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Consulting physician		Patient		Sample	
Provider	General Hospital	Name	Michelle Doe	Accession Number	7-SP17-9111-B1-RNA_HighConfidenceVariants.zip
Physician	Dr. E Smith	Age	58		
Pathologist	Dr. R Jones	Gender	Female		
Report Date	May 20, 2020	Diagnosis	Breast carcinoma	Collection site	Breast
		Stage	IV	Type	Biopsy
				Collection date	May 11, 2020

Panel Analysis: Somatic cancer

Description of panel, purpose and what ever we need to tell the patient / oncologist in order to introduce the scope and relevance of the report. Somatic Cancer Panel is a comprehensive genomic profiling test designed to identify somatic mutations, copy numbers, fusions across 456 genes in tumor samples.

Overall comment

Patient specific comment to be added. Please note the interactions of mutations on clinical outcome.

Analysis results: Positive

1 Biomarker	Approved treatments	Other findings
Tumor Mutation Burden: TMB-low (5.7 Mutations/Megabase)	-	-
2 Variants of strong clinical significance, Tier 1	**Approved treatments**	**Other findings**
ERBB2: amplification, Pathogenic	DS-8201a Lapatinib Neratinib Pertuzumab Trastuzumab Trastuzumab emtansine	**Resistance: cetuximab, erlotinib, osimertinib** Trials: 3 Phase 3 6 Phase 2 1 Early Phase 1
PIK3CA: p.H1047R, Pathogenic	Alpelisib/fulvestrant	**Resistance: vemurafenib** Trials: 1 Expanded Access 2 Phase 2 1 Phase 1/Phase 2 6 Phase 1
2 Variants of potential clinical significance, Tier 2	**Approved treatments**	**Other findings**
CCND1: amplification, Pathogenic	-	Trials: 3 Phase 2
TP53 †: p.L348*, Pathogenic	-	-
2 Variants of biological significance, Tier 3	**11 Variants of uncertain significance, Tier 3**	
FGF10: amplification, Likely Pathogenic		
MYCN: amplification, Pathogenic		

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

Interactions

Clinically relevant co-occurring variants are reported in the "interactions" section starting on page 2.

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 2.

Approval

Electronically signed on: May 20, 2020 by Dr. Jones

Report content

GUIDELINES

The NCCN Guidelines (v.2.2020) note that Her2-positive breast carcinoma patients may consider adjuvant chemotherapy plus trastuzumab, regardless of hormone receptor status, depending on the physician's evaluation of the individual patient; in certain situations, regimens including pertuzumab, ado-trastuzumab emtansine, or lapatinib may also be considered. The NCCN Guidelines (v.3.2020) list fulvestrant plus alpelisib as a preferred second-line therapy (category 1) for hormone receptor-positive, Her2-negative breast cancer patients with tumors harboring a PIK3CA mutation.

INTERACTIONS

PI3K pathway activation, as evidenced by the presence of activating PIK3CA mutations or decreased expression of Pten, has been associated with resistance to Her2-targeted therapies in some clinical studies, though in other studies no association was found (Guarneri et al., 2015; 26245675, Cescon and Bedard, 2015; 25559805, Majewski et al., 2015; 25559818, Pogue-Geile et al., 2015; 25559813, Chandarlapaty et al., 2012; 23092874, Sueta et al., 2014; 25542038) [PMID:26245675, PMID:25559805, PMID:25559818, PMID:25559813, PMID:23092874, PMID:25542038].

TREATMENT OPTIONS

Therapies with potential clinical benefit (7)

DS-8201A

Fam-trastuzumab deruxtecan-nxki, a HER2-directed antibody and topoisomerase inhibitor conjugate, is FDA-approved for treating adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

LAPATINIB

Lapatinib, a kinase inhibitor, in combination with capecitabine, is FDA- and EMA-approved for treating patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab; in combination with letrozole for treating postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated; lapatinib, in combination with trastuzumab, is EMA-approved for treating patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy.

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

NERATINIB

Neratinib, a kinase inhibitor, is FDA- and EMA-approved as a single agent for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer, to follow adjuvant trastuzumab based therapy; neratinib, in combination with capecitabine, is FDA-approved for treating adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

PERTUZUMAB

Pertuzumab, a HER2/neu receptor antagonist, in combination with trastuzumab and docetaxel, is FDA- and EMA-approved for treating patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease; in combination with trastuzumab and chemotherapy, for treating patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as neoadjuvant treatment as part of a complete treatment regimen for early breast cancer; and in combination with trastuzumab and chemotherapy, for treating patients with HER2-positive early breast cancer at high risk of recurrence as adjuvant treatment.

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

TRASTUZUMAB

Trastuzumab, a HER2/neu receptor antagonist, is FDA- and EMA-approved for treating HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

TRASTUZUMAB EMTANSINE

Therapies with potential clinical benefit (7)

Trastuzumab emtansine, a HER2-targeted antibody and microtubule inhibitor conjugate, is FDA- and EMA-approved for treating patients with HER2-positive metastatic breast cancer as detected by an FDA-approved companion diagnostic who previously received trastuzumab and a taxane, separately or in combination (patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy); trastuzumab emtansine is also FDA-approved for the adjuvant treatment of patients with HER2-positive early breast cancer as detected by an FDA-approved companion diagnostic who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

ALPELISIB/FULVESTRANT

Alpelisib, a kinase inhibitor, in combination with fulvestrant, an estrogen receptor antagonist, is FDA-approved for treating postmenopausal female, and male, patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (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.

