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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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.

**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**October 2022
Clinical/Medical**

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

Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>*

and/or

*Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
<https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**October 2022
Clinical/Medical**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	IMMUNE-MEDIATED SAFETY DATA COLLECTION AND EVALUATION	2
	A. Identifying Potential imARs.....	3
	B. Protocol and Case Report Form Considerations Related to imARs.....	4
	C. Sponsor Classification of Adverse Events as imARs.....	5
	D. NDA or BLA - Additional imAR Safety Data Considerations	6
	E. Labeling Recommendations.....	6
	1. WARNINGS AND PRECAUTIONS Section.....	7
	2. DOSAGE AND ADMINISTRATION Section	8

1 **Characterizing, Collecting, and Reporting Immune-**
2 **Mediated Adverse Reactions in Cancer Immunotherapeutic**
3 **Clinical Trials**
4 **Guidance for Industry¹**
5

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

6
7
8 **I. INTRODUCTION**
9

10 Cancer immunotherapeutic drugs and biological products (hereafter referred to as cancer
11 immunotherapeutic drugs) can modulate (i.e., stimulate or suppress) the endogenous immune
12 system to produce an anticancer effect. Adverse events² that are consistent with an autoimmune
13 etiology should be evaluated as potential immune-mediated adverse reactions (imAR)³ to guide
14 patient management and inform the drug labeling or investigator brochure, as applicable.

15
16 For the purpose of this guidance, the term imAR refers to adverse reactions that occurred in the
17 context of exposure to a cancer immunotherapeutic drug and are consistent with the development
18 of an autoimmune reaction, and are not attributable to another cause (e.g., infection, trauma,
19 other drugs). While corticosteroids and other immunosuppressive drugs are regularly used to
20 manage imARs in cancer clinical trials, the absence of a history of immunosuppressive treatment
21 for an adverse reaction does not preclude its characterization as an imAR, especially for low-
22 grade imARs that result in dose interruption.
23

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).

Contains Nonbinding Recommendations

Draft—Not for Implementation

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

30
31 This guidance provides recommendations regarding the data that should be collected and
32 evaluated to assess whether adverse events qualify as imARs and the data on imARs that should
33 be included in a new drug application (NDA) or biologics license application (BLA) for a cancer
34 immunotherapeutic drug.

35
36 The contents of this document do not have the force and effect of law and are not meant to bind
37 the public in any way, unless specifically incorporated into a contract. This document is
38 intended only to provide clarity to the public regarding existing requirements under the law.
39 FDA guidance documents, including this guidance, should be viewed only as recommendations,
40 unless specific regulatory or statutory requirements are cited. The use of the word should in
41 Agency guidances means that something is suggested or recommended, but not required.

42
43

II. BACKGROUND

44
45

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

61
62

III. IMMUNE-MEDIATED SAFETY DATA COLLECTION AND EVALUATION

63
64

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

Contains Nonbinding Recommendations

Draft—Not for Implementation

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

73
74 Sponsors developing cancer immunotherapeutic drugs should discuss collection,
75 characterization, and reporting of immune-mediated safety data with the clinical review division
76 early in development and prior to implementing a cancer immunotherapeutic drug trial.

A. Identifying Potential imARs

77
78
79
80 Sponsors should develop a prespecified list of potential imARs consisting of groupings of
81 Medical Dictionary for Regulatory Activities (MedDRA) terms describing the same medical
82 concept using all levels of the MedDRA hierarchy including Standardized MedDRA Queries
83 (SMQs) on which data should be collected to characterize a potential imAR. This list should be
84 updated throughout the development program and included in relevant documents (e.g., in the
85 protocol, investigator brochure, safety analysis plan). When developing this list, the sponsor
86 should consider the:

- 87
- 88 • Mechanism of action of the drug and prior experience with the same or similar
89 immunotherapeutics in oncology, as well as other disease settings
 - 90 • Immunologic impact of the cancer or prior cancer therapy.

