Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Julia Beaver at 240-402-0489 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
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Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
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Guidance for Industry[1]

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I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products[2] regulated by CDER and CBER for the treatment of cancer.[3] Specifically, this guidance includes recommendations regarding the inclusion of patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient

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

[2] For the purposes of this guidance, references to drugs and drug and biological products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological drug products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[3] Topics of the other three guidances are related to eligibility criteria for patients with brain metastases, minimum age for pediatric patients, and patients with organ dysfunction or prior or current malignancies.

accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.[4,5]

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice without jeopardizing patient safety.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and 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

HIV and HBV infections can be chronically managed and HCV infections can be cured with contemporary anti-viral therapy. These viral infections may increase the risk of development of several malignancies. However, exclusion of patients with HIV, HBV, or HCV infections from cancer clinical trials remains common in most studies of investigational drugs. Expanding cancer clinical trial eligibility to be more inclusive of patients with HIV, HBV, or HCV infections is justified in many cases, and may accelerate the development of effective therapies in cancer patients with these chronic infections. Designing cancer clinical trials that include patients with HIV, HBV, or HCV infections and then including this information in the labeling promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice.

III. RECOMMENDATIONS

Thoughtful consideration should be given to the potential inclusion of patients infected with HIV, HBV, or HCV in cancer clinical trials. Eligibility criteria that address requirements regarding relevant concurrent antiviral and other therapies (e.g., antibiotic prophylaxis) and degree of immunocompetence in patients with HIV, HBV, or HCV infections should be designed in a manner that is appropriate for a given cancer, investigational drug, and intended use population.[6] In cases where there is a strong rationale for exclusion, the rationale should be addressed in the trial protocol.

[4] Beaver JA, Ison G, Pazdur R, 2017, Reevaluating Eligibility Criteria- Balancing Patient Protection and Participation in Oncology Trials, NEJM, 376:1504-1505.

[5] Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, JCO, 35(33): 3737-3744.

[6] Uldrick T, Ison G, Rudek M, et al., 2017, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group, JCO, 35(33): 3774–3780.

The following recommendations for eligibility criteria for patients with cancer and concurrent HIV infection are focused on evaluation of immune function and HIV therapy. The following recommendations for eligibility criteria for patients with cancer who have evidence of chronic HBV or with current or history of HCV are focused on liver-related laboratories and HBV/HCV therapy.

A. Recommendations for patients with HIV infection

1. Evaluation of immune function

- **Eligibility based on CD4+ T-cell counts**

  - Patients with CD4+ T-cell (CD4+) counts ≥ 350 cells/uL should generally be eligible for any study.

  - Patients with a lower CD4+ count (< 350 cells/uL) should generally be eligible if the patient has a potentially curable malignancy or for interventions in a later stage of development that have demonstrated prior activity with a given cancer.

- **Eligibility based on history of AIDS (acquired immunodeficiency syndrome)-defining opportunistic infections**

  - Patients without a history of AIDS-defining opportunistic infections should generally be eligible for any study.

  - Patients with a history of AIDS-defining opportunistic infections may be eligible, taking into account the time frame and cancer type:

    - In general, patients should be eligible if they have not had an opportunistic infection within the past 12 months.

    - For studies of patients with a history of AIDS-defining cancers (e.g., Kaposi's sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer) with curative potential, exclusion of patients with uncontrolled opportunistic infections may be appropriate.

    - Patients on prophylactic antimicrobials should be included, although patients taking specific antimicrobial drugs where there may be drug-drug interactions or overlapping toxicities should be excluded.

2. HIV therapy[7]

- **Timing of antiretroviral therapy (ART) initiation** – Eligibility criteria specifying timing of initiation of ART should be based on study goals and take into consideration patients recently diagnosed with HIV or patients not on effective ART. Effective ART is defined as a drug, dosage, and schedule associated with reduction and control of the viral load.

    - **For advanced cancer settings in which there is not curative intent:** To ensure that effective ART is tolerated and that toxicities are not confused with investigational drug toxicities, trial participants should be on established ART for at least four weeks and have an HIV viral load less than 400 copies/mL prior to enrollment.

    - **For therapies given in a potentially curative setting:** Participants should have no evidence of documented multidrug resistance that would prevent effective HIV therapy and should agree to adhere to ART based on protocol defined treatment guidelines.

- **Exclusion of specific ART drugs** – It may be necessary or appropriate to exclude patients taking certain ART drugs based on demonstrated or predicted drug-drug interactions that affect absorption, distribution, metabolism, and excretion of the investigational drug (or the ART) or for potential overlapping toxicities.

