ContextualGenomics

Sonic Genetics
Quality is in our DNA

Melanie Citizen

LAB ID 987654321 DOB 02/03/1965 (53Y Female)

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Referring Doctor	Dr John Medico
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Address	123 Main Street, SUBURBTOWN NSW 2000
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Contextual Genomics Report
FIND IT® Full Panel (30 genes)

Summary

- Activating PIK3CA variant detected.
- The SOLAR-1 trial suggests potential response to treatment with PI3K inhibitor (alpelisib) + fulvestrant; however, this combination is not yet approved in Australia

MUTATIONS DETECTED*

Gene	cDNA change	Amino Acid Change	Exon	Allelic ratio (%)	Therapeutic implication	Level of evidence
PIK3CA	c.1633G>A (NM_006218.3)	E545K p.(Glu545Lys)	10	8.6	May be associated with resistance to trastuzumab therapy	Tier: II.D Literature
					May be responsive to PI3K/AKT/mTOR inhibitors	Tier: II.C Literature Clinical trials

* All hotspot mutations detected in this specimen are shown in the Mutations Detected table, above. All tested mutations are listed in the "Hotspot Panel" table (below, after Methodology). Mutations listed in the "Hotspot Panel" but not presented above were tested, but were not detected in this specimen.

Interpretation

The presence of an activating PIK3CA variant, typically in exon 9 or 20, has been observed in all breast cancer sub-types (16-45%) but has been primarily associated with hormone receptor-positive and HER2-positive breast cancers. PIK3CA variants are less frequent in triple negative (basal-like) breast tumours (8%) (Stemke-Hale K, 2008).

None of the other FIND IT hotspot variants were detected in this tumour DNA (see Hotspot Panel, below Methodology section, for a full list). Note that the FIND IT panel does not test for variants in HR DNA repair genes such as BRCA1 and BRCA2.

Implications of PIK3CA Variants In Breast Cancer

i) Treatment with PI3K inhibitors:

Studies have reported that presence of a PIK3CA variant is predictive of response to alpelisib (alpha-specific PI3K inhibitor) therapy in advanced breast cancers (Elkabets M, 2013; Fritsch C, 2014). The efficacy of this treatment has been evaluated in a phase III clinical trial (SOLAR-1) following early positive results in postmenopausal women with ER-positive metastatic breast cancer who had received prior endocrine therapy (Juric D, 2016).

Analyses from the SOLAR-1 trial show that alpelisib in combination with fulvestrant extended progression-free survival compared with fulvestrant alone (Andre F, 2018). Based on this data, alpelisib and fulvestrant has been granted FDA approval for PIK3CA mutant, HR+/HER2- advanced or metastatic breast cancer, following progression on or after an endocrine-based regimen. However, this combination is not currently approved by the TGA or funded by the PBS in Australia.

The efficacy of other PI3K inhibitors (e.g. buparlisib and taselisib) in HR+ breast cancer patients is being actively investigated in clinical trials, along with other agents targeting the PI3K/AKT/mTOR pathway.

ii) Treatment with mTOR inhibitors:

The presence of a PIK3CA variant in breast cancers has been reported as predictive of response to mTOR inhibitors everolimus or temsirolimus (Wheler JJ, 2014; Moroney J, 2012): however, response to these therapies has also been found independent of PIK3CA status (Zhang H, 2014; Moynahan ME, 2017). Strong response to temsirolimus treatment or to rapamycin treatment was observed in triple-negative breast cancer xenograft tumours irrespective of the presence or absence of a PIK3CA variant (Zhang H, 2014).

iii) Treatment of HER2 overexpressing breast cancers:

In breast tumours positive for HER2 protein overexpression, the presence of PIK3CA variants has been associated with resistance to trastuzumab treatment (Berns K, 2007; Esteva FJ, 2010). In contrast, lapatinib treatment was found to be independent of PIK3CA mutation status, and more patients achieved a pathologic complete response on lapatinib than on trastuzumab treatment (Dave B, 2011).

iv) Other therapeutic considerations:

The presence of a PIK3CA variant had no significant effect on the outcome of tamoxifen therapy of hormone receptor-positive breast cancer patients (Stemke-Hale K, 2008).

