose is also maximally effective. Although this was reasonable for cytotoxic agents, this association cannot be assumed for immunotherapies. Figure 3 shows several possible relationships between dose and dose-limiting toxicity (DLT) for anti-cancer therapies with different levels of toxicity (all with the same relationship between dose and clinical response). Assumptions for the maximum tolerated dose (MTD) being the optimal dose have been based on the shape and relative location of the dose-toxicity curve (traditional) and dose-efficacy curve (clinical response). There is a therapeutic window for dose that is relatively narrow—only a few doses have activity that is not overly toxic (dose levels 3 and 4 in figure 3). For other scenarios described by flat or right-shifted dose-toxicity curves, there are doses lower than the MTD that show high ORRs with relatively low toxicity. Dose optimization strategies for immunotherapies should seek to understand both the dose toxicity and the dose efficacy relationships. In figure 3, dose level 6 would be optimal for the shifted or flat toxicity curve scenarios: it has high efficacy at dose level 6 with almost no gain in efficacy at higher doses and the toxicity is below an acceptable threshold for the DLT rate.

While understanding the relationship between dose and efficacy and between dose and toxicity is critical to drug development, it may be determined that a broad range of doses have similar efficacy and/or toxicity and, thus, there is not a single dose that could be deemed "optimal" for IO therapies. Using PD-1 ICIs as an example, neither pembrolizumab[27] nor nivolumab[28] reached an MTD in phase 1 studies, and both drugs were active at doses much lower than the highest doses administered and with a relatively flat dose-response curve.

One strategy for dose optimization promoted by the FDA Project Optimus incorporates both efficacy and toxicity. A somewhat traditional phase 1 study design might be used to explore toxicity rates for a range of dose levels using dose escalation with relatively few patients per dose level. Based on observed toxicities (both low and high grades in early cycles), pharmacokinetics, and pharmacodynamics at various dose levels, two or more doses would be selected for further evaluation in a dose-ranging study. The dose-ranging study may have a different patient population than the phase 1 study and would have primary endpoints of efficacy and tolerability (including long-term safety and tolerability endpoints) to help select an optimal dose. Another approach of considerable interest to patient advocates is to provide a range of potential doses that can be individually titrated for each patient.

Along these lines, the FDA Oncology Center for Excellence (OCE) has initiated various projects relevant to the development of cancer immunotherapies.[29] They span different aspects of drug development and approval to promote optimization, expediency, and to ensure approved agents provide more than incremental clinical benefit. Those of most relevance are provided in table 2, with more information available on the OCE website.

The role of patient advocates in clinical trials

Involving patient advocates in the planning, conduct, and dissemination of clinical trial results helps to ensure that trials answer questions important to patients, that the burden of trial participation is minimized, and that communication about the trial occurs in a patient-friendly way (box 1), thus facilitating rapid accrual and excellent compliance. Advocate input is especially essential in two areas that directly impact participants: patient-reported outcomes (PROs), and trial-related communication. PROs directly assess participants' perceptions of adverse events and their Health-Related Quality of Life (HR-QoL). The collection of PROs is becoming standard practice in oncology clinical trials. The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)[30] is a commonly used instrument that assesses patients' experience of toxicities in oncology trials. However, it is not focused specifically on toxicities associated with immunotherapies, where late-occurring toxicities are more likely. The distinct pattern and timing of immune-related adverse events warrant the development of PRO instruments specifically tailored to immunotherapies.[31 32] In addition to PROs, advocates can provide critical input to guide the development of non-technical,

Table 2 Summary of the Food and Drug Administration's Oncology Center for Excellence projects

