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Towards high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Cancer Genome-based Medicine Course
Lecture Title : Expert Panel System/Molecular Tumor Board in Japan
Speaker : Takafumi Koyama

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Takafumi Koyama, M.D.

Attending Physician, Oncologist and Hematologist

Department of Experimental Therapeutics

Position/Title	Name and Location of Institution	Dates
Current Attending Physician / Dept of Experimental Therapeutics	National Cancer Center Hospital (Chuo-ku, Tokyo, Japan)	May/2018– Present
Previous Research Fellow / Dept of Experimental Therapeutics	National Cancer Center Hospital (Chuo-ku, Tokyo, Japan)	Apr/2018
Previous Resident / Dept of Experimental Therapeutics	National Cancer Center Hospital (Chuo-ku, Tokyo, Japan)	Apr/2016– Mar/2018
Previous Attending Physician / Dept of Medical Oncology	Kameda Medical Center (Kamogawa-shi, Chiba, Japan)	Apr/2011– Mar/2016
Previous Clinical Fellow / Dept of Medical Oncology	Kameda Medical Center (Kamogawa-shi, Chiba, Japan)	Apr/2008– Mar/2011
Previous Resident / Dept of General Internal Medicine	Kishiwada Tokusyukai Hospital (Kishiwada, Osaka, Japan)	Apr/2006– Mar/2008

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- ✓ **Role of the expert panel**
  - What is an expert panel?
  - Expert panels and the cancer genome-based medicine system in Japan
- ✓ **Treatment strategies based on the results of oncogene panel tests**
  - Selection of treatment
  - Role of clinical trials
  - Treatment strategies decided by attending physicians

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Tests for Investigating Genes
Companion Diagnostic vs Next-Generation Sequencing

Type	Companion Diagnostic	Next-Generation Sequencing
Definition	• Diagnostic used to preliminarily test whether a treatment is applicable to the target patient and to increase the efficacy and safety of specific drugs.	Test method for simultaneously measuring changes in multiple genes related to cancer.
Target gene	• One gene related to cancer	• Multiple genes related to cancer (100–500 genes)
Connection with treatment	• Genes for which corresponding therapeutic agents have been developed	• Also includes genes for which corresponding therapeutic agents have not been developed
Clinical efficacy	• Established, and there is a corresponding therapeutic agent for the gene mutation	• Has reached the level where it can be employed in clinical practice, and some drugs respond to gene mutations (many are not covered by insurance, unapproved drugs)
Use in clinical practice	• Covered by insurance	• Covered by insurance ● OncoGuideNCC Oncopanel System ● FoundationOneCDx Cancer Genome Profile ● Oncomine Dx Target Test Multi CDx System • Some medical expenses are not covered by insurance

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Necessity of Expert Panels

Ovarian cancer – a patient in her 50s

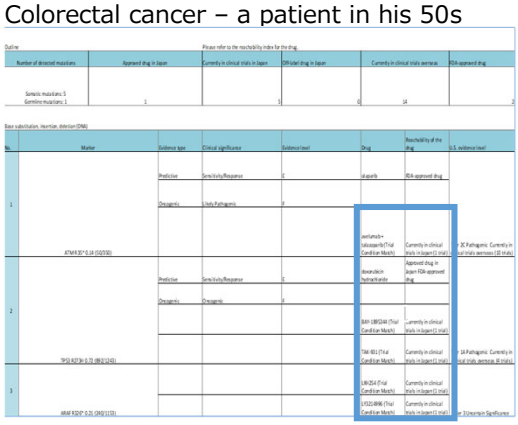
Foundation One CDx

Biomarker findings	ACTIONABILITY	
Microsatellite status - MS-Stable	No therapies or clinical trials. See Biomarker Findings section	
Tumor Mutational Burden -TMB-Low (5 Muts/Mb)	No therapies or clinical trials. See Biomarker Findings section	
Genomic findings	**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**
ATM-Q3038*	Niraparib Olaparib Rucaparib	Talazoparib
10 Trials see p.13		
PALB2-L9F	Niraparib Olaparib Rucaparib	Talazoparib
10 Trials see p.16		
PIK3CA - H1047R	None	Alpelisib Everolimus Temsirolimus
10 Trials see p.19		
ARID1A - Y471*, Q546*	None	None
6 Trials see p.12		

Does it really have pathogenic significance? Could it be a germline mutation?

