Introduction of Taiho R&D

Oct. 10, 2019
Outline

< R&D Strategy (In-house Drug Discovery & External R&D Collaboration)>

• **In-house Drug Discovery: Taiho’s Approach in the Oncology Arena**
  – Evolution from “futraful (FT)” an oral antimetabolite
    • FT → UFT → S-1 → Lonsurf →
  – Molecular targeted drugs
    • Build, strengthen and expand a unique drug discovery platform
  – Cysteinomix

• **Introduction of Products in Clinical Development**
  – Introduction of three representative products
    • Futibatinib (TAS-120)
    • TAS3681
    • TAS-115

• **External R&D Collaboration: Access to Innovative Drugs**
R&D STRATEGY
(IN-HOUSE DRUG DISCOVERY & EXTERNAL R&D COLLABORATION)
IN-HOUSE DRUG DISCOVERY: TAIHO’S APPROACH IN THE ONCOLOGY ARENA
Changing Era/Technology Innovations
From Cytotoxic Drugs to Molecular Targeted Drugs and Immuno-oncology Drugs


“Drugs using the different growth rates between cancer cells and normal cells”

Cytotoxic Drugs 1940’s~
- Alkylating agents
- Antimetabolites
- Plant alkaloids
- Antitumor antibiotics
- Platinum antitumor agents
- Taxanes
- Synthetic antitumor agents
- Topoisomerase inhibitors

“Drugs targeting molecules which accelerate growth of cancer cells”

Molecular Targeted Drugs 1990’s ~
- Monoclonal antibodies
- Protein kinase inhibitors
- Epigenetic agents

“Drugs using the built-in immune system to eliminate cancer cells”

Immunotherapy 1970’s ~
- Non-specific immune stimulator
- Cytokine therapy

Immuono-oncology Drugs 2010 ~
- Increase the power of immunity → Disrupting Immune Suppression
- Immune-checkpoint blockade
Battle to Develop **Oral Anticancer Drugs**: Maximizing the Antitumor Effect by combining the **Chemical Modulators**

- **1974** Launched Futraful Capsule
- **1969** Licensed in Futraful
- **1974** Launched Futraful Capsule
- **1984** Launched UFT Capsule
- **1999** Launched TS-1 Capsule
- **2014** Launched Lonsurf Tablet
- **2010** Launched Aloxi Launched Abraxane

**Introduction of Crucial Drugs for Japanese Cancer Patients**

**Improvement QOL of Cancer Patients: Aloxi**

Anticancer drug approved in > 70 countries: Abraxane
Taiho’s Anticancer Drug Development History: Evolution from Oral Anti-metabolite Futraful

- **Oral anticancer drug**
- **Combination product**

**1st Gen Futraful (1974~)**

- Tegafur (5-FU prodrug)
  - High oral absorbability

**2nd Gen UFT (1984~)**

- Tegafur (5-FU prodrug)
  - Keeps high 5-FU blood concentration

**3rd Gen TS-1 (1999~)**

- Gimeracil (DPD inhibitor)
  - Keeps high 5-FU blood concentration

- Oteracil potassium (OPRT inhibitor)
  - Reduce GI toxicity

Maximizing the Potential of 5-FU

- Treatment switch from hospitalization to outpatient through oral administration
- Overcame difficulties of determining and proofing the combination ratio → Other companies could not imitate.
Research and Development of Antimetabolites: Lonsurf

**Lonsurf combination tablet**

- **Trifluridine**
  - (FTD: thymidine analog)
  - metabolized through phosphorylation in cancer cells, then incorporated into DNA.