Project	Goal
Project Optimus	To reform the dose optimization and selection paradigm in oncology drug development. Draft guidance has been released that emphasizes the need for evidence to support dose selection using various metrics (not just toxicity).[84]
Project Catalyst	To provide resources to support the development of directed and novel anticancer therapies with a focus on guidance and educational materials for small pharmaceutical companies and academic life science incubators and accelerators.
Project Endpoint	To enhance the development of endpoints in oncology, including early and novel endpoints, and to advance the use of long-term endpoints (eg, overall survival).
Project Pragmatica	To encourage and demonstrate efficiencies and patient-centric aspects of clinical trials by using pragmatic design elements. These may include flexibility in the delivery of intervention, broadened eligibility and patient-centric outcomes.
Project Orbis	To provide a framework for concurrent submission and review of oncology therapies to international regulatory agencies. Establishing a greater uniformity of new global standards of treatment, leading to the optimal design of these important trials.

visually attractive, balanced, patient-facing trial materials, and help shape informed consent discussions. Advocates can also assist in crafting plain-language summaries of trial results for patients and the public.

BIOMARKER OPPORTUNITIES

With thousands of cancer IO drugs under investigation, biomarker development is critical to identify the right therapy for the right patient at the right time. Incorporating biomarkers into drug development at the earliest stages should accelerate clinical research and optimize routine clinical practice after drug approval. Biomarkers are biologic data associated with the likelihood that a patient will respond to a given treatment (predictive biomarkers) or that convey a better or worse prognosis with currently available therapies (prognostic biomarkers). Some biomarkers are both predictive and prognostic (for example, peripheral soluble PD-L1 across cancers, and somatic *STK11* mutations co-occurring with *KRAS* mutations in lung cancer).[33 34] Biomarker development has historically relied on the collection of tumor tissue and blood samples. Profiling to define static biomarkers at baseline as well as dynamic changes on treatment can lend deep insights into the mechanism of action and efficacy of a drug. Examples of dynamic biomarkers are ctDNA kinetics and cytokine signatures in the blood, which may better capture systemic tumor burden and quality of the antitumor immune response, respectively.[35 36] While biomarkers are often developed for patient selection, there is increasing interest in on-treatment biomarkers as early indicators of response, biomarkers of toxicity, and biomarkers associated with the pharmacodynamic activity of the drug.

There are only a few validated biomarkers to guide IO decisions (figure 4). PD-L1 is a biomarker approved by the FDA to guide therapeutic decisions in certain tumor types such as triple-negative breast cancer (TNBC)[37] and NSCLC.[38] In metastatic TNBC, PD-L1 expression guides the selection of patients for treatment with PD-1 blockade and chemotherapy, and in NSCLC it dictates whether chemotherapy should be included with PD-1 blockade, or if combination immunotherapies should be pursued. It is not employed in some other tumor types where it is not predictive, such as melanoma[39] or hepatocellular carcinoma.[40] TMB, routinely computed by many commercial NGS panels, is also an FDA-approved biomarker. Although the optimal cut-off for TMB remains debated, patients with high TMB may benefit from IO regardless of tumor histology.[13] Importantly, these predictive biomarkers do not always predict a clinical response, as there is a sizeable fraction of cancers with either PD-L1 expression or a high TMB that do not regress with IO. Cancers with MSI by NGS or mismatch repair deficiency (dMMR) by immunohistochemistry are hypermutated and typically

Box 1 Strategies for maximizing benefit and minimizing burden on trial participants

Maximize benefit

- ⇒ Power trials to achieve large benefits
- ⇒ Allow patients to cross over
- ⇒ Include patient-reported outcomes and Quality of Life measures
- ⇒ Minimize the number of patients who receive a placebo or standard of care
- ⇒ Ensure the trial will be completed rapidly to remain meaningful to future patients
- ⇒ Broaden eligibility requirements
- ⇒ Provide personalized treatments
- ⇒ Return results (aggregate and individual)
- ⇒ Allow patients to donate their tissue/data for future research

Minimize burden

- ⇒ Schedule an appointment for patient convenience
- ⇒ Improve access by opening sites convenient for diverse patient groups
- ⇒ Prioritize the most important research procedures
- ⇒ Be mindful of direct and indirect financial burdens of trial participation, and provide appropriate compensation
- ⇒ Be proactive about providing supportive care for toxicities

