STATISTICAL ANALYSIS

original reports abstract

Implementation of the Time-to-Event Continuous Reassessment Method Design in a Phase I Platform Trial Testing Novel Radiotherapy-Drug Combinations—CONCORDE

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PURPOSE CONCORDE is the first phase I drug-radiotherapy (RT) combination platform in non–small-cell lung cancer, designed to assess multiple different DNA damage response inhibitors in combination with radical thoracic RT. Time-to-event continuous reassessment method (TiTE-CRM) methodology will inform dose escalation individually for each different DNA damage response inhibitor-RT combination and a randomized calibration arm will aid attribution of toxicities. We report in detail the novel statistical design and implementation of the TiTE-CRM in the CONCORDE trial.

METHODS Statistical parameters were calibrated following recommendations by Lee and Cheung. Simulations were performed to assess the operating characteristics of the chosen models and were written using modified code from the R package dfcrm.

RESULTS The results of the simulation work showed that the proposed statistical model setup can answer the research questions under a wide range of potential scenarios. The proposed models work well under varying levels of recruitment and with multiple adaptations to the original methodology.

CONCLUSION The results demonstrate how TiTE-CRM methodology may be used in practice in a complex dose-finding platform study. We propose that this novel phase I design has potential to overcome some of the logistical barriers that for many years have prevented timely development of novel drug-RT combinations.

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INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide with approximately 46,000 new patients diagnosed annually in the United Kingdom alone.[1,2] Of these patients, approximately 40,000 will present with stage III non–small-cell lung cancer (NSCLC). Concurrent chemoradiotherapy (CTRT) is considered standard of care in unresectable stage III NSCLC,[3] but most patients are not suitable for this treatment on the basis of tumor bulk, location, or fitness.[4,5] For patients not suitable for concurrent CTRT, sequential CTRT is considered, but local control and survival rates are inferior compared with concurrent CTRT.[6] A promising strategy is to combine novel agents that act synergistically with radiotherapy (RT) with respect to tumor cell killing, in a concept known as radiosensitization. Recent investment by pharmaceutical companies has generated a portfolio of potent and specific DNA damage response inhibitors (DDRi)[7] that may be combined with RT.[8-10] A major challenge when developing drug-RT combination trials is to integrate efficient trial designs with robust statistical strategies.[10] These challenges have delayed and restricted the development of new drug-RT combinations with only two agents licensed at present.[11,12]

The available portfolio of DDRis presents an opportunity to efficiently investigate multiple DDRi-radiotherapy (DDRi-RT) combinations in NSCLC within a single platform trial using a master protocol,[13,14] in a more efficient and scientifically rich manner than studying each combination individually,[15,16] and allowing additional arms to adapt to evolving standards of care.

A challenge of dose-finding trials of RT interventions is that commonly used designs[17] such as the 3 + 3 design and continual reassessment method (CRM) are not appropriate for this setting,[18] because of the need to evaluate late toxic effects of RT. An extension to the CRM, the time-to-event continual reassessment method (TiTE-CRM), allows continued recruitment while accruing

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Application of complex phase I statistical methodology to a platform trial in non–small-cell lung cancer provides an efficient approach to evaluating a portfolio of DNA damage response inhibitors in combination with radiotherapy. Practical implementation of the time to event continuous reassessment method in a randomized controlled phase I platform trial is described, encouraging researchers to adopt and implement more efficient methods compared with conventional approaches.

Knowledge Generated

Implementation of novel phase I designs requires multidisciplinary collaboration. A significant investment of time, knowledge, and resource is needed to identify an appropriate design and evaluate its performance.

Relevance

Determining recommended phase II doses of novel agents combined with radiotherapy is the first stage of clinical evaluation on the route to registration of the combination. The practical application of novel statistical methods described in this setting is highly relevant to researchers developing phase I trials of these combinations.

follow-up for participants currently on trial.[19] This time-to-event extension uses weights to represent partial follow-up of participants and allows for greater efficiency by allowing robust estimation of the recommended phase II dose (RP2D) when late-onset toxicities are present, thus lending itself to the RT setting.[10,18] Usage of TiTE-CRM methodology has become increasingly popular, with various trials having implemented the TiTE-CRM, in the RT combination setting[20-24] and more widely.[25-27]

Application of the TiTE-CRM requires up-front specification of a target toxicity level (TTL), denoting an acceptable dose limiting toxicity (DLT) probability with the treatment under investigation. Typically this is based on review of current literature and expected DLT probabilities with standard of care treatment. Attribution of toxicity is essential in defining this target. A difficulty for phase I drug-RT combination trials in the NSCLC sequential CTRT setting is the lack of contemporaneous studies providing detailed treatment and toxicity data with the use of modern RT techniques, making it difficult to set a TTL and attribute toxicity.[28] To mitigate these issues, consideration may be given to the inclusion of a control, or calibration, arm in which patients receive RT alone.

CONCORDE is a novel phase Ib platform study designed to assess multiple DDRis in combination with radical thoracic RT, using TiTE-CRM to inform dose escalation while incorporating a randomized calibration arm. CONCORDE is the first phase I drug-RT combination platform in NSCLC, developed through national collaboration of clinicians, scientists, biostatisticians, patients, and industry partners, under the auspices of the National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Research Working Group (CTRad) and NCRI Lung Group. The protocol is described in elsewhere.[29] Here, we report in detail the statistical design and implementation of the TiTE-CRM (ISRCTN10142971).

