Towards High-quality Clinical Trials And
Implementation Of Genomic Medicine

ATLAS Training Program

Course : Characteristics Of Cancer Clinical Trials (General)

Speaker : Noboru YAMAMOTO, MD, PhD

ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

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Education

- MD from Hiroshima University in 1991
- PhD from Hiroshima University in 2000

Professional Positions

- 2019-Present Deputy Director
- 2019-Present Director / Clinical Research Support Office
- 2013-Present Director / Department of Experimental Therapeutics
- 2010-Present Head of Physician / Department of Thoracic Oncology
- 2017-2019 Director / Clinical Research Coordinating Division
- 2012-2016 Head / Clinical Trial Management Office
- 2000-2010 Staff physician / Department of Thoracic Oncology
- 1998-2000 Senior Resident / Department of Internal Medicine
- 1995-1998 Resident / Department of Internal Medicine

Area of Expertise

- Early Drug Development (phase I trial)
- Thoracic Oncology
- Clinical Pharmacology

Contents

- Overview of clinical studies and clinical trials
- Phase I trial
- Phase II trial
- Phase III trial
- Recent trends in anticancer drug development

Overview of **Clinical Research**

What are clinical trials?

- Investigation of patients (humans)
- Prospectively planned research to identify the optimal treatment for future patients matching specific medical conditions

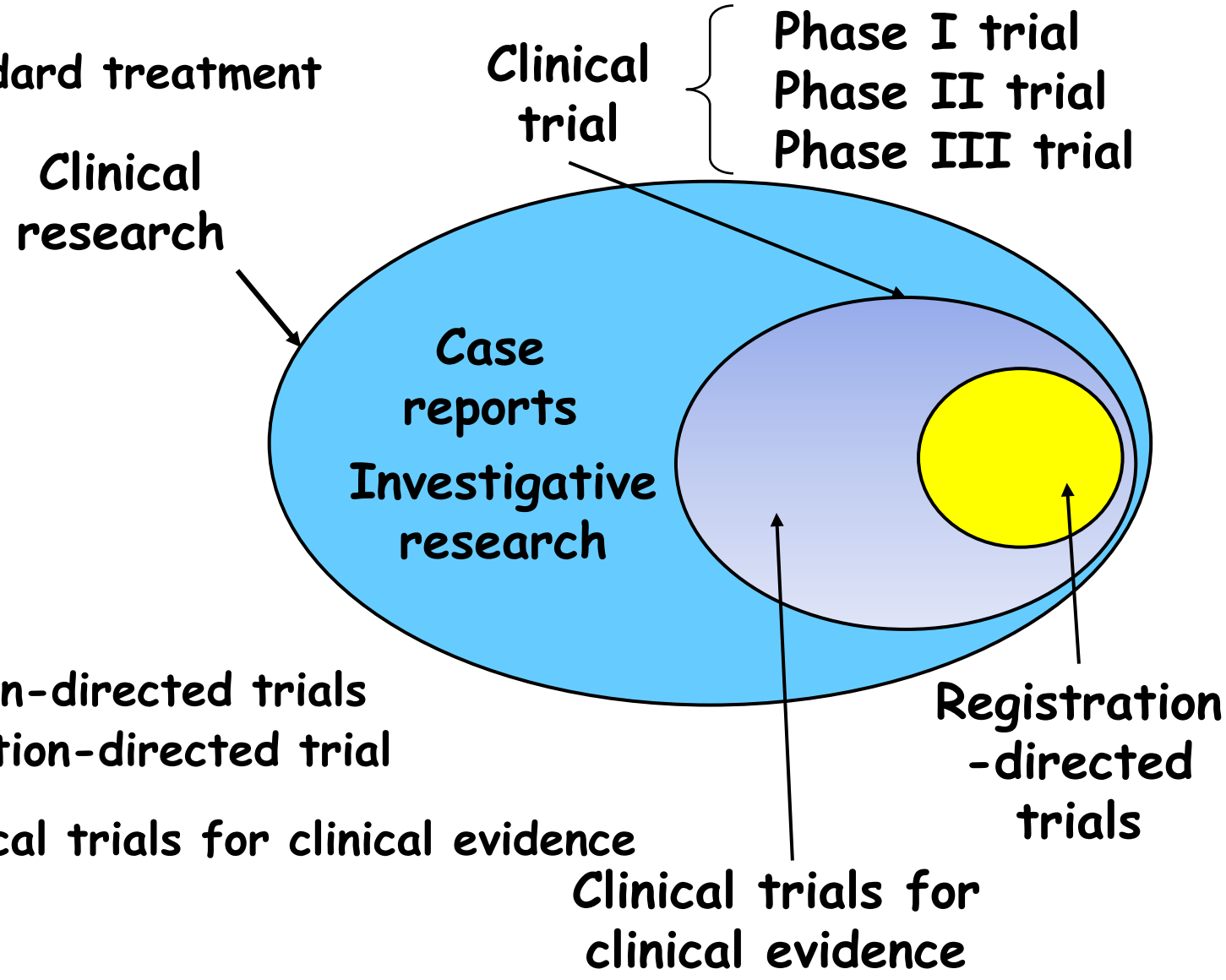
    - Essential to consider human rights
        - Declaration of Helsinki
        - Ethical guidelines

    - IRB approval is required

    - Informed consent is required
        - Easy-to-understand explanation
        - Decision-making by the participating patients

Classifications Of Clinical Studies/Trials

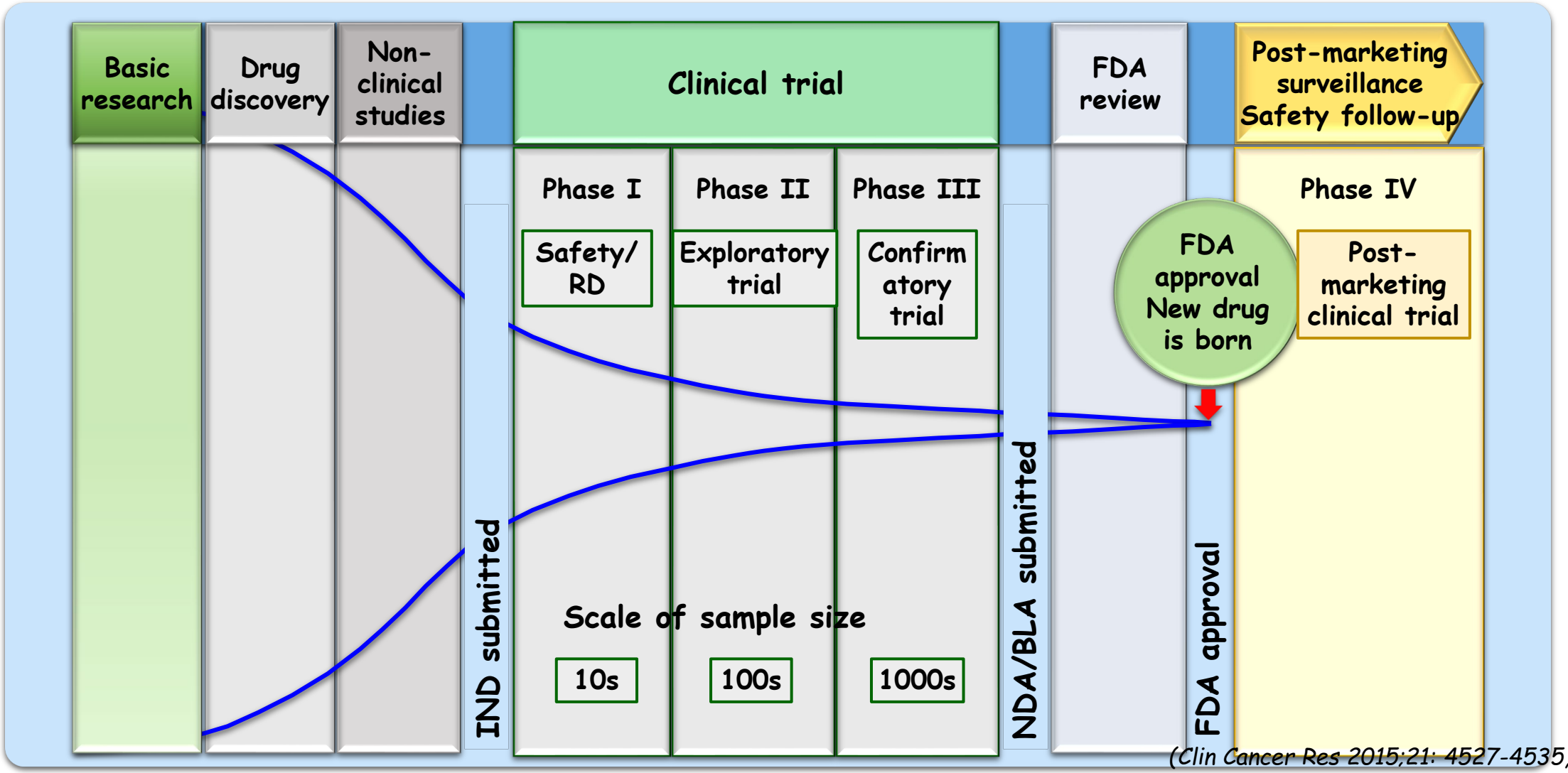
- Phases･･･Clinical introduction → Standard treatment
  - Phase I trial
  - Phase II trial
  - Phase III trial



- Types of clinical trials
  - Registration-directed trials
    - Industry-sponsored registration-directed trials
    - Investigator-initiated registration-directed trial
  - Post-marketing Clinical trials/Clinical trials for clinical evidence

Long Road To The Emergence Of A New Anticancer Drug

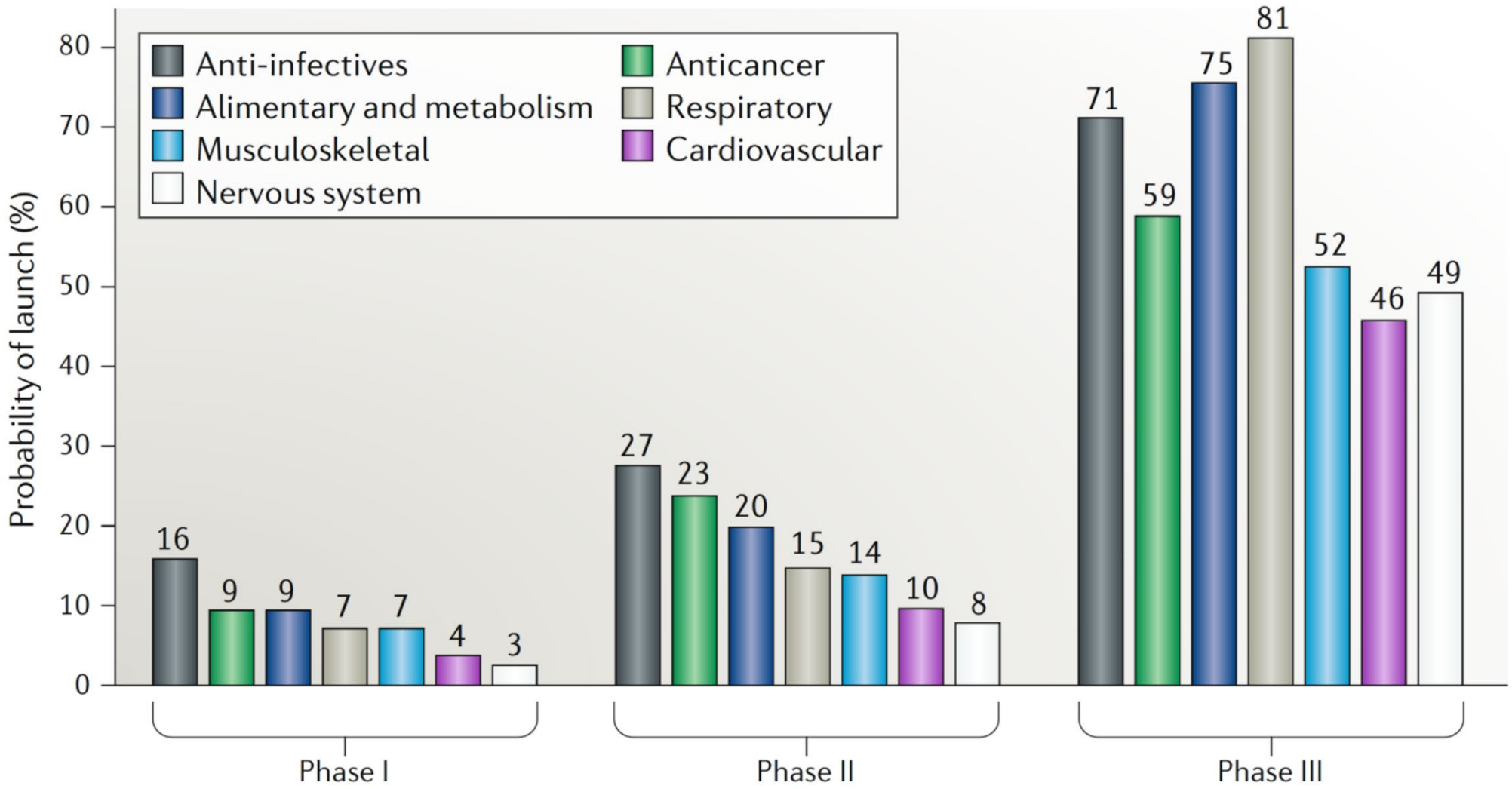
- It has been said that "One new drug is born from among 5000–10,000 candidate products"…



(Clin Cancer Res 2015;21: 4527-4535, revised)

Not All Anticancer Drugs Are Approved

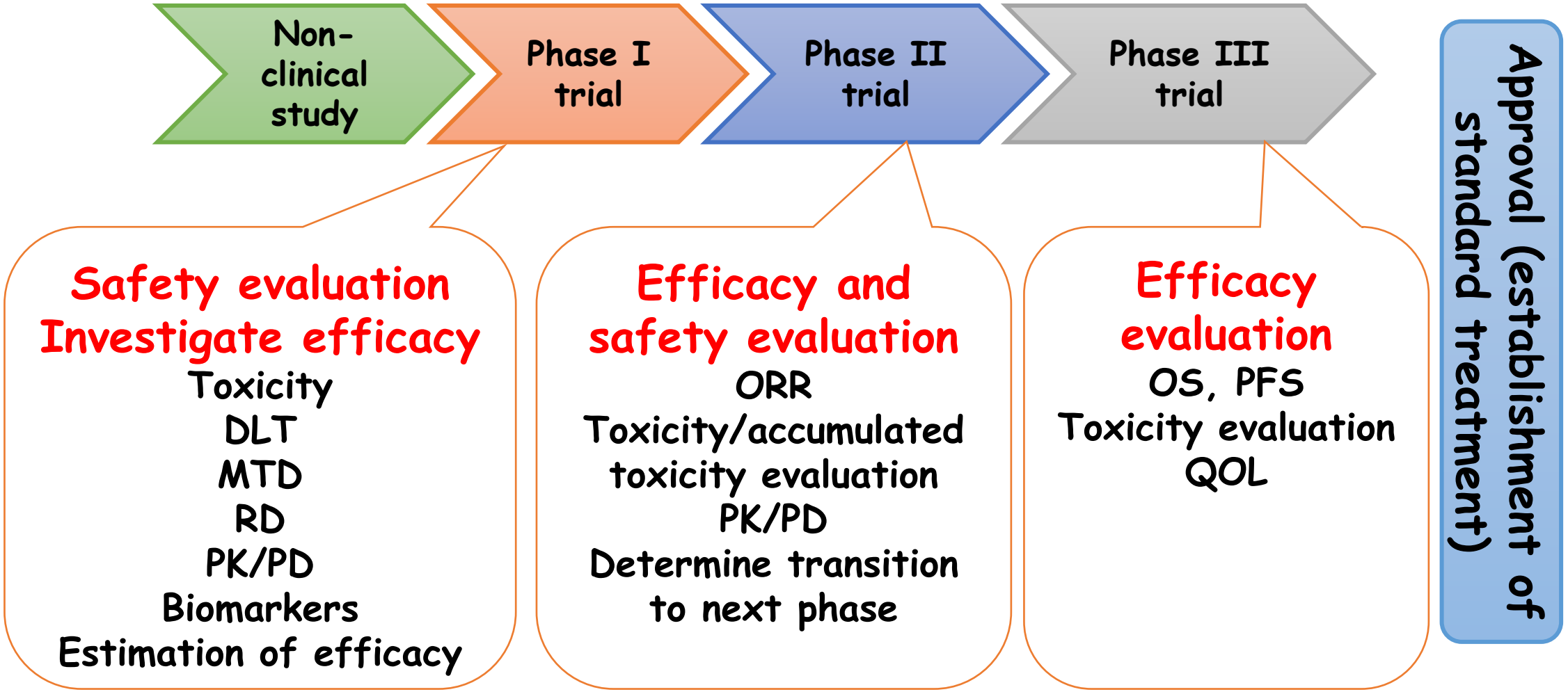
- Approval rate of development from 2010 to 2017



(Nat Rev Drug Discov 18: 495-496, 2019)

Development Process Of Anticancer Drugs

- From non-clinical study to clinical trial (Phase I→Phase II→Phase III)



Clinical Study Phases

Items	Phase I	Phase II	Phase III
Purpose	Decide whether to progress to Phase II	Decide whether to progress to Phase III	Determine standard treatment
	Determine RD	Efficacy screening Enhance toxicity profile	Comprehensive risk/ benefit evaluation
Primary endpoint	Toxicity (MTD, DLT)	Response rate, survival rate, relapse-free survival rate	Overall survival
Secondary endpoint	Efficacy	Safety	PFS, Safety etc.
Study design	Toxicity-based dose-escalation trial	Single-arm trial Randomized trial	Randomized controlled trial
Sample size	15–30 cases (100–200 cases when an expansion cohort is included)	60–100 (200) cases	200–3,000 cases
Participating facilities	Fewer study sites	Medium-scale (mainly specialized hospitals)	Large-scale, multicenter, multinational (mainly general hospitals)

Phase I Trial

Clinical Trial Phases

Items	Phase I	Phase II	Phase III
Purpose	Decide whether to progress to Phase II	Decide whether to progress to Phase III	Determine standard treatment
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Phase I Clinical Trial: Overview And Purpose

