Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group

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ABSTRACT

Purpose: Washout periods and concomitant medication exclusions are common in cancer clinical trial protocols. These exclusion criteria are often applied inconsistently and without evidence to justify their use. The authors sought to determine how washout period and concomitant medication allowances can be broadened to speed trial enrollment and improve the generalizability of trial data to a larger oncology practice population without compromising the safety of trial participants.

Experimental Design: A multistakeholder working group was convened to define problems associated with excessively long washout periods and exclusion of patients due to concomitant medications. The group performed a literature search and evaluated study data from the Pancreatic Cancer Action Network (PanCAN), Emory University School of Medicine (Atlanta, GA), and the FDA to understand recent approaches to these eligibility criteria. The group convened to develop consensus recommendations for broadened eligibility criteria.

Results: The data analysis found that exclusion criteria based on washout periods and concomitant medications are frequently inconsistent and lack scientific rationale. Scientific rationale for appropriate eligibility criteria are presented in the article; for washout periods, rationale is presented by treatment type.

Conclusions: Arbitrary or blanket washout and concomitant medication exclusions should be eliminated. Where there is evidence to support them, clinically relevant washout periods and concomitant medication–related eligibility criteria may be included.

See related commentary by Giantonio, p. 2369

Introduction

Patient access to evidence-based experimental treatments is associated with improved outcomes in the cancer population (1). Expediting enrollment into therapeutic clinical trials in cancer is dependent on removing barriers to patient participation, such as overly restrictive eligibility criteria. Trials that adopt criteria safely reflecting populations most commonly seen in daily practice are more likely to accrue rapidly and be applicable to greater numbers of patients.

Approximately 20% of patients are ineligible for trials on the basis of commonly employed eligibility criteria (2). This makes a strong case for critical analysis of areas where eligibility criteria may be expanded safely. Prior work by American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) recommended numerous areas where expanded eligibility should be employed (3). This list was extensive, but a number of barriers remain. Our working group was formed to evaluate two commonly perceived barriers: washout periods from recent therapies/interventions and prohibited concomitant medications.

A washout period is defined as a time between treatment periods that is intended to prevent misinterpreting observations about study-related treatments that were actually due to prior therapies. Generally, washout/waiting periods prior to enrollment are employed in cancer trials following surgery, radiation, cytotoxic chemotherapy, small-molecule/tyrosine kinase inhibitors, monoclonal antibodies (with and without drug conjugates), and immunotherapies.

Prohibited concomitant medications create eligibility and timing challenges, because patients receiving anticancer therapies often have comorbidities that require drug therapy, such as pain, diabetes, or gastrointestinal or cardiovascular disorders. While some medications may be necessarily prohibited early in investigational agent development, prolonged prohibition across trial phases reduces the applicability of a therapy to a broader patient population in trials and following approval.

Current applications of washout period and concomitant medication eligibility criteria are discussed in **Table 1**. Reducing and/or eliminating a need to include time-based washout periods and prohibit concomitant medications may facilitate both clinical trial participation and greater generalizability of the research findings to a larger oncology practice population.

Process

The multistakeholder group identified concerns regarding washout periods and prohibited medications, with a focus on broadening eligibility criteria as much as possible to increase

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Translational Relevance

Washout periods for prior treatments and interventions limit timely accrual and evidence generation and may prevent patient enrollment without adding safety measures or preventing misinterpretation of efficacy results. Exclusion of patients who require concomitant medications for comorbidity or supportive care management prevents early understanding of investigational agent tolerability and dosing in those likely to receive the treatment after approval. Less restrictive requirements for prior therapy washout periods and concomitant medication use, in many instances, should be considered and may facilitate both clinical trial participation and greater generalizability of the research findings to a larger oncology practice population.

efficiency of enrollment and potentially diversify enrolled populations to include greater numbers of patients with comorbidities and chronic medication management needs. The group's observations of current and ideal eligibility criteria and trial design related to washout periods and concomitant medications are described in **Table 2**.

