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The Future of Clinical Trials Design in Oncology

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Abstract

Clinical trials represent a fulcrum for oncology drug discovery and development to bring safe and effective medicines to patients in a timely manner. Clinical trials have shifted from traditional studies evaluating cytotoxic chemotherapy in largely histology-based populations, to become adaptively designed and biomarker driven evaluations of molecularly targeted agents and immune therapies in selected patient subsets. This review will discuss the scientific, methodological, practical and patient-focused considerations to transform clinical trials. A call to action is proposed to establish the framework for next generation clinical trials that strikes an optimal balance of operational efficiency, scientific impact and value to patients.

Introduction

Clinical trials are critical engines for the discovery and development of new therapies. They represent a cornerstone to provide objective and evidence-based answers to the most important questions. Over the past decade, clinical trials have evolved extensively to translate biological drivers of cancer and their vulnerabilities into therapeutic opportunities. Notable trends that mark the current generation of clinical trials include a shift from the evaluation of cytotoxic agents to an increasing number of investigations focusing on molecularly targeted agents and immuno-oncology compounds. From a scientific perspective, the testing of new drugs or drug combinations has shifted from empiricism to hypothesis-driven and biomarker-based studies. These studies are enhanced in their patient selection and endpoint determination through the application of innovative trial design and integration of modern technology. While cooperative groups remain as key trial sponsors, especially for large randomized phase III studies that evaluate potential practice-changing approaches against standard of care, the pharmaceutical sector has played a growing role in all phases of clinical research. Regulatory agencies have been responsive to these trends by providing guidance in many facets of clinical trials, as well as establishing new paths for accelerated drug approval. Patient-reported outcomes are being actively incorporated into clinical trials using instruments and digital tools that are user-friendly. To a large extent, these changes in clinical trials are driven by the urgency to bring effective medicines to patients while maintaining close monitoring of patient safety and pharmacovigilance.

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Continued efforts from all stakeholders are required to overcome many challenges that persist in clinical research, including the modest success rates from human entry to approval, low clinical trial participation rates especially in minority and underserved populations, increasing complexity and demands for trial operations, inadequate infrastructure and limited funding to support research, and difficulties in the knowledge translation of trial data to meaningful clinical practice.

This overview will focus on scientific, methodological, and practical considerations to transform clinical trials in the next era. In addition, it will emphasize the importance of data sharing and post-approval surveillance, address emerging priorities in clinical research, and highlight the need to train and mentor early career investigators as future leaders (Figure 1). Lastly, a call to action is articulated to invigorate the clinical trials framework to strike an optimal balance of operational efficiency, scientific impact and value to patients.

Key Considerations for Innovation in Clinical Trials

Scientific Considerations

Increase in Forward and Backward Translation—The traditional drug development paradigm is linear with nonclinical testing using *in vitro* and *in vivo* models for candidate selection based on therapeutic index, followed by human evaluation in a stepwise manner to determine safety, antitumor activity and comparative efficacy versus standard treatment. Correlative studies are an important component of clinical trials to establish proof of mechanism and identify predictive biomarkers in tumor and surrogate tissues. An example of traditional linear drug development is illustrated by the multikinase inhibitor sorafenib. Nonclinical evaluation of sorafenib focused on its inhibitory effects on Raf1 kinase, even though its *in vitro* IC_{50} values were subnanomolar for multiple kinase targets including VEGFR1, 2 and 3, PDGFRβ, c-Kit and RET. *In vivo* testing in a cell line colorectal cancer xenograft model demonstrated tumor growth inhibition without a detectable reduction in phosphorylated ERK, implicating an alternative mechanism of antiproliferative effects, rather than via blockade of the mitogen-activated protein kinase (MAPK) pathway (1). Four phase I clinical trials in patients with advanced solid malignancies identified objective responses in renal cell and hepatocellular cancers (2). Such antitumor activity led to the rethinking of sorafenib being a multikinase antiangogenic agent rather than a Raf kinase inhibitor as was originally conceived. Multiple phase II and III studies ensued and led to the drug's approval for advanced renal cell cancer in 2005. The overall development timeline from initial lead compound identification to regulatory approval took eleven years (1).

A circular drug development pathway that includes iterative feedback from bench to bedside and back, may expedite the process in several steps along the way. For instance, molecularly characterized *in vivo* and *in vitro* models such as patient-derived organoids and patient-derived xenografts may reveal histologies and genomic aberrations that are most sensitive or resistant to the investigational drug or drug combinations, thus offering additional insights into putative mechanisms of action. The United States National Cancer Institute (NCI) has established a Patient-Derived Models Repository that is available for distribution to the research community through material transfer agreements (https://pdmr.cancer.gov/models/database.htm). Tumor biopsies and circulating tumor cells prospectively collected from

cancer patients following progression on treatment can be used to create patient-derived models to assess mechanisms of primary and acquired resistance. This type of "bedside-to-bench" evaluation was exemplified by the work of Cocco et al. (3) in patients with *NTRK* fusion-positive tumors with acquired resistance to larotrectinib but were not found to harbor *TRK* kinase domain mutations. Nonclinical evaluation of patient-derived xenografts from biological samples collected at disease progression detected off-target resistance, mediated by genomic alterations that led to activation of the MAPK pathway. Such data garnered from biological samples of patients enrolled in clinical trials testing new drugs may inform on optimal combinations to pre-empt therapeutic resistance. The treatment of *BRAF V600E*-mutant colorectal cancer using a combination of EGFR, BRAF and MEK inhibitors is another example of how a continuous feedback loop between laboratory research and clinical testing led to an effective regimen to overcome resistance to BRAF inhibitor therapy in this setting (4,5).

Modern Technologies for Molecular, Immune and Imaging Characterization— Clinical trials have evolved with advances in technology which have provided the tools necessary to characterize tumor cells, their microenvironment and immune contexture. Tumor molecular characterization using next-generation sequencing (NGS) is increasingly performed in routine practice to enable biomarker-selected clinical trials, even during the earliest phase of dose finding with first-in-human investigational agents. Despite these advances, trial eligibility criteria remain generally narrow with molecular selection typically based on the detection of single gene alterations or protein expression in archival tumor specimens; and antitumor efficacy is often evaluated with static, linear measurements of target lesions. In the future, integration of novel, multi-dimensional biomarkers, such as whole exome or genome-based mutation signatures (6), digital spatial profiling of proteins or RNA in the tumor immune microenvironment (7), and radiomic analysis of quantitative features extracted from standard-of-care imaging (8), will be applied to improve patient stratification. These platforms might be particularly relevant to identify druggable targets for patients whose tumors lack clinically actionable oncogenic driver mutations. Artificial intelligence (AI) and machine learning platforms (9) along with the ability to track clonal dynamics with circulating tumor (ct)DNA monitoring (10) may allow for trials testing personalized drug-combinations with adaptive drug dosing that balances competitive interactions between drug-sensitive and drug-resistant clones (11). Post-progression tumor biopsies, ctDNA collection, and research rapid autopsy programs (12) will increasingly be applied to understand mechanisms of adaptive resistance to experimental drug treatments.

