Product Overview of ROZLYTREK®

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ROZLYTREK® Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

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.
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

Gene name  Protein Name
NTRK1 = TRKA
NTRK2 = TRKB
NTRK3 = TRKC

TRK (neurotrophin receptors)

Source: Rozlytrek package insert, Rozlytrek product information
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
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.

Source: ROZLYTREK product information
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.

**Adults**
- Salivary gland cancer: 80.0-100%[^8][^9]
- Non-small cell lung cancer: 0.2-3.3%[^17][^24]
- Secretory breast carcinoma: 80.0-100%[^4][^7]
- Invasive breast cancer: 0.1%[^7]
- Melanoma: 0.3%[^17]
- Malignant melanoma (Spitzoid melanoma): 21.2%[^11]
- Uterine sarcoma: 4.1%[^30]

**Children**
- Astrocytoma: 3.1%[^13]
- Low grade glioma: 0.4%[^17]
- Glioblastoma multiforme: 0.6-2.6%[^17][^20][^22]
- Head and neck cancer: 0.5%[^17]
- Thyroid cancer: 2.4%[^17]
- Papillary thyroid carcinoma: 2.0-12.6%[^15][^16]
- Sarcoma: 1.0%[^17]
- Inflammatory myofibroblastic tumor: 2.8%[^14]
- Gastrointestinal stromal tumor: 0.5-%[^14]
- Biliary cancer: 3.6%[^12]
- Pancreatic cancer: 0.4%[^23]
- Appendiceal cancer: 2.1%[^25]
- Colorectal cancer: 0.5-1.5%[^17][^19]
- Non-brainstem high-grade glioma (<3 years): 40.0%[^28]
- Diffuse intrinsic pontine glioma: 3.5%[^28]
- Papillary thyroid carcinoma: 25.9%[^29]
- Infantile fibrosarcoma: 87.2-100%[^1][^3][^30]
- Mesoblastic nephroma: 66.7-83.3%[^2][^10]

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
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.

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/m² (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.
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

## Safety Specification

### Important Identified Risks
- Cardiac disturbance (excluding QT prolongation)
- Cognitive Impairment / Ataxia

### Important Potential Risks
- QT prolongation
- Syncope
- Interstitial lung disease
- Growth and developmental retardation

### Important Missing Information
- Use in patients with hepatic dysfunction

## Efficacy concerns

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

## Pharmacovigilance Plan

**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)

**Periodic site visits for six months post-launch**

## 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)

**General drug use surveillance (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.

**Additional activities**
- 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

Prepared: Sep. 2019
From Organ Specific to Gene Specific Cancer Treatment
- Expectations on ROZLYTREK for NTRK Fusion-Positive Solid Tumors -

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Co-principal investigator, GI-SCREEN-Japan

September 5th, 2019
Disclosure of Conflict of Interests

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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
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."

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.

Cancers with a Large Number of Patients and Rare Cancers

- Stomach cancer
- Lung cancer
- Colorectal cancer
- Breast cancer
- Prostate cancer, etc.
- Oral cancer
- Ovarian cancer
- Urinary tract cancer
- Soft tissue sarcomas
- Gliomas
- Salivary gland cancer, etc.
- Pediatric cancers

Illustrated and modified from in-hospital cancer registration (2008-2011),

○ ▲ : patients with gene mutation
Drug Development to Date

Drugs are developed for cancers with many patients and cancer subtypes with frequent gene mutations.

Challenges in Drug Development in Rare Cancers

Stomach cancer
Lung cancer
Colorectal cancer
Breast cancer
Prostate cancer, etc.
Oral cancer
Ovarian cancer
Urinary tract cancer
Soft tissue sarcomas
Gliomas
Salivary gland cancer, etc.
Pediatric cancers

Rare fractions
(Newly identified mutations with low frequency)

Confirmatory or large-scale trails targeting gene mutations are infeasible because patient numbers are small

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).

What are Rare Cancers?

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

Rare cancers account for 10-20% of all new cancer patients.

