A Road Map for Designing Phase I Clinical Trials of Radiotherapy–Novel Agent Combinations

Sarah R. Brown[1], Samantha Hinsley[2], Emma Hall[3], Chris Hurt[4], Richard D. Baird[5], Martin Forster[6], Andrew F. Scarsbrook[7], and Richard A. Adams[8]

ABSTRACT

Radiotherapy has proven efficacy in a wide range of cancers. There is growing interest in evaluating radiotherapy–novel agent combinations and a drive to initiate this earlier in the clinical development of the novel agent, where the scientific rationale and preclinical evidence for a radiotherapy combination approach are high. Optimal design, delivery, and interpretation of studies are essential. In particular, the design of phase I studies to determine safety and dosing is critical to an efficient development strategy. There is significant interest in early-phase research among scientific and clinical communities over recent years, at a time when the scrutiny of the trial methodology has significantly increased. To enhance trial design, optimize safety, and promote efficient trial conduct, this position paper reviews the current phase I trial design landscape. Key design characteristics extracted from 37 methodology papers were used to define a road map and a design selection process for phase I radiotherapy–novel agent trials. Design selection is based on single- or dual-therapy dose escalation, dose-limiting toxicity categorization, maximum tolerated dose determination, subgroup evaluation, software availability, and design performance. Fifteen of the 37 designs were identified as being immediately accessible and relevant to radiotherapy–novel agent phase I trials. Applied examples of using the road map are presented. Developing these studies is intensive, highlighting the need for funding and statistical input early in the trial development to ensure appropriate design and implementation from the outset. The application of this road map will improve the design of phase I radiotherapy–novel agent combination trials, enabling a more efficient development pathway.

Introduction

Despite a wealth of preclinical data demonstrating the radiosensitizing properties of several biological agents, none have made a significant impact to clinical care. In 2012, Ataman and colleagues (1) provided a pharmaceutical perspective on the clinical development of molecularly targeted agents in combination with radiotherapy, hypothesizing a lack of pharmaceutical investment in such studies as a reason for so few outputs. Although several perceived development barriers were highlighted, efficient collaboration between pharmaceutical companies and academia was noted as a key mechanism to drive forward this area of research. A series of consensus recommendations to increase the number of radiotherapy–novel agent studies affecting patient outcomes have been published (2, 3). The American Society for Radiation Oncology published a policy review and guideline (4) supporting the concept that with the rising technical power of radiotherapy to safely increase the local control of many solid tumors, it is an opportune time to rigorously explore the potential benefits of combining radiotherapy with molecular targeted agents and immunotherapies to improve cancer survival outcomes.

A prioritized, robust preclinical evaluation is essential to progressing radiotherapy–novel agent combinations efficiently, and guidelines summarize core data sets required to progress to phase I clinical evaluation (5). Although the need to optimize a phase I trial design is acknowledged (1–3, 5), the statistical and practical considerations needed to enable an effective evaluation have not been sufficiently addressed. The ability to produce robust, reliable safety results and dosing information during phase I studies ultimately speeds up the clinical development pathway, ensuring a sound evidence base from which to progress.

Deutsch and colleagues proposed determining the maximum tolerated dose (MTD) of an agent based on acute toxicity (defined as within 90 days of starting radiotherapy, following the RTOG definition; ref. 6), and incorporating late toxicities when determining the recommended phase II dose (7). "Late" toxicity has been variably defined, with a 2010 review of radiotherapy dose escalation trials (8) indicating over 80% of phase I studies define "late" as >3 months after radiotherapy and 5% as >6 months.

Challenges faced when designing phase I clinical trials of radiotherapy–drug combinations, which are not encountered in standard phase I studies of drug–drug combinations, have been highlighted (5). These include: (i) consideration of disease site(s) and normal organs exposed to the combination treatment, and how this affects toxicity evaluation(s); (ii) routine observation of grade 3 toxicities with curative intent radiotherapy, and the difficulty this causes in defining dose-limiting toxicities (DLT); and (iii) the time frame for observing toxicities being longer, for both acute and late toxicities. They emphasized that the most important consideration when designing phase I clinical trials of radiotherapy–drug combinations is to avoid delays in the delivery of radiotherapy, averting

[1]Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom. [2]Clinical Trials Unit Glasgow, University of Glasgow, Glasgow, United Kingdom. [3]Clinical Trials and Statistics Unit, The Institute of Cancer Research, London, United Kingdom. [4]Centre for Trials Research, Cardiff University, Cardiff, United Kingdom. [5]Cancer Research UK Cambridge Centre, Cambridge, United Kingdom. [6]University College Hospital, London, United Kingdom. [7]Radiotherapy Research Group, Leeds Institute of Medical Research at St James's, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom. [8]Centre for Trials Research, Cardiff University and Velindre Cancer Centre, Cardiff, United Kingdom.

Corresponding Author: Sarah R. Brown, Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds LS2 9JT, United Kingdom. E-mail: S.Brown@leeds.ac.uk

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serious effects on the probability of achieving tumor control. Defining DLTs appropriately is, therefore, difficult but crucial.

There is ample literature describing and reviewing various statistical approaches to phase I clinical trial designs in oncology (9–14), frequently dominated by the discussion of rule-based (e.g., 3 + 3) versus model-based [e.g., continuous reassessment method (CRM)] designs. Rule-based designs typically recruit patients in cohorts of 1 to 3, pause recruitment for a prespecified DLT period, and make dose-escalation decisions based on the number of DLTs observed within that cohort. In comparison, model-based designs use statistical modeling to estimate the relationship between dose and DLT risk, which informs dose-escalation decisions, considering a prespecified target DLT rate (the accepted proportion of patients expected to have a DLT at MTD). It is commonly accepted that model-based approaches have superior operating characteristics to rule-based designs; however, an assumption that these designs are more complex and challenging to implement has limited their use in practice (15). More recently, model-assisted designs, combining the advantages of rule-based and model-based designs, have been adopted in practice (16). A series of papers aimed at breaking down barriers to implementing statistically robust designs has recently been published (17–19).

The discussion of appropriate trial designs for radiotherapy–novel agent combination phase I trials has consistently highlighted the need to move away from the 3 + 3 design, and recommendations of using the time-to-event CRM (TiTE-CRM) or flip-flop approaches have been suggested (2, 5, 7, 13). TiTE-CRM offers a modification to the original CRM accounting for the timing of late-onset toxicities, enabling patients to be recruited while previous patients are being observed, ultimately resulting in a comparatively shorter trial duration.

Equally important considerations are selection of endpoints, definition of DLTs, target DLT rate, and follow-up period. With the challenge of potential delayed toxicity occurring after radiotherapy, the key factor in limiting radiation dose, phase I trials of radiotherapy–drug combinations must tackle this issue with a view to identifying a recommended phase II dose (RP2D). The safe identification of an appropriate phase II dose requires the setting of target DLT rates and relevant attributions and timings for the evaluation of given DLTs. Consideration must be given to whether dose-escalation decisions should be driven solely by toxicity or by the incorporation of other endpoints such as efficacy. Finally, the inclusion of differing patient subgroups, potentially with varied radiotherapy field size or biomarker-defined subgroups, and the impact on determining an MTD or RP2D should be addressed to determine whether dose escalation across multiple subgroups should be formally incorporated into the statistical design. Notably, radiotherapy is a precision-targeted therapy that is tailored to the individual, with generally minimal systemic effects, unlike most drugs. Although individual genetic factors result in interindividual variations in acute and late toxicities the ability to select or stratify patients based upon the radiation dose and fractionation schedule delivered to organs at risk is of key relevance in radiotherapy combination studies. Knowledge of the mechanism of action and preclinical normal tissue effects is key to the phase I setting to optimally assess the proposed combination and will inform decisions as to whether the initial approach should be in the palliative, neoadjuvant, or definitive setting. These aspects can be evaluated through a careful study of the mechanism of action of the drug, and its interaction with radiotherapy, in the preclinical work-up.

To enhance the design of radiotherapy–novel agent combination trials, optimize the potential for trials funding, and promote efficient trial conduct, we review the current phase I trial design landscape. We present a road map to facilitate future trial development, from the consideration of the research question and intervention to identifying a statistical design. Finally, illustrative case studies utilizing the road map are provided to inform those involved in the phase I radiotherapy–novel agent trial design, as well as key stakeholders participating throughout the development pathway.

