

YOUR LAB

Consulting physician		Patient		Sample	
Provider	General Hospital	Name	Michelle Doe	Accession Number	TSO500 QCI Interpret
Physician	Dr. E Smith	Age	67		One demo Report
Pathologist	Dr. R Jones	Gender	Female	Collection site	Breast
Report Date	May 7, 2020	Diagnosis	Breast carcinoma	Type	Biopsy
		Stage	IV	Collection date	May 7, 2020

## Panel Analysis: TruSight™ Oncology 500

### Overall comment

Patient specific information for this case can be described here

### Analysis results: Positive

2 Variants of strong clinical significance, Tier 1	Approved treatments	Other findings
ERBB2: amplification, Pathogenic	DS-8201a Lapatinib Neratinib Pertuzumab Trastuzumab Trastuzumab emtansine	<b>Resistance: cetuximab, erlotinib, osimertinib</b> Trials: 3 Phase 3 6 Phase 2 1 Early Phase 1
PIK3CA: p.H1047R, Pathogenic	Alpelisib/fulvestrant	<b>Resistance: vemurafenib</b> 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	-	Other Indications: bortezomib /rituximab, lenalidomide/rituximab, rituximab
1 Variant of biological significance, Tier 3	12 Variants of uncertain significance, Tier 3	
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

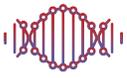
Potentially relevant guidelines are reported in the "guidelines" section starting on page 2.

### Approval

Electronically signed on: May 7, 2020 by Dr. Jones

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## 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 (10)

#### 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
<b>ERBB2</b>	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
<b>ERBB2</b>	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
<b>ERBB2</b>	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
<b>ERBB2</b>	Tier 1A Pathogenic	amplification

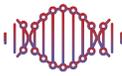
#### TRASTUZUMAB

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
<b>ERBB2</b>	Tier 1A Pathogenic	amplification

#### TRASTUZUMAB EMTANSINE



## Therapies with potential clinical benefit (10)

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
<b>ERBB2</b>	Tier 1A Pathogenic	amplification

### ALPHELISIB/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
<b>PIK3CA</b>	Tier 1A Pathogenic	p.H1047R c.3140A>G

### BORTEZOMIB/RITUXIMAB

-

### Sensitive

Gene	Classification	Variant
<b>TP53</b>	Tier 2C Pathogenic	p.L348* c.1043T>A

### LENALIDOMIDE/RITUXIMAB

Lenalidomide, a thalidomide analogue, in combination with rituximab, a CD20-directed cytolytic antibody, is FDA- and EMA-approved for treating patients with previously treated follicular lymphoma (FL); lenalidomide, in combination with rituximab, is FDA-approved for treating patients with previously treated marginal zone lymphoma (MZL).

### Sensitive

Gene	Classification	Variant
<b>TP53</b>	Tier 2C Pathogenic	p.L348* c.1043T>A

### RITUXIMAB

Rituximab, a CD20-directed cytolytic antibody, is FDA-approved for treating adult patients with relapsed or refractory, low grade or follicular, CD20-positive B cell Non-Hodgkin's Lymphoma (NHL) as a single agent; previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy; non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens; previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide; rituximab is EMA-approved for treating adult patients with previously untreated stage III-IV follicular lymphoma in combination with chemotherapy; follicular lymphoma (maintenance therapy) responding to induction therapy; stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy; CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy; and previously untreated and relapsed/refractory chronic lymphocytic leukaemia in combination with chemotherapy.

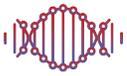
### Sensitive

Gene	Classification	Variant
<b>TP53</b>	Tier 2C Pathogenic	p.L348* c.1043T>A

## 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



## Therapies associated with resistance (4)

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
<b>ERBB2</b>	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
<b>ERBB2</b>	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
<b>ERBB2</b>	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.

### Resistance

Gene	Classification	Variant
<b>PIK3CA</b>	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
<b>PIK3CA</b>	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

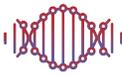
Randomized, Double-blind, Phase 3 Study of Tucatinib or Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Subjects With Unresectable Locally-advanced or Metastatic HER2+ Breast Cancer (HER2CLIMB-02)

[NCT03975647](#)

#### Qualifying variant

#### Contact

United States: AZ, CA, CO, DE, FL, GA, IL, MD, MI, MO, NE, NJ, OR,



## Phase 3 clinical trials (3)

Gene	Classification	Variant	TN, TX, VA
<b>ERBB2</b>	Tier 1A Pathogenic	amplification	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			Contact
Gene	Classification	Variant	
<b>ERBB2</b>	Tier 1A Pathogenic	amplification	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			Contact
Gene	Classification	Variant	
<b>ERBB2</b>	Tier 1A Pathogenic	amplification	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
Gene	Classification	Variant	
<b>ERBB2</b>	Tier 1A Pathogenic	amplification	United States: AK, AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IA, ID, 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;
<b>PIK3CA</b>	Tier 1A Pathogenic	p.H1047R c.3140A>G	
<b>CCND1</b>	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			Contact
Gene	Classification	Variant	
<b>ERBB2</b>	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 Trial

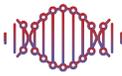
[NCT02422641](#)

Qualifying variant			Contact
Gene	Classification	Variant	
<b>ERBB2</b>	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](#)



## Phase 2 clinical trials (8)

Qualifying variant

Gene	Classification	Variant
<b>ERBB2</b>	Tier 1A Pathogenic	amplification

Contact

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
<b>ERBB2</b>	Tier 1A Pathogenic	amplification

Contact

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
<b>ERBB2</b>	Tier 1A Pathogenic	amplification
<b>CCND1</b>	Tier 2C Pathogenic	amplification

Contact

United States: PA  
Peter O Dwyer, MD; PennCancerTrials@emergingmed.com;  
855-216-0098;

## GDC-0084

Genomically-Guided Treatment Trial in Brain Metastases

[NCT03994796](#)

Qualifying variant

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

Contact

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

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

Gene	Classification	Variant
<b>CCND1</b>	Tier 2C Pathogenic	amplification

Contact

United States: MA  
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

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

Contact

United States: CA, NY, OH, RI  
Bayer Clinical Trials Contact; clinical-trials-contact@bayer.com;  
(+1)-888-84 22937;

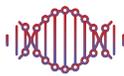
## Phase 1 clinical trials (6)

## COPANLISIB, DURVALUMAB, OLAPARIB

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

[NCT03842228](#)