- **Tipiracil (TP inhibitor)**
  - keeps the plasma FTD levels high

**Futuraful**
- 1974 launched

**UFT**
- 1984 launched

**TS-1**
- 1999 launched

**Lonsurf**
- 2014 launched in Japan
- 2015 launched in the USA

**Cumulative Experience and Technologies in Antimetabolite Drug Discovery**

+ Establishment of New Drug Discovery Platforms

**Novel anticancer drug**

Trifluridine (FTD: thymidine analog) is metabolized through phosphorylation in cancer cells, then incorporated into DNA. Tipiracil (TP inhibitor) keeps the plasma FTD levels high. Lonsurf combination tablet consists of Trifluridine and Tipiracil. Lonsurf was launched in Japan in 2014 and in the USA in 2015. This success is attributed to the cumulative experience and technologies in antimetabolite drug discovery, including the establishment of new drug discovery platforms.
Establishment of Platforms for Molecular Targeted Drug Discovery

“Drugs using the different growth rates between cancer cells and normal cells”

Cytotoxic Drugs 1940’s ~

Cumulative Experience and Technology in Antimetabolites Drug Discovery + Molecular Targeted Drug Discovery Platforms

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Advances in Drug Discovery Technology
Human Genome
Immune-checkpoint


“Drugs using the different growth rates between cancer cells and normal cells”

“Drugs targeting molecules which accelerate growth of cancer cells”

“Drugs using the built-in immune system to eliminate cancer cells”
Small ~ Medium Sized Molecule Drug Discovery Driven by In-house Platform Technologies

- **DNA Encoded Chemical Library**: 2016 ~
- **Drug Discovery Platform**: 2017 ~
- **Collaboration with Dana-Farber Cancer Institute**
- **Drug Discovery Platform**: 2018 ~
- **Collaboration with MD Anderson Cancer Center**
- **Natural Product Drug Discovery**: 2014 ~
- **Collaboration with X-CHEM**
- **Structure Based Drug Discovery**: 2015 ~
  - **Fragment Based Drug Discovery**: 2009 ~
- **Cysteinomix Drug Discovery**: 2010 ~
- **Launched**: **Clinical**
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~medium-sized molecules

• Covalent Binding Drugs
  Drugs that specifically captures 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 forms a covalent bond with the target cysteinome.
Futibatinib: The World’s First Covalent FGFR Inhibitor

Figure 4B

Futibatinib (TAS-120)

% Control

FGFR: Fibroblast growth factor receptor

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. Aims to achieve early approval
DEVELOPMENT PIPELINE
Development Pipeline (As of Jun. 30, 2019)

**Pre-clinical**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease Area</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB928 (JPN)</td>
<td>A2AR/A2BR Antagonist</td>
<td>Co-development with Helsinn</td>
</tr>
<tr>
<td>TAS6417/CLN-081</td>
<td>EGFR inhibitor</td>
<td>Out-licensed to Cullinan Pearl</td>
</tr>
</tbody>
</table>

**Phase 1**

| TAS3681 | Novel AR antagonist | Prostate, US, EU |
| TAS0728 | Her2 inhibitor | Solid Tumor, US, EU |
| TAS4464 | NAE inhibitor | Solid Tumor, Hematological Cancer, JPN, US, EU |
| ET-743 | DNA minor groove binder | Ovarian, JPN |

**Phase 2**

| TAS117 | Allosteric Akt inhibitor | Solid Tumor, JPN |
| TAS119 | Aurora A inhibitor | Solid Tumor, US, EU |
| TAS0313 | Peptide Vaccine | Urothelial, JPN |

**Phase 3**

| TAS114 | dUTPase inhibitor | NSCLC, JPN, US, EU |
| TAS115 | Multi tyrosine kinase inhibitor | Prostate, JPN |
| TAS116 | Multi tyrosine kinase inhibitor | Prostate, JPN |
| TAS118 | A2AR/A2BR Antagonist | In-licensed from Arcus Biosciences |

**Oncology**

- **Cytotoxic**
- **Molecular targeted**
- **Supportive care**

**Other Disease Area**

- **Molecular targeted**
- **Others**
Introduction of Three Representative Products

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

◆ **TAS3681**
  - Pure AR antagonist with AR downregulating activity
  - Potential First-in-class drug
  - Indication (under development): Castration resistant prostate cancer

◆ **TAS-115**
  - Multi tyrosine kinase inhibitor
  - Potential Best-in-class drug
  - Indication (under development): Idiopathic pulmonary fibrosis, Prostate cancer and others
FUTIBATINIB (TAS-120)
Characteristics of FGFRs as Cancer Treatment Targets

