Section Editors: Jeannine M. Brant, Constance Visovsky, Steven H. Wei, and Rita Wickham

Clinical Trial Design and Drug Approval in Oncology: A Primer for the Advanced Practitioner in Oncology

SANDRA E. KURTIN, PhD, ANP-C, AOCN®, and RASHIDA TAHER, MPH, PA-C

From [1]The University of Arizona Cancer Center, Tucson, Arizona; [2]Lifespan Cancer Institute, Providence, Rhode Island

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Sandra Kurtin, PhD, ANP-C, AOCN®, The University of Arizona Cancer Center, 3838 N. Campbell Avenue, Tucson, AZ 85719-1454. E-mail: sandra.kurtin@bannerhealth.com

https://doi.org/10.6004/jadpro.2020.11.7.7

Abstract

Evidenced-based practice requires timely and accurate integration of scientific advances. This presents a challenge for the oncology clinician given the robust pace of scientific discovery and the increasing number of new drug approvals and expanded indications for previously approved drugs. All currently available antineoplastic therapies have been developed through the clinical trials process. Advanced practitioners (APs) in oncology are often involved in the conduct of clinical trials as primary investigators, sub-investigators, study coordinators, or in the delivery and monitoring of care to patients enrolled in these trials. A prerequisite to evidenced-based practice is understanding how clinical trials are conducted and how to critically analyze published results of studies leading to U.S. Food & Drug Administration approval. Any AP involved in the clinical management and supportive care of patients receiving antineoplastic therapies should be able to critically review published data to glean findings that warrant a change in practice. The goals of this manuscript are to summarize key elements of the clinical trial process for oncology drug development and approval in the United States and to provide a primer for the interpretation of clinical data.

Translating research into clinical practice is a challenging and valuable skill for the advanced practitioner (AP) in oncology. Recent analysis of 585 trials registered in the National Cancer Institute Clinical Trials database showed that 29% remained unpublished within 5 years of completion of the study (Jones et al., 2013). A second study showed that among 1,075 abstracts describing 378 randomized and 697 nonrandomized clinical trials presented as abstracts at the American Society of Clinical Oncology (ASCO) meeting, only 75% of randomized and 54% of nonrandomized trials (61% overall) were ever published (Massey, Wang, Prasad, Bates, & Fojo, 2016). The average time from completion of a trial and publication among 809 trials closed to accrual between 2009 and 2013 was 47 months, with only 18.8%

J Adv Pract Oncol 2020;11(7):736–751

of these being published within 2 years of trial completion (Chapman et al., 2017). Unpublished results limit our ability to integrate the findings of these trials into practice, favorable or unfavorable, and diminish the efforts made by patients participating in those trials. Only 2% to 4% of all adults with cancer participate in clinical trials, the majority being under the age of 65 (Denson & Mahipal, 2014). Given the small number of patients participating in clinical trials today, publication of results should be a priority. Furthermore, the robust pace of scientific discovery in oncology places renewed emphasis on the ability of clinicians and scientists to critically review published data to allow appropriate and effective integration of the findings into the mainstream delivery of care.

Advanced practitioners in oncology are involved in the clinical management and supportive care of patients receiving antineoplastic therapies. Advanced practitioners are often involved in the conduct of clinical trials as primary investigators (PIs), sub-investigators, study coordinators, or in the delivery and monitoring of care to patients. Although the work is arduous, requiring meticulous assessment, documentation, and adherence to the protocol design, bringing a new therapy to trial and in some cases to market is one of the greatest privileges in oncology practice. Understanding evidence-based practice requires the systematic analysis of the scientific process evident in published works. The ability to independently, critically, and effectively articulate published data allows the AP the ability to glean findings that warrant a change in practice. Fortunately, summaries provided by various professional organizations, educational groups, or pharmaceutical companies allow for rapid dissemination of clinical trial results. However, the ability to independently review and effectively articulate trial results to colleagues and patients is an invaluable skill for APs. Concepts from the peer review and journal club processes offer practical and well-established criteria for critical appraisal of scientific literature.

The goals of this manuscript are to summarize key elements of the clinical trial process for new oncology drug development and approval in the United States and to provide a primer for the interpretation of clinical data. Part two and three of this series will apply this information to recent U.S. Food & Drug Administration (FDA) approvals in oncology with discussion of the implications for practice in both hematologic malignancies and solid tumors.

KEY ELEMENTS OF CLINICAL TRIALS CONSIDERED IN DRUG APPROVAL

Clinical trials are used to test drugs, vaccines, and other medical interventions. Each clinical trial starts with a question or hypothesis generated based on clinical expertise, collaboration, and review of extant literature. It is incumbent on the PI(s) to select a question that will expand knowledge, offer clinical benefit to study participants (efficacy) and improve or sustain quality of life (safety). The trial design will be dictated by the question at hand and the available relevant science. The phase of clinical trial is indicative of the question at hand and the state of science relative to that question (Table 1). The phase of trial indicates the maturity of the science relative to the stated hypothesis and most often guides the study design (Table 2).

Interventional trials provide the foundation for new drug approvals in the United States. The randomized controlled trial (RCT) provides the most precise, thorough, and reliable characterization of therapeutic interventions by limiting bias through randomization (Simon et al., 2015). Blinded RCTs reduce bias further as clinicians are not told whether the patient will receive drug A or drug B. If there is a significant benefit in one arm of the trial at a predefined interim data analysis, crossover to the arm using the newer treatment may be allowed, and the trial will be unblinded at that time. Trials that include a crossover design with unblinding where clinicians may be more inclined to take patients off the control arm may confound analysis of progression-free survival (PFS; Simon et al., 2015). This is in part due to the challenges of recruitment but may also be driven by the selected endpoints and the time required to enroll enough subjects to reach statistical significance. Overall survival (OS) is generally the gold standard for the primary endpoint in RCTs, although reaching statistically significant OS can take many years in selected diseases. Demonstrating a survival advantage is logistically difficult in diseases with relatively favorable overall survival

Table 1. Phases of Clinical Trials and Primary Objectives

Phase or type	Main objectives
I	• Determine the MTD, DLT, and recommended phase II dose, including schedules and modes of administration • Characterize specific side effects and target organs for toxicity relative to the MTD and DLTs, including grade, duration, and reversibility • Pharmacokinetics and pharmacodynamics related to target effects and adverse effects, relative to routes of administration • Generally, cancer populations without an established therapeutic option or where new options may be feasible
II	• Build on success of phase I trials • May be used for FDA approval, most often with the caveat of continued study • Most often focused on a single disease
III	• Confirmatory trials aimed at comparing a currently approved standard of care with a new agent, regimen, or route of administration that has been proven in phase I/II trials
IV	• Conducted after FDA approval to obtain additional information, including the drug's risks, benefits, and optimal use
Biosimilar analysis	• Agent must demonstrate biosimilarity to the reference product based on totality of the evidence. If a proposed biosimilar is truly highly similar to the reference product, it is expected that all aspects of its therapeutic effects, including efficacy, safety, and immunogenicity, would also be similar. • The type and extent of data required to demonstrate biosimilarity may vary and will be determined on a case-by-case basis • Extrapolation of indications is based an analysis of efficacy and safety data including demonstrated mechanism of action • Generally conducted in target patient population, using endpoints that can detect any clinically meaningful differences between the proposed biosimilar and the reference product

Note. MTD = maximum tolerated dose; DLT = dose-limiting toxicity. Information from Curigliano, O'Connor, Rosenberg, & Jacobs (2016); Ellimoottil, Vijan, & Flanigan (2015); Simon et al. (2015).

(patients lost to follow-up) and is very costly. As a result, PFS has been increasingly used as a surrogate to OS to allow earlier drug approval with many trials continuing their analysis post approval to achieve OS data. It is important to understand the differences and implications of different primary and secondary endpoints with regard to drug approval.

Although the RCT is considered the gold standard, there are instances in which this study design is not feasible. These include trials for drugs that target rare cancers where there are limited available therapies, trials in which there is a known actionable biomarker, and trials where the currently available therapies are highly toxic and/or marginally effective (Simon et al., 2015).

Single-arm trials, although limited by inherent bias, are often used in these cases. Single-arm trials generally focus on overall response rates based on the understanding that without treatment, the underlying disease would inevitably progress. Effective single-arm trials often move on to a randomized trial for validation. All RCTs and single-arm interventional trials are built on the foundation of early phase trials necessary for drug development. The rapid expansion of tailored therapies, with proof of therapeutic concept verified in laboratory models using cell lines derived from the science of cloning, has led to an increase in first-in-human trials approved by the FDA (Prowell, Theoret, & Pazdur, 2016). Rapid expansion of dosing cohorts to establish maximum tolerated dose and efficacy endpoints more efficiently are strategies used to accelerate the drug development process in these trials (Mayawala, Tse, Rubin, Jain, & de Alwis, 2017).