Qualifying variantContact



## Phase 1 clinical trials (6)

Gene	Classification	Variant	United States: CO, MA, TX
<b>PIK3CA</b>	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
<b>PIK3CA</b>	Tier 1A Pathogenic	p.H1047R c.3140A>G	Geoffrey Shapiro, MD; <a href="mailto:Geoffrey_Shapiro@dfci.harvard.edu">Geoffrey_Shapiro@dfci.harvard.edu</a> ; 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
<b>PIK3CA</b>	Tier 1A Pathogenic	p.H1047R c.3140A>G	Reference Study ID Number: GO39374 <a href="http://www.roche.com/about_roche/roche_worldwide.htm">www.roche.com/about_roche/roche_worldwide.htm</a> ; <a href="mailto:global-roche-genentech-trials@gene.com">global-roche-genentech-trials@gene.com</a> ; 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
<b>PIK3CA</b>	Tier 1A Pathogenic	p.H1047R c.3140A>G	ArQule, Inc.; <a href="mailto:ClinicalTrials@arqule.com">ClinicalTrials@arqule.com</a> ; 781-994-0300;

## 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
<b>PIK3CA</b>	Tier 1A Pathogenic	p.H1047R c.3140A>G	Pfizer CT.gov Call Center; <a href="mailto:ClinicalTrials.gov_Inquiries@pfizer.com">ClinicalTrials.gov_Inquiries@pfizer.com</a> ; 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](#)

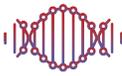
Qualifying variant			Contact
Gene	Classification	Variant	United States: FL, MI, MO
<b>PIK3CA</b>	Tier 1A Pathogenic	p.H1047R c.3140A>G	Angela Capriati Corporate Director, PhD MD; <a href="mailto:acapriati@menarini-ricerche.it">acapriati@menarini-ricerche.it</a> ; +390555680 x9990;

## Early Phase 1 clinical trials (1)

## PEMBROLIZUMAB

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

[NCT02872025](#)



## Early Phase 1 clinical trials (1)

Qualifying variant

Gene	Classification	Variant
<b>ERBB2</b>	Tier 1A Pathogenic	amplification

Contact

United States: CA  
Laura Esserman; cancertrials@ucsf.edu;  
877-827-3222;

## VARIANT DETAILS

## Variants of strong clinical significance (2)

## ERBB2 amplification

**Gene:** ERBB2**Amino Acid:** amplification**Classification:** Tier 1A**Assessment:** PathogenicTreatment 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 [70]. Activation of Her2 as a result of mutation or amplification of ERBB2 can lead to excessive proliferation and tumor formation [70]. ERBB2 gene amplification or mutation, or Her2 overexpression may predict sensitivity to Her2 inhibitors [126, 193]. 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 [PMID:23020162, PMID:29244528, PMID:29146401, PMID:22149875, 178]. Trastuzumab has additionally been FDA-approved for the treatment of Her2-positive gastric and gastroesophageal junction carcinoma [11].

**Disease summary:** ERBB2 amplification assessed by FISH in breast cancer has been correlated with Her2 overexpression as assessed by immunohistochemical analysis [PMID:15722788, 141]. Her2 expression has been associated with increased tumor aggressiveness and risk of recurrence in breast cancer [PMID:24783266, PMID:22139081, PMID:3798106]. 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 [PMID:30066480, PMID:27767099]. 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 [PMID:18508484, PMID:23908178].

**Molecular function:** Amplification of the ERBB2 gene often correlates with increased Her2 expression in several cancer types [PMID:24186136, PMID:23599643, PMID:23455784, PMID:21676436, PMID:27753660].

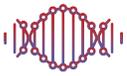
**Incidence:** Putative high-level amplification of ERBB2 has been reported in 9.7-34% of Breast carcinoma cases (cBioPortal for Cancer Genomics, Jan 2019). ERBB2 amplification has been reported in 11-30% of breast carcinoma cases analyzed [PMID:23875536, 141, 157, PMID:27567228]. ERBB2 amplification assessed by FISH in breast cancer has been correlated with Her2 overexpression as assessed by immunohistochemical analysis [PMID:15722788, 141]. Large-scale studies have reported positive Her2 expression in 13-20% of breast cancer samples [PMID:30066480, 141, PMID:27767099, PMID:26817902].

**Role in disease:** Activation of ERBB2 by amplification or mutation has been reported to play a role in several types of cancer [69]. Her2 expression has been associated with increased tumor aggressiveness and risk of recurrence in breast cancer [PMID:24783266, PMID:22139081, PMID:3798106]. 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 [PMID:30066480, PMID:27767099].

**Diagnostic significance:** Unknown.**Prognostic significance:** Unknown.

**Drug sensitivity:** Activating ERBB2 alterations may predict sensitivity to Her-targeted drug therapies. A number of therapies, including antibodies, small molecule inhibitors, and tyrosine kinase inhibitors, have been approved in various indications; these and other agents are under investigation [11, PMID:19959074, PMID:22149875, PMID:23020162, PMID:25779558, 170, 181]. Her2-directed chimeric antigen receptor (CAR) T-cell therapies are additionally being investigated in glioblastoma and other diseases expressing ERBB2/Her2 [PMID:28977984, PMID:28426845]. However, PI3K pathway activation, as reported in this case, has been associated with lack of response to certain Her2-targeted therapies.

**Drug resistance:** ERBB2 amplification has been linked to chemoresistance in breast, ovarian, cervical, and endometrial cancers [PMID:23529353]. Her2 overexpression in ER-positive breast cancer has been associated with resistance to endocrine therapy [PMID:1346366, PMID:10098763, PMID:18227529, PMID:18216219]. High ERBB2/CEP17 amplification ratio has been significantly associated with decreased disease-free survival in patients treated with standard trastuzumab-based chemotherapy in a study of 332 patients with Her2-positive breast cancer [PMID:27463363].

