PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The [18F]-Fluoroethyl-L-tyrosine (FET) in Glioblastoma (TROG 18.06 FIG) study: protocol for a prospective, multicentre PET/CT trial
AUTHORS	Koh, Eng-Siew; Gan, Hui; Senko, Clare; Francis, Roslyn; Ebert, Martin; Lee, Sze Ting; Lau, Eddie; Khasraw, M; Nowak, Anna; Bailey, Dale; Moffat, Bradford; Fitt, Greg; Hicks, Rodney; Coffey, Robert; Verhaak, Roel; Walsh, Kyle; Barnes, Elizabeth; De Abreu Lourenco, Richard; Rosenthal, Mark; Adda, Lucas; Foroudi, Farshad; Lasocki, Arian; Moore, Alisha; Thomas, Paul; Roach, Paul; Back, Michael; Leonard, Robyn; Scott, Andrew

VERSION 1 – REVIEW

REVIEWER	Tonn, Jörg-Christian University Hospital Munich, Department of Neurosurgery
REVIEW RETURNED	02-Mar-2023

GENERAL COMMENTS	The authors have to be congratulated to set up a large prospective study to evaluate FET-PET in the context of radiation planning and differential diagnosis of recurrent tumor in GBM. One could emphasize a little bit more the issue that tissue based diagnosis of recurrent tumor should be favoured and time to peak (TTP) as an objective parameter describing the slope of the tracer uptake should be used.

REVIEWER	Wang, Qun Chinese Peoples Liberat Army Gen Hosp, Neurosurgery
REVIEW RETURNED	02-Mar-2023

GENERAL COMMENTS	The authors performed a a prospective and multicentre PET/CT trial for [18F]-Fluoroethyl-L-tyrosine (FET) in Glioblastoma (TROG 18.06 FIG) study, and this study are firstly to investigate how the addition of FET-PET versus standard MRI impacts RT volume delineation and secondly to determine the accuracy and management impact of FET-PET in distinguishing pseudoprogression from true tumour progression and/or tumour recurrence. The manuscript is well written. And the study involved about 10 sites centers in Australia. This manuscript could be considered for publishing. 1. As a protocol study, the study design and methodology is very important, the study registration number were listed in the Registration section. That's good.

	2. For the appendices, PET device information and the including sequences in different centers should be clarified as a imaging study.

REVIEWER	Eisenstat, David University of Alberta, Oncology
REVIEW RETURNED	13-Mar-2023

GENERAL COMMENTS	Koh et el present the TROG 18.06 FIG Study protocol, a prospective, multi-centre PET/CT trial investigating FET (18F-fluoroethyl-L-tyrosine) in newly diagnosed adults with glioblastoma. The trial will be open in 10 sites within Australia. Overall, the protocol and accompanying manuscript are well-written and the study hypotheses, aims and objectives are clearly outlined. However, a few revisions are recommended as follows: Comments: 1. The justification for selecting the three time-points (FET-1, FET-2 and FET-3) should be added to the protocol manuscript. For example, what is the potential impact of surgery on timepoint FET-1? of chemoradiation on timepoint FET-2? 2. The accompanying protocol Figure 2 should be added to the protocol manuscript. 3. Although evident in the accompanying protocol, there is no mention of the (optional) FDG-PET at timepoint FET-3 other than under Exploratory Objectives, Page 8, line 59 in one sentence. The timing (i.e. separate days from FET-PET) should be explicitly stated as well as that this study is optional as per each study site's investigator. If FET-PET is potentially going to be incorporated into clinical practice, comparisons to both MRI and FDG-PET will be important considerations. 4. What are the implications, if any, for the pending utilisation of FET-PET combined with MRI versus CT? 5. Please add a brief paragraph in the protocol manuscript regarding the planned Health Economic analyses which are cleared outlined in the accompanying study protocol. Other Concerns: 1. Introduction, Page 5, line 22: Spell out "LAT-1" in full for first use. 2. Line 27: Add "contrast" after "Gadolinium". 3. Primary Aim 2, Page 6, paragraph 3. For the Maurer study, please comment on the relative utility of FET-PET between grades II, III and IV glioma. 4. Secondary Aim, Page 8, Paragraph 1, line 21. As written "FET-PET proved to be the most important parameter for recurrence prediction" is too vague. Please be more specific. 5. Exploratory Aims, Page 8, line 44: Some specific details regarding "multi-omics" should be provided. For example, will you consider DNA methylation to subgroup the GBMs? There is a NATA-accredited test at the VCGS in Melbourne, Australia linked to the Heidelberg brain tumour classifier. 6. Study Interventions, Page 10, paragraph 1, lines 21-22: Delete "1)" after "Group 1 participant" as this is confusing as written. 7. Inclusion Criteria, Page 11, line 33: Add "a" prior to "previous". 8. Patient and Public Involvement, Page 12, line 36: Add "a" prior to "consumer investigator".

