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REVIEW

Seamless Designs: Current Practice and Considerations for Early-Phase Drug Development in Oncology

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Abstract

Traditionally, drug development has evaluated dose, safety, activity, and comparative benefit in a sequence of phases using trial designs and endpoints specifically devised for each phase. Innovations in drug development seek to consolidate the phases and rapidly expand accrual with "seamless" trial designs. Although consolidation and rapid accrual may yield efficiencies, widespread use of seamless first-in-human (FiH) trials without careful consideration of objectives, statistical analysis plans, or trial oversight raises concerns. A working group formed by the National Cancer Institute convened to consider and discuss opportunities and challenges for such trials as well as encourage responsible use of these designs. We reviewed all abstracts presented at American Society of Clinical Oncology annual meetings from 2010 to 2017 for FiH trials enrolling at least 100 patients. We identified 1786 early-phase trials enrolling 57 559 adult patients. Fifty-one of the trials (2.9%) investigated 50 investigational new drugs, were seamless, and accounted for 14.6% of the total patients. The seamless trials included a median of 3 (range = 1–13) expansion cohorts. The overall risk of clinically significant treatment-related adverse events (grade 3–4) was 49.1% (range = 0.0–100%), and seven studies reported at least one toxic death. Rapid expansion of FiH trials may lead to earlier drug approval and corresponding widespread patient access to active therapeutics. Nevertheless, seamless designs must adhere to established ethical, scientific, and statistical standards. Protocols should include prospectively planned analyses of efficacy in disease- or biomarker-defined cohorts of sufficient rigor to support accelerated approval.

Advances in biology and immunology continue to refine our understanding of cancer, elucidating potential mechanisms of tumor cell growth, survival, angiogenesis, and systematic suppression of cancer immunity. Nevertheless, with US Food and Drug Administration (FDA) approval bestowed on 5.1% of oncology drugs initiating trials between 2006 and 2015, translating advances in preclinical knowledge into effective cancer treatments has been difficult historically (1). An average of 9.1 years was required to develop agents receiving US regulatory approval between 1990 and 2005 (2). More recent data (1998–2014) suggest

that timelines for cytotoxic agents remained slow (median of 9.4 years), although targeted therapies required a median duration of 5.4 years (3). The immune checkpoint inhibitor pembrolizumab, however, received accelerated approval in only 3.7 years.

Attempting to expedite development timelines, pharmaceutical companies have launched first-in-human (FiH) studies devised to acquire a breadth of patient data that far exceeds the size of a typical phase I design. The FDA identified more than three dozen Investigational New Drugs involving expansive FiH

trials (3,4). Several trials have accrued more than a thousand patients, and a few have enrolled nearly 2000 (5). Although diverse in their details, these trials often assess efficacy at various doses and schedules as well as incorporate multiple expansion cohorts spanning a variety of organ- or biomarker-defined tumor subtypes. Attempting to consolidate clinical phases of drug development into a single, repeatedly amended, FiH protocol, sponsors have conducted these trials in ways that can be described as "seamless designs (4)."

Although the oncology community appreciates the efficiencies of this model, concerns have emerged. The Clinical Trials Design Task Force of the National Cancer Institute's Investigational Drug Steering Committee formed a working group to elucidate challenges arising from the growing adoption of these trials. This article summarizes the discussions from the perspectives of multiple stakeholders and provides recommendations to encourage responsible use of these designs.

Current Oncologic Drug Development Landscape

The traditional drug development paradigm partitioned primary evaluations of safety in phase I from analysis of preliminary efficacy in phase II and assessment of benefit relative to the existing standard of care with randomized comparison in phase III. Conventional discrete development programs have intrinsic inefficiencies and pause between phases of research while investigators interpret results, design, and initiate the next study. Moreover, while enrolling trial participants exhibiting diverse comorbidities, treatment histories, and cancer microenvironments, conventional designs rely on sample averages to guide dose selection and project benefit to the broader target patient population. Trials devised to infer average behavior may not elucidate the extent to which a treatment strategy confers benefit to individual patients and specific subpopulations.

Recent emphasis on precision medicine, with drugs targeting particular genetic alterations that activate pathways mediating proliferation and cell survival or promote anti-cancer immunity, has accelerated the development of tumor agnostic noncytotoxics and prompted innovations in trial design. Pembrolizumab achieved the first tissue-agnostic drug approval in 2017, expanding the indication to any unresectable or metastatic solid tumor with microsatellite instability. The tropomyosin receptor kinase inhibitor larotrectinib received priority review status from the FDA for tumors with an neurotrophic tropomyosin receptor kinases gene fusion, regardless of tissue of origin.

