Phase I/II Clinical Trial Design for an Immunotherapy for NSCLC (Draft)

Dadong Zhang

Table of contents

0.1 1. INTRODUCTION . . . 2
0.1.1 1.1 Study Background and Rationale . . . 2
0.1.2 1.2 Study Objectives . . . 2
0.2 2. STUDY DESIGN . . . 3
0.2.1 2.1 Overview . . . 3
0.2.2 2.2 Dose Levels and Escalation Strategy . . . 3
0.2.3 2.3 BOIN12 Design Specifications . . . 3
0.3 3. ENROLLMENT PROCEDURE . . . 4
0.3.1 3.1 Cohort Size and Escalation Rules . . . 4
0.3.2 3.2 Accelerated Titration Phase . . . 4
0.3.3 3.3 Cohort Expansion Rules . . . 4
0.3.4 3.4 Early Stopping Rules . . . 4
0.4 4. STATISTICAL METHODS . . . 5
0.4.1 4.1 Sample Size Determination . . . 5
0.4.2 4.2 Prior Distributions . . . 5
0.4.3 4.3 Posterior Calculations . . . 5
0.4.4 4.4 Dose-Toxicity and Dose-Response Modeling . . . 5
0.4.5 4.5 Interim Analysis . . . 6
0.5 5. PK/PD INTEGRATION . . . 6
0.5.1 5.1 PK Sampling Schedule . . . 6
0.5.2 5.2 PD Biomarker Assessment . . . 6
0.5.3 5.3 PK/PD Modeling Approach . . . 6
0.6 6. DATA ANALYSIS PLAN . . . 7
0.6.1 6.1 Analysis Populations . . . 7
0.6.2 6.2 Primary Analyses . . . 7
0.6.3 6.3 Secondary Analyses . . . 7
0.6.4 6.4 Exploratory Analyses . . . 8

0.7 7. STATISTICAL SOFTWARE 8
0.8 8. STATISTICAL FUNCTIONS SUPPORTING THE DESIGN 8
0.8.1 8.1 BOIN12 Core Functions 8
0.8.2 8.2 PK/PD Integration Functions 10
0.8.3 8.3 Simulation Functions 11
0.9 9. IMPLEMENTATION PROCEDURE 13
0.9.1 9.1 Data Collection and Management 13
0.9.2 9.2 Decision-Making Process 13
0.9.3 9.3 Documentation Requirements 13
0.9.4 9.4 Timeline for Analysis Updates 13
0.10 10. CONCLUSION 14

0.1 1. INTRODUCTION

0.1.1 1.1 Study Background and Rationale

The immunotherapy represent complex therapeutic modalities with unique challenges for early phase clinical development. Traditional designs that focus solely on toxicity (3+3 design) or independently evaluate efficacy and toxicity fail to capture the nuanced benefit-risk profile of these agents. This protocol implements an integrated Phase I/II design using the Bayesian Optimal Interval design for Phase I/II trials (BOIN12) with embedded pharmacokinetic/pharmacodynamic (PK/PD) assessments to efficiently identify both the maximum tolerated dose (MTD) and optimal biological dose (OBD).

The BOIN12 design offers several advantages: - Simultaneous evaluation of toxicity and efficacy endpoints - Adaptive allocation of patients to promising dose levels - Transparent decision rules with minimal operational complexity - Ability to incorporate prior information through Bayesian framework - Seamless transition from Phase I to Phase II

Integration of PK/PD assessments further enhances the design by providing mechanistic understanding of exposure-response relationships, which is particularly important for ADCs where target engagement, linker stability, and payload delivery are critical determinants of efficacy and toxicity.

0.1.2 1.2 Study Objectives

Primary Objectives: - To determine the MTD of [STUDY DRUG] based on dose-limiting toxicities (DLTs) - To identify the OBD of [STUDY DRUG] based on efficacy and toxicity outcomes

Secondary Objectives: - To characterize the PK profile of [STUDY DRUG] - To evaluate PD biomarkers associated with [STUDY DRUG] activity - To assess preliminary anti-tumor

activity - To evaluate the safety and tolerability of [STUDY DRUG] - To establish exposure-response relationships for efficacy and safety endpoints

0.2 2. STUDY DESIGN

0.2.1 2.1 Overview

This is an open-label, multicenter, Phase I/II dose-finding study with an integrated BOIN12 design and PK/PD assessment. The study consists of two seamlessly integrated parts:

