Toward high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course: Phase 1 Trial Development Course

Lecture title: Basic Knowledge and Practical Consideration of Phase I Trials in Oncology

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- Work Experience
  - 2009-2012 University of Texas at Austin, Austin TX, USA
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  - 2012-2016 Department of Medical Oncology,
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- Specialty
  - Medical Oncology, Early Phase I Drug Development

Basic Knowledge and Practical Consideration of Phase I Trials in Oncology

Outline and Purpose of Phase I trial

- Outline
  - **First administration of novel anticancer drugs in human (FIH：First-in-human)**
  - Determining the optimal dose and administration method
  - Dose escalation test using toxicity as an index
- Purpose
  1. Conducting safety assessment
  2. Determining DLTs (dose-limiting toxicities)
  3. Estimating MTD (maximum tolerated dose)
  4. Determining RD (recommended dose) and administration method
  5. Examining pharmacokinetic (PK) and pharmacodynamic (PD) markers
  6. Determining administration method (such as schedule)
  7. Examining biomarkers
  8. Evaluating therapeutic effects (preliminary anti-tumor activity)

Phase I Trial: Recent Eligibility Criteria

1. Refractory to standard treatment or no effective treatment/standard treatment
2. ECOG performance status 0-1
3. No effect of previous treatment (recovery of toxicity to grade 1 or less), preservation of major organ function
4. In case of history of immune-related adverse events (requiring steroid treatment), first exclude...
5. In case of history of drug-induced pneumonitis, first exclude…
6. Measurable lesions (not required, but often required...)
7. Tumor biopsy possible (although not mandatory, the number of clinical trials requesting biopsy has increased significantly recently...)

- **Toxicity is almost certain to occur, as the dose increases**
- **Unexpected toxicity may occur**
- **Uncertainty about treatment efficacy**
- **Lethal doses may be reached before effective doses**

Treatment/participation intention is essential for patients (only patients who want to participate are included)

Sufficient ethical consideration is required in case selection because the primary objective is not therapeutic efficacy (the patient's purpose is considered as "effect")

Phase 1 trial: Dose-Limiting Toxicity (DLT)

- Toxicity criteria for dose escalation
  - Toxicity to determine that no further dose escalation is possible
  - Usually addresses acute and subacute toxicity, such as during the DLT evaluation period in the first cycle (cycle 1)
  - It is defined according to each test (protocol), whose contents are slightly different

- What are the common DLT criteria? (based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE))
  - Grade 4 hematological toxicity
  - Grade 3 non-hematological toxicity
    - Conditions such as nausea, vomiting, anorexia, hair loss, or transient electrolyte disturbance may be excluded

Phase I trial: Maximum Tolerated Dose (MTD)

- Maximum tolerated dose（MTD）
  - Defined by DLT frequency per protocol
    - DLT expression dose level in ≥2 of 3-6 patients
    - DLT expression dose level in ≥3 of 3-6 patients
    - DLT expression dose level greater than 33%
  - Determining acceptable frequency/severity of toxicity depends on pharmacological and clinical assesment

- MTD is a relative concept
  - It may be affected by the specificity and prognosis of the target disease
  - Once established, MTD may be revised upward with subsequent supportive care
  - It may be changed after safety information is accumulated in the dose escalation part + expansion part

Phase I Trial: Recommended Dose (RD)

- Recommended dose（RD）
  - (1) “Recommended dose” ＝ “MTD－1 Level”？
  - (2) “Recommended dose” ＝ “MTD”?
    - Both are correct
    - Ideally defined by protocol
    - Compared to previous data, the trend in recent years is that “recommended dose” = “MTD” is more common
    - In previous Phase I trials, (1) was more common
    - Recently, it is almost unified to (2)
  - **Determined by considering the toxicity in the second cycle (continuous cycles after the DLT observation period) and beyond**
  - Final decisions may be carried over to subsequent phases such as Phase II
    - Molecularly targeted drugs, etc.

Pharmacokinetic (PK) Studies

“What is the body doing to the drug?”

