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SAMPLE INFORMATION

Name:		**Date Sp. Extracted:**	
Medical ID:		**Req. Physician:**	
Date Of Birth:		**Report No:**	
Material #1:	PLASMA	**Date Received:**	
Material #2:		**Date Of Report:**	
Sample #1 ID:		**Tumor type:**	BREAST CANCER

Com.Pl.i.t. DX Liquid Biopsy Breast | Comprehensive Panel for Individualized Treatment

Report Summary

12	Unique Genes analyzed	**1**	Genomic alterations identified in tumor
1	Biomarker related approved therapies for indication	**1**	Biomarker related therapies with potential benefit
0	Biomarker related therapies with potential resistance	**18**	Biomarker related Clinical Trials

Results and Interpretation*

Biomarker	Result	Approved therapies for indication	Therapies with potential benefit	Therapies with potential resistance/toxicity	Clinical Trials
PIK3CA	Exon 10 c.1633G>A (p.E545K)	Alpelisib+Fulvestrant (1A.1)	Everolimus (2C.1)	-	yes

*Note: Variants' Level of Evidence (LoE) (e.g. 1A.1, 2C.1, 1B etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

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Genomic Alterations Identified

***PIK3CA:* c.1633G>A (p.E545K)**	**VAF*:1,5%**	**OncoKB**	**CIViC**	**PMKB**

Treatment information

Alpelisib in combination with fulvestrant is approved by the FDA for postmenopausal women, and men, with hormone receptor (HR)-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. Approval was based on the SOLAR-1 study (NCT02437318), a randomized, double-blind, placebo-controlled trial of alpelisib plus fulvestrant versus placebo plus fulvestrant. Among a subset of patients with PIK3CA mutations, the median PFS by local assessment was 11.0 months (95% CI, 7.5-14.5) for those who received the alpelisib combination compared with 5.7 months (95% CI, 3.7-7.4) for those who received placebo plus fulvestrant. Those results, assessed after a median follow-up of 20 months, translated into a 35% reduction in the risk of progression or death, with a hazard ratio of 0.65 in favor of alpelisib (95% CI, 0.50-0.85; P = .00065). There was no advantage to alpelisib on median PFS in patients without a PIK3CA mutation. PIK3CA activating mutations or amplification may predict sensitivity to inhibitors of the PI3K-AKTmTOR pathway. The mTOR inhibitor everolimus is FDA approved, in combination with the aromatase inhibitor exemestane, to treat postmenopausal women with hormonereceptor- positive, HER2-negative advanced breast cancer. These therapies and other mTOR inhibitors are in clinical trials in breast cancer and other solid tumor types. Inhibitors of PI3K and AKT, alone or in combination with other therapies are also in clinical trials in solid tumors. Activating mutations in PIK3CA may also confer resistance to anti-HER2 therapies.

Gene information

PIK3CA is a gene that encodes the protein phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform, a subunit of the PI3K protein. Phosphatidyl 3-kinases (PI3K) are a family of lipid kinases involved in many cellular processes, including cell growth, proliferation, differentiation, motility, and survival. Mutant PIK3CA has been implicated in the pathogenesis of several cancers, including colon cancer, glioma, gastric cancer, breast cancer, endometrial cancer, and lung cancer (PMID: 15016963). PIK3CA mutations are positive prognostic factors in breast cancer. The somatic mutations found thus far in PIK3CA are oncogenic, and the majority of them are clustered within exon 10 and 21 (helical and kinase domains), with 80% of the identified mutations found within three hotspot: E542K, E545K, and H1047R (PMID: 17376864, 21266528). These mutations in PIK3CA lead to increased PI3K activity (PMID: 22422409), which may promote tumorigenesis in an AKT/mTOR-dependent or independent manner (PMID: 19573809).

Variant information

The PIK3CA p.Glu545Lys (E545K) detected in this patient is one of the most common PIK3CA hotspot mutations in multiple tumor types (https://cancer.sanger.ac.uk/cosmic). This alteration induces cellular proliferation, colony formation, cellular invasiveness, and conveys strong in vivo oncogenic potential.