Most recently, noninferiority trials have emerged to substantiate alternative routes of administration, schedules for administration, and biosimilar agents. The standards for noninferiority trials are different than those for RCTs such that the design and analysis of outcomes must be evaluated within the context of each trial (Dunn, Copas, & Brocklehurst, 2018; Ganju & Rom, 2017). It is not within the scope of this paper to address the scientific principles and processes used in the development and approval of biosimilar agents. The reader is referred to several recent publica-

Table 2. The Hierarchy of Clinical Data

Study type	Description	Advantages	Disadvantages
Secondary Studies			
Systematic review	• Systematic reviews with homogeneity of RCTs can summarize the existing clinical research on a topic • Level of evidence: 1a	• Useful in summarizing extant literature and translating clinical research into practice	• Retrospective
Meta-analyses	• Data from systematic reviews (multiple studies on a specific disease or treatment) are analyzed • Practice guidelines such as the National Comprehensive Cancer Center (NCCN) Guidelines for treatment by cancer site are generated via meta-analysis • Level of evidence: 1a	• Useful in translating clinical research into practice • The results of a meta-analysis are usually stronger than the results of any study by itself	• Retrospective
Primary Studies (Randomized)			
Randomized controlled trial (interventional)	• Clinical trial in which at least two interventions are simultaneously evaluated • Groups are randomly assigned to minimize bias • Considered the gold standard in establishing the effect of an intervention • Most common primary endpoint is overall survival • Level of evidence: 1b	• Unbiased distribution of confounders • Blinding more likely • Randomization facilitates statistical analysis and the ability to interpret the differences in outcomes caused by the intervention and not by chance	• Expensive • Volunteer bias ethically problematic at times
Primary Studies (Nonrandomized)			
Single-arm prospective trial (interventional)	• Clinical trial in which enrolled patients are assigned to a single intervention • Commonly used in trials seeking accelerated approval • Most common primary endpoint is objective response rate	• Ethically safe • More rapid accrual and reporting supporting accelerated approval • Eligibility criteria and outcome assessments can be standardized • Administratively easier and cheaper than RCT	• Inherent bias • Most receive approval with the requirement for postmarketing confirmatory analysis and/or phase III trials
Prospective cohort study (interventional)	• Data are obtained from groups who have been exposed, or not exposed, to the intervention • No allocation of exposure is made by the researcher • Best for study of the effect of predictive risk factors on an outcome	• Ethically safe • Subjects can be matched • Can establish timing and directionality of events • Eligibility criteria and outcome assessments can be standardized • Administratively easier and cheaper than RCT	• Controls may be difficult to identify • Exposure may be linked to a hidden confounder • Blinding is difficult • For rare disease, large sample sizes or long follow-up necessary
Case control studies (observational, descriptive)	• Patients with a certain outcome or disease and an appropriate group of controls without the outcome or disease are selected • Information is obtained on whether the subjects have been exposed to the factor under investigation • Useful in generating ideas, hypotheses, and techniques that can then be tested in a clinical trial	• Comparably inexpensive • Only feasible method for very rare disorders or those with long lag between exposure and outcome • Fewer subjects needed than cross-sectional studies	• Reliance on recall or records to determine exposure status • Confounders • Selection of control groups is difficult • Potential bias: recall, selection

Table 2. The Hierarchy of Clinical Data (cont.)

Study type	Description	Advantages	Disadvantages
Primary Studies (Nonrandomized) (cont.)			
Cross-sectional survey (analytic and comparative, observational)	• Examines the relationship between diseases/characteristics and other variables of interest as they exist in a defined population at one particular time • Best for quantifying the prevalence of a disease or risk factor, and for quantifying the accuracy of a diagnostic test	• Comparably inexpensive • More simplistic design • Ethically safe	• Establishes association at most, not causality • Recall bias susceptibility • Group sizes may be unequal
Case report	• A detailed report of the diagnosis, treatment, and follow-up of an individual patient	• Useful in reporting postmarketing exposure to approved interventions generating ideas, hypotheses, and techniques that can then be tested in a clinical trial	• Not generalizable

Note. RCT = randomized controlled trial. Information from Blumenthal et al. (2015); Ho, Peterson, & Masoudi (2008); Howick et al. (2011); Maymone, Gan, & Bigby (2014); Simon et al. (2015).

tions (Nabhan, Parsad, Mato, & Feinberg, 2018; Rifkin & Peck, 2017).

Inclusion and exclusion criteria must be defined based on established literature and clinical practice guidelines to ensure a homogenous study group and exclude patients who are at increased risk for adverse events based on what is known about the drug regimen and the disease being investigated. It is important to note that these patients, in most cases, are not representative of the general population where the presence of comorbidities or other factors excluded in the trial are prevalent. More recently, therapies tailored to specific targets or pathways have limited inclusion criteria such that recruitment may take a prolonged period of time. It is critical for clinicians to consider the inclusion and exclusion criteria in the postmarketing setting to safely integrate new therapies into practice with patients who may be at a higher risk for adverse events.

Safety must be evaluated in every study prior to FDA approval. The Common Terminology Criteria for Adverse Events (CTCAE) are applied across studies to summarize tolerability, safety, and patient-reported outcomes systematically (Shepshelovich et al., 2019; U.S. Department of Health and Human Services, 2017). The CTCAE criteria are subdivided by organ system and common adverse events. Each adverse event (AE) is graded on a scale of 1 (minor) to 5 (death). This process is critical in interpreting the risks and benefits of each treatment and is used to develop the AE profiles printed in package inserts for drugs approved by the FDA. The CTCAE has published multiple versions, and it is important to note the version being used in the trial to effectively interpret the AEs reported. To reduce the subjectivity inherent in clinicians' attribution of AEs, patient-reported outcomes (PRO) have gained importance to better describe safety and tolerability across the life of a trial (Kluetz, Chingos, Basch, & Mitchell, 2016). The Patient-Reported Outcomes Version of the CTCAE (PRO-CTCAE) incorporates 78 patient-reported symptomatic AEs to collect subjective symptoms directly from patients, including measures for health-related quality of life (HRQOL).

CLINICAL TRIAL ENDPOINTS

Researchers must select primary and secondary endpoints for each study. The primary endpoint is the major focus of the study and is essentially what is expected to happen or the primary aim of the study. Secondary endpoints are outcomes expected to add to the significance of the new therapy being investigated. These endpoints are selected based on analysis of the existing literature, treatment landscape, the anticipated fit of the treatment being studied, power analysis, and the research interests and expertise of the research team. Overall survival, PFS, PFS2, event-

free survival (EFS), objective response rate, duration of response (DOR), time to progression (TTP), time to treatment failure (TTF), and depth of response are the most common primary and secondary endpoints (Table 3; Hickey et al., 2013). Patient-centered endpoints include OS and HRQOL, both affecting a patient's feeling of well-being and directing patient clinical benefit. Tumor or disease-specific endpoints include PFS or depth of response. Although OS is considered the hallmark of success, data to support statistically significant improvement of OS may require years of data collection/monitoring based on the expected survival in selected tumor types; PFS always precedes OS and has become a more common primary endpoint in clinical trials today. If PFS or TTP is selected as a primary endpoint, OS should be reported as a secondary endpoint and vice versa. Importantly, OS reporting may be confounded by subsequent therapies (Estey, Othus, Lee, Appelbaum, & Gale, 2016). In the era of accelerated approvals, overall response rate is the standard for a primary endpoint (Blumenthal et al., 2015; Chen, Raghunathan, & Prasad, 2019).

Criteria for response should be based on various disease-specific working group consensus statements. These must be articulated prior to study approval. These criteria provide the foundation for claims of efficacy. The specific response criteria and version must be noted, as these criteria are regularly updated based on emerging data. The ability to generalize results will be limited by the study design. Comparing two published trials with similar but not exactly the same methods and sample is not recommended.

