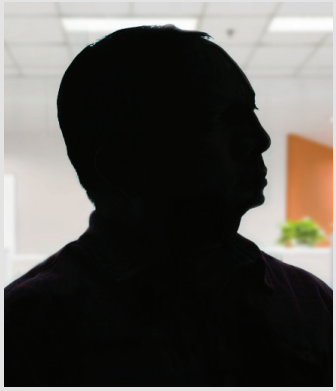
CASE STUDY

Comprehensive Analysis of Lung Cancer Specimens: Enabling Early Choice of the Most Appropriate Therapies

Quick Summary



- Mr. Daftari* (59 years) was diagnosed with lung cancer (NSCLC) and was prescribed the StrandAdvantage Lung Tissue-Specific Test (TST) for molecular analysis of the cancer (Oct 2017). The test is designed to probe for expression of proteins, detection of gene amplifications as well as NGS analysis.
- Results from the molecular characterization of the tumor provided decision support for sequential as well as combinatorial choices of targeted therapeutic drugs, in addition to generic chemotherapy.
- A comprehensive tissue-specific panel comprising of NGS, FISH and IHC techniques provided a rapid evaluation of the tumor. This molecular profile has a distinct advantage over single-gene tests in creating a therapeutic roadmap for personalized treatment of a cancer patient.

Strand Advantage Lung TST	*Identified Molecular Marker*	*Targeted Therapeutics*		*Monitoring Liquid Biopsy*
		First Line Therapy	**Second Line Therapy**	
NGS	*EGFR*^{L858R}	Gefitinib, Erlotinib	Afatinib	EGFR-Sense / Resist Tests
	EGFR^{L858R} and *EGFR*^{T790M}			
FISH	*ALK* +	Crizotinib		
			Brigatinib	
			Alectinib	
			Ceritinib	
IHC	*PD-L1*	Nivolumab		
		Pembrolizumab		
			Atezolizumab	

Table 1. Decision Support for Choice of Targeted Therapeutics Provided by the StrandAdvantage Lung Tissue-Specific Test

Introduction

Lung cancer is characterized by high and fast fatality, with overall survival time of afflicted patients barely crossing the 1-year mark. In India, this is the second most common cancer in men and sixth most frequent cancer in women (Noronha et al. 2016).

** Name changed to protect patient privacy*

In fact, analysis of 5-year survival trends in data collected from several Indian registries shows that lung and stomach cancers have the poorest survival rates amongst various cancers (Figure 1) (Takiar & Jayant 2013). The realistic survival time of a lung cancer patient is 12-13 months, post diagnosis.

Therefore, choice of appropriate first-line therapy, aided by sensitive and accurate molecular tests, is of utmost importance. Given that the operational freedom for choice of therapy is limited, rapid and accurate molecular analyses of lung cancer are the need of the hour. Strand Life Sciences offers tests for genetic analyses of cancer that provide a list of actionable cellular and genetic markers present in the cancer tissue.

Prevalence / Incidence Ratio for Cancers In India

CANCER	PREVALENCE / INCIDENCE RATIO (Takiar & Jayant 2013)
Breast	5
Cervix	5
Ovary	3
Stomach	1
Lung	1
Mouth	4
Lifetime	3

Table 1. Prevalence / Incidence Ratio for Lung Cancer is the lowest in India (Takiar & Jayant 2013).

Patient Profile

Mr. Farrokh Daftari, aged 59 years and a lawyer by profession, suffered from a persistent cough for a few months before he decided to consult his general physician. His voice had been growing hoarse for some time and that was a serious impediment to his profession as well. He had been losing weight steadily and although that seemed like a good thing initially, the weight loss became a cause of concern. Persistent coughing would also cause him to bring up rust-colored sputum, from time-to-time. Mr. Daftari's general physician ruled out infectious causes of these breathing difficulties and referred him to a renowned physician in Mumbai.

Medical investigations revealed that Mr. Daftari had developed lung cancer. The specific subtype of the cancer - Non-Small Cell Lung Cancer (NSCLC) – was confirmed using histopathological analyses. Mr. Daftari was also advised to undergo tests for genetic and immunohistochemical analyses of his tumor tissue. These tests are expected to yield information about the mutation profile of the tumor as well as about expression of cell-surface proteins that can be targeted by specific drugs.

