HHS Public Access

Author manuscript

JAMA Oncol. Author manuscript; available in PMC 2021 May 17.

Published in final edited form as:

JAMA Oncol. 2020 January 01; 6(1): 133–141. doi:10.1001/jamaoncol.2019.4117.

Eligibility and Radiologic Assessment for Adjuvant Clinical Trials in Kidney Cancer

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Obtained funding: Apolo.

Administrative, technical, or material support: Agrawal, Bagheri, Lane, Hammers, Bratslavsky, Kim, Cross, Liu, Pazdur, Blumenthal, Choueiri, Apolo.

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Abstract

PURPOSE—To harmonize the eligibility criteria and radiologic disease assessment definitions in clinical trials of adjuvant therapy for renal cell carcinoma (RCC).

METHOD—On November 28, 2017, US-based experts in RCC clinical trials, including medical oncologists, urologic oncologists, regulators, biostatisticians, radiologists, and patient advocates, convened at a public workshop to discuss eligibility for trial entry and radiologic criteria for

assessing disease recurrence in adjuvant trials in RCC. Multiple virtual meetings were conducted to address the issues identified at the workshop.

RESULTS—The key workshop conclusions for adjuvant RCC therapy clinical trials were as follows. First, patients with non–clear cell RCC could be routinely included, preferably in an independent cohort. Second, patients with T3–4, N+M0, and microscopic R1 RCC tumors may gain the greatest advantages from adjuvant therapy. Third, trials of agents not excreted by the kidney should not exclude patients with severe renal insufficiency. Fourth, therapy can begin 4 to 16 weeks after the surgical procedure. Fifth, patients undergoing radical or partial nephrectomy should be equally eligible. Sixth, patients with microscopically positive soft tissue or vascular margins without gross residual or radiologic disease may be included in trials. Seventh, all suspicious regional lymph nodes should be fully resected. Eighth, computed tomography should be performed within 4 weeks before trial enrollment; for patients with renal insufficiency who cannot undergo computed tomography with contrast, noncontrast chest computed tomography and magnetic resonance imaging of the abdomen and pelvis with gadolinium should be performed. Ninth, when feasible, biopsy should be undertaken to identify any malignant disease. Tenth, when biopsy is not feasible, a uniform approach should be used to evaluate indeterminate radiologic findings to identify what constitutes no evidence of disease at trial entry and what constitutes radiologic evidence of disease. Eleventh, a uniform approach for establishing the date of recurrence should be included in any trial design. Twelfth, patient perspectives on the use of placebo, conditions for unblinding, and research biopsies should be considered carefully during the conduct of an adjuvant trial.

CONCLUSIONS AND RELEVANCE—The discussions suggested that a uniform approach to eligibility criteria and radiologic disease assessment will lead to more consistently interpretable trial results in the adjuvant RCC therapy setting.

Substantial variability exists in the eligibility criteria of multiple ongoing trials for the adjuvant treatment of renal cell carcinoma (RCC). The eligibility criteria for patients in trials of novel agents, including immunotherapy with checkpoint inhibitors, are often the same as those historically applied to patients in trials of adjuvant therapy with tyrosine kinase inhibitors. Eligibility criteria should be revisited to limit the unnecessary exclusion of patients for whom these adjuvant therapies would be advantageous. Further complicating this landscape is the lack of consensus regarding the radiologic definitions used to define study eligibility or radiologic disease recurrence commonly used in adjuvant trials. Data to support these definitions are scarce, and so the definitions often vary among trials. Methods for determining the date of recurrence in these trials may also differ, and this variance can have implications for trial outcomes. These issues make interpreting trial results, applying trial results to the general population, and making comparisons across trials more difficult. Reconciling these differences would allow for more consistent interpretation of future trials.

On November 28, 2017, the US Food and Drug Administration (FDA) and the National Cancer Institute, with support from the Society of Urologic Oncology, convened at the National Institutes of Health in Bethesda, Maryland, a group of experts in genitourinary cancer clinical trials for a public workshop on adjuvant clinical trials in RCC and bladder cancer. The RCC component focused on 3 topics: (1) the role of patient and disease characteristics, (2) criteria for radiologic eligibility, and (3) the definition of disease

recurrence in adjuvant RCC therapy trials. The state of the science was reviewed by multiple stakeholders, including investigators, patient advocates, biostatisticians, industry representatives, regulators, and the public. Multiple virtual meetings were used to outline these issues.

We report on the discussions from these virtual meetings and the public workshop. The companion manuscript[1] about the bladder cancer component of the workshop addresses many of the same issues as the RCC component. The key discussion points from the workshop are explained in this article and summarized in Table 1.