Clinical trials

Australia	Study
PIK3CA Mutation Present	
A Double-Blind, Placebo-Controlled, Randomized Phase III Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Patients With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor-Positive, HER2-Negative Breast Cancer	NCT03337724

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Other Relevant Trials	
A Phase Ib, Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Ipatasertib in Combination With Rucaparib in Patients With Advanced Breast, Ovarian, or Prostate Cancer	NCT03840200

The clinical trials included in the report are sourced from Australian trials listed on clinicaltrials.gov and anzctr.org.au. We select trials based on tumour histotype and mutation status, with a specific focus on trials of targeted therapy. The inclusion of a trial in our report does not necessarily mean that the patient would be eligible. Patients' eligibility for a trial, and the benefit that they may derive from it, will depend on additional factors that must be assessed by the oncologist. Conversely, the list of potentially relevant trials in our report may not be complete. We may have overlooked relevant trials on these websites, or there may be relevant trials listed elsewhere. Please let us know if you identify a trial of targeted therapy that could have been included in a patient's report.

Specimen Information

Specimen Type: FFPE Block

Specimen Source: Biopsy

Primary Site of Tumour: Breast

Histologic Type: Adenocarcinoma

Referral Reason : Therapeutic Target Identification

Biopsy Site : Left breast

Block ID #: BLOCK #12345

Tumour Cellularity: 10%

Methodology and Limitations

This test involves targeted sequence analysis of hotspot mutations/coding exons of the requested genes and transcripts (listed below, see Hotspot Panel table). DNA is extracted and targets of interest amplified using a highly multiplexed in-house designed PCR assay, sequenced using Illumina technology and analysed using a validated, custom-built bioinformatics pipeline. Hotspot variants are categorised into clinical significance tiers as per Li et al. 2017 (PMID 27993330). Variants of strong or potential clinical significance (tier I or II) will be reported. VUS and likely benign variants (tier III and IV) will not be reported. Please contact the laboratory if tier III or IV variants are required.

Single nucleotide changes, insertions (1-18 bp) and deletions (1-24 bp) are detected by this assay. Limit of detection is approximately 5% variant allele ratio; the ability to detect a particular mutation may depend upon the tumour content of the tested sample and the proportion of the mutant tumour clone. Rare genetic variation can interfere with this assay. CNVs (e.g. gene amplification or large deletions) and gene rearrangement events (e.g. gene fusions) will not be detected by this assay. Approximately 20% of MET exon 14 skipping mutations are large deletions, and will not be detected. BRCA gene mutations, MSI and tumour mutational burden are not assessed in this assay. This assay does not differentiate between germline (hereditary) and somatic mutations.

Hotspot Panel

Gene	Hotspot	Transcript	Gene	Hotspot	Transcript
AKT1	E17	NM_001014432.1	KIT	T670, D816, D820, N822, Y823, A829, exons: 9, 11, 13	NM_000222.2
ALK	T1151, L1152, C1156, F1174, L1196, L1198, G1202, D1203, S1206, G1269, R1275	NM_004304.4	KRAS	G12, G13, A59, Q61, K117, A146	NM_004985.4
AR	F877, H875, L702H, S741, T878, V716, W742	NM_000044.3	MAP2K1	Q56, K57, K59, D67, C121, P124, P387	NM_002755.3
BRAF	Q201, G466, F468, G469, Y472, D594, G596, L597, V600, K601	NM_004333.4	MAP2K2	F57, Q60, K61, L119	NM_030662.3
CTNNB1	D32, S33, G34, S37, T41, S45	NM_001904.3	MET	Y1253, exons: 13, 14+25, 14-50, 14, 18	NM_001127500.2
DDR2	L239, I638, S768	NM_001014796.1	NRAS	G12, G13, A59, Q61, K117, A146	NM_002524.4