Cancer Interception Trials for Molecular Residual Disease—After the establishment of safety and tolerability in early phase studies, initial efficacy evaluations of novel agents or combinations are typically conducted in patients with advanced metastatic disease. With some notable exceptions, such as molecularly agents that target oncogenic drivers (e.g. EGFR inhibitors in *EGFR* mutant non-small cell lung cancer) and anti-PD-1/L1 antibodies in inflamed tumors, most active new drugs produce only modest benefits in patients with recurrent and/or metastatic cancers. In order to achieve larger magnitude gains in survival, promising regimens must be tested in patients with curable malignancies who have undergone definitive treatment but are at high risk of relapse. Cancer interception is the

active intervention of cancers at an early stage, offering an opportunity to eliminate molecular residual disease (MRD) before clinical relapse (13). MRD describes the state in which cancer-derived biomarkers are detectable, typically using highly sensitive and specific molecular assays in blood or other body fluids that are below the threshold of detection by conventional tests such as radiological imaging (14). Interception or “nip in the bud” clinical trials that evaluate adjuvant or maintenance treatment in MRD settings are challenging to conduct. These studies must not only identify patient subsets who would benefit from additional interventions with an acceptable therapeutic index, but they often require lengthy follow-up to observe sufficient events in time-based endpoints such as relapse-free survival. The choice of systemic agents being administered should be justified based on the biological rationale and their therapeutic index. For instance, as hyperprogression has been reported as a pattern of disease progression in some patients with immune checkpoint inhibitors and there is no clear-cut way to pre-identify such patients (15), thus the use of these agents in interception trials must be carefully considered and accompanied by close ctDNA monitoring.

The emergence of liquid biopsies coupled with ultra-sensitive assays to detect low levels of ctDNA has led to the development of interception clinical trials (e.g. *ACTRN12615000381583,* NCT03145961, NCT03832569, NCT04385368). While not all tumors at risk of recurrence shed ctDNA into the bloodstream or other body fluids, the ability to quantify those that do, enables the application of ctDNA clearance as a short-term surrogate endpoint to correlate with relapse-free survival. In a recent pan-cancer cohort of 73 patients with advanced solid tumors treated with the PD-1 immune checkpoint inhibitor pembrolizumab, early clearance of ctDNA measured using a tumor-informed bespoke (individualized) 16-variant panel identified patients with long-term overall survival (OS) (16). These findings have been corroborated using other ctDNA platforms besides bespoke panels (17). Integration of additional blood-based biomarkers (e.g. blood-based tumor mutational burden, immune cell proportions) with ctDNA kinetics may further improve the accuracy of immunotherapy response prediction (18). Other technologies that have demonstrated potential relevance in the MRD setting include whole genome sequencing of ctDNA based on the cumulative signals from thousands of somatic mutations harbored by many solid tumors (19). It is expected that over time, an increasing number of interception clinical trials will be conducted, investigating new drugs or drug combinations that have demonstrated an adequate safety profile as well as established evidence of antitumor activity in the recurrent or metastatic setting.

Another area of growing interest is the use of genome-wide epigenetic profiling that simultaneously assesses multiple cancer-specific DNA-methylation marks in liquid biopsies. Distinct patterns of differentially methylated regions can be measured within plasma ctDNA for different cancer types and subtypes. This approach is actively being pursued in early cancer detection (*e.g.* NCT02889978 and NCT03085888) and may ultimately lead to a new generation of primary prevention studies when the sensitivity of such assays become sufficiently high to justify their cost utility (20). Furthermore, the application of methylated ctDNA in the evaluation of MRD is of great interest, as it has the potential to provide a greater sensitivity than mutation-based ctDNA testing, and may enable detection in tumor

types where there is a low frequency of somatic mutations without the need for bespoke panels (21).

Design and Methodological Considerations

Phase I-II-III Paradigm: What Needs to Stay, What Needs to Go?—Clinical trials are divided into phases to provide key decision points during the drug development path of an investigational agent to continue or stop. Phase III trials represent the most costly step with respect to resource utilization and financial expenditure, due to their large sample size as well as their long duration of enrollment and follow-up before analysis of the primary endpoint. As such, at least two main checkpoints are in place to decide if an investigational treatment should be tested in a large randomized phase III trial. The first checkpoint is the phase I-II transition when safety, tolerability and preliminary antitumor activity have been evaluated, to determine if a new treatment should be examined for efficacy in histology-based or histology-agnostic, molecular-based cohorts of modest size, as either single-arm or randomized studies. The second checkpoint involves a go-no-go decision based largely on efficacy signals observed at the completion of focused phase II trials, which typically employ objective response rate (ORR) as an endpoint in single-arm studies, or progression-free survival (PFS) in randomized studies. Despite these checkpoints, the success rate of new anticancer agents that enter clinical testing that achieve regulatory approval is low. A recent review by Wong et al. analyzed 17,368 drug development paths (defined as the investigation of a particular drug for a single indication) from January 1, 2000 to October 31, 2015 and reported an overall probability of success rate of only 3.4% in oncology (22). Importantly, the overall success rate was much higher in those utilizing biomarkers as a selection strategy than those that did not (10.7% *versus* 1.6%).

In the last decade, seamless oncology clinical trials have emerged which blur the lines between the three sequential phases of drug development. To some extent, this phenomenon is driven by the urgency to expedite drug approvals to transform cancer care (23). There are notable examples of first-in-human seamless trials (e.g. KEYNOTE-001, CHECKMATE-040) that have achieved accelerated approval of promising anticancer agents in record time (24,25). Conversely, many other agents tested in large, seamless phase I/II trials with multiple parallel cohorts have failed to produce clear readouts of antitumor activity to inform future clinical development decisions. Drugs or drug combinations with compelling signals of antitumor activity observed during dose escalation may benefit most from the efficiency of seamless trial designs, especially for rare disease types or biomarker subsets.

Tissue-agnostic drug development represents another paradigm that has evolved in recent years due to an increasing understanding that specific oncogenic drivers or dependencies are shared across multiple tumor types. Histology-agnostic basket trials have led to accelerated approvals for pembrolizumab in microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors, or those with high tumor mutational burden; as well as larotrectinib and entrectinib in *NTRK*-fusion positive advanced solid tumors. These are typically single-arm studies consisting of multiple tumor types lacking a comparator arm as it is challenging to have a common control therapy, and the high objective response rates

achievable with these drugs preclude randomization in patients with limited alternate options. These agents may subsequently be evaluated in randomized, histology-specific studies in earlier disease settings, such as KEYNOTE-177 which compared pembrolizumab against standard chemotherapy as first-line therapy in patients with unresectable or metastatic MSI-H/dMMR colorectal cancer (26).

Clinical trial designs should not be “one size fits all”, the dynamic assessment of safety and early efficacy signals from dose and schedule finding studies may inform on the most optimal next steps. This may take the path of the traditional paradigm of distinctive trial phases, or morph to seamless or tissue-agnostic designs to speed up subsequent steps. Regardless of the strategy, investigators must comply with established scientific, ethical and biostatistical principles and standards to ensure data integrity and study subject protection (27).

Adaptive and Agile Clinical Trial Design—The speed of medical innovation can outpace the conduct of traditional randomized clinical trials (RCTs), rendering their results less relevant. The KEYLYNK-010 (NCT03834519) study in men with metastatic castration resistant prostate cancer is an example of an RCT impacted by the shifting landscape of standard of care options during its lifetime. This phase III trial randomizes patients who have received an androgen signaling targeted inhibitor (abiraterone or enzalutamide) and docetaxel chemotherapy to either olaparib (poly-ADP ribose polymerase inhibitor) with pembrolizumab or the comparator ‘physician’s choice treatment’ arm (abiraterone or enzalutamide, whichever not administered prior). Almost a year after the study launched, the CARD trial (28) published in December 2019, established cabazitaxel as the new standard of care, thus rendering the KEYLYNK-010 comparator arm as outdated. Adaptive study designs such as the multi-arm multi-stage (MAMS) design utilized in the STAMPEDE trial (NCT00268476) or the platform design used in the I-SPY2 trial (NCT01042379) may provide solutions to address these issues. STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) is a multi-national, randomized phase III trial that evaluates multiple treatments in separate cohorts for patients with high risk or metastatic castration sensitive prostate cancer. Similarly, I-SPY-2 (Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2) randomizes patients with locally advanced breast cancer to receive one of several experimental regimens in the neoadjuvant setting, in addition to a number of exploratory biomarker and imaging investigations.