Sensitive

Gene	Classification	Variant
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G

Therapies associated with resistance (4)

CETUXIMAB

Cetuximab, an epidermal growth factor receptor antagonist, is FDA-approved for treating patients with locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy; recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU; recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy; KRAS wild-type, EGFR-expressing, metastatic colorectal cancer in combination with FOLFIRI for first-line treatment, or in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan; cetuximab is EMA-approved for treating patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan; squamous cell cancer of the head and neck in combination with radiation therapy for locally advanced disease, and in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

Resistance

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

ERLOTINIB

Erlotinib, a kinase inhibitor, is FDA- and EMA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen; and locally advanced, unresectable or metastatic pancreatic cancer (first-line treatment), in combination with gemcitabine.

Resistance

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

OSIMERTINIB

Osimertinib, a kinase inhibitor, is FDA-approved for treating patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test; metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy; osimertinib is EMA-approved for treating adult patients with locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer; and locally advanced or metastatic NSCLC (first-line treatment) with activating EGFR mutations.

Resistance

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

VEMURAFENIB

Vemurafenib, a kinase inhibitor, is FDA-approved for treating patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test, and Erdheim-Chester Disease with BRAF V600 mutation; vemurafenib is EMA-approved for treating adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Therapies associated with resistance (4)

Resistance

Gene	Classification	Variant
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G

AVAILABLE CLINICAL TRIALS

Expanded Access clinical trials (1)

ALPELISIB

INST UNM 1601: Compassionate Use of BYL 719 Alpelisib
NCT03941782

Qualifying variant

Gene	Classification	Variant
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G

Contact
United States: NM
Ian Rabinowitz, MD; irabinowitz@salud.unm.edu;
505 925-0412;

Phase 3 clinical trials (3)

TRASTUZUMAB EMTANSINE, TUCATINIB

Randomized, Double-blind, Phase 3 Study of Tucatinib or Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Subjects With Unresectable Locally-advanced or Metastatic HER2+ Breast Cancer (HER2CLIMB-02)
NCT03975647

Qualifying variant

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

Contact
United States: AZ, CA, CO, DE, FL, GA, IL, MD, MI, MO, NE, NJ, OR, TN, TX, VA
Seattle Genetics Trial Information Support; clinicaltrials@seagen.com;
866-333-7436;

DS-8201A, TRASTUZUMAB EMTANSINE

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of DS-8201a (Trastuzumab Deruxtecan), an Anti-HER2 Antibody Drug Conjugate (ADC), Versus Ado Trastuzumab Emtansine (T-DM1) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With Trastuzumab and Taxane
NCT03529110

Qualifying variant

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

Contact
United States: CA, DC, FL, GA, IL, KY, MA, MD, MO, NC, NE, NY, OH, PA, TN, TX, WA
(For Sites in Asia Only) Daiichi Sankyo Contact for Clinical Trial Information; dsclinicaltrial@daiichisankyo.co.jp;
+81-3-6225-1111;

VINORELBINE, ERIBULIN, TRASTUZUMAB, LAPATINIB, CAPECITABINE, SYD985

A Multi-centre, Open-label, Randomized Clinical Trial Comparing the Efficacy and Safety of the Antibody-drug Conjugate SYD985 to Physician's Choice in Patients With HER2-positive Unresectable Locally Advanced or Metastatic Breast Cancer
NCT03262935

Qualifying variant

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

Contact
United States: AL, AZ, CA, FL, IL, KS, MD, MI, MO, NC, OH, OR, PA, TX, VA
Evelyn van den Tweel, PhD; clinicaltrials@synthon.com;
+31 24 372 7700;

Phase 2 clinical trials (8)

TRASTUZUMAB EMTANSINE, TRASTUZUMAB, PERTUZUMAB

Molecular Analysis for Therapy Choice (MATCH)
NCT02465060

Qualifying variants

Contact
United States: AK, AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IA, ID,

Phase 2 clinical trials (8)

Gene	Classification	Variant	IL, IN, KS, KY, LA, MA, MD, ME, MI, MN, MO, MS, MT, NC, ND, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY Keith T Flaherty;
ERBB2	Tier 1A Pathogenic	amplification	
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	
CCND1	Tier 2C Pathogenic	amplification	

CARBOPLATIN, TRASTUZUMAB, PERTUZUMAB, PACLITAXEL

A Phase II Study of Breast Cancer Treatment Using Weekly Carboplatin + Paclitaxel With Pertuzumab + Trastuzumab (HER2+) or Bevacizumab (HER2-) in the Neoadjuvant Setting
NCT02436993

Qualifying variant

Gene	Classification	Variant	Contact
ERBB2	Tier 1A Pathogenic	amplification	United States: CA UC Irvine Health Chao Family Comprehensive Cancer Center; UCstudy@uci.edu;