	9. Time to event, toxicity and QOL measures, Page 15, line 8: Please provide an example or two of potential suspected reactions to FET, acknowledging that these are relatively uncommon in clinical practice.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Jörg-Christian Tonn, University Hospital Munich
Comments to the Author:
The authors have to be congratulated to set up a large prospective study to evaluate FET-PET in the context of radiation planning and differential diagnosis of recurrent tumor in GBM.
One could emphasize a little bit more the issue that tissue based diagnosis of recurrent tumor should be favoured and time to peak (TTP) as an objective parameter describing the slope of the tracer uptake should be used.
We have clarified the importance of obtaining tissue (when available) after completion of treatment to assist with confirming progression vs pseudoprogression (page 11), and time to peak has been clarified (page 6).

Reviewer: 2

Dr. Qun Wang, Chinese Peoples Liberat Army Gen Hosp
Comments to the Author:
The authors performed a a prospective and multicentre PET/CT trial for [18F]-Fluoroethyl-L-tyrosine (FET) in Glioblastoma (TROG 18.06 FIG) study, and this study are firstly to investigate how the addition of FET-PET versus standard MRI impacts RT volume delineation and secondly to determine the accuracy and management impact of FET-PET in distinguishing pseudoprogression from true tumour progression and/or tumour recurrence. The manuscript is well written. And the study involved about 10 sites centers in Australia. This manuscript could be considered for publishing.

1. As a protocol study, the study design and methodology is very important, the study registration number were listed in the Registration section. That's good.
2. For the appendices, PET device information and the including sequences in different centers should be clarified as a imaging study.
The protocol for PET imaging has been included as Supplementary file 3, and for MRI scans included as Supplementary file 4.

Reviewer: 3
Dr. David Eisenstat, University of Alberta
Comments to the Author:
Koh et el present the TROG 18.06 FIG Study protocol, a prospective, multi-centre PET/CT trial investigating FET (18F-fluoroethyl-L-tyrosine) in newly diagnosed adults with glioblastoma. The trial will be open in 10 sites within Australia.
Overall, the protocol and accompanying manuscript are well-written and the study hypotheses, aims and objectives are clearly outlined.

However, a few revisions are recommended as follows:
Comments:

1. The justification for selecting the three time-points (FET-1, FET-2 and FET-3) should be added to the protocol manuscript. For example, what is the potential impact of surgery on timepoint FET-1? Of chemoradiation on timepoint FET-2?

The timing of surgery in relation to FET-PET1 was designed to be post-operatively, with the time from surgery to adjuvant chemo-radiation commencement within standard clinically acceptable timeframes. FET-PET2 at four weeks post concurrent phase completion is designed to test the impact of chemo-radiation on FET-PET appearance and used for comparison to FET-PET3 for interpretation of possible progression versus pseudoprogression.

The following text has now been included pages 11 of the manuscript.

"The timing of FET-PET1 is aligned with literature establishing the potential role of FET-PET in delineating the extent of residual tumour (12,13). FET-PET2 timing was to establish a baseline after chemo-radiation, and to compare to FET-PET3 which is timed for when clinical suspicion of progression versus pseudoprogression arises."

2. The accompanying protocol Figure 2 should be added to the protocol manuscript.
   Accompanying protocol Figure 2 has now been referred to the manuscript on p5 and renamed Figure 1.
   Study schema has now been renamed as Figure 2.

3. Although evident in the accompanying protocol, there is no mention of the (optional) FDG-PET at timepoint FET-3 other than under Exploratory Objectives, Page 8, line 59 in one sentence. The timing (i.e. separate days from FET-PET) should be explicitly stated as well as that this study is optional as per each study site's investigator. If FET-PET is potentially going to be incorporated into clinical practice, comparisons to both MRI and FDG-PET will be important considerations.

   Further text has been added in page 11 and reads as:

   "At the time of suspected recurrent disease, in addition to FET-PET3 and MRI3, study participants are requested to undergo a FDG-PET scan, which has been made optional, as although a direct comparison of FDG-PET with FET-PET is planned, the study protocol requirements for participants are already quite substantial, with the FET-PET and MRI taking precedence".

