




**REPORT**

# Current state of therapeutic development for rare cancers in Japan, and proposals for improvement

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This article discusses current obstacles to the rapid development of safe and effective treatments for rare cancers, and considers measures required to overcome these challenges. In order to develop novel clinical options for rare cancers, which tend to remain left out of novel therapeutic development because of their paucity, efficient recruitment of eligible patients, who tend to be widely dispersed across the country and treated at different centers, is necessary. For this purpose, it is important to establish rare cancer registries that are linked with clinical studies, to organize a central pathological diagnosis system and biobanks for rare cancers, and to consolidate patients with rare cancers to facilities that can conduct clinical studies meeting international standards. Establishing an all-Japan cooperative network is essential. Clinical studies of rare cancers have considerable limitations in study

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design and sample size as a result of paucity of eligible patients and, as a result, the level of confirmation of the efficacy and safety shown by the studies is relatively low. Therefore, measures to alleviate these weaknesses inherent to external conditions need to be explored. It is also important to reform the current research environment in order to develop world-leading treatment for rare cancers, including promotion of basic research, collaboration between industry and academia, and improvement of the infrastructure for clinical studies. Collaboration among a wide range of stakeholders is required to promote the clinical development of treatment for rare cancers under a nationwide consensus.

**KEYWORDS**

cancer registry, evaluation method, rare cancer, rare subtype of cancer, therapeutic development

## 1 | INTRODUCTION

A rare cancer is defined as a cancer with an approximate morbidity (incidence) of <6 per 100 000 population, which has more unsolved clinical and therapeutic problems compared to other cancers because of the limited number of patients.<sup>1</sup>

As for actual clinical practice for rare cancers in Japan, as a limited number of patients are dispersed across the country and treated at different sites in different clinical areas, the patients have difficulty in receiving the newest evidence-based treatment at the right time and clinical studies are difficult to promote.<sup>2</sup> Development of guidelines for rare cancers also tends to be delayed compared to more common cancers and, as a result, treatment satisfaction and performance in patients with rare cancers have been reported to be poorer than those in patients with more common cancers.<sup>3</sup>

However, even among more common cancers, rare variants characterized by specific molecular abnormalities have been identified through recent dramatic advances in genomic analysis technology. As a result, cancers that have not previously been considered to be rare are now regarded as an assembly of rare subtypes of cancer based on different molecular abnormalities. If each of these rare subtypes required specific diagnosis, treatment and therapeutic development, the limited number of patients would lead to problems similar to those for rare cancers.

Although Guidance on the Clinical Development of Ultra-orphan Drugs<sup>4</sup> (report by Narukawa's team, 2016) and Investigation Committee on the Desirable State of Medical Treatment and Support for Rare Cancers<sup>1</sup> (Hotta's report, 2015) have been compiled as efforts to fight rare diseases, they were not always focused on cancers or on the clinical development of treatments. Herein, on the basis of the report Issues and Proposals for the Promotion of Clinical Development for Rare Cancers 2017 compiled by the Subcommittee on Rare Cancers<sup>5</sup> (Chairperson, Ryuzo Ueda) under the direction of the Pharmaceuticals and Medical Devices Agency (PMDA) Science Board (Chairperson, Kyosuke Nagata), we discuss possible challenges in accelerating the rapid development of treatment for rare cancers and consider measures that are required to overcome these challenges.

PMDA Science Board was established in 2012 in order to respond to the rapid progress of medical innovations in recent years and to properly address scientific challenges in the field of advanced science and technology. It previously published a paper regarding the use of non-clinical studies in the regulatory evaluation of oncology drugs.<sup>6</sup> In addition, reports on several other topics are indicated on the PMDA website.<sup>7</sup>

## 2 | RARE CANCERS AND RARE SUBTYPES OF CANCER

In this article, we broadly discuss rare cancers, which are defined as both rare cancers in the narrow sense and rare subtypes of cancer. The former is narrowly defined as an anatomically and clinicopathologically recognized cancer that occurs rarely (approximate morbidity of <6 per 100 000 population) in accordance with the report of the Investigation Committee on the Desirable State of Medical Treatment and Support for Rare Cancers<sup>1</sup> described above.