Could any of these drugs be administered? What is the evidence for the efficacy of these drugs?

Colorectal cancer – a patient in his 50s



A large number of clinical trials is listed, but how should we make a judgement?

At present, some elements must still be **judged by experts**.

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Expert Panel Members

- **Discussion topics by expert panels**

  Expert panels conduct multifaceted discussions on appropriate treatment based on genetic abnormality results while considering the patient's clinical information.

- **Members: Specialists from each field**

  A) Clinicians with specialized knowledge of cancer drug therapy

  B) Doctors with specialized knowledge of genetic medicine

  C) People with genetic medicine counseling skills

  D) Pathologists

  E) People with knowledge of molecular genetics and genomic medicine

  F) Bioinformatician

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What an Expert Panel Meeting Looks Like

- **Outline:** 1 hour/session/week (web conference)
  1: Moderator briefly presents information including the diagnosis name, medical history, family history, and treatment history.
  2: Researcher explains the results.
  3: Genetic specialist comments on germline mutations, if needed.
  4: Moderator summarizes the recommended treatment.

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Detailed Matters Examined in Expert Panel Meetings

(contd. from the previous slide)

- On the general test quality
  - Quality of the sample and data
- On each genetic abnormality
  - ① Biological significance is assigned to each genetic abnormality (whether it contributes to the acquisition of specific traits, such as cancer potential).
  - ② Therapeutic drugs whose mechanism of action indicates that they can be used to correct/manage the genetic abnormality are confirmed.
  - ③ An availability rank is allocated based on specific candidate drugs corresponding to the genetic abnormality, evidence level, approval conditions, and clinical trials status of drugs*, after considering the patient's basic information (age, gender, cancer type, etc.).

    * It is preferable to regularly collect information regarding the status of clinical trials in Japan, and search as widely as possible for candidate drugs corresponding to the genetic abnormality
  - ④ When necessary, the panel contemplates whether any candidate drugs listed in ③ are preferentially recommended, based on the patient condition and drug availability.
  - ⑤ Diagnosis- and prognosis-related evidence is interpreted.
  - ⑥ If germline genetic abnormalities are detected (or suspected), the significance of the findings and a suitable response is considered in accordance with guidelines, guidance, and recommendations.

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Differences between Expert Panels in Terms of the Treatments Recommended

Example》 Treatment recommendations made in response to a simulated case at 11 core hospitals
(Health and Labour Sciences Research Grant – Yoshino Subgroup research)
Simulated case: colorectal cancer, *BRAF* V600E, *ATM* R35*, *TP53* R273H, *APC* c.1312+1G>A

Site	Recommended therapy	Considered therapy
A	Dabrafenib+Trametinib	LXH254, TP0903, olaparib, Talazoparib+Avelumab, BAY1895344, TAK-931
B	Dabrafenib+Trametinib	–
C	Binimetinib + Cetuximab + Encorafenib	–
D	Dabrafenib+Trametinib	–
E	Binimetinib + Cetuximab + Encorafenib, Dabrafenib+Trametinib, Talazoparib＋Avelumab, BAY1895344	–
F	Dabrafenib+Trametinib, TP0903, BAY1895344	Trametinib
G	–	Dabrafenib+Trametinib
H	Dabrafenib+Trametinib	–
I	Binimetinib + Cetuximab + Encorafenib, Dabrafenib+Trametinib, TP0903	–
J	Dabrafenib+Trametinib	–
K	Binimetinib + Cetuximab + Encorafenib, Dabrafenib+Trametinib, PARP inhibitor	–

Sunami K, Naito Y et al. *IJCO* accepted

Even if a particular treatment is recommended at another facility, the investigator may not decide that it is indicated.