Materials and Methods

Search strategy and selection criteria

A search of the MEDLINE/PubMed databases was performed for articles on phase I trial designs for radiotherapy–novel agent combinations published between October 2009 and February 2021. The following search terms were used: ((longitudinal[Title/Abstract] AND toxicity[Title/Abstract]) AND phase I[Title/Abstract]) OR (time to event[Title/Abstract] AND phase I[Title/Abstract])) OR (TITE[Title/Abstract]). Pearl growing from cited references within selected papers was also performed, on the basis of titles. The focus was specifically on key design components relevant to radiotherapy–novel agent phase I trials and the ability to incorporate long-term toxicity data into dose-escalation decision-making. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria were adhered to (20).

Abstracts were reviewed by one author (SB) to determine applicability to the setting of phase I radiotherapy–novel agent trials, and full texts of all potentially eligible abstracts were reviewed in detail by at least two authors (at least one statistician and one clinician). Papers describing clinical trial protocols or results, reviews, or those not applicable to oncology or clinical trials were excluded. Given the purpose of the review, free-text information was extracted from each paper as follows: timing of DLT period and timing of assessment; definition of toxicity; endpoints and categorization; MTD determination; inclusion of subgroups or biomarkers; statistical methodology backbone; software availability and practicality discussion; simulations or performance evaluation; the number of citations identified via Web of Science. An initial assessment by each reviewer of the relevance to radiotherapy–novel agent combinations and the practical application of the design was also performed.

Information extracted was recorded in a spreadsheet for data summary. A consensus discussion of all papers enabled the grouping of designs by the following aspects: MTD determination (toxicity, toxicity and efficacy, multiple outcomes); DLT categorization (binary over fixed period, ordinal over fixed period, cumulative/longitudinal, total toxicity profile); intervention to be escalated (drug, drug and radiotherapy dose/schedule); inclusion of subgroups (yes formally, no/yes but no information borrowing required/model independently); software availability (yes, no); performance evaluation (good, further evaluation required, poor). Based on these groupings, a road map was developed to provide a step-by-step approach to considering key components of the phase I trial design, with the overall aim of identifying an appropriate statistical design.

Quality assessment

A traffic light system was used to categorize designs based on software availability and performance evaluation, defined by simulation studies performed for each design. Simulation studies where a comparator design was incorporated, and/or there was a detailed discussion of desirable operating characteristics, where the time frame of DLT evaluation was at least three months (6, 7) or where the logistic difficulty index (LDI) was at least 6, and where at least five dose-toxicity scenarios were considered, were classed as having a good performance evaluation. When addressing the period of DLT evaluation, the LDI was calculated to take into account the accrual rate in the context of the

DLT window (21, 22), with an LDI of at least 6 (i.e., at least six patients recruited within the DLT evaluation time frame) deemed a sufficiently high value to evaluate a long-term toxicity approach (21). Designs highlighted in the original design paper as having poor performance compared with other designs were classed as poor. Designs with software readily available for implementation and with good performance evaluation were categorized as "green," being immediately accessible and relevant to radiotherapy–novel agent phase I trials; those with software available but requiring further performance evaluation, or no software available but good performance evaluation, were categorized as "amber"; and those with no software available and poor, or requiring further, performance evaluation were categorized as "red." Designs not relevant to radiotherapy–novel agent combinations were excluded from the road map selection.

Understanding the application of novel statistical designs is important to determine the practicalities associated with implementing them within a research environment (17, 18). Building on the road map developed from the literature review, two examples of designs in practice were identified by informally searching clinicaltrials.gov and are presented to demonstrate the usability of the road map, promote best practice, and outline logistical considerations for their implementation.

Results

Literature search

The literature search identified 99 abstracts, for which 33 full-text articles were deemed of appropriate fit and were retrieved as full texts. A review of full texts found 29 to be eligible for inclusion, and 4 were excluded. An additional eight articles were identified via citation searching. **Figure 1** displays the number of citations, full-text papers, and design categorizations identified from each stage of the review. Most papers excluded at abstract review described trial protocols or were not relevant to the oncology or clinical trial setting.

The design characteristics of the 37 papers are summarized in **Table 1**. Overall, 29 of 37 papers described designs whereby MTD determination was based on toxicity only, with the majority (29/37) categorizing DLTs as a binary outcome over a fixed period. Some designs extended this to incorporate adaptations such as the inclusion of time to treatment discontinuation (23) or wait times between patients (24). Only two papers described designs incorporating the dose escalation of both radiotherapy dose/schedule *and* drug (25, 26), and three incorporated formal subgroup analysis (27–29). Software was noted as available to apply the design in over 70% of studies (27/37). Design performance was rated as "good" in 20 of 37 designs, with further performance evaluation required in 16 of 37 and poor performance in 1 of 37 design.

Developing a design road map

The design characteristics summarized in **Table 1** were used to produce a road map (**Fig. 2**), providing researchers with a step-by-step approach of specific points to consider in the process of identifying and selecting an appropriate trial design for a phase I radiotherapy–drug combination trial. This was then used to group the methods identified through the literature search, to facilitate design selection. The road map consists of four components:

i. Determining the DLT assessment format
ii. Determining the MTD
iii. Practical considerations in design selection
iv. Additional points to consider

Determining the DLT assessment format

An initial consideration in identifying a phase I design for a radiotherapy–drug combination trial is to determine which aspects of the treatment will be escalated. Typically, this would be expected to be the dose of drug only; however, dual components may also be considered (e.g., two-drug combination with radiotherapy). Determining whether a single or dual component of therapy is to be escalated will refine design selection.

Defining DLT criteria is an essential aspect of phase I trial design. Individual DLT definitions may be disease-specific and should be defined with consideration of the mechanism of action of the treatment under consideration and the expected interaction with radiotherapy. This may depend upon and determine the clinical setting in which the combination is evaluated, i.e., palliative, neoadjuvant, or definitive setting. The categorization of DLTs for the purpose of endpoint evaluation may be considered as (i) binary over a fixed time, i.e., did the patient experience a DLT within a prespecified time frame, yes/no; (ii) ordinal over a fixed period e.g., did the patient experience no toxicity, moderate toxicity, or DLT, or ordinal toxicity as graded by Common Terminology Criteria for Adverse Events v5.0 (CTCAE; ref. 30); (iii) cumulative or longitudinal, e.g., cumulative toxicity over multiple cycles, or worst grade of toxicity experienced at each treatment cycle; (iv) a total toxicity profile i.e., a quasi-continuous score capturing multiple types and grades of toxicity (31, 32). Selecting which endpoint is most appropriate can be dependent on the mechanism of action of the radiotherapy–drug combination, the expected toxicity profile of these alone and in combination, and the disease in question. Specification of the DLT evaluation window is essential in determining the DLT assessment format, and further discussion of this specific aspect is provided under "Additional points for consideration," where selection between identified designs is required.