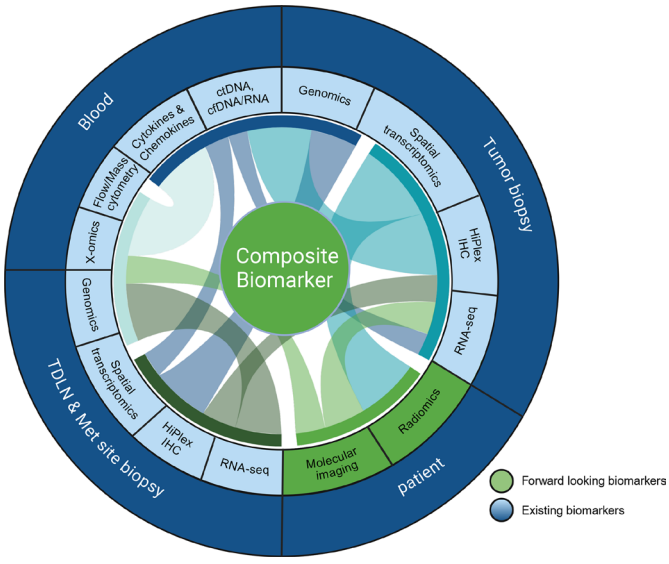

Figure 4 Cancer immunotherapy biomarkers. A variety of biomarker analyses that assess DNA, RNA, and protein can be performed on biopsies of the primary tumor, TDLN, sites of metastasis, and/or blood samples. Emerging methods allow for minimally invasive biomarker assessments and include liquid biopsies, molecular imaging and radiomics. Ultimately, it is likely that distinct technologies will be combined to generate composite biomarkers that most accurately reflect the active tumor-immune dynamic within a given patient. The present and future landscape of immunotherapy biomarker analyses is represented by this theoretical circos plot, which highlights both the potential and likely complexity of future biomarker assessments. Created in BioRender. Staff, S. (2025) https://BioRender.com/o83j407. cfDNA, cell-free DNA; cfRNA, cell-free RNA; ctDNA, circulating tumor DNA; IHC, immunohistochemistry; Met, metastatic; RNA-seq, RNA sequencing; TDLN, tumor draining lymph node.

harbor an exceptionally high TMB that drives deep and durable responses to IO;[12 41 42] however, even MSI-high is an imperfect predictive biomarker.

As TMB represents only a crude measure of tumor foreignness, emerging approaches that capture mutations, co-mutations and mutational signatures uniquely associated with ICI response hold promise.[43–45] Similarly, novel transcriptomic signatures based on bulk RNA sequencing may identify tumors with an inflamed tumor microenvironment (TME) that can drive tumor elimination in the context of ICI.[46] At a deeper level, machine learning methodologies are now enabling bulk and single-cell resolution assessment of the transcriptomic, epigenetic, and metabolic state of tumor cells, stromal cells and infiltrating immune cells, and cells in the neighboring parenchyma and draining lymph nodes and lymphatics (figure 4).[47] Additionally, spatial proteomic and transcriptomic platforms can provide a snapshot of the TME architecture. Spatial determinants of response to IO might include the excluded or inflamed immunophenotype, or the presence and maturation status of tumor-associated tertiary lymphoid structures (TLS). TLS has been shown to correlate with response to checkpoint blockade.[46 48]

