towards high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course: CRC Training Course

Lecture Title: Support for Phase 1 Cancer Clinical Trials

Speaker: Tomomi Tsuchiya

Tomomi Tsuchiya

Clinical Research Coordinator at the Clinical Trial Support Office
National Cancer Center Hospital

■ Work Experience
- 2013–present National Cancer Center Hospital

■ Qualification
- Pharmacist

Support for Phase 1 Cancer Clinical Trials

Content of today's lecture

- ✓Phase 1 Trials in Cancer Clinical Trials
- ✓Preparation for Starting Clinical Trials
- ✓Administration of Study Drug
- ✓Summary

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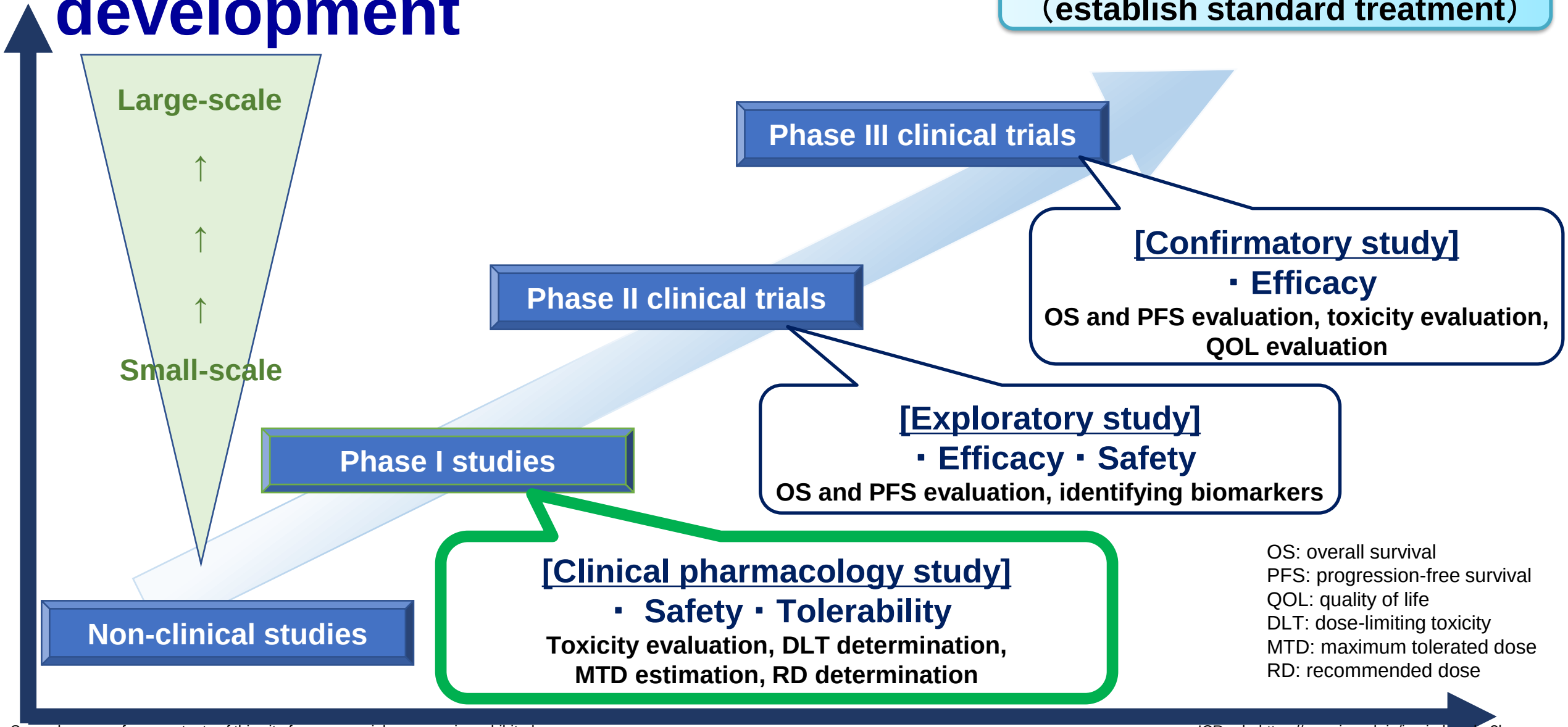
Stages of anticancer drug development



OS: overall survival
PFS: progression-free survival
QOL: quality of life
DLT: dose-limiting toxicity
MTD: maximum tolerated dose
RD: recommended dose

Target patients in Phase I studies

① Patients with cancer are the trial participants (general drugs are tested in healthy males)
② No effective/standard treatment
③ Performance status (PS) is maintained
④ Adequate organ function is maintained
⑤ No effect of previous treatment
⑥ Ability to provide consent

