VIEWPOINT

Molecular Marker Testing in Curable Non–Small Cell Lung Cancer—Practice Necessarily Precedes Data

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Emerging Data and Evolving Implications

Over the past decade, the differentiation of advanced non–small cell lung cancer (NSCLC) into multiple subgroups defined by the presence or absence of driver sequence variations and tumor expression of programmed cell death ligand 1 (PD-L1) has transformed outcomes. Comprehensive molecular genotyping using next-generation sequencing is recommended during the initial workup of advanced NSCLC based on established improvement in survival and an overall reduction of toxic effects for many patients. Optimal molecular testing strategies in early-stage NSCLC, however, have yet to be defined.

Recently, 3 key trials have changed the paradigm of treating patients with resectable NSCLC through the introduction of targeted therapy and immunotherapy in the perioperative setting. In 2020, the US Food and Drug Administration granted approval for osimertinib following surgical resection for NSCLC with a sensitizing epidermal growth factor receptor (*EGFR*) sequence variant.[1] In 2021, atezolizumab became the first immune checkpoint inhibitor (ICI) to be approved for adjuvant use following surgical resection and chemotherapy in patients with PD-L1–expressing tumors.[2] Most recently, neoadjuvant combination chemoimmunotherapy was approved for patients with early-stage resectable NSCLC without an *EGFR* mutation or *ALK* translocation.[3] These approvals require biomarker testing, including PD-L1 testing and determination of at least *EGFR* and *ALK* mutations to guide management in the perioperative setting. This is a departure from current practice, in which the performance of molecular testing is largely dependent on stage and histologic findings. At present, however, the limited and inconsistent data on molecular genotyping and patient selection to enrich or exclude certain patients based on stage and histologic findings requires the oncology community to draw inferences and follow our best judgment about optimal biomarker testing, invariably landing between overtesting or undertesting.

We argue that in a setting in which direct evidence is lacking, broad molecular marker testing combined with PD-L1 testing should be a preferred strategy for patients in whom treatment beyond local therapy alone is likely indicated, while acknowledging that this strategy may leave many open questions.

The Debatable Value of Molecular Data

The support in favor of broad, panel-based, next-generation sequencing in early-stage NSCLC with a nonsquamous histology is that, in addition to informing the decision around perioperative therapy, knowing the molecular profile may also provide valuable and readily accessible information in anticipation of disease relapse to avoid further treatment delays. However, is this argument valid for all patients with early-stage NSCLC? One of the core tenets of medicine is to eschew tests for which the results would not alter management. This is particularly true when the test in question has a cost of several thousand dollars and may not be covered by all payers. Moreover, data obtained in patients with a stage of disease for which systemic therapy is not indicated may adversely alter management decisions. For instance, if a patient is found to have *RET*-rearranged stage II NSCLC, the oncologist or patient may be tempted to administer a *RET* inhibitor, extrapolating data from the clinical trial of adjuvant osimertinib but in a setting in which the effectiveness of *RET*-directed therapy remains untested. In a patient with very early NSCLC, for whom no systemic therapy is indicated, molecular testing may be considered; but the risk of harm, including financial adverse effects, may well exceed anticipated benefit if the probability of relapse is low.

Confirming the Value of Molecular Testing Where Systemic Therapy Is Indicated

For patients with stage I to III NSCLC in whom systemic therapy beyond local therapy is warranted, clinical trials provide evidence-based support for testing PD-L1 expression along with *EGFR* and *ALK* mutations. Beyond these biomarkers, however, we would contend that there is now value in comprehensive molecular genotyping. While testing policies for specific trials on stage I to III NSCLC have been piecemeal, we would argue that lessons learned in the stage IV NSCLC setting should be applied to the curative setting. Specifically, a growing constellation of data support the premise that ICIs directed at either programmed cell death 1 or PD-L1 are less effective and even ineffective against cancers that harbor many, but not all, driver sequence variations.[4,5] As a general premise, patients with genomic alterations that have highly active associated targeted therapies should be preferentially treated with targeted therapy, even in the presence of high PD-L1 expression. That said, we should avoid advocating one strategy for all subgroups, as data indicate that NSCLC positive for *KRAS* or *BRAF* V600E sequence variants appears to respond comparably to immunotherapy as does wild-type NSCLC.[4,5]

Identifying patients with early-stage cancers associated with a driver sequence variation is not only valuable because it can identify patients for whom immunotherapy is likely to be ineffective, it can also identify patients in whom immunotherapy is likely to be harmful. For many of these same patients, immunotherapy may pose a significant risk of harm if their cancer

demonstrates relapse or progression while they are taking or have just completed ICI therapy due to the long half-life of these agents and the common finding of serious and even potentially life-threatening adverse effects from the interaction of these targeted therapies with concurrently or recently administered ICIs.[5] Based on this concern, many thoracic oncology experts are disinclined to recommend durvalumab to patients with a known driver sequence variation despite the fact that the PACIFIC trial[6] (which confirmed the efficacy benefit of consolidation durvalumab after concurrent chemoradiation for unresectable stage III NSCLC) did not specifically test for or exclude patients based on the presence or absence of a driver sequence variation. At the same time, retrospective data from the PACIFIC trial suggest that the efficacy of consolidation durvalumab did not extend to patients with tumor PD-L1 expression less than 1%, making it appropriate to know a patient's tumor PD-L1 expression when personalizing a recommendation for or against this treatment.[7] In addition, molecular genotyping represents a uniquely attractive path for those patients in whom an incidental driver sequence variation is found for which there is a relevant clinical trial available. For those without a trial-based option, we can expect new data in the coming years to help guide our practice, with patients and their oncologists left to weigh the potential off-protocol options vs surveillance off of treatment as an alternative. Given the probability that these concerns apply to patients with a growing array of driver sequence variations and associated targeted therapies, we believe it is appropriate to prioritize broad panel-based molecular genotyping for any thoughtful and individualized discussion of anticipated risk vs benefit among systemic therapy options.

By Necessity, Practical Management Precedes Data

Our current practice in the setting of early-stage NSCLC leaves us in the unenviable situation of being forced to decide on biomarker testing with insufficient data to guide us. In this void, we must apply our best judgment and recognize that we can err by either overgenotyping or undergenotyping. It is most appropriate to discuss the nuances and implications of these decisions with patients, as it is quite possible that results may unwittingly lead to future clinical decisions that lack evidence-based answers. On balance, while the use of comprehensive molecular genotyping is questionable for patients with such early-stage disease in whom systemic therapy is not indicated, we believe it is most appropriate to seek a full picture of the potentially relevant molecular markers for those in whom systemic therapy is indicated, enabling oncologists and patients to make optimally informed care decisions in the face of ambiguity.

ARTICLE INFORMATION

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