

CSRC Think Tank: Detection, Assessment and Risk Mitigation of Cardiac  
Safety Signals in Oncology Drug Development

# Cardiovascular Safety Assessments in Early Phase Oncology Clinical Trials

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# Rationale and Underlying Assumptions

- Similar to all other systemic therapies, cardiovascular (CV) safety profile of all anticancer drugs should be characterized, including Electrophysiology (ECG/QT), LV Function (Imaging/BM) and Hemodynamic (BP) effects, and any other potential MACE, as relevant.
- Potential CV safety liabilities of investigational anticancer drugs should be defined early in their development, ideally prior to exposing large populations in late phase clinical trials.
- Wherever possible, CV safety assessments should be integrated into routine early-phase oncology clinical trials with minimal disruption to study design, conduct and interpretation/analysis.

# “Disclaimer”

- Oncology studies do not necessarily, or no longer, conform with the traditional development phases (I, II, III and IV) and this talk will therefore broadly refer to ‘early’ and ‘late’ development clinical trials.
- This talk will not address specific study designs for oncology clinical trials involving CV safety assessments, but rather discuss the integration of CV safety assessments in routine oncology studies employing standard or innovative designs.
- Due to time considerations the talk will focus on ECG/QT monitoring, but may be extended to other CV safety parameters - including LV function, hemodynamic and other relevant MACE.

# Example: Drug X – Study Design

## ▶ Study design

- FiH, two-part, open-label, multicenter phase 1 study in patients with advanced malignancies
- **Part 1:** accelerated dose escalation plan to establish DLT, MTD, and RP2D
  - accelerated single-patient cohort design, followed by a standard “3 + 3” design
- **Part 2:** a cohort expansion phase, adding patients and assessing activity of the RP2D

## ▶ Population: Patients with a variety of solid tumors.

- Required to have a normal LV function (LVEF of >50%) and QT/QTc (<470ms).
- 24 patients were recruited for Part 1 and 81 for Part 2

## ▶ ECG monitoring and PK sampling:

- ECGs and PK collected on multiple timepoints at baseline and on Day 1 and Day 15 of Cycle 1

## ▶ ECG/QTc Analysis Plan:

- Lowest (sub therapeutic) dose used as a surrogate for placebo
- Exposure response modelling developed, using robust model criteria and assumptions
- Assessment of Appropriateness of the Primary Model and Robustness Analyses performed
- Standard categorical and morphological analysis completed

# Example: Drug X - results

*Unpublished data; this study is being submitted for publication*

# Early Phase (PI) Oncology Studies

## **Objectives:**

- Primary: evaluate safety/toxicity, define PK profile
- Secondary: collect early evidence of a clinical response

## **Endpoints:**

- Maximum Tolerated Dose (MTD); employ dose-escalation designs to find a MTD, often using small cohorts of patients (3-6)
- Dose Limiting Toxicity (DLT); Determine the overall toxicity profile by counting DLT events during the dose-escalation phase
- Recommended Phase 2 Dose (RP2D); Suggest a RP2D at the end of the study, based on clinical, safety, PK and PD data

# Early Phase (P11) Oncology Studies

## **Primary Goals**

- Evaluate activity
- Further safety (adverse events) evaluation at the MTD

## **Endpoints**

- Response
  - Complete Response (CR)
  - Partial Response (PR)
  - Stable Disease (SD)
  - Progressive Disease (PD)
- Additional safety data

# Early Phase (PI) Oncology Standard Design

- Open label, non-randomized, dose escalation
- Low starting dose, unlikely to cause serious toxicity
  - 1/10th the lethal dose (LD10) in the most sensitive species tested
- 3-6 patients per cohort
- Increase dose gradually
- Most common scheme is a Modified Fibonacci