Purpose of Phase I studies

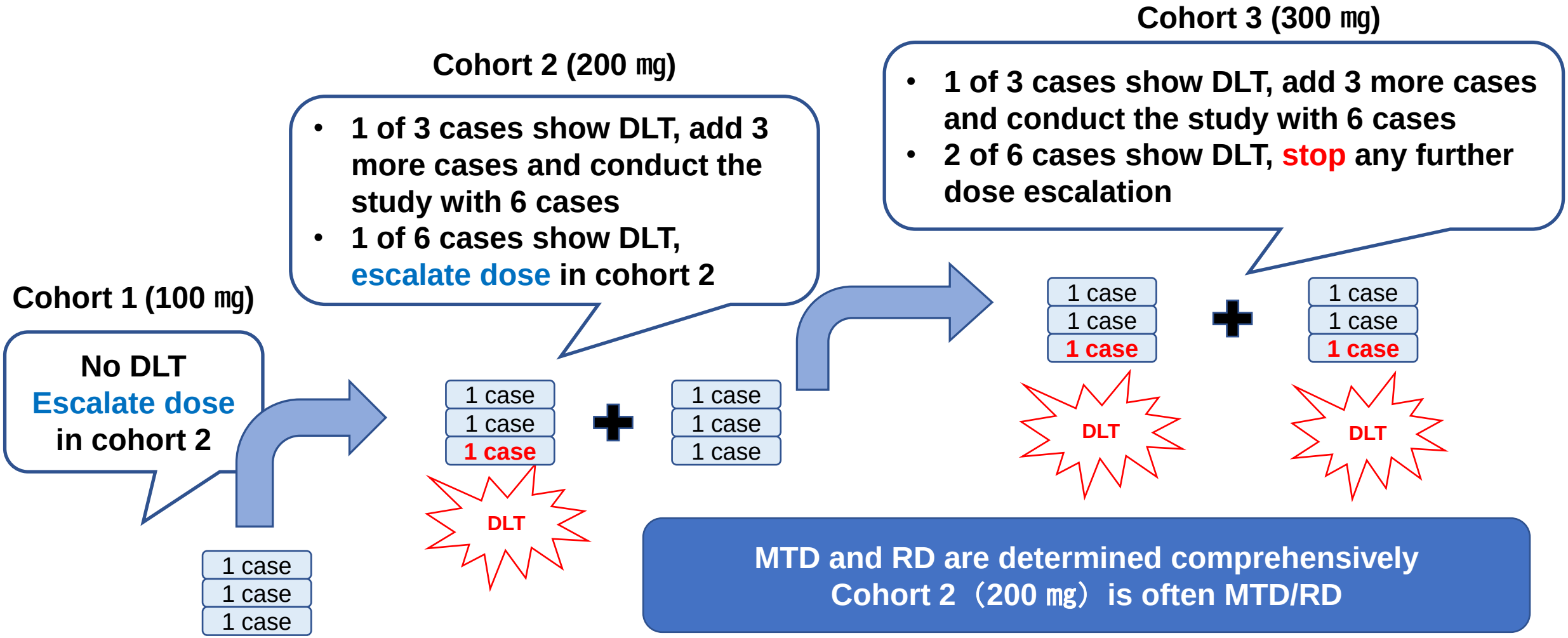
■Purpose

※The primary endpoint of Phase I studies is not the attainment of a therapeutic effect

① Safety evaluation
② Determination of dose-limiting toxicity (DLT)
③ Estimation of maximum tolerated dose（MTD)
④ Determination of recommended dose (RD)
⑤ Pharmacokinetic study (pharmacokinetic/pharmacodynamic)
⑥ Determination of dosing method
⑦ Investigation of biomarkers

Phase I study methods（3+3 design）

～Dose-escalation study with toxicity as an index～



DLT evaluation

- DLT: dose limiting toxicity
- Patients: Participants who completed the DLT evaluation period after starting administration of the study drug
- Evaluation period: Up to completion of the first dose (course 1)
- Definition: Adverse events considered as possibly being related to the study drug that occur at any time during the evaluation period as specified in the protocol.

[General DLT criteria（based on NCI-CTCAE）]

- Grade 4 hematotoxicity
- Grade 3 non-hematotoxicity
- Nausea, vomiting, anorexia, alopecia（conditions such as transient electrolyte imbalance may be excluded）

DLT evaluation

＜Overall study＞

- Determination of the MTD and RD
- Determination of transition to the next cohort based on the number of patients with DLT