Sharing FAQ among participating facilities, matching awareness of annotations associated with major mutations
(Outside the test: Creation of consensus annotation using simulated cases for major mutations (Yoshino subgroup research) etc.)

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Report on the Results of Investigations Made by the Expert Panel

- Quality of the sample and data
- Biological significance of the detected genetic abnormality
- Evidence level and specific candidate drugs whose mechanism of action enables the management conditions arising as a result of the genetic abnormality
- Indication status of the candidate drug and reachability rank of the drug based on clinical trial information
- Whether there are germline mutations that need to be explained to the patients, and the frequency of these mutations
- Points judged to require modification and/or addition to the testing organization's report, etc.
- Scope of the report
- Breakdown of the knowledge database used to assign significance and the access date

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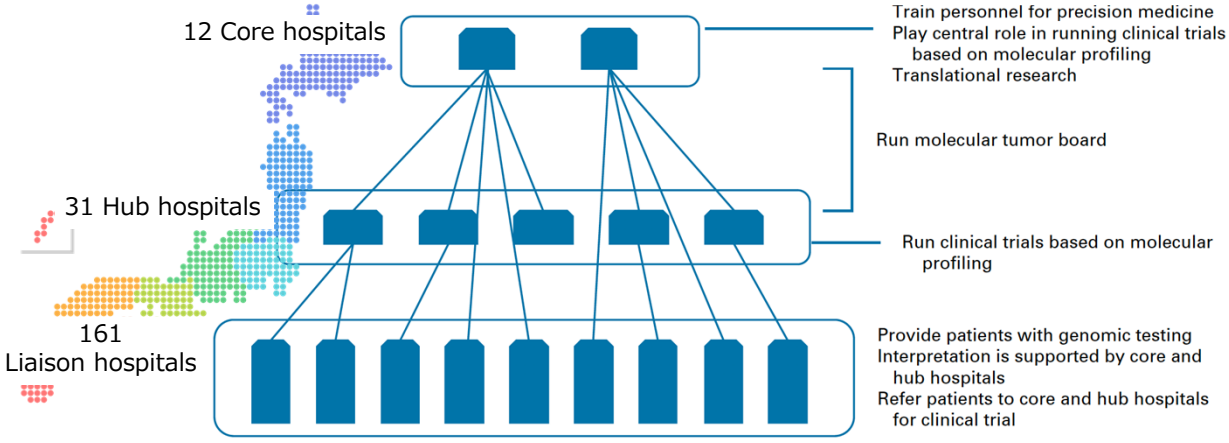
Three-tier Structure of the Institutes Designated for Precision Oncology



Partial modification in "Ebi H, Bando H. Precision Oncology and the Universal Health Coverage System in Japan. *JCO Precis Oncol*. 2019;3."

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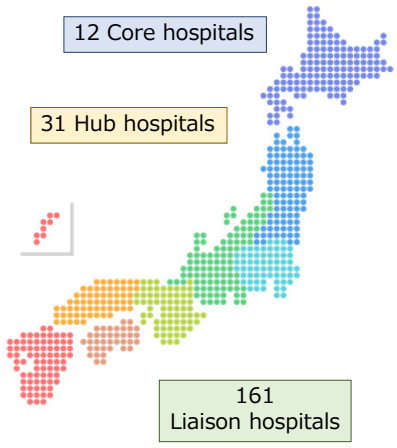
Requirements for Core and Hub Hospitals



