Toward high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course: Phase1 Trial Development Course

Lecture: Current trends in Phase I trials

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■Work experience

2020~present

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History of pharmaceutically approved anti-cancer drugs in Japan

● : Cytotoxic agent
● : Hormonal agent
● : Small-molecule targeted agent
● : Immuno-oncology agent
● : Antibody, Antibody-drug conjugate
● : Others

1950–70s

Busulfan（1957）
Cyclophosphamide（1962）
Mitomycin C（1963）
5-FU（1967）
Vincristine（1968）
Vinblastine（1968）
Methotrexate（1968）
Cytarabine（1971）
Doxorubicin（1975）
Melphalan（1979）

1980–90s

Tamoxifen（1981）
Cisplatin（1983）
UFT（1984）
Ifosfamide（1985）
Dacarbazine（1986）
Etoposide（1987）
Epirubicin（1989）
Carboplatin（1990）
Mercaptopurine（1991）
Irinotecan（1994）
Nedaplatin（1995）
Paclitaxel（1997）
Docetaxel（1997）
Gemcitabine（1999）
S-1（1999）

2000s

Fludarabine（2000）
Arimidex（2001）
Rituximab（2001）
Trastuzumab（2001）
Gefitinib（2002）
Exemestane（2002）
Amrubicin（2002）
Capecitabine（2003）
Oxaliplatin（2005）
Imatinib（2005）
Letrozole（2006）
Temozolomide（2006）
Bortezomib（2006）
Pemetrexed（2007）
Erlotinib（2007）
Bevacizumab（2007）
Nilotinib（2007）
Cetuximab（2008）
Sunitinib（2008）
Sorafenib（2008）
Thalidomide（2009）
Lapatinib（2009）
Dasatinib（2009）

2010–2015

Bendamustine（2010）
Nab-paclitaxel（2010）
Everolimus（2010）
Temsirolimus（2010）
Panitumumab（2010）
Eribulin（2011）
Crizotinib（2012）
Axitinib（2012）
Pazopanib（2012）
Ofatumumab（2013）
Pertuzumab（2013）
Regorafenib（2013）
Afatinib（2014）
Alectinib（2014）
T-DM1（2014）
Nivolumab（2014）
Vemurafenib（2014）
Ramucirumab（2015）
Lenvatinib（2015）
Ipilimumab（2015）
Trabectedin（2015）

2016–2020

Osimertinib（2016）
Ceritinib（2016）
Bexarotene（2016）
Dabrafenib（2016）
Trametinib（2016）
Carfilzomib（2016）
Pembrolizumab（2016）
Ponatinib（2016）
Ibrutinib（2016）
Ibrutinib（2016）
Romidepsin（2017）
Palbociclib（2017）
Avelumab（2017）
Olaparib（2018）
Atezolizumab（2018）
Durvalumab（2018）
Lorlatinib（2018）
Dacomitinib（2019）
Entrectinib（2019）
Venetoclax（2019）
Necitumumab（2019）
Daratumumab（2019）
Quizartinib（2019）
Abemaciclib（2019）
Tisagenlecleucel (2019)
Tepotinib（2020）
Trastuzumab deruxtecan（2020）
Tirabrutinib（2020）
Cabozantinib（2020）
Isatuximab (2020)
Capmatinib (2020)
Niraparib (2020)
Cetuximab sarotalocan (2020)

2020–current

- Acalabrutinib (2021)
- Brigatinib (2021)
- Denileukin diftitox (2021)
- Larotrectinib (2021)
- Daratumumab (2021)
- Polatuzumab vedotin (2021)
- Pemigatinib (2021)
- Tazemetostat (2021)
- Lutetium oxodotreotide (2021)
- Dinutuximab (2021)
- Tucidinostat (2021)
- Selpercatinib (2021)
- 3-Iodobenzylguanidine (2021)
- Enfortumab vedotin (2021)
- Teserpaturev (2021)
- Idecabtagene vicleucel (2021)
- Axicabtagene ciloleucel (2021)
- Lisocabtagene maraleucel (2021)
- Sotorasib (2022)
- Asciminib (2022)
- Valemetostat (2022)
- Darinaparsin (2022)
- Pimitespib (2022)

updated 02/Dec/2022

Rationale underlying changes in anti-cancer drug categories

- Development of targeted therapy
  - Molecularly targeted drugs
  - Immune-checkpoint inhibitors
- Development of treatments using new technologies
  - Regenerative medicine therapy (CAR-T therapy, virus) and immunotherapy
  - Improvement in existing drugs, such as antibody-drug conjugates (ADCs) and BiTE
  - PROTAC, molecular glue (targeted protein degradation/activation inducer)
    - Target proteins without pockets