METHOTREXATE

Traditional Incision and Drainage of Cutaneous Abscess Vs. Minimally Invasive Incision and Drainage With Vessel Loop: A Randomized Controlled Trail
NCT02422641

Qualifying variant

Gene	Classification	Variant	Contact
ERBB2	Tier 1A Pathogenic	amplification	United States: MD, MO, NC Cindy Miller; cytmill@wakehealth.edu;

CYCLOPHOSPHAMIDE, TRASTUZUMAB, PACLITAXEL

A Phase II Study of Neoadjuvant Chemotherapy With and Without Trastuzumab in Patients With Breast Cancer
NCT01750073

Qualifying variant

Gene	Classification	Variant	Contact
ERBB2	Tier 1A Pathogenic	amplification	United States: NE Elizabeth Reed;

NERATINIB, CAPECITABINE

A Phase II Trial of HKI-272 (Neratinib), Neratinib and Capecitabine, and Ado-Trastuzumab Emtansine for Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer and Brain Metastases
NCT01494662

Qualifying variant

Gene	Classification	Variant	Contact
ERBB2	Tier 1A Pathogenic	amplification	United States: CA, DC, MA, MD, MI, MN, NC, PA, TX Rachel Freedman, M.D., M.P.H.; rafreedman@partners.org; 6176322335;

PALBOCICLIB

Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer
NCT01037790

Qualifying variants

Gene	Classification	Variant	Contact
ERBB2	Tier 1A Pathogenic	amplification	United States: PA Peter O Dwyer, MD; PennCancerTrials@emergingmed.com; 855-216-0098;
CCND1	Tier 2C Pathogenic	amplification	

GDC-0084

Genomically-Guided Treatment Trial in Brain Metastases
NCT03994796

Qualifying variant

Gene	Classification	Variant	Contact
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	United States: AK, AR, CA, CO, CT, FL, GA, IA, ID, IL, KY, LA, MA, MI, MN, MO, MS, MT, NC, NE, NJ, NM, NY, OH, OK, OR, PA, TX, UT, VA, VT, WA, WI, WY Priscilla Brastianos, MD; pbrastianos@partners.org; 617-724-1074;

ABEMACICLIB

Phase 2 clinical trials (8)

A Phase II Study of the CDK4/6 Inhibitor Abemaciclib in Patients With Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6
NCT03310879

Qualifying variant			Contact
Gene	Classification	Variant	United States: MA
CCND1	Tier 2C Pathogenic	amplification	Geoffrey Shapiro, MD, PhD; geoffrey_shapiro@dfci.harvard.edu; 617-632-4942;

Phase 1/Phase 2 clinical trials (1)

COPANLISIB, NIVOLUMAB

An Open-label, Multi-center, Phase 1b/2 Study to Evaluate the Safety and Efficacy of Copanlisib in Combination With Nivolumab in Patients With Advanced Solid Tumors.
NCT03735628

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, NY, OH, RI
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	Bayer Clinical Trials Contact; clinical-trials-contact@bayer.com; (+)1-888-84 22937;

Phase 1 clinical trials (6)

COPANLISIB, DURVALUMAB, OLAPARIB

A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors
NCT03842228

Qualifying variant			Contact
Gene	Classification	Variant	United States: CO, MA, TX
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	Timothy A Yap;

GEDATOLISIB, PALBOCICLIB

Phase I Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors
NCT03065062

Qualifying variant			Contact
Gene	Classification	Variant	United States: MA
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	Geoffrey Shapiro, MD; Geoffrey_Shapiro@dfci.harvard.edu; 617-632-4942;

GDC-0077

A Phase I, Open-Label, Dose-Escalation Study Evaluating the Safety, Tolerability, and Pharmacokinetics of GDC-0077 as a Single Agent in Patients With Locally Advanced or Metastatic PIK3CA-Mutant Solid Tumors and in Combination With Endocrine and Targeted Therapies in Patients With Locally Advanced or Metastatic PIK3CA-Mutant Hormone-Receptor Positive Breast Cancer
NCT03006172

Qualifying variant			Contact
Gene	Classification	Variant	United States: MA, NY, TN
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	Reference Study ID Number: GO39374 www.roche.com/about_roche /roche_worldwide.htm; global-roche-genentech-trials@gene.com; 888-662-6728 (U.S. and Canada);

FULVESTRANT, PACLITAXEL, ARQ 751

A Phase 1b Study of ARQ 751 as a Single Agent or in Combination With Other Anti-Cancer Agents in Adult Subjects With Advanced Solid Tumors With PIK3CA / AKT / PTEN Mutations
NCT02761694

Qualifying variant			Contact
Gene	Classification	Variant	United States: OK, SC, TN, TX
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	ArQule, Inc.; ClinicalTrials@arqule.com; 781-994-0300;

Phase 1 clinical trials (6)

GEDATOLISIB, DOCETAXEL, DACOMITINIB, CISPLATIN

A PHASE 1B OPEN-LABEL THREE-ARM MULTI-CENTER STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF PF-05212384 (PI3K/MTOR INHIBITOR) IN COMBINATION WITH OTHER ANTI-TUMOR AGENTS
NCT01920061

