Expanding Access to Lung Cancer Clinical Trials by Reducing the Use of Restrictive Exclusion Criteria: Perspectives of a Multistakeholder Working Group

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Abstract

Low rates of adult patient participation have been a persistent problem in cancer clinical trials and have continued to be a barrier to efficient drug development. The routine use of significant exclusion criteria has contributed to this problem by limiting participation in studies and creating significant clinical differences between the study cohorts and the real-world cancer patient populations. These routine exclusions also unnecessarily restrict opportunities for many patients to access potentially promising new therapies during clinical development. Multiple efforts are underway to broaden eligibility criteria, allowing more patients to enroll in studies and generating more robust data regarding the effect of novel therapies in the population at large. Focusing specifically on lung cancer as an example, a multistakeholder working group empaneled by the LUNGevity Foundation identified 14 restrictive and potentially outdated exclusion criteria that appear frequently in lung cancer clinical trials. As a part of the project, the group evaluated data from multiple recent lung cancer studies to ascertain the extent to which these 14 criteria appeared in study protocols and played a role in excluding patients (screen failures). The present report describes the working group's efforts to limit the use of these routine exclusions and presents clinical justifications for reducing the use of 14 criteria as routine exclusions in lung cancer studies, potentially expanding trial eligibility and improving the generalizability of the results from lung cancer trials.

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Introduction

Low rates of adult patient participation in cancer clinical trials have continued to be a barrier to efficient drug development. The routine use of significant exclusion criteria to limit participation in these studies affects the generalizability of the study results, creating important differences among the study cohort and the overall lung cancer patient population.[1-3] These routine exclusions also unnecessarily restrict opportunities for many patients to access potentially promising new therapies during clinical development. Furthermore, some eligibility criteria are antiquated and might not be relevant given the specific mechanism of action for the agents under study.

Multiple efforts are underway to streamline the eligibility criteria, allowing more patients to enroll in studies and generating more robust data about the effect of novel therapies in the population at large. In the past year, Friends of Cancer Research, American Society of Clinical Oncology, LUNGevity Foundation (LUNGevity),

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and the Food and Drug Administration (FDA) have developed proposals for broadening the eligibility among patients with a history of previous cancer, brain metastases, human immunodeficiency virus (HIV), organ dysfunction, and poor performance status.[4-7]

In 2018, LUNGevity convened a working group through its Scientific and Clinical Research Roundtable (SCRT), including leading clinicians, FDA officials, and industry representatives to address the topic of outdated or unnecessary lung cancer clinical trial restrictions. This effort was launched in response to concerns expressed by leading lung cancer clinicians that some exclusion criteria appearing routinely in lung cancer study protocols are not necessary to protect the safety of the patients or the integrity of the study. Clinicians have posited that these exclusions are perpetuated from one study to the next through a common practice of "cutting and pasting" text from previous protocols.[8] In addition, although the therapeutic landscape for lung cancer has changed dramatically with the advent of drugs with novel mechanisms of action (including targeted therapies and immunotherapy agents), certain trial exclusion criteria developed specifically for cytotoxic agents and radiation therapy have continued to remain common in clinical study protocols.

The present report summarizes the activities and recommendations made by the 2018 LUNGevity SCRT working group to provide trial sponsors with a list of exclusion criteria that should be thoughtfully considered and justified when used for a specific study with a specific agent, rather than routinely incorporated into the study protocol. It is our hope that the spirit with which these recommendations are made—moving away from outdated and unnecessary exclusions to expand the opportunities for patients to participate in trials—will be embraced. It is our view that if these recommendations are adopted into practice, patients with lung cancer will benefit from greater access to clinical trials moving forward.

Materials and Methods

LUNGevity surveyed the multistakeholder participants of the SCRT (including the foundation's scientific and clinical leadership, representatives from leading sponsors of lung cancer trials, and regulatory officials) in December 2017 to compile a list of exclusion criteria that appear frequently in clinical study protocols that could be considered unnecessary, outdated, or redundant in today's lung cancer therapy development landscape. From the survey feedback, an initial list of 18 criteria was developed. This list was reviewed by the expert working group and refined to its final form of 14 criteria (Table 1).

Justifications

The 14 eligibility criteria identified by the expert panel were reviewed by an independent group of thoracic oncologists who routinely conduct therapeutic phase I to III lung cancer clinical trials. The thoracic oncologist panel surveyed the reported data to identity situations in which a criterion might no longer be applicable. The panel considered the mechanism of action of the drug, the types of pharmacokinetic and pharmacodynamic data available when determining the eligibility criteria for late-phase trials (for new molecular entities with phase I safety data), and the type of supportive care that could be used for patients with specific medical conditions. The panel's proposals are summarized in Table 1. As noted in Table 1, the parameters related to laboratory tests have specific limits. These are general considerations; however, they could need to be modified based on information such as drug-specific characteristics and the clinical development stage. For example, some eligibility criteria for the dose-finding cohorts of the first-in-human trials might be more stringent than those in later trials because (1) little is known about the pharmacokinetics, safety, and activity of the drug and (2) confounding the maximum tolerated dose determination and dose selection for later trials should be avoided to the extent possible. For convenience, the 14 eligibility criteria have been categorized into 4 groups: clinical history, treatment history, laboratory values, and "other."

Clinical History

The clinical history category includes information on the diagnoses of conditions that have previously required, or currently require, active treatment.

Venous Thromboembolic Events. Lung cancer clinical trial eligibility criteria frequently exclude patients with a history of venous thromboembolic events in the preceding 6 months. This stipulation prevents a relatively large number of patients with lung cancer from participation in clinical trials. In a study that evaluated the frequency of thromboembolic events in 673 patient with newly diagnosed lung cancer, 13.2% of the patients had experienced a thromboembolic event during the 3 months preceding the lung cancer diagnosis.[9] The rate was 20% for patients with stage IV lung cancer.[9] Other studies have also reported a higher rate of thromboembolic events in patients with stage IV lung cancer compared with patients with early-stage or locally advanced disease.[10] Other factors associated with higher rates of thromboembolic events in patients with lung cancer include adenocarcinoma histologic subtype, emergency hospital admission, and leukocytosis.[9,10]

Compared with older oral anticoagulant agents, treatment with low-molecular-weight heparin has reduced the frequency of new venous thromboembolic events in patients with cancer and preexisting deep vein thrombosis and/or pulmonary emboli.[11] Also, direct oral anticoagulant agents have been approved to treat venous thromboembolic events.[11]

Venous thromboembolic events are frequent, and current anticoagulant therapies are effective in preventing subsequent thrombotic events. Therefore, we recommend including these patients in clinical trials if they are receiving adequate anticoagulation therapy, the experimental agent does not interact adversely with the anticoagulant therapy, and the agent is not expected to increase the risk of venous thromboembolic events or excessively increase the rates of serious bleeding.

