October 20, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2025-D-1757; Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development; Guidance for Industry; Draft Guidance

To Whom It May Concern:

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each year[i] and over 600,000 Americans living with the disease[ii], we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development**."

This draft guidance continues the important work the Agency began surrounding dosage optimization and provides additional clarifications for identifying an optimized dosage for radiopharmaceutical therapies (RPTs) in oncology. Dosage optimization is crucial to ensure that patients receive efficacious treatments without being subjected to unnecessary toxicities. We agree that RPTs require unique considerations for dosage optimization, given their mechanism of action and concern for long-term toxicities. While RPTs have not yet been widely used for the treatment of lung cancer, we are excited by ongoing trials and research in this space. Therefore, LUNGevity applauds the FDA's issuance of the draft guidance, which will help ensure efficiency in the development of RPTs across broader cancer indications in the future, and provides additional feedback on areas for clarification and granularity.

Recognition of the Relationship between RPTs and EBRT

LUNGevity appreciates the Agency's distinction between RPTs and external beam radiation therapy (EBRT) and the draft guidance's acknowledgment that RPTs' administered activities may not need to adhere strictly to absorbed dose limits based upon EBRT organ tolerances. It is important that studies establish RPT-specific organ tolerances, which should not be limited to EBRT organ tolerances to ensure that the optimized dosage is appropriate.

Rather, we emphasize that clinical data should be leveraged for dosage selection rather than the EBRT organ tolerances.

Further, we recognize that many patients with lung cancer will receive EBRT as part of their treatment. We agree with the draft guidance's recommendations to include previously EBRT-treated patients in clinical trials for RPTs, given their potential for clinical benefit. Previously EBRT-treated patients should be included if their organ function meets eligibility requirements and their cumulative exposure does not raise toxicity concerns. However, we recognize there is the potential for overlapping toxicities, and agree with the Agency's suggestion of maintaining separate cohorts based on previous EBRT treatment. We would caution, however, that the potentially small sizes of these subgroups may pose challenges to data interpretability. Further, accurate cumulative exposure from EBRT documentation may not be present for all patients enrolling in clinical trials, and flexibility may be warranted to include these patients if their organ function meets eligibility criteria.

Long-Term Toxicities and Safety Monitoring

As noted in the draft guidance, traditional dose-escalation designs focus on acute and subacute, rather than long-term, toxicities. We acknowledge that awareness of long-term toxicities is important for shared decision-making with clinicians and providers, including for quality-of-life considerations. However, depending on the patient population, the natural history of the disease may preclude any risks of long-term toxicities, and in a patient's risk-benefit analysis, the efficacy of the treatment may outweigh the potential for long-term side effects. Indeed, many cancer therapies, such as chemotherapy, also cause long-term toxicities such as neuropathies, renal toxicity, and hearing loss. However, these therapies are still widely used, indicative of patients' willingness to accept some long-term toxicity to treat their cancer. Therefore, careful consideration should be given on the need to fully characterize long-term toxicities in early phase dose-escalation studies. While renal toxicity, for instance, may be of considerable concern given the kidney's particular radiosensitivity, it is usually not detectable until almost a year from administration. We are concerned about the necessity of collection of long-term safety data posing inappropriate delays to the progression of promising therapies out of early phase studies.

This concern with assessment of long-term toxicities with delayed onset highlights the need to define and analyze meaningful endpoints for late toxicities. We agree with the Agency about the importance of finding these early markers, which may help to predict long-term toxicities in initial early phase studies and allow for justification past EBRT limits while ensuring organ function.

We do acknowledge that long-term safety follow-up should be required for RPTs, albeit the data collection should not necessarily preclude promising therapies from moving into later phases of study and subsequently receiving approval. Long-term monitoring for late radiation adverse events is critical to understand the safety profile of emerging RPTs and may be best suited for post-market surveillance. In addition to CTCAE, the guidance may offer consideration for including patient reported outcomes (PROs) to capture long-term toxicities and impact on patients.

Lastly, we encourage additional granularity on the types of data that may be used to support long-term safety data collection. Registries may serve as a possible mechanism to collect long-term safety data to satisfy any post-market requirements. The Agency should also consider opportunities to leverage real-world data (RWD) for safety monitoring. Given the expectation of data collection at least 5 years, as stated in the guidance, a pragmatic approach to data collection which introduces the least amount of burden to patients will be important, and should be reflected by the frequency of labs and assessments. Balancing the rigor of long-term data collection with reduced burden is important to continue studies and clinical trials in RPTs.

Justification and Evidence to Support Administered Activities

The draft guidance states that adequate justification is needed for RPT administered activities to exceed EBRT organ tolerances or previously characterized RPT dosages. While "existing clinical data" is suggested for the justification, further guidance from the FDA on what clinical data would be adequate (including safety, efficacy dosimetry, PK/PD, etc.), as well as what nonclinical data and simulations/modeling may be appropriate, would be helpful.

Additionally, the FDA OCE's Oncology Dosing Tool Kit has been a beneficial resource to support dosage optimization, although in its current form it is not fully applicable to RPTs. The Agency could consider amending the tool kit or making an RPT-specific tool kit for considerations to support dosage optimization for these therapies.

LUNGevity appreciates the opportunity to comment on this important draft guidance. Oncology RPTs offer an exciting possible therapeutic option for many patients with cancer, and this field will only continue to expand. The Agency's guidance on the appropriate dosage optimization during clinical development for these exciting therapies will help support their robust characterization and development, ensuring that patients receive the appropriates dosages while minimizing unnecessary long-term toxicities. With the

proposed additional clarifications and considerations, we support this draft guidance. Please feel free to reach out to me at bmckelvey@lungevity.org with any questions.

Sincerely,

Brittany McKelvey

Brittany Avin McKelvey
Senior Director, Regulatory Policy
On Behalf of LUNGevity Foundation

---

[i] Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.

[ii] Centers for Disease Control and Prevention. United States Cancer Statistics. Available at https://gis.cdc.gov/Cancer/USCS/#/Prevalence/