

Document title: **Independent Review Charter:
PET Methodology Extracted**

Document version: **Final**

Trial sponsor: **Abraxis BioScience, LLC, a wholly-owned
subsidiary of Celgene Corporation**

Protocol identifier: **CA046**

Protocol description: A randomized phase III study of weekly ABI-007 plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas

1 Image Acquisition and Collection

Patients enrolled in the CA046 trial protocol¹ will undergo radiological imaging studies for tumor assessment according to the visit schedule specified in the trial

protocol. All radiographic images performed for tumor assessment will be submitted to the imaging vendor, including CT (use of triphasic CT of the abdomen is strongly recommended), MRI, and ^{18}F -FDG-PET (for a target total of approximately 200 subjects). The imaging vendor firmly advises sites to ensure consistency in modality, patient positioning, scanning parameters, and PET scanner usage per patient across time points.

Note: If PET/CT imaging equipment is adequate, CT from PET/CT can replace diagnostic CT (first, low-dose CT for PET attenuation correction/registration will be performed, then higher dose contrast-enhanced CT will be performed in same scanner for diagnostic quality). When this is done, CT data must be encoded twice.

1.1 Imaging Manual and Data Transmittal

The imaging vendor authors and disperses to the investigational sites a modality-specific ^{18}F -FDG-PET Imaging Manual and a Radiology Imaging Manual approved by the trial sponsor that includes the following:

- Complete instructions for image acquisition, documentation according to GCP, query resolution, archiving, and shipment of image data to the imaging vendor.
- Imaging Data Transmittal Forms (DTFs).
- Pre-addressed courier labels.
- Study labels for the digital and film media.
- Complete contact information.
- A web portal may be used to upload images utilizing an electronic DTF.

1.1.1 Data Transmittal Forms

The imaging vendor designs a modality-specific 2-part DTFs to accompany the image data with each subject at each time point delivered. Sites are required to enter minimal, essential information on these forms. Typical information recorded on a DTF includes subject information, imaging site information, anatomical areas imaged, basic imaging parameters applied, and any variations from established imaging protocols and type of archival media. DTFs are located within the provided Imaging Manuals.

1.1.2 Image Acquisition Parameters

Appendix B: Image Acquisition outlines the Image Acquisition Parameters provided in the Imaging Manuals for radiology and PET imaging. Any re-versioning of the Imaging Manuals will not be an immediate cause for updating the Independent Review Charter, unless substantive changes affect the scope of the Independent Review protocol. During each successive imaging session, every effort will be made to replicate baseline imaging anatomies and techniques in order to characterize with consistency each reported lesion. All scans will be performed according to protocol

using a standardized acquisition plan, as outlined in the Imaging Manuals supplied to the study centers (sites).

1.1.3 Site Training

The imaging vendor provides site-training via teleconference covering all aspects of each Imaging Manuals' content. Training sessions are documented according to standard operating procedures (SOPs) and updates will be provided via bi-weekly reports. Within the Imaging Manuals and during Site Training teleconferences, sites are instructed to ensure consistency of techniques across time points, stressing that the following types of quality checks are ensured:

- Consistent anatomical coverage across time points.
- Proper and consistent patient positioning, eg, supine position with arms extended above head.
- Correct and consistent radiologic parameters used at all time points, ie, slice thickness, spacing, views, sequences, and plane acquired. **Note:** The imaging vendor recommends that sites use fields of view (FOV) that accommodate individual body habitus.
- Consistent contrast injection dose, method, speed, and timing.
- Correct and consistent ^{18}F -FDG-PET parameters at all required time points, ie, scanner, dose, uptake time, and acquisition and reconstruction parameters.
- Images checked and archiving success checked prior to releasing the patient.

The imaging vendor will perform site retraining for new staff and equipment if Abraxis BioScience requests and notifies the imaging vendor of such changes. **Note:** Training on the PET requirements will only be conducted at sites participating in the PET portion of the protocol.