Patient and Disease Characteristics

Genomic Classification of RCC

Most RCC cases are clear cell RCC; however, more than 40 non–clear cell RCC types are described in the World Health Organization classification.[6,7] Indiscriminately grouping patients with histologically diverse cancers in clinical trials and ignoring the tumors' biological signatures have seriously hampered efforts to find treatments for these cancers. Integrated histopathologic and molecular classification of RCC is needed.[8] Patients with non–clear cell RCC, especially with a relevant driver mechanism, should be included in trials of patients with clear cell RCC, preferably as an independent cohort, because integration of non–clear cell RCC into prospective clinical trials may enrich the variety of altered tumorigenic pathways and thus provide more opportunities for breakthrough discoveries in subset analyses of tumor-profiling data. This integration may better inform the evaluation and development of targeted therapies based on molecular and genomic features across various histologic subtypes.

High-risk Disease Stages

The advantage of adjuvant therapy for patients with localized RCC after nephrectomy has not been established but is being actively investigated. Previous adjuvant RCC therpay trials have enrolled patients with stages T1b (grade 3–4)-T3N1–3.[9–13] Selecting the ideal patient with high risk of RCC recurrence on the basis of TNM staging for enrollment into an adjuvant clinical trial can be difficult. Many prognostic factors, such as tumor size, grade, and presence of symptoms at presentation, among other factors, may play an important role in outcomes. Several models and clinical nomograms have been developed to estimate the risk of disease recurrence and progression. However, even these methods vary in their predictive ability over time.[14] Currently, patients with T3–4, N+M0, and microscopic R1 RCC tumors have a high risk of recurrence[15–18] and consequently may gain the greatest advantage from adjuvant therapy.

Renal Function

Patients with RCC considered for adjuvant trials have had previous nephrectomy and are usually older, and between 20% and 40% of these patients have stage III or worse chronic kidney disease at presentation.[19] Trials of therapeutic agents that are not renally excreted should not exclude these patients if adequate imaging can be performed using lower doses of contrast with hydration and if renal function limitations do not have implications for other

aspects of the trial. Drugs that do not place the patient at risk for further renal damage should not preclude the patient from accessing the potential advantage of an experimental therapy. Differences in renal function are relevant to overall survival analysis, as severe chronic kidney disease is associated with limited life expectancy.[20]

Surgical Considerations

Timing and Length of Adjuvant Therapy

The de facto standard has become the administration of adjuvant systemic therapy within the first 12 weeks after the surgical procedure. According to clinical experience and prospective collaborative data (eg, the American College of Surgeons National Surgical Quality Improvement Program), substantive recovery and perioperative risks are acceptably low in most patients with RCC by day 30 after the surgical procedure.[21] The rationale for supporting a specific interval to initiate adjuvant therapy is unknown, given that the perioperative kinetics of circulating tumor cells, acquisition of invasive phenotypes, and timing of an angiogenic switch are all unclear. Given these facts, adjuvant therapy should begin as soon as the patient has recovered adequately from the surgical procedure and can still be initiated up to 16 weeks after the procedure to allow for more inclusivity. Similarly, although a duration of 9 to 12 months has become standard for adjuvant therapy, no data exist that support this practice. Shorter duration of adjuvant therapy may not be inferior.[22] The appropriate length of adjuvant therapy in RCC is unknown owing to the lack of data.

Surgical Technique

Most trials appropriately accept patients who have undergone open or minimally invasive surgical procedures. However, no data suggest that one procedure type is inferior to the other. Important differences, such as likelihood of blood transfusion and extent of lymph node dissection, may become factors in trial outcomes and should be balanced by randomization or addressed with stratification. Patients undergoing radical or partial nephrectomy should be equally eligible, assuming the preservation of adequate renal function and R0 resection, because no data suggest that one nephrectomy type is inferior to the other. However, existing data suggest that for higher-risk disease (>pT3), local recurrence may be more likely after partial nephrectomy.[23–27] Therefore, adjuvant trial eligibility criteria and interpretation should account for potential differences in recurrence rates between higher- and lower-risk disease.

Positive Microscopic Surgical Margins

The verification of negative surgical margins requires keen intraoperative observation to distinguish normal tissue from tumor and can be plagued by sampling error and poor communication between surgeon and pathologist. A particularly common margin issue is that of vascular margins in the setting of venous thrombus. A positive margin on the thrombus can be confusing when interpreting pathological findings, and a false positive finding may inappropriately render patients ineligible for trial participation. In cases of tumor thrombus, venous wall invasion should be assessed as the true margin. Patients with microscopically positive soft tissue or vascular margins as opposed to gross residual disease should be judiciously included in adjuvant trials because these therapies may be

advantageous for these patients. However, such potential advantages need to be balanced against the possibility of worse clinical outcomes in this group, an important point to consider during trial design and interpretation.