- **Go/No Go decisions:**
  - When the drug concentration does not reach the therapeutic range・・・・・・・
    Development is discontinued
    (e.g., formulation and bioavailability concerns)
  - When the drug concentration is saturated (saturation/plateau)
- **Dosing method (schedule) study:**
  - Use of loading dose (quickly reach a steady state)
  - Dosing frequency/interval (e.g., drugs with short half-lives)
- **Toxicity/PD profile and PK parameter correlation analysis:**
  - Cmax, AUC, etc.
- **Interaction (pharmacologic effects) studies:**
  - **Food effect**
  - **Drug-drug interaction (DDI)**

Pharmacodynamic (PD) Studies

“What is the drug doing to the body”?

- **Exploration and usefulness of optimal biological dose (OBD)**

  ⇒ If toxicity is minor, if MTD is not reached (if DLTs do not occur)

- **Exploration and demonstration of the mechanism of action of drugs (investigational drug)**
  - Confirmation of “clinical” target inhibition (inhibition of protein phosphorylation, receptor occupancy, etc.)
  - Changes in tumor tissue or normal surrogate tissue
  - Molecular imaging

- **Early exploratory “identification” of optimal patient populations**
  - Biomarker predictor

Phase I Trial: Starting Dose

Remarks: Preclinical toxicity test (safety test)

- Repeated toxicity test (4 weeks)
- Antibody formulation vs small-molecule compound, etc.
- What is the reproducibility of preclinical (organ-specific) toxicity in humans?
  [Hematopoietic/GI, Liver/kidney (false positive)? Immunity-related]

Generally,

1) 1/10 of mouse LD_{10}
   - ➢ 1/10 dose of 10% lethal dose in mice
2) 1/3 of dog TDL (toxic dose low)
3) No severe toxicity when non-rodent species are sensitive species

One-sixth of the maximum dose (HNSTD) is usually considered as the starting dose for initial clinical trials.

HNSTD: highest dose that does not cause death, life-threatening toxicity, or irreversible toxicity

- **Toxicity parameters**
  - **NOAEL- No Observed Adverse Effects Level**
  - **HED- Human Equivalent Dose**

LD_{10}: lethal dose 10%
HNSTD: Highest Non-Severely Toxic Dose

In the case of advanced development overseas

- ➢ Low doses with no toxicity may be skipped...what if later?
- ➢ About 50% of MTD confirmed overseas is a guideline, such as for Phase I trials in Asians

Phase I: Starting Dose
NOAEL vs MABEL

The first-in-human (FIH) initial dose should be scientifically supported by all available non-clinical data (pharmacokinetics, pharmacodynamics, toxicity, etc.).

Extrapolation from preclinical toxicity studies

- **FIH Starting dose: 10% of the HED/NOAEL**

Equivalent Surface Area Dosage Conversion Factors

	MOUSE 20g	RAT 150 g	MONKEY 3.0 kg	DOG 8 kg	MAN 60 kg
Mouse	1	½	¼	1/6	1/12
Rat	2	1	½	¼	1/7
Monkey	4	2	1	3/5	1/3
Dog	6	4	5/3	1	½
Man	12	7	3	2	1

Initial dose selection using the Minimum Anticipated Biological Effect Level (MABEL) should be considered.
e.g., Compounds that act on the immune system (Immune-oncology agents, etc.)

