towards high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course : Methods of utilizing NGS test results
(off-label, clinical trial, etc.)

Speaker : Tatsunori Shimoi

Tatsunori Shimoi, M.D., Ph.D.

Department of Medical Oncology, National Cancer Center Hospital

EDUCATION

Gifu City University School of Medicine, Japan

Juntendo University Graduated School of Medicine, Japan

WORK EXPERIENCE

Senior Resident, Respiratory Medicine and Medical Oncology, Tokyo Metropolitan Komagome Hospital (2009–2013)

Chief Resident, Department of Breast and Medical Oncology, National Cancer Center (2013–2015)

Staff, Department of Breast and Medical Oncology, National Cancer Center (2015–2017)

Deputy Director, Health Insurance Bureau, Ministry of Health, Labor and Welfare. (2017–2019)

Staff, Department of Breast and Medical Oncology, National Cancer Center (2019–2020)

Head of Physician, Department of Breast and Medical Oncology, National Cancer Center (2020–2022)

Head of Physician, Department of Medical Oncology (name change of department), National Cancer Center Hospital (2022–Present)

Director, International Medical Care Section, Department of International Clinical Development (2020–Present)

BOARD CERTIFICATION

Diplomate, Subspecialty Board of Medical Oncology, JSMO (2015)

Fellow of the Japanese Society of Internal Medicine (2015)

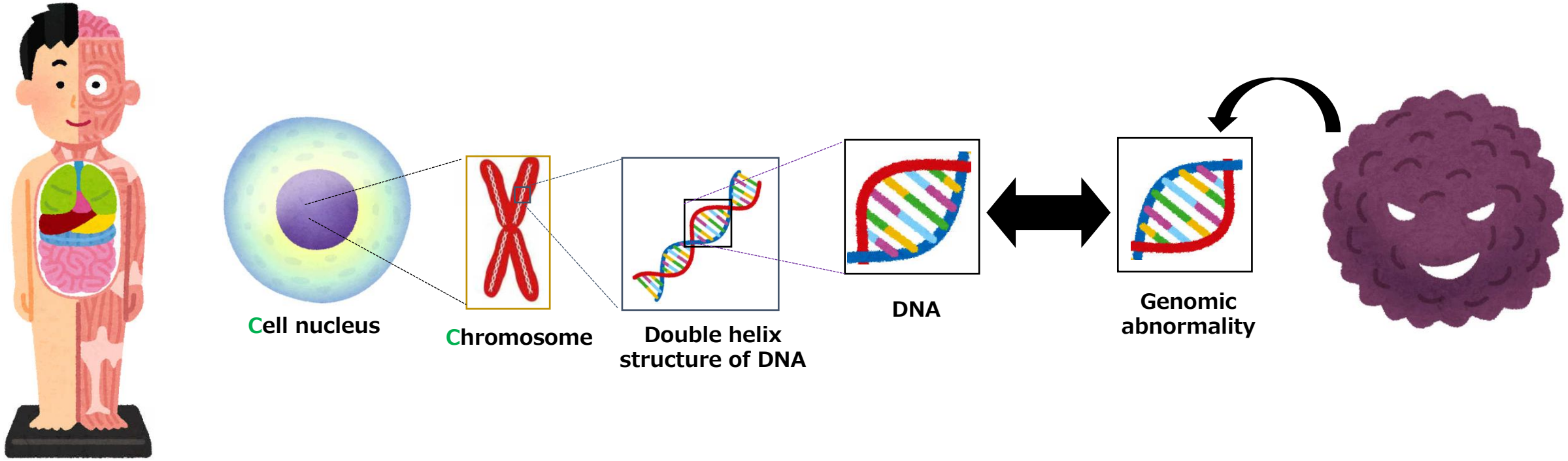
Faculty, Subspecialty Board of Breast Oncology, Japanese Breast Cancer Society (2021)

Topics

1. Cancer genomic medicine and comprehensive genomic profiling (CGP) test

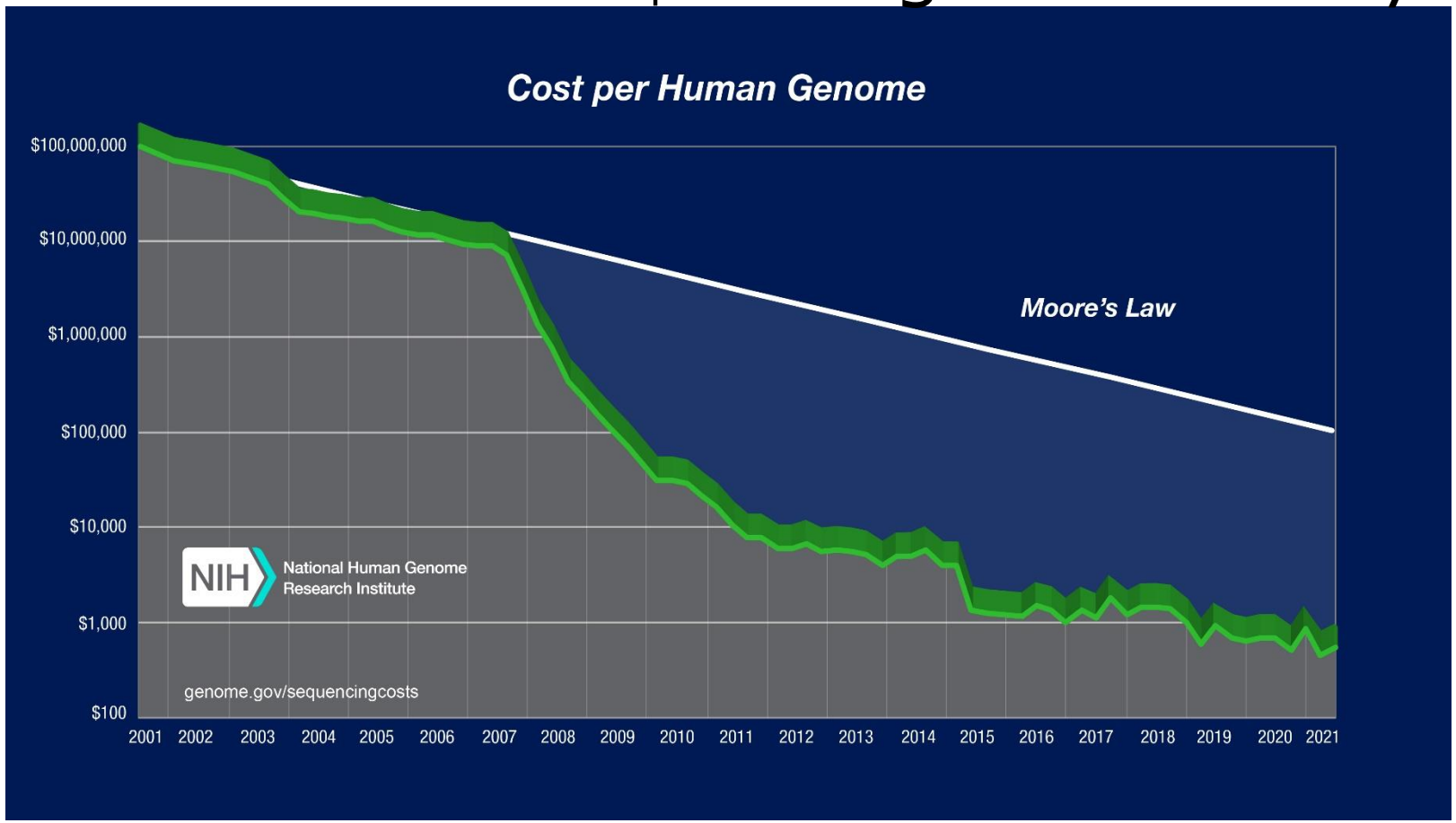
2. Treatment based on cancer genomic profiling

Cancer genomic test and cancer genomic medicine



- The Human Genome Project was completed in 2003. Since then, numerous cancer-specific genomic abnormalities have been analyzed
- Investigating genomic abnormalities in cancer and applying the results in clinical practice, such as in diagnosis and treatment, is known as cancer genomic medicine