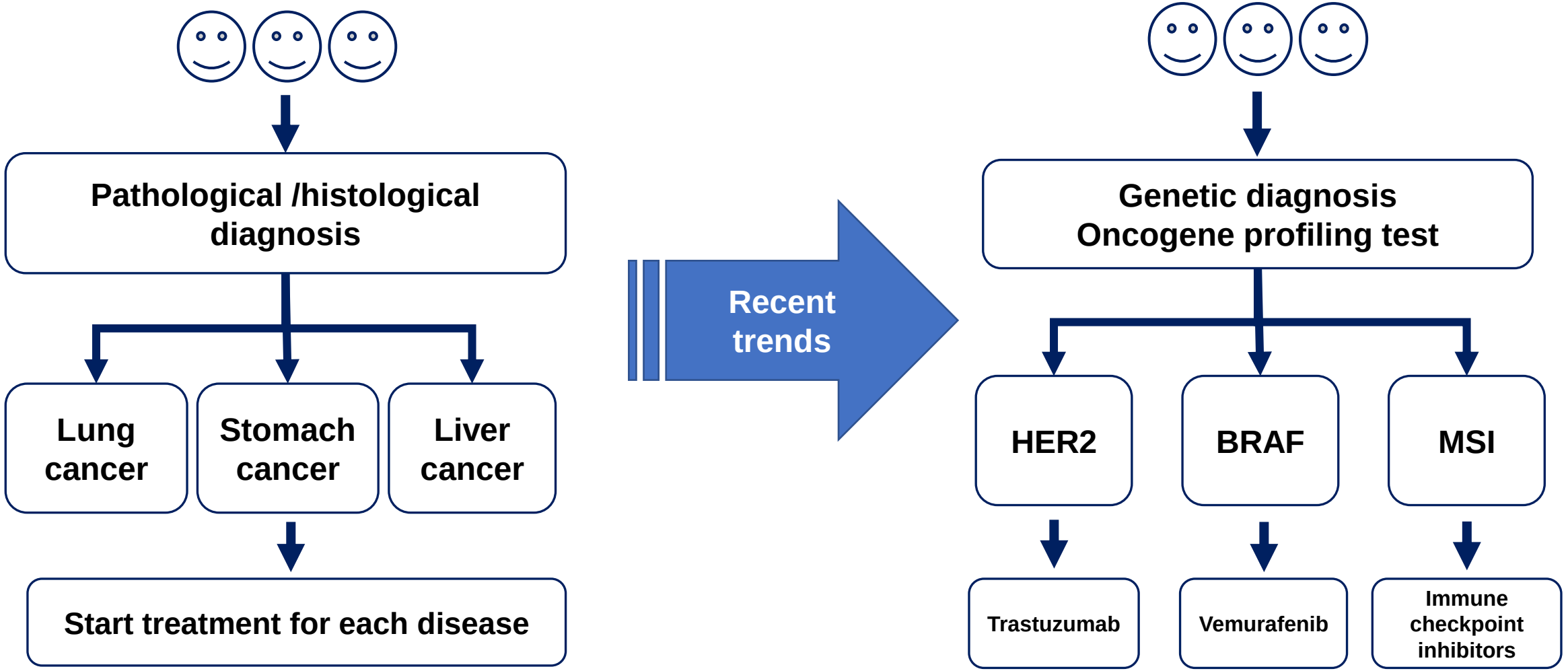
＜Patients＞

- Risk of unknown adverse reactions

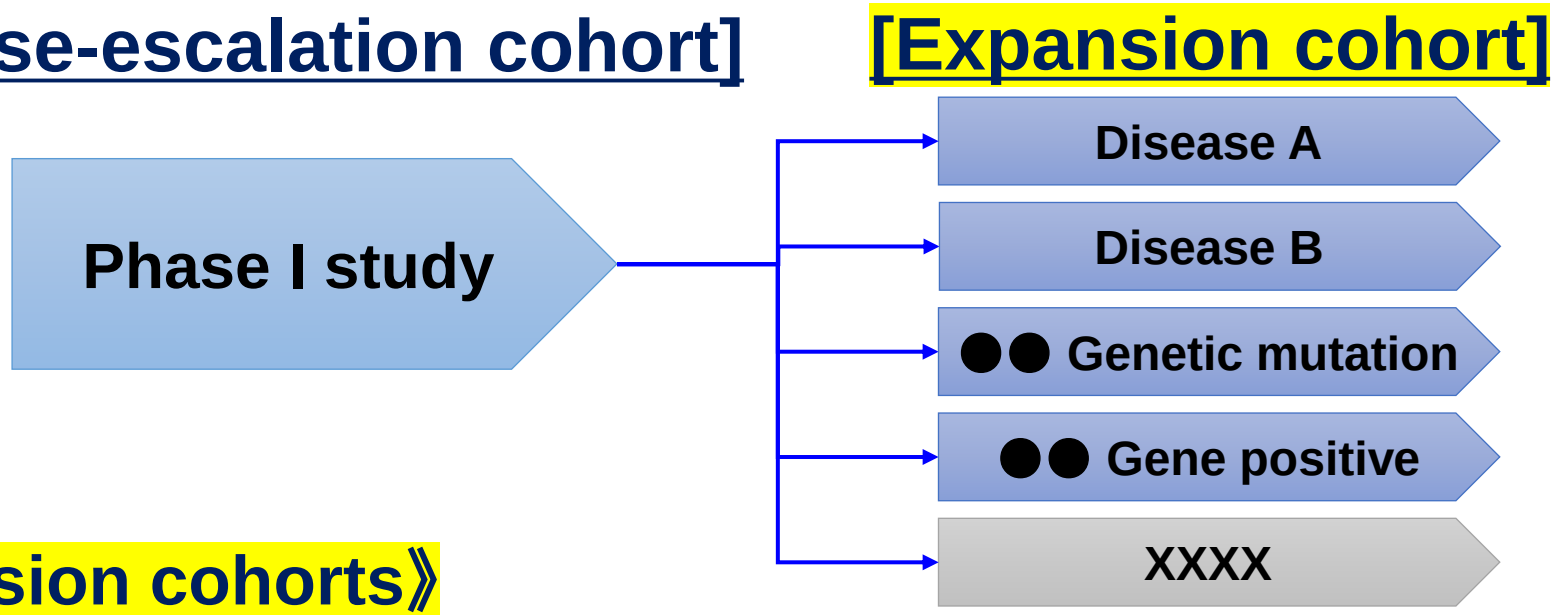
＜Doctor/CRC＞

- Sufficient knowledge and experience in clinical trials

Recent trends in Phase I studies (individualization)



Characteristics of recent protocols



《Setting expansion cohorts》

- Expansion cohorts are set “by disease” or “by genetic mutation”
- If preparations are not made at the new stage, Expansion cohort will not be ready in time

