COMMENTARY

Making Lung Cancer Clinical Trials More Inclusive: Recommendations for Expanding Eligibility Criteria

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Introduction

Cancer clinical trials institute multiple patient inclusion and exclusion criteria intended to create a somewhat homogenous group of patients with an expected outcome based on the current standard of care to which the newer therapy can be benchmarked, while addressing safety considerations. These criteria are based on scientific, clinical, and sponsor business considerations.

Regulations governing the U.S. Food and Drug Administration (FDA) do not include specific requirements for eligibility criteria other than stating that a clinical trial protocol should contain criteria for patient selection. Regulatory approval for a new drug is then predicated on data pertinent to enrolled patients and relevant to the U.S. population in U.S. medical practice.[1]

The FDA cannot mandate specific trial criteria, but it does encourage trial sponsors to consider eligibility criteria that can yield trial results generalizable to a broader U.S. population by defining cohorts of patient who may be appropriate to receive an investigational therapy within the context of a trial.[2] The FDA emphasizes that trial eligibility criteria should protect patient safety, facilitate accrual, and permit patient access to investigational agents as appropriate.[3]

The American Society of Clinical Oncology (ASCO) in collaboration with Friends of Cancer Research (Friends) and the FDA recently published recommendations for broadening clinical trial eligibility across multiple types of cancer.[4] The objective for the LUNGevity Working Group was to apply these recommendations specifically to advanced lung cancer trials and to promote discussion regarding eligibility criteria involving brain metastases, history of previous malignancy, and reduced performance

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status. When defined as exclusion criteria, these three conditions in aggregate could exclude as many as 50% of lung cancer patients from participating in clinical trials.[5–7]

Background for LUNGevity Foundation Eligibility Criteria Initiative

LUNGevity Foundation is a nonprofit patient advocacy organization committed to increasing quality of life and survivorship of people with lung cancer. In 2016, the LUNGevity Foundation launched its Scientific and Clinical Research Roundtable (SCRT) initiative to define and implement streamlined clinical trials for lung cancer, leveraging work begun through an International Association for the Study of Lung Cancer–FDA educational symposium in 2015.[8]

Comprised of leaders from across the lung cancer ecosystem in North America and Europe, the LUNGevity SCRT initially focused on three specific areas: expanding eligibility criteria, developing a prospective common control arm, and addressing unnecessary adverse event reporting.

This report is limited to recommendations made by the LUNGevity Eligibility Criteria Working Group. Our objective was to develop recommendations to expand trial access, while minimizing patient risk and not jeopardizing approval of effective drugs.

The Case for Expanding Eligibility Criteria

An ASCO survey of academics and clinicians found that 87% view clinical trial exclusions as impeding efforts to accrue patients to molecularly driven trials, and half agree such trials should include a provision for performance status (PS) 2 patients.[9] Nonetheless, trials still frequently exclude significant numbers of patients. A recent analysis of approximately 250 oncology Investigational New Drug (IND) submissions by Jin et al. reported that 96% included a strict performance status requirement, with 60% requiring Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and 35% allowing PS 2, whereas 77% excluded known, active, or symptomatic brain metastases, and 47% allowed treated or stable brain metastases.[10]

The impact of such exclusion criteria remains an ongoing point of controversy in the lung cancer arena, where poor performance status, brain metastases, and history of prior malignancy are common in the patient population. For example, approximately 13% to 22% of lung cancer patients have brain metastases at diagnosis,[7] 21% of patients are PS 2 at diagnosis,[6] and almost 15% of stage 4 lung cancer patients have a history of prior malignancy.[5] Kim et al. cited a recent Kaiser Permanente analysis of non–small-cell lung cancer patients in which 80% failed to meet eligibility criteria requirements for ongoing chemotherapy and antiangiogenic therapy trials.[4]

Brain Metastases

Exclusions of patients with brain metastases continue to appear in lung cancer clinical trials despite evidence that the relative impact of brain metastases on overall survival is modest after accounting for other factors such as number of metastatic sites.[11] In addition, response rates of untreated lung cancer brain metastases to systemic therapies are not substantially different than response rates at extracranial sites.[12]