Bridging the biology of antitumor immune responses with innovative technologies that provide real-time, minimally invasive monitoring of systemic tumor burden, liquid biopsies provide a window into both tumor clonal evolution and the systemic immune milieu across diverse metastatic sites.[36] Molecular response based on ctDNA detection during ICI consistently predicts clinical outcomes and is now often tested in interventional clinical trials.[22] A growing body of ctDNA studies supports the potential clinical utility of ctDNA molecular response as an early endpoint of ICI response. Thus, liquid biopsy-tailored approaches may facilitate drug development by providing a rapid read-out of therapeutic efficacy. Moreover, ctDNA-informed treatment escalation or de-escalation can be evaluated in clinical trials. As IO enters the therapeutic arena of early-stage cancers, minimal residual disease (MRD) detected by ctDNA may serve as a real-time monitor for disease burden during neoadjuvant or perioperative IO, and predict long-term outcomes.[49 50] As the analytical and clinical sensitivity of MRD assays continues to improve, ctDNA MRD may enable the navigation of an expanding clinical trial landscape for patients with early-stage cancers.[51] Blood-based profiling can also enhance our understanding of the systemic immune milieu. The neutrophil-to-lymphocyte ratio (NLR) is both prognostic and predictive,[52] and an even deeper analysis of systemic lymphoid and myeloid populations reveals further biologic granularity. In tandem, profiling peripheral cytokines and chemokines can identify both biomarkers and therapeutic targets. Many studies have evaluated inflammasome cytokines, such as IL-1. Measuring and potentially manipulating Type 1 (Th1) or Type 2 (Th2) cytokines, known to promote or stymie antitumor immunity respectively, is also under intensive investigation.[53] It is likely that composite biomarkers that incorporate aspects of both tumor and host immunobiology will be most informative (figure 4).

While the technologies to query the TME and systemic immune milieu in patients at baseline and on therapy have rapidly progressed, these new approaches have highlighted several challenges that currently limit the implementation of tissue-based and blood-based biomarkers into clinical trials. One key limitation is the lack of standardization. First, even among trials within a single sponsor or cooperative group, each trial may collect different biospecimens at different time points, and potentially process and preserve samples in disparate manners. Second, blood and tissue analyses are often performed using distinct platforms. The use of specific platforms and modes of analysis is heterogeneous due to significant expense, thus limiting cross-trial comparisons. Third, when relatively limited assessments are selected for logistical or financial reasons (predefined cytokine or flow cytometry panels for example), generalizability is often limited due to heterogeneity between patients, and among disease sites within a given patient. This highlights the importance of sampling multiple sites of disease when evaluating biomarkers, as biomarker expression between

two biopsies within the same patient may diverge. Biologic differences based on stage add further complexity. It is unclear the extent to which resected tumors from patients with early-stage disease may represent the TME of widely metastatic disease. Furthermore, the immunobiology of premalignant tissue is likely to be even more distinct. While neoadjuvant and window-of-opportunity trials are invaluable given the sheer volume of tumors available for biomarker testing, biomarker findings in the perioperative setting must always be validated across the disease spectrum, where the local and systemic immune milieus may differ. The neoadjuvant setting further represents a unique opportunity to relate tumor-based biomarkers to liquid biopsy-based biomarkers in a time-efficient manner.

Ideally, biological samples for biomarker development are assessed at baseline, on treatment, and at disease progression. As this requires multiple tissue biopsies and/or blood samples from a given patient, the ethics of this have been widely discussed by researchers, ethicists, and patient advocates.[54 55] The value of the information gained versus the risk to participants must be weighed. While patients are often willing to donate biologic samples, sites are often reluctant to request them due to logistical burdens on both the patient and the study team, the extra resources required, and a lack of understanding of the potential value of the information gained. Blood-based biomarkers and non-invasive biomarkers such as radiomics and molecular imaging may be less cumbersome and risky than tissue biopsies, and thus likely to be more readily implemented.

Biomarker assays must be validated across patient samples and clinical settings, ideally in biospecimens with standardized, straightforward collection procedures. The biologic signal of interest should be highly stable, so that tissue formalin fixation time, or time from blood collection to centrifugation and/or cryopreservation, will not significantly alter a protein or genomic signal. The biomarker assay must be performed consistently across locations and operators, and ideally not require highly specialized training. Finally, while significant investment is required for assay development and standardization, the ultimate biomarker for clinical use should incur minimal expense to facilitate future global implementation to guide routine clinical use of the drug.