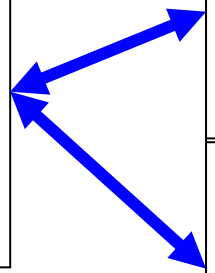
- Overview
  - New anticancer drugs are administered to humans for the first time
  - Optimal dose and dosing method are determined
  - Dose-escalation trial using toxicity as an index
  - Endpoint is toxicity

- Purpose
  - Toxicity and qualitative/quantitative evaluation
  - Determine dose-limiting toxicity (DLT)
  - Estimate maximum tolerated dose (MTD)
  - Determine recommended dose (RD) and dosing method for next phase
  - Analysis of pharmacokinetics (PK/PD)
  - Observe therapeutic effect
  - Identify predictive markers of therapeutic effect (molecular-targeted drugs)

Phase I Clinical Trial: Eligible Subjects

- For cancer patients
  - General drugs…healthy males
- No effective treatment method/standard treatment
- Good Performance Status (PS) (PS ≤ 2, almost all recent PS ≤ 1)
- Preservation of organ function with no effect from prior therapy
- Age: ≥legal age (the upper limit was previously set at ≤75 years)
- Informed consent

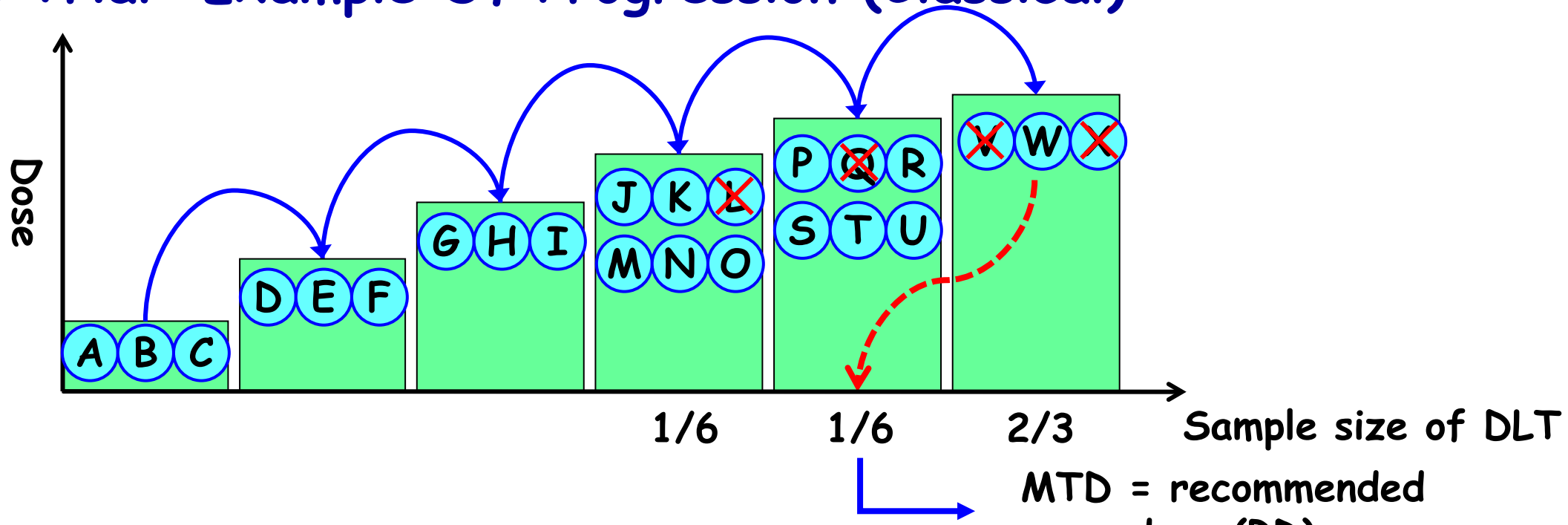
- Toxicity is almost certain as the dose increases
  Unexpected toxicity may also be observed
- Therapeutic effect is uncertain
  Fatal dose may be reached before the effective dose is reached



Intention to treat and participate is indispensable for patients
(only patients who wish to enroll participate in the trial)

The primary purpose is not the therapeutic effect, so adequate ethical consideration is required for patient selection
(The patient's purpose is "effect")

Phase I Trial: Example Of Progression (Classical)



Number of DLT cases

Number of DLT cases

3 cases registered → 0/3 → Dose escalation

3 cases registered → 1/3 → 3 more cases included → 1/6 → Dose escalation

3 cases registered → 1/3 → 3 more cases included → ≥2/6 → No dose escalation

3 cases registered → ≥2/3 → No dose escalation

Phase I Trial: Starting Dose

- Generally
  - ① 1/10 of LD_{10} in mice
    - ➢ 1/10 dose of 10% lethal dose in mice
  - ② 1/3 of TDL (toxic dose low) in dogs
    - ➢ 1/3 of the dose that causes minimal reversible toxicity in beagles
  - ➢ Normally, if potent toxicity is not observed after administration of the dose in ① to beagles, ① is set as the starting dose
  - ➢ If toxicity is observed, ② is set as the starting dose, which is a lower dose than ①

- If there is previous development overseas (US, EU, etc.)
  - Low-doses with no toxicity may be skipped
  - Approximately 50% of the MTD confirmed overseas is used as the benchmark

Phase I Trial: Dose Limiting Toxicity (DLT)

- Toxicity criteria that govern dose escalation
  - Toxicity is used to determine that no further dose escalation is possible
  - Normally deals with acute and subacute toxicity
  - Stipulated by each study (protocol), and the content differs slightly

- What are the common DLT standards? (based on NCI-CTCAE)
  - Grade 4 hematotoxicity
  - Grade 3 non-hematotoxicity
    - Nausea, vomiting, loss of appetite, alopecia, and transient electrolyte imbalances may be excluded

Phase I Trial: Supportive Care For Toxicity

- Supportive therapy for toxicity (adverse events) is clearly stated in the protocol
  - Drugs that may be used for treatment differ depending on the trial

- Previously in Phase I trials (particularly corporate clinical trials)
  - Supportive therapy was not provided until DLT was observed
    - Example: Grade 2 diarrhea·····monitor progress
    - Example: Grade 3 diarrhea····· supportive therapy is (may be) started once determined as DLT

- Now in Phase I trials (particularly corporate clinical trials)
  - Supportive therapy may be started once toxicity (adverse events) is observed
    - This enables evaluation in a format closer to actual clinical practice

Phase I Trial: Maximum Tolerated Dose (MTD), Recommended Dose (RD)

- Maximum tolerated dose (MTD)
  - MTD is defined for each protocol depending on the incidence of DLT
    - DLT onset dose level in 2 or more cases of 3–6 cases
    - DLT onset dose level in 3 or more cases of 3–6 cases
    - DLT onset dose level exceeding 33%
  - Determining the acceptable range of frequency and severity of toxicity differs depending on pharmaceutical and clinical judgements
  - MTD is a relative concept
    - May be affected by the characteristics and prognosis of the target disease
    - Once an MTD is determined, it may be revised upward with subsequent supportive therapy

- Recommended dose (RD)
  - In many studies, MTD = RD
  - The final decision may be carried over to the Phase II trial

Phase I Trial: Escalation Method

- Classical method
  - Modified Fibonacci sequence

- Dose escalation methods have been proposed to overcome the limitations associated with the classical method
  - PK guided dose escalation: PGDE
  - mCRM (Bayesian Optimal Interval [BOIN] design)
  - Accelerated titration design

Phase I Trial: Modified Fibonacci Sequence

- Conventional method
- Starting dose is set as "n"
- Rate of dose escalation decreases as the dose increases

- Advantages
  - Safety can be adequately considered
- Disadvantages
  - Ten or more steps may be needed to reach MTD
  - Large sample size and long study period are needed

Dosing level	Dose	Increase ratio (%)
Level 1	n	-
Level 2	2.0 n	100
Level 3	3.3 n	67
Level 4	5.0 n	50
Level 5	7.0 n	40
Level 6	9.0 n	33
Level 7	12.0 n	33
Level 8	16.0 n	33

Phase I Trial: mCRM (1)

- **M**odified **C**ontinual **R**eassessment **M**ethod
  - O'Quigley. *Biometrics* 46: 33, 1990

- Models the relationship between dose and adverse reactions based on previous information and sequentially tests the probability of expected toxicity onset close to the estimated dose for each case to estimate the posterior distribution.
  - Bayesian style approach
    - Recently, this approach has been referred to as the BOIN (Bayesian Optimal INterval) design
  - Goal is to increase the proportion of patients receiving treatment close to the MTD

- What is previous information?
  - Results of preceding Phase I trials
    - Dosing schedule may differ
  - Overseas results
  - Results of clinical trials on the mother compound when developing a derivative

Phase I Trial: mCRM (2)

- Advantages
  - The sample size registered at a low dose level can be reduced, and it is (should be) possible to reach close to the MTD in relatively few steps
  - This increases the proportion of patients receiving (close to) the optimal dose

- Disadvantages
  - In contrast, more time may be required to estimate the posterior distribution by adding events for each case
  - The number of patients treated with a dose above the recommended dose may increase depending on the estimation results

- This method does not always outperform the conventional method

Phase I Trial: Accelerated Titration Design

- Goal
  - Reduce the sample size on doses below the therapeutic range (low dose)
  - Reach the MTD with a small sample size, and accelerate the progression of the trial

Design 1

- The dose escalation increase is 40% with the normal modified Fibonacci method (A)

Design 2

- One case is registered at each dose level, and the dose is escalated. The trial transitions to design 1 when there is one case with DLT or two or more cases with grade 2 or higher toxicity in the first course (B)

Design 3

- One case is registered at each dose level, and the dose is escalated 100% each time. The trial transitions to design 1 when there is one case with DLT or two or more cases with grade 2 or higher toxicity in the first course (B)

Design 4

- One case is registered at each dose level, and the dose is escalated 100% each time. The trial transitions to design 1 when there is one case with DLT or two or more cases with grade 2 or higher toxicity in all treatment courses (B)

➢ (A) No intra-patient dose escalation

➢ (B) Intra-patient dose escalation is possible if the toxicity is grade 1 or lower

(Simon R. *JNCI* 89; 1138, 1997)

Precautions For Dose Escalation Trials (1)

- DLT is greatly affected by patient selection
  - DLT can appear artificially
  - It is essential to consider the patient's age and physique in response to high doses (particularly with drugs for which the dosage is calculated using BSA "mg/body")
- Escalation method
  - Recently, the use of model-based designs such as CRM and EWOC is increasing (particularly in corporate clinical trials), but there appears to be no significant difference even when using a rule-based design
- Biomarker evaluation with dose escalation is now indispensable
  - Previously, it was sufficient to employ toxicity only as an index (≒cytotoxic agent)
  - However, this approach is no longer adequate
    - Blood (PK/PD, PBMC) and tissue (normal, tumor) are essential
    - It may not be possible to determine the MTD based on toxicity alone

Precautions For Dose Escalation Trials (2)

- What MTD should be aimed for in Phase I trials?
  - It is only to decide on the dose to be used in the next phase, and not to determine the dose at approval
  - Is the aim a dose that can be repeated many times?
  - Is the aim a dose that can be administered in one course?

  } Need to discuss with researchers and sponsor

- What should you aim for?
  - Dose-escalation trial to clearly determine how much of the drug can be administered
    - First and last chance
    - Further dose escalation is difficult in the next and subsequent phases
    - Dose modification for the second and subsequent courses may be decided later

  - How much of the respective drug can be administered to a living person should be clarified
  - "Effective drugs, even with some adverse reactions" are required in medical practice

Phase I Trial: Pharmacokinetics

- Pharmacokinetics analysis
  - Blood concentration measurement for the first time in humans
  - Small sample size, but full sampling
    - 10–13 points/case
  - Investigate the relationship between pharmacokinetics parameters and toxicity/effect (PK/PD analysis)
  - Investigation of linearity/non-linearity

- What is important?
  - Pharmacokinetics in humans does not always match the data from preclinical (animal) studies
  - There may be ethnicity-related differences (Japanese vs. Westerners)
  - One opportunity to observe the dose response from a low dose
    - Important for confirming whether there is linearity
    - Important when considering subsequent combination therapy and clinical application

Phase I Trial (for all patients with solid carcinoma): Observation Of The Therapeutic Effect (Story from the past)

- Conclusions regarding the effect cannot be made based on Phase I trials
  - Even some drugs that showed no effect in Phase I trials were confirmed to have efficacy in Phase II trials and later
- Generally, the response rate is low, approximately 4–5%····A partial response ("PR") is observed in 1 in 20 people
  - Almost all registered cases have had multiple previous treatments
  - Ultimately, a large proportion of cases is treated with a dose below the effective dose

Report	Period	Number of trials	Sample size	Response rate (%)
NCI	1974–1982	187	6447	4.2
M.D. Anderson	1991–1993	23	610	3
ASCO	1991–2002	213	6474	3.8
NEJM	1976–1993	363	12076	4.1
CTEP	1991–2002	178	4315	4.3
NCCH	1996–2012	54	777	6.2

(Mizugaki, et al: JCO 2015)

Do Phase I Clinical Trials Have A Therapeutic Impact?

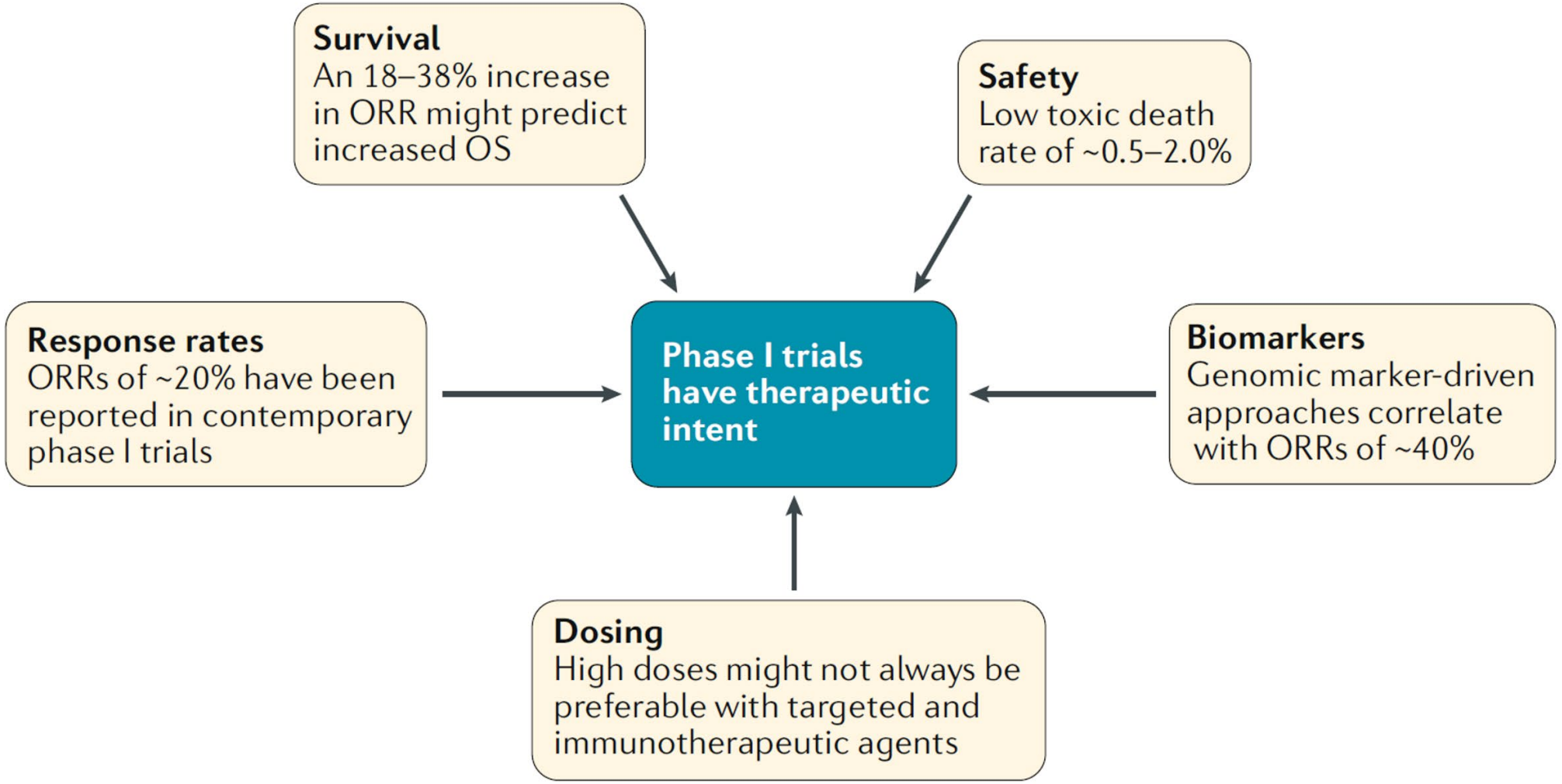
- Effectiveness of Phase I trials have been limited
  - Response rate: 4–5%
- The response rate has improved with advancements in drug discovery technology and progression in the development of individualized treatment following the identification of molecular targets

Series	Period covered	Trials included (n)	Patient (n)	Agents Tested (n)	ORR (%)	Gr 5 AEs (%)
Estey et al. (1986)	1974–1982	187	NR	54	4.2	NR
Decoster et al. (1990)	1972–1987	211	6639	87	4.5	0.5
Horstmann et al. (2005)	1991–2002	460	11935	NR	10.6	0.49
Roberts et al. (2004)	1991–2002	213	6474	149	3.8	0.54
Mizugaki et al. (2015)	1996–2012	54	777	NR	6.2	0.3
Schwaederle et al. (2016)	2011–2013	Biomarker-driven: 57	2655		31.1	1.9
		Non-biomarker-driven, targeted: 177	10548		5.1	NR
		Non-biomarker-driven, cytotoxic: 116			4.7	2.2
Waligora et al. (2018)	2004–2015	170	4604	NR	10.29	2.09
Chakiba et al. (2018)	2014–2015	224	NR	224	19.8	NR

(Mizugaki, JCO 2015, Nat Rev Clin Oncol, 2019)

Do Phase I Trials Have A Therapeutic Impact?

