Provisional Translation (as of June 2026)*

Information Regarding Explanations to Driver Mutations in the Development of Anti-cancer Drugs （Early Consideration）

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1. Purpose

The purpose of this Early Consideration is to clearly state the Pharmaceuticals and Medical Devices Agency (PMDA) current views on the information to be presented when providing explanations regarding so-called driver mutations during PMDA's clinical trial consultations or application forms for developing anti-cancer drugs, based on the following background. It should be noted that the perspective presented in this Early Consideration is formulated based on knowledge available to date and may be subject to change depending on new knowledge obtained in the future.

- In developing anti-cancer drugs, efficacy and safety usually need to be demonstrated using a primary endpoint such as overall survival in phase III studies (confirmatory randomized controlled studies). On the other hand, if high clinical utility is expected in exploratory studies corresponding to phase II studies, etc., there are cases in which the drug is approved based on the relevant clinical data.
- “Guidelines for Clinical Evaluation of Anti-cancer Drugs” (PSEHB/PED Notification No.0331-1, March 31, 2021), anti-cancer drugs targeting mutations particularly important for cancer development (hereafter referred to as "driver mutations") also state that “Certain drugs targeting driver mutations particularly important for cancer development have proven highly effective, leading to the development of drugs against functional changes based on less frequent gene mutations. In the clinical development of anti-cancer drugs for these rare molecular subtypes, it is often difficult to conduct a confirmatory randomized controlled study using overall survival as the primary endpoint, and the primary evaluation of the efficacy of some drugs and subsequent approval is based on the tumor response observed in a phase II study.” [1)]
- In addition, when considering the criteria[*1] for designation of orphan drugs, etc., there are cases in which the explanations for driver mutations may influence the determination of whether the target disease corresponds to "salami slicing"[*2].

  *1 : The number of subjects of the criteria of orphan drugs, etc. designation is less than 50,000 in Japan.

  *2 : In the case where the total number of patients with the target disease is more than 50,000 but the treatment with the study drug is applicable only to a limited population based on biomarkers, etc. for anti-cancer drugs (limited to cases where the limitation is scientifically sound, e.g., expression level of target protein or genetic alteration is biologically significant), it is acceptable to consider that such restriction of target population is not deemed "salami slicing" [2), 3)].

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* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

2. Driver Mutations

As is known from the multi-step carcinogenesis model for colorectal cancer, it is generally believed that the development and progression of malignant tumors, especially solid malignancies, is caused by the multistep accumulation of mutations or epigenetic mutations in multiple genes (hereafter referred to as “cancer-related genes”) in normal cells, which ultimately leads to the transformation of normal cells into cancer cells. The types of mutations that accumulate in these cancer-related genes vary among individual genes, and the contribution of mutations to the development and progression of malignant tumors depends on the original functions of individual genes and the roles of genetic aberrations in carcinogenesis. In a broad sense, among cancer-related gene mutations, mutations that are particularly important for cancer development are referred to as driver mutations.

However, there is no clear definition of what is called a driver mutation when there is a significant contribution to cancer development. Therefore, in this Early Consideration, PMDA refers to mutations as driver mutations that can be determined to have high scientific and rational clinical utility from a tumor biological point of view in the development of anti-cancer drugs.

More specifically, in principle, phase III studies intended for regulatory approval need to verify the clinical benefits of the drug. However, there are cases in which regulatory approval has been granted based on the results of clinical studies at the early stage of development. Therefore, driver mutations shall be deemed to refer to mutations for which the degree of oncogene addiction is high and the drug efficacy can reasonably be predicted, by evaluating the results together with clinical studies at the early stage of development.

Based on the above, mutations accumulating in individual cancer-related genes should not be classified as driver mutations. On the other hand, when the cause (mutations) and the result (carcinogenesis, etc.) have a one-to-one relationship[*3] rather than a multi-step carcinogenesis model, an anti-cancer drug targeting the cancer-related gene that is the cause of cancer development is expected to exert a remarkable antitumor effect [4),5)], and therefore PMDA considers such mutations to be driver mutations, at least in the case of such a relationship.

*3 : Genetic aberrations caused by chromosomal translocations, such as *ALK* fusion genes and *ROS1* fusion genes, are considered to be highly mutually exclusive and strongly oncogenic in isolation.

As mentioned above, PMDA has not conclusively determined a driver mutation only if the cause (mutations) and result (carcinogenesis, etc.) are in a one-to-one relationship. When claiming the relevance of driver mutations, it is necessary to rationally explain the scientific evidence based on the tumor biology, so the biological significance of the genetic aberration should be explained together with the results of clinical studies at the early stage of development.

3. Information Regarding Explanations to Driver Mutations in the Development of Anti-cancer Drugs

Next, in the development of anti-cancer drugs (PMDA's clinical trial consultations or an application

for approval), when the consulter or applicant claims the relevance of a driver mutation because of a one-to-one relationship between the cause (mutation) and result (carcinogenesis, etc.) as described above, PMDA considers that the consulter or applicant needs to adequately explain all of the points described in the following 3.1-3.3 as the evidence for tumor biology. The specific examples regarding driver mutations are listed below, so they can be used for your reference. In planning the development program, it is recommended to consult with PMDA as necessary when considering the relevance to driver mutations.

3.1. Expression of protein derived from genes with driver mutations targeted by anti-cancer drugs

When abnormalities occur in genes of normal cells, it is considered to result in the acquisition of malignant phenotypes (cancer development) due to functional abnormalities associated with quantitative or qualitative changes in the translated protein, and thus explain the expression of proteins derived from the gene with aberrations in indicated cancer types.