91
92 As an example of immunologic impact of prior cancer therapy, in allogeneic hematopoietic stem
93 cell transplantation (HSCT), multiple non-randomized trials evaluating PD-1 targeted antibodies
94 in patients either before or after undergoing allogeneic HSCT demonstrated an increased risk of
95 transplant related complications, even after PD-1 targeted antibody treatment had been
96 discontinued. Therefore, examples of potential imARs that should be prespecified for data
97 collection in this setting include hyperacute graft versus host disease (GVHD), acute GVHD,
98 chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and
99 steroid-requiring febrile syndrome (without an identified infectious cause).

100
101 Attributing certain adverse events to a cancer immunotherapeutic can be challenging when
102 overlapping toxicities are expected with other drugs or anticipated for the population under
103 study. Sponsors should consider patient- and treatment-related factors in assessing causality,
104 including but not limited to:

- 105
- 106 • Current organs/sites involved with disease.
 - 107
 - 108 • Previous therapy, e.g., radiation therapy.
 - 109
 - 110 • Any medical history of immune based pathologies, e.g., rheumatoid arthritis, Crohn's
111 disease, systemic lupus erythematosus, or other autoimmune diseases.
- 112

Contains Nonbinding Recommendations

Draft—Not for Implementation

- 113 • Combination therapy with chemotherapy or other drugs that have known toxicities in
114 specific organs.
115

116 In some circumstances, individual case assessment can be clarified by a rechallenge (if
117 appropriate), or follow-up response to immunosuppressive therapy. Causality, however, may not
118 be clear until sufficient exposure reveals an increase in incidence or severity of the specific
119 imAR within the arm of interest. Increased surveillance (e.g., defining the potential imAR as an
120 Adverse Events of Special Interest(AESI))⁴ in subsequent trials for suspected imARs is
121 appropriate to facilitate a causality assessment. In addition, when immunotherapeutic drugs with
122 a mechanism that decreases the threshold for disrupting peripheral immunological tolerance are
123 used in combination with a drug infrequently associated with an organ specific toxicity, a
124 marked increase in the frequency of organ specific toxicity should be considered an imAR until
125 proven otherwise (e.g., evaluate for immune-mediated nephritis rather than attribute to
126 chemotherapy-induced acute renal failure in a patient receiving an immunotherapeutic plus
127 chemotherapy combination regimen). These considerations should also be included in protocols
128 to assist investigators in determining whether there is a reasonable possibility that the drug
129 caused the adverse event.⁵
130

B. Protocol and Case Report Form Considerations Related to imARs

131
132 The protocol should include the following:
133
134

- 135 • Instructions for how clinical investigators should evaluate adverse events to assess
136 immunological causality, including tissue biopsy or other laboratory test results to
137 determine whether the adverse event is an imAR.
138
139 • Descriptions of the imAR-related data that should be collected. Data on potential imARs
140 should be collected for at least 90 days after the last dose of an immunotherapeutic drug.
141 Sponsors should have a predefined plan for capturing information regarding imARs that
142 are known to occur beyond this period.
143

144 CRFs should include fields for documenting information about potential imARs.⁶ For example,
145 data elements should include, but are not limited to, the following:
146