Qualifying variant			Contact
Gene	Classification	Variant	United States: AL
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	Pfizer CT.gov Call Center; ClinicalTrials.gov_Inquiries@pfizer.com; 1-800-718-1021;

TRASTUZUMAB, CH 5132799

Open-label, Multicentre, Phase Ib Dose-escalation Study of MEN1611, a PI3K Inhibitor Combined With Trastuzumab With or Without Fulvestrant, in Subjects With PIK3CA Mutated HER2 Positive Locally Recurrent Unresectable (Advanced) or Metastatic (a/m) Breast Cancer Progressed to Anti-HER2 Based Therapy
NCT03767335

Qualifying variant			Contact
Gene	Classification	Variant	United States: FL, MI, MO
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	Angela Capriati Corporate Director, PhD MD; acapriati@menarini-ricerche.it; +390555680 x9990;

Early Phase 1 clinical trials (1)

PEMBROLIZUMAB

Testing the Ability of Pembrolizumab to Alter the Tumor Immune MicroEnvironment (TIME) of High Risk DCIS
NCT02872025

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA
ERBB2	Tier 1A Pathogenic	amplification	Laura Esserman; cancertrials@ucsf.edu; 877-827-3222;

VARIANT DETAILS

Biomarker (1)

Tumor Mutation Burden: TMB-low (5.7 Mutations/Megabase)

Biomarker: TMB-low
Classification: Tier 3
Assessment: Uncertain Significance

Biomarker summary: The functional consequences of Tumor Mutational Burden-low are unknown.

Clinical relevance: Deregulation of multiple cellular processes is capable of introducing DNA alterations during tumorigenesis. Genetic mutations in tumor cells have been reported to result in the production of neoantigens, which are immunogenic peptides recognized by tumor-infiltrating lymphocytes (TILs) [134, 6, 197, 68]. Studies have shown high tumor mutational burden or high levels of neoantigens to be associated with high expression of cytotoxic T-cell markers; thus, immunotherapies may be relevant in tumors with high tumor mutational burden [93, 68, 32, 179]. Indeed, high tumor mutational burden has been associated with increased clinical benefit of several immune checkpoint inhibitors, including pembrolizumab, nivolumab, nivolumab plus ipilimumab, and atezolizumab in studies of NSCLC, urothelial carcinoma, and other solid tumors [177, 35, 65, 176, 60, 82, 245, 180, 105, 73, 188]. However, as the functional consequences of low tumor mutational burden are unclear, the relevance of any therapeutic approach is unknown.

Disease summary: Increased tumor mutational burden has been correlated with higher tumor grade and was more common in triple negative and hormone receptor (HR)-negative/Her2-positive tumors as compared with HR-positive/Her2-negative tumors in one study of 687 primary breast cancers [33].

Molecular function: A test result demonstrating low tumor mutational burden has been reported in this sample.

Incidence: A study has reported a median tumor mutational burden of 3.8 mutations per megabase (mut/Mb) in 4722 breast carcinoma cases, specifically 3.6 mut/Mb in 4297 invasive ductal breast carcinoma, 2.7 mut/Mb in 142 metaplastic breast carcinoma, and 2.7 mut/Mb in 520 invasive lobular carcinoma cases [38]. A study of 3689 breast cancer cases from multiple publicly available databases has reported a median tumor mutational burden of 1.55 mut/Mb.

Variants of strong clinical significance (2)

ERBB2 amplification

Gene: ERBB2
Amino Acid: amplification
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
6 Sensitive
10 Trials

Biomarker summary: ERBB2-amplification is an activating alteration.

Clinical relevance: ERBB2 (also known as HER2/neu) encodes the receptor tyrosine kinase Her2, in the same family as Egfr [83]. Activation of Her2 as a result of mutation or amplification of ERBB2 can lead to excessive proliferation and tumor formation [83]. ERBB2 gene amplification or mutation, or Her2 overexpression may predict sensitivity to Her2 inhibitors [147, 221]. Numerous therapies have been approved by the EMA, PMDA, and/or FDA for use in Her2-overexpressing or ERBB2-amplified breast cancer, including ado-trastuzumab emtansine, lapatinib, neratinib, pertuzumab, and trastuzumab as well as several biosimilars [226, 107, 142, 20, 208]. Trastuzumab has additionally been FDA-approved for the treatment of Her2-positive gastric and gastroesophageal junction carcinoma [18].

Disease summary: ERBB2 amplification assessed by FISH in breast cancer has been correlated with Her2 overexpression as assessed by immunohistochemical analysis [206, 160]. Her2 expression has been associated with increased tumor aggressiveness and risk of recurrence in breast cancer [121, 169, 207]. Her2 positivity has been significantly associated with ER/PR-negative status, invasive ductal subtype, younger age, higher histologic grade, as well as increased tumor size and nodal status in large-scale breast carcinoma studies [49, 185]. Cross-talk between Her2 and ER signaling has been reported in breast cancer cells, and Her2 expression has been associated with resistance to endocrine therapy [23, 149].