A rare subtype of cancer is defined as a rare disease entity extracted through identification of a specific molecular abnormality in an anatomically and clinicopathologically recognized cancer entity.<sup>8-10</sup> Although rare cancers and rare subtypes of cancer are both rare disease groups with a limited number of patients, in some respects, they have different clinicopathological backgrounds and require different considerations in terms of drug development and implementation of clinical studies (Table 1).

## 3 | PATHOLOGICAL DIAGNOSIS AND BIOBANK FOR RARE CANCERS

Accurate pathological diagnosis is absolutely fundamental to treatment/research of rare cancers including clinical studies. However, questions have been raised about the accuracy of pathological diagnosis for rare cancers because of their intrinsically unusual nature,

**TABLE 1** Rare cancers and rare subtypes of cancer

	Rare cancers in the narrow sense	Rare subtypes of cancer
Definition	A cancer that has been recognized as an entity anatomically and clinicopathologically, which occurs rarely (approximate morbidity of <6 per 100 000 population).	A rare disease group extracted through identification of a common molecular abnormality from among a cancer type that is anatomically and clinicopathologically recognized as an entity.
Disease examples	Soft tissue sarcoma, osteosarcoma, ocular malignancy, small intestinal cancer, neuroendocrine tumor, central nervous system glioma etc.	Rare fractions of lung adenocarcinoma: ALK gene translocation (5%), RET fusion gene (1%), ROS1 gene translocation (1%), and BRAF mutations (1%) etc.
Characteristics	<ul style="list-style-type: none"> <li>• In many cases, the molecular abnormality characterizing each rare cancer type is absent or remains unknown</li> <li>• It is difficult to expect that a drug targeting a single molecule would show marked therapeutic efficacy</li> <li>• The physician or the department in charge may not always be specialized in cancer treatment</li> <li>• In order to improve the quality of clinical practice and promote clinical research, measures including consolidation and networking are considered to be effective</li> </ul>	<ul style="list-style-type: none"> <li>• As each rare subtype has a common molecular abnormality, dramatic therapeutic efficacy can be expected by targeting a single molecule</li> <li>• Proof of concept for drug vs efficacy is clear</li> <li>• Many of the physicians and departments in charge of the treatment of the underlying cancers are specialized in cancer treatment</li> <li>• In order to improve the quality of clinical practice, measures including development of guidelines are considered to be effective</li> </ul>

shortage of expert pathologists, and the paucity of pathologists experienced in the relevant cancer type at each institution.

For example, the rate of diagnostic agreement for sarcomas, representative rare cancers, between expert and non-expert pathologists has been reported to be 50%-70% overseas, causing therapeutically significant diagnostic disparity in 10%-20% of cases.<sup>11,12</sup> In Japan, the accuracy of such pathological diagnoses in a routine clinical setting has not been validated.

One way to address these diagnostic problems related to rare cancers is to establish a central diagnostic system for rare cancers to be shared by medical institutions throughout the country, thereby improving diagnostic accuracy and facilitating required molecular biological analyses such as next-generation sequencing. To meet this goal, specific approaches should be considered, including the linking of human resources and organizations virtually through the internet, and reforming the centralization structure without disrupting the existing one, rather than attempting to centralize human resources and organizations. Such reform of the diagnostic system would be expected to encourage and facilitate enrolment of patients into registries of rare cancers, and also into appropriate clinical studies.

Moreover, because the relationship between genomic information and therapeutic efficacy/clinical course remains poorly understood in rare cancers, archiving of biological samples (biobank) aimed at future research or therapeutic development is essential. Use of a reinforced national pathological diagnostic system for organization of such rare cancer biobanks represents another important concern.