- Phase I trials now have an adequate impact on treatment



(*Nat Rev Clin Oncol*, 16: 773-778, 2019)

Phase II Trial

Clinical Trial Phases

Items	Phase I	Phase II	Phase III
Purpose	Decide whether to progress to Phase II	Decide whether to progress to Phase III	Determine standard treatment
	Determine RD	Efficacy screening Enhance toxicity profile	Comprehensive risk/ benefit evaluation
Primary endpoint	Toxicity (MTD, DLT)	Response rate Survival rate, relapse-free survival rate	Overall survival
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Participating facilities	Fewer study sites	Medium-scale (mainly specialized hospitals)	Large-scale, multicenter, multinational (mainly general hospitals)

Phase II Trial: Overview And Purpose

- Overview
  - Efficacy screening (exploratory evaluation using surrogate endpoint/short-term indicators)
  - Implementation of treatment using the RD for each cancer
  - Decision as to whether to progress to Phase III trial

- Purpose
  - Evaluate the efficacy of a drug (or new therapy) for a specific cancer
  - Evaluate safety, including accumulated toxicity
  - Further investigation of pharmacokinetics (PK/PD)
  - Determine whether to progress to Phase III trial
  - Investigate predictive markers for therapeutic effect (molecular-targeted drugs)

Phase II Trial: Endpoints And Eligible Subjects

- Endpoints
  - Use surrogate endpoints
    - Response rate
      ORR/DCR/CR
    - One-year relapse-free survival rate····Postoperative chemotherapy, etc.

- Targets
  - Specific cancers with a pathological diagnosis (limited)
  - Good PS (PS: 0–2), major organ function is preserved
  - Age: Set for each trial
  - It must be possible to evaluate the treatment efficacy…Necessity of measurable lesions by RECIST
  - Rules regarding prior treatment
    - Cancers with standard treatment…Recurrent cases/refractory cases
    - Cancers without effective treatment…Untreated cases
  - Informed consent

Phase II Trial: Ethical Considerations

- Statistical design
  - The study is designed to disprove that the respective drug (or therapy) is ineffective

- Low response rate
  - The response rate obtained in a Phase II trial using the new drug as monotherapy is significantly lower than the patient's expected response rate (was often the case previously)

- Balancing rules regarding prior treatment with efficacy evaluation
  - Including untreated subjects in a trial aimed at efficacy evaluation may be unethical for cancers for which effective standard combination chemotherapy is available
  - Evaluation of efficacy may be difficult when examining treated cases

Phase II Trial: Efficacy And Safety Evaluation And Pharmacokinetics

- Efficacy evaluation
  - Effect determination…RECIST
  - Confirmed by an Independent Data Monitoring Committee

- Safety evaluation
  - NCI-CTCAE v5.0
  - Evaluate toxicity for all treatment courses, including accumulated toxicity
  - Rules for dose reduction criteria and supportive therapy are determined for each trial

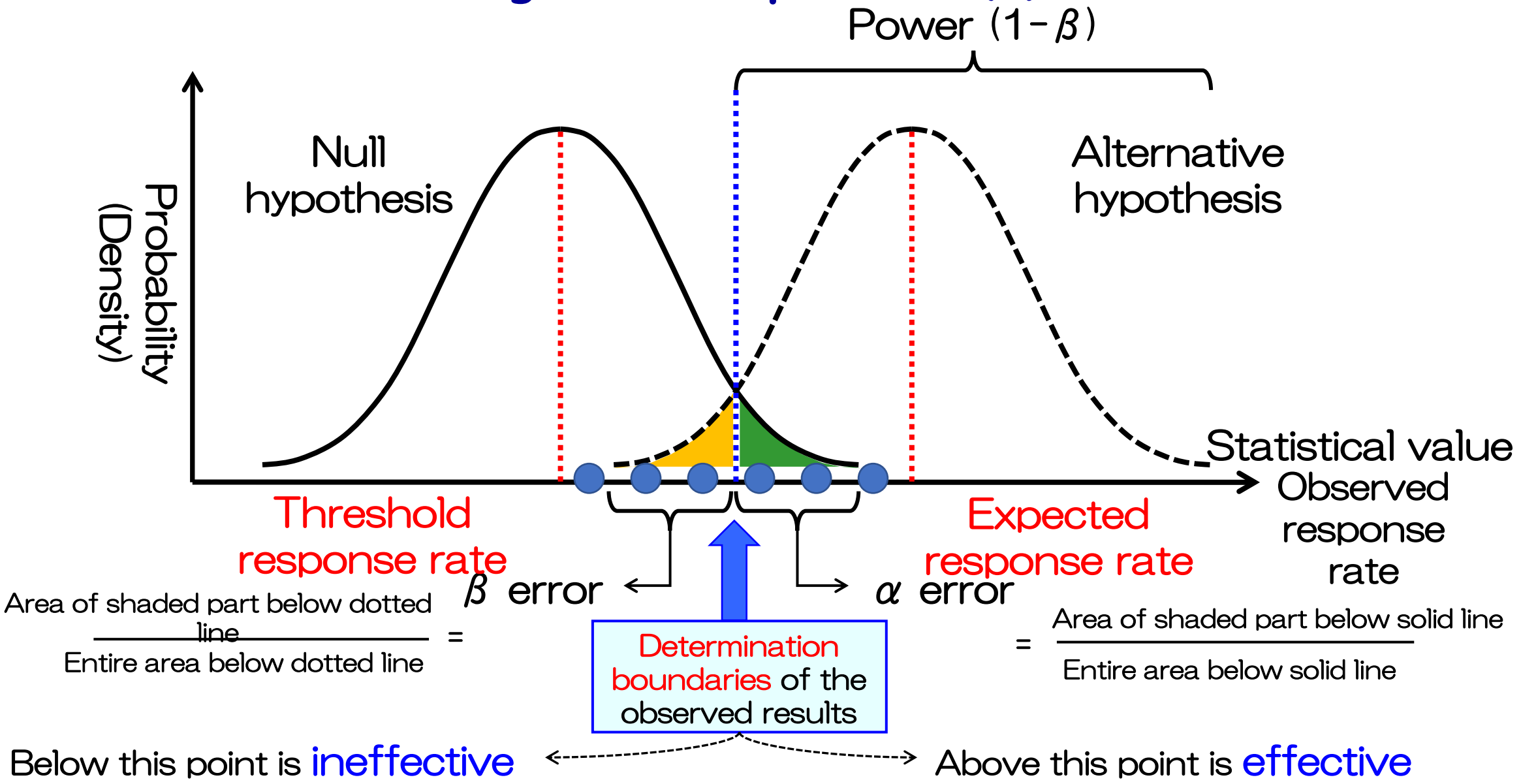
- Pharmacokinetics
  - Number of samplings for each case is small
  - Evaluation of variations in the recommended dose and analysis of the determinant factors
    - Investigate the optimal dose and dosing method

Phase II Trial: Setting The Sample Size (1)

- Establishing a sample size
  - Method of setting based on tests… Establishing the threshold response rate and expected response rate
  - Method of setting based on estimation…The confidence interval of the obtained response rate falls within a certain range
- Calculation based on binomial distribution
  - Threshold response rate (p_0)･･･null hypothesis (H_0)
  - Expected response rate (p_1)･･･alternative hypothesis (H_1)
  - α error･･･Probability of the mistaken acceptance of an actually false null hypothesis
  - β error･･･Probability of the mistaken rejection of an actually true null hypothesis
  - The lower limit of the confidence interval of the expected response rate is set to exceed the threshold response rate

		Respective drug (new therapy)	
		Effective	Ineffective
Decision-making for the hypothesis	Reject	1-β (power) Sensitivity	α False-positive
	Do not reject	β False-negative	1-α Specificity

Phase II Trial: Setting The Sample Size (2)

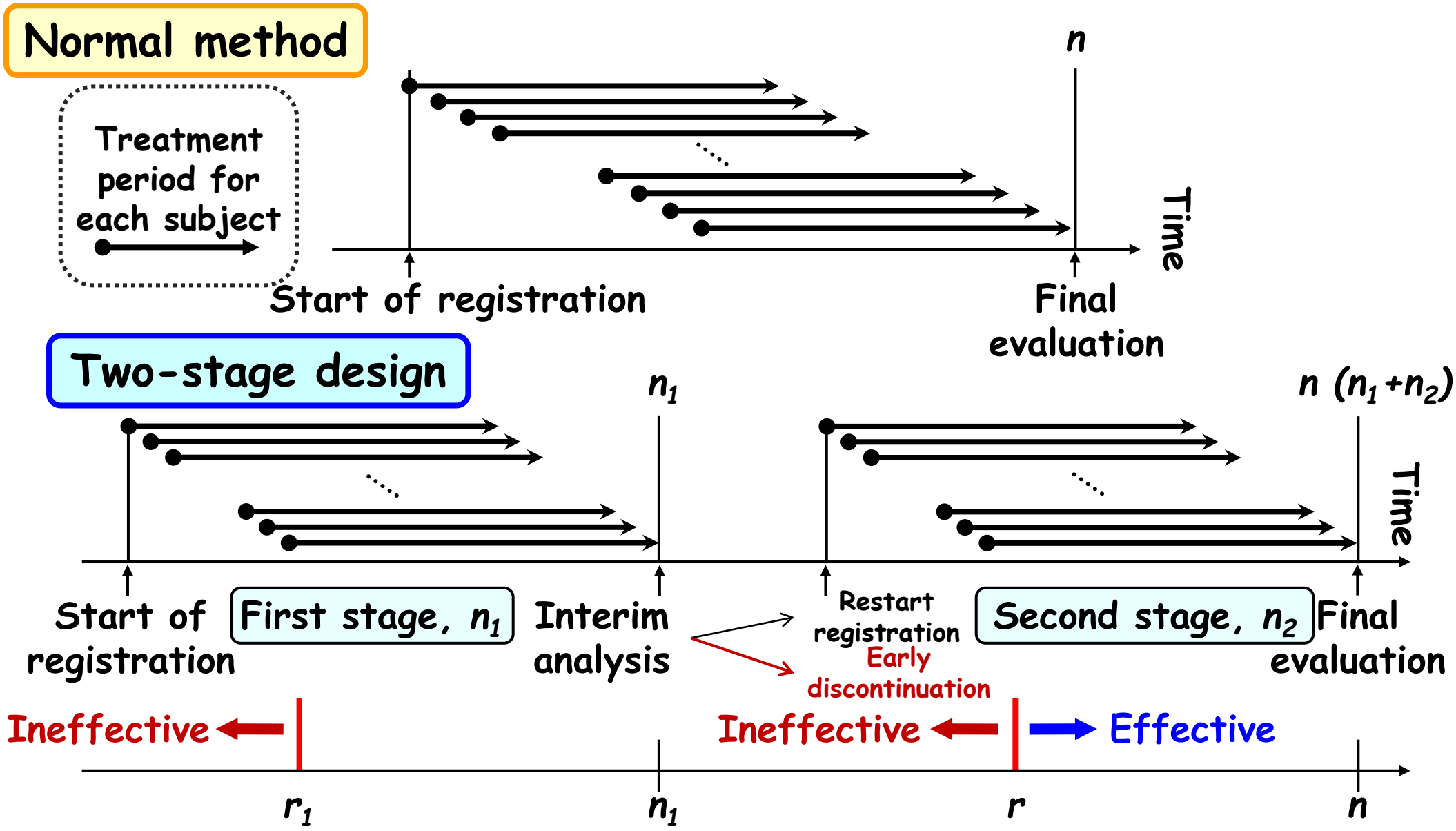


Phase II Trial: Setting The Sample Size And A Two-stage Design (1)

- Not all developed drugs (or new therapies) are effective
  - Few effective anticancer drugs are available
  - Because of ethical considerations, it is essential to make judgements about terminating development as soon as possible with a small number of patients

- Two-stage designs setting early termination due to ineffective treatment
  - Fleming design
  - Simon's design
    - Optimal design…Minimize the mean sample size considering the threshold
    - Minimax design…Minimize the sample size in the final stage
  - SWOG design
    - Assuming variation in the number of registered cases at each stage
    - Conduct tests with an alternative hypothesis at a significance level of 0.02 for cases registered in the first stage
    - Test the null hypothesis during final analysis at p = 0.05

Phase II Trial: Setting The Sample Size And A Two-Stage Design (2)



Phase II Trial: Setting The Sample Size And A Two-Stage Design (3)

Simon's two-stage design (Optimal design) (p1 - p0 = 0.2, α = 0.05) (partial excerpt)

Threshold response rate p0	Expected response rate p1	β error	r_1	n_1	r	n
0.05	0.25	0.2	0	9	2	17
		0.1	0	9	3	30
0.10	0.30	0.2	1	10	5	29
		0.1	2	18	6	35
0.20	0.40	0.2	3	13	12	43
		0.1	4	19	15	54
0.30	0.50	0.2	5	15	18	46
		0.1	8	24	24	63
0.40	0.60	0.2	7	16	23	46
		0.1	11	25	32	66

As the first-stage, treatment is provided to n_1 subjects. If the number of responsive cases is less than r_1 , the drug is determined to be "ineffective" and the trial is discontinued. If there r_1 or more responsive cases, the clinical trial progresses to the second stage, in which n cases (total sample size) are treated. If the number of effective cases is less than r, the drug is determined to be "ineffective", whereas if the number of effective cases is r or more, the drug is determined to be "effective".

Phase II Trial: Websites For Establishing The Sample Size

- **SWOG**: https: //stattools.crab.org/

CRAB Cancer Research And Biostatistics

SWOG CANCER RESEARCH NETWORK

STATISTICAL TOOLS | DESIGN | ANALYSIS | PROBABILITIES | OTHER TOOLS | ABOUT US

Statistical Tools

Design	Analysis
One Arm Binomial	Frequency Table
One Arm Normal	Binomial Confidence Interval
One Arm Survival	**Probabilities**
One Arm Expected Events	Binomial
Two Stage	Normal
Two Arm Binomial	Poisson
Two Arm Normal	Chi-Square
Two Arm Survival	Probability of Observing a Rare Event
Two Arm Expected Events	**Other Tools**
Binomial Interaction	Prognostic Mixture
Survival Interaction	Survival Converter
Binomial Noninferiority	
Survival Noninferiority	
Continuous Marker Prognostic Power	

- **NCI**: https: //linus.nci.nih.gov/brb/samplesize/default.htm

NIH NATIONAL CANCER INSTITUTE
DCTD Division of Cancer Treatment & Diagnosis

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BRP Biometric Research Program

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Predictive Biomarkers in Phase II/III Clinical Trials
Biomarker Targeted Randomized Design
Biomarker Stratified Randomized Design
Optimal Two-Stage Designs For Phase II Clinical Trials
Integrated Phase II/III Study
Sample Size Planning for Developing Classifiers Using High Dimensional Data
Design, Monitoring and Analysis of Bayesian Basket Discovery Trials
Bayesian Phase II Single Arm Clinical Trials

Online Sample Size Calculation

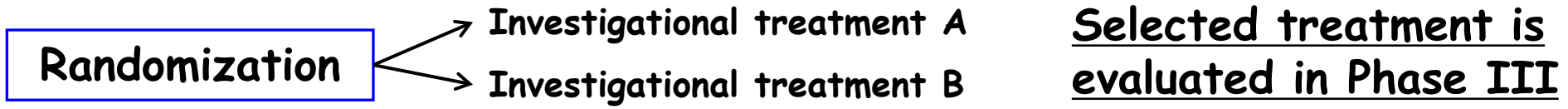
Last Updated: 11/22/16

Online Sample Size Calculation

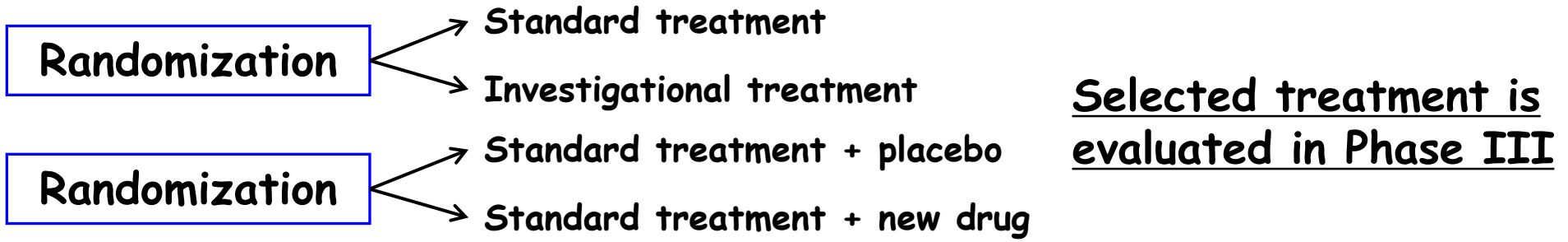
- Predictive Biomarkers in Phase II/III Clinical Trials
  - Biomarker Targeted Randomized Design
  - Biomarker Stratified Randomized Design
- Optimal Two-Stage Designs for Phase II Clinical Trials
- Integrated Phase II/III Study
- Sample Size Planning for Developing Classifiers
- Design, Monitoring and Analysis of Bayesian Basket Discovery Trials
- Bayesian Phase II Single Arm Clinical Trials

Phase II Trial: Randomized Phase II Trial

- A priority order is allocated to several candidate treatments
- The response should be confirmed before the next phase (Phase III)
- Selection design···Select promising candidates from among several candidate treatments
  - Endpoints: Response rate, survival time (1-year survival rate), etc.



- Screening design···α error/β error are set to large values to confirm the response
  - Endpoints: Progression-free survival, overall survival, response rate, etc.