*VAF: Variant Allele Frequency

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Associated Treatments Information

Alpelisib

DrugBank

Alpelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with potent antitumor activity. It works by selectively inhibiting class I PI3K p110a, which is the catalytic subunit of PI3K, a lipid kinase that plays a role in various biological processes, including proliferation, survival, differentiation, and metabolism. Alpelisib was designed to target this enzyme that appears to be mutated at a rate of nearly 30% in human cancers, leading to hyperactivation. There are several isoform-specific PI3K inhibitors that are under clinical development or currently approved, such as used for chronic lymphocytic leukemia (CLL). Approved by the FDA in May 2019, alpelisib is the first approved PI3K inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer in combination with for postmenopausal women and male patients. To initiate alpelisib therapy, it is required that the presence of a PIK3CA mutation in the tissue and/or liquid biopsy sample collection should be confirmed via FDA-approved diagnostic tests. Studies evaluating the therapeutic effectiveness of alpelisib in other cancers, such as ovarian cancer and colorectal cancer, are under ongoing investigations. Alpelisib was granted FDA approval on 24 May 2019.

Alpelisib is indicated in combination with fulvestrant to treat postmenopausal women, and men, with advanced or metastatic breast cancer. This cancer must be hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, and PIK3CA mutated. The cancer must be detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Fulvestrant

DrugBank

Fulvestrant is a drug treatment of hormone receptor (HR)-positive metastatic breast cancer in post-menopausal women with disease progression following anti-estrogen therapy. It is an estrogen receptor antagonist with no agonist effects, which works both by down-regulating and by degrading the estrogen receptor. While it is used as monotherapy for the treatment of breast cancers, it is also used in combination with for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer

For the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy, as monotherapy or in combination with other antineoplastic agents.

Everolimus

DrugBank

Everolimus is a derivative of Rapamycin (sirolimus) and works similarly to Rapamycin as an mTOR (mammalian target of rapamycin) inhibitor. It is currently used as an immunosuppressant to prevent rejection of organ transplants. In a similar fashion to other mTOR inhibitors Everolimus' effect is solely on the mTORC1 protein and not on the mTORC2 protein.

Everolimus is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or

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anastrozole; indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease; indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib; indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery; indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

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Clinical Trials to consider

PIK3CA associated clinical trials

NCT04191499	Phase 2|Phase 3
Title	A Study Evaluating the Efficacy and Safety of Inavolisib + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer
Treatment	Inavolisib| Placebo| Palbociclib| Fulvestrant
Location	United States, Australia, Austria, Belgium, Canada, China, Denmark, France, Germany, Greece, Hong Kong, Hungary, Italy, Korea, Republic of, Malaysia, New Zealand, Poland, Portugal, Russian Federation, Singapore, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom

NCT05631795	Phase 4
Title	Study to Assess the Safety of Alpelisib Plus Fulvestrant, in Men and Post-menopausal Women With HR-positive, HER2-negative, Advanced Breast Cancer (aBC) With PIK3CA Mutation, Whose Disease Progressed on or After Endocrine Treatment
Treatment	Alpelisib| Fulvestrant
Location	India

NCT03264547	Phase 3
Title	A Study to Compare Eribulin Mesylate + Pertuzumab + Trastuzumab With Paclitaxel or Docetaxel + Pertuzumab + Trastuzumab
Treatment	Pertuzumab| Trastuzumab| Docetaxel| Paclitaxel| Eribulin
Location	Japan

NCT05090358	Phase 2
Title	Preventing High Blood Sugar in People Being Treated for Metastatic Breast Cancer
Treatment	Ketogenic Diet| Low Carbohydrate Diet| Alpelisib| Fulvestrant| Canagliflozin
Location	United States

NCT04524000	Phase 2
Title	Study Assessing the Efficacy and Safety of Treatment With Alpelisib Plus Fulvestrant in Japanese Men and Postmenopausal Women With Advanced Breast Cancer
Treatment	Alpelisib| Fulvestrant

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Location	Japan

NCT04544189	**Phase 2**
Title	Study Assessing the Efficacy and Safety of Treatment With Alpelisib Plus Fulvestrant Versus Placebo Plus Fulvestrant in Chinese Men and Postmenopausal Women With Advanced Breast Cancer
Treatment	Alpelisib| Fulvestrant| Placebo
Location	China

NCT05660083	**Phase 2**
Title	Alpelisib/iNOS Inhibitor/Nab-paclitaxel in Patients With HER2 Negative Metaplastic Breast Cancer (MpBC)
Treatment	L-NMMA
Location	United States