Determining the MTD

Typically, within phase I trials, the MTD will be determined based on the occurrence of DLTs, as defined according to considerations discussed in the paragraph above. However, the incorporation of additional measures such as treatment efficacy may be appropriate where a trade-off between toxicity and efficacy is important in selecting a dose to take forward for further evaluation. Consideration should be given to the mechanism of action and the clinical development pathway for the radiotherapy–drug combination and the patient population under consideration, when determining the basis for the MTD. A tailored selection of patients for specific drug treatments is increasingly based upon biological knowledge or predictive biomarkers, which means even phase I studies may recruit based upon these criteria. Although a more typical approach would be to determine MTD more broadly and then expand into cohorts of selected patients dependent upon early signals of activity either biologically or clinically (33, 34), where biomarker screening or immune profiling may be expected to affect treatment tolerability, designs incorporating multiple subgroups may be considered. In terms of efficacy and toxicity as a combined endpoint in single-arm, early-phase, combination therapy studies, it is relevant to explore the concepts that interactions between radiotherapy and drug may require some process adaptation. As an example, if we look at immunotherapies and radiotherapy, it is possible that a novel combination will be relevant for a biomarker-selected cohort of patients. It may be prehypothesized that the incidence of, for instance, novel autoimmune toxicities, might only be relevant and increased in frequency in those with the relevant biomarker. In this scenario, it would be key to explore relevant toxicities separately as well as jointly across subgroups. Should the inclusion of multiple subgroups

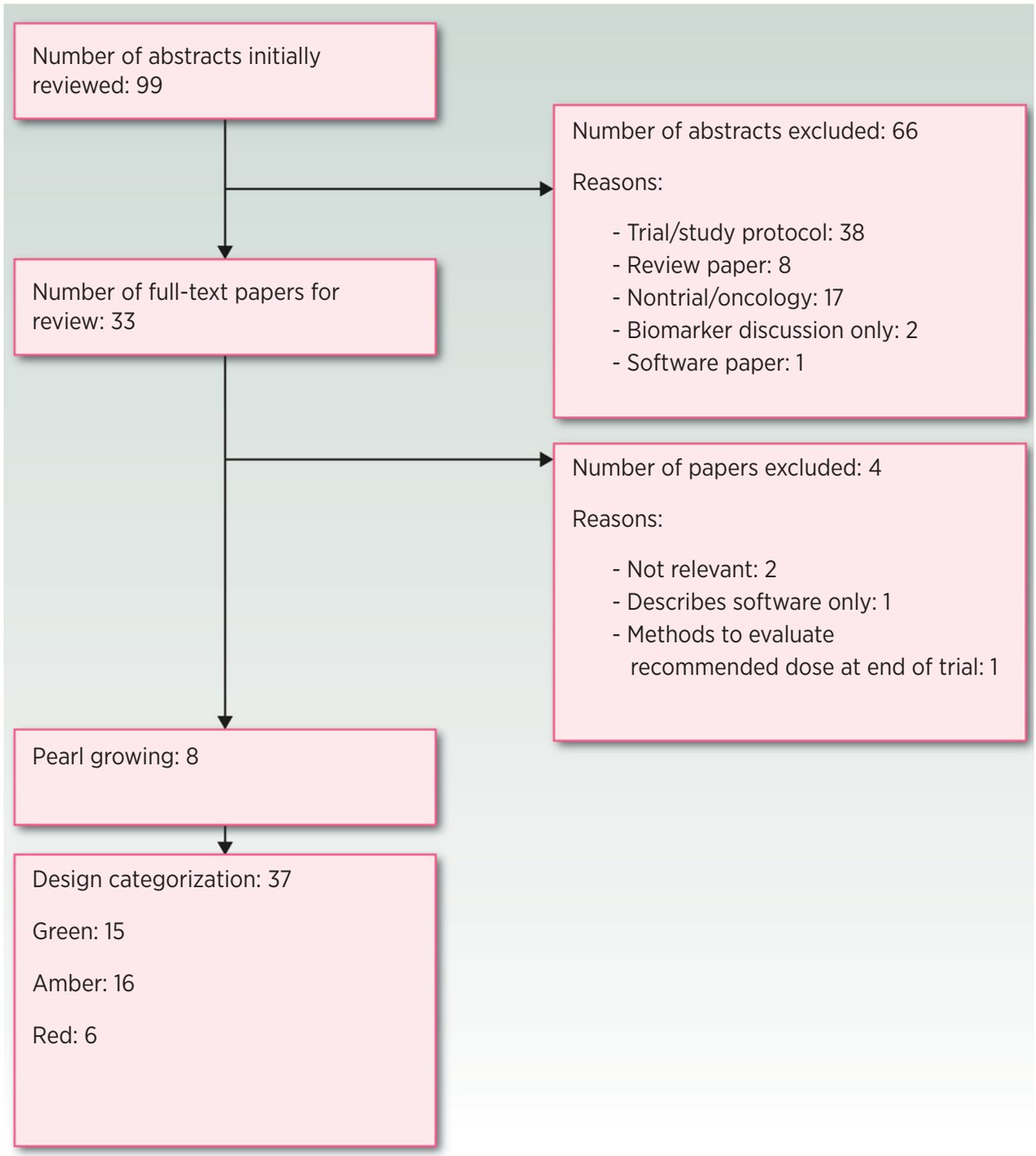

Figure 1.
PRISMA flow diagram of papers in review.

be necessary in determining the MTD, this may be incorporated into the design by allowing subgroup information to be formally included in the dose-escalation model or enabling the borrowing of information across groups. It is also possible to utilize the same statistical design across multiple subgroups independently, therefore widening the number of applicable designs in this setting.

Practical considerations in selecting a design

Grouping of identified phase I designs has been made based on software availability and performance evaluation. Additional practical considerations when considering design selection are covered in the following section. A key barrier to the implementation of novel phase I designs is often the availability of statistical design software and the

Table 1. Number of designs for each data item extracted, overall and by rating ($n = 37$).

	Green	Amber	Red	Overall
Total	**15**	**16**	**6**	**37**
MTD determination				
Toxicity	14	12	3	29
Toxicity and efficacy	1	3	3	7
Multiple outcomes	0	1	0	1
DLT categorization				
Binary fixed period	13	11	5	29
Ordinal fixed period	1	1	0	2
Total toxicity profile	1	2	0	3
Cumulative/longitudinal	0	2	1	3
Escalation of				
Drug	14	15	6	35
Drug and radiotherapy dose/schedule	1	1	0	2
Incorporation of subgroups				
Yes, formally	1	2	0	3
No/model independently	14	14	6	34
Software available				
Yes	15	11	1	27
No	0	5	5	10
Number of citations, median (range)	9 (0–291)	7 (0–57)	4 (0–36)	7 (0–291)
Performance evaluation via simulation				
Good	15	5	0	20
Further evaluation required	0	11	5	16
Poor	0	0	1	1

capability to adapt this to trial-specific design requirements. When selecting a model to implement, attention should be given to ease of application, and to published design performance metrics. It is essential that the performance of a design is evaluated for the specific requirements of a trial via extensive simulation. The resource requirements to undertake this evaluation should not be underestimated; therefore, understanding the current practical application and more general design performance is beneficial when selecting an appropriate methodology. Approaches to design evaluation and simulation have previously been published (35, 36).

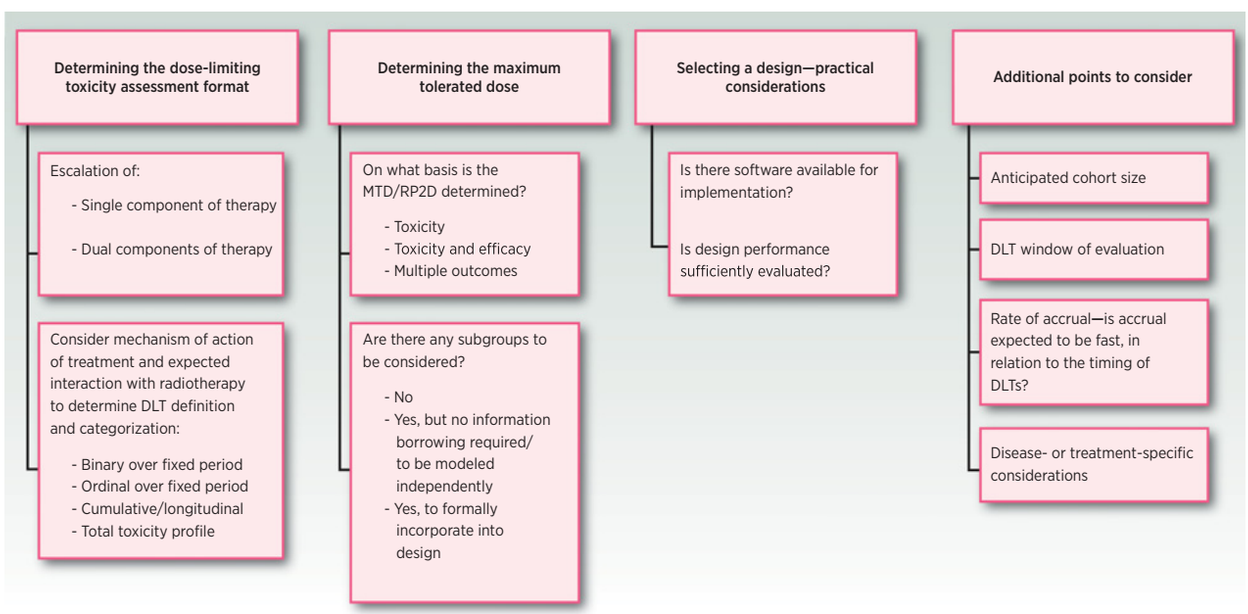

Figure 2.
Road map of points for consideration when designing phase I radiotherapy–drug combination trials. MTD, maximum tolerated dose; DLT, dose-limiting toxicity; RP2D, recommended phase II dose.