《Frequent protocol revisions》

- Procedures are changed and cohorts are added through protocol revisions rather than as a new protocol
- The inclusion/exclusion criteria, test items and PK points differ for each cohort

PK（Pharmacokinetics）

Importance of PK in Phase 1 studies

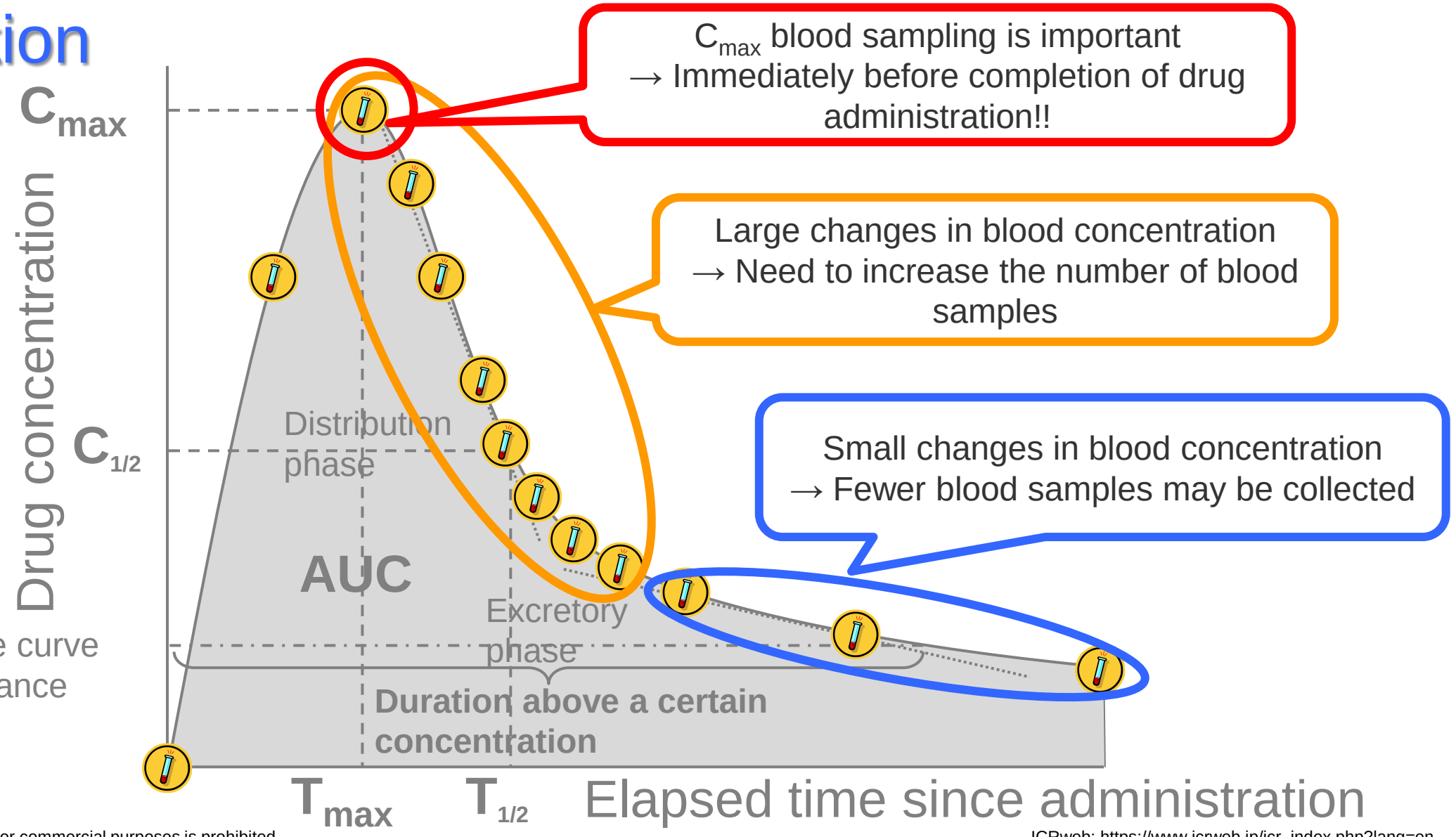
- **Phase 1 information on drugs administered for the first time in humans is fundamental for subsequent drug development**