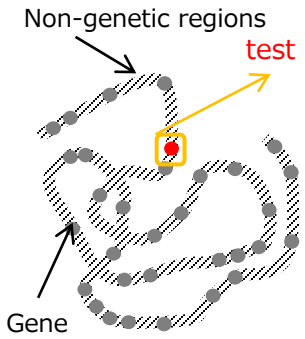
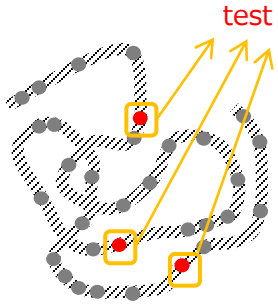
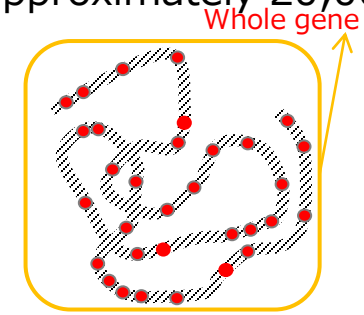
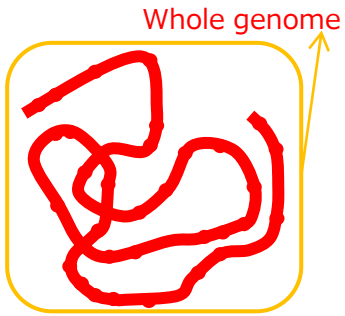
Towards the era of $1000 genome analysis



- Proposed by Intel co-founder Gordon Moore based on his observations that 'computer performance tends to double every two years, hence halving its price'
- A grant from the US National Human Genome Research Institute led to rapid improvements in genome analysis technology that exceeded the rate of Moore's law as well as to the development of devices known as next-generation sequencers

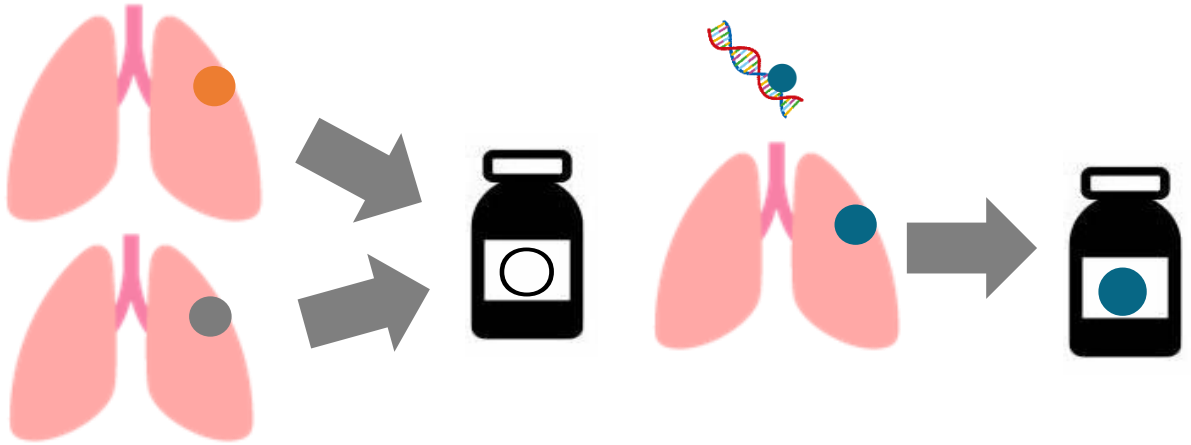
Nature. 2014;507:294-5.

Types of Cancer Genomic Testing in Japan

Type of test	Single gene test	**Comprehensive genomic profiling (CGP)**	Whole-exome sequencing	Whole-genome sequencing
Target	• One gene 	• Multiple genes associated with cancer 	• Whole gene • (approximately 20,000) 	• Whole genome 
Relationship with treatment	• Genes for which corresponding therapeutic agents have been established	• **Including genes for which no corresponding drug therapy has been established**	• Most genes for which no corresponding drug therapy has been established	• Most areas have no known function
Relationship with medical insurance	• Partially covered by insurance	• Partially **covered by insurance** • Research such as Advanced medical care B	• Research use only	• Research use only

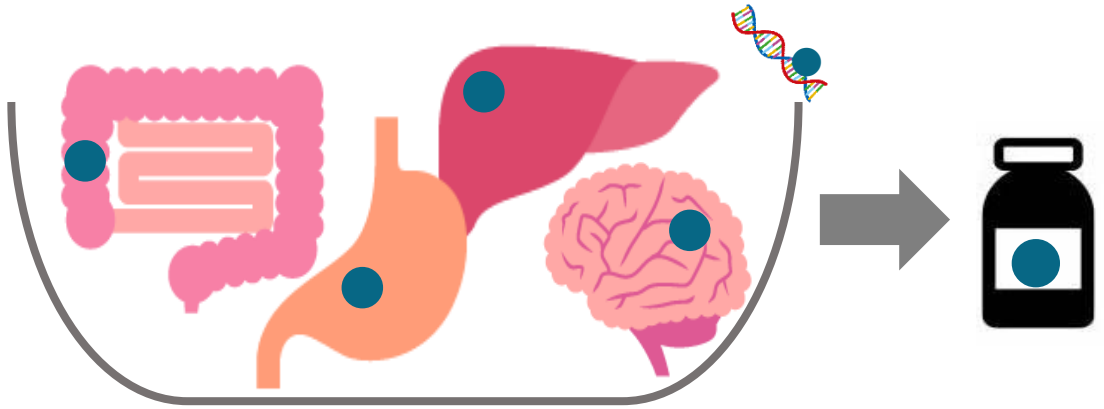
From treatment selection by cancer type to treatment selection by genetic abnormality

Conventional treatment selection



Conventionally, anticancer drugs were selected based on the organ from which the cancer was derived. In recent years, however, anticancer agents have been selected based on genetic abnormalities in some cancers originating in certain organs.

Organ-independent treatment selection based on genetic abnormalities



If the same genetic abnormality is present, the same anticancer drug is selected regardless of the affected organ.

FoundationOne® CDx
がんゲノムプロファイル
総合製品ガイド

FoundationOne® CDx がんゲノムプロファイル

【警告】
本品による検査を実施する際には、関連する指針等に提示される施設要件を満たすことを確認するとともに、関連学会が作成したガイドライン等の最新の情報を参考にすること。

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体細胞遺伝子変異解析プログラム（抗悪性腫瘍薬適応判定用）

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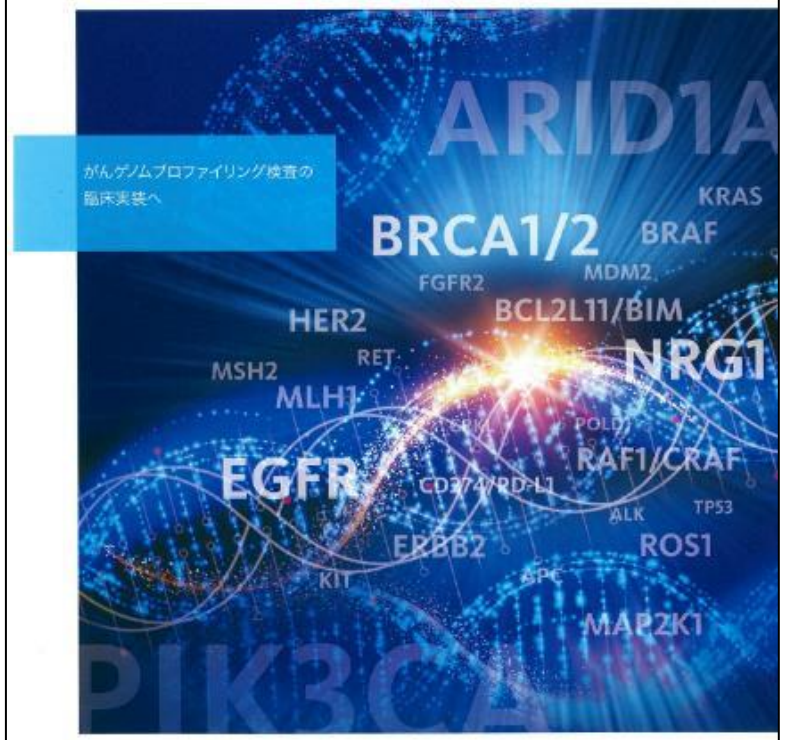
OncoGuide™
NCCオンコパネル システム