Autoimmune Disease. The eligibility criterion of no history of autoimmune disease affects a relatively large proportion of the lung cancer population because the baseline autoimmunity could predispose to malignancy, including lung cancer.[12] Specifically, autoimmune disorders might promote carcinogenesis through chronic inflammation and/or decreased immune surveillance among patients receiving immunosuppressive medications. In one recent study,

Table 1 List of Recommendations for 14 Eligibility Criteria in Lung Cancer Clinical Trials

Criterion No.	Criterion	Clinical Recommendations for Allowing These Patients in Trials (Routine)	Clinical Considerations for Excluding These Patients From Trials (Justification)
1	Previous cardiovascular events (eg, acute MI, CHF, CVA, TIA) in previous > 3 mo	Low-risk cardiac disease with events that occurred >3 mo before investigational treatment	Investigational agent known or suspected to cause vascular complications
			New-onset CHF with reference to NYHA- or LVEF-based criteria
			Recent TIA or stroke if no recovery from neurologic deficits, PS requirement not met, study agent is associated with thrombotic or hemorrhagic complications, or swallowing ability is compromised (for oral agents)
2	Previous PE/DVT or another clotting event	Pre-existing DVT and/or PE concurrently treated with anticoagulant therapy	Investigational agent suspected or known to cause thrombotic effects
3	Minimal blood count (eg, ANC > 1500 cells/μL, platelet count > 100K cells/μL, Hb > 9 g/dL)	Hb ≥ 8.0 g/dL; platelet count ≥ 75K cells/μL, and ANC ≥ 1.0 cells/μL	Investigational agent suspected or known to have myelosuppressive or hematologic effects
		Drugs with low likelihood of causing hematologic effects (< 3% incidence of grade 3-4 treatment-related events)	
4	Recent blood transfusion	A history of recent blood transfusion, provided other eligibility criteria are met	Investigational agent suspected or known to cause anemia and patient is transfusion dependent
5	Life expectancy of ≥ 12 wk	Other eligibility criteria met and ECOG PS of 0-1 or 2 (for specific trials)	NA
6	Any history of pneumonitis	Infections (pneumonia) that have resolved spontaneously or with antibiotics	Investigational agent suspected or known to cause lung inflammation
		Radiation pneumonitis that has subsided and does not require ongoing corticosteroid treatment	Usual interstitial pneumonitis
			Nonspecific interstitial pneumonitis
			Pulmonary fibrosis (diffuse) from any cause
			Acute hypersensitivity pneumonitis
			Chronic hypersensitivity pneumonitis
			Acute radiation pneumonitis requiring corticosteroids
7	Supplemental oxygen requirements	Other eligibility criteria met and ECOG PS of 0-1 or 2 (for specific trials)	Investigational agent suspected or known to cause pulmonary toxicity
		Subcategory: supplemental oxygen required because of COPD, previous surgery, pulmonary fibrosis limited to radiation field, or restrictive lung disease secondary to successful treatment of malignant pleural effusion	When oxygen required for interstitial lung disease
8	Renal insufficiency (eg, CrCl > 50-60 mL/min)	eGFR ≥ 45 mL/min/1.73 m^2 or CrCL≥ 45 mL/min	Investigational agent suspected or known to cause nephrotoxicity
		eGFR ≥ 30 mL/min/1.73 m^2 or CrCL ≥ 30 mL/min if renal clearance not a significant component of drug's elimination pathway	Investigational agent known to be renally metabolized and/or no data available on renal metabolism (ie, phase I trial)
9	Liver function abnormalities (eg, total bilirubin elevation in patients with Gilbert syndrome)	AST or ALT elevation cutoff of ≤ 3 times institutional ULN without liver metastases and ≤ 5 times ULN with liver metastatic disease	Investigational agent suspected or known to cause hepatotoxicity (eg, > 3% incidence of grade ≥ 3 hepatitis)
		Total bilirubin ≤ 1.5 times institutional ULN; for patients with Gilbert syndrome, total bilirubin should be ≤ 3 times institutional ULN	For medications metabolized by glucuronidation, exclusion based on total bilirubin ≤ 1.5 times institutional ULN might be appropriate even if Gilbert syndrome present
10	Long washouts from chemotherapy and radiotherapy	< 14 or 21 d for chemotherapy (assuming blood count recovery)	Longer half-life of drug (eg, immunotherapy with half-life of ~25 d)
		Radiotherapy with palliative intent	Radiotherapy with risk of pneumonitis
11	Line of therapy	Previous lines of therapy, especially for phase I studies	Exclusion should be determined by PS and laboratory test results

Table 1 Continued

Criterion No.	Criterion	Clinical Recommendations for Allowing These Patients in Trials (Routine)	Clinical Considerations for Excluding These Patients From Trials (Justification)
12	Bacterial, fungal or viral infection (eg, hepatitis B and C, HIV, AIDS-related illness)	Well-controlled infections (antibiotic therapy, no active fever, no evidence of systemic inflammatory response syndrome), including HIV and "cured" hepatitis C	Drug known to be immunosuppressive
			Active infection present
			Concern for potential drug—drug interactions, specific offending agents (eg, antibiotic/antiviral agents) should be explicitly excluded
13	History of autoimmune disease	Irreversible autoimmune disorders unlikely to be exacerbated by therapy (eg, type 1 diabetes, hypothyroidism)	Exclude baseline autoimmune disorders in early-phase studies of cancer immunotherapies, especially when evaluating novel combinations—only for immunotherapy trials
		Baseline autoimmune disorders (nonimmunotherapy trials)	Active autoimmune disorders requiring ongoing immunosuppression—only for immunotherapy trials
14	Previous stem cell transplantation	Other eligibility criteria met and ECOG PS of 0-1 or 2 (for specific trials)	High risk of GVHD (eg, immunotherapy drugs)

Abbreviations: AIDS = acquired immunodeficiency virus; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; CVA = cerebrovascular accident; DVT = deep vein thrombosis; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; GVHD, graft versus host disease; Hb = hemoglobin; HIV = human immunodeficiency virus; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = not applicable; PE = pulmonary embolism; PS = performance status; TIA = transient ischemic attack; ULN = upper limit of normal.