- Randomized Phase II trials are not confirmatory trials like Phase III trials
- Should be conducted only with the premise of progressing to a Phase III trial

Phase III Trial

Clinical Trial Phases

Items	Phase I	Phase II	Phase III
Purpose	Decide whether to progress to Phase II	Decide whether to progress to Phase III	Determine standard treatment
	Determine RD	Efficacy screening Enhance toxicity profile	Comprehensive risk/ benefit evaluation
Primary endpoint	Toxicity (MTD, DLT)	Response rate Survival rate, relapse-free survival rate	Overall survival
Secondary endpoint	Efficacy	Safety	PFS, Safety, etc.
Study design	Toxicity-based dose-escalation trial	single-arm trial Randomized trial	Randomized controlled trial
Sample size	15–30 cases (100–200 cases when an expansion cohort is included)	60–100 (200) cases	200–3,000 cases
Participating facilities	Fewer study sites	Medium-scale (mainly specialized hospitals)	Large-scale, multicenter, multinational (mainly general hospitals)

Phase III Trial: Overview

- Determine standard treatment

- Compare new drugs, treatments, or new uses of drugs with the current standard treatment
  - Does not compare new treatments with unconfirmed effect
  - Control arm…Current standard treatment (only)

- Randomly allocate the treatment
  - Factors other than the treatment are the same between groups…"Difference in result is because of the difference in treatment"
  - Analyze as assigned…intention to treat

- Confirmatory trial: Reach a conclusion
  - New treatment is set as the new standard treatment, or the standard treatment remains
  - Superiority trial…New treatment must be better
  - Non-inferiority trial…New treatment can be said to be better, but not worse

Phase III Trial: Targets

- Investigation of specific cancers
  - Recent studies often designate specific cancers + biomarkers

- When investigating subject with prior therapies
  - Certain criteria should be established for prior therapies

- Eligibility criteria for participating in phase III trials are slightly more lenient than those for participating in Phase I and II trials
  - The obtained results will be directly applicable in routine practice

Phase III Trial: Endpoints

- Primary endpoint: Life-extending effect
  - Overall survival (OS)…Representative of life-extending effect indicators
    - OS = "Date of death due to any cause" — "Randomization time/Registration date"

- Relapse-free survival (RFS)
- Progression-free survival (PFS)
  - May be used in groups with good prognosis
  - When a large number of patients is registered, long-term tracking is required to evaluate the OS
  - The next best measure
  - Soft indicator that may change significantly depending on the observer, examination and hospital visit intervals, and definitions
    - Requires careful setting in the trial plan

- What is QOL?
  - Conceptually, it is an indicator of patient benefit
  - No method has been established for measuring the QOL with adequate reliability and reproducibility

Phase III Trial: Randomization

- Phase III trials are implemented as randomized controlled trials
  - Randomized controlled trial: RCT
- Randomization
  - Minimizes bias between treatment groups based on known factors as well as unknown factors that cannot be measured or evaluated
  - Best method for creating comparable groups where the differences between each group are attributed to the differences in treatment
    - Difference in result is due to difference in treatment

- Reference: Matching
  - Used in observational, epidemiological, and exploratory trials
  - Data are collected and analyzed to ensure that both the control group and new treatment group have the same number of known prognostic factors
  - Only known factors are matchable
  - It cannot be guaranteed that unknown prognostic factors would not have bias

→It is necessary to verify the findings obtained with matching

Phase III Trial: Randomization

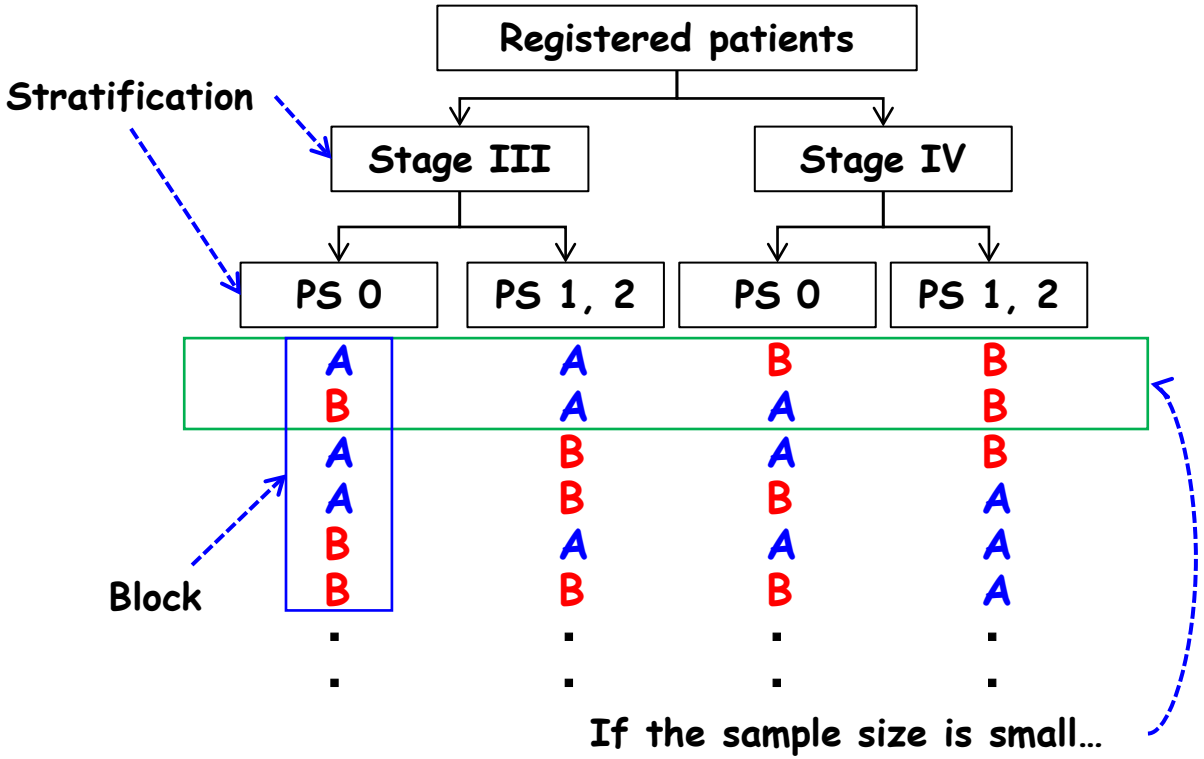
- Simple randomization
  - Allocates treatment to all registered patients with equal probability (2 groups: 50% vs. 50%)
  - When there are important prognostic factors
    - Differences in known prognostic factors may be larger than expected differences in prognosis between treatment groups
      - Example: PS, stage
    - Differences between treatment groups may be suspected to be due to bias in prognostic factors

    →Necessary to ensure that the groups are balanced

- Methods for balancing between groups (adjusted allocation) (known as stratification)
  - Stratified allocation
  - Dynamic allocation

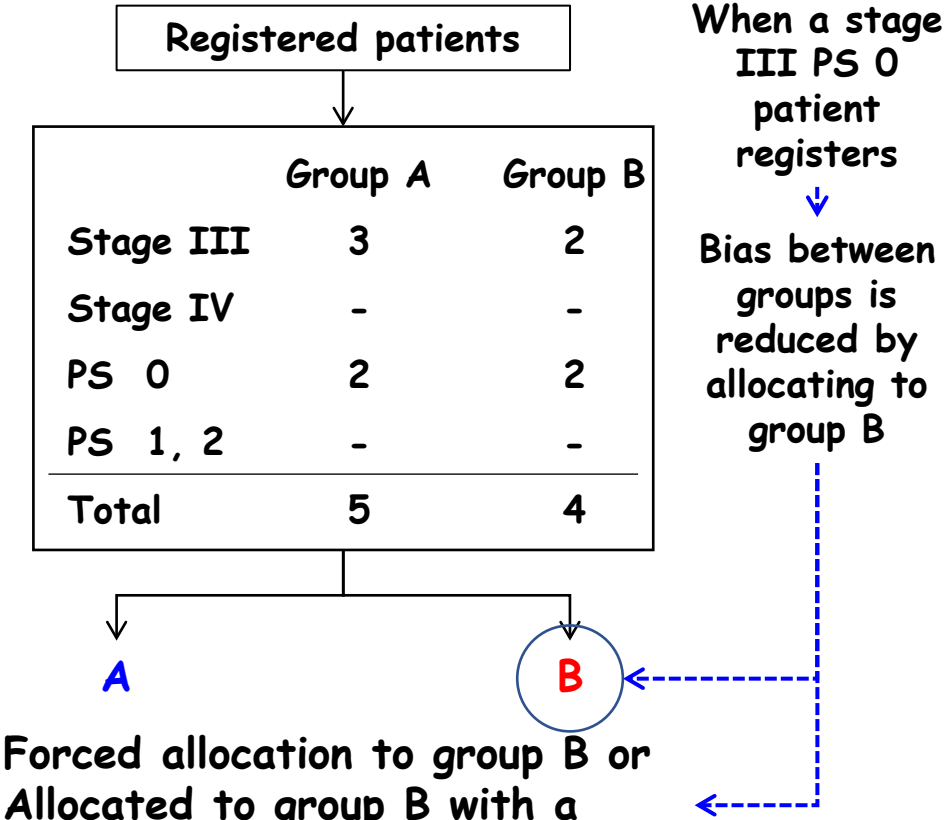
Phase III Trial Randomization: Achieving A Balance Between Groups

- Stratified allocation (Example: Block method)



- Allocation table is created in advance
- Block length is decided in advance
  Same number allocated to groups A and B in the block
  The block length is not known to the researcher
- Suitable for large-scale trials on circulatory organs, etc.

- Dynamic allocation (Example: Minimization method)



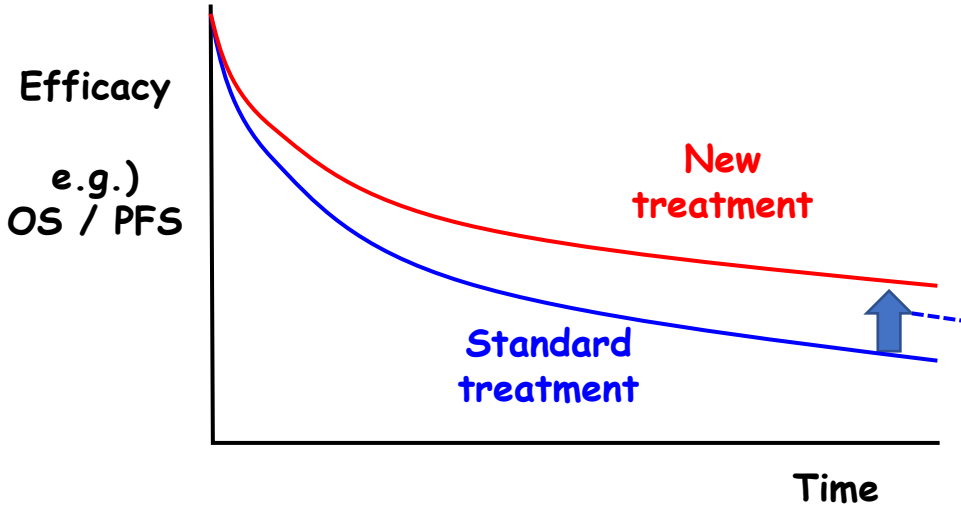
- Each time a patient is registered, decide whether he/she is allocated to group A or B
- Suitable for medium-scale cancer clinical trials

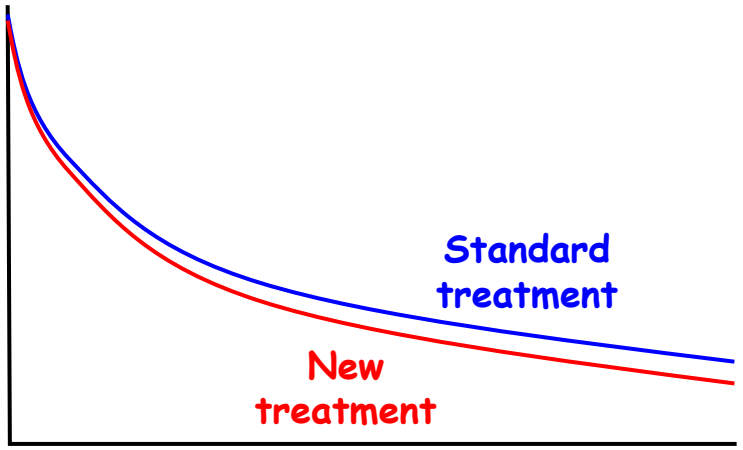
Phase III Trial: Trial Types

- Standard vs. Toxic New
  - New treatment…High toxicity but also potent life-extending effect
  - Uses a superiority trial design

- Standard vs. Less Toxic New
  - New treatment…Equal life-extending effect, but less toxic
  - Uses a non-inferiority trial design

Standard vs. Toxic New





Only as much as the drawback associated with the degree of toxicity
The new treatment must have better efficacy

Clinically significant difference

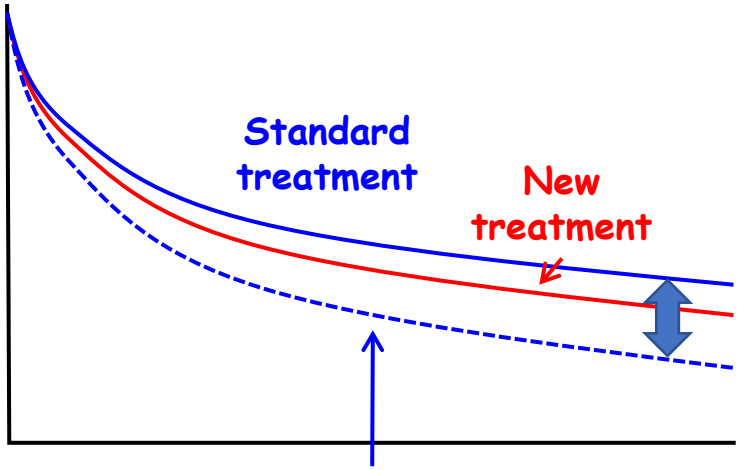
If the efficacy exceeds this level, then the treatment is selected as a new treatment
Less than the clinically significant difference, and the standard treatment remains

Phase III trials are used to statistically verify whether there is a "clinically significant difference"

When a new highly toxic treatment is lower
Whether it is "significantly" inferior is not a concern

→ Determination to not use the test
→ Statistically, a **superiority trial** for a "one-sided" hypothesis

Standard vs. Less Toxic New



Rule out levels lower than this

This is not a test to "verify that the treatments are the same"

In other words…

Superiority trial with new treatment elevated

or

Superiority trial with standard treatment handicapped

Scenarios where a new treatment does not need to be superior, and it is sufficient to be not inferior, verify that the treatment does not fall below the lower tolerance limit to demonstrate "non-inferiority"

= non-inferiority trial

When the life-extending effect is approximately the same but there are other advantages (example: less toxic) = new treatment is concluded to be superior

Consider only whether it is above the lower tolerance limit

= one-sided hypothesis

Cannot be handled with a normal log-rank test

Test whether the hazard ratio exceeds the tolerance limit in the proportional hazard model (apparently)

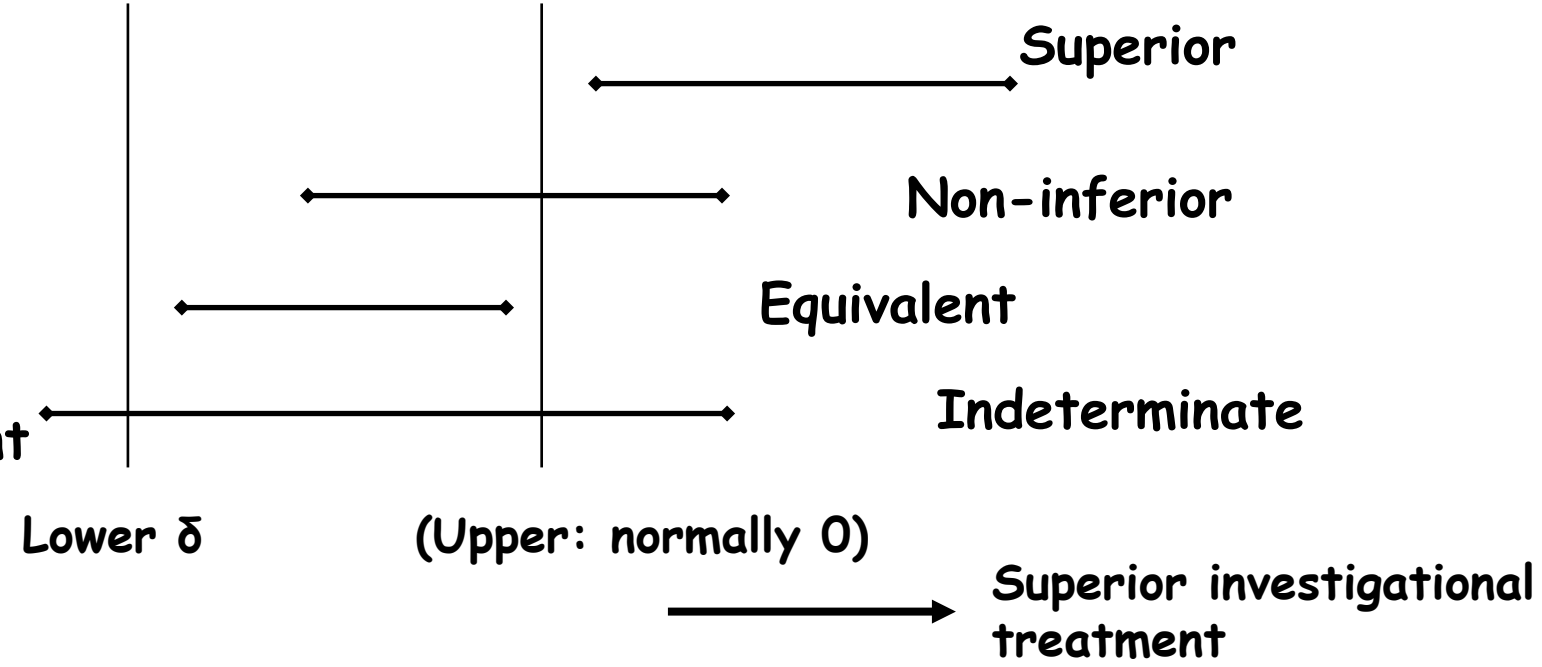
= Performed by a statistician

Superiority Trial And Non-inferiority Trial

Difference in the therapeutic effect and confidence interval: Difference in the therapeutic effect of the investigational treatment and standard treatment "δ (delta)"

Confidence interval

(normally 95%)
If this value does not contain 0, it is "statistically significant (5%)"

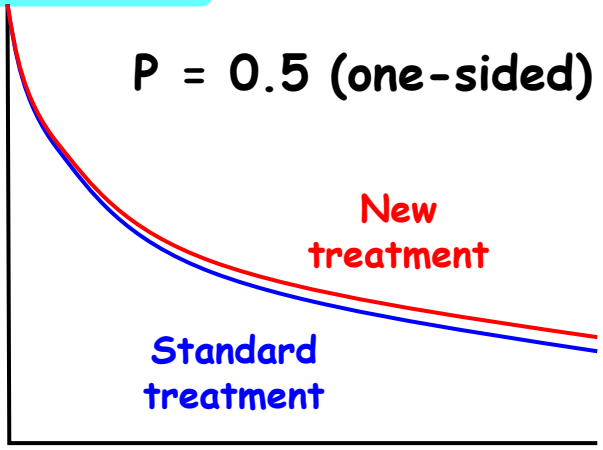


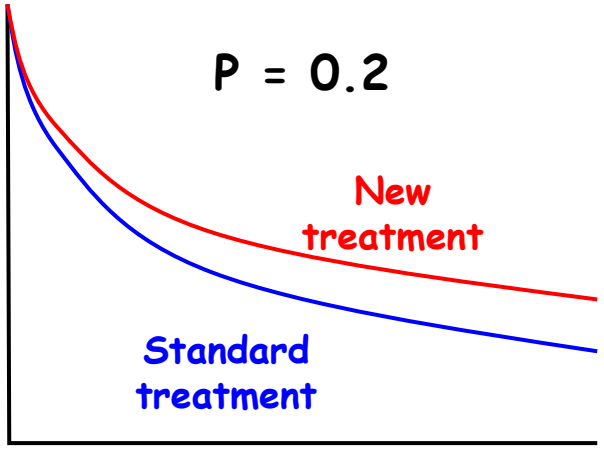
How is δ selected?