Molecular function: Amplification of the ERBB2 gene often correlates with increased Her2 expression in several cancer types [195, 80, 139, 253, 132].

Incidence: Putative high-level amplification of ERBB2 has been reported in 9.7-34% of Breast carcinoma cases (cBioPortal for Cancer Genomics, Jan 2019). ERBB2 amplification has been reported in 11-30% of breast carcinoma cases analyzed [97, 160, 182, 150]. ERBB2 amplification assessed by FISH in breast cancer has been correlated with Her2 overexpression as assessed by immunohistochemical analysis [206, 160]. Large-scale studies have reported positive Her2 expression in 13-20% of breast cancer samples [49, 160, 185, 239].

PIK3CA H1047R

Gene: PIK3CA
Exon: 21
Nucleotide:
NM_006218.4:
g.178952085A>G
c.3140A>G
Amino Acid: p.H1047R
Allelic Fraction: 32.0% (of 2977 reads)
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
1 Sensitive
10 Trials

Biomarker summary: PIK3CA-H1047R is an activating mutation.

Clinical relevance: PIK3CA encodes the protein p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival [189, 56]. Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials [99, 143]. In addition, the p110-alpha inhibitor alpelisib has been approved by the FDA for the treatment of postmenopausal women, and men, with PIK3CA-mutated, hormone receptorpositive, Her2-negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy [10].

Disease summary: A study of 1394 early stage breast cancer samples reported that positive p110-alpha expression was associated with higher tumor grade, larger tumor size, nodal involvement, and vascular invasion. Higher p110-alpha expression was associated with basal-like breast cancer, Her2-positive breast cancer, and triple negative non-basal tumors [5]. Additional studies have reported that p110-alpha-positivity is associated with lower grade disease in breast cancer samples [113, 166, 184]. A pooled analysis of 10319 breast cancer patients from 19 studies has reported that PIK3CA mutation was associated with ER positivity, lower tumor grade, and smaller tumor size [251]. PIK3CA mutations and activation of the PI3K pathway may play a role in resistance to hormonal therapy in ER-positive breast cancers, as well as to Her2-targeted therapies in Her2-positive breast cancers, although some studies have reported no association between activation of the PI3K pathway and resistance to Her2-targeted therapies [62, 103, 155, 172, 236, 19, 122].

Molecular function: PIK3CA H1047R is a missense alteration that occurs in the kinase domain of the p110-alpha protein (UniProt). H1047R is a commonly reported hotspot mutation in the PIK3CA gene, and has been reported to result in increased lipid binding, elevated kinase activity, and oncogenic transformation in preclinical studies [111, 88, 14, 96, 162].

Incidence: PIK3CA mutations have been reported in 27% (4981/18180) of Breast carcinoma samples analyzed in COSMIC (Jan 2019). PIK3CA mutations have been reported in 27-48% of Breast carcinoma samples (cBioPortal for Cancer Genomics, Jan 2019). Literature studies have reported PIK3CA mutations in 26-40% of breast carcinoma samples overall [163, 61, 249, 153, 146]. In addition, PIK3CA mutations have been reported in 29-38% of hormone receptor-positive breast cancer samples and in 9-14% of triple negative breast cancer (TNBC) samples [61, 55, 21, 2].

Variants of potential clinical significance (2)

CCND1 amplification

Gene: CCND1
Amino Acid: amplification
Classification: Tier 2C
Assessment: Pathogenic

Treatment options
3 Trials

Biomarker summary: CCND1-amplification is an activating alteration.

Clinical relevance: CCND1 encodes Cyclin D1, a G1/S-specific cell cycle regulator. Activating alterations in CCND1 and overexpression of Cyclin D1 may lead to increased cellular proliferation [115, 15, 161, 192]. CCND1 amplification, activating mutations, and Cyclin D1 overexpression may predict sensitivity to Cdk4/6 inhibitors [72].

Disease summary: High CCND1 amplification (copy number greater than or equal to eight) has been reported to be associated with higher breast cancer tumor grade [137, 34, 183, 17, 4, 209]. Cyclin D1 expression has also been correlated with CCND1 amplification and estrogen receptor expression in breast cancer samples [137, 54, 175, 183, 130].

Molecular function: Amplification of CCND1 has been described in multiple tumor types and correlated with overexpression of the Cyclin D1 protein, cell cycle progression, and cell proliferation [159, 1, 171, 54, 22, 51, 126].

Incidence: Putative high-level amplification of CCND1 has been reported in 15-46% of Breast carcinoma cases (cBioPortal for Cancer Genomics, Jan 2019). Scientific studies have reported CCND1 amplification in 10-22% of breast carcinoma samples analyzed, including a study of male breast cancer cases [1, 136, 178, 54, 4, 130]. Studies have variably reported high Cyclin D1 expression in 12-81% of breast cancer cases examined [250, 229, 41, 54, 175, 90, 130].

TP53 L348*

Gene: TP53
Exon: 10
Nucleotide:
NM_000546.5:
g.7573984A>T
c.1043T>A
Amino Acid: p.L348*
Allelic Fraction: 56.0% (of 1989 reads)
Classification: Tier 2C
Assessment: Pathogenic

Biomarker summary: TP53-L348* is an inactivating mutation.