The concept of Breakthrough Therapy designation established by the FDA Safety and Innovation Act has further precipitated deviation from conventional drug development strategies (6). The intent of the pathway was to expedite development of the most promising agents for life-threatening diseases. Since 2012, the FDA awarded breakthrough designation to 101 cancer therapies from 82 unique cancer drugs in 98 unique indications (7). The result has been multiple accelerated approvals granted based on single-arm cohorts, including several studies that blur the distinction between dose selection and efficacy evaluation (8,9).

Merck's FiH trial of pembrolizumab (KEYNOTE-001, NCT01295827) opened to accrual in January 2011. Initially designed as a conventional 3 + 3 dose-escalation study, multiple amendments to the original protocol resulted in enrollment of 1235 patients across two dozen expansion cohorts (10–12). CheckMate-040 (NCT01658878) (13), a study initially designed to evaluate the safety of nivolumab in patients with hepatocellular carcinoma, was modified to add cohorts evaluating single-agent activity in sorafenib-naïve and sorafenib-treated patients (14). Subsequent amendments added cohorts to assess single-agent safety and efficacy in Child-Pugh B patients as well as a randomized comparison of dose and schedule for the ipilimumab and nivolumab combination. In total, the study treated 262 eligible patients.

Attempting to carry out an entire drug development program within a single, repeatedly amended FiH protocol has the potential to expose both patients and drug developers to avoidable risks. Traditional phase I studies evaluate safety at a limited number of centers, enroll a small number of patients, and involve frequent communication among the sites and sponsor. In contrast, traditional phase III trials activate globally with individual investigators observing only a small fraction of participants. Because adverse event (AE) profiles are typically well-established by the launch of a phase III trial, the potential risk to patients of having investigators with less individual experience with the study drug is minimized.

Large, early-phase, seamless designs pose new challenges to existing infrastructure for oversight, analysis, and real-time recognition and dissemination of emerging safety and efficacy data. As safety databases expand rapidly beyond the size of a typical phase I study, synthesis and analysis become practically challenging. Additionally, frequent protocol modifications add complexity, requiring more frequent communication between stakeholders. As a result, the FDA has proposed that seamless trials be reserved for drugs demonstrating sufficient preliminary evidence to support a breakthrough designation (4–6,15). A draft guidance document providing more clarity with respect to the use of seamless designs for oncology drug development was released by the FDA in August 2018 (16).

Extent of Use of Seamless Designs

We reviewed all abstracts presented at the American Society of Clinical Oncology annual meeting from 2010 to 2017 for FiH trials enrolling at least 100 patients to get a sense of the prevalence of such large early studies. Search and extraction methods are given in the Supplementary Materials. The analysis excluded clinical studies of pediatric populations and abstracts reporting trials in progress. A total 1786 early-phase trials enrolling 57 559 adult patients were identified (Figure 1). Most of these studies (86.3%) included patients with advanced solid tumors. Targeted and immunotherapy agents were investigated in 64.2% and 15.1% of these studies, respectively. Of 1786 trials, 51 were identified as seamless (Figure 1; Table 1). The seamless trials included a median of three (range = 1–13) expansion cohorts. As depicted in Figure 2, seamless trials accounted for only 2.9% of total oncology trials (n = 1786) but 14.6% of total trial participants (8423/57 559).