1.2 Protocol Imaging

1.2.1 Radiology

For this trial, contrast-enhanced CT (use of triphasic abdominal CT is strongly recommended) is the preferred imaging modality for use in evaluating clinical efficacy. CT/MRI should be performed per site standard of care. The same mode of imaging must be used throughout the study.

Unless intravenous (IV) contrast is contraindicated (eg, due to contrast sensitivity or renal insufficiency), contrast media must be used for CT and MRI. Throughout the duration of the study, the same mode of imaging, anatomical coverage, patient positioning, techniques, contrast usage, and timing employed at baseline must be repeated at each visit. Consistency of modality and contrast use is integral for accurate and reliable review. An exception may be made for patients in whom intravenous CT contrast is contraindicated. In such a case, contrast-enhanced MRI

of the abdomen and pelvis may be performed, thereby superseding CT with the exception of the chest, for which unenhanced CT is acquired. This combination of imaging modalities is acceptable in order to provide the highest sensitivity and specificity.

1.2.1.1 Scheduled Imaging

Per protocol, anatomical coverage including the chest, abdomen, and pelvis will be imaged by CT, and MRI as needed, at baseline, Cycle 1 day 1 (within 14 days prior to Cycle 1 Day 1). Thereafter imaging will be done every 8 weeks (at any time during that week) and at end of study (if required per the defined study imaging schedule).

1.2.1.2 Unscheduled Imaging

In order to confirm objective response, an unscheduled CT scan will be allowed 4 weeks (a minimum of 28 days) from the initial documented complete or partial response. For such patients, all subsequent CT scans should return to the original schedule performed every 8 weeks starting from the date of first dose of study therapy. An unscheduled CT scan for suspected progression may be performed at any time.

1.2.2 ¹⁸F-FDG-PET

¹⁸F-FDG-PET will be performed to obtain standard uptake values (SUVs). Imaging will be performed at baseline (after randomization, within 14 days prior to Cycle 1 Day 1). PET scans will be performed every 8 weeks up to Week 16. The original target total (200 patients who have had 2 ¹⁸F-FDG-PET evaluations and who have completed a minimum of 16 weeks of treatment) according to the following parameters:

- ¹⁸F-FDG-PET scans will be obtained at baseline for patients enrolled prior to the date that Amendment X of the protocol was implemented.
- Follow-up ¹⁸F-FDG-PET scans will be obtained for patients who have obtained a baseline ¹⁸F-FDG-PET scan and are still actively receiving treatment.
- Follow-up ¹⁸F-FDG-PET scans for active patients will be obtained up to Week 16, but no further ¹⁸F-FDG-PET scans will be obtained after Week 16.

Patients who have had at least 2 PET evaluations (imaging at baseline and Week 8 at a minimum) will be included in the Independent Review. The area of coverage will be from the mid-thigh to the base of the skull. Accurate FDG injection and scan times, as well as weight height, and fasting time, must be recorded. Times and dose must be established at baseline; thereafter, there must be less than 10% deviation in comparison to baseline values.

1.2.3 Post-Study Follow-up for Disease Progression

Patients who are discontinued from treatment in the absence of disease progression (eg, patients removed for unacceptable toxicity or patient/investigator discretion) will undergo repeat imaging (CT/MRI) and tumor response assessments every 8 weeks

(at any time during that week), regardless of regimen, until disease progression is documented. It is recommended that subsequent therapy not be instituted until disease progression is documented. **Note:** For patients randomized to ABI-007 plus gemcitabine, if ABI-007 is discontinued but gemcitabine is continued, this should be considered as continuation of the study regimen and imaging should continue. If the imaging vendor receives images acquired after the patient received subsequent therapy, the tumor assessment Independent Review will still be conducted until progression is noted on site.

1.3 Off-Protocol Imaging

If sites submit image data outside of the scope of the protocol-specified imaging described above, the imaging vendor will log-in, encode, and perform nominal quality control (QC) to document receipt of the image data. The imaging vendor will not present these images for independent review unless otherwise instructed by Abraxis BioScience during data reconciliation. **Note:** Ultrasound is not an acceptable imaging modality for this trial.

