日本標準商品分類番号 874291

抗悪性腫瘍剤／チロシンキナーゼ阻害剤

劇薬、処方箋医薬品*

新発売

薬価基準収載

ロズリートレク®カプセル100mg、200mg

ROZLYTREK® Capsules
entrectinib

エヌトレクチニブカプセル

*注意－医師等の処方箋により使用すること

®F.ホフマン・ラ・ロシュ社（スイス）登録商標

Product Overview of ROZLYTREK®

Yoshito Nakanishi
ROZLYTREK® Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

ROZLYTREK®
entrectinib

Prepared: Sep. 2019

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends.

Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

ROZLYTREK®
entrectinib

About ROZLYTREK

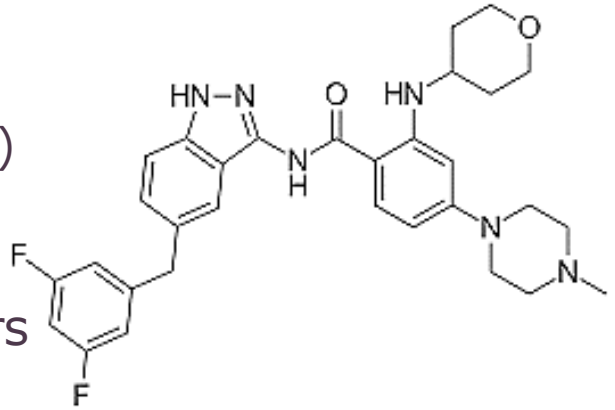
ROZLYTREK is a small molecule tyrosine kinase inhibitor that selectively blocks kinases including TRK family.

Nonproprietary name: entrectinib (JAN)

Target: TRK kinase family (TRKA, TRKB, TRKC)

Target cancer:

TRK; *NTRK* fusion–positive solid tumors



Structural formula

Gene name		Protein Name	
NTRK1	=	TRKA	
NTRK2	=	TRKB	
NTRK3	=	TRKC	TRK (neurotrophin receptors)

Source: Rozlytrek package insert, Rozlytrek product information
Khotskaya YB, et al.: Pharmacol Ther. 2017;173:58-66

ROZLYTREK® entrectinib

History of Development

2012	Nerviano Medical Sciences started clinical trials in Italy
2013	Ignyta Inc. started development of entrectinib
May 2017	U.S. FDA granted Breakthrough Therapy Designation
Oct. 2017	EMA granted Medicins designation
Dec. 2017	Roche agreed to acquire Ignyta
March 2018	MHLW granted *Sakigake* designation
July 2018	Chugai signed in-licensing agreement
Dec. 2018	Chugai submitted regulatory application for *NTRK* fusion-positive solid tumor
June 2019	Chugai obtained regulatory approval in *NTRK* fusion-positive solid tumor for the first time in the world
Sep. 2019	ROZLYTREK was listed on the National Health Insurance reimbursement price list and launched

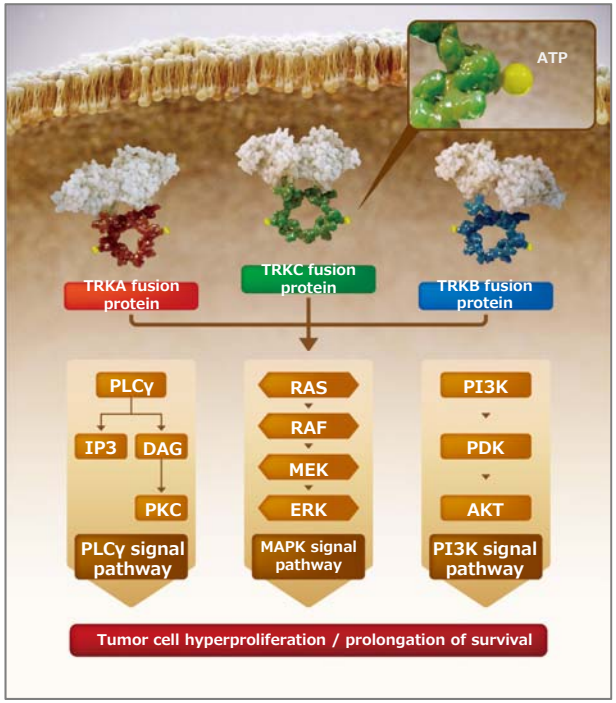
ROZLYTREK®
entrectinib

Mode of Action

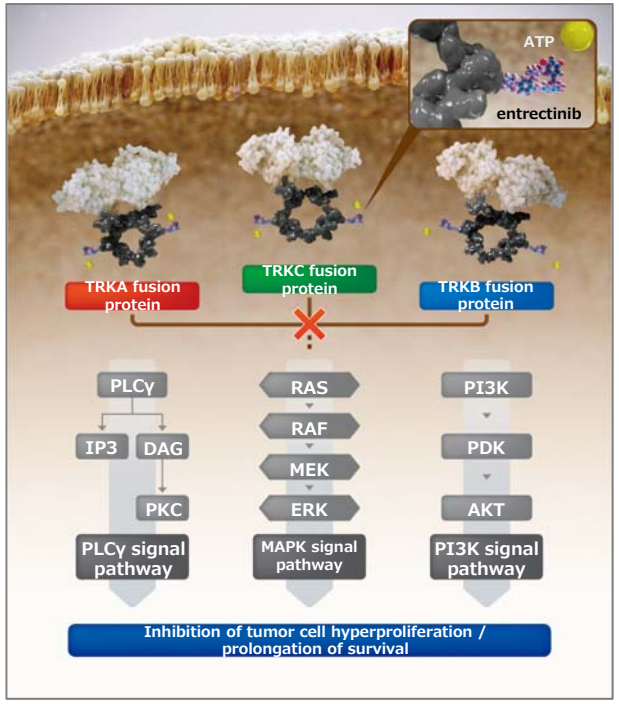
ROZLYTREK inhibits abnormally-activated TRK fusion kinase protein and blocks TRK signal pathway, suppressing excessive growth and prolongation of survival of cancer cells.

(Conceptual illustration)

●Tumor growth mechanism by TRK fusion protein



●MOA of signal suppression by entrectinib

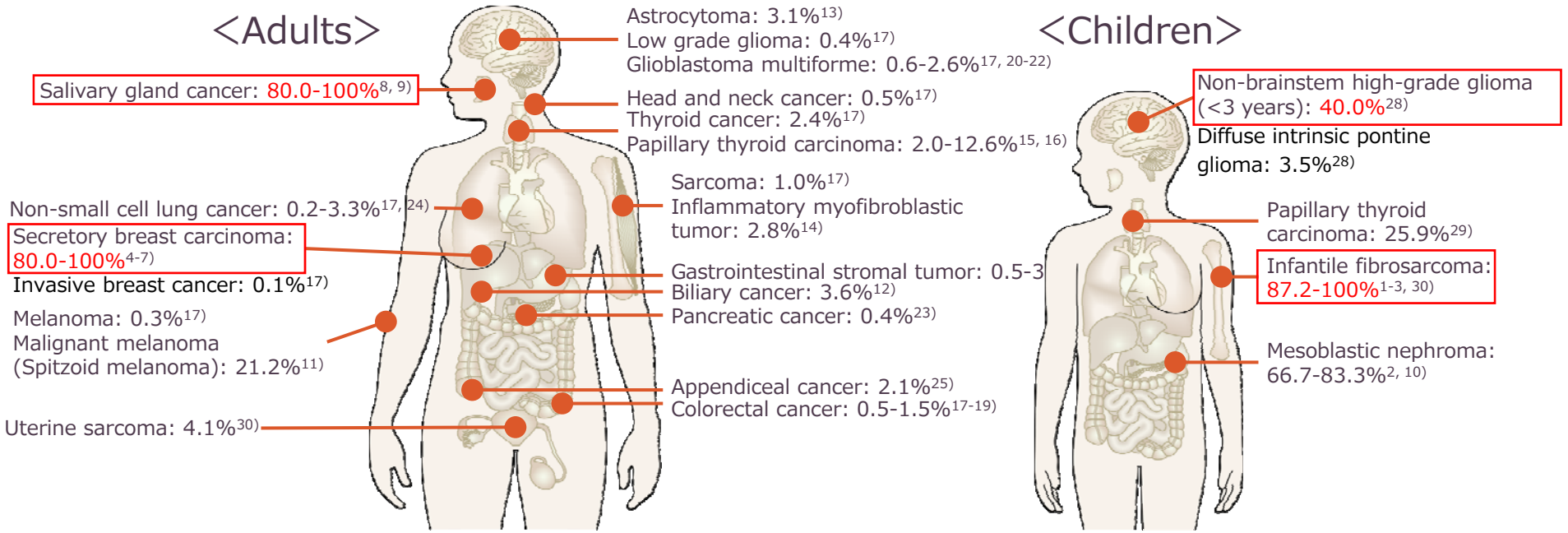


ROZLYTREK® entrectinib

Source: ROZLYTREK product information
Vaishnavi A, et al. Cancer Discov. 2015; 5 (1): 25-34.
Kheder ES, et al. Clin Cancer Res. 2018; 24 (23): 5807-5814.
Rolfo C, et al. Expert Opin Investig Drugs. 2015; 24 (11): 1493-1500.

Proportion of *NTRK* Fusion-Positive Cancers

The number of eligible patients is estimated to be very small since the incidence of NTRK fusions tends to be low in common cancers and high in rare cancers.



1) Knezevich SR, et al.: Nat Genet. 1998; 18 (2): 184-187. 2) Rubin BP, et al.: Am J Pathol. 1998; 153 (5): 1451-1458. 3) Bourgeois JM, et al.: Am J Surg Pathol. 2000; 24 (7): 937-946. 4) Del Castillo M, et al.: Am J Surg Pathol. 2015; 39 (11): 1458-1467. 5) Makretsov N, et al.: Genes Chromosomes Cancer. 2004; 40 (2): 152-157. 6) Tognon C, et al.: Cancer Cell. 2002; 2 (5): 367-376. 7) Laé M, et al.: Mod Pathol. 2009; 22 (2): 291-298. 8) Skálová A, et al.: Am J Surg Pathol. 2016; 40 (1): 3-13. 9) Bishop JA, et al.: Hum Pathol. 2013; 44 (10): 1982-1988. 10) Knezevich SR, et al.: Cancer Res. 1998; 58 (22): 5046-5048. 11) Wiesner T, et al.: Nat Commun. 2014; 5: 3116. 12) Ross JS, et al.: Oncologist. 2014; 19 (3): 235-242. 13) Jones DT, et al.: Nat Genet. 2013; 45 (8): 927-932. 14) Yamamoto H, et al.: Histopathology. 2016; 69 (1): 72-83. 15) Musholt TJ, et al.: Surgery. 2000; 128 (6): 984-993. 16) Leeman-Neill RJ, et al. Cancer. 2014; 120 (6): 799-807. 17) Stransky N, et al.: Nat Commun. 2014; 5: 4846. 18) Ardini E, et al.: Mol Oncol. 2014; 8 (8): 1495-1507. 19) Creancier L, et al.: Cancer Lett. 2015; 365 (1): 107-111. 20) Kim J, et al.: PLoS One. 2014; 9 (3): e91940. 21) Frattini V, et al.: Nat Genet. 2013; 45 (10): 1141-1149. 22) Zheng Z, et al.: Nat Med. 2014; 20 (12): 1479-1484. 23) Zehir A, et al.: Nat Med. 2017; 23 (6): 703-713. 24) Vaishnavi A, et al.: Nat Med. 2013; 19 (11): 1469-1472. 25) Chen Y, et al.: J Hematol Oncol. 2018; 11 (1): 78. 26) Shi E, et al.: J Transl Med. 2016; 14 (1): 339. 27) Brenca M, et al.: J Pathol. 2016; 238 (4): 543-549. 28) Wu G, et al.: Nat Genet. 2014; 46 (5): 444-450. 29) Prasad ML, et al.: Cancer. 2016; 122 (7): 1097-1107. 30) Chiang S, et al.: Am J Surg Pathol. 2018; 42 (6): 791-798. 31) Orbach D, et al.: Eur J Cancer. 2016; 57: 1-9.

ROZLYTREK® entrectinib

Indications

Neurotrophic tyrosine receptor kinase (*NTRK*) fusion–positive advanced or recurrent solid tumors

Precautions concerning Indications

1. The efficacy and safety of ROZLYTREK in adjuvant therapy have not been established.
2. Select candidate patients after carefully reading 17. “CLINICAL STUDIES” (regarding details such as the tumor types of patients included in clinical studies) to gain a thorough understanding about the efficacy and safety of ROZLYTREK and carefully considering treatments other than ROZLYTREK.
3. Administer ROZLYTREK to patients with tumors confirmed to be *NTRK* fusion–positive by a pathologist or clinical laboratory with the necessary experience. Use an approved testing method such as an *in vitro* diagnostic agent.
4. Carefully determine the advisability of administering ROZLYTREK to pediatric patients after carefully reading 9.7 “Pediatric Use” and 17. “CLINICAL STUDIES” regarding the ages of patients included in clinical studies.

Approved companion diagnostic: FoundationOne® CDx Cancer Genomic Profile

ROZLYTREK®
entrectinib

Product Outline

ROZLYTREK capsules 100 mg: 30 capsules
ROZLYTREK capsules 200 mg: 90 capsules

Regulatory classification
Powerful drug, prescription drug
Caution: Use only as prescribed by a physician, etc.

Storage
Store at room temperature

Shelf life
24 months

Precautions for handling
ROZLYTREK is hygroscopic. Protect capsules from moisture during storage after the bottle is opened.

Precautions for storage
Instruct patients to keep the product out of the reach of children in order to avoid swallowing by mistake.

ROZLYTREK
entrectinib

Source: ROZLYTREK product information
ROZLYTREK package insert

Dosage and Administration

The usual adult dosage is 600 mg entrectinib administered orally once a day. Reduce the dose as necessary depending on the patient's condition.

The usual pediatric dosage is 300 mg/m^2 (body surface area) entrectinib administered orally once a day. However, the dose should not exceed 600 mg. Reduce the dose as necessary depending on the patient's condition.

ROZLYTREK®
entrectinib

Approval Conditions

1. A drug risk management plan is to be prepared and appropriately implemented.

2. Given that the number of patients in clinical studies in Japan was extremely limited, postmarketing drug use surveillance of all patients receiving ROZLYTREK should be conducted until data for a certain number of patients have been accumulated, in order to understand background information on patients receiving ROZLYTREK, collect early data on the safety and efficacy of ROZLYTREK, and take necessary measures for appropriate use of ROZLYTREK.

Overview of ROZLYTREK RMP

Prepared: Sep. 2019

Safety Specification

Important Identified Risks

- Cardiac disturbance (excluding QT prolongation)
- Cognitive Impairment / Ataxia

Important Missing Information

- Use in patients with hepatic dysfunction

Important Potential Risks

- QT prolongation
- Syncope
- Interstitial lung disease
- Growth and developmental retardation

Efficacy concerns

Efficacy against *NTRK* fusion-positive advanced/recurrent solid tumor in the state of actual use

Pharmacovigilance Plan

Periodic site visits for six months post-launch

Routine activities

- Collection and evaluation of individual cases
- Collection and evaluation of literature etc.
- Collection and evaluation of information on overseas regulatory actions
- Signal detection and evaluation through means such as data mining techniques for adverse events (including deaths)

Additional activities

- Early post-marketing phase vigilance (EPPV)
- Drug use surveillance programs
- Specific use results survey (pediatric)

- **General drug use surveylance (all-case survey):** 200 subjects
- **Specific drug use surveillance (pediatric):** All of the pediatric patients treated with this product in seven years post-launch, if possible.

