Designs for clinical trials on cancer

Part 1 of 2

Junki Mizusawa
Statistics Section, JCOG(*) Data Center

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*** Japan Clinical Oncology Group** (https://jcog.jp/en/)

JCOG
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ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

Outline

- Anticancer drug development flow and endpoints
- Phase I designs
- Phase II designs
- Phase III designs

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Flow of Clinical Trials on Cancer

Phase Ⅲ

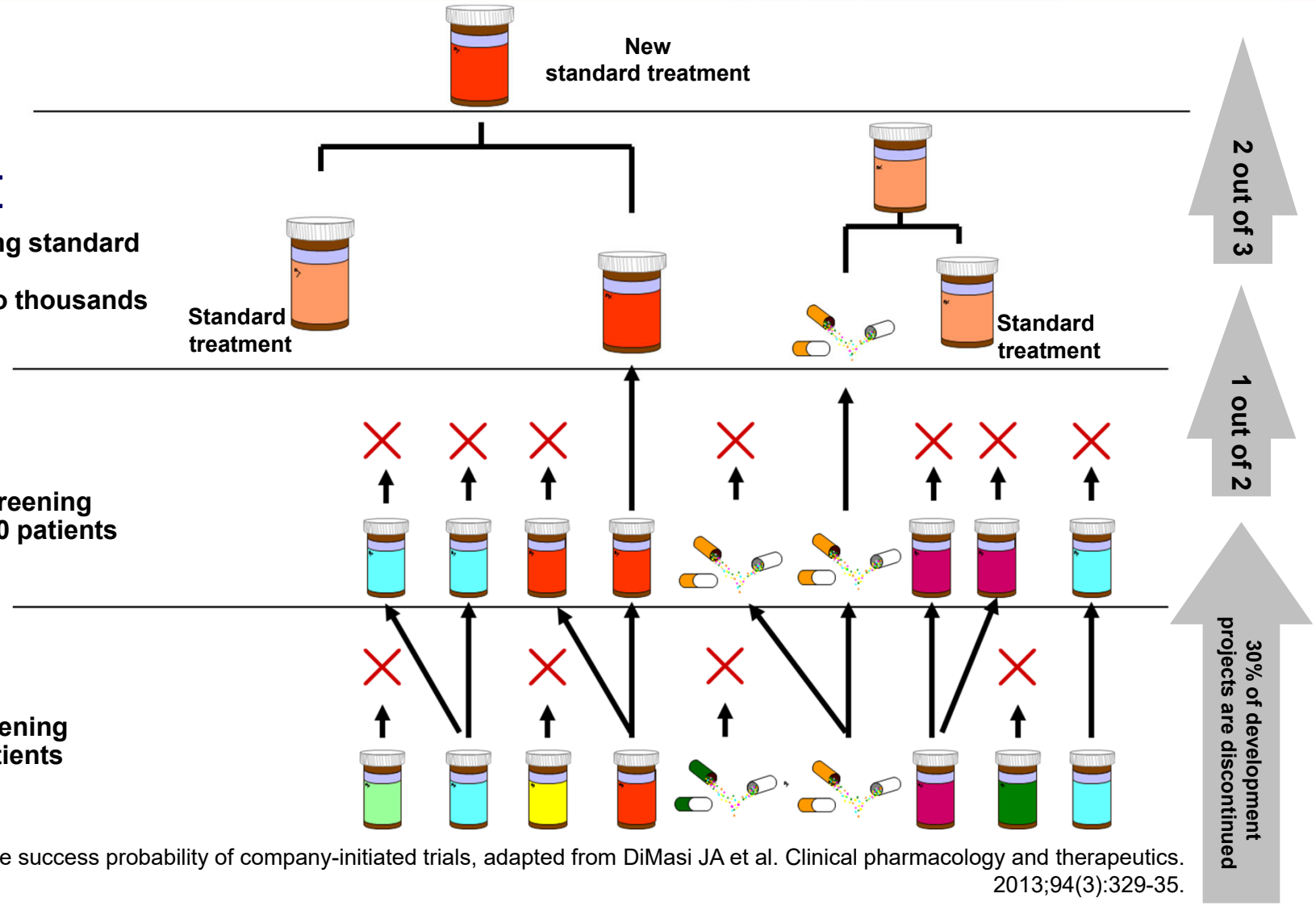
- Determining standard treatment
- Hundred to thousands of patients

Phase Ⅱ

- Efficacy screening
- 20-30 to 200 patients

Phase Ⅰ

- Safety screening
- 10 to 40 patients



Data on the success probability of company-initiated trials, adapted from DiMasi JA et al. Clinical pharmacology and therapeutics. 2013;94(3):329-35.