14% to 25% of patients with a diagnosis of lung cancer had a concomitant autoimmune disorder.[13] Common autoimmune disorders among this patient population include rheumatoid arthritis, psoriasis, and polymyalgia rheumatica.[13]

Eligibility criteria excluding patients with autoimmune disorders have been common in clinical trials evaluating cancer immunotherapy, most notably immune checkpoint inhibitors. Although such agents have dramatically transformed the management of lung cancer in recent years,[14,15] a theoretical concern exists that immune checkpoint inhibitors could exacerbate underlying autoimmune disorders and/or predispose patients to develop more severe and/or frequent immune-related adverse events (irAEs). Because of these restrictions on clinical trial enrollment, data on the safety of immune checkpoint inhibitors in lung cancer patients with autoimmune disorders are limited. One recent retrospective analysis studied 56 patients with non—small-cell lung cancer (NSCLC) and autoimmune disease who were treated with programmed cell death 1 (PD-1) and/or programmed cell death ligand 1 (PD-L1) inhibitors. Of the 56 patients, 23% experienced a flare in their underlying autoimmune disorder and 38% developed irAEs.[16] In these patients, the irAEs were generally manageable and only infrequently led to discontinuation of immune checkpoint blockade. Likewise, in melanoma, retrospective analyses have shown that PD-1/PD-L1 inhibitors can be safety administered to patients with underlying autoimmune disorders.[17] This is also consistent with the results from an FDA analysis of patients with baseline autoimmune diseases treated with PD-1/PD-L1 immunotherapy agents.[14]

Retrospective studies have suggested that immune checkpoint inhibitors can be safely administered to patients with baseline autoimmune disorders.[16-18] However, data from large series and longer term follow-up are limited. Although it is reasonable to continue to exclude baseline autoimmune disorders in early-phase studies of cancer immunotherapies, especially when evaluating novel combinations, this exclusion would, optimally, be defined narrowly. For example, the exclusion criterion could be restricted to patients with active autoimmune disorders or the need for ongoing immunosuppression. In contrast, patients with irreversible autoimmune disorders unlikely to be exacerbated by the therapy (eg, type 1 diabetes, hypothyroidism, rheumatoid arthritis) could remain eligible. Furthermore, for cancer immunotherapy agents in the later stages of testing, it would be reasonable to consider including dedicated safety cohorts for patients with baseline autoimmunity or additional safety monitoring if included in the overall study population.

Finally, outside of clinical trials evaluating agents with immune-based mechanisms of action, patients with baseline autoimmune disorders who meet all other eligibility criteria should not be excluded from trials.

Chronic Kidney Disease. Lung cancer clinical trials frequently exclude patients with a history of moderate chronic kidney disease (CKD; eg, estimated creatinine clearance [CrCl] using the Cockcroft-Gault equation of $\leq$ 60 mL/min). A recent analysis of $>$ 90 therapeutic lung cancer trials from 2012 to 2017 found that 90% of these trials had excluded patients with CKD.[19] The exclusions had occurred regardless of the phase of the clinical trial, class of agent (ie, cytotoxic, target therapy, monoclonal antibody), and suspicion that the drug was nephrotoxic.[19] In addition, a significant number of trials will use the serum creatinine level to define the exclusion criterion. Multiple studies have shown that serum creatine is a relatively poor measure of the glomerular filtration rate (GFR). Also, more accurate formulas to estimate the GFR (eg, CrCl and estimated GFR [eGFR] using the Modification of Diet in Renal Disease equations) are already in routine clinical use in oncology clinics.[20] This is concerning because the prevalence of CKD at the diagnosis of cancer has ranged from 12% to 53%[20,21] and malignancy is the cause of death in 32% of patients with CKD.[22] Furthermore, patients with CKD appear to have a greater risk of the development of lung cancer.[23] Thus, the routine exclusion of

patients with CKD prevents a relatively large number of patients with lung cancer from participation in clinical trials.

Many FDA-approved and commonly used cytotoxic agents with known renal toxicity (eg, pemetrexed, cisplatin) have been approved for use in patients with CKD and a CrCl of $\geq$ 45 mL/min or creatinine of $\leq$ 1.5 of the upper limit of normal (ULN) or were approved without guidance (eg, gemcitabine). Mild to moderate CKD (CrCl $\geq$ 45 mL/min) is common in patients with lung cancer, and these patients regularly receive nephrotoxic cytotoxic agents in the first-line setting. Thus, an arbitrary CrCL cutoff (CrCl $\geq$ 60 mL/min) in the absence of known or suspected nephrotoxicity is an unnecessarily restrictive exclusion criterion. Efforts are necessary to include this common patient population with an eGFR of $\geq$ 45 mL/min/1.73 m^2 or CrCl of $\geq$ 45 mL/min in lung cancer clinical trials unless the agent is suspected to cause nephrotoxicity. When the pharmacokinetics of the drug are expected to increase in patients with impaired renal function, the inclusion of such patients could be facilitated by a dose reduction to produce systemic exposure similar to that for patients with relatively preserved renal function. If renal clearance is not a significant component of the drug's elimination pathway (eg, monoclonal antibodies) and the drug is not suspected to cause nephrotoxicity, the patients with an eGFR of $\geq$ 30 mL/min/1.73 m^2 or CrCl of $\geq$ 30 mL/min could also be included in the clinical trials. Characterizing the drug elimination pathways early in the drug development process could help avoid unnecessary exclusion criteria in later trials.

Supplemental Oxygen Use. Lung cancer clinical trial eligibility criteria frequently exclude patients with supplemental oxygen use even when their oxygen use for chronic obstructive pulmonary disease (COPD) predates the diagnosis of lung cancer. COPD and emphysema are well established risk factors for the development of lung cancer.[24] More than one third of patients in the National Lung Screening trial had COPD as determined by pulmonary function test results.[25] In addition, an estimated 33% to 52% of patients with lung cancer will have a diagnosis of COPD.[25-27] Almost one third of patients with COPD will be excluded from clinical trials by their long-term oxygen use.[28] Therefore, this criterion prevents a relatively large number of patients with lung cancer from participating in clinical trials.

For patients who otherwise meet the eligibility criteria with an Eastern Cooperative Oncology Group performance status of 0-1 (or 2 if allowed), exclusion solely because of the use of long-term oxygen lacks scientific or clinical justification. We recommend including this common patient population unless the agent is suspected to cause pulmonary toxicity.

HIV and Hepatitis Infection. Although HIV and hepatitis infection exclusion criteria are appropriate when applied to clinical trials of drugs known, or expected, to cause immunosuppression, they might not be necessary for all trials and could be incorporated selectively into the eligibility criteria.

HIV and hepatitis infections are relatively common and frequently co-occur with a diagnosis of lung cancer. For example, according to the Centers for Disease Control and Prevention estimates, HIV affects ~1.1 million adults in the United States[29] and is even more common in other parts of the world. Current antiviral therapies are highly effective and have successfully turned HIV into a chronic illness, leading to an increasing number of patients living with HIV. However, patients with HIV generally have an increased risk of malignancy, and of lung cancer in particular.[30] It is well-known that patients with HIV and cancer are less likely to receive cancer-directed treatment than are those without HIV.[31] Many studies have confirmed the safety of both chemotherapy[32] and immunotherapy[33] in this population. For example, emerging data have suggested that immune checkpoint inhibitors can be safely used in patients with HIV and lung cancer. In a recent retrospective review of 73 patients with HIV treated with immunotherapy (anti-PD-1 or anti-CTLA4, or both), no new or increased safety signals were seen, and 93% of the patients maintained a suppressed HIV viral load during treatment.[33] Ongoing trials are further evaluating both the safety and the efficacy of immune checkpoint inhibitors in this population.