Clinical relevance: TP53 is a tumor suppressor that encodes the p53 protein; alterations in TP53 may result in a loss of p53 function, yet an increase in the expression and stability of the mutant p53 protein in the nucleus, sometimes leading to oncogenic effects, including genomic instability and excessive cell proliferation [128, 238, 123, 116, 92, 156]. At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines [196, 227, 186]. Tumors with TP53 mutations may be sensitive to the Wee1 inhibitor adavosertib (MK-1775), and clinical trials are currently underway for patients with solid tumors and hematologic malignancies [84, 28]. Aurora kinase A inhibitors are another therapeutic approach under investigation for TP53-mutated cancers [228, 131, 114, 218, 109].

Disease summary: TP53 is considered a breast cancer susceptibility gene; TP53 germline mutation carriers have an 18-60 fold increased risk of early onset breast cancer as compared to the general population [94, 232, 66, 12].

Molecular function: This mutation is expected to truncate the p53 protein within the tetramerization domain; this truncation is expected to result in the loss of a portion of the tetramerization domain and the entire C-terminal regulatory domain [104]. The tetramerization domain is thought to be critical to normal p53 function [110]. In addition, the C-terminal regulatory domain has been shown to be required for DNA binding and transcriptional activation by p53 [120]. Therefore, this mutation is predicted to be inactivating.

Incidence: TP53 mutations have been reported in 27% (4056/15008) of Breast carcinoma samples analyzed in COSMIC (Jan 2019). TP53 mutations have been reported in 27-48% of Breast carcinoma samples (cBioPortal for Cancer Genomics, Jan 2019). TP53 is one of the most commonly mutated genes in breast cancer; TP53 mutations have been reported in 13-29% of breast tumors analyzed in the scientific literature [61, 203, 9, 47, 165].

Variants of biological significance (2)

FGF10 amplification

Gene: FGF10
Amino Acid: amplification
Classification: Tier 3
Assessment: Likely Pathogenic

Biomarker summary: FGF10-amplification is predicted to be an activating alteration.

Clinical relevance: FGF10 is an oncogene encoding fibroblast growth factor 10 (Fgf10), a ligand of Fgfr2 and Fgfr1, implicated in promoting tumorigenesis, cell migration and invasion [220, 63, 37, 102, 214, 157, 252]. FGF10 amplification or activating mutation may induce Fgf receptor (Fgfr) activation; therefore, Fgfr inhibitors may be relevant in a tumor with FGF10 alteration [158, 117, 252]. Several multi-kinase inhibitors that target Fgfrs, including pazopanib, ponatinib, regorafenib, and lenvatinib, have been FDA-approved for certain

Variants of biological significance (2)

indications and continue to be studied in clinical trials [212, 151, 194, 255, 43, 76, 46]. Additional agents that target Fgfrs are also being studied in clinical trials [154, 101, 224, 215, 174, 13].

Disease summary: Amplification of FGF10 has been reported in 2% (21/1033) of samples in the Breast Invasive Carcinoma TGCA dataset (cBioPortal for Cancer Genomics, Oct 2014). Increased FGF10 mRNA expression has been reported in 10% of primary human breast carcinoma samples in one study [220].

Molecular function: Amplification of FGF10 has been reported in multiple cancer types and is expected to result in increased Fgf10 expression and function [52, 37, 102, 187, 157].

Incidence: Putative high-level amplification of FGF10 has been reported in 1.2-2.7% of Breast carcinoma cases (cBioPortal for Cancer Genomics, Jan 2019). Increased FGF10 mRNA expression has been reported in 10% of primary human breast carcinoma samples in one study [220]. In addition, increased Fgf10 expression has been reported in four bone-metastatic breast cancer cases as compared with four breast cancer cases without bone metastasis as well as in breast cancer samples as compared with four benign fibroadenoma tissues examined in one study [213].

MYCN amplification

Gene: MYCN
Amino Acid: amplification
Classification: Tier 3
Assessment: Pathogenic

Biomarker summary: MYCN-amplification is an activating alteration.

Clinical relevance: MYCN is a transcription factor that is expressed during embryonic development and B-cell development in adults; it is frequently amplified and overexpressed in a number of cancers [164]. Multiple approaches are in preclinical development to target MYCN in cancers, including inhibition of N-Myc expression, as well as synthetic lethal strategies of inhibiting Cdks and Aurora kinases [205, 222, 193, 89, 29, 71, 148, 244, 91]. Inhibitors of the BET family of chromatin adapters were shown to suppress transcription of MYC and MYCN, and to have anti-tumorigenic effects in MYC- or MYCN-driven tumor models [144, 241].

Disease summary: Studies have reported MYCN mRNA expression in breast cancer samples, with increased expression reported in samples from younger women as compared with older women, and in inflammatory breast cancer (IBC) as compared with non-IBC [106, 24].

Molecular function: MYCN copy number increase or amplification has been correlated with increased N-Myc expression [152, 57, 39, 26, 237, 124, 222].