  （setting dose and dosing method, concomitant use with other drugs, etc.）

- **The only opportunity to observe dose-response starting at a low dose**

  - PK may differ in humans and animals
  - Confirmation of racial differences（Japanese vs. Caucasians）

Measurement of blood drug concentration



AUC
Area under the concentration-time curve
AUC = dose/clearance

PK（worksheet）

[Implementation order] ①VS→②ECG→③PK

Day	schedule time		PK	ECG Loan ECG	Urine collec
C1D1	pre	8：30—9：00	:	☐ 3 times in a row	
	administration 09:00				
	15 min（±5 min）	9:15	:	☐ 3 times in a row	[Urine coll
	30 min（±10 min）	9:30	:	☐ 3 times in a row	① 9：00–15 Urine volu （mL）
	1 h（±10 min）	10:00	:	☐ 3 times in a row	
	2 h（±10 min）	11:00	:	☐ 3 times in a row	② 15：00–21 Urine vol （mL）
	4 h（±10 min）	13:00	:		
	6 h（±10 min）	15:00	:		
	8 h（±60 min）	17:00	:	☐ 1 time only	
	24 h（±60 min）	21:00	:	☐ 1 time only	

VS: vital signs

[In-hospital PK worksheet]

Summarized in one table

- ECG time points
- Order of Vital Signs, ECG, PK
- Other tests

Shared among the ward, clinical laboratory department, CRC

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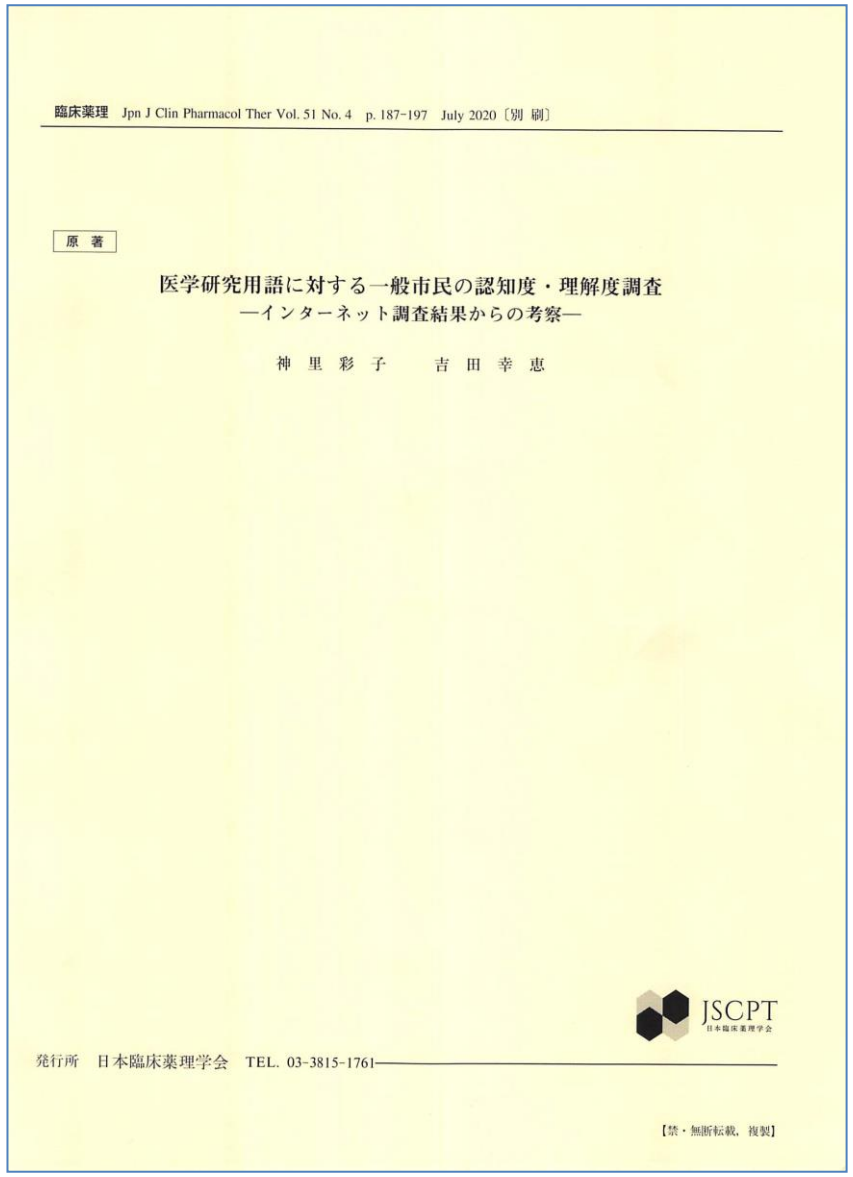