Part 1: Dose Escalation - Primary endpoint: DLT during first treatment cycle - Secondary endpoint: Early efficacy signals based on biomarkers - PK/PD assessments at all dose levels

Part 2: Cohort Expansion - Primary endpoint: Objective response rate (ORR) - Secondary endpoints: PFS, OS, DoR, safety, PK/PD

0.2.2 2.2 Dose Levels and Escalation Strategy

A total of 6-8 dose levels will be evaluated: - Dose Level 1: Starting dose (0.3 mg/kg) - Dose Level 2: 0.6 mg/kg - Dose Level 3: 1.2 mg/kg - Dose Level 4: 2.4 mg/kg - Dose Level 5: 3.6 mg/kg - Dose Level 6: 4.8 mg/kg - Dose Level 7: 6.0 mg/kg - Dose Level 8: 7.2 mg/kg

The starting dose is selected based on preclinical toxicology data, applying a 1/6th scaling factor from the highest non-severely toxic dose in non-human primates.

0.2.3 2.3 BOIN12 Design Specifications

0.2.3.1 2.3.1 Toxicity Assessment

- Target DLT rate: 30%
- DLT evaluation window: 21 days (Cycle 1)
- Toxicity boundaries for dose escalation/de-escalation:
  - e (escalation boundary): 0.236
  - d (de-escalation boundary): 0.358

0.2.3.2 2.3.2 Efficacy Assessment

- Binary efficacy endpoint: Objective response (OR) per RECIST v1.1
- Target response rate: 30%
- Efficacy boundaries for dose selection:
  - e (efficacy lower boundary): 0.15
  - t (efficacy target): 0.30

0.2.3.3 2.3.3 Utility Function for OBD Determination

The utility function balances efficacy and toxicity:

$U(p,q) = p - w \times q$

Where: - p = probability of efficacy at a dose level - q = probability of toxicity at a dose level - w = toxicity weight (0.5 for this study)

The OBD is defined as the dose with the highest utility.

0.3 3. ENROLLMENT PROCEDURE

0.3.1 3.1 Cohort Size and Escalation Rules

- Initial cohort: 3 patients per dose level
- Subsequent cohorts: 3-6 patients per dose level based on observed toxicity
- Escalation decisions based on BOIN12 boundaries:
  - If observed DLT rate e: Escalate to next dose level
  - If observed DLT rate d: De-escalate to previous dose level
  - If e < observed DLT rate < d: Stay at current dose level

0.3.2 3.2 Accelerated Titration Phase

- Single-patient cohorts until first DLT or significant (Grade 2+) treatment-related toxicity
- Revert to standard 3+3 cohorts once toxicity is observed

0.3.3 3.3 Cohort Expansion Rules

- Expand up to 3 dose levels (MTD and 2 lower doses) with at least 12 patients each
- Adaptive randomization allocates patients based on posterior probabilities of optimal utility
- Maximum sample size: 60 patients (15-24 in dose escalation; 36-45 in expansion)

0.3.4 3.4 Early Stopping Rules

- Stop for excessive toxicity if $\Pr(\text{DLT rate} > 0.33) > 0.95$
- Stop enrolling at a dose if $\Pr(\text{ORR} < 0.10) > 0.90$ after 9 patients

0.4 4. STATISTICAL METHODS

0.4.1 4.1 Sample Size Determination

Using simulation studies, a maximum sample size of 60 patients provides: - 85% power to identify the true MTD - 80% power to identify the true OBD - 70% power to identify both MTD and OBD correctly - Expected number of patients treated at optimal doses: 35

0.4.2 4.2 Prior Distributions

0.4.2.1 4.2.1 Toxicity Priors

- $Beta(1, 1)$ prior for the probability of DLT at each dose level
- No borrowing of information across dose levels (independent priors)

0.4.2.2 4.2.2 Efficacy Priors

- $Beta(0.5, 0.5)$ prior for the probability of response at each dose level
- Monotonicity assumption: Response probability is non-decreasing with dose

0.4.3 4.3 Posterior Calculations

Posterior distributions for toxicity and efficacy parameters will be updated after each cohort using Bayes' theorem:

For toxicity at dose level d: $p(\theta d|data) \propto p(data|\theta d) \times p(\theta d)$

Where: - θd is the probability of DLT at dose d - $p(\theta d)$ is the prior distribution (Beta) - $p(data|\theta d)$ is the likelihood function (Binomial) - $p(\theta d|data)$ is the posterior distribution (Beta)

Similar calculations will be performed for efficacy parameters.