Table 2. Design identification following the road map.

Escalation of:	DLT definition and categorization	MTD/RP2D determined based on:	Subgroups?	Selecting a design: Practical considerations
Single component	Binary over fixed period	Toxicity	Yes, formally	**Green:** Chapple and Thall, 2018 (29) **Amber (further evaluation):** Salter et al., 2015 (27)
			No/model independently	**Green:** Yuan et al., 2018 (22), Andrillon et al., 2020 (23), Polley, 2011 (24), Lin and Yuan, 2019 (41), Yin and Yang, 2020 (42), Bekele et al., 2008 (43), Cheung and Chappell, 2000 (44), Lin and Yin, 2016 (45), Yin et al., 2013 (46), North et al., 2019 (47) **Amber (further evaluation):** Biard et al., 2021 (48), Ivanova et al., 2016 (49), Mauguen et al., 2011 (50), Tighiouart et al., 2014 (51), Zheng et al., 2016 (52), Liu et al., 2013 (53)
		Toxicity and efficacy	No/model independently	**Amber (software):** Jin et al., 2014 (21), Altzerinakou and Paoletti, 2020 (54), Yuan and Yin, 2009 (55)
	Ordinal over fixed period	Toxicity	No/model independently	**Green:** Lee et al., 2019 (56)
		Multiple outcomes	Yes, formally	**Amber (further evaluation):** Thall, 2019 (28)
	Cumulative/longitudinal	Toxicity	No/model independently	**Green:** Huang and Kuan, 2014 (57) **Amber (further evaluation):** Paoletti et al., 2015 (58) **Amber (software):** Doussau et al., 2013 (59)
	Total toxicity profile	Toxicity	No/model independently	**Amber (further evaluation):** Yin et al., 2017 (32) **Amber (software):** Yin et al., 2017 (31)
		Toxicity and efficacy	No/model independently	**Green:** Du et al., 2019 (60)
Dual component	Binary over fixed period	Toxicity	No/model independently	**Green:** Wages et al., 2013 (25) **Amber (further evaluation):** Wheeler et al., 2019 (26)

Additional points to consider

Cohort size

Rationally, cohort size in an early-phase trial should be sufficient to provide confidence for an optimum, safe schedule to take forward to phase II, and this is no different in a radiotherapy combination study. The caveats in this scenario are the well-documented noncontiguous toxicities, which often raise additional anxieties as to the need to inflate the size of cohorts to ensure late effects are adequately anticipated.

Cohort sizes of between 1 and 3 are typically used in phase I dose-escalation trials, although deviation from prespecified cohort sizes has been shown to have little effect on the operating characteristics of model-based or model-assisted designs (37). Perhaps more important to consider is the minimum number of patients required to have completed at least some period of follow-up for DLTs prior to dose escalation being permitted, ensuring large numbers of patients are not exposed to overly toxic doses. This is particularly relevant when considering the rate of accrual in the context of DLT windows, as discussed below, and the total follow-up time available at the point of dose-escalation decision-making. The LDI, defined by Jin and colleagues as the accrual rate multiplied by the length of the DLT window of evaluation (21), provides a benchmark for assessing difficulty relating to the amount of information available at the point of dose-escalation decision-making. An LDI ≤ 1 represents no or minimal logistic difficulty, with larger values >1 reflecting increasing difficulty. Consideration to the LDI should be given when evaluating design performance and selecting between multiple possible designs.

DLT window of evaluation

Recommendations of a minimum three-month DLT window of evaluation have previously been made (6, 7). It is particularly important to consider whether a longer DLT period, extending into the "late" side-effect period, may be necessary for a specific trial, and therefore the performance of potential designs in that setting. This is especially relevant in the neoadjuvant or definitive/radical setting where consideration of a minimum six-month DLT period may be appropriate. It is widely acknowledged that late effects of radiotherapy are dependent on a range of factors, including the dose and fractionation schedule—though increasingly the fractionation schedule, including the role of hypofractionation, is being challenged, with notable evidence in prostate, breast, and rectal cancer over recent years (38–40). The most significant underlying factors are likely to be genetic, not unlike drug metabolism but dissimilar in the sense that pharmacokinetic and pharmacodynamic data can be used to relatively inform interindividual variation; this is not yet practical in the radiotherapy setting in relation to late effects.

Rate of accrual

Although the use of the methodologies included in the road map can increase trial efficiency where toxicity evaluation is over a long time period, it is essential to consider the impact of recruitment rate on the performance of the selected design. Where accrual is fast relative to the DLT window, it is possible a large proportion of patients may be recruited to low doses before dose-escalation decisions can be made reliably. Consideration of the LDI (21, 22) and evaluation of design performance under varying rates of accrual must be addressed, to ensure fast accrual relative to the DLT window does not result in poor performance or negate the long-term follow-up features of the design itself. Consideration to restricting recruitment must be given to ensure enough patients remain available from the overall sample size to explore all dose levels under investigation. Indeed, it is this consideration that has encouraged the use of flip-flop designs in which two separate drugs are evaluated in combination with radiotherapy in the same clinical setting, enabling toxicity data to accrue and inform modeling in drug A while patients can still be recruited to the study

Table 3. Design name and software availability, by category.

Category		Reference	Design name/backbone	Software details/link	GUI or script
Green	**15**	Chapple and Thall, 2018 (29)	Sub-TITE	SubTite on CRAN at http://cran.r-project.org	Script
		Cheung and Chappell, 2000 (44)	TITE-CRM	titecrm function in R package dfcrm	Script
		Bekele et al., 2008 (43)	Predicted risk of toxicity	https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/69	GUI
		Polley, 2011 (24)	Modified TITE-CRM	R-program for simulating operating characteristics available upon request to authors	Script
		Yin et al., 2013 (46)	Fractional CRM	Shiny App available: https://demoyang.shinyapps.io/clinicaltrialdesignapp_fcrm/, as well as R software code on GitHub: https://github.com/ZhaoYangCICAMS/fCRM	Both
		Andrillon et al., 2020 (23)	Surv-CRM and iSurv-CRM	R code for the use of the Surv-CRM, the iSurv-CRM, and the associated benchmark is to be made freely available on GitHub	Script
		North et al., 2019 (47)	STARPAC	R package bcrm (61)	Script
		Lin and Yin, 2016 (45)	fNOC	https://github.com/ruitaolin/NOC	Script
		Yuan et al., 2018 (22)	TITE-BOIN	https://www.trialdesign.org/	GUI
		Lin and Yuan, 2019 (41)	TITE-Keyboard/TITE-mTPI	R codes for implementation available on Github (https://github.com/ruitaolin/TITE-MAD). Software also freely available at http://www.trialdesign.org	Both
		Yin and Yang, 2020 (42)	Fractional CRM	Shiny App available: https://demoyang.shinyapps.io/clinicaltrialdesignapp_fcrm/, as well as R software code on GitHub: https://github.com/ZhaoYangCICAMS/fCRM	Both
		Lee et al., 2019 (56)	TITE-CRMMC	Software in the form of R code is available on GitHub and can be requested from the corresponding author (sml2114@cumc.columbia.edu)	Script
		Huang and Kuan, 2014 (57)	Modified TITE-CRM	R code in supplementary material	Script
		Du et al., 2019 (60)	Extension of RMD	R package: phase1RMD at https://cran.r-project.org/web/packages/phase1RMD/index.html	Script
		Wages et al., 2013 (25)	PO-TITE	Appendix has R code for MCMC implementation titesim function in R package dfcrm	Script
Amber	**16**	Salter et al., 2015 (27)	Two-group TITE-CRM	SAS code, Supplementary data to Salter 2015 (62)	Script
		Biard et al., 2021 (48)	Modified TITE-CRM	Implemented using the R package dfcrm	Script
		Ivanova et al., 2016 (49)	Rapid Enrolment Design (RED)	Web-based software available at http://cancer.unc.edu/biostatistics/program/ivanova/	GUI
		Mauguen et al., 2011 (50)	TITE-EWOC	R graphical interface, GUIP1, that combines different model-guided adaptive designs (CRMB, CRML, EWOC, TITE-CRM, TITEEWOC) for simulating and conducting phase I cancer clinical trials	GUI
		Tighiouart et al., 2014 (51)	EWOC-PH	https://biostatistics.csmc.edu/ewocWeb.php R package ewoc_d1ph from https://cran.r-project.org/web/packages/ewoc/index.html	Both
		Zheng et al., 2016 (52)	Three-parameter logistic method	The CRM methods implemented using the R package dfcrm and the Bayesian logistic model implemented using the R package MCMCpack	Script
		Liu et al., 2013 (53)	DA-CRM	https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/132	GUI
		Altzerinakou and Paoletti, 2020 (54)	Joint model for longitudinal biomarkers and time-to-event toxicity	None listed	
		Jin et al., 2014 (21)	Late Onset- EffTox	None listed	
		Yuan and Yin, 2009 (55)	Joint probability models for toxicity and efficacy as TITE outcomes	*None listed*	
		Thall, 2019 (28)	Nonproportional odds and proportional odds unstratified, model-based designs	A computer program Nkcelldosefinding for implementing this methodology is available from https://users.soe.ucsc.edu/∼juheelee/ and also http://wileyonlinelibrary.com/journal/rss-datasets.	Script
		Paoletti et al., 2015 (58)	POMM-CRML and LMM-CRML	Simulations were carried out with an R-program and packages ordinal for fitting POMMand lme4 for fitting logistic model on repeated binary data	Script

