Characterizing, Collecting, and Reporting Immune-Mediated Adverse Reactions in Cancer Immunotherapeutic Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (OCE/CDER) Marc Theoret at 301-796-4099 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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Food and Drug Administration
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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page

I. INTRODUCTION

Cancer immunotherapeutic drugs and biological products (hereafter referred to as cancer immunotherapeutic drugs) can modulate (i.e., stimulate or suppress) the endogenous immune system to produce an anticancer effect. Adverse events[2] that are consistent with an autoimmune etiology should be evaluated as potential immune-mediated adverse reactions (imAR)[3] to guide patient management and inform the drug labeling or investigator brochure, as applicable.

For the purpose of this guidance, the term imAR refers to adverse reactions that occurred in the context of exposure to a cancer immunotherapeutic drug and are consistent with the development of an autoimmune reaction, and are not attributable to another cause (e.g., infection, trauma, other drugs). While corticosteroids and other immunosuppressive drugs are regularly used to manage imARs in cancer clinical trials, the absence of a history of immunosuppressive treatment for an adverse reaction does not preclude its characterization as an imAR, especially for low-grade imARs that result in dose interruption.

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] An *adverse event* means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related (21 CFR 312.32(a)). See also guidance for industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2006). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] An *adverse reaction* is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. See 21 CFR 201.57(c)(7).

This guidance is intended for sponsors of cancer immunotherapeutic drugs that modulate the endogenous immune system and may disrupt immunologic tolerance to normal organs and tissues. Examples of such cancer immunotherapeutic drugs include monoclonal antibodies, anticancer vaccines, and cytokines. Adoptively transferred cell-based cancer immunotherapeutics that target a tumor-associated antigen (TAA) and directly exert an anticancer effect (e.g., a TAA-directed genetically modified T-cell immunotherapy) are outside the scope of this guidance.

This guidance provides recommendations regarding the data that should be collected and evaluated to assess whether adverse events qualify as imARs and the data on imARs that should be included in a new drug application (NDA) or biologics license application (BLA) for a cancer immunotherapeutic drug.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Cancer immunotherapeutic drugs utilize the immune system to exert an anti-cancer treatment effect. Recently, cancer immunotherapeutic drugs have demonstrated safety and efficacy across a wide breadth of cancer types and are becoming standard of care treatments—as monotherapy and as part of combination therapy regimens—for patients with hematologic and solid tumor malignancies. In general, the safety concerns of cancer immunotherapeutic drugs predominantly consist of immune-mediated risks, which are off-tumor immune responses generated as a result of exposure to the drug, with the spectrum of toxicities reflecting the underlying mechanism of action of the drug. For example, immunotherapeutic drugs that activate the endogenous immune system by breaking peripheral tolerance may lead to inflammation involving almost any organ system, whereas immunotherapeutic drugs that direct the immune system with specificity for a TAA may lead to toxicities of normal tissues that share the same target (e.g., off-tumor, on-target toxicity) or a molecularly similar target (e.g., cross reactivity based on sequence or structural homology). Adverse events that are unrelated to the drug may also occur during a trial, and it is critical to have a comprehensive understanding of imARs to allow an assessment of the benefits and risks of the drug and to provide information in the drug labeling to inform clinical use.

III. IMMUNE-MEDIATED SAFETY DATA COLLECTION AND EVALUATION

When designing trials evaluating cancer immunotherapeutic drugs, sponsors should develop a prospective approach for collecting and characterizing imARs. Sponsors should prospectively design the protocol and case report form (CRF) to capture the information needed to determine whether an adverse event is an imAR. Evaluation of a potential imAR involves consideration of

how to discriminate between 1) effects of the immunotherapeutic and 2) effects not related to the immunotherapeutic such as those attributable to the underlying disease itself, another condition (e.g., infection, trauma), or another drug. It is also important to consider potential interactions among these factors.

Sponsors developing cancer immunotherapeutic drugs should discuss collection, characterization, and reporting of immune-mediated safety data with the clinical review division early in development and prior to implementing a cancer immunotherapeutic drug trial.

A. Identifying Potential imARs

Sponsors should develop a prespecified list of potential imARs consisting of groupings of Medical Dictionary for Regulatory Activities (MedDRA) terms describing the same medical concept using all levels of the MedDRA hierarchy including Standardized MedDRA Queries (SMQs) on which data should be collected to characterize a potential imAR. This list should be updated throughout the development program and included in relevant documents (e.g., in the protocol, investigator brochure, safety analysis plan). When developing this list, the sponsor should consider the:

- Mechanism of action of the drug and prior experience with the same or similar immunotherapeutics in oncology, as well as other disease settings
- Immunologic impact of the cancer or prior cancer therapy.

As an example of immunologic impact of prior cancer therapy, in allogeneic hematopoietic stem cell transplantation (HSCT), multiple non-randomized trials evaluating PD-1 targeted antibodies in patients either before or after undergoing allogeneic HSCT demonstrated an increased risk of transplant related complications, even after PD-1 targeted antibody treatment had been discontinued. Therefore, examples of potential imARs that should be prespecified for data collection in this setting include hyperacute graft versus host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause).