CAR-T: Chimeric antigen receptor-T cell
ADC: Antibody-drug conjugate
BiTE: Bispecific T-cell engager
PROTAC: Proteolysis targeting chimera

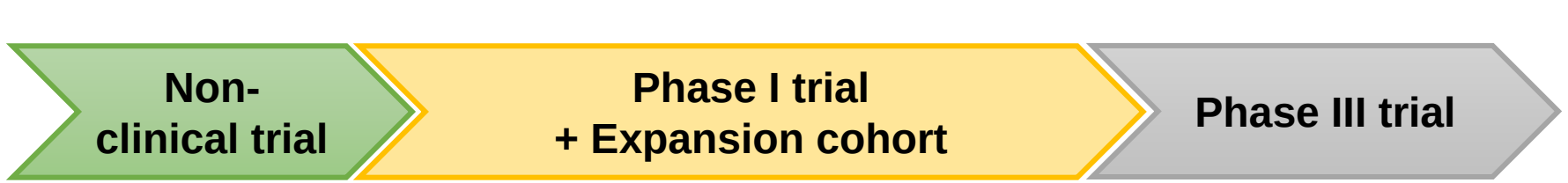
Conventional anti-cancer drug development process

	Phase I trial	Phase II trial	Phase III trial
Primary endpoint	Toxicity (DLT determination, MTD estimation)	Response rate	Overall survival
Secondary endpoint	Efficacy, PK analysis, biomarker discovery	Toxicity/accumulative toxicity evaluation, PK analysis	Toxicity evaluation, progression-free survival, QOL evaluation
Trial design	Dose escalation trial	Single-arm trial	Randomized controlled trial
Number of cases	20–80 cases	200–1,000 cases	200–3,000 cases
Participating institutions	One center to several centers	Medium-scale, mainly specialized centers	Large-scale, multi-center, including general hospitals

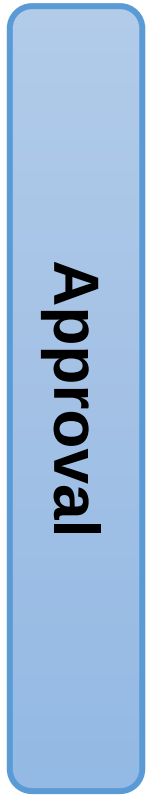
DLT: Dose Limiting Toxicity, MTD: Maximum Tolerated Dose, PK: Pharmacokinetics, QOL: Quality of Life

Recent trend: diversification of development process

- Larger Phase I trial, setting expansion cohort
  - Added efficacy search function



- Pharmaceutical approval obtained in some cases without conducting Phase III trial
  - Difficult to recruit patients for Phase III trials due to rarity of cases
  - Need to demonstrate “clear target + high efficacy”



What is an expansion cohort?

- Cohort with its own purpose and rationale, following the dose escalation part
  - Evaluation of efficacy in specific cancer types
  - Evaluation of efficacy of specific biomarkers
  - Evaluation of dietary effects and drug interactions
  - Further evaluation of RP2D safety

- Three or more cohorts
- Upper limit of one cohort is approximately 40 cases (Simon's two-stage model)
- Cohorts may include hundred to thousand participants
- Attention should be paid to type I errors when interpreting results

RP2D: Recommended Phase 2 Dose
First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry, March 2022

Recent trend: faster development

- Acceleration of development: more efficient drug discovery
- Seamless trial design
  - Efficacy also evaluated by P1 + expansion cohort within the same protocol rather than with P1 and P2 (e.g., KEYNOTE-001, JAVELIN trial)
- Faster and more flexible drug approval process for regulatory agencies
  - Conditional early approval system
  - SAKIGAKE designation

Basis of starting dose: toxicological approach

Calculation according to the GLP compliance trial (in accordance with ICH-S9)

①1/10th of STD10 in rodents (mice)

②1/6th of HNSTD in non-rodents (e.g., monkeys, dogs)

③ Human equivalent dose should be calculated using NOAEL and multiplied by a safety factor (often 10) to determine the maximum recommended dose