臨床薬理 Jpn J Clin Pharmacol Ther Vol. 51 No. 4 p. 187-197 July 2020〔別 刷〕

原 著

医学研究用語に対する一般市民の認知度・理解度調査
—インターネット調査結果からの考察—

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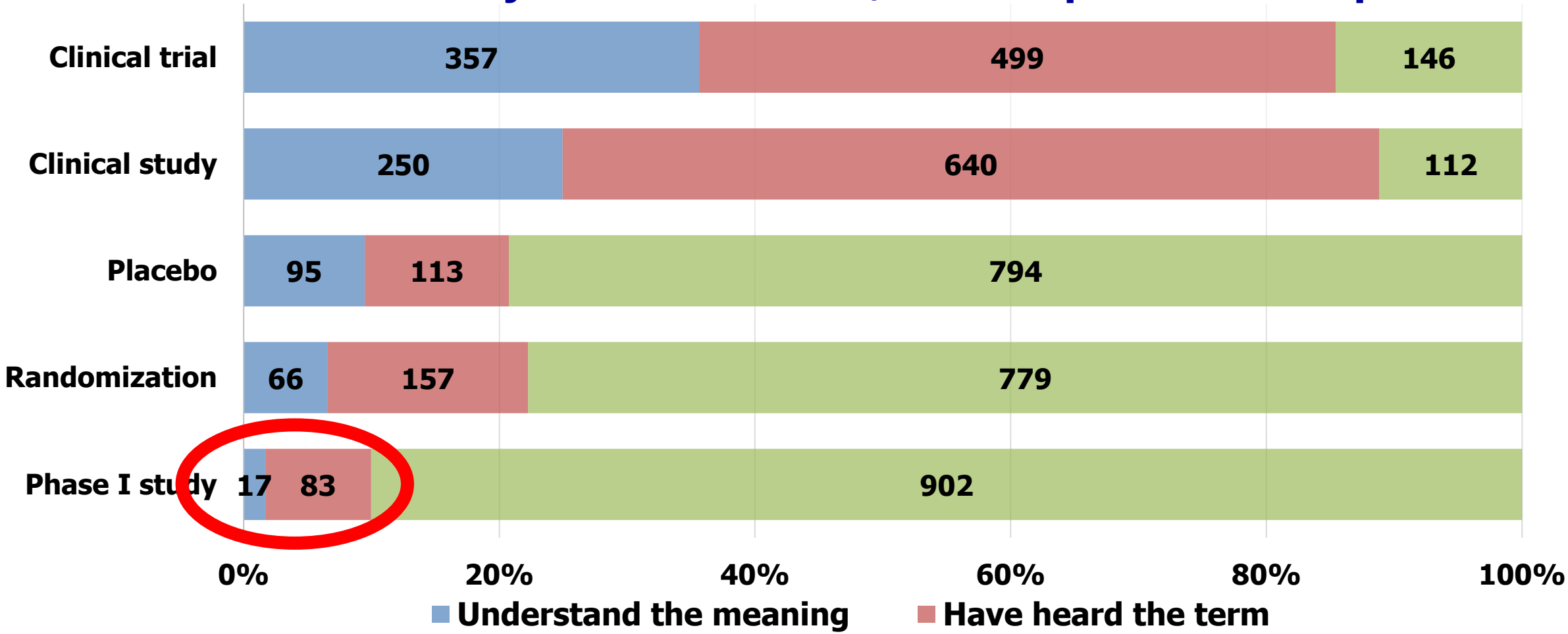
Survey of general public's level of awareness and understanding of medical research terminology

- Ascertaining the general public's level of awareness and understanding of medical research terminology
- Internet-based survey
  - Random sampling
  - 2018/12/05–12/07
  - n = 7,847
  - Exclude people working in industries, such as pharmaceuticals, health food, healthcare, welfare, mass media, advertising, newspaper, broadcasting

Survey of general public's level of awareness and understanding of medical research terminology
— survey results（n = 1,002） （partial excerpt）



Select patients to participate

[Conferences are held each week]

- Pick up studies in pre-registration
- Make a list of patients referred to Phase 1 from each clinical department and from other facilities
- Share information on the study progress
- Decide on candidate studies based on the list of in-progress studies

[CRCs ascertain the following]

- Detailed inclusion/exclusion criteria
- Recent registration availability (remaining cohort slots in ongoing trials)

Informed consent

Patients who were selected as candidates at the conference will be asked to come to the hospital to determine whether they can actually participate in the study

[Doctor, CRC]

◆Determine whether a patient can safely participate in the clinical study

- Confirm inclusion/exclusion criteria
- Confirm PS（pain, appetite, personal chores）
- Confirm eligibility for study participation
- Is a long hospital stay or frequent hospital visits possible?（remote living location, work situation)
- Check peripheral blood vessels（secure route for frequent PK blood sampling)

Informed consent

[Patient]

- This study is my only option.
- I heard during genetic testing that there is a study that suits me perfectly.
- I definitely want to get better.

