We would like to introduce Daiichi Sankyo’s approach to developing cancer targeted medicines with special reference to the drug discovery strategy, global discovery activities and external research collaboration leading to generation of innovative drugs for cancer patients. We are developing 14 clinical projects for cancer treatment and three of them have been previously approved. These are mostly targeted for growth and survival signals of cancer cells. To overcome the drug resistance mechanism derived from the heterogeneous nature of cancer, we are developing selective inhibitors in three major clusters of signal pathways which may allow future rational combinations of oncology products. In addition to the main research facility in Japan, research sites in the EU and the USA provide us with different technical expertise and diversified ideas of drug discovery. To access novel drug targets, we are facilitating research collaboration with leading academia and successful cancer research scientists. In conclusion, we intend to focus more on developing innovative personalized medicines for better treatment of cancer.

Key words: drug discovery – targeted medicine – Daiichi Sankyo

DISCOVERY FOCUS IN ONCOLOGY

In 2009, we restructured and more narrowed focused therapeutic disease areas in drug discovery based upon the future trend of unmet medical needs and in-house research capability in drug discovery (Fig. 1). One of the two newly focused disease areas was oncology where better treatment is still highly demanded (1). By selecting more limited disease areas, we intended to accelerate the creation of innovative drugs without delaying novel scientific findings emerging in tumor biology.

We previously developed topoisomerase-I inhibitor Irinotecan (CPT-11) with Yakult Co. in Japan and with Pfizer in the USA. The drug has meaningfully contributed to the treatment of colorectal cancer especially in the West. However, the successful R&D for cancer targeted medicine today requires largely different knowledge and technology from that utilized for chemotherapeutic agents in the past.

All 14 drugs in the pipeline, both marketed and under development, are molecular targeted medicines (Table 1). Denosumab is an anti-RANKL monoclonal antibody that inhibit osteoclast activation in bone. In addition to the treatment of osteoporosis, Denosumab prevents skeletal-related events and potentially represents a novel treatment option in men with bone metastases from castration-resistant prostate cancer (2,3). Vemrafenib is a mutant BRAF kinase inhibitor approved for the first-line treatment of advanced melanoma. We thus have supported treatment of colorectal cancer, melanoma and bone metastasis with these three approved products.

It has been shown that drug discovery in oncology from compound selection through drug approval is least successful according to a survey in major therapeutic disease areas, and only 2% of the research programs can get approval for commercialization (4). To reduce such a high attrition rate in drug development, we first established a clear vision and a focused discovery strategy in cancer drug discovery. We are pursuing tumor biology-guided drug discovery and development especially for attacking cancer-driving molecular targets and identification of rational drug combinations. In parallel with drug development, we are increasing activity to develop diagnostic strategies and tools for the selection of right patients.
CHALLENGES IN DEVELOPING CANCER TARGETED MEDICINES

Cancer is a complicated disease and the cancer cell usually has a heterogeneous nature with multiple gene mutations. According to the recent genome analysis of clinical cancer, different mutations were found not only in primary and metastatic tumors but also in a tumor mass itself (5). Cross-talk and activation of alternative signaling pathways often induces de novo or acquired drug resistance. Gatekeeper mutation in the kinase molecule occurs after repeated treatment with its selective kinase inhibitor. Treatment with a target-selective single agent is thus not always effective and in most cases drug combination is required.

Approach toward personalized treatment is a critical success factor in cancer and it requires utilization of predictive and prognostic biomarkers for the selection of right products and right patients.

CREATION OF SELECTIVE TARGETED MEDICINES FOR THE CLUSTER OF MAJOR SIGNALING PATHWAYS

We first selected major growth and survival signal pathways as the drug target. We then created a number of target-selective inhibitors against either kinases or surface membrane receptors for each selected pathway (Fig. 2). We believe that this comprehensive approach will support to choose best combination for each patient who has a variety of different gene mutations/deletions/amplifications in their tumor. A highly selective compound with a sufficient safety profile enables a drug combination to provide strong and prolonged signaling blockade.