A literature search was performed to understand the historical rationale and background of common eligibility criteria, particularly for washout periods. Because of the relative lack of information obtained, additional data were pursued from three datasets: a series of trials in the Pancreatic Cancer Action Network (PanCAN) portfolio, a sampling of trials performed at the Winship Cancer Institute of Emory University (Atlanta, GA), and a review of new approvals in 2018 by the FDA.

Data Analysis

PanCAN trial dataset

Eligibility criteria for industry-, institutional-, and NCI-sponsored metastatic pancreatic adenocarcinoma treatment studies were reviewed to evaluate the need for specific recommendations related to washout periods and concomitant medications. Eligibility criteria from 16 phase III (including one seamless phase II/III) trials in the PanCAN database between 2010 and 2019 were evaluated (**Table 3**). Eligibility criteria from corresponding phase I and II trials studying treatments that advanced to phase III trials listed in PanCAN's database or on clinicaltrials.gov were also evaluated. In total, 34 trials studying 15 unique investigational agents were evaluated.

Studies were evaluated for washout periods for prior radiotherapy, chemotherapy, monoclonal antibodies, immunotherapy, and investigational agents. Washout periods for surgery, corticosteroids, blood cell stimulating drugs, antibiotics, and hormone therapy were also noted when indicated. When treatment-specific washout periods were not available as a result of inadequate details about entry criteria, more general exclusion criteria that would likely include these specific treatments were included (e.g., "washout from all prior systemic treatment").

Results showed a lack of consistency in washout periods from trial to trial, regardless of study phase and type of therapy, with most trials not mentioning a washout period in eligibility criteria. There was also a lack of consistency when reviewing how washout periods for therapies change over time as an investigational agent moves from earlier phase to later phase trials. While the washout periods often stayed the same for many types of therapies as an investigational agent moved to later phase testing, in some instances the washout periods decreased, increased, or were removed altogether. A rationale for washout periods was rarely provided. Our review demonstrated that about 50% of studies included time-based washout periods from 14 to 28 days.

Table 1. Definitions and applications of washout periods and prohibited concomitant medications.

Washout periods
Definition: a washout period is defined as a time between treatment periods that is intended to prevent clouding of information from one intervention to the next.
Application: washout/waiting time periods prior to enrollment are identified in protocols following surgery, radiation, cytotoxic chemotherapy, small-molecule/tyrosine kinase inhibitors, monoclonal antibodies (with and without drug conjugates), and immunotherapies.
Historical rationale: each aspect of a protocol-required washout period may have a different historical rationale, including prevention of untoward adverse events (e.g., wound healing after surgery and cytopenias), drug interactions (e.g., tyrosine kinase inhibitors overlapping with investigational agents), and incorrect adverse event attribution (e.g., late effects with immunotherapies). While in many cases these may be associated with theoretical concerns, they are often irrelevant to clinical practice.
Example: protocol-based treatment vs. clinical practice, a protocol may require a 21-day washout period from a daily oral EGFR-directed tyrosine kinase inhibitor; whereas in practice, a patient would be rapidly transitioned to next-line therapy after knowledge of progressive disease, with the only interval between doses being that required for insurance approval. These agents have short half-lives, and in some instances, discontinuation may be associated with a disease flare, making rapid transitions to next-line therapies critical (19, 20).
Concomitant medications
Definition: a concomitant medication is any drug or dietary supplement that a study participant uses in addition to the treatment under investigation.
Application: on average, patients with cancer take five chronic noncancer medications, not including those that may be used to manage adverse events associated with anticancer therapy (21). As patients age, the prevalence of comorbidities and associated polypharmacy increases (22).
Historical rationale: exclusion of concomitant medications is intended to prevent adverse drug interactions that may affect pharmacokinetics assessment, increase adverse event risks, and in rarer cases, reduce anticancer agent efficacy.
Example: protocol-based treatment vs. clinical practice, protocols often prohibit patients from taking ondansetron in any dose or route due to fears of QTc prolongation with an investigational agent; however, oral ondansetron is used widely and commonly in practice. The risk of QTc prolongation is solely due to high-dose intravenous ondansetron use and has not been shown with the oral route (23).

