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## **Summary of discussion on the assessment of the current status of personalized medicine related to development and regulatory review**

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### **1. Introduction**

The joint committee of the Science Board, Pharmaceuticals Subcommittee and Bio-products Subcommittee of the Pharmaceuticals and Medical Devices Agency (PMDA) held continuous discussions, from a scientific viewpoint, on methods for actively promoting personalized medicine and accumulating further scientific evidence of pharmaceuticals related to personalized medicine. The results of the discussions were summarized.

Personalized medicine refers to treatment for diseases in individual patients with an emphasis on individual variations for the selection of treatment methods, as a whole. Recently, in particular, personalized medicine has come to be inferred as the use of the genome information of patients and their disease cells as well as the gene expression information to predict the effect and efficacy of the drug. Selecting patients responsive to drugs is likely to be useful in increasing the treatment effect, in contributing to the reduction of the medical cost, and in increasing the success rate of the development of innovative new drugs. For anticancer drugs, the so-called molecular-targeted drugs in particular, specific oncogene products resulting from the translocation of specific genes and the presence of specific mutations have been shown to affect the efficacy of these drugs, and detecting such genetic changes plays an important role in determining the treatment option. Similar possibilities have increased for drugs used in cancer and other therapeutic areas and, as a result, their importance in drug development is currently considered with emphasis.

The “healthcare policy” was established on June 14, 2013, upon agreement of relevant

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ministers. The strategies proclaims promotion of research and development by leading-edge technologies, including (i) promotion of the simultaneous development of molecular-targeted drugs and *in vitro* diagnostics (companion diagnostics) for predicting the efficacy of the drugs and their adverse reactions, (ii) promotion of research related to the methods for evaluating the companion diagnostics in coordination with drug review, and (iii) reinforcement of research on the development and evaluation methods to promote the practical application of personalized medicine.

Taking account of the above, the joint subcommittee has made continuous discussions on (i) possible impacts of the emphasis on personalized medicine on the development and use of drugs, (ii) development of basic technologies for personalized medicine, particularly the development of companion diagnostics, and problems associated with their use, (iii) roles of biomarkers in evaluating the efficacy of drugs, and (iv) the possibility of using these biomarkers as endpoints of clinical trials. The following is the summary of the discussions.

## **2. Current status and problems of drug development pertaining to personalized medical therapy**

### **2.1. Personalized medicine in cancer therapy**

#### **2.1.1. Roles of cancer genome information in personalized medicine**

Development of analytical devices such as the next-generation sequencers is rapidly progressing in the field of cancer genome analysis, and is now about to usher in the age of the personal genome. Together with the progress in the technologies for new drug development centered on molecular-targeted drugs, driver gene mutations and selective inhibitors such as imatinib against *BCR-ABL* and *c-Kit* mutations, gefitinib and erlotinib against *EGFR* mutation, crizotinib against *EML4-ALK* fusion gene, and vemurafenib against *BRAF* gene mutation, exhibit potent antitumor activity, and are examples for successful cases of personalized medicine based on genome analysis. Personalized medicine is the most advanced in the treatment of pulmonary adenocarcinoma and the development of personalized medicine utilizing driver genes mutations such as *EGFR*, *ALK*, *RET*, and *ROS1* is presently ongoing. Currently, a technique called “clinical sequencing” is available. In this technique, tumor tissues are obtained from individual patients, utilized for detecting gene abnormalities which serve as targets for molecular-targeted drugs, and, accordingly select the appropriate drugs. This technique has rapidly propagated from leading institutions in the United States, and is now opening the door to genome diagnosis and treatment system which could be the ultimate personalized medicine. Based on these changes, there are attempts in clinical studies to develop therapeutic drugs not based on cancer types but based on genome abnormality across individual organs. However, there is also a problem in this approach. For example, *BRAF* inhibitor vemurafenib shows high response rate against malignant melanoma, a cancer with *BRAF* gene mutation (V600E), whereas it shows only weak response rate against colon cancer, a cancer with the same gene mutation, when used alone. The difference is due to the presence

of collateral pathways and *EGFR* activation in colon cancer. In order to overcome this problem, a study has been initiated for coadministration of 2 to 3 different drugs including molecular-targeted drugs which suppress other active sites. Thus, genome abnormalities unique to each cancer types or individual tumors within the same cancer type are suggested, and it is necessary to elucidate these issues in future clinical studies. In any case, personalized medicine based on genome analysis will generate a number of rare populations, necessitating large-scale screenings in drug development and, as a result, the increased cost and prolonged study period are becoming formidable challenges.