We acknowledge that cautious evaluation of novel therapies known or expected to be immunosuppressive could be necessary for patients with viral infections, including HIV and hepatitis. For such studies, excluding patients with known active or recent hepatitis or HIV infection might be appropriate. However, for therapies that are unlikely to cause significant immunosuppression, we recommend including patients with well-controlled HIV and hepatitis if they have met the other eligibility criteria and no potential or predicted drug–drug interactions are expected. In addition, if data are available suggesting a drug–drug interaction between the investigational agent or agents and the antiviral drugs the patients are taking, appropriate instructions (eg, avoidance of certain concomitant medications) should be included in the protocol.

Previous Cardiovascular or Arterial Thrombotic Event. Cardiovascular and arterial thrombotic events include acute myocardial infarction (MI), congestive heart failure (CHF), cerebrovascular accident (CVA), and transient ischemic attack (TIA). The exclusion of patients with previous cardiovascular or arterial thrombotic events might not be necessary, unless the drug under study is suspected to cause vascular or thrombotic complications.

Cardiac disease remains the most common cause of death for women and men in the United States and worldwide, just barely greater than that for carcinoma, even with improvements in cardiac survival and related interventions. Cardiac disease and central nervous system arterial thrombus (ie, CVA, TIA) share the primary risk factor of tobacco use with lung carcinoma. The substantial overlap between patients with a cardiac or central nervous system event history and lung cancer has significant implications for clinical trial eligibility.

Although a dearth of data exists on the best methods to manage cardiac risk with cancer care and clinical trials,[34] this should not preclude consideration of logical and evidence-based changes to traditional exclusion criteria. The growing field of cardio-oncology could also offer new data and a different clinical perspective that would be valuable in lung cancer clinical trial design.[35]

Currently, per an FDA analysis, ~55% of lung cancer trials have included a previous MI or cardiac event within 3 or 6 months before randomization as an exclusion criterion. However, frequently, no

Table 2 Analysis of 14 LUNGevity Criteria in FDA Pilot Analysis

LUNGevity Outdated Eligibility Criteria	Pilot Study Analysis		
	Medical Category	Exclusion Criteria	Frequency and Analysis of Criteria Within Pilot Study
Previous cardiovascular events (eg, acute MI, CHF, CVA, TIA) in previous > 3 mo (unless drug suspected to cause vascular complications)	Cardiovascular	MI event within 3 or 6 mo before randomization	56% of trials; 60%, 3 mo; 40%, 6 mo
		Multiple criteria: LVEF; NYHA; other (eg, CHF within 3 mo before randomization)	56% of trials; 40%, LVEF; 50%, NYHA; 60%, other
		CVA, including TIAs within 3 or 6 mo before randomization	89% of trials; 50%, 3 mo; 50%, 6 mo
Previous PE/DVT or other clotting event (unless drug suspected to cause thrombotic effects)	Cardiovascular	Any arterial thrombotic event within 6 mo before randomization	6% of trials
Normal blood count (eg, ANC > 1500 cells/μL, platelet count > 100K cells/μL, Hb > 9 g/dL; unless drug suspected to cause bone marrow suppression)	Hematology	Hb ≤ 8-10 g/dL	78% of trials; 7%, Hb ≤ 8 g/dL; 7%, Hb ≤ 8.5 g/dL; 57%, Hb ≤ 9 g/dL; 14.5%, Hb ≤ 9.5 g/dL; 14.5%, Hb ≤ 10 g/dL
		ANC ≤ 1500 cells/μL	89% of trials
		Platelet count ≤ 75,000-100,000 cells/μL	89% of trials; 88%, 100,000 cells/μL; 12%, 75,000 cells/μL
Recent blood transfusion (unless drug suspected to cause anemia and transfusion dependent)	Hematology	Blood transfusion within 2 wk (14 d) to 4 wk (28 d) of first dose	11% of trials
		Blood transfusion within 120 d of date of genetic sample collection	11% of trials; 50%, 3 mo; 50%, 6 mo
Life expectancy of ≥ 12 wk	Other	Life expectancy < 2 or 3 mo	53% of trials; 89%, 3 mo; 11%, 2 mo
Any history of pneumonitis	Pulmonary	Radiation, hypersensitivity, drug-induced, and/or history of or known pneumonitis	35% of trials; 17%, radiation; 33%, hypersensitivity; 67%, drug-induced; 50%, history or known pneumonitis
Renal insufficiency (eg CrCl > 50-60 mL/min; unless drug suspected to be nephrotoxic)	Nephrology	CrCl or eGFR (calculated)[a]	77% of trials; 7%, calculated CrCl ≤ 40 mL/min; 21%, calculated CrCl ≤ 45 mL/min; 36%, calculated CrCl ≤ 50 mL/min; 36%, calculated CrCl ≤ 60 mL/min
		Serum Cr	47% of trials; 75%, serum Cr > 1.5 × ULN; 25%, serum Cr > 2.0 × ULN
Liver function abnormalities (eg, total bilirubin elevations in patients with Gilbert syndrome; unless drug suspected to be hepatotoxic)	Hepatic and biliary system (gastroenterology)	Transaminases	• 84% of trials; 20%, AST/ALT > 1.5 × ULN; 60%, AST/ALT > 2.5 × ULN; 20%, AST/ALT > 3.0 × ULN
		Transaminases if transferase elevation in presence of liver metastases or underlying malignancy	50% of trials; 78%, liver metastases; 22%, underlying malignancy; AST/ALT > 5 × ULN
		Total bilirubin	89% of trials; 31%, bilirubin > ULN; 13%, bilirubin > 1.0 × ULN; 56%, bilirubin > 1.5 × ULN
		Total bilirubin levels for patient with known Gilbert syndrome	22% of trials; bilirubin > 3 × ULN
		ALP	11% of trials
		ALP levels in presence of exclusive bone metastases and absence of any liver disorder	6% of trials
Bacterial, fungal or viral infection (eg hepatitis B and C, HIV, AIDS-related illnesses) (unless the study drug is suspected to cause immunosuppression)	Infectious	Active hepatitis B or hepatitis C[b]	44% of trials
		Known HIV infection or AIDS-related illness	66% of trials