Risk Minimization Plan

Routine activities

- Preparation of package insert (revisions)
- Medication Guide for Patients

Additional activities

- Provision of information from EPPV
- Provision of information to healthcare providers (Guidance for Appropriate Use)
- Provision of information to patients

1. Requirements for facilities
2. Requirements for physicians
3. Preliminary explanation to physicians and healthcare professionals by medical representatives (MR)
4. Request for cooperation from hospital pharmacies and dispensing pharmacies
5. Restriction of distribution
6. Request for cooperation from wholesalers

ROZLYTREK® entrectinib

From Organ Specific to Gene Specific Cancer Treatment

- Expectations on ROZLYTREK for *NTRK* Fusion-Positive Solid Tumors -

Takayuki YOSHINO, MD, PhD
Director, Department of Gastroenterology and Gastrointestinal Oncology,
National Cancer Center Hospital East (NCCE), Japan
Co-principal investigator, GI-SCREEN-Japan

NCC NATIONAL CANCER CENTER JAPAN
EPOC
Exploratory Oncology Research & Clinical Trial Center

September 5th, 2019

Disclosure of Conflict of Interests

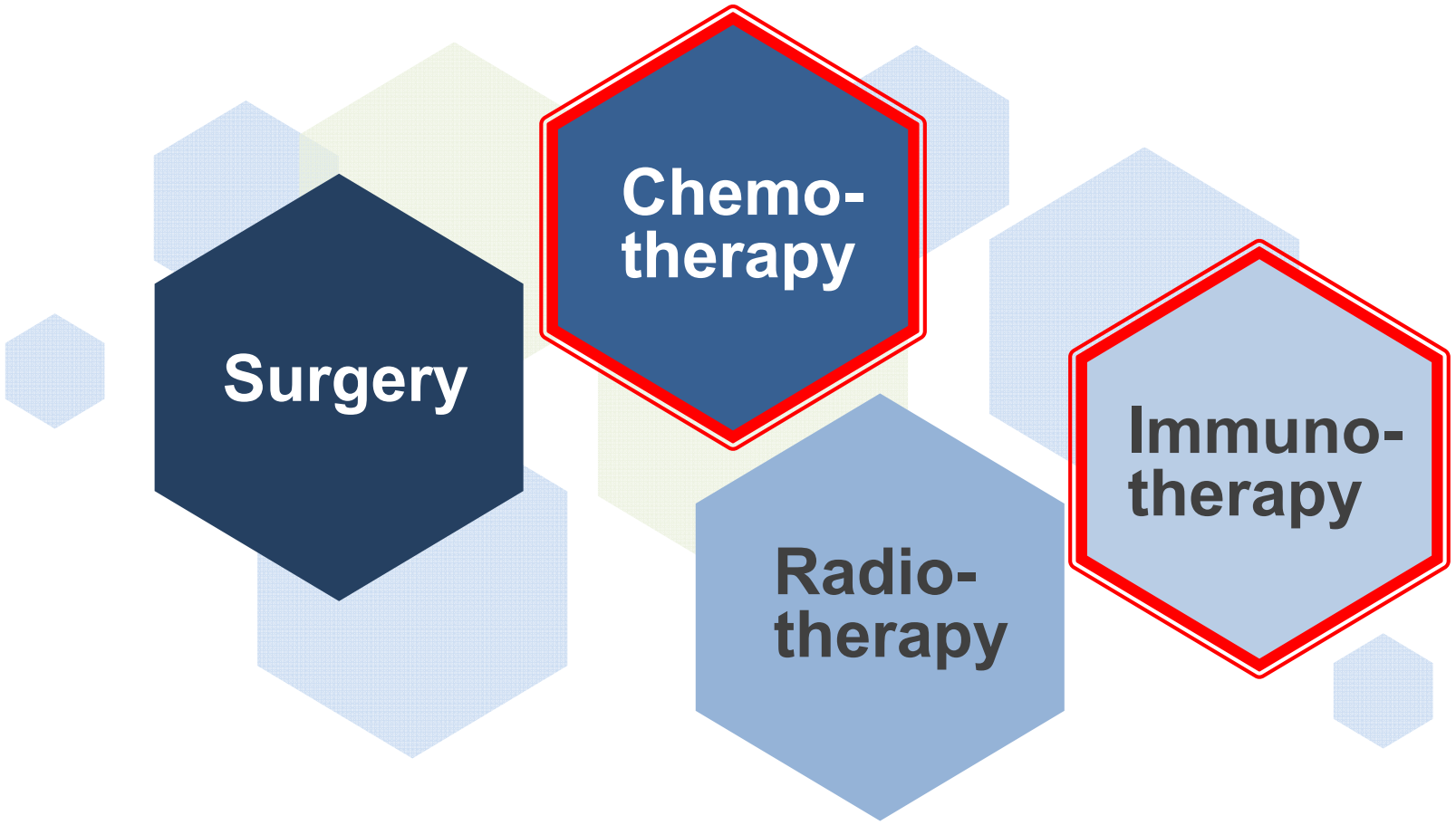
Name: Takayuki Yoshino

Research Funding: Novartis Pharma K.K.
MSD K.K.
Sumitomo Dainippon Pharma Co., Ltd.
CHUGAI PHARMACEUTICAL CO., LTD.
Sanofi K.K.
DAIICHI SANKYO COMPANY, LIMITED
PAREXEL International Inc.
ONO PHARMACEUTICAL CO., LTD.

Agenda

- Development of therapeutic drugs in the cancer genome era and challenges to date
- Change in cancer treatment from organ specific to gene specific
- *NTRK* fusion genes and entrectinib

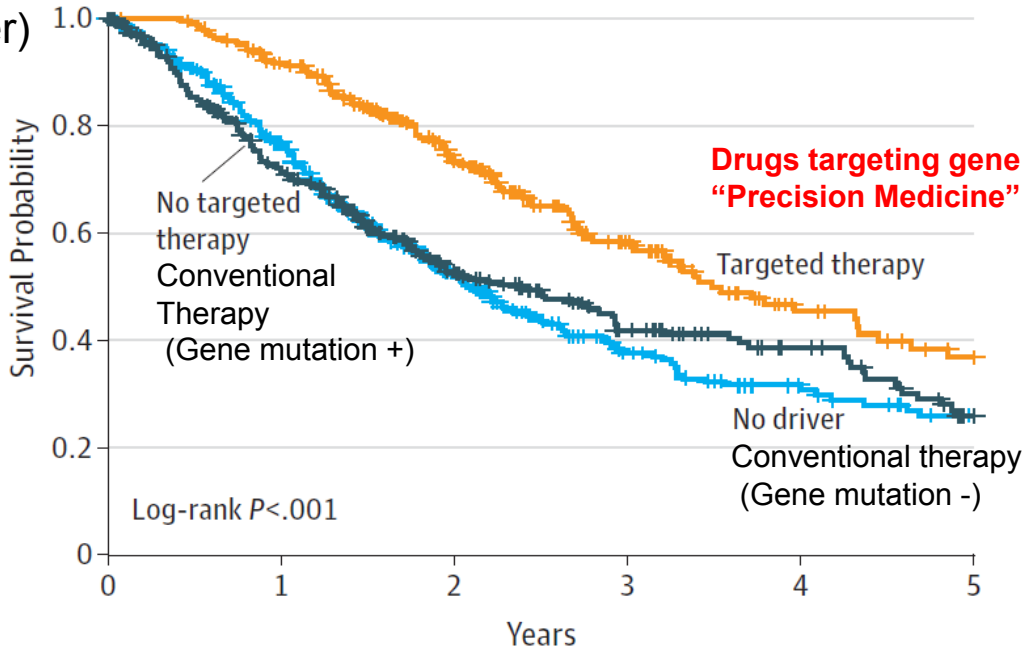
Chemo- and Immuno-Therapy are Central to Advanced Diseases



Treatment Goal for Advanced Cancer

- In the United States, President Obama announced the Precision Medicine Initiative in the State of the Union Address in 2015.
- Cancer prevention method and treatments considering individual differences in gene, environment and lifestyle are established, evolving from conventional cancer treatment designed for "Average patients."

(e.g. Lung cancer)



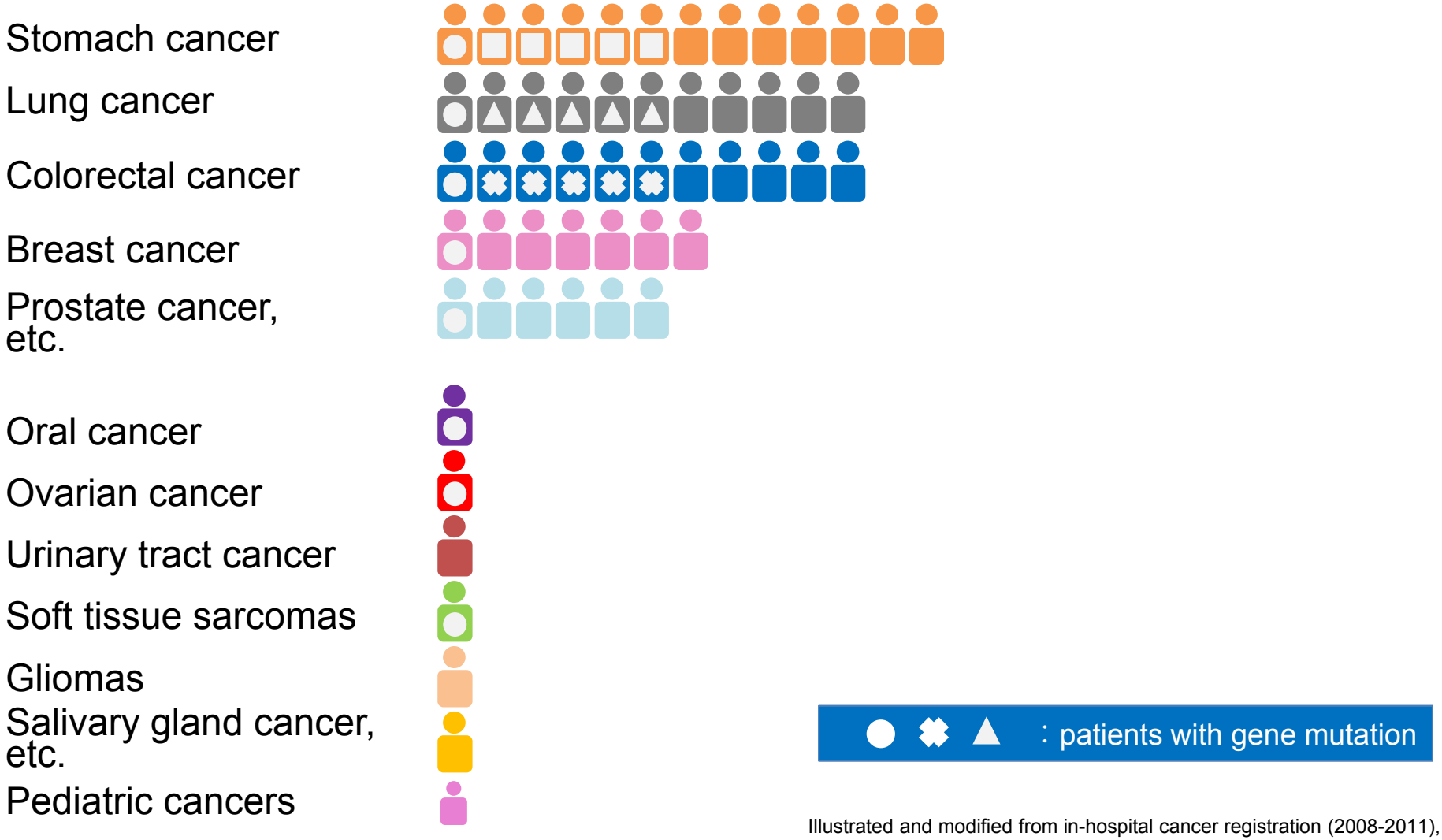
Drugs targeting gene mutation/alteration
"Precision Medicine"

Drugs targeting gene mutation/alteration improve survival for cancer patients

<Subject / Method>
Ten driver genes such as ERBB2, EGFR, ALK in 1,007 patients with recurrent / metastatic lung adenocarcinoma with PS 0-2 who underwent one or more genetic tests at 14 US institutions from 2009 to 2012 were tested the frequency of driver gene expression, the rate of molecular target therapy, and survival time were prospectively observed.

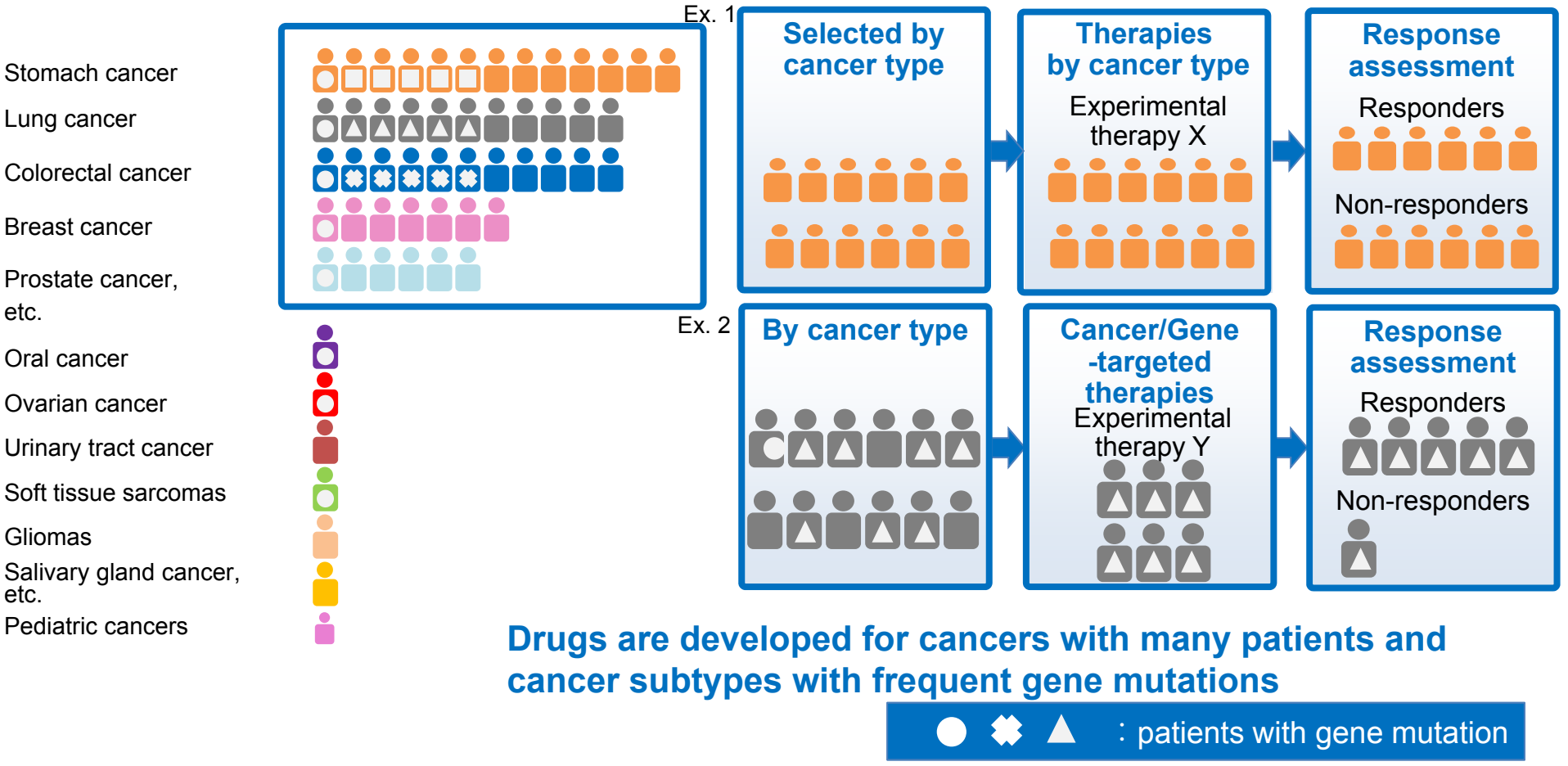
Kris MG, et al.: JAMA. 2014;311(19):1998-2006

Cancers with a Large Number of Patients and Rare Cancers



Illustrated and modified from in-hospital cancer registration (2008-2011),
Modified from Semin Cancer Biol. 2019;55:16-27

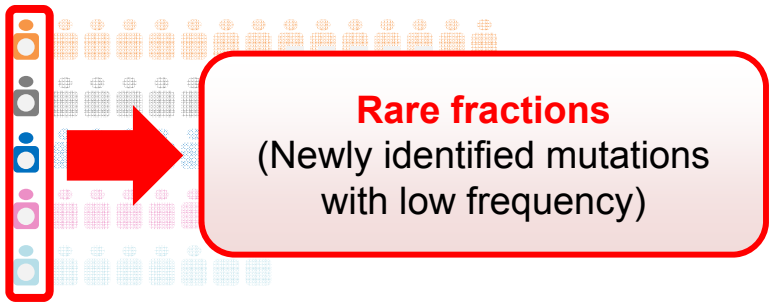
Drug Development to Date



Illustrated and modified from in-hospital cancer registration (2008-2011), Modified from Semin Cancer Biol. 2019;55:16-27

Challenges in Drug Development in Rare Cancers

Stomach cancer
Lung cancer
Colorectal cancer
Breast cancer
Prostate cancer, etc.



