REPLY: We appreciate the opportunity to respond to the comments on our phase 2 LuCAP trial and thank Tuncel et al. for their thoughtful insights. The LuCAP trial evaluated low-dose capecitabine as a radiosensitizer for ^{177}Lu-DOTATATE in grade 1/2 advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The primary endpoint, objective response rate, was 33.3% in the combination arm versus 30.6% in the monotherapy arm, a nonsignificant difference (*1*). Given the overall negative results, subgroup analyses in limited samples must be interpreted with caution.

Tuncel et al. suggest improved responses with capecitabine in patients with a Ki-67 of at least 10% and pancreatic neuroendocrine tumors (NETs). However, the reported risk ratios (<1) indicate a lower probability of the outcome, that is, response with add-on capecitabine in these subgroups, not an improvement. More importantly, the 95% CIs crossed the line of no effect, confirming nonsignificance. We acknowledge that our study comprised a small proportion of patients with pancreatic NETs and Ki-67 values of at least 10%, and hence, the subgroup analyses were not adequately powered for meaningful interpretations.

Tuncel et al. also propose higher-dose capecitabine and temozolomide. However, capecitabine was used as a radiosensitizer in this study, not as a definitive therapy in itself. The 1,250 mg/m^2 dose was consistent with prior studies and more appropriate for our patient population (*2–5*). While CAPTEM (capecitabine plus temozolomide) is an effective treatment regimen for NETs, its combination with ^{177}Lu-DOTATATE has primarily been explored in high-grade and FDG-avid tumors (*6,7*). Moreover, temozolomide's long-term risk of myelodysplasia makes its omission justified in our study, which included only grade 1/2 GEP-NETs and excluded patients with discordant somatostatin receptor–negative, FDG-positive disease (*8*).

We agree that longer follow-up is needed for survival analysis, and the same is planned. However, our findings remain robust, particularly in gastrointestinal NETs with a Ki-67 less than 10%, indicating that capecitabine does not enhance response rates in these indolent tumors. Further studies are indeed required for higher-grade tumors and pancreatic NETs. However, we must emphasize here the results of the subgroup analyses of the phase 3 NETTER-2 trial, wherein objective response with ^{177}Lu-DOTATATE was higher in patients with grade 3 NETs (48.1% vs. 40.4% in grade 2) and pancreatic NETs (51.2% vs. 26.7% in small-bowel NETs), although the progression-free survival was expectedly lower in these subgroups (*9*). Considering these findings, it is important that future studies carefully evaluate the long-term benefits and risks of combining chemotherapy with ^{177}Lu-DOTATATE. A key question remains whether concurrent chemotherapy should be preferred with ^{177}Lu-DOTATATE in aggressive tumors or whether a sequential approach would offer better or similar long-term outcomes while preserving patients' quality of life.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Satapathy S, Aggarwal P, Sood A, et al. ^{177}Lu-DOTATATE plus capecitabine versus ^{177}Lu-DOTATATE alone in patients with advanced grade 1/2 gastroenteropancreatic neuroendocrine tumors (LuCAP): a randomized, phase 2 trial. *J Nucl Med.* 2025;66:238–244.
2. Glynne-Jones R, Dunst J, Sebag-Montefiore D. The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? *Ann Oncol.* 2006;17:361–371.
3. Ballal S, Yadav MP, Damle NA, Sahoo RK, Bal C. Concomitant ^{177}Lu-DOTATATE and capecitabine therapy in patients with advanced neuroendocrine tumours: a long term-outcome, toxicity, survival, and quality-of-life study. *Clin Nucl Med.* 2017;42:e457–e466.
4. Satapathy S, Mittal BR, Sood A, Sood A, Kapoor R, Gupta R. Peptide receptor radio nuclide therapy as first-line systemic treatment in advanced inoperable/metastatic neuroendocrine tumors. *Clin Nucl Med.* 2020;45:e393–e399.
5. Satapathy S, Mittal BR, Sood A, et al. ^{177}Lu-DOTATATE plus radiosensitizing capecitabine versus octreotide long-acting release as first-line systemic therapy in advanced grade 1 or 2 gastroenteropancreatic neuroendocrine tumors: a single institution experience. *JCO Glob Oncol.* 2021;7:1167–1175.
6. Yordanova A, Ahrens H, Feldmann G, et al. Peptide receptor radionuclide therapy combined with chemotherapy in patients with neuroendocrine tumors. *Clin Nucl Med.* 2019;44:e329–e335.
7. Parghane RV, Ostwal V, Ramaswamy A, et al. Long-term outcome of "sandwich" chemo-PRRT: a novel treatment strategy for metastatic neuroendocrine tumors with both FDG- and SSTR-avid aggressive disease. *Eur J Nucl Med Mol Imaging.* 2021;48:913–923.
8. Scaringi C, De Sanctis V, Minniti G, Enrici RM. Temozolomide-related hematologic toxicity. *Onkologie.* 2013;36:444–449.
9. Singh S, Halperin D, Myrehaug S, et al. First-line efficacy of [^{177}Lu]Lu-DOTA-TATE in patients with advanced grade 2 and grade 3, well-differentiated gastroenteropancreatic neuroendocrine tumors by tumor grade and primary origin: subgroup analysis of the phase III NETTER-2 study. *Ann Oncol.* 2024;35:S92–S93.

