TAIHO PHARMA R&D

Sep. 29, 2020

Taiho Pharmaceutical Co., Ltd.
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Agenda

◆ R&D Activity Summary
  ➢ Major Progresses since “R&D Meeting” on Oct. 10, 2019
  ➢ Development Pipeline
  ➢ Open Innovation and Venture Investment

◆ Development Pipeline Updates
  ➢ Futibatinib (TAS-120)
  ➢ TAS-115

◆ Drug Discovery Research Updates
  ➢ Expansion of Cysteinomix (from Kinases to RAS Drug Discovery)
  ➢ Brain Metastasis Drug Discovery (Partnering with MD Anderson Cancer Center)
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## Taiho Pharma R&D: Major Progresses since last R&D Meeting

<table>
<thead>
<tr>
<th>Basic research collaboration</th>
<th>Small molecules against several drug targets including KRAS</th>
<th>Initiate collaboration with Astex and MSD</th>
<th>Jan. 6, 2020 News Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-license</td>
<td>Zimberelimab (AB122; anti-PD-1 antibody)</td>
<td>Obtain development and commercialization rights of an anti-PD-1 antibody, AB122 in Japan and certain other territories in Asia (excluding China) from Arcus Biosciences</td>
<td>Feb. 27, 2020 News Release</td>
</tr>
<tr>
<td>Basic research collaboration</td>
<td>Brain metastasis drug discovery</td>
<td>Partner with MD Anderson Cancer Center</td>
<td>Sep. 24, 2020 News Release</td>
</tr>
<tr>
<td>Clinical development</td>
<td>Futibatinib (TAS-120; FGFR inhibitor)</td>
<td>Publish the result of interim analysis of a Phase 2 study in patients with intrahepatic cholangiocarcinoma</td>
<td>ASCO2020 Oral Presentation</td>
</tr>
</tbody>
</table>
Taiho, Astex and MSD Establish Strategic Oncology Collaboration

Taiho Pharmaceutical Co. Ltd., ("Taiho") today announce an exclusive worldwide research collaboration and license agreement with Astex Pharmaceuticals (UK), a wholly owned subsidiary of Otsuka Pharmaceutical Co., Ltd. ("Astex"), and a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, known as MSD outside the United States and Canada ("MSD") focused on the development of small molecule inhibitors against several drug targets, including the KRAS oncogene, which are currently being investigated for the treatment of cancer.

"Taiho has used its unique and proprietary drug discovery platform to generate a number of small molecule inhibitors," said Teruhiro Utsugi, Ph.D., managing director at Taiho. "This alliance builds on our KRAS research up to now, and together with MSD it allows us to combine expertise to significantly accelerate the global research, development and commercialization of a number of our mutant KRAS programs by accessing external talent and resources."

Under the terms of the agreement, Taiho, Astex and MSD will combine preclinical candidates and their data with knowledge and expertise from their respective research programs. In exchange for providing MSD an exclusive global license to their small molecule inhibitor candidates, Taiho and Astex will receive an aggregate upfront payment of $50 million and will be eligible to receive approximately $2.5 billion contingent upon the achievement of preclinical, clinical, regulatory and sales milestones for multiple products arising from the agreement, as well as tiered royalties on sales. MSD will fund research and development and will be responsible for commercialization of products globally. Taiho has retained co-commercialization rights in Japan and an option to promote in specific areas of South East Asia.
Taiho Pharmaceutical and MD Anderson announce collaboration to accelerate development of novel therapies for brain metastasis and other unmet medical needs

Three-year collaboration to focus on therapies for brain metastases, refractory cancers

TOKYO and HOUSTON— Taiho Pharmaceutical Co., Ltd. and The University of Texas MD Anderson Cancer Center today announced a three-year strategic collaboration to accelerate the development of treatments for significant unmet medical needs in oncology, including patients with brain metastases and those with cancers refractory to available therapies.