Rare fractions
(Newly identified mutations with low frequency)

Oral cancer
Ovarian cancer
Urinary tract cancer
Soft tissue sarcomas
Gliomas
Salivary gland cancer, etc.

Rare cancers

Pediatric cancers

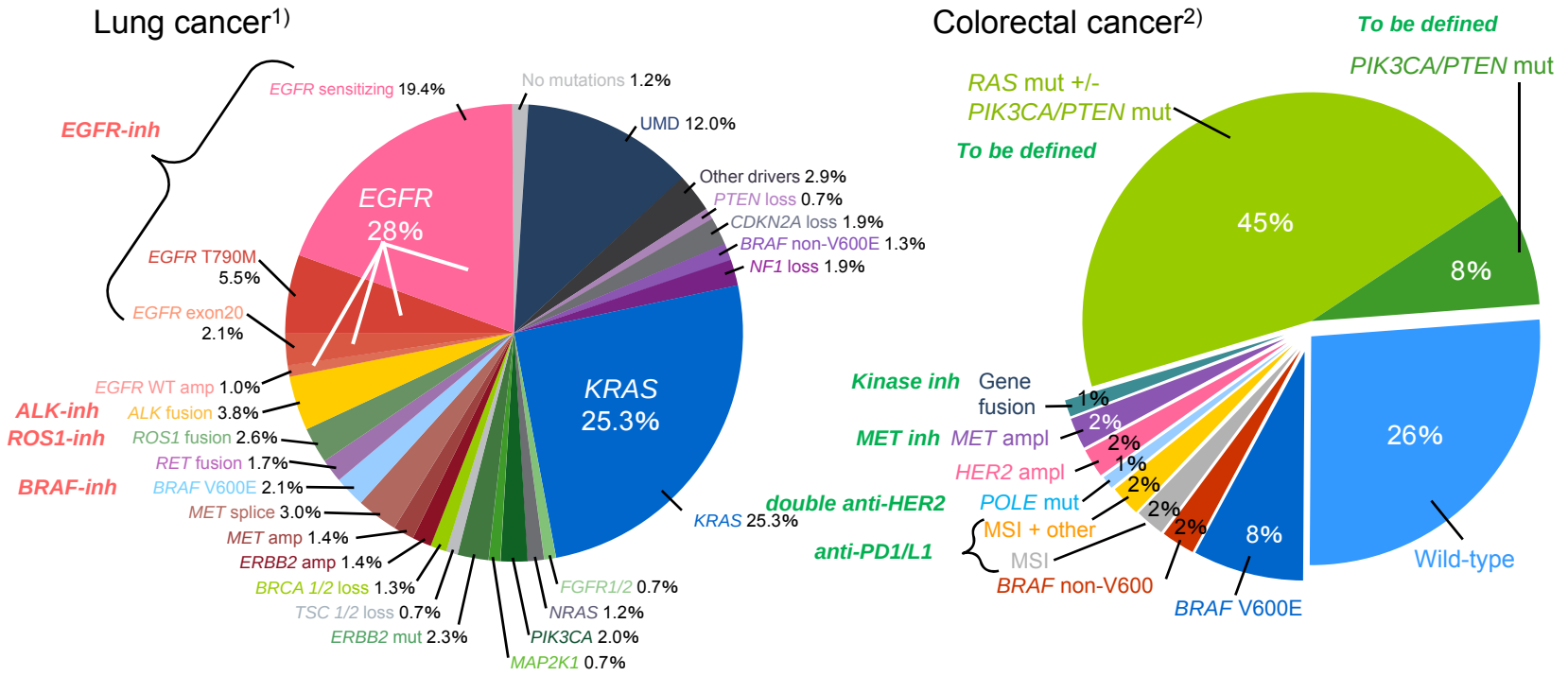
Pediatric cancers

<u>Confirmatory or large-scale trails</u> targeting gene mutations are infeasible because patient numbers are small

● ✸ ▲ : Gene mutation

"The Current State of Therapeutic Development for Rare Cancers in Japan, and Proposals for Improvement
Illustrated and modified from in-hospital cancer registration (2008-2011), Modified from Semin Cancer Biol. 2019;55:16-27

Proportion of Gene Alterations Identified in Lung and Colorectal Cancer



Treatments targeting these gene alterations may be developed in the future.

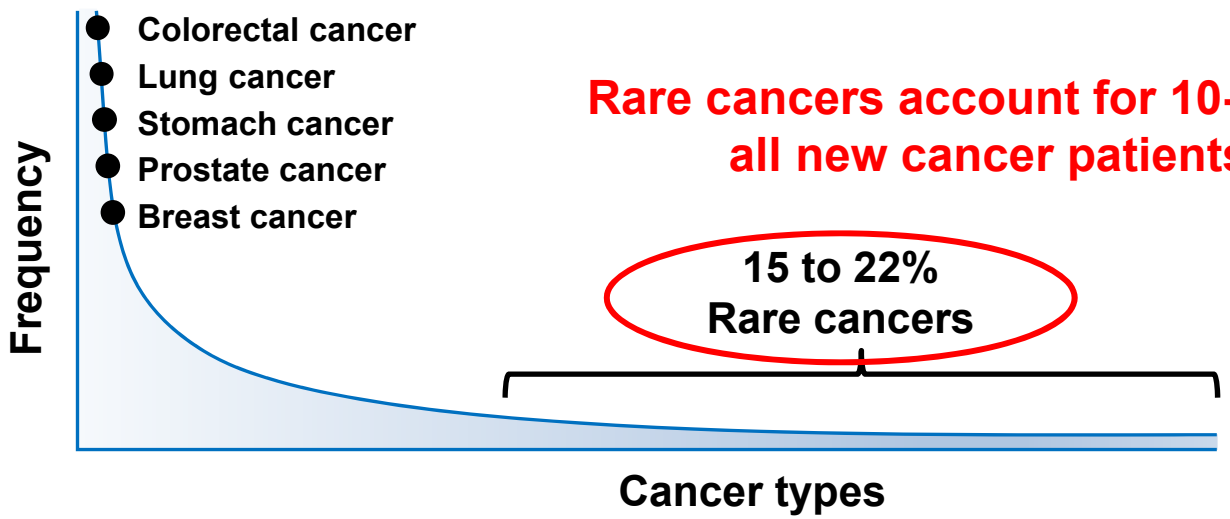
<Subjects / Methods>
Genetic information was identified by NGS for 860 lung cancer (adenocarcinoma) patients (left) and colorectal cancer patients (right).

1）Jordan EJ, et al.: Cancer Discov. 2017; 7: 596-609, 2）Dienstmann R, et al.: ASCO Educational Book 2018

What are Rare Cancers?

Defined as cancers newly diagnosed in fewer than six patients per year per 100,000 population

(Conceptual illustration)



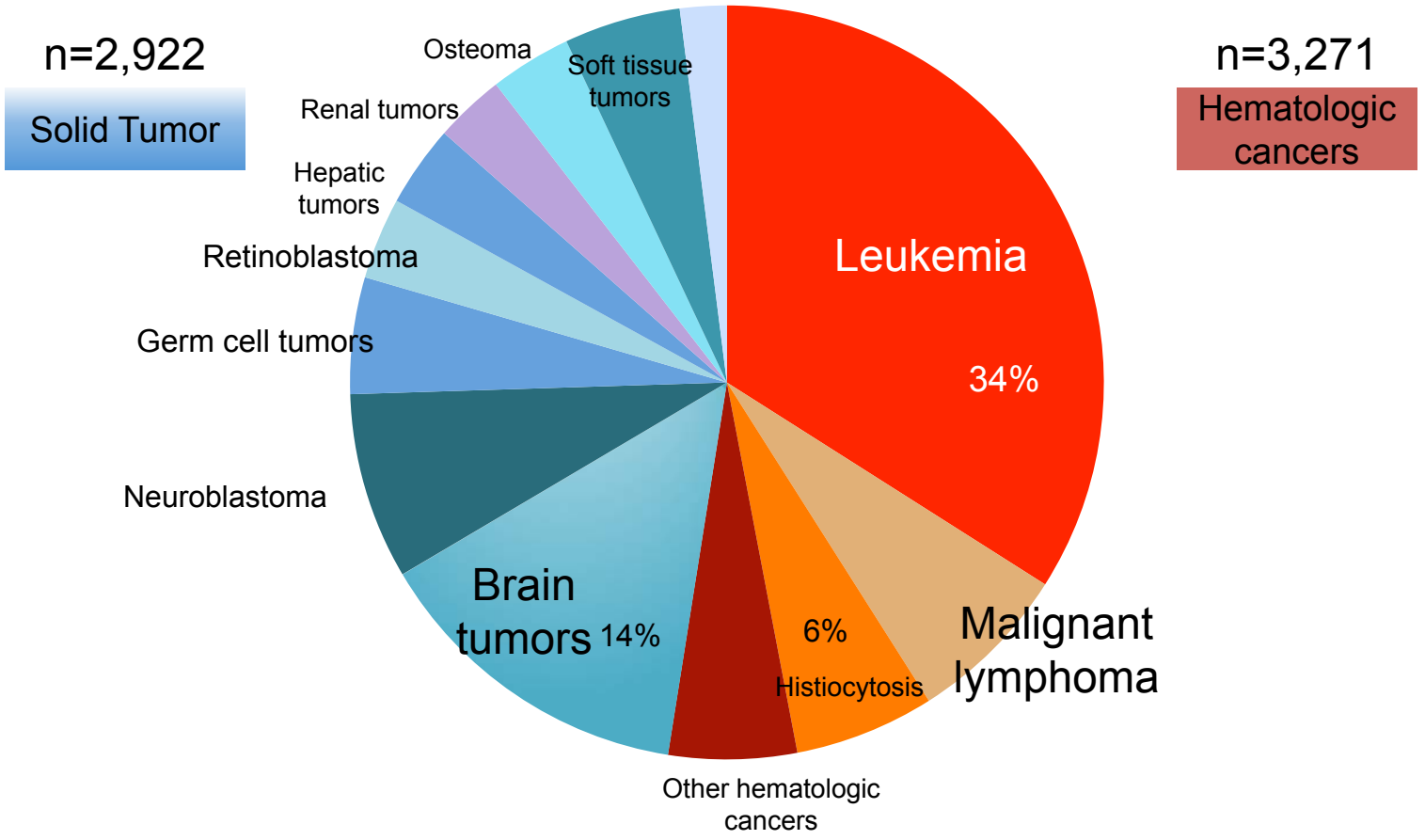
National Cancer Center: https://www.ncc.go.jp/jp/ri/division/rare_cancer_research/20161206100630.html

Establishing standard treatment or guidelines are difficult in rare cancers since the limited number of patients makes it difficult to conduct clinical research and trials difficult.

Therapeutic outcomes and treatment satisfaction are known to be lower in rare cancers than in more common cancers due to lack of proper diagnosis, optimal treatment and benefits from the latest medical findings.

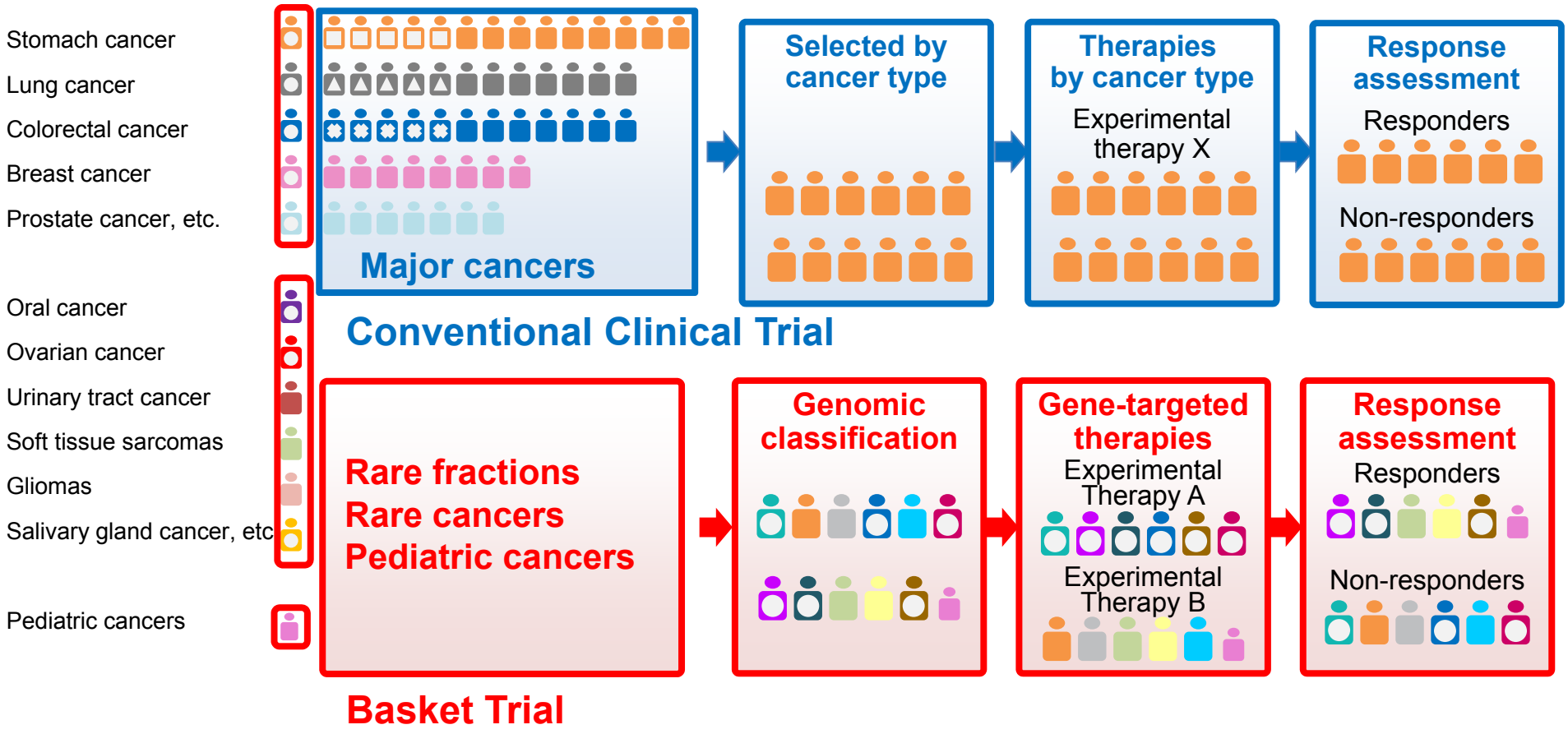
Source: Challenges and suggestions to promote clinical studies in rare cancers 2017