(Continued on the following page)

Table 3. Design name and software availability, by category. (Cont'd)

Category		Reference	Design name/backbone	Software details/link	GUI or script
		Doussau et al., 2013 (59)	POMM-CRML	None listed	
		Yin et al., 2017 (32)	RMD	R package: phase1RMD at https://cran.r-project.org/web/packages/phase1RMD/index.html	Script
		Yin et al., 2017 (31)	RMD	None listed	
		Wheeler et al., 2019 (26)	TITE-PIPE	https://cran.r-project.org/web/packages/pipe.design/index.html	Script
Red	**6**	Chapple et al., 2019 (63)	TITE-IR	The titeIR package is available on CRAN and provides the necessary infrastructure for the design of phase I trials	Script
		Chen et al., 2014 (64)	EWOC-NETS-TITE	Manuscript states software being developed	
		Koopmeiners and Modiano, 2014 (65)	Joint probability model for efficacy and toxicity as TITE outcomes	None listed	
		Takeda et al., 2020 (66)	TITE-BOIN-ET	None listed	
		Yan et al., 2019 (67)	Generalization of TITE-CRM to bivariate outcomes–TITE-B	None listed	
		Braun, 2006 (68)	Generalization of TITE-CRM assuming toxicity times have a beta distribution	None listed	

Abbreviations: BOIN, Bayesian optimal interval; CRM, continual reassessment method; CRMMC, continual reassessment method with multiple constraints; DA-CRM, data augmentation-CRM; ET, efficacy and toxicity; EWOC, escalation with overdose control; fNOC, fractional nonparametric overdose control; IRL, isotonic regression; iSurv-CRM, informative survival CRM; LMM, logistic mixed-effects model; MAD, model-assisted designs; mTPI, modified toxicity probability interval; NETS, normalized equivalent toxicity score; PH, proportional hazards; PIPE, product of independent beta probabilities escalation; PO, Partial Orders; POMM-CRML, proportional odds mixed effect regression model–continual reassessment method with likelihood inference; RMD, repeated-measures design; Surv-CRM, survival CRM; TITE, time to event.

involving drug B. Similarly, the use of platform studies with multiple radiotherapy–drug combination arms will mitigate the risk of suspending recruitment should the accrual rate be too high relative to the DLT window.

Disease- or treatment-specific considerations

Additional aspects that may be related directly to the treatment or disease under consideration may be important to incorporate in the trial design where this may affect dosing recommendations. For example, consideration of overdose control, incorporation of censoring due to treatment discontinuation or disease progression or weighting of DLT periods in the model.

Phase I trial design selection

The designs identified through the literature review were grouped according to a traffic light system, as previously described. Characteristics of the designs, by grouping, are shown in **Table 1**. Using key components of the road map designs are further stratified to facilitate targeted selection, as presented in **Table 2**. Combined with the road map, this presents a practical tool for researchers to identify appropriate phase I designs relevant to the specific components of their trial. Categorization of each design identified is presented in **Table 3** , along with design name and software information.

Fifteen of the 37 (41%) designs were categorized as "green," having software availability and good performance. A further 16 (43%) designs were categorized as "amber," either requiring software to be developed or made accessible (5) or requiring further performance evaluation (11). Six (16%) designs identified were categorized as "red," based on no available software and further performance evaluation being required, or performance being noted as poor.

Application of phase I designs

Below two examples of the practical application of designs identified as "green" or "amber" are illustrated, applying the road map and design selection tool to demonstrate how these may be used in practice. **Tables 4** and **5** describe the practical application of designs considering the dose escalation of the drug only with DLTs categorized as a binary outcome, highlighting the use of both model-based and model-assisted designs, respectively.

Discussion

This review provides a practical overview of methodologies that offer optimal approaches to an early-phase trial design in which novel therapies are combined with radiotherapy. Methods lacking sufficient evidence or credibility for current use and requiring further work to establish their potential merits are clearly defined. The 15 designs achieving a green rating met objective quality assessment criteria and are more suitable for immediate clinical application. Specific domains evaluated in this quality assessment process included: methodology for determining DLT and MTD; comparison with alternative models in terms of efficiency and safety; demonstrated performance over a minimum of three months toxicity evaluation or a sufficiently high accrual relative to DLT time period; provision of software for simulation/modeling the design prior to clinical implementation. Of the designs rated as green or amber there are nuances in relation to each that may make them more suitable for specific elements of the trial in hand, which are factored into the road map. The time frame of toxicity evaluation used to categorize a design as green was taken to be a minimum of three months, based on definitions of DLT periods suggested by Deutsch and colleagues (7) and the RTOG definition (6). Where this was less than three months, we also considered design performance under varying accrual rates, relative to the chosen DLT window (22). Where accrual rate is expected to be particularly slow relative to this, consideration to designs requiring complete follow-up before dose-escalation decisions are made may be possible. Given the long DLT windows required for radiotherapy studies, these scenarios are expected to be few and far between.

Table 4. Practical application of the road map for a phase I trial using TiTE-CRM in a platform setting.