The MAMS design permits many agents (multi-arm) of interest to be tested simultaneously against a standard control arm in a RCT, with recruitment discontinued in arms that do not show sufficient activity based on an appropriate surrogate endpoint (29). In contrast, arms that demonstrate sufficient activity can continue recruitment until enough patients are enrolled to assess the primary endpoint. In STAMPEDE, once the docetaxel arm demonstrated superiority over the control arm, the study was amended to discontinue enrollment on the “old” control arm and to perform new pair-wise comparisons between the docetaxel arm (“new control”) and the currently recruiting experimental arms. This design in the phase III setting can result in drug approval and registration, as demonstrated by the European Medicine Agency (EMA)’s approval of abiraterone and docetaxel for men with

metastatic castration sensitive prostate cancer, based on the STAMPEDE results. Furthermore, using the MAMS design, a trial can adapt and add new therapies of interest without having to design and launch a new, separate study. In the example of KEYLYNK-010, to address the evolving standard of care, a MAMS trial could add a new arm (cabazitaxel) or drop an arm (androgen inhibitor). Similar to multi-arm designs, multi-stage (e.g. phase II/III) designs can be cost efficient due to their flexibility to transform phase II into phase III arms such that results may be acquired faster and requiring fewer patients overall.

Adaptive platform trials can investigate multiple experimental therapies for a specific tumor indication in a continual manner, with different pharmacological interventions added or removed based on predefined thresholds for success or failure (30). In addition, further adaptations can be implemented such as: 1) response-adaptive randomization whereby rules to assign participants to an arm with a higher degree of success based on specific patient or tumor related features; 2) adaptive sample size enrollment that uses the amassed data to re-estimate treatment effect and consequently the optimal study sample size; and 3) interim updates which permit the adaptive design to be updated based on the accrued information from the trial. The I-SPY-2 trial is a well-known example of the adaptive platform design and to date this study has tested 17 experimental regimens combined with one chemotherapy regimen in the neoadjuvant setting in locally advanced breast cancer patients with ten predefined biomarker profiles (31). Over the last ten years, the I-SPY-2 trial has graduated six regimens through to phase III trials each with a high probability of statistical success (https://www.ispytrials.org/results/past-agents).

To be successful, MAMS and adaptive platform studies require significant collaboration between multiple industry, regulatory and academic stakeholders, as demonstrated by the STAMPEDE and I-SPY2 studies. Innovative clinical trial designs and approaches that are adaptive and dynamic are needed to advance this rapidly growing field, taking the two most important resources into consideration, our patients and their time.

Designing “Smart” Clinical Trials Based on Big Data Initiatives and Real World Evidence—RCTs are the gold standard for evaluating new cancer treatments. With the rise of precision medicine, there are a growing number of rare indications for which RCTs are infeasible. Trials that randomize to an investigational treatment versus an active control (standard therapy or placebo) can be hampered by slow accrual or a high rate of dropout in the control arm when the investigational treatment, or other treatments in the same drug class, are accessible “off study”. External control arms with patient-level matched data from historical clinical trials, or electronic medical record (EMR) and administrative claims information from routine practice can be used to evaluate the comparative and cost-effectiveness of new cancer treatments. These data are often utilized to support regulatory applications (32), label expansion (33) and health technology applications for reimbursement in publicly funded health care systems (34). Commercial enterprises, such as Roche’s Flatiron Health, Medidata Systems’ Acorn AI, and IQVIA, have recently demonstrated the value of aggregating diverse sources of “big data” to generate real world evidence (RWE) to accelerate drug development. The United States Food and Drug Administration (FDA) (https://www.fda.gov/regulatory-information/search-fda-guidance-

documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance), EMA (https://www.ema.europa.eu/en/documents/other/hma-ema-joint-big-data-taskforce-phase-ii-report-evolving-data-driven-regulation_en.pdf), and Health Canada (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html) have recently published guidance for the application of RWE to regulatory decision making. Successful examples of RWE to support a new indication or label expansion approved by the FDA include blinatumomab for Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia, avelumab for metastatic Merkel cell carcinoma, and palbociclib for hormone receptor positive, HER2-negative, metastatic male breast cancer.

Deciphering RWE from the experience of patients outside of RCTs is challenging (35). Patients frequently receive medical care at multiple hospitals during their cancer journey, with stand-alone EMR systems that are not interconnected. Genomic testing may be performed by commercial laboratories, with results that are not linked to hospital EMRs. Pathology, drug treatment, toxicity, and radiographic response data may exist in free-text physician dictated clinical notes, as well as unstructured pathology and radiology reports that require manual curation for research use. Protection of identifiable patient information from privacy attacks in aggregated genomic data sets can also be problematic (36). Notwithstanding these complexities, several academic consortia have been formed, such as The Cancer Genome Atlas (TCGA), the American Society of Clinical Oncology (ASCO)'s CancerLinQ, the American Association for Cancer Research (AACR) Project GENIE, Moffitt Cancer Center's ORIEN, and the International Cancer Genome Consortium (ICGC), to enable clinical and genomic data sharing. However, clinical annotation of genomic records is often rudimentary, with information restricted to age, gender, tumor type, and the tissue sample profiled. Generation of RWE from these registries that includes longitudinal information about treatment and survival outcomes requires trained personnel available at academic medical centers to curate EMRs on an ongoing basis. Natural language processing (NLP) technologies capable of automated data extraction brings promise to assist with, or ultimately replace such tasks. AACR Project GENIE recently demonstrated that such deep clinical curation is feasible to better define the natural history of a rare genomic subtype of breast cancer (*AKT1 E17K* mutation) (37). Aggregating data across multiple institutions for large cohorts is complicated, and several initiatives, such as ASCO's mCODE (https://mcodeinitiative.org/) and PRISSMM (38) from the Dana Farber Cancer Institute, are developing standardized data elements that can be applied to EMR data using NLP and AI-based tools. Enabled by collaboration with the pharmaceutical industry, a larger scale initiative through Project GENIE is ongoing to curate detailed clinical and genomic records from more than 50,000 patients using the PRISSMM data model that will be made publicly available (39). Greater access to data can help oncologists make evidence-informed treatment recommendations for patients with clinically actionable genomic alterations when trial-level results do not exist and enable more streamlined biomarker-focused clinical trials. Informatics tools that link patient-specific information from EMRs to genomically-annotated clinical trial registries (40–42) may also facilitate individual patient matching to accelerate accrual to clinical trials for rare genomic sub-populations.

Patient Reported Outcomes (PROs)—Incorporation of patients' perspective in clinical trials can provide vital information on the burden of symptoms, the tolerability of treatment related side effects and the impact of interventions on patients' health related quality of life (HRQOL). To be effective, such patient reported outcomes (PRO) need to be collected by validated tools such as the Functional Assessment of Cancer Therapy-General (FACT-G) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), then analyzed and reported correctly. However, several challenges exist with integration of PROs in clinical trials such as, inadequate description and design of PRO content in protocols; delayed or under-reported PRO data; missing data especially from patients who become too unwell to provide PROs due to disease progression or drug related adverse events; lack of longitudinal data collection particularly in patients lost to follow-up or unable to attend in person visits; and assessment of clinical actionability of data collected in real-time from PRO items (43). To address these and other issues, the Patient Reported Outcome Tools: Engaging Users and Stakeholders (PROTEUS) Consortium seeks to guide the appropriate use of PRO tools and reporting of PRO data to ensure that this information from clinical trials is disseminated to patients, clinicians and regulators to drive treatment decisions. The Consortium recommends specific tools and resources such as the Standard Protocol Items: Recommendations for Interventional Trials-PRO Extension (SPIRIT-PRO) guidelines, Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAOQOL) and International Society for Quality of Life Research (ISOQOL) standards to improve PRO measurement, implementation, analysis and reporting in clinical trials in order to maximize the value of these data (44–46). PROs are critical to the assessment of the risk benefit balance of investigational therapies and new strategies to enhance their collection represent key priorities in this area of research.