As of July 2022, two arms are open to recruitment and two are in development. Twenty-five patients have been recruited and dose escalation decisions successfully made in both arms open.

METHODS

Design Summary

CONCORDE is designed using a Bayesian adaptive model-based approach to dose escalation, with separate TiTE-CRM models for each experimental arm.[29]

The primary objective is to determine the RP2D for each DDRi in combination with radical thoracic RT of 60 Gy in 30 fractions, on the basis of observed DLTs, defined in the Data Supplement. The DLT monitoring period is 13.5 months from the start of RT, divided into two periods: acute (up to 4.5 months post-RT start) and long (4.5 months to 13.5 months post-RT start). At least one patient is required to have completed the acute period from a dose level (DL) before the next higher DL can be allocated.

Randomized Calibration Arm

A contemporary RT-alone calibration arm is incorporated to ensure safety, and toxicity data are interpretable. This also aids attribution of toxicities and is not intended to facilitate formal comparison between arms as part of the primary analysis but will allow this to be investigated in an exploratory manner.[30] Further detail is provided in the Data Supplement.

Sample Size

A maximum sample size of 30 evaluable DDRi-RT patients is defined for each arm, to allow robust determination of the RP2D in a reasonable period for future drug development. Simulations were performed to confirm this sample size sufficient under various scenarios to reliably determine the RP2D on the basis of the prespecified TTL. With five experimental arms in the platform, approximately 210 evaluable patients will be recruited: 150 to DDRi-RT and up to 60 RT alone.

Time-to-Event Continual Reassessment Method

The TiTE-CRM is an extension of the CRM, which allows for dose escalation or de-escalation decisions and recruitment of patients without requiring all patients to be fully followed up.[31] Each treatment arm within CONCORDE represents a separate phase I dose escalation study. Here, we outline the clinical and statistical parameters used to determine the model.

DLs

Five DLs were initially considered for each arm during design development. To allow flexibility, additional DLs were incorporated into the first two arms (Tables 1 and 2). Additional detail regarding selection of DLs is given in the Data Supplement.

CONCORDE-A uses olaparib, a poly (ADP-ribose) polymerase inhibitor licensed for maintenance therapy in ovarian cancer after platinum-containing chemotherapy and for which flexibility in dose escalation was limited by commercially available doses.[32] CONCORDE-A incorporates six DLs.

CONCORDE-B uses the ATM-inhibitor AZD1390 which is earlier in clinical development, with the first in-human study dose escalating in combination with RT to the brain (ClinicalTrials.gov identifier: NCT03423628), where different toxicity profiles are seen compared with RT to the lung and adjacent organs. AZD1390 is a much more potent radiosensitiser than olaparib, and it may not be feasible or necessary to administer this agent with every fraction of RT. CONCORDE-B introduces intermittent DLs situated between the daily DLs (DLs 1-5), which will be referred to as intermittent levels from hereon. Only one intermittent level will be explored during dose allocation; hence, 10 DLs are incorporated into the CONCORDE-B model, but a maximum of seven will be explored in practice.

Model Setup

The initial model is developed using the clinical parameters in Table 3. A TTL of 25% is prespecified on the basis of clinical consensus and target DLT rates in phase I studies of novel systemic therapies.

TABLE 1. DLs for CONCORDE-A (Olaparib)

DL	Dose
–1	100 mg o.d.[a] (1 week day only)
–0.5	100 mg o.d.[a] (Monday/Thursday only)
1	100 mg o.d.[a](alternate days Monday/Wednesday/Friday and not at weekends)
2	100 mg o.d.[a] (including weekends)
3	100 mg b.d.[b] (including weekends)
4	150 mg b.d.[b] (including weekends)

Abbreviation: DL, dose level.
[a]Once daily.
[b]Twice daily.

The middle DL is the prior RP2D, where –0.5 DL on CONCORDE-A and all intermittent levels on CONCORDE-B have been excluded. This represents no prior anticipation of the RP2D. When there are two middle main doses (eg, CONCORDE-B), the lower was chosen to be conservative. The starting dose for all models is taken to be DL 1 for safety. No dose skipping of untested doses is permitted. Patients are recruited in cohorts of 1, meaning a dose escalation decision is made on all available data at the time of each patient being recruited.

DLTs are monitored from the start of treatment (DDRi-RT or RT) to 13.5 months after the start of RT to capture both acute and long-term toxicities related to the DDRi-RT combination. DLTs are collected for the RT-alone arm to aid interpretation and attribution of toxicities but are not included in any models.

Piecewise linear weights are used within the model. A participant is weighted 90% when followed up to 4.5 months post-RT start as it is anticipated that approximately 90% of DLTs will have been experienced by this point on the basis of a review of toxicity in locally advanced NSCLC from the Radiation Therapy Oncology Group database.[33] Participants are weighted 100% when they are either followed up to 13.5 months or have experienced a DLT. Full follow-up to 13.5 months is required for all patients, where possible, before confirmation of the RP2D.

The details regarding the functional form of the dose toxicity model and approach to determining the corresponding statistical parameters are provided in the Data Supplement. Model recommendations for dose allocation are made on the basis of the posterior probability of toxicity at each DL, recommending the dose with probability closest to the TTL (or lower, should lower doses not yet have been explored, to avoid dose skipping).