Fifty investigational new drugs (66.7% targeted therapy, 17.6% immunotherapy, 9.8% antibody-drug conjugate, 2.0% chemotherapy, 3.9% other therapy) were studied in the 51 trials, either as single agents (52.9%) or in combination with other therapies (47.1%) (Table 1). The majority of these trials (64.7%) were presented in the last 3 years (2014–2017), and 32 (62.7%) had published results by March 2018. Of these 32 studies, 68.8% lacked reported or publicly available statistical justification of the expansion cohorts' sample sizes. The overall rate of clinically significant treatment-related AEs (grade 3–4) was 49.1% (range = 0.0–100.0%), and at least one toxic death was reported in seven of these studies. The average response rate (complete plus partial responses) per study was 20.0% (range = 0.9–77.0%).
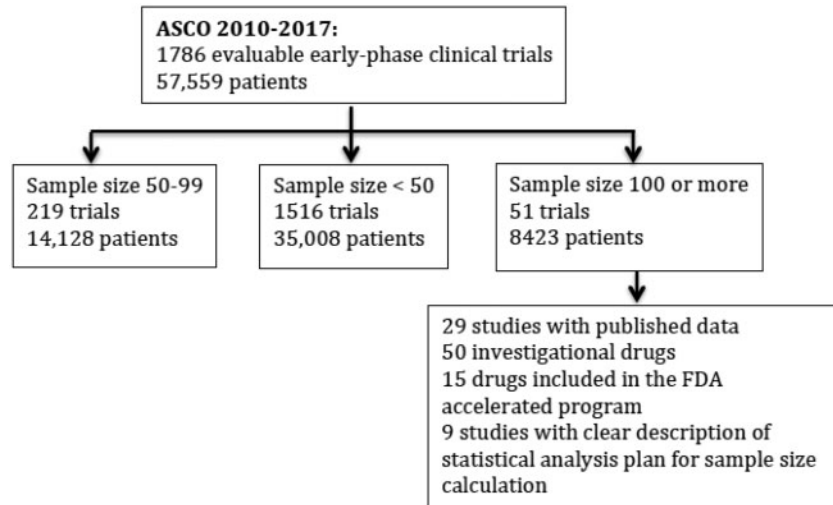
Figure 1. Flow diagram of study selection. ASCO = American Society of Clinical Oncology; FDA = US Food and Drug Administration.

Table 1. Seamless phase I/II studies with 100 or more patients

Variable	No. of studies (%)
Total	51 (100.0)
Primary tumor	
Hematologic	4 (7.8)
Mixed	3 (5.9)
Solid tumor	44 (86.3)
Clinical trial (single agent/combination of agents)	
Single agent	27 (52.9)
Combination regimen	24 (47.1)
Mechanism of action of investigational drug	
Targeted therapy	34 (66.7)
Immunotherapy	9 (17.6)
Antibody-drug conjugate	5 (9.8)
Chemotherapy	1 (2.0)
Other	2 (3.9)
Median number cohorts (range)	3 (1–13)
Pooled overall response rate (expansion/phase 2)	
0%	0 (0.0)
>0% and <10%	13 (25.5)
≥10% and <20%	15 (29.4)
≥20% and <40%	8 (15.7)
≥40%	8 (15.7)
Not available	7 (13.7)
Pooled clinically significant adverse events	
Studies with G3-4 (%)	34 (66.7)
Average G3-4, % (range)	49.1 (0.0–100.0)
Studies with any G5 (%)	7 (13.7)
Average G5, % (range)	7.5 (0.6–18.8)
Not available (%)	17 (33.3)
US Food and Drug Administration program	
Accelerated approval/number with same tumor indication	11 (21.6) / 8 (15.7)
Priority review	1 (2.0) / 1 (2.0)
Orphan drug status/number with same tumor indication	3 (5.9) / 0 (0.0)
Industry sponsorship	
Yes	40 (78.4)
No	11 (21.6)

By March of 2018, the FDA had granted accelerated approval to eight drugs and regular approval to five (17).

Dose Selection and Expansion Cohort Considerations

Most seamless designs begin with dose selection to identify the maximum tolerated dose (MTD) or a recommended dose for future study. For immunotherapies and targeted agents, dose-response and dose-toxicity relationships often fail to adhere to the monotonic assumptions that justify escalation designs for cytotoxic strategies. Dose-limiting toxicities (DLTs) are often not observed with these agents, and, therefore, an MTD may not be determined at the end of dose escalation. In the case of nivolumab, for instance, the original 3 + 3 design did not identify a MTD among doses 1, 3, and 10 mg/kg (18).

Seamless designs might benefit from new approaches for identifying safe and effective single-agent or combination doses (19–24). Integration of randomized dose-ranging stages may better refine regimens for molecularly targeted or immuno-oncology agents than conventional dose escalation approaches (19,20). Further efficiency can be gained if dose escalation strategies incorporate an "effect marker" to address efficacy if the goal is locating an effective dose (21,22,25,26). Because phase I studies tend to enroll more refractory patients than phase II studies, seamless designs devised to interrogate both safety and efficacy may require analyses that adjust for trial participants' characteristics, such as prognostic status or previous lines of therapies.