Table 2 Continued

LUNGevity Outdated Eligibility Criteria	Pilot Study Analysis		
	Medical Category	Exclusion Criteria	Frequency and Analysis of Criteria Within Pilot Study
		Infections described as active, uncontrolled and active, ongoing and active, or severe	56% of trials
History of autoimmune disease (requires further discussion)	Immunology	Autoimmune disease (defined as active, known, or suspected history of autoimmune disease); nonspecific language (history of autoimmune disease, including but not limited to); specific exceptions (eg, type 1 diabetes mellitus, skin disorders (eg, vitiligo, psoriasis, alopecia) not requiring systemic treatment; conditions not expected to recur in absence of external trigger permitted to enroll	28% of trials
Previous stem cell transplantation	Other	Previous allogeneic bone marrow transplantation	22% of trials
		Previous solid organ transplantation	17% of trials
Long washouts from chemotherapy and radiotherapy	Oncology	Multiple chemotherapy criteria with variable duration[c]	61% of trials; 18%, 2 wk; 9%, 3 wk; 45%, 4 wk; 27%, NS
		Multiple radiotherapy criteria with variable duration[d]	55% of trials; 25%, 2 wk; 37%, 4 wk; 13%, 12 wk; 13%, 24 wk; 13%, NS
Supplemental oxygen requirements	Other	The pilot study could not find criteria for supplemental oxygen requirements within protocol of selected trials	
Line of therapy (recommend no limit on previous therapies, especially in phase I study)	Other	This criterion could not be properly assessed in the pilot study, which surveyed phase III studies, with trial-specific requirements found	

Several categorizations could be used within the same trial (eg, LVEF and NYHA), such that the total could exceed the sum of 100%.
Abbreviations: AIDS = acquired immunodeficiency virus; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CHF = congestive heart failure; Cr = creatinine; CrCl = creatinine clearance; CVA = cerebrovascular accident; DVT = deep vein thrombosis; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; Hb = hemoglobin; HIV = human immunodeficiency virus; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NS = not specified; PE = pulmonary embolism; TIA = transient ischemic attack; ULN = upper limit of normal.
[a]Calculation method per institutional standard (eg, Cockcroft-Gault, modification of diet in renal disease study formula, chronic kidney disease epidemiology collaboration equation).
[b]Active hepatitis B infection can be defined with hepatitis B serologic testing; active hepatitis C infection can be defined with hepatitis C serologic and quantitative hepatitis C virus RNA testing.
[c]Criteria definition issues: general (any previous chemotherapy, any investigational therapy, previous systemic anticancer therapy); specific cancer history (previous chemotherapy for relapsed or metastatic non–small-cell lung cancer); toxicity oriented (recovered from any previous therapy-related toxicity to Common Toxicity Criteria for Adverse Event grade ≤ 1); duration variability (specific for washout period; duration criteria used to permit previous treatment with neoadjuvant or adjuvant chemotherapy); no specific duration noted.
[d]Criteria definition issues: general (any previous radiation); location specific (chest irradiation); toxicity oriented (previous radiotherapy allowed, provided the patient had recovered from any toxic effects); treatment specific (radiotherapy to $> 30\%$ of bone marrow); combination (if patients had received radiotherapy of > 30 Gy, they must have recovered from toxicity and/or complications from the intervention).

distinction between non–ST-elevation MI, unstable angina, or ST-elevation MI will be specified. Data are increasing on the best interventions for cardiac syndromes, and patients with non–ST-elevation MI or unstable angina with negative catheterization findings have had excellent outcomes.[36,37]

Given these data, for clinical trials including MI or a previous cardiac event as an exclusion criterion, we recommend consideration of including patients with low-risk cardiac events that occurred > 3 months before randomization. It is challenging to predict the cardiac impact of multiple novel agents given that late-phase healing after an MI can occur ≤ 6 months after the event.[38] Data have not strongly favored 3 months versus 6 months as an exclusion criterion, and studies of lung cancer are split 40%/60% for the use of 3 versus 6 months after a cardiac event. Further studies are needed to determine the optimal screening timing and criteria for inclusion of patients with previous cardiac events in lung cancer trials.

The eligibility criteria for other cardiac complications, such as CHF, are somewhat unclear, with approximately one third of lung cancer clinical trials excluding patients with a history of CHF within 3 to 6 months of randomization or with "uncontrolled" or "ongoing" CHF. Harmonization and standardization of the exclusion criteria for CHF and cardiomyopathy would be beneficial using criteria such as the New York Heart Association classification for CHF and the left ventricular ejection fraction for cardiomyopathy. Determination of eligibility according to a history of CHF or cardiomyopathy would then be determined by the potential for cardiac myocyte damage with the investigational product.

Patients with lung cancer have the highest stroke risk of the most common cancers, with a 6-month incidence of 8.3% compared with 2.4% in controls.[39] This very high incidence might partially explain why $< 25\%$ of NSCLC pivotal trials evaluated by the FDA had incorporated CVA or TIA as exclusion factors. Additionally, any patient with a recent serious CVA is unlikely to meet the Eastern Cooperative Oncology Group eligibility for a clinical trial because of their functional status during recovery. Chemotherapy can also increase the stroke risk in this already at-risk population.[40]

Given these issues, for novel medications without a known safety profile (eg, phase I), agents likely to induce a pro-inflammatory state or endothelial changes, and cytotoxic agents, the exclusion of patients with a recent TIA or stroke might be reasonable. In general, better specificity of the eligibility criteria for arterial thrombotic events, with liberalization of the exclusion criteria for low-risk cardiac events occurring > 3 months before randomization and for patients with stable and compensated CHF with good functional status, should be considered.

Treatment History and Comorbidity

History of Pneumonitis. Many patients with lung cancer have a history of pneumonitis. Also, this condition has frequently been listed as an exclusion criterion in lung cancer clinical trials because many systemic treatments for lung cancer are associated with pulmonary toxicity. Patients who have had pneumonia or bronchitis that has resolved, either spontaneously or as a result of treatment with antibiotics, should be included in lung cancer trials, providing they have an adequate performance status and have met the other eligibility requirements.

Similarly, we recommend that patients with radiation pneumonitis that does not require corticosteroids or that has resolved after a course of corticosteroids should be included in lung cancer trials. In a recent clinical trial, within 2 to 6 weeks of completing chest radiotherapy and concurrent chemotherapy, patients with stage III NSCLC were randomized to treatment with durvalumab versus observation. The rate of serious pulmonary toxicity was 3%, and no differences were observed between the patients assigned to durvalumab and those assigned to observation.[41]

Interstitial lung disease is another type of pneumonitis often listed as an exclusion criterion in lung cancer clinical trials. A recent review has summarized the relationship between interstitial lung disease and lung cancer.[42] The relative risk of developing lung cancer is 3.5 to 7.3 times greater for individuals with interstitial lung disease. The presence of interstitial lung disease has been found in 2.4% to as high as 24% of patients with a diagnosis of lung cancer.[42] Interstitial lung disease is a heterogeneous group of pulmonary disorders associated with inflammation and fibrosis.[43] In some cases, such as sarcoidosis and autoimmune disease, the etiology of the pulmonary inflammation and scarring can be identified. However in other cases, no obvious cause will be identified, and the disease is classified as idiopathic interstitial pneumonia.[43,44] The common diagnoses grouped under idiopathic interstitial pneumonia include the usual interstitial pneumonia, nonspecific interstitial pneumonia, and hypersensitivity pneumonitis. Interstitial lung disease with or without an unknown cause can develop into progressive, irreversible pulmonary fibrosis.