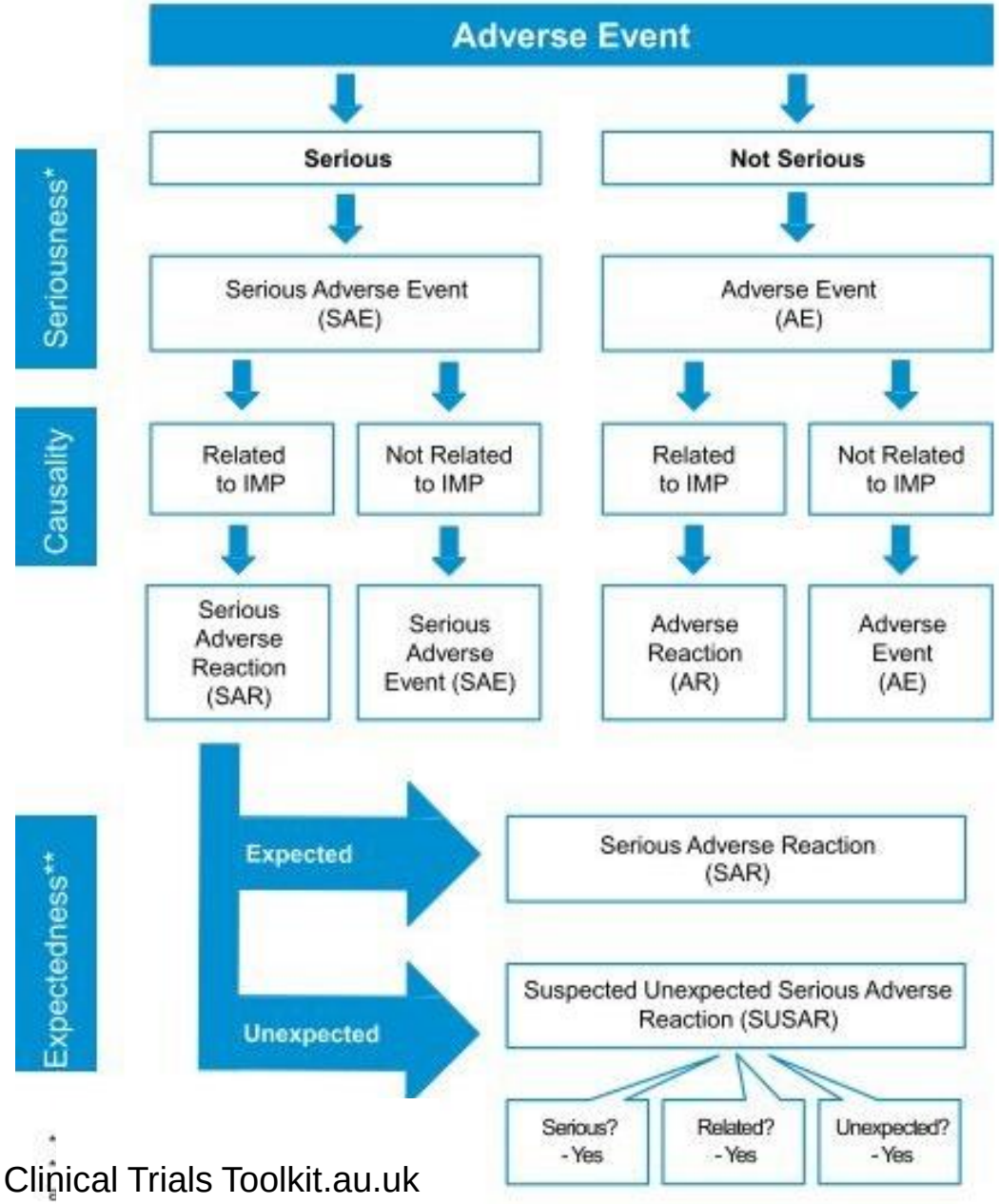
2006: Case of anti-CD28 agonist antibody (TGN1412)
Phase I, double-blind, randomized, placebo-controlled, healthy adult males aged 18-40 years, 8 subjects for each dose (active drug 6, placebo 2)

The starting dose (0.1 mg/kg) was set as 1/500 of the NOAEL
→ A receptor occupancy of 90.6% was reported.

Phase I Trial: Dose Escalation Method

Framework (type)	Technique (method)	Pros	Cons
Rule-based	• **3+3 design** • Accelerated titrated design (ATD) • Rolling 6	Simple and easy operation	Risk of (occasionally) inaccurate MTD estimates
Model-based	• Continual reassessment methods (CRM), modified **CRM** • Escalation with overdose control **(EWOC)** • Bayesian logistic regression model **(BLRM)**	Possibility of accurate MTD estimation	Statistical expert support required (e.g., parametric model for dose-toxicity curve) (Do you actually see some cases where clinical consistency is not achieved?)
Model-assisted	• Modified toxicity probability interval **(mTPI)** • Keyboard • Bayesian optimal interval design **(BOIN)**	Combination of accuracy and convenience	Same with model-based design?