The shift toward precision medicine, immunotherapies, and other treatments with novel mechanisms of action has shifted the traditional definition of progression and response. The phenomenon of pseudoprogression seen in trials using immunotherapies has required redefinition of progression (Hochmair, Schwab, Burghuber, Krenbek, & Prosch, 2017). For patients with rare or extensive disease, stable disease or even a slow progression is considered acceptable outside of a clinical trial (Kaufmann, Pariser, & Austin, 2018). Similarly, the integration of depth of response, specifically achieving undetectable minimal residual disease status in hematologic malignancies has been correlated with PFS and OS and is now being integrated into the response criteria for selected diseases (Gormley et al., 2016; Hallek et al., 2018; Heuser, Mina, Stein, & Altman, 2019; Kovacs et al., 2016; Medeiros, 2018; Molica, Giannarelli, & Montserrat, 2019). Although these new criteria have been defined, the application in general practice for patients treated outside of a clinical trial is not clearly defined in many cases. Caution is recommended prior to changing therapies where there is no clear data to support loss of undetectable minimal residual disease as progression.

The duration of response, although not often a primary endpoint, is critical to evaluating treatment options over time. The durability of a treatment option including tolerability is often lost in a new drug approval where the data cutoff points are focused on achievement of the primary and secondary endpoints to support approval. Both long-term responses, survival, and late relapses are not captured in trials that do not monitor patients over time or where patients are lost to follow-up (Cuzick, 2015). In addition, many blinded trials are unblinded at predetermined data cutoff points to facilitate statistical analysis, making long-term analysis of outcomes more difficult. Case reports and anecdotal data are often the mainstay for reporting outcomes in the subset of patents that achieve the most durable responses to investigational agents that are subsequently approved (Kurtin & List, 2009).

CONDUCT OF CLINICAL TRIALS

A site initiation visit is conducted by the study monitor to ensure that all clinicians and clinical trials staff are registered on the study, fully trained on all aspects of the study, and understand the processes for conducting the study, including reporting of unexpected adverse events or deviations. Consent forms, data monitoring processes and forms, and safety requirements are outlined in detail. Once the study is open at an individual site, patient accrual begins. Patient recruitment requires a coordinated team approach to inform clinicians about the trial and facilitate patient screening. This requires a level of knowledge on the part of the primary clinical team to effectively articulate the value of a clinical trial in the treatment selection process to the patient and their

Table 3. Common Clinical Trial Endpoints

Endpoint	Type of endpoint	Recommended study design	Advantages	Disadvantages
Overall survival	• Clinical • Time to event	• Randomized	• Easily and precisely measured • Generally based on objective and quantitative assessment	• May be affected by switch-over of control to treatment or subsequent therapies • Needs longer follow-up • Includes noncancer deaths
Progression-free survival	• Clinical • Surrogate endpoint for therapeutic and accelerated approval	• Randomized	• Generally assessed earlier and with smaller sample size compared with survival studies • Measurement of stable disease included • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Balanced timing of assessments among
Disease-free survival or event-free survival	• Clinical • Surrogate endpoint for therapeutic and accelerated approval • Time to event	• Randomized	• Generally assessed earlier and with smaller sample size compared with survival studies • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Balanced timing of assessments among treatment arms is critical • Includes noncancer deaths
Objective response rate	• Clinical • Surrogate endpoint for therapeutic and accelerated approval	• Randomized • Single-arm • Independent blinded review	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumor attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Many tumor or disease specific response criteria have changed the definitions of response limiting application to trials using earlier criteria • Frequent radiological or other assessments • May not always correlate with survival
Complete response	• Clinical • Surrogate endpoint for therapeutic and accelerated approval	• Randomized • Single-arm • Independent blinded review	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumor attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival
Symptom endpoints (patient-reported outcomes)	• Clinical • Time to event	• Randomized	• Generally assessed earlier and with smaller sample size compared with survival studies	• Blinding is important for assessing this endpoint • Subject to assessment bias, particularly in open-label studies • Lack of validated instruments in many disease areas • Definitions vary among studies • Balanced timing of assessments across treatment arms is critical • Application and validation of the PRO-CTCAE is in the early phases of application

Note. PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events. Information from Beaver et al. (2018; Chen et al. (2019); Fiteni et al. (2014); Hickey et al. (2013); Kluetz et al. (2016); McKee, Farrell, Pazdur, & Woodcock (2010); Pocock, Clayton, & Stone (2015a, b, c); Simon et al. (2015); U.S. Department of Health and Human Services (2018).

caregivers. If a patient is eligible for a trial, it is always a preferred option, as accessibility and eligibility for trials can change quickly. Applying the mantra "Never exclude a treatment option" will offer the patient the best opportunity to receive all available therapies.

For those patients interested in participating in a clinical trial, a detailed process of screening ensures application of the predefined inclusion and exclusion criteria. If eligible, the clinical trial is then submitted for insurance approval for the individual patient. Unfortunately, despite federal legislation, not all insurance plans approve investigational treatment. The number of open trials in the United States and the number of FDA approvals in oncology over the past decade contribute to challenges in the recruitment of patients. In many instances, patients are not referred to tertiary centers for clinical trial participation if FDA-approved drugs are available for use.

Each trial includes a schema, or a calendar of events with a detailed step-by-step process for conducting the trial. The schema includes any diagnostic imaging, laboratory or tissue testing, clinical visits, and medication reconciliation. Also included in most studies are patient journals to facilitate self-reporting of any adverse events. Physical exams and evaluation of AEs are included in these prespecified visits and must also be reported for any unexpected visits or admission to urgent care, the emergency room, or to the inpatient setting. Patients are queried for HRQOL indices at prespecified intervals to evaluate patient-reported outcomes. Reviewing the schema and the intensity of visits is critical to guide the patient in making the decision to participate. For some patients, the intensity of a trial, particularly phase I trials that require frequent pharmacokinetic testing, may dissuade the patient from participation.

Safety monitoring is at the core of managing patients on clinical trials and requires attention to detail. Advanced practitioners are often designated as Co-PIs or sub-investigators on these trials and see patients for trial-related visits. These visits require a detailed review of systems to capture any changes from baseline, details of any new clinical or symptom findings, and capture of any missed doses or medications added for symptom management. Adverse events must be attributed as to system, causality, and estimated severity (Tables 4 and 5). These attributions are the primary source for reporting safety and are used to create the tables and charts included in package inserts for FDA-approved drugs. Patients who require urgent or emergent care or hospitalization require immediate reporting and are automatically considered to have serious adverse events that must be reported to the medical monitor for the study within 24 to 48 hours. This requires a coordinated effort on the part of the research team, the patient, and their caregivers. Accurate and timely reporting is essential to avoid adverse events related to the investigational regimen across all study sites. Despite ongoing efforts to refine the definitions to limit variability in attributions, the system remains imperfect and open to subjective interpretation (George et al., 2019). Postmarketing reporting is critical to integrate continued observations for approved drugs, flag any sentinel events, and continue to ensure the safety of the public at large.

THE FDA APPROVAL PROCESS

Prior to 1992, FDA approval was only granted through the standard process for review and in the majority of cases required completion of a RCT. The FDA established the Oncology Center of Excellence (OCE) in January 2017 to streamline the development of cancer therapies through expedited review of drugs, biologics, and devices (Goldberg, Blumenthal, McKee, & Pazdur, 2018). The accelerated approval pathway utilizes surrogate measures such as biomarkers, objective overall response, and in some cases, clinical benefit (Chen et al., 2019; Gyawali, Hey, & Kesselheim, 2019). This is in response to the transformative effect of biomarker-driven therapies, the field of immunology, and the desire to make these drugs available to the public.

Between December 11, 1992, and May 31, 2017, the FDA granted accelerated approval for drugs considered to be transformative in areas of high unmet need based on phase II data and on endpoints other than OS (Beaver et al., 2018; Bloomfield et al., 2018). Among 64 malignant hematology and oncology products for 93 new indications, the most common primary endpoints included response rate (n = 81, 87%), PFS or TTP (n = 8, 9%), and disease-free survival (n = 4, 4%). Importantly,

Table 4. Adverse Event Attribution in Clinical Trials

CTCAE grade	Definition
Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe or medically significant but not immediately life-threatening
Grade 4	Life-threatening consequences
Grade 5	Death related to adverse event

Note. CTCAE = Common Terminology Criteria for Adverse Events

single-arm trial designs were the most common (n = 67, 72%; Beaver et al., 2018). For many trials with accelerated approval, postmarketing validation via long-term follow-up or conduct of a phase III randomized trial may be required for continued approval. In this analysis, at a median of 3.4 years after the accelerated approval, 55% (n = 51) had fulfilled their postmarketing requirement and verified benefit, 40% (n = 37) had not yet completed the confirmatory trials, and 5% (n = 5) had been withdrawn from the market.