This collaboration will bring Taiho’s unique portfolio of preclinical and clinical brain-penetrant therapies together with both the industry-scale translational research capabilities of MD Anderson’s Translational Research to Advance Therapeutics and Innovation in Oncology (TRACTION) platform as well as insights and clinical development infrastructure from MD Anderson’s Brain Metastasis Clinic.
Technology Enabled Drug Discovery in Taiho

- **Brain Metastasis**
  - Brain Cancer
  - 1993~
  - 2017~
- **DNA-encoded Library**
  - 2016~
- **Natural Product**
  - 2014~
- **RAS**
  - 2012~
- **Covalent Binders Cysteinomix**
  - 2010~
- **SBDD/FBDD**
  - 2009~
  - 2015~
- **UFT TS-1 Lonsurf**
  - 2009~
- **Kinase Inhibitors**
  - 2009~
- **TAS-114 TAS-115 TAS-117 TAS-119**
- **TAS-116 TAS3681**
- **TAS1440**
- **TAS-110**
- **TAS-116**
- **TAS-117**
- **TAS-119**
- **TAS-120 TAS5315 TAS6417 TAS0728**

**Approved Clinical**
### Development Pipeline (As of Jun. 30, 2020)

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TAS0953/HM06</strong>&lt;br&gt;RET inhibitor Co-development with Helsinn&lt;br&gt;IND</td>
<td><strong>TAS1440</strong>&lt;br&gt;LSD1 inhibitor&lt;br&gt;AML US</td>
<td><strong>TAS3681</strong>&lt;br&gt;Novel AR antagonist&lt;br&gt;Prostate Cancer US, EU</td>
<td><strong>TAS116</strong>&lt;br&gt;HSP90 inhibitor&lt;br&gt;GIST etc. JPN</td>
</tr>
<tr>
<td><strong>TAS0728</strong>&lt;br&gt;Her2 inhibitor&lt;br&gt;Solid Tumor US, EU</td>
<td><strong>TAS-117</strong>&lt;br&gt;Allosteric AKT inhibitor&lt;br&gt;Solid Tumor US, EU</td>
<td><strong>TAS-114</strong>&lt;br&gt;dUTPase/DPD inhibitor&lt;br&gt;NSCLC</td>
<td><strong>Pro-NETU</strong>&lt;br&gt;NK1RA&lt;br&gt;Chemotherapy-induced Nausea &amp; Vomiting JPN</td>
</tr>
<tr>
<td><strong>TAS-119</strong>&lt;br&gt;Aurora A inhibitor&lt;br&gt;Out-licensed to VITRAC Therapeutics</td>
<td><strong>TAS6417/CLN-081</strong>&lt;br&gt;EGFR inhibitor&lt;br&gt;Out-licensed to Cullinan Pearl</td>
<td><strong>TAS0313</strong>&lt;br&gt;Peptide Vaccine&lt;br&gt;Urothelial Cancer</td>
<td><strong>TAS-115</strong>&lt;br&gt;Multi tyrosine kinase inhibitor Prostate Cancer etc. JPN</td>
</tr>
<tr>
<td><strong>ET-743</strong>&lt;br&gt;DNA minor groove binder&lt;br&gt;Ovarian Cancer JPN&lt;br&gt;In-licensed from PharmaMar</td>
<td><strong>TAC-302</strong>&lt;br&gt;Neuroprotective Agent&lt;br&gt;Detrusor low activity&lt;br&gt;Overactive Bladder JPN&lt;br&gt;In-licensed from Meiji</td>
<td><strong>TAS-120</strong>&lt;br&gt;FGFR inhibitor&lt;br&gt;iCCA, Breast Cancer etc. JPN, US, EU</td>
<td><strong>TAS-118</strong> Development discontinued</td>
</tr>
<tr>
<td><strong>AB122</strong>&lt;br&gt;PD-1 inhibitor&lt;br&gt;In-licensed from Arcus Biosciences</td>
<td><strong>TAS-205</strong>&lt;br&gt;Prostaglandin D2 synthase inhibitor&lt;br&gt;Duchenne Muscular Dystrophy JPN</td>
<td><strong>TAS0728</strong>&lt;br&gt;ALK inhibitor&lt;br&gt;NSCLC US, EU</td>
<td><strong>TAS5315</strong>&lt;br&gt;BTK inhibitor&lt;br&gt;Rheumatoid Arthritis JPN</td>
</tr>
<tr>
<td><strong>AB928</strong>&lt;br&gt;A2AR/A2BR Antagonist&lt;br&gt;In-licensed from Arcus Biosciences</td>
<td><strong>TAS-303</strong>&lt;br&gt;Selective NA Re-uptake inhibitor&lt;br&gt;Stress Urinary Incontinence JPN</td>
<td><strong>TAS0953/HM06</strong>&lt;br&gt;RET inhibitor Co-development with Helsinn&lt;br&gt;IND</td>
<td><strong>TAS116</strong>&lt;br&gt;HSP90 inhibitor&lt;br&gt;GIST etc. JPN</td>
</tr>
</tbody>
</table>