Newly Diagnosed Pediatric Cancer in 3 years



Source: 2008-2010 Japanese Society of Pediatric Hematology/Oncology enrollments

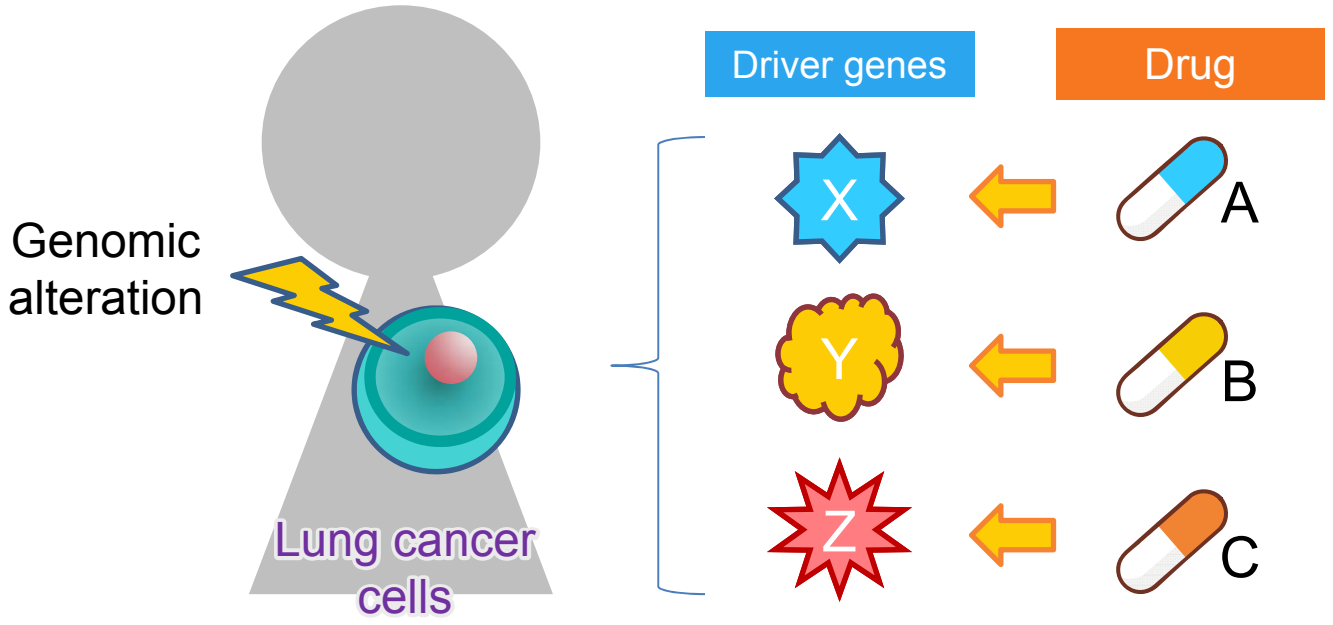
Drug Development in Rare Fractions/Cancers, and Pediatric Cancer



Modified from Semin Cancer Biol. 2019;55:16-27

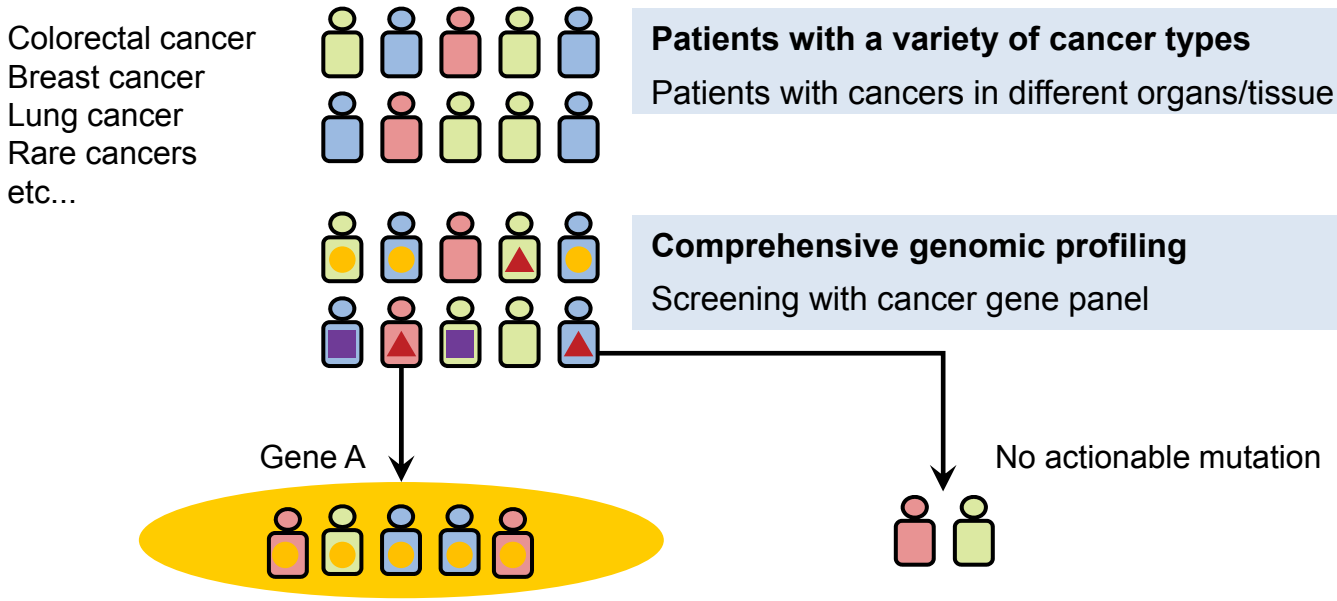
Cancer Genomic Medicine: Cancer Medicine Based on Genomic Information

- The single disease entity “lung cancer” has a variety of driver genes that require different drugs for treatment.
- Genomic medicine seeks to identify the driver mutations to allow more effective therapeutic drugs to be selected, leading to “personalized healthcare” tailored to each patient.



Overview and Significance of Basket Trials

In a basket trial, patients with an actionable driver mutation or characteristic biomarker such as genomic instability are recruited across organ types, and a drug which targets specific driver genes is developed. This clinical trial design consolidates rare fractions into a single trial.

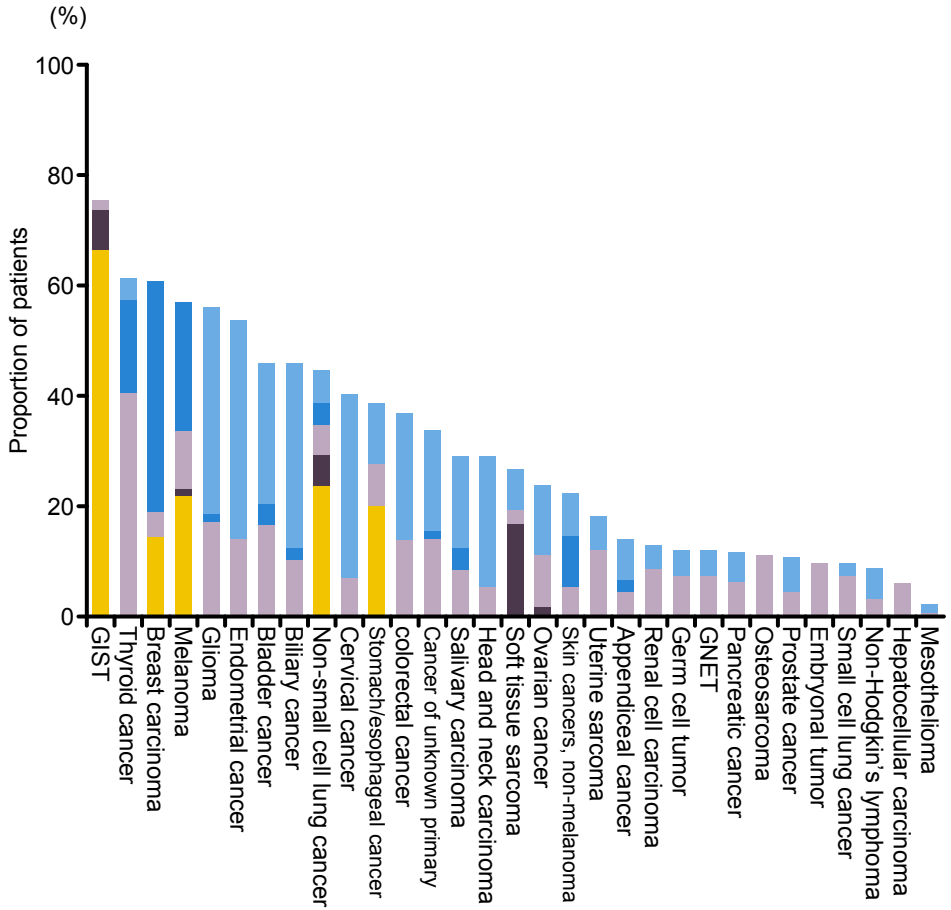


Simon R, Ann Intern Med. 2016;165(4):270-8, Tao JJ, et al.: Annu Rev Med. 2018;69:319-331

Proportion of Actionable Gene Alterations

Case of MSK-IMPACT (a hybridization capture–based NGS panel)

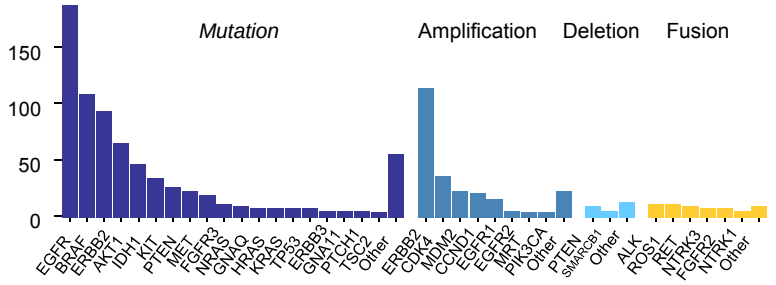
Proportion of patients with gene alterations among 11,369 patients with advanced solid cancers



Evidence levels of gene alterations as a predictor of drug efficacy

Level 1	FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker for an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication

Number of patients with gene alterations

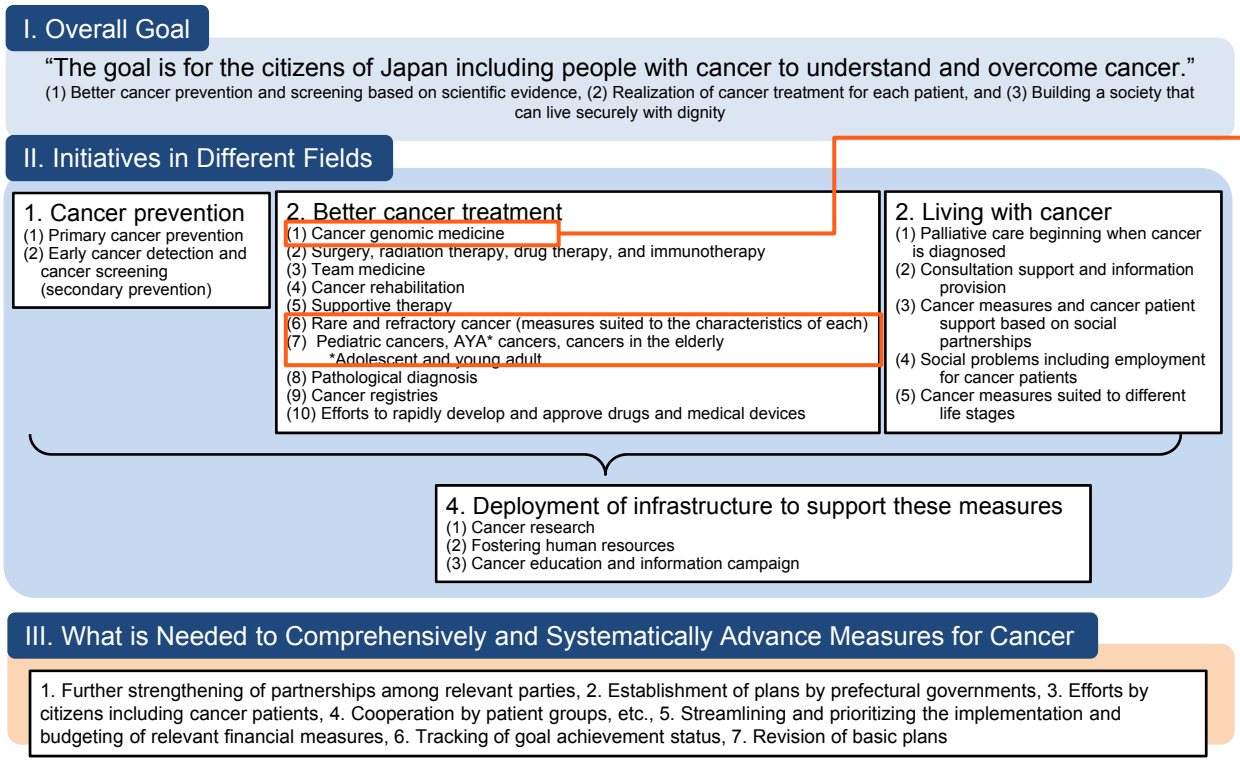


GIST: Gastrointestinal stromal tumor, GNET: Gastrointestinal neuroendocrine tumor

Zehir A, et al: Nat Med 23（6）: 703-713, 2017

The 3rd Phase Basic Plan to Promote Cancer Control Programs

The 3rd Phase Basic Plan to Promote Cancer Control Programs (approved by Japanese Cabinet on March 9, 2018) (summary) [1)]



2. Better cancer medicine (excerpt) [2)]

(1) Cancer genomic medicine

Current status and issues: **Genomic medicine** that factors in individual differences based on the genomic information of individuals has recently shown increasing promise, and a range of related efforts are underway in and outside Japan. ... What will be needed to bring about cancer genomic medicine at core hospitals and pediatric cancer core hospitals are the establishment of standards for ensuring the quality and precision of **genomic analysis with next-generation sequencers** and the development of systems for interpreting (establishing the clinical significance of) the analytical results and for properly providing relevant information to patients.

For "better cancer medicine" in the 3rd phase basic plan to promote cancer control programs, concrete goals have been set for cancer genomic medicine as an area to be advanced.

1) MHLW: Summary of 3rd phase basic plan to promote cancer control programs (March 2018) https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000196974.pdf (accessed in December 2018)
2) MHLW: 3rd phase basic plan to promote cancer control programs(March 2018) https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000196975.pdf (accessed in December 2018)

Gene Panel Tests Granted National Insurance Coverage in June

OncoGuide™ NCC Oncopanel System

Cancer Gene Panel Test OncoGuideTM NCC Oncopanel System added to Health Insurance Coverage list

May 29, 2019
National Cancer Center

in Japanese

OncoGuide™ NCC Oncopanel System (hereinafter, "NCC Oncopanel Test") has been listed for coverage under national health insurance from June 2019. NCC Oncopanel Test was developed jointly by the National Cancer Center (President: Hitoshi Nakagama, Location: Chuo-ku, Tokyo, Japan) and Sysmex Corporation (Chairman and CEO: Hisashi Ietsugu; HQ: Kobe, Japan) as a type of gene panel testing*1 designed specifically for Japanese cancer genome mutations.

The NCC Oncopanel Test uses next-generation sequencers*2 to test 114 genes where Japanese people are prone to express cancer mutations, in a single round. Comprehensive examination of gene mutations causing various types of solid tumors including childhood cancers, aids in patient diagnosis, in therapeutic drugs selection and realizes cancer genomic medicine*3.

Comment from Hitoshi Nakagama, President - National Cancer Center

"Insurance coverage of cancer genomic medicine, allowing optimal treatments for individuals based on cancer genome mutation information is groundbreaking. The Center for Cancer Genomics and Advanced Therapeutics (C-CAT)*4 will aggregate the generated cancer genome information with clinical details. A framework to make the most out of the available information, sharing with academia, pharmaceutical and medical devices companies, while safeguarding data protection, is being put together. With nationwide collaboration, we shall take cancer genomic medicine in Japan to the global forefront."

Clinical Utility

NCC Oncopanel Test detects mutations in 114 genes, evaluates the tumor mutation burden*6 affecting treatment effects of immune checkpoint inhibitors, while differentiating mutations cancer patients are born with (germline mutations*7) and mutations present only in cancer cells (somatic gene mutations). Consequently, in some cases test results can help diagnose hereditary cancers.

At TOP-GEAR Project*8study at the National Cancer Center Hospital, which verifyied this test, gene mutations than can guide therapeutic decisions*9 were detected in approximately half the patients. Anti-cancer drugs were administered to more than 10% of patients

FoundationOne® CDx Cancer Genomic Profile

Press Release

Chugai Launches Genomic Mutation Analysis Program, FoundationOne CDx Cancer Genomic Profile

TOKYO, June 3, 2019 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced today that it has launched FoundationOne® CDx Cancer Genomic Profile, (hereafter "the Program") a next-generation sequencing based gene mutation analysis program. Also, SRL Inc. has started providing testing services for the Program today.

FoundationOne CDx is the first cancer genomic test in Japan which obtained regulatory approval for the two functions of gene mutation analysis program (for use in cancer genome profiling) for solid tumors, and somatic gene mutation analysis program (for use in assessing anticancer drug indications). The approval was granted by the Ministry of Health, Labour and Welfare on December 27, 2018.