Lymph Node Dissection

A randomized clinical trial demonstrated no survival advantage for routine lymph node dissection in localized RCC with no suspicious lymph nodes on imaging.[28] Nevertheless, consensus is lacking regarding the staging and therapeutic advantage of resecting clinically suspicious lymph nodes. The areas of debate include radiologically defined node-positive disease, management of patients with suspicious nodes, indications for complete lymphadenectomy compared with more limited lymph node sampling, and precise templates for lymphadenectomy. With no clear survival advantage for lymph node dissection and some potential to reduce trial eligibility owing to pathological outcomes or surgical issues (ie, bleeding or lymphatic leak that may prolong recovery), many surgeons resect lymph nodes sparingly.[29] This variability in surgical practice could have implications for the outcomes of adjuvant trials if not addressed. The utility of routine lymph node dissection in adjuvant trials is unclear, but in the absence of data, the following principles were agreed on in workshop discussions.

First, all suspicious regional cN+ (clinically node-positive) nodes should be fully resected for accurate staging, with the goal of rendering the patient macroscopically R0 or tumor free. Second, the extent of lymph node dissection and the number of lymph nodes sampled before trial entry should be documented and communicated to investigators. Third, when lymph node metastases and/or locally advanced (T3–4) RCC are present, the use of a template for retroperitoneal lymph node dissection would be helpful but difficult to standardize.

Radiologic Considerations

Equivocal lesions noted on imaging before enrollment or on trial surveillance imaging make the determination of disease status difficult. Workshop discussion focused on this issue, and agreement was reached on the following general principles. First, biopsy should be performed to determine whether any residual disease is present. Considerations for obtaining biopsies[30–37] are summarized in the Box. Second, if a biopsy is not safe or feasible, indeterminate radiologic lesions should be managed uniformly so that patients who have no confirmed evidence of disease but are at a high risk of recurrence are not unnecessarily excluded from adjuvant therapy trials. Third, in general, more inclusive criteria should be used for enrolling patients in trials to enhance the efforts to find successful therapies in this space and thus give more patients the opportunity to gain the potential advantage from these adjuvant therapies. Fourth, the eligible postoperative period should be extended to allow for the follow-up of suspicious radiologic abnormalities.

Radiologic Eligibility

No standard criteria are currently available to adjudicate equivocal findings on radiologic imaging before adjuvant trial enrollment. Workshop discussion included a review of

available literature. The principles outlined in the Response Evaluation Criteria in Solid Tumors (RECIST)[38] and technical standards published in Quantitative Imaging Biomarkers Alliance guidelines[5] support use of the following general radiologic criteria during initial evaluation: (1) A nonnodal lesion 1.0cm or larger in the long axis and a nodal lesion 1.0cm or larger in the short axis is considered suggestive of malignant disease, and (2) equivocal lesions are assumed to be benign if smaller than 1.0cm in the long axis for all non–lymph node lesions and in the short axis for lymph nodes.

The 1.0-cm threshold may not capture all suspicious lesions or may lead to further diagnostic evaluation of lesions that are actually benign. However, this threshold represents a size that is reasonably sensitive and specific for identification of potential malignant neoplasm in radiologic practice,[39,40] allows for reliable characterization of lesions on computed tomography,[5] and represents a rate of growth of subcentimeter lesions that outpaces the rate of growth of typically benign lesions.

Given the lack of data in radiologic tumor assessment in the adjuvant setting, patient eligibility for these trials should not be based solely on discrete numeric cutoffs. Rather, these thresholds provide an example of what could reasonably prompt further evaluation before enrollment. Table 2 summarizes the agreements from the workshop on site-specific findings that warrant additional radiologic evaluation or biopsy to exclude malignant disease before enrollment.

Radiologic Disease Recurrence

RECIST are well-established criteria for assessing the response to treatment in patients with metastatic disease; however, no specific criteria exist for identifying new radiologic lesions. [38] Applying a model similar to RECIST to the adjuvant setting would be helpful for uniformly assessing new and highly suspicious yet indeterminate radiologic lesions when biopsy is not feasible to confirm malignant disease. The goal in identifying common thresholds to define recurrence is to permit more consistent evaluation of adjuvant trial outcomes, given that the application of varying response criteria may lead to differences in trial outcomes.[51] More consistent evaluation would also allow patients with disease progression during an adjuvant therapy trial to either receive standard-of-care treatment or enroll in trials for metastatic disease.