4. What are the implications, if any, for the pending utilisation of FET-PET combined with MRI versus CT?

   Current standard of care adjuvant radiation involves MRI-derived target volumes and CT-based planning. The FIG study will establish if FET-PET provides information that impacts on outcomes of patients with glioblastoma at the time of treatment planning for chemo-radiation following initial surgery, and in distinguishing recurrent tumour versus pseudoprogression after chemo-radiation treatment. FET-PET may be complementary to MRI in these clinical scenarios. In future, it is feasible that CT-based radiation planning may become redundant in the setting of MR alone (+/- FET-PET) based treatment planning).

5. Please add a brief paragraph in the protocol manuscript regarding the planned Health Economic analyses which are cleared outlined in the accompanying study protocol.

The text has been updated on p15 to read:

"The cost consequences of incorporating FET-PET imaging in the management of GBM patients will be evaluated by quantifying the resource use associated with these tests. Data will include resource use associated with the delivery and interpretation of FET-PET scans; chemo-radiation and subsequent treatment utilisation. Resource use associated with all multimodal imaging (FET-PET, MRI) as well as radiation therapy treatment plans will be available from trial based CRFs. Data on outpatient and community-based services (pharmaceuticals and medical) will also be collected as well as prescribing data. Additionally, based on 10 of the 15 dimensions of the QLQ-C30, the QLU-C10D is a newly developed, cancer-specific multi-attribute utility instrument (MAUI) included in the EORTC assessment

system and will be used for the health economic evaluations in cost-utility analyses (CUA) relating to FIG trial participants.

Other Concerns:

1. Introduction, Page 5, line 22: Spell out "LAT-1" in full for first use. Text now updated.

2. Line 27: Add "contrast" after "Gadolinium". Text now updated.

3. Primary Aim 2, Page 6, paragraph 3. For the Maurer study, please comment on the relative utility of FET-PET between grades II, III and IV glioma.

The following text has been added to the manuscript, page 6: “The accuracy of FET PET was significantly higher in IDH-wild-type gliomas. The diagnosis based on FET-PET turned out to be incorrect in 33% of the IDH-mutant tumours, but in only 9% of the IDH-wild-type tumours. The F-FET PET rating, the WHO grade, the IDH status, and the Karnofsky performance status remained independent prognostic factors. MGMT promoter methylation did not significantly affect the diagnostic performance of FET PET.”

4. Secondary Aim, Page 8, Paragraph 1, line 21. As written "FET-PET proved to be the most important parameter for recurrence prediction" is too vague. Please be more specific.
This has been addressed with additional text: “The most pronounced correlations were observed for FDG and FET uptake in contrast-enhancing lesions and non-contrast-enhancing lesions. Voxel-wise modelling of recurrence probability resulted in area under the receiver operating characteristic curve of 0.77 from scans prior to therapy.”

5. Exploratory Aims, Page 8, line 44: Some specific details regarding "multi-omics" should be provided. For example, will you consider DNA methylation to subgroup the GBMs? There is a NATA-accredited test at the VCGS in Melbourne, Australia linked to the Heidelberg brain tumour classifier.
   This has been addressed with inclusion of text on page 15.

6. Study Interventions, Page 10, paragraph 1, lines 21-22: Delete "1)" after "Group 1 participant" as this is confusing as written.
   Text now updated.

7. Inclusion Criteria, Page 11, line 33: Add "a" prior to "previous".
   Text now updated.

8. Patient and Public Involvement, Page 12, line 36: Add "a" prior to "consumer investigator". Text now updated.

9. Time to event, toxicity and QOL measures, Page 15, line 8: Please provide an example or two of potential suspected reactions to FET, acknowledging that these are relatively uncommon in clinical practice.
The text has been updated on p15 to read:
“The incidence of significant toxicities is anticipated to be very low, but could include a local reaction at the tracer injection site or minor systemic symptoms.”

Upon submission of the R1 manuscript, the Editorial team have subsequently advised on May 8th, 2023 that Table 3 can be no wider than 9 columns. For this reason, Table 3 has been retained with the final column to the right removed. The contents have been transferred with tracked edits to page 13 under 'Schedule of Assessments' to now read:

"Post progression follow up consists of survival status verification at one year post chemo-radiation completion and 6 monthly thereafter. For those participants proceeding to second surgery, tissue and serum blood biomarkers will be collected".

VERSION 2 – REVIEW

REVIEWER	Eisenstat, David University of Alberta, Oncology
REVIEW RETURNED	28-May-2023

GENERAL COMMENTS	Corresponding author ES Koh, on behalf of the author team, have submitted a comprehensive and detailed response to each of the external peer reviewers comments and concerns. The resubmitted manuscript reflects these revisions and is significantly improved, especially since it is a study protocol based manuscript. No further revisions are requested.