### Preparing Clinical Development in Japan/Asia (ex. China)

- **AB122**<br>PD-1 inhibitor<br>In-licensed from Arcus Biosciences
- **AB928**<br>A2AR/A2BR Antagonist<br>In-licensed from Arcus Biosciences

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**Oncology**
- Cytotoxic
- Molecular targeting
- Supportive care
- Immunooncology

**Other Disease Area**
- Molecular targeting
- Others
Access to Highly “Innovative” Drugs: A Multifaceted Approach

Access to Innovative Drugs through Venture Investment

**Business Development**
- Oncology, Immunology/Allergy, Urology

**Tsukuba Research Center**
- Oncology, Immunology/Allergy, Urology

**TAIHO INNOVATIONS**
- Oncology, Immunology/Allergy, Urology
- Small Molecule
- Medium Sized Molecule
- Oncology
- Immunology/Allergy
- Urology

**TAIHO VENTURES**
- Mainly Oncology
- Antibody
- Vaccine
- Cancer (Innovative Treatments)

**REMIGES VENTURES**
- Wide range of disease areas
- Cell Therapy
- Rare Diseases

Obtaining innovative technologies and innovative development concepts not available in-house.
# Taiho Ventures’ Portfolio Companies

<table>
<thead>
<tr>
<th>Immuno-Oncology</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Checkpoint inhibitor</td>
<td>TCR-T cell therapy</td>
<td>T-cell engager</td>
<td>TME immune stimulant</td>
<td></td>
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<tr>
<td><img src="image1" alt="ARCUS Biosciences" /></td>
<td><img src="image2" alt="Next Cure" /></td>
<td><img src="image3" alt="PACT Pharma" /></td>
<td><img src="image4" alt="HARPOON Therapeutics" /></td>
<td><img src="image5" alt="Werewolf Therapeutics" /></td>
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<tr>
<td>(RCUS)</td>
<td>(NXTC)</td>
<td>(HARP)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Oncology</th>
<th></th>
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<tbody>
<tr>
<td>RNA epigenetics</td>
<td>Cancer resistance</td>
<td>DNA damage response</td>
<td>Oncogenic driver</td>
<td></td>
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<tr>
<td><img src="image6" alt="STORM Therapeutics" /></td>
<td><img src="image7" alt="ORIC" /></td>
<td><img src="image8" alt="BREAKPOINT Therapeutics" /></td>
<td><img src="image9" alt="Cullinan Pearl" /></td>
<td></td>
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<tr>
<td>(ORIC)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Microbiome</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><img src="image10" alt="AXIAL Biotherapeutics" /></td>
<td></td>
</tr>
</tbody>
</table>

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Taiho Ventures will have a first right to negotiate for an exclusive license related to the new oncology programs.

Spin-out TAS6417 to Cullinan Pearl to accelerate its clinical development.