Design reference	Time-to-event continuous reassessment method (44)	
Trial reference	CONCORDE: A phase I platform study of novel agents in combination with conventional radiotherapy in non–small cell lung cancer (69) https://clinicaltrials.gov/ct2/show/NCT04550104	
Trial summary	**Setting**: Non–small cell lung cancer **Interventions**: Radiotherapy alone or in combination with one of five DNA-damage repair inhibitors (DDRi): Current—olaparib, AZD1390; planned—up to 3 additional DDRis **DLT period**: 13.5 months **Number of doses/schedules**: Olaparib: up to 6; AZD1390: up to 7 **Target toxicity level:** 25% **Number of patients**: 30 per arm	
Road map application	**Trial consideration**	**Decision**
Determining the DLT assessment format		
Escalation of: Single component; dual components	Adapted from Walls et al. (69): The trial is designed to evaluate the safety of multiple novel drug–RT combinations in locally advanced NSCLC and aims to inform how DNA-damage response inhibitors (DDRi) can be combined with radical RT in patients unfit for concurrent CRT. Five components of the DNA damage signaling pathway will be targeted using novel systemic agents, in combination with the international RT dose fractionation of 60 Gy delivered in 2-Gy once-daily fractions. While the biology underpinning the intrinsic radioresistance of NSCLC remains incompletely defined, repair of radiation-induced DNA damage is considered a fundamental component. These pathways are actionable: potent novel agents targeting DNA damage response pathways are becoming clinically available, and strategies for synergistic combination of systemic agents with RT are being realized across tumors.	Single component
DLT categorization: binary; ordinal; cumulative/longitudinal; TTP	Anticipate DLTs to occur in both the acute and late setting. Standard approach to defining DLTs, which are listed in the manuscript. Dosing limited by the occurrence of any of the events, rather than informed by e.g., ordinal grading or accumulation of events.	Binary
Determining the MTD		
MTD based on: Toxicity; toxicity and efficacy; multiple outcomes	The aim of the trial is to find RP2Ds for the DDRi–radiotherapy combination, on the basis of toxicity alone.	Toxicity only
Subgroups to be considered:	The population under consideration is expected to be homogeneous in terms of toxicity response.	No subgroups
Practical considerations	Of the green and amber designs identified through the literature review, 16 designs are suitable to inform dose escalation with DLTs defined as binary outcomes, based on toxicity only and with no subgroups.	
Software available:	16 designs have available software	
Performance evaluation:	10 designs have good performance	
Additional points to consider	**Cohort size:** Dose escalation decisions to be made after every patient **DLT window:** Time frame for toxicity is 13.5 months, split into acute (up to 4.5 months) and late toxicity. Weighting incorporated for each of these periods in the model, based on clinical experience (acute 90%, late 10%), and requirement for at least 1 patient to be followed up for the acute toxicity period before dose escalation can commence. **Rate of accrual:** Not expected to be fast in relation to the toxicity time frame, and patients are recruited across multiple arms. **Disease or treatment-specific considerations:** The trial is run as a platform trial with 5 arms; therefore, methods need to be easily implemented.	
Design selection	Given the need to apply a design across five experimental arms within the platform, for ease of implementation, designs with software available may be prioritized. **Possible designs:** (22–24, 41–53)	CONCORDE is designed using the original TiTE-CRM method of Cheung and Chapple (44)

It is the role of a phase I trial to explore interactions between radiotherapy and drug therapies safely and efficiently. An important consideration relates to the specifics of radiotherapy having an enhanced, or altered, impact upon the systemic effect of a systemic therapy. For example, augmentation of the immune system may have negative toxicity effects, or positive abscopal effects, or both. Evaluating the interaction of combination therapies on potential side effects is critical to the design of the phase I trial. Considering overlapping radiotherapy and systemic therapy effects, and the potential for either treatment to modulate the effects of the other, is important in defining DLTs, setting DLT periods, and defining target toxicity levels. We have provided the necessary insights and tools relevant to the selection of an appropriate methodology to account for these unknowns.

Designs were categorized based on the availability of software to enable implementation, either as noted in the manuscript or identified

Table 5. Practical application of the road map for a phase I trial using TiTE-BOIN in a radiotherapy–novel agent combination trial.

Design reference	Time-to-event Bayesian optimal interval design (22)	
Trial reference	Phase I study of talazoparib in combination with radiation therapy for locally recurrent gynecologic cancers (70) https://clinicaltrials.gov/ct2/show/record/NCT03968406?term=NCT03968406&draw=2	
Trial summary	**Setting:** Multiple gynecologic cancers—recurrent (patients with refractory or recurrent ovarian, fallopian tube, primary peritoneal, cervical, vaginal, or endometrial carcinoma) **Interventions:** Radiotherapy in combination with talazoparib (PARPi). Two cohorts of patients will be enrolled based on radiotherapy field size (large-field vs. limited-field), and dosing may be limited according to DLTs observed in differing subgroups. **DLT period:** 6.5 months **Number of doses/schedules:** up to 4 **Target toxicity level:** 30% **Number of patients:** 24 in total (18 large-field, 6 limited-field)	
Road map application	**Trial consideration**	**Decision**
Determining the DLT assessment format		
Escalation of: Single component; dual components	Adapted from Lakomy et al. (70): In this phase I study, we aim to determine the safety, tolerability, and MTD of talazoparib when delivered concurrently with radiotherapy in women with recurrent gynecologic cancers. The role of radiotherapy in the management of recurrent ovarian and endometrial cancers has expanded in the last decade, with several retrospective studies documenting its effectiveness. A radiosensitizer in conjunction with radiotherapy could be utilized to widen the therapeutic ratio; one class of such agent includes the poly-ADP-ribose-polymerase (PARP) inhibitors. Talazoparib is a novel, potent inhibitor of PARP. It is particularly notable among other PARP inhibitors due to the lower concentrations needed to generate antitumor cell responses. Preclinical work has shown that talazoparib monotherapy has remarkable antitumor activity and can sensitize a variety of tumor types to radiation.	Single component
DLT categorization: binary; ordinal; cumulative/longitudinal; TTP	Anticipate DLTs to occur in both the acute (treatment) and late (1–5 months post-treatment) setting. Standard approach to defining DLTs, which are listed in the manuscript. Dosing limited by the occurrence of any of the events, rather than informed by e.g., ordinal grading or accumulation of events.	Binary
Determining the MTD		
MTD based on: Toxicity; toxicity and efficacy; multiple outcomes	The aim of the trial is to find the MTD of the talazoparib–radiotherapy combination, based on toxicity alone.	Toxicity only
Subgroups to be considered:	Toxicity will vary depending upon radiotherapy field—protocol stipulates radiotherapy dose and fractionation for each of these, and dose escalation takes place in each cohort independently. Acceptable toxicity in the large field may enable dose escalation in the limited field. No other subgroups specified, though a series of biomarkers are being explored.	Two subgroups—consider both formally incorporating AND independent modeling
Practical considerations	Of the green and amber designs identified through the literature review, 16 designs are suitable to inform dose escalation with DLTs defined as binary outcomes, based on toxicity only and with independent modeling in each subgroup. A further 2 designs are suitable to incorporate subgroups formally.	
Software available:	18 designs have available software	
Performance evaluation:	11 designs have good performance	
Additional points to consider	**Cohort size:** Dose-escalation decisions assumed to be made after every patient **DLT window:** Time frame for toxicity is 6.5 months, split into acute (during treatment) and late toxicity (up to 5 months after end of treatment). **Rate of accrual:** Not detailed (accrual period assumed 3 years) **Disease or treatment-specific considerations:** Dose escalation is to be considered in 2 separate cohorts with relatively small patient numbers and potentially only 2 doses in one cohort. A model-assisted design may lend itself to this scenario to avoid overly complex model specification with limited doses.	
Design selection	For ease of implementation, designs with software available may be prioritized. **Possible designs:** (22–24, 27, 29, 41–53) Based on the small number of doses and patients, a model-assisted design may be considered, avoiding the need for complex statistical models to be determined while offering comparable performance (16). A model-assisted design in each subgroup independently, with additional rules to limit dose escalation by field size, was selected by the researchers.	The trial is designed using the TiTE-BOIN design of Yuan et al. (22).

by authors via internet searching. Notably, a number of software packages listed are in script format requiring an element of interpretation and adaptation to be implemented in practice. The availability of software is an essential aspect to ensure wide-scale adoption of new methods by applied statisticians, with designs facilitated by user-friendly, easily adapted software often favored. Dinart and colleagues have developed a user-friendly R package, GUIP1, combining multiple dose-escalation designs in a central platform (71), and numerous phase I design software are available through www.trialdesign.org, in addition to the software links provided in **Table 3**. These offer useful tools to explore multiple design options, including via extensive simulation.

The review identified a variety of phase I designs covering both model-based and model-assisted statistical designs. For those new to phase I trials or with limited statistical support available throughout the conduct of the trial, model-assisted designs provide an opportunity to implement novel adaptive methods without the complex computational requirements of some of the more complicated model-based approaches. Yuan and colleagues provide a review of state-of-the-art model-assisted designs showcasing freely available user-friendly software and providing practical examples, to facilitate wider adoption of these methods (16).