Technology presents opportunities to obtain important patient data on cardiac, respiratory, dietary and general function in addition to other aspects of HRQOL that trial treatment may impact. Wearable devices that contain sensors, smart phone and computerized applications for symptom monitoring, digital questionnaires, virtual teleconferencing and telemedicine, AI and cloud-based platforms are among some of the innovations that can be integrated into clinical trials to facilitate PRO data collection. These technologies will enable PRO data integration to identify meaningful trends that would provide a better evaluation of the efficacy and value of clinical trial treatments. Incomplete questionnaires and missing data have been a major limitation for PRO collection. The missing data problem may be mitigated by an ePRO pilot app that has been developed by the NCI. This app can be downloaded onto android and iOS devices to prompt patients to complete items from the PRO-Common Terminology Criteria for Adverse Events (PRO-CTCAE) at protocol defined time points (https://ctep.cancer.gov/initiativesprograms/docs/ePRO_ETCTN_Supplement_Announcement.pdf). The goal of the PRO-CTCAE is to provide the patient experience of symptomatic adverse events and is designed to complement data collected by clinicians using the CTCAE. As of October 2020, clinicaltrials.gov listed 51 completed or active oncology trials that utilized wearable technologies including Fitbit, Everion, mHealth and Actigraph amongst other devices. In addition to providing more PRO information, these technologies may facilitate trial conduct

by allowing more comprehensive remote patient assessments, reducing unnecessary in-person visits and decreasing the burden of trial participation on patients. Despite the obvious practical advantages, wearable technologies are yet to be widely implemented in oncology clinical trials due to the perceived challenges of managing, storing and interpreting the large volumes of data generated; concerns around safety, security and privacy of the data collected; differences in data standards across various devices leading to harmonization and reliability concerns (47). To deal with these issues, regulatory agencies such as the US FDA have provided a framework to establish standards for wearable technologies with clinical and research applications (https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/UCM568735.pdf). PROs and mobile health technologies present opportunities to capture and measure more accurately the patient experience on clinical trials, which will provide crucial information on the risk-benefit assessment for all experimental interventions.

Post-Approval Surveillance and Data Sharing

Importance of Post Approval Surveillance and Reporting—The development and approval of cancer drugs is a long and arduous process. Health regulators have taken initiatives to speed up the approval process for new medicines. These accelerated approval pathways allow approval of investigational cancer drugs through the demonstration of benefit based on surrogate measures (e.g. ORR or PFS) instead of definitive endpoints (e.g. OS), enabling drugs to be rapidly available to patients. Within the US FDA, accelerated approval of oncology drugs has increased steadily since its inception in 1992 (https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review) (48), with over 120 different indications (48,49). Table 1 demonstrates an increasing proportion of initial FDA approvals of oncology drugs via the accelerated approval mechanism in the past five years. In one report, the FDA accelerated approval program hastened oncology early drug accessibility by an average of 3.9 years, compared to regular drug approval (50). Despite the apparent advantage, it is crucial to recognize the clinical and scientific trade-offs of accelerated approval pathways in oncology.

Most accelerated approval pathways require a subsequent confirmatory post-approval clinical trial. Failure to complete this could result in the removal of the accelerated approval indication from the market. Despite this requirement, the due diligence in conducting post-approval trials to confirm clinical benefit has been suboptimal. In a review of 47 accelerated approvals, confirmatory trials were not reported for 14 of these indications, with several exceeding five years with no report (50). Furthermore, only approximately 20% of accelerated approval indications subsequently report confirmatory trials with an OS benefit (51). Of greater concern, there was no change in regulatory approval despite the failure of confirmatory trials to show an OS advantage, with examples being provided in Gill et al (49). For instance, the initial accelerated approval for nivolumab in metastatic small-cell lung cancer, based on the CHECKMATE-032 trial (NCT01928394), was continued despite the negative results of the phase III CHECKMATE-331 trial (NCT02481830).

Some steps may be implemented to enable the challenging tasks faced by the regulatory authorities in balancing patients' needs for novel therapies against the safety and meaningful

benefit of drugs. First, accelerated regulatory approvals should only be granted once confirmatory trials have commenced with strict adherence to planned timelines and milestones to maintain approval status. Accelerated approval should only be granted if following the regular approval pathway would result in a significant delay for patient access, such as when a confirmatory trial result is not likely to be available in the foreseeable future. Second, when considering surrogate endpoints for accelerated approvals, the validity of the surrogacy, as it pertains to disease site or treatment type, must weigh heavily on the approval decision to reduce the risk of approving ineffective agents. Third, accelerated approvals should genuinely address areas of unmet need. Multiple approvals for the same drug class in same disease type without a clear improvement in therapeutic index should be avoided. Fourth, the drug regulatory agencies will need continued vigilance and diligence for removing agents based on the results collected from post-approval confirmatory trials and/or RWE in a swift and timely manner. Failure to do so may not only lead to financial costs but may cause harm to patients due to unnecessary drug exposure. While regulatory decisions to continue or discontinue an approval can be complex and based on multiple factors such as shifts in standard of care, they must be made with transparency and flexibility if the evidence changes. Lastly, the lofty, but not impossible goal to achieve agreements between different national drug regulatory agencies on approval, and to enforce close monitoring of accelerated approval status should be strongly considered. Such cooperation will eliminate redundancies and streamline the post-marketing confirmatory studies that are required for the transition to full approval.

Data Sharing of Clinical Trial Results—Regulations for mandatory registration and results disclosure of clinical trials to centralized, publicly accessible databases such as clinicaltrials.gov and EudraCT have facilitated opportunities for clinical trial participation and improved transparency of reporting. At the completion of a clinical trial, positive and negative results must be shared with the scientific community through presentations and publications to facilitate knowledge transfer and translation. In an analysis of 94 phase III trials conducted over three decades from 1985 to 2014 by the Southwest Oncology Group, primary articles from positive trials were published in higher impact factor journals. However, when the scientific impact based on the number of citations of all publications associated with the trials were compared, there was no difference between positive and negative trials (52). This finding underscores the importance of making all trial results available such that advances can be achieved not only via practice-changing trials reporting positive results, but also through negative studies by avoiding ineffective treatments.

Many scientific journals mandate the deposition of raw data in appropriate public repositories to support transparency, and to allow the reuse and mining of the data for continued learning. Such repositories are available for the deposition of genomics, proteomics, microarray, flow cytometry data; software and code; among others. General public databases such as Mendeley Data exist to enable the sharing of any original data not deposited in another repository (https://data.mendeley.com/). For clinical trials, the US FDA mandates that scientific and administrative information related to trial results from Applicable Clinical Trials (ACT) must be submitted to the ClinicalTrials.gov results database no later than 12 months after the primary completion date. ACT is defined as trials

of drugs and biologics subject to FDA regulation that are undergoing controlled clinical investigations, other than phase I investigations, with primary completion date after December 26, 2007 (https://clinicaltrials.gov/ct2/manage-recs/fdaaa). Moving forward, the systematic sharing of results from clinical trials must be more globalized and seamless. Individual-level data from clinical trials in the post-competitive space should not become "dark matter" and should be more broadly shared. To maximize the knowledge that can be leveraged from completed clinical trials, raw clinical and correlative sciences data from all trials independent of their phases, sponsors, and outcome (positive or negative) should be made available in publicly accessible and searchable repositories.