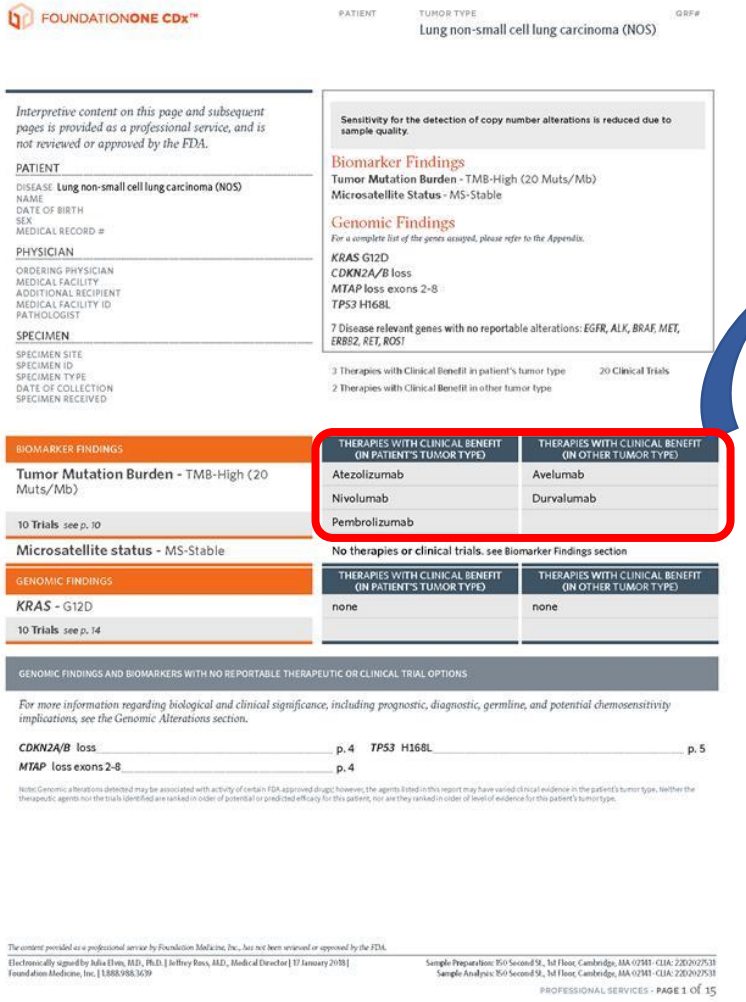


www.sysmex.co.jp

Features of the Cancer Genomic Profiling Test

Testing parameters	FoundationOne® CDx	FoundationOne® Liquid CDx	OncoGuide NCC™ Oncopanel
Specimen	Tumor tissue (Formalin-fixed, paraffin-embedded, FFPE)	Blood	Tumor tissue (FFPE) + reference normal tissue (blood)
Sample requirement	4–5 μm × 10 slides (≥25 mm²) Tumor content ≥30% (≥20%)	Peripheral blood 17 mL	5 μm × 10 slides (≥16 mm²) Tumor content ≥20%
Number of genes	324	324	124
Functions as a companion test	NSCLC: *EGFR* (ex19del, L858R, T790M), *ALK* fusion, *ROS1* fusion, *MET* skipping mutation Malignant melanoma: *BRAF* V600E/K Breast cancer: *ERBB2* CNV Colorectal cancer: *KRAS/NRAS* WT Solid tumor: *NTRK1/2/3* fusion Ovarian cancer, prostate cancer: *BRCA1/2* Bile duct cancer: *FGFR2* fusion	NSCLC: *EGFR*(ex19del, L858R, T790M), *ALK* fusion, *ROS1* fusion, Solid tumor: *NTRK1/2/3* fusion Prostate cancer: *BRCA1/2*	—
Tumor mutation burden	○	○ (Outside scope of regulatory approval)	○
Microsatellite instability	○	○ (Outside scope of regulatory approval)	○

Treatment strategy according to the results of cancer genomic profiling tests



FOUNDATIONONE CDx™

PATIENT | TUMOR TYPE: Lung non-small cell lung carcinoma (NOS) | ORR#

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT
DISEASE Lung non-small cell lung carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Sensitivity for the detection of copy number alterations is reduced due to sample quality.

Biomarker Findings
Tumor Mutation Burden - TMB-High (20 Muts/Mb)
Microsatellite Status - MS-Stable

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.
KRAS G12D
CDKN2A/B loss
MTAP loss exons 2-8
TP53 H168L

7 Disease relevant genes with no reportable alterations: *EGFR, ALK, BRAF, MET, ERBB2, RET, ROS1*

3 Therapies with Clinical Benefit in patient's tumor type — 20 Clinical Trials
2 Therapies with Clinical Benefit in other tumor type

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
Tumor Mutation Burden - TMB-High (20 Muts/Mb)	Atezolizumab	Avelumab
10 Trials see p. 10	Nivolumab	Durvalumab
	Pembrolizumab	
Microsatellite status - MS-Stable	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)
KRAS - G12D	none	none
10 Trials see p. 14		

GENOMIC FINDINGS AND BIOMARKERS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Alterations section.

CDKN2A/B loss p. 4 — *TP53* H168L p. 5
MTAP loss exons 2-8 p. 4

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

The content provided as a professional service by Foundation Medicine, Inc., has not been reviewed or approved by the FDA.

Electronically signed by Julia Elvin, M.D., Ph.D. | Jeffrey Ross, M.D., Medical Director | 17 January 2018 | Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 3rd Floor, Cambridge, MA 02141 - CLIA: 22D2027538
Sample Analysis: 150 Second St., 3rd Floor, Cambridge, MA 02141 - CLIA: 22D2027538

PROFESSIONAL SERVICES - PAGE 1 OF 15

Cancer has the A genetic alteration

A gene alteration

Anticancer drug A is recommended

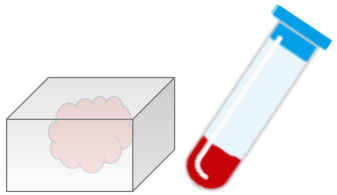
Drug A'

① Drug 'A' is a candidate for the A gene abnormality....
Why is 'A' recommended?
(pathophysiology and molecular biology of cancer)
② How much and how effective can we expect the drug to be?
(search for past clinical trial results)
③ How can the drug be administered?
(information on current clinical trials not reimbursed by insurance, etc.)
④ Is there a possibility of germline findings?

https://www.sec.gov/Archives/edgar/data/1488613/000156459018004758/fmi-10k_20171231.htm

Flow of the Cancer Genomic Profiling test

Test explanation and obtaining consent



Collection and selection of samples for analysis

Cancer genomic testing

Expert panel = molecular tumor board

Explanation of results Treatment selection

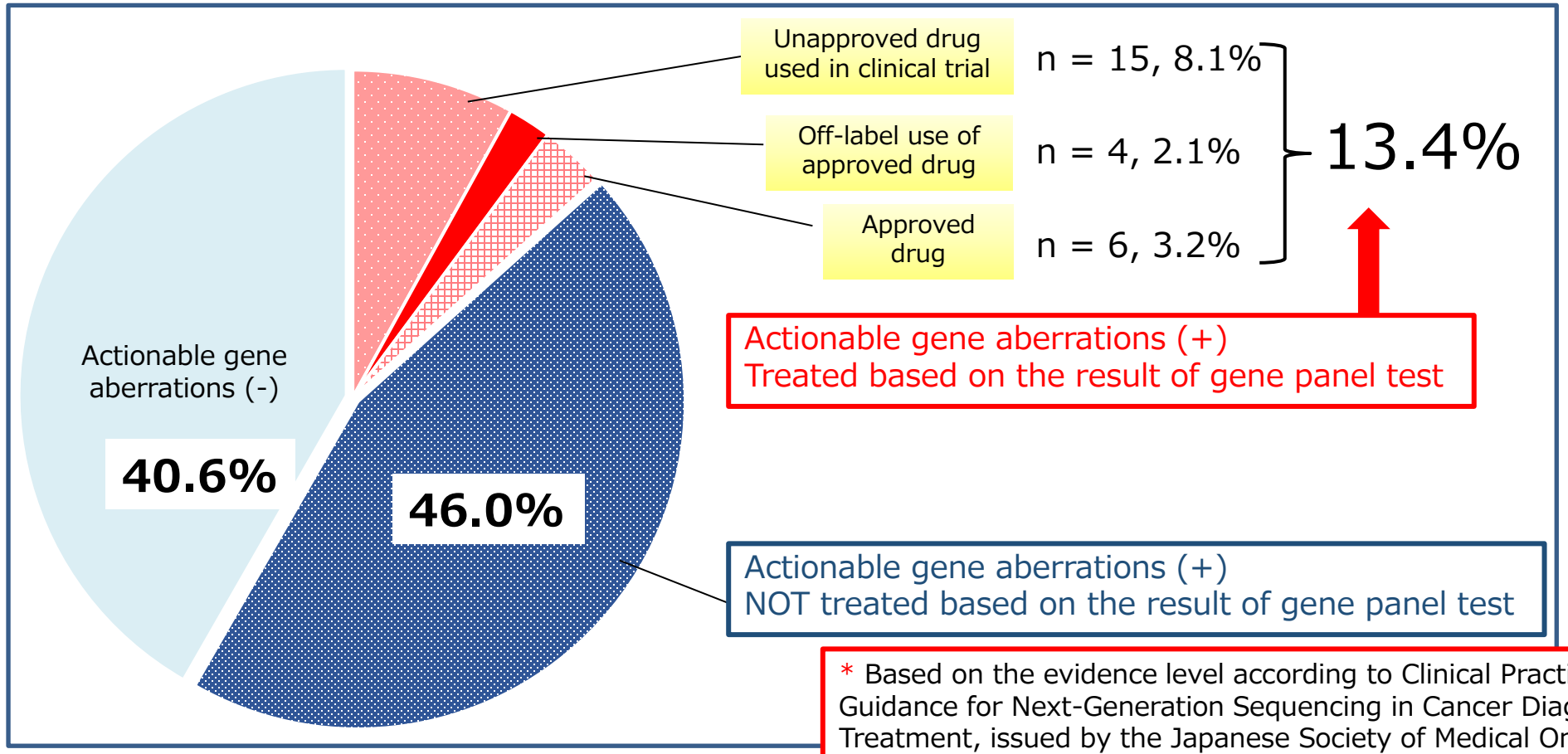
Particularly, medical institutions that provide genomic medicine must provide treatment, have a system that can adequately refer patients to clinical trial sites in Japan based on the test results, and provide genetic counseling.