Results of Molecular Characterization Tests

Strand offers a lung-cancer specific test called StrandAdvantage Lung Tissue Specific Test. In addition to the genetic analysis by NGS, the TST can also be used for identifications of genetic rearrangements of the *ALK* (anaplastic lymphoma kinase) and *ROS1* genes as well as immunological detection of *PD-L1*, in the biopsy sample.

In Mr. Daftari's case, the TST yielded some significant results.

Therapy	Tested Marker(s)	Relevant Marker(s)	Likelihood of Response**
Alectini	*ALK*	*ALK* $^{FISH+}$	*Enhanced*
Brigatinib	*ALK*	*ALK* $^{FISH+}$	*Enhanced*
Crizotinib	*ALK, MET, ROS1*	*ALK* $^{FISH+}$	*Enhanced*
Ceritinib	*ALK*	*ALK* $^{FISH+}$	*Enhanced*
Afatinib	*EGFR, ERBB2, KRAS, MET*	*ALK* ^{L858R}	*Enhanced*
Gefitinib	*EGFR, ERBB2, KRAS, MET*	*EGFR* ^{L858R}	*Enhanced*
Erlotinib	*EGFR, ERBB2, KRAS, MET*	*EGFR* ^{L858R}	*Enhanced*
Nivolumab	*PD-L1*	*PD-L1* $^{IHC+}$	*Enhanced*
Pembrolizumab	*PD-L1*	*PD-L1* $^{IHC+}$	*Enhanced*
Atezolizumab	*PD-L1*	*PD-L1* $^{IHC+}$	*Enhanced*

Salient Results and Therapeutic Implications

- In this case, genomic rearrangements in the *ALK* gene were detected using fluorescence in situ hybridization (FISH). This confirmation indicates that drugs such as Alectinib, Brigatinib, Crizotinib, and Ceritinib are likely to be effective in halting the progression of cancer.
- Crizotinib is a first-line inhibitor therapy that is usually prescribed for *ALK*+ lung cancers (Ou et al. 2012).
- Going forward, if Mr. Daftari develops resistance to Crizotinib, Brigatinib, Alectinib, and Ceritinib can be prescribed to him. Each of these new therapeutic drugs provides targeted treatment for specific rearrangements in the *ALK* gene (Sullivan & Planchard 2017; Sabari et al. 2017; Friboulet et al. 2014). Therefore, several therapeutic options to target NSCLC cells that express various mutant forms of the *ALK* gene, are available.
- A characteristic mutation in the *EGFR* gene, namely, *EGFR*^{L858R} was identified using next-generation sequencing (NGS) techniques. Irreversible inhibitors of *EGFR*^{L858R}, Erlotinib and Gefitinib, can be prescribed to Mr. Daftari. A second-generation inhibitor – Afatinib - is an effective first-line therapy against lung cancer cells expressing this mutation (Lee et al. 2016). Afatinib is an irreversible inhibitor of *EGFR*^{L858R} and is more effective than Gefitinib and Erlotinib (Barron et al. 2016; Lee et al. 2016).
- The expected response to Afatinib therapy is the emergence of the *EGFR*^{T790M} mutation in the resistant clones (Tseng et al. 2016).
- Strand also offers liquid biopsy tests to assess the progression of the cancer post initiation of Afatinib therapy.
- Strand EGFR-Sense is designed to identify the prevalence of the *EGFR*^{L858R} mutation in a patient's blood sample.
- Strand EGFR-Resist is designed to identify the emergence of *EGFR*^{T790M} mutation in a liquid biopsy.
- A combination of these tests is expected to provide an indication of the suitable time point for switching therapy from Afatinib (against *EGFR*^{L858R}) to Osimertinib (against *EGFR*^{T790M}).
- *PD-L1* was also detected in the lung biopsy sample. Therefore, antibody drugs like Nivolumab, Pembrolizumab and Atezolizumab can be prescribed for Mr. Daftari (Rizvi et al. 2016; Seetharamu et al. 2017; Dang et al. 2016).
- Overall, the comprehensive analysis of Dr. Daftari's tumor sample has provided adequate decision support for the choice of targeted therapeutics as alternatives to generic chemotherapy.

StrandAdvantage Lung Tissue Specific Test

The StrandAdvantge Lung Tissue Specific Test is a comprehensive panel of NGS, IHC and FISH tests designed to identify mutations, gene rearrangements and expression of cell surface markers in lung cancer cells. These chosen genes are molecular targets with specific therapies designed against cells expressing these markers. The comprehensive panel offers more therapeutic options than doing sequential single-gene tests.

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