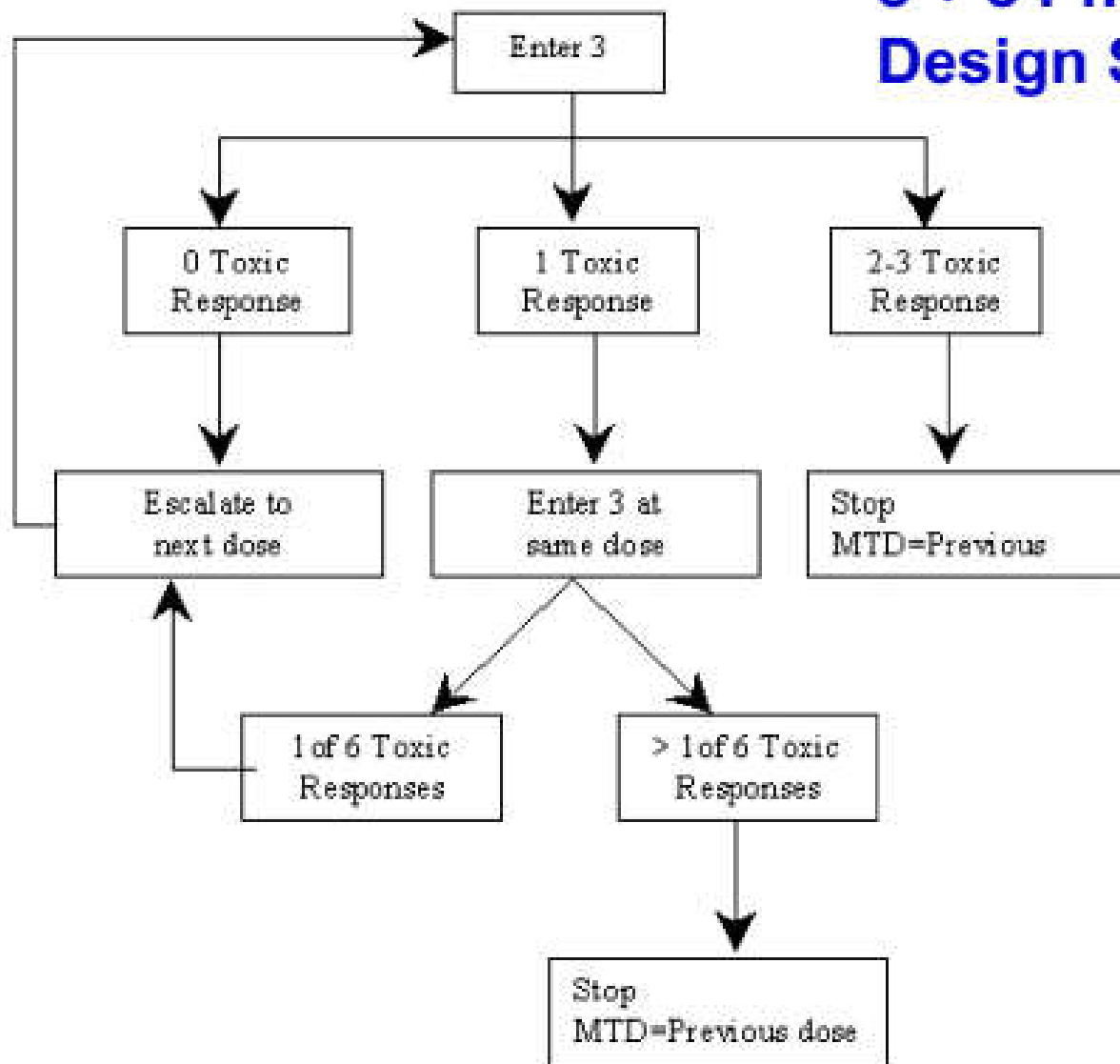


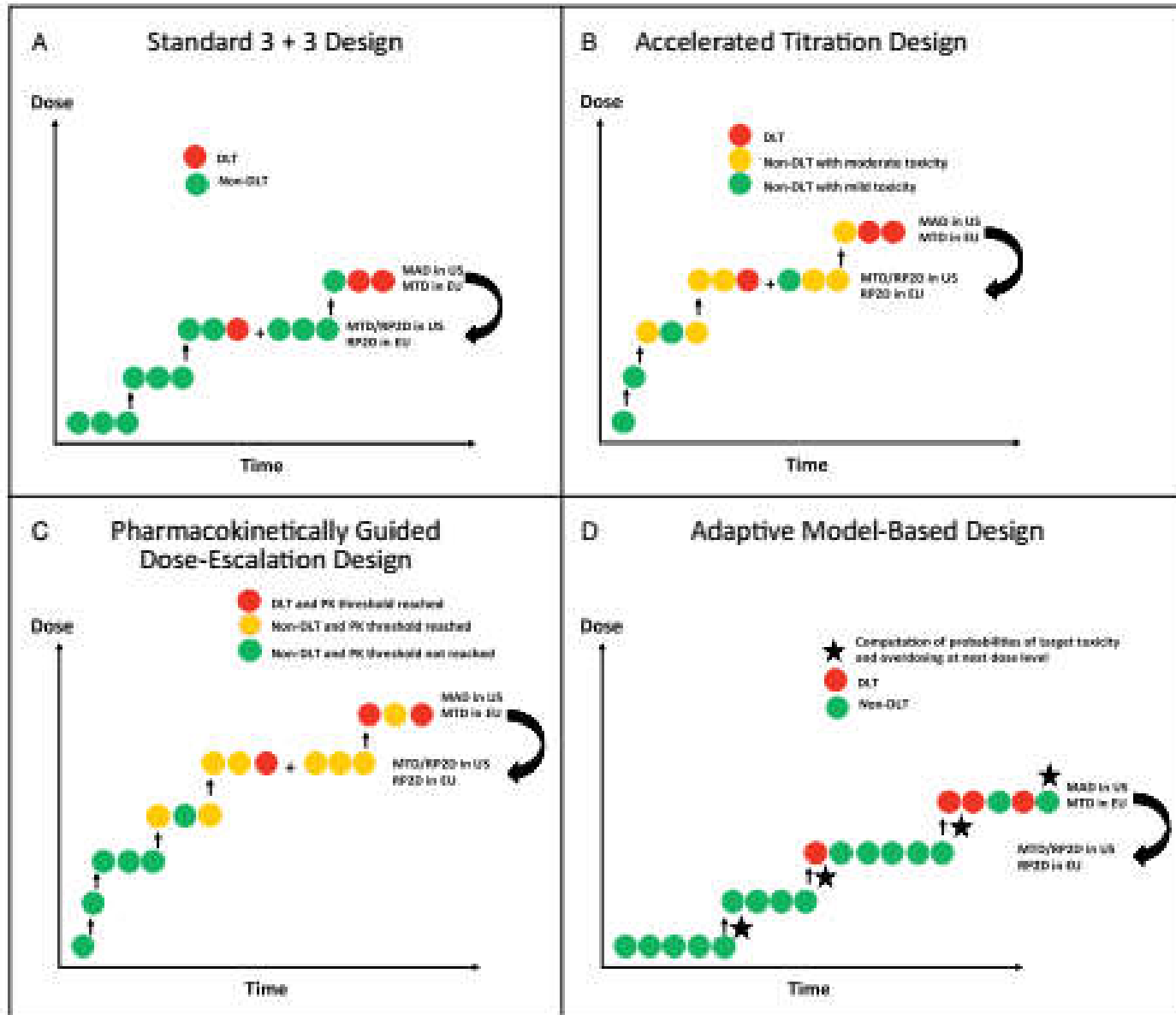
# Early Phase (PI) Dose-escalation Approaches

- Two broad classes of dose-escalation designs in phase 1 cancer trials:
  1. Rule-based (or up-and down) designs – e.g., the “3+3” design
    - developed in the era of predominantly cytotoxic drugs
    - assume that both efficacy and toxicity increase simultaneously with dose
    - no underlying assumption of an expected maximum tolerated dose (MTD)
  2. Model-based designs
    - assign patients to doses based on est. probability of achieving target toxicity
    - data derived from nonclinical dose–toxicity relationship or class effect data
    - uses all available data to model dose–toxicity curves for the RP2D

The traditional “3+3” design remains the most common design for oncology phase 1 trials (J Natl Cancer Inst 2009;101:708–720)