15 to 22% Rare cancers

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

- **Solid Tumor**:
  - Neuroblastoma
  - Retinoblastoma
  - Germ cell tumors
  - Brain tumors (14%)
  - Osteoma
  - Renal tumors
  - Hepatic tumors
  - Soft tissue tumors

- **Hematologic cancers**:
  - Leukemia (34%)
  - Malignant lymphoma
  - Other hematologic cancers
  - Histiocytosis (6%)

**Counts**:
- Solid Tumor: n=2,922
- Hematologic cancers: n=3,271
Drug Development in Rare Fractions/Cancers, and Pediatric Cancer

Major cancers

- Stomach cancer
- Lung cancer
- Colorectal cancer
- Breast cancer
- Prostate cancer, etc.
- Oral cancer
- Ovarian cancer
- Urinary tract cancer
- Soft tissue sarcomas
- Gliomas
- Salivary gland cancer, etc.
- Pediatric cancers

Conventional Clinical Trial

- Selected by cancer type
- Therapies by cancer type
- Experimental therapy X
- Response assessment
  - Responders
  - Non-responders

Basket Trial

- Rare fractions
- Rare cancers
- Pediatric cancers

- Genomic classification
- Gene-targeted therapies
  - Experimental Therapy A
  - Experimental Therapy B
- Response assessment
  - Responders
  - Non-responders

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.

Colorectal cancer
Breast cancer
Lung cancer
Rare cancers etc...

Gene A

Patients with a variety of cancer types
Patients with cancers in different organs/tissue types

Comprehensive genomic profiling
Screening with cancer gene panel

Evaluation by individual mutation
Patients with the target driver mutation are enrolled to receive the matched investigational drug

No actionable mutation

Patients without the target mutation are excluded
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

Mutation  Amplification  Deletion  Fusion
The 3rd Phase Basic Plan to Promote Cancer Control Programs

I. Overall Goal

“The goal is for the citizens of Japan including people with cancer to understand and overcome cancer.”

1) Better cancer prevention and screening based on scientific evidence, (2) Realization of cancer treatment for each patient, and (3) Building a society that can live securely with dignity

II. Initiatives in Different Fields

1. Cancer prevention
   (1) Primary cancer prevention
   (2) Early cancer detection and cancer screening (secondary prevention)

2. Better cancer treatment
   (1) Cancer genomic medicine
   (2) Surgery, radiation therapy, drug therapy, and immunotherapy
   (3) Team medicine
   (4) Cancer rehabilitation
   (5) Supportive therapy

2. Living with cancer
   (1) Palliative care beginning when cancer is diagnosed
   (2) Consultation support and information provision

3. Rare and refractory cancer (measures suited to the characteristics of each)
   (7) Pediatric cancers, AYA* cancers, cancers in the elderly
   (8) Pathological diagnosis
   (9) Cancer registries
   (10) Efforts to rapidly develop and approve drugs and medical devices

4. Deployment of infrastructure to support these measures
   (1) Cancer research
   (2) Fostering human resources
   (3) Cancer education and information campaign

III. What is Needed to Comprehensively and Systematically Advance Measures for Cancer

1. Further strengthening of partnerships among relevant parties, 2. Establishment of plans by prefectural governments, 3. Efforts by citizens including cancer patients, 4. Cooperation by patient groups, etc., 5. Streamlining and prioritizing the implementation and budgeting of relevant financial measures, 6. Tracking of goal achievement status, 7. Revision of basic plans

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.
Gene Panel Tests Granted National Insurance Coverage in June

OncoGuide™ NCC Oncopanel System

FoundationOne® CDx Cancer Genomic Profile

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

Press Release

Chugai, Inc. – June 3, 2019 – Chugai Pharmaceutical Co., Ltd. (TYO:4519) announced today that it has launched FoundationOne® CDx Cancer Genomic Profile, GenomiKei® ("the Program")—a next-generation sequencing based gene mutation analysis program. Also, SEI 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 genomics profiling) for solid tumor, 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 location for personalized cancer care. I am delighted that the program is now available for patients and healthcare providers in Japan," said Tatsumi Kaneko, Chugai’s President and CEO. "Through this program, Chugai will further strive to realize advanced and personalized patient-centric healthcare by providing 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, insertions and deletions, and copy number alterations in 350 genes and select gene rearrangements, as well as germline signatures including hereditary susceptibilities (HCM) and tissue- and constitutional tumors (CTM) using DNA isolated from patient’s tumor tissue. As a comprehensive companion diagnostic function, it can also be used as a companion diagnostic for certain indications approved in Japan.