How do we interpret the CGP report??
Check the ICR web → Dr. Sunami's and Dr. Hirata's lecture

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

Subsequent treatment after CGP test in Japan

- Actionable gene aberrations*: 111/187 cases (59.3%)
- Treated based on gene panel test results: 25/187 cases (13.4%)



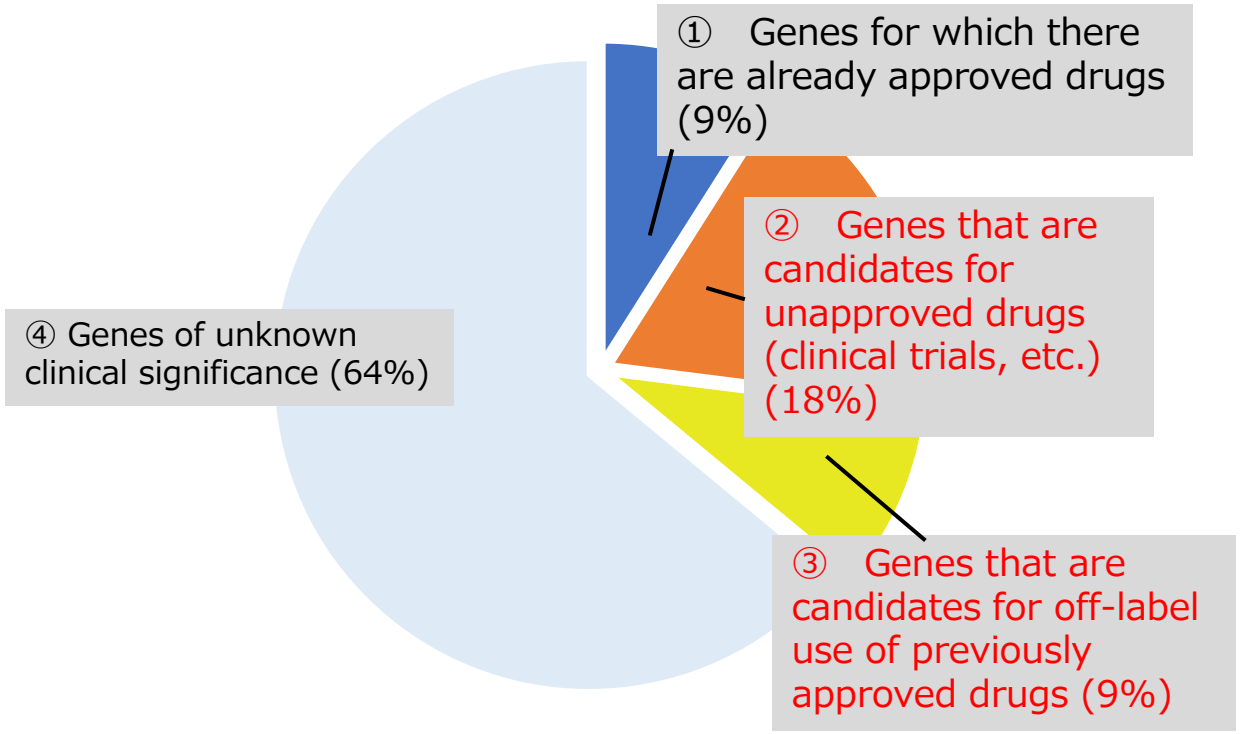
* Based on the evidence level according to Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment, issued by the Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and the Japanese Cancer Association

Sunami K et al. Cancer Sci. 2019 Apr;110(4):1480-1490
Figure is modified, with permission, from Dr. Sunami at NCCH

Results of Cancer Genomic Profiling Test and Treatment

- The results of a cancer gene panel test involving more than 10,000 patients at Memorial Sloan Kettering Cancer Center (USA) showed that 36% of genetic abnormalities were related to treatment. The breakdown of subsequent treatments is as follows.

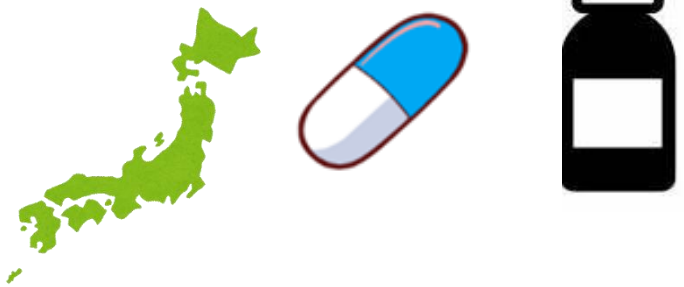
Results of clinical study of MSK-IMPACT



※Only 11% of patients received treatment

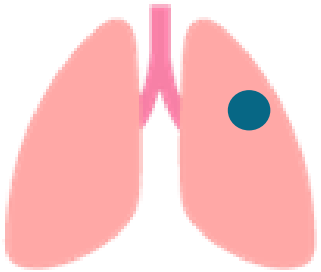
Nat Med. 2017;23:703-713. Figure6

Off-label drugs and Unlicensed drugs



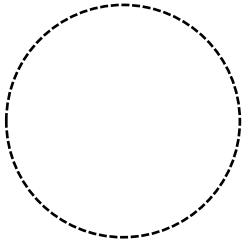
New drugs

Approval
by the authority



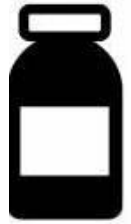
Ex., this drug is
approved
for lung cancer

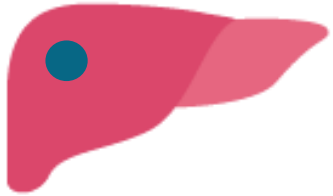
Approved indications
(indications in the package insert)



Unlicensed drugs

No indication itself
(No national manufacturing
or marketing authorization)