"FoundationOne CDx Cancer Genomic Profile will open up a new horizon for personalized cancer care. I am delighted that the program is now available for patients and healthcare providers in Japan," said Tatsuro Kosaka, Chugai's President and CEO. "Through this program, Chugai will further strive to realize advanced and sustainable patient-centric healthcare by promoting access to treatments optimized to each patient."

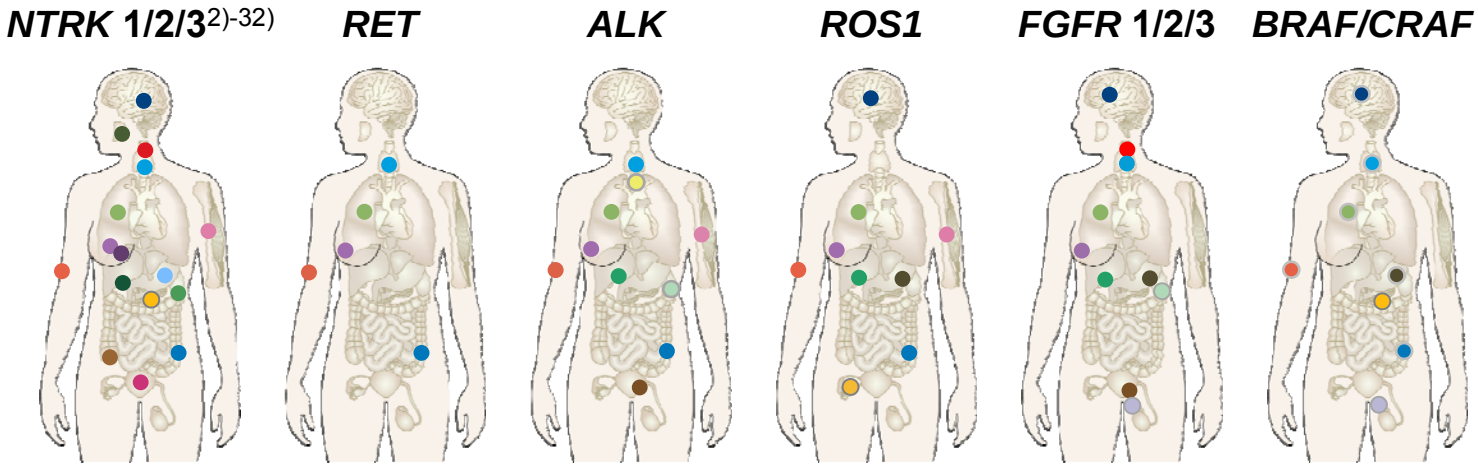
Developed by Foundation Medicine Inc., FoundationOne CDx Cancer Genomic Profile is a next-generation sequencing based *in vitro* diagnostic device for the detection and analysis of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from patient's tumor tissues. As a comprehensive companion diagnostic function, it can be also used as a companion diagnostic for certain molecular-targeted drugs approved in Japan.

As a leading company in the field of oncology, Chugai is committed to realize advanced personalized oncology care and contribute to patients and healthcare providers through comprehensive genomic profiling.

National Cancer Center press release dated May 29, 2019, Chugai Pharmaceutical Co., Ltd. press release dated June 3, 2019

Fusion Genes Expressed Across Cancer Types

Cancer types expressing fusion genes[1)]



1）Schram AM, et al.: Nat Rev Clin Oncol. 2017; 14（12）: 735-748 2）Orbach D, et al.: Eur J Cancer. 2016; 57: 1-9 3）Knezevich SR, et al.: Nat Genet. 1998; 18（2）: 184-187 4）Rubin BP, et al.: Am J Pathol. 1998; 153（5）: 1451-1458 5）Bourgeois JM, et al.: Am J Surg Pathol. 2000; 24（7）: 937-946 6）Del Castillo M, et al.: Am J Surg Pathol. 2015; 39（11）: 1458-1467 7）Makretsov N, et al.: Genes Chromosomes Cancer. 2004; 40（2）: 152-157 8）Tognon C, et al.: Cancer Cell. 2002; 2（5）: 367-376 9）Laé M, et al.: Mod Pathol. 2009; 22（2）: 291-298 10）Skálová A, et al.: Am J Surg Pathol. 2016; 40（1）: 3-13 11）Bishop JA, et al.: Hum Pathol. 2013; 44（10）: 1982-1988 12）Knezevich SR, et al.: Cancer Res. 1998; 58（22）: 5046-5048 13）Wu G, et al.: Nat Genet. 2014; 46（5）: 444-450 14）Prasad ML, et al.: Cancer. 2016; 122（7）: 1097-1107 15）Wiesner T, et al.: Nat Commun. 2014; 5: 3116 16）Musholt TJ, et al.: Surgery. 2000; 128（6）: 984-993 17）Leeman-Neill RJ, et al.: Cancer. 2014; 120（6）: 799-807 18）Chiang S, et al.: Am J Surg Pathol. 2018; 42（6）: 791-798 19）Ross JS, et al.: Oncologist. 2014; 19（3）: 235-242 20）Jones DT, et al.: Nat Genet. 2013; 45（8）: 927-932 21）Yamamoto H, et al.: Histopathology. 2016; 69（1）: 72-83 22）Stransky N, et al.: Nat Commun. 2014; 5: 4846 23）Vaishnavi A, et al.: Nat Med. 2013; 19（11）: 1469-1472 24）Shi E, et al.: J Transl Med. 2016; 14 （1）: 339 25）Brenca M, et al.: J Pathol. 2016; 238（4）: 543-549 26）Kim J, et al.: PLoS One. 2014; 9（3）: e91940 27）Frattini V, et al.: Nat Genet. 2013; 45（10）: 1141-1149 28）Zheng Z, et al.: Nat Med. 2014; 20（12）: 1479-1484 29）Chen Y, et al.: J Hematol Oncol. 2018; 11（1）: 78 30）Ardini E, et al.: Mol Oncol. 2014; 8（8）: 1495-1507 31）Creancier L, et al.: Cancer Lett. 2015; 365（1）: 107-111 32）Zehir A, et al.: Nat Med. 2017; 23（6）: 703-713

Toward the Era of Tumor-Agnostic Indications
(shifting from treatment by organ to treatment by gene)

Proportion positive (%)	Non-small cell lung cancer	Breast cancer	Colorectal cancer	Malignant melanoma	Thyroid cancer	Ovarian cancer	Endometrial cancer	Head and neck carcinoma	Cancer of unknown primary
	n=1,668	n=1,324	n=1,007	n=365	n=231	n=224	n=218	n=186	n=186
***EGFR* mutation**	18.65%	1.36%	2.09%	6.58%	-	0.45%	4.13%	2.15%	3.23%
***ROS1* fusion**	1.62%	-	-	-	-	0.89%	-	-	0.54%
***BRAF* mutation**	5.16%	0.3%	11.52%	30.41%	38.1%	1.34%	4.13%	0.54%	5.91%
***HER2* amplification**	21.7%	13.22%	2.38%	1.1%	-	3.57%	7.34%	2.69%	4.3%
***PIK3CA* mutation**	6.89%	34.59%	19.17%	4.11%	6.06%	10.27%	40.37%	19.35%	9.14%
***BRACA1/2* mutation**	5.22%	5.29%	8.54%	12.6%	1.73%	3.13%	7.63%	5.38%	5.46%
MSI-H	**0.06%**	**0.08%**	**6.54%**	**-**	**0.44%**	**-**	**8.53%**	**0.56%**	**0.63%**
***NTRK* fusion**	**0.06%**	**-**	**0.31%**	**0.29%**	**0.88%**	**-**	**-**	**-**	**0.63%**

Tumor-agnostic approach

Qin BD, et al.: Front Oncol. 2019 12;9:229, Zehir A, et al.: Nat Med. 2017;23(6):703-713

Examples of Tumor-Agnostic Indications

Indication of pembrolizumab (MSI-H solid tumors) (approved in December 2018)

Indication:

Advanced/recurrent MSI-high solid tumors that have progressed after chemotherapy (only if refractory or intolerant to standard therapies)

Appropriate Use Guide for Pembrolizumab: Solid tumors with microsatellite instability-high (MSI-high) (June 2019 revision), Keytruda Package insert July 2019 (Version 12)

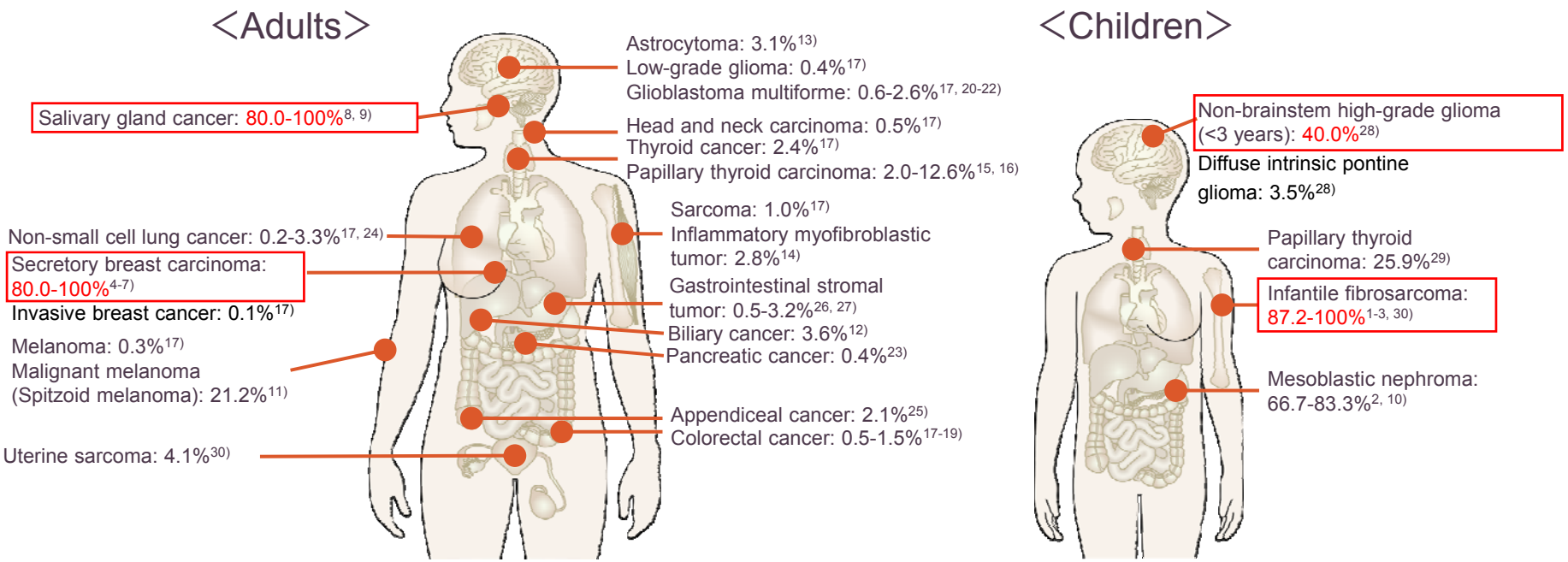
Indication of ROZLYTREK (approved in June 2019)

Indication:

Neurotrophic tyrosine receptor kinase (*NTRK*) fusion–positive advanced or recurrent solid tumors

ROZLYTREK Package insert June 2019 (Version 1)

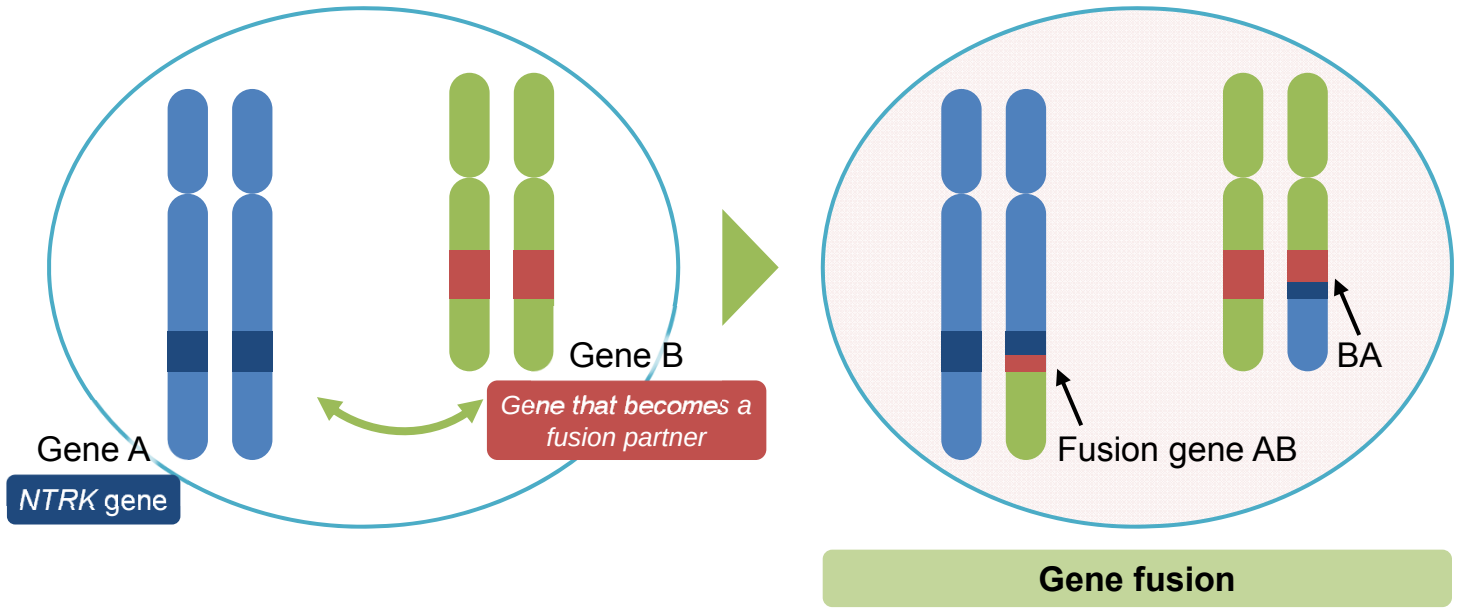
Proportion of *NTRK* Fusion-Positive Cancers



1）Knezevich SR, et al.: Nat Genet. 1998; 18 (2): 184-187. 2）Rubin BP, et al.: Am J Pathol. 1998; 153 (5): 1451-1458. 3）Bourgeois JM, et al.: Am J Surg Pathol. 2000; 24 (7): 937-946. 4）Del Castillo M, et al.: Am J Surg Pathol. 2015; 39 (11): 1458-1467. 5）Makretsov N, et al.: Genes Chromosomes Cancer. 2004; 40 (2): 152-157. 6）Tognon C, et al.: Cancer Cell. 2002; 2 (5): 367-376. 7）Laé M, et al.: Mod Pathol. 2009; 22 (2): 291-298. 8）Skálová A, et al.: Am J Surg Pathol. 2016; 40 (1): 3-13. 9）Bishop JA, et al.: Hum Pathol. 2013; 44 (10): 1982-1988. 10）Knezevich SR, et al.: Cancer Res. 1998; 58 (22): 5046-5048. 11）Wiesner T, et al.: Nat Commun. 2014; 5: 3116. 12）Ross JS, et al.: Oncologist. 2014; 19 (3): 235-242. 13）Jones DT, et al.: Nat Genet. 2013; 45 (8): 927-932. 14）Yamamoto H, et al.: Histopathology. 2016; 69 (1): 72-83. 15）Musholt TJ, et al.: Surgery. 2000; 128 (6): 984-993. 16）Leeman-Neill RJ, et al. Cancer. 2014; 120 (6): 799-807. 17）Stransky N, et al.: Nat Commun. 2014; 5: 4846. 18）Ardini E, et al.: Mol Oncol. 2014; 8 (8): 1495-1507. 19）Creancier L, et al.: Cancer Lett. 2015; 365 (1): 107-111. 20）Kim J, et al.: PLoS One. 2014; 9 (3): e91940. 21）Frattini V, et al.: Nat Genet. 2013; 45 (10): 1141-1149. 22）Zheng Z, et al.: Nat Med. 2014; 20 (12): 1479-1484. 23）Zehir A, et al.: Nat Med. 2017; 23 (6): 703-713. 24）Vaishnavi A, et al.: Nat Med. 2013; 19 (11): 1469-1472. 25）Chen Y, et al.: J Hematol Oncol. 2018; 11 (1): 78. 26）Shi E, et al.: J Transl Med. 2016; 14 (1): 339. 27）Brenca M, et al.: J Pathol. 2016; 238 (4): 543-549. 28）Wu G, et al.: Nat Genet. 2014; 46 (5): 444-450. 29）Prasad ML, et al.: Cancer. 2016; 122 (7): 1097-1107. 30）Chiang S, et al.: Am J Surg Pathol. 2018; 42 (6): 791-798. 31）Orbach D, et al.: Eur J Cancer. 2016; 57: 1-9.