Safety Reporting Assessment



Clinical Trials Toolkit.au.uk

Serious adverse event (SAE)

Definition: Adverse events are classified as:

- Events leading to death
- Life-threatening events
- Events requiring hospitalization or extension of hospitalization period for treatment
- Events leading to permanent or marked disability/malfunction
- Events leading to congenital anomalies
- Other events judged to be serious based on medical and scientific grounds

If an SAE occurs, the investigator should promptly (within 24 hours of the investigator's or sub investigator's knowledge) report the event to the sponsor and the head of the site, along with the necessary treatment for the subject.
(Each report has a respective format)

Assessing the Efficacy in Early Phase I Trials in Oncology

Categorical endpoints

- Objective response rate (ORR)
- Complete response (CR) rate
- Clinical benefit rate
- Durable response rate
- Landmark rates of time-to-event endpoints

Time-to-event endpoints

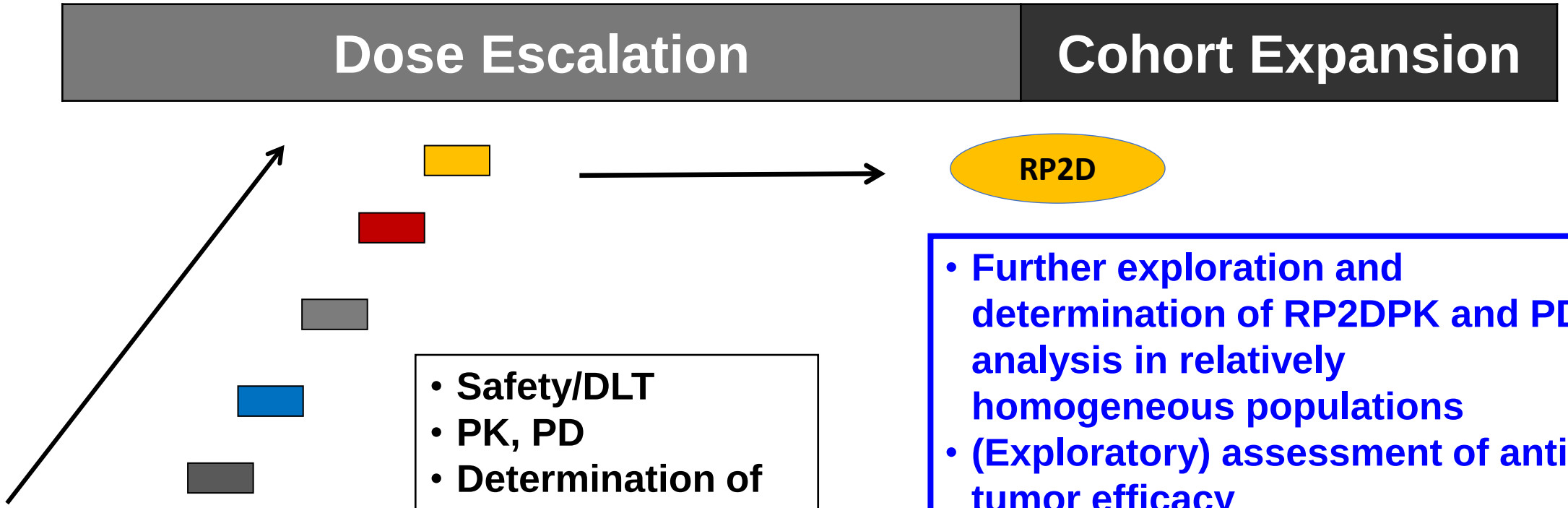
- Progression-free survival/time to progression
- Duration of response (DoR)

Pharmacodynamics

- Biomarkers, in general, including those for minimal residual disease
- Optimal biological dose (mostly a safety-related outcome)

