Renal Cell Carcinoma: Developing Drugs and Biologics for Adjuvant Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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I. INTRODUCTION

This guidance provides recommendations to sponsors regarding the development of drugs and biologics,[1] regulated by CDER and CBER for the adjuvant treatment of renal cell carcinoma. The guidance includes recommendations regarding eligibility criteria, choice of comparator, follow-up imaging assessments, determination of disease recurrence, analyses of disease-free survival (DFS), and interpretation of trial results. Although FDA may consider endpoints other than DFS for the adjuvant treatment of renal cell carcinoma, this guidance is focused on clinical trials with DFS as the primary efficacy endpoint.

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

Significant variability exists in the design, conduct, and analysis of trials for the adjuvant treatment of renal cell carcinoma, including the eligibility criteria, radiological disease assessments, the definition of disease recurrence, and the date used to define the DFS endpoint. Consistency in these aspects within and across trials may facilitate interpretation of trial results. These issues were discussed at an FDA-NCI public workshop held on November 27, 2017.[2]

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

[2] Agrawal S, Haas NB, Bagheri M, et. al., 2019, Eligibility and Radiologic Assessment for Adjuvant Clinical Trials in Kidney Cancer, JAMA Oncol, epub ahead of print November 21, 2019, doi: 10.1001/jamaoncol.2019.41141.

III. RECOMMENDATIONS

A. Trial Eligibility Criteria

- Patients with non-clear cell subtypes of renal cell carcinoma, including those with a sarcomatoid component should be included. It may be appropriate to study patients with non-clear cell histologies in cohorts separately from patients with clear cell histologies to account for variations in response.

- Patients with microscopically positive soft tissue or vascular margins without gross residual disease should be included when the clinical trial ensures that the number of patients at high-risk for recurrence achieves balance between arms through stratified randomization procedures.

- The protocol should require documentation of tumor stage, nodal and vascular involvement, and the number of lymph nodes sampled at the time of nephrectomy to ensure that eligibility criteria are met. Case report forms should be designed to capture this information.

- Patients who have undergone radical or partial nephrectomy should be included.

- See section III.C for recommendations regarding imaging assessments relevant to eligibility criteria.

- For recommendations on eligibility regarding renal function, see section III.A.1 of the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies*.[3]

- Patients with residual or recurrent malignant disease should be excluded.

    - Any lesions on imaging that could possibly represent residual or recurrent kidney cancer should be biopsied prior to enrollment, if safe and feasible, to assess for the presence of malignant disease and to document eligibility.

    - When biopsy is not safe or feasible, it may be necessary to use imaging to establish absence of disease at baseline prior to enrollment to document eligibility. The radiological definition of "no evidence of disease" should be prespecified in the protocol. For example, for patients entering these trials with enlarged lymph nodes or sub-centimeter lesions in the visceral organs that are not amenable to biopsy, the protocol should contain criteria regarding the size or other characteristics of these lesions that establish absence of disease for the purpose of determining eligibility in the trial.

[3] July 2020. 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.

- A blinded independent central review (BICR) of baseline scans prior to study entry is recommended to ensure the absence of metastatic disease.

B. Choice of Comparator

- The appropriate choice of comparator should be discussed with the Agency prior to study initiation and should be consistent with standards of care and with practice patterns in the community.

C. Imaging Assessments

- The protocol should specify acceptable methods of imaging acquisition, display, and radiological interpretation technique for use in determination of DFS. The protocol should specify that the same modality should be used throughout the trial for an individual patient.

- Initial imaging studies should be completed within 4 weeks of trial enrollment.

- Imaging assessment frequency should be the same on all treatment arms as asymmetrical frequencies may bias the assessment of DFS. The anticipated magnitude of effect on DFS necessary to demonstrate clinical benefit should be considered in planning the frequency of imaging assessments. The anticipated magnitude of DFS improvement should be substantially greater than the imaging frequency for DFS to be interpretable.

D. Determination of Disease Recurrence

- The determination of disease recurrence for DFS should be based on the assessment by a BICR.

- Radiological findings suggestive of disease recurrence should be supported by tumor biopsies to confirm malignant disease, whenever safe and feasible.

- The radiological definition of recurrence by site (e.g., tumor bed, lymph nodes, bone metastases, visceral disease) should be prespecified, in case biopsy is not safe or feasible to confirm recurrence. The definition should include the location, size, and the number of lesion(s) that define radiological recurrence. The definition should be applied uniformly by investigators and the BICR to ensure consistency in criteria for recurrent disease in the absence of histologic confirmation.

- The definition of disease recurrence should address the development of localized disease such as a new lesion in the contralateral kidney or at a site away from the original resection in the ipsilateral kidney after partial nephrectomy in the absence of the development of overtly metastatic disease.

- The algorithm for assigning date of recurrence should be prespecified and consistently applied. For example,

    - When both an image and biopsy document recurrence, the earlier date should be used for date of recurrence.

    - When confirmatory imaging is required to document disease recurrence in the absence of a biopsy, the date of recurrence should be the date the lesion(s) was first identified.

E. Trial Analysis

- The protocol and statistical analysis plan (SAP) should contain a detailed description of the trial assumptions and statistical methods for analysis of DFS and overall survival (OS).

- Procedures should be put in place to minimize missing data for DFS.

- The SAP should specify the primary analysis and sensitivity analyses with different censoring rules to evaluate the impact of missing observations, imaging assessment frequency, and other factors on the results.

F. Interpretation of Trial Results

- Interim analyses of DFS are not recommended because immature data may lead to over- or underestimation of magnitude of improvement.

- The trial design (e.g., add-on design, active versus placebo control) and conduct, toxicity profile observed, study population, and the overall benefit-risk evaluation all factor in to the magnitude of improvement in DFS required to support drug approval.

- While FDA approval does not require demonstration of an OS benefit, the protocol and SAP should include a plan for a formal interim analysis of OS at the time of final DFS analysis. To support a favorable benefit-risk assessment, this analysis should demonstrate a favorable numeric trend and provide assurance that OS is not adversely affected by the treatment. In addition, FDA expects continued follow-up to allow conduct of the final OS analysis.