2 Image Data Receipt, Tracking, and Quality Control

The imaging vendor works directly with each investigational center (site), the trial sponsor, and its associates to manage the collection of all subject image data through completion of this trial. Sites will acquire all images in accordance with the trial protocol and will submit them to the imaging vendor for quality assurance, standardization, assignment of a random number, and subject de-identification prior to independent review. The imaging vendor requires that each site deliver to the imaging vendor all original digital imaging data for each subject at each visit. A completed DTF must accompany each data transfer.

2.1 Quality Control Data Checks

According to general procedures and protocol-specific requirements for each anticipated imaging modality, QC encompasses the following items that require verification:

- Correlation of patient identity between image data, DTF, and enrollment information.
- Compliance and consistency with imaging requirements, eg, missing time points, anatomy and sequences.
- Proper documentation.

- Technical quality of CT/MRI.
 - Proper depiction of the anatomy of interest.
 - Patient motion.
 - Patient positioning.
 - Proper signal-to-noise ratio.
 - Proper slice thickness (ie, ≤ 5 -8 mm [preferably under 5] for spiral CT and ≤ 10 mm for conventional CT, and consistent for each time point).
 - Proper use of intravenous and oral contrast medium.
 - Measurement scale included on each image for hardcopy films.
 - Consistent parameters between visits.
- Technical quality compliance with ^{18}F -FDG-PET requirements.
 - Complete coverage and required views.
 - Missing images or time point datasets.
 - Radiopharmaceutical use within range.
 - Uptake time within range.
 - Proper acquisition and reconstruction parameters.
 - Use of same scanner and consistent parameters across visits.
- Submission quality compliance with the use of film for archiving (CT/MR only)
 - Measurement scale included on each image for hardcopy films.
 - Proper window level/width and acceptable print quality for hard copy films.
 - Consistent filming format between visits.
- from disease at baseline are missing at a subsequent time point, the response assessment will be based on the available scans of other regions.

3 ¹⁸F-FDG-PET Functional Review Design and Methodology

3.1 Purpose

¹⁸F-FDG-PET studies will be performed to evaluate functional tumor response, determine SUV at baseline, and evaluate for correlation between objective tumor response based on CT scans (using RECIST criteria)² and functional tumor response based on ¹⁸F-FDG-PET scans (using EORTC criteria)³.

3.2 Review Paradigm

For the ¹⁸F-FDG-PET review component of the IRC, 1 nuclear medicine physician or radiologist specializing in nuclear medicine will separately review an individual's subject data sequentially by time point.

3.3 Review Population

¹⁸F-FDG-PET scans will be performed per the defined study imaging schedule for a target of 200 patients. The patients must have undergone at least 2 PET evaluations (at baseline and at Week 8 at a minimum) to be included in the blinded central image review using the EORTC criteria.

3.4 eCRF for ¹⁸F-FDG-PET

For training and actual trial subject image analysis, the Independent Reviewer will employ an eCRF.

The configuration of electronic systems used by the Reviewer will consist of a nuclear-medicine-specific data display system and the same data capture system used for the radiology review. Assessment of ¹⁸F-FDG-PET data will be facilitated by the system; however, ¹⁸F-FDG-PET images will be archived to nuclear-medicine-specific image review software prior to the start of a given read session and the Reviewer will manually select the images for review. The imaging vendors review system will create the eCRF import list to drive the review. The eCRF will work in conjunction with the nuclear-medicine-specific software to allow access to the derived values.

3.5 Handling Unavailable or Inadequate Image Data

If an entire dataset was not submitted that was required according to the tumor evaluation schedule within the protocol, a "black screen" will announce the missing data and the Reviewer will be instructed to enter an overall image quality rating of "Not Readable" and provide an overall assessment of UE.

