EA8191/INDICATE
Phase III Study of Local or Systemic Therapy **IN**tensification **DI**rected by PET in Prostate **CA**ncer Patients with Post-Prosta**TE**ctomy Biochemical Recurrence **(INDICATE)**

EA8191/INDICATE Frequently Asked Questions

Key Topics for Site Investigators and Staff

This document answers frequently asked questions about requirements for EA8191, the INDICATE study; it is not meant to substitute for the protocol. Should you have any additional questions, please email **EA8191team@jimmy.harvard.edu**.

Q1. Does EA support remote consenting procedures?

Yes. Remote consenting may be utilized while participating in EA studies. Due to the current COVID-19 public health emergency, expanded use of remote consenting has been granted by the NCI CIRB. Please refer to item #8 in the below link for a detailed list of the NCI CIRB approved remote consenting procedures:

https://ncicirb.org/announcements/frequently-asked-questions-regarding-covid-19-and-cirb

You can also contact the ECOG-ACRIN audit team with any other related questions at AskEAAudit@ecog-acrin.org.

Q2. Which patients are eligible for this trial?

Prostate cancer patients who are post-prostatectomy with PSA levels of at least 0.2ng/mL if within 12 months of surgery, or at least 0.5ng/mL if > 12 months since surgery—**regardless of surgical pathology findings—**are eligible. These thresholds were selected to help enrich for patients with potential findings on PET, based on current fluciclovine radiotracer performance characteristics. These PSA eligibility thresholds may be adjusted in the future following the availability and addition of more sensitive FDA-approved radiotracers to the protocol. Enrolled patients must have no evidence of metastases on conventional imaging; must be candidates for standard of care salvage therapy (pelvic radiation and short-term androgen deprivation [ADT]); and must have a baseline PET scan performed prior to initiation of salvage therapy.

Q3: Why is the salvage treatment standardized as whole pelvis radiation therapy (WPRT) plus short-term androgen deprivation therapy (ADT) for 6 months?

The study population comprises patients with post-prostatectomy biochemical recurrence and negative conventional imaging who are candidates for curative-intent standard of care (SOC) RT and short-term ADT. The ADT is standardized to 6 months to remove the duration as a confounder. All four arms will thus get the same total duration of ADT, and only the +/- apalutamide aspect will vary

in Arm A vs. Arm B. All patients in Arms C and D will receive apalutamide in recognition of their PET-only findings of extrapelvic disease, despite negative conventional imaging.

Similarly, WPRT is required to avoid the potential confounder of variable RT fields. Preliminary results from the RTOG-0534 (SPPORT) clinical trial (reported ASTRO 2018) demonstrated a failure-free survival benefit with WPRT plus 6 months of ADT in the salvage therapy setting (i.e., post-prostatectomy patients with rising PSA levels). If updated RTOG-0534 results officially report no benefit with WPRT (in contrast to the 2018 abstract), the protocol will revise the SOC to prostate bed RT + 6 months of ADT.

Q4: Who is providing the apalutamide?

Although stated on CTSU that apalutamide is commercial, Janssen is providing the apalutamide, and ordering instructions are in Section 8.1.11 of the protocol. All orders will need to go through the ECOG-ACRIN Drug Team, and institutions should allow up to 3 business days for drug to reach your site once drug has been submitted to the ECOG-ACRIN team; please refer to protocol for full details. If commercial apalutamide is used on this study, it would be considered serious non-compliance.

Q5: When can a patient start apalutamide?

As a suggested guidance, apalutamide should be started within 1 week (+/-) of starting the GnRH agonist, and both can start up to 3 months prior to RT, but no later than the first day of RT. This language will be updated in an upcoming amendment.

Q6. Can a site use any PET/CT scanner to complete PET1 and PET2 ^{18}F-fluciclovine PET/CT scans?

No, the PET1 and PET2 ^{18}F-fluciclovine PET/CT scans must be performed on a PET Body (PTBO) qualified scanner through ACR.

Q7. How does a site qualify a PET/CT scanner?

Scanner qualification requirements and directions are outlined in the EA8191 Site Imaging Manual. The EA8191 Site Imaging Manual is located on the EA8191 CTSU page under the *Documents/Miscellaneous* tab.