What are Fusion Genes?

■ Gene fusion[1)]



- *NTRK* gene translocation results in fusion with another gene and the consequent production of a fusion protein[1)]
- *NTRK* fusion genes are driver genes that induce durable signalling[2)]

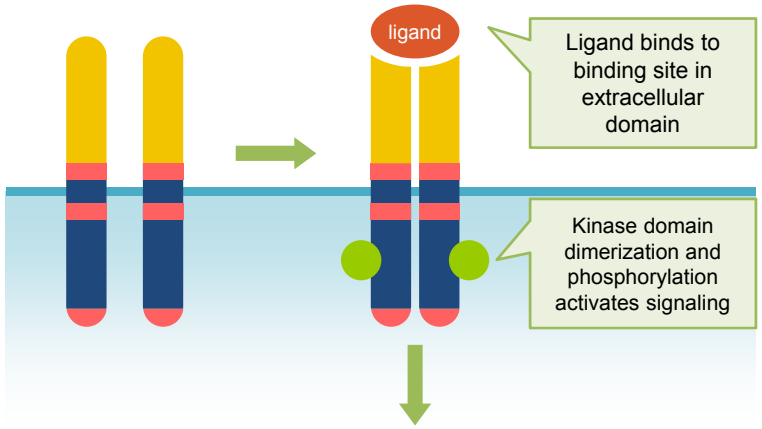
NTRK: Neurotrophic tyrosine receptor kinase

1) Kato M, Motoi T: J Clin Exp Med [Japanese] 2015; 254 (4): 276-284
2) Katsuya T, Shimizu T: Clin Oncol [Japanese] 2017; 19 (6): 674-680

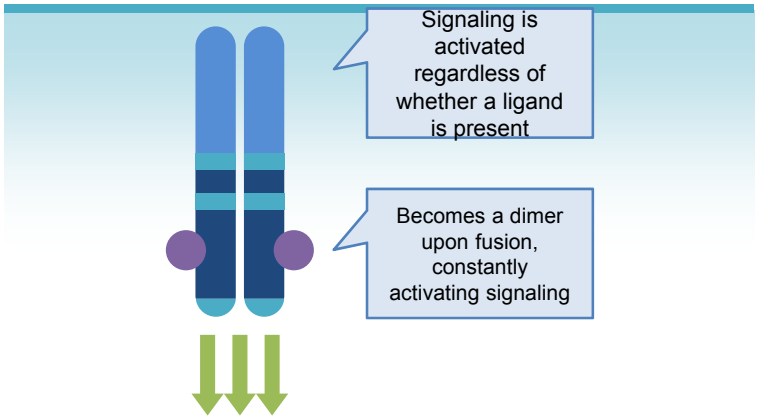
TRK Receptor Function and Signaling

TRK receptor is expressed in healthy and cancerous tissues[1)]

TRK receptor coded by normal *NTRK* gene



TRK receptor coded by *NTRK* fusion gene

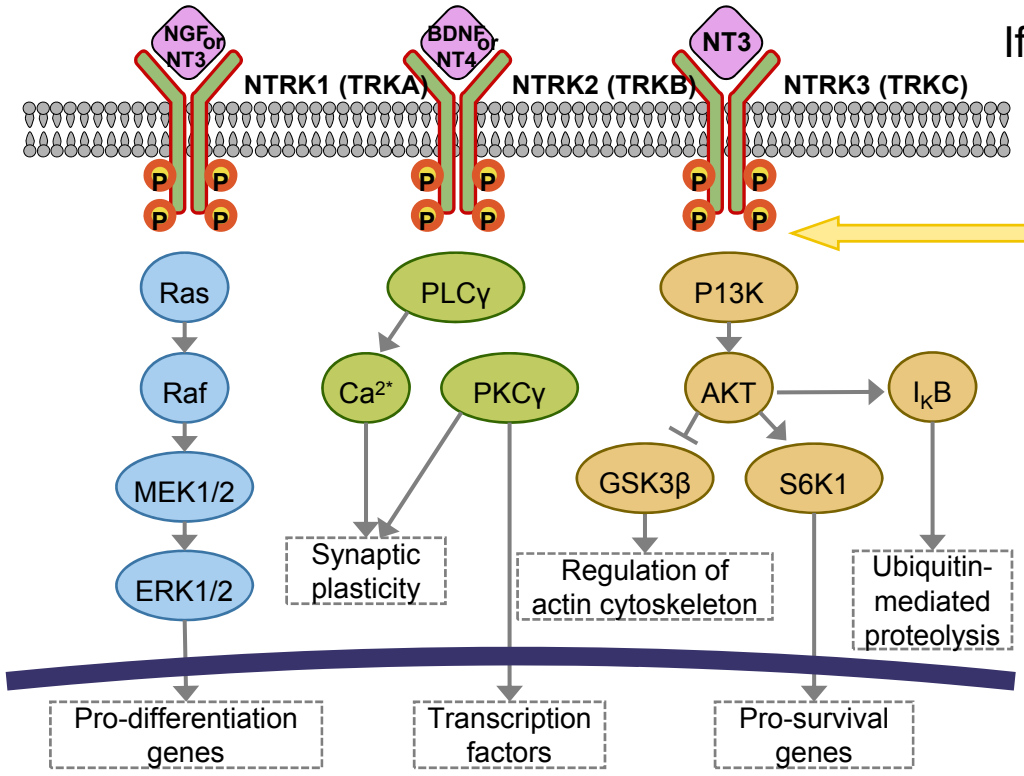


Normal TRK receptor function[2)]

TRKA receptor coded by *NTRK1*	Pain, thermoregulation
TRKB receptor coded by *NTRK2*	Movement, memory, mood, appetite, weight
TRKC receptor coded by *NTRK3*	Sensory nerve sensation (e.g., muscles, tendons, labyrinth)

Adapted from 1) Katsuya T, Shimizu T: Clin Oncol [Japanese] 2017; 19 (6): 674-680
Adapted from 2) Furukawa T, Naito Y: Clin Oncol [Japanese] 2018; 22 (3): 348-354

Mechanism of Cancer Proliferation by *NTRK* Fusion Genes and Mode of Action of ROZLYTREK



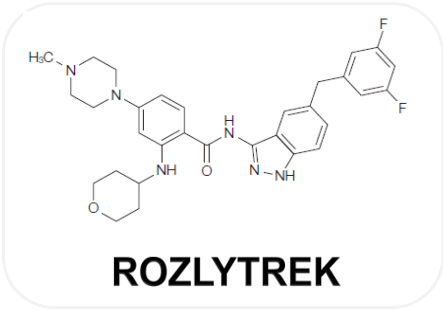
If *NTRK* fusion gene present

TRK fusion protein translation

Ligand-independent tyrosine kinase activation

Signaling pathway constant activation

Cancer cell proliferation

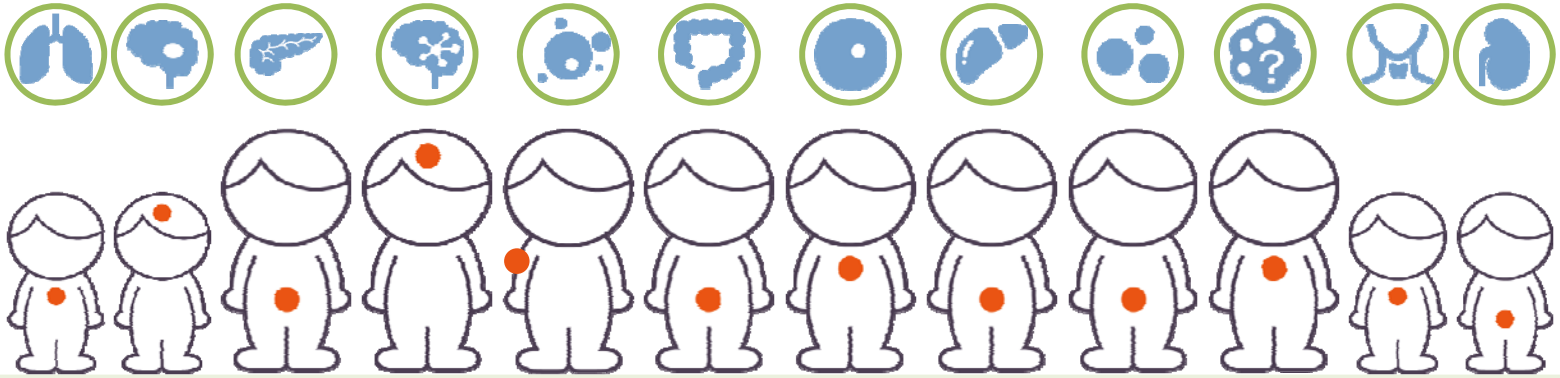


June 18, 2019
Approval in Japan

NGF: Nerve growth factor
BDNF: Brain-derived neurotrophic factor
NT: NeuroTrophin

Khotskaya YB, et al.: Pharmacol Ther. 2017;173:58-66, Rozlytrek Summary of Product Characteristics

ROZLYTREK is Japan's First Drug Targeting *NTRK* Fusion Genes across Different Cancer Types



ROZLYTREK has national insurance coverage for a variety of *NTRK* fusion-positive solid cancers in patients from children to adults.

Product Summary (ROZLYTREK/entrectinib)

Molecule	ROZLYTREK, a small molecule drug that selectively blocks tyrosine kinases such as **TRK A/B/C**
Dosage form	Oral capsules (Nos. 0 and 2)
Indication	***NTRK*** fusion-positive advanced/recurrent **solid cancers**
Dosage regimen	**600 mg** as entrectinib once daily for adults **300 mg/m^2 (body surface area)** as entrectinib once daily **for children**
Companion testing	When testing, use an approved companion diagnostic. **FoundationOne CDx Cancer Genomic Profile (F1CDx)**
Data for approval review	**Global Phase 2 (STARTRK-2, adults: still underway)** Efficacy analysis: 51 patients with 10 cancer types (May 2018 cutoff), 1 Japanese patient Safety analysis: 206 patients, 16 Japanese patients **Phase 1/1b (STARTRK-NG, children: still underway)** Efficacy analysis: 5 patients (October 2018 cutoff, *NTRK* positive and evaluable) Safety analysis: 16 patients (May 2018 cutoff), no Japanese patients
Major adverse events	Cardiac disorder, QT interval prolongation, cognitive disorder/ataxia, interstitial lung disease
Others	Developed by Ignyta

100 mg
30-capsule bottle (enough for 5 days)

200 mg
90-capsule bottle (enough for 30 days)

Major Clinical Studies of ROZLYTREK

Clinical study	Study design	Study patients	Country	Enrollments	Primary endpoint
ALKA	**Phase I** Multicenter, open label, dose escalation study	Patients with recurrent or metastatic solid cancer positive for *NTRK1/2/3*, *ROS1*, or *ALK* mutation	Italy	58 patients	• DLT • MTD
STARTRK-1	**Phase I** Global, Multicenter, open label, dose escalation study	Dose-escalation cohort: Patients with locally advanced or metastatic solid cancer of any type Expansion cohort: Patients with locally advanced or metastatic solid cancer positive for *NTRK1/2/3, ROS1*, or *ALK* mutation	United States, Spain, South Korea	76 patients	• Dose escalation: DLT/MTD • Expansion: Response rate
STARTRK-2	**Phase II** Global, multicenter, open label, basket trial	Patients with locally advanced or metastatic solid cancer positive for *NTRK1/2/3*, *ROS1*, or *ALK* fusion	United States, 7 EU nations, United Kingdom, Australia, Taiwan, South Korea, Hong Kong, Japan, Singapore	207 patients	• Response rate
STARTRK-NG	**Phase I/Ib** Multicenter, open label, dose escalation, expansion	Patients with recurrent or refractory solid cancer 2 to 21 years of age (including patients with *NTRK1/2/3*, *ROS1*, and *ALK* fusion genes)	United States	Application dossier: 16 patients (May 2018 cutoff) ASCO2019: 29 patients (October 2018 cutoff)	• MTD • RP2D

DLT: Dose limiting toxicity, MTD (Maximum torelated dose, RP2D: Recommended phase 2 dose

The STARTRK-2 study
(Open-label, multicenter, global Phase II basket trial)

An open-label, multicenter, global Phase II basket trial of entrectinib in patients with *NTRK1/2/3*, *ROS1*, or *ALK* fusion-positive locally advanced or metastatic solid cancer

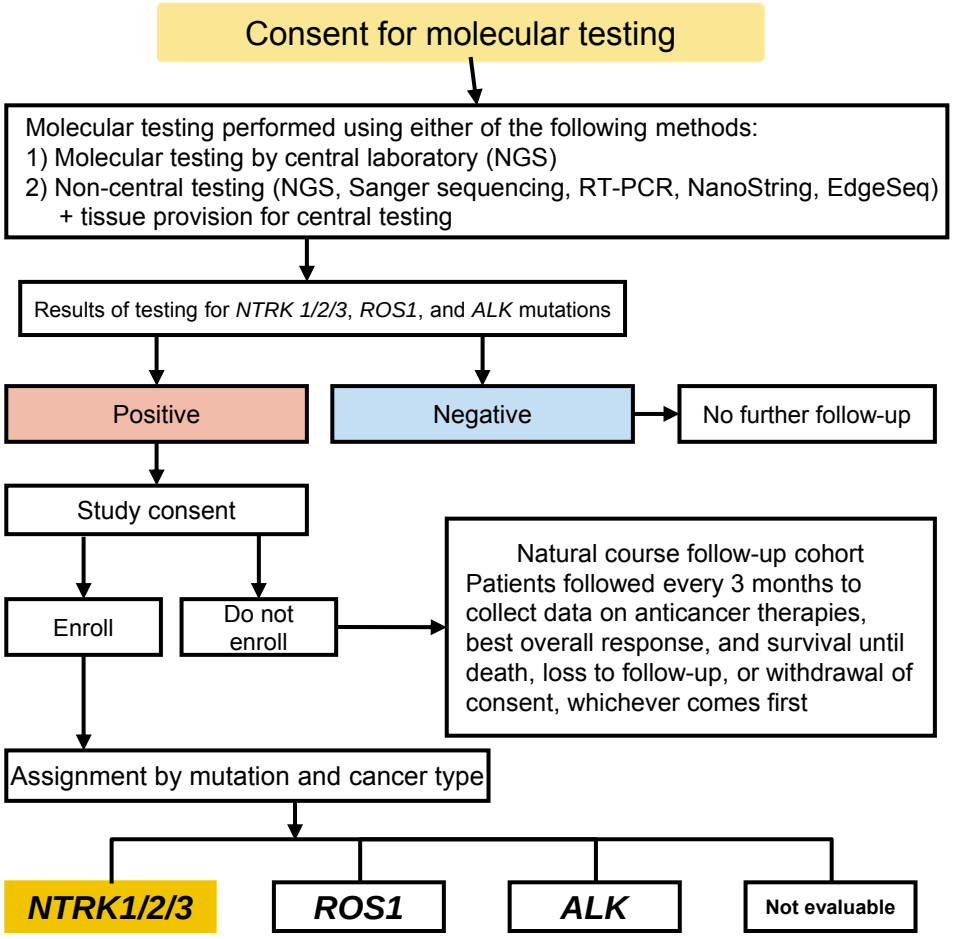
Primary endpoint
- Response rate (evaluation of ORR, BICR)

Secondary endpoints
- Clinical benefit rate (CBR), duration of response (DOR), progression free survival (PFS), overall survival (OS), intracranial overall response rate (IC-ORR), intracranial progression free survival (IC-PFS), etc.

  Subgroup analyzes of patients with brain metastases at baseline and cancer type were planned in advance.