- Nobody has used this drug before. I’m scared.
- I don’t want to spend one month in the hospital.

But…this is my only remaining option, so I’ll participate!

I just have to do it!

Informed consent

[CRC]

◆To enable patients to participate in the study with peace of mind

[Eliminate patient's anxiety]

- About the disease（will it be cured?）
- About the treatment（how long will it continue?）
- About the adverse reactions（what types of adverse reactions are there?）
- About the cost（how much will it cost?）

[Consent based on adequate understanding and acceptance]

- Provide explanation suited to the patient's level of understanding and living environment
- Eliminating the effects of anxiety on subsequent clinical study treatment

[Duality of CRCs]
Examine patients from the clinical study side

Consideration of patients from the clinical practice side

Informed consent

[CRC]

◆Patients make choices without regret

Participating in Phase 1 studies is not everything.

Ensure that patients do not feel “it wasn’t supposed to be like this…”

Providing the explanation often takes an hour or more…

This is natural because it is a life-changing decision for the patient

Schedule management

[Features of Phase 1 schedules]

≪Protocol factors≫

- Cohort registration frequently opens/closes
- Long hospital stay for initial administration
- Many hospital visits
- Many specific tests
- Many biopsies

≪Study site factors≫

- Check with sponsor each time whether IC is possible
- Bed control with other studies
- Check on national holidays several months in advance
- Advance in-hospital adjustments (few appointment slots)
- Highly invasive, may require hospitalization

IC: Informed Consent

Schedule management

Schedule adjustment is one of the important tasks performed by CRCs

How can administration of the study drug be started smoothly within a short timeframe?

◆Affects subsequent progress of the study overall

◆Shortens the period of time patients are untreated

hospitalization

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Worksheet (initial administration of study drug)

[Implementation order] ①VS→②ECG→③PK

Day	schedule time		PK	ECG 貸与心電計	Urine collecti
C1D1	pre	8:30—9:00	:	□ 3 times in a row	
	administration 09:00				
	15 min (±5 min)	9:15	:	□ 3 times in a row	[Urine collec
	30 min (±10 min)	9:30	:	□ 3 times in a row	①9:00–15:0 Urine volum (mL)
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	8 h (±60 min)	17:00	:	□ 1 time only	
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VS: vital signs

[In-hospital PK worksheet]

Summarized in one table

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Shared among the ward, clinical laboratory department, CRC

Full PK blood collection tubes

①

Blood collection tubes required for a single blood sampling

②

① is prepared for each blood sampling

③

② is prepared in a box in the order of blood sampling time starting from the front

Admission instruction sheet (1)

[Admission Instruction sheet]

It is important to provide specific instructions as to who, when, and how the procedures are to be performed that day

*CRCs create the instruction sheet while visualizing actual movement within the hospital

≪Within 60 min before administration of study drug≫

- Contact the laboratory technician once preparation is complete (**)
- Implement in the following order within 60 minutes before administration
  - ① VS（blood pressure, heart rate, body temperature, SpO_2）
  - ② ECG（measure three times in a row）
  - ③ PK blood sampling

Admission instruction sheet (2)

≪10:00≫ [Start study drug]

- Administration time: 30 min（-5 min to +10 min）
- Prime with saline for flush
- Use in-line filter dedicated for clinical trial use

(provided by Department of Pharmacy with the study drug)

- Pump ON = administration start time

*Administration may be started after 10:00

(however, administration must be completed within 4 h of preparation)

*Fine adjustment of flow rate is possible

≪10:30≫ [End administration]

- Administration end time ＝ 6 min after switching to saline

* Planned flow rate：240 mL/h （flow rate can be adjusted between 225 and 255 mL/h）

Create procedures that anyone can implement

Instructions that can be interpreted in different ways by different people lead to deviations!

（Example）PK blood sampling for 2-h infusion

◆ Written instructions are “within 5 min after administration”

→ 5 min after starting administration?

→ 5 min after ending administration?

Just one word can cause a large error!!