3.6 Patient Data Available to the Reviewer

The eCRF will provide the Reviewer access to patient data pertinent to the ^{18}F -FDG-PET analysis. Subject demographic and clinical data presented will include: subject height and weight, lean body mass (LBM—calculated for gender), injection time, scan start time, net injected activity (MBq), and glucose concentration level at time of injection.

3.7 Functional Evaluation of Baseline Data

Functional evaluation of ^{18}F -FDG-PET baseline images will be conducted in accordance to the EORTC ^{18}F -FDG-PET study guidelines. SUVs will be calculated from ROIs drawn around lesions that have been identified by the Reviewer. The Reviewer will select up to a maximum of 5 representative lesions in accordance with the parameters set forth by the protocol and procedures developed.

The Reviewer's interpretation and values measured will be reported on the eCRF, which will be programmed based on the SRS to adhere to the requirements of the protocol and the EORTC guidelines. After reviewing and approving all baseline evaluation entries recorded on the eCRF, the Reviewer will lock the data. The Reviewer will evaluate follow up images for the same subject following the same methodology used for the baseline evaluation.

SUVs are derived from the ROI in accordance to EORTC guidelines. The exact outlining and placement of the ROI has a major effect on the derived value. In order to ensure the highest level of accuracy and reproducibility in establishing tumor volumes, the Reviewer will be trained in using the steps and guidelines detailed below to evaluate the target lesions.

3.7.1 Tumor Identification

Each identified lesion will be documented and tracked with a lesion number, with a maximum of 5 lesions being identified. The Reviewer may select lesions that have a tumor-to-background ratio (TBR) of $\geq 2:1$. The Reviewer will be instructed to select the ^{18}F -FDG-PET slice with the greatest amount of ^{18}F -FDG accumulation for the placement of the ROI. An ROI will be centered around the highest concentration of ^{18}F -FDG accumulation in the identified lesion; the region of highest concentration represents viable tumor. The exact position of the hot spot identified at baseline will not necessarily be the same in the follow-up time point. At subsequent visits the most intense area may be in a different location within the lesion. Additionally, background uptake values for normal muscle tissue of the thigh will be reported as $_{\text{LBM}}\text{SUV}_{\text{avg}}$, and will be utilized in the tumor to background analysis, the background regions must be ≥ 20 mm in the longest dimension.

3.7.2 Standard Uptake Value Evaluation

The SUV is defined by tumor activity per dose injected per body mass.

A TBR will be calculated for each individual lesion using the tumor ${}_{LBM}SUV_{max}$ and the background average ${}_{LBM}SUV_{avg}$.

It is suggested that the computed SUV_{max} be corrected using LBM because the lean body tissue appears to more closely represent the distribution volume of the ${}^{18}F$ -FDG. LBM (L: kg) can be estimated from height (H: cm) and weight (W: kg) and for gender where⁴:

for men:

$$L = 1.10 W - 128 \left(\frac{W}{H} \right)^2$$

and for women:

$$L = 1.07 W - 148 \left(\frac{W}{H} \right)^2$$

The Reviewer is expected to choose only those lesions that have a TBR of approximately 2:1 or greater. Training will be provided in selecting the region within the lesion with the greatest accumulation of ${}^{18}F$ -FDG and in drawing an appropriate ROI. If a subject only has lesions at baseline with a TBR of less than approximately 2:1, they will be considered non-evaluable. The exact position of the area of greatest accumulation of ${}^{18}F$ -FDG does not have to be the same in the baseline study as in the follow-up studies; the most intense area may be in a different location within the lesion at the subsequent visits.