On the other hand, results of the whole-exome analysis, which are currently being reported in a rapidly increasing number, indicate the limit of molecular-targeted drugs. Thus, the frequency of driver gene abnormality is low among solid tumors as a whole. Instead, multiple gene abnormalities are observed in the same disease in a majority of cases, posing a limitation to personalized medicine based only on genome analysis. In order to practically impliment personalized cancer therapy, an all-inclusive approach encompassing epigenomic analysis and other omics analyses are expected to be accelerated, resulting in diversification of cancer drugs.

### **2.1.2. Role of non-genomic information in personalized medicine**

Personalized medicines of biological products, such as antibody preparations, mainly targeting the expression of cell surface proteins, such as trastuzumab against HER2 and rituximab against CD20, has already become widely used in medical practice. Diagnosis has mainly been performed by methods such as immunostaining and fluorescence *in situ* hybridization (FISH). However, the extent of correlation between *in situ* hybridization (ISH), immunostaining, and transcriptome analysis, etc. with clinical efficacy varies depending on individual situations and, as a result, effective method for diagnosis is determined based on the results of clinical studies. With the ongoing propagation of the use of diagnostic panels which include gene amplification and fusion genes in addition to the above clinical sequencing, there are now attempts for achieving personalized medicine therapy based upon comprehensive diagnosis not only based on driver gene mutations.

Another recent movement is to achieve personalized medicine based on multi-level omics analysis by combining proteome, metabolome, transcriptome, epigenome analyses, etc. The practicalization of such type of personalized medicine faces arduous challenges, including the creation of numerous novel drugs, securing the manpower of bioinformatics for analyzing massive quantity of data, and cost reduction. To address these issues, it is necessary not only to conduct individual tests in drug development but also to create an efficient drug development strategy taking into account of the entire aspects of cancer therapy including cost-benefit performance, accompanied by the evaluation of the efficiency of such strategy.

### **2.1.3. Problems in the development of companion diagnostics for cancer**

In the current development of cancer drugs, development of companion diagnostics based on the identification of biomarkers that accurately predict the efficacy of the drugs is a critically important factor in maximizing the efficacy of the drugs and increasing the success rate of tests in drug development. For this purpose, it is necessary to carefully plan and conduct a proof-of-concept (POC) study, i.e., a study to investigate the mechanism of action of the drug and verify the efficacy during the early stage of development. Ideally, it is desirable to establish a biomarker diagnostic method for predicting the efficacy before starting the phase III comparative study. Realistically, it is necessary to assess the correlation between the biomarker and the clinical efficacy with a limited sample size during the short follow-up period in early stage of drug development. Particularly for ISH and immunostaining, flexible approaches using various methods are required in order to establish objective and effective diagnostic methods. Also, development of precise analytical method that could eliminate the effects of ununiformity in tissues and so-called liquid biopsies such as diagnosis by circulating tumor cells (CTCs) using blood samples and exome analysis of blood samples is expected to make further progresses in future.

In the area where drugs are developed based on multiple driver gene abnormalities, as seen in pulmonary adenocarcinoma, new problems have emerged, such as (i) whether we should use individual companion diagnosis, multiplex diagnostic panel that simultaneously diagnoses multiple gene abnormalities, or comprehensive genome analysis panel, etc., and (ii) whether or not to perform individual companion diagnosis after the prescreening using a multiplex diagnostic panel or a comprehensive genome analysis panel. In drug development, clinical trials based on each driver gene abnormality are ongoing simultaneously. Therefore, in order to increase the efficiency of drug development, it is essential to conduct comprehensive screenings and information sharing. To promote such streamlining, consensus among companies and effective use of data in regulatory activities will be necessary.

The importance of the development of companion diagnostics and the challenges it faces as described above also apply to the development of anticancer drugs targeting immunomodulatory molecules which is currently being increasingly pursued.