Stopping Rules

The following stopping rules have been incorporated into the design of each experimental treatment arm:

TABLE 2. DLs for CONCORDE-B (AZD1390)

DL	Dose	Schedule
–1	X mg	Monday, Wednesday, and Friday
1	X mg	Monday-Friday
1a	2X mg	Monday, Wednesday, and Friday
2	2X mg	Monday-Friday
2a	4X mg	Monday, Wednesday, and Friday
3	4X mg	Monday-Friday
3a	6X mg	Monday, Wednesday, and Friday
4	6X mg	Monday-Friday
4a	9X mg	Monday, Wednesday and Friday
5	9X mg	Monday-Friday

Abbreviation: DL, dose level.

TABLE 3. Clinical Parameters Used in Development of the Initial Time-to-Event Continuous Reassessment Method Model

Parameter	Input for CONCORDE
Target toxicity probability (p_T)	0.25
Number of test doses (K)	Dependant on specific DDRi. Expected to be no more than five for most treatment arms, including a DL –1 drop-down dose. Models have been calibrated for 3, 4, and 5 DLs as well as for intermittent dosing models with 6 and 10 DLs
Prior RP2D (v)	Middle main DL, excluding DL –0.5 on CONCORDE-A and intermittent levels on CONCORDE-B. This represents no clear prior anticipation of the RP2D
Starting DL	For the majority of trial arms, given the novel combination and lack of supporting data, we expect that dose escalation will start at DL 1 for safety. Where this is not the case, further calibration and simulations would be required
Maximum sample size	30 per DDRi
Dose skipping	No skipping of any untested doses will be permitted
Cohort size	1

Abbreviation: DDRi, different DNA damage response inhibitor; DL, dose level; RP2D, recommended phase II dose.

1. Stop after 10 patients at top dose if no DLTs seen.
2. Terminate if the lower limit of the 95% credible interval around the DLT probability at the lowest dose (–1) is above 0.3 or if 3 DLTs are seen at DL –1.

Evaluating Model Performance

Simulations were performed to assess operating characteristics under several scenarios (Table 4). Model performance was evaluated on the basis of the probability of each dose being recommended as the phase II dose, the average number of patients treated at each dose, and the average toxicity rate at each dose. The probability of stopping early is calculated as 1 minus the probability of each dose being selected as the RP2D. Three differing recruitment scenarios representing fast (four patients/month), average (two patients/month), and slow (0.7 patients/month) recruitment were simulated for each scenario. All simulations used 5,000 replicates and were performed using edited code from the R package, dfcrm.[34] Specific modifications are detailed in the Data Supplement.

Results of Simulations

A web interface of the simulation results is available at CONCORDE Simulation Results.[35]

The key results for CONCORDE-A (six DLs) and CONCORDE-B (10 DLs) are presented in Tables 5 and 6, respectively; additional results are presented in the Data Supplement. Corresponding results considering the original five DLs are in presented in the Data Supplement. Fast, average, and slow accrual results in an average duration of 21, 28.5, and 54 months, respectively, for both arms.

Under the primary model assumptions, Table 5 shows that the model chooses the correct RP2D(s) with a probability of 25%-65% across majority of scenarios, regardless of accrual rate. When considering RP2Ds within 5% of the TTL, this increases to 60%-80%, since where multiple DLs are close to the TTL, the model struggles to choose between two, as expected. More patients are treated at DLs with true toxicity closer to the target when accrual rates are slower. With fast accrual, the model explores all safe DLs adequately, and the probability of correctly choosing the RP2D is similar to that seen with slower accrual in the majority of scenarios, with fewer patients treated at the RP2D. Where all doses are too toxic, the model chooses the lowest doses –1 or –0.5 as the RP2D with 80% probability when accrual is slow, selecting higher doses as accrual rates increase and stopping early only 5% of the time, under the assumption of uniform DLT occurrence. Simulating under the assumption of 90% DLTs within 4.5 months, lowest doses are selected with 66% probability, stopping 26% of the time. In scenario 6, where DL1 and DL2 are too toxic, we see the model selects these as the RP2D with 87% probability with fast recruitment under the assumption of uniform DLT occurrence; however, this reduces to 32% when we reflect the expected distribution of 90% within 4.5 months, with 47% probability of selecting the correct dose (DL –0.5).

Incorporating intermittent dosing in CONCORDE-B inevitably reduces model performance, since with more doses it becomes harder to identify the correct RP2D. The model chooses the correct RP2D with a probability of 18%-46% across majority of scenarios, increasing to 37%-61% when considering RP2Ds within 5% of the TTL. Across all scenarios, few patients are treated at intermittent dosing levels, and these are not likely to be chosen as the RP2D even when they are the correct RP2D. However, the model is often close and chooses DLs closest to this intermittent level. If recruitment is fast, the prior has more influence on the model; hence, the intermittent level nearest the prior RP2D is more frequently used and often chosen as the RP2D in some scenarios. During slow recruitment, intermittent levels closest to the true RP2D are used the most, but with few patients treated at these DLs. As with CONCORDE-A, where all doses are too toxic, the model selects the lowest two doses the majority of time, stopping early 4% of the time, under uniform DLT occurrence. Assuming 90% DLTs within 4.5 months, early stopping increases to 28%.

When toxicities mostly occur toward the end of the DLT window, as simulated under the truncated normal distribution in the Data Supplement, for five DLs, the RP2D is chosen within 5% of the TTL with high probability (> 64%) in scenarios 4 and 5. Where all doses are too toxic (scenario 2), the model escalates to higher doses because of longer observation time of DLTs.