INTERPRETATION OF STUDY RESULTS: EFFICACY

The efficacy of each trial is based on meeting both primary and secondary endpoints defined prior to submission for Institutional Review Board approval. Although the science sometimes moves faster than the enrollment process as previously discussed, the primary hypotheses of the study cannot be modified. The most common strategies for communicating outcomes include both statistical descriptions and graphic display (Table 6). Understanding how to interpret written and graphical displays of data is essential to critical review and application of the study results to practice. Specific examples of recent FDA-approved therapeutics for hematologic malignancies and the published pivotal trials will be presented in part two of this series. Specific examples of recent FDA-approved therapeutics for solid tumors and the published pivotal trials will be presented in part three of this series.

INTERPRETATION OF STUDY RESULTS: SAFETY

Efficacy without safety is not an acceptable outcome in clinical trials or in standard of care treatment. The CTCAE reporting structure (Table 4) in clinical trials has required continued editing to reflect knowledge gained across medical specialties relevant to organ function, degree of organ damage, and the potential causative agent. Publication of pivotal trials provides the most complete publicly available resource for summarizing adverse events. Reading the package insert and the published registration trial is recommended to integrate new therapies into practice and to guide estimates of risk and benefits. Understanding the grading system for AEs, the criteria for specific toxicities, and the population studied in the pivotal trial will improve APs' ability to safely integrate new therapies into practice. Importantly, package inserts include all trials registered for the approved agent and must be interpreted in the context of the specific diseases and any combination regimens.

Adverse events are generally summarized in publications and in the package insert as all-grade or grade ≥ 3. Grade 1 AEs are generally bothersome but not life-threatening and may or may not require interventions but should be mon-

Table 5. Attribution Codes Describing, in the Opinion of the Investigator, the Likelihood That the Adverse Event Is Due to the Intervention

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	1 - Unrelated	The AE is *clearly not related* to the intervention
	2 - Unlikely	The AE is *doubtfully related* to the intervention
Related to investigational agent/intervention	3 - Possible	The AE *may be related* to the intervention
	4 - Probable	The AE is *likely related* to the intervention
	5 - Definite	The AE is *clearly related* to the intervention

Note. AE = adverse event.

Table 6. Common Graphs and Diagrams Used to Display Data Generated From Clinical Trials

Reporting technique	Outcome measures	Application in reporting outcomes	Limitations/discussion
Kaplan-Meier curve (Figures 1 and 2)	OS, PFS, DOR, cumulative benefit	• Allows estimation of survival and comparison of two treatment groups based on selected categories	• Univariate analysis, which may be confounded by censoring differences between groups
Forest plot (Figure 3)	Treatment effects	• Helps determine behaviors of different subgroups within a larger dataset • Displayed using HR	• Subject to error if there are only a small number of data points within subgroup analysis resulting in false interpretation
Waterfall plot (Figure 4)	Tumor response	• Summarizes the typical response size and the fraction of patients experiencing benefit. Reveals interpatient heterogeneity of response	• Only shows one measurement in time, and tumor response size may not represent actual patient benefit in terms of OS or PFS
Swimmer plot (Figure 5)	Tumor response	• Tumor response and time frame of response displayed	• May become cluttered and uninformative if too many subjects are included or too many variables are included
Spider plot (Figure 6)	Tumor response	• Allows visualization of data points across time rather than at a specified time point	• Does not allow for formal statistical inference; difficult to interpret if there is a large number of data points
Hazard ratio	Statistical method	• The HR determines the treatment effect by comparing the difference between intervention A and intervention B • The hazard is the chance of an event (x) occurring at a specific time (t) • The farther away the HR is from 1.0, the greater the difference is between the intervention and control groups	• A reduction in the HR for death means that survival is prolonged, but not that the risk of death has been averted completely • Time specific and not cumulative, which confounds interpretation across trials that have different time points
Confidence interval	Statistical method	• The CI provides a range of possible values for the effect of the intervention • It can be obtained by estimating the precision of the estimate using the standard error of the effect Standard error can be determined from • The variability in the data and the sample size	• *p* value is commonly misused and misinterpreted • The CI and the *p* value are mathematically related • The 95% CI means that when we repeat a study many times in similar samples, the observed CI will cover the true • Risk ratio 95% of the times • Conversely, a *p* value of .05 means that if the null hypothesis were true and we were to repeat a study, a similar or more extreme risk ratio would be observed only 5% of the times.
p value	Statistical method	*p* < .05 means that the null hypothesis is true Interpretation of *p* values < .001 — Overwhelming evidence .001 to ≤ .01 — Strong evidence .01 to ≤ .05 — Some evidence .05 to ≤ .10 — Insufficient evidence ≥ .10 — No evidence	

Note. OS = overall survival; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval. Information from Gillespie (2012); Medeiros (2018); Miclaus (2018); Pocock, McMurray, & Collier (2015); Sashegyi & Ferry (2017); van Rijn et al. (2017).

itored closely to avoid more severe AEs. Grade 2 AEs may require interventions to control symptoms, but do not generally require dose modifications. Grade 3 or 4 AEs represent serious toxicities that require careful assessment of cause and consideration of options for mitigation and management. In some cases, the drug will need to be held, dose reduced, or discontinued based on the

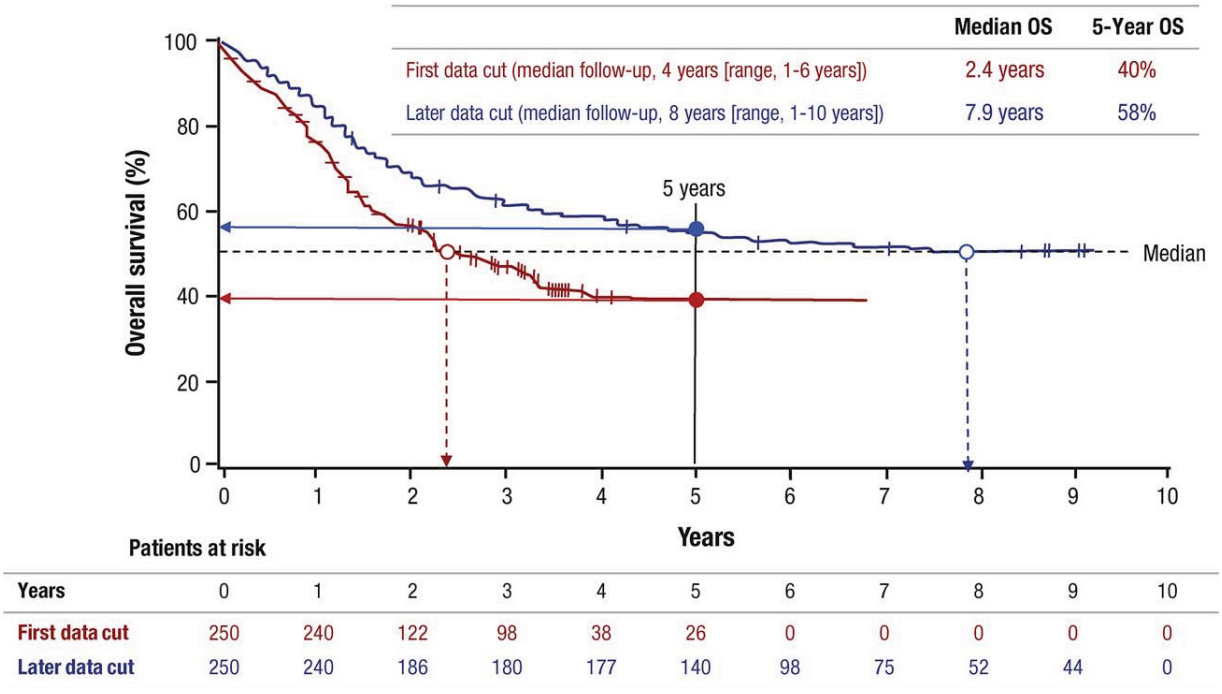

Figure 1. Example Kaplan-Meier curves of overall survival (OS) from an original data set (red) plus a follow-up analysis set (blue). As more patients completed the protocol and had additional follow-up, the median survival and 5-year OS increased. The dotted lines and open circles indicate the median survival for the original data set (red) and follow-up analysis set (blue), respectively. The 5-year survival estimates (solid black line) for the original data set and follow-up analysis set are represented by the red- and blue-filled circles, respectively. Note that the median (dotted black line) intersects with the "plateau" of events for the blue cohort and is therefore less informative than the median for the red cohort. Censored patients are indicated with vertical lines on the curves. The black dotted line is the median, colored dotted lines and open circles are where the KM curve and median intersect, and filled circles represent the 5-year OS estimate. Reprinted with permission from Medeiros, B. C. (2018). Interpretation of clinical endpoints in trials of acute myeloid leukemia. *Leukemia Research, 68*, 32–39. https://doi.org/10.1016/j.leukres.2018.02.002

individual guidelines for that drug and regimen. Unfortunately, many treatments are prematurely discontinued without application of all available strategies available for mitigation and management, effectively limiting potential benefit due to the fear of AEs.