The first cluster is a receptor tyrosine kinase (RTK) that transduces cancer-inducing growth/survival signals such as EGFR and its ligand HB-EGF, HER3 and c-MET. The clinical pipeline is the mixture of antibody and small chemical tyrosine kinase inhibitor (TKI) aligning with a preferred nature of tumor biology. It has been known that c-MET induces drug resistance in EGFR-TKI therapy for non-small-cell lung cancer (NSCLC) (6). Tivantinib (ARQ 197) is a small molecule chemical inhibitor interacting with c-MET and is under late-stage development in collaboration with ArQule. Tivantinib physically interacts with a unique site of c-MET in an ATP pocket and it stabilizes c-MET in an inactivated kinase form (7) which is different from other ATP-competitive kinase inhibitors. This unique way of inhibition may exhibit different phenotypes of c-MET or common kinase inhibitor. Meanwhile, it has been shown by recent publications questioning whether the MOA of Tivantinib is c-Met inhibition or not (8). We realize the possibility that there are additional MOAs other than c-Met, which needs to be further clarified.

In preclinical studies, Tivantinib has shown antitumor activity in many c-MET-positive tumor models including lung cancer. Tivantinib showed better efficacy in a Phase 2 clinical study for c-MET-positive NSCLC when combined with erlotinib (9). Recently, similar clinical response to Tivantinib was shown in c-MET-high hepatocellular carcinoma (HCC) patients in second-line treatment (10). Study met primary endpoint in second-line HCC for the ITT population, with statistically significant improvement in time to progression [hazard ratio (HR) = 0.64, 6.9 versus 6.0 weeks, \( P = 0.04 \)]. A c-MET-high subpopulation showed almost twice long overall survival (HR = 0.38, 7.2 versus 3.8 months; Fig. 3). Its placebo-controlled, double-blind, Phase 3 clinical trial is under way for registration in second-line HCC as a single agent against best supportive care (11).

Table 1. Clinical pipeline in oncology as of August 2013

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>U3-1565 (HB-EGF)</td>
<td>CS-1008 (DR5)</td>
<td>Tivantinib (c-MET)</td>
<td>Vemurafenib (BRAF)</td>
</tr>
<tr>
<td>DS-2248 (HSP90)</td>
<td>U3-1287 (HER3)</td>
<td>DE-766 (EGFR)</td>
<td>Denosumab (RANKL)</td>
</tr>
<tr>
<td>DS-7423 (PI3K/mTOR)</td>
<td>PLX 3397 (FMS/c-KIT)</td>
<td></td>
<td>Irinotecan (TOPO-1)</td>
</tr>
<tr>
<td>ARQ 092 (AKT)*</td>
<td></td>
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<tr>
<td>DS-3078a (TORC1/2)</td>
<td></td>
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<tr>
<td>DS-3032b (MDM2)</td>
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MOA is shown in parenthesis and the antibody is shown in italics.

*aReturned to ArQule in 2013.*
HER3 is an RTK that only physically interacts with PI3K in the HER family and it forms a heterodimer with other HER family RTKs to strengthen cancer growth signals (12). Antibody is a feasible approach for drug discovery since HER3 itself does not have kinase activity in the subcellular domain. While the ligand of HER2 is not known, Hereglin is the ligand of HER3 and around half of patients showed significant expression of Hereglin in tumors. Recently, it was shown that targeting HER3 could be a potential strategy for personalized treatment of cancer (12).
in the clinical study that the level of Hereglin in tumor tissues can be a possible predictive biomarker for a HER3 blocking drug (13). Also, somatic mutation of HER3 in advanced cancers is reported (14). U3-1287 is an anti-HER3 monoclonal antibody under Phase 2 clinical development for second-line NSCLC and first-line metastatic breast cancer. It was well tolerated and it exhibited stable disease in almost half of the patients in Phase 1 (Fig. 4) (15). Both hypothesis-free and hypothesis-driven biomarker strategies are under development to enrich the patient population for further drug development. The activation of HER3 is associated in some TKI drug resistance. The combination therapy of U3-1287 with other molecular targeted medicines will be explored based on these new findings.