### **2.1.4. Problems caused by the mitigation of cancer population size due to personalized cancer therapy**

Personalized medicine based on driver gene abnormalities and the corresponding drugs have generated a numerous number of rare populations. The frequency of these patients is often lower than that of patients with the so-called orphan cancer and, ongoing development on these personalized drugs are facing problems similar to those experienced in development of orphan cancers. For example, in pulmonary adenocarcinoma, gene abnormality occurs in  $\leq 5\%$  of patients except for *EGFR* mutation. Therefore, it is necessary to screen more than 10,000 patients in order to conduct a phase III comparative study with a sample size of

several hundreds. Thus, it is essential to construct a large-scale screening network and to develop a comprehensive diagnostic screening test in order to reduce the huge cost for testing. Thorough discussion will be necessary on whether or not phase III comparative studies covering all rare populations are practically feasible, whether or not drugs could be approved based on phase II study results and, if this is considered appropriate, how the criteria for approval should be defined, including the methods for ensuring the safety.

Genome analysis, multi-level omics analysis, and other advanced techniques are currently performed only in a limited number of leading institutions. However, development of methods for treating these rare populations will not be feasible unless comprehensive diagnostic systems become widely available.

## **2.2. Personalized medicine in immunological/inflammatory diseases**

### **2.2.1. Types of biomarkers contributing to the promotion of personalized medicine in immunological/inflammatory diseases**

Samples taken from patients are used to measure biomarkers for predicting and assessing the treatment effect against immunological/inflammatory diseases and classifying individual patients, but the biomarkers differ depending on the types of the drugs. The current status and future prospect of the use of biomarkers for personalized medicine will be presented below with an example of rheumatoid arthritis (RA), a representative immunological/inflammatory disease against which molecular-targeted therapy is making marked progress.

### **2.2.2. Clinical assessment and treatment of RA**

RA is characterized by destructive arthritis that occurs with a background of autoimmunological mechanism. Unless appropriate treatment is provided, approximately half of the RA patients are expected to result in a bed-ridden condition after 10 years. Their average remaining life expectancy is considered to be shorter by approximately 10 years. The prime factor defining the poor prognosis is joint destruction which is caused by cumulative disease activities. The treatment approach taken is first to control the disease activity, thereby suppressing the joint destruction. Overall evaluation of disease activities is performed using Disease Activity Score, 28 (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), etc. DAS28, and SDAI include Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP) as biomarkers. Evaluation of joint destruction is conducted using the van der Heijde modified Total Sharp Score (mTSS) of plain radiograph, but scoring should be performed by an experienced radiographic interpreter. For the evaluation of physical function, Health Assessment Questionnaire-Disability Index (HAQ-DI) is used. It is recognized that the primary objective of RA treatment is to achieve clinical remission, and the “Treat to Target (T2T)” is to prevent the progression of joint destruction

and maximize the physical function for a prolonged period of time.

Methotrexate (MTX) is the most preferred first-line drug unless contraindicated. In treating highly active RA patients with poor prognostic factors, consideration is given for coadministration of a TNF inhibitor, a biological product, with MTX. Biological products other than TNF inhibitors have also been introduced. Therefore, accurate clinical evaluations for the above are critical for the treatment and essential in the development of new drugs. On the other hand, these diversified drugs do not necessarily act in a similar manner in all patients, and have high incidence of adverse reactions. In addition, they impose an economic burden because of the high price. Thus, personalized medicine is a necessity in this disease area in order to appropriately select drugs and to predict the prognosis to decide whether or not the treatment should be discontinued.

### **2.2.3. Prediction of efficacy and safety of RA drugs by biomarkers**

Biomarkers used in immunological/inflammatory diseases include acute-phase reactants (ESR and CRP), rheumatoid factors (autoantibodies), and anti-citrullinated protein antibodies (anti-CCP antibodies). Rheumatoid factors and anti-CCP antibodies are useful in routine diagnosis as poor prognostic factors as well. With the advancement of drugs, biomarker with higher specification is in demand. Biomarkers with high efficacy are expected to contribute to the selection of better suited drugs in routine clinical practice and to the development of drugs. For example, polyglutamated MTX level in the blood has been shown to reflect the amount of MTX incorporated into cells, and attempts are being made to clarify the relationship with efficacy or safety. Attempts are also being made to evaluate how the blood levels of inflammatory cytokines, known to play key roles in the pathogenesis of RA, are correlated with the treatment effect of MTX and the results suggest the usefulness as biomarkers of IL-6, CRP, and MMP-3 in the blood of patients being treated with MTX.