The importance of creating tools

Procedure manuals created by CRCs are important both in hospitals and clinical trials

Direct connection with safe implementation of clinical trials by other departments and ensuring the reliability of clinical trial data

Create accurate and easy-to-understand tools

Electronic data capture (EDC) input

[Vast amount of input data]

- Large number of previous treatments
- Many pre-existing medical conditions and complications
- Many concomitant drugs
- Many adverse events
- Frequent severe adverse events

Patients who have completed all standard treatments participate in these studies

↓

Disease is advanced

↓

General condition is deteriorating

↓

Many patients have a history of previous treatment, complications, and adverse events

Techniques for completing medical charts (use template)

(O) 治験登録前評価

【人種】
日本人

【現病歴】
（初回診断時）
初回診断日：2015/7/2
癌腫：肺癌 Lung cancer
組織診断：腺癌 Adenocarcinoma
TNM分類：AJCC 7th T4N2M0
Stage：Stage3B
Histological Grade：N/A

（治験登録時）
直近の再発日：2017/3/15
病変部位：肝、骨 Liver and bone
TNM分類：AJCC 7th TxNxM1
Stage：Stage4
Histological Grade：N/A

【前治療歴】
・手術
術式：右下葉、上葉切除 Right lung upper and lower
日付：2015/8/11
目的：原疾患の治療 Definitive surgery

・放射線治療
部位：右骨盤 Righgt pelvis
総照射線量：30Gy
照射期間：2017/2/3-2/10
目的：緩和照射 Palliative radiation

・化学療法
レジメン種類：Cisplatin, Vinorelbine
投与期間：2015/10/8-2015/12/9
最良効果：PD
目的：術後補助療法 Adjuvant chemotherapy

レジメン種類：Nivolumab
投与期間：2016/2/22-2016/7/15
最良効果：PD
目的：緩和化学療法 Palliative chemotherapy

レジメン種類：Carbiplatin+Pemetrexed+Avastin
投与期間：2016/8/1-2016/11/ukn
最良効果：SD
目的：緩和化学療法 Palliative chemotherapy

レジメン種類：Pemetrexed
投与期間：2016/12/1
最良効果：PD
目的：緩和化学療法 Palliative chemotherapy

【既往症】
診断名：右卵巣境界悪性腫瘍 Right ovarian boderlin
発症日：2012/1/ukn

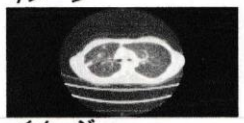
(O) 【治験RECIST1.1】
検査日：2017/3/15CT

一回目効果判定（baseline）

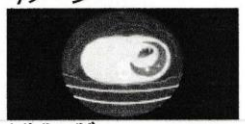
TL	部位	image	径mm
TL①	右肺S4 RIght lung S4	29/82	17.7mm
TL②	左肺S10 Left Lung S10	59/82	13.6mm
TL③	肝S6 Liver segmet 6	74/82	30.0mm
TL④	肝S8 Liver segment 8	58/82	25.1mm
TL⑤			
長径和	**mm （登録時 86.4mm） （最小径 **mm）		
縮小率	**%		
増大率	**%		
判定			
NTL	部位	Image	判定
NTL①	左肺門リンパ節 Left lung hilar lymph node		
NTL②	多発肺転移 Multiple lung metestases		
NTL③	多発肝転移 Multiple liver metastases		
NTL④	多発骨転移 Multiple bone metastases		
NTL⑤	腹腔内リンパ節 Abdominla lymph nodes		

新病変：無 有の場合は部位
RECIST総合効果：
irRECIST総合効果（該当する場合）：

(A) イメージ



(A) イメージ



Complete medical charts using a template

↓

Unification of patient information

↓

- **Ensure quality of source material**
- **Speeds up EDC input and reduces errors**

Specimen material management

visit名	使用期限	個数	特記事項
Screening (15)	2022/7/25	5	
C1D1 (2)	2022/5/31	2	
	2022/7/31	2	
C1D2 (3)	2022/5/31	2	
	2022/7/31	2	
C1D4 (4)	2022/5/31	2	
	2022/7/31	2	
C1D8 (5)	2022/5/31	2	
	2022/7/31	2	
C1D15 (6)	2022/5/31	2	
	2022/7/31	2	
C2D1 (7)	2022/5/31	2	
	2022/7/31	2	
C2D8 (16)	2022/5/31	2	
	2022/7/25	2	
C2D15(17)	2022/1/27	2	
	2022/7/25	2	
C3D1 (10)	2022/2/28	3	
	2022/7/31	2	
C3D2 (11)	2022/2/28	3	
	2022/7/31	2	
C3D4 (12)	2022/2/28	3	
	2022/7/31	2	
C3D8 (13)	2022/2/28	4	次回発注予定
C3D15 (14)	2022/2/28	5	次回発注予定
C4+D1 (T-9)	2022/1/27	2	
	2022/5/31	6	
	2022/7/25	3	
EOT (T-10)	2022/5/31	3	次回発注予定
30-Day-FU (T-6)	2022/1/31	5	
Every 3 Months FU (T-7)	2022/1/31	5	
Unscheduled (T-13)	2022/4/30	8	
	2022/7/25	2	
COVID-19 Biomarker Sample Kit (T-12)	2022/2/14	7	
Part 2 Exploratory Biomarker (T-4)	2021/12/31	4	
	2022/4/30	20	
ILD PK(T-11)	2022/2/28	5	
Archival Tssue (T-1)	2050/12/31	7	
Fresh Tssue (T-2)	2050/12/31	20	
Part 2 Fresh Tssue		0	

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CRCs in Phase I studies

- Support the patients
- Understand the study drug and protocol
- Create in-hospital tools