DISCUSSION

CONCORDE adopts a Bayesian adaptive model-based design including a calibration arm to overcome limitations typically

TABLE 4. Simulation Scenarios for Each CONCORDE Design

Scenario	True Toxicity Probability at Each DL	Time to Toxicity (T) Distribution
Original design (five DLs)	{DL-1, DL1, DL2, DL3, DL4}	
1: Low toxicity	{0.05, 0.1, 0.15, 0.2, 0.25}	Uniform
2. High toxicity	{0.4, 0.5, 0.6, 0.7, 0.8}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$ 90% acute: TruncNorm(0, 2.75) $0 < T < 13.5$ 60% acute: TruncNorm(0, 4) $0 < T < 13.5$
3. Reasonable toxicity	{0.05, 0.1, 0.15, 0.2, 0.3}	Uniform
4. Top doses too toxic	{0.05, 0.1, 0.25, 0.5, 0.7}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$
5. Difficult choice	{0.1, 0.25, 0.3, 0.4, 0.5}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$ 90% acute: TruncNorm(0, 2.75) $0 < T < 13.5$ 60% acute: TruncNorm(0, 4) $0 < T < 13.5$
CONCORDE A (six DLs)	{DL-1, DL-0.5, DL1, DL2, DL3, DL4}	
1: Low toxicity	{0.05, 0.075, 0.1, 0.15, 0.2, 0.25}	Uniform
2. High toxicity	{0.4, 0.45, 0.5, 0.6, 0.7, 0.8}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$ 90% acute: TruncNorm(0, 2.75) $0 < T < 13.5$ 60% acute: TruncNorm(0, 4) $0 < T < 13.5$
3. Reasonable toxicity	{0.05, 0.075, 0.1, 0.15, 0.2, 0.3}	Uniform
4. Top doses too toxic	{0.05, 0.075, 0.1, 0.25, 0.5, 0.7}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$
5. Difficult choice	{0.1, 0.175, 0.25, 0.3, 0.4, 0.5}	Uniform Late: TruncNorm(13.5,4) $0 < T < 13.5$
6. Top doses too toxic, DL-0.5 RP2D	{0.1, 0.25, 0.4, 0.45, 0.5, 0.6}	Uniform Late: TruncNorm(13.5,4) $0 < T < 13.5$ 90% acute: TruncNorm(0, 2.75) $0 < T < 13.5$ 60% acute: TruncNorm(0, 4) $0 < T < 13.5$
CONCORDE B (10 DLs)	{DL-1, DL1, DL1a, DL2, DL2a, DL3, DL3a, DL4, DL4a, DL5}	
1: Low toxicity	{0.05, 0.1, 0.125, 0.15, 0.175, 0.2, 0.225, 0.25, 0.3, 0.45}	Uniform
2. High toxicity	{0.4, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.825, 0.85}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$ 90% acute: TruncNorm(0, 2.75) $0 < T < 13.5$ 60% acute: TruncNorm(0, 4) $0 < T < 13.5$
3. Reasonable toxicity	{0.05, 0.1, 0.125, 0.15, 0.175, 0.2, 0.25, 0.3, 0.35, 0.4}	Uniform
4. Top doses too toxic	{0.05, 0.1, 0.175, 0.25, 0.375, 0.5, 0.6, 0.7, 0.75, 0.8}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$
5. Difficult choice	{0.1, 0.25, 0.275, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$ 90% acute: TruncNorm(0, 2.75) $0 < T < 13.5$ 60% acute: TruncNorm(0, 4) $0 < T < 13.5$
6. Difficult choice, DL2a RP2D	{0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5}	Uniform Late: TruncNorm(13.5, 4) $0 < T < 13.5$

Abbreviations: DL, dose level; RP2D, recommended phase II dose.

faced when applying more commonly used designs to a phase I drug-RT combination trial. The platform enables continuous recruitment to the trial without requiring excessive pauses in recruitment to allow efficient toxicity observation for dosing decisions. Recruitment will need to be monitored, especially in the early stages of each arm, to ensure that excessive numbers of patients are not recruited to the lowest DLs, should higher DLs later be proven safe, and conversely to ensure that higher doses are not explored too quickly should lower doses be shown to be too toxic. Although the model can mitigate some of these concerns to a degree, particularly where overly toxic doses are of concern, the ability of the safety review committee (SRC) to pause, or slow, recruitment is paramount.

TABLE 5. Simulation Results: Uniform Time to Toxicity, Six DLs (CONCORDE-A)