Incidence: Putative high-level amplification of MYCN has been reported in 0.2-1.3% of Breast carcinoma cases (cBioPortal for Cancer Genomics, Jan 2019). MYCN amplification was not reported in any of 41 breast cancer samples analyzed in an additional study [225]. Studies have reported MYCN mRNA expression in breast cancer samples, with increased expression reported in samples from younger women as compared with older women, and in inflammatory breast cancer (IBC) as compared with non-IBC [106, 24].

Variants of uncertain significance (11)

Gene	Variant	Allelic fraction	Classification
ABRAXAS1	c.763G>C p.E255Q	13.0% (of 1969 reads)	Tier 3, Uncertain Significance
APC	c.2593C>T p.P865S	56.0% (of 3192 reads)	Tier 3, Uncertain Significance
ARID1A	c.126_128delGGC p.A45del	8.06% (of 186 reads)	Tier 3, Uncertain Significance
ARID1A	c.126_128dupGGC p.A45dup	6.13% (of 212 reads)	Tier 3, Uncertain Significance
CTNNB1	c.2056G>C p.E686Q	15.0% (of 3322 reads)	Tier 3, Uncertain Significance
FANCI	c.3931G>T p.A1311S	38.0% (of 1699 reads)	Tier 3, Uncertain Significance
FLT1	c.2117-10897_2117-10895dupCAT	12.0% (of 1784 reads)	Tier 3, Uncertain Significance
JAK3	c.115dupC p.Q39fs*13	8.14% (of 921 reads)	Tier 3, Uncertain Significance
JAK3	c.115delC p.Q39fs*108	6.95% (of 1093 reads)	Tier 3, Uncertain Significance
MDM4	c.326T>C p.L109S	46.0% (of 1435 reads)	Tier 3, Uncertain Significance
PIK3CA	c.667G>A p.E223K	14.0% (of 3502 reads)	Tier 3, Uncertain Significance

REPORT INFORMATION

Genes tested (523)

DICER1, DHX15, DDX41, DDR2, DCUN1D1, DAXX, CYLD, CXCR4, CUX1, CUL3, CTNNB1, CTNNA1, CTLA4, CTCF, CSNK1A1, CSF3R, CSF1R, CRLF2, CRKL, CREBBP, CIC, CHEK2, CHEK1, CHD4, CHD2, CENPA, CEBPA, CDKN2C, CDKN2B, CDKN2A, CDKN1B, CDKN1A, CDK8, CDK6, CDK4, CDK12, CDH1, CDC73, CD79B, CD79A, CD74, CD276, CD274, CCNE1, CCND3, CCND2, CCND1, CBL, CBFB, CASP8, CARD11, CALR, BTK, BTG1, BRIP1, BRD4, BRCA2, BRCA1, BRAF, BMPR1A, BLM, BIRC3, BCR, BCORL1, BCOR, BCL6, BCL2L2, BCL2L11, BCL2L1, BCL2, BCL10, BBC3, BARD1, BAP1, B2M, AXL, AXIN2, AXIN1, AURKB, AURKA, ATRX, ATR, ATM, ASXL2, ASXL1, ARID5B, ARID2, ARID1B, ARID1A,