Study population
- *NTRK* efficacy analysis set:
  51 of the 63 patients enrolled in the cohort, or all except 12 ineligible patients
- Safety analysis set:
  206 of the 207 patients enrolled, or all except 1 untreated patient

Methods
- Orally administer 600 mg once every day over a cycle of 4 weeks
- Continue treatment until toxicity occurs or PD is assessed by blinded central independent review (BICR)



Study for evaluation in regulatory reviewC

The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Patient Baseline Characteristics (*NTRK* efficacy analysis set)

		Number of patients (%), n=51
Sex	Male	21 (41.2)
	Female	30 (58.8)
Median age, years [IQR: interquartile range]		58.0 [48.0-67.0]
ECOG PS	0	23 (45.1)
	1	22 (43.1)
	2	6 (11.8)
Disease extent/degree	Locally advanced	2 (3.9)
	Metastatic	49 (96.1)
Site of metastasis	Bone	16 (31.4)
	Brain	11 (21.6)
	Liver	20 (39.2)
	Lungs	31 (60.8)
	Lymph nodes	29 (56.9)
	Skin	3 (5.9)
	Other	13 (25.5)

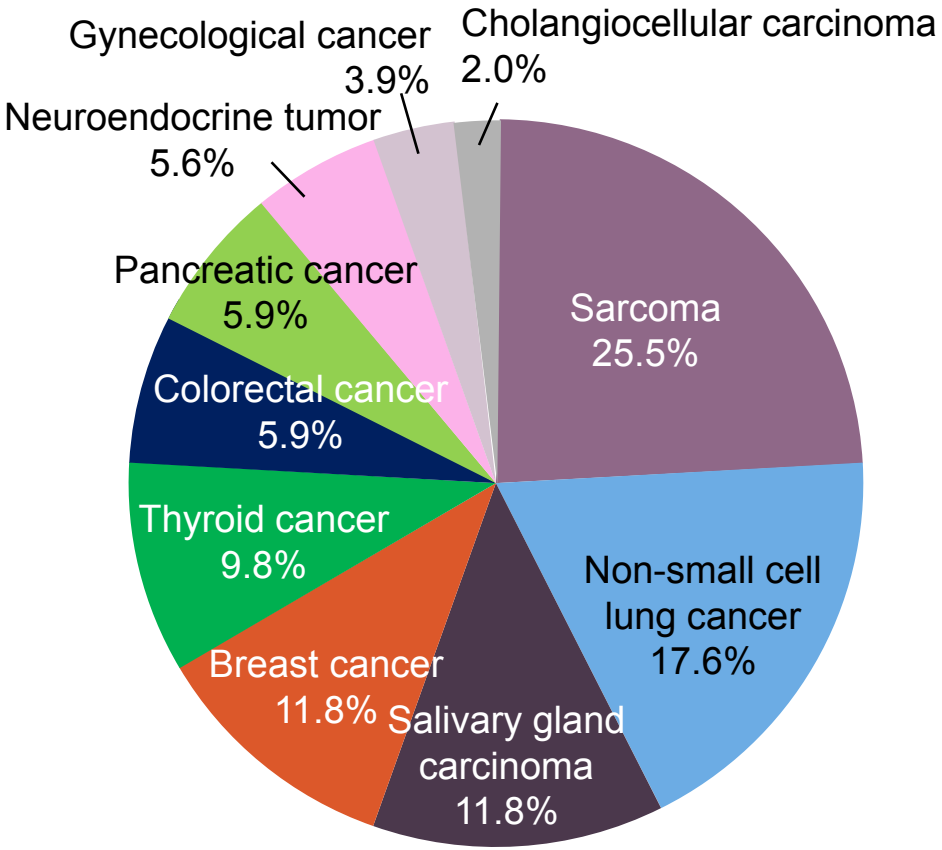
		Number of patients (%), n=51
Prior treatment history	Yes	45 (88.2)
	Chemotherapy	43 (84.3)
	Immunotherapy	6 (11.8)
	Molecular targeted drug	11 (21.6)
	Endocrine therapy	9 (17.6)
Number of lines of prior therapy for advanced recurrent solid cancer	0	20 (39.2)
	1	11 (21.6)
	2	14 (27.5)
	3	3 (5.9)
	4	2 (3.9)
	>4	1 (2.0)
History of radiotherapy		35 (68.6)
History of surgery		41 (80.4)
Brain metastatic lesions at baseline	Measurable lesions present	1 (2.0)
	Yes	10 (19.6)
	No	40 (78.4)

The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Patient Baseline Characteristics (*NTRK* efficacy analysis set)

Breakdown of cancer types

n (%)	*NTRK* efficacy analysis set (n=51)
Sarcoma	13 (25.5%)
Non-small cell lung cancer	9 (17.6%)
Salivary gland cancer	6 (11.8%)
Breast cancer	6 (11.8%)
Thyroid cancer	5 (9.8%)
Colorectal cancer	3 (5.9%)
Pancreatic cancer	3 (5.9%)
Neuroendocrine tumors	3 (5.9%)
Gynecological cancer*	2 (3.9%)
Cholangiocellular carcinoma	1 (2.0%)



*Ovarian cancer, endometrial cancer, one case each

The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Response Rate (ORR) [primary endpoint, BICR], Clinical Benefit Rate (CBR)* [secondary endpoint, BICR]

ORR, CBR*（n=51）

	Responders	Response rate
ORR	29	56.9%
CBR*	33	64.7%
CR	4	7.8%
PR	25	49.0%
SD	9	17.6%
PD	3	5.9%
Non CR/PD	3	5.9%
Unknown or not evaluable	7	13.7%

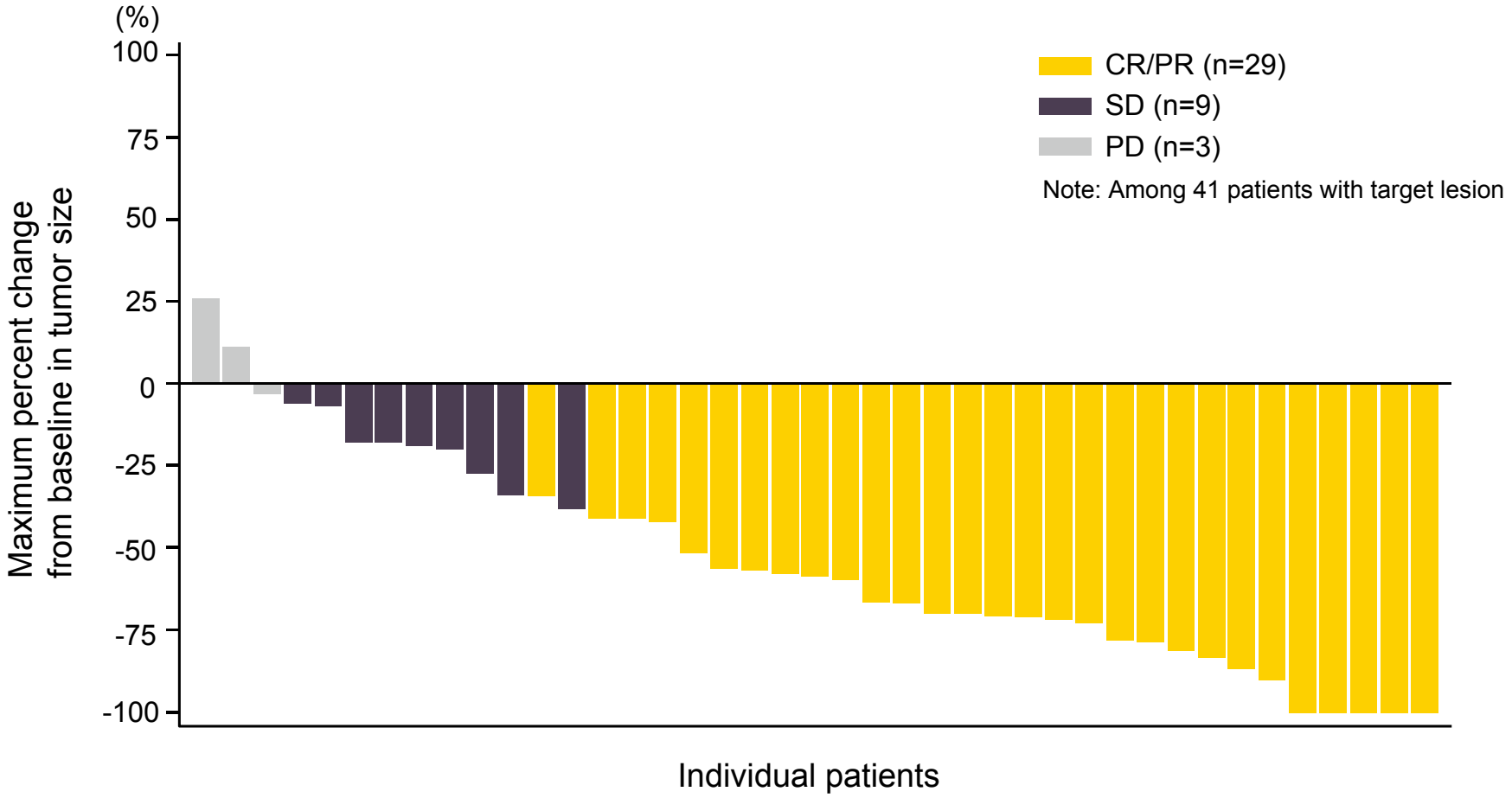
ORR by cancer type [subgroup analysis] (n=51)

Cancer type	Responders/ patients	Response rate
Sarcoma	6/13	46.2%
Non-small cell lung cancer	6/9	66.7%
Breast cancer	5/6	83.3%
Salivary gland cancer	5/6	83.3%
Thyroid cancer	1/5	20.0%
Colorectal cancer	1/3	33.3%
Neuroendocrine tumors	1/3	33.3%
Pancreatic cancer	2/3	66.7%
Gynecological cancer	1/2	50.0%
Cholangiocellular carcinoma	1/1	100.0%

CBR: Proportion of patients who experienced CR, PR, or SD in 6 months after first entrectinib dose

The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Maximum Percent Change from Baseline in Tumor Size (Waterfall plot)



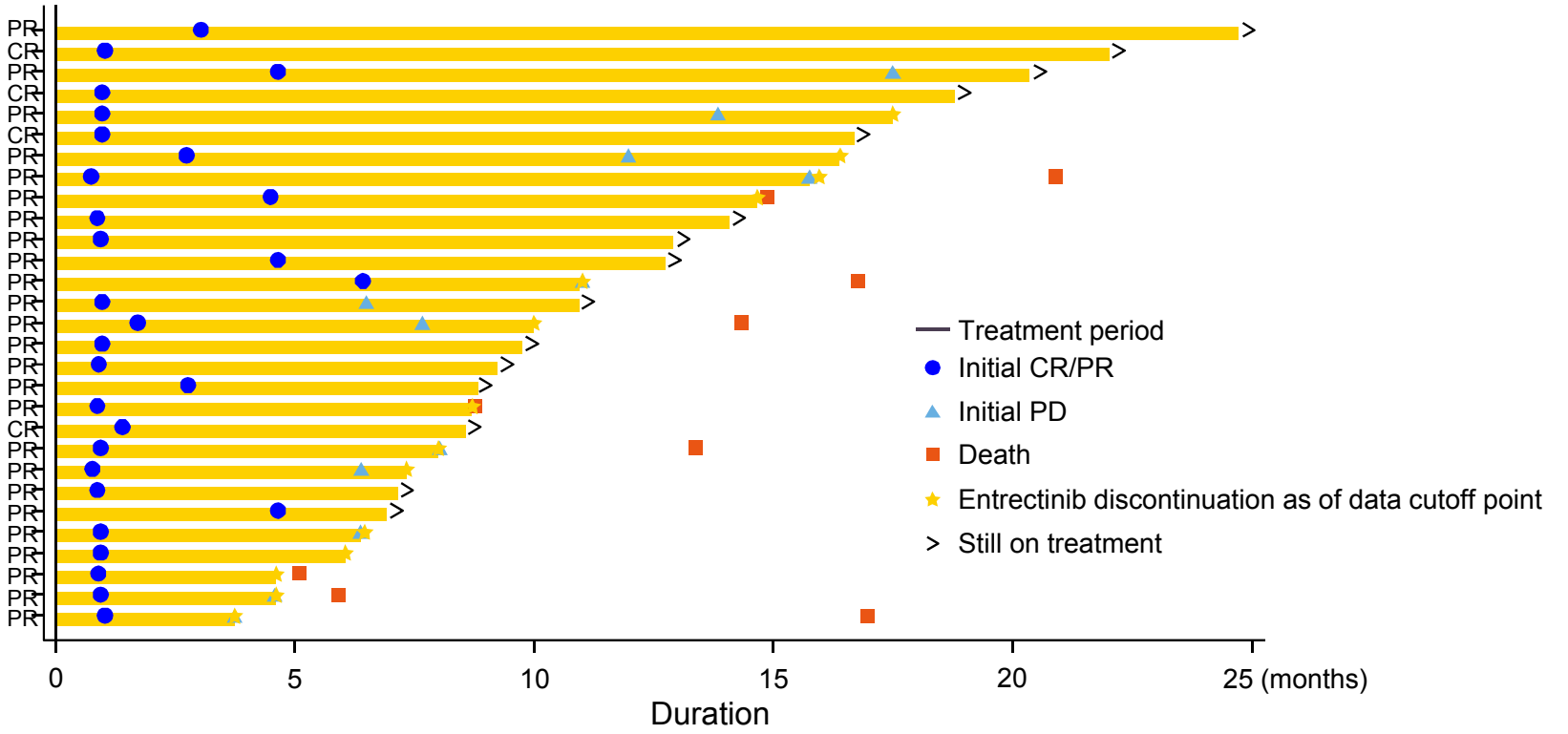
The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Duration of Response (DOR) [secondary endpoint, BICR] (responders n=29)

Median DOR: 10.4 months (95% CI: 7.1-15.0)

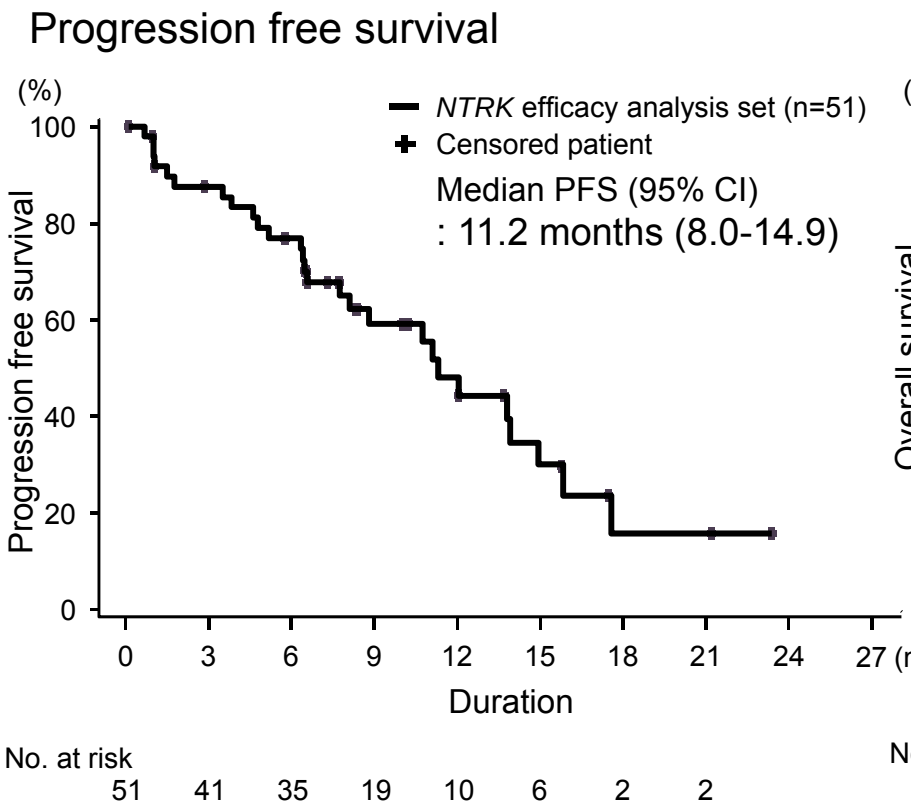
Data cutoff date: May 31, 2018
Median duration of follow-up: 12.9 months