Attributing certain adverse events to a cancer immunotherapeutic can be challenging when overlapping toxicities are expected with other drugs or anticipated for the population under study. Sponsors should consider patient- and treatment-related factors in assessing causality, including but not limited to:

- Current organs/sites involved with disease.
- Previous therapy, e.g., radiation therapy.
- Any medical history of immune based pathologies, e.g., rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, or other autoimmune diseases.

- Combination therapy with chemotherapy or other drugs that have known toxicities in specific organs.

In some circumstances, individual case assessment can be clarified by a rechallenge (if appropriate), or follow-up response to immunosuppressive therapy. Causality, however, may not be clear until sufficient exposure reveals an increase in incidence or severity of the specific imAR within the arm of interest. Increased surveillance (e.g., defining the potential imAR as an Adverse Events of Special Interest(AESI))[4] in subsequent trials for suspected imARs is appropriate to facilitate a causality assessment. In addition, when immunotherapeutic drugs with a mechanism that decreases the threshold for disrupting peripheral immunological tolerance are used in combination with a drug infrequently associated with an organ specific toxicity, a marked increase in the frequency of organ specific toxicity should be considered an imAR until proven otherwise (e.g., evaluate for immune-mediated nephritis rather than attribute to chemotherapy-induced acute renal failure in a patient receiving an immunotherapeutic plus chemotherapy combination regimen). These considerations should also be included in protocols to assist investigators in determining whether there is a reasonable possibility that the drug caused the adverse event.[5]

B. Protocol and Case Report Form Considerations Related to imARs

The protocol should include the following:

- Instructions for how clinical investigators should evaluate adverse events to assess immunological causality, including tissue biopsy or other laboratory test results to determine whether the adverse event is an imAR.

- Descriptions of the imAR-related data that should be collected. Data on potential imARs should be collected for at least 90 days after the last dose of an immunotherapeutic drug. Sponsors should have a predefined plan for capturing information regarding imARs that are known to occur beyond this period.

CRFs should include fields for documenting information about potential imARs.[6] For example, data elements should include, but are not limited to, the following:

- Date of onset (i.e., Start Date).

[4] See guidance for industry: International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use and Draft Guidance, *Optimisation of Safety Data Collection E19* (April 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[5] See 21 CFR 312.64

[6] Additional data elements may be needed in the CRF for other purposes. For example, fields regarding whether an adverse event is serious, whether an adverse event is expected and unrelated to the study drug, and an assessment of causality regardless of whether the adverse event is immune-mediated, are needed for the purpose of IND safety reporting.

- Common Terminology Criteria for Adverse Events (CTCAE)[7] grade
  - If CTCAE is not adequate to grade a specific imAR, the CRF should provide the grading system to be used.

- Action taken with study drug(s)

- Outcome of the imAR

- Concomitant medications (including steroids, other immunosuppressive drugs, and hormone replacement therapy) with doses and duration used to treat the potential imAR and the ability to link the concomitant medication to the specific imAR.

- Date of resolution as defined as resolution of symptoms or return to baseline and no longer requiring medical management (e.g., corticosteroids) or hormone replacement.

- Detailed data on baseline (i.e., preexisting) medical conditions (e.g., thyroid, renal, hepatic, cardiac function, GVHD).

- Prior treatment history that may predispose a patient to experience an imAR.

- Clinical investigator's final assessment of whether an adverse event is an imAR (e.g., [Yes/No] data field on the CRF) and a required field to document the rationale for this assessment, such as a description of the response to immunosuppressive or other therapy, rechallenge information, clinicopathologic results, increase in frequency or severity of an imAR with a pattern suggesting synergism, or other (option for free text).

C. Sponsor Classification of Adverse Events as imARs

As described in Section IIIA, sponsors should have a prespecified method for classifying adverse events as imARs throughout the drug development program. This method should be systematic and reproducible to allow comparison across trials and development programs. Key principles of this method are the following:

- Sponsors should update and revise the list of potential imARs as described in Section IIIA to accurately and fully capture and characterize these adverse events if (1) the investigator assesses the adverse event to be an imAR, regardless of whether the patient received corticosteroids, other immunosuppressive drugs, and/or hormone replacement therapy, and (2) the sponsor agrees with this assessment, which may require an evaluation of data across the development program. Events for which imAR-directed therapy was instituted, but later stopped in favor of an alternative cause for the event should not be included in this category.

[7] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- Adverse events that were not prespecified can be added to the relevant imAR category that describes a similar medical concept. Sponsors should consider any treatment-emergent adverse event as an imAR if
    - the patient received steroids, other immunosuppressive drugs, and/or hormone replacement therapy and
    - the sponsor assessed the adverse event to be an imAR, taking into account the investigator assessment and rationale.

- Sponsors should document the rationale for their agreement or disagreement with the investigator on classification of an adverse reaction as an imAR.

D. NDA or BLA - Additional imAR Safety Data Considerations

In addition to the information recommended in section III.A and III.B. of this guidance, the analysis datasets in an NDA or BLA should include:

- A variable in the adverse event dataset specifying the imAR if the individual event collected is part of a grouped set of MedDRA Preferred Terms (PTs) included in the prespecified imAR term.