#### 4 | RARE CANCER REGISTRY

To initiate clinical studies of rare cancers, eligible patients with rare cancers who are widely dispersed across the country and treated at different centers must be efficiently recruited at study sites. For this

purpose, an all-Japan patient referral system that extends beyond individual facilities would be needed.

This approach would require information about the patients with rare cancers who are treated at each institution. Such information would need to have real-time immediacy (and also interactivity), in contrast to so-called epidemiological registries. A system different from that used for population-based epidemiological registries would be essential for registries for clinical studies of rare cancers.

However, registries for rare cancers are expected to be used not only for patient recruitment into clinical studies but also as an external source of control data. If it becomes possible to leverage external control data by using the registry, the burden associated with assessment of a new drug in clinical studies of rare cancers, which are ill-fitted with comparator-based efficacy assessment, would also be reduced.

An example of a recent approach in Japan for addressing this problem includes the MASTER KEY Project, which has been comprehensively collecting genetic and treatment information and prognostic data for patients with rare cancers to create a large-scale basic database that can be applied to clinical studies.<sup>13</sup> Case registration for rare subtypes of cancer has also been started through SCRUM-Japan, a genomic screening project for lung cancer and gastrointestinal cancer, which has been founded by more than 10 pharmaceutical companies and organized by National Cancer Center.<sup>14</sup> The MASTER KEY Project and SCRUM-Japan are both oriented to construction of a large-scale patient registry of rare cancers and rare subtypes that integrates clinical and genomic information. This research is expected to establish globally compatible rare cancer genomic data registries that could cover future global trials.

#### 5 | CLINICAL STUDIES OF RARE CANCERS

In clinical studies of rare cancers, study design is considerably restricted as a result of the paucity of patients, compared to clinical

**TABLE 2** Study designs applicable for rare cancer clinical trials

Study design	Outline of the design
Umbrella study	A method in which a clinical study platform (umbrella) with genomic analysis for patient selection is constructed, and the patients are assigned to multiple arms (rare fractions) according to actionable driver mutations and receive a matched molecular targeting drug in order to assess them simultaneously. Examples include NCI-MATCH by the NCI in USA
Basket study	A method in which patients with common actionable driver mutations across organs (rare fractions of each organ cancer) are collected to promote the development of a drug corresponding to the relevant genomic abnormality. The aim is to obtain a therapeutic indication across organs based on a specific genomic abnormality. Examples include a clinical study of BRAF inhibitor in cancers with BRAF mutations and a clinical study of an immune checkpoint inhibitor for cancers with abnormalities in DNA repair (microsatellite instability-positive: MSI-H or dMMR).
N-of-1 study	A study in which multiple treatments are applied to 1 patient at different times to compare the effects of these treatments. Although an assessment can be made in a small number of subjects (rare cancers, rare fractions) by comparing the treatments in the same individual (under the same conditions), it has limitations similar to those of a cross-over study
Adaptive design	A study design in which specific factors are changed based on the data obtained during the study, as planned in advance (selection of dose groups, change in the probability of assignment to a specific treatment group, change in the sample size etc.)
Bayesian design	An assessment can be carried out with a relatively small number of subjects by introducing a prior distribution that represents biological findings and/or data of previous research to a parameter such as therapeutic efficacy etc. Unlike conventional statistical inference (hypothesis testing and confidence interval by the frequentist approach), consistent inference procedures and criteria on therapeutic efficacy may be applied consecutively across analysis time points (without adjustment for the multiplicity of analysis), based on the posterior distribution combining the prior distribution and study data. It can also be applied to umbrella, basket, or N-of-1 studies, as well as those with adaptive designs

studies of more prevalent cancers. Specifically, it is restricted in terms of setting up a concurrent control group, selection of the primary endpoint, and establishment of the sample size (level of significance and power). As a result of these kinds of external restrictions, the level of confirmation of the efficacy and safety of study treatment indicated by the clinical study becomes relatively low.

