Review Article

Role and room for biomarkers in non-small cell lung cancer

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Abstract: While molecular profiling of tumor tissue from patients with advanced cancer has been ordered by physicians to assist with treatment decision making, it is important to note that the cancer theranostics literature is rampant with many improperly validated biomarkers for prognostic and/or predictive features. This review outlines commonly assessed biomarkers in non-small cell lung cancer (NSCLC) associated with a clinical benefit. Overall, there remains room for improvements in this field and the undertaking to have validated and reproducible biomarkers associated with a clinical benefit is not a trivial undertaking.

Keywords: Advanced non-small cell lung cancer (advanced NSCLC); next-generation sequencing (NGS); somatic mutation; biomarkers; theranostics

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For several years, molecular profiling of tumor tissue from patients with advanced cancer has been ordered by physicians to assist with treatment decision making. It is important to note that the cancer theranostics literature is rampant with many improperly validated biomarkers for prognostic and/or predictive features (1,2). The most commonly used non-small cell lung cancer (NSCLC) biomarkers for which there are validated studies conducted by more than one group using clinically-annotated samples from prospective clinical trials are listed in *Table 1*. These are mainly somatic mutations or gene rearrangements of known oncogene drivers in cancer.

The association of biomarkers with clinically meaningful endpoints, defined as conferring an overall survival (OS) benefit, are even more limited. Endpoints that patients care about are OS or quality of life improvements, in contrast to those that they have been told are important, such as progression-free survival (PFS) or overall response rate (ORR) (3). While PFS and ORR are criteria considered by regulatory authorities for drug approval, they often do not correlate with an OS advantage (4,5). Furthermore, the reported substantial time saved for bringing new drugs to market utilizing surrogate endpoints compared with OS appears to be exaggerated (6). This is particularly salient when the likelihood of regulatory withdrawal of an approved anticancer drug for lack of efficacy is rare.

Use of next-generation sequencing (NGS) platforms, with their ability to measure hundreds of biomarkers, are increasingly touted as cost-effective relative to assessing a limited panel of more clinically meaningful biomarkers (7-10). However, the cost to patients and/or payor often exceeds thousands of dollars per NGS test, not including the cost of tissue/blood acquisition and the associated facility/provider fees that can be extraordinarily high. Determination of utility, particularly with the dearth of randomized clinical trials testing the superiority of NGS relative to routine testing has been challenging (8,11).

The Food & Drug Administration (FDA) has either approved or authorized two different molecular profiling platforms for tumor tissue testing in 2017 (12). A summary of commercially available NGS platforms both for tumor tissue and blood are listed in *Table 2*. Several papers have evaluated the concordance between NGS platforms. Few of these have focused on DNA level changes and contemporaneously collected matched sample pairs of tumor and/or blood (13,14). Longer time intervals between paired sample collection from the same patient (months or years) increases the probability of altered clonal changes and a different mutational profile (15,16).

There are many other theranostic biomarkers under evaluation that are considered exploratory at this point in time. These include non-coding RNA, exosomes,

Table 1 Commonly assessed biomarkers in NSCLC associated with a clinical benefit

Biomarker	Feature associated with clinical benefit	Linkage to approved drug class in NSCLC
EGFR	Gene mutation	EGFR inhibitor
ALK	Gene rearrangement	ALK inhibitor
ROS1	Gene rearrangement	ROS1 inhibitor
BRAF	Gene mutation	BRAF + MEK inhibitor
NTRK	Gene rearrangement	NTRK inhibitor
PD-L1	Protein expression	PD-1 or PD-L1 inhibitor
Tumor mutation burden	Numerical cutoff	PD-1 or PD-L1 inhibitor +/– CTLA-4 inhibitor

NSCLC, non-small cell lung cancer.

Table 2 Sample of commercially-available NGS platforms

Platform Name	Manufacturer	Type of analyte	Amount of material	Number of genes	Typical turnaround in calendar days
FoundationOne®	Foundation Medicine (Cambridge, MA)	Tumor tissue	11 slides, 25 mm^2	Entire coding sequence of 315 genes, introns of 28 genes	8–14 days
MSK-IMPACT	Memorial Sloan Kettering (New York, NY)	Tumor tissue and matching whole blood	5–20 unstained 10-µm thick sections, blood volume not specified-minimum 50 ng DNA input	468 genes	20 days
Caris Intelligence	Caris (Phoenix, AZ)	Tumor tissue	25 unstained 4-µm thick sections, 25 mm^2	592 genes	14 days
PCDx™	Paradigm (Phoenix, AZ)	Tumor tissue	1–2 4 µm slides, 3 mm^2	234 genes	3–5 days
PlasmaSELECT™-R64	Personal Genome Diagnostics (Baltimore, MD)	Plasma	6–10 mL	64 genes	14–21 days
Circulogene Genomics Profiling	Circulogene (Birmingham, AL)	Plasma	0.5 mL	53 genes	5–7 days
FoundationOne® Liquid	Foundation Medicine (Cambridge, MA)	Whole blood	17 mL	70 genes	<14 days

NGS, nest-generation sequencing.

and microbiota. Other types of analytes that have been examined beyond tumor and blood include urine, bronchial lavage, stool, and saliva. Limitations of biomarker discovery and validation include the use convenient samples that are readily available to investigators at the time of research and were collected without the previous intent for biomarker discovery, use of invalid surrogate endpoints, insufficient sample size, low quality samples, and/or the inability to reproduce results in independent cohorts (2).

Two commonly cited predictive biomarkers for benefit with immunotherapy in NSCLC are PD-L1 immunohistochemistry (IHC) staining and tumor mutation burden (TMB). The KEYNOTE-024 (KN-024) trial of checkpoint inhibitor pembrolizumab *vs.* chemotherapy in first-line advanced NSCLC with PD-L1 IHC ≥50% met its primary endpoints for both overall survival (OS) and PFS (17). While there are several different IHC stains and criteria, one of the most prevalently used is the commercially available 22C3 pharmDx assay as a result of the KN-024 and subsequent supporting prospective trials

involving its use in NSCLC. TMB has been proposed as a predictive biomarker based on data suggesting that the prevalence of somatic mutations leads to increased novel peptide epitopes that may result in enhanced tumor immunogenicity. Discordances between assays for mutation calling, reproducibility of threshold cut-offs, and turnaround time for results are factors that weigh in on TMB's broad applicability as a predictive biomarker (18). To date, TMB has not been validated to predict OS benefit in NSCLC.

While there are many NSCLC theranostics reported as promising in the literature, an overwhelming majority do not pan out after rigorous validation. There remains room and it is a nontrivial endeavor for improvements in this field, either with linkage of existing drugs and previously identified biomarker targets or future yet uncharacterized biomarkers and undeveloped anti-cancer agents.

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Footnote

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