- Many types of genetic abnormalities compared with other genes; Point mutation, Translocation, Gene amplification and Overexpression
- FGFR genetic abnormalities found in many types of cancer; Cholangiocarcinoma(CCA), Breast cancer, Lung cancer, and Gastric cancer
- Impact on the tumor microenvironment; Forms a unique tumor microenvironment through not only tumor cells but also fibroblasts, and is attracting particular attention from the viewpoint of tumor immunity
- Contribution in drug resistance mechanisms; Resistance mechanisms of various chemotherapeutic and immunotherapeutic drugs (Expectations as a combination therapy partner)
Key Profiles of Futibatinib

- Inhibits all 4 family receptors (FGFR1-4); Expected to show effects in cancer types that do not respond to other drugs
- 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
Futibatinib Demonstrates Meaningful Clinical Benefit in CCA Patients with FGFR2 Gene Fusions

**Waterfall plot in CCA patients with FGFR2 gene fusions (n=28)**

- 24 patients were evaluable for efficacy
- 20 had tumor shrinkage
- 7 had confirmed partial response (26% ORR)
- 15 had stable disease
- Disease control rate = 78.6%

* Prior FGFR inhibitor

**Kaplan-Meier plot of time on treatment in CCA patients with FGFR2 gene fusions**

- Median duration of treatment: 7.4+ months
- 15/28 patients are ongoing

Response rate: 25%, Disease control rate: 78.6%
Progression free survival: 7.4 month

Currently conducting Global Phase 2 study aiming early approval

ESMO World Congress on Gastrointestinal Cancer, 2018
Abstract O-001 F. Meric-Bernstam et al.
Overcoming Acquired Resistance in Patient with FGFR2 Gene Fusion

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

Response and stable disease on TAS-120 for over one year

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 ctDNA 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 (NS49T) FGFR2 (NS549H) FGFR2 (M537i)</td>
<td>-22.1%</td>
<td>2.9+ months, ongoing</td>
</tr>
</tbody>
</table>

Many more cases of response with TAS-120 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 TAS-120.

AACR Annual Meeting 2019, Abstract CT239, L. Goyal et al.
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.
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.

**Anticancer drug resistance**

By combination with futibatinib, IO-drug’s efficacy will increase!

Combination study of futibatinib with IO drugs planned.

Combination studies of futibatinib with various anticancer agents planned (ongoing, in part).
TAS3681
A NOVEL PURE AR ANTAGONIST WITH AR DOWNREGULATING ACTIVITY
AR Agents in Prostate Cancer Treatment Tree

Androgen deprivation therapy
- LH-RH agonist/antagonist
- Additional HR therapy
- Bicalutamide

2nd gen AR agents
- Abiraterone
- Enzalutamide
- Darolutamide
- Apalutamide

Chemotherapy
- Docetaxel
- Cabazitaxel

Death due to CRPC

Local treatment

Additional HR therapy

Non metastatic
Metastatic

Asymptomatic
Symptomatic

ADT success
Castration Resistant Prostate Cancer (CRPC)

Death

CRPC: Castration resistant prostate cancer
mHSPC: metastatic hormone sensitive Prostate cancer

Modified from EAU2012 P. Mulders et al.
Urgent Issues on CRPC Treatment

- Cross resistance between Enzalutamide and Abiraterone
- Compounds with the same MOA currently in development have the same issue

One of the main resistant mechanism of the two drugs is AR splicing variants such as AR-V7 which lacks the ligand binding domain.

**PSA response to Abiraterone**

- AR-V7 positive
- AR-V7 negative

**PSA response to Enzalutamide**

- AR-V7 positive
- AR-V7 negative

Due to the lack of LBD, both drugs do not function against splicing variant ARs.

*Full length AR*  
DNA binding domain  
AR binding domain

*AR-V7*  
NTD  
DBD  
LBD

Key Profiles of TAS3681

TAS3681 has an AR antagonist activity comparable to enzalutamide,

In addition, it downregulates NOT only the full length AR but also the splicing variant ARs,

Which leads to efficacy in enzalutamide resistant models with AR-V7

(A) Cell growth

(B) PSA production

Results are expressed as the mean ± SD (n = 3).