LD: Lethal dose
TDL: Toxic dose low
STD: Severely toxic dose
HNSTD: Highest non-severe toxic dose
NOAEL: No-observed adverse effect level

Starting dose for antibody drugs: pharmacological approach

- For antibody drugs, calculations using STD and NOAEL may not be able to accurately evaluate toxicity.
  - TGN1412 incident caused by CD28 agonists (TGN1412)
  - Rennes incident caused by FAAH inhibitors (BIA10-2474)

- MABEL：minimum anticipated biological effect level
  - Dose or concentration at onset of dose-response curve in humans
  - Starting dose should not be “substantially higher” than MABEL
  - Approach to evaluate on-target effect
  - Estimation method
    - Receptor/target binding and occupancy
    - Pharmacological dose-response relationship
    - Estimated exposure
    - *Ex vivo* (effect on human tissue), in vitro, and *in vivo* evaluations

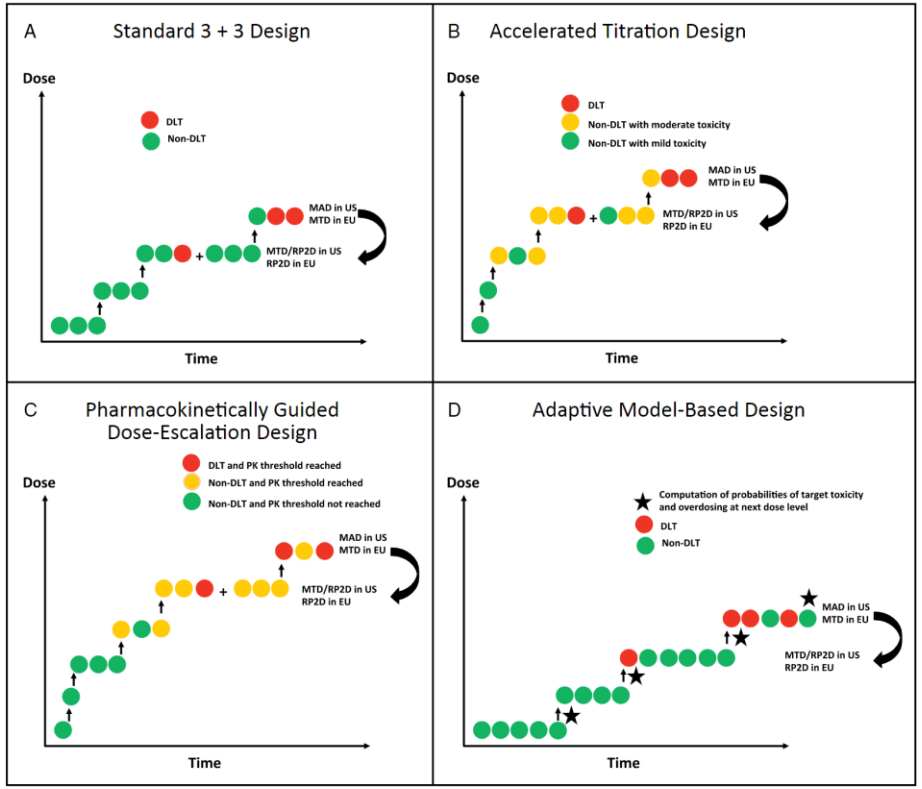
Optimal dosage for small molecules

- Differences between molecularly targeted drugs and cytotoxic anti-cancer drugs
  - Dosage is not proportional to anti-tumor effect
  - May not have MTD
  - Evaluation of accumulative toxicity with long-term administration is needed
- From the use of conventional MTD approaches to improved dose selection strategies
    - Guided by a drug's pharmacokinetics (PK) and pharmacodynamics (PD)
    - Randomized evaluations of a range of doses in trials for dose optimization

Reference: Project Optimus from U.S.Food and Drug Administration
(Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases)

Changes in statistical analysis

- Classic method: rule-based design
  Simple, but concerns about accuracy of MTD estimation "slow and steady"
  - 3+3 design
  - Modified Fibonacci method
- Improved method: model-based design
  - Accelerated titration design by Simon
    "cheap and cheerful"
  - Pharmacologically guided dose escalation by Collins
    "hard-to-get"
  - Continual reassessment method by O'Quigley
    "fast and loose"
  - Bayesian optimal interval (BOIN) design by Yuan
    "lower risk of overdosing"