Given the inherent flaws of clinician-only reporting of AEs using the CTCAE criteria, the PRO-CTCAE has been developed (Kluetz et al., 2016). Familiarity with the PRO-CTCAE will become a necessary component of conducting clinical trials in oncology to optimize benefit and limit risk. Adverse events attributed to immunotherapies have required development of specific criteria to estimate severity (Michot et al., 2016; Wang & Xu, 2019; Yu et al., 2019).

IMPLICATIONS FOR THE AP

All currently available therapies for cancer patients have been derived through the conduct of clinical trials. Advanced practitioners in oncology play an integral role in the conduct of clinical trials and in the integration of new therapies into mainstream practice. Review and synthesis of the plethora of clinical trial outcome data has become an arduous yet essential task. Applying general concepts and strategies for review will assist in the interpretation and clinical application of the emerging data. Familiarity with the hierarchy of clinical trial design, the shifting of desired endpoints in the era of precision medicine and robust clinical development, and the necessity of incorporating patient-reported outcomes will be necessary for all oncology clini-

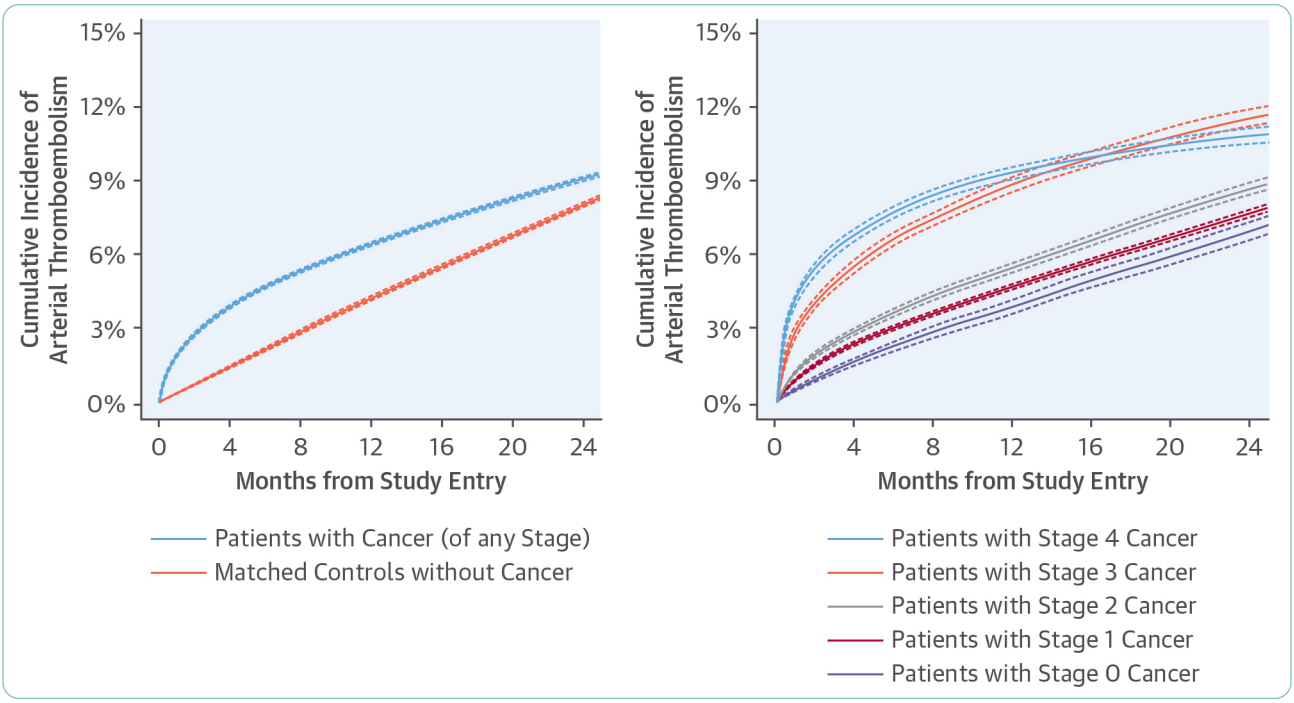

Figure 2. Example Kaplan-Meier curves displaying cumulative incidence. Cumulative incidence of arterial thromboembolism (composite of myocardial infarction and ischemic stroke) in patients with cancer compared to matched control patients (left panel) and when stratified by cancer stage at the time of cancer diagnosis (right panel). Competing risk survival statistics were used to calculate incidence. Dashed lines are used to indicate 95% confidence intervals. Reprinted with permission from Navi et al. (2017). Risk of arterial thromboembolism in patients with cancer. *Journal of the American College of Cardiology, 70*(8), 926–938. https://doi.org/10.1016/j.jacc.2017.06.047

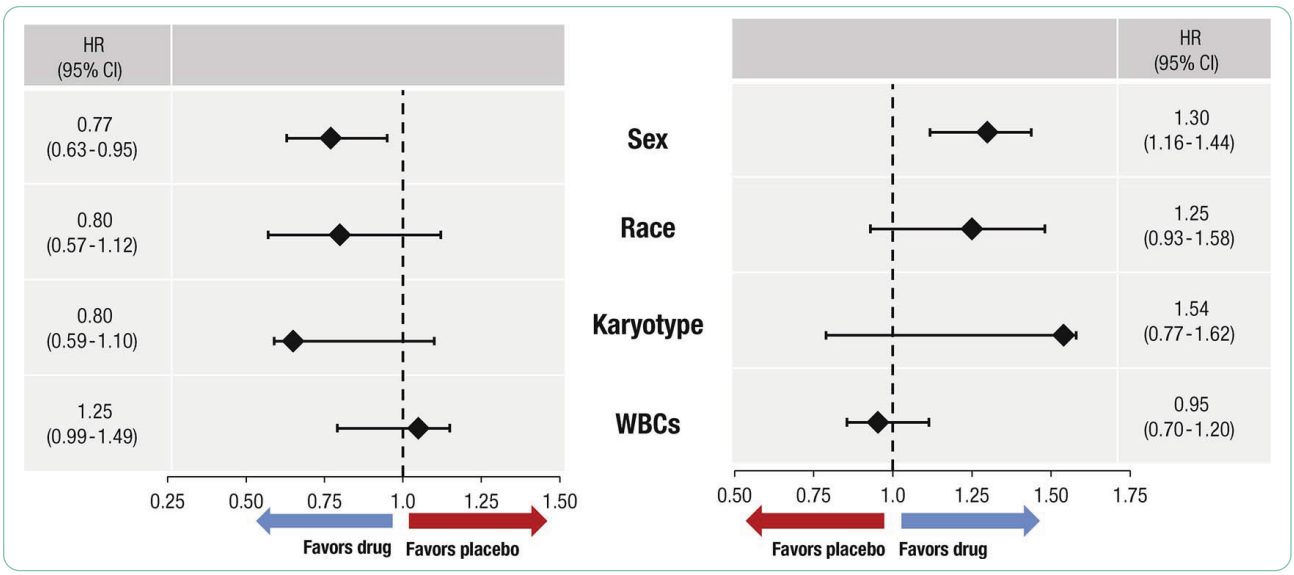

Figure 3. Example of a forest plot. Examples of the same multivariate analysis data plotted with both ratio options (i.e., drug or placebo as the reference group). In either case, the further away the hazard ratio (HR) is from 1.0, the greater the difference is between the drug and placebo. WBC = white blood cell. Reprinted with permission from Medeiros, B. C. (2018). Interpretation of clinical endpoints in trials of acute myeloid leukemia. *Leukemia Research, 68*, 32–39. https://doi.org/10.1016/j.leukres.2018.02.002