The ${}_{LBM}SUV_{avg}$ (or total tumor uptake) is derived from the ROI drawn around the entire lesion volume. This method of evaluation gives an average value of the ${}^{18}F$ -FDG accumulation within the lesion but may not accurately represent the actual metabolic activity of the lesion. A lesion may be made up of various tissue types that have varying affinities for ${}^{18}F$ -FDG accumulation.⁵

3.7.3 Evaluation of Subsequent Visit Data

Following completion of the baseline evaluation, images from the follow-up imaging visit will be presented to the Reviewer in coordination with the eCRF. The Reviewer will proceed by using methods consistent with the baseline capture of TBRs. The lesions selected at baseline will pre-populate the eCRF screen for the time point. For each existing area of interest, the Reviewer will record updated SUV_{max} and ${}_{LBM}SUV_{max}$ values. The highest concentration of ${}^{18}F$ -FDG in a lesion may be in a different location in the follow up images; therefore, the placement of the ROI on the lesion may be different from baseline to the follow up images. The ${}_{LBM}SUV_{avg}$ values will be derived and recorded as well for each lesion and for the background normal muscle tissue of the thigh.

If New lesions appear at any timepoint post baseline, the Reviewer will be able to include up to 2 individual new incidences of disease on the lesion table and provide the corresponding SUV values; they will be identified in the database as the appearance of new disease and should elicit the categorization of progressive metabolic disease (PMD).

Upon the basis of the EORTC criteria for determining response level according to the relative change of the summed $_{lbm}SUV_{max}$ over time, the eCRF will auto-calculate the corresponding response-level at the follow up time point.

The Reviewer must provide any required or voluntary comments and the chosen time point response level before committing the case to the database by entering his or her electronic signature.

3.7.4 Assignment of Functional Response Level

Table 5 indicates parameters based on the EORTC ^{18}F -FDG-PET criteria to evaluate functional tumor response levels utilizing $_{LBM}SUV_{max}$.

3.7.5 Summary Page

The eCRF will produce a summary page upon the completion of all available time point data. Response levels assigned previously will populate the lesion table (the Reviewer will have the option to provide a comment).

Table 1: EORTC Response Criteria for ^{18}F -FDG-PET

Response Level	Description
Complete Response (CR)	Complete resolution of ^{18}F -FDG uptake within the tumor volume so that it is indistinguishable from surrounding normal tissue.
Partial Response (PR)	A reduction of a minimum of 15-25% in tumor ^{18}F -FDG SUV after 1 cycle of chemotherapy (after 51 days on-study), and > 25% after more than 1 treatment cycle. (A reduction in the extent of the tumor ^{18}F -FDG uptake is not a requirement for PR.)
Stable Disease (SD)	An increase in tumor ^{18}F -FDG SUV of < 25% or a decrease of < 15% after 1 cycle of chemotherapy and < 25% after more than 1 treatment cycle and no visible increase in extent of ^{18}F -FDG tumor uptake. (Neither PD, PR, or CR)
Progressive Disease (PD)	An increase in ^{18}F -FDG tumor SUV of > 25% within the tumor region defined on the baseline scan, or the appearance of new ^{18}F -FDG uptake in metastatic lesions. ^{18}F -FDT-PET scans will not be used as a criterion for patient withdrawal from the study. Only CT scans or MRI will be used for this purpose.

Response Level	Description
Unable to Evaluate (UE)	A lesion present at baseline that was not assessed or that was not evaluable, leading to an inability by the Reviewer to determine the status of that particular tumor for the time point in question. If the SUV cannot be determined at a time point, and the rules for PD do not apply, a response of CR, PR, or SD cannot be assigned for that time point and the time point response will be UE.

4 References

¹ Abraxis BioScience, LLP. Protocol CA046: *A Randomized Phase III Study of Weekly ABI-007 plus Gemcitabine versus Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas*. Amendment 6. 12 December 2011.

² Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. *J Natl Cancer Inst*, 2000;92:205-216

³ Young H, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Euro J Cancer* 1999;35:1773-1782.

⁴ Hallynck TH and Soep HH et al. Should clearance be normalised to body surface or to lean body mass? *Br J Clin Pharmacol* 1981;11:523-526.

⁵ Zasadny KR, Wahl RL. Standardised uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-d-glucose: variations with body weight and a method for correction. *Radiology* 1993;189:847-850.