The molecular targets of biological products that have so far been developed in the world for the treatment of RA are inflammatory cytokines (TNF $\alpha$ , IL-6, IL-1 $\beta$ ) and cell surface molecules (CD20, CD80/86). Taking account of TNF $\alpha$  and IL-6 as molecular targets, since the two cytokines form a network within the bodies of RA patients, clinical effect of TNF $\alpha$  inhibition will be maximized when both cytokines are suppressed. This suggests that patients responsive to TNF $\alpha$ -targeted treatment and those responsive to IL-6-targeted treatment are most likely to largely overlap. The second factor that determines the efficacy is the blood trough level of biological products, cytokine inhibitors in particular. Based on these results, attempts are being made to clinically use the baseline level of the target molecule, blood drug concentration, anti-drug antibody, and affinity to Fc receptor as biomarkers for predicting the efficacy and safety. For the development of the next generation RA drugs, it will become necessary to subclassify patients by these biomarkers from the beginning of drug development.

#### **2.2.4. Significance of patient subclassification in immunological/inflammatory diseases**

Although biological products against RA are more effective than conventional drugs, response varies among patients, as is evident from the following findings: (i) remission induction to all patients is not feasible, since its rate is 0 to 70% depending on the products with different targets, (ii) remission, even if achieved, cannot be maintained in all patients, and (iii) remission is maintained only in 20% to 40% of patients after drug withdrawal after maintenance of remission. Also, serious adverse reactions occur in 2.5% to 7.5% of patients within 6 months of treatment, with discrepancies in the incidence rate among different molecular-targeting drugs. In immunological/inflammatory diseases including RA, attempts to identifying patients who respond to existing drugs such as those targeting TNF $\alpha$ , IL-6, IL-12p40, CD80/86 (T cell activator), CD20 (B cell receptor), and BAFF (B cell activating factor) and those who respond to drugs with new targets(IL-17, IL-20, GM-CSF) which are undergoing development will provide great benefits to individual patients. Also, it offers effective treatments to patients in the society as a whole, and at the same time discards unnecessary treatment procedures, which will have a substantial health economic significance.

Immunity and inflammation are associated with numerous factors including various immunocompetent cells and molecules such as cytokines, and there is no clearly established direction for personalized medicine. However, for RA as an example, 101 disease-related gene loci have been identified, and RA may possibly be subclassified according to the combinations of these loci. In patients who share a common amino acid sequence at a particular region of the HLA-DR molecule (shared epitope), joint destruction definitely prones to progress. Also, there are numerous markers that finely subclassify patients, such as genes expressed in each type of cells derived from patients, expressed proteins, and types of autoantibodies produced. In fact, disease activity and joint destruction are clearly different between anti-CCP antibody positive and negative RA, and there is now a widespread opinion from medical practices that patients with anti-CCP antibody positive RA should be more promotively treated with biological products.

### **2.3. Pharmacogenomics and drug development**

#### **2.3.1. Roles of genomic biomarkers**

Application of pharmacogenomics in personalized medicine was discussed regarding the following three aspects: (i) prediction of adverse reactions due to individual variation, (ii) roles of genomic biomarkers in personalized medicine, and (iii) roles in drug development. Pharmacogenomics is a method used for elucidating the effects of genetic factors on the individual variations of protein expression related to pharmacokinetics (PK) such as drug absorption, distribution, metabolism, and excretion, as well as of protein expression related to pharmacodynamics (PD) such as the therapeutic efficacy and adverse reactions. Regarding the effects of polymorphism of PK-related genes on blood exposure, progress has been made on

the analysis for important metabolic enzymes and transporters and, as a result, it is now possible to predict the effects of genetic factors on new drugs to be developed in future. In order to accurately make these predictions, it is important to know the contribution rates of metabolic enzymes and transporters to relevant pharmacokinetic processes in in vitro studies. For metabolic enzymes, inhibitors specific to individual isoforms are known, allowing highly precise prediction. Studies on transporter are also making rapid progress, and it is expected that, in the near future, predictions will be possible in a similar extent of precision as in the cases of metabolic enzymes.

### **2.3.2. Prediction of adverse reactions, etc.**

In recent years, there have been movements to apply, for the decision making on the necessity of clinical studies and on dosage, the pharmacokinetics prediction by mathematical modeling such as physiologically-based pharmacokinetic (PBPK) modeling which allows prediction of pharmacokinetics including blood concentration-time curve, target tissue concentration, and tissue concentration related to adverse reactions. In confirming the appropriateness of the treatment regimen and treatment design and in setting appropriate precautions such as drug interactions, it is important to predict the pharmacokinetics of drugs in patients with various background characteristics as precisely as possible. For this purpose, it is desirable to recognize the importance of the analysis based on mathematical models, such as the PBPK model, and to organize regulatory review systems which enable these analyses.