In the EU and USA, discussions are held at various forums to promote development of pharmaceutical products for rare diseases including cancers. For example, Rare Cancers Europe (RCE) initiative presented considerations for clinical study design and alternative endpoints for rare cancers.<sup>15</sup> The International Rare Cancers Initiative (IRCI) has highlighted characteristic approaches used in previous clinical studies of relevant rare cancers, and proposed that a study should be regarded as a "Phase III study" if it is meant to be definitive or practice-changing, despite weakness of the trial design.<sup>16</sup>

It is important to actively discuss and implement measures to alleviate weakness as a result of external conditions associated with clinical studies of rare cancers as much as possible. Specifically, these measures include: (i) the use of clinical studies based on genomic information (umbrella/basket study) and active introduction of new study designs including self-controlled study (such as N-of-1 study), adaptive design, and Bayesian design (Table 2); (ii) consolidation of study facilities/expertise and promotion of patient enrolment through sharing of study implementation status; (iii) construction of a system to facilitate access to clinical study information; and (iv) construction of patient registries and a system to visualize and promote the use of such registries. In addition, investigation would be needed on a desirable state of regulatory approval (labeled indication) based on such data.<sup>17,18</sup>

Rare cancers requiring global collaborative research are not uncommon. In order for patients not to suffer disadvantages from being left out of treatment opportunities, we should make every

effort to participate in and/or take the initiative in planning such global studies. There is an urgent need for organizing the treatment/research structure for rare cancers to enable participation in global research, including consolidation of patients with rare cancers at facilities where precision could be controlled at an international level.

However, as the low level of confirmation of the efficacy and safety of the study treatment cannot completely be overcome by the above measures, it is also important to organize the scheme and regulations to continuously review clinical usefulness of the treatment, including use of a conditional early approval system premised on planning and implementation of post-marketing special safety measures and active use of real-world data including various medical information databases and patient registries.

However, from the standpoint of the developer of pharmaceutical products, the level of predictability of the clinical data package for regulatory approval has a major effect on decision-making of the development (whether or not to start the development, and priority and timing). For this purpose, guidance documents etc. should be organized to describe conditions and situations where restrictions on the study design may be alleviated, such as acceptance of single-arm study design, use of an alternative endpoint such as the response rate, or increased probability of type 1 and 2 errors in clinical studies of rare cancers.

In addition, for regulatory approval of these products, it is important to actively transmit information to society and obtain understanding regarding the presence of disadvantages associated with the approval based on limited information (that the efficacy and safety are not highly reliable), even though there may be major advantages, especially in the field of life-threatening cancer, of prompt delivery of pharmaceutical products. It must be said that there is no completely correct answer for the development and assessment of pharmaceutical products.

## 6 | APPLICATION OF INNOVATIVE SCIENTIFIC TECHNOLOGIES

It is expected that innovative scientific technologies including next-generation sequencing, induced pluripotent stem (iPS) cells, immunotherapy, gene therapy and cell-based therapy would considerably change the development of pharmaceutical products for rare cancers.

### 6.1 | Next-generation sequencing technology

Innovation in sequencing technology has enabled decoding of whole exons, whole genome and whole transcriptomes in rare cancers, comprehensively revealing genomic abnormalities. Representative examples include identification of the CIC-BCOR fusion gene-positive group in small round cell tumors and identification of BRAF gene mutations in rare hematological tumors.<sup>19</sup> In addition, in brain tumors for which various pathological classifications exist, it is reported that attempts have been made to reconstruct the existing histopathological classification based on genomic abnormalities by systematic genomic analysis.

In contrast, the development of molecular targeting therapy has led to the promotion of genomic medicine, whereby cases are stratified and treated based on the presence or absence of a given genomic abnormality, as well as clinical studies such as umbrella and basket studies using genomic biomarkers. It is expected that rare subtypes having relatively homogeneous genomic abnormalities will be effectively treated with molecular targeting drugs targeting disease-specific genomic abnormalities. It will also be important in the future to promote clinical development based on various stratifications including other molecular information/pathway activation such as immunoprofiling, epigenomics and metabolomics, in addition to genomic diagnosis.