（Example）

＜*ALK* fusion gene expression in non-small-cell lung cancer (NSCLC)＞

- It is reported that 3% to 5% of patients with NSCLC have an *ALK* fusion gene which is detected by fluorescent *in situ* hybridization (FISH), immunohistochemical staining (IHC) methods, etc. (Guidance for Biomarker Testing in Lung Cancer Patients, Version 2.7.1 [edited by Biomarker Committee, The Japanese Lung Cancer Society]).

3.2. Effects of driver mutations targeted by anti-cancer drugs on cancer development

Explanation how genetic aberrations act as oncogenic factors in the indicated cancer types, based on the following points:

- Have malignant phenotypes (anchorage-independent growth ability, enhancement of proliferation ability, etc.) been acquired by introducing the gene with aberrations to normal cells?
- Have tumors been formed by introducing the gene with aberrations to normal cells and transplanting the cells into immunodeficient mice?

（Example）

＜Acquisition of malignant transformation (loss of contact-inhibition, the ability to exhibit anchorage-independent growth, etc.) by introduction of *ALK* fusion gene＞

- The loss of contact-inhibition was elicited by introducing *echinoderm microtubule-associated protein-like 4 (EML4)-ALK* gene fusion into murine fibroblasts (Cancer Res 2008; 68: 4971–6).
- Subcutaneous implantation of murine fibroblasts transduced with *EML4-ALK* gene fusion into nude mice led to development of tumors (Nature 2007; 448: 561-6).

3.3. Relationship between a driver mutation targeted by certain drugs alone and cancer development

(causal relationship)

Discuss the causal role of genetic aberrations targeted by anti-cancer drugs without being affected by other factors in contributing to the cancer development and progression. For example, explanations of whether tumors have formed in normal tissues (organs) derived from indicated cancer types, using a model such as animal genetically modified to express the gene with a driver mutation[*4].

*4 : Disease model mice produced to develop a single gene abnormality that is considered to be the cause of carcinogenesis in a specific tissue (organ) by using a tissue specific promoter or a drug-inducible promoter, etc.

（Example）

＜Contribution of *ALK* fusion gene to oncogenesis in NSCLC＞

- Lung adenocarcinomas developed at 3 weeks after birth in transgenic mice forced to express the *EML4-ALK* fusion gene in lung alveolar epithelial cells by modifying the promoter region of the *surfactant protein C (SPC)* gene[*5] (Proc Natl Acad Sci USA 2008; 105: 19893-7).

＜Contribution of *ROS1* fusion gene to oncogenesis in NSCLC＞

- Lung tumors developed at 2 to 4 weeks after birth in transgenic mice forced to express the *ezrin (EZR)-ROS1*, *CD74-ROS1*, or *syndecan 4 (SDC4)-ROS1* fusion gene in lung alveolar epithelial cells by modifying the promoter region of the *SPC* gene[*5] (PLoS One 2013; 8: e56010; Carcinogenesis 2016; 37: 452-60).

＜Contribution of *human epidermal growth factor receptor 2 (HER2)* exon 20 insertion mutant to carcinogenesis in NSCLC＞

- Lung tumors developed within 2 weeks after doxycycline administration in conditional knock-in mice to express the *HER2* exon 20 insertion mutant in response to doxycycline-induced activation of *Clara cell secretory protein (CCSP)* gene[*6] promoter (Proc Natl Acad Sci USA 2009; 106: 474-9).

*5 : *SPC* gene expressed in alveoli of normal human lungs.
*6 : *CCSP* gene expressed in epithelial cells of normal human lungs.

4. Driver Mutations in the Development of Anti-cancer Drugs Across Cancer Types

In the development of anti-cancer drugs across cancer types, the role of genetic aberrations in the carcinogenesis of each cancer type (organ) and the basis for the common biological significance of genetic aberrations among cancer types can be useful information for clinical development, rather than the conventional anti-cancer drug development specified for conducting non-clinical pharmacological studies on the efficacy for indicated cancer types. Therefore, it is important to obtain as much data as possible on the tumor biology differences between the target cancer types and consider them from multiple perspectives, and to rationally explain the relevance of driver mutations across cancer types (organs).

5. Reference

1） Guidelines for Clinical Evaluation of Anti-cancer Drugs (PSEHB/PED Notification No.0331-1, March 31, 2021) (Cancer Sci 2021; 112: 2563–77)
2） Partial Revision of “Designation of Orphan Drugs etc.” (PSB/PED Notification No. 0116-1, PSB/MDED Notification No. 0116-1, January 16, 2024)
https://www.pmda.go.jp/files/000268408.pdf (last accessed: June 16, 2026)
3） Questions and Answers (Q&A) for Designation of Orphan Drugs etc. (Administrative Notice, January 16, 2024)
https://www.pmda.go.jp/files/000268407.pdf (last accessed: June 16, 2026)
4） Summary of Discussion on Non-clinical Pharmacology Studies on Anticancer Drugs, dated December 10, 2013, by the Pharmaceuticals and Bio-products Subcommittees, Science Board
https://www.pmda.go.jp/files/000152906.pdf (last accessed: June 16, 2026)
5） Report on the use of non-clinical studies in the regulatory evaluation of oncology drugs, dated February 29, 2016, by the Subcommittee on Non-clinical Studies, Science Board (Cancer Sci 2016; 107: 189-202)