HB-EGF is a ligand of EGFR and HER4. U3-1565 neutralizing antibody of HB-EGF is under development in Phase 1. U3-1287 and U3-1565 have originated from U3 Pharma in our group company. Nimotuzumab (DE-766) is an anti-EGFR antibody with limited skin toxicity and is approved overseas for head and neck cancer, glioma and esophagus cancer. Two Phase 3 studies of Nimotuzumab for EGFR-high stomach cancer and lung cancer combined with chemoradiation are underway in Japan. PLX 3397 is an FMS/c-KIT kinase inhibitor in Phase 2 for several advanced tumors and it has originated from Plexxikon in our group company.

The second category is the PI3K pathway, which is widely activated in cancer (16). Its activation is so common that it does not seem to be a major driver despite the fact that it is known to be involved in PI3K gene mutation or inactivation of PTEN. It, however, is often the case that activation of PI3K pathway is associated in some drug resistance of TKI. In combination with inhibitor of PI3K pathway, major-driver inhibitor may restore its response to the resistant cancer cells. We have recently developed three selective inhibitors in this pathway targeting PI3K/mTOR (DS-7423), AKT (ARQ 092) and mTORC1/2 (DS-3078a) to identify the best indications for drug combination of each compound with the standard of care. The right of AKT inhibitor ARQ 092 was returned to ArQule after the Phase 1 study. There are a variety of compounds under development for inhibiting growth and survival signals in the PI3K pathway. Since target molecules in this pathway are not a strong driver in cancer, rational combination is under examination for further development.

The third category is the RAF/MEK/ERK pathway. BRAF V600E mutation is a hallmark of the tumor-initiating gene in metastatic melanoma. An overwhelming response rate of the BRAF selective kinase inhibitor, Vemurafenib was noted in the development (Fig. 5) and it was quickly approved in the USA and the EU in 2011 (17,18). We are exploring expansion of Vemurafenib for other indications that are known to have the BRAF mutation. The challenge to the resistance caused by signal cross-talks or kinase mutations is the next focus of study in the RAF/MEK/ERK field of kinase inhibitors. Also, a next generation BRAF inhibitor that does not have a paradoxical activation of the MAPK pathway that induces benign cutaneous tumors will be of benefit for melanoma patients.

Beyond growth/survival signals, we are expanding discovery activity to emerging MOAs such as metastasis, cancer stemness and epigenetic regulation.
In the cluster of cell-death or apoptosis area, DR5 antibody CS-1008 is under development in the Phase 2 stage. Combination studies are under examination based on preclinical experiments (19,20). Recently, we initiated a Phase 1 study of MDM2 inhibitor DS-3032b for p53 wild-type patients. MDM2 is an E3 ligase selective to p53 and it is often activated in cancers harboring wild-type p53 for preventing tumor suppressor activity of p53. DS-3032b inhibits interaction of MDM2 with p53 and it inhibits p53 ubiquitination in preclinical studies. DS-3032b shows strong antitumor activity in a variety of p53 wild-type tumor models. The common side effect of MDM2 inhibitor in experimental animals is hematological toxicity.

DISCOVERY SPEED FOR APPLYING NOVEL SCIENTIFIC FINDINGS TO CANCER TREATMENT

Our second approach is the accelerated speed in discovery. As previously mentioned, cancer is a complicated disease and there are many theories and hypotheses to be tested in the clinical setting. It requires quick development of new innovative drugs to show hypothesis-free clinical evidences and immediately bring clinical benefit to critically sick patients. Global Executive Meeting of R&D (GEMRAD) in Daiichi Sankyo is the decision-making body with members of senior managements across functions including business, license and production. Each project team directly reports to GEMRAD and this monthly meeting makes timely and strategically go/no-go decisions of development projects from the preclinical stage through drug approval. We are improving the process of drug discovery by taking a biotech approach in order to shorten the research period up to that of a first-in-human study. In oncology, we have an in-house research target of 3 years from compound screening through achieving a first-in-human study.

To participate in global Phase 3 clinical study and register NDA filing simultaneously with other regions, early initiation of Phase 1 study is further accelerated in Japan. Most of the projects that recently entered into FIH study took a parallel approach in Japan and overseas. Clinical development in Asia is primarily managed by Tokyo, but clinical studies for regional registration will be increasing in Asia in collaboration with regional development function.

