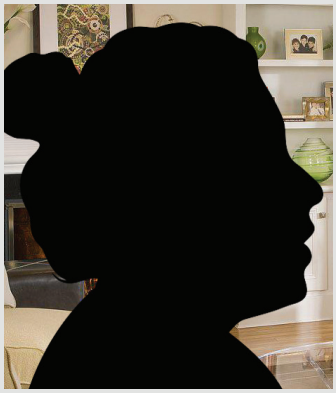
CASE STUDY

Comprehensive Assessment of Genetic Profile of Breast Cancer: StrandAdvantage 152-gene test Yields The Best Therapeutic Options

Quick Summary



- Ila Jindal*, aged 58 years, presented with breast cancer.
- Genetic analysis facilitated by the StrandAdvantage 152-gene test helped to identify targeted drugs namely - Sorafenib, Selumetinib, Temsirolimus, Everolimus, AZD5363, LY2780301, PD0325901, AZD2014, and AZD1775 – as viable and potentially highly effective therapies for her treatment.
- A complete assessment of the mutation profile of Ila's breast cancer also helped to identify drugs with the least possibility of effect, namely - with Lapatinib, Neratinib, Everolimus, Palbociclib, Ribociclib, Tamoxifen, Trastuzumab and Pertuzumab.
- Likewise, the effectiveness of non-targeted chemotherapy was also judged to be no greater than the population average effect owing to the lack of mutations in certain genes.
- A comprehensive profile of Ila's tumor was provided by the StrandAdvantage 152 gene test, which helped to arrive at a new strategy for treatment using 9 targeted therapeutics.
- Genetic testing provided a highly accurate rationale for choosing very specific targeted therapies over chemotherapy. This represents significant savings in time as well as financial resources spent in cancer therapy.

Introduction

Breast cancer is all set to become a significant health problem for Indian women, in the forthcoming decade. As a global health problem, the annual incidence of new breast cancer cases is the highest in the US, followed by China and then by India. However, an estimate of the mortality (number of patients lost to the disease) of breast cancer shows that India loses the most patients to breast cancer, followed by China and then the US. The survival of women (predominantly, since the rate of incidence of male breast cancer is rather low) who are diagnosed with breast cancer is the lowest in India, owing to several factors. Most cases are diagnosed very late because of lack of awareness of breast cancer amongst women (Khokhar, 2012, 2013). There are hereditary genes that, when mutated, can increase a woman's chances of suffering from breast as well as ovarian cancer. The prevalence of such genes (19 genes) is also high in the Indian population (Mannan et al., 2016).

In addition to inherited mutations, breast cancer is also caused by sporadic or chance mutations. In fact, several genes have been known to play a role in causing breast cancer (Perou et al., 2000).

A thorough understanding of the genetic profile of somatic breast cancer can therefore help in the choice of best suitable drugs. Genetic tests like the StrandAdvantage 152-gene test can provide a comprehensive picture of mutations that can be identified in a patient's biopsy, thereby guiding the selection of targeted therapies with optimal benefit.

*Name changed to protect patient privacy

Patient Profile

Ila Jindal, a 58-year-old owner of a chain of small fashion boutiques, was looking forward towards setting up a new outlet in a town 50 kms out of Delhi. She had always maintained her health with a watchful diet and regular exercise. Recently, she had noticed bouts of fatigue and also occasional pain in her breasts.

These small signs prompted her to consult her gynecologist and thereafter an oncologist. A mammogram and breast MRI showed the presence of some lumps in her breast tissue. Ila was advised to undergo a breast biopsy for pathological analysis. Additionally, her oncologist also suggested that a small sample of the biopsy be sent for genetic analysis.

Results of Genetic Testing

Ila's family history was documented by a trained genetic counselor from Strand Life Sciences in order to understand whether she can benefit from a hereditary or a somatic genetic test. Ila's family- immediate and extended- had several health problems but cancer was certainly not one of them. Concluding that her breast cancer was caused by a chance occurrence, Ila was prescribed the StrandAdvantage 152-gene test.