Patient Accrual	Result	DL −1	DL −0.5	DL 1	DL 2	DL 3	DL 4
Scenario 1. True P(tox): Uniform		0.05	0.075	0.1	0.15	0.2	0.25
Fast	P(RP2D)	0.000	0.001	0.061	0.284	0.311	0.343
	N patients	0.017	0.047	1.688	7.540	8.388	12.320
	Avg toxicity	0.080	0.064	0.099	0.150	0.200	0.250
Average	P(RP2D)	0.001	0.001	0.044	0.339	0.322	0.295
	N patients	0.027	0.061	1.629	5.791	7.744	14.747
	Avg toxicity	0.067	0.088	0.101	0.149	0.197	0.252
Slow	P(RP2D)	0.001	0.002	0.053	0.182	0.340	0.423
	N patients	0.039	0.100	1.890	5.419	9.474	13.078
	Avg toxicity	0.057	0.080	0.100	0.150	0.202	0.248
Scenario 2. True P(tox): Uniform		0.4	0.45	0.5	0.6	0.7	0.8
Fast	P(RP2D)	0.101	0.110	0.536	0.247	0.006	0.000
	N patients	0.636	1.737	6.430	11.637	6.965	2.594
	Avg toxicity	0.407	0.442	0.502	0.599	0.703	0.802
Average	P(RP2D)	0.274	0.221	0.410	0.087	0.003	0.001
	N patients	1.873	3.841	8.442	9.533	4.711	1.572
	Avg toxicity	0.401	0.458	0.503	0.604	0.699	0.804
Slow	P(RP2D)	0.613	0.187	0.111	0.028	0.012	0.001
	N patients	9.654	6.578	6.188	4.335	2.229	0.514
	Avg toxicity	0.401	0.452	0.499	0.603	0.700	0.785
Scenario 2. True P(tox): T ~ TruncNorm(0, 2.75) 0 < T < 13.5		0.4	0.45	0.5	0.6	0.7	0.8
Fast	P(RP2D)	0.712	0.127	0.100	0.039	0.000	0.000
	N patients	13.270	5.699	5.085	4.861	0.786	0.023
	Avg toxicity	0.402	0.446	0.504	0.599	0.703	0.796
Average	P(RP2D)	0.692	0.093	0.087	0.040	0.001	0.000
	N patients	15.272	5.228	4.296	3.305	0.560	0.021
	Avg toxicity	0.402	0.453	0.503	0.601	0.710	0.757
Slow	P(RP2D)	0.565	0.093	0.061	0.020	0.001	0.000
	N patients	14.087	4.963	3.824	1.977	0.472	0.020
	Avg toxicity	0.400	0.453	0.497	0.609	0.690	0.800
Scenario 3. True P(tox): Uniform		0.05	0.075	0.1	0.15	0.2	0.3
Fast	P(RP2D)	0.000	0.001	0.065	0.294	0.320	0.320
	N patients	0.021	0.060	1.737	7.598	8.304	12.280
	Avg toxicity	0.047	0.080	0.102	0.151	0.195	0.305
Average	P(RP2D)	0.001	0.001	0.050	0.346	0.314	0.289
	N patients	0.024	0.051	1.558	5.821	8.092	14.454
	Avg toxicity	0.076	0.070	0.104	0.149	0.200	0.303
Slow	P(RP2D)	0.001	0.002	0.058	0.196	0.375	0.369
	N patients	0.046	0.108	1.896	5.775	10.364	11.811
	Avg toxicity	0.052	0.065	0.102	0.149	0.200	0.301
Scenario 4. True P(tox): Uniform		0.05	0.075	0.1	0.25	0.5	0.7
Fast	P(RP2D)	0.001	0.001	0.190	0.691	0.116	0.000
	N patients	0.035	0.093	2.397	9.693	10.302	7.480
	Avg toxicity	0.040	0.064	0.099	0.251	0.503	0.700

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TABLE 5. Simulation Results: Uniform Time to Toxicity, Six DLs (CONCORDE-A) (Continued)

Patient Accrual	Result	DL −1	DL −0.5	DL 1	DL 2	DL 3	DL 4
Average	P(RP2D)	0.002	0.003	0.211	0.653	0.130	0.001
	N patients	0.052	0.111	2.861	10.288	10.629	6.060
	Avg toxicity	0.039	0.088	0.101	0.254	0.502	0.698
Slow	P(RP2D)	0.007	0.012	0.228	0.673	0.079	0.001
	N patients	0.158	0.482	6.375	13.480	7.350	2.154
	Avg toxicity	0.042	0.077	0.101	0.250	0.502	0.700
Scenario 5. True P(tox): Uniform		0.1	0.175	0.25	0.3	0.4	0.5
Fast	P(RP2D)	0.003	0.013	0.246	0.575	0.148	0.014
	N patients	0.071	0.235	2.930	9.750	9.368	7.646
	Avg toxicity	0.090	0.162	0.252	0.298	0.401	0.502
Average	P(RP2D)	0.006	0.020	0.274	0.507	0.172	0.022
	N patients	0.117	0.384	3.578	9.627	9.570	6.724
	Avg toxicity	0.099	0.166	0.251	0.301	0.398	0.504
Slow	P(RP2D)	0.019	0.079	0.362	0.380	0.146	0.014
	N patients	0.445	1.671	7.083	10.597	7.302	2.902
	Avg toxicity	0.107	0.177	0.251	0.299	0.400	0.510
Scenario 6. True P(tox): Uniform		0.1	0.25	0.4	0.45	0.5	0.6
Fast	P(RP2D)	0.029	0.060	0.434	0.439	0.037	0.002
	N patients	0.214	0.767	4.632	11.014	8.618	4.755
	Avg toxicity	0.112	0.249	0.399	0.451	0.498	0.599
Average	P(RP2D)	0.062	0.106	0.451	0.338	0.041	0.002
	N patients	0.437	1.496	6.424	10.794	7.363	3.486
	Avg toxicity	0.102	0.252	0.400	0.447	0.501	0.600
Slow	P(RP2D)	0.120	0.373	0.356	0.119	0.029	0.003
	N patients	2.090	6.108	9.321	7.408	3.866	1.203
	Avg toxicity	0.102	0.249	0.399	0.450	0.505	0.606
Scenario 6. True P(tox): T ~ TruncNorm(0, 2.75) 0 < T < 13.5		0.1	0.25	0.4	0.45	0.5	0.6
Fast	P(RP2D)	0.199	0.474	0.260	0.062	0.004	0.000
	N patients	5.189	8.440	8.299	6.478	1.476	0.112
	Avg toxicity	0.100	0.250	0.400	0.450	0.502	0.597
Average	P(RP2D)	0.181	0.518	0.238	0.055	0.007	0.000
	N patients	5.075	9.969	8.373	5.108	1.312	0.143
	Avg toxicity	0.102	0.251	0.402	0.450	0.497	0.584
Slow	P(RP2D)	0.155	0.558	0.228	0.046	0.007	0.000
	N patients	4.530	11.594	8.765	3.772	1.106	0.130
	Avg toxicity	0.099	0.255	0.402	0.453	0.506	0.618

Abbreviations: Avg toxicity, average toxicity rate; DL, dose level; N patients, number of patients treated; P(RP2D), probability of correctly selected the true RP2D; P(tox), probability of toxicity; RP2D, recommended phase II dose.