#	Requirements	Core	Hub
1	Quality-assured multigene panel testing (outsourcing is acceptable)	○	○
2	Own molecular tumor board for medical interpretation of multigene panel testing (cooperation with external experts is some areas is acceptable, such as pediatric cancer)	○	○
3	Provide genetic counseling for hereditary cancer syndromes	○	○
4	Have a sufficient number of patients eligible for multigene panel testing	○	○
5	Can ascertain and manage test results and clinical information securely and can relay the required information to Center for Cancer Genomics and Advanced Therapeutics	○	○
6	Store fresh frozen surgical and other biospecimens that express biomarkers	○	○
7	Capability to manage a robust trial portfolio including investigator-initiated clinical trials, trials related to advanced medical care, and international trials	○	
8	Provide patient and family member consultation service with respect to future clinical trials and use of clinical information	○	○
9	Train fellows and clinical coordinators and to be involved in translational research	○	

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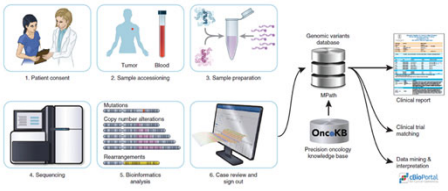
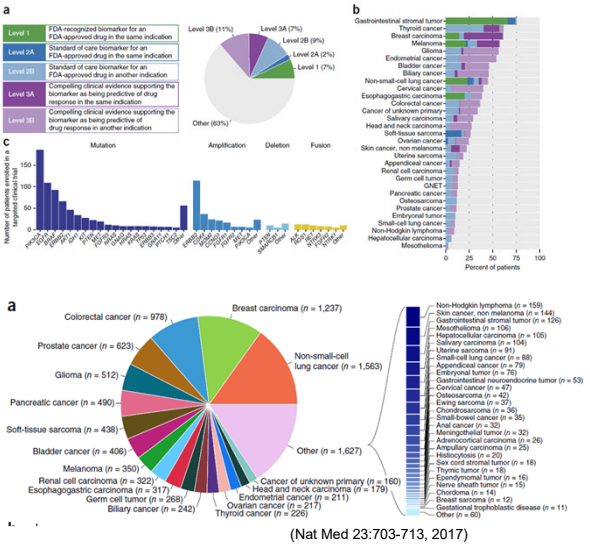
MSK-IMPACT

MSK-IMPACT clinical workflow



- Implemented between January 2014 and March 2016
- 10,945 samples sequenced
- Cases with treatment matched to the genetic abnormality
- 11%



(Nat Med 23:703-713, 2017)

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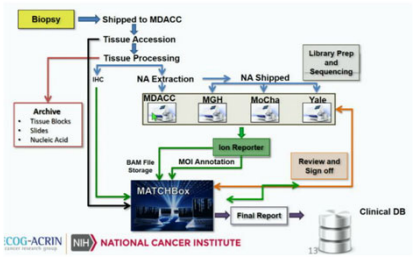
NCI-MATCH

NCI-MATCH clinical workflow



- Case registration
  - Phase 1: 2015/08–2015/11
  - Phase 2: 2016/05–2017/07
  - n = 6,000
- Cases matched to a genetic abnormality: 18%
  - Actually enrolled: 12.4% (689/5560)

NCI-MATCH Central Screening Summary

# Registered for Screening	# With Samples Submitted	# With Testing Complete	# Assigned to Rx	# Enrolled on Rx
6397	5962	5560	992	689

Cases with samples/# enrolled	93%
Assay successful/# with samples	93%
Assigned to Rx/Assay successful	18%
Enrolled on Rx/Assigned	69%

(AACR-NCI-EORTC, OCT 26-30, 2017)