The principles of RECIST,[38] as well as the technical standards defined by Quantitative Imaging Biomarkers Alliance,[5] were considered and support the following formula, which can be applied to patients with highly suspicious radiologic findings that are not amenable to biopsy. Patients who meet the following criteria can reasonably be considered as having unequivocal recurrence, assuming the complete exclusion of an alternative clinical explanation beyond malignant neoplasm: (1) any new lesion 1.0 cm or larger that was absent on initial evaluation, (2) any preexisting lesion (a) 1.0 cm or larger that demonstrates more than 50% growth on 2 consecutive radiologic examinations with 5 mm absolute increase or greater or (b) 1.0 cm or larger that demonstrates 50% growth on a single examination, or (3) multifocal lesions smaller than 1.0 cm that demonstrate geographic distribution or radiologic

or metabolic features that are pathognomonic for metastatic disease (Table 2). Follow-up imaging for indeterminate lesions should occur at 6- to 8-week intervals.

Designating the recurrence of small tumors (<1.0 cm) or a single lesion 1.0 cm or larger on the basis of these criteria may be problematic and could lead to the overestimation of recurrence. However, as noted earlier, the 1.0-cm threshold represents a size that is reasonably sensitive and specific for identifying potential malignant neoplasms in radiologic practice,[39,40] allows for reliable characterization of lesions on computed tomographic imaging,[5] and represents a rate of growth of subcentimeter lesions that outpaces the rate of growth of typically benign lesions. Protocols using different numeric thresholds may be reasonable but should be consistent. Accurate and uniform application of the trial criteria for unequivocal recurrence is essential in reporting outcomes.

The development of a new lesion in the contralateral kidney or at a site away from the original resection in the ipsilateral kidney parenchyma after partial nephrectomy also requires careful consideration. Such lesions may not be considered progression events in adjuvant trials because they likely reflect multifocality. Alternatively, lesion growth during an adjuvant trial may be considered a failure of the adjuvant therapy to control disease and therefore could be considered a progression event. Further evidence is needed to ascertain whether these new lesions should be categorized as progression events; however, an agreement was reached that the approach to these lesions should be prospectively addressed and specified in protocols.

Date of Recurrence

Multiple potential methods may be used to establish a date of recurrence in patients previously under observation and deemed to have no evidence of disease. Some trials have backdated recurrence to the date when new lesions were first noted on imaging, because this date is most closely associated with the actual time of recurrence. However, for the purposes of a clinical trial, backdating may be difficult and could lead to inconsistency in defining the date of recurrence. The first appearance of a lesion may not be entirely clear, or backdating could potentially identify patients who were ineligible for an adjuvant trial on a retrospective basis, as progression might be backdated to imaging findings that did not meet the criteria for disease at trial entry.

Using the date at which the prespecified criteria for unequivocal recurrence were met prevents these issues, and applying criteria such as those outlined in Table 2 to specific disease sites is a more consistent method of assigning the date of radiologic disease recurrence. However, this method may not identify recurrence in a temporally accurate manner. Although no agreement was reached at the workshop on which method to use, it was decided that the method should be clearly stated in the protocol and applied consistently to establish and document the date of recurrence, as doing so is essential for reporting outcomes in adjuvant trials.

Recurrence may also be dated to the time of histologic confirmation, if available, or the time of investigator-assessed clinical progression. When both an imaging date and a biopsy date

are available, the imaging date is preferable as the date of radiologic recurrence because a biopsy is typically prompted by suspicious findings on imaging. Further considerations for biopsy are listed in the Box.

Patient Perspectives

Patients must be informed of what is known about the study therapy and what is unknown about its efficacy and potential adverse effects. Clear verbal communication and written consent documents improve accrual and participation. Reminding patients that clinical trials must provide at least the current standard of care and assuring them of thorough and consistent monitoring of their status throughout the trial can help to alleviate anxiety. Placebo-based, blinded, and biopsy-driven trials can be particularly concerning for patients.

Placebo-Based Trials

Unblinded clinical trials can successfully mitigate dropout if the patient and investigator verify before randomization that the patient is committed to the trial and scheduled follow-up even if assigned to the observation arm. Balancing the accrual deterrence of placebo with the actual accrual rate of the observational control arm is critical to successful trial design. The FDA, in general, does not require the use of placebo for control in trials of adjuvant cancer therapies and has stated that, if possible, active control is preferred over placebo. For adjuvant trials that involve a unique product class, such as a cancer vaccine, use of a placebo control might be desirable. The appropriate choice of comparator should be discussed with the FDA before study initiation.