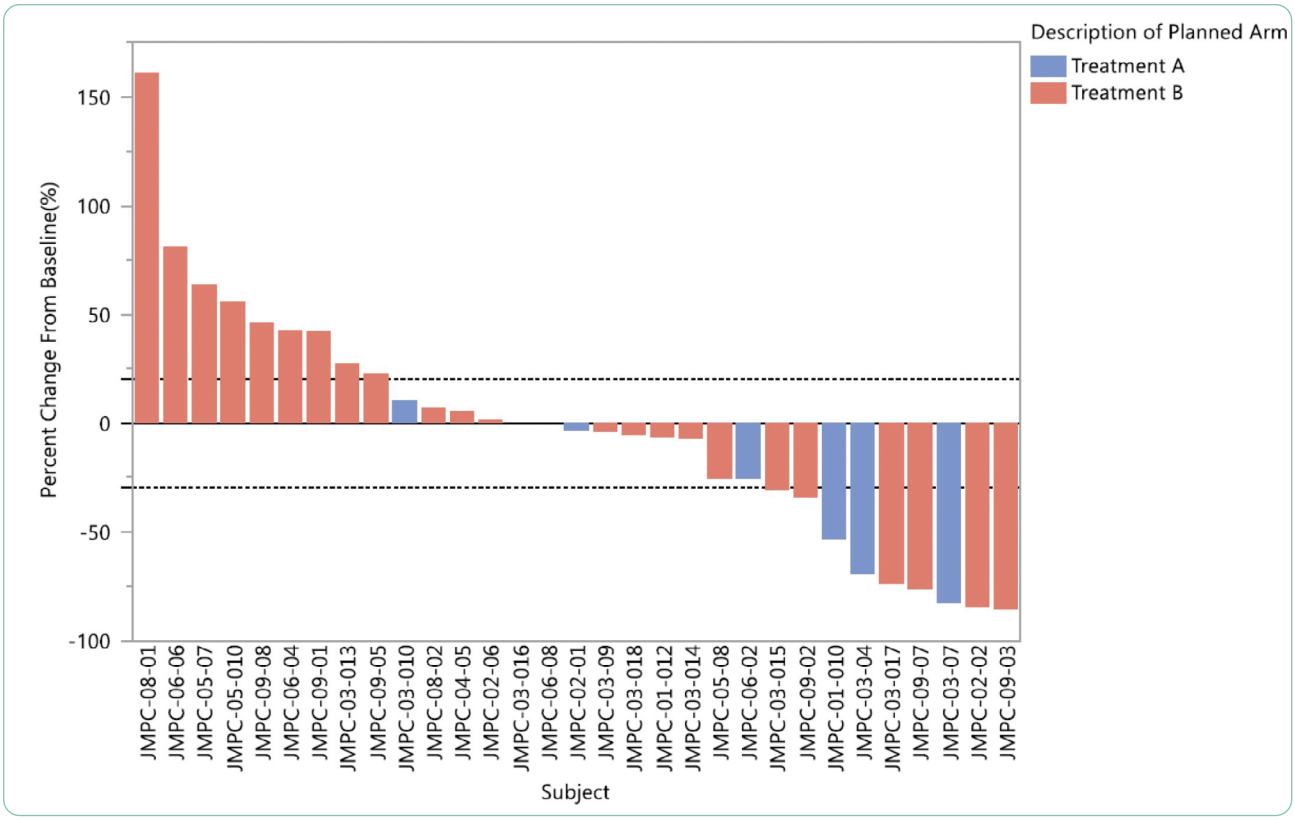

Figure 4. Example of a waterfall plot. A waterfall plot displays patients, ordered by their best response in tumor shrinkage, with y-axis as percent change from baseline of target lesions (Gillespie, 2012). Waterfall plots typically sort the x-axis by the same value displayed on the y-axis like a cascade of water. In this illustration, subjects are sorted in descending order so patients on the right (with large negative values in percent change from baseline) represent those responding well to treatment (tumor shrinkage), while those on the left typically represent those with potential disease progression. Each bar represents a single patient. These may be colored according to add further detail to the waterfall plot. Adapted from Miclaus, K., & Li, L. (2018). *Leveraging Standards for Effective Visualization of Early Efficacy in Clinical Trial Oncology Studies.* Paper presented at the PharmaSUG 2018 China.

cians, including the AP. For those APs involved in the conduct of clinical trials, familiarity with new definitions of response, changes in the attestation of AEs, including patient-reported outcomes, will be imperative to the effective conduct and reporting of the trial. There is an opportunity for all APs in oncology to play a larger role in the reporting of adverse events and development of strategies for the management of AEs in the postmarketing phase.

Disclosure

The authors have no conflicts of interest to disclose.

References

Beaver, J. A., Howie, L. J., Pelosof, L., Kim, T., Liu, J., Goldberg, K. B.,...Kluetz, P. G. (2018). A 25-year experience of US Food and Drug administration accelerated approval of malignant hematology and oncology drugs and biologics: A Review. *JAMA Oncology, 4*(6), 849–856. https://doi.org/10.1001/jamaoncol.2017.5618

Bloomfield, C. D., Estey, E., Pleyer, L., Schuh, A. C., Stein, E. M., Tallman, M. S., & Wei, A. (2018). Time to repeal and replace response criteria for acute myeloid leukemia? *Blood Reviews, 32*(5), 416–425. https://doi.org/10.1016/j.blre.2018.03.006

Blumenthal, G. M., Karuri, S. W., Zhang, H., Zhang, L., Khozin, S., Kazandjian, D.,...Pazdur, R. (2015). Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. *Journal of Clinical Oncology, 33*(9), 1008–1014. https://doi.org/10.1200/jco.2014.59.0489

Chapman, P. B., Liu, N. J., Zhou, Q., Iasonos, A., Hanley, S., Bosl, G. J., & Spriggs, D. R. (2017). Time to publication of oncology trials and why some trials are never published. *PLoS One, 12*(9), e0184025. https://doi.org/10.1371/journal.pone.0184025

Chen, E. Y., Raghunathan, V., & Prasad, V. (2019). An over-

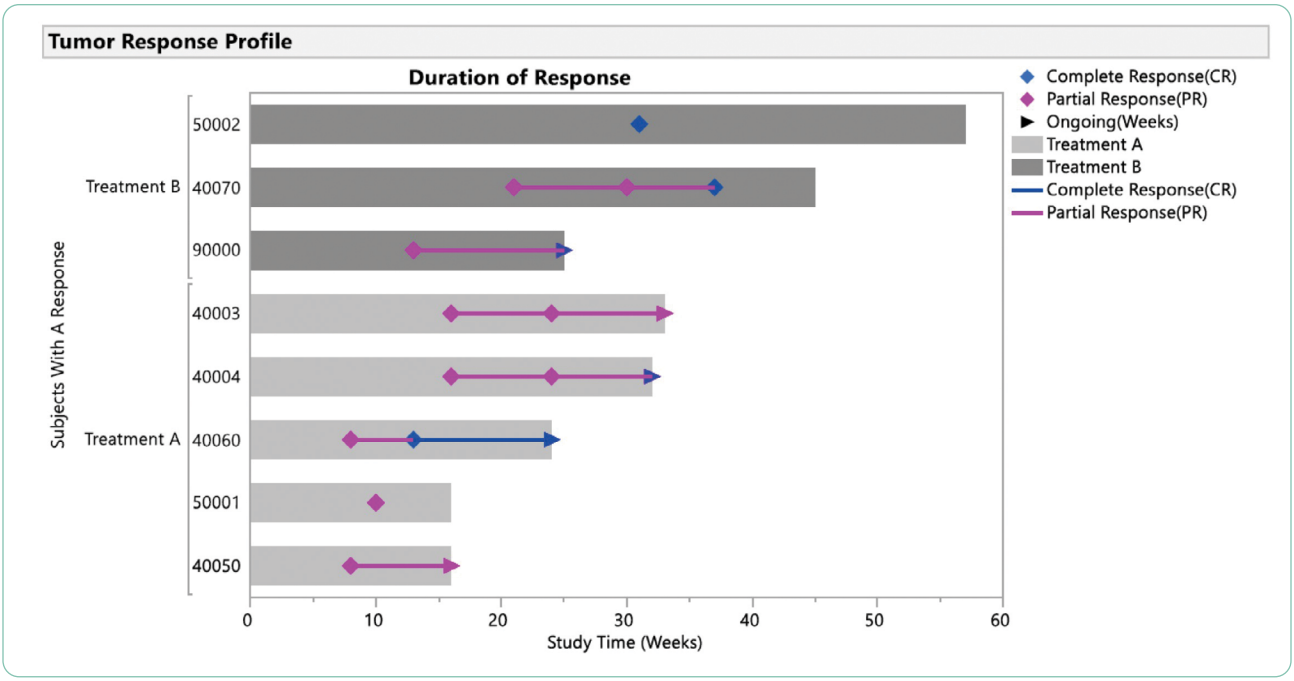

Figure 5. Example of a swimmer plot**.** This example shows use of a swimmer plot to illustrate tumor response over time by treatment A or B with details added for depth of response for each subject. Adapted from Miclaus, K., & Li, L. (2018). *Leveraging Standards for Effective Visualization of Early Efficacy in Clinical Trial Oncology Studies.* Paper presented at the PharmaSUG 2018 China.