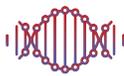


## Variants of strong clinical significance (2)

**FDA approved:** Lapatinib. Neratinib. Trastuzumab. Ado-trastuzumab emtansine. Pertuzumab.

**Phase 3:** A Phase 3 study that randomized 808 Her2-positive metastatic breast cancer patients who had not received prior chemotherapy or anti-Her2 therapy for metastatic disease to trastuzumab, docetaxel, and pertuzumab versus trastuzumab, docetaxel, and placebo reported an improvement in median progression-free survival (18.7 months vs. 12.4 months) and overall survival (56.6 months vs. 40.8 months) for the pertuzumab-containing arm [PMID:25693012, 13]. A Phase 3 study of afatinib plus vinorelbine or trastuzumab plus vinorelbine in 508 Her2-positive metastatic breast cancer patients resistant to trastuzumab reported a median progression free survival of 5.5 months and 5.6 months in the afatinib and trastuzumab group, respectively; an unfavorable benefit-risk ratio was reported for the afatinib group, leading to early stopping of this trial [PMID: 26822398]. Secondary analysis of a Phase 3 trial of 647 Her2-positive metastatic breast cancer patients reported that tumors with low levels of stromal tumor-infiltrating lymphocytes had a lower risk of progression when treated with trastuzumab as compared with lapatinib [PMID:28750133]. High ERBB2 mRNA expression has been significantly associated with greater progression-free survival with ado-trastuzumab emtansine as compared with treatment of physician's choice in the Phase 3 TH3RESA study of 602 patients with Her2-positive advanced breast cancer [101]. A randomized, double-blind, placebo-controlled Phase 3 trial of adjuvant chemotherapy and trastuzumab treatment with or without pertuzumab in 4805 women with node-positive or high-risk node-negative Her2-positive breast cancer reported a small but statistically significantly higher three-year invasive disease-free survival rate for the pertuzumab arm as compared with the placebo arm (94.1% versus 93.2%) [PMID:28581356]. A Phase 3 study of capecitabine with lapatinib or trastuzumab in Her2-positive breast cancer patients without baseline CNS metastases reported a similar incidence of CNS metastases as first site of relapse of 3% (8/251) and 5% (12/250) in patients who received lapatinib-capecitabine and trastuzumab-capecitabine, respectively [PMID:25605838]. A Phase 3 study of first line lapatinib versus trastuzumab in combination with taxanes in 652 breast cancer patients, including 537 Her2-positive patients, reported an inferior median intention-to-treat (ITT) progression-free survival (PFS) of 9.0 months with lapatinib as compared to 11.3 months with trastuzumab; in patients with Her2-positive tumors, median PFS of 9.1 and 13.6 months was reported with lapatinib and trastuzumab, respectively [PMID: 25779558]. A Phase 3 study of lapatinib (LAP) plus trastuzumab (TRAS) combined with an aromatase inhibitor (AI) versus LAP or TRAS combined with AI in 355 Her2-positive/HR-positive metastatic breast cancer patients has reported superior median progression-free survival with LAP+TRAS+AI versus TRAS+AI, 11 versus 5.7 months, respectively, and with LAP+AI versus TRAS+AI, 8.3 versus 5.7 months, respectively. Serious adverse events were reported similarly across the three treatment groups [PMID:29244528]. A Phase 3 randomized, double-blind, placebo-controlled trial of neratinib for 12 months after standard chemotherapy and trastuzumab in 2840 women with Her2-positive early breast cancer reported significantly fewer invasive disease-free survival events in the neratinib than in the placebo group, and a five-year invasive disease-free survival rate of 90.2% for neratinib and 87.7% for placebo, without significant differences in long-term toxicity in the two arms [PMID:29146401]. Trastuzumab was approved for breast cancer on the basis of a Phase 3 randomized clinical trial comparing the combination of trastuzumab and chemotherapy to chemotherapy alone; the addition of trastuzumab was associated with significant improvements in time to progression, objective response rate, duration of response, and overall survival [178]. A randomized Phase 3 trial of ado-trastuzumab emtansine (T-DM1) versus capecitabine plus lapatinib in 991 patients with Her2-positive unresectable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane reported that median overall survival was longer in the T-DM1 treatment arm (29.9 months versus 25.9 months); in addition, grade 3 or higher adverse events were less common in the T-DM1 arm [PMID:28526536]. The Phase 3 MARIANNE study of T-DM1 with or without pertuzumab versus trastuzumab plus taxane (TT) as first-line therapy for patients with Her2-positive metastatic breast cancer (n=1095) reported median overall survival (mOS) of 53.7, and 51.8, and 50.9 months in the T-DM1, T-DM1 plus pertuzumab, and TT arms, respectively; in patients with objective responses, mOS was 64.4, not reached, and 56.3 months. Grade 3 or higher adverse events were reported in 47.1%, 48.6%, and 55.8%, respectively [PMID:31318460]. The Phase 3 KATHERINE study of T-DM1 or trastuzumab in 1486 Her2-positive early breast cancer patients with residual invasive disease after treatment with neoadjuvant therapy plus trastuzumab reported a significantly increased invasive disease-free survival at 3 years of 88.3% in patients who received T-DM1 as compared with 77% in patients who received trastuzumab. Invasive breast cancer or death was reported in 12.2% of patients treated with T-DM1 and 22.2% of patients treated with trastuzumab. Adverse events were reported to be more frequent with T-DM1 as compared with trastuzumab [PMID:30516102]. The approval of pertuzumab in Her2-positive breast cancer was based on a Phase 3 randomized trial which demonstrated that the combination of pertuzumab and trastuzumab (with docetaxel) results in a significant improvement in progression-free survival, with a trend toward improvement in overall survival, compared to trastuzumab and docetaxel alone [PMID:22149875].

**Phase 2:** A Phase 2 study of tucatinib, or placebo, in combination with trastuzumab and capecitabine in Her2-positive metastatic breast cancer patients previously treated with Her2-targeted therapies has reported one-year progression-free survival rate of 33.1% and 12.3%, median progression-free survival of 7.8 months and 5.6 months, two-year overall survival rate of 44.9% and 26.6%, and median overall survival of 21.9 months and 17.4 months, in the tucatinib and placebo combination arms, respectively. In the subset of patients with brain metastases, one-year progression-free survival rate was 24.9% and 0% and median progression-free survival was 7.6 months and 5.4 months, in the tucatinib and placebo combination arms, respectively. Grade 3 or higher diarrhea and elevated aminotransferase levels were more common in the tucatinib combination arm



## Variants of strong clinical significance (2)

[PMID:31825569]. In a Phase 2 study of neratinib plus vinorelbine in 79 patients with metastatic breast cancer with ERBB2 amplification and prior trastuzumab treatment, 41% (23/56) of evaluable patients with no prior lapatinib and 8% (1/12) of patients with prior lapatinib exhibited a partial response [PMID:22967996]. A Phase 2 study of 68 evaluable Her2-positive trastuzumab-pretreated metastatic breast cancer patients receiving neratinib in combination with capecitabine has reported complete and partial responses in 12% (8/68) and 51% (35/68) of patients, respectively. Approximately 60% of patients experienced a grade 3/4 adverse event, with the most common being diarrhea (26%) [PMID:25287822]. A Phase 2 clinical trial of afatinib in Her2-negative metastatic breast carcinoma reported no objective responses [PMID:22763464]. A Phase 2 clinical trial of afatinib in Her2-positive metastatic breast carcinoma reported a 46% clinical benefit rate [PMID:22418700]. A Phase 2 study of afatinib plus letrozole in 28 ER-positive hormone-refractory metastatic breast cancer patients resistant to letrozole monotherapy reported that 14% (4/28) of patients remained progression-free at 16 weeks, including two patients known to be Her2-negative; a best response of stable disease was reported in 54% (15/29) of patients [PMID:26835225]. A Phase 2 trial of afatinib in Her2-positive inflammatory breast carcinoma reported clinical benefit in 35% (9/26) of cases. Combination treatment with afatinib and vinorelbine following disease progression resulted in clinical benefit in 2/10 of patients [59].