- Flags for investigator and sponsor assessment of imARs.

- Outcome of the imAR at the time of data cut-off.

- Links between the specific imAR(s) and the concomitant medication(s) used to treat the imAR(s).

- Rechallenge information, including a designation (flag) for an imAR that recurs after a rechallenge with any study drugs.

The narrative safety portion of an NDA or BLA should also include a discussion of the sponsor's assessment of whether adverse events are imARs and the rationale for the sponsor's assessment, e.g., in the Integrated Summary of Safety.

E. Labeling Recommendations

This section of the guidance summarizes labeling recommendations on how to incorporate imAR information into the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of labeling for cancer immunotherapeutic drugs. The recommendations for this section of this guidance are not intended to be exhaustive. Information about imARs may be included in other sections of labeling (e.g., PATIENT COUNSELING

INFORMATION). For developing these and other sections of labeling, applicants should refer to statutory and regulatory labeling requirements and other FDA guidance recommendations.[8]

1. WARNINGS AND PRECAUTIONS Section

Clinically significant imARs should be incorporated into one numbered subsection in the WARNINGS AND PRECAUTIONS section of labeling (e.g., **5.1 Severe and Fatal Immune-Mediated Adverse Reactions**). Clinically significant imARs include those that occurred with the subject drug as well as those that occurred with drugs in the same class (e.g., same mechanism of action), as appropriate. When imARs are based on a pooled safety database, to reduce redundancy from providing a detailed description of pooled safety data multiple times in labeling, FDA recommends including this information in the *Clinical Trials Experience* subsection in the ADVERSE REACTIONS section, instead of the imAR subsection in the WARNINGS AND PRECAUTIONS section. The imAR subsection should cross-reference to the *Clinical Trials Experience* subsection for the detailed description of pooled safety data. In the imAR subsection in the WARNINGS AND PRECAUTIONS section, FDA recommends:

- Consolidating information that is applicable to different imARs (e.g., recommendations on how to prevent, mitigate, and monitor for or manage imAR(s)) in the beginning of this subsection rather than repeating this information for each imAR. This subsection should cross-reference to the DOSAGE AND ADMINISTRATION section for detailed recommendations on dosage modifications intended to reduce the risk of an imAR.

- Organizing information about specific common imAR(s) that are clinically significant under non-numbered headings (e.g., Immune-Mediated Pneumonitis, Immune-Mediated Hepatitis).

- Listing less common serious imARs (e.g., incidence of <1%) that do not need further description under a non-numbered heading (e.g., "Other Clinically Significant Immune-Mediated Adverse Reactions") and grouping them by organ/site. Subsequent to approval of the NDA/BLA, less common, nonserious imARs should usually be only listed in the ADVERSE REACTIONS section of labeling; however, if such imARs are otherwise clinically significant (e.g., requires new patient monitoring or management) they should also be listed in under this heading in the imAR subsection in the WARNINGS AND PRECAUTIONS section.

- If a cancer immunotherapeutic drug is approved for monotherapy and as part of a combination regimen or therapy:
  - Including clinically significant imAR information associated with monotherapy and

[8] See Prescription Drug Labeling Resources website at https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources.

- Only including clinically significant imAR information associated with concomitant use when there are novel clinically significant imAR(s) or more frequent or severe clinically significant imAR(s) compared to those that occurred with monotherapy.

- If a cancer immunotherapeutic drug is approved for use in multiple cancer subpopulations:
  - Including clinically significant imAR information from the pooled cancer populations, and
  - Only including clinically significant imAR information for specific cancer subpopulation(s) if the imAR is novel, severe, or occurs at a significantly higher incidence compared to those from the pooled cancer populations.

- For each clinically significant imAR under the appropriate heading within this subsection, including the following information, as applicable:

  - A statement(s) regarding how the imAR was defined.
  - Frequency of imARs for all grades and by toxicity severity grade (2, 3, 4, and 5) to characterize the risk at each grade and provide management actions for each grade, if applicable (e.g., Grade 2 dosage modification, Grade 4 permanent discontinuation).
  - Time of imAR onset (median and range) in relation to start of the drug when sufficient information is available for a specific imAR.
  - Frequency of permanent discontinuation and withholding of the drug due to the imAR.
  - Number and percentage of patients with the imAR who required immunosuppressive treatment categorized by type of therapy (local corticosteroids, systemic corticosteroids, tumor necrosis factor inhibitors, etc.).
  - Number and percentage of patients in whom the imAR did not resolve.
  - Number and percentage of patients who reinitiated the drug after symptom improvement (after withholding for the imAR) and the number and percentage of these patients who had an imAR recurrence.

2. DOSAGE AND ADMINISTRATION Section

Recommendations on dosage modification intended to reduce the risks of imARs (e.g., dosage reduction, dosage interruption, or permanent discontinuation) should be included in the DOSAGE AND ADMINISTRATION section. Such information is generally displayed in this section in a three-column table (e.g., Adverse Reaction, Severity, Dosage Modification). This section should also include a cross-reference to the imAR subsection in the WARNINGS AND PRECAUTIONS section.