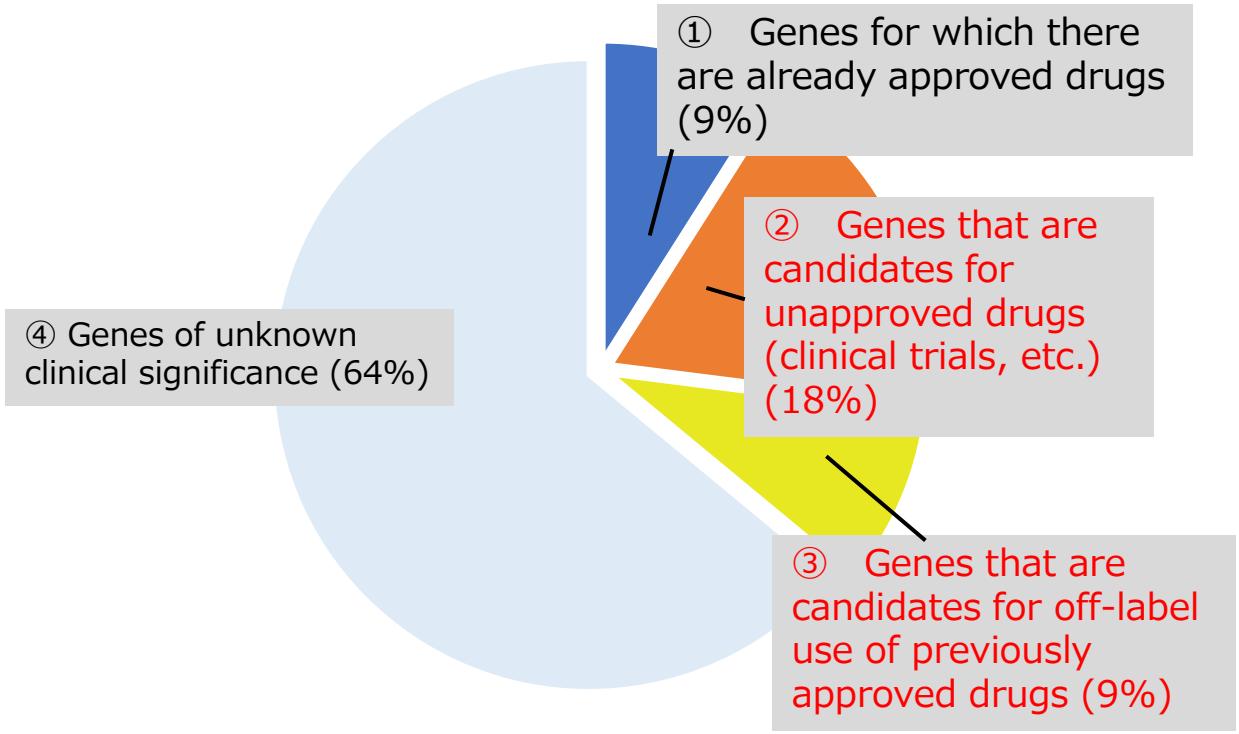
Off-label drugs

Diseases other than
those indicated

Results of Cancer Genomic Profiling Test and Treatment

- The results of a cancer gene panel test involving more than 10,000 patients at Memorial Sloan Kettering Cancer Center (USA) showed that 36% of genetic abnormalities were related to treatment. The breakdown of subsequent treatments is as follows.

Results of clinical study of MSK-IMPACT

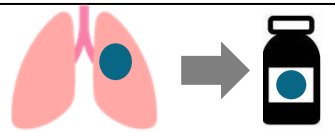


※Only 11% of patients received treatment

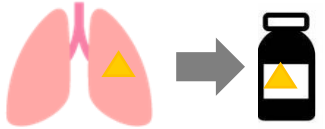
Nat Med. 2017;23:703-713. Figure6

Treatments option based on genomic test results

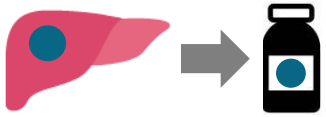
① Insurance treatment (for use within indications)



② New drug development, clinical trials, etc.



③ Clinical trials of off-label drugs



Trends in administration of off-label use of cancer drugs worldwide

- Study to provide an overview of off-label drug use prevalence in oncology.
- Studies were conducted in nine countries, USA (n = 11), Italy (n = 3), France (n = 2), Australia (n = 2), Spain, Canada, China, Switzerland, and Israel.
- Overall, 13–71% of adult patients with cancer received a minimum of one off-label chemotherapy during the treatment course.
- Off-label drug use unsupported by standard treatment guidelines or drug compendia was 7–31%.
- The availability of off-label administration of drugs depends on the coverage of the patient's medical insurance. In Japan, off-label use of drugs is not permitted (reimbursed) under the universal health insurance system, except for in some clinical trials.

→ Clinical trials with off-label drugs are required, along with platform-type trials to match the genomic era.

J Clin Pharm Ther. 2017 Jun;42(3):251-258. JCO Oncol Practv. 2021 Mar;17(3):e416-e425.

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IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.

Find a study (all fields optional)

Status

- ○ Recruiting and not yet recruiting studies
- ● All studies

Condition or disease (For example: breast cancer)

Other terms (For example: NCT number, drug name, investigator name)

Country

Search | Advanced Search

https://clinicaltrials.gov/

Examples of clinical trials for pan-solid tumors in Japan

Biomarker	Drugs	Trial phase	Clinical trial number
HRRm- or HRD-positive	Pembrolizumab+olaparib	Phase2 SIT	NCT04123366 jRCT2011200025
BRCA gene mutation	Niraparib	Phase2 IIT	jRCT2011200023
BRCA or ATM gene mutation	Tralasoparib+avelumab	Phase2 SIT	NCT03565991 JapicCTI-194898
FGF/FGFR abnormalities	TAS-120	Phase2 SIT	NCT02052778 JapicCTI-184178
Activating FGFR mutations or translocations	Pemigatinib	Phase2 SIT	NCT03822117 JapicCTI-194976
FGFR gene mutation or fusion gene	Erdafitinib	Phase2 SIT	NCT04083976 JapicCTI-205204
FGFR gene abnormalities in circulating tumor DNA in blood	TAS-120	Phase2 SIT	JapicCTI-194624
Positive for FGFR4 and KLB expression	Roblitinib (FGF401)	Phase1/2 SIT	NCT02325739 JapicCTI-152932
FGFR gene abnormalities (fusion genes), activating gene mutations, gene amplification	E7090	Phase2 SIT	jRCT2031210043
HER2 active mutation-positive	Trastuzumab delxtecan	Phase2 SIT	NCT04639219 jRCT2031210132
HER2No evidence of overexpression/amplification HER2 mutated tumors	Tucatinib Trastuzumab combination therapy	Phase2 SIT	NCT04579380 jRCT2031210113
KRAS p.G12C mutation	Sotorasib	Phase1/2 SIT	NCT03600883 JapicCTI-194823
KRAS p.G12C mutation	Sotorasib	Phase1/2 SIT	NCT04185883 jRCT2031210121
BRAF V600E	Dabrafenib + trametinib	Phase2 SIT	NCT02034110 JapicCTI-173743

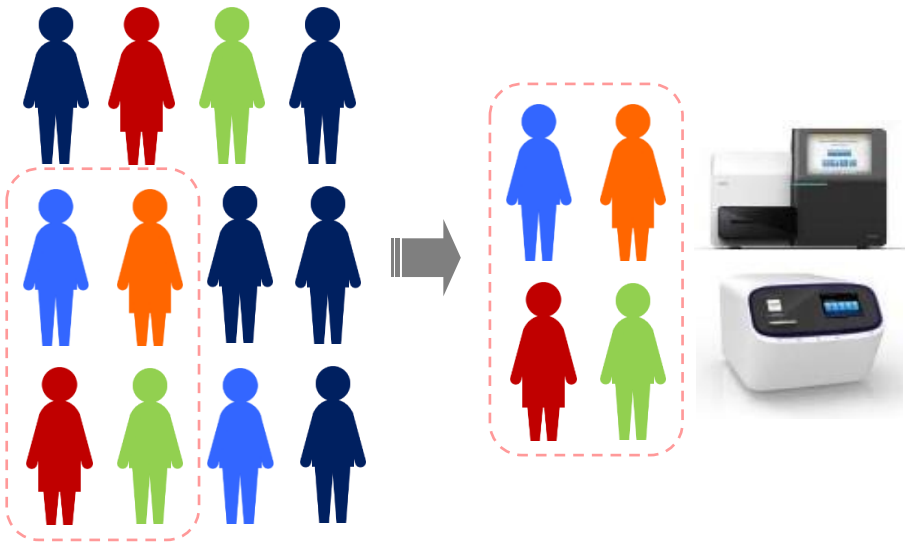
https://rctportal.niph.go.jp/ Accessed Nov. 1, 2021