As of Aug. 31, 2020
Arcus Biosciences Anti-PD-1 antibody Zimberelimab (AB122): Obtained Rights to Develop and Commercialize in Japan and Certain Other Territories in Asia

Taiho Pharmaceutical Concludes Option and License Agreement with Arcus Biosciences

Taiho Pharmaceutical obtains an option to in-license exclusive marketing rights of Arcus’s portfolio in Asia (excluding China) and aims to develop innovative cancer immunotherapies

Taiho Pharmaceutical Enters into Development of a Novel Immuno-Oncology Therapy with Arcus Biosciences

Taiho Pharmaceutical has obtained the exclusive right to develop and commercialize Arcus’s adenosine receptor antagonists in Japan and certain other territories in Asia (excluding China)

Obtain development and commercialization rights of an Adenosine Receptor Antagonist → Preparing clinical development in Japan/Asia
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Clinical Pipeline Update

◆ **Futibatinib (TAS-120)**
  - Covalent FGFR inhibitor
  - Potential Best-in-class drug
  - Indications (under development): Intrahepatic cholangiocarcinoma, Breast cancer, Gastric cancer, and others

◆ **TAS-115**
  - Multi tyrosine kinase inhibitor
  - Potential Best-in-class drug
  - Indications (under development): Idiopathic pulmonary fibrosis, Osteosarcoma, and others
FUTIBATINIB (TAS-120)
Key Profiles of Futibatinib

- The only covalently-binding FGFR inhibitor in clinical development stage
- Expected to have high antitumor activity with few side effects
- Expected to be effective in patients who have acquired resistance mutations to other drugs
- Inhibits all 4 family receptors (FGFR1-4); Expected to show effects in cancer types that do not respond to other drugs
Overcoming Acquired Resistance in Patients with FGFR2 Gene Fusion

Recurrence 1 year after response to the FGFR inhibitor (BGJ398)

Response and stable disease on futibatinib for over one year

Patient #2: Response to TAS-120

<table>
<thead>
<tr>
<th>Patient</th>
<th>73 yo Female with ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>FGFR2-SORBS1 fusion</td>
</tr>
<tr>
<td>PFS on BGJ-398</td>
<td>12.4 months</td>
</tr>
<tr>
<td>PFS on TAS-120</td>
<td>25.9 months</td>
</tr>
</tbody>
</table>

Response to BGJ398

Response to TAS120

Table 1: Patients With Benefit From TAS120 After Prior FGFR Inhibitor

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>FGFR Fusion</th>
<th>Prior FGFR Inhibitor</th>
<th>Best Response on Prior FGFR</th>
<th>Time on Prior FGFR</th>
<th>FGFR2 mutations that arose on cDNA or biopsy after prior FGFR</th>
<th>Best response on TAS120</th>
<th>Time on TAS120</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FGFR2-ZMYM4</td>
<td>BGJ-398</td>
<td>-49.9%</td>
<td>5.6 months</td>
<td>FGFR2 (V564F) FGFR2 (K659M) FGFR2 (E565A) FGFR2 (N549H/K)</td>
<td>+8.7%</td>
<td>7.4 months</td>
</tr>
<tr>
<td>2</td>
<td>FGFR2-SORBS1</td>
<td>BGJ-398</td>
<td>-68.2%</td>
<td>12.4 months</td>
<td>FGFR2 (K659M) FGFR2 (K714R)</td>
<td>-76.7%</td>
<td>15.9 months</td>
</tr>
<tr>
<td>3</td>
<td>FGFR2-NRAP</td>
<td>BGJ-398</td>
<td>-40.0%</td>
<td>7.1 months</td>
<td>Not assessed</td>
<td>-47.7%</td>
<td>9.0+ months, ongoing</td>
</tr>
<tr>
<td>4</td>
<td>INA-FGFR2</td>
<td>Debio 1347</td>
<td>-46.0%</td>
<td>11.2 months</td>
<td>FGFR2 (N549T) FGFR2 (N549H) FGFR2 (M537I)</td>
<td>-22.1%</td>
<td>2.9+ months, ongoing</td>
</tr>
</tbody>
</table>

Many more cases of response with futibatinib after recurrence with other FGFR inhibitors.