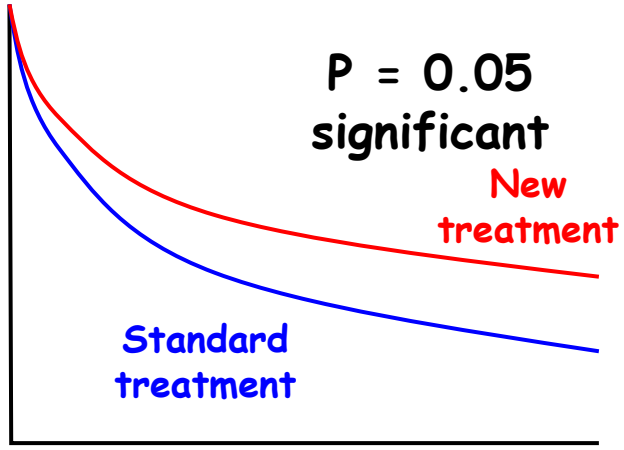
Clinically negligible differences in the therapeutic effect
Regional differences, characteristics of standard treatment (toxicity, cost)…
No undisputed decision method

Superiority Trial And Non-inferiority Trial

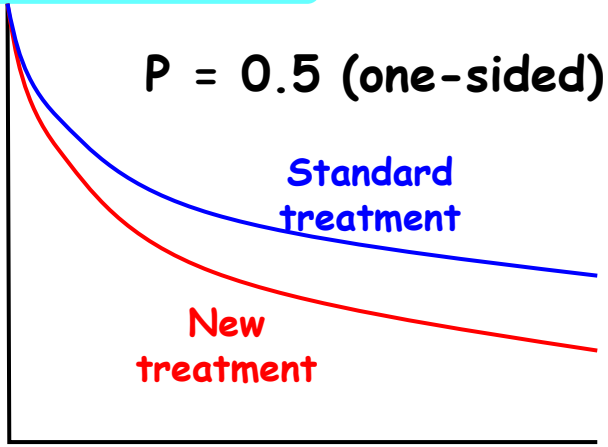
Superiority trial

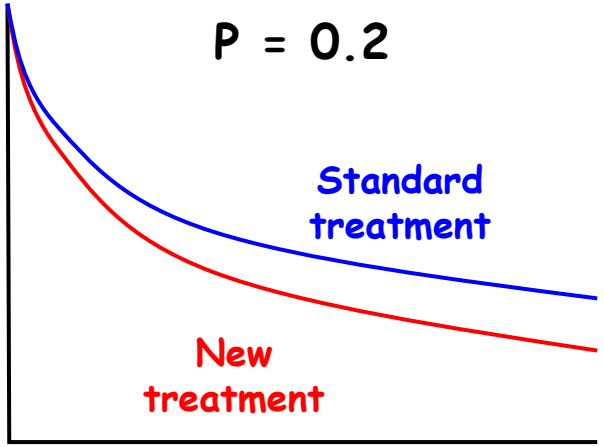


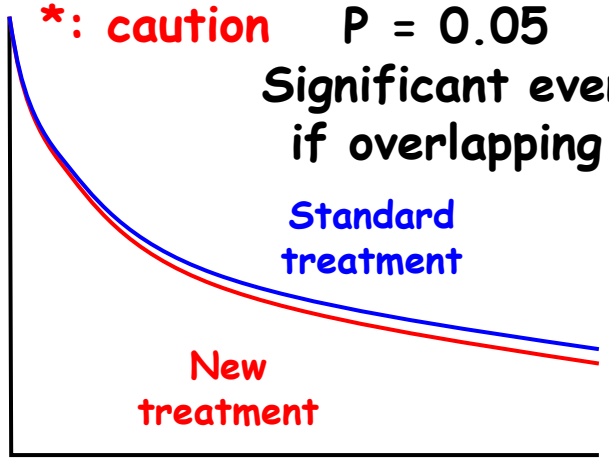




Non-inferiority trial



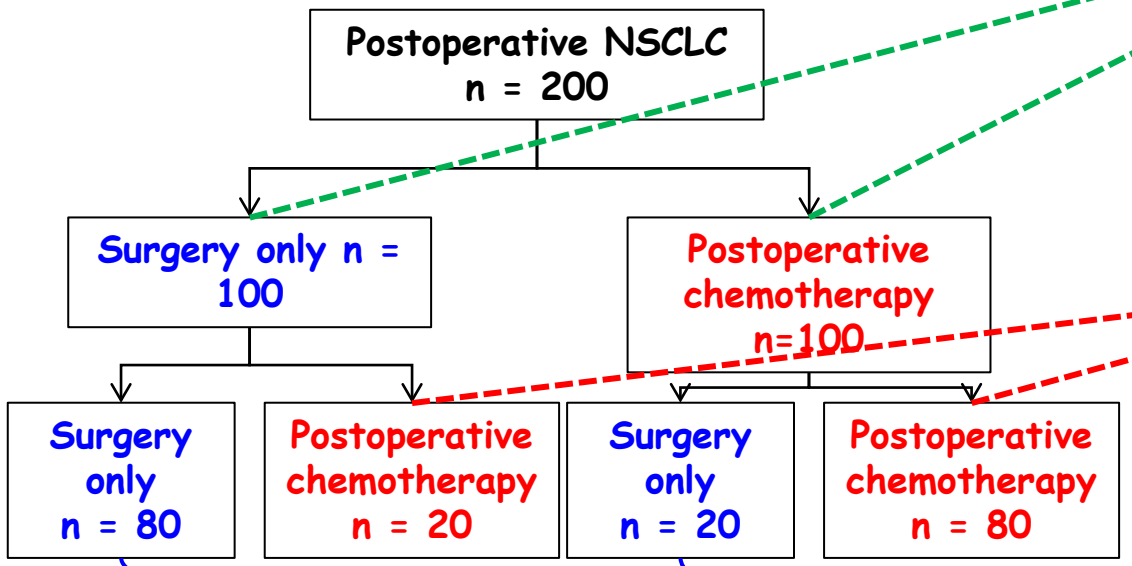




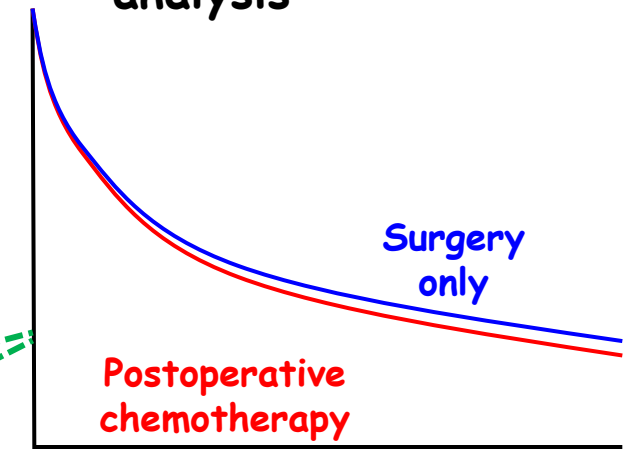
*: When evaluating a less toxic new treatment in a superiority trial, the treatment will be discarded even if it is demonstrated to be non-inferior.

Phase III Trial: Intention To Treat

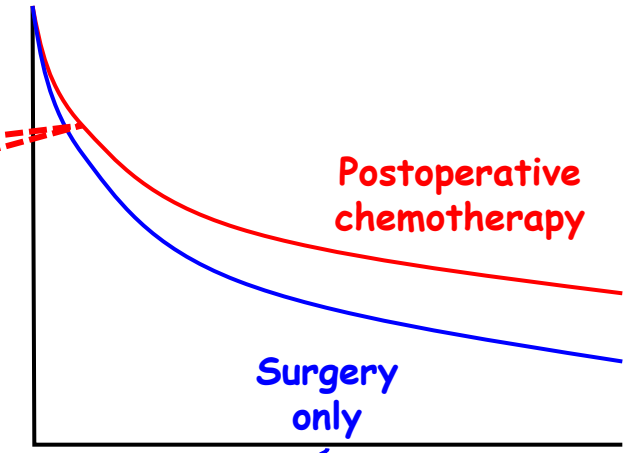
- All randomized patients are included in analysis
- It is permitted to set the primary analysis as all eligible patients after excluding the ineligible patients (example: patients with gastric malignant lymphoma enrolled in a stomach cancer trial) from all randomized patients
  - Not good if many patients are ineligible → Bias ↑
  - Necessary to create a protocol that will not generate ineligible cases



Intention to treat analysis



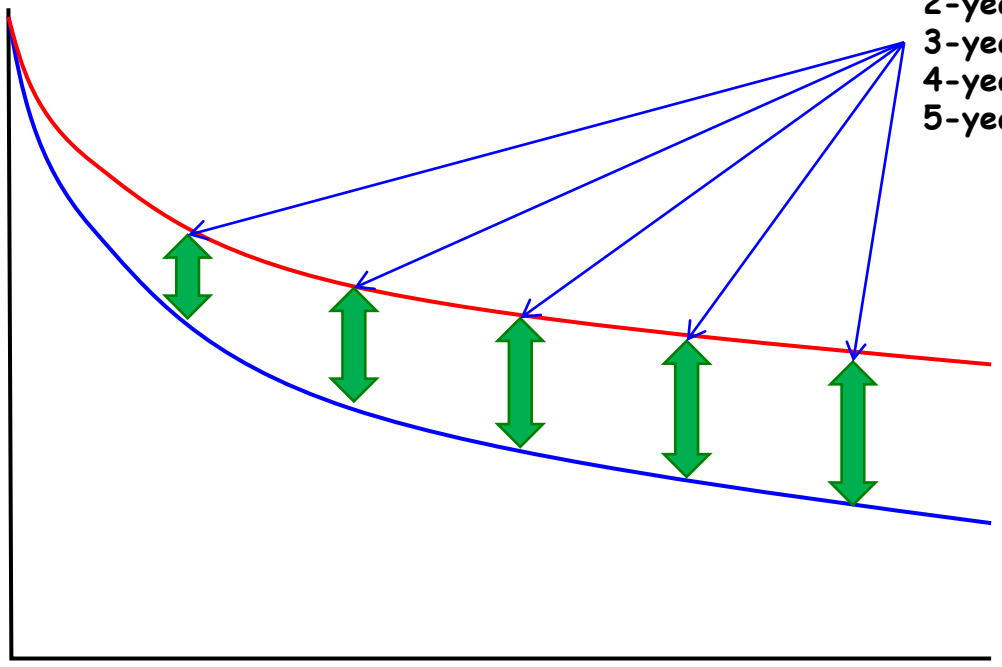
Per-protocol analysis



Bias is introduced into the treatment selection procedure after randomization and comparability is lost

Phase III Trial: Comparison Of Survival Time

Log-rank test is commonly used



1-year survival rate
2-year survival rate
3-year survival rate
4-year survival rate
5-year survival rate

These are not being compared

↓

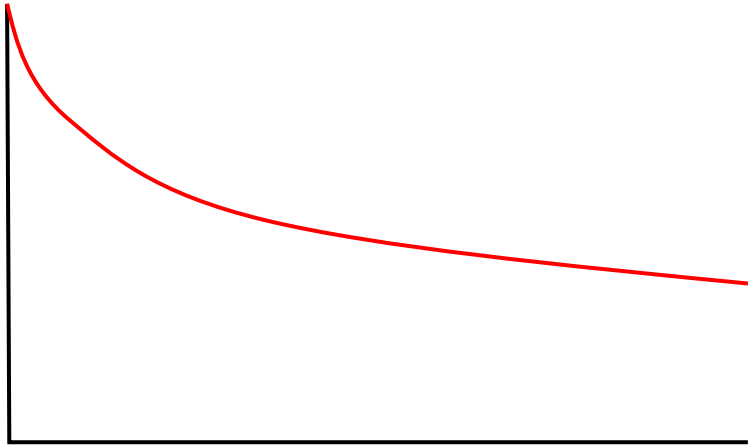
Calculated by totalling the difference between the "number of observed events" and "number of expected events" at all points in time when an event (death) occurred

↓

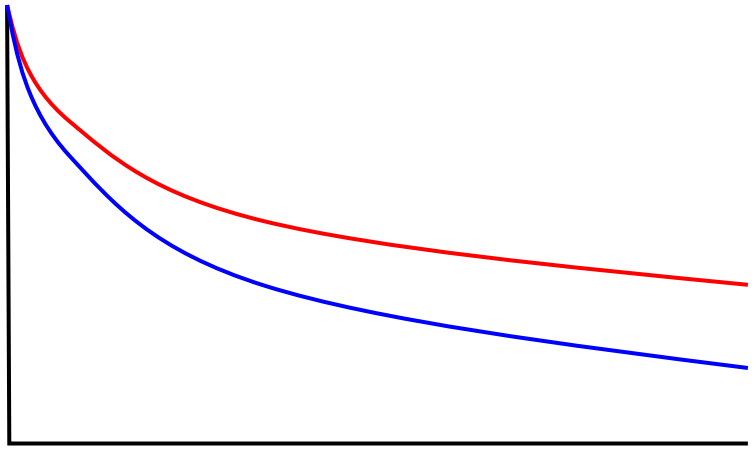
One P-value is obtained by comparing the entire survival curve

Phase III Trial: Sample Size Calculation Assumptions

- Exponential distribution/exponential curve
  - Instantaneous mortality rate is constant regardless of time
  - Slope eases smoothly
  - Once the instantaneous mortality rate and starting point are decided, the curve is uniquely decided

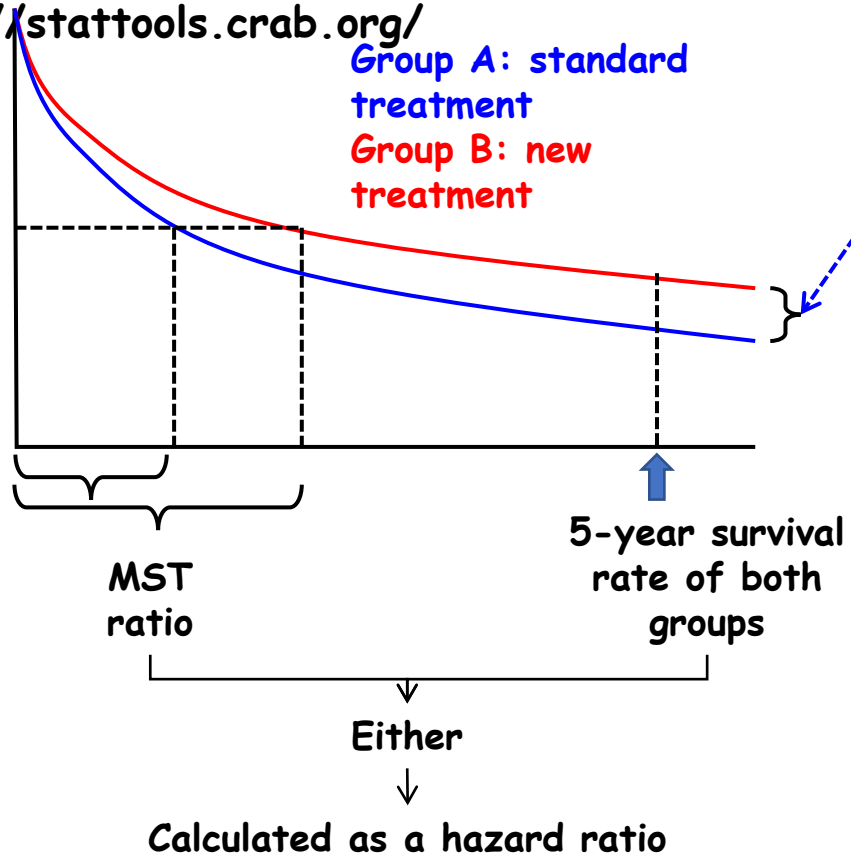


- Assuming a constant hazard ratio
  - Ratio of instantaneous mortality rate between groups is constant
  - "Slope ratio" of both curves is constant
  - Gap between both groups widens smoothly



Phase III Trial: Setting The Sample Size (Superiority Trial)

- Assuming an exponential distribution, calculate the number of events required for testing and number of registered cases required to obtain that number of events
- Website for calculating the sample size (SWOG)
- https://stattools.crab.org/



- Standard treatment data
  - ● Annual survival rate or MST
- "Difference" you want to detect
  - Clinically significant difference
  - "When the difference is smaller than this, the new treatment is ineffective, and the standard treatment remains"
  - Δ% difference in ● annual survival rate
  - ● Months difference in MST
- Significance level (α error)
  - Risk of mistakenly judging a new treatment as effective, when it is actually ineffective
  - Normally 5% or 2.5% one-sided
- Power (1−β)
  - Probability of correctly judging that a new treatment is effective, when it is actually effective
  - Normally 80–90%
- Registration period/follow-up period
  - Ability to accumulate from past registration results
  - When should the decision be made?