Platform-type trials

Genomic medicine = medicine based on patient genomic information

Patient selection

CGP test



Participate in a platform-type trial

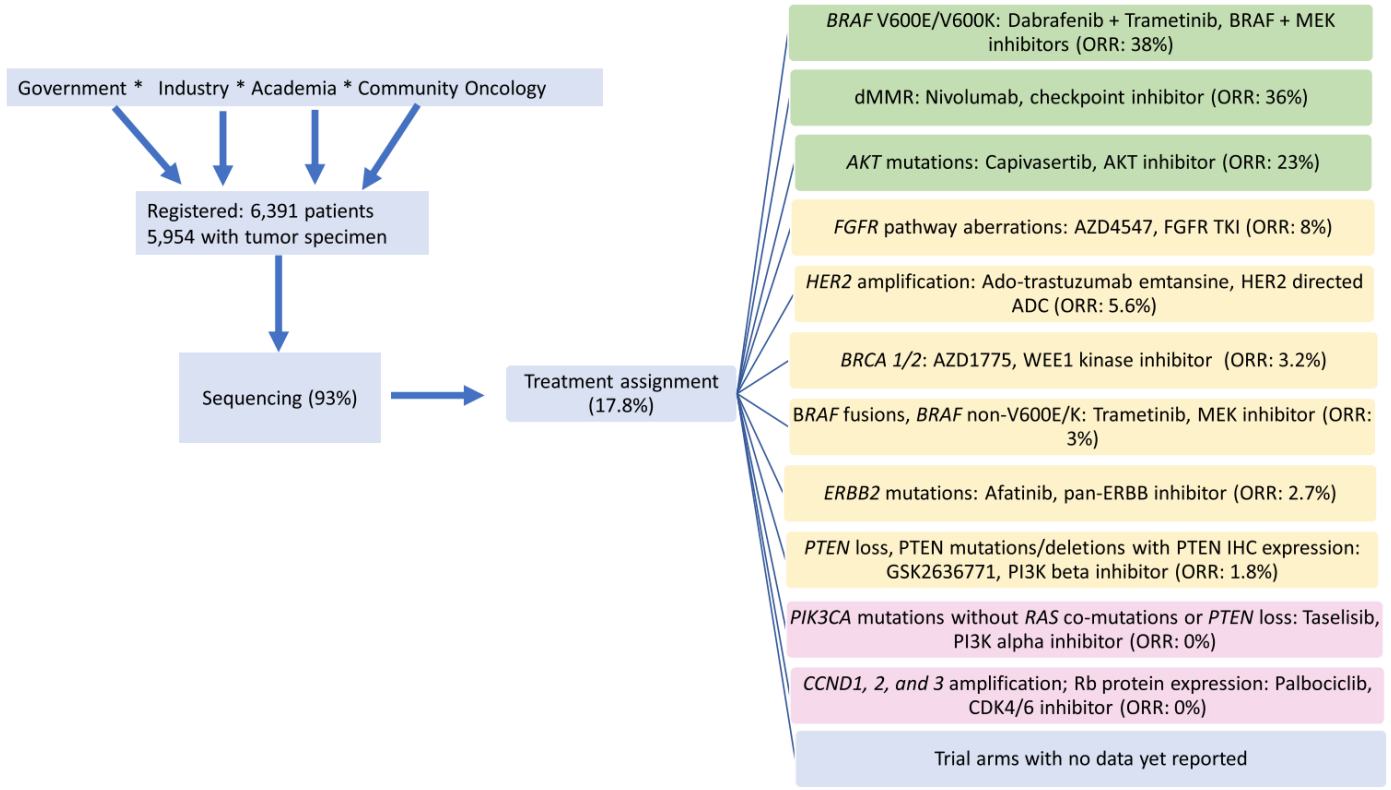
Treatment selection based on genetic abnormalities

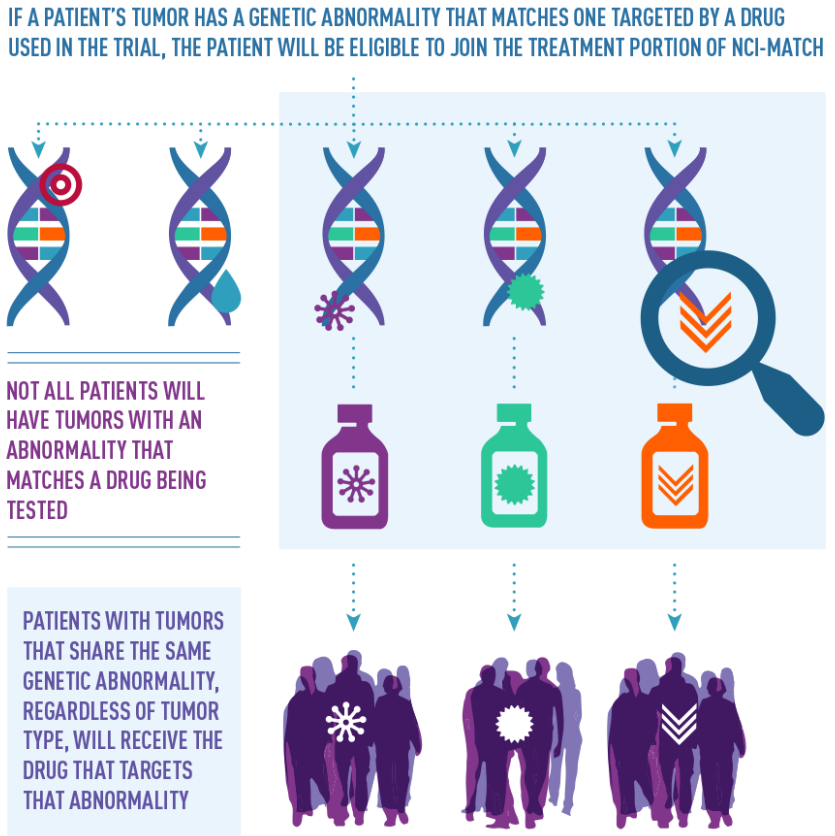
A gene alteration	Clinical trial for drug A′
B gene alteration	Clinical trial for drug B′ + X
C gene alteration	Clinical trial for drug C′
D gene alteration + Z gene alteration	Clinical trial for drug D′ + Z′

Platform-type trials for genomic medicine

Representative trials	Design details	Biomarker used	Aim	Published data
MD Anderson IMPACT1	Navigational	Sequencing and immunohistochemistry	Use of tumor molecular profiling to optimize the selection of targeted therapies for patients who will participate in a phase I clinical trial program	*Am Soc Clin Oncol Educ Book. 2014:61–9. JCO Precis Oncol. 2017;2017:PO.17.00002.*
TAPUR	Non-randomized, open label	ALK, ROS1, MET, mTOR, TSC, HER2, BRCA, ATM, RET, VEGFR1/2/3, KIT, PDGFRβ, BRAF[b]	Evaluate the efficacy of FDA-approved, targeted agents in patients whose tumors have actionable genomic alterations known to be targeted by the respective drug	J Clin Oncol. 2020;38(4_suppl):122. J Clin Oncol 2020;38(4_suppl):132. J Clin Oncol. 2020;38(4_suppl):133.
NCI-MATCH	Non-randomized, open label, parallel assignment	EGFR, HER2, MET, ALK, ROS1, BRAF[b], PIK3CA, FGFR, PTENNF1, cKIT	Evaluate the efficacy of matched targeted treatments in patients with refractory cancers, irrespectively of their cancer histology	J Clin Oncol. 2020;38(3):214–22. Ann Oncol. 2019;30(11):1821–30. Cancer Res. 2019;79(13 Supplement):CT138-CT.
MD Anderson IMPACT2	Randomized phase II study	Tumor molecular profiling	Compare progression-free survival in patients with advanced cancer who received matched treatments based on tumor genomic profiling results vs. those whose treatment was not selected based on genomic analysis	NCT02152254 NPJ Precis Oncol. 2021;5(1):21.
I-PREDICT UCSD	Prospective navigation	Molecular alterations, PD-L1, tumor mutation burden, and microsatellite instability	Assess whether personalized treatment with combination therapies would improve outcomes in patients with refractory malignancies	Nat Med. 2019;25(5):744–50.
SHIVA	Randomized, controlled, phase II	Alterations in hormone receptors and PI3K/AKT/mTOR and RAF/MEK pathways	Assess the efficacy of molecularly targeted treatments matched to tumor molecular alterations versus conventional therapy	Lancet Oncol. 2015;16(13):1324–34.
NCI-MPACT	Randomized, phase II	Alterations in DNA repair and PI3K and RAS/RAF/MEK pathways	Assess the utility of selecting treatment based on tumor DNA sequencing in patients with advanced cancer compared to that of not-matched treatment	JCO Precis Oncol. 2021 Jan 12;5:PO.20.00372.
DART	Multiple cohorts, phase II	Immunotherapy for rare cancers; biomarkers are assessed as correlated	Assess response rates of nivolumab and ipilimumab combination in multiple cohorts of rare and ultra-rare cancers	Clin Cancer Res. 2020;26(10):2290–6. Cancer. 2021;127(17):3194–201. Clin Cancer Res. 2022;28(2):271–8. J Immunother Cancer. 2021 Aug;9(8):e002990.
BELIEVE	Non-randomized, open label, parallel assignment	Tumor molecular profiling	Evaluate the efficacy of matched targeted treatments in patients with refractory cancers, irrespectively of the cancer histology	Pediatr Blood Cancer 66:S14,2019 (suppl 5)

