with severe cystic fibrosis (CF)-related lung disease after commencing elexacaftor–tezacaftor–ivacaftor (1). We congratulate the authors on capturing real-world population data in this key group of patients with FEV_1 <40% who have significant potential to benefit from these treatments but were excluded from the pivotal phase 3 trials. The authors demonstrated significant and rapid improvements in lung function, nutritional parameters, and treatment burden in line with previous studies (2–4). Importantly, they are the first to describe a significant reduction in the need for lung transplantation, with 11 of 16 patients removed from the lung transplant waiting list and a remarkable 36 of 37 removed from consideration of transplant within the next 3 months.

Therefore, at a population level, there are many reasons to be optimistic, but clinicians must remain cautious in their expectations and not prematurely alter their practice, which is a message that was not highlighted in the manuscript. Our own experience and that of others (2–4) suggests that not every patient will experience such a dramatic improvement in lung function, because of either lack of response or medication intolerance. For example, in one phase 3 trial of triple therapy, 1% of subjects had to cease the medication because of adverse events, 11.6% developed elevated liver enzymes, and 10.9% developed a rash (3). In addition, nonresponding cases may not be reported as frequently because of publication bias. Enthusiasm for this class of medications may also be heightened because of the widespread involvement of CF care teams (including the authors of this letter) in the clinical trials and the frequent conflict of interests that have developed consequently through associations with manufacturers. As clinicians we must remain alert to all possible outcomes and continue to follow existing standards of care, which currently include early referral for consideration of lung transplantation.

The importance of continuing to consider lung transplantation is a key aspect of management, as early engagement with transplant services leads to better outcomes (5). In addition, early involvement with palliative care services can benefit patients with severe, end-stage lung disease considerably. The Cystic Fibrosis Foundation recommends that discussions about lung transplantation should occur when FEV_1 declines below 50%, and lung transplant referral should occur for those with advanced but not end-stage lung disease (5). Lung transplantation is a major undertaking, and consideration includes significant education, support, and joint decision-making over time. Although CFTR modulator therapies such as elexacaftor–tezacaftor–ivacaftor now play an important role in discussions about disease trajectory and treatment options, we suggest that the practice of early transplant discussion and referral should continue.

Despite the remarkable outcomes described in this paper and the optimistic promise of future CFTR modulator therapies, we must remain cautious about changing our practice and continue to prepare and offer options for those who do not tolerate or respond to triple therapy. ■

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Reply to Kuek *et al.*

From the Authors:

We thank Dr. Kuek and colleagues for their letter in reference to our recent publication (1). They suggest that our manuscript contains many reasons to be optimistic but that it does not highlight that clinicians must remain cautious with their expectations and should not prematurely alter their practice standards. As stated in our original manuscript, our study provided the first data describing the effects of initiating elexacaftor–tezacaftor–ivacaftor in a large cohort

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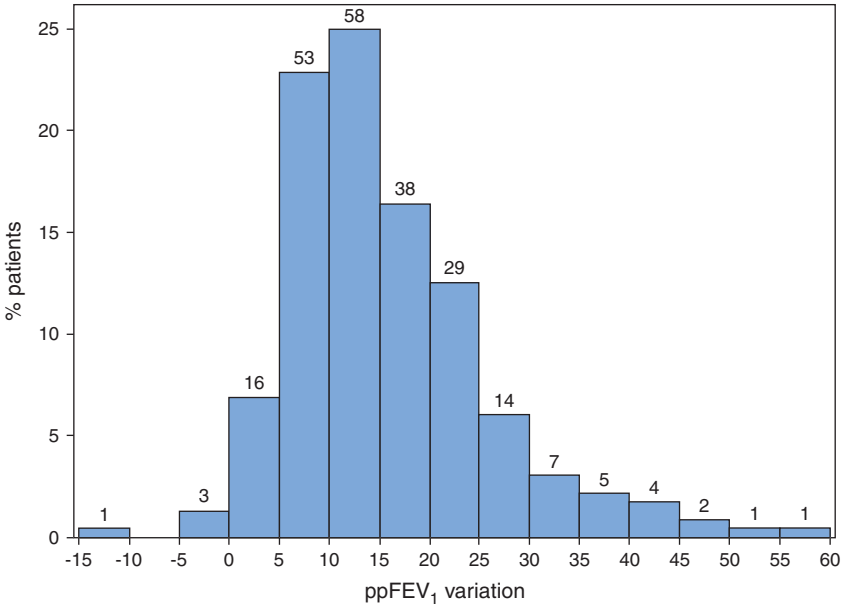

Figure 1. Distribution of the difference between the best $ppFEV_1$ after starting elexacaftor–tezacaftor–ivacaftor compared with baseline $ppFEV_1$ (n = 232 patients). Numbers of patients are indicated on top of the bars. Data are from Reference 1. $ppFEV_1$ = percentage predicted FEV_1.

of patients with cystic fibrosis (CF) and advanced pulmonary disease (1). Because our manuscript reported early experience with this novel medication, we purposefully did not discuss the consequences in terms of change in daily clinical practice and highlighted the fact that our data should be confirmed over a longer period of time and in multiple countries (1).