Emerging Needs and Priorities in Clinical Research

Setting Priorities on Existent Gaps in Clinical Trials—Cancer research endeavors have transcended many different challenges across the decades. The main priorities have always been an improvement in the prevention, diagnosis and treatment of cancer, translating to patients living longer with better quality of life. However, despite substantial scientific advances made over time, these gains have not been equally realized by all populations of cancer patients. One crucial area is clinical trial inequalities which comprise a lack of trial participation in rare tumors, disadvantaged socioeconomic groups as well as minorities. Rare tumors account for over 20% of cancer diagnoses, with a disproportionately low percentage of clinical research investment (53). Trial participation for rare tumors should be coordinated via rare research consortia to avoid duplication of efforts, accelerate therapeutic developments and maximize the impact of research for the limited resource available. The International Rare Disease Research Consortium (IRDiRC) (https://irdirc.org), as well as the International Rare Cancers Initiative (ICRI) (54), are two examples of efforts advocating research for rare tumors. However, for these efforts to be transformative, such consortia should be empowered to work and coordinate their efforts with grant-awarding bodies, cooperative research institutions as well as health regulators within high and middle/low income nations. The lack of trial participation of lower socioeconomic groups and minorities have been well document in cancer (55,56). The NCI has multiple initiatives directed at eliminating these disparities with some degree of success. Programs aimed at patient and community education as well as increased incentives for trial participation are relevant initiatives in promoting research participation within low socioeconomic and minority populations. Ultimately, global oncology research opportunities must be facilitated in low socioeconomic neighborhoods/countries to enable increased trial participation (57).

Another area in cancer clinical trials that remains a significant gap is to define what constitutes clinically meaningful impact. Measuring impact is inherently valuable as cancer research is costly, and a return of investment can only be useful if it results in clinically meaningful benefits for patients. Additionally, measuring impact creates accountability for the research community and allows for work prioritization and funding allocation. Within cancer clinical trials, there is no formal agreed methodology to assess impact. The European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a structured methodology which derives a relative ranking of the magnitude of clinically meaningful benefit that can be expected from anticancer treatments (58). This tool enables

the distinction of substantial clinical benefit within positively reported trials, which in turn can be used to demonstrate impact. In one analysis of 694 randomized clinical trials, only one-third of the favorably reported clinical trials were associated with a clinically meaningful clinical benefit when analyzed via the ESMO-MCBS criteria (59). At present, there is no clear role for tools such as the ESMO-MCBS to be applied in all phases of clinical trials. However, one would envisage that the reporting and publication of late phase trials should incorporate such tools to demonstrate impact.

Globalization of Clinical Trials—Historically, the globalization of clinical trials with involvement of low and middle-income countries has been promoted by large pharmaceutical companies to maximize accrual, reduce operational costs, and expedite the completion of studies to support the development and regulatory approval of new anticancer agents (60). In low-income countries, global clinical trials may provide earlier access to novel investigational agents otherwise unavailable. Clinicians in these communities are able to garner expertise in the field of drug development, build new infrastructures and train study team members, leading to a potential overall benefit in global health (61).

For investigator-initiated studies, clinical trial globalization represents a unique opportunity to accelerate cancer research within academic centers worldwide. Many of these studies address important questions that have pharmacoeconomic implications, especially in societies where many anticancer drugs are not affordable. However, global clinical trials face a variety of challenges, most notably, lack of funding for many of these initiatives. Furthermore, heterogeneous legislations and regulatory environments; pharmacogenomic variations; geographical, cultural, political, lifestyle differences; and socio-economic boundaries of diverse societies pose additional barriers (62). Through support provided by charitable groups and peer-reviewed grants, these trials foster the collaborative research alliances among investigators worldwide. Attempts to facilitate investigator-initiated clinical trials are available in major international organization websites, with general guidelines that are easily accessible regarding basic requirements to build strong partnerships and effective research programs to establish infrastructure to sustain clinical trials. As an example, the ASCO Research Community Forum Development Task Force provides an updated library of assets to centralize resources to facilitate the development, conduct and management of clinical trials (https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/2020-ASCO-RCF-Library-Basic-Requirements.pdf). Although funding support remains limited, initiative such as Global Oncology and International Development Education Awards incentivize international research to be conducted in low- and middle-income countries. Yet the development of investigator-initiated clinical trials requires a concrete and established framework and financial oversight to fuel global discoveries and fight cancer health disparities.

To conduct global investigator-initiated trials, the study design may need to account for imbalances in accrual from diverse geographical sites, as well as differences in ethnicity, culture, lifestyle, genetic profile, diet, and metabolism. The eligibility criteria may vary based on accessible treatments in the jurisdiction for the patient populations under investigation. The delivery of investigational agents and safety of study subjects can be impacted by sanitary conditions, available supportive care, the presence of endemic

infections, and life expectancy of the patient population. Ultimately, continuous oversight is critical to guarantee research quality, protection of subjects and correct interpretation of clinical outcome (61).

The undertaking of globalizing academic clinical trials requires broad and well-established networks, where large cancer centers partner with institutions in low- and middle-income countries to provide appropriate research training and guidance, and promote the development of local leaders and key players (63). Cooperative group and intergroup models such as the US NCI, Canadian Clinical Trials Group, EORTC, Australasian Gastro-Intestinal Trials Group, among others, can provide the framework and resources to conduct global trials and play a central role in coordinating the efforts while maintaining central supervision. The International Duration Evaluation of Adjuvant Therapy (IDEA) is a successful example of an international academic collaboration of 12 countries, with an independent data center and without commercial support. This study involved six individual randomized adjuvant phase III trials and 12,834 patients with stage III colon cancer, evaluating the role of adjuvant regimens of FOLFOX versus CAPOX (64). Ultimately, global investigator-initiated clinical trials can foster collaborations and alliances, leverage and maximize expertise, ensure equitable distribution of resources, and promote data sharing. Rather than competing to address the same research question, these initiatives can build capacity to enable scientifically worthwhile projects with minimal resources. As government-based funding is often very limited or absent, pharmaceutical partnerships and philanthropic donations may serve as a solid base to support the advancement of global academic trials.

Increasing Efficiency in Clinical Trials—The urgency to bring effective therapies to patients requires the design of smart clinical trials that demonstrate operational and scientific efficiencies to address questions of highest priority and impact. In the current era, the administrative burden to activate, run and close out clinical trials is often excessive requiring many regulatory procedures. A reinvigoration by key stakeholders such as investigators, regulatory bodies, sponsors, and patient advocates to streamline clinical trial processes is critical to expedite oncology drug development (65).

The coronavirus disease 2019 (COVID-19) pandemic, as declared by the World Health Organization on March 11, 2020, has led to unprecedented global measures in an effort to stop the spread of this zoonotic infection. In oncology, COVID-19 has impacted not only cancer care but also the conduct of clinical trials. Examples of trial modifications in response to the pandemic include virtual patient assessments using platforms such as telemedicine or by phone; omission of physical examinations during virtual visits; courier services for delivery of oral trial medications to patients' homes; collection of study-related biospecimens from their homes or at local laboratories; administration of parenteral study treatment and performance of study-related investigations in local centers when appropriate; digital signatures; electronic consents; and remote study monitoring. Electronic systems for remote data capture and monitoring are now widely used to enable more sophisticated data analyses, rapid communication of safety signals to investigators, and informed decisions to be conducted in real-time. Increasing use of wearable technologies that remotely monitor vital signs and telemetry recordings, and ePRO questionnaires may also reduce the burden of

travel for trial participants. It is uncertain whether any or all of these decentralized measures will be extended as the “new normal” in clinical trials, but this pandemic has raised the possibilities of allowing flexibility in these practices while maintaining patient safety and trial integrity.