CLINICAL TRIAL OPERATIONS AND ECOSYSTEM OPPORTUNITIES

The complexity of biobanking processes, procedures, and ethics during the conduct of clinical trials reflects the clinical trials operations landscape beyond IO and cancer, which is fraught with inefficiencies and challenges. The focus of the manuscript is US-centric, but it is critical to recognize that inefficiencies in systems supporting clinical trials also affect the clinical trial enterprise outside the USA. Some of these inefficiencies are shared with the USA, but others are unique, and often related to differences in regulatory oversight between countries. Difficulties in protocol development, regulatory approvals, site selection, patient enrollment, retention, and data collection/analysis are so significant that only approximately 12% of clinical trials are ultimately successful.[56] The intricacies of trial execution and design preclude many community sites from participating in clinical trials, thereby limiting both patient access and the diversity of patients enrolled in potentially life-saving cancer therapies. Ultimately, this slows the approval of new therapies. Indeed, cancer clinical trial offices at North American cancer centers have a median annual operating budget of US$8.2 million and more than 100 employees to accommodate the required financial, regulatory, clinical and data operations requirements.[57] While many patients with cancer express interest in participating in clinical trials, especially those with poor prognosis and limited treatment options, other patients do not trust the medical establishment that sponsors clinical trials and fear they will be treated as "guinea pigs". Patients who are interested in trial participation often have difficulty identifying trials for which they are eligible, or encounter financial, travel, time, or other impediments that discourage them.

One proposed strategy to improve trial operational efficiency is the centralization of clinical research resources required for site selection and study start-up. Currently, trial sponsors and contract research organizations routinely request redundant and/or non-essential information, causing delays, increased burdens on research staff, and increased costs. Recommendations from a 2020 American Society of Clinical Oncology (ASCO) Task Force, formed to assess burdens and challenges with feasibility assessments (FAs), include: (1) implementing a streamlined and uniform FA process across trials and sponsors; (2) minimizing and standardizing questions; and (3) leveraging technology to centralize FAs, facilitate communications, and reduce redundancies.[58] Implementing these strategies will allow greater focus on factors identified as crucial site-related qualities, including the ability to reach enrollment goals and meet necessary data quality standards.[59]

Achieving enrollment goals is also contingent on reasonable and applicable eligibility criteria. In the current competitive cancer therapy approval landscape, eligibility criteria have become increasingly restrictive, creating unnecessary barriers to patient access.[60–62] A recent systematic evaluation of the effect of different eligibility criteria on cancer trial populations and outcomes with real-world data using an AI computational framework suggests that many patients who were not eligible under the established trial criteria actually could potentially benefit from the investigational treatments.[63] Additionally, trials with more relaxed eligibility thresholds (eg, bilirubin, platelets, hemoglobin and alkaline phosphatase) did not have increased treatment withdrawals due to adverse events compared with trials with more stringent eligibility thresholds across different types of cancer.[63] Similarly, a 2022 LUNGevity Foundation working group, convened to streamline lung cancer

clinical trials, identified 13 common eligibility categories with key factors to consider during development to prevent unnecessary limitations.[60]