**Phase 1:** A Phase 1 clinical trial of the pan-ErbB inhibitor dacomitinib in advanced, solid tumor patients reported that 1/13 evaluable patients had a partial response (a lung adenocarcinoma patient) and 9/13 had stable disease for at least six weeks [186].

**Preclinical:** The pan-ErbB inhibitor dacomitinib was reported to inhibit cell proliferation in breast cancer cell lines with ERBB2 amplification, including cell lines with resistance to trastuzumab or lapatinib [PMID:22761403]. A preclinical study has reported that abemaciclib, a CDK4/6 inhibitor, can overcome lapatinib or trastuzumab resistance in Her2-positive breast cancer cell and mouse models [58].

## 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.

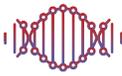
**Clinical relevance:** PIK3CA encodes the protein p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival [162, 47]. Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials [PMID:21216929, PMID:23551097]. 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 receptor-positive, Her2-negative advanced or metastatic breast cancer who experience disease progression on or following an endocrine-based therapy [PMID:31091374].

**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 [4]. Additional studies have reported that p110-alpha-positivity is associated with lower grade disease in breast cancer samples [92, PMID:27283966, 159]. 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 [PMID:29470143]. 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 [PMID:23087906, 84, 137, 152, 202, 12, 101].

**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 [90, 75, PMID:16432179, 80, 143].

**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 [144, 51, 214, 134, PMID:27388585]. 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 [51, PMID:26603012, PMID:27806348, 2].

**Role in disease:** PIK3CA mutations are not mutually exclusive with EGFR or KRAS or BRAF mutations, and are associated with increased PI3K signaling and increased activation of Akt [207, 81]. 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 [4].



## Variants of strong clinical significance (2)

Additional studies have reported that p110-alpha-positivity is associated with lower grade disease in breast cancer samples [92, PMID:27283966, 159]. 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 [PMID:29470143].

**Diagnostic significance:** Unknown.

**Prognostic significance:** Unknown.

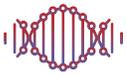
**Drug sensitivity:** Activating PIK3CA alterations may predict sensitivity to PI3K/Akt/mTOR pathway inhibitors, several of which are currently being tested in clinical trials [PMID:21216929, PMID:23551097]. While PIK3CA activating alterations have been suggested to predict sensitivity to the mTOR inhibitors everolimus and temsirolimus, results from clinical studies have been mixed, with several reporting no associations between PIK3CA mutational status and response to therapy [PMID:21216929, PMID:23301057, 118, 76, 131]. Other agents that target mTOR, including dual mTORC1/mTORC2 inhibitors and dual PI3K/mTOR inhibitors, are currently in preclinical and clinical development [38, 54, PMID:25432176]. 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 [PMID:31091374].

**Drug resistance:** PIK3CA mutations and activation of the PI3K pathway may play a role in resistance to hormonal therapy in ER-positive breast cancers [PMID:23087906]. PI3K pathway activation, as evidenced by the presence of activating PIK3CA mutations or decreased expression of PTEN, has also been associated with resistance to Her2-targeted therapies in some clinical studies, though in other studies no association was found [84, 137, 152, 202, 12, 101]. In preclinical models of mammary carcinoma bearing PIK3CA H1047R mutations, response to PI3K inhibitors is variable; preclinical studies suggest that amplification of MYC and MET may contribute to resistance [125, 113, PMID:21876152].

**FDA approved:** Alpelisib (approved for HR-positive, Her2-negative breast carcinoma).

**Phase 3:** The Phase 3 SOLAR-1 study of alpelisib plus fulvestrant compared with placebo plus fulvestrant in 572 hormone receptor (HR)-positive, Her2-negative breast cancer patients has reported that, among the 341 patients with PIK3CA mutation, the median progression-free survival (PFS) was 11.0 months in the alpelisib arm and 5.7 months in the placebo arm; a response rate of 36% was reported in PIK3CA-positive patients treated with alpelisib and 16% in PIK3CA-positive patients treated with placebo. PFS assessment in patients lacking PIK3CA mutation did not meet the predefined proof of concept endpoint [PMID:31091374]. Two randomized Phase 3 trials (BELLE-2 and BELLE-3) of buparlisib or placebo in combination with fulvestrant in HR-positive/Her2-negative advanced breast cancer patients have reported a significant increase in progression-free survival with combination therapy as compared with fulvestrant alone; however, due to the negative safety profile of combined fulvestrant and buparlisib treatment, further development of this combination is not expected [PMID:30241001, 14, PMID:29223745].

**Phase 2:** A Phase 1/2 trial of alpelisib plus nab-paclitaxel in Her2-negative metastatic breast cancer patients has reported an overall response rate of 57% (24/42) and stable disease for 16 weeks or longer in 21% of evaluable patients. Patients with PIK3CA mutations had longer progression-free survival of 13 months, as compared with 7 months in patients without PIK3CA mutations, and an overall response rate of 65%. A Phase 2 study of letrozole combined with either alpelisib or placebo in post-menopausal, HR-positive, early stage breast cancer patients reported similar objective response rates in both treatment arms, regardless of PIK3CA mutational status [PMID:30723140]. A randomized Phase 2 trial of ipatasertib plus paclitaxel versus paclitaxel alone as first-line treatment in 124 metastatic triple negative breast cancer patients has reported a median progression-free survival (PFS) of 6.2 months in the ipatasertib arm as compared with 4.9 months in the control arm. Among patients with low Pten expression, the median PFS was 6.2 months with ipatasertib as compared with 3.7 months with paclitaxel alone [PMID:28800861]. A randomized Phase 2 trial (FAIRLANE) of neoadjuvant ipatasertib with paclitaxel in 151 early triple negative breast cancer patients have shown a small, non-significant increase in pathologic complete response (pCR) rate with addition of ipatasertib to paclitaxel, with pCR observed in 17% (13/76) of patients treated with ipatasertib and paclitaxel, and 13% (10/75) of patients treated with paclitaxel alone. The pCR rate was also non-significantly increased in ipatasertib-treated patients in groups with low Pten expression by IHC or PIK3CA/AKT1/PTEN alterations by NGS. Grade 3 or higher adverse events were reported in 32% and 16% of patients in the ipatasertib and placebo arms, respectively [PMID:31147675]. A Phase 2/3 trial (BELLE-4) of paclitaxel with buparlisib (n=207) or placebo (n=209) in Her2-negative advanced breast cancer patients reported median progression-free survival of 8.0 and 9.2 months for the buparlisib and placebo arms, respectively. In patients with PI3K pathway activation, median progression-free survival was 9.1 and 9.2 months, respectively. The study was terminated prior to Phase 3, due to futility [PMID:27803006]. A Phase 1b/2 study in patients with advanced breast cancer has reported a median progression-free survival (PFS) of 10.9 and 8.4 months in 110 evaluable patients treated



## Variants of strong clinical significance (2)

with paclitaxel in combination with either capivasertib (AZD5363) or placebo, respectively. Additionally, in a subset analysis of 51 patients harboring a PIK3CA mutation, the PFS was reported to be 10.9 and 10.8 months in patients receiving the same treatment regimens, respectively [PMID:30860570].