Education and Training

Mentorship and Training in Clinical Research—The task of advancing cancer research is contingent on the renewal of its work force through training of the next generation of clinical investigators. This critical process requires a strong and dynamic research mentor-mentee relationship, in addition to open access to knowledge, and exposure to high quality academic discussion and networking (66,67). The role of successful mentorship should extend beyond scientific and technical training of clinical skills and medical knowledge, but also on leadership development. Mentor-mentee mutual respect and open communication play a pivotal role in building the perfect “mentorship chemistry” for a successful career in academia.

Within oncology, the early phase clinical trial setting still remains a relatively selected niche, where centers of excellence have the ability and the responsibility to provide domestic and international trainees with the opportunities to advance methods of clinical practice, perform cutting edge research, develop ideas and flourish as independent investigators. As a testimonial of the pivotal role of mentorship, international associations including ASCO, AACR, ESMO, amongst others have instituted mentorship initiatives and tailored workshops where participants are paired with mentors across the globe to support learning, promote professional growth and academic career development (Table 2). These represent a unique opportunity to learn the necessary clinical trial development skills and expertise, and a valuable platform for networking and fostering new collaborations. Participants around the world are matched with key opinion leaders who provide direct mentorship in areas important to personal career development, as well as insightful advice including avoidance of burnout and maintenance of a healthy work-life balance.

Conclusions

The aforementioned key considerations encompass different facets in the design, conduct, analysis, reporting, implementation and data sharing of clinical trials. Advances in various areas such as molecular biology, immunology, biotechnology and patient-reported outcomes will be the drivers that determine the most relevant questions to be addressed by future studies. Currently, one of the most pressing need is a call to action to establish the anticipated framework and path forward for next generation clinical trials (Table 3). These guidances are relevant to empower the research community to prioritize resources, optimize efficiency and increase the impact of clinical trials.

Advancing into the next decade, the journey of a clinical trial participant (Figure 2) will be dynamic and adaptive by leveraging scientific, technical and methodological innovations to pre-empt the emergence of therapeutic resistance. While precision cancer medicine will remain central to provide individualized strategies, the clinical and molecular data as well as patient-reported outcomes collected from each patient will rapidly contribute to AI-assisted

learning systems to enhance overall knowledge. The integration between bench and bedside will be seamless and robust to ensure there is constant translational feedback to help tailor treatment and to inform target discovery and drug development. The success of next generation clinical trials will be based on the fundamental principles of acting locally to learn globally, and treating participants individually to advance the field collectively.

More than ever, future clinical trials will be patient-centric and incorporate the perspectives of patients, advocates and survivors in their design and conduct. Patients will actively participate in clinical data generation through wearable devices, virtual care and ePROs. Importantly, the input of patients must be integrated to ensure that the most pertinent questions with tangible outcomes are addressed to increase cancer control and cure.

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Statement of Significance

The future of cancer clinical trials requires a framework that can efficiently transform scientific discoveries to clinical utility through applications of innovative technologies and dynamic design methodologies. Next generation clinical trials will offer individualized strategies which ultimately contribute to globalized knowledge and collective learning, through the joint efforts of all key stakeholders including investigators and patients.

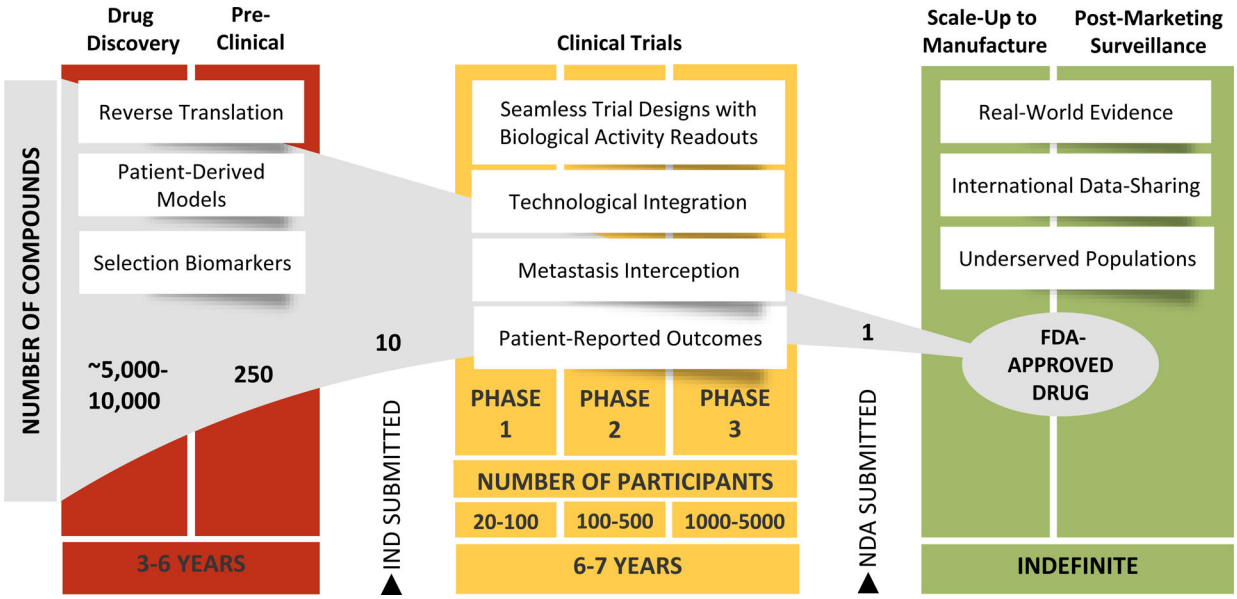

Figure 1: Key Considerations and Clinical Trials Framework from Drug Discovery, to Clinical Trials, to Post Market Surveillance.

The current drug development pathway, including the number of compounds entering clinical testing, number of study participants in phase I, II, and III trials, and the timeline from preclinical testing to market approval is provided. Advances in trial design, conduct and analysis (summarized in white boxes) may lead to more focused trials involving fewer participants with an accelerated timeline for clinical development.