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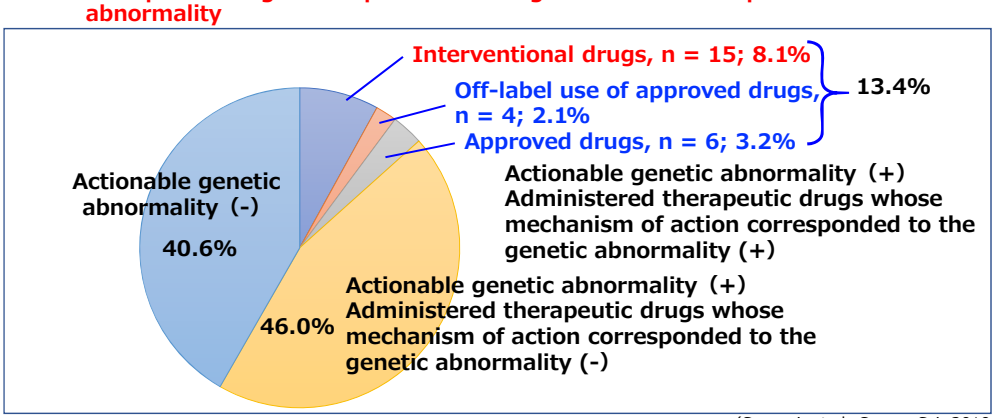
TOP-GEAR

- 187 patients enrolled between May 2016 to May 2017
  - 1 or more genetic abnormality detected : 156 patients (83.4%)
  - 3A or higher based on the 3-association guidance : 111 patients (59.4%)
  - Tumor Mutational Burden<10/Mb : 17 patients (9.1%)
  - The mechanism of action of the administered therapeutic drugs corresponded to the genetic abnormality : 25 patients (13.4%)



(Sunami, et al: Cancer Sci. 2019 Feb 11)

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Treatment Selection Based on the Results of Oncogene Panel

- Approved drug
- Interventional drug
- Off-label use

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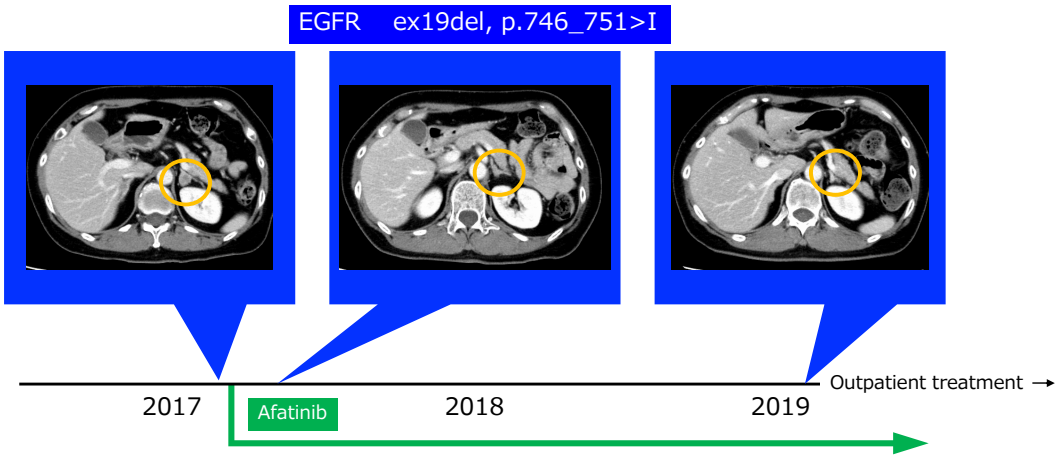
Use of Approved Drugs for Rare Gene Mutations

PS2 woman in her 50s with recurrent lung adenocarcinoma and brain metastasis 3 months after postoperative adjuvant chemotherapy.
The patient was found to be negative for EGFR mutation and ALK fusion gene using the companion test.