Unblinding

Prohibiting unblinding of patient assignment after patients discontinue study participation presents challenges in that patients will not be able to use information from their trial participation when making future decisions about therapy. Although patients may discontinue their participation for any reason at any time, most of them leave only after experiencing toxic effects or recurrence or progression. Placebo-based studies should allow for patient- and investigator-level unblinding after cessation of study treatment, and consent forms should contain explicit language regarding this consideration to optimize patient care.

Mandatory Biopsies

Researchers must carefully weigh the importance of a biopsy in a trial against the biopsy's accrual effect and potential harms. The rationale for the biopsy must be scientifically sound and carefully explained to patients during the initial and consent interviews. Researchers must be mindful that transparency and honesty build trust, and trust supports patient accrual and retention.

Planning for the Future

The public workshop concluded that a uniform approach to defining eligibility criteria and assessing residual and recurrent disease will allow the scientific community to reduce unnecessary variability in the conduct of adjuvant RCC therapy trials. Data to support

specific radiologic criteria are currently lacking; thus, these definitions may require adjustment as more data become available and as the FDA recommends continuing dialogue during trial design and development. The scientific community needs to account for the rapidly changing landscape of the science when considering the conduct of clinical trials for adjuvant RCC therapies.

Funding/Support:

This study was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health.

Role of the Funder/Sponsor:

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest Disclosures:

Dr Hammers reported receiving grants, personal fees, and travel expenses from Bristol Myers-Squibb; personal fees and travel expenses from Merck; personal fees from Eli Lilly and Co, Exelixis, Pfizer, Novartis, and Armo Biosciences outside the submitted work. Dr Maher reported currently working at DataRevive and being employed by the Food and Drug Administration during preparation of this manuscript. Dr Plimack reported receiving personal fees from Acceleron, AstraZeneca, Bristol-Myers Squibb, Clovis, Dendreon, Exelexis, Genentech/Roche, Horizon Pharma, Inovio, Merck, Novartis, Pfizer, Synergene, Eli Lilly and Co; receiving grants from Acceleron, Aveo, Bristol-Myers Squibb, Eli Lilly and Co, Merck, Peloton, and Pfizer outside the submitted work; conducting institutional and personal research for Analysis Group, AstraZeneca, Alexion, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc, Exelixis, Ipsen, Tracon, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Eli Lilly and Co, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Calithera, Sanofi, and Takeda; receiving honoraria from Analysis Group, AstraZeneca, Alexion, Sanofi, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc, Exelixis, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Heron Therapeutics, Eli Lilly and Co, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, National Comprehensive Cancer Network (NCCN), Analysis Group, Michael J. Hennessy Associates Inc, L-path, Kidney Cancer Journal, Clinical Care Options, Platform Q, Navinata Healthcare, Harborside Press, American Society of Medical Oncology, *New England Journal of Medicine*, and *Lancet Oncology*; filling a consulting or advisory role for Analysis Group, AstraZeneca, Alexion, Sanofi, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc, Exelixis, Genentech, Heron Therapeutics, Eli Lilly and Co, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, and NCCN; serving in leadership or membership roles at Dana-Farber Cancer Institute, NCCN Kidney Panel, GU Steering Committee, Kidney Cancer Association Medical and Scientific Steering Committee; holding International Patent Application No. PCT/US2018/12209 (PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response, filed January 3, 2018; claiming priority to US Provisional Patent Application No. 62/445,094, filed January 11, 2017) and International Patent Application No. PCT/US2018/058430 (Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy, filed October 31, 2018; claiming priority to US Provisional Patent Application No. 62/581,175, filed November 3, 2017); and receiving medical writing and editorial assistance support from communications companies funded by pharmaceutical companies. Dr Choueiri reported receiving research support (institutional and personal) from AstraZeneca, Alexion, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Ipsen, Tracon, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Eli Lilly and Co, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Calithera, Analysis Group, Sanofi, Takeda, the National Cancer Institute, the National Institutes of Health, and the Department of Defense; honoraria from AstraZeneca, Alexion, Sanofi, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, Michael J. Hennessy Associates Inc, Research to Practice, L-path, Kidney Cancer Journal, Clinical Care Options, Platform Q, Navinata Healthcare, Harborside Press, American Society of Medical Oncology, *New England Journal of Medicine*, *Lancet Oncology*, Heron Therapeutics, Eli Lilly and Co, the American Society of Clinical Oncology, and the European Society for Medical Oncology; consulting or advisory compensation for AstraZeneca, Alexion, Sanofi, Bayer, Bristol Myers-Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Heron Therapeutics, Eli Lilly and Co, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, NCCN, Analysis Group, Pionyr, and Tempest; stock ownership in Pionyr and Tempest; present or past leadership roles including Director of GU Oncology Division at Dana-Farber

