Estimating prognosis in patients with resected non–small cell lung cancer (NSCLC) remains an area of active research, as risk of recurrence is substantial. Even with the addition of adjuvant platinum-based chemotherapy, the risk of recurrence or death remains high.1 Findings from prior studies on the prognostic impact of epidermal growth factor receptor (EGFR) alterations in early stage NSCLC are conflicting, and factors associated with recurrence risk in patients with EGFR-positive NSCLC need further elucidation. The cohort study by Tan et al2 included patients with EGFR-positive and wildtype EGFR early-stage NSCLC with the primary goal to compare disease-free survival (DFS) between cohorts and identify clinicopathologic and molecular factors associated with recurrence among patients with EGFR-positive NSCLC. Tan et al2 found that 2-year DFS was similar between patients with EGFR-positive NSCLC (70.2%) and those with wildtype EGFR NSCLC (67.6%), and several risk factors for recurrence were identified in the EGFR-positive population. This research is especially timely and relevant, given the recent Food and Drug Administration (FDA) approval in December 2020 of adjuvant osimertinib in patients with stage IB to IIIA resected EGFR-positive NSCLC. The impressive DFS benefit with adjuvant osimertinib seen in the ADAURA trial3 in patients with resected EGFR-positive NSCLC led to this approval; however, many researchers still await mature overall survival data from this landmark study.

In this large pre-ADAURA cohort, Tan et al2 found DFS to be similar between the wildtype EGFR and altered EGFR groups, which questions the prognostic significance of EGFR alterations in terms of recurrence risk. However, overall survival was significantly improved in EGFR-positive NSCLC compared with wildtype EGFR NSCLC, which is likely explained by the number of efficacious targeted treatment options in the metastatic setting for EGFR-positive NSCLC. Tan et al2 found similar DFS for patients with stage IA (81%) and IB (78%) NSCLC in the EGFR-positive cohort. This is notable, given that patients with stage IA NSCLC were not included in ADAURA3 and are otherwise not eligible for osimertinib, per the FDA label. Even among patients with very early-stage disease, nearly 20% of patients still experience early recurrence or death. On the other hand, Tan et al2 note that 37% of their overall cohort of patients with stage IB to IIIA NSCLC were disease free at 5 years and cured, without the benefit of receiving adjuvant osimertinib.2 Since the publication of the ADAURA findings,3 much debate has been centered around which patients benefit most from adjuvant osimertinib, given the differences in absolute DFS benefits observed by stage. Many oncologists admit a greater enthusiasm for offering this additional therapy to patients with stage II to IIIA disease and acknowledge the need for more nuanced discussions regarding the risks and benefits in stage I disease. The findings by Tan et al2 highlight that stage of disease is only a part of this equation and support the need for further research on individual risk profiling and prognostic modeling for recurrence.

To further our knowledge on this, Tan et al2 conducted multivariable analyses to identify clinicopathological features associated with recurrence. Largely consistent with traditionally accepted high-risk features in a general NSCLC population,4 they found higher stage, sublobar resection, positive resection margins, lymphovascular invasion, and nonacinar and nonlepidic adenocarcinoma histological subtypes to be associated with recurrence in patients with EGFR-positive NSCLC. In an exploratory analyses of a subgroup of 85 patients with EGFR-positive NSCLC, whole-exome and transcriptome sequencing data integrated with histopathological information...
were used to develop a prognostic model for recurrence. Their model identified alterations in RHPN2, CTNNB1, and micropapillary subtype to be associated with increased risk of recurrence, while loss of RB1 was associated with decreased risk. As Tan et al note, micropapillary subtype and CTNNB1 alterations have been traditionally associated with a poor prognosis. Conversely, the finding of RB1 loss as having a protective association is surprising, given that prior studies have linked it to adverse survival and small cell transformation. Molecular sequencing is an integral part of initial diagnostic testing in advanced metastatic NSCLC. Since ADAURA, more patients may now be receiving such testing immediately after surgical resection to identify EGFR alterations. Thus, whole-genome sequencing may be a plausible strategy and readily adaptable to assess for molecular risk-signatures in such patients with early-stage cancer in the future.

Over the past decade, the landscape of NSCLC treatment has changed dramatically to include the use of targeted agents in advanced disease. One of the biggest success stories has been targeted therapy in the EGFR-positive population, which has transformed a disease with previously short survival to a well-managed chronic disease that many patients may live with for years. Much focus recently has been on patients with early-stage EGFR-positive NSCLC and preventing recurrence after definitive therapy. The study by Tan et al characterizes such patients with early-stage EGFR-positive NSCLC in one of the largest pre-ADAURA cohorts to date, with several clinicopathological and molecular factors identified as associated with recurrence risk. Continued work on individualized risk stratification, including prospective studies and research that incorporates cell-free DNA techniques as measures of risk, is needed to better inform oncologists' decision-making regarding adjuvant therapy use after resection.

ARTICLE INFORMATION
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