NCT04589845	**Phase 2**
Title	Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study
Treatment	Entrectinib| Entrectinib| Alectinib| Atezolizumab| Ipatasertib| Trastuzumab emtansine| Idasanutlin| Inavolisib| Belvarafenib| Pralsetinib
Location	United States, Australia, Belgium, Brazil, Canada, China, Denmark, France, Germany, Hong Kong, Israel, Italy, Japan, Korea, Republic of, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Singapore, Spain, Swaziland, Switzerland, Taiwan, United Kingdom

NCT03297606	**Phase 2**
Title	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)
Treatment	Olaparib| Dasatinib| Nivolumab plus Ipilimumab| Axitinib| Bosutinib| Crizotinib| Palbociclib| Sunitinib| Temsirolimus| Erlotinib| Trastuzumab plus Pertuzumab| Vemurafenib plus Cobimetinib| Vismodegib| Tucatinib
Location	Canada

NCT04317105	**Phase 1|Phase 2**
Title	Testing the Addition of an Anti-cancer Drug, Copanlisib, to the Usual Immunotherapy (Nivolumab With or Without Ipilimumab) in Patients With Advanced Solid Cancers That Have Changes in the Following Genes: PIK3CA and PTEN
Treatment	Biopsy| Biospecimen Collection| Computed Tomography| Copanlisib Hydrochloride| Echocardiography| Ipilimumab| Nivolumab| X-Ray Imaging
Location	United States, Canada

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NCT03939897	Phase 1|Phase 2
Title	Testing the Addition of Copanlisib to Usual Treatment (Fulvestrant and Abemaciclib) in Metastatic Breast Cancer
Treatment	Abemaciclib| Copanlisib Hydrochloride| Fulvestrant
Location	United States

NCT05768139	Phase 1|Phase 2
Title	First-in-Human Study of STX-478 as Monotherapy and in Combination With Other Antineoplastic Agents in Participants With Advanced Solid Tumor
Treatment	STX-478| Fulvestrant
Location	United States

NCT03805399	Phase 1|Phase 2
Title	FUSCC Refractory TNBC Umbrella (FUTURE)
Treatment	Pyrotinib with Capecitabine| AR inhibitor combined with everolimus(B1) or CDK4/6 inhibitor(B2),or EZH2 inhibitor (B4)| anti PD-1 with nab-paclitaxel| PARP inhibitor included therapy| BLIS with anti-VEGFR included therapy| MES with anti-VEGFR included therapy| mTOR inhibitor with nab-paclitaxel
Location	China

NCT03006172	Phase 1
Title	To Evaluate the Safety, Tolerability, and Pharmacokinetics of Inavolisib Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer
Treatment	Inavolisib| Fulvestrant| Letrozole| Palbociclib| Metformin| Trastuzumab| Pertuzumab
Location	United States, Canada, France, Spain, United Kingdom

NCT05300048	Phase 1
Title	Combination of Serabelisib and Insulin Suppressing Diet With or Without Nab-paclitaxel in Subjects With Advanced Solid Tumors With PIK3CA Mutations
Treatment	Serabelisib| Insulin Suppressing Diet| Nab paclitaxel
Location	United States

NCT05307705	Phase 1
Title	A Study of LOXO-783 in Patients With Breast Cancer/Other Solid Tumors
Treatment	LOXO-783| Fulvestrant| Imlunestrant| Abemaciclib| Anastrozole, Exemestane, or Letrozole| Paclitaxel

Location	United States, Australia, Canada, Japan, Singapore

NCT05504213	**Phase 1**
Title	A Phase Ib Study of HS-10352 Plus Fulvestrant in Patients With Advanced Breast Cancer
Treatment	HS-10352 combined with fulvestrant (Stage 1)| HS-10352 combined with fulvestrant (Stage 2)
Location	China

NCT05216432	**Phase 1**
Title	First-in-Human Study of Mutant-selective PI3KÎ± Inhibitor, RLY-2608, as a Single Agent in Advanced Solid Tumor Patients and in Combination With Fulvestrant in Patients With Advanced Breast Cancer
Treatment	RLY-2608| Fulvestrant
Location	United States, Spain

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Methodology

NGS analysis

DNA was extracted from the sample under investigation using the QIAamp Circulating Nucleic Acid Kit (Qiagen).

Mutation hotspot regions of 12 genes were amplified using Oncomine Breast cell free total nucleic acid assay (Thermo Fisher Scientific). Copy number variations, SNPs, and indels were analyzed. Sequencing was carried out using the Next Generation Sequencing platform Ion GeneStudio S5 Prime System (ThermoFisher). The variant detection limit of the assay is 0.1%, with 90% sensitivity and >98% specificity for SNV hotspots and indels.