Following dose escalation, phase I studies commonly use expansion cohorts to further interrogate tolerability, evaluate pharmacology and biomarkers, and obtain additional data to assess therapeutic activity across tumor subtypes (27). Facilitating simultaneous investigations of multiple dose levels, schedules, and patient subtypes with expansion cohorts, seamless designs may be useful for refining regimens for future study. This strategy has been successfully employed to develop immune checkpoint inhibitors and molecularly targeted therapies (Table 2). Although multiple expansion cohorts may be advantageous for rapidly acquiring patient data, prespecified statistical analysis plans are essential to maintain statistical rigor and avoid

Distribution of cohort by number of patients (n=57,559)

- ☷ CT < 50   ☐ CT 50-99   ■ CT 100+
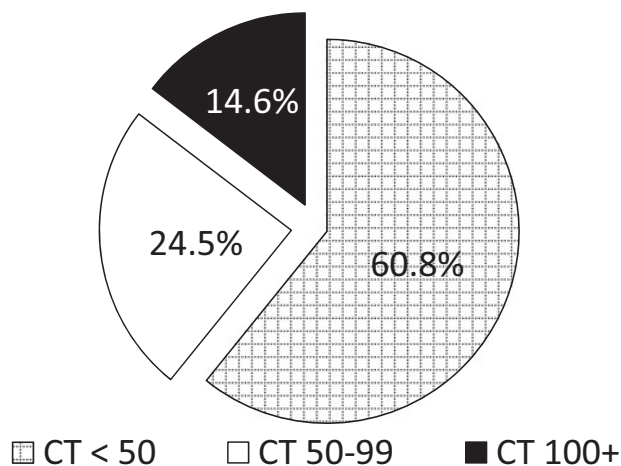
Distribution of total cohort by number of clinical studies (n=1786)
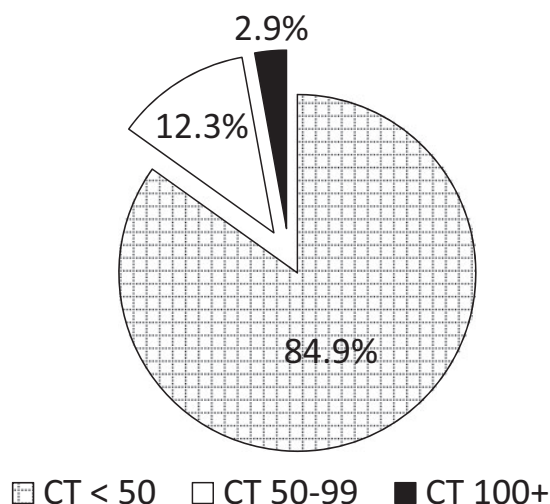

- ☷ CT < 50   ☐ CT 50-99   ■ CT 100+

Figure 2. Distribution of phase I/II trials. **A)** Distribution by number of patients and **B)** by number of clinical trials is shown. CT = clinical trial sample size.

erroneous conclusions of efficacy due to uncontrolled type 1 error. Some seamless early-phase trials have included randomization (10) to reduce allocation bias and confounding (60). Of the studies in Table 2, only Keynote-001 (pembrolizumab) and the Morpheus (atezolizumab combination) trials included randomization.

Late-Onset DLTs and Combination Therapies

Phase I clinical studies have traditionally focused on identifying AEs during the first cycle of treatment. Additionally, DLT definitions are generally based on acute AEs that are considered prohibitive for continued dosing. Although potentially dose limiting, late or delayed AEs occurring outside the prespecified evaluation timeframe may be overlooked when selecting the

most appropriate dose for future study (61,62). Late or delayed toxicity has occurred with immuno-oncology and molecularly targeted agents. In a pooled analysis of 576 patients with advanced melanoma receiving nivolumab (63), the median time to onset for treatment-related AEs of any grade ranged from 5.0 to 15.1 weeks. Among 2084 patients treated in 54 phase I trials of targeted agents (64), nearly one-half of the 599 patients developed their first DLT after the first cycle. For grade 2 AEs such as diarrhea, fatigue, and neutropenia, the highest incidence was observed in treatment cycles 3 to 6. With multiple expansion cohorts opening concurrently and sequentially, seamless trials may accrue over a longer duration than conventional early-phase studies. As a result, these studies may better elucidate risks of chronic low-grade AEs and late or delayed DLTs. For example, the phase I study of ceritinib for anaplastic lymphoma kinase gene (ALK)-rearranged, non-small cell lung cancer (58) could have proceeded to 900 mg daily according to the protocol. Instead, the recommended phase II dose was lowered because of grade 3 transaminitis and persistent grade 2 gastrointestinal toxicities observed beyond the protocol-specified DLT assessment period (Table 2).