Principles of Clinical Trials

Clinical trials involve "**Comparisons**"

Phase III

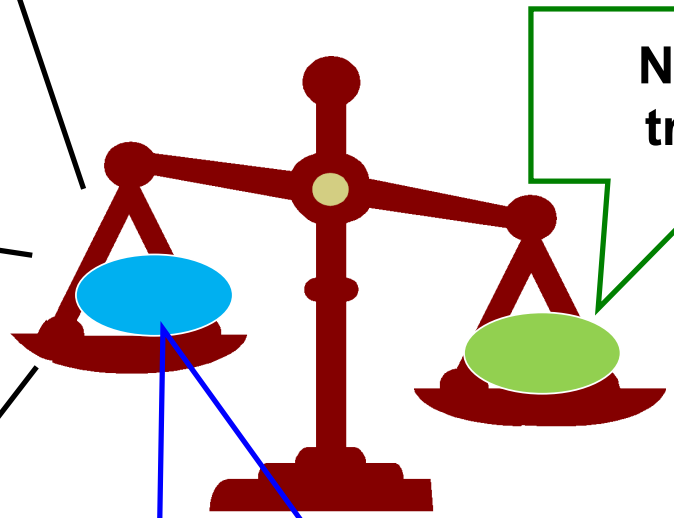
Comparison of **overall efficacy and safety** of new drug/treatment to those of standard drug/treatment

Phase II

Comparison of **efficacy objectives** derived from past data

Phase I

Comparison of **acceptable level of safety** derived from past data (acceptable toxicity percentage)



New drug/ treatment

Comparisons are always made against standard drug/treatment

What Do We Compare?

- **Comparing patient benefit**
  - Compared to conventional standard drugs, the new study drug should have
    - Greater efficacy ・・ **Efficacy** comparison
    - Fewer side effects ・・ **Safety** comparison
    - Lower cost ・・ **Economic efficiency** comparison

* However, there is no international consensus on cost-benefit, and medical insurance differs greatly depending on the social system. Thus, generalization is not possible.

How do we measure benefit?