The PBPK model is about to be utilized for the prediction of drug interactions as well as for the prediction of pharmacokinetics and therapeutic efficacy in cases of PK-related gene mutations, in elderly patients, in pediatric patients, and in patients with impaired renal or hepatic function. The central idea in these practice is that it is impossible to conduct clinical studies on all combinations of various drugs and various patient background characteristics. Based on such idea, it is necessary to separately estimate the active uptake clearance to the tissues responsible for drug's therapeutic efficacy and adverse reactions, clearance by passive transport, excretion clearance from cells, and intracellular metabolic clearance. It is difficult to detect rare adverse reactions or to conduct clinical pharmacokinetic studies in pediatric patients. From this, it is expected that these events can also be predicted by generating computerized virtual person based on the database encompassing the complete genome information including genetic polymorphism, taking account of the factors such as ethnic factor, lifestyle, and functional variations of organs such as the liver and kidney.

It is also expected that accumulation of data on pathophysiological condition-associated changes in the amount and quality of various metabolic enzymes, transporters, and druggable proteins will lead to the future development of drugs that can evade drug interactions, drugs less affected by individual variations or disease conditions, and drugs with a wide therapeutic range.

### **3. Current status and problems in clinical studies based on personalized medicine, particularly the issues on handling of patient information and genetic information accompanied by the promotion of personalized medicine**

It is expected that, the promotion of personalized medicine in the future will result in the accumulation of a vast amount of personal information not limited to genomic information but also including epigenomic, proteomics, and lipidomics information, as well as clinical information. It will be necessary to create a system in which patients participating in clinical trials can benefit from their own genomic and other omics information. Thus, when a company plans to develop a drug based on the whole genomic information or on other omics information, discussion should be made on whether such information belongs to the sponsor, to the patients themselves, or to the whole nation. At present, all ownership of the sample and information obtained from the sample in clinical studies are monopolized by the pharmaceutical companies under consent of the patients. There are differences in interest between Japan and other countries in the method of obtaining consent and in whether or not the collected samples can be subjected to secondary use. Disclosure of genomic data of Japanese subjects obtained in multi-regional clinical trials to foreign countries also poses a problem. Another problem is that the information that should preliminarily belong to patients themselves is monopolized by one company. In the development of drugs, effective use of information that was obtained in previous development of drugs for similar diseases will contribute not only to labor saving but also to the development of drugs on a more scientifically sound basis.

From these viewpoints, it is expected that a system should be established to restore the clinical data obtained from Japanese people and associate samples as the property of citizens, and a national organization should be implemented to perform such authorized activities. It is necessary that the information and samples related to drug development are handled as the common property shared within the nation and becomes available for later scientific research and for the development of new drugs. Thus, discussion will be necessary to form a national consensus on this project and on the system which enables such project. A drug development information system such as BioBank led by the Japanese government, once established, is expected to make dramatic progress in these fields. For example, in current clinical studies, only related genes are analyzed in the genomic analysis. However, the system of shared genomic information is desired whereby the whole genome information is analyzed and stocked in the bank as a database, and researchers authorized by the third-party committee can have access to the database.

### **4. Conclusions**

Medical treatment fundamentally aims for the treatment of individual patients, and therefore it embodies an aspect of discretion. As the background of the recent awareness of personalized medicine, there is the recognition of the genetic diversity of human discovered

by the progress of genomic sciences. As discussed in the text above, genetic diversity has significant effects on the onset and progression of many diseases. From the viewpoint of the efficacy of drugs, genetic diversity of genes directly involved in diseases and molecules associated with drug absorption, distribution, metabolism, excretion, etc., are found to cause individual variation in the treatment efficacy and the incidence of adverse events. This scientific background should be utilized to deliver effective drugs to a greater number of patients. This summary selected three relatively advanced research fields and described that the directions for the future progress required for regulatory science differ from one another. Further research will be required in order to apply these findings to the regulatory review process. This summary is published to evaluate the current status and present the issues, but is subject to additional changes and revisions in future.