Swayamjeet Satapathy
Ashwani Sood*
**Post Graduate Institute of Medical Education and Research*
Chandigarh, India
Email: sood99@yahoo.com

Published online Apr. 24, 2025.
DOI: 10.2967/jnumed.125.270026

FDA Reconsiders Rules Around Radiation Dosimetry for First-in-Human Studies of Investigational PET Radiopharmaceuticals

TO THE EDITOR: Radiopharmaceuticals for PET imaging are regulated as drugs by the U.S. Food and Drug Administration (FDA) through several offices within the Center for Drug Evaluation and Research, including the Office of New Drugs and the Office of Generic Drugs. Within this framework, radiopharmaceuticals follow the same general drug development pathway as pharmaceuticals. Thus, investigational new drug (IND) applications are required for first-in-human (FIH) studies, as well as subsequent phase 2 and 3 clinical trials intended to demonstrate safety and efficacy. Marketing authorization is then obtained through approval of a new drug application. Alternatively, in the case of generic drugs, marketing authorization is obtained via approval of an abbreviated new drug application.

Despite using the same general regulatory framework as nonradioactive drugs, because of the unique characteristics of radiopharmaceuticals (radioactive as well as pharmaceutical doses need considering, short half-lives, microdosing [≤100 μg], low administered activity [AA], final product testing of every batch, etc.), there are some contents of regulatory filings such as INDs that are specific to this class of drugs. For example, dosimetry is a means to quantify the absorbed dose (AD), expressed in Grays or rads, associated with the AA of a PET drug. Historically, 21CFR§312.23(a)(10)(ii) has required that IND applications include sufficient data from animal

COPYRIGHT © 2025 by the Society of Nuclear Medicine and Molecular Imaging.

(or human) studies to allow reasonable estimation of AD to critical organs and effective dose to the patient to justify the lowest AA that can be given to obtain a usable PET image (*1*).

Dosimetry estimates are typically obtained by conducting biodistribution studies in rodents and using these data, in conjunction with radiation dosimetry software such as OLINDA/EXM (Hermes Medical Solutions) (*2*), to estimate the radiation AD for different organs within the body from the proposed AA for a given radiopharmaceutical. After approval of an IND, the FDA requires that the first few human studies (e.g., $n = 4$; 2 men/2 women) consist of whole-body scans to determine actual human dosimetry. However, stakeholders in new PET drug development have expressed that pre-IND animal dosimetry studies are burdensome, contain assumptions or uncertainties given the extrapolation from animal data to human estimates (e.g., rats do not have a gallbladder), and are potentially unnecessary given both the established safety record of PET drugs and the availability of human dosimetry immediately on initiating FIH studies.

In response to this, the FDA convened a meeting of its Medical Imaging Drugs Advisory Committee in August 2023 to reevaluate what dosimetry data are needed to support the initial clinical study in an original IND for certain new PET drugs (the meeting summary is provided at http://jnm.snmjournals.org) (*3*). Their goals were to conduct a systematic review of clinical dosimetry estimates of PET drugs derived from preclinical and clinical dosimetry studies and to determine AA amounts that could be used safely in FIH studies of new PET drugs without prior animal dosimetry studies. This review included human organ AD and whole-body effective dose estimates extrapolated from animal dosimetry studies and also calculations based on human dosimetry studies, from a total of 322 radiopharmaceuticals, including several approved by FDA. The study found good agreement between animal-derived and human-measured dosimetry.