Investigators attempting to identify optimal doses and schedules for multiple therapies administered in combination face additional challenges. Combination studies require strategies for managing toxicities, especially when the true MTD may not be known of each single agent. Because immunotherapies target the host immune system rather than the tumor, combination studies with immuno-oncology agents should consider late toxicities and endpoints. Extending accrual and observation periods with seamless design may facilitate more detailed pharmacokinetic and pharmacodynamic profiling of drug interactions (65).

Statistical Considerations and Challenges

Seamless trials require rigorous, prespecified, statistical analysis plans and sample sizes commensurate with the objectives and endpoints under study. Several factors, including variation inherent in study subpopulations, within-tumor molecular heterogeneity, clinical prognostic heterogeneity, comorbidities, and outcome assessment, determine the extent to which any trial provides reliable statistical estimates. Design modifications arising from post-hoc, data-driven analyses are sensitive to chance imbalances, yielding biased and potentially erroneous estimates of treatment effect size.

Seamless studies must also clearly define efficacy endpoints. Interim design modifications should be guided by objective decision thresholds that have been prespecified in the trial protocol. Similarly, researchers should select patients for the primary analysis population prior to reviewing study data. Protocols and amendments should clearly specify the maximum number of patients to be enrolled. Some have proposed criteria other than statistical power for choosing sample sizes, and these approaches may be useful for designing seamless trials (66–68).

Interim safety monitoring, required to protect patients enrolling into a conventional dose escalation study, should continue with subsequent evaluations of activity, biomarkers, and late-onset toxicities in expansion cohorts. Moreover, large seamless trials devised to assess measures of efficacy and clinical endpoints require interim futility analyses to limit enrollment of patients to ineffective regimens, combinations, or dose levels.

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Table 2. Selected examples of seamless phase I/II studies of immunotherapy and targeted agents

Drug study	Dose/schedule*	Tumor types	Reference	Role of expansion cohort(s)†
Pembrolizumab NCT 01295827 (Keynote 1)	2, 10 mg/kg q3w; 10 mg/kg q2w	Melanoma (n = 135) (28), expansion n = 173 (29) NSCLC (n = 495)	Hamid et al., 2013 (28) Robert et al., 2014 (29) Garon et al., 2015 (10)	D, S, T
Nivolumab NCT 00730639	0.1, 0.3, 1, 3, 10 mg/kg q2w	Melanoma (n = 104) NSCLC (n = 127 including initial n = 122) RCC (n = 34) CRC (n = 19) Prostate cancer (n = 17)	Topalian et al., 2012 (18) Brahmer et al., 2013 (30) Drake et al., 2013 (31)	D, T
NCT 01658878 (CheckMate 040)	0.1, 0.3, 1, 3, 10 mg/kg q2w	HCC (n = 262)	El-Khoueiry et al., 2017 (13)	D, T
Atezolizumab NCT 01375842	≤1, 10, 15, 20 mg/kg q3w 3, 10, 15, 20 mg/kg q3w; 1200 mg q3w 15 mg/kg q3w; 1200 mg q3w 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 15, 20 mg/kg q3w; 1200 mg/kg q3w	Melanoma (n = 45) NSCLC (n = 53) RCC (n = 70) Bladder cancer (n = 68, expansion n = 95) Multiple tumors (n = 23)	Hamid & Lawrence, 2013 (32) Spigel et al., 2013 (33) McDermott et al., 2016 (34) Powles et al., 2014 (35) Petrylak et al., 2017 (36) Herbst et al., 2014 (37)	D, T
Atezolizumab as part of various doublet and triplet combinations NCT 03424005 (Morpheus-TNBC)	1200 mg q3w; 840 mg days 1 + 15 q4w	TNBC (n = 260‡)	ClinicalTrials.gov (38)	D, S, T
NCT 03337698 (Morpheus-Non-Small Cell Lung Cancer)		NSCLC (n = 292‡)		
NCT 03280563 (MORPHEUS)		Hormone receptor positive HER-2 negative breast cancer (n = 111‡)		
NCT 03555149 (Morpheus-CRC) NCT 03193190 (Morpheus-Pancreatic Cancer) NCT 03281369 (Morpheus)-Gastric Cancer)		CRC (n=120‡'§) Pancreatic cancer (n = 185‡) Gastric/gastro-esophageal junction tumors (n = 357‡)		
Tremelimumab NCT 00086489	3, 6, 10 mg/kg q4w; 15 mg/kg q12w	Melanoma (n = 117)	Camacho et al., 2009 (39)	D, S, T
Durvalumab NCT 01693562	10 mg/kg q2w	Multiple tumors (n = 26; n = 288) including expansion in NSCLC (updated n = 198), melanoma, HCC, SCCHN (updated n = 62, esophageal, pancreatic cancers, TNBC), bladder cancer expansion (n = 61)	Lutzky et al., 2014 (40) Segal et al., 2014 (41) Rizvi et al., 2015 (42) Segal et al., 2016 (43) Massard et al., 2016 (44)	T
Durvalumab + tremelimumab NCT 02000947	Durvalumab 3, 10, 15, 20 mg/kg q4w; 10 mg/kg q2w Tremelimumab 1, 3, 10 mg/kg q4w X6→ q12w X3	NSCLC (n = 102)	Antonia et al., 2016 (45)	D, S, T