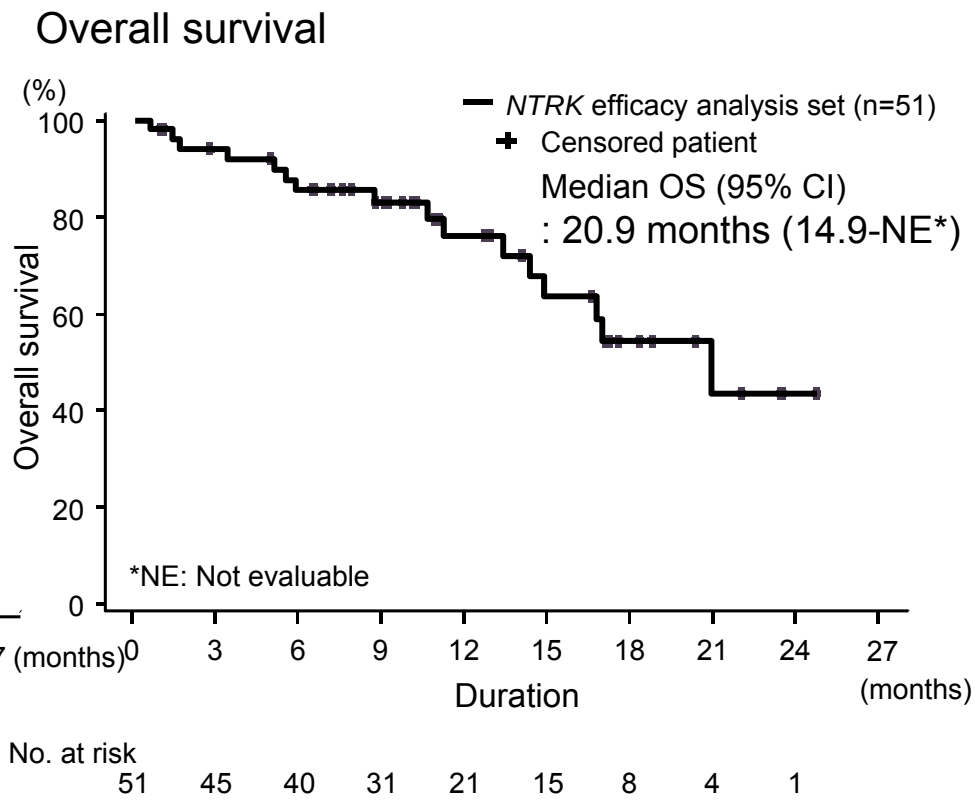
Swimmer plot of responders



The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Progression Free Survival (PFS) and Overall Survival (OS) [secondary endpoints, BICR]





Data cutoff date: May 31, 2018, median duration of follow-up: 12.9 months

The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Efficacy in Brain Lesions of Patients with Brain Metastatic Lesions at Baseline (n=10)
Intracranial Overall Response Rate (IC-ORR), Intracranial Progression Free Survival (IC-PFS)

[secondary endpoints, BICR, subgroup analysis]

	n=10
Brain lesion responders	5
IC-ORR (95% CI)	50.0% (18.7-81.3)
CR	2 (20.0%)
PR	3 (30.0%)
SD	1 (10.0%)
PD	1 (10.0%)
Non CR/PD	2 (20.0%)
Unknown or not evaluable	1 (10.0%)
Median IC-PFS (95% CI)	14.3 months (5.1-14.3)

The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

Adverse Events（Safety analysis set: n=206）

	n=206	
	All grades	≥ Grade 3
All adverse events	205(99.5%)	131(63.6%)
Constipation	110(53.4%)	1(0.5%)
Dysgeusia	95(46.1%)	1(0.5%)
Diarrhea	80(38.8%)	5(2.4%)
Dizziness	78(37.9%)	3(1.5%)
Fatigue	76(36.9%)	10(4.9%)
Peripheral edema	67(32.5%)	2(1.0%)
Increased body weight	63(30.6%)	20(9.7%)
Anemia	61(29.6%)	22(10.7%)
Increased blood creatinine	59(28.6%)	3(1.5%)
Dyspnea	59(28.6%)	12(5.8%)
Nausea	55(26.7%)	0
Arthalgia	46(22.3%)	1(0.5%)
Cough	44(21.4%)	0
Pyrexia	42(20.4%)	1(0.5%)
Pneumonia	15(7.3%)	11(5.3%)

MedDRA ver. 18.0, CTCAE ver. 4.0

Adverse events leading to treatment suspension
45.1%

Adverse events leading to dose reduction
35.0%

Adverse events leading to withdrawal
10.2%

*Data cutoff date: May 31, 2018

Serious adverse events occurred in 81 cases (39.3%). The events observed in ≥3% were pneumonia (10 cases (4.9%)) and pleural effusion (9 cases (4.4%)). There were 13 deaths due to adverse events (6.3%), 2 each for acute respiratory failure, cardiopulmonary arrest, sepsis and pneumonia, 1 each for dyspnea, attempted suicide, cardiogenic shock, cerebral infarction and septic shock.

Major Clinical Studies of ROZLYTREK

Clinical study	Study design	Study patients	Country	Enrollments	Primary endpoint
ALKA	**Phase I** Multicenter, open label, dose escalation study	Patients with recurrent or metastatic solid cancer positive for *NTRK1/2/3*, *ROS1*, or *ALK* mutation	Italy	58 patients	• DLT • MTD
STARTRK-1	**Phase I** Global, Multicenter, open label, dose escalation study	Dose-escalation cohort: Patients with locally advanced or metastatic solid cancer of any type Expansion cohort: Patients with locally advanced or metastatic solid cancer positive for *NTRK1/2/3*, *ROS1*, or *ALK* mutation	United States, Spain, South Korea	76 patients	• Dose escalation: DLT/MTD • Expansion: Response rate
STARTRK-2	**Phase II** Global, multicenter, open label, basket trial	Patients with locally advanced or metastatic solid cancer positive for *NTRK1/2/3*, *ROS1*, or *ALK* fusion	United States, 7 EU nations, United Kingdom, Australia, Taiwan, South Korea, Hong Kong, Japan, Singapore	207 patients	• Response rate
STARTRK-NG	**Phase I/Ib** Multicenter, open label, dose escalation, expansion study	Patients with recurrent or refractory solid cancer 2 to 21 years of age (including patients *with NTRK1/2/3*, *ROS1*, and *ALK* fusion genes)	United States	Application dossier: 16 patients (May 2018 cutoff) ASCO2019: 29 patients (October 2018 cutoff)	• MTD • RP2D

DLT: Dose limiting toxicity, MTD (Maximum torelated dose, RP2D: Recommended phase 2 dose

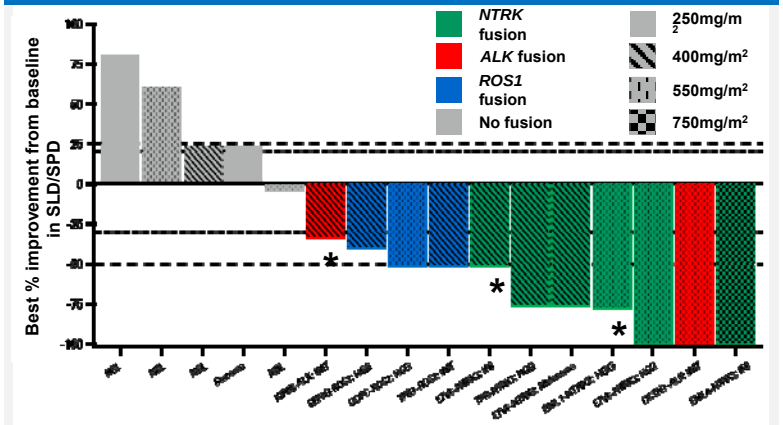
The STARTRK-NG study (P1/P1b)

Efficacy of ROZLYTREK in Children and Adolescents in *NTRK*, *ROS1* or *ALK* Fusion-Positive Solid Tumors

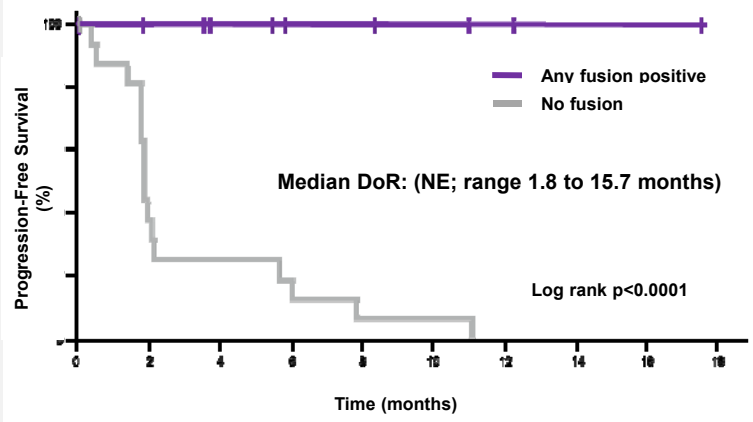
- All patients with *NTRK*, *ROS1* or *ALK* fusions showed durable responses without relapse (ORR 100%)
- 5 patients with primary high-grade CNS tumors were included, and 2 patients[1] showed complete responses
- Major adverse events: elevated creatinine (41%), weight gain (28%), dysgeusia (21%), ataxia/falling (<10%)

[1] high-grade glioma or sarcoma

Response rate in pediatric solid tumors
ORR 100% in patients with fusions (11/11)[2]



PFS for all patients with and without gene fusion-positive solid tumors (n=29)



Data cut-off October 31, 2018; [2] Investigator assessed: includes only patients with measureable disease at baseline and tumor assessment; *unconfirmed response at time of data cut-off; Median duration of therapy was 85 days (6–592 days) for all patients; 56 days (6–338 days) for non-responders; and 281 days (56–592 days) for responders

CNS, central nervous system; SLD, sum of the longest diameters; SPD, sum of the products of diameters; NE, not estimable; ORR, overall response rate; PFS, progression-free survival

Note: No participation from Japanese facilities in this study

Source: ASCO 2019 presentation, Roche Analyst Event at ASCO 2019 presentation (partially modified)

MONSTAR-SCREEN

Nationwide Cancer Genome Screening Project
under Industry-Academia Partnership

Stage 3: Beginning in July 2019

GI-SCREEN revised into MONSTAR-SCREEN

Gastrointestinal tumors + skin tumors, gynecological tumors, head and neck tumors, mammary gland tumors, urological tumors

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The 3rd-Stage MONSTAR-SCREEN

	SCRUM-Japan GI-SCREEN	SCRUM-Japan MONSTAR-SCREEN
Period	until Mar 2019	Apr 2019 - Mar 2021
Number	6,391 patients (CRC 3,439, non-CRC 2,952)	2,000 patients
Field	GI cancers	GI, breast, skin, head and neck, Gynecological, urological
Aims	Promoting new drugs/devices Creating large-scale database Screening for clinical trials	Promoting new drugs/devices Promoting translational research Screening for clinical trials for treatment resistant mechanisms

GI cancers ⇒ All solid tumors

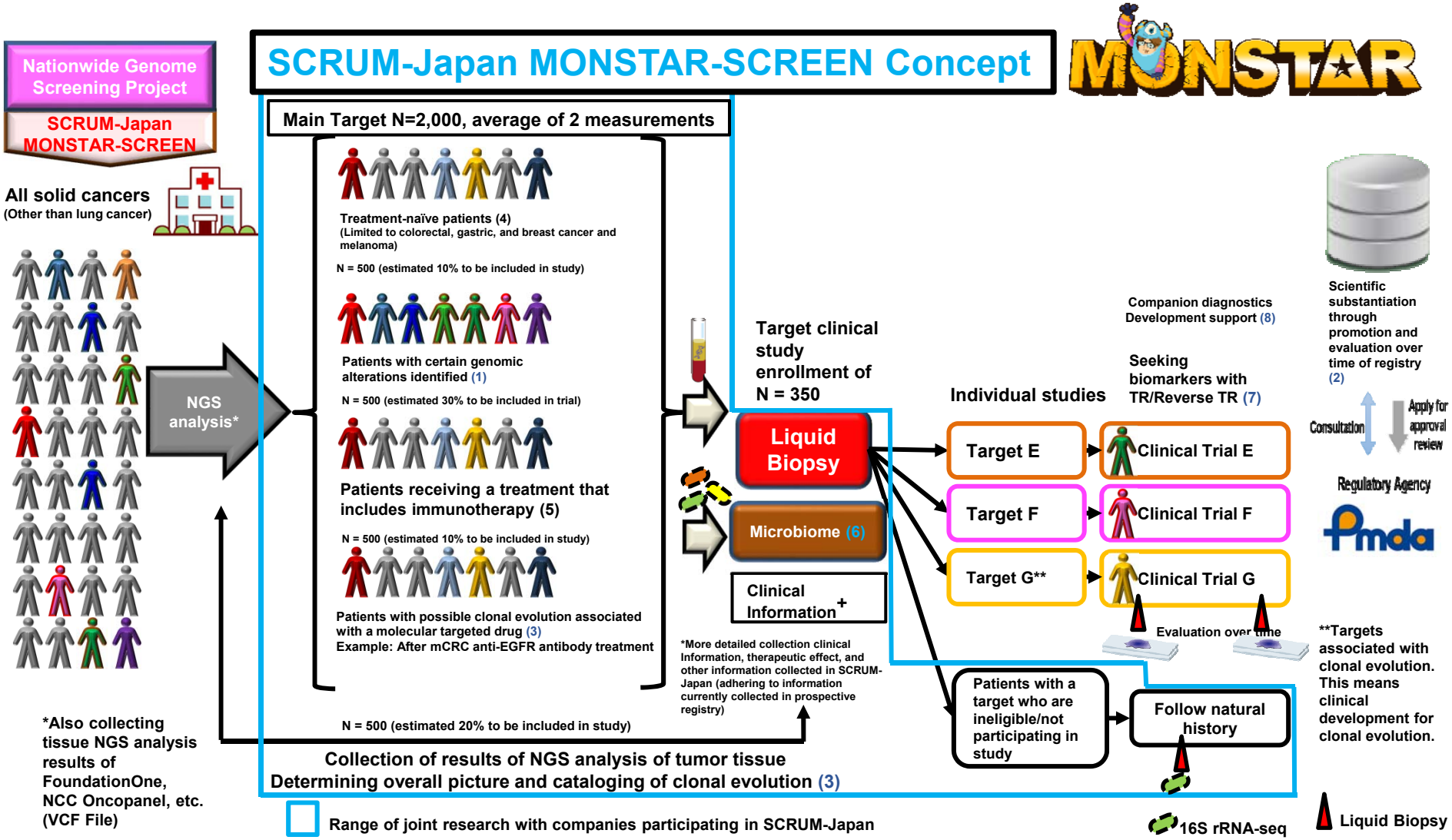
Screening system ⇒ Monitoring system

Platform of translational research to develop new drugs

The 3rd-Stage MONSTAR-SCREEN

- Target Populations: Patients in all advanced solid tumors
- Period: two-years from June 2019 to March 2021 (As a precondition, the Foundation One will be reimbursed at June 2019)
- Assay to be introduced: Liquid Biopsy and Microbiome
- Planning Tumor-Agnostic Basket-type Clinical Trials: FGFR, HER2, ROS1
- Promotion of SCRUM-Japan Prospective Registry that can be used for the regulatory approval applications

Joint Research with Companies Participating in SCRUM-Japan



Conclusion

- To date, drug development has been carried out for cancers with a large number of patients and gene mutations that occur frequently. For this reason, large-scale clinical trials have been difficult in rare cancers, rare fractions, and pediatric cancer because of the small number of patients.
- The following are the solutions to further advance cancer genomic medicine.
  - Basket clinical trials targeting common gene mutations across organs
  - Clinical trials that identify causative gene mutations and select appropriate treatments
- Pembrolizumab for MSI-High and ROZLYTREK for *NTRK* fusion-positive are drugs with tumor-agnostic indications.
- MONSTAR-SCREEN, tumor-agnostic basket clinical trial, is ongoing for patients with advanced solid tumor. Going forward, tumor-agnostic treatment is expected to progress further instead of organ-specific treatment.