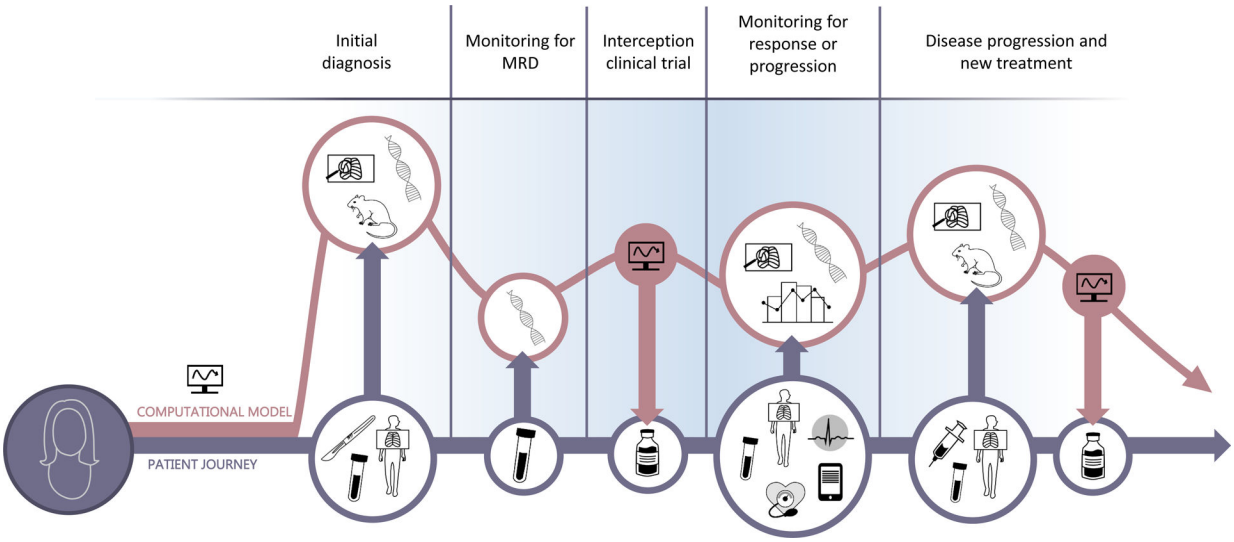

Figure 2: The Journey of a Clinical Trial Participant in the Next Decade

As cancer clinical trials continue to evolve over the next decade to transform patient care, a forward looking vision into the journey of a cancer clinical trial participant in 2030 helps to set an inspirational goal (top pathway in red): A patient undergoes curative surgery in a local hospital with tumor specimen and germline blood immediate processing in a centralized laboratory for multi-omic molecular evaluation, digital spatial profiling and immunophenotyping. In addition to engrafting the tumor in patient-derived models, blood and other body fluid samples and conventional radiological imaging are collected pre- and post-surgery for ctDNA and radiomic analyses. All deidentified clinical, molecular and radiological data are entered into an international database with an integrated computational model for AI-based prediction of relapse risk. These results are deliberated via a virtual tumor board with clinical input from the local treating physician teams to recommend the best course of action. Persisting ctDNA as quantified by a tumor-informed, ultrasensitive assay suggests the evidence of molecular residual disease (MRD). The patient is recruited to an interception clinical trial with an anticancer drug combination based on analysis from the multidimensional characterization of resected tumor, as well as from functional drug sensitivity testing of the patient-derived models. There are frequent dynamic assessments of ctDNA to determine if there is molecular response or clearance. Any increase in ctDNA and changes in radiomic profile, upon repeat confirmation, signify molecular progression. Clinical samples at molecular progression and patient-derived models that have been treated with the same drugs are interrogated to suggest treatments that can be used to pre-empt acquired clinical resistance. In this clinical trial, the patient alternates between virtual visits and in person visits, based on risks and occurrences of any treatment emergent adverse events. Throughout the duration of the clinical trial, the patient provides regular update through an ePRO app on a smart phone and wears a device that collects vital signs, cardiac rhythm, and blood glucose on a continuous basis. These data and all clinical information collected in the patient's EMR are electronically compiled into summary statistics that can be generated into reports for specified time intervals. If any of the ePRO entries or physical measures reach a reportable threshold, an electronic alert is sent to the patient as well as treating physician. Upon publication of the clinical trial results, individual level data

collected are deposited into an international database with open and controlled access to enable sharing with the public, as well as researchers and investigators respectively. In addition, the data are entered into a rapid learning system to understand how this case compares to other similar cases that have been collected on clinical trials as well as from RWE.

Table 1:

Initial Oncology Drug Approvals by the US FDA 2015–2020 (as of October 12, 2020) (https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications)

Drug	Approval Date	Indication	Accelerated Approval
Palbociclib	2/3/2015	Advanced hormone receptor-positive, HER2-negative breast cancer	Yes
Lenvatinib	2/13/2015	Progressive, differentiated thyroid cancer with radioactive iodine refractory disease	
Panobinostat	2/23/2015	Multiple myeloma	
Dinutuximab	3/10/2015	Pediatric patients with high-risk neuroblastoma	
Sonidegib	7/24/2015	Locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or who are not candidate for surgery or radiation therapy	
Trifluridine and tipiracil	9/22/2015	Advanced colorectal cancer	
Trabectedin	10/23/2015	Soft tissue sarcoma that cannot be removed by surgery or is metastatic	
Cobimetinib and Vemurafenib	11/10/2015	Advanced BRAF V600 E/K melanoma	
Osimertinib	11/13/2015	Advanced non-small cell lung harboring an EGFR T790M mutation	
Daratumumab	11/16/2015	Multiple myeloma post at least three prior therapies	
Ixazomib	11/20/2015	Multiple myeloma post at least one prior therapy	
Necitumumab	11/24/2015	Advanced squamous non-small cell lung cancer, in combination with gemcitabine and cisplatin, in patients who have not previously received medication to treat advanced lung cancer	
Elotuzumab	11/30/2015	Multiple myeloma post one to three prior therapies	
Alectinib	12/11/2015	ALK-positive non-small cell lung cancer	
Venetoclax	4/11/2016	Chronic lymphocytic leukemia with chromosome 17p deletion and post at least one prior therapy	
Atezolizumab	5/18/2016	Platinum-refractory or platinum-ineligible urothelial carcinoma	
Olaratumab	10/19/2016	Soft tissue sarcoma	
Rucaparib	12/19/2016	Advanced ovarian cancer with BRCA mutation and post two or more prior chemotherapies	
Ribociclib	3/13/2017	Advanced hormone receptor-positive, HER2-negative breast cancer	
Avelumab	3/23/2017	Merkel cell carcinoma	Yes
Niraparib	3/27/2017	Maintenance treatment for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers	
Brigatinib	4/28/2017	ALK-positive non-small cell lung cancer who have progressed on or are intolerant to crizotinib	Yes
Durvalumab	5/1/2017	Locally advanced or metastatic urothelial carcinoma	Yes
Neratinib	7/17/2017	HER2-positive breast cancer previously treated with trastuzumab	
Enasidenib	8/1/2017	Relapsed or refractory IDH2 mutant acute myeloid leukemia	
Inotuzumab Ozogamicin	8/17/2017	Relapsed or refractory B-cell acute lymphoblastic leukemia	
Copanlisib	9/14/2017	Relapsed follicular lymphoma	Yes
Abemaciclib alone or in combination with fulvestrant	9/28/2017	Advanced hormone receptor-positive, HER2-negative breast cancer	

Drug	Approval Date	Indication	Accelerated Approval
Acalabrutinib	10/31/2017	Mantle cell lymphoma post at least one prior therapy	Yes
Lutetium Lu 177 dotatate	1/26/2018	Gastroenteropancreatic neuroendocrine tumors	
Apalutamide	2/14/2018	Non-metastatic prostate cancer	
Blinatumomab	3/29/2018	B-cell acute lymphoblastic leukemia in first or second complete remission with minimal residual disease great than or equal to 0.1%	Yes
Binimetinib and Encorafenib	6/27/2018	Advanced BRAF V600 E/K melanoma	
Ivosidenib	7/20/2018	Relapsed or refractory IDH1 mutant acute myeloid leukemia	
Mogamulizumab	8/8/2018	Mycosis fungoides or Sezary syndrome post at least one prior therapy	
Moxetumomab pasudotox	9/13/2018	Hairy cell leukemia post at least two prior therapies	
Duvelisib	9/24/2018	Relapsed or refractory chronic lymphocytic leukemia, small lymphocytic leukemia and follicular lymphoma	
Dacomitinib	9/27/2018	Advanced non-small cell lung cancer with EGFR exon 19 deletion or exon 21 L858R substitution	
Cemiplimab	9/28/2018	Cutaneous squamous cell carcinoma	
Talazoparib	10/26/2018	Locally advanced or metastatic breast cancer with a germline BRCA mutation	
Lorlatinib	11/2/2018	ALK-positive non-small cell lung cancer	Yes
Glasdegib	11/21/2018	Newly diagnosed acute myeloid leukemia	
Larotrectinib	11/26/2018	Solid tumors with NTRK fusions	Yes
Gilteritinib	11/28/2018	Relapsed or refractory FLT3 mutant acute myeloid leukemia	
Calaspargase pegol-mknl	12/20/2018	Acute lymphocytic leukemia	
Tagraxofusp	12/21/2018	Blastic plasmacytoid dendritic cell neoplasm	
Erdafitinib	4/12/2019	Advanced FGFR mutant urothelial carcinoma	Yes
Alpelisib	5/24/2019	Advanced hormone receptor-positive, HER2-negative, PIK3CA mutant breast cancer	
Polatuzumab vedotin	6/10/2019	Relapsed or refractory diffuse large B-cell lymphoma	Yes
Selinexor	7/3/2019	Relapsed or refractory multiple myeloma	Yes
Darolutamide	7/30/2019	Non-metastatic castrate resistant prostate cancer	
Pexidartinib	8/2/2019	Symptomatic tenosynovial giant cell tumor	
Entrectinib	8/15/2019	ROS1-positive non-small cell lung cancer and solid tumors with NTRK fusions	Yes
Fedratinib	8/16/2019	Intermediate-2 or high risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis	
Zanubrutinib	11/14/2019	Mantle cell lymphoma post at least one prior therapy	Yes
Enfortumab Vedotin	12/18/2019	Advanced urothelial carcinoma post anti-PD1/PD-L1 antibody and a platinum-containing chemotherapy	Yes
Fam-Tratuzumab Deruxtecan	12/20/2019	Advanced HER2-postiive breast cancer post at least two prior anti-HER2 regimens	Yes
Avapritinib	1/9/2020	Advanced gastrointestinal stromal tumor	
Tazemetostat	1/23/2020	Epithelioid sarcoma	Yes
Isatuximab	3/2/2020	Advanced multiple myeloma post at least two prior therapies	

