Dropping bars or rising hoops – phase III outcomes of NSCLC

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Over the past three decades, the interpretation of clinical trial outcomes in studies of advanced-stage non-small-cell lung cancer has changed. The robustness of findings from these trials has been called into question. We believe this change is a reflection of the improved understanding of molecular-based therapeutics and continued advances in this field.

Advanced-stage non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related death in the world.1,2 As such, effective systemic treatment for patients with NSCLC has been a subject of intense investigation over the past decades with the hope to improve survival. Sacher and colleagues recently published a retrospective analysis of the changes in study design and interpretation of randomised phase III trials in patients with advanced-stage NSCLC over time, particularly noting the changes in the primary endpoint of such trials, study outcomes, statistical significance and conclusions.3 For the purpose of comparison and analysis, trials were arbitrarily divided into three categories, based on the decade of publication: 1980–1990, 1991–2000, and 2001–2010. In their analysis of over 200 trials, the authors commented that overall survival remained the most common primary endpoint in all trials, although more trials from the past decade have used progression-free survival (PFS) instead of overall survival as the primary endpoint (0% in 1980–1990; 13% in 2001–2010, \(P=0.002\)).3 The interpretation of trials has also changed. The percentage of trials reporting a positive outcome that did not meet their primary endpoints has increased from 30% in 1980–1990 to 53% in 2001–2010 (\(P<0.001\)). Trials were reported as “positive” based on improvements seen in secondary endpoints, such as PFS and adverse effects. More importantly, the trials from the past decade have also been seen to assert non-inferiority despite a lack of a statistically appropriate non-inferiority design or had recommended further study on the basis of a nonsignificant trend in primary outcome. A trend toward decreasing magnitude of survival gain in trials reporting a statistically significant survival improvement was seen over time (3.9 months in 1980–1990, 2.5 months in 2001–2010, \(P=0.11\)). There has also been an increase in sample size of clinical trials over time, indicating that ‘statistical significance’ was only achieved owing to the accrual of a larger number of patients, but leading to a lower magnitude of survival gain per patient. Specifically, when all trials deemed positive were considered, the decreasing magnitude of improvement in survival was even more apparent, with median net survival of 3.9 months in 1980–1990 compared with only 0.9 months from trials from the period 2001–2010.

The authors of this study conclude by warning that “the bar is dropping” with a significant shift in the past three decades in the design and interpretation of randomised phase III trials in patients with advanced-stage NSCLC.
advanced-stage NSCLC. This shift is evidenced by the declining use of overall survival as the primary measure of benefit, and the magnitude of benefit itself.

While we appreciate their efforts and agree that the trend of randomised phase III trials in patients with advanced-stage NSCLC have changed considerably over the past three decades, we are hesitant to concur with the belief that this has a negative impact on drug development for NSCLC as a whole, and we disagree with the authors’ conclusion that the bar is dropping. There is an overriding concern about the design of the analysis of Sacher and colleagues. Specifically, there is no mention of the rationale of why clinical trials were arbitrarily ‘pigeon-holed’ into the three categories based on their decades of publication. To the best of our knowledge, there is no justification to use these specific time points as cut-offs, apart from ‘rounding off’ these numbers for analysis purely for convenience. There is no reason to believe that the nature of a trial and the attitude of the authors may switch according to the decade. Categorising trials on the basis of their publication dates inherently introduces bias into the subsequent data analysis and conclusions.

Notably, specific landmark advances in science would change clinical trial design. There have been significant changes in the systemic management of patients with advanced-stage NSCLC over the past three decades. The key milestones of these changes are the discovery in 2004 of driver oncogenes such as EGFR and in 2007 the identification of the translocation mutation of anaplastic lymphoma kinase (ALK). With a better understanding of molecular subtypes of NSCLC, specific tyrosine kinase inhibitors, such as gefitinib, were shown to be superior to standard platinum-based cytotoxic chemotherapy, whereas treatment outcomes were the opposite in patients without EGFR mutation. Since then, patient selection according to the tumour molecular profile has become a crucial component of many monumental phase III trials in patients with advanced-stage NSCLC. We believe that if an analysis of patterns and interpretation of NSCLC trials is to be done fairly, these particular milestones should be taken into account and grouping of trials should be based on the disease biology.

As we move towards a new era of molecular targeted therapy trials according to the genetic profile of each patient, it is only natural to adopt PFS as the primary study endpoint. Improvement in overall survival might not be reflected in these clinical trials given that it would be unethical not to offer the experimental drug to patients (with the driver oncogene) in the control arm upon a clear PFS advantage. For example, Kwak and colleagues have established in a phase I study that patients with an ALK mutation attained high tumour response rates (overall response rate 57%, stable disease 33%) and prolonged PFS (probability of 6-month PFS is 72%) with crizotinib. Thus, in the randomised phase III study comparing crizotinib with single-agent chemotherapy, Shaw et al. intentionally (and ethically) allowed all patients to receive crizotinib upon disease progression following chemotherapy. This study has successfully demonstrated prolongation of PFS, which proves the true efficacy of crizotinib, whereas the lack of overall survival benefit is merely a reflection of the crossover-effect.

The proposal that the ‘bar is dropping’ could be correct if lung cancer remained a homogenous disease. Clinical trials that used overall survival as the primary endpoint might have made a small impact on survival in the past. However, the one-size-fits-all approach of large phase III trials comprising of a ‘basket’ of NSCLC patients with diverse molecular subtypes is unlikely to provide further improvement in clinical outcomes. As we understand more about the heterogeneity of NSCLC and its reliance on different driver oncogenes for propagation, we believe the pendulum will swing towards smaller and molecular-based trials.

We, therefore, believe that the bar is not dropping; rather, the opposite effect is true. The design and interpretation of clinical trials for NSCLC will likely become more stringent and complex given the smaller numbers of patients available as we break NSCLC down into numerous molecular subtypes. Further advances in the science of this disease will likely produce more bars and possibly even hoops, which we will need to overcome.

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