- 147 • Date of onset (i.e., Start Date).
148

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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 149 • **Common Terminology Criteria for Adverse Events (CTCAE)⁷ grade**
150 - If CTCAE is not adequate to grade a specific imAR, the CRF should provide the
151 grading system to be used.
152
- 153 • Action taken with study drug(s)
154
- 155 • Outcome of the imAR
156
- 157 • Concomitant medications (including steroids, other immunosuppressive drugs, and
158 hormone replacement therapy) with doses and duration used to treat the potential imAR
159 and the ability to link the concomitant medication to the specific imAR.
160
- 161 • Date of resolution as defined as resolution of symptoms or return to baseline and no
162 longer requiring medical management (e.g., corticosteroids) or hormone replacement.
163
- 164 • Detailed data on baseline (i.e., preexisting) medical conditions (e.g., thyroid, renal,
165 hepatic, cardiac function, GVHD).
166
- 167 • Prior treatment history that may predispose a patient to experience an imAR.
168
- 169 • Clinical investigator's final assessment of whether an adverse event is an imAR (e.g.,
170 [Yes/No] data field on the CRF) and a required field to document the rationale for this
171 assessment, such as a description of the response to immunosuppressive or other therapy,
172 rechallenge information, clinicopathologic results, increase in frequency or severity of an
173 imAR with a pattern suggesting synergism, or other (option for free text).
174

C. Sponsor Classification of Adverse Events as imARs

175
176
177 As described in Section IIIA, sponsors should have a prespecified method for classifying adverse
178 events as imARs throughout the drug development program. This method should be systematic
179 and reproducible to allow comparison across trials and development programs. Key principles of
180 this method are the following:
181

- 182 • Sponsors should update and revise the list of potential imARs as described in Section
183 IIIA to accurately and fully capture and characterize these adverse events if (1) the
184 investigator assesses the adverse event to be an imAR, regardless of whether the patient
185 received corticosteroids, other immunosuppressive drugs, and/or hormone replacement
186 therapy, and (2) the sponsor agrees with this assessment, which may require an
187 evaluation of data across the development program. Events for which imAR-directed
188 therapy was instituted, but later stopped in favor of an alternative cause for the event
189 should not be included in this category.
190

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

Contains Nonbinding Recommendations

Draft—Not for Implementation

- 191
- 192
- 193
- 194
- 195
- 196
- 197
- 198
- 199
- 200
- 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

201

202

203

204 In addition to the information recommended in section III.A and III.B. of this guidance, the

205 analysis datasets in an NDA or BLA should include:

206

- 207
- 208
- 209
- 210
- 211
- 212
- 213
- 214
- 215
- 216
- 217
- 218
- 219
- 220
- 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.

221 The narrative safety portion of an NDA or BLA should also include a discussion of the sponsor's

222 assessment of whether adverse events are imARs and the rationale for the sponsor's assessment,

223 e.g., in the Integrated Summary of Safety.

224

E. Labeling Recommendations

225

226

227 This section of the guidance summarizes labeling recommendations on how to incorporate imAR

228 information into the WARNINGS AND PRECAUTIONS and DOSAGE AND

229 ADMINISTRATION sections of labeling for cancer immunotherapeutic drugs. The

230 recommendations for this section of this guidance are not intended to be exhaustive. Information

231 about imARs may be included in other sections of labeling (e.g., PATIENT COUNSELING

Contains Nonbinding Recommendations

Draft—Not for Implementation

232 INFORMATION). For developing these and other sections of labeling, applicants should refer
233 to statutory and regulatory labeling requirements and other FDA guidance recommendations.⁸
234

235 1. WARNINGS AND PRECAUTIONS Section

236
237 Clinically significant imARs should be incorporated into one numbered subsection in the
238 WARNINGS AND PRECAUTIONS section of labeling (e.g., **5.1 Severe and Fatal Immune-**
239 **Mediated Adverse Reactions**). Clinically significant imARs include those that occurred with
240 the subject drug as well as those that occurred with drugs in the same class (e.g., same
241 mechanism of action), as appropriate. When imARs are based on a pooled safety database, to
242 reduce redundancy from providing a detailed description of pooled safety data multiple times in
243 labeling, FDA recommends including this information in the *Clinical Trials Experience*
244 subsection in the ADVERSE REACTIONS section, instead of the imAR subsection in the
245 WARNINGS AND PRECAUTIONS section. The imAR subsection should cross-reference to
246 the *Clinical Trials Experience* subsection for the detailed description of pooled safety data. In
247 the imAR subsection in the WARNINGS AND PRECAUTIONS section, FDA recommends:
248