**Phase 1:** In a Phase 1 clinical trial of onatasertib (CC-223), an expansion cohort of HR-positive/Her2-negative breast cancer patients reported partial responses in target lesions in three of 13 evaluable patients, all of whom harbored PIK3CA mutations; six patients had stable disease after two treatment cycles, one lasting over 24 weeks. A study of 729 breast cancer patients treated with neoadjuvant chemotherapy reported that the rate of pathological complete response was significantly lower in those with PIK3CA mutations (14.6%, 30/206) than in those with wild-type PIK3CA (21.4%, 112/523) [214]. A Phase 1 study of alpelisib plus ado-trastuzumab emtansine in 17 Her2-positive metastatic breast cancer patients after trastuzumab and taxane therapy has reported an overall response rate of 43% and 30%, and clinical benefit rate of 71% and 60% in 14 evaluable patients overall and in the subset of ten patients with prior treatment and progression on ado-trastuzumab emtansine, respectively [PMID:29850984]. The PanHER phase 1b study of copanlisib and trastuzumab in 12 patients with pretreated recurrent or metastatic Her2-positive breast cancer reported a best response of stable disease in 75% (9/12) of patients and continued treatment for at least 16 weeks in six patients; no dose-limiting toxicities were reported. Preliminary results from a Phase 1b study of ipatasertib with atezolizumab and either paclitaxel or nab-paclitaxel in patients with triple-negative breast carcinoma reported confirmed responses in 73% (19/26) of patients; responses were irrespective of PD-L1 expression or PIK3CA/PTEN/AKT1 alteration status. Grade 3 or higher adverse events were reported in 54% (14/26) of patients. Enrollment is ongoing. A Phase 1b study of the combination treatment of paclitaxel and MK-2206 included 14 metastatic breast cancer patients (one in dose-escalation and 13 in dose expansion). In breast cancer subjects, partial responses were reported in the one patient in the dose-escalation arm and in two of the dose expansion patients; stable disease of at least four weeks was reported in three breast cancer patients in dose expansion. Of note, two breast cancer patients in the dose expansion arm discontinued therapy, either due to disease progression or grade 4 toxicity [PMID:25688104]. A Phase 1 trial combining the Akt inhibitor MK-2206 with the anti-Her2 antibody trastuzumab in 31 patients with Her2-overexpressing tumors reported one complete response in a patient with metastatic breast cancer; one other breast cancer patient experienced a partial response and five patients (four with breast cancer) experienced stable disease for at least four months [79]. A Phase 1 trial of MK-2206 in combination with anastrozole or fulvestrant in 26 evaluable postmenopausal patients with ER-positive metastatic breast cancer reported clinical benefit in 11 patients (42%), with two partial responses and stable disease of at least six months occurring in nine patients [117].

**Preclinical:** A preclinical study reported that treating a mouse model of PIK3CA H1047R breast cancer with the Egrf-inhibitor gefitinib resulted in lower tumor volume and reduced ERK phosphorylation [211]. Treatment with capivasertib (AZD5363) has been reported to reduce tumor growth on its own, and to enhance sensitivity to ErbB pathway inhibitors in Her2-positive breast cancer preclinical models. In addition, combined treatment with capivasertib and fulvestrant was observed to synergistically reduce tumor growth in ER-positive patient-derived breast cancer xenograft models [33, PMID:26116361, 29, PMID:23844554].

## Variants of potential clinical significance (2)

### CCND1 amplification

**Gene:** CCND1

**Amino Acid:** amplification

**Classification:** Tier 2C

**Assessment:** Pathogenic

Treatment options

3 Trials

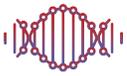
**Biomarker summary:** CCND1-amplification is an activating alteration.

**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 [95, 9, 142, 166]. CCND1 amplification, activating mutations, and Cyclin D1 overexpression may predict sensitivity to Cdk4/6 inhibitors [60].

**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 [PMID:22475046, PMID:24862872, 158, PMID:21327470, PMID:15574759, PMID:27666519]. Cyclin D1 expression has also been correlated with CCND1 amplification and estrogen receptor expression in breast cancer samples [PMID:22475046, 45, PMID:16648863, 158, PMID:27069548].

**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 [PMID:29140993, 1, 150, 45, PMID:21746927, 41, PMID:25907675].

**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, PMID:



## Variants of potential clinical significance (2)

30819233, 154, 45, PMID:15574759, PMID:27069548]. Studies have variably reported high Cyclin D1 expression in 12-81% of breast cancer cases examined [PMID:28797035, PMID:29177689, PMID:24744797, 45, PMID:16648863, PMID:25312293, PMID:27069548].

**Role in disease:** CCND1, located on chromosome 11q13, has been reported to be amplified (and/or overexpressed) in several tumor types, including bladder, breast, squamous cell carcinoma, non-small cell lung cancer (NSCLC), pancreatic adenocarcinoma, and hemangioma [89, 129, 132, 136, 74, 15]. D-type Cyclins, such as Cyclin D1, activate Cdk6, leading to the phosphorylation of Rb and subsequent release of transcription factor E2F; E2F activation then leads to the transcription of a host of genes which lead to cell cycle G1 progression. Overexpression or amplification of Cyclin D1 may therefore lead to excessive proliferation [107, 65, 182]. High CCND1 amplification (copy number greater than or equal to eight) has been reported to be associated with higher breast cancer tumor grade [PMID:22475046, PMID:24862872, 158, PMID:21327470, PMID:15574759]. Multiple studies have reported that expression of Cyclin D1 is significantly correlated to positive expression of the estrogen and/or progesterone receptor in breast cancer samples [45, PMID:16648863, 158, PMID:11870541, PMID:25313758, 145, PMID:24744797, PMID:27499632, PMID:27069548, PMID:26981504].

**Diagnostic significance:** Unknown.

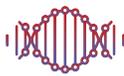
**Prognostic significance:** Unknown.

**Drug sensitivity:** There are currently no approved therapies that directly target the activation of CCND1 or overexpression of Cyclin D1; however, these tumors may be sensitive to inhibitors of Cdk4/6, several of which are being studied in clinical trials [60]. Palbociclib has been FDA-approved in combination with letrozole or fulvestrant for the treatment of female and male patients with hormone receptor positive, Her2 negative breast cancer [48, PMID:26030518]. Ribociclib has been FDA-approved for the treatment of hormone receptor positive, Her2 negative breast carcinoma in combination with an aromatase inhibitor in postmenopausal women with advanced/metastatic disease [PMID:27717303]. Abemaciclib has been FDA-approved for hormone receptor-positive, Her2-negative breast cancer as a front-line therapy in postmenopausal women in combination with an aromatase inhibitor, as a second-line therapy in women with disease progression following endocrine therapy in combination with fulvestrant, and as a single agent in women and men with disease progression following endocrine therapy and prior chemotherapy [PMID:28533223, PMID:28580882, PMID:28968163].