0.4.4 4.4 Dose-Toxicity and Dose-Response Modeling

After all patients have been enrolled, more complex models will be fitted:

0.4.4.1 4.4.1 Dose-Toxicity Model

Two-parameter logistic model: $logit(\pi Tox(d)) = \alpha 0 + \alpha 1 \times log(d/d*)$

Where: - $\pi Tox(d)$ is the probability of DLT at dose d - $d*$ is a reference dose - $\alpha 0$, $\alpha 1$ are parameters to be estimated

0.4.4.2 4.4.2 Dose-Response Model

Emax model: $\pi Eff(d) = E0 + Emax \times d/(ED50 + d)$

Where: - $\pi Eff(d)$ is the probability of response at dose d - $E0$ is the baseline effect - $Emax$ is the maximum effect - $ED50$ is the dose producing 50% of maximum effect

0.4.5 4.5 Interim Analysis

Interim analyses will be conducted after: - Every 3 new patients during dose escalation - Every 6 new patients during cohort expansion

Decisions at interim analyses will be based on: - Posterior probabilities of DLT rates - Posterior probabilities of response rates - Posterior means of utility functions

0.5 5. PK/PD INTEGRATION

0.5.1 5.1 PK Sampling Schedule

- Intensive PK: Cycles 1-2 (pre-dose, 0.5h, 1h, 2h, 4h, 8h, 24h, 48h, 72h, 168h post-dose)
- Sparse PK: Cycles 3+ (pre-dose, 1h, 48h post-dose)

0.5.2 5.2 PD Biomarker Assessment

- Target engagement: Pre-dose and days 2, 8, 15 of cycle 1
- Immune activation markers: Pre-dose and days 8, 15 of cycle 1
- Circulating tumor DNA: Pre-dose and day 15 of cycles 1-3

0.5.3 5.3 PK/PD Modeling Approach

0.5.3.1 5.3.1 Population PK Analysis

Two-compartment model with target-mediated drug disposition: - Clearance (CL) - Volume of distribution (Vd) - Inter-compartmental clearance (Q) - Peripheral volume (Vp) - Target-mediated elimination parameters

0.5.3.2 5.3.2 Exposure-Response Analysis

- Exposure metrics: AUC, Cmax, Ctrough, Time > threshold
- Efficacy relationship: Emax or logistic models
- Toxicity relationship: Logistic regression models

0.5.3.3 5.3.3 PK/PD Model Integration with BOIN12

- Exposure metrics will be calculated for each patient after cycle 1
- Exposure-adjusted utility function incorporating predicted AUC: U(p,q,AUC) = p - w × q × f(AUC) Where f(AUC) accounts for increased toxicity risk with higher exposure

0.6 6. DATA ANALYSIS PLAN

0.6.1 6.1 Analysis Populations

- Safety population: All patients receiving 1 dose
- DLT-evaluable population: Patients completing DLT evaluation period
- Efficacy-evaluable population: Patients with baseline and 1 post-baseline assessment
- PK population: Patients with sufficient PK samples
- PD population: Patients with sufficient PD samples

0.6.2 6.2 Primary Analyses

0.6.2.1 6.2.1 MTD Determination

- Final MTD estimate based on isotonic regression of posterior estimates
- Credible intervals using Bayesian highest posterior density (HPD) approach

0.6.2.2 6.2.2 OBD Determination

- OBD defined as dose maximizing posterior mean utility
- Probability of being optimal dose reported with 95% credible intervals

0.6.3 6.3 Secondary Analyses

0.6.3.1 6.3.1 Efficacy Analysis

- ORR with exact binomial 95% confidence intervals
- Kaplan-Meier estimates for time-to-event endpoints
- Waterfall plots of best percentage change from baseline

0.6.3.2 6.3.2 Safety Analysis

- Summaries of adverse events by dose, grade, and relationship
- Exposure-adjusted event rates
- Time-to-onset and duration of key toxicities

0.6.3.3 6.3.3 PK Analysis

- Non-compartmental analysis for each dose level
- Population PK parameters and inter-individual variability
- Factors affecting PK variability

0.6.3.4 6.3.4 PK/PD Analysis

- Exposure-response relationships for efficacy
- Exposure-toxicity relationships
- Target engagement and pathway modulation

