YOUR LAB

Your Lab Genetics Lab
123 Nathan Street, San Mateo, CA 94401
ylgenetics.com / (650) 484 4040
A trusted partner for your health

Consulting physician		Patient		Sample	
Provider	General Hospital	Name	Michelle Doe	Accession Number	TSO500 QCI Interpret One demo Report
Physician	Dr. E Smith	Age	67		
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	**Resistance: cetuximab, erlotinib, osimertinib** Trials: 3 Phase 3 6 Phase 2 1 Early Phase 1
PIK3CA: p.H1047R, Pathogenic	Alpelisib/fulvestrant	**Resistance: vemurafenib** Trials: 1 Expanded Access 2 Phase 2 1 Phase 1/Phase 2 6 Phase 1
2 Variants of potential clinical significance, Tier 2	**Approved treatments**	**Other findings**
CCND1: amplification, Pathogenic	-	Trials: 3 Phase 2
TP53 †: p.L348*, Pathogenic	-	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

Report content

GUIDELINES

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

INTERACTIONS

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

TREATMENT OPTIONS

Therapies with potential clinical benefit (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
ERBB2	Tier 1A Pathogenic	amplification

LAPATINIB

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

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

NERATINIB

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

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

PERTUZUMAB

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

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

TRASTUZUMAB

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

Sensitive

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

TRASTUZUMAB EMTANSINE

Therapies with potential clinical benefit (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
ERBB2	Tier 1A Pathogenic	amplification

ALPELISIB/FULVESTRANT

Alpelisib, a kinase inhibitor, in combination with fulvestrant, an estrogen receptor antagonist, is FDA-approved for treating postmenopausal female, and male, patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Sensitive

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

BORTEZOMIB/RITUXIMAB

-

Sensitive

Gene	Classification	Variant
TP53	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
TP53	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
TP53	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
ERBB2	Tier 1A Pathogenic	amplification

ERLOTINIB

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

Resistance

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

OSIMERTINIB

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

Resistance

Gene	Classification	Variant
ERBB2	Tier 1A Pathogenic	amplification

VEMURAFENIB

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

Resistance

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

AVAILABLE CLINICAL TRIALS

Expanded Access clinical trials (1)

ALPELISIB

INST UNM 1601: Compassionate Use of BYL 719 Alpelisib
NCT03941782

Qualifying variant

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

Contact

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

Phase 3 clinical trials (3)

TRASTUZUMAB EMTANSINE, TUCATINIB

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

Qualifying variant

Contact

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

Phase 3 clinical trials (3)

Gene	Classification	Variant	
ERBB2	Tier 1A Pathogenic	amplification	TN, TX, VA Seattle Genetics Trial Information Support; clinicaltrials@seagen.com; 866-333-7436;

DS-8201A, TRASTUZUMAB EMTANSINE

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

NCT03529110

Qualifying variant

Gene	Classification	Variant	Contact
ERBB2	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

Gene	Classification	Variant	Contact
ERBB2	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

Gene	Classification	Variant	Contact
ERBB2	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;
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	
CCND1	Tier 2C Pathogenic	amplification	

CARBOPLATIN, TRASTUZUMAB, PERTUZUMAB, PACLITAXEL

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

NCT02436993

Qualifying variant

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

METHOTREXATE

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

NCT02422641

Qualifying variant

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

CYCLOPHOSPHAMIDE, TRASTUZUMAB, PACLITAXEL

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

NCT01750073

Phase 2 clinical trials (8)

Qualifying variant			Contact
Gene	Classification	Variant	United States: NE
ERBB2	Tier 1A Pathogenic	amplification	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			Contact
Gene	Classification	Variant	United States: CA, DC, MA, MD, MI, MN, NC, PA, TX
ERBB2	Tier 1A Pathogenic	amplification	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			Contact
Gene	Classification	Variant	United States: PA
ERBB2	Tier 1A Pathogenic	amplification	Peter O Dwyer, MD; PennCancerTrials@emergingmed.com; 855-216-0098;
CCND1	Tier 2C Pathogenic	amplification	

GDC-0084

Genomically-Guided Treatment Trial in Brain Metastases
NCT03994796

Qualifying variant			Contact
Gene	Classification	Variant	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;
PIK3CA	Tier 1A Pathogenic	p.H1047R c.3140A>G	

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

Phase 1/Phase 2 clinical trials (1)

COPANLISIB, NIVOLUMAB

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

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

Phase 1 clinical trials (6)

COPANLISIB, DURVALUMAB, OLAPARIB

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

Qualifying variant	Contact

Phase 1 clinical trials (6)

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

GEDATOLISIB, PALBOCICLIB

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

NCT03065062

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

GDC-0077

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

NCT03006