At the time of recurrence, a resistance mutation appeared in the blood, but the clone disappeared after administration of futibatinib

AACR Annual Meeting 2019, Abstract CT239, L. Goyal et al.
Futibatinib Demonstrates Meaningful Clinical Benefit in iCCA Patients with FGFR2 Gene Fusions

- Response rate: 37.3%, Disease control rate: 82.1%
- Progression-free survival (median): 7.2 months

Completed enrollment of Global Phase 2 study aiming early approval. Currently Planning Phase 3 study for 1st line iCCA.
## Futibatinib: Adverse Events

<table>
<thead>
<tr>
<th>MedDRA (v18.1) preferred term</th>
<th>All patients (N=67), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Patients with at least one AE</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (26.9)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>19 (28.4)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15 (22.4)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>13 (19.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (14.9)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>6 (9.0)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>10 (14.9)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>9 (13.4)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (11.9)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>8 (11.9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>6 (9.0)</td>
</tr>
</tbody>
</table>
Expansion to Other Types of Cancers as a Single Agent

In the Phase 1 study, multiple cases of tumor reduction in other cancer types (including gastric cancer) have been observed.

Currently planning multiple Phase 2 studies.
Tumor Agnostic Phase 2 Study is Ongoing

**Cohort A**
Advanced/metastatic solid tumors with *FGFR1-*4 rearrangements* (n=60)

**Cohort B**
Advanced/metastatic gastric or GEJ cancer with *FGFR2* amplification (n=35)

**Cohort C**
MLN with *FGFR1* rearrangements (n=20)

Futibatinib
20 mg QD orally in 28-day cycles

**Primary endpoint**
- Cohort A, B: Objective response rate
- Cohort C: Complete response rate

GEJ: Gastroesophageal junction
MLN: Myeloid or lymphoid neoplasms
* Brain tumors and iCCA are excluded.

https://clinicaltrials.gov/ct2/show/NCT04189445
**Futibatinib: Development Strategy for Combination Therapy**

- Recent studies have revealed that FGFRs play many roles including tumor microenvironment and drug resistance. Taiho currently aims to achieve clinical efficacy in combination therapies.

### Tumor microenvironment

FGFR inhibitors reduce the number of myeloid-derived suppressor cells (MDSC) via fibroblasts and attenuate tumor immune resistance.


- **FGFR**

### Anticancer drug resistance

- **Fluvestrant**

- **Futibatinib**

- **PI3K**
- **RAS**
- **AKT**
- **RAF**
- **MEK**
- **ERK**

- **HR positive breast cancer**
- **K-Ras mutant lung cancer**

- **Resistance**

**Combination study of futibatinib with IO drugs planned.**

**Combination studies of futibatinib with various anticancer agents planned (ongoing, in part).**
Futibatinib (TAS-120) : Ongoing Studies of Combination Therapy

- **TAS-120 monotherapy/TAS-120+fulvestrant**
  - Phase 2 study for FGFR mutated Breast Cancer
    (NCT04024436)

- **TAS-120+pembrolizumab**
  - Phase 1 study for FGFR mutated Solid Tumor
    (JapicCTI-195063)

- **TAS-117+TAS-120**
  - Phase 1/2 study for FGFR mutated Solid Tumor
    (JapicCTI-194864)
TAS-115(PAMUFETINIB) (MULTI TYROSINE KINASE INHIBITOR)
Idiopathic Pulmonary Fibrosis (IPF)

**Idiopathic pulmonary fibrosis**
A type of Idiopathic Interstitial Pneumonia defined in the National Registry of Designated Intractable Diseases in Japan
- Poor prognostic, idiopathic lung disease. Irreversible honeycomb form as a result of severe fibrosis
- Dyspnea and progressive decline in respiratory function are known as the typical symptom

Annual incidence and prevalence of IPF
- **[Japan]**
  - Approximately 14,000 pts
  - Annual incidence 2.23 patients/100K
  - Prevalence 10.0 patients/100K

Annual incidence 4.6-8.8 patients/100K
Prevalence 14.0-27.9 patients/100K

**[US/EU]**
- Annual incidence 4.6-8.8 patients/100K
- Prevalence 14.0-27.9 patients/100K

Median overall survival in IPF is reported as approximately 3 years after diagnosis.