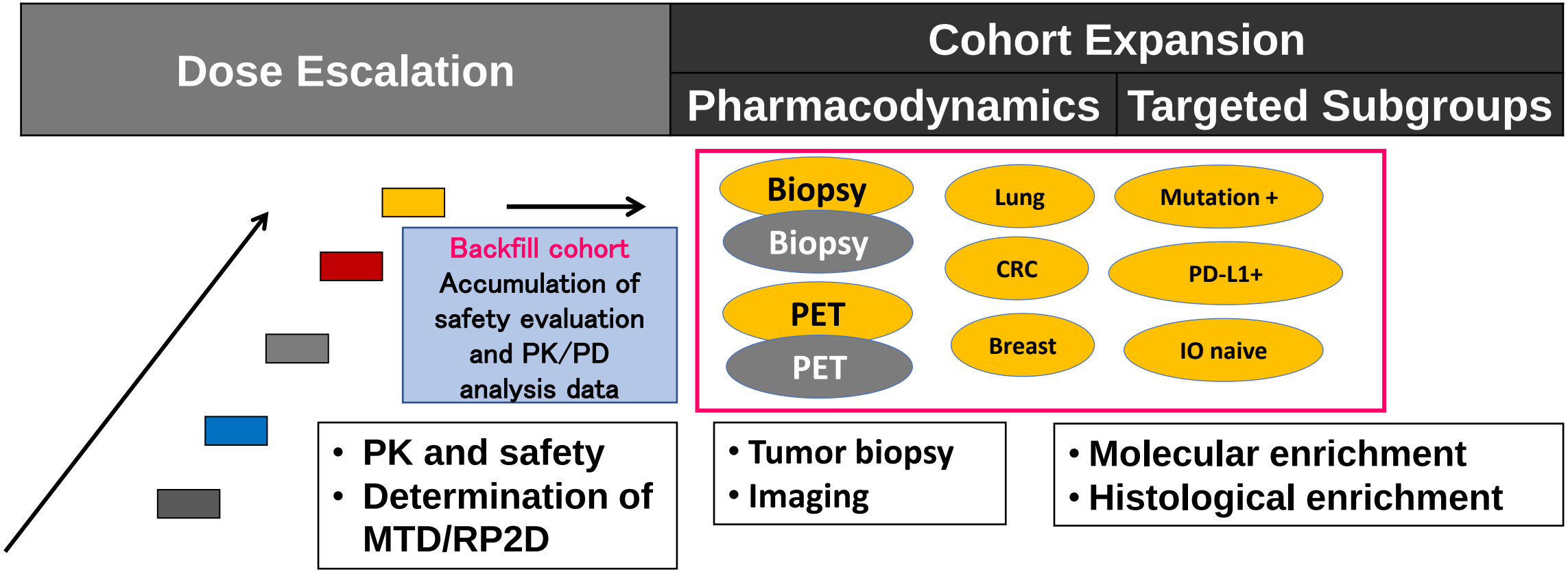
Traditional Phase I Trial Design –

Dose escalation part･･･All comer (no specific patient selection)
Expansion part･･･Relatively small scale, recommended dose (RP2D) search purpose



Current Phase I Trial Design –

Dose escalation part: Combined with and without specific patient selection (all comer frames tend to decrease); Expansion part: Relatively large scale (each group: 20 to 50 subjects: Additions and deletions, as appropriate as can be)