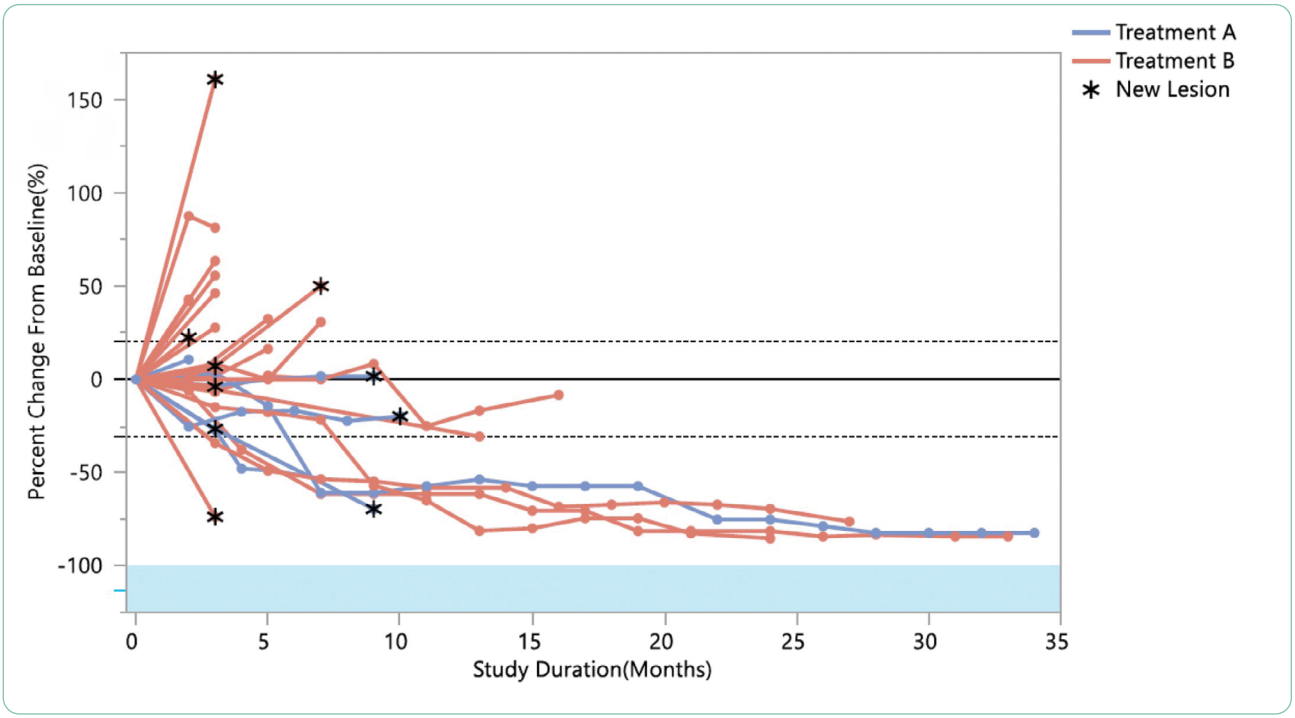

Figure 6. Example of a spider plot. Visualization of patient response trends across time is commonly called a spider or spaghetti plot. This plot is very useful to see changes and duration of quantitative tumor response to treatment, including the occurrences of a new lesion. Adapted from Miclaus, K., & Li, L. (2018). *Leveraging Standards for Effective Visualization of Early Efficacy in Clinical Trial Oncology Studies.* Paper presented at the PharmaSUG 2018 China.

view of cancer drugs approved by the US Food and Drug Administration based on the surrogate end point of response rate. *JAMA Internal Medicine, 179*(7), 915–921. https://doi.org/10.1001/jamainternmed.2019.0583

Curigliano, G., O'Connor, D. P., Rosenberg, J. A., & Jacobs, I. (2016). Biosimilars: Extrapolation for oncology. *Critical Reviews in Oncology/Hematology, 104*, 131–137. https://doi.org/10.1016/j.critrevonc.2016.06.002

Cuzick, J. (2015). Statistical controversies in clinical research: Long-term follow-up of clinical trials in cancer. *Annals of Oncology, 26*(12), 2363–2366. https://doi.org/10.1093/annonc/mdv392

Denson, A. C., & Mahipal, A. (2014). Participation of the elderly population in clinical trials: Barriers and solutions. *Cancer Control, 21*(3), 209–214. https://doi.org/10.1177/107327481402100305

Dunn, D. T., Copas, A. J., & Brocklehurst, P. (2018). Superiority and non-inferiority: Two sides of the same coin? *Trials, 19*(1), 499. https://doi.org/10.1186/s13063-018-2885-z

Ellimoottil, C., Vijan, S., & Flanigan, R. C. (2015). A primer on clinical trial design. *Urologic Oncology, 33*(3), 116–121. https://doi.org/10.1016/j.urolonc.2014.12.014

Estey, E., Othus, M., Lee, S. J., Appelbaum, F. R., & Gale, R. P. (2016). New drug approvals in acute myeloid leukemia: What's the best end point? *Leukemia, 30*(3), 521–525. https://doi.org/10.1038/leu.2015.262

Fiteni, F., Westeel, V., Pivot, X., Borg, C., Vernerey, D., & Bonnetain, F. (2014). Endpoints in cancer clinical trials. *Journal of Visceral Surgery, 151*(1), 17–22. https://doi.org/10.1016/j.jviscsurg.2013.10.001

Ganju, J., & Rom, D. (2017). Non-inferiority versus superiority drug claims: the (not so) subtle distinction. *Trials, 18*(1), 278. https://doi.org/10.1186/s13063-017-2024-2

George, G. C., Barata, P. C., Campbell, A., Chen, A., Cortes, J. E., Hyman, D. M.,...Hong, D. S. (2019). Improving attribution of adverse events in oncology clinical trials. *Controversy, 76*, 33–40. https://doi.org/10.1016/j.ctrv.2019.04.004

Gillespie, T. (2012). Understanding waterfall plots. *Journal of the Advanced Practitioner in Oncology, 3*(2), 106–111. https://doi.org/10.6004/jadpro.2012.3.2.6

Goldberg, K. B., Blumenthal, G. M., McKee, A. E., & Pazdur, R. (2018). The FDA Oncology Center of Excellence and precision medicine. *Experimental Biology and Medicine (Maywood), 243*(3), 308–312. https://doi.org/10.1177/1535370217740861

Gormley, N. J., Turley, D. M., Dickey, J. S., Farrell, A. T., Reaman, G. H., Stafford, E.,...Marti, G. E. (2016). Regulatory perspective on minimal residual disease flow cytometry testing in multiple myeloma. *Cytometry Part B: Clinical Cytometry, 90*(1), 73–80. https://doi.org/10.1002/cyto.b.21268

Gyawali, B., Hey, S. P., & Kesselheim, A. S. (2019). Assessment of the clinical benefit of cancer drugs receiving accelerated approval. *JAMA Internal Medicine, 179*(7), 906–913. https://doi.org/10.1001/jamainternmed.2019.0462

Hallek, M., Cheson, B. D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Dohner, H.,...Kipps, T. J. (2018). iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood, 131*(25), 2745–2760. https://doi.org/10.1182/blood-2017-09-806398

Heuser, M., Mina, A., Stein, E. M., & Altman, J. K. (2019). How precision medicine is changing acute myeloid leukemia therapy. *American Society of Clinical Oncology Educational Book, 39*, 411–420. https://doi.org/10.1200/edbk_238687

Hickey, R., Vouche, M., Sze, D. Y., Hohlastos, E., Collins, J., Schirmang, T.,...Salem, R. (2013). Cancer concepts and principles: primer for the interventional oncologist-part I. *Journal of Vascular Interventional Radiology, 24*(8), 1157–1164. https://doi.org/10.1016/j.jvir.2013.04.024

Ho, P. M., Peterson, P. N., & Masoudi, F. A. (2008). Evaluating the evidence: Is there a rigid hierarchy? *Circulation, 118*(16), 1675–1684. https://doi.org/10.1161/circulationaha.107.721357