The design simulations showed that if toxicity occurs in a roughly uniform manner across the DLT window, the TiTE-CRM model results in acceptable operating characteristics, acknowledging within the context of a phase I trial we cannot expect to see high probabilities of identifying the correct dose exactly, when patient numbers are inherently low. Accepting a RP2D with toxicity rates within 5% of the target toxicity level gave increased probability of correct selection in the region of 60%-80% across most scenarios for CONCORDE-A and 37%-61% for CONCORDE-B. Where all doses are too toxic, the model chooses the lowest dose as the RP2D, the majority of the time when accrual is slow, under the assumption of uniform DLT occurrence. However, a limitation of the model, even when

TABLE 6. Simulation Results: Uniform Time to Toxicity, 10 DLs (CONCORDE-B)

Patient Accrual	Result	DL −1	DL 1	DL 1a	DL 2	DL 2a	DL 3	DL 3a	DL 4	DL 4a	DL 5
Scenario 1. True P(tox): Uniform		0.05	0.1	0.125	0.15	0.175	0.2	0.225	0.25	0.3	0.35
Fast	P(RP2D)	0.006	0.044	0.001	0.161	0.129	0.071	0.001	0.317	0.000	0.271
	N patients	0.265	1.590	0.035	3.823	3.481	3.333	0.011	5.972	0.000	11.489
	Avg toxicity	0.057	0.097	0.098	0.151	0.176	0.199	0.298	0.255	NA[a]	0.349
Average	P(RP2D)	0.004	0.056	0.003	0.175	0.011	0.125	0.010	0.213	0.029	0.375
	N patients	0.222	1.425	0.143	3.751	0.496	4.040	0.381	5.360	1.036	13.146
	Avg toxicity	0.050	0.102	0.115	0.151	0.179	0.203	0.219	0.250	0.292	0.351
Slow	P(RP2D)	0.004	0.053	0.005	0.110	0.020	0.230	0.044	0.245	0.048	0.241
	N patients	0.183	1.724	0.184	3.140	0.666	5.944	1.322	5.872	1.425	9.539
	Avg toxicity	0.057	0.097	0.115	0.151	0.178	0.200	0.224	0.250	0.308	0.352
Scenario 2. True P(tox): Uniform		0.4	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.825	0.85
Fast	P(RP2D)	0.311	0.316	0.001	0.260	0.055	0.029	0.000	0.022	0.000	0.006
	N patients	3.857	5.233	0.206	6.524	4.291	3.785	0.009	3.748	0.000	2.344
	Avg toxicity	0.406	0.507	0.518	0.601	0.653	0.703	0.891	0.796	NA[a]	0.852
Average	P(RP2D)	0.532	0.214	0.008	0.157	0.004	0.053	0.001	0.021	0.000	0.005
	N patients	7.492	6.057	0.825	6.054	1.068	3.831	0.225	2.426	0.159	1.809
	Avg toxicity	0.402	0.503	0.552	0.600	0.648	0.707	0.771	0.800	0.832	0.847
Slow	P(RP2D)	0.783	0.033	0.002	0.082	0.002	0.049	0.000	0.005	0.000	0.002
	N patients	17.188	4.373	0.331	2.867	0.183	2.517	0.083	1.041	0.015	0.822
	Avg toxicity	0.401	0.498	0.534	0.605	0.641	0.705	0.758	0.791	0.800	0.855
Scenario 2. True P(tox): T ~ TruncNorm(0, 2.75) 0 < T < 13.5		0.4	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.825	0.85
Fast	P(RP2D)	0.781	0.014	0.000	0.142	0.041	0.002	0.000	0.001	0.000	0.000
	N patients	20.628	3.313	0.048	3.251	1.612	0.536	0.000	0.276	0.000	0.035
	Avg toxicity	0.402	0.502	0.479	0.598	0.651	0.702	NA[a]	0.809	NA	0.874
Average	P(RP2D)	0.772	0.014	0.002	0.110	0.000	0.018	0.000	0.002	0.000	0.000
	N patients	21.063	3.061	0.218	2.780	0.082	1.051	0.001	0.247	0.000	0.048
	Avg toxicity	0.401	0.494	0.550	0.592	0.639	0.702	0.714	0.772	NA	0.864
Slow	P(RP2D)	0.670	0.014	0.001	0.029	0.000	0.009	0.000	0.000	0.000	0.000
	N patients	18.562	3.040	0.166	1.598	0.040	0.884	0.002	0.132	0.000	0.040
	Avg toxicity	0.402	0.506	0.555	0.596	0.663	0.703	0.889	0.814	1.000	0.894
Scenario 3. True P(tox): Uniform		0.05	0.1	0.125	0.15	0.175	0.2	0.25	0.3	0.35	0.4
Fast	P(RP2D)	0.005	0.056	0.000	0.170	0.139	0.087	0.001	0.323	0.000	0.220
	N patients	0.305	1.606	0.035	3.814	3.517	3.483	0.018	6.187	0.000	11.036
	Avg toxicity	0.047	0.105	0.115	0.150	0.174	0.197	0.239	0.303	NA[a]	0.402
Average	P(RP2D)	0.003	0.078	0.002	0.196	0.013	0.158	0.012	0.226	0.021	0.292
	N patients	0.202	1.427	0.139	3.896	0.517	4.394	0.455	5.590	1.084	12.297
	Avg toxicity	0.044	0.103	0.115	0.151	0.175	0.203	0.251	0.300	0.351	0.401
Slow	P(RP2D)	0.003	0.057	0.005	0.133	0.023	0.280	0.058	0.243	0.037	0.160
	N patients	0.232	1.845	0.232	3.524	0.718	6.720	1.515	6.086	1.284	7.844
	Avg toxicity	0.048	0.097	0.111	0.151	0.166	0.203	0.251	0.300	0.356	0.400
Scenario 4. True P(tox): Uniform		0.05	0.1	0.175	0.25	0.375	0.5	0.6	0.7	0.75	0.8