TAS3681

• Currently under Phase 1 trial
TAS-115 (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

[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.

Treatment option for IPF is limited. Nintetanib is the only approved drug recommended in the International Treatment Guideline.
Key Profiles of TAS-115

Mechanism of action of TAS-115

- **Inhibition of Fibrosis in preclinical IPF model**
  - Comparison with nintedanib

**VEGF**

**PDGF**

**VEGFR**

**PDGFR**

Nintedanib

TAS-115

Endothelial cells growth

Fibroblasts growth

Growth signal inhibition

* VEGFR: Vascular endothelial growth factor receptor

** PDGFR: Platelet-derived growth factor receptor

Efficacy: Significant Suppression of FCV Decline in Phase 2 Study

Pre-TAS-115 treatment

TAS-115 treatment period

- After nintedanib
- After pirfenidon
- No prior treatment

Remarkable responder

Baseline
FVC ; 71.6%

Week 26
FVC ; 75.1%

Forced vital capacity (FVC, %)

Decline of vital capacity

Prevention of vital capacity loss

Data cut-off date is Jul 2, 2019

ERS International Congress 2019, Abstract PA1296, T. Ogura et al.
Safety: Adverse Events (≥5%) in Phase 2 Study

As of Jun 30, 2019

Four treatment-related SAEs (pyrexia, interstitial lung disease, idiopathic pulmonary fibrosis and rash) were observed in four patients. The most commonly observed AE was skin rash, which was controllable following interruption or dose modification of TAS-115.

The commonly observed digestive symptoms (such as diarrhea and nausea) of nintedanib were much less frequent in TAS-115.
TAS-115 : Future Plan

• Planning Phase 3 trial in IPF
• Planning clinical trials to confirm antitumor activity
EXTERNAL R&D COLLABORATION: ACCESS TO INNOVATIVE DRUGS
Further Actions to Discover and Develop Innovative Drugs

“Drugs using the different growth rates between cancer cells and normal cells”

Cytotoxic Drugs 1940’s~

“In-house Drug Discovery Platforms

Molecular Targeted Drugs 1990’s ~

Monoclonal antibodies, Protein kinase inhibitors Epigenetic agents

Immune checkpoint blockade

Immuno-oncology Drugs 2010 ~

Increase the power of immunity → Disrupting Immune Suppression

Non-specific immune stimulator
Cytokine therapy

Immuno-oncology
Drugs 2010 ~

“Drugs targeting molecules which accelerate growth of cancer cells”

“Drugs using the built-in immune system to eliminate cancer cells”

Advances in Drug Discovery Technology

Human Genome

Immune-checkpoint

External Innovations

Launched Futrafal
Launched UFT
Launched S-1
Launched Lonsurf

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Drugs 2010 ~
Access to Highly “Innovative” Drugs: A Multifaceted Approach

Access to Innovative Drugs through Venture Investment

Development Stage

Early
Late

Business Development

Oncology, Immunology/Allergy, Urology

Obtaining innovative technologies and innovative development concepts not available in-house.

Mainly Oncology

Wide range of disease areas

REMIGES VENTURES

TAIHO VENTURES

Oncology, Immunology/Allergy, Urology

TAIHO INNOVATIONS

Japanese only
+Healthcare

Example) Types of Drugs

Small Molecule
Medium Sized Molecule

Antibody
Vaccine
Cell Therapy

Example) Disease Area

Cancer (Innovative Treatments)
Rare Diseases

Oncology
Immunology/Allergy
Urology

Tsukuba Research Center

Example) Disease Area

Oncology
Immunology/Allergy
Urology

TAIHO PHARMACEUTICAL CO., LTD.

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Taiho Ventures’ Portfolio Companies

Please visit Taiho Ventures, LLC’s Website

http://www.taihoventures.com/portfolio.html
Agreements with Arcus Biosciences, One of Taiho Ventures’ Portfolio

News Releases

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)