Hochmair, M. J., Schwab, S., Burghuber, O. C., Krenbek, D., & Prosch, H. (2017). Symptomatic pseudo-progression followed by significant treatment response in two lung cancer patients treated with immunotherapy. *Lung Cancer, 113*, 4–6. https://doi.org/10.1016/j.lungcan.2017.08.020

Howick, J., Chalmers, I., Glasziou, P., Greenhalgh, J., Heneghan, C., Liberati, A.,...Thornton, H. (2011). The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document). Retrieved from https://www.cebm.net/index.aspx?o=5653

Jones, C. W., Handler, L., Crowell, K. E., Keil, L. G., Weaver, M. A., & Platts-Mills, T. F. (2013). Non-publication of large randomized clinical trials: Cross sectional analysis. *BMJ, 347*, f6104. https://doi.org/10.1136/bmj.f6104

Kaufmann, P., Pariser, A. R., & Austin, C. (2018). From scientific discovery to treatments for rare diseases - the view from the National Center for Advancing Translational Sciences - Office of Rare Diseases Research. *Orphanet Journal of Rare Diseases, 13*(1), 196–196. https://doi.org/10.1186/s13023-018-0936-x

Kluetz, P. G., Chingos, D. T., Basch, E. M., & Mitchell, S. A. (2016). Patient-reported outcomes in cancer clinical trials: Measuring symptomatic adverse events with the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *American Society of Clinical Oncology Educational Book, 35*, 67–73. https://doi.org/10.14694/edbk_159514

Kovacs, G., Robrecht, S., Fink, A. M., Bahlo, J., Cramer, P., von Tresckow, J.,...Bottcher, S. (2016). Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic leukemia (CLL) who achieve partial response: Comprehensive analysis of two phase III studies of the German CLL Study Group. *Journal of Clinical Oncology, 34*(31), 3758–3765. https://doi.org/10.1200/jco.2016.67.1305

Kurtin, S. E., & List, A. F. (2009). Durable long-term responses in patients with myelodysplastic syndromes treated with lenalidomide. *Clinical Lymphoma and Myeloma, 9*(3), E10–E13. https://doi.org/10.3816/CLM.2009.n.053

Massey, P. R., Wang, R., Prasad, V., Bates, S. E., & Fojo, T. (2016). Assessing the eventual publication of clinical trial abstracts submitted to a large annual oncology meeting. *Oncologist, 21*(3), 261–268. https://doi.org/10.1634/theoncologist.2015-0516

Mayawala, K., Tse, A., Rubin, E. H., Jain, L., & de Alwis, D. P. (2017). Dose finding versus speed in seamless immuno-oncology drug development. *Journal of Clinical Pharmacology, 57*(S10), S143–S145. https://doi.org/10.1002/jcph.1001

Maymone, M. B. C., Gan, S. D., & Bigby, M. (2014). Evaluat-

ing the strength of clinical recommendations in the medical literature: GRADE, SORT, and AGREE. *Journal of Investigative Dermatology, 134*(10), 1–5. https://doi.org/10.1038/jid.2014.335

McKee, A. E., Farrell, A. T., Pazdur, R., & Woodcock, J. (2010). The role of the U.S. Food and Drug Administration review process: Clinical trial endpoints in oncology. *Oncologist, 15(Suppl 1)*, 13–18. https://doi.org/10.1634/theoncologist.2010-S1-13

Medeiros, B. C. (2018). Interpretation of clinical endpoints in trials of acute myeloid leukemia. *Leukemia Research, 68*, 32–39. https://doi.org/10.1016/j.leukres.2018.02.002

Michot, J. M., Bigenwald, C., Champiat, S., Collins, M., Carbonnel, F., Postel-Vinay, S.,...Lambotte, O. (2016). Immune-related adverse events with immune checkpoint blockade: A comprehensive review. *European Journal of Cancer, 54*, 139–148. https://doi.org/10.1016/j.ejca.2015.11.016

Miclaus, K., & Li, L. (2018). *Leveraging Standards for Effective Visualization of Early Efficacy in Clinical Trial Oncology Studies*. Paper presented at the PharmaSUG 2018 China.

Molica, S., Giannarelli, D., & Montserrat, E. (2019). Minimal residual disease and survival outcomes in patients with chronic lymphocytic leukemia: A systematic review and meta-analysis. *Clinical Lymphoma, Myeloma, and Leukemia, 19*(7), 423–430. https://doi.org/10.1016/j.clml.2019.03.014

Nabhan, C., Parsad, S., Mato, A. R., & Feinberg, B. A. (2018). Biosimilars in oncology in the United States: A Review. *JAMA Oncology, 4*(2), 241–247. https://doi.org/10.1001/jamaoncol.2017.2004

Navi, B. B., Reiner, A. S., Kamel, H., Iadecola, C., Okin, P. M., Elkind, M. S.,...DeAngelis, L. M. (2017). Risk of arterial thromboembolism in patients with cancer. *Journal of the American College of Cardiology, 70*(8), 926–938. https://doi.org/10.1016/j.jacc.2017.06.047.

Pocock, S. J., Clayton, T. C., & Stone, G. W. (2015a). Design of major randomized trials: Part 3 of a 4-part series on statistics for clinical trials. *Journal of the American College of Cardiology, 66*(24), 2757–2766. https://doi.org/10.1016/j.jacc.2015.10.036

Pocock, S. J., McMurray, J. J., & Collier, T. J. (2015b). Making sense of statistics in clinical trial reports: Part 1 of a 4-part series on statistics for clinical trials. *Journal of the American College of Cardiology, 66*(22), 2536–2549. https://doi.org/10.1016/j.jacc.2015.10.014

Pocock, S. J., McMurray, J. J. V., & Collier, T. J. (2015c). Statistical controversies in reporting of clinical trials: Part 2 of a 4-part series on statistics for clinical trials. *Journal of the American College of Cardiology, 66*(23), 2648–2662. https://doi.org/10.1016/j.jacc.2015.10.023

Prowell, T. M., Theoret, M. R., & Pazdur, R. (2016). Seamless oncology-drug development. *New England Journal of Medicine, 374*(21), 2001–2003. https://doi.org/10.1056/NEJMp1603747

Rifkin, R. M., & Peck, S. R. (2017). Biosimilars: Implications for clinical practice. *Journal of Oncology Practice, 13*(9_suppl), 24s–31s. https://doi.org/10.1200/jop.2017.025734

Sashegyi, A., & Ferry, D. (2017). On the interpretation of the hazard ratio and communication of survival benefit. *Oncologist, 22*(4), 484–486. https://doi.org/10.1634/theoncologist.2016-0198

Shepshelovich, D., McDonald, K., Spreafico, A., Razak, A. R. A., Bedard, P. L., Siu, L. L.,...Hansen, A. R. (2019). Feasibility assessment of using the complete Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library. *Oncologist, 24*(4), e146–e148. https://doi.org/10.1634/theoncologist.2018-0332

Simon, R., Blumenthal, G. M., Rothenberg, M. L., Sommer, J., Roberts, S. A., Armstrong, D. K.,...Pazdur, R. (2015). The role of nonrandomized trials in the evaluation of oncology drugs. *Clinical Pharmacology & Therapeutics, 97*(5), 502–507. https://doi.org/10.1002/cpt.86

U.S. Department of Health and Human Services. (2017). *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0*. Retrieved from https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

U.S. Department of Health and Human Services. (2018). Clinical trial endpoints for the approval of cancer drugs and biologics: Guidance for industry. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics

van Rijn, M. H. C., Bech, A., Bouyer, J., & van den Brand, J. (2017). Statistical significance versus clinical relevance. *Nephrology Dialysis Transplantation, 32*(suppl_2), ii6–ii12. https://doi.org/10.1093/ndt/gfw385

Wang, Q., & Xu, R. (2019). Immunotherapy-related adverse events (irAEs): Extraction from FDA drug labels and comparative analysis. *JAMIA Open, 2*(1), 173–178. https://doi.org/10.1093/jamiaopen/ooy045

Yu, Y., Ruddy, K. J., Tsuji, S., Hong, N., Liu, H., Shah, N., & Jiang, G. (2019). Coverage evaluation of CTCAE for capturing the immune-related adverse events leveraging text mining technologies. *AMIA Joint Summits on Translational Science, 2019*, 771–778. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6568118/pdf/3056004.pdf

APSHO Members

Visit APSHO.org to download an APSHO Educator Module on this topic, specially created by the authors. You'll find a slide deck and accompanying presenter notes: a valuable resource for you to educate your team!