    - Drug-drug interactions with ART occur via many mechanisms, with CYP3A4-mediated interactions being the most common. The absorption, distribution, metabolism, and excretion data known to date for the investigational drug should be assessed. Exclusion of patients on specific ART drugs should then be based on the potential for clinically significant drug-drug interactions using known information (see Appendix 2). The protocol should include tables of any drugs, including ART and other drugs, that are prohibited for patients while participating in the study, and therefore would be considered part of the exclusion criteria for the study. For sensitive CYP3A4 substrates, patients who are using concurrent strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat) or strong inducers could be switched to an alternate effective ART regimen (with minimal drug-drug interaction potential) before study participation or should be excluded from the study if their regimen cannot be altered. Otherwise eligible study participants could be switched to an alternate effective ART regimen before study participation.

[7] See Appendix 1 for references regarding management of concurrent HIV infection.

- Consider exclusion of patients on specific ART drugs based on toxicity (e.g., tenofovir (renal dysfunction), atazanavir (PR prolongation and AV block), efavirenz (depressed mood)) if overlapping toxicities with investigative drugs is expected.

- **Exceptions to concurrent ART** – Although effective ART is recommended in patients with HIV infection, exceptions to concurrent ART should be considered in both development of eligibility criteria and conduct of studies, as follows:[8]

  - In studies enrolling patients with curable malignancies where cancer therapy requires prioritization, eligibility criteria should permit enrollment, since treatment interruption or deferred initiation of ART is appropriate in curable malignancies when ART may compromise intended full-dose cancer therapy with investigational drug(s).

  - For treatment interruptions for toxicity management.

  - For treatment interruptions to meet scientific objectives of the study.

B. Recommendations for patients with evidence of chronic HBV infection or patients with current or history of HCV infection

1. Liver-related laboratories

- Liver-related laboratory eligibility criteria should generally be the same as that for the general population.

  - Exception: AST/ALT and bilirubin criteria may be less stringent in patients with hepatocellular carcinoma and cholangiocarcinoma in whom hepatic function based on Child-Pugh score should be used.

2. HBV/HCV therapy

- HBV: Eligibility criteria for patients with serologic evidence of chronic HBV infection should generally require patients to have an HBV viral load below the limit of quantification and should address the requirement for concurrent viral suppressive therapy.[9]

[8] Uldrick T and Little R, 2015, How I Treat Classical Hodgkin Lymphoma in Patients Infected with Human Immunodeficiency Virus, Blood, 125(8):1226-1235.

[9] Reddy K, Beavers K, Hammond S, et al., 2015, American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy, Gastroenterology, 148(1): 215-219.

- HCV: Eligibility criteria for patients with a history of HCV infection should require patients to have completed curative antiviral treatment and require HCV viral load below the limit of quantification.

- HCV: Eligibility criteria for patients on concurrent HCV treatment should generally require patients to have HCV below the limit of quantification.

APPENDIX 1: REFERENCES FOR MANAGEMENT OF CONCURRENT HIV

1. Department of Health and Human Services (HHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV[10]

2. HHS Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[11]

[10] Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0, accessed February 26, 2019.
[11] Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf, accessed February 26, 2019.

APPENDIX 2: REFERENCES FOR AVAILABLE ANTIRETROVIRAL DRUGS AND RELEVANT PHARMACOLOGY TO AVOID DRUG-DRUG INTERACTIONS

1. Literature[12,13]

2. University of Liverpool HIV Drug Interaction Website Searchable Database[14]

3. FDA's Website – Antiretroviral Drugs Used in the Treatment of HIV Infection[15]

[12] Rudek M, Flexner C, Ambinder R, 2011, Use of Antineoplastic Agents in Patients with Cancer Who Have HIV/AIDS, Lancet Oncol, 12(9): 905-912. The article includes tables on drug interaction potential of antiretroviral drugs.

[13] Berretta M, Caraglia M, Martellotta F, et. al., 2016, Drug-Drug Interactions Based on Pharmacogenetic Profile between Highly Active Antiretroviral Therapy and Antiblastic Chemotherapy in Cancer Patients with HIV Infection, Front. Pharmacol., epub March 30, 2016, doi: 10.3389/fphar.2016.00071.

[14] Available at https://www.hiv-druginteractions.org/, accessed February 26, 2019.

[15] Available at https://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm118915.htm, accessed February 26, 2019.