Clinical trials that provide treatment options based on next-generation sequencing results, such as NCI-MATCH, are being conducted in the US





Cancer Cell. 2021 Jan 11;39(1):22-24.

https://www.aacr.org/blog/2015/08/19/nci-match-trial-opens/

Results of NCI-MATCH

Number	Treatment details	Inclusion criteria	Sample size	ORR (%)	DCR (%)	Survival results
1	Nivolumab (anti-PD-1 antibody)	Types of deficient mismatch repair non-colon cancers (for example, endometrial cancer, prostate cancer, uterine carcinosarcoma)	42	36	57	18-month PFS rate: 31.4% Median OS: 17.3%
2	AZD4547 (FGFR inhibitor)	Tumors with FGFR amplification, mutation, or fusion (for example, breast cancer, urology, endometrium)	50	5	51	6-month PFS rate: 17%
3	Capivasertib (pan-AKT inhibitor)	Tumors with AKT1 E17K mutation (for example, breast cancer, endometrial cancer)	35	23	69	6-month PFS rate: 52%
4	Trastuzumab emtansine (HER2 targeted antibody-drug conjugate)	HER2 amplification tumors, excluding breast cancer and stomach cancer	36	5.6	52.6	6-month PFS rate: 23.6%
5	Taselisib (PI3 kinase inhibitor)	Tumors with activating mutation in PIK3CA	65	0	NR	6-month PFS rate: 27%
6	GSK2636771 (PI3K β-selective inhibitor)	Arm N:PTEN mutation/deletion Arm P:Tumors with PTEN loss	22 34	4.5 0	36.5 37.5	Median PFS: Both groups 1.8 months
7	Afatinib (pan-HER inhibitor)	Patients with HER2 mutation other than in non-small cell lung cancer	40	2.7	NR	6-month PFS rate: 11%
8	Palbociclib (cyclin-dependent kinase 4/6 inhibitor)	CCND1-3 amplification cancer	40	0	38.9	Median PFS: 1.8 months
9	AZD1775 (Wee1 kinase inhibitor)	Tumors with mutations in BRCA 1-2	33	3.2	NR	6-month PFS rate: 19%

https://ecog-acrin.org/nci-match-eay131-findings/

1) J Clin Oncol. 2020;38(3):214–22. 2) J Clin Oncol. 2020 Jul 20;38(21):2407-2417. 3) JAMA Oncol. 2021 Feb 1;7(2):271-278. 4) Ann Oncol. 2019 Nov 1;30(11):1821-1830. 5) JCO Precis Oncol. 2022 Feb;6:e2100424. 6) Ann Oncol 2018;29(Suppl 8):viii137.
7) Cancer Res. 2019; 79 (abstract CT139) 8) Cancer Res 2019;79(Suppl). (abstract LB – 010) 9) Cancer Res 2019;79(Suppl). (abstract CT138.) 10) J Clin Oncol. 2020 Nov 20;38(33):3895-3904. 11) Clin Cancer Res. 2020 Apr 15;26(8):1812-1819.
12) J Clin Oncol. 2022 May 10;40(14):1552-1561. 13) Clin Cancer Res. 2021 Jun 1;27(11):2996-3004. 14) J Clin Oncol. 2022 May 10;40(14):1552-1561.
15) JCO Precis Oncol. 2022 Feb;6:e2100424. 16, 17) NPJ Precis Oncol. 2022 Mar 1;6(1):13. 18) JCO Precis Oncol. 2022 Aug;6: e2200165.

Results of NCI-MATCH

Number	Treatment details	Inclusion criteria	Sample size	ORR (%)	DCR (%)	Survival results
10	Dabrafenib (BRAF inhibitor) Trametinib (MEK inhibitor)	Tumors with BRAF V600E/K mutation (colorectal cancer and thyroid cancer, excluding melanoma)	35	38	75.9	Median PFS: 11.4 months Median OS: 28.6 months
11	Trametinib (MEK inhibitor)	Pre-set fusions or non-V600 mutations	32	3	15.6	Median PFS: 1.8 months Median OS: 5.7 months
12	Copanlisib (PI3 kinase inhibitor)	Cancer with PIK3CA mutations (± PTEN loss) excluding HER2-positive breast cancer and lymphoma	35	16	52	Median PFS: 3.2 months Median OS: 5.9 months
13	Binimetinib (MEK inhibitor)	Codons 12, 13, vs 61 NRAS-mutation	47	2.1	51	Median PFS: 1.7 vs 4.9 months Median OS: 5.0 vs 15.1 months
14	Copanlisib (PI3K inhibitor)	PIK3CA mutations (with or without PTEN loss)	35	16	52	Median PFS: 3.4 months Median OS: 5.9 months
15	Taselisib (PI3K inhibitor)	PIK3CA mutation (excluding breast cancer, squamous cell lung cancer, or cancer with *KRAS* or *PTEN* mutations)	61	0	32	Median PFS: 3.2 months Median OS: 7.2 months
16	Critpzinib (ALK, ROS1, MET, HGFR inhibitor)	Rare cancers with ALK rearrangement	4	50	75	Median PFS: 3.8 months Median OS: 4.3 months
17	Critpzinib (ALK, ROS1, MET, HGFR inhibitor)	Rare cancers with ROS1 rearrangement	4	25	50	Median PFS: 4.3 months Median OS: 6.2 months
18	Afatinib	Solid cancers with ERBB2-activating mutations	59	2.7	40.5	Median PFS: 1.7 months Median OS: 6.5 months

https://ecog-acrin.org/nci-match-eay131-findings/

1) J Clin Oncol. 2020;38(3):214–22. 2) J Clin Oncol. 2020 Jul 20;38(21):2407-2417. 3) JAMA Oncol. 2021 Feb 1;7(2):271-278. 4) Ann Oncol. 2019 Nov 1;30(11):1821-1830. 5) JCO Precis Oncol. 2022 Feb;6:e2100424. 6) Ann Oncol 2018;29(Suppl 8):viii137.
7) Cancer Res. 2019; 79 (abstract CT139) 8) Cancer Res 2019;79(Suppl). (abstract LB – 010) 9) Cancer Res 2019;79(Suppl). (abstract CT138.) 10) J Clin Oncol. 2020 Nov 20;38(33):3895-3904. 11) Clin Cancer Res. 2020 Apr 15;26(8):1812-1819.
12) J Clin Oncol. 2022 May 10;40(14):1552-1561. 13) Clin Cancer Res. 2021 Jun 1;27(11):2996-3004. 14) J Clin Oncol. 2022 May 10;40(14):1552-1561.
15) JCO Precis Oncol. 2022 Feb;6:e2100424. 16, 17) NPJ Precis Oncol. 2022 Mar 1;6(1):13. 18) JCO Precis Oncol. 2022 Aug;6: e2200165.