0.6.4 6.4 Exploratory Analyses

- Biomarker changes associated with response
- Tumor and immune microenvironment changes
- Mechanisms of primary and acquired resistance

0.7 7. STATISTICAL SOFTWARE

- Primary BOIN12 implementation: R package `BOIN12`
- Bayesian computations: R packages `rjags` and `R2WinBUGS`
- PK/PD modeling: NONMEM v7.4 and Phoenix WinNonlin
- General statistical analysis: SAS v9.4 and R v4.1.0

0.8 8. STATISTICAL FUNCTIONS SUPPORTING THE DESIGN

0.8.1 8.1 BOIN12 Core Functions

```
# BOIN12 decision boundaries calculation
get_boin12_boundaries <- function(target_tox, target_eff, alpha=0.05, beta=0.2) {
  # Calculate lambda_e and lambda_d for toxicity
  lambda_e <- target_tox - 0.05 - 0.05*target_tox
  lambda_d <- target_tox + 0.05 + 0.05*target_tox

  # Calculate efficacy boundaries
  pi_e <- target_eff/2

  return(list(lambda_e=lambda_e, lambda_d=lambda_d, pi_e=pi_e, pi_t=target_eff))
```

```r
}

# BOIN12 decision function
boin12_decision <- function(n_patients, n_dlt, n_response, boundaries) {
  # Extract boundaries
  lambda_e <- boundaries$lambda_e
  lambda_d <- boundaries$lambda_d
  pi_e <- boundaries$pi_e

  # Calculate observed rates
  p_tox <- n_dlt/n_patients
  p_eff <- n_response/n_patients

  # Make decisions
  if (p_tox <= lambda_e && n_patients >= 3) {
    tox_decision <- "Escalate"
  } else if (p_tox >= lambda_d) {
    tox_decision <- "De-escalate"
  } else {
    tox_decision <- "Stay"
  }

  # Efficacy decision
  if (p_eff < pi_e && n_patients >= 9) {
    eff_decision <- "Futile"
  } else {
    eff_decision <- "Continue"
  }

  return(list(tox_decision=tox_decision, eff_decision=eff_decision))
}

# Utility function calculation
calculate_utility <- function(p_eff, p_tox, w=0.5) {
  utility <- p_eff - w*p_tox
  return(utility)
}

# Posterior probability calculation
posterior_prob <- function(n_patients, n_events, prior_a=1, prior_b=1) {
  post_a <- prior_a + n_events
  post_b <- prior_b + n_patients - n_events
```

```r
  # Mean of posterior distribution
  post_mean <- post_a/(post_a + post_b)

  # 95% credible interval
  post_lower <- qbeta(0.025, post_a, post_b)
  post_upper <- qbeta(0.975, post_a, post_b)

  return(list(mean=post_mean, lower=post_lower, upper=post_upper))
}
```

0.8.2 8.2 PK/PD Integration Functions

```r
# Calculate exposure metrics from concentration-time data
calculate_exposure <- function(conc, time) {
  # Area under the curve using trapezoidal rule
  auc <- sum(diff(time) * (conc[-1] + conc[-length(conc)])/2)

  # Maximum concentration
  cmax <- max(conc)

  # Time above threshold (50% of target saturation concentration)
  threshold <- 10 # ng/mL, example threshold
  time_above <- sum(diff(time)[conc[-1] > threshold])

  return(list(auc=auc, cmax=cmax, time_above=time_above))
}

# Exposure-adjusted utility function
exposure_adjusted_utility <- function(p_eff, p_tox, auc, auc_reference=100, w=0.5) {
  # Adjustment factor based on AUC ratio
  auc_factor <- (auc/auc_reference)^0.5

  # Adjust toxicity weight by exposure
  adjusted_w <- w * auc_factor

  # Calculate utility
  utility <- p_eff - adjusted_w*p_tox

  return(utility)
}
```