Q8: If a patient has a PET/CT from another site on an unqualified scanner, can the scan be used for the PET1 timepoint if it is within 12 weeks of Step 0 registration?

The PET/CT scan from another site can be used, as long as it was performed on an ACR PTBO-qualified scanner. If the scan was not completed on an ACR PTBO-qualified scanner, a new PET/CT scan will require completion on one. Patients completing the PET2 scan must have the scan performed on the same scanner as PET1. PET scans from ACR PTBO-qualified scanners done prior to Step 0 Registration can be used if performed within 12 weeks of Step 0 Registration.

Q9: Are there training requirements for the interpreting radiologists/nuclear medicine physicians reviewing PET1 and PET2 ^{18}F- Fluciclovine scans?

Yes! All radiologists/nuclear medicine physicians reviewing PET1 and PET2 scans utilizing ^{18}F-fluciclovine must complete the Society of Nuclear Medicine and Molecular Imaging on Interpretation (SNMMI) Training with Axumin™. You can access the training (free recorded webinar and post-assessment) here: https://www.snmmilearningcenter.org/Activity/4521746/Detail.aspx.

Upon successful completion, the training certificate must be uploaded to the CTSU for site approval of EA8191. See protocol Section 4.0, Protocol Specific Requirements, for how to upload all training certificates to the CTSU.

During audit as part of the regulatory compliance review, ECOG-ACRIN will review all training certificates of radiologists reviewing PET1 and PET2 scans on this trial.

Q10: How will images be submitted for EA8191?

All imaging must be submitted through TRIAD, ACR's image exchange application. TRIAD provides sites a secure method to transmit DICOM RT, DICOM formatted image files, and other objects. Section 4.5 of the protocol outlines TRIAD installation instructions.

Any staff submitting images through TRIAD will need to be registered with CTEP, have a valid and active CTEP-IAM account, and be registered as an A, AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures in Section 4 for instructions on how to request a CTEP-IAM account and complete registration in RCR.

Q11: Can a site perform imaging with another radiotracer outside of ^{18}F-fluciclovine (Axumin™)?

As of the date of this FAQ, ^{18}F-fluciclovine (Axumin™) is the only FDA-approved radiotracer for prostate cancer that is an established PET agent widely available for a multicenter trial, and thus is the only one used on this trial for now. As other radiotracers (e.g., PSMA-based) receive FDA approval and become commercially available for distribution, the study team will evaluate them for inclusion in the trial, as the findings are intended to be agnostic of the PET tracer. For a given patient, PET1 and PET2 scans must be completed with the same radiotracer.

Q12: Are the PET/CT scans covered by the study?

The baseline PET (PET1) is considered standard of care, and the scan and ^{18}F-fluciclovine (Axumin™) should be billed to the patient or patient's insurance. The PET2 scan (Arms C & D only) is considered research and thus the PET2 PET/CT scan will be reimbursed at $1500 to your site; you will order ^{18}F-fluciclovine (Axumin™) through ECOG-ACRIN and PETNET (directions included in the protocol section 8.2.8).

Q13: Why are Arms C and D receiving a second PET?

As required for study eligibility, the patients in Arms C and D have negative conventional imaging (CIM) but evidence of extrapelvic metastases on PET. There may be a subgroup of these patients who have a more aggressive natural history, closer to that seen with CIM-positive patients. Performing a second PET at the 12-month time point after completion of the assigned systemic therapy (or sooner in the event of early PSA progression) will allow for post-therapy response assessment and the opportunity for treating physicians to intervene in a timely fashion if evidence of disease progression on the second PET. Assessment of PET2 will be performed as a secondary objective to address the research questions regarding patterns of progression and response in patients with extrapelvic PET-positive metastatic disease.

Q14: Are the clinical imaging modality (CIM) time points outlined in Section 7.7 billable to insurance?

For all patients in whom PSA progression is confirmed, restaging CIM will be performed within 6 weeks of the most recent PSA value (section 6.1)*. Routine clinical imaging may be continued every 6 months as long as there is a documented clinical indication.
*PSA progression (section 6.1) - *PSA progression is defined as a PSA level that is ≥0.5 ng/mL higher than the nadir value and confirmed on a second PSA test, with the second value being equal to or higher than the first.*