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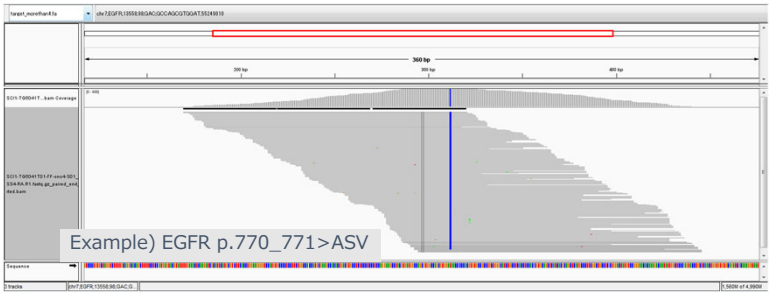
Detecting EGFR Rare Variants

Oncogene panel tests can detect rare variants that cannot be detected using companion diagnostics



Reviewing recommendation of EGFR-TKI treatment by the expert panel

No.	Tumor type	Gene	Aberration	CDx detection	EGFR-TKI treatment
1	Lung	EGFR	ex20ins, p.773_774>GH	-	No data
2	Lung	EGFR	ex19del, p.751_759>N	-	Gefitinib, Erlotinib
3	Lung	EGFR	ex19del, p.746_751>I	-	Afatinib
4	Lung	EGFR	ex19del, p.752_759del	-	No data
5	Lung	EGFR	ex19del, p.746_752>V	-	No data
6	Lung	EGFR	ex20ins, p.767_768insTLA	-	No data

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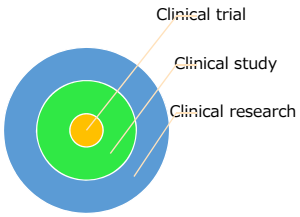
What Are Cancer Clinical Trials?



Clinical studies conducted to obtain approval for a drug or medical device from an authorized organizations are called “Clinical Trials”.

- ✓ Cancer affects all of us
- ✓ Research studies involving people
- ✓ Try to answer scientific questions and find better ways to prevent, diagnose, or treat cancer
- ✓ Clinical trials translate the results of basic scientific research to enable the prevention, diagnosis, or treatment of cancer
- ✓ Greater the number of individuals enrolled in a trial, the faster we can
  - Answer critical research questions
  - Find better treatments and strategies to prevent cancer

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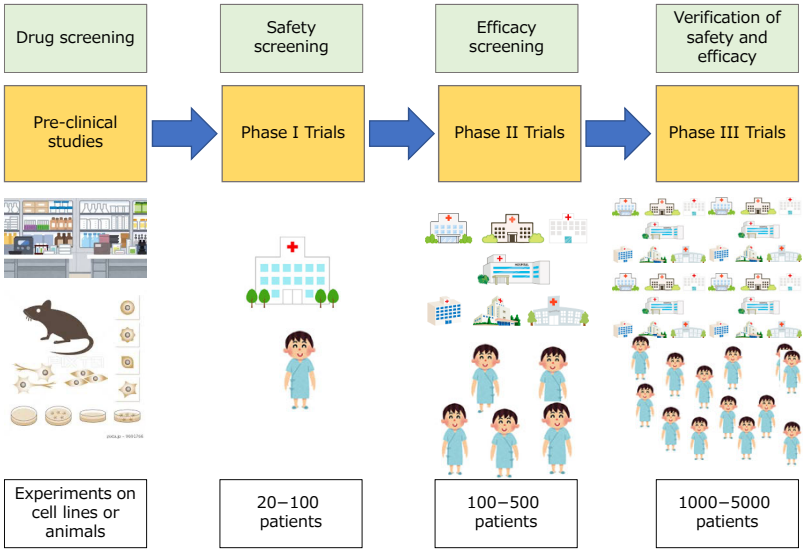
Various Clinical Trial Phases



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Common Eligibility Criteria and Exclusion Criteria in Early Clinical Studies (Phase I, Ib)