Cancer Institute and past president of medical staff at Dana-Farber Cancer Institute, member of NCCN Kidney panel and the GU Steering Committee, and past chairman of the Kidney Cancer Association Medical and Scientific Steering Committee; holding International Patent Application No. PCT/US2018/12209 (PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response), filed January 3, 2018, claiming priority to US Provisional Patent Application No. 62/445,094, filed January 11, 2017, and International Patent Application No. PCT/US2018/058430 (Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy), filed October 31, 2018, claiming priority to US Provisional Patent Application No. 62/581,175, filed November 3, 2017; and mentoring several non-US citizens on research projects with potential funding (in part) from non-US sources or foreign components outside the submitted work. Dr Uzzo reported receiving personal fees from Pfizer, funding for investigator-initiated trials from Novartis and Genentech, and personal fees from Janssen outside the submitted work. No other disclosures were reported.

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Box.

Considerations in Obtaining a Biopsy to Test for Residual or Recurrent Disease

- Biopsy remains the standard for determining tumor recurrence.
- Proper patient selection as well as pre- and postprocedural management are paramount to optimizing patient experience, maximizing tissue yield, and minimizing risk.[30]
- Trials should use practices consistent with national medical society practice guidelines that specifically address tissue biopsy. Both the Society of Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe have published standards-of-practice guidelines for percutaneous needle biopsy.[30,31]
- Quality improvement thresholds for biopsy success and complication rates are available and can serve as benchmarks31 and enable biopsy risk to be categorized by location. The benchmarks, in turn, can guide the optimization of patient selection and management, especially with respect to coagulation status and hemostasis.[31–33]
- With continued improvements in technology, new tools are now available for biopsy of lesions that are difficult to distinguish or are radiologically occult with standard imaging modalities.[34]
- Coaxial devices may decrease the risk of tract seeding of tumor cells, but they have not been shown to have an improved safety profile.[30,35]
- Although numerous factors are associated with biopsy success and complication rates, fine needle aspiration alone has been shown to have a lower diagnostic tissue yield, sensitivity, and accuracy as well as higher diagnostic failure rate compared with core needle biopsy.[36,37]

Table 1.