As a leading company in the field of oncology, Chugai is committed to realize advanced personalized, oncology care and contributes 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

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

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

Tumor-agnostic approach
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

### Adults

- **Salivary gland cancer**: 80.0-100%[^8][^9]
- **Low-grade glioma**: 0.4%[^17]
- **Glioblastoma multiforme**: 0.6-2.6%[^17][^20-^22]
- **Head and neck carcinoma**: 0.5%[^17]
- **Thyroid cancer**: 2.4%[^17]
- **Papillary thyroid carcinoma**: 2.0-12.6%[^15][^16]
- **Sarcoma**: 1.0%[^17]
- **Inflammatory myofibroblastic tumor**: 2.8%[^14]
- **Gastrointestinal stromal tumor**: 0.5-3.2%[^26][^27]
- **Biliary cancer**: 3.6%[^12]
- **Pancreatic cancer**: 0.4%[^23]
- **Appendiceal cancer**: 2.1%[^25]
- **Colorectal cancer**: 0.5-1.5%[^17][^19]

### Children

- **Non-brainstem high-grade glioma (<3 years)**: 40.0%[^28]
- **Diffuse intrinsic pontine glioma**: 3.5%[^28]
- **Papillary thyroid carcinoma**: 25.9%[^29]
- **Infantile fibrosarcoma**: 87.2-100%[^1][^3][^30]
- **Mesoblastic nephroma**: 66.7-83.3%[^1][^10]

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What are Fusion Genes?

- **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
**TRK Receptor Function and Signaling**

TRK receptor is expressed in healthy and cancerous tissues\(^1\)

<table>
<thead>
<tr>
<th>Normal TRK receptor function(^2)</th>
<th>TRK receptor coded by normal NTRK gene</th>
<th>TRK receptor coded by NTRK fusion gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRKA receptor coded by NTRK1</td>
<td>Ligand binds to binding site in extracellular domain</td>
<td>Signaling is activated regardless of whether a ligand is present</td>
</tr>
<tr>
<td>TRKB receptor coded by NTRK2</td>
<td>Kinase domain dimerization and phosphorylation activates signaling</td>
<td>Becomes a dimer upon fusion, constantly activating signaling</td>
</tr>
<tr>
<td>TRKC receptor coded by NTRK3</td>
<td>Pain, thermoregulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Movement, memory, mood, appetite, weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensory nerve sensation (e.g., muscles, tendons, labyrinth)</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of Cancer Proliferation by \textit{NTRK} Fusion Genes and Mode of Action of ROZLYTREK

If \textit{NTRK} fusion gene present

- TRK fusion protein translation
- Ligand-independent tyrosine kinase activation
- Signaling pathway constant activation
- Cancer cell proliferation


genes

- Pro-differentiation
- Pro-survival

factors

- Transcription

other proteins

- PLGγ
- PKCγ
- Ca2+
- GSK3β
- S6K1
- Regulation of actin cytoskeleton
- Ubiquitin-mediated proteolysis

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


June 18, 2019
Approval in Japan
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)

<table>
<thead>
<tr>
<th><strong>Molecule</strong></th>
<th>ROZLYTREK, a small molecule drug that selectively blocks tyrosine kinases such as TRK A/B/C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage form</strong></td>
<td>Oral capsules (Nos. 0 and 2)</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>NTRK fusion-positive advanced/recurrent solid cancers</td>
</tr>
<tr>
<td><strong>Dosage regimen</strong></td>
<td>600 mg as entrectinib once daily for adults &lt;br&gt;300 mg/m² (body surface area) as entrectinib once daily for children</td>
</tr>
<tr>
<td><strong>Companion testing</strong></td>
<td>When testing, use an approved companion diagnostic. &lt;br&gt;FoundationOne CDx Cancer Genomic Profile (F1CDx)</td>
</tr>
<tr>
<td><strong>Data for approval review</strong></td>
<td><strong>Global Phase 2 (STARTRK-2, adults: still underway)</strong>&lt;br&gt;Efficacy analysis: 51 patients with 10 cancer types (May 2018 cutoff), 1 Japanese patient&lt;br&gt;Safety analysis: 206 patients, 16 Japanese patients</td>
</tr>
<tr>
<td></td>
<td><strong>Phase 1/1b (STARTRK-NG, children: still underway)</strong>&lt;br&gt;Efficacy analysis: 5 patients (October 2018 cutoff, NTRK positive and evaluable)&lt;br&gt;Safety analysis: 16 patients (May 2018 cutoff), no Japanese patients</td>
</tr>
<tr>
<td><strong>Major adverse events</strong></td>
<td>Cardiac disorder, QT interval prolongation, cognitive disorder/ataxia, interstitial lung disease</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Developed by Ignyta</td>
</tr>
</tbody>
</table>
## Major Clinical Studies of ROZLYTREK