Drug	Approval Date	Indication	Accelerated Approval
Tucatinib	4/17/2020	Advanced HER2-postiive breast cancer post at least one or more prior anti-HER2 regimens, in combination with trastuzumab and capecitabine	
Pemigatinib	4/17/2020	Advanced cholangiocarcinoma with FGFR2-fusion	Yes
Sacituzumab govitecan	4/22/2020	Triple negative breast cancer post at least two prior therapies	Yes
Capmatinib	5/6/2020	Advanced non-small cell lung cancer with MET exon 14 skipping mutation	Yes
Selpercatinib	5/8/2020	Non-small cell lung cancer, medullary thyroid cancer and other types of thyroid cancers which harbor a RET mutation or fusion	Yes
Ripretinib	5/15/2020	Advanced gastrointestinal stromal tumor	
Lurbinectedin	6/15/2020	Advanced small cell lung cancer post platinum-based chemotherapy	Yes
Decitabine and Cedazuridine	7/7/2020	Myelodysplastic syndrome	
Tafasitamab-cxix	7/31/2020	Diffuse large B-cell lymphoma not otherwise specified, including those arising from low grade lymphoma, who are not eligible for autologous stem cell transplant	Yes
Belantamab mafodotin-blmf	8/5/2020	Relapsed or refractory multiple myeloma post at least four lines of therapy	Yes
Carfilzomib and Daratumumab and dexamethasone	8/20/2020	Relapsed or refractory multiple myeloma post at least one to three lines of therapy	
Pralsetinib	9/4/2020	RET-fusion positive non-small cell lung cancer	Yes

Note: Approvals of cell therapies are not included in this table

Table 2:

Examples of International Organization-Driven Mentorship Opportunities and Workshops

Organization	Type	Target Audience	Objectives
ASCO	ASCO Virtual Mentoring Program	• Practicing Oncologists • Population Underrepresented in Medicine • Women in Oncology • Oncologists in training	Long-term and situational mentoring support of individual learning; growth and professional development needs
	ASCO Diversity Mentoring Program	• Medical students • Residents	Career and education guidance
AACR/ASCO EORTC/ESMO/ AACR	Methods in Clinical Cancer Research Workshop	• Oncology Clinical Fellows • Oncology Junior Faculties	Essentials of effective clinical trial designs of therapeutic interventions in the treatment of cancer
AACR	Translational Cancer Research for Basic Scientists	• Pre-doctoral Student • Post-Doctoral Fellows • Early Career Scientists • Senior Scientists in transition to translational Research	Introduction to translational cancer research, including cancer medicine, the clinical cancer research environment, and collaborative team science
AACR/ASCO	Molecular Oncology in Clinical Biology	• Aspiring Physician Scientists	Overview of molecular biology, translational cancer research, current laboratory techniques, career development, and the best practices of grant writing
AACR	ACORD: Australia & Asia Pacific Oncology Research Development Workshop	• Oncology Clinical Fellows • Oncology Junior Faculties	Clinical trial design and methodology; protocol development
ESMO	Virtual Mentorship Program	• Medical/Clinical Oncologist Young Investigator	Skill development; career, publication advice; implementation of research interests
EORTC	ECI: Early Career Investigator's Leadership Program	• Early Career Investigators	Strategic thinking leadership; communication skills and capabilities
FDA	Oncology center of Excellence Fellows Program	• Hematology/Oncology Fellows • Radiation Oncology Residents	Type of FDA submissions; clinical trial design and drug development; Regulatory requirements for drug approval; clinical considerations in risk-benefit analysis

ASCO: American Society of Clinical Oncology; AACR: American Association for Cancer Research; EORTC: European Organisation for Research and Treatment of Cancer; ESMO: European Society of Medical Oncology; FDA: Food and Drug Administration

Table 3:

A Call to Action to Establish the Framework for Next Generation Clinical Trials

Actions	Expected Outcomes
Framework and Impact	
• Engage key stakeholders in an open dialogue to exchange new concepts, scientific knowledge and best practices for next generation clinical trials	• Establish a forum where ideas for next generation clinical trials can be shared
• Promote collaboration between regulatory bodies, cancer societies, patients and advocacy groups to anticipate the impact of next generation clinical trials on cancer patients and payers	• Establish prospective value frameworks to inform clinical trial designs to assess clinically meaningful differences in outcome
Protocol and Consent Form Development	
• Establish trusted networks to provide systematic guidance and connected infrastructure, such as tools to accelerate protocol development, build data-driven rationale and logic into decisions e.g. eligibility criteria restrictions; enable clear and concise digital informed consent process	• Enable streamlined protocol development and consent process
Data Collection and Monitoring	
• Focus data collection on the most clinically relevant data points, enhance opportunities for remote data monitoring, consolidate clinical trials that are no longer recruiting patients into an institutional follow-up protocol	• Increase efficiency and minimize waste of resources, time, and patients in clinical trials
Reducing Trial Burden	
• Reduce burden of trial participation on patients and their caregivers – eliminate “non-essential” travel visits to treatment facility; enable wearable technologies for data collection and electronic patient-reported outcomes; integration of community hospitals/oncologists for safety assessments within local trial teams; remote delivery of trial medications; treatment at local infusion centers; “at home” collection services for correlative samples	• Reduce trial burden for participants and increase participation in clinical trials
Data Sharing and Rapid Learning System	
• Increase awareness, transparency and sharing of clinical trial information as well as real world data to create a rapid learning system, leveraging advances in artificial intelligence and machine learning	• Create iterative learning from clinical trial data and real world evidence
Clinical Trial Navigation	
• Promote trial nurse navigators to link patients receiving standard of care treatment(s) at community sites with trial participation opportunities at referral centers; facilitate outreach to minority and underserved populations	• Enhance clinical trial navigation and participation, especially for minority and underserved groups
Knowledge Translation	
• Enforce post approval surveillance of how clinical trial data are being applied in clinical practice, and collect this information to add to real world evidence, in order to identify ways to increase knowledge translation	• Track and improve how clinical trial results are translated into practice and knowledge