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Hotspot Panel					
Gene	**Hotspot**	**Transcript**	**Gene**	**Hotspot**	**Transcript**
EGFR	S492, exons: 18, 19, 20, 21	NM_005228.3	PDGFRA	D842, L839_Y849, N659, R560_E571	NM_006206.4
ERBB2	G309, S310, L755, exons: 20	NM_004448.3	PIK3CA	R88, E542, E545, Q546, D549, M1043, N1044, A1046, H1047, G1049	NM_006218.3
ESR1	K303, S463, V534, P535, L536, Y537, D538	NM_001122742.1	POLE	Exons: 9, 10, 11, 12, 13, 14	NM_006231.3
GNA11	Q209	NM_002067.4	PTCH1	W844, G1093	NM_000264.3
GNAQ	Q209	NM_002072.4	PTEN	R130	NM_000314.4
GNAS	R201	NM_000516.5	RET	C634, V804, M918	NM_020975.4
HRAS	G12, G13, Q61	NM_005343.3	ROS1	L2026, G2032	NM_002944.2
IDH1	R132	NM_005896.3	SMO	D473, S533, W535	NM_005631.4
IDH2	R140, R172	NM_002168.3	TP53	Exons: 4, 5, 6, 7, 8, 9	NM_000546.5

References

- Andre F, Ciruelos EM, Rubovszky G et al. Alpelisib (ALP) + fulvestrant (FUL) for advanced breast cancer (ABC): results of the phase III SOLAR-1 trial. Ann Oncol 2018; 29(Suppl 8) 5411
- Berns K, Horlings HM, Hennessy BT, et al. "A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer." 2007 Oct . Cancer Cell - PMID17936563
- Dave B, Migliaccio I, Gutierrez MC, et al. "Loss of phosphatase and tensin homolog or phosphoinositol-3 kinase activation and response to trastuzumab or lapatinib in human epidermal growth factor receptor 2-overexpressing locally advanced breast cancers." 2011 Jan 10. J. Clin. Oncol. - PMID21135276
- Elkabets M, Vora S, Juric D, et al. "mTORC1 inhibition is required for sensitivity to PI3K p110□ inhibitors in PIK3CA-mutant breast cancer." 2013 Jul 31. Sci Transl Med - PMID23903756
- Esteva FJ, Guo H, Zhang S, et al. "PTEN, PIK3CA, p-AKT, and p-p70S6K status: association with trastuzumab response and survival in patients with HER2-positive metastatic breast cancer." 2010 Oct . Am. J. Pathol. - PMID20813970
- Fritsch C, Huang A, Chatenay-Rivauday C, et al. "Characterization of the novel and specific PI3K□ inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials." 2014 May . Mol. Cancer Ther. - PMID24608574
- Janku F, Hong DS, Fu S, et al. "Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors." 2014 Jan 30. Cell Rep - PMID24440717
- Moroney J, Fu S, Moulder S, et al. "Phase I study of the antiangiogenic antibody bevacizumab and the mTOR/hypoxia-inducible factor inhibitor temsirolimus combined with liposomal doxorubicin: tolerance and biological activity." 2012 Oct 15. Clin. Cancer Res. - PMID22927482
- Moynahan ME, Chen D, He W, et al. "Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR+, HER2- advanced breast cancer: results from BOLERO-2." 2017 Mar 14. Br. J. Cancer - PMID28183140
- Presented at Miami Breast Cancer Conference; March 10-13, 2016; Miami, FL. Abstract 334 5219
- Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, et al. "An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer." 2008 Aug 01. Cancer Res. - PMID18676830
- Wheler JJ, Moulder SL, Naing A, et al. "Anastrozole and everolimus in advanced gynecologic and breast malignancies: activity and molecular alterations in the PI3K/AKT/mTOR pathway." 2014 May 30. Oncotarget - PMID24912489
- Zhang H, Cohen AL, Krishnakumar S, et al. "Patient-derived xenografts of triple-negative breast cancer reproduce molecular features of patient tumors and respond to mTOR inhibition." 2014 Apr 07. Breast Cancer Res. - PMID24708766