### 6.2 | iPS cells

Rare diseases can be the target of development of pharmaceutical products using the characteristics of iPS cells. The development of pharmaceutical products for rare diseases is associated with many difficulties including a paucity of pathological and biological data of relevant diseases and uncertainty about returns from investment for the research and development. In this context, there are high expectations that iPS cell technology will be able to overcome these difficulties.<sup>20</sup>

Fibrodysplasia ossificans progressiva is a very rare genetic disease characterized by generalized heterotopic ossification that progresses from childhood. It is caused by missense mutations in the ACVR1/ALK2 gene coding the bone morphogenetic protein (BMP) receptor, although the pathological mechanism is not known. As a characteristic of this disease, resection of the lesion exacerbates the symptoms and thus it is difficult to collect research materials. Toguchida et al overcame this problem by deriving pathologically responsible cells from iPS cells established from the peripheral blood of a patient. As a result, they discovered that an unexpected molecular

mechanism, induction of heterotopic ossification by activin-A, was responsible for the disease and, furthermore, based on these findings, they succeeded in identifying rapamycin as a drug with potential therapeutic application.<sup>21,22</sup>

Clarification of the pathology of rare cancers and subsequent therapeutic development are associated with many difficulties: (i) difficulty obtaining clinical samples as a result of disease rarity; (ii) delayed study of the disease as a result of its rarity and inability to proceed to development of a therapeutic agent because the pathological mechanism is unknown; and (iii) difficulty in conducting studies to validate efficacy and safety etc. These difficulties can be overcome with iPS cells. An inexhaustible supply of iPS cells that can replace difficult-to-obtain clinical samples is expected to make an enormous contribution to a variety of aspects including elucidation of the pathology of rare cancers, screening of candidate drugs, and conducting clinical studies to validate efficacy/safety.

### 6.3 | Gene therapy, cell-based therapy and immunotherapy

Gene therapy, cell-based therapy and immunotherapy for malignancies including rare cancers have enabled remarkable clinical achievements to be made in the last few years, as though emerging from a long tunnel. Genetically modified T-cell therapy has recently been attempted by using the T-cell receptor (TCR therapy) approach and the chimeric antibody receptor (CAR-T) approach against rare cancers including malignant melanoma and synovial sarcoma.<sup>23,24</sup> The development of virotherapy, which destroys tumors using genetically engineered viruses, has also been promoted in recent years.<sup>25</sup> In addition, development has recently been promoted for immunotherapy targeting somatic genes with malignant mutations, called neoantigens, and clinical studies of combination immunotherapy and gene therapy are now being started.

Future advances in molecular/pathological elucidation of rare cancers may lead to further progress in the development of new gene therapy, cell-based therapy, and immunotherapy, as well as their clinical applications. For rare subtypes characterized by common genetic abnormalities or common tumor antigens etc., therapeutic efficacy of gene therapy, cell-based therapy, and immunotherapy may well be expected.

## 7 | EXPERIENCES OF JAPAN CHILDREN'S CANCER GROUP (JCCG)

Pediatric cancers, which comprise various tumor types, are also considered to be rare cancers. In the field of pediatric cancer, efforts have long been made by separate clinical research groups for individual tumor types. In 2015, based on a decision to organize clinical research groups for pediatric cancers into an all-Japan organization, the Japan Children's Cancer Group (JCCG) was established.<sup>26</sup> At present, nearly 90% of patients newly diagnosed with pediatric cancer in Japan every year (about 2500 cases annually) are treated at

JCCG-affiliated centers. JCCG is operated as a community by functionally integrating treatment facilities and universities located around the country to organize infrastructure/support centers to aid optimization of research and improve quality, including a central diagnostic center, data center and biobank.

The philosophy of JCCG that any single facility- or group-based structures are inadequate given the regional expansion and rarity of the cases and that a collaborative clinical research structure to consolidate rare cases under an all-Japan structure is needed, as well as the strategy of JCCG to promote basic research and clinical studies using patients accumulated through the central diagnostic service, may directly serve as an excellent model for clinical development of other rare cancer treatment.