GLOBAL SITES OF DISCOVERY RESEARCH IN ONCOLOGY

The main research site is located in Tokyo where target validation, compound screening, chemical synthesis and animal studies are conducted (Fig. 6). Production of chemicals and biologics is centralized: in Hiratsuka, Kanagawa Prefecture for chemicals and Tatebayashi, Gunma Prefecture for biologics.

U3 Pharma located in Munich is a group company investigating innovative cancer therapy by creating antibody medicine. They originally developed HER3 monoclonal antibody that intervenes with HER3-mediated robust growth signals which are primarily associated with EGFR/HER2. U3 Pharma focuses on translational research-driven antibody development. Networking with local academia and the surrounding biotech industry for basic and discovery research in cancer is another important function for U3.

Plexxikon is a scaffold-based drug discovery company in San Francisco. They are focusing on drug screening and compound optimization by co-crystallization of target protein with interacting chemical compounds. Plexxikon discovered an inhibitor of mutant BRAF kinase and they brought revolutionary benefit to melanoma patients who have such mutation. They also develop other products by themselves up to POC achievement.

These two overseas cancer research sites, which are well connected to the local academia, will provide Daiichi Sankyo
with a supplemental pipeline by keeping own biotech research management and culture.

Translational research connecting discovery research and clinical research is crucial for simultaneous development of companion diagnostics together with drugs. A PD marker optimizes dosing regimen and a predictive biomarker secures selection of enriched beneficial patients. We recently opened a translational research laboratory in Munich, Tissue and Cell Research Munich, for increasing biomarker analysis using clinical human tissue samples. We continue to examine biomarker identification, assay development and development of companion diagnostics seamlessly in drug development.

Through a robust network of global group companies with diversity of approaches and ways in different cultures, Daiichi Sankyo will further expand activities of cancer discovery for bringing innovative personalized treatment in cancer.

**FACILITATION OF OPEN INNOVATION**

Open innovation is a critical success factor for the discovery of innovative first-in-class drug discovery. We launched a competition machinery of academia research funding named TaNeDS in 2011. It is a web-based fund application system for academic researchers and we select projects to harvest drug seeds from such academic research collaboration. The area of TaNeDS is now expanding to the West.

We initiated broad scope of collaboration with the Japanese National Cancer Research Center (NCRC) for facilitating drug discovery research. Previously, several research collaborations were independently done with the organization. Now, cancer research scientists in the NCRC can introduce their drug discovery ideas to a collaboration basket so that we timely select prioritized discovery programs from the basket with clinical researchers in the NCRC. Research collaboration with Medical and Science Research Institute at Tokyo University follows a similar approach in open innovation.

Although it took a long time, we have established academia networks with leading research scientists to accelerate drug generation from novel biological findings in basic research to clinical application for patient treatment. The DR5 antibody program originated from multiple years of research collaboration with University of Alabama (UAB). We have been partnering as an adviser with Prof. Dr Frank McCormick, director at the UCSF Cancer Center and a founder of ONYX, and with Prof. Dr Axel Ullrich, director of Biochemistry at Max Planck Institute and a founder of Sugen, U3 Pharma and others. They have amazingly contributed to cancer treatment by discovery of novel basic science and generation of innovative cancer drugs including Tratuzumab, Sunitinib and Sorafenib in their biotech companies.

A number of post-doc research fellows in our company joined one-by-one these collaboration laboratories in USCF and UAB and they have learned world-class research in tumor biology in the laboratories over the past two decades. Many of them created our clinical-stage projects in the oncology pipeline after returning to our research facilities. It is most important that we have a collaboration network with great cancer scientists in academia who have also been founders of biotech venture companies and who apply their scientific discoveries...
to cancer therapy. Many of our projects in the current clinical and discovery pipeline are derived from collaboration with such leaders in academia.

Recently, we launched an annual numerical target for novel drug development in all disease areas as a goal of the next 5-year business plan: approval of two major indications, initiation of four Phase 3 indications and initiation of nine Phase 1 compounds. Our mission in oncology is to contribute to cancer therapy by achieving these company goals in the near future.

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**Conflict of interest statement**

None declared.

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1. IMS Institute for healthcare informatics; therapy forecaster, May 2011.