Kuek and colleagues also state that dramatic improvement in lung function occurred at the population level, but that their experience and previous studies suggest that not every patient will experience such a dramatic improvement. We agree that lung function response to CFTR (cystic fibrosis transmembrane conductance regulator) modulators is heterogeneous; however, a remarkable finding in our study was that initiation of elexacaftor–tezacaftor–ivacaftor resulted in an unprecedented median (quartile 1 to quartile 3) increase in percentage predicted FEV_1 ($ppFEV_1$) by +13 (+8 to +20; n = 232 patients; $P < 0.0001$). These results are remarkable in comparison to the trends presented in a previous comparable study evaluating the effectiveness of lumacaftor–ivacaftor in patients with $ppFEV_1$ <40, in which the median increase in $ppFEV_1$ was +0.5 (−2.2 to +4.3; n = 77 patients; $P = 0.03$) with only 22% and 7% of patients showing an increase in $ppFEV_1$ ⩾5 and ⩾10, respectively (2). The distribution of increase in $ppFEV_1$ with elexacaftor–tezacaftor–ivacaftor observed in our recent study (1) is provided in Figure 1. As the graph shows, although a limited number of patients had no increase in $ppFEV_1$, 91% and 69% of patients had an increase in $ppFEV_1$ ⩾5 and ⩾10, respectively. Clearly, these findings indicate that the majority of patients with advanced respiratory disease will show a significant increase in lung function with elexacaftor–tezacaftor–ivacaftor. Furthermore, lack of improvement in lung function is not synonymous with a lack of response to therapy, as patients with no increase in $ppFEV_1$ can show improvement in nutritional status and exacerbation rates (2, 3).

Kuek and colleagues also suggest that medication intolerance may prevent treatment with elexacaftor–tezacaftor–ivacaftor, as 1% of subjects (two subjects) had to discontinue the medication because of adverse events (one rash, one portal hypertension in a patient with preexisting cirrhosis), 11.6% developed elevated liver enzymes, and 10.9% developed a rash in the phase 3 study by Middleton and colleagues (4). Importantly, treatment discontinuation due to adverse effects is clearly a problem when no alternative treatment exists. For example, our group reported a 28.2% discontinuation rate in patients with $ppFEV_1$ <40 treated with lumacaftor–ivacaftor, an older-generation CFTR modulator (5), who were left with no alternative treatment at that time. In addition, our recent study with elexacaftor–tezacaftor–ivacaftor reported an overall good safety profile with minor adverse events. These included a localized rash in 7.2% and generalized rash in 3.8% of patients, and a liver enzyme increase ⩾3, the upper limit of normal, in less than 3% of patients (1). Importantly, these adverse events were generally manageable and no patient had to discontinue treatment. Large-scale data in patients with preexisting liver cirrhosis are needed, as these subjects were generally excluded from phase 3 trials and accounted for only 5% of patients in our study. Furthermore, we suggest that improved knowledge on the management of adverse effects (e.g., cutaneous rash) may allow most patients to continue treatment.

Dr. Kuek and colleagues further suggest that nonresponding cases may not be reported as frequently because of publication bias. Although this statement is generally true, it does not apply to our CFTR real-world studies in which all patients, regardless of their outcomes (favorable or not!), are systematically reported by all 47 centers in France (1, 2, 5).

Finally, Kuek and colleagues underscored the importance of continuing to consider lung transplantation as a key aspect of management for patients with CF. We agree that lung transplantation remains an important aspect of the clinical management of patients with CF in whom no other treatment options are available. This group of patients includes patients with advanced pulmonary disease in whom symptomatic treatment directed toward lung infection and respiratory insufficiency, nutritional support, and CFTR modulators provides insufficient improvement. Of note, approximately 15% of

patients have CFTR genotypes that do not respond to current CFTR modulators. Additional follow-up data, collected over a longer period of time, are clearly necessary to fully establish the effects of elexacaftor–tezacaftor–ivacaftor on lung transplantation in eligible patients with advanced disease. Nevertheless, our data suggest that clinically significant improvements in lung function, body weight, and gas exchange as well as symptoms and quality of life will allow healthcare teams to postpone lung transplantation in many patients.

The data provided in our study therefore support granting access to elexacaftor–tezacaftor–ivacaftor to all eligible patients throughout the world and seem paramount in the care of patients with CF, albeit with a careful monitoring of long-term effectiveness and potential adverse outcomes. ■

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Informing Healthcare Decisions with Observational Research Assessing Causal Effect: An American Thoracic Society Statement Not Ready for Implementation

To the Editor:

A recently published American Thoracic Society Statement concluded that observational studies (OS) should be included in guideline development and used in clinical decision-making in absence of high-quality randomized controlled trials (RCTs) and can "contribute compelling evidence for causal inference" (1). The authors contend that OS have better generalizability and/or external validity, less publication bias, imprecision, and inconsistency, and lower cost; enroll larger sample sizes; have fewer limitations resulting from lack of equipoise; and can be used to assess cause and effect. A more evenly balanced consideration of these contentions is needed.

The authors propose that OS produce higher levels of generalizability/external validity because efficacy RCTs are frequently conducted in academic centers and use numerous inclusion and exclusion criteria. These are not problems with RCTs *per se*, however, as investigators can specify sites where studies should be conducted and can define inclusion criteria as narrowly or broadly as they wish (2). The authors correctly note that pragmatic RCTs address many of these concerns and these preserve the critical element of randomization. Accordingly, the benefits of randomization need not be killed on the altar of generalizability/external validity.

The authors state that publication bias, imprecision, inconsistency, and lack of equipoise adversely affect RCTs, but these concerns apply to

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