Summary of Workshop Discussion on the Conduct of Adjuvant RCC Therapy Trials

Section	Workshop Discussion
Patient/Disease Characteristics	
Histologic subtypes	• Enrollment of patients with non-clear cell RCC is encouraged, preferably in an independent cohort.
Stage	• T3–4, N+M0, and microscopic R1 RCC tumors have a high risk of recurrence, and patients with these tumors consequently may gain the greatest advantage from adjuvant therapy.
Renal function	• Patients with renal insufficiency need not be excluded from adjuvant RCC therapy trials if the study agents are not renally metabolized. • Differences in renal function may require attention during survival analysis.
Surgical considerations	• Patients undergoing radical or partial nephrectomy should be equally eligible. • Adjuvant trial eligibility and interpretation should account for potential differences in recurrence rates between higher- and lower-risk disease. • Patients with microscopically positive soft tissue or vascular margins without gross residual disease can be included in adjuvant trials, and the possibility of worse clinical outcomes in this group may be taken into account during trial design and interpretation. • The preferred type of lymph node dissection is not clear; however, all suspicious regional lymph nodes should be fully resected for accurate staging, with the goal of rendering the patient macroscopically R0.
Timing of adjuvant therapy	• Adjuvant therapy can be initiated as soon as the patient recovers from the surgical procedure and can be initiated up to 16 weeks after the procedure.
Duration of adjuvant therapy	• The appropriate length of therapy in adjuvant clinical trials of RCC is currently unknown.
Radiologic Considerations	
Principles of radiologic imaging	• Chest CT should be done before the surgical procedure for clinically high-risk patients and is favored over chest radiography, because evidence demonstrates that chest radiography is less sensitive in detecting pulmonary primary/metastatic disease compared with chest CT.[2–4] • Patients should have CT imaging of the chest, abdomen, and pelvis within 4 weeks before entering an adjuvant trial. • If patients cannot receive CT imaging with contrast, they should undergo noncontrast CT of the chest and MRI of the abdomen and pelvis with gadolinium.
Documentation of serial imaging	• Archiving of each patient's previous imaging scans should be undertaken. As many examination results as possible should be archived, including reports and a clinical history documenting any previous acute and chronic diseases as well as previous operations and interventions. • Trials should adhere to image acquisition, display, and interpretation techniques as advised by QIBA.[5]
Defining radiologic eligibility for an adjuvant RCC therapy trial and radiologic recurrence	• Biopsy should be done, when safe and feasible, to determine whether malignant disease is present. • Trials should implement common thresholds in the radiologic assessment of patients for trial eligibility and progression of disease (Table 2).
Considerations in obtaining biopsy	• Biopsy should be undertaken after discussion in a multidisciplinary setting with an interventional radiologist. Further biopsy considerations are listed in the Box.
Defining date of recurrence	• Noting the date when the prespecified size criteria for metastatic lesions are met is the most consistent method for determining the date of recurrence in the absence of histologic confirmation, and backdating introduces inconsistency. However, this method lacks temporal accuracy as to the development of recurrent disease. No agreement exists on which method to use, but whichever method is used should be applied consistently and accurately throughout the trial.
Managing New Second Primary Tumors in Contralateral or Ipsilateral Kidney After Partial Nephrectomy	
Second primary tumors as treatment failure	• Whether these lesions constitute a progression event owing to the failure of adjuvant therapy to control disease or are a reflection of multifocality requires more evidence generation.
Patient Perspectives	
Biopsy	• Biopsies solely for research purposes should be carefully balanced with the best interests of the patient.
Placebo	• Trial designs that eliminate placebo, more heavily weight the observation group with action or an active agent, or allow crossover when justified by trial data are preferred by patients.
Blinding	• Patients agree to blinding; however, unblinding is generally warranted for disease progression and certain toxic effects requiring a specific intervention.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; QIBA, Quantitative Imaging Biomarkers Alliance; RCC, renal cell carcinoma.

Table 2.

Radiologic Considerations for Evaluating Patient Eligibility During Initial Evaluation and Unequivocal Radiologic Recurrence During Adjuvant Trial Imaging Surveillance

Anatomic Location	Site-Specific Considerations	Initial Evaluation: Findings Warranting Customized Radiologic Workup, Repeat Radiologic Evaluation, or Biopsy Before Enrollment	Adjuvant Trial Surveillance: Findings Qualifying as Unequivocal Radiologic Disease Recurrence	Additional Workshop Discussion Points
Lung	• In RCC, 45% of metastases are to the lung, presenting as multiple nodules in 75% of cases and less commonly as a solitary lesion.[41,42] • Nodules <1.0 cm in diameter are less likely to be metastatic.[43] • Micronodules can be a form of metastasis if other potential explanations of a miliary pattern, such as tuberculosis and fungal infections, are ruled out.	Indeterminate pulmonary nodule ≥1.0 cm in the long axis	• New nodule ≥1.0 cm that was absent on initial evaluation • Preexisting nodule: (1) If <1.0 cm in previous examination, >50% growth in the long axis on 2 consecutive examinations with ≥5 mm absolute increase, or (2) if ≥1.0 cm in previous examination, >50% growth in the long axis on a single examination • Multifocal nodules measuring <1.0 cm that demonstrate geographic distribution or radiologic/metabolic features pathognomonic for metastatic disease	Guidelines, such as those published by the Fleischner Society[44] and the American College of Radiology Incidental Findings Committee,[45] should be reviewed and may be helpful when retrospectively evaluating indeterminate lesions on images acquired before the initial evaluation for trial, with the understanding that these guidelines were designed with the assumption that the patient has no underlying malignant neoplasm.
Lymph nodes	• In RCC, lymph nodes are the second most common site of metastasis.[46] • Increasing size and nonhomogenous enhancement is suspicious for tumor involvement.	Lymph node ≥1.0 cm in the short axis	• New lymph node ≥1.0 cm that was absent on initial evaluation • Preexisting lymph node: (1) If <1.0 cm in previous examination, >50% growth in the short axis on 2 consecutive examinations with ≥5 mm absolute increase, or (2) if ≥1.0 cm in previous examination, >50% growth in the short axis on a single examination	• Lymph nodes ≥1.0 cm, but <1.5 cm inthe short axis are suspicious. However, they can be difficult to interpret and may not be convincing enough to call recurrence on imaging alone. • Lymph nodes ≥1.5 cm in the short axis are highly suspicious for malignant disease involvement, especiallywhen exhibiting growth on multiple scans.
Liver	• Liver metastasis is seen in 20% of patients with metastatic RCC.[41] • Characteristically benign lesions, such as hemangiomas and focal perfusion variations, should be excluded. • Metastatic liver lesions are usually hypervascular, occasionally with central necrosis (hypodense with peripheral enhancement).[46]	Indeterminate lesion ≥1.0 cm in the long axis	• New lesion ≥1.0 cm that was absent on initial evaluation • Preexisting lesion: (1) If <1.0 cm in previous examination, >50% growth in the long axis on 2 consecutive examinations with ≥5 mm absolute increase, or (2) if ≥1.0 cm in previous examination, >50% growth in the long axis on a single examination • Multifocal lesions measuring <1.0 cm that demonstrate geographic distribution or radiologic/metabolic features pathognomonic for metastatic disease	Any new enhancing lesions, even those <1.0 cm, are considered suspicious.
Other solid visceral organs (including spleen, pancreas, and adrenal glands) and peritoneum,	• Peritoneal and retroperitoneal metastases account for 7% of RCC metastasis.[41] • Lesions may appear as enhancing nodules/ masses with or without central necrosis.[47]	Indeterminate lesion ≥1.0 cm in the long axis	• New lesion ≥1.0 cm that was absent on initial evaluation • Preexisting lesion: (1) If <1.0 cm in previous examination, >50% growth in the long axis on 2 consecutive examinations with ≥5 mm absolute increase, or (2) if ≥1.0 cm in previous examination, >50% growth in the long axis on a single examination • Multifocal lesions measuring <1.0 cm that demonstrate	Any new and/or enhancing mass in the abdominal/pelvic cavity on CT or MRI is considered suspicious, especially when associated with lymphadenopathy.