Analysis of recommended AA values (mean AA from package inserts of approved radiopharmaceuticals) and published dosimetry data suggest that if the planned AA of a FIH study with a new radiopharmaceuticals labeled with ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N is no more than 299 MBq (8 mCi), 555 MBq (15 mCi), 158 MBq (4.3 mCi), 148 MBq (4 mCi), 1440 MBq (39 mCi), and 552 MBq (15 mCi), respectively, sufficient data are available to justify omitting preclinical dosimetry studies and proceeding directly to required phase 1 human dosimetry studies to establish radiation safety. Although the recommendations in the dossier do not necessarily represent the final position of the agency, several of us have recently used this new approach, filing an IND application for a FIH study with a ^{64}Cu-labeled radiopharmaceutical without a preclinical dosimetry package, and were gratified that the FDA is following this approach and approved the study to proceed. Notably, radiopharmaceuticals labeled with longer-lived radionuclides such as ^{89}Zr and ^{124}I were also considered but are not presently included in the exemption of preclinical dosimetry requirements because of the potential for higher radiation risks. ^{15}O was also excluded because there are currently no ^{15}O-labeled PET drugs with FDA approval.

Besides human studies under an IND, many PET radiopharmaceuticals are used under the auspices of a local Radioactive Drug Research Committee (RDRC) (*4*). Conducting research in humans using radiopharmaceuticals under RDRC approval requires that the research is basic science and not intended to demonstrate safety or efficacy or for diagnostic purposes, that the pharmacologic dose to be administered is known to cause no clinically detectable pharmacologic effect in humans, and that the radiation dose is justified and within specified annual limits (≤3 rem for whole body, active blood-forming organs, lens of the eye, and gonads, and ≤5 rem for other organs for a single dose).

In many instances, when dosimetry has been previously published (*5*), RDRC approval is straightforward to obtain. However, in the event that a radiopharmaceutical has been used in humans previously, but dosimetry has not been published and cannot be accessed (e.g., legacy dosimetry has been lost, contact cannot be made with original lab, or parties are unwilling or unable to share), then sites are forced to undertake burdensome preclinical estimates of dosimetry themselves, negating benefits offered by 21CFR§361 and the RDRC mechanism in the first place. Given that radiopharmaceuticals used under RDRC must have already been in humans at or above the proposed pharmacologic dose and have shown no adverse events, they are as safe as new radiopharmaceuticals being translated under an IND application. Therefore, we close this letter by respectfully requesting that the FDA also consider adopting this new flexibility in omitting animal dosimetry studies in the case of PET drugs used in basic clinical research under the RDRC mechanism.

DISCLOSURE

Steven Zigler is an employee of Siemens PETNET Solutions. In addition to their primary employment, Steven Zigler, Sally Schwarz, Henry VanBrocklin, and Peter Scott hold volunteer leadership positions at the Coalition of PET Drug Manufacturers, a 501(c)(6) trade association operating as a not-for-profit organization dedicated to the advancement of scientific and regulatory principles associated with the manufacturing and distribution of safe and effective drugs for diagnostic PET imaging. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Title 21, Chapter I, Subchapter D, Part 312—Investigational New Drug Application. Code of Federal Regulations website. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312. Updated March 25, 2025. Accessed April 1, 2025.
2. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med.* 2005;46:1023–1027.
3. PET Diagnostic Radiopharmaceutical Drugs: Medical Imaging Drugs Advisory Committee Meeting. U.S. Food and Drug Administration website. https://www.fda.gov/media/170658/download. Published August 1, 2023. Accessed April 1, 2025.
4. Guidance for Industry and Researchers. The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application. U.S. Food and Drug Administration website. https://www.fda.gov/media/76286/download. Published August 2010. Accessed April 1, 2025.
5. Jackson IM, Lee SJ, Sowa AR, et al. Use of 55 PET radiotracers under approval of a Radioactive Drug Research Committee (RDRC). *EJNMMI Radiopharm Chem.* 2020;5:24.

Marianna Dakanali
Steven S. Zigler
Sally W. Schwarz
Michael L. Nickels
Reiko Oyama
Henry F. VanBrocklin
Peter J. H. Scott*
**University of Michigan*
Ann Arbor, Michigan
E-mail: pjhscott@umich.edu

Published online Apr. 17, 2025.
DOI: 10.2967/jnumed.125.269885