Maximizing the efficiency of clinical research operations is also key to implementing clinical trials, accruing participants, obtaining quality data, and delivering new IO drugs to patients. The National Cancer Institute (NCI) Clinical Trials and Translational Research Advisory Committee (CTAC) put together a Strategic Planning Working Group in 2019 to work toward a vision of "flexible, faster, simpler, less expensive, high-impact trials that seamlessly integrate with clinical practice".[64] Recommendations from their Streamlining Clinical Trials Working Group provide a framework to build on and include streamlining data collection, use of standard practice data principles and data elements, and optimizing the use of electronic health records (EHR) to support clinical trials through efforts such as data extraction and EHR study builds.[65] These recommendations directly impact clinical trial sites and their participation in studies. Ensuring that sites have a voice in the development of these key strategies is critical at both the national as well as the local level. The inclusion of site research leaders and study coordinators at every level of protocol design and implementation will also help facilitate better operational clarity and feasibility. This practical, real-world line-of-sight could reduce logistical barriers, provide feedback to improve study processes such as slot and cohort management, and identify potential budget, contractual, billing, and compliance issues that could lead to delays and future protocol amendments. Participating in networks and consortia such as the National Cancer Institute Clinical Trials Network (NCTN) is one way to maximize access to trials and the efficiency of clinical research operations while potentially reducing administrative and regulatory redundancies. This allows research staff more time to focus on meeting enrollment goals and working with investigators to ensure good clinical practice and care.

Increasing diversity in clinical trials is a pressing priority in cancer research. Recognizing that people enrolled in oncology clinical trials tend to be younger, healthier, and less racially, ethnically, and geographically diverse than people seen in clinics, the FDA issued a draft guidance for diversity plans to improve enrollment of trial participants from underrepresented racial and ethnic populations.[66 67] As about 20% of drugs have different effects based on a patient's race, concerted efforts are urgently needed to recruit diverse patient populations to investigational studies to ensure that approved cancer therapies are safe for all.[68] Ochsner Health, comprised of 46 hospitals and 370 clinics and urgent care centers in Louisiana, prioritized minority enrollment in clinical trials as an institutional goal in 2023. To achieve this goal, they conducted a multimedia campaign to educate patients, created a Center of Health Equity with Xavier University, engaged the community, formed a patient council, implemented housing and transportation programs to reduce barriers to clinical trial enrollment, and created a pipeline of research staff from the community. Through these efforts, which have been similarly validated in other settings, Ochsner achieved 36% minority enrollment in clinical trials for 2023.[69] Additional considerations for achieving diversity in clinical trials include LGBTQ+, elderly, and disabled patients. Emerging guidance[70] and support for the implementation of Decentralized Clinical Trial activities will also provide research sites with greater ability to provide some trial-related activities at locations beyond traditional clinical trial sites, thus broadening access for patients and community partners.

Workforce shortages have affected goals for efficient and representative clinical trial enrollment, with 63% of US-based clinical research sites identifying staffing and retention as the top research challenge.[71] Due to a lack of career development opportunities, key members of the clinical trial team, such as data managers, study coordinators and research nurses, work in these settings for short periods of time before moving on to a better-defined career path.[72] Opportunities to reduce dissatisfiers include improved clarity in protocols and data submission requirements, reduced collection of unnecessary data, streamlined regulatory and rostering processes, increased consistency and standardization between sponsors and research bases, improved clinical trial accessibility for underserved populations, centrally provided protocol-specific EHR treatment plans, and centralized training for research staff and investigators. These recommendations were developed by a cross-network Research Operations Working Group, comprised of representatives from NCI Oncology Research Program (NCORP)/NCTN Research Bases (Southwest Oncology Group (SWOG), Alliance, NRG [**NRG** Oncology is a NCTN group created through the coordinated efforts of the National Surgical Adjuvant Breast and Bowel Project (**N**SABP), the Radiation Therapy Oncology Group (**R**TOG), and the Gynecologic Oncology Group (**G**OG)] and Eastern Cooperative Oncology Group-American College of Radiology Imaging Network [ECOG-ACRIN]), then shared with NCTN, NCORP and CTAC leaders, and are currently being implemented. Pilot projects are also underway with several NCTN groups related to direct electronic medical record to electronic data capture data collection.