JAMA Oncol. Author manuscript; available in PMC 2021 May 17.

Anatomic Location	Site-Specific Considerations	Initial Evaluation: Findings Warranting Customized Radiologic Workup, Repeat Radiologic Evaluation, or Biopsy Before Enrollment	Adjuvant Trial Surveillance: Findings Qualifying as Unequivocal Radiologic Disease Recurrence	Additional Workshop Discussion Points
omentum, or mesentery			geographic distribution or radiologic/metabolic features pathognomonic for metastatic disease	
Tumor resection bed	• Postsurgical enhancement can be seen up to 12 mo after the surgical procedure.[48] • Evaluation of the tumor bed in the arterial phase of a CT scan is helpful to differentiate a hypervascular tumor from postsurgical changes.[49] • More medial growing masses in the surgical bed should also be considered for the possibility of an involved lymph node.	Indeterminate soft tissue lesion of any size	• New lesion ≥1.0 cm that was absent on initial evaluation • Preexisting lesion: (1) If <1.0 cm in previous examination, >50% growth in the long axis on 2 consecutive examinations with ≥5 mm absolute increase, or (2) if ≥1.0 cm in previous examination, >50% growth in the long axis on a single examination	Imaging should be performed >4 weeks after surgical resection to allow for resolution of postsurgical inflammation.
Pleural effusion or ascites	No radiologic study can definitively differentiate between benign and malignant processes. In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.	In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.	In the absence of coexisting nonmalignant clinical disease, indeterminate fluid should be sampled.	In the absence of coexisting nonmalignant clinical disease, indeterminate pleural and ascitic fluid should undergo cytologic evaluation, if safe and feasible.
Bone	Bone metastases account for 30% of metastatic disease in patients with RCC.[41] Bone metastases are most common in the axial skeleton, where they can cause severe pain and morbidity.[46,50]	Indeterminate bone lesion	• New lytic or sclerotic bone lesion that was absent on initial evaluation • Multifocal lesions that demonstrate geographic distribution or radiologic/metabolic features pathognomonic for metastatic disease	Osseous metastases commonly demonstrate nonspecific features on CT images. In the absence of multifocal stereotypical features of osteolytic or osteoblastic metastases, indeterminate lesions should be further evaluated by radiography, MRI, or nuclear medicine imaging.
Brain	Patients with metastatic RCC are at risk for brain metastasis, and any new lesion in the brain noted on imaging is highly suggestive of metastatic disease.	Indeterminate lesion of any size	Anytypical brain or leptomeningeal lesion of any size, particularly a lesion with ringlike enhancement that is hemorrhagic and/or associated with vasogenic edema	Any new brain lesions are considered highly suggestive of brain metastases, and biopsy is not considered necessary to diagnose recurrence in patients with classic radiologic findings of brain metastatic disease.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; RCC, renal cell carcinoma.