Table 2. Working group observations related to washout period- and concomitant medication–based trial design.

Current state
Real-time learning of adverse event profiles and pharmacology applicable to washout periods and concomitant medication prohibition is often not reflected in updated protocols.
A lack of data exists regarding patients not enrolled on trials due to extensive washout periods or inability to change or discontinue a prohibited medication.
Washout periods are essentially nonspecific surrogates for a clinical (e.g., adverse event) or laboratory (e.g., absolute neutrophil count) measurement that are included to ensure participant safety and prevent confounding of observations (safety or efficacy) on trial.
Lack of rationale for or specificity regarding washout period and concomitant medication exclusions can cause patient confusion about why they are ineligible for certain trials.
Optimal state
Although postmarketing development of drugs occurs, it is optimal and possible to have complete data on concomitant medication allowances at approval.
Evaluating potential safety and pharmacology interactions, such as QT interval prolongation studies and drug–drug interaction studies, early in drug development can liberalize concomitant medication allowances during later phases of drug development.
Nonclinical tools, such as *in silico* modeling, should be optimized to potentially minimize exclusion of medications and/or reduce required sample sizes in trials.

In reviewing the concomitant medications data, the most commonly excluded concomitant medications were infectious disease treatments and anticoagulants. As with washout periods, rationale for the exclusion of these concomitant medications was rarely provided.

Emory dataset

A series of 102 trials, across phases, was retrospectively evaluated for both washout periods and allowance of concomitant medications (**Table 4**). The majority were early-phase trials with pharmaceutical sponsors, and primarily included investigational oral small molecules alone or in combinations. Each trial was assessed for required washout periods for surgery, radiation, chemotherapy, monoclonal antibodies, immunotherapy, and investigational agents. Of the 102 trials, 36 were silent for a washout period from surgery. The remainder are listed in **Table 4**. Overall, washout periods varied; however, many categories had similar proportions in the ≤14 and

Table 3. Summary of PanCAN data review.

	Washout periods as I/E criteria			
	14 days	21 days	28+ days	No washout period I/E criteria
Radiation	11.76%	2.94%	26.47%	58.82%
Chemotherapy	23.53%	5.88%	5.88%	64.71%
Monoclonal antibodies	11.76%	5.88%	2.94%	79.41%
Immunotherapy	14.71%	5.88%	2.94%	76.47%
Investigational agents	20.59%	5.88%	20.59%	52.94%
Surgery	8.82%	14.71%	47.06%	29.41%

	Change in washout periods with later-phase trials					
	Shorter	Same	Longer	Not allowed	Silent	Added
Radiation	6.67%	33.33%	0.00%	40.00%	13.33%	6.67%
Chemotherapy	0.00%	33.33%	6.67%	33.33%	13.33%	13.33%
Monoclonal antibodies	0.00%	40.00%	0.00%	33.33%	0.00%	26.67%
Immunotherapy	0.00%	40.00%	0.00%	33.33%	6.67%	20.00%
Investigational agents	6.67%	13.33%	0.00%	26.67%	20.00%	33.33%
Surgery	0.00%	66.67%	20.00%	0.00%	6.67%	6.67%

Most commonly excluded concomitant medications	
Antibiotics	35.29%
Other anti-infectives	29.41%
Antifungals	26.47%
Anticoagulants	17.65%
Corticosteroids	2.94%
Growth factors	2.94%

Abbreviation: I/E, inclusion/exclusion.

Table 4. Summary of Emory data review.