## 8 | FUTURE PERSPECTIVES

We reviewed some concerns related to therapeutic development for rare cancers that should be addressed, clarifying the definition of rare cancers.

The first concern is the development of an efficient structure for treatment and clinical research of rare cancers. As patients will be disadvantaged by the absence of accurate pathological diagnosis, there is an urgent need to improve the accuracy of pathological diagnosis of rare cancers. In the field of rare cancers, it is also particularly important to organize biobanks to facilitate new research and therapeutic development and to construct case registries to facilitate clinical studies. In the context of present clinical settings for rare cancer treatment where a limited number of patients are dispersed across the country and treated at different locations in different clinical departments, achieving the above points is a major challenge.

The second concern is the problem of the evaluation method in clinical studies of rare cancers. Compared to clinical studies of diseases

with many patients, there are considerable restrictions in clinical studies of rare cancers in terms of design and sample size and, as a result, the level of confirmation of the efficacy and safety shown by the study is relatively low.<sup>7</sup> Measures should be taken to alleviate weaknesses of these studies as a result of external conditions.

As measures to overcome these problems and promote the development of effective treatments and drugs for rare cancers, we propose the following specific action goals from the aspects of: (i) acquisition of accurate patient information and establishment of developmental bases; (ii) use of biomarkers; (iii) environmental considerations for promotion of therapeutic development for rare cancers; and (iv) rearrangement of the evaluation methods (Table 3).

The Ministry of Health, Labour and Welfare (MHLW) is also working to promote construction of the base for drug development through various policies. The Act on the Safety of Regenerative Medicine<sup>27</sup> was enacted in November 2014, together with The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.<sup>28</sup> In addition, a new approval system for regenerative medicine, including conditional approval, was started in line with the practical application of regenerative medicine. In October 2017, a conditional early approval system was also started for pharmaceutical products.<sup>29</sup>

In order to provide effective treatments to patients with rare cancers as early as possible, advocacy of the patient association is also very important. Advocacy refers to "increasing awareness about an important and interesting issue". The patient association must have a clear vision of current health care, participate actively in discussions, and cooperate with various associations working towards the same goal, particularly in the field of rare cancers with a limited number of patients.

Recent advances made in the field of life science have been remarkable; from the perspective of clinical development for rare

**TABLE 3** Proposed action goals for promoting clinical development for rare cancers

Objective	Action goals
Acquisition of accurate patient information and establishment of developmental bases	(a) Construction of an all-Japan cooperative network (b) Organization of a central pathological diagnosis system and biobank (c) Promotion of rare cancer registries that are linked with clinical studies (d) Consolidation of patients with rare cancers to facilities that can conduct clinical studies meeting international standards
Use of biomarkers	(a) Promotion of clinical studies that use biomarkers (genomic information etc.) (b) Promotion of development of companion diagnostics
Environmental considerations for promotion of therapeutic development for rare cancers	(a) Promotion of basic research for rare cancers (b) Promotion of industrial participation, and industry-academia collaborative work (c) Establishment of infrastructure for clinical studies of rare cancers including centralization of institutional review board (d) Education and development of clinicians specializing in rare cancers (e) Participation of patient advocates, and discussions involving the whole nation
Rearrangement of evaluation methods	(a) Listing of approaches for various measures to alleviate weakness as a result of external conditions on the study design (b) Provision of ideas to improve the efficacy and efficiency of clinical trial consultation (c) Provision of ideas for the method of collection of post-marketing safety and efficacy information and systematic confirmation of the results

cancer treatment, there has been new progress which previously could not have been imagined. Although the concepts discussed in the present article will not always be easy to realize, effective and substantive therapeutic development for rare cancers should eventually become possible through nationwide consensus-based cooperation and active exchange of ideas among a wide range of stakeholders in the field, including scientific societies, health-care professionals, patient advocates, pharmaceutical companies and regulatory authorities.

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## CONFLICT OF INTEREST

Authors declare no conflicts of interest for this article.

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