<table>
<thead>
<tr>
<th>Clinical study</th>
<th>Study design</th>
<th>Study patients</th>
<th>Country</th>
<th>Enrollments</th>
<th>Primary endpoint</th>
</tr>
</thead>
</table>
| **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/b 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 tolerated 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)

Consent for molecular testing

Molecular testing performed using either of the following methods:
1) Molecular testing by central laboratory (NGS)
2) Non-central testing (NGS, Sanger sequencing, RT-PCR, NanoString, EdgeSeq)
   + tissue provision for central testing

Results of testing for NTRK 1/2/3, ROS1, and ALK mutations

- Positive
- Negative
- No further follow-up

Study consent

Enroll

Do not enroll

Assignment by mutation and cancer type

NTRK1/2/3

ROS1

ALK

Not evaluable

Natural course follow-up cohort
Patients followed every 3 months to collect data on anticancer therapies, best overall response, and survival until death, loss to follow-up, or withdrawal of consent, whichever comes first
The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

**Patient Baseline Characteristics (NTRK efficacy analysis set)**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21 (41.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30 (58.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median age, years</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>[IQR: interquartile range]</td>
<td>58.0 [48.0-67.0]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>23 (45.1)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22 (43.1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (11.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease extent/degree</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced</td>
<td>2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>49 (96.1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of metastasis</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>16 (31.4)</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>11 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>20 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>31 (60.8)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>29 (56.9)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>3 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13 (25.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior treatment history</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>45 (88.2)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>43 (84.3)</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>6 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Molecular targeted drug</td>
<td>11 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>9 (17.6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of lines of prior therapy for advanced recurrent solid cancer</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20 (39.2)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (21.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14 (27.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (5.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>1 (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of radiotherapy</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 (68.6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of surgery</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41 (80.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brain metastatic lesions at baseline</th>
<th>Number of patients (%)</th>
<th>n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurable lesions present</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (19.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40 (78.4)</td>
<td></td>
</tr>
</tbody>
</table>
### The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

**Patient Baseline Characteristics (NTRK efficacy analysis set)**

#### Breakdown of cancer types

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma</td>
<td>13 (25.5%)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>9 (17.6%)</td>
</tr>
<tr>
<td>Salivary gland cancer</td>
<td>6 (11.8%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>6 (11.8%)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Gynecological cancer*</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>Cholangiocellular carcinoma</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>

*Ovarian cancer, endometrial cancer, one case each*

![Pie chart depicting cancer types distribution](chart.png)
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]

<table>
<thead>
<tr>
<th>ORR, CBR* (n=51)</th>
<th>Responders</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>29</td>
<td>56.9%</td>
</tr>
<tr>
<td>CBR*</td>
<td>33</td>
<td>64.7%</td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
<td>7.8%</td>
</tr>
<tr>
<td>PR</td>
<td>25</td>
<td>49.0%</td>
</tr>
<tr>
<td>SD</td>
<td>9</td>
<td>17.6%</td>
</tr>
<tr>
<td>PD</td>
<td>3</td>
<td>5.9%</td>
</tr>
<tr>
<td>Non CR/PD</td>
<td>3</td>
<td>5.9%</td>
</tr>
<tr>
<td>Unknown or not evaluable</td>
<td>7</td>
<td>13.7%</td>
</tr>
</tbody>
</table>

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

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)

Note: Among 41 patients with target lesion
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)

Swimmer plot of responders

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)

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

Progression free survival

- NTRK efficacy analysis set (n=51)
- Censored patient

Median PFS (95% CI): 11.2 months (8.0-14.9)

Overall survival

- NTRK efficacy analysis set (n=51)
- Censored patient

Median OS (95% CI): 20.9 months (14.9-NE*)

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)

<table>
<thead>
<tr>
<th>Brain lesion responders</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IC-ORR (95% CI)</strong></td>
<td>50.0% (18.7-81.3)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td><strong>Non CR/PD</strong></td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td><strong>Unknown or not evaluable</strong></td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td><strong>Median IC-PFS (95% CI)</strong></td>
<td>14.3 months (5.1-14.3)</td>
</tr>
</tbody>
</table>
The STARTRK-2 study (Open-label, multicenter, global Phase II basket trial)

**Adverse Events** (Safety analysis set: n=206)

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

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.