(continued)

Table 2. (continued)

Drug study	Dose/schedule*	Tumor types	Reference	Role of expansion cohort(s)†
Avelumab NCT 01772004	10 mg/kg q2w	Multiple tumors (n = 53)NSCLC (n = 184) expansion Bladder cancer (n = 44) expansion	Heery et al., 2017 (46) Gulley et al., 2017 (47) Apolo et al., 2017 (48)	T
Dabrafenib NCT 00880321	≤75, 100, 150, 200, 300 mg bid; 100 mg tid	Melanoma (n = 156) Multiple tumors (n = 28)	Falchook et al., 2012 (49)	D, S, T
Trametinib NCT 00687622	0.125–4 mg qd various regimens including 21/7, loading dose, daily with or without 15 days run-in dose	Melanoma (n = 81)Multiple tumors (exclude melanoma) (n = 125)	Falchook et al., 2012 (50) Infante et al., 2012 (51)	D, S, T
Cobimetinib NCT 00467779	0.05, 0.1, 0.2 mg/kg 21/7; 10, 20, 40, 60, 80 mg 21/7; 60, 80, 100, 125 mg 14/14	Multiple tumors (n = 97)	Rosen et al., 2016 (52)	D, S
Vemurafenib + cobimetinib NCT 01271803	Vemurafenib 720, 960 mg bid cobimetinib 60, 80, 100 mg qd 14/14, 21/7, 28/0	Melanoma BRAF V600+ (n = 129)	Ribas et al., 2014 (53)	D, S, T
Dabrafenib ±trametinib NCT 01072175	Dabrafenib 75, 150 mg bid trametinib 1, 1.5, or 2 mg qd	Melanoma BRAF V600+ (n = 247)	Flaherty et al., 2012 (54)	D, T
Crizotinib NCT 00585195	50 mg qd – 300 mg bid; 250 mg bid expansion	Multiple tumors (n = 37) NSCLC ALK+ (n = 143, includes initial report of n = 82) expansion	Kwak et al., 2009 (55) Camidge et al., 2012 (56) Kwak et al., 2010 (57)	D, S, T
Ceritinib NCT 01283516	50–750 mg qd	NSCLC ALK+ (n = 130)	Shaw et al., 2014 (58)	D, A, T
Niraparib NCT 00749502	30–400 mg qd	Multiple tumors enriched for BRAC+, expand in HGSOC and prostate cancer (n = 100)	Yap et al., 2010 (59)	D, A, T

*xx/yy denotes schedules where patients receive therapy for xx days followed by period off-therapy for yy days. q2w = every 2 weeks; q3w = every 3 weeks; qd = once a day; bid = twice a day; tid = three times a day; HCC = hepatocellular carcinoma; HGSOC = high grade serous ovarian cancer; NSCLC = non-small cell lung cancer; SCCHN = squamous cell cancer of head and neck; TNBC = triple negative breast cancer.

†A = elucidate delayed adverse events; D = dose refinement; S = schedule refinement; T = obtain further efficacy, toxicity, pharmacokinetic/pharmacodynamic data at one dose and schedule in one or more tumor subtypes.