Although the amount of data is small, it appears that the response rates to chemotherapy in patients with NSCLC with or without interstitial lung disease are similar.[41] However, inferior survival has been observed in patients with interstitial lung disease. Although the explanation for the shorter survival of patients with interstitial lung disease is not clear, it could be that chemotherapy exacerbated the underlying interstitial lung disease. Therefore, at present time, we recommend excluding patients with clinically significant interstitial lung disease from clinical trials testing agents, such as stereotactic body radiotherapy, that are associated with pulmonary toxicity.

The sequence of, and interval between, systemic treatments could have significant implications for the development of pneumonitis. A recent report described a high rate of pneumonitis when patients with NSCLC were treated with an immune checkpoint inhibitor, followed by treatment with osimertinib, an EGFR tyrosine kinase inhibitor (TKI), within 3 months.[45] This observation suggests that these patients might have had asymptomatic pneumonitis that was not detectable by chest computed tomography scans and that subsequent treatment with this TKI exacerbated occult pneumonitis.

Chemotherapy and Radiation Washout. Previous treatment regimens and clearance are a significant issue in lung cancer care. Lung cancer has specific issues with enrollment for radiation and chemotherapy washout, given that many patients have received multiple previous lines of therapy and could have significant toxicities from previous therapies. Patient enrollment has been limited by the widely variable washout timings between different studies. The LUNGevity survey identified the use of multiple definitions and language as a persistent issue, with some studies noting "any prior chemotherapy," others noting "any investigational therapy" or "prior systemic anti-cancer therapy." Almost all clinical trials in lung cancer have noted washout and previous therapy recommendations for radiation and previous treatments.

Regarding these issues, the specific language can depend on the specific study and investigational agent. The primary safety concerns are the potential for drug—drug interactions or the potential for additive toxicity. Also, the biologic half-life of previous treatments is worth consideration. Chemotherapy regimens will have negligible systemic levels within 30 days after treatment, although the toxicities can linger. Immunotherapy or antibody regimens can have substantially prolonged half-lives. For example, nivolumab has a half-life of ~25 days.[46] Small molecular drugs can have very short half-lives of several hours to days. Biologic agents such as CAR-T can remain biologically active and present in patients for the rest of their lives. Thus, it would be appropriate for exclusion language to specify either traditional chemotherapy agents versus biological versus small molecule-based therapies, as appropriate, according to the mechanism of action of the novel agent. Regarding traditional chemotherapy, the washout periods should be < 14 to 21 days and the washout time could be minimized, depending on the toxicity, bone marrow recovery, and immune reconstitution.[47]

The second major reason for washout in clinical trials is related to the potential for additive toxicity. Recovery from previous therapy-related toxicity to Common Terminology Criteria for Adverse Events grade 1 is commonly used language that is appropriate, especially in phase I trials of agents with less well-characterized toxicity profiles. However, these criteria are likely overly restrictive in the phase II and phase III setting for chronic toxicities secondary to therapy, which are unlikely to interfere with the tolerability for therapy (eg, chronic peripheral neuropathy secondary to paclitaxel or cisplatin treatment or hearing loss secondary to cisplatin). The duration of washout and recovery from previous treatment-related toxicities could be important. It might, therefore, be useful to grade the toxicities defined in the protocol for agents that could have overlapping toxicities with previous treatments. Again, the suggested focus is to be as inclusive as possible while maintaining patient safety.

Radiotherapy washout protocols and durations also varied significantly among the different studies examined and often included location data, toxicity, and intent (palliative vs. curative). Exceptions for palliative radiation therapy unlikely to interfere with therapy are recommended. Again, the level of baseline caution should be higher for phase I studies, given the risk of pneumonitis, even years after radiation,[48] with immunotherapies or TKI therapy. To the extent possible, we recommend minimizing radiation washout periods, especially for phase II and III studies, if toxicities have resolved.

Previous Lines of Treatment. The exclusion criteria relating to previous lines of treatment unnecessarily limit some patients with lung cancer from enrolling in clinical trials. Recent advances in lung cancer treatment have led to significant improvements in the median survival of patients with this disease, with many patients now living years after their initial diagnosis. For example, the 3-year follow-up of the phase I KEYNOTE-001 study with pembrolizumab reported a median overall survival of 34.9 months for patients with PD-L1$^+$ lung cancer treated with first-line pembrolizumab.[49] Improved outcomes have also been observed for patients treated with targeted therapies, including both ALK$^+$ NSCLC, for which alectinib leads to an estimated median progression-free survival of 34.8 months,[50] and EGFR$^+$ NSCLC, for which the combination of the EGFR inhibitor gefitinib and chemotherapy led to an estimated overall survival of 52.2 months.[51] Given the increasing number of effective lung cancer therapies and improving survival times for patients with lung cancer, patients are able to receive more lines of therapy during their lifetime.

Exclusion criteria limiting the number of previous lines of therapy have sometimes been used as a surrogate to exclude patients with more advanced cancer and poor overall functional status. Such patients could be at an increased risk of toxicities with treatment. However, the number of previous therapies does not necessarily reflect a more compromised clinical status, in particular, because many treatments now have very favorable side effect profiles. Other eligibility criteria, most notably the patient's current performance status and laboratory parameters of organ function, can be more effectively used to evaluate the status of the patient and exclude those who might be too ill for clinical trial enrollment.

Because patients with lung cancer are living longer and receiving increasing numbers of treatments during their lifetime, we recommend considering limits on the use of clinical trial exclusions based on the number of previous treatments received, especially for phase I trials in which the efficacy of a particular treatment is unknown. Instead, other markers such as performance status and laboratory parameters and/or bone marrow recovery, and possibly even neutrophil lymphocyte ratios and serum albumin, could be used to select patients healthy enough to participate in clinical trials.[52,53]

History of Stem Cell Transplantation. Exclusions for a history of stem cell transplantation affect a relatively large population of patients, because it has been estimated that there are roughly 500,000 survivors of hematopoietic cell transplantation (HCT) worldwide.[54] HCT plays a critical role in the management of a variety of hematologic diseases; however, long-term survivors face a range of late effects that can compromise their quality of life and survival.[55] The life expectancy of 5-year HCT survivors is ~30% lower than that of the general population.[56] The late effects of HCT include recurrent malignancy, chronic graft versus host disease, infection, lung disease (eg, bronchiolitis obliterans syndrome, cryptogenic organizing pneumonia, pulmonary hypertension), and secondary malignancy, among others.