The suite of designs identified and incorporated in the road map selection is limited by the restrictions of the systematic review, particularly in relation to the time window used (October 2009–February 2021) and the use of specific terminology relating only to "longitudinal" or "time to event" methods, albeit incorporating citation searching. As the review was designed to be informative rather than exhaustive, these restrictions were incorporated for practical reasons. The proposed road map and the suite of designs may be expanded in the future to incorporate additional methods that predate the search and were not identified by citation searching, as well as future designs developed.

It is important to consider that only some of the green- and amber-rated studies are in current use in early-phase radiotherapy combination studies. A practical implementation of the road map for two recent studies, both currently in recruitment (69, 70), is presented. Importantly, the acid test that provides reassurance and confidence in methodologies developed *in silico* comes from successful implementation in the clinical setting. A novel adaptation of the TITE-CRM design proposed by Huang and Kuan (57), which includes an adaptive weight function, has been implemented in two studies. The weight function is continually updated from existing patients' cyclical safety data and is a natural function to describe the cycle-toxicity pattern due to the unique mechanism of action of the experimental treatment. This design has been implemented in an ongoing phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable or partially resectable glioblastoma (72) and a completed phase Ib study of utomilumab in combination with mogamulizumab in patients with advanced solid tumors (73). These studies highlight that with appropriate statistical input and a willingness to adopt new methods, novel designs can be successfully implemented. As uptake of these novel designs increases, it is important to disseminate practical experiences and lessons learned from their implementation. Recent such examples include those of Tidwell and colleagues (74) in the setting of radiotherapy combinations in pancreatic cancer with the implementation of the late-onset EffTox design (21), and van Dijk and colleagues (75) in the setting of head and neck cancer with the implementation of the TITE-BOIN design (22). Notably, very few of the methods identified have yet reported their outcomes and more specifically have yet to be taken through to a "safe" and deliverable phase II study based on phase I results. This apparent failing no doubt relates to a number of phenomena, including the contemporaneous review undertaken over an 11-year period, with the duration of time to establish, run and report on studies but probably more importantly the relatively slow uptake of novel methodologies by regulators, the pharmaceutical industry, ethical review boards, funders and clinicians who are likely to be conservative in their approach to adopting designs which have not been robustly evaluated.

The road map presented has been developed to inform the development of phase I radiotherapy–novel agent combination studies, from consideration of the research question and intervention through to identifying a statistical design that is fit for purpose. It offers a practical, user-friendly approach to enhancing trial design, aiming to facilitate and encourage an interactive approach between clinical researchers and statisticians, and consequently optimizing the potential for funding, and promoting efficient trial conduct.

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References

1. Ataman OU, Sambrook SJ, Wilks C, Lloyd A, Taylor AE, Wedge SR. The clinical development of molecularly targeted agents in combination with radiation therapy: a pharmaceutical perspective. Int J Radiat Oncol Biol Phys 2012;84:e447–54.
2. Sharma RA, Plummer R, Stock JK, Greenhalgh TA, Ataman O, Kelly S, et al. Clinical development of new drug-radiotherapy combinations. Nat Rev Clin Oncol 2016;13:627–42.

3. Ahmad SS, Crittenden MR, Tran PT, Kluetz PG, Blumenthal GM, Bulbeck H, et al. Clinical development of novel drug–radiotherapy combinations. Clin Cancer Res 2019;25:1455–61.
4. Bristow RG, Alexander B, Baumann M, Bratman SV, Brown JM, Camphausen K, et al. Combining precision radiotherapy with molecular targeting and immunomodulatory agents: a guideline by the American Society for Radiation Oncology. Lancet Oncology 2018;19:E240–E51.
5. Harrington KJ, Billingham LJ, Brunner TB, Burnet NG, Chan CS, Hoskin P, et al. Guidelines for preclinical and early phase clinical assessment of novel radiosensitisers. Br J Cancer 2011;105:628–39.
6. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
7. Deutsch E, Soria JC, Armand JP. New concepts for phase I trials: evaluating new drugs combined with radiation therapy. Nat Clin Pract Oncol 2005;2:456.
8. Pijls-Johannesma M, van Mastrigt G, Hahn SM, De Ruysscher D, Baumert BG, Lammering G, et al. A systematic methodology review of phase I radiation dose escalation trials. Radiology and Oncology 2010;95:135–41.
9. Braun TM. The current design of oncology phase I clinical trials: progressing from algorithms to statistical models. Chin Clin Oncol 2014;3:2.
10. Le Tourneau C, Gan HK, Razak ARA, Paoletti X. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. PLoS One 2012;7:e51039.
11. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst 2009;101:708–20.
12. Riviere MK, Le Tourneau C, Paoletti X, Dubois F, Zohar S. Designs of drug-combination phase I trials in oncology: a systematic review of the literature. Ann Oncol 2015;26:669–74.
13. Rivoirard R, Vallard A, Langrand-Escure J, Mrad MB, Wang G, Guy J-B, et al. Thirty years of phase I radiochemotherapy trials: latest development. Eur J Cancer 2016;58:1–7.
14. Zhu Y, Hwang W-T, Li Y. Evaluating the effects of design parameters on the performances of phase I trial designs. Contemp Clin Trials Commun 2019;15:100379.
15. Ree AH, Hollywood D. Design and conduct of early-phase radiotherapy trials with targeted therapeutics: lessons from the PRAVO experience. Radiother Oncol 2013;108:3–16.
16. Yuan Y, Lee JJ, Hilsenbeck SG. Model-assisted designs for early-phase clinical trials: simplicity meets superiority. JCO Precision Oncology 2019:1–12.
17. Love SB, Brown S, Weir CJ, Harbron C, Yap C, Gaschler-Markefski B, et al. Embracing model-based designs for dose-finding trials. Br J Cancer 2017;117:332–9.
18. van Werkhoven E, Hinsley S, Frangou E, Holmes J, de Haan R, Hawkins M, et al. Practicalities in running early-phase trials using the time-to-event continual reassessment method (TiTE-CRM) for interventions with long toxicity periods using two radiotherapy oncology trials as examples. BMC Med Res Method 2020;20:162.
19. Wheeler GM, Mander AP, Bedding A, Brock K, Cornelius V, Grieve AP, et al. How to design a dose-finding study using the continual reassessment method. BMC Med Res Method 2019;19:18.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
21. Jin IH, Liu S, Thall PF, Yuan Y. Using data augmentation to facilitate conduct of phase I–II clinical trials with delayed outcomes. J Am Statist Assoc 2014;109:525–36.
22. Yuan Y, Lin R, Li D, Nie L, Warren KE. Time-to-event Bayesian optimal interval design to accelerate phase I trials. Clin Cancer Res 2018;24:4921–30.
23. Andrillon A, Chevret S, Lee SM, Biard L. Dose-finding design and benchmark for a right censored endpoint. J Biopharm Stat 2020;30:948–63.
24. Polley MY. Practical modifications to the time-to-event continual reassessment method for phase I cancer trials with fast patient accrual and late-onset toxicities. Stat Med 2011;30:2130–43.
25. Wages NA, Conaway MR, O'Quigley J. Using the time-to-event continual reassessment method in the presence of partial orders. Stat Med 2013;32:131–41.
26. Wheeler GM, Sweeting MJ, Mander AP. A Bayesian model-free approach to combination therapy phase I trials using censored time-to-toxicity data. J R Stat Soc Ser C Appl Stat 2019;68:309–29.
27. Salter A, O'Quigley J, Cutter GR, Aban IB. Two-group time-to-event continual reassessment method using likelihood estimation. Contemp Clin Trials 2015;45:340–5.
28. Thall PF. Bayesian cancer clinical trial designs with subgroup-specific decisions. Contemp Clin Trials 2019:105860.
29. Chapple AG, Thall PF. Subgroup-specific dose finding in phase I clinical trials based on time to toxicity allowing adaptive subgroup combination. Pharm Stat 2018;17:734–49.
30. NIH NIoH. 2017 Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
31. Yin J, Paoletti X, Sargent DJ, Mandrekar SJ. Repeated measures dose-finding design with time-trend detection in the presence of correlated toxicity data. Clin Trials 2017;14:611–20.
32. Yin J, Qin R, Ezzalfani M, Sargent DJ, Mandrekar SJ. A Bayesian dose-finding design incorporating toxicity data from multiple treatment cycles. Stat Med 2017;36:67–80.
33. Iasonos A, O'Quigley J. Dose expansion cohorts in phase I trials. Stat Biopharm Res 2016;8:161–70.
34. Mokdad AA, Xie X-J, Zhu H, Gerber DE, Heitjan DF. Statistical justification of expansion cohorts in phase 1 cancer trials. Cancer 2018;124:3339–45.
35. Iasonos A, Gönen M, Bosl GJ. Scientific review of phase I protocols with novel dose-escalation designs: how much information is needed? J Clin Oncol 2015;33:2221–5.
36. Wages NA, Petroni GR. A web tool for designing and conducting phase I trials using the continual reassessment method. BMC Cancer 2018;18:133.
37. Park M, Liu S, Yap TA, Yuan Y. Evaluation of deviation from planned cohort size and operating characteristics of phase 1 trials. JAMA Net Open 2021;4:e2037563.
38. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM-K, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29–42.
39. Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017;35:1884–90.
40. Brunt AM, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet North Am Ed 2020;395:1613–26.
41. Lin R, Yuan Y. Time-to-event model-assisted designs for dose-finding trials with delayed toxicity. Biostatistics 2020;21:807–24.
42. Yin G, Yang Z. Fractional design: an alternative paradigm for late-onset toxicities in oncology dose-finding studies. Contemp Clin Trials Commun 2020;19:100650.
43. Bekele B, Ji Y, Shen Y, Thall PJB. Monitoring late-onset toxicities in phase I trials using predicted risks. Biostatistics 2008;9:442–57.
44. Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics 2000;56:1177–82.
45. Lin R, Yin G. Nonparametric overdose control with late-onset toxicity in phase I clinical trials. Biostatistics 2016;18:180–94.
46. Yin G, Zheng S, Xu J. Fractional dose-finding methods with late-onset toxicity in phase I clinical trials. J Biopharm Stat 2013;23:856–70.
47. North B, Kocher HM, Sasieni P. A new pragmatic design for dose escalation in phase 1 clinical trials using an adaptive continual reassessment method. BMC Cancer 2019;19:632.
48. Biard L, Cheng B, Manji GA, Lee SM. A simulation study of approaches for handling disease progression in dose-finding clinical trials. J Biopharm Stat 2021;31:156–67.
49. Ivanova A, Wang Y, Foster MC. The rapid enrollment design for phase I clinical trials. Stat Med 2016;35:2516–24.
50. Mauguen A, Le Deley MC, Zohar S. Dose-finding approach for dose escalation with overdose control considering incomplete observations. Stat Med 2011;30:1584–94.
51. Tighiouart M, Liu Y, Rogatko A. Escalation with overdose control using time to toxicity for cancer phase I clinical trials. PLoS One 2014;9:e93070.
52. Zheng W, Zhao Y, Lu Y, Miao H, Liu H. A Bayesian three-parameter logistic model for early- and late-onset DLTs in oncology phase I studies. J Biopharm Stat 2016;26:339–51.