Study for evaluation in regulatory review
# Major Clinical Studies of ROZLYTREK

<table>
<thead>
<tr>
<th>Clinical study</th>
<th>Study design</th>
<th>Study patients</th>
<th>Country</th>
<th>Enrollments</th>
<th>Primary endpoint</th>
</tr>
</thead>
</table>
| ALKA           | Phase I      | 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      | 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     | 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/b    | 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 tolerated 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)**

<table>
<thead>
<tr>
<th>Fusion Type</th>
<th>Dose (mg/m(^2))</th>
<th>Best % Improvement from Baseline</th>
<th>NTRK fusion</th>
<th>ROS1 fusion</th>
<th>ALK fusion</th>
<th>No fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>250mg/m(^2)</td>
<td>-15 - 35</td>
<td>40 - 60</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
</tr>
<tr>
<td>400mg/m(^2)</td>
<td>-15 - 35</td>
<td>60 - 80</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
</tr>
<tr>
<td>550mg/m(^2)</td>
<td>-15 - 35</td>
<td>80 - 100</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
</tr>
<tr>
<td>750mg/m(^2)</td>
<td>-15 - 35</td>
<td>100 - 120</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
<td>250mg/m(^2)</td>
</tr>
</tbody>
</table>

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

- Median DoR: (NE; range 1.8 to 15.7 months)
- Log rank p=0.0001

Data cut-off October 31, 2018; \(^2\) Investigator assessed: includes only patients with measurable 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

tyoshino@east.ncc.go.jp
The 3rd-Stage MONSTAR-SCREEN

<table>
<thead>
<tr>
<th>Scrum-Japan GI-SCREEN</th>
<th>Scrum-Japan MONSTAR-SCREEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Period</strong></td>
<td>Apr 2019 - Mar 2021</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>2,000 patients</td>
</tr>
<tr>
<td><strong>Field</strong></td>
<td>GI, breast, skin, head and neck, Gynecological, urological</td>
</tr>
<tr>
<td><strong>Aims</strong></td>
<td>Promoting new drugs/devices</td>
</tr>
<tr>
<td></td>
<td>Creating large-scale database</td>
</tr>
<tr>
<td></td>
<td>Screening for clinical trials</td>
</tr>
<tr>
<td></td>
<td>Promoting translational research</td>
</tr>
<tr>
<td></td>
<td>Screening for clinical trials for treatment resistant mechanisms</td>
</tr>
</tbody>
</table>

GI cancers $\Rightarrow$ All solid tumors

Screening system $\Rightarrow$ 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

**SCRUM-Japan MONSTAR-SCREEN Concept**

Main Target N=2,000, average of 2 measurements

- **Liquid Biopsy**
- **Microbiome**
- **Clinical Information**

**Collection of results of NGS analysis of tumor tissue**
Determining overall picture and cataloging of clonal evolution (3)

- **Target clinical study enrollment of N = 350**
- **Individual studies**
  - Target E
  - Target F
  - Target G**

**Range of joint research with companies participating in SCRUM-Japan**

- **Nationwide Genome Screening Project**
- **SCRUM-Japan MONSTAR-SCREEN**

**All solid cancers (Other than lung cancer)**

- NGS analysis*

**Companion diagnostics Development support (8)**

- Seeking biomarkers with TR/Reverse TR (7)

**Scientific substantiation through promotion and evaluation over time of registry (2)**

**Follow natural history**

- 16S rRNA-seq

**Targets associated with clonal evolution. This means clinical development for clonal evolution.**

- **Compliance
- **Regulatory Agency
- **Pmda

*Also collecting tissue NGS analysis results of FoundationOne, NCC Oncopanel, etc. (VCF File)
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.