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EDITORIAL

The Ever-Increasing Number of Trial Eligibility Criteria: Time to Bend the Curve

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The purposes of trial eligibility criteria are to create a homogenous patient population and ensure patient safety. Previous trial eligibility criteria were developed to reduce the risks associated with chemotherapy and radiation therapy. Patients with lung cancer have been divided into molecularly defined patient populations, and with the development of antiangiogenesis agents, molecularly targeted therapy, and immunotherapy, the number of eligibility criteria has progressively increased. Garcia et al. analyzed the 74 lung cancer trials (including surgical, medical, and radiation trials) activated in the Eastern Cooperative Oncology Group from 1986 to 2016 and found a statistically significant increase in the median number of eligibility criteria (medians of 16 for 1986–1995, 19 for 1996–2005, and 27 for 2006–2016).[1] The primary cause of the increase in the eligibility criteria is medical oncology trials, specifically, laboratory testing. The increasing number of eligibility criteria is not surprising, but a median number of 27 eligibility criteria is cause for concern. The consequences of the increased number of eligibility criteria include fewer patients being able to participate in trials and the patient population enrolled possibly not representing the population of patients with lung cancer who are seen in routine care. Previous studies of the National Cancer Institute National Clinical Trials Network (NCTN) found that elderly patients were underrepresented in cancer clinical trials and that eligibility criteria were a contributing factor.[2]

The study by Garcia et al.[1] raises the question of whether it is time to reevaluate, simplify, and standardize some of the eligibility criteria for lung cancer trials. One area for improvement could be the elimination of "legacy" criteria from previous trials, such as hematological parameters for immunotherapy or molecularly targeted therapy trials when hematological adverse events are uncommon. Eligibility criteria related to prothrombin time and partial prothrombin time are frequently included but should be restricted to agents that increase the risk for bleeding, and urinalysis should be restricted to drugs known to cause proteinuria or another specific toxicity that requires a urinalysis. Perhaps the most problematic are the eligibility criteria related to "unstable" conditions, which can include a wide variety of conditions. These criteria are included in many protocols, but they are ambiguous, are open to widely different interpretation, and can be difficult to implement. If there are specific comorbidities of concern related to a study agent, a more specific eligibility criteria could be used (e.g., myocardial infarction within the last 6 months).

The eligibility criteria related to prior malignancy cancer are problematic, and they were included in more than 80% of protocols in this study. In a review of the Surveillance, Epidemiology, and End Results Medicare registry, approximately 15% of patients with lung cancer had a history of prior cancer, approximately 75% of prior cancers were localized or at the regional stage, and the median time from lung cancer diagnosis to prior cancer diagnosis was 4.7 years.[3] Importantly, among patients with stage IV lung cancer, a history of prior cancer did not adversely affect overall survival or lung cancer survival regardless of prior cancer stage, type, or timing of the prior malignancy. More recent trials have reduced the time requirement and allowed patients with in situ cancers of the breast or cervix and nonmelanoma skin cancer to enroll, but this definition remains an impediment to enrollment. For patients with stage IV lung cancer, the eligibility requirement could be changed to exclude patients receiving active therapy for other cancer or with concurrent metastatic cancer.

For locally advanced stage III NSCLC, common exclusion criteria used for clinical trials that may limit patient enrollment include strict timelines for recent

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imaging (i.e., positron emission tomography/computed tomography within 60 days of enrollment), fairly strict pretreatment pulmonary function criteria (forced expiratory volume in 1 second >1.2 L/s), Zubrod performance status of 0 or 1, prior lobectomy with current nodal recurrence, and unintentional weight loss exceeding 10% of body mass. These criteria are intended to select the best patient performers with the intent of achieving the best possible survival rates and/or the lowest toxicity outcomes. However, they do limit clinical trial participation. If the intent of the trial is to compare one systemic therapy against the other by measuring progression-free or overall survival, many of these limiting eligibility criteria could be loosened, enabling the study question to be answered more expediently. Ideally, some of the more important prognostic factors could be balanced between arms through stratification.

With regard to early-stage lung cancer, a recent retrospective observational analysis of the National Cancer Database examining the timing of adjuvant chemotherapy after a curative resection for stage IB to IIIA NSCLC showed that adjuvant chemotherapy given for up to 18 weeks was efficacious.[4] This suggests that future clinical trials of adjuvant chemotherapy should extend their current timing criteria from 12 weeks to 18 weeks. By allowing this simple extension, more patients, including the elderly (who may need more time to recover), can be enrolled onto trials. Adjuvant trials are of utmost importance because they have the best chance to increase the cure rate of lung cancer.

Biomarker-based trials present additional challenges. Most of these studies were performed before archival tissue collection or a specific biomarker were mandated as part of the eligibility criteria. In a retrospective study, of 250 patients with advanced NSCLC who were considered for biomarker-driven trials; in 40% of the samples analyzed, a biomarker of interest was identified and 15% of patients were enrolled in clinical trials.[5] The mean time between signing informed consent and receiving the biomarker analysis was 24.4 calendar days, the mean time for preparation of the slide by the pathology laboratory was 9.1 calendar days, and the time of biomarker testing in the central laboratory was 12.8 calendar days. The low rate of enrollment and the prolonged delays related to biomarker clinical testing are concerning. More recent National Cancer Institute trials have included a prescreening component to allow testing for biomarker testing, which may be useful if the trial is a study of second-line therapy, such as Lung-MAP (NCT02154490), or adjuvant therapy, such as ALCHEMIST (NCT02194738).

Most of the future trials will have translational medicine investigations integrated into the trial design, and patients are required to have a tumor sample available for trial participation. These translational medicine investigations are critical to our understanding of the activity of the therapy and disease biology, as well as for future biomarker development. Unfortunately, many times the tumor sample has been exhausted as part of routine clinical care and additional samples are not available. This often requires that the patient undergo an additional biopsy and delays the initiation of therapy. If the number and thickness of slides could be standardized and reduced to the bare minimum, it would facilitate trial participation. The ability of studies to routinely cover the cost of repeat biopsies to satisfy eligibility requirements would facilitate study enrollment.

The study by Garcia et al.[1] reminds us of the need to reevaluate our eligibility criteria for each study. For future clinical trials and those in development, we should make sure that the criteria are relevant, are concisely and simply worded, have appropriate time lines, and are standardized when possible across the National Clinical Trials Network lung cancer portfolio.

References

1. Garcia S, Bisen A, Yan J, et al. Thoracic oncology clinical trial eligibility criteria and requirements continue to increase in number and complexity. *J Thorac Oncol*. 2017;12:1489–1495.
2. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21:1383–1389.
3. Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. *J Natl Cancer Inst*. 2015;107:djv002.
4. Salazar MC, Rosen JE, Wang Z, et al. Association of delayed adjuvant chemotherapy with survival after lung cancer surgery. *JAMA Oncol*. 2017;3:610–619.
5. Vrancken A, Lepers S, Peeters L, et al. The challenge of molecular testing for clinical trials in advanced non-small cell lung cancer patients: analysis of a prospective database. *Lung Cancer*. 2016;102:96–100.