Genes Analyzed

10 gene alterations									
AKT1	EGFR	ERBB2 (HER2)	ERBB3	ESR1	FBXW7	KRAS	PIK3CA	SF3B1	TP53

3 Copy number genes						
CCND1	ERBB2 (HER2)	FGFR1				

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Appendix

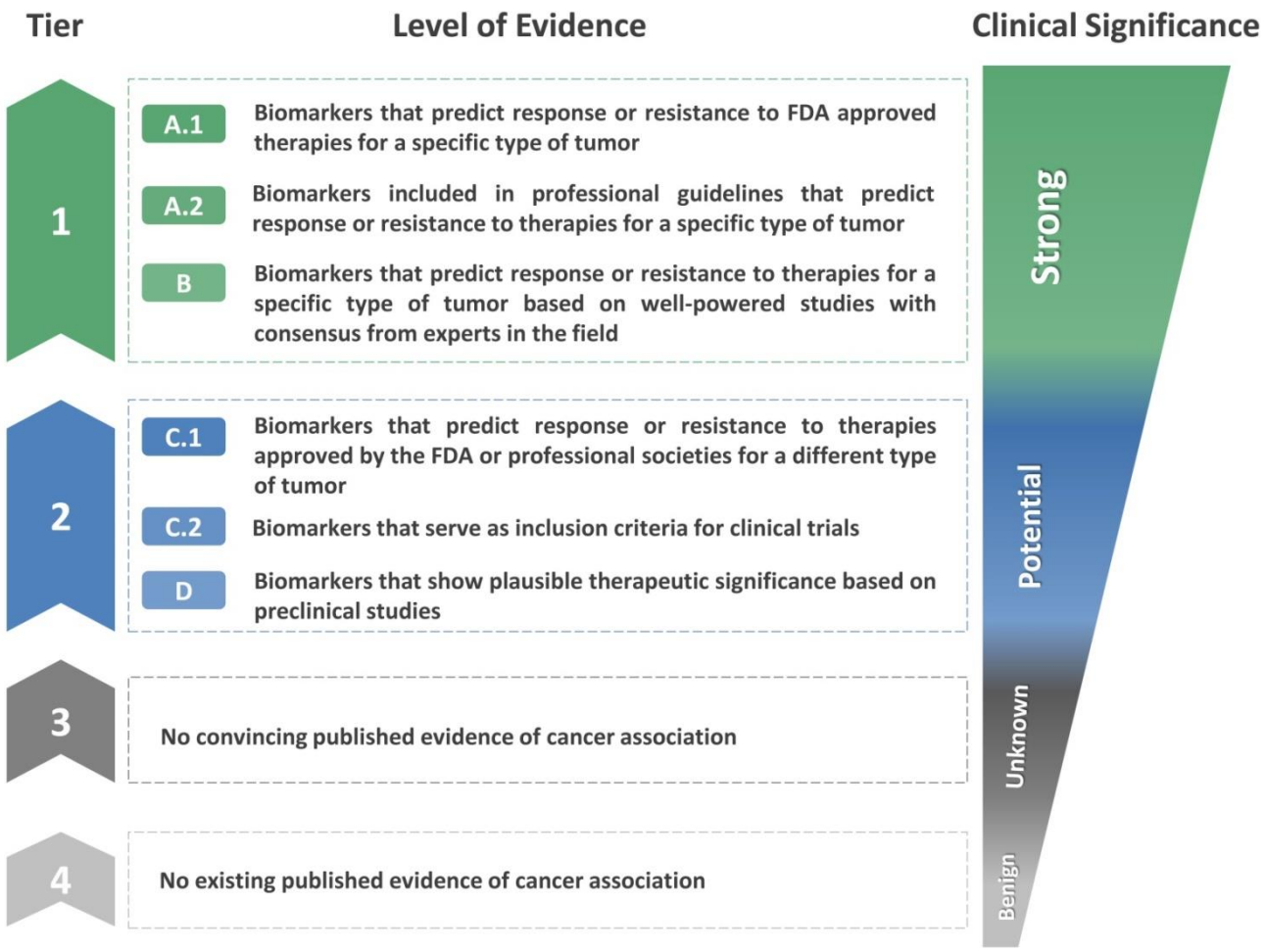

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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