(Continued on following page)

TABLE 6. Simulation Results: Uniform Time to Toxicity, 10 DLs (CONCORDE-B) (Continued)

Patient Accrual	Result	DL −1	DL 1	DL 1a	DL 2	DL 2a	DL 3	DL 3a	DL 4	DL 4a	DL 5
Fast	P(RP2D)	0.020	0.218	0.000	0.435	0.210	0.080	0.000	0.032	0.000	0.004
	N patients	0.525	2.464	0.048	5.113	4.494	5.063	0.021	6.560	0.000	5.711
	Avg toxicity	0.050	0.101	0.192	0.249	0.378	0.495	0.632	0.698	NA[a]	0.801
Average	P(RP2D)	0.030	0.247	0.017	0.457	0.041	0.163	0.001	0.036	0.001	0.007
	N patients	0.630	3.233	0.419	6.827	1.495	6.503	0.651	5.033	0.575	4.635
	Avg toxicity	0.055	0.098	0.181	0.247	0.380	0.504	0.594	0.702	0.755	0.799
Slow	P(RP2D)	0.069	0.242	0.078	0.408	0.036	0.138	0.001	0.021	0.000	0.007
	N patients	2.249	7.099	1.546	7.916	1.206	5.266	0.478	2.215	0.088	1.939
	Avg toxicity	0.050	0.099	0.163	0.252	0.364	0.499	0.577	0.701	0.754	0.799
Scenario 5. True P(tox): Uniform		0.1	0.25	0.275	0.3	0.35	0.4	0.45	0.5	0.55	0.6
Fast	P(RP2D)	0.034	0.187	0.001	0.364	0.170	0.081	0.001	0.130	0.000	0.031
	N patients	0.874	2.645	0.102	5.018	4.164	4.534	0.022	6.120	0.000	6.519
	Avg toxicity	0.100	0.245	0.260	0.302	0.349	0.401	0.459	0.503	NA[a]	0.597
Average	P(RP2D)	0.040	0.227	0.013	0.342	0.027	0.194	0.006	0.118	0.003	0.029
	N patients	0.967	3.115	0.569	6.098	1.200	6.046	0.635	5.079	0.725	5.567
	Avg toxicity	0.098	0.250	0.266	0.302	0.357	0.402	0.457	0.499	0.549	0.604
Slow	P(RP2D)	0.084	0.323	0.031	0.269	0.019	0.191	0.007	0.056	0.001	0.018
	N patients	2.938	6.505	1.206	6.694	1.063	5.574	0.676	2.665	0.245	2.431
	Avg toxicity	0.097	0.248	0.280	0.300	0.344	0.400	0.452	0.502	0.567	0.599
Scenario 5. True P(tox): T ~ TruncNorm(0, 2.75) 0 < T < 13.5		0.1	0.25	0.275	0.3	0.35	0.4	0.45	0.5	0.55	0.6
Fast	P(RP2D)	0.178	0.356	0.013	0.303	0.083	0.037	0.000	0.026	0.000	0.003
	N patients	8.318	7.330	0.405	6.522	3.383	2.182	0.011	1.438	0.000	0.405
	Avg toxicity	0.101	0.248	0.270	0.306	0.350	0.401	0.536	0.499	NA	0.610
Average	P(RP2D)	0.147	0.381	0.056	0.260	0.028	0.090	0.001	0.030	0.000	0.005
	N patients	7.172	7.869	1.860	6.564	1.091	3.317	0.138	1.388	0.044	0.538
	Avg toxicity	0.100	0.252	0.275	0.301	0.344	0.399	0.431	0.489	0.545	0.598
Slow	P(RP2D)	0.137	0.417	0.066	0.203	0.030	0.111	0.005	0.019	0.000	0.004
	N patients	6.206	9.023	2.028	5.917	1.013	3.682	0.333	1.121	0.062	0.511
	Avg toxicity	0.100	0.254	0.283	0.304	0.350	0.398	0.437	0.492	0.503	0.607
Scenario 6. True P(tox):		0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
Fast	P(RP2D)	0.010	0.104	0.002	0.269	0.176	0.103	0.001	0.239	0.000	0.097
	N patients	0.420	1.921	0.055	4.209	3.772	3.996	0.016	6.481	0.000	9.131
	Avg toxicity	0.054	0.099	0.139	0.204	0.249	0.296	0.275	0.402	NA[a]	0.504
Average	P(RP2D)	0.005	0.136	0.006	0.279	0.020	0.211	0.013	0.205	0.012	0.114
	N patients	0.257	1.764	0.229	4.662	0.867	5.497	0.606	5.958	1.092	9.068
	Avg toxicity	0.054	0.103	0.157	0.200	0.237	0.302	0.351	0.400	0.458	0.497
Slow	P(RP2D)	0.011	0.113	0.023	0.260	0.038	0.306	0.033	0.146	0.009	0.061
	N patients	0.477	3.184	0.598	5.962	1.191	7.416	1.328	4.627	0.663	4.553
	Avg toxicity	0.051	0.102	0.154	0.203	0.248	0.300	0.350	0.398	0.451	0.502