Survivors of HCT have a greater risk of developing solid tumors compared with the general population.[55] Therefore, it is important that these patients have the opportunity to participate in clinical trials, provided they meet the remaining criteria with respect to end organ function and the agent or agents under study do not have a mechanism of action that could pose a theoretical risk of excess complications within the HCT survivor population (eg, immunotherapy in the setting of chronic graft vs. host disease).[57]

Laboratory Values

Liver Function Abnormalities. Lung cancer clinical trials often exclude patients with isolated elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels. Most exclusion criteria are a level of 2.5 times the ULN for AST or ALT, and many trials will exclude all patients with levels of 1.5 $\times$ the ULN. This can prevent many otherwise eligible patients from participating in clinical trials and obtaining safe access to new therapies. Many asymptomatic patients with good liver function will be excluded using these criteria. For example, nonalcoholic steatohepatitis or nonalcoholic fatty liver disease is the most common form of liver disease in the United States. Both are extremely common with an incidence of ~20% to 30% of the population of the United States.[58] Furthermore, $\geq$ 40% of these patients will have ALT levels $>$ 1.5 times the ULN, which would mean that many clinical trials are excluding $>$ 10% of the US population from enrollment despite these patients being asymptomatic with intact liver function. Also, newly discovered liver enzyme elevations in asymptomatic patients with intact liver function can be clinically followed up without biopsy and reevaluated as long as the elevations are $<$ 2 to 3 times the ULN and no other signs of cirrhosis are present.[59]

For drugs not suspected to be hepatotoxic, an isolated AST or ALT elevation cutoff of $>$ 3 times the ULN for patients without liver metastases and $>$ 5 times for patients with liver metastases could be implemented. Given that most patients with nonalcoholic steatohepatitis will have AST/ALT levels of $<$ 4 times the ULN and ~80% of trials will exclude patients with an AST or ALT level $>$ 2.5 times the ULN and 20% will exclude patients with an AST or ALT $>$ 1.5 times the ULN, this change in the cutoffs will improve patient enrollment for this significant cohort of patient in the United States. We recommend considering HIV, active hepatitis B, and hepatitis C testing, where appropriate, especially when the liver enzymes are elevated, because these infections can result in independent risks for patients in clinical trials.

Regarding the total bilirubin levels, it is important to note that Gilbert syndrome is another common cause of abnormal liver laboratory study results (per the National Library of Medicine, 3%-7% of the US population have Gilbert syndrome).[60] Gilbert syndrome is a genetic syndrome with changes in the expression of an enzyme responsible for bilirubin glucuronidation. It most commonly leads to an asymptomatic mild elevation of unconjugated bilirubin.[61] This will be a benign finding in most cases, although the drugs that rely mostly on glucuronidation by this enzyme, such as irinotecan, could result in increased toxicity in these patients. Patients with asymptomatic, chronic mild unconjugated hyperbilirubinemia consistent (eg, total bilirubin level $<$ 3 times the institutional ULN) with Gilbert syndrome should be included in lung cancer trials, with caution exercised for drugs metabolized by glucuronidation.

Normal Blood Counts and Recent Blood Transfusion. Many lung cancer clinical trials will exclude patients with hematologic indexes that are less than the lower limits of normal (eg, absolute neutrophil count [ANC] > 1500 cells/μL, platelet count > 100K cells/μL, hemoglobin > 9 g/dL) but are at levels that would not require intervention (eg, blood product transfusion or growth factor support). Recent receipt of a blood transfusion (within 7-28 days of study treatment day 1) is another frequent exclusion criterion despite not resulting in an immediate effect on the delivery of antineoplastic medicines in clinical practice.

Many clinical trials enrolling patients with lung cancer involve immune checkpoint antibodies or molecularly targeted agents that have little effect on the hematologic indexes. For example, in the recent KEYNOTE-024 trial, severe neutropenia or thrombocytopenia was not observed in patients treated with pembrolizumab, although 5.4% of patients treated with pembrolizumab had developed any grade of anemia.[15] In the recent FLAURA trial, ~1% of all patients enrolled to receiver either osimertinib or standard EGFR-TKI developed clinically significant anemia and < 1% of all patients enrolled developed neutropenia or thrombocytopenia.[62] The low level of hematologic toxicity reported in these studies could have been foreseen from the extensive phase I and II experience with immune checkpoint antibodies and TKIs. Despite this previous experience, both studies excluded any patient with an ANC of ≤ 1500 cells/μL, platelet count < 100K cells/μL, or hemoglobin < 9 g/dL. In addition, the FLAURA trial excluded any patient who had received a recent blood transfusion. A review of the FDA labels for osimertinib and pembrolizumab reinforced these low levels of hematologic toxicity.[63,64]

The enrollment of patients with hemoglobin of ≥ 8.0 g/dL, platelet count of ≥ 75K cells/μL, and ANC of ≥ 1.0 cells/μL could be acceptable in lung cancer trials of novel agents, provided the agents are not known to affect the hematologic parameters or are known to have a low likelihood of doing so (< 3% incidence of grade 3-4 treatment-related events). In addition, we recommend including otherwise eligible patients who have had recent transfusion of red blood cells.

Other Eligibility Criteria: Life Expectancy of ≥ 12 Weeks

Lung cancer clinical trial eligibility criteria frequently include a stipulation that "the patient is expected to be alive in 12 weeks." This factor is not straightforward to assess and will depend on age, comorbid medical problems, and extent of lung cancer. The expectation of being alive in 12 weeks cannot be measured using a blood test or computed tomography scan. Thus, fulfilling this criterion is often based on the clinician's "educated guess."

Several important arguments exist for removing this criterion from clinical trials. First, the risk of lung cancer increases with age, with more than one half of lung cancer cases diagnosed in patients aged > 65 years.[65] With age, comes the inherent risk of death from other age-related disease processes (eg, heart disease, stroke). Second, an inherent bias is associated with using age and life expectancy as criteria to exclude elderly patients from clinical trials, because these patients represent a highly select population that must satisfy the strict inclusion criteria. Because lung cancer is most frequently diagnosed among people aged 65 to 74 years, with a median age of diagnosis of 70 years,[66] excluding these patients from clinical trials could reduce the generalizability of results for a large segment of the lung cancer population.[67] Third, because the spectrum of different modalities to treat patients with lung cancer has continued to increase with the development of improved biomarkers and new systemic therapies beyond cytotoxic chemotherapy alone, patients with lung cancer have begun to live longer. For example, in the phase II study of nivolumab, the estimated 5-year overall survival rate was 16%,[68] with most of the long-term survivors actually no longer taking the drug. In addition, recent data have shown that for patients with ALK^+ metastatic lung cancer the median overall survival time from the diagnosis of stage IV disease was 81 months (6.8 years).[69] Ultimately, we believe that flexibility regarding the treating clinician's judgment about whether it is appropriate to enroll an older patient in a clinical trial is critical given that older age is associated with changes in CrCl and other comorbidities, which in turn, can affect a patient's health and ability to participate in a clinical trial.

FDA Pilot Review

In support of the present project and to ascertain the extent to which these 14 criteria appeared in recent lung cancer studies, the FDA conducted a pilot review of protocols within its database.