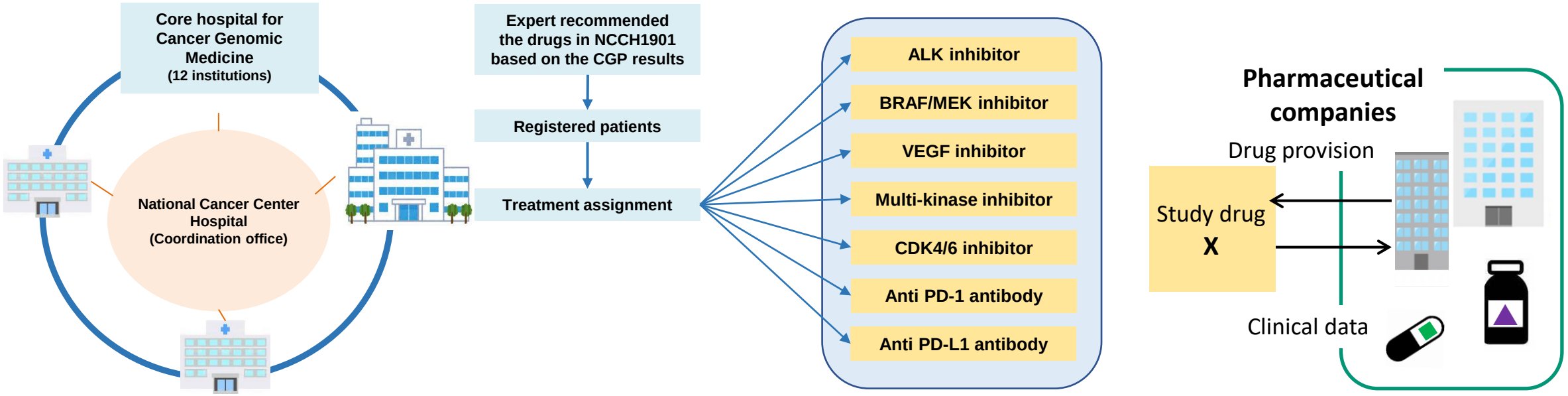
Results of TAPUR trial

Number	Treatment details	Inclusion criteria	Sample size	Objective response rate (%)	Disease control rate (%)	Survival results
1	Cetuximab (anti-EGFR antibody)	Wild-type *KRAS*, *NRAS*, *BRAF*	Breast cancer n = 10	0	0	PFS 6.7 weeks OS 14.1 weeks
			Non-small cell lung cancer n = 10	0	0	PFS 8.0 weeks, OS 22.7 weeks
			Ovarian cancer n = 29	0	14	PFS 8.0 weeks, OS 21.6 weeks
2	Palbociclib (cyclin-dependent kinase 4/6 inhibitor)	CDKN2A loss/mutation	Pancreatic cancer n = 12	0	0	PFS 7.2 weeks, OS 12.4 weeks
			Biliary tract n = 10	0	0	PFS 7.3 weeks, OS 11.1 weeks
		CDKN2A change	Non-small cell lung cancer n = 29	3.4	31	PFS 8.1 weeks, OS 21.6 weeks
3	Olaparib (PARP inhibitor)	BRCA1/2 inactivating mutation in germ-line cell/somatic-line cell	Prostate cancer n = 29	52	68	PFS 75.3 weeks, OS 41.7 weeks
			Pancreatic cancer n = 30	7	31	PFS 8.1 weeks, OS 43.0 weeks
			Solid cancer n = 32	25	41	PFS 15.7 weeks, OS 45.0 weeks
	Olaparib (PARP inhibitor)	ATM mutation/deletion	Solid cancer n = 39	8	25	PFS 8.4 weeks, OS 40.4 weeks
4	Trastuzumab＋Pertuzumab (anti-HER2 antibody)	ERBB2 amplification/overexpression	Colorectal cancer n = 28	25	50	PFS 17.2 weeks, OS 108.6 weeks
			Lung cancer n = 28	11	37	PFS 16.1 weeks, OS 54.4 weeks
5	Pembrolizumab (anti-PD- 1 antibody)	TMB-high (≥9 mutations/Mb)	Breast cancer n = 28	21	37	PFS 10.6 weeks, OS 30.6 weeks
			Colorectal cancer n = 28	11	28	PFS 9.3 weeks, OS 51.9 weeks
6	Sunitinib (multi-kinase inhibitor)	FLT-3 mutation/amplification	Colorectal cancer n = 10	0	20	PFS 10.1 weeks, OS 38 weeks
7	Vemurafenib (BRAF inhibitor) Cobimetinib (MEK inhibitor)	BRAF_V600E/D/K/R mutation	Colorectal cancer n = 30	29	57	PFS 15.8 weeks, OS 38.9 weeks
			Solid cancer n = 31	57	68	PFS 23.3 weeks, OS 60.9 weeks
8	Temsirolimus	mTOR mutation	Solid cancer n = 29	8	46	PFS 13.6 weeks, OS 45.3 weeks
9		PIK3CA mutation	Colorectal cancer n = 10	0	10	PFS 8.1 weeks, OS 8.7 weeks
10	Nivolumab, ipilimumab (anti-PD-1 antibody, CTLA4 antibody)	TMB-High (≥9 mutations/Mb)	Colorectal cancer n = 12	10	10	PFS 13.6 weeks, OS 42.9 weeks

JCO Precis Oncol. 2018;2018:10.1200/PO.18.00122. 1) Target Oncol. 2020 Dec;15(6):733-741. 2) JCO Precis Oncol. 2020 Nov;4:757-766. JCO Precis Oncol. 2019 Dec;3:1-8.
3) J Clin Oncol 2020;38(Suppl).(abstract 5567) J Clin Oncol 2020;38(Suppl). (abstract 4637) Ann Oncol 2022; VOLUME 33, SUPPLEMENT 7, S583-S584, Cancer Res (2022) 82 (12_Supplement): CT110.
4) J Clin Oncol 2020;38(Suppl).(abstract 132) , Ann Oncol 2022; VOLUME 33, SUPPLEMENT 7, S997-S998, 5) J Clin Oncol. 2021 Aug 1;39(22):2443-2451.
6) Target Oncol. 2020 Dec;15(6):743-750. 7) J Clin Oncol 2020;38(Suppl). (abstract 122) J Clin Oncol 2022;40, no. 16_suppl3008-3008 8) J Clin Oncol 2022;40, no. 16_suppl3114-3114.
9) J Clin Oncol 2022;40, no. 4_suppl106-106 10) J Clin Oncol 2022;40, no. 4_suppl107-107

Prospective trial of patient-proposed healthcare services with multiple targeted agents based on the results of gene profiling in multigene panel test (BELIEVE trial/code name: NCCH1901)

jRCT Japan Registry of Clinical Trials
臨床研究実施計画・研究概要公開システム
jRCTs031190104



- Objective: To increase treatment options after gene panel testing
- Off-label treatment with multiple molecular targeted drugs conducted in patient-proposed healthcare services
- Clinical trials conducted within a single protocol (master protocol)
- Started on October 1, 2019

NCCH1901/BELIEVE trial cohort list

No.	Classification	Generic name	Brand name	Provided by	Pediatric application
1	ALK inhibitor	Ceritinib	ZYKADIA tablets 150 mg	Novartis Pharma K.K.	—
2	BCR-ABL tyrosine kinase inhibitor	Imatinib	Glivec tablets 100 mg		—
3	mTOR inhibitor	Everolimus	AFINITOR tablets 2.5 mg/5 mg AFINITOR dispersible tablets 2 mg/3 mg		Available
4	BRAF inhibitor	Dabrafenib	Tafinlar capsules 50 mg/75 mg		—
5	MEK inhibitor	Trametinib	Mekinist tablets 0.5 mg/2 mg		—
6	VEGF inhibitor	Pazopanib	Votrient tablets 200 mg		—
7	BRAF inhibitor	Dabrafenib	Tafinlar capsules 50 mg/75 mg		—
	MEK inhibitor	Trametinib	Mekinist tablets 0.5 mg/2 mg		
8	BCR-ABL tyrosine kinase inhibitor	Nilotinib	Tasigna capsules 50 mg/150 mg/200 mg		Available
9	JAK inhibitor	Ruxolitinib	JAKAVI tablets 5 mg/10 mg		—
10	ALK inhibitor	Alectinib	ALECENSA capsules 150 mg	CHUGAI Pharmaceutical Co., Ltd.	Available
11	Anti HER2 monoclonal antibody	Trastuzumab	HERCEPTIN for intravenous infusion 150 mg		—
12	Anti PD-L1 monoclonal antibody	Atezolizumab	TECENTRIQ for intravenous infusion 1200 mg		—
13	TRK inhibitor	Entrectinib	ROZLYTREK capsules 100 mg/200 mg		Available
14	Anti PD-1 monoclonal antibody	Nivolmab	OPDIVO I.V. infusion 240 mg	ONO Pharmaceutical Co., Ltd.	—
15	BRAF inhibitor	Encorafenib	BRAFTOVI capsules 50 mg		—
	MEK inhibitor	Binimetinib	MEKTOVI tablets 15 mg		—
16	ALK inhibitor	Crizotinib	XALKORI capsules 200 mg/250 mg	Pfizer Japan, Inc.	—
17	BCR-ABL tyrosine kinase inhibitor	Ponatinib	ICLUSIG tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	—
18	Cyclin-dependent kinase 4/6 inhibitor	Abemaciclib	VERZENIO tablets 50 mg/100 mg/150 mg	Eli Lilly and Company	—
19	PARP inhibitor	Niraparib	ZEJURA tablets	Takeda Pharmaceutical Company	—

https://www.ncc.go.jp/jp/ncch/genome/90/index.html

Today's summary

- The CGP test is being conducted worldwide.
- To provide treatment opportunities after CGP testing, platform-type trials and basket trials are underway globally.
- BELIEVE trial: Japanese version of NCI-MATCH, which is the largest clinical trial for pan-solid tumors to evaluate the efficacy and safety of the off-label use of drugs in Japan.

Thank you for your attention

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