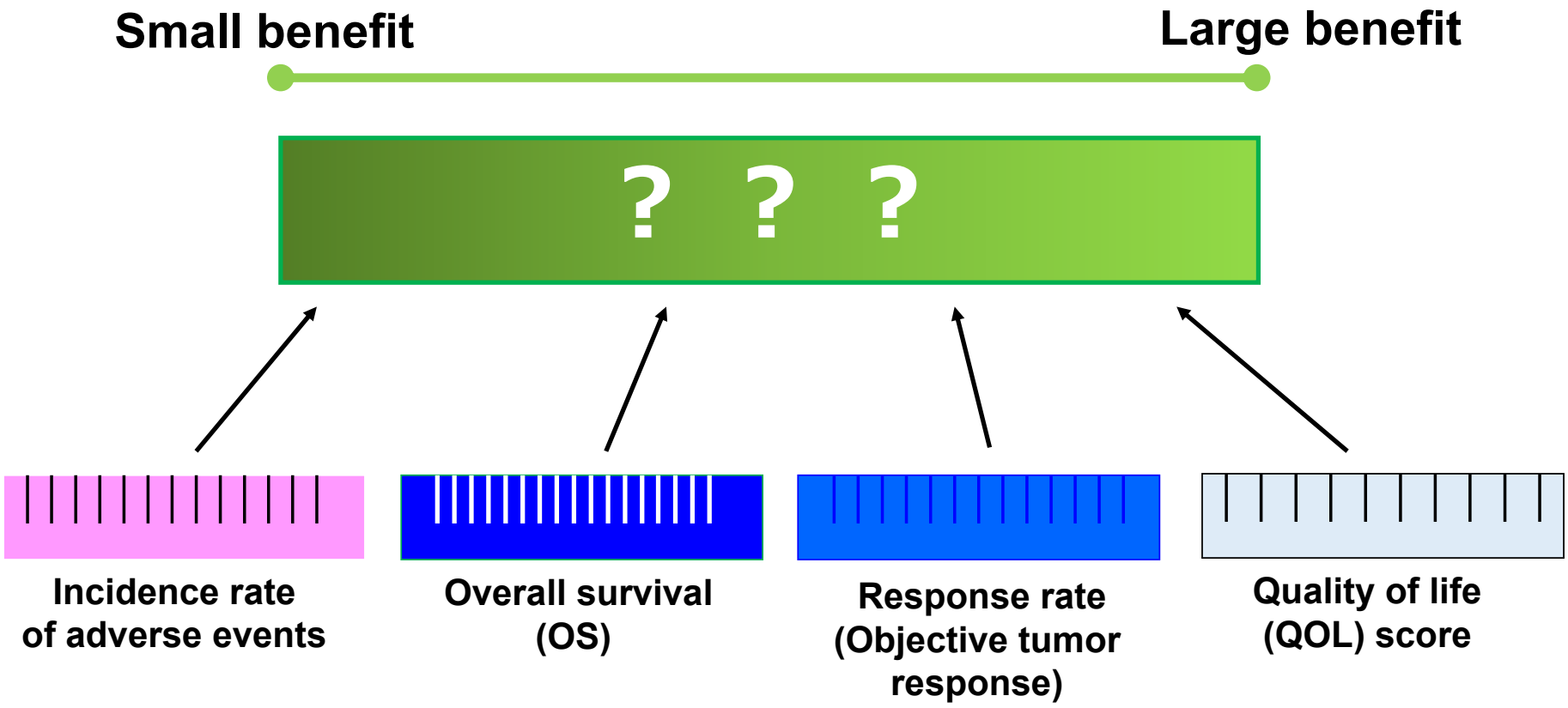
- **Endpoint** (evaluation index, evaluation item)

"A **'Ruler'** for measuring patient benefit"

"Criterion by which patient benefit is measured"

- Richard Simon

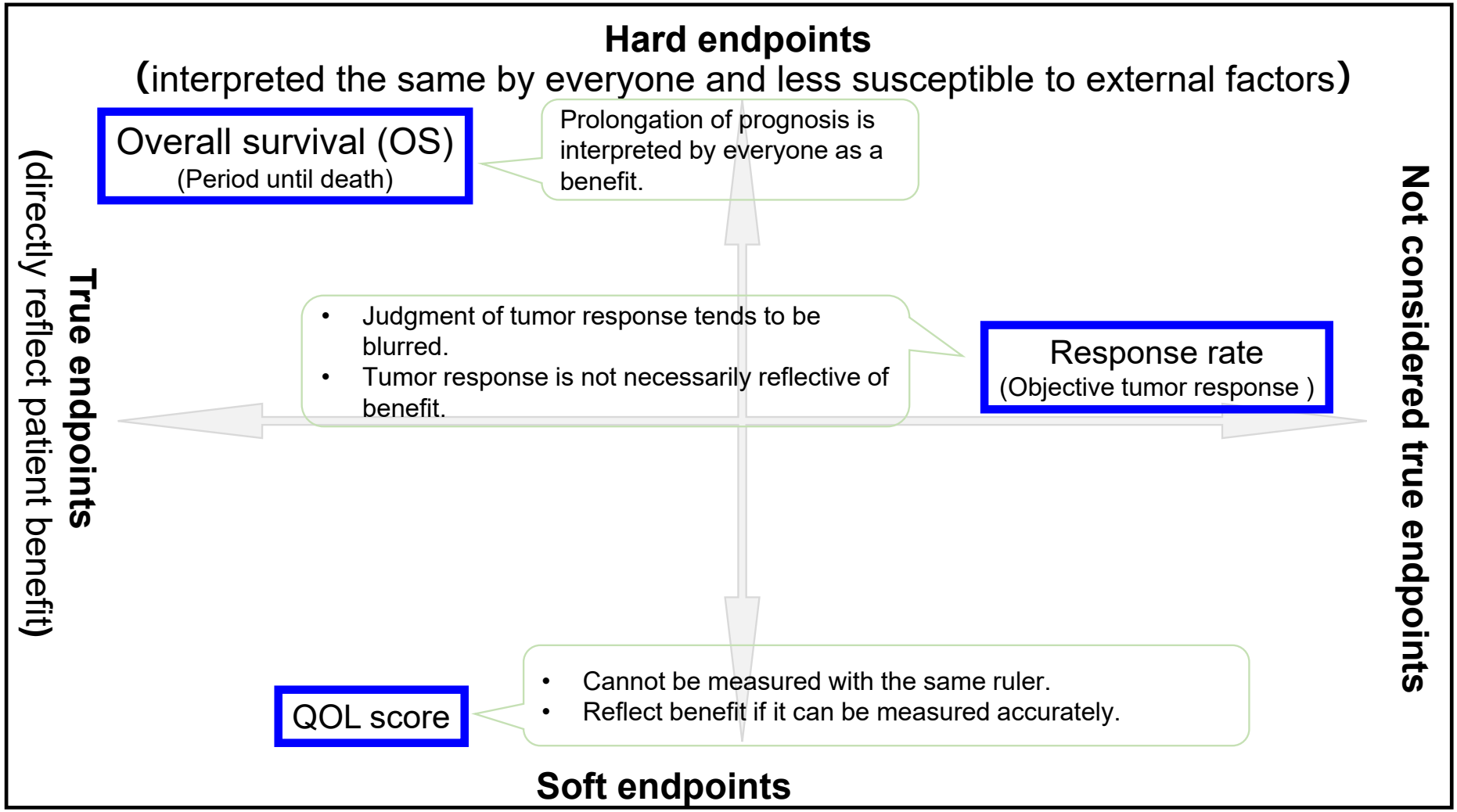
Endpoint (Ruler)