‡Numbers of study subjects are estimates only because trials are ongoing.

§This study has not yet commenced recruiting.

Studies comprising parallel histology-specific expansion cohorts may benefit from more efficient designs, such as platform trials or basket trials (69–71). These innovative trial designs have evolved to estimate the relative impact of a tumor's molecular characteristics on a targeted agent's activity (72,73). Platform designs consolidate inter-study controls, enabling randomized comparisons while assigning a greater number of patients to experimental agents (74,75). Basket designs study heterogeneity among tumors harboring a common genetic alteration, facilitating statistical inferences for specific clinical and molecular subpopulations (76). Additionally, by integrating information across subgroups rather than treating the cohorts as de facto separate trials, basket designs promote efficiency (77). Seamless trials evaluating targeted therapies among doses, schedules, and patient subpopulations may benefit from the application of Bayesian multivariate modeling (78) and sequential monitoring strategies used in basket trials, which enable information sharing while controlling the study's overall probability of falsely declaring superiority of a treatment in the study, a risk that increases with multiple comparisons (79).

Reporting Practices and Oversight

Reports of seamless trials should transparently present the study's design, its evolution over time (ie, amendments), planned decision points, interim data analyses, and oversight. In some cases, a study report may need to include a fuller *Methods* section, even if in the supplementary materials, detailing design considerations. Seamless studies without randomized controls will require additional scrutiny given the potential

Table 3. Summary comparison of discrete phases I and II and seamless designs

Aspect of study conduct	Discrete early-phase design		Seamless design	
	Advantages	Challenges	Advantages	Challenges
Administration and infrastructure	Feasibility, because can activate in a limited number of sites Clear study endpoint and processes for disseminating data to investigators, clinical sites, and review boards	Pauses between phases for analysis, pharmacokinetic, safety review Requires additional protocols, regulatory and institutional review board approvals	Reduced duration between phases Compelling activity may lead to accelerated or full approval more expeditiously	Activates across many sites adding complexities Relies on a central medical monitor requiring evaluations of data submitted from many sites Often lacks formal study endpoint Lacks processes for formal review and dissemination to investigators, sites, and review boards
Statistical design	Prespecified statistical analyses Established methods for evaluating statistical power, sample size selection, and evaluating other operating characteristics Interim monitoring simplified with fewer enrolling sites Clear hypotheses	Enrolls only a limited number of sites In the presence of intersite clinical and patient heterogeneity, findings may not describe target treatment populations Often lacks randomization and thus difficult to project treatment activity benefit	Seamless phase transitions expedite acquisition of efficacy markers Enables rapid accrual over longer duration Facilitates expansion to many doses, schedules, combinations, and patient subpopulations May include randomization across expansion cohorts facilitating estimation of predictive activity benefit	May lack a formal design for expansion cohorts Imprecise operating characteristics as well as methods for design Interim safety and futility monitoring may be difficult with many expansion cohorts across many sites
Statistical inference	Established methods for hypothesis testing and analysis	Conventional analyses require assumptions of inter-patient exchangeability Relies on sample averages to guide dose selection and project benefit to the broader target patient population	Facilitates statistical inferences for specific clinical and molecular subpopulations with multivariate modelling applied to expansion cohorts	May overemphasize nonrandomized efficacy estimates Should use more complex analyses to adjust for drift in the prognostic status of trial participants across phases
Oversight	Established frameworks for transparency and monitoring by all stakeholders, including institutional review boards and regulatory reviewers	Small companies with a single drug may have limited experience monitoring ongoing trials	Allows more frequent communication between stakeholders about larger cohorts of patients	May expand rapidly without a formal process for review of initial safety data Decisions to incorporate novel cohort, dose, or combination may be ad hoc with no oversight Trial complexity and frequent modifications and multi-site data consolidation may make institutional review board and institutional oversight infeasible

Table 3. (continued)