**Drug resistance:** Cyclin D1 is a target gene of the estrogen receptor (ER), and overexpression of Cyclin D1 has been associated with resistance to endocrine therapy in preclinical studies of breast cancer cell lines [PMID:21613412, PMID:19701242, PMID:16113099]. One study reported that high levels of CCND1 mRNA expression were correlated with failure to achieve a pathological complete response after preoperative treatment with chemotherapy and trastuzumab in Her2/ER-positive breast cancer patients, but not in Her2-positive/ER-negative patients [189].

**FDA approved:** Palbociclib (hormone receptor-positive, Her2-negative breast carcinoma). Ribociclib (hormone receptor-positive, Her2-negative breast carcinoma). Abemaciclib (hormone receptor-positive, Her2-negative breast carcinoma).

**Phase 3:** Palbociclib has been approved for use in combination with fulvestrant for the treatment of hormone receptor-positive, Her2-negative breast cancer patients resistant to endocrine therapy based on the Phase 3 PALOMA-3 trial of fulvestrant in combination with palbociclib or with placebo in this population (n=521). A greater progression-free survival (9.2 and 3.8 months) and an improved clinical benefit rate (response or prolonged stable disease; 34% and 19%) were reported in patients treated with fulvestrant and palbociclib as compared with control therapy, respectively; neutropenia was the most frequent grade 3-4 adverse event in patients who received palbociclib, and was managed with dose modification without loss of efficacy [PMID:27368881, PMID:26030518]. A Phase 3 trial (MONALEESA-2) of first-line letrozole plus ribociclib or placebo in 668 women with HR-positive, Her2-negative recurrent or metastatic breast cancer reported 18-month progression-free survival rate of 63.0% versus 42.2% in the ribociclib and placebo arms, respectively. Overall response rates were 52.7% and 37.1%, and treatment discontinuation was reported in 7.5% and 2.1%, respectively [PMID:27717303]. Second interim analysis of the Phase 3 MONALEESA-3 study of fulvestrant in combination with ribociclib or placebo in 726 post-menopausal HR-positive, Her2-negative advanced breast cancer patients has reported improved estimated overall survival rate at 42 months with ribociclib as compared with placebo (57.8% versus 45.9%), with benefit observed across first-line and second-line treatment subgroups. Higher rates of grade 3/4 neutropenia (57.1% versus 0.8%) and leukopenia (15.5% versus 0%) were observed in the ribociclib arm as compared with the placebo arm [PMID:31826360]. The Phase 3 MONALEESA-7 study of ribociclib combined with endocrine therapy (tamoxifen or NSAID and goserelin) as a front-line therapy in pre- and perimenopausal women with HR-positive, Her2-negative breast cancer has reported a significantly improved median progression-free survival (PFS) of 23.8 months in the ribociclib arm as compared with 13.0 in the placebo arm; treatment discontinuation due to adverse events occurred in 4% and 3% of the ribociclib and placebo arms, respectively [PMID:29804902]. Follow-up analysis of the



## Variants of potential clinical significance (2)

MONALEESA-7 study has reported that the addition of ribociclib to endocrine therapy was associated with significantly increased 3.5-year overall survival as compared with endocrine therapy alone (70.2% vs. 46.0%) [PMID:31166679]. A Phase 3 (MONARCH2) trial of fulvestrant with abemaciclib or placebo in 669 hormone receptor-positive, Her2-negative advanced breast cancer patients following progression on prior therapies reported objective response rates of 48.1% and 21.3%, respectively, and significantly improved median progression-free survival (16.4 versus 9.3 months) and overall survival (46.7 versus 37.3 months) in the fulvestrant plus abemaciclib arm as compared with the fulvestrant plus placebo arm [PMID:28968163, PMID:31563959]. A Phase 3 (MONARCH3) trial of a nonsteroidal aromatase inhibitor (anastrozole or letrozole) with abemaciclib or placebo in 493 hormone receptor-positive, Her2-negative advanced breast cancer patients reported significantly improved objective response rates (59% and 44%, respectively), and significantly improved progression-free survival following nonsteroidal aromatase inhibitor with abemaciclib versus with placebo (not reached and 14.7 months, respectively) [PMID:28968163].

**Phase 2:** Palbociclib has received accelerated FDA approval for use in combination with letrozole for the treatment of hormone receptor-positive, Her2-negative advanced breast cancer in postmenopausal women based on the randomized PALOMA-1/TRIO-18 Phase 2 trial of first-line letrozole with or without palbociclib in this population (n=165); significantly improved progression-free survival was reported for the palbociclib plus letrozole group compared with the letrozole only group (20.2 vs. 10.2 months) as well as a trend towards improved overall survival in the palbociclib group [48]. An updated analysis of the PALOMA-1/TRIO-18 Phase 2 trial of first-line letrozole with or without palbociclib in 165 postmenopausal women with ER-positive/Her2-negative advanced breast cancer reported median overall survival of 37.5 months and 34.5 months (statistically non-significant) in 66 patients who received palbociclib plus letrozole or letrozole alone, respectively; median overall survival of 35.1 months for palbociclib plus letrozole and 35.7 months for letrozole alone (statistically non-significant) was reported in part 2 of the study in 99 patients additionally screened for CCND1 amplification and/or loss of p16INK4a. A Phase 2 (MONARCH1) trial of abemaciclib monotherapy in 132 hormone receptor-positive, Her2-negative metastatic breast cancer patients following progression on prior therapies reported an objective response rate of 19.7%, a clinical benefit rate of 42.4%, median progression-free survival of 6.0 months, and median overall survival of 17.7 months; discontinuation due to adverse events was seen in 7.6% [PMID:28533223].

**Phase 1:** A Phase 1 clinical trial of alvocidib in combination with FOLFIRI in 63 evaluable patients with advanced cancers reported stable disease in 35% (22/63) of patients, two partial responses (small bowel and bladder cancer), and a complete response in a melanoma patient [PMID:20953860]. A Phase 1 study of docetaxel followed by alvocidib in 27 evaluable solid tumor patients has reported one complete response (pancreatic cancer patient), four partial responses (pancreatic, ovarian, and two breast cancer patients), and stable disease in ten patients. Grade 3 or higher toxicities included mucositis and neutropenia [PMID:17908977]. A Phase 1 study of roniciclib in ten patients with advanced solid tumors reported stable disease for a duration of 5.0 months in one patient with melanoma, and stable disease for a duration of 2.5-3.0 months in three patients (thyroid cancer, colorectal cancer, esophageal squamous cell cancer). Low tolerability of this treatment has been reported and trial enrollment was stopped. A Phase 1 study of roniciclib in 12 Japanese patients with advanced solid tumors reported one partial response and stable disease in four patients for a disease control rate of 42%; no grade 4 or 5 drug-related treatment-emergent adverse events were reported, and grade 3 events occurred in three patients.