Phase III Trial: Multiplicity

- Conducting comparisons multiple times increases the possibility of finding differences
  - Many tests, many endpoints, many subgroups
- Number of comparisons (tests) and probability of obtaining a "significant difference $p < 0.05$"
  - Conducting tests with a significance level of 5% based on a null hypothesis (no difference):

Number of comparisons	Probability of a "significant difference $p < 0.05$" appearing (%)
1	5.0
2	9.7
3	14.3
4	18.5
5	22.6
10	40.0
20	64.1

- Concluding that a treatment is effective when $p < 0.05$ is found in one analysis of 20 subgroups also means that "there is probability of 2/3 (64%) of making an incorrect judgment"

Phase III Trial: Interpretation When There Is A Significant Difference

- There are two types of test results

- A significant difference was observed ($p < 0.05$)
  - Difference due to causes other than the treatment
    - There were more people with good prognosis in the investigational treatment group
  - The difference was a coincidence…a error
  - There was a difference in the therapeutic effect

- No significant difference was observed ($p > 0.05$)
  - Difference was hidden by factors other than the treatment
    - There were more people with poor prognosis in the investigational treatment group, i.e., the results were distorted
  - There was a real difference, but it was concealed by error…β error
  - There was no difference in the therapeutic effect

Phase III Trial: Interpretation When There Is A Significant Difference

- There are two types of test results

- A significant difference was observed ($p < 0.05$)
  - ~~Difference due to causes other than the treatment~~
    - ~~There were more people with good prognosis in the investigational treatment group~~
  - ~~The difference appeared as a coincidence…a error~~
  - There was a difference in the therapeutic effect

- No significant difference was observed ($p > 0.05$)
  - ~~Difference was hidden by factors other than the treatment~~
    - ~~There were more people with poor prognosis in the investigational treatment group, distorting the results~~
  - ~~There was a real difference, but it was concealed by error…β error~~
  - There was no difference in the therapeutic effect

- Reliable conclusions are obtained by managing the study design and data

Bias
Minimize with randomization

Random error
Minimize with adequate sample size

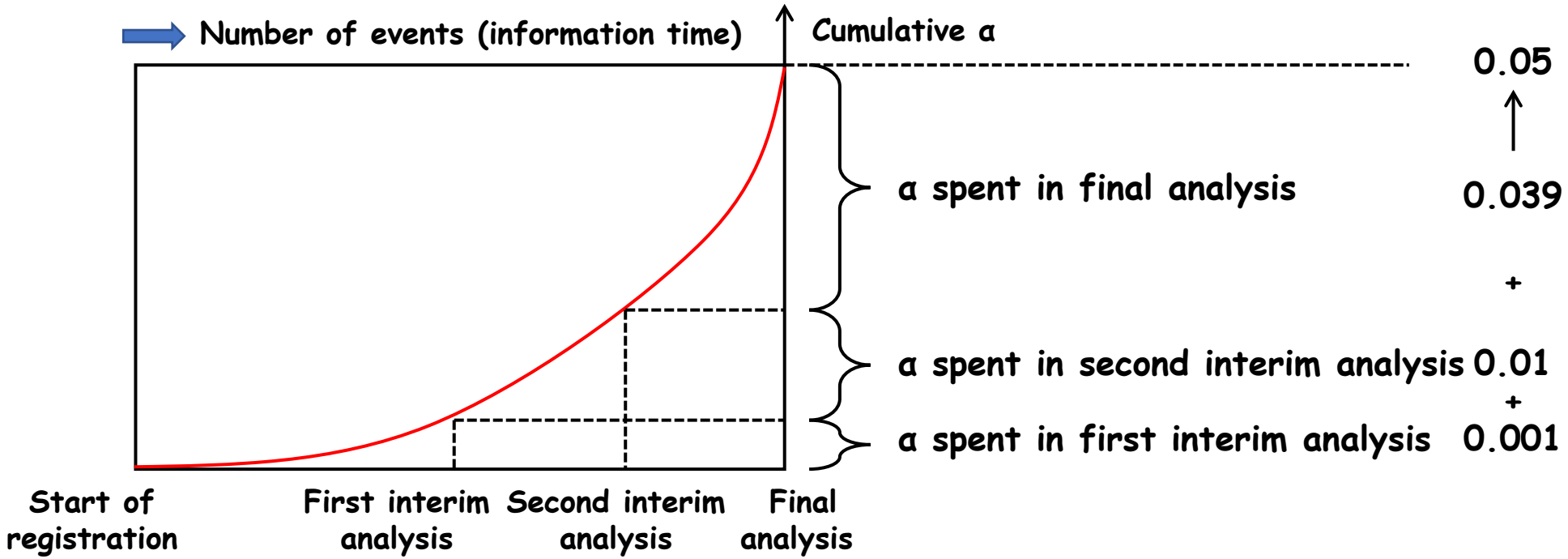
Phase III Trial: Dealing With Multiplicity

- Use only pre-declared analysis for judgment
  - Only subgroup analysis decided on initially is used for the conclusion
  - Ad hoc (hindsight) analyses are all "exploratory" → Confirm in a separate trial/with different subjects

- Multiplicity adjustment
  - Bonferroni correction: α = divide 0.05 by the number of comparisons
    - 10 subgroup analyses: $p < 0.005$ is considered "significant"
  - Alpha-spending function (α-spending function, Lan & DeMets)
    - Time-series multiplicity in survival time analysis (time-to-event analysis)

Phase III Trial: Interim Analysis

- Multiplicity considerations: Keep α error at 0.05 throughout the trial
  - Do not perform multiple evaluations needlessly, small number of pre-determined interim analyses
  - Time-series multiplicity adjustment: α-spending function (alpha-spending function)



- Only an independent data monitoring committee (third party) views the results
  - If researchers are cognizant of this information, it affects case registration and treatment

Phase III Trial: Summary

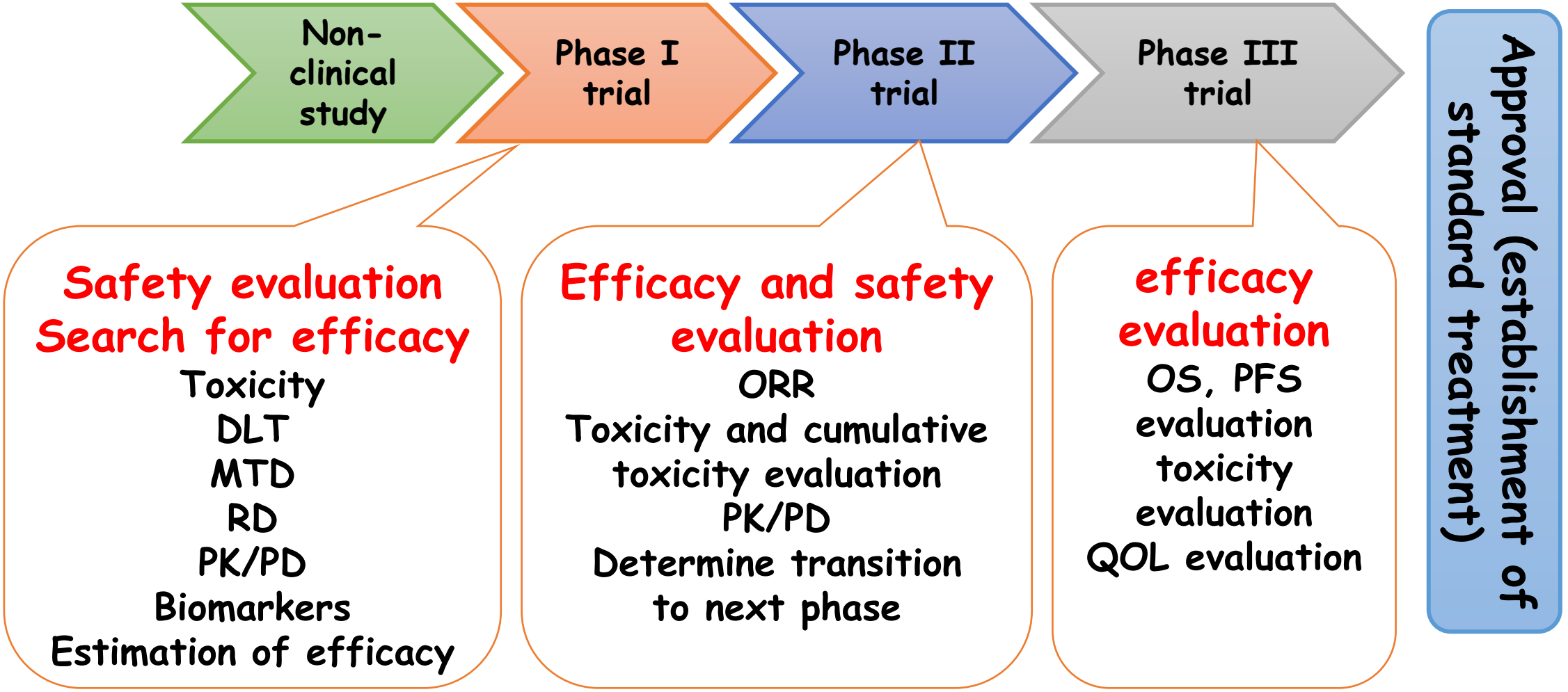
- Confirmatory trial to determine standard treatment by randomly comparing new treatments with standard treatments
- Random allocation
  - Stratification using minimization (dynamic allocation) is common in oncology
- Survival
  - Compare the entire survival curve (log-rank test)
  - Intention-to-treat analysis
  - Superiority trial, non-inferiority trial
- Required parameters for calculating the sample size
  - Standard treatment data, clinically significant differences, α, β, registration period, follow-up period
  - https://stattools.crab.org/
  - Adjustment of multiplicity is necessary
- Interim analysis
  - Do not stop unless a large difference is observed
  - The researchers do not view the results

Anticancer Drug Development

Recent Trends

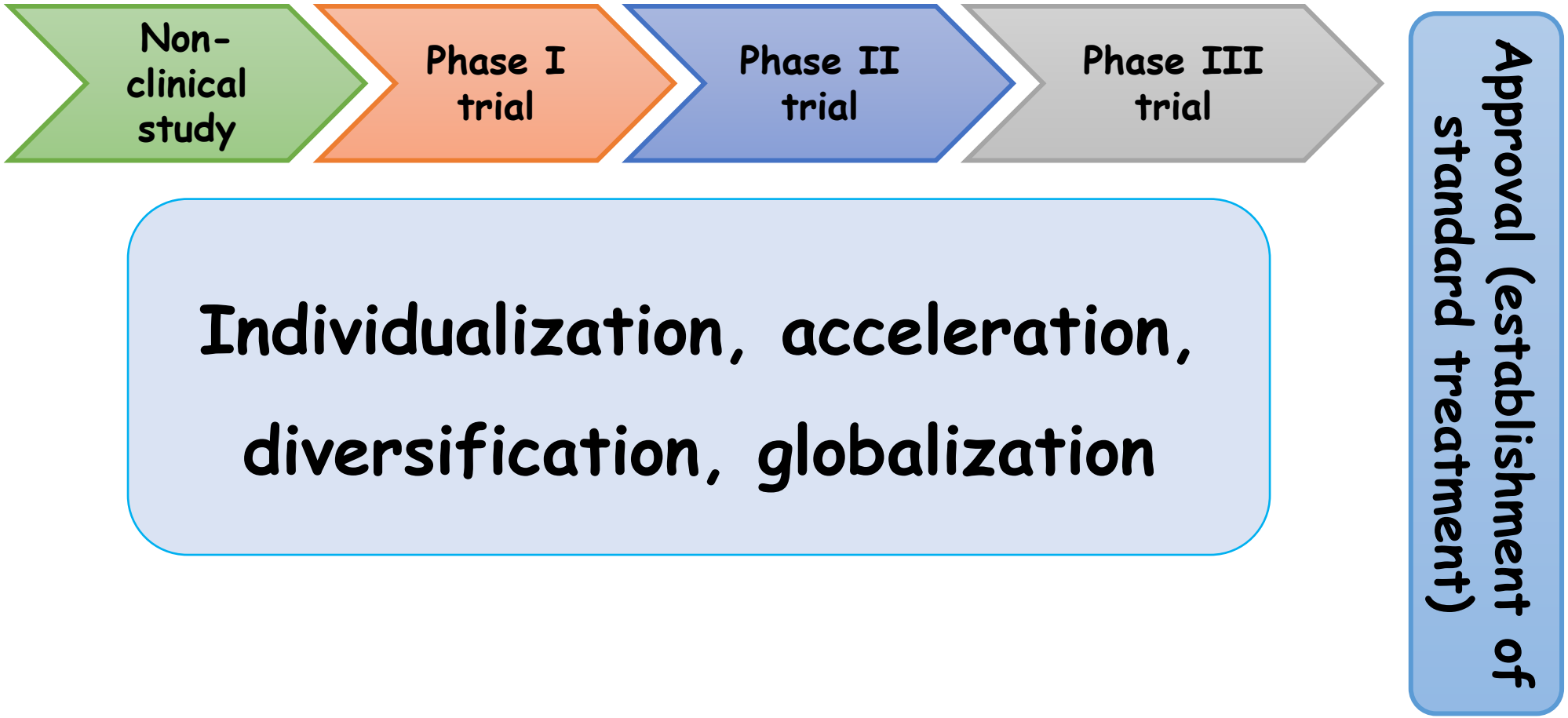
Anticancer Drug Development Process

- From non-clinical study to clinical trial (Phase I→Phase II→Phase III)



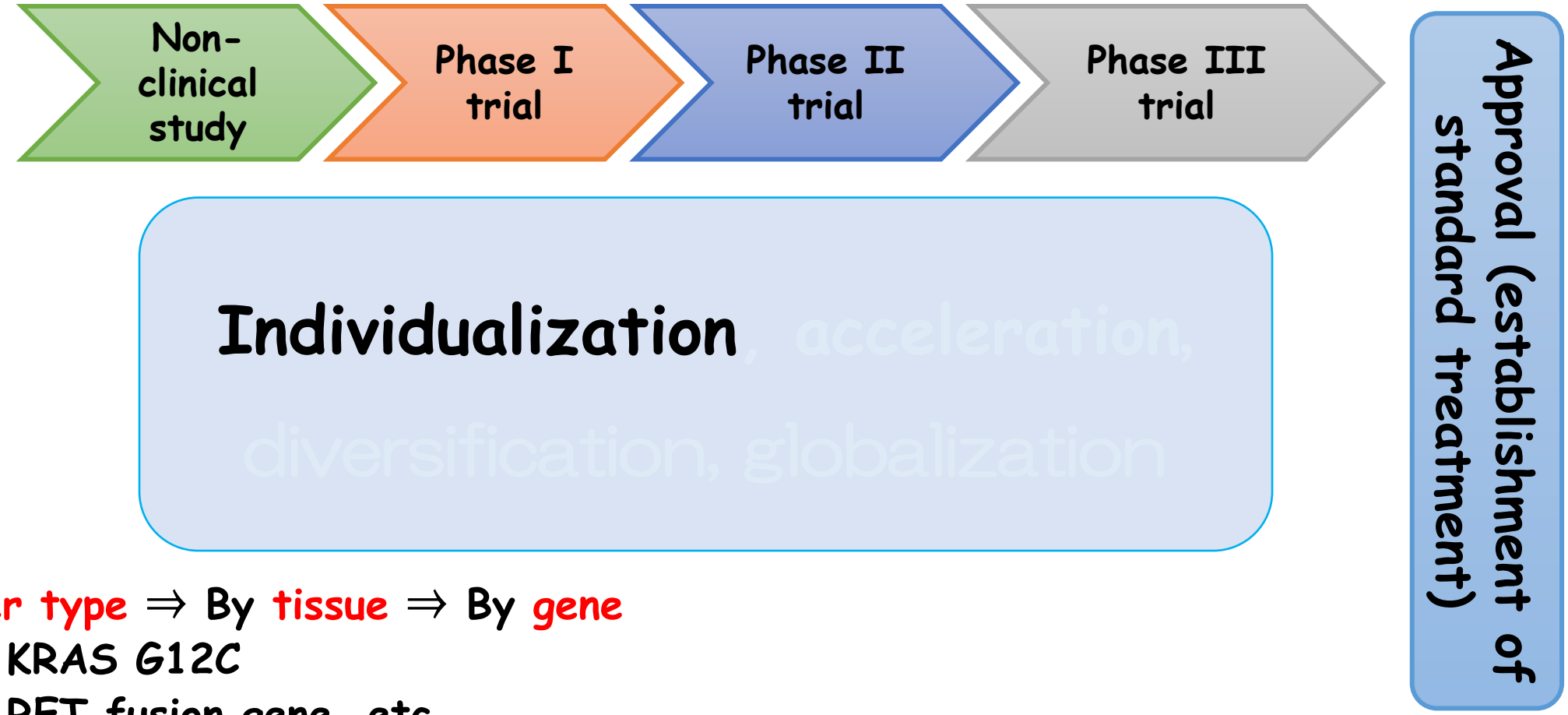
Recent Trends In Anticancer Drug Development

- From non-clinical study to clinical trial (Phase I→Phase II→Phase III)



Recent Trends In Anticancer Drug Development

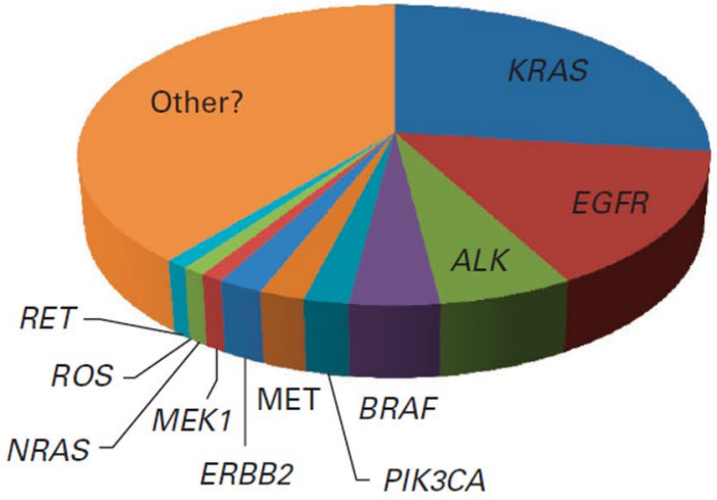
- From non-clinical study to clinical trial (Phase I→Phase II→Phase III)



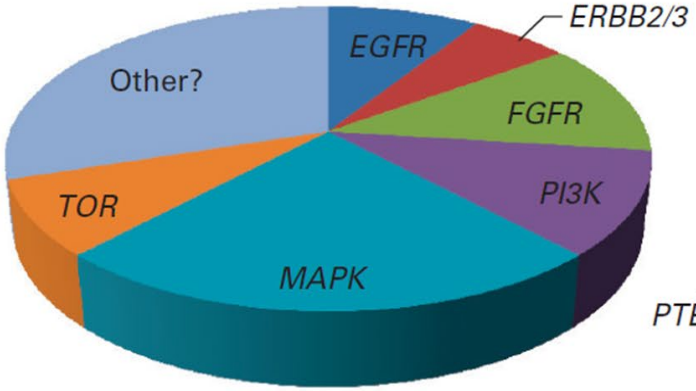
- By cancer type ⇒ By tissue ⇒ By gene
  - Only KRAS G12C
  - Only RET fusion gene, etc.