Choice of Targeted Therapies

Therapy	*Relevant Markers*	*Approved Indications*	*Trials*
Akt Inhibitor	*AKT1* ^{E17K}	None	NCT02299999, NCT02576444
Akt Inhibitor	*AKT1* ^{E17K}		
PD0325901	*KRAS* ^{amp}		NCT02022982
Sorafenib	*KRAS* ^{amp}, *NF1* $^{c.1260+2dup}$	Hepatooellular carcinoma, Kidney Cancer Thyroid cancer	NCT02029001, NCT02143401, NCT01724606
Selumetinib	*KRAS* ^{amp}, *NF1* $^{c.1260+2dup}$	None	NCT02299999, NCT02586987
Everolimus	*NF1* $^{c.1260+2dup}$	Pancreatic Neuroendo online Tumor. Gastrointes tinal Neuroendocrine Tumor. Lung Neuroendocrine Tumor, Kidney Cancer.	NCT01061788, NCT01624766, NCT01582191, NCT01827384
Temsirolimus	*NF1* $^{c.1260+2dup}$	Kidney Cancer	NCT01529593, NCT02215720, NCT01552434
mTOR Kinase Inhibitor AZD2014	*NF1* $^{c.1260+2dup}$	None	NCT02583542, NCT02299999
WEE1 inhibitor AZD1775	*TP53* ^{V274fs}	None	NCT01748825, NCT02576444, NCT01827384

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

Mutations in *AKT1, KRAS, NRAS, NF1* and *TP53* genes were identified in the breast cancer biopsy.

Drugs that can act specifically against cells bearing these mutations are being tested in various other solid tumors. A cross-recommendation of such therapies to other tumors with similar genetic mutations is possible, and the same was provided in the report.

Elimination of Unsuitable Therapies

In addition to the identified mutations, the StrandAdvantage 152-gene test was also used to understand genes that were normal (not mutated) in Ila's breast cancer.

Therapy	Tested Marker(s)	
Lapatinib	*ERBB2, HER2*	None
Neratinib	*ERBB2, HER2*	None
Pertuzumab	*ERBB2, HER2*	None
Trastuzumab	*ERBB2, HER2*	None
Everolimus	*ER, HER2*	None
Palbociclib	*ER, HER2*	None
Ribocidib	*ER, HER2*	None
Tamoxifen	*ER*	None

Table 2. Mutation Status of Other Genes Associated with Breast Cancer

As seen in table 2, drugs such as Lapatinib, Neratinib, Everolimus (different gene target than the one shown in Table 1), Palbociclib, Ribociclib and Tamoxifen are unlikely to be effective against Ila's cancer. Similarly, targets for antibody-based therapeutics like Trastuzumab and Pertuzumab were also not identified.

Response to Chemotherapy

Therapy	Tested Marker(s)	Relevant Marker(s)	
Doxorubioin	*TOP2A*	None	Standard
Epirubion	*TOP2A*	None	Standard
Fluorouracil	*SMAD4*	None	Standard
Cisplatin	*BRCA1, BRCA2*	None	Standard

Table 3. Prediction of Response to Chemotherapy

Chemotherapy drugs that disrupt the DNA replication process also remain a viable option for cancer treatment. In Ila's case, mutations in *TOP2A, SMAD4* and *BRCA1* and *BRCA2* genes were not identified. Therefore, the response to treatment with Doxorubicin, Epirubicin, Fluorouracil and Cisplatin was not likely to be significantly better that the population average response.

Conclusions

- Ila Jindal, aged 58 years, presented with breast cancer.
- Genetic analysis facilitated by the StrandAdvantage 152-gene test helped to identify targeted drugs namely - Sorafenib, Selumetinib, Temsirolimus, Everolimus, AZD5363, LY2780301, PD0325901, AZD2014, and AZD1775 – as viable and potentially highly effective therapies for her treatment.
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StrandAdvantage 152 Gene Test

The StrandAdvantage 152-gene test is a pan-cancer test that is designed to identify mutation hotspots in 152 genes that are frequently mutated in most solid tumors. This is a laboratory-developed test that has been designed and tested at the Strand Center for Genomics and Personalized Medicine, Bangalore, India. This test has been benchmarked by an independent organization against similar tests from three other leading US laboratories. Results from the StrandAdvantage 152-gene test have been found to be at par with those provided by other US genomic diagnostic tests (Mori, Levenson, &

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Strand Life Sciences Pvt. Ltd.
5th Floor, Kirloskar Business Park, Bellary Road, Hebbal, Bangalore - 560 024
Phone: 1800-1022-695, support.strandx@strandls.com, www.strandls.com

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