Aspect of study conduct	Discrete early-phase design		Seamless design	
	Advantages	Challenges	Advantages	Challenges
				Small companies with a single drug may have limited experience monitoring ongoing trials
				Frequent modifications add complexity reducing clarity for investigators and review boards
				Requires more frequent communication between stakeholders
Reporting	Established frameworks for reporting findings for conventional designs	None	None	Requires the dissemination of large body of patient data without established reporting practices
Selection of dose and schedule	Established methodology and decision rules	Often algorithmic based with limiting assumptions of dose-response and dose-toxicity relationships	May better facilitate refined dose selection through the integration of randomized dose-ranging stages	Requires efficient consolidation of data from many sites that many not observe all toxicities
			May capture regimen benefit heterogeneity for molecularly targeted or immuno-oncology agents beyond the conventional dose escalation approaches	
			Prolonged accrual and observation periods may facilitate more detailed profiling of drug interactions via pharmacokinetics or pharmacodynamics	
Late onset toxicities	None	Late or delayed adverse events that occur outside the prespecified dose-limiting toxicity evaluation timeframe are often missed	Refine regimens for future study with extended accrual over a longer duration	None
			May better elucidate risks of chronic low-grade adverse events and late or delayed dose-limiting toxicities	

for bias. When reporting results, investigators should provide full presentation of enrolled patients to allow clinicians to extrapolate data relevant to their patients. Dissemination of a meaningful body of safety data from concurrent standard-of-care therapies is especially important for FIH seamless trials administering drugs that are first-in-class.

Oversight of clinical trials is a responsibility shared by many stakeholders, including sponsors, institutional review boards (IRBs), trial steering committees, data safety monitoring committees (DSMCs), participating investigators, and regulators. Each institution has its own specific policies and operational principles, but all IRBs are required to "assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research" (80).

With limited numbers of patients, investigators, participants, and sites, traditional phase I designs often forgo external DSMCs. Larger and more decentralized seamless designs warrant more formal processes for external oversight, and some research bodies, such as the National Cancer Institute (81,82), require certain trials to have formal DSMCs. Neither Good Clinical Practice (83) nor the FDA (84) require a DSMC or trial steering committee for all trials, although the recent FDA guidance on expansion cohorts in FiH trials calls for independent

monitoring committees. Institutions, IRBs, and investigators need to ensure that the safety monitoring plan is robust and appropriate for potential modifications and expansion. Amendments involving substantial design changes should undergo full IRB review and approval. For large phase I trials, defined here as those enrolling more than 100 patients, primary investigators should provide regular full updates (similar to Development Safety Update Reports submitted to Health Authorities) (85) to IRBs and participating sites. Sponsors should develop a formal plan to ensure reliable and efficient dissemination of emerging safety information to all investigators. When effective standard therapies exist, institutional oversight and regulatory committees should continue to encourage comparative trials.

The Patient's Perspective

Opinions differ among advocates on how to balance the urgency for new therapies against the need to ensure safety and efficacy. For example, some advocates, but by no means all (c.f., Friends of Cancer Research) (86), have supported passage of "Right to Try" legislation, allowing terminally ill patients to try experimental treatments that have completed phase I evaluation. Some advocacy organizations argue against early stopping of trials that show exceptional efficacy, reasoning that stopping may preclude identification of rare toxicities. Although virtually all patients who participate in oncology clinical trials do so with the hope of personal benefit, most nonetheless appreciate the nature of the overarching goal of early clinical studies—to characterize the efficacy and safety of drugs for the greater benefit of society and future patients. Most patients and advocates applaud innovations like seamless trial designs that have the potential to accelerate the development and approval of new drugs to treat cancer; however, they also expect well-designed and monitored clinical studies that protect participants and sufficiently characterize benefit and risk to support potential drug approval and enable future patients to make well-informed decisions about their treatment.

Discussion

A summary of the advantages and challenges of a seamless design compared with discrete early-phase designs is shown in Table 3. Experimental targeted and immuno-oncology agents have demonstrated substantial activity in early phase trials. Development of these noncytotoxic agents has challenged conventional assumptions about dose-response and inter-patient exchangeability that underlie traditional designs and methods for statistical analysis. The US regulatory landscape has also changed, with a growing number of accelerated approvals, especially in solid tumors, on the basis of single-arm trials. These phenomena have prompted innovations in trial design and consolidation of phases in the traditional paradigm. This review highlights many of the considerations for discrete phase and seamless study.

Appropriately designed and conducted clinical studies, however, remain a critical societal need (87). The rapid expansion of FiH trials may lead to earlier drug approvals and corresponding widespread patient access to active therapeutics. Nevertheless, seamless designs must adhere to established ethical, scientific, and statistical standards to ensure appropriate attention to benefits and risks for patients and the scientific community. Protocols should include prospectively planned analyses of efficacy in disease- or biomarker-defined cohorts of sufficient rigor to support accelerated approval.

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