Primary endpoint: The most important study endpoint to draw conclusions from

Secondary endpoints: Other endpoints

Classification of Endpoints



Definition of Time-to-Event Type Endpoint

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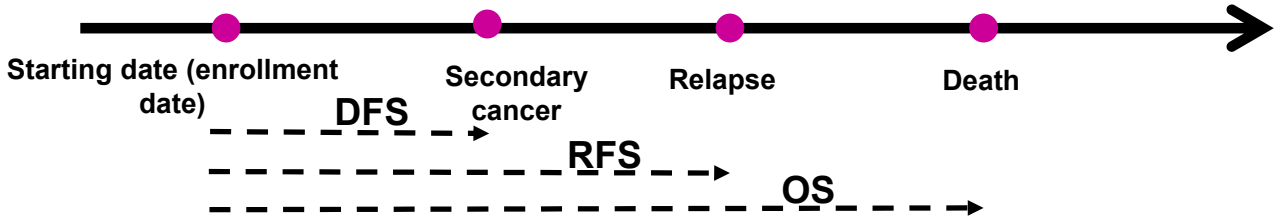
- Time-to-event: The period from a point in time (starting date) to the event of interest that occurs first

Endpoint		Event (whichever occurs first)		
Overall survival (OS) (true)		Death (hard)	-	-
Progression-free survival (PFS) (non-true)	Cancer-bearing status at enrollment	Death	Progression (soft)	
Relapse-free survival (RFS)	Non-cancer-bearing status at enrollment	Death	Relapse (hard)	
Disease-free survival (DFS)	Non-cancer-bearing status at enrollment	Death	Relapse	Secondary cancer