## 3 + 3 Phase 1 Study Design Schematic





# Early Phase (PII) Oncology Study Designs

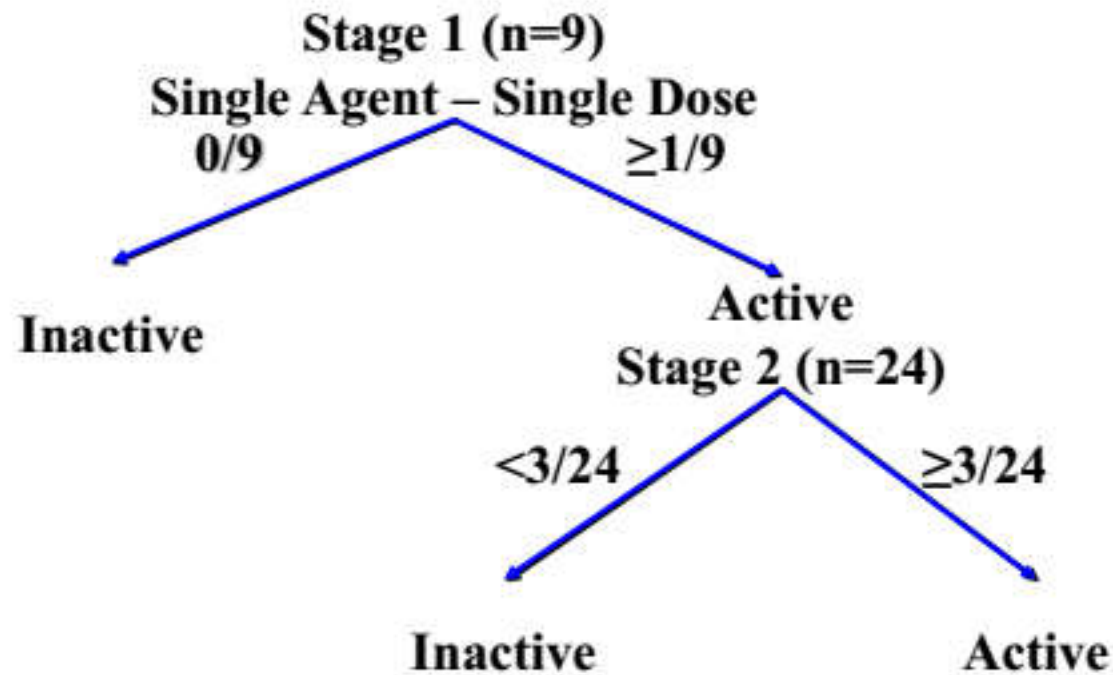
Type of Statistical Design Used in Randomized Phase II Trials (N=123)

- 1-stage design - 39.0%
- 2-stage design\* - 44.7%
- 3-stage design - 3.3%
- Randomized phase II\*\* - 10.6%
- Others - 2.4%
  - Bayesian binomial
  - Group sequential binomial

\*Two-stage design with early stopping rule for efficacy or futility

\*\*SWE (=Simon, Wittes, Eilenberg) randomised design

# Early Phase (PII) Oncology Standard Design



Two-stage design with early stopping rule for efficacy or futility

# Challenges with Incorporating CV Safety Assessments in Early Phase Oncology Trials

- Early phase (PI) studies, including FiH, are conducted in cancer patients
  - Patients may have already been exposed to other toxic treatments
  - Relatively small patient numbers (underpowered trials)
  - Mostly open-label, non-randomized designs
  - High potential for patient selection bias
  - No control (standard of care or placebo) arms
  - First patients may be treated at sub-therapeutic doses
  - Inconsistency in endpoints and study outcome definitions
- and the list goes on...

# Oncology QT Study Design Considerations

## ▶ **Patient population**

- Cancer patients vs. healthy volunteers

## ▶ **Study setting**

- Oncology department vs. experienced CPU

## ▶ **Study design**

- Part of early or late phase study vs dedicated Phase I QT study
- Inclusion of comparator groups - placebo and positive control
- Method of blinding (yes/no, single/double)
- Intensity and duration of PD (ECG/QT) and PK sampling; No of cycles
- Number of baseline and on-treatment ECGs; replicate ECGs (Y/N)

## ▶ **Data analysis**

- Central tendency and categorical analysis plus ERM vs descriptive/summary statistics

# ECG Monitoring Checklist

- ▶ Use appropriate Baseline ECG collection
- ▶ Obtain ECGs at all exposure/dose levels
- ▶ Collect serial ECGs at first dose and steady-state
- ▶ Obtain replicate ECGs (typically triplicate) per time point
- ▶ Ensure concomitant PK sampling at all ECG time points
- ▶ Obtain post-treatment ECGs to assess reversibility of effect
- ▶ Wherever possible use a control group – placebo or active
- ▶ Avoid concomitant medication with known QT effect
- ▶ Perform manually adjudicated ECG reading as cancer patients may have highly abnormal ECGs which can affect performance of ECG algorithms