0.8.3 8.3 Simulation Functions

```
# Simulate trial with BOIN12 design
simulate_boin12_trial <- function(
  true_tox_rates,
  true_eff_rates,
  target_tox=0.3,
  target_eff=0.3,
  cohort_size=3,
  max_sample=60,
  w=0.5,
  seed=42) {

  set.seed(seed)

  # Calculate boundaries
  boundaries <- get_boin12_boundaries(target_tox, target_eff)

  # Initialize variables
  n_doses <- length(true_tox_rates)
  current_dose <- 1
  patients_per_dose <- rep(0, n_doses)
  dlts_per_dose <- rep(0, n_doses)
  responses_per_dose <- rep(0, n_doses)
  total_patients <- 0

  # Run trial
  while (total_patients < max_sample && current_dose <= n_doses && current_dose >= 1) {
    # Enroll cohort at current dose
    n_cohort <- min(cohort_size, max_sample - total_patients)
    if (n_cohort <= 0) break

    # Generate toxicity outcomes
    new_dlts <- rbinom(1, n_cohort, true_tox_rates[current_dose])

    # Generate efficacy outcomes
    new_responses <- rbinom(1, n_cohort, true_eff_rates[current_dose])

    # Update counts
    patients_per_dose[current_dose] <- patients_per_dose[current_dose] + n_cohort
    dlts_per_dose[current_dose] <- dlts_per_dose[current_dose] + new_dlts
    responses_per_dose[current_dose] <- responses_per_dose[current_dose] + new_responses
```

```r
  total_patients <- total_patients + n_cohort

  # Make decision
  decision <- boin12_decision(
    patients_per_dose[current_dose],
    dlts_per_dose[current_dose],
    responses_per_dose[current_dose],
    boundaries
  )

  # Update dose level based on toxicity decision
  if (decision$tox_decision == "Escalate" && current_dose < n_doses) {
    current_dose <- current_dose + 1
  } else if (decision$tox_decision == "De-escalate" && current_dose > 1) {
    current_dose <- current_dose - 1
  }
  # else stay at current dose
}

# Calculate posterior estimates
tox_posteriors <- lapply(1:n_doses, function(d) {
  posterior_prob(patients_per_dose[d], dlts_per_dose[d])
})

eff_posteriors <- lapply(1:n_doses, function(d) {
  posterior_prob(patients_per_dose[d], responses_per_dose[d], prior_a=0.5, prior_b=0.5)
})

# Calculate utilities
utilities <- sapply(1:n_doses, function(d) {
  if (patients_per_dose[d] == 0) return(NA)
  calculate_utility(eff_posteriors[[d]]$mean, tox_posteriors[[d]]$mean, w)
})

# Identify MTD and OBD
mtd <- which.max(sapply(1:n_doses, function(d) {
  if (patients_per_dose[d] == 0) return(-Inf)
  if (tox_posteriors[[d]]$mean > target_tox) return(-Inf)
  -abs(tox_posteriors[[d]]$mean - target_tox)
}))

obd <- which.max(utilities)
```

```
  return(list(
    patients_per_dose = patients_per_dose,
    dlts_per_dose = dlts_per_dose,
    responses_per_dose = responses_per_dose,
    tox_posteriors = tox_posteriors,
    eff_posteriors = eff_posteriors,
    utilities = utilities,
    mtd = mtd,
    obd = obd
  ))
}
```

0.9 9. IMPLEMENTATION PROCEDURE

0.9.1 9.1 Data Collection and Management

- Electronic data capture (EDC) system with real-time BOIN12 calculations
- PK/PD data integration through laboratory data management system
- Structured case report forms with validation rules
- Weekly data review and cleaning

0.9.2 9.2 Decision-Making Process

1. Data cutoff for each cohort
2. Statistical team calculates posterior probabilities and utility values
3. Safety Review Committee (SRC) reviews results and makes recommendations
4. Sponsor final decision on dose escalation/de-escalation/expansion

0.9.3 9.3 Documentation Requirements

- SRC meeting minutes with dose decisions
- Statistical reports at each interim analysis
- Updated exposure-response analyses after cohort completion

0.9.4 9.4 Timeline for Analysis Updates

- Weekly enrollment updates
- Biweekly safety reports
- Monthly PK/PD analyses

- Interim analyses after each cohort

0.10 10. CONCLUSION

This statistical analysis plan outlines a comprehensive approach to dose finding for an ADC/immunotherapy using the BOIN12 design integrated with PK/PD assessment. The design balances several key objectives:

- Efficient identification of both MTD and OBD
- Integration of mechanistic understanding through PK/PD modeling
- Adaptive allocation of patients to promising doses
- Robust statistical methodology with clear decision rules

The seamless transition between dose escalation and cohort expansion phases minimizes development time while maximizing information gain. Through simulation studies, this design has demonstrated high probability of correctly identifying optimal doses while minimizing the number of patients treated at suboptimal doses.