Trial characteristics ($N = 102$)	
Phase	%
I	37%
I/II	22%
II	28%
III (2 seamless trials)	13%
Sponsor	
Pharmaceutical	77%
National Cancer Institute (NCI)	11%
Academic center	11%
Performance status allowed	
0–1	42%
0–2	55%
0–3	3%
Investigational agent type	
Small molecule[a]	66%
Monoclonal antibody[a]	21%
Chemotherapy[a]	8%
Antibody–drug conjugate	5%

Trial washout periods for prior treatments			
	≤14 days	21 days	≥28 days
Radiation ($n = 87$)	47%	9%	27%
Chemotherapy ($n = 93$)	34%	20%	37%
Monoclonal antibody (non-IO; $n = 78$)	24%	7%	45%
Immunotherapy ($n = 75$)	30%	12%	31%
Investigational agent ($n = 88$)	19%	16%	46%

Exclusions for concomitant medications			
CYP isozyme	Inducers	Inhibitors	Substrates
3A4/5	39%	40%	9%
2D6	2%	2%	2%
2C8/9	2%	3%	3%
1A2	4%	10%	2%
2C19	2%	3%	1%

[a]Includes combinations.

≥28 day timeframes, suggesting periods were not uniformly selected regardless of investigational agent mechanism of action (MOA).

Exclusions for concomitant medications were also evaluated, and common classes leading to ineligibility included corticosteroids (60%), antifungal agents (36%), anticoagulants (15%), human immunodeficiency virus therapy (13%), other anti-infectives (12%), and gastrointestinal medications (11%). Drug–drug interactions leading to exclusions were also evaluated, with a focus on agents that are metabolized by or affect the cytochrome P450 (CYP) enzyme system. Of 102 trials, 49 excluded some type of CYP agent. The most common isozyme leading to exclusions was CYP 3A4/3A5, with similar numbers for agents that induce and inhibit the pathway. The frequency of this exclusion aligns with this isozyme's role in the metabolism of approximately 60% of orally administered drugs (4, 5).

FDA data

The FDA analysis focused on new molecular entities (NME) that were approved in 2018 across all therapeutic areas within the Office of Hematology and Oncology Products (6). The rationale for this selection method of recently approved NMEs was to obtain a sample of products spanning a diverse range of molecules, novel targets, and therapeutic areas. The FDA working group members reviewed characteristics of registrational trials specific to concomitant medications and washouts, as outlined in the publicly available FDA product reviews and product labeling. For washouts, the FDA analysis included whether trials included periods for chemotherapy agents, monoclonal antibodies, immuno-oncology agents, prior investigational agents, and radiotherapy. For concomitant medications, the FDA analysis focused on whether CYP exclusions, drug–drug interactions, and concomitant medication allowances were included in registrational trial protocols.

The FDA analysis evaluated a variety of products, including therapies for solid and hematologic malignancies. A variety of types of molecular entities were reviewed for this analysis, including small molecules, monoclonal antibodies, radiolabeled analogues, and enzymes. Of the 19 NMEs approved in 2018, there was a wide range of washout periods specified in the registrational trials. Frequently, protocols included blanket language encompassing prior chemotherapy, radiation, and surgery. The most frequently used washout period ranged between 14 and 28 days, however, some protocols did not specify any washout period, and the longest washout period was 3 months. Overall, there was heterogeneity in washout periods specified in registrational protocols, even among similar therapeutic classes and diseases, and absence of rationale was common.

Prohibited concomitant medications were also specified in a heterogenous manner. Many trials of small molecules prohibited the use of CYP3A4 substrate medications, and washout periods varied greatly. For example, one trial used clear language regarding CYP3A4: "the concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A are not allowed," whereas another protocol used less definitive language: "coadministration with moderate/strong CYP3A4 inhibitors was not recommended. However, such medications could be used with caution and only if considered medically necessary. . ." As with washout periods, this analysis revealed a dearth of rationale for prohibited concomitant medications included in these registrational trials.

Recommendations

The consensus recommendations below are made in consideration of the benefits and risks to broadening criteria described above. These recommendations should inform sponsors and investigators as they draft study eligibility criteria, but are not intended as template language for trial protocols. Eligibility criteria should be tailored to the investigational treatment and patient population. For that reason, the recommendations are inclusive, rather than specific and prescriptive. Recommended language such as "clinically significant expected adverse event" should be replaced or supported by disease- and drug-specific, evidence-based examples.