Lung diffusion capacity is also declined in IPF patients

Treatment option for IPF is limited. Nintedanib and pirfenidone are approved drug recommended in the International Treatment Guideline.
【IPF】Efficacy: Significant Suppression of FVC Decline in Phase 2 Study

We are currently planning a Phase 3 study.

**Pre-TAS-115 treatment**

**TAS-115 treatment period**

- After nintedanib
- After pirfenidone
- No prior treatment

Remarkable responder

Baseline  FVC: 71.6%

Week 26   FVC: 75.1%

**ERS International Congress 2019, Abstract PA1296, T. Ogura et al.**

Phase 3 Study of TAS-115 in Patients with Osteosarcoma has Started

Osteosarcoma

- Bone sarcomas include osteosarcoma, chondrosarcoma, Ewing's sarcoma, and giant cell tumor of bone.
- The annual incidence of osteosarcoma in Japan is said to be 200 to 300. Many cases occur in teens to 20s.


Treatments for unresectable / metastatic osteosarcoma are limited and medical needs are high.

Efficacy of TAS-115 for Osteosarcoma

TAS-115 has a unique kinase inhibition spectrum and high antitumor activity against osteosarcoma and bone metastasis.

In some cases, the treatment period with TAS-115 is longer than that of the previous treatment. We have started a Phase 3 study.
Phase 3 Study Design

**R cohort**
- ≥15 years old
- Osteosarcoma
- Refractory or intolerance to MAP regimen or similar ones
- Unable curative resection due to metastatic lesion
- Primary lesion has been removed completely

Target sample size: 60

- TAS-115
- Placebo
- PD

**P cohort**
- 7-15 years old
- Osteosarcoma
- Refractory or intolerance to MAP regimen or similar ones
- Unable curative resection due to metastatic lesion
- Body weight is over 30 kg

Target sample size: 6

- TAS-115

Primary endpoint: Progression-free survival based on blinded central radiological review, Overall survival
Expected duration of study: June 2020 - June 2023

MAP: Methotrexate + Doxorubicin + Cisplatin
PD: Progressive Disease

JapicCTI-205335
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Technology Enabled Drug Discovery in Taiho

DNA-encoded Library
2016～

Brain Metastasis Brain Cancer
2017～

Nucleic Acids
1993～

Kinase Inhibitors
2009～

Natural Product
2014～

RAS
2012～

Covalent Binders Cysteinomix
2010～

SBDD/FBDD
2009～

Approved
Clinical

TS-1
Lonsurf
TAS-114
TAS-115
TAS-117
TAS-119
TAS-120
TAS5315
TAS6417
TAS0728
TAS-116
TAS3681
TAS1440

TAS-120
TAS5315
TAS6417
TAS0728
Expansion of Cysteinomix
~from Kinases to RAS Drug Discovery~
Cysteinomix Drug Discovery Platform

• **Cysteinome**
  Druggable proteins that have reactive amino acid residues (ex. Cys) located inside or adjacent to the binding sites of small to medium-sized molecules

• **Covalent Binding Drugs**
  Drugs that specifically capture reactive amino acid residues (ex. Cys) by forming covalent bonds
Cysteinomix Drug Discovery Platform

- **Cysteinomix**
  Taiho’s proprietary technology platform to identify drugs that specifically form a covalent bond with the target cysteinome
Futibatinib was found to show potent and selective inhibition of FGFR1, 2, 3, and 4 by forming a covalent bond with the targeted Cys in FGFR1, 2, 3, and 4.