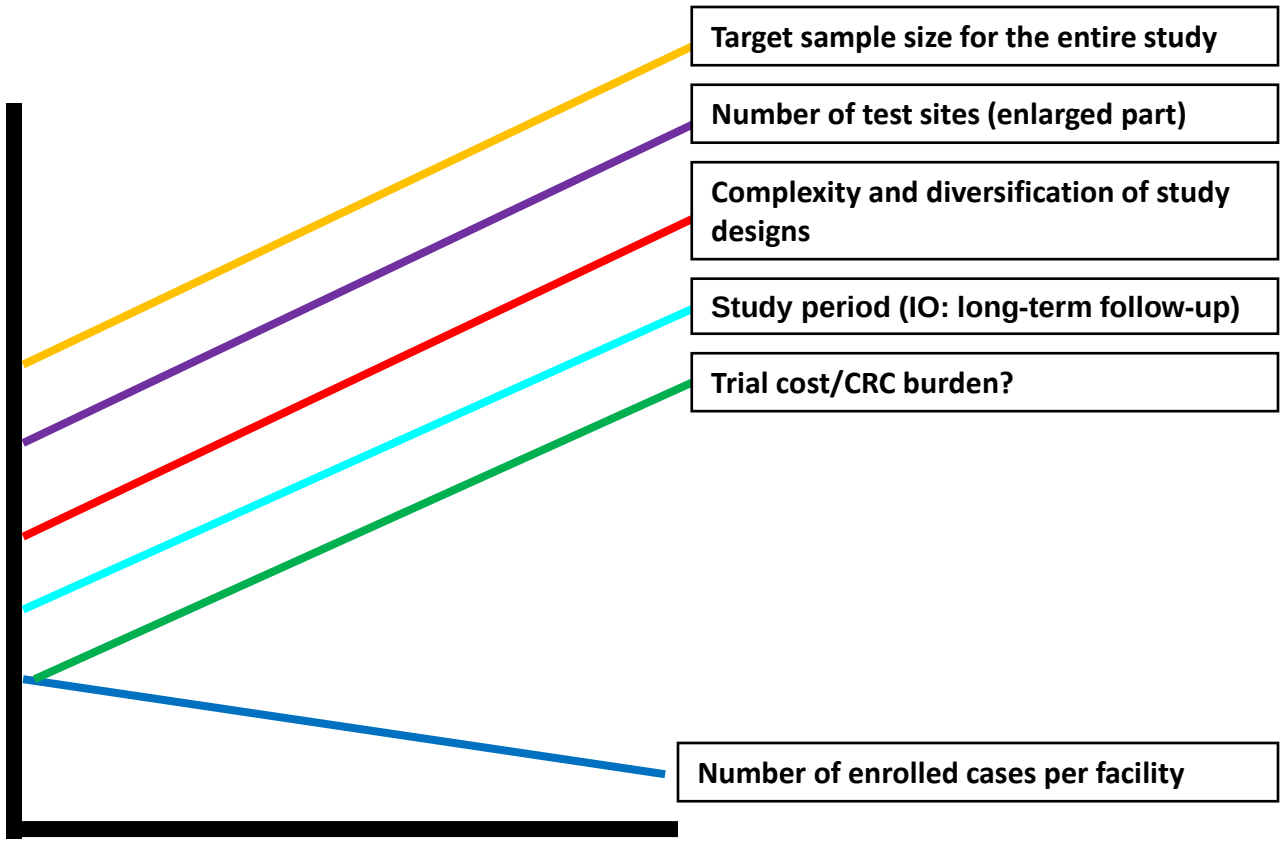
Current Phase I Trial Design – Unselected/Selected Patients in Dose Escalation followed by <u>Multiple</u> Specific Expansion Cohorts.

Phase I Trial: Major Changes in Target Cancer Setting

（C→B→A→AA→not possible）

- **Difficulty C**：In other words, all comer Phase I trial
  - Patient enrollment is easy (recently declining…)
- **Difficulty B**：Set depending on cancer type
  - E.g.： NSCLC, head and neck cancer, gastric cancer, breast cancer (excluding sarcoma)
  - E.g.： Breast cancer, ovarian cancer … limited to gynecologic cancer
  - E.g.： Gastric cancer, esophageal cancer … limited to gastrointestinal cancer
- **Difficulty A**：Set by genetic abnormality
  - E.g.： MDM2 gene abnormality (high expression, mutation, etc. can be incorporated)
  - E.g.： FGFR gene abnormality (mutation of FGFR1-4, high expression, etc. can be incorporated)
  - E.g.： MAPK pathway gene abnormalities (NRAS, KRAS, NF1, BRAF, CRAF, MEK, GNAQ, etc., multiple candidates)
- **Difficulty AA**： Setting by low-frequency genetic abnormality
  - E.g.： KRAS G12C mutation (only), IDH1 R132 mutation (only)
  - E.g.： EGFR exon 20 mutation (only)

Recent Changes in “Logistics” in Phase I Trials (oncology)



- Should sites accept many Phase I trials if offered? (for financially viability?, to secure constant requests? or?)
- Frequent IRB support (protocol revisions, SUSARs, etc.)
- Long-term safety follow-up period (Long-term support for both facilities and clients)
- Increase in clinical trial costs (per case)
- Insufficient experience of investigators and facilities (for new class drugs)
- Insufficient experience of the client (pharmaceutical company) (for new class of drugs)

Sample Preparation Time for a Global FIH Phase I trial

In one test, three large boxes containing the initial 80 x 60 x 60 cm kit are brought in.