Advanced practitioners (APs) (including nurse practitioners and physician assistants) represent a growing and critical component of the oncology workforce with more than 80% of US oncology practices employing APs, many of whom function in research roles.[73] Recent revisions in NCI's Cancer Therapy Evaluation Program (CTEP) policies allow APs to register as enrolling investigators and sign treatment orders for investigational agents without a physician co-signature.[73] Future research frameworks should consistently include AP researchers in critical research activities including feasibility reviews, assessment of enrollment goals, site initiation visits and investigator meetings. Successful diversification of the clinical trial workforce must include a broad array of professions. Opportunities to foster professional advancement for all

members of the research team should be identified and implemented.

CONCLUSION

Cancer IO has clearly demonstrated its power over the last decade as the first wave of immune-based drugs transformed the patient experience. The field is now clearly at an inflection point. Discovery and translational researchers effectively leveraged the science of IO to create a robust and heterogeneous pipeline of highly innovative, first-in-class immunotherapies with significant therapeutic promise. These unique agents clearly require further innovations in clinical, manufacturing, and regulatory science for their effective delivery to patients and providers. A major barrier in bringing these new IO drugs to patients is the clutter and redundancy built into the current clinical trials ecosystem. SITC highlighted this challenge in its program on the Crisis in Clinical Research, advocating for key reforms that will streamline clinical trial operations across the stakeholders in the drug development ecosystem. From a research perspective, deploying efficiencies in clinical trial design and incorporating the use of surrogate clinical endpoints that reflect long-term clinical benefit at early time points will accelerate clinical progress. Appropriate patient stratification based on clinical variables, histopathological features, or discrete biomarker expression in clinical trials will further hasten drug development. The analysis of baseline, on-treatment, and post-progression clinical trial biospecimens will lend important insights into mechanisms of IO response, resistance, and toxicity, enabling biomarker-driven patient selection and management. Safely moving investigational therapies from advanced disease into the neoadjuvant or adjuvant settings should also accelerate progress since the therapeutic impact in the early disease setting is likely much greater. The landscape of promising immune-based strategies for the interception of developing malignancy and upfront immunoprevention in high-risk individuals is also growing.

SITC has prioritized multiple programs designed to capitalize on these opportunities by maintaining open dialog and integrating the thinking of key drug development stakeholders. The SITC Drug Development Symposium in fall 2024 is newly updated. It is designed to deliver foundational information, and facilitate vibrant and open discussion among key around the most impactful opportunities and pressing challenges in IO drug development today. Programming at SITC's 2024 Annual Meeting included a symposium on TIL therapy, and a workshop on immunoengineering. The SITC Spring Scientific in 2025 will focus on cell therapy for solid tumors. Society initiatives designed to inform patient stratification and selection are focused on primary and secondary IO drug resistance, and the critical role of informative biomarkers in accelerating IO drug development. The Society has convened roundtables with biotech, pharma, and the FDA to discuss surrogate clinical endpoints as a near-term measure of long-term clinical benefit to hasten drug approval timelines, and release criteria for complex biologics such as cell-based therapies. SITC has a major focus and investment in developing the next generation of discovery, translational, and clinical investigators, and offers numerous programs to support them. We offer numerous travel awards to the annual meeting, and the prestigious Presidential award goes to the highest-ranked abstract by an early career investigator. We have also implemented a 1 day program at the annual meeting designed to introduce biomedical research and practice to undergraduates from underrepresented groups in the community where the annual meeting is held. We also support the careers of new investigators through research fellowship awards, the annual SITC Winter School focused on fundamental IO and the concurrent SITC Clinical Immuno-Oncology Network (SCION) program focused on developing high-quality clinical protocols. SITC collaborates with the Association of Cancer Care Centers (ACCC) to reach community clinicians, and offers clinician training through its Advances in Cancer Immunotherapy (ACI) program. SITC will continue to use its "big tent" approach to foster dialog that engages and integrates diverse members of the drug development community, including academia, biotech, pharma, the financial community, the FDA, the NCI, community oncologists, and patients themselves, with the goal of synergistically working together to rapidly bring the latest innovative cancer immunotherapies to the patients waiting for them.

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