→ Currently in Phase 2 and aim to achieve early approval.

FGFR: Fibroblast growth factor receptor
Cysteinomix Drug Discovery Platform

- Cysteinome Identification Platform
  Proprietary technology for genome-wide screening of druggable Cysteinome

**INFORMATICS PLATFORM**
Genome Wide Search of Targetable Cysteinome

**MS PLATFORM**
Experimentally Validate the Reactivity of Target Cys in Cysteinome

Disease related genome (Kinome, Epigenome, GTPase family etc.)

**Target Cysteinome**

Cysteinomix Drug Discovery Targeting Small GTPase Family

- **Protein kinase family (518)**
  - FGFR (TAS-120)
  - EGFR exon20 (TAS6417)
  - BTK (TAS5315)
  - HER2 (TAS0728)

- **Small GTPase family (160)**
  - KRAS G12C

\[ \frac{188}{518} \text{ Cysteinome} \]

\[ \frac{29}{160} \text{ Cysteinome} \]

The 188 kinases and 217 locations are shown in different colors and symbols

**Mutant RAS driven cancers are high unmet medical needs**

- Frequently mutated in deadly cancers (lung, pancreatic, colon, etc.)
- Remained as undruggable targets despite 30 years challenges
- Involved in highly complicated intracellular protein-protein interactions

*Drug Discovery Targeting RAS Oncogene*

Oncogenic KRAS Mutations Are Highly Valuable Targets

**KRAS G12 mutation**

**Pancreatic**
- 91% G12
- 35% G12V, 17% G12D, 13% G12C

**Colorectal**
- 68% G12
- 30% G12C, 45% G12D, 25% G12A, G12F, G12C

**Adenocarcinoma**
- 85% G12
- 23% G12C, 17% G12D, 46% G12A, G12F, G12C

Incidence of KRAS Mutations in Three Human Cancers

<table>
<thead>
<tr>
<th></th>
<th>All KRAS</th>
<th>G12C</th>
<th>G12D</th>
<th>G12V</th>
<th>G13D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>60,000</td>
<td>5,700</td>
<td>25,000</td>
<td>15,700</td>
<td>13,600</td>
</tr>
<tr>
<td>Lung</td>
<td>45,600</td>
<td>23,000</td>
<td>9,200</td>
<td>11,900</td>
<td>1,500</td>
</tr>
<tr>
<td>Pancreas</td>
<td>32,200</td>
<td>1,000</td>
<td>19,500</td>
<td>11,500</td>
<td>200</td>
</tr>
<tr>
<td>Total new cases/year</td>
<td>137,800</td>
<td>29,700</td>
<td>53,700</td>
<td>39,100</td>
<td>15,300</td>
</tr>
</tbody>
</table>

Percentages of KRAS mutations that are in codon 12 by tissue type for pancreatic, colorectal and lung adenocarcinoma


Cysteinomix Screening of KRAS G12C Covalent Binders

Target Cysteinome

- KRAS G12C (Cancer Cell)
- KRAS wild-type (Normal Cell)

Off target

Discovery of covalent binding
KRAS modulators

KRAS G12C – Compound X

High speed MS binding assay
Taiho, Astex and MSD Establish Strategic Oncology Collaboration

Taiho Pharmaceutical Co., Ltd., ("Taiho") today announce an exclusive worldwide research collaboration and license agreement with Astex Pharmaceuticals (UK), a wholly owned subsidiary of Otsuka Pharmaceutical Co., Ltd. ("Astex"), and a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, known as MSD outside the United States and Canada ("MSD") focused on the development of small molecule inhibitors against several drug targets, including the KRAS oncogene, which are currently being investigated for the treatment of cancer.

"Taiho has used its unique and proprietary drug discovery platform to generate a number of small molecule inhibitors," said Teruhiro Utsugi, Ph.D., managing director at Taiho. "This alliance builds on our KRAS research up to now, and together with MSD it allows us to combine expertise to significantly accelerate the global research, development and commercialization of a number of our mutant KRAS programs by accessing external talent and resources."