- 249 • Consolidating information that is applicable to different imARs (e.g.,
250 recommendations on how to prevent, mitigate, and monitor for or manage imAR(s))
251 in the beginning of this subsection rather than repeating this information for each
252 imAR. This subsection should cross-reference to the DOSAGE AND
253 ADMINISTRATION section for detailed recommendations on dosage modifications
254 intended to reduce the risk of an imAR.
255
- 256 • Organizing information about specific common imAR(s) that are clinically significant
257 under non-numbered headings (e.g., Immune-Mediated Pneumonitis, Immune-
258 Mediated Hepatitis).
- 259 • Listing less common serious imARs (e.g., incidence of <1%) that do not need further
260 description under a non-numbered heading (e.g., “Other Clinically Significant
261 Immune-Mediated Adverse Reactions”) and grouping them by organ/site. Subsequent
262 to approval of the NDA/BLA, less common, nonserious imARs should usually be
263 only listed in the ADVERSE REACTIONS section of labeling; however, if such
264 imARs are otherwise clinically significant (e.g., requires new patient monitoring or
265 management) they should also be listed in under this heading in the imAR subsection
266 in the WARNINGS AND PRECAUTIONS section.
267
- 268 • If a cancer immunotherapeutic drug is approved for monotherapy and as part of a
269 combination regimen or therapy:
 - 270 ○ Including clinically significant imAR information associated with monotherapy
271 and
272

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

Contains Nonbinding Recommendations

Draft—Not for Implementation

- 273 ○ Only including clinically significant imAR information associated with
274 concomitant use when there are novel clinically significant imAR(s) or more
275 frequent or severe clinically significant imAR(s) compared to those that occurred
276 with monotherapy.
277
- 278 ● If a cancer immunotherapeutic drug is approved for use in multiple cancer
279 subpopulations:
- 280 ○ Including clinically significant imAR information from the pooled cancer
281 populations, and
282 ○ Only including clinically significant imAR information for specific cancer
283 subpopulation(s) if the imAR is novel, severe, or occurs at a significantly higher
284 incidence compared to those from the pooled cancer populations.
285
- 286 ● For each clinically significant imAR under the appropriate heading within this
287 subsection, including the following information, as applicable:
288
- 289 ○ A statement(s) regarding how the imAR was defined.
290 ○ Frequency of imARs for all grades and by toxicity severity grade (2, 3, 4, and 5)
291 to characterize the risk at each grade and provide management actions for each
292 grade, if applicable (e.g., Grade 2 dosage modification, Grade 4 permanent
293 discontinuation).
294 ○ Time of imAR onset (median and range) in relation to start of the drug when
295 sufficient information is available for a specific imAR.
296 ○ Frequency of permanent discontinuation and withholding of the drug due to the
297 imAR.
298 ○ Number and percentage of patients with the imAR who required
299 immunosuppressive treatment categorized by type of therapy (local
300 corticosteroids, systemic corticosteroids, tumor necrosis factor inhibitors, etc.).
301 ○ Number and percentage of patients in whom the imAR did not resolve.
302 ○ Number and percentage of patients who reinitiated the drug after symptom
303 improvement (after withholding for the imAR) and the number and percentage of
304 these patients who had an imAR recurrence.
305

2. DOSAGE AND ADMINISTRATION Section

306 Recommendations on dosage modification intended to reduce the risks of imARs (e.g., dosage
307 reduction, dosage interruption, or permanent discontinuation) should be included in the
308 DOSAGE AND ADMINISTRATION section. Such information is generally displayed in this
309 section in a three-column table (e.g., Adverse Reaction, Severity, Dosage Modification). This
310 section should also include a cross-reference to the imAR subsection in the WARNINGS AND
311 PRECAUTIONS section.
312
313