Washout periods

(i) Time-based washout periods should be removed from protocol eligibility criteria in most cases. Any inclusion of time-based washout periods should be scientifically justified and clearly specified.

(ii) Relevant clinical and laboratory parameters should be used in place of time-based washout periods to address safety considerations.

(iii) Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

Table 5. Historical rationale for common time-based washout period eligibility criteria and key considerations for scientifically justified washout eligibility criteria, by treatment type: chemotherapy, small-molecule inhibitors, monoclonal antibodies, and antibody–drug conjugates.

Treatment type	Key shortcomings of common/historical washouts	Key considerations for scientifically justified washouts
Chemotherapy	• Many protocols include requirements for washout periods from prior therapy, often ranging from 14 to 28 days, yet a literature search yielded little in the way of published rationale for time-based washout periods from cytotoxic chemotherapy. • Treatment delays are a risk to patients who demonstrate radiographic progression, and screening periods may be employed to establish required intervals between radiographic evaluation.	• The typical 28-day washout period on the basis of the anticipated time for patients to recover from side effects of prior chemotherapy is no longer scientifically justified in many cases. – For example, in the era of growth factors, 3–4 weeks are not necessarily required for myelosuppression recovery.
Small-molecule inhibitors (including, but not limited to TKIs, serine and threonine kinase inhibitors, cyclin-dependent kinase inhibitors, MEK inhibitors, and tropomyosin kinase inhibitors)	• EC are not routinely updated to reflect differing MOAs, elimination half-lives, and toxicity profiles of targeted therapies. • Much of the trial language surrounding kinase inhibitors is the same as cytotoxic agents, antibodies, or other cancer treatments with prolonged washouts without justification. • The rationale for the differences with agents with minimal acute and chronic toxicity profiles is not well elucidated. • An approach to ensure patient safety from treatment withdrawal complications has yet to infiltrate protocol design, despite extensive documentation of effects, such as TKI withdrawal disease flare. – For example, gastrointestinal stromal tumors have a unique biology with rapid disease progression when imatinib is removed after prolonged benefit (9).	• Many targeted agents have rapid time-to-peak concentration, as well as abbreviated elimination half-lives, a unique property (e.g., compared with monoclonal antibodies). • The MOA of a given TKI on the tumor and the effects of any specific TKI on other factors related to the natural history of a given cancer or anticipated clinical course of a trial participant must be understood prior to initiation of treatment. This is imperative for the safety of the patient not only for treatment-related side effects, but also for treatment withdrawal effects. – For example, when outcomes of patients with advanced renal cell carcinoma treated with TKIs before and after cytoreductive nephrectomy are compared, complication rates are variable, but most note potential delayed wound healing and exacerbation of underlying medical conditions specific to perioperative VEGF-targeting TKIs (8).
Monoclonal antibodies (therapeutic tumor-targeted proteins with variable fragments engineered for epitope binding and based on IgG1 or IgG4 backbones)	• Monoclonal antibody therapies have more pharmacologic consistency than other agents (e.g., oral therapies), allowing for more predictable distribution and elimination, with typical half-lives ranging from 14 to 21 days (12). Despite this consistency, washout periods in EC are highly variable, suggesting history rather than pharmacology-driven timing.	• Concerns of clouding investigational therapeutic efficacy are minimal when the most recent therapy has failed the patient. • Because of the target specificity, concrete consideration of adverse events associated with monoclonal antibodies and their impact on next treatments may be determined in the absence of an arbitrary time period.
ADCs (a subset of monoclonal antibodies that comprise a monoclonal antibody, a linker, and a therapeutic payload)	• Payloads utilized to date have been agents such as maytansinoids and topoisomerase inhibitors that are in actuality chemotherapeutic agents, with cytopenias and other conventional acute adverse effects. Washout periods following these agents have varied and have often not been specified for this class; however, their growing use warrants discussion.	• For eligibility purposes, ADCs may be considered for washout periods as two different drugs, the monoclonal antibody and the payload. • The targeted component of the monoclonal antibody portion of the ADC can be considered for its specificity and contribution to a potential adverse event for an investigational agent or regimen. • Like cytotoxic chemotherapy, recovery from toxicities following ADCs are best measured by laboratory and clinical parameters, rather than timeframes. Rarely will a simple time period be justified, adequate, or necessary for ensuring safe and clear management of patients enrolled on trials.