53. Liu S, Yin G, Yuan Y. Bayesian data augmentation dose finding with continual reassessment method and delayed toxicity. Ann Appl Stat 2013;7:2138–56.
54. Altzerinakou MA, Paoletti X. An adaptive design for the identification of the optimal dose using joint modeling of continuous repeated biomarker measurements and time-to-toxicity in phase I/II clinical trials in oncology. Stat Methods Med Res 2020;29:508–21.
55. Yuan Y, Yin G. Bayesian dose finding by jointly modelling toxicity and efficacy as time-to-event outcomes. J R Stat Soc Ser C Appl Stat 2009;58:719–36.
56. Lee SM, Ursino M, Cheung YK, Zohar S. Dose-finding designs for cumulative toxicities using multiple constraints. Biostatistics 2019;20:17–29.
57. Huang B, Kuan PF. Time-to-event continual reassessment method incorporating treatment cycle information with application to an oncology phase I trial. Biom J 2014;56:933–46.
58. Paoletti X, Doussau A, Ezzalfani M, Rizzo E, Thiebaut R. Dose finding with longitudinal data: simpler models, richer outcomes. Stat Med 2015;34:2983–98.
59. Doussau A, Thiebaut R, Paoletti X. Dose-finding design using mixed-effect proportional odds model for longitudinal graded toxicity data in phase I oncology clinical trials. Stat Med 2013;32:5430–47.
60. Du Y, Yin J, Sargent DJ, Mandrekar SJ. An adaptive multi-stage phase I dose-finding design incorporating continuous efficacy and toxicity data from multiple treatment cycles. J Biopharm Stat 2019;29:271–86.
61. Sweeting M, Mander A, ST bcrm.: Bayesian continual reassessment method designs for phase I dose-finding trials. J Statist Softw 2013;54:1–26.
62. Salter A, Morgan C, Aban IB. Implementation of a two-group likelihood time-to-event continual reassessment method using SAS. Comput Methods Programs Biomed 2015;121:189–96.
63. Chapple AG, Wojcik JJ, McDaniel LS. A regression based phase I clinical trial for late-onset toxicities without clinician elicitation. Contemp Clin Trials Commun 2019;14:100327.
64. Chen Z, Cui Y, Owonikoko TK, Wang Z, Li Z, Luo R, et al. Escalation with overdose control using all toxicities and time to event toxicity data in cancer phase I clinical trials. Contemp Clin Trials 2014;37:322–32.
65. Koopmeiners JS, Modiano J. A Bayesian adaptive phase I-II clinical trial for evaluating efficacy and toxicity with delayed outcomes. Clin Trials 2014;11:38–48.
66. Takeda K, Morita S, Taguri M. TITE-BOIN-ET: Time-to-event Bayesian optimal interval design to accelerate dose-finding based on both efficacy and toxicity outcomes. Pharm Stat 2020;19:335–49.
67. Yan D, Tait C, Wages NA, Kindwall-Keller T, Dressler EV. Generalization of the time-to-event continual reassessment method to bivariate outcomes. J Biopharm Stat 2019;29:635–47.
68. Braun TM. Generalizing the TITE-CRM to adapt for early- and late-onset toxicities. Stat Med 2006;25:2071–83.
69. Walls GM, Oughton JB, Chalmers AJ, Brown S, Collinson F, Forster MD, et al. CONCORDE: a phase I platform study of novel agents in combination with conventional radiotherapy in non-small-cell lung cancer. Clin Transl Radiat Oncol 2020;25:61–6.
70. Lakomy DS, Urbauer DL, Westin SN, Lin LL. Phase I study of the PARP inhibitor talazoparib with radiation therapy for locally recurrent gynecologic cancers. Clin Transl Radiat Oncol 2020;21:56–61.
71. Dinart D, Fraisse J, Tosi D, Mauguen A, Touraine C, Gourgou S, et al. GUIP1: a R package for dose escalation strategies in phase I cancer clinical trials. BMC Med Inf Decis Making 2020;20:134.
72. Lesueur P, Lequesne J, Grellard JM, Dugué A, Coquan E, Brachet PE, et al. Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable or partially resectable glioblastoma: OLA-TMZ-RTE-01 trial protocol. BMC Cancer 2019;19:198.
73. Cohen EEW, Pishvaian MJ, Shepard DR, Wang D, Weiss J, Johnson ML, et al. A phase Ib study of utomilumab (PF-05082566) in combination with mogamulizumab in patients with advanced solid tumors. J Immunother Cancer 2019;7:342.
74. Tidwell RSS, Thall PF, Yuan Y. Lessons learned from implementing a novel bayesian adaptive Dose-finding design in advanced pancreatic cancer. JCO Precis Oncol 2021:1719–26.
75. van Dijk LV, Frank SJ, Yuan Y, Gunn B, Moreno AC, Mohamed ASR, et al. Proton Image-guided radiation assignment for therapeutic escalation via selection of locally advanced head and neck cancer patients [PIRATES]: a phase I safety and feasibility trial of MRI-guided adaptive particle radiotherapy. Clin Transl Radiat Oncol 2022;32:35–40.