Diseases with good prognoses, in which secondary cancer becomes a concern



Review Questions: Please choose YES or NO

1. Overall survival is representative of the soft and true endpoint.

2. Multiple secondary endpoints are usually set for one trial.

3. If patients are in the cancer-bearing status at enrollment, PFS is used rather than RFS.

4. RFS is used if the events include death, relapse, and secondary cancer.

Review Questions: Please choose YES or NO

1. Overall survival is representative of the soft and true endpoint. **NO**

2. Multiple secondary endpoints are usually set for one trial. **YES**

3. If patients are in the cancer-bearing status at enrollment, PFS is used rather than RFS. **YES**

4. RFS is used if the events include death, relapse, and secondary cancer. **NO**

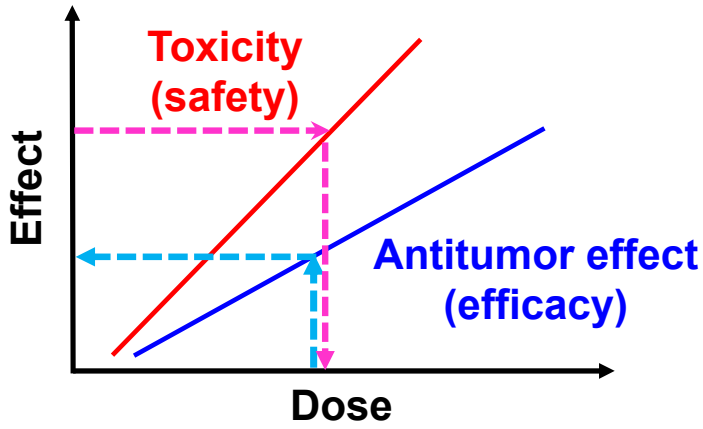
Outline

- Anticancer drug development flow and endpoints
- **Phase I designs**
- Phase II designs
- Phase III designs

Purpose and Overview of Phase I Trials

- Purpose: To decide whether to proceed to phase II
  - Determination of the recommended dose (RD) of the study treatment for phase II and subsequent phases

- Typical design
  - Target: Advanced-stage patients with normal organ function who have received standard treatment
  - Number of patients enrolled: 10-40 patients
  - Participating facilities: Single to multiple specialized facilities
  - Screening by **toxicity**
    - Premise: Toxicity is an alternative for efficacy.
      - Efficacy increases with higher toxicity



Traditional Phase I Trial Design: 3+3 Design

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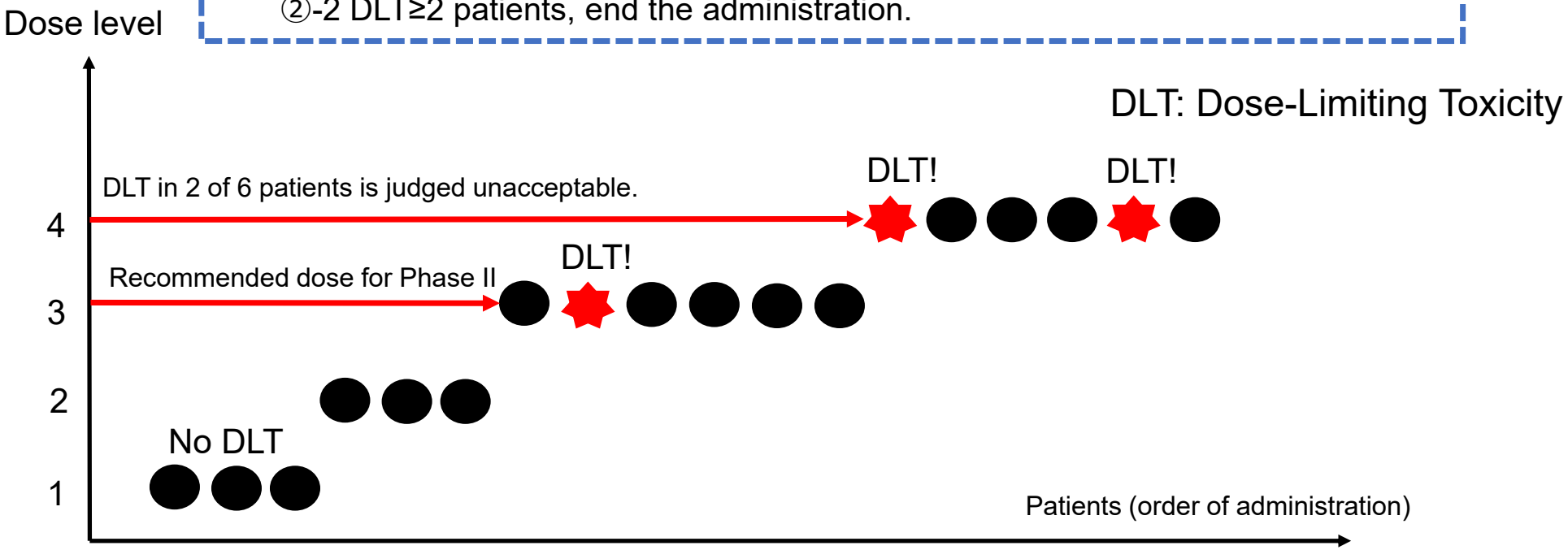
Dose escalation rule

① Administer to 3 patients at a certain dose level. If out of the 3 patients,
  ①-1 DLT=0 patient, proceed to the next dose level. To ①.
  ①-2 DLT=1 patient, add 3 more patients. To ②.
  ①-3 DLT≥2 patients, end the administration.
② Administer to 3 additional patients. If out of the 6 patients,
  ②-1 DLT=1 patient, proceed to the next dose level. To ①.
  ②-2 DLT≥2 patients, end the administration.