Examples exist of recent trials in which these patients were included without jeopardizing successful results. Two such examples involving brain metastases are the recently completed and successful studies of alectinib versus crizotinib[12] (an international, randomized, open-label, phase 3 trial also known as GLOBAL ALEX) and of osmertinib versus first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) (an international, double-blind, phase 3 trial also known as FLAURA).[13] In both studies, there was no compromise in the progression-free survival benefits observed, whether brain involvement existed or not; nor did these patients experience higher rates of toxicity. Both osimertinib and alectinib have produced high response rates in brain metastases.[13,14] However, there is evidence that the blood-brain barrier is disrupted by metastases potentially enabling tumor permeation by multiple classes of systemic therapy.[15]

Our group and an increasing number of thoracic oncologists believe that allowing patients with untreated, asymptomatic brain metastases to participate in clinical trials provides an opportunity to identify potentially effective systemic treatments for intracranial disease and could reduce the need for whole brain radiation, while providing important safety information in the patient population that will inevitably be seen in clinical practice.

Prior Malignancy

A Surveillance, Epidemiology, and End Results data base study showed that a history of previous malignancy was associated with superior survival in stage 4 lung cancer.[5] Superior survival was observed even if the previous malignancy was diagnosed within a year of the lung cancer diagnosis.[5] Although excluding prior malignancy in the prior 5 years might make sense in the curative setting where the time horizon to outcome is long, these exclusions make little sense in the palliative setting where median survival historically has been less than 15 to 18 months and where the likelihood of death from a pre-existing cancer is extraordinarily unlikely.

Poor Performance Status

Exclusion of poor performance status (PS) (ECOG PS + 2) in ECOG trials was based on the observation that the rate of treatment related deaths was 10% in stage IV

non–small-cell lung cancer patients treated with chemotherapy versus 3% in patients with ECOG PS 0/1.[14] This restriction may be unnecessary with new, less toxic targeted and immunotherapeutic agents and with improved supportive care. The Working Group recommends that sponsors consider feasibility of expansion cohorts or separate safety studies specifically targeting PS 2 patients who are analyzed separately from the trials conducted for regulatory purposes.

LUNGevity Working Group Recommendations

The Working Group assessed current literature and clinical experience in developing recommendations to broaden trial eligibility for advanced lung cancer patients while minimizing safety concerns and business risks for sponsors. These recommendations permit earlier use of systemic therapy and provide data regarding activity in central nervous system metastases those with prior malignancy or compromised PS. Table 1 presents the Working Group's recommendations.

Conclusions

Consensus is developing within the oncology field, and specifically in thoracic oncology, that clinical trial eligibility criteria are overly restrictive. By relaxing criteria involving history of previous early stage malignancy, brain metastases, and reduced performance status, the LUNGevity Working Group believes that more advanced lung cancer patients, who are typical of the real world, will have access to novel, experimental therapies. Also, we believe that adopting a more inclusive eligibility philosophy is likely to reduce the time to complete advanced-stage lung cancer trials. The information generated through the inclusion of these populations could also be valuable for both patients and prescribers at the time of drug approval.

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Table 1. LUNGevity Working Group Recommendations

Condition	Frequent Practice	Recommendations (Lung Cancer–Specific, Metastatic or Recurrent Disease Trials)
Brain metastases	General exclusions and pre-treatment requirements	Include: • Untreated asymptomatic brain metastases (except brain stem metastases) • Stable, previously radiated or resected brain metastases (not requiring corticosteroids) Exclude/limit pre-treatment requirement to: • Symptomatic brain metastases • Lesions larger than 1 cm • Large posterior fossa metastases • Solitary brain metastasis with no other sites of metastatic disease or no secure diagnosis
Prior malignancy	General exclusions of most prior malignancy (except skin)	Include: • Any history of prior malignancy (regardless of time interval) except for invasive, active malignancy requiring ongoing therapy
Poor performance status	General exclusions of patients with PS 2 or higher	Not suggested for phase 1 or registrational studies Consider including PS 2 patients: • When drug has been well-studied and safety has been established in a different tumor type • In studies for different disease states (such as stage 3 lung cancer with radiotherapy) • In selected investigator-initiated trials • In combination studies when both agents have well established safety Use PS as a stratification factor for trials with randomization, or, in the context of phase II trials, as "expansion cohorts."

Abbreviations: PS, performance status.

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