The aim of FDA's pilot study was to understand the patient eligibility criteria used in recently approved therapeutic products for NSCLC. The objective was to survey the inclusion and exclusion criteria used in key clinical trials with results that supported product approval. The pilot study included 18 pivotal and supportive trials for 11 therapeutic products covering 13 organ systems (eg, cardiovascular, renal) and, within those systems, 43 specific criteria (eg, previous MI within a defined period, calculated CrCl less than a certain threshold).

Inconsistency and heterogeneity of language and parameters described in the protocols surveyed were found. For example, renal insufficiency could be determined using the serum creatinine or CrCl. Also, for each of these parameters, the cutoffs used to inform eligibility varied. Similarly, nonspecific language was often used that could lead to variability in interpretation by the investigator. For example, patients with infections would be excluded if the infections were "uncontrolled and active," "severe," "active," or "ongoing and active"; however, no definitions were provided for these categories. Consequently, some of the criteria might be overly restrictive. The eligibility criteria were also found to be unstructured within some protocols.

The 14 criteria identified by LUNGevity as being unnecessarily restrictive and outdated were evaluated further in the FDA pilot study (Table 2). The results support our conclusions that these criteria are generally outdated, can be unnecessarily restrictive, and could hinder the enrollment of a broader patient population in clinical trials supporting therapeutic product registration. We recognize that our analysis complements the FDA's support for expanding the common cancer clinical trial eligibility criteria to broaden the patient populations included in trials and aligned with the recent guidance documents issued by the FDA.[70-74]

Screen Failures

In addition to assessing the recent protocols, the LUNGevity working group sought to understand the effect these exclusion

Table 3 Analysis of Screen Failures in Lung Cancer Clinical Trials Conducted by Eli Lilly

Clinical Trial	Inclusion or Exclusion	LUNGevity Criterion No.	Patients With Screen Failure, n
I4T-MC-JVCY	Exclusion	X	74
	Inclusion	3, 8, and 9	14
	Exclusion	2, 9, and 12	11
	Inclusion	X	10
	Inclusion	10	8
	Inclusion	X	5
	Exclusion	X	5
	Inclusion	X	5
	Exclusion	X	3
	Exclusion	6	3
I4T-MC-JVBA	Exclusion	X	144
	Exclusion	X	63
	Inclusion	3, 8, and 9	48
	Exclusion	X	28
	Inclusion	10 and 11	26
	Inclusion	X	25
	Exclusion	12	25
	Inclusion	X	17
	Exclusion	2	15
I3Y-MC-JPBK[a]	Inclusion	X	1572
	Inclusion	X	216
	Inclusion	X	74
	Inclusion	10 and 11	58
	Inclusion	X	50
	Exclusion	X	35
	Inclusion	3, 8, and 9	13
	Inclusion	5	12
	Inclusion	X	9
	Exclusion	12	7
I3Y-MC-JPBX	Inclusion	3, 8, and 9	8
	Inclusion	X	7
	Inclusion	X	4
	Inclusion	X	3
	Inclusion	10 and 11	2
	Exclusion	X	1
	Inclusion	X	1
	Inclusion	X	1
	Exclusion	X	1
	Inclusion	X	1

Numbers on column 3 correspond to individual criteria described in Table 1. X = Screen failure unrelated to LUNGevity criterion
[a]Top 2 reasons for screen failures were related to a KRAS mutation requirement.

criteria would have had on the enrollment of patients in recent sponsored lung cancer studies. To the best of our knowledge, this is the first report of data collected from screen failure data from a clinical trial of lung cancer. Eli Lilly, in consultation with the authors of the project, identified 4 contemporaneously randomized clinical trials of patients with lung cancer, in which data on screen failures were collected. All of the trials were globally conducted trials, and 3 were of registrational intent (ClinicalTrials.gov identifiers, NCT01168973, NCT02450539, NCT02152631, NCT02411448). Before any evaluation of any data, the 4 trial designs were evaluated for relevance to our project.

The goal of this effort was to evaluate the frequency of screen failures stemming from these criteria (ie, subjects who had signed an informed consent document and were entered in the trial but did not meet the protocol inclusion and exclusion criteria). The combined number of subjects across the 4 studies that had entered trial screening was 5535 (inclusive of a small number of rescreened patients). The total number of screen failures and enrolled patients across the trials was 2845 and 2408, respectively (Table 3). One trial had had an especially high screen failure rate because the inclusion criteria required a positive biomarker level before enrollment.

The most common reasons for screen failures across these 4 trials were brain metastases (254 subjects), line of therapy and/or long washout before starting therapy (94 subjects), abnormal laboratory test results (eg, renal tests, liver function tests, hematologic tests; 83 subjects), and poor performance status (79 patients). A less common reason was previous cardiovascular events (17 subjects). In most of the trials, many of the criteria were collapsed into a single exclusion criterion (eg, previous pulmonary embolism/deep vein thrombosis and bacterial/HIV infections were joined to other exclusion criteria). Although the subjects had failed the screening process for the aggregate criteria, it was not possible to isolate the specific, underlying reason as part of our analysis.

The results must be considered with 2 important caveats: (1) prescreened patients were not included and (2) a history of pneumonitis, oxygen requirements, a history of autoimmune disease, and previous stem cell transplantation could not be accurately measured because they were not listed as protocol exclusion criteria across most of the 4 studies. Thus, owing to these gaps in data, the effect of the exclusion criteria on screen failures for these studies could have been underestimated.

Conclusions

Trial sponsors should be cautious about reusing previous trial protocol templates when designing new studies, because outdated or unnecessary exclusion criteria could be present that are needlessly restricting enrollment. We would urge lung cancer trial sponsors to search for methods to expand the opportunities to include more patients in their trials, within the appropriate constraints for patient safety. Patients with lung cancer continue to seek options for access to novel therapy approaches, including participation in clinical trials, and trial sponsors expend time and resources to recruit and enroll patients in their studies. Through a multistakeholder effort evaluating the exclusion criteria and assessing the safety considerations, the LUNGevity working group identified 14 examples of frequent trial exclusions that might no longer be appropriate for routine use in lung cancer studies. We hope that this effort to identify and provide clinical justifications for removing potentially outdated or overly restrictive exclusion criteria from lung cancer clinical trials will contribute to expanded opportunities for patients to access novel therapies through clinical trials and help to develop an evidence base regarding the effect of investigational therapies among a broader population of patients. These recommendations are meant to serve as guidelines for sponsors. Treating physicians

should maintain the ultimate judgment regarding their patients' suitability for enrollment in a clinical trial, with consideration of an individual patient's health and the specific clinical trial setting (eg, distinctions should be made for late-stage clinical trials for which significant information is already available on the pharmacokinetics, metabolism, and unique adverse effects of the investigational agent or agents under consideration).

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