Disadvantages of 3+3 Design

- Many patients are administered drugs at low doses.
  - The enrolled patients expect efficacy even in the Phase I stage.
  - The aim is to minimize the number of patients administered low doses (≒ low efficacy)

The number of patients and dose level at the initial human administration of various drugs in Phase I trials

Drug name	FDA approval year	Number of patients	Dose level
Paclitaxel	1992	34	11
Gemcitabine	1996	47	12
Imatinib	2001	83	14
Pemetrexed	2004	38	10
Panitumumab	2006	96	13

RD is considered to be high dose level. Therefore, high dose levels suggest that patients administered drugs at low dose levels received significantly lower doses than RD.

Adapted from Le Tourneau C, Lee JJ, Siu LL. J Natl Cancer Inst. 2009;101(10):708-20.

Continual Reassessment Method (CRM)

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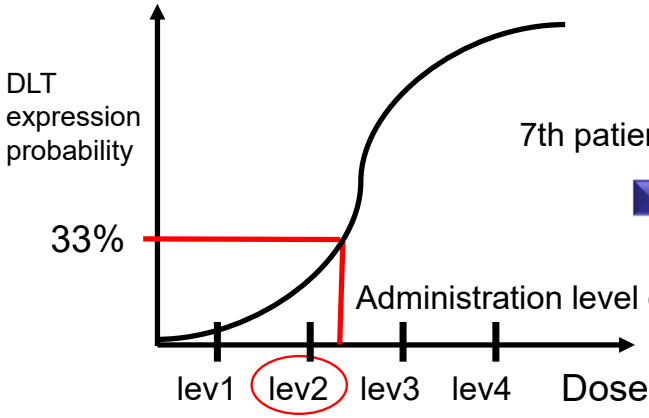
- Setting up a **mathematical model** for the relationship between dose and toxicity
- Updating the mathematical model with information on the presence/absence of DLT in enrolled patients
- The next enrolled patients are administered at the highest level that does not exceed a DLT of 33% based on the mathematical model.

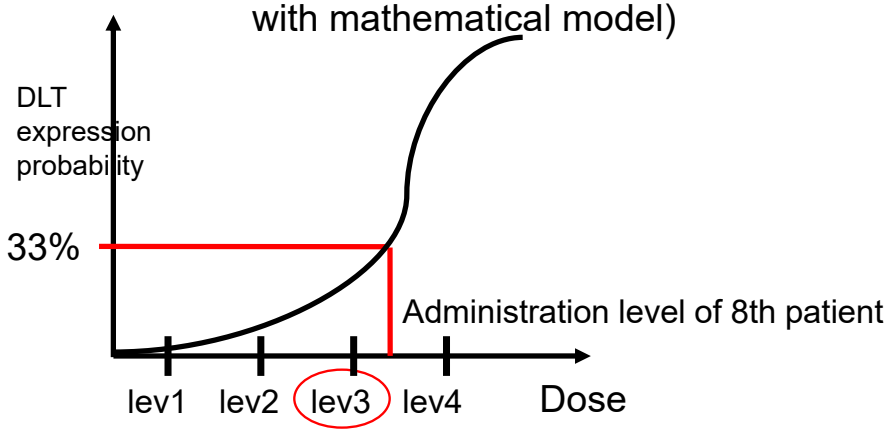
O ' Quigley J et al.,Biometrics.1990;46 (1):33–48
Graphs and values are hypothetical.