Gene Profiling For Solid Tumors In General

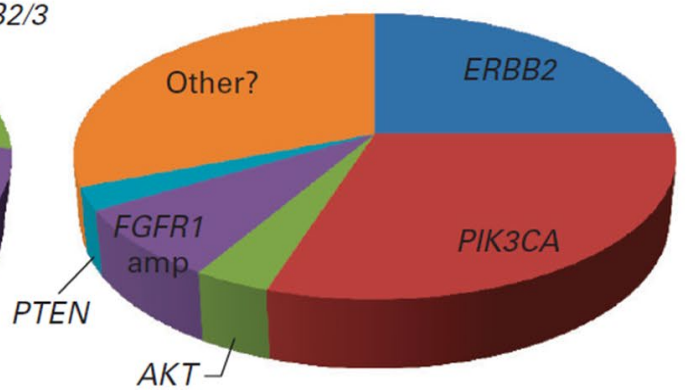
Lung adenocarcinoma



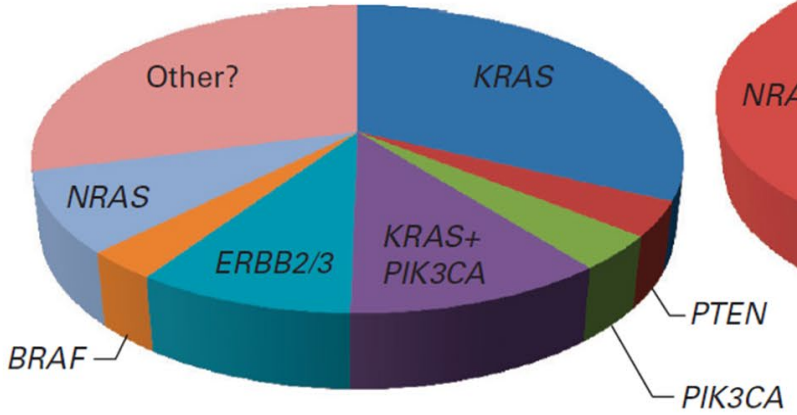
Lung squamous cell carcinoma



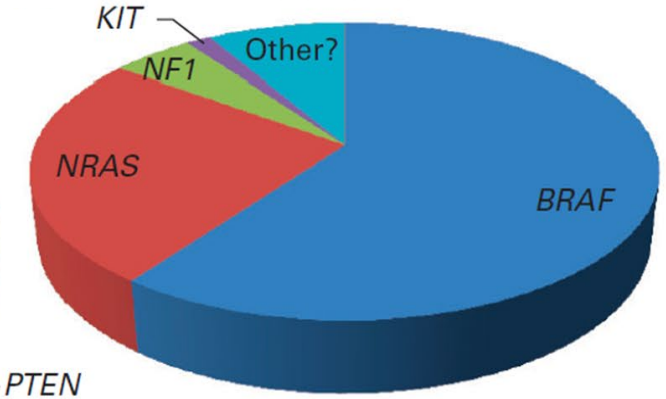
Breast cancer



Colorectal cancer

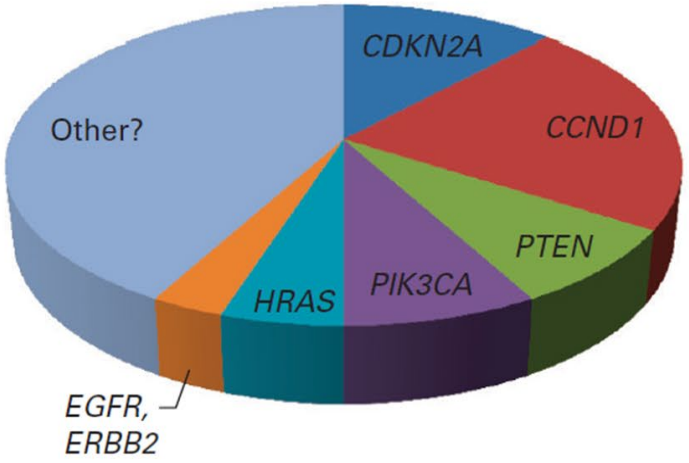


Melanoma



(*PTEN* and *CDKN2A* are frequently inactivated)

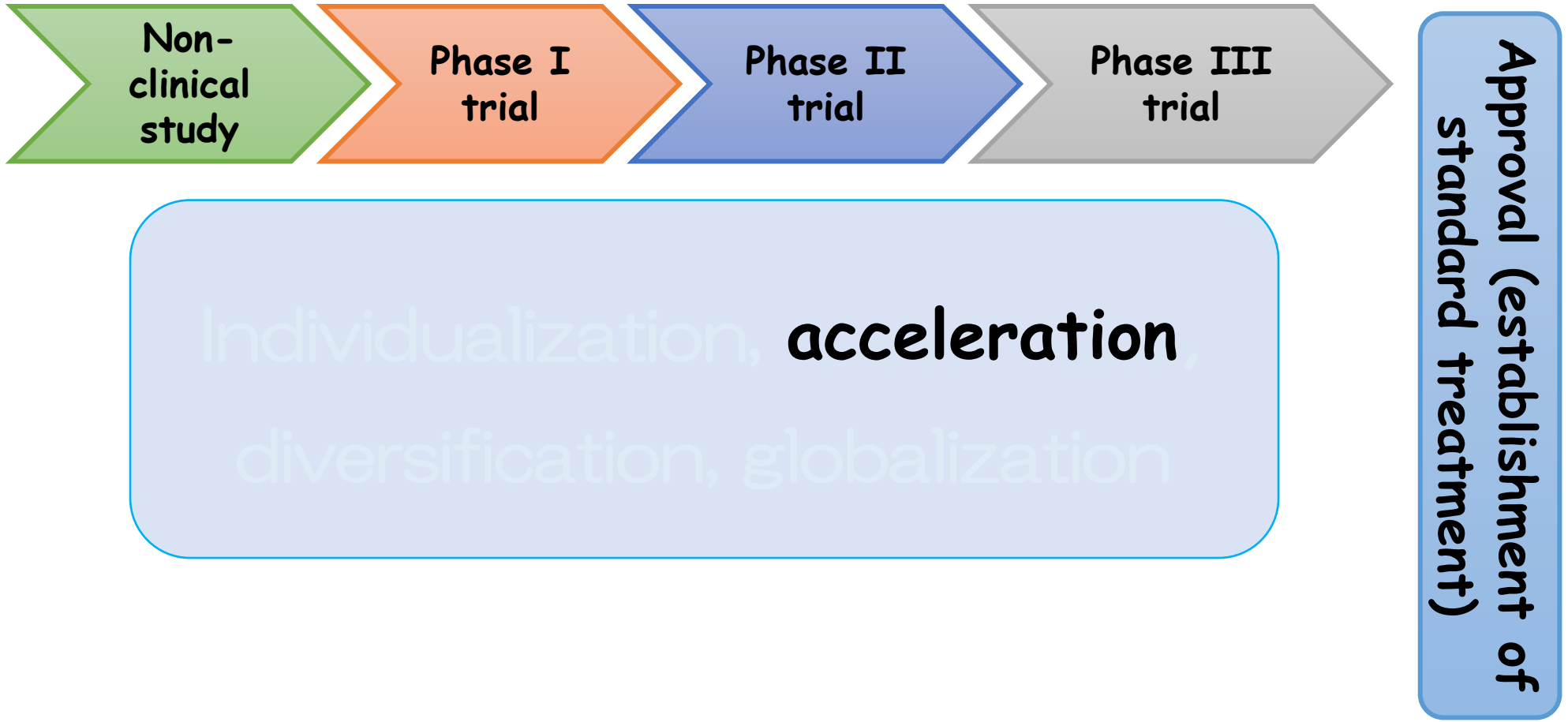
Head and Neck cancer



(J Clin Oncol 31: 1806-1814, 2013)

Recent Trends In Anticancer Drug Development

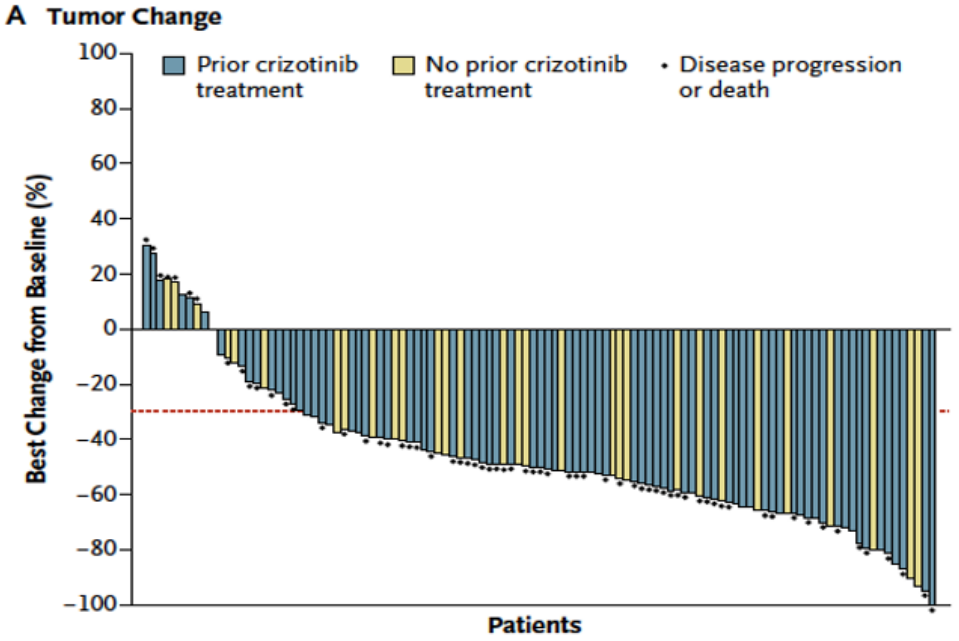
- From non-clinical study to clinical trial (Phase I→Phase II→Phase III)

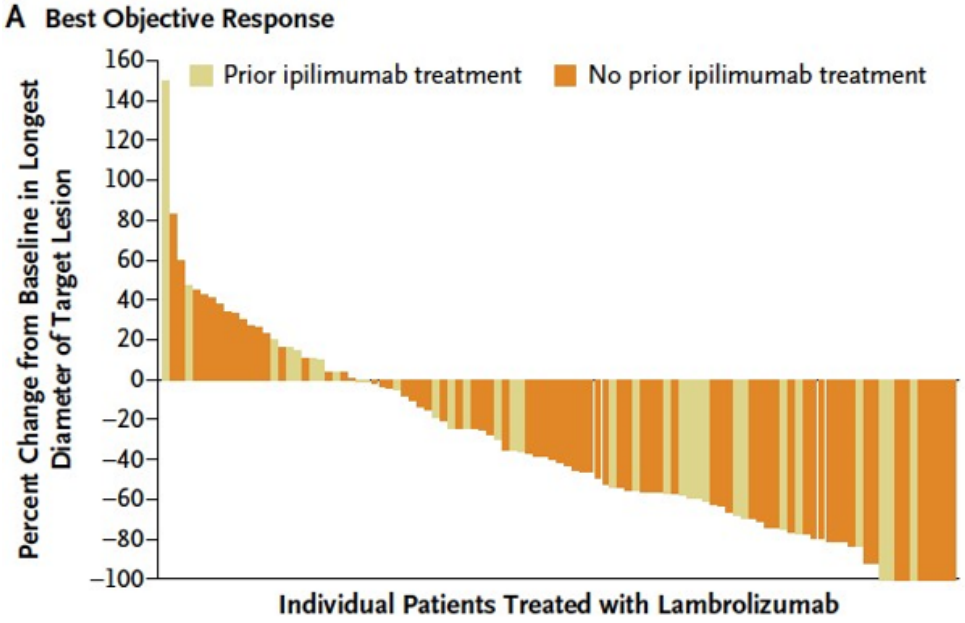


US: Accelerated Approval

- The accelerated approval system has further shortened the time from development to approval in the US

Drug	Phase I to approval by FDA	Time (years)
Pembrolizumab (Keytruda)	February 2011 to September 2014	3.6 yrs.
Ceritinib (Zykadia)	January 2011 to April 2014	3.3 yrs.



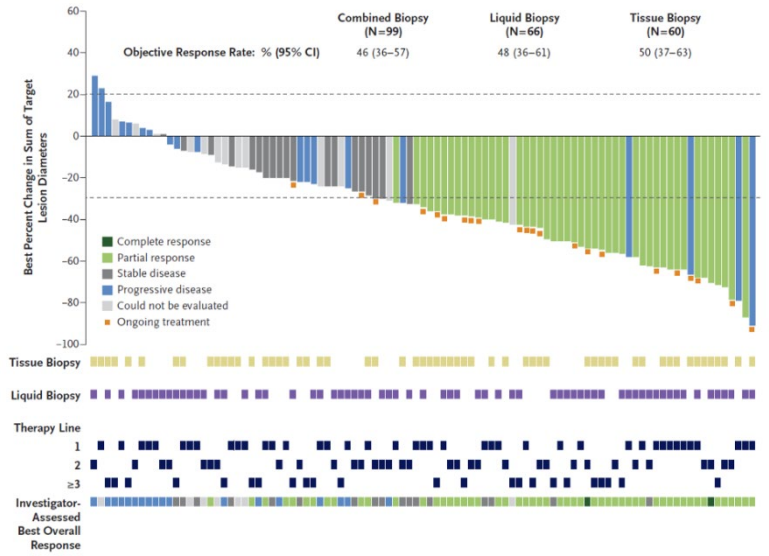


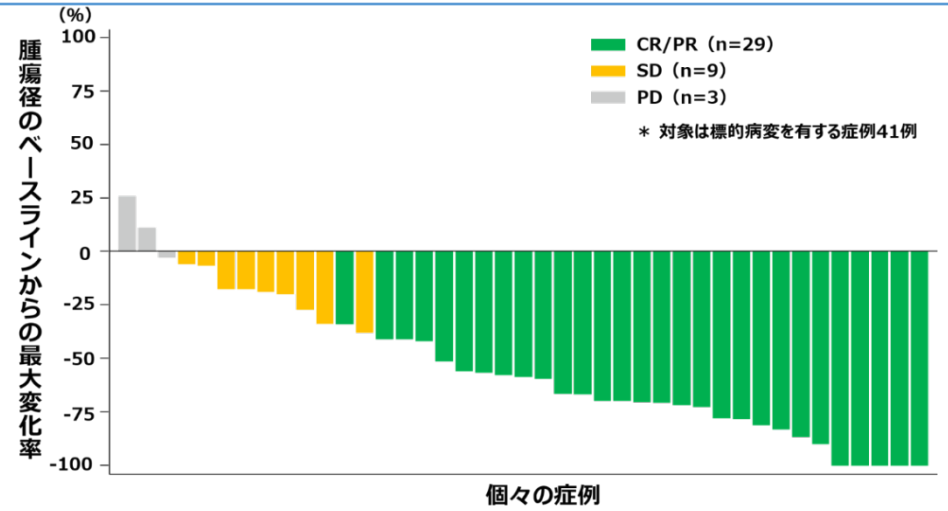
(N Engl J Med 369: 134-144, 2013, N Engl J Med 370: 1189-1197, 2014)

Japan: Approval Example Under The *Sakigake* Designation System

- Shortening the time from application to approval using the Sakigake designation system

Drug	Target disease	Application to approval
Tepotinib (Tepmetko)	Unresectable advanced/recurrent non-small cell lung cancer positive for MET gene exon 14 skipping mutation	3.5 months
Entrectinib (Rozlytrek)	Advanced/recurrent NTRK fusion-positive solid tumors	5.4 months