When disposing of unnecessary kits, sort them into medical waste, general waste, and shredder.

0.6 X 0.42 X 0.23＝
0.05796 m³

Volume becomes about 1/3

0.27 X 0.42 X 0.18＝
0.020412 m³

This process takes about 60 minutes.
Even for tests that are relatively easy to enter, it takes about 60 minutes to enter the EDC during screening. Organizing small boxes is a lot of work.

Other settings for full PK settings
Collection slips, filling in Spitz/dispensing tubes, setting according to hospital rules

Consider 50 minutes per patient
(If it is a new test, it may take 90 minutes due to confirmation work)

Time Difference in a Web Conference・・・

You can participate in the meeting anytime from anywhere with your smartphone (iPhone, etc.), but...

AGENDA

Agenda for meeting	Timing	Discussion Leader
Roll call & Meeting objectives	10 min	CTL
Review of clinically relevant patient data from current cohort - Adverse Events (incl. DLTs) - Laboratory values - Dosing delays or modifications - Con meds - Other information	20 min	PIs and CPL
Preliminary pharmacokinetic data	10 min	LPK
Statistical Modeling	5 min	TS
Dose decision and next steps	10 min	CPL
Summary	**5 min**	CTL

- Global FIH Phase I trials have many online meetings
  - ➢ Generally called “PI calls” or “safety calls”
- Frequency of conferences varies, such as weekly, bi-weekly, and dose levels
- When held simultaneously in the United States, Europe, and Asia, conferences are often held early in the morning or late at night.
- The duration varies (from 5 minutes to 60 minutes or more)

US FDA Finalizes Several Guidance on Cancer-related Trials in line with Biden's "Moonshot"

4164-01-P

This document is scheduled to be published in the Federal Register on 03/02/2022 and available online at federalregister.gov/d/2022-04397, and on govinfo.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-2777]

Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products

Draft Guidance for Industry

4164-01-P

This document is scheduled to be published in the Federal Register on 03/02/2022 and available online at federalregister.gov/d/2022-04398, and on govinfo.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-3292]

Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

Bispecific Antibody Development Programs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
Pharmaceutical Quality/CMC

Challenges and Future Prospects Required for Clinical Trial Sites in the Changing Early Development of New Drugs (especially FIH Phase I Trials)

- **What are the recent trends in site selection? ?**

Early 2010's…..

- Investigator, speed (IRB, contract, etc.), clinical trial fee, subject registration, TR facility, etc.

Mid 2010's…..

- What has changed? / What additional elements are needed?
- Comprehensive partnership agreement, strategic agreement (pharmaceutical company - academia/facility)
- Sponsor's "preferred" sites (Phase I designated / preferred sites)

After 2023…..???

Challenges and Future Prospects Required for Clinical Trial Sites in the Changing Early Development of New Drugs (especially FIH Phase I Trials)

- In conjunction with the understanding of the disease, **the simple profile of the investigational drug and the understanding of the trial ...**
- What stage is the trial at?
  - What is the enrollment status at overseas facilities?
  - What are the common problems in enrollment and clinical trial implementation both in Japan and overseas?
- Target diseases/patients (subjects)?
  - Should I actively participate in this trial?
  - What are the risks and benefits of participating?
- Is the purpose clear?
  - Purpose of trial, purpose of facility

"Understanding and integration of clinical trials!"

Conclusions

- The importance of FIH Phase I trials in the development of new cancer drugs has increased considerable in recent years.
  (Especially Go/No-Go Decisions at development companies...)
- (FIH) Many elements of Phase I trials have changed significantly in recent years (complexity, diversification, etc.), and flexibility is required for sponsors (companies), clinical trial sites, CROs, etc.
- Always consider the position of “stakeholders” (subjects, IRB, hospital-related departments, collaborating medical institutions, clients, CROs, etc.) and be mindful of “understanding and assimilating trials (clinical trials)”!
- Let us be constantly aware of globalization (although it is taken for granted now...)
- (FIH) All researchers and medical staff engaged in Phase I trials should always be aware and take pride in the fact that they are at the forefront of new drug development!