Abbreviations: ADC, antibody–drug conjugate; EC, eligibility criteria; TKI, tyrosine kinase inhibitor.

Table 6. Historical rationale for common time-based washout period eligibility criteria and key considerations for scientifically justified washout eligibility criteria, by treatment type: radiotherapy, surgery, and immunotherapies.

Treatment type	Key shortcomings of common/historical washouts	Key considerations for scientifically justified washouts
Radiotherapy		• CNS edema postradiation: to realize all the potential benefits of enrolling patients with brain metastases and gather real-world experience of such patients, eligibility requirements should establish a 14-day washout after stereotactic radiotherapy or whole-brain radiotherapy for patients as a standard (13). • Myelosuppression risk: postradiotherapy myelosuppression risk is based on the percentage of active bone marrow irradiated, so the percentage of total bone marrow activity by bony site is helpful in determining the RR of marrow acute side effects from radiotherapy (14). • Acute mucosal membrane reactions to radiation: defined washout period times following standard palliative radiotherapy to mucosal or other surfaces are better replaced by clinical observation, particularly because adverse events will be low-grade and self-limited in nature in most patients.
Surgery	• As noted in the PanCAN dataset, eligibility washout timeframes following surgery vary greatly, and are often not mentioned, even within a single cancer type (**Table 1**). • Differing approaches (laparoscopic vs. open), invasiveness, anesthesia employed, and anatomic location are some of the variables that may impact recovery from the variety of surgeries that patients with cancer may undergo prior to trial enrollment. This heterogeneity suggests that the underlying rationale for including a specified number of days or weeks, rather than more specific parameters for recovery following a procedure, is arbitrary and should be removed from protocols.	• Specific clinical and medical assessment should be employed to ensure potential trial volunteers are functionally prepared and healed to safely receive investigational therapies. • For postsurgery treatment as with other treatments, arbitrary time periods do not reflect or replace clinical judgment, are part of a combination of EC that often overlap to ensure safety (e.g., laboratory values and performance status), and cannot be expected to be broadly applicable across multiple patients and procedures.

Immunotherapies	• Trials should not default to historical washout periods based on time or pharmacokinetic parameters (e.g., half-life), as this approach is both impractical and may not be in the patient's best interests, particularly since a new regimen on a trial has most likely been selected because of cancer progression.	• Pharmacologically, this class of agents includes a variety of molecules designed to modulate antitumor immune responses, and that often have an extended period of time for onset of both clinical activity and adverse events.
		• The tempo of median onset and resolution of irAEs have to be considered when patients transition from immunotherapies on trials or in the clinic to investigational agents.
		  • Median time to resolution of irAEs of 12 weeks has been generally consistent among immune checkpoint inhibitor agents (e.g., initial reports of ipilimumab; ref. 10).
		• Data support rapid subsequent trial enrollment when coupled with an initial understanding of investigational agent adverse event profiles and experience in adverse event attribution.
		  • A recent study showed that up to 25% of patients may experience new or worsening irAEs (most commonly hypothyroidism) after 6 or more months of therapy, but only 2.5% will experience a deepening of response after 6 months (23).
		• Late occurring irAEs that may cloud attribution to a single drug or regimen on study have to be accounted for prior to enrollment.
		• A thorough history of agent(s) given, timing of treatment, irAEs experienced, and understanding of the timing of common late effects may assist in differentiating late effects from prior therapies versus new effects from investigational ones.
		• It may be more useful to stratify study participants based on prior immunotherapy use and to avoid washout periods in the absence of unresolved irAEs that threaten participant safety.

Abbreviations: CNS, central nervous system; EC, eligibility criteria; irAE, immune-related adverse events.