Inclusion criteria	Patients with advanced cancer for whom the standard treatment is ineffective, or no suitable treatment exists
	ECOG PS*is 0 or 1 (*: Eastern Cooperative Oncology Group Performance Status)
	Retaining proper organ function White blood cells ≧3,000/mm^3 Neutrophils ≧1500–2,000/mm^3 Hemoglobin ≧9.0 g/dL AST≦2 ~2.5-fold times the facility reference standard ALT≦ 2 ~2.5-fold the facility reference standard Serum creatinine ≦1.2 mg/dL
	Measurable lesion (not essential, but often required)
	Able to undergo biopsy (not essential, but recently an increasing number of clinical trials require this)
	Preferable that toxicity due to pre-treatment has recovered to ≦Grade 1
Exclusion criteria	Patients unable to understand participation in experimental (exploratory) treatment
	Patients with symptomatic brain metastasis (asymptomatic patients are permitted, but post-treatment is preferred. Not possible if steroids are used to control cerebral edema. Not possible if anticonvulsants are used to control epilepsy arising as a result of brain metastasis)
	Patients unable to go once or twice per week to the facility where the clinical trial is being conducted Trials often require the subjects to be hospitalized during the first cycle of treatment (approximately 3–4 weeks), so patients who cannot be hospitalized for 3–4 weeks are also excluded
	Patients with pulmonary fibrosis, interstitial pneumonia, or drug-induced pneumonia
	Patients with uncontrolled fluid retention (pleural effusion, ascites, pericardial effusion)
	Patients incapable of oral intake
	Patients with clinically unstable conditions (expected to become clinically unstable after 6–8 weeks in the absence of treatment)

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Comparison of Clinical Trials (Especially Phase I trials) and General Medical Care

Point	Clinical trial	General medical care
Purpose	Evaluation of drug safety Evaluation of drug effect	Radical treatment with preoperative and postoperative therapy Pain relief and prolongation of life with recurrence of metastasis
Start of treatment	Specified in the protocol	Based on the judgement of each attending physician
Dose	Specified in the protocol	There is a standard dose, but it can be changed at the discretion of the attending physician based on the patient's PS, age, kidney function, and liver function
Change of dose	Once the dose is decreased, it is often impossible to increase the dose again	Dose can be increased again after decreasing
Dosing intervals	Specified in the protocol (dosing is discontinued if postponed for a long period)	Can be restarted even if postponed for a long period
Caution for concomitant drugs	Drugs exhibiting pharmacokinetic interactions with each other are often contraindicated in the protocol, even general drugs	Drugs that affect the concentration of co-administered drugs must be used with caution
Top priority	Patient safety	Patient safety

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Decisions Regarding Treatment Strategies Made by the Attending Physicians

- Molecular biological validity of the pharmacological action from the perspective of the genetic abnormality
- Drug efficacy and adverse reactions
- Social background of the patient

  (Ideal end-of-life scenario, support from family, etc.)

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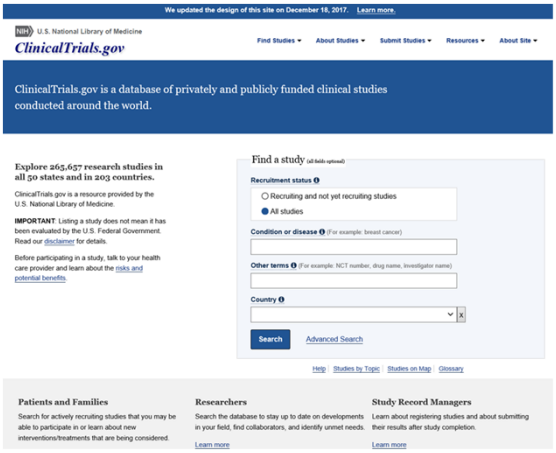
Clinical Trial Search Site

- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home)
- Site operated by the U.S. National Institutes of Health (NIH)



- Advantages
  - ✓ Mainly based in the US, but also covers clinical trials and clinical studies almost worldwide
  - ✓ Also provides information on facilities implementing clinical trials
- Disadvantage
  - ✓ English (technical terms) input only

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Summary

- ✓ Role of the expert panel
  - ■ What is an expert panel?
  - ■ System of cancer genome-based medicine in Japan and expert panels
- ✓ Treatment based on the results of oncogene panel tests
  - ■ Selection of treatment
  - ■ Role of clinical trials
  - ■ Treatment strategies decided by attending physicians

References

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