ARFRP1, ARAF, AR, APC, ANKRD26, ANKRD11, ALOX12B, ALK, AKT3, AKT2, AKT1, ACVR1B, ACVR1, ABL2, ABL1, H3-5, H3-3B, H3-3A, GSK3B, GRM3, GRIN2A, GREM1, GPS2, ADGRA2, GNAS, GNAQ, GNA13, GNA11, GLI1, GID4, GEN1, GATA6, GATA4, GATA3, GATA2, GATA1, GABRA6, FYN, FUBP1, FRS2, FOXP1, FOXO1, FOXL2, FOXA1, FLT4, FLT3, FLT1, FLI1, FLCN, FH, FGFR4, FGFR3, FGFR2, FGFR1, FGF9, FGF8, FGF7, FGF6, FGF5, FGF4, FGF3, FGF23, FGF2, FGF19, FGF14, FGF10, FGF1, FBXW7, FAT1, FAS, FANCL, FANCI, FANCG, FANCF, FANCE, FANCD2, FANCC, FANCA, TENT5C, ABRAXAS1, AMER1, EZH2, EWSR1, ETV6, ETV5, ETV4, ETV1, ETS1, ESR1, ERRFI1, ERG, ERCC5, ERCC4, ERCC3, ERCC2, ERCC1, ERBB4, ERBB3, ERBB2, EPHB1, EPHA7, EPHA5, EPHA3, EPCAM, EP300, EMSY, EML4, EIF4E, EIF4A2, EIF1AX, EGFR, EGFL7, EED, E2F3, DOT1L, DNMT3B, DNMT3A, DNMT1, DNAJB1, DIS3, MST1R, MST1, MSH6, MSH3, MSH2, MRE11, MPL, MLLT3, KMT2A, MLH1, MITF, MGA, MET, MEN1, MEF2B, MED12, MDM4, MDM2, MDC1, MCL1, MAX, MAPK3, MAPK1, MAP3K4, MAP3K14, MAP3K13, MAP3K1, MAP2K4, MAP2K2, MAP2K1, MALT1, MAGI2, LZTR1, LYN, LRP1B, LMO1, LATS2, LATS1, LAMP1, KRAS, KMT2D, KMT2C, KMT2B, KLHL6, KLF4, KIT, KIF5B, KEL, KEAP1, KDR, KDM6A, KDM5C, KDM5A, KAT6A, JUN, JAK3, JAK2, JAK1, IRS2, IRS1, IRF4, IRF2, INSR, INPP4B, INPP4A, INHBA, INHA, IL7R, IL10, IKZF1, IKBKE, IGF2, IGF1R, IGF1, IFNGR1, IDH2, IDH1, ID3, ICOSLG, HSP90AA1, HSD3B1, HRAS, HOXB13, HNRNPK, HNF1A, HLA-C, HLA-B, HLA-A, H3-4, H3C13, H3C14, H3C15, H3C12, H3C11, H3C10, H3C8, H3C7, H3C6, H3C4, H3C3, H3C2, H3C1, H2BC5, H1-2, HGF, RBM10, RB1, RASA1, RARA, RANBP2, RAF1, RAD54L, RAD52, RAD51D, RAD51C, RAD51B, RAD51, RAD50, RAD21, RAC1, RAB35, QKI, PTPRT, PTPRS, PTPRD, PTPN11, PTEN, PTCH1, PRSS8, PRKDC, PRKCI, PRKAR1A, PREX2, PRDM1, PPP6C, PPP2R2A, PPP2R1A, PPM1D, PPARG, POLE, POLD1, PNRC1, PMS2, PMS1, PMAIP1, PLK2, PLCG2, PIM1, PIK3R3, PIK3R2, PIK3R1, PIK3CG, PIK3CD, PIK3CB, PIK3CA, PIK3C3, PIK3C2G, PIK3C2B, PHOX2B, PHF6, PGR, PDPK1, PDK1, PDGFRB, PDGFRA, PDCD1LG2, PDCD1, PBRM1, PAX8, PAX7, PAX5, PAX3, PARP1, PRKN, PALB2, PAK5, PAK3, PAK1, NUTM1, NUP93, NTRK3, NTRK2, NTRK1, NSD1, NRG1, NRAS, NPM1, NOTCH4, NOTCH3, NOTCH2, NOTCH1, NKX3-1, NKX2-1, NFKBIA, NFE2L2, NF2, NF1, NEGR1, NCOR1, NCOA3, NBN, NAB2, MYOD1, MYD88, MYCN, MYCL, MYC, MYB, MUTYH, MTOR, ZRSR2, ZNF703, ZNF217, ZFHX3, ZBTB7A, ZBTB2, YES1, YAP1, XRCC2, XPO1, XIAP, WT1, CCN6, VTCN1, VHL, VEGFA, U2AF1, TSHR, TSC2, TSC1, TRAF7, TRAF2, TP63, TP53, TOP2A, TOP1, TNFRSF14, TNFAIP3, TMPRSS2, TMEM127, TGFBR2, TGFBR1, TFRC, TFE3, TET2, TET1, TERT, TERC, TCF7L2, TCF3, ELOC, TBX3, TAF1, SYK, SUZ12, SUFU, STK40, STK11, STAT5B, STAT5A, STAT4, STAT3, STAG2, STAG1, SRSF2, SRC, SPTA1, SPOP, SPEN, SOX9, SOX2, SOX17, SOX10, SOCS1, SNCAIP, SMO, SMC3, SMC1A, SMARCD1, SMARCB1, SMARCA4, SMAD4, SMAD3, SMAD2, SLX4, SLIT2, SHQ1, SH2D1A, SH2B3, SF3B1, SETD2, SETBP1, SDHD, SDHC, SDHB, SDHAF2, SDHA, RYBP, RUNX1T1, RUNX1, RPTOR, RPS6KB2, RPS6KB1, RPS6KA4, ROS1, RNF43, RIT1, RICTOR, RHOA, RHEB, COP1, RET, REL, RECQL4

Methods and limitations

EXAMPLE Statement including sample type (FFPE, etc), method of extraction, amplification reactions, panel targeted regions, sequencing technology, etc. Additionally, a description of the data analysis software(s), genome of reference and the sensitivity of the methods should be described.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (6.0.20200519), Ingenuity Knowledge Base (X-release), CADD (v1.4), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2019-10-01), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2020-04-09 23:48:02.0), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (X-release), PolyPhen-2 (v2.2.2), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Apr 10 11:25 iva-1.0.1426.jar), PhyloP hg18 (2009-11), PhyloP hg19 (2009-11), DbSNP (151), TargetScan (7.2), GENCODE (Release 31), CentoMD (5.3), OMIM (May 26, 2017), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2019-11-06), DGV (2016-05-15), COSMIC (v89), HGMD (2019.3), OncoTree (oncotree_2019_03_01), SIFT4G (2016-02-23)

Clinical significance of variants based on AMP / ASCO / CAP guidelines*

Strong clinical significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential clinical significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain clinical significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

*Adapted from PMID:27993330 jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf

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