Concomitant medications

(i) Concomitant medication use should only exclude patients from trial participation when clinically relevant known or predicted drug–drug interactions or potential overlapping toxicities will impact the safety of trial participants or compromise efficacy.

Scientific Rationale for Washout Periods by Treatment Type

Arbitrary time periods do not reflect or replace clinical judgment, are part of a combination of eligibility criteria that often overlap to ensure safety (e.g., laboratory values and performance status), and cannot be expected to be broadly applicable across multiple patients and procedures. Sponsors and investigators should provide the scientific rationale for washout periods when developing and implementing protocols, rather than relying on historic precedent that may not be appropriate for the treatment or disease being studied.

The group reviewed the rationale for common time period–based washout eligibility criteria for seven treatment types [chemotherapy, small-molecule inhibitors (1, 2 , 4, 5, 8, 9), immunotherapies (3, 10, 11), monoclonal antibodies (12), antibody–drug conjugates, radiotherapy (6, 7, 13–15), and surgery], where it was available. **Tables 5** and **6** outline the shortcomings of these common eligibility criteria and present key patient responses and safety considerations (e.g., potential risk of and recovery from clinically significant adverse events) that should guide clinical assessment of patient readiness for initiation of a new treatment.

Scientific Rationale for Excluding Certain Medications

As with washout periods, exclusion of concomitant medications during protocol-driven treatment should be supported by scientific rationale. Clearance and elimination of many investigational agents are predictable based on agent type, molecular weight, and/or other physicochemical characteristics. These more predictable agents (e.g., monoclonal antibodies) have known pharmacokinetic properties, and have a very low *a priori* likelihood of being involved in drug interactions. Other drugs under investigation, such as many oral small molecules, have a higher likelihood of being substrates, inducers, or inhibitors of metabolic clearance or transporter pathways, and therefore, must be approached more conservatively when considering which concomitant medications should be allowed. Although the preclinical ability to predict interactions has improved over time, no model or approach has sufficiently replaced dedicated studies in patients (16). Another consideration is actual oral bioavailability of a novel formulation and the effects of coadministration of agents that affect gastric pH (antacids, H2 antagonists, and proton pump inhibitors) and/or gastric emptying (food). Because these are unknown, many trials require patients to fast for 2–8 hours prior to and up to 4 hours following ingestion of an investigational agent, as well as prohibit agents that affect gastric pH. Also, as these drugs are available over the counter and prescribed in up to 55% of patients with cancer, it is important to mitigate the effect on investigational agents as early as possible in development and allow for their use in a general population (17).

Because the presence of concomitant medications can result in drug–drug interactions that affect the safety profile and interpretation of efficacy of an investigational drug, there are understandable concerns regarding loosening restrictions on concomitant medications in clinical trials. Unfortunately, polypharmacy tends to be common in patients with cancer, who also tend to be an older population, with multiple comorbid conditions that may require medical management. A review conducted by LeBlanc and colleagues reported the number of prescribed drugs in patients ranged from 3 to 9.1 (18). Without prior nonclinical knowledge of the potential effects of concomitant medications on investigational drug's pharmacokinetics and pharmacodynamics, many concomitant drugs are prohibited in early-phase clinical trials to ensure patient safety, reduce variability of responses, and ensure optimal conditions for proof of concept. This stringent exclusion of concomitant medications is often duplicated in later phases of drug development without much consideration of how growing nonclinical or clinical knowledge may support broader inclusion of concomitant medications.

Clinical pharmacology studies should be conducted as early as possible in drug development to inform concomitant medication use in eligibility criteria. Formulations of oral investigational agents should be optimized as early as possible in drug development to minimize absorption interactions and pharmacokinetic variability and inform allowance of concomitant medications as early as possible. Concomitant medication allowances should be broadened in later phase trials so that safety is assessed in the premarket setting.