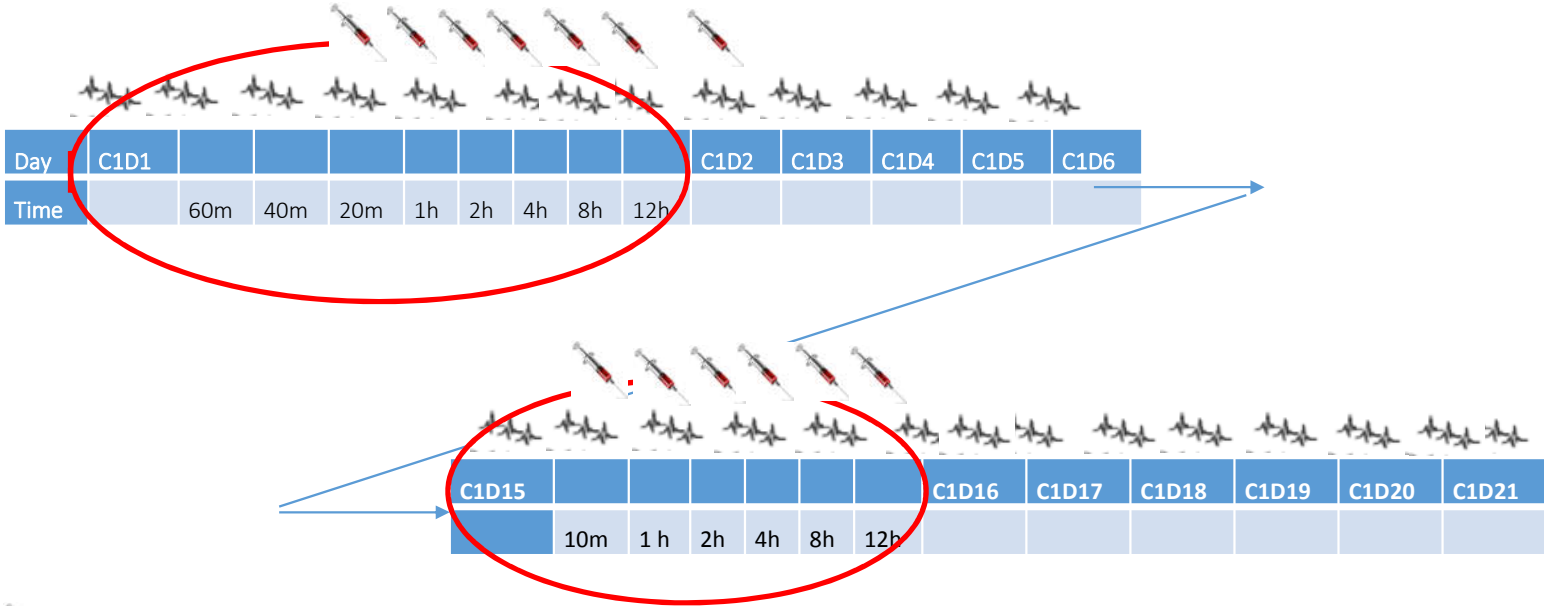




# Thorough QT (TQT) vs Intensive QT (IQT) Studies in Oncology Drug Development

	<b>Thorough QT (TQT) Studies</b>	<b>Intensive QT (IQT) studies</b>
Toxicity profile	Drugs with no known systemic toxicity	Drugs with documented systemic toxicity
Clinical phase	Phase 1 dedicated clinical trials	Incorporated into early or late phase trials
Subjects	Typically performed in healthy subjects	Typically performed in cancer patients
Design	ICH-E14 (X-over/parallel-group) design	Intensive ECG/PK sampling with ER modelling in routine oncology trials
Data analysis	E14 IUT, complemented by ER analysis	Primarily Exposure-Response modelling
Exemption	May be waived if intensive ECG/PK assessment available	Typically required of all drugs, unless established QT prolongation

# Example 2: Sulfatinib ECG and PK Sampling Plan

## Cycle 1



-  PK Blood Sample
-  Triplicate ECG Sample

# Consider Also Monitoring:

- ▶ LV Function
  - Imaging (GLS)
  - Serum Biomarkers
- ▶ Blood Pressure
  - Ambulatory, office or home
  - Advanced hemodynamic parameters (PWV, CAP, AI, etc.)
- ▶ Other MACE (major adverse cardiac events)
  - Venous/arterial thrombosis, ischemia, etc.

Thank you for your attention

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