Abbreviations: Avg toxicity, average toxicity rate; DL, dose level; N patients, number of patients treated; P(RP2D), probability of correctly selected the true RP2D; RP2D, recommended phase II dose.

[a]NA as no patients treated at this dose.

incorporating stopping rules, is the difficulty to stop early. Within CONCORDE, we expect 90% of toxicities to occur within the first 4.5 months of the DLT window.[36] Simulating DLT occurrence to reflect this shows the model significantly improves in its ability to stop early, under slow recruitment; however, this still remains low at 26%. This is likely because, with more DLs, the model takes longer to reach DL −1 (where the toxicity stopping rules kick in), reducing the ability to stop early since many of the patients will have been recruited by this time. As some of the lower DLs are close in toxicity probability, the model may also spend time flip-flopping between these doses rather than terminating. In this situation, it would be key for the SRC to reflect on whether it is more appropriate to stop recruitment or pause for longer follow-up periods to allow more safety data to accrue and similarly where high toxicity is seen in lower DLs to prevent overdosing of patients. To alleviate the issue of fast recruitment, restriction on the number of patients recruited before dose decisions are made may be included, such as restriction to cohort sizes of only two patients for the first four or six patients. In combination, these additional recruitment restrictions and stopping rules will control recruitment to accrue more safety data before making escalation decisions, thus reducing the chances of treating at too toxic doses.

For CONCORDE-B, the addition of intermittent dosing inevitably reduces the ability of the model to select the correct dose, since fewer patients are treated at each dose. This limitation is an acceptable tradeoff to allow exploration of more appropriate dosing. In some settings, it may be feasible to consider adding more patients to the RP2D in a further expansion phase to the study, where only few patients have been treated at that dose. Within CONCORDE, this is not possible since recruitment to an arm will have closed before the RP2D is determined. During slow recruitment, intermittent levels closest to the true RP2D are used most, but few patients are treated at these. This may be due to an intermittent level being used too soon and locking out all other intermittent levels, as only one will be explored throughout the trial. During the trial, this will likely not be such an issue, as the SRC will have some flexibility to postpone investigation of an intermittent level until later in the trial, when more safety data have been accrued. This is not included in simulations.

Although the simulations performed reflect the study design and conduct as closely as possible, we acknowledge not all elements have been incorporated, relating to very specific scenarios. This decision was taken on the basis of recommendations of the CHARIOT TiTE-CRM study, suggesting not programming minor details not readily available in existing software where their impact will be minimal.[22]

At the final analysis for each arm, the RP2D will be calculated based on observed toxicity rates, to account for only few patients being treated at a dose, where prior estimates may be informing the posterior probability of toxicity. We acknowledge this as a limitation; however, this was chosen due to simulation results showing up to 20% of cases recommending the incorrect phase II dose on the basis of posterior probabilities. In practice, model estimates of the β parameter and corresponding posterior probabilities of toxicity and credible intervals will also be calculated for each dose. These estimates, combined with the RP2D on the basis of observed toxicity as well as broader information on safety and toxicity and potentially efficacy, will be used to inform the decision regarding the dose to take forward to subsequent trials.

There are challenges in applying this design. The setup of TiTE-CRM models requires substantial statistical resource, with extensive simulation work needed to calibrate the model and check its operating characteristics, exploring many scenarios. Logistically, having multiple experimental arms open at once and enabling patients to enter at any point during the trial means that the SRC must meet regularly and the trial statistician must run the models to determine dose recommendations more frequently than in a single-arm phase I dose escalation trial. Because of the complexity of the TiTE-CRM, the SRC also includes a statistician to provide independent statistical input. Communication of TiTE-CRM output to a multidisciplinary team can be difficult because of potential unfamiliarity with using this model. It is, however, important to note that the TiTE-CRM output is a model recommendation to the SRC, whereby dose escalation recommendations may be overruled should the SRC decide more follow-up of current patients is required. This allows clinical expertise to integrate with statistics. These are challenges we accept in running a trial of this design.

In conclusion, we have demonstrated how TiTE-CRM methodology may be used in practice in a complex dose-finding platform study. Key features of this novel platform trial provide an opportunity to study multiple targeted therapies in the same disease area in a more efficient manner. CONCORDE will enable ongoing recruitment despite long DLT periods, investigation of multiple DDRi-RT combinations, and accumulation of quality-assured standard-of-care RT data for this setting. We propose that this novel phase I design has potential to overcome logistical barriers that for many years have prevented timely development of novel drug-RT combinations.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

The simulation data are available at https://github.com/rachelphillipctru/concordesims.

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