**Preclinical:** In preclinical studies, metformin has also been shown to inhibit Cyclin D1 expression (and activate AMPK), and lead to reduced proliferation of breast cancer cells [PMID:19046439, PMID:19221498, PMID:19440038]. A preclinical study has reported that alvocidib inhibited the growth of triple negative breast cancer cells resistant to both Akt and MEK inhibitors [PMID:31527768].

## TP53 L348\*

**Gene:** TP53**Exon:** 10**Nucleotide:**

NM\_000546.5:

g.7573984A&gt;T

c.1043T&gt;A

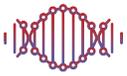
**Amino Acid:** p.L348\***Allelic Fraction:** 56.0% (of 1989 reads)**Classification:** Tier 2C**Assessment:** PathogenicTreatment options

3 Sensitive

**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 [109, 203, 103, 96, 77, 138]. 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 [168, PMID:21541192, PMID:24982341]. 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 [PMID:20107315, PMID:21799033]. Aurora kinase A inhibitors are another therapeutic approach under investigation for TP53-mutated cancers [PMID:25398437, 111, 94, 190, PMID:24091768].

**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 [PMID:32091585, 197, PMID:15637391, 8].



## Variants of potential clinical significance (2)

**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 [PMID:18410249]. The tetramerization domain is thought to be critical to normal p53 function [88]. In addition, the C-terminal regulatory domain has been shown to be required for DNA binding and transcriptional activation by p53 [100]. 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 [51, 176, PMID:18465328, PMID:23014189, 146].

**Role in disease:** Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers [22]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias [120, 183, 165]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [203, 103, 96, 77, 138]. 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 [PMID:32091585, 197, PMID:15637391, 8].

**Diagnostic significance:** Unknown.

**Prognostic significance:** Unknown.

**Drug sensitivity:** 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 [168, PMID:21541192, PMID:24982341]. Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function [PMID:21087899, PMID:20107315, PMID:21799033]. Clinical trials of the Wee1 inhibitor adavosertib (MK-1775) are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors [PMID:25398437, 111, 94, 190, PMID:22611192, PMID:23955083]. A preclinical study in breast cancer cell lines suggests that Tlr4 inhibition may have a synthetic lethal effect on tumors with TP53 mutations [66].

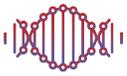
**Drug resistance:** Mutations in TP53 may increase resistance to ionizing radiation therapy [PMID:14576853, 127].

**FDA approved:** None.

**Phase 3:** None.

**Phase 2:** A Phase 2 trial of a p53 adenoviral vector in combination with docetaxel and doxorubicin as neoadjuvant therapy in 13 patients with locally advanced breast cancer, including eight patients with TP53 mutation (of 11 patients analyzed), was terminated early due to a lack of pathologic complete response in any of the patients. However, serial biopsies did show an increase in TP53 mRNA in the tumors [30]. A Phase 2 trial of ENMD-2076 in patients with advanced triple-negative breast carcinoma (TNBC) reported a six-month clinical benefit rate of 16.7%, with partial responses and stable disease in 5.6% (2/36) and 38.9% (14/36) of patients, respectively [37]. A Phase 2 study of single agent alisertib included a cohort of 53 breast cancer patients. Of the 49 who were evaluable, nine (18%) had an objective response (all partial), ten (20%) had stable disease for six months or more, and median progression-free survival was 5.4 months. The most common drug-related grade 3/4 adverse events in the breast cancer patients were neutropenia (53%), leukopenia (34%), and stomatitis (15%) [PMID:25728526]. A Phase 1/2 study of paclitaxel with or without alisertib in 191 patients with advanced breast cancer or recurrent ovarian cancer has reported documented progression-free survival (PFS) event at data cutoff in 75% (107/142) of patients, specifically in 71% (52/73) of patients in the alisertib plus paclitaxel arm compared with 80% (55/69) of patients in the paclitaxel monotherapy arm. In addition, the median PFS were 6.7 months and 4.7 months in the alisertib plus paclitaxel and the paclitaxel monotherapy arms, respectively. Grades 3 or higher treatment-related adverse events were reported in 86% (63/73) and 20% (14/69) of patients in the alisertib plus paclitaxel and paclitaxel monotherapy arms, respectively [PMID:30347019].

**Phase 1:** A Phase 1 trial of adavosertib (AZD1775, MK-1775) in 21 evaluable patients with refractory solid tumors, including seven patients with documented BRCA1/2 mutations, reported confirmed partial responses in



## Variants of potential clinical significance (2)

one head and neck cancer and one ovarian cancer patient, both harboring BRCA1 mutations; however, no responses were seen in any of five patients with confirmed TP53 mutations [39]. A Phase 1 trial of adavosertib alone or in combination with chemotherapy in patients with refractory solid tumors has reported confirmed or unconfirmed partial responses in 10% (17/176) of patients overall, including in patients with ovarian cancer, melanoma, breast cancer, head and neck cancer, colorectal cancer, and cutaneous squamous cell carcinoma. In patients with archived tumor tissue evaluable for sequence analysis, partial responses were reported in 21% (4/19) and 12% (4/33) of TP53 mutant and TP53 wild-type cases, respectively. Stable disease was reported in 53% (94/176) of patients overall [PMID:27601554]. A Phase 1 trial of alisertib with fulvestrant in nine patients with endocrine-resistant, ER-positive metastatic breast carcinoma reported a six-month clinical benefit rate of 77.8% and median progression-free survival of 12.4 months. The combination was well-tolerated [PMID:29289986]. A Phase 1 trial of SGT-53 in 11 patients with refractory cancer reported that the gene therapy complex was well tolerated with stable disease achieved in seven patients at six weeks and a median survival of 340 days; in addition, one tumor which was previously classified as inoperable was able to be resected [PMID:23609015]. A Phase 1 trial of SGT-53 in combination with docetaxel in 14 patients with advanced cancer has reported three partial responses and two stable diseases per RECIST [PMID:27357628].