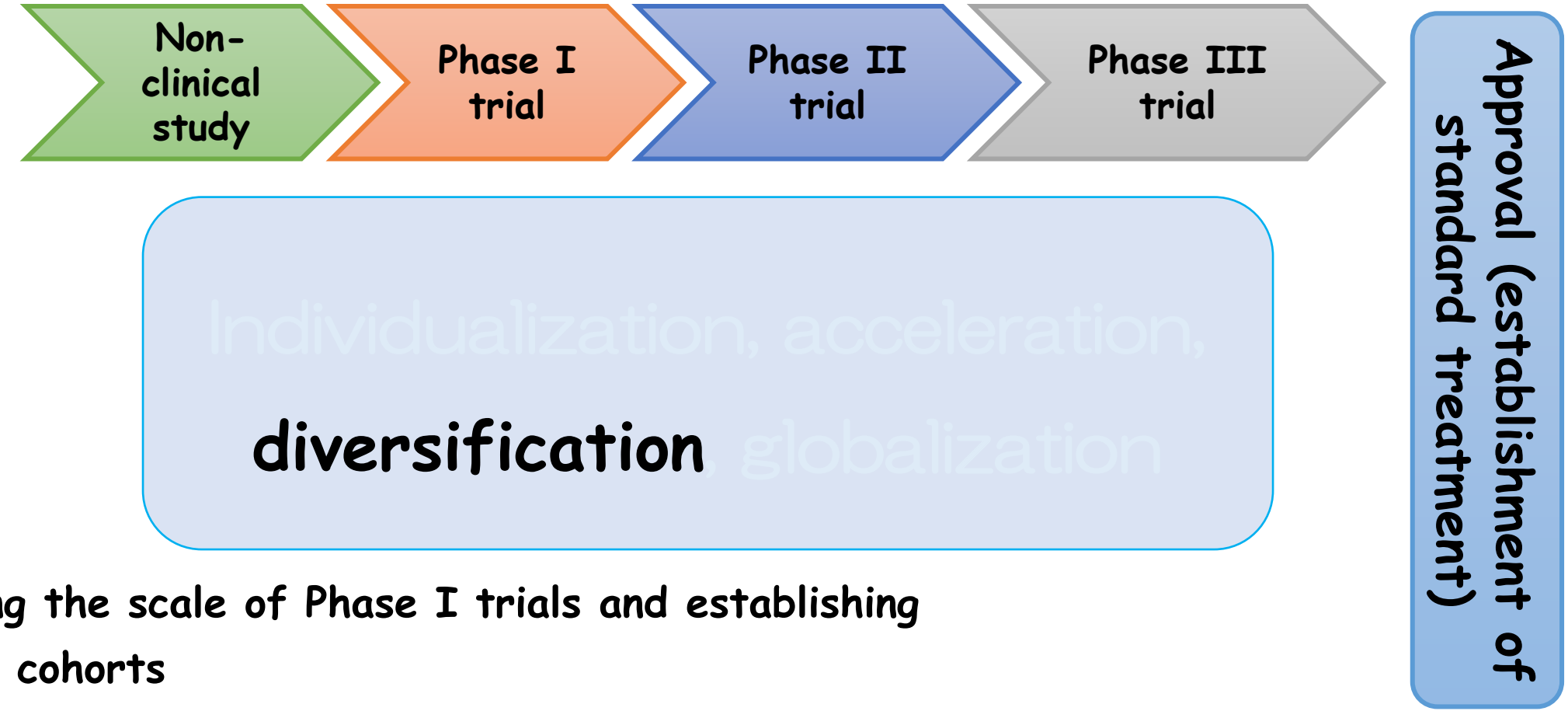
(STARTRK-2 study, N Engl J Med 383: 931-943, 2020)

Reference: Special Regulatory Measures (Japan, Europe, US)

Country/Region	Special regulatory measures
Japan	Priority Review Accelerated Review Orphan Sakigake Designation System Conditional Early Approval System
US	Priority Review Accelerated Approval Orphan Fast Track Breakthrough Therapy
Europe	Accelerated Assessment Orphan Conditional Approval Exceptional Circumstances PRIME

Recent Trends In Anticancer Drug Development

- From non-clinical study to clinical trial (Phase I→Phase II→Phase III)

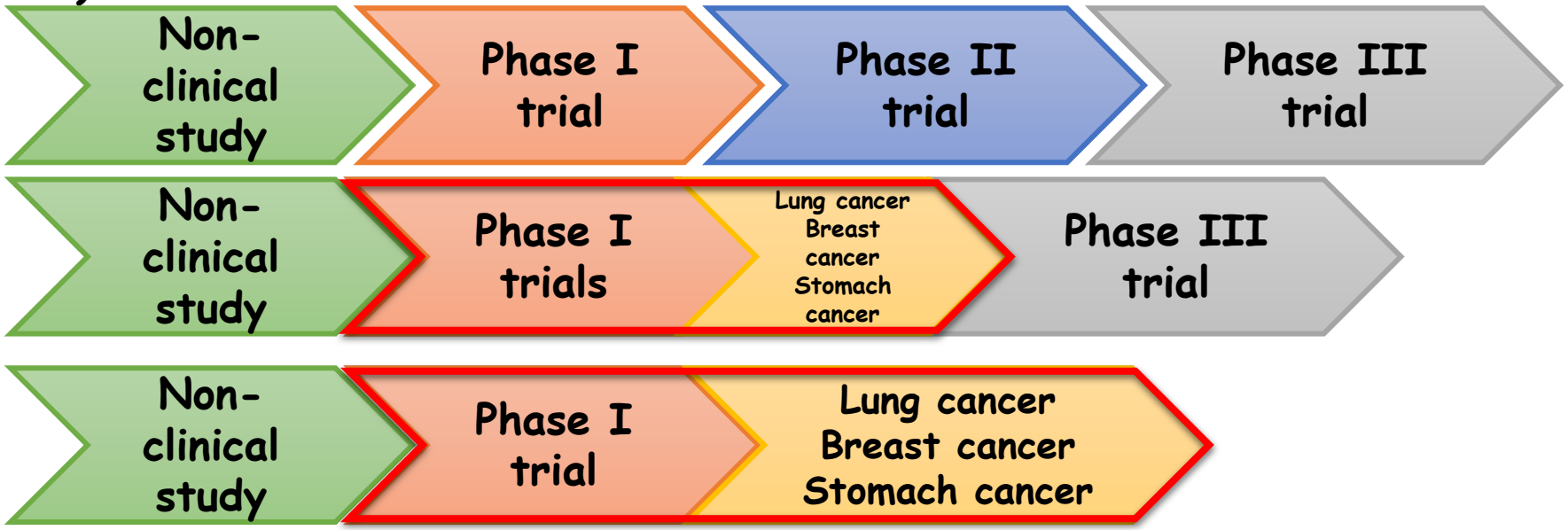


- Expanding the scale of Phase I trials and establishing expansion cohorts
- Frequent protocol amendments

Diversification Of Anticancer Drug Development

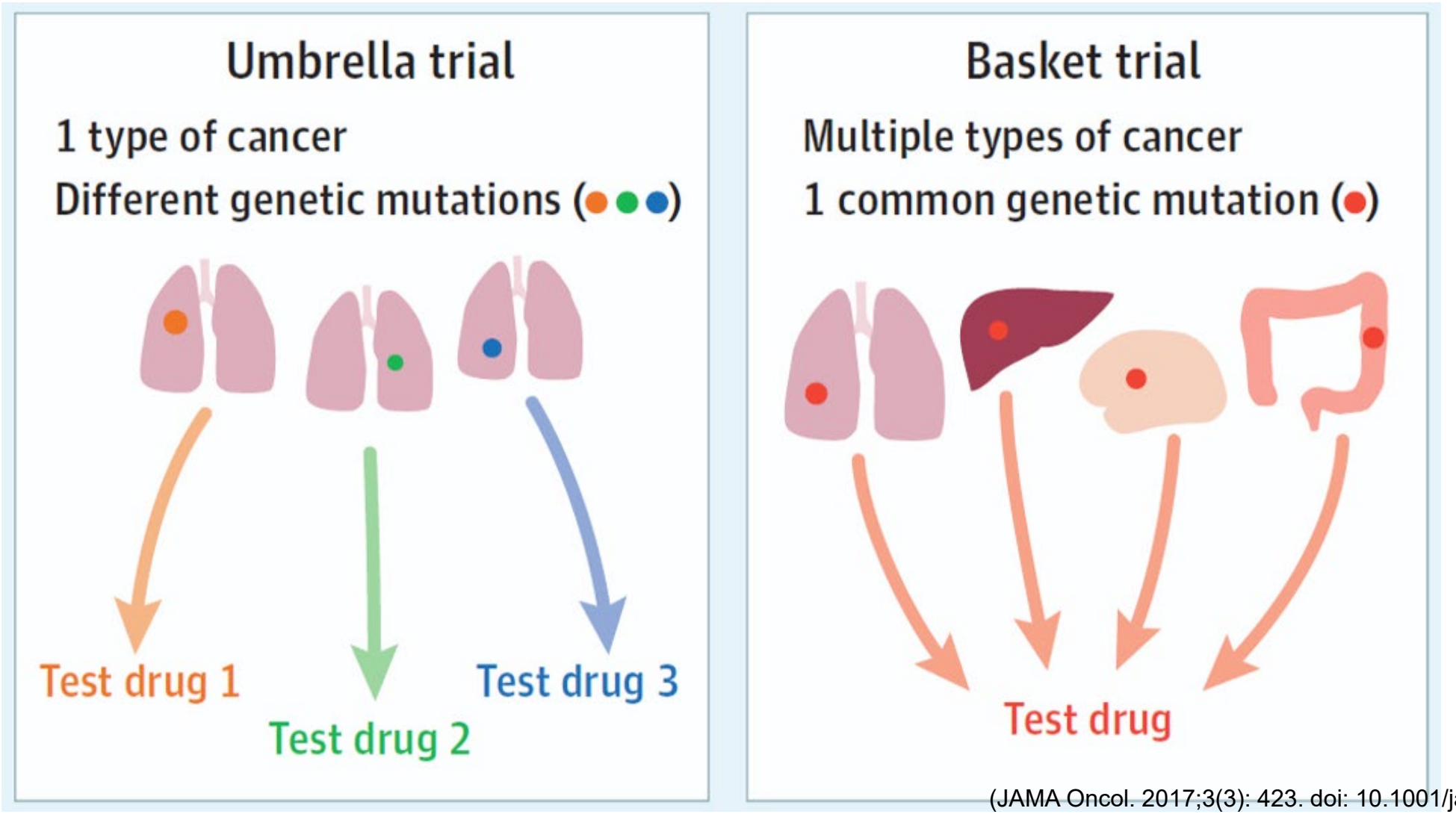
- Previous anticancer drug development: Phase I→Phase II→Phase III

- Recent trends
  - Establishing expansion cohorts…Incorporating efficacy exploratory component in Phase I trials
  - Enlarging the scale of Phase I trials and applying for approval as-is (skipping Phase III)



Diversification Of Anticancer Drug Development

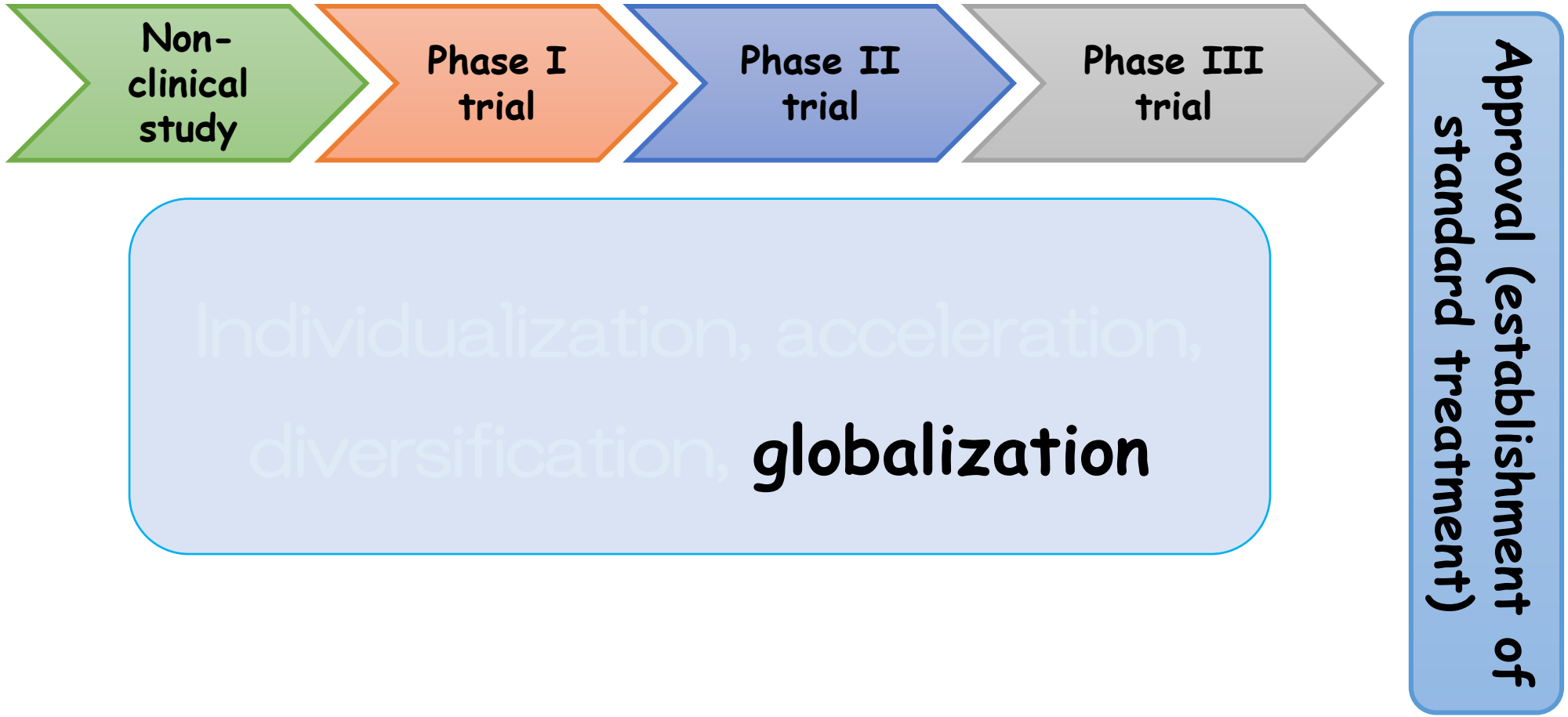
- Increase in basket trials, umbrella trials



(JAMA Oncol. 2017;3(3): 423. doi: 10.1001/jamaoncol.2016.5299)

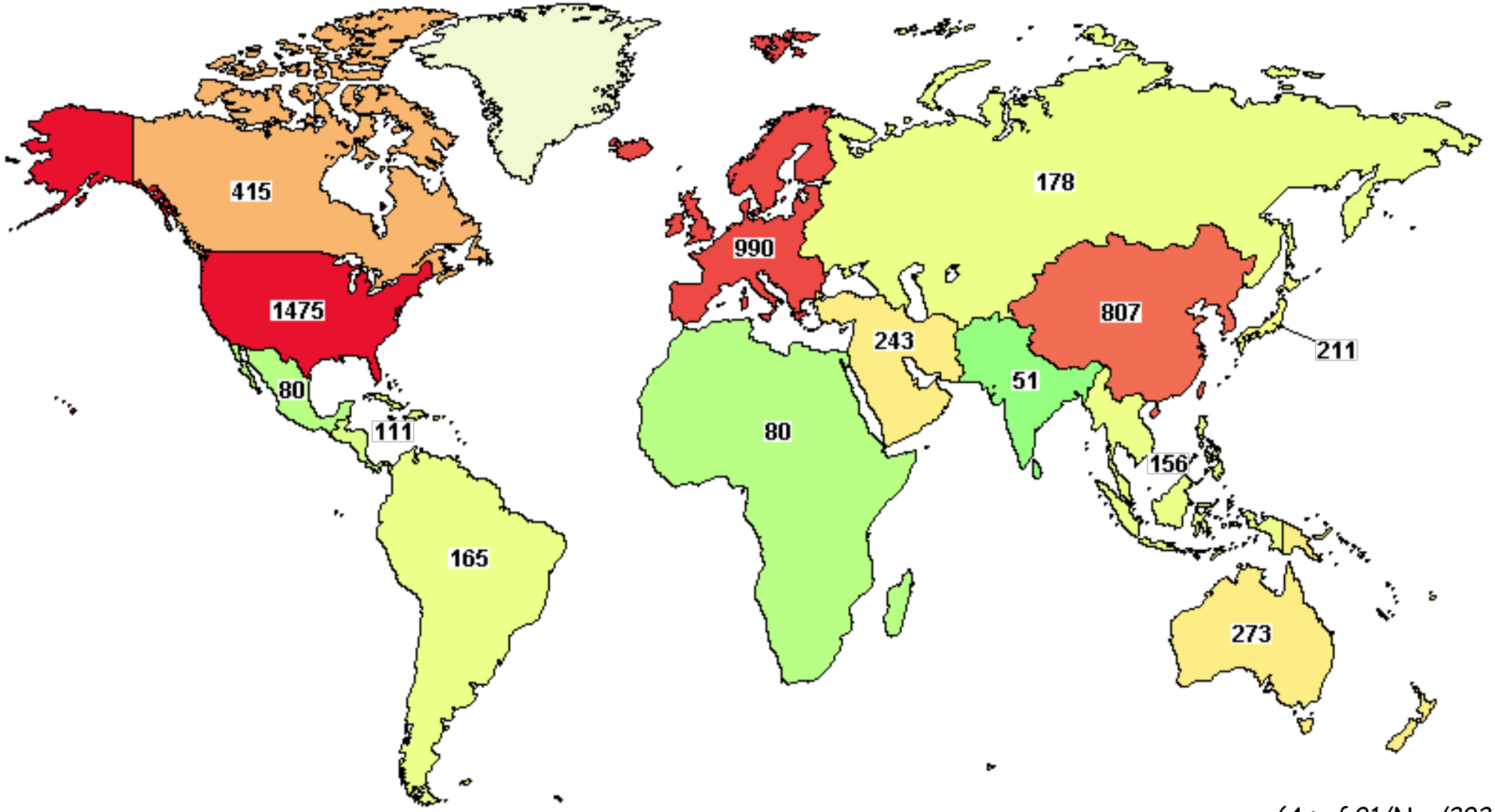
Recent Trends In Anticancer Drug Development

- From non-clinical study to clinical trial (Phase I→Phase II→Phase III)



Anticancer Drug Development: International Joint Study Is The Standard

3040 studies found for: **global, oncology | Recruiting, Not yet recruiting Studies | Interventional Studies**



(As of 01/Nov/2021. ClinialTrials.gov)

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Contents

- Overview of clinical studies and clinical trials
- Phase I trial
- Phase II trial
- Phase III trial
- Recent trends in anticancer drug development