Under the terms of the agreement, Taiho, Astex and MSD will combine preclinical candidates and their data with knowledge and expertise from their respective research programs. In exchange for providing MSD an exclusive global license to their small molecule inhibitor candidates, Taiho and Astex will receive an aggregate upfront payment of $50 million and will be eligible to receive approximately $2.5 billion contingent upon the achievement of preclinical, clinical, regulatory and sales milestones for multiple products arising from the agreement, as well as tiered royalties on sales. MSD will fund research and development and will be responsible for commercialization of products globally. Taiho has retained co-commercialization rights in Japan and an option to promote in specific areas of South East Asia.
Technology Enabled Drug Discovery in Taiho

Brain Metastasis
Brain Cancer
1993～2009～
2017～

DNA-encoded Library
2016～

Nucleic Acids
1993～

Covalent Binders Cysteinomix
2010～

Kinase Inhibitors
2009～

SBDD/FBDD
2009～

RAS
2012～

Natural Product
2014～

UFT TS-1 Lonsurf
TAS-114

TAS-115 TAS-117

TAS-119

TAS-116 TAS3681

TAS1440

TAS-120 TAS5315 TAS6417 TAS0728

Approved Clinical

DNA-encoded Library
2016～

Brain Metastasis Brain Cancer
1993～2009～
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Approved Clinical
Brain Metastasis and Brain Cancers
Advance in Cancer Therapy Leads to Increased Brain Metastasis

**Metastatic Brain Tumor**

** Newly diagnosed cases of brain metastases**
- US: 200,000 patients/year
- Japan: ~80,000 patients/year

**Frequency of brain metastasis according to primary site**

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Occupancy(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>50-60%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>20-30%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>5-10%</td>
</tr>
<tr>
<td>Gastric, Esophageal, Prostate, Ovarian Cancer</td>
<td>In total 5-10%</td>
</tr>
</tbody>
</table>

**Brain Cancers**

** Newly diagnosed cases**
- US: 23,890 patients/year
- Japan: ~80,000 patients/year

**Prognosis and Treatment**

*Glioblastoma*

- Glioblastoma is an almost incurable disease with a median survival of 14.6 months, even in patients who can be treated with standard treatment.
- Treatment for glioblastoma is limited to temozolomide and bevacizumab.

Our Strategy to Tackle Brain Metastasis

Discovery Brain Penetrant Compounds

Drug Discovery Platforms Targeting Brain Metastasis

Pioneering Basic and Clinical Brain Metastasis Research

Research Collaboration with MD Anderson Cancer Center

Tim Heffernan, Ph.D.
- TMACTION Platform Leader
- Executive Director and Head, Oncology Research

Michael A. Davies, M.D., Ph.D.
- Professor and Chairman of the Department of Melanoma Medical Oncology

John F. de Groot, M.D.
- Professor of the Department of Neuro-Oncology, Division of Cancer Medicine

Hussein A. Tawbi, M.D., Ph.D.
- Co-director of MD Anderson’s Brain Metastasis Clinic
- Director of Melanoma Clinical Research and Early Drug Development
Taiho Pharmaceutical and MD Anderson announce collaboration to accelerate development of novel therapies for brain metastasis and other unmet medical needs
Three-year collaboration to focus on therapies for brain metastases, refractory cancers

TOKYO and HOUSTON— Taiho Pharmaceutical Co., Ltd. and The University of Texas MD Anderson Cancer Center today announced a three-year strategic collaboration to accelerate the development of treatments for significant unmet medical needs in oncology, including patients with brain metastases and those with cancers refractory to available therapies.

This collaboration will bring Taiho’s unique portfolio of preclinical and clinical brain-penetrant therapies together with both the industry-scale translational research capabilities of MD Anderson’s Translational Research to Advance Therapeutics and Innovation in Oncology (TRACTION) platform as well as insights and clinical development infrastructure from MD Anderson’s Brain Metastasis Clinic.