Conclusion

Washout periods and concomitant medication exclusions are common in cancer clinical trial protocols. These exclusion criteria are often applied inconsistently (across trials and between protocol-driven vs. off-protocol treatment) and without evidence to justify their use. Arbitrary or blanket washout period and concomitant medication exclusions should be eliminated. Where there is evidence to support them, clinically relevant washout periods and concomitant medication–related eligibility criteria may be included.

Information gained from preclinical studies and earlier trials about investigational agent adverse event profiles and pharmacology should be incorporated as early as possible in drug development to minimize washout periods and liberalize concomitant medication allowances.

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Disclaimer

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References

1. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. Am Soc Clin Oncol Educ Book 2016;35:185–98.
2. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst 2019;111: 245–55.
3. Kim ES, Bruinooge SS, Roberts S, Ison G, Lin NU, Gore L, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research joint research statement. J Clin Oncol 2017;35:3737–44.
4. Rendic S. Summary of information on human CYP enzymes: human P450 metabolism data. Drug Metab Rev 2002;34:83–448.
5. Zimmerlin A, Trunzer M, Faller B. CYP3A time-dependent inhibition risk assessment validated with 400 reference drugs. Drug Metab Dispos 2011;39: 1039–46.
6. Blumenthal GM, Pazdur R. Approvals in 2018: a histology-agnostic new molecular entity, novel end points and real-time review. Nat Rev Clin Oncol 2019;16:139–41.
7. Evans SR. Clinical trial structures. J Exp Stroke Transl Med 2010;3:8–18.
8. Carvalho FLF, Zheng C, Witmer K, O'neill J, Lynch JH, Kowalczyk KJ. Complications associated with perioperative use of tyrosine kinase inhibitor in cytoreductive nephrectomy. Sci Rep 2019;9:15272.
9. Le Cesne A, Ray-Coquard I, Bui BN, Adenis A, Rios M, Bertucci F, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. Lancet Oncol 2010;11:942–9.
10. Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab. Cancer 2013;119:1675–82.
11. Hall KH, Liu Y, Jiang C, Harvey RD. New and worsening long-term immune-related adverse events with PD-1/PD-L1 pathway agents in patients with cancer. Pharmacotherapy 2020;40:133–41.
12. Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. CPT Pharmacometrics Syst Pharmacol 2017;6:576–88.
13. Lin NU, Prowell T, Tan AR, Kozak M, Rosen O, Amiri-Kordestani L, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group. J Clin Oncol 2017;35:3760–73.
14. Hayman JA, Callahan JW, Herschtal A, Everitt S, Binns DS, Hicks RJ, et al. Distribution of proliferating bone marrow in adult cancer patients determined using FLT-PET imaging. Int J Radiat Oncol Biol Phys 2011; 79:847–52.
15. Klopp AH, Moughan J, Portelance L, Miller BE, Salehpour MR, Hildebrandt E, et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. Int J Radiat Oncol Biol Phys 2013;86: 83–90.
16. Obach RS, Walsky RL, Venkatakrishnan K. Mechanism-based inactivation of human cytochrome P450 enzymes and the prediction of drug-drug interactions. Drug Metab Dispos 2007;35:246–55.
17. Planchard D. Can an acidic beverage reduce interactions between proton pump inhibitors and erlotinib? J Clin Oncol 2016;34:1292–4.
18. LeBlanc TW, McNeil MJ, Kamal AH, Currow DC, Abernethy AP. Polypharmacy in patients with advanced cancer and the role of medication discontinuation. Lancet Oncol 2015;16:e333–41.
19. Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with *EGFR*-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res 2011;17:6298–303.
20. Riely GJ, Kris MG, Zhao B, Akhurst T, Milton DT, Moore E, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. Clin Cancer Res 2007;13:5150–5.
21. Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, et al. Prevalence and factors associated with polypharmacy in older people with cancer. Support Care Cancer 2014;22:1727–34.
22. Balducci L, Goetz-Parten D, Steinman MA. Polypharmacy and the management of the older cancer patient. Ann Oncol 2013;24:vii36–vii40.
23. Harvey RD. Managing drug interactions with oral anticancer agents: signals, noise, and echoes. J Oncol Pract 2019;15:91–2.