January 27, 2025

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

RE: Docket No. FDA-2024-D-4643; Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products, Guidance for Industry—Draft Guidance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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products**."

Data collection to understand long-term toxicities in patients treated with anti-cancer therapies is critical for patients and providers to make informed decisions on the best treatment for an individual patient. We applaud the Agency for providing recommendations for measurement of ovarian toxicity in relevant oncology clinical trials enrolling premenopausal adults. In 2021, almost 5,000 people under the age of 50 were diagnosed with lung cancer.[iii] Further, younger women under 54 are being diagnosed with lung cancer at higher rates than men.[iv] As patients live longer with their disease,[v] long-term toxicities, including ovarian toxicities for premenopausal women, play an increasingly important role in treatment decision-making and quality of life considerations. Therefore, it is critical for patients to have as much robust data as possible to make informed decisions, which can include family planning and reproductive measures prior to treatment when considering ovarian toxicity. We support the recommendations in the draft guidance and have a few areas where additional guidance would be beneficial.

Additional Clarification on Defining Terms in the Draft Guidance

The draft guidance does not stipulate what is defined as "premenopausal age". Menopause is diagnosed retrospectively by a patient's history and biomarker status and will vary by individual. Given that the draft guidance states the recommendations are for "relevant cancer clinical trials that enroll premenopausal adults", additional clarification on how the Agency defines premenopausal will be valuable (e.g., requirement for test of ovarian function for all women at screening, a general age range, etc.). Additionally, further clarification on what constitutes "relevant clinical trials" would be helpful. The draft guidance notes the application in settings "where life expectancy based on tumor type is of a sufficient time where ovarian toxicities may be relevant". Further clarification on determination of what is a "sufficient" time is needed, which may be based on overall survival metrics, be age dependent, and consider child-bearing potential. Leveraging language and definitions previously provided by the Agency, such as in the Pregnancy and Lactation Labeling Final Rule[vi] on females of reproductive potential may help add clarification to the guidance.

Data Collection Considerations for Assessment of Ovarian Function

The draft guidance specifies that the methodology used for ascertainment of laboratory biomarkers be standardized across trial sites. While ideal, this may create undue burden on patients, trial sponsors, and sites by requiring the same assay that may differ from the assay used in routine care. Assay methodology standardization is critical on a patient level, to ensure the ability to compare assessments over time, therefore we suggest the recommendation should be at minimum to use the same methodology on a per patient basis to allay concerns of heterogeneity.

Additionally, the draft guidance notes that laboratory biomarkers should be assessed on specific days of a patient's menstrual cycle. This may require additional visits for the patients which are not timed with treatment administration or other follow-up, which may create additional burden for patients and sites. Patients' cycles may also be dysregulated due to anti-cancer therapies which may impact the feasibility of precise collection during the menstrual cycle. Further, as this testing is only for premenopausal women, there is the potential for bias by creating uneven patient follow-up burden across enrolled participants with extra testing for a subset of participants which may impact enrollment and retention of premenopausal women. To alleviate some of the burden of additional testing, the guidance could recommend the use of local testing for patients to not have to travel to a study site.

The guidance could also consider the option of only the assessment of clinical measures/gynecological history and confounders if laboratory biomarkers are prohibitive.

Lastly, there may be the opportunity to include patient-reported outcomes (PROs) and/or digital health technologies (DHTs) to add additional context to ovarian function and toxicity, given the individualized nature of the toxicities and menstrual status. The guidance could include leveraging menstrual diaries or PROs for events such as abnormal bleeding that allow the capture of relevant information to be done remotely, by the patients.

Interpretation of Data

Further guidance is needed from the Agency on how ovarian toxicity as a safety endpoint should be considered in the statistical analysis plan. This includes further clarification of the impact of the phase of the trial to the relevance of the safety endpoint. The draft guidance notes the sponsor should assess toxicity in "at least a subset of premenopausal study participants (e.g., N=40) if there is an identified risk of ovarian toxicity with a specific agent. Further guidance is needed to understand how this analysis should be statistically powered. The cancer type and proportion of patients that are premenopausal will impact the ability to conduct meaningful subset analyses and further clarification is needed on expectations.

Lastly, the draft guidance does not note how the data collected will be leveraged for the label. Patients and clinicians use the labelling information to make informed decisions about treatments. Further information from the Agency on how the data collected will be used to inform the label will be valuable.

LUNGevity appreciates the opportunity to comment on this important guidance. For patients to make the most informed decisions with their providers on the best treatment options, understanding long-term toxicities is critical. The Agency's guidance on including ovarian toxicity data collection in oncology clinical trials will greatly benefit patients. Please feel free to reach out to me at bmckelvey@lungevity.org with any questions.

Sincerely,

Brittany Avin McKelvey

Senior Director, Regulatory Policy
On Behalf of the LUNGevity Foundation

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[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/
[iii] U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in June 2024.
[iv] Fu Y, et al. (2023). Gender disparities in lung cancer incidence in the United States during 2001–2019. Scientific Reports, 13(1). https://doi.org/10.1038/s41598-023-39440-8
[v] SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. Accessed at https://seer.cancer.gov/explorer/ on Jan 23, 2024.
[vi] Department of Health and Human Services, Food and Drug Administration. 21 CFR Part 201. Pregnancy and Lactation Labeling (Drugs) Final Rule | FDA