**Preclinical:** A preclinical study reported that ENMD-2076 treatment was associated with antiproliferative activity in a panel of breast cancer cell lines, with greater activity in cell lines without increased Her2 expression and those negative for estrogen receptor expression [PMID:23136197]. Adavosertib has been shown to increase the sensitivity of p53-defective, but not p53-wild-type, breast cancer cell lines to radiation [PMID:21799033]. Adavosertib has been reported to induce apoptosis in breast cancer cell lines; adavosertib in combination with paclitaxel synergistically induced apoptosis [PMID:28562324]. A preclinical study reported that treatment of breast cancer, non-small cell lung cancer, and glioblastoma mouse models with SGT-53 resulted in sensitivity to anti-PD1 antibodies; the combination therapy resulted in greater activation of tumor infiltrating lymphocytes and synergistic tumor growth inhibition as compared with either treatment alone [PMID:30288347].

## Variant of biological significance (1)

### 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 [PMID:15975048]. 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 [PMID:22174364, PMID:22065083, 167, PMID:22222631, 19, PMID:17589519, PMID:19525400, 208, PMID:22430491]. 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 [123, PMID:24009722].

**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 [PMID:25999348, PMID:15501955].

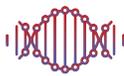
**Molecular function:** MYCN copy number increase or amplification has been correlated with increased N-Myc expression [PMID:29464082, PMID:28453467, PMID:9815553, PMID:9779703, PMID:23901000, PMID:26171843, PMID:22065083].

**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 [PMID:3330785]. 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 [PMID:25999348, PMID:15501955].

**Role in disease:** MYCN encodes N-Myc, a transcription factor that is thought to act as an oncoprotein by preventing cell differentiation and promoting cell proliferation, in part by altering transcription of many target genes [31, 114]. MYCN gene amplification and/or protein overexpression have been reported in many tumor types in the scientific literature [21, 160, 130, 93, 133, 46, 128].

**Diagnostic significance:** Unknown.

**Prognostic significance:** Unknown.



## Variant of biological significance (1)

**Drug sensitivity:** Multiple different approaches are in preclinical development to target MYCN in cancers, including inhibition of N-Myc expression and indirect targeting of N-Myc [PMID:22174364, PMID:22065083, 167]. Preclinical studies have suggested several synthetic lethal strategies to indirectly target Myc, including synthetic lethal interactions between Myc overexpression and inhibition of Cdk1, Cdk2, or Aurora kinases. Cdk inhibitors and Aurora kinase inhibitors are under investigation in clinical trials [PMID:22430491, PMID:22222631, PMID:17589519, 208, PMID:19525400, 19]. 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 [123, PMID:24009722].

**Drug resistance:** None.

**FDA approved:** None.

**Phase 3:** None.

**Phase 2:** A Phase 2 trial of ENMD-2076 in patients with advanced triple-negative breast carcinoma (TNBC) reported a six-month clinical benefit rate of 16.7%, with partial responses and stable disease in 5.6% (2/36) and 38.9% (14/36) of patients, respectively [37]. A Phase 2 study of dinaciclib or capecitabine in previously treated advanced breast cancer patients was stopped after an interim analysis reported that the time to tumor progression with dinaciclib was inferior compared to capecitabine [PMID:24393852]. A Phase 2 study of single agent alisertib included a cohort of 53 breast cancer patients. Of the 49 who were evaluable, nine (18%) had an objective response (all partial), ten (20%) had stable disease for six months or more, and median progression-free survival was 5.4 months. The most common drug-related grade 3/4 adverse events in the breast cancer patients were neutropenia (53%), leukopenia (34%), and stomatitis (15%) [PMID:25728526]. A Phase 1/2 study of paclitaxel with or without alisertib in 191 patients with advanced breast cancer or recurrent ovarian cancer has reported documented progression-free survival (PFS) event at data cutoff in 75% (107/142) of patients, specifically in 71% (52/73) of patients in the alisertib plus paclitaxel arm compared with 80% (55/69) of patients in the paclitaxel monotherapy arm. In addition, the median PFS were 6.7 months and 4.7 months in the alisertib plus paclitaxel and the paclitaxel monotherapy arms, respectively. Grades 3 or higher treatment-related adverse events were reported in 86% (63/73) and 20% (14/69) of patients in the alisertib plus paclitaxel and paclitaxel monotherapy arms, respectively [PMID:30347019].

**Phase 1:** A Phase 1 study of roniciclib in ten patients with advanced solid tumors reported stable disease for a duration of 5.0 months in one patient with melanoma, and stable disease for a duration of 2.5-3.0 months in three patients (thyroid cancer, colorectal cancer, esophageal squamous cell cancer). Low tolerability of this treatment has been reported and trial enrollment was stopped. A Phase 1 study of roniciclib in 12 Japanese patients with advanced solid tumors reported one partial response and stable disease in four patients for a disease control rate of 42%; no grade 4 or 5 drug-related treatment-emergent adverse events were reported, and grade 3 events occurred in three patients. A Phase 1 trial of alisertib with fulvestrant in nine patients with endocrine-resistant, ER-positive metastatic breast carcinoma reported a six-month clinical benefit rate of 77.8% and median progression-free survival of 12.4 months. The combination was well-tolerated [PMID:29289986].

**Preclinical:** A preclinical study reported that ENMD-2076 treatment was associated with antiproliferative activity in a panel of breast cancer cell lines, with greater activity in cell lines without increased Her2 expression and those negative for estrogen receptor expression [PMID:23136197].

## Variants of uncertain significance (12)

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
FGF10	amplification	-	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, ERRF1, 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, HNRNP, 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, MYO1D1, MYD88, MYCN, MYCL, MYC, MYB, MUTYH, MTOR, ZRSR2, ZNF703, ZNF217, ZFH3, 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, TGFB2, TGFB1, 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 (6.0.20200507), 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

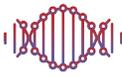
## Potential clinical significance

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

Tier 3 Biomarker has uncertain clinical significance and not known to be likely benign or benign

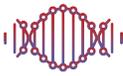


## significance

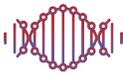
\*Adapted from PMID:27993330 [jmd.amjpathol.org/article/S1525-1578\(16\)30223-9/pdf](http://jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf)

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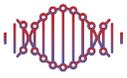
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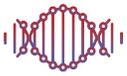
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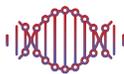
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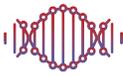
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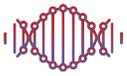
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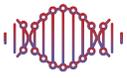
- Optimization of Orally Bioavailable Enhancer of Zeste Homolog 2 (EZH2) Inhibitors Using Ligand and Property-Based Design Strategies: Identification of Development Candidate (R)-5,8-Dichloro-7-(methoxy(oxetan-3-yl)methyl)-2-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-3,4-dihydroisoquinolin-1(2H)-one (PF-06821497). *J Med Chem*. 2018 Feb 08;61(3):650-665. Epub 2017 Dec 27 ([PMID: 29211475](#))
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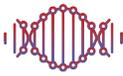
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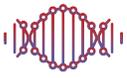
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