Relationship between dose and toxicity at the time of administration to 6 patients
(determined by the mathematical model)



7th patient was "No DLT"

Relationship between dose and toxicity at the time of administration to 7 patients
(updating the relationship between dose and toxicity with mathematical model)



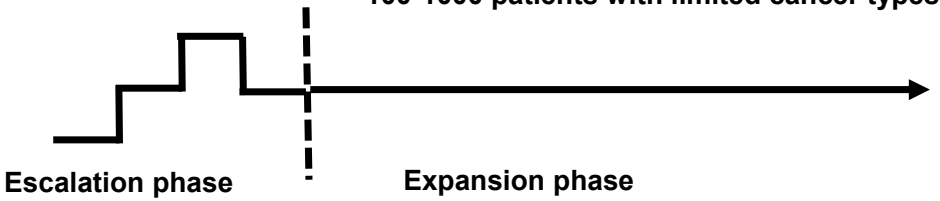
Because CRM allows for rapid escalation of dose levels, relatively fewer patients may be administered at lower doses, and the number of patients receiving near-optimal doses may increase.

Expansion Cohort

- A method of confirming the safety and efficacy of drugs, by adding the required number of patients to a cohort according to its purpose after the dose escalation phase.
  - Re-examination of safety at the recommended dose (e.g.: pazopanib)
  - Examination of efficacy for different cancer types showing objective tumor response (ex: pembrolizumab)
- Use of expansion cohorts is increasing due to the emergence of molecularly targeted drugs, immune checkpoint inhibitors, and accelerated drug development.
  - Increasing the number of drugs that are likely to be effective and identifying patients who exhibit effectiveness are the keys to successful development.
  - Used in 12% of trials in 2006 → 38% in 2011
  - Lower cost than conducting another trial

Manji A.,J Clin Oncol 2013;31:4260–7.

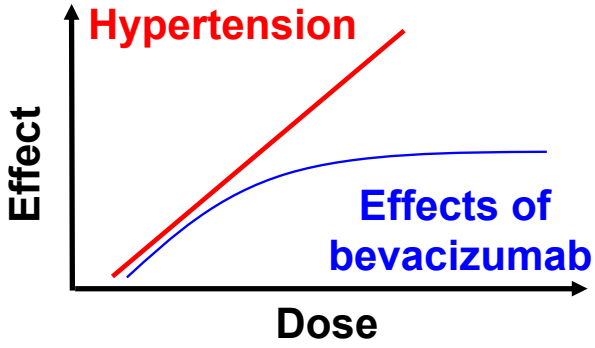
- **20-30 patients (cytotoxic drugs)**
- **30-300 patients with limited cancer types and biomarkers (molecular target drugs)**
- **100-1000 patients with limited cancer types and immune biomarkers (immunotherapy)**

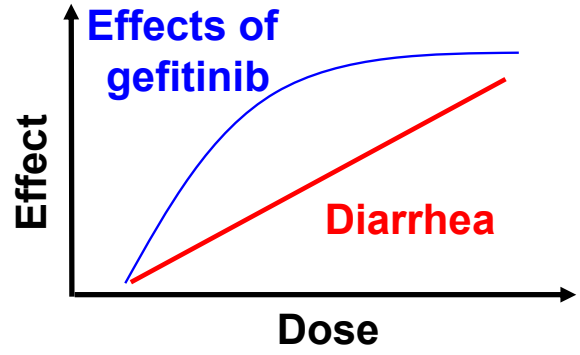


Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry
https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm616325.pdf

Endpoints for Molecularly Targeted Drugs, etc.

- Toxicity may not be a suitable alternative for efficacy.
  - Example 1: Hypertension with bevacizumab
    - Toxicity is dose-dependent, while efficacy is dose-independent.
  - Example 2: Diarrhea and rash with gefitinib
    - Effect plateaus before toxicity occurs.
- The recommended dose may be decided by indices other than toxicity.
  - Indices reflecting the amount of drugs in the blood (AUC, Cmax, etc.)
  - Expression of effects expected for target molecules in the blood
  - Objective tumor response by judging effects on images (CT, MRI, PET, etc.)





Clinical Oncology, 4(5):445-453,2009

Summary of Phase I Trial Designs

- Phase I trials primarily involve screening of candidate drugs for **safety**.
  - In 97% of cytotoxic drugs and 58% of molecularly targeted drugs, recommended doses are determined by toxicity.

Jardim DL, et al. Clinical cancer research. 2014;20(2):281-8.

- From a statistical point of view, **CRM** is preferable to a **3+3 design**.
  - Decrease the number of patients receiving low doses
  - Increase the number of patients receiving near-optimal doses

- The use of **expansion cohorts** is increasing for efficient treatment development.