Hansen et al, 2014

Changes due to genomic medicine

- 2019: Clinical introduction of next-generation sequencer (NGS) gene panel testing
- Changes in target cancer types for Phase I trials
  - From “solid cancer” for which standard treatment has been completed to “genetic abnormality-specific” trial design
    - Toward pharmaceutical approval at an earlier trial stage
- Enables cross-organ development
  - Drug development for rare conditions
  - Tumor agnostic approval
    - Only if there is a clear biomarker and rationale
    - MSI-high, NTRK, RET, BRAF

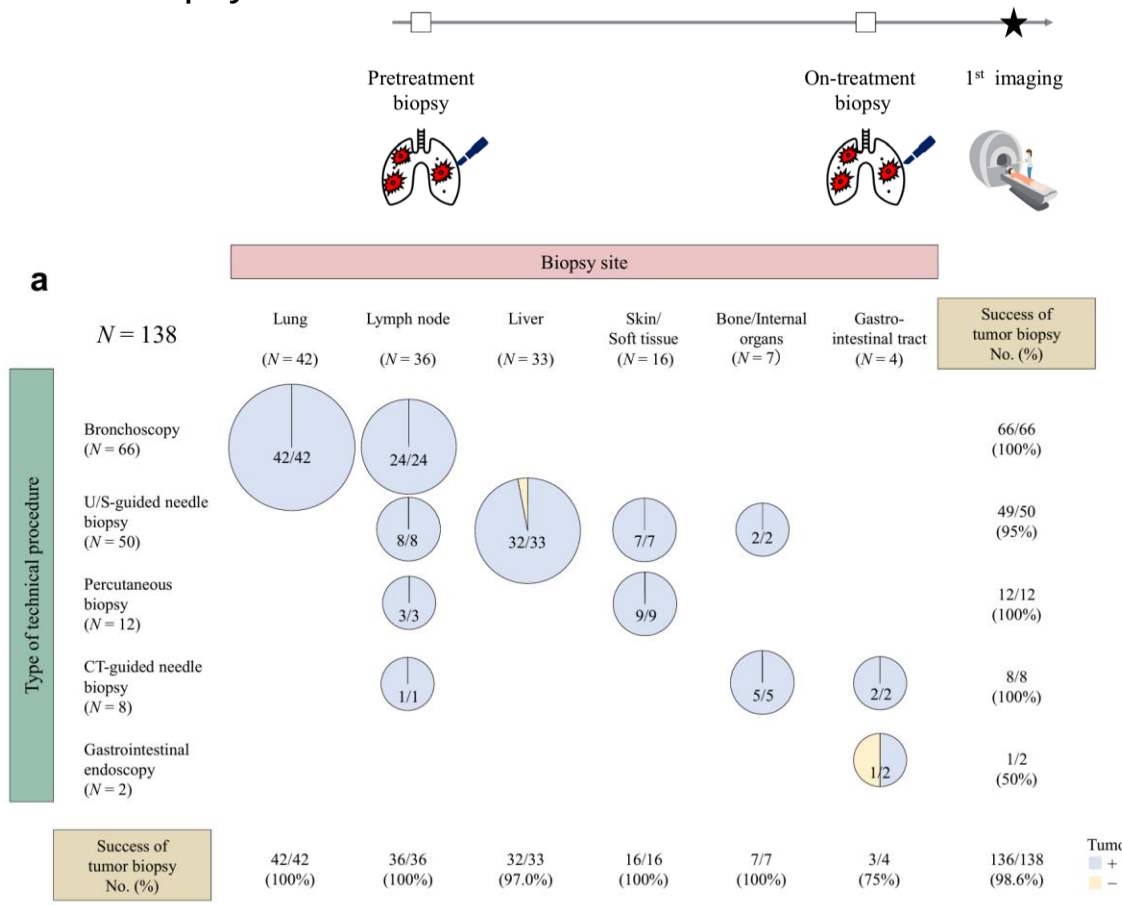
NGS: Next-generation sequencer

Biomarker discovery

- Increasing number of trials requiring specimen sampling
  - Increase in serial biopsies
  - Biomarker discovery is essential for high efficacy
- Collaboration with IVR and endoscopy teams is essential

IVR: Interventional radiology

Serial biopsy: conducted in about 30% of FIH trials



Koyama et.al, Investigational New Drugs 2022

Conclusions

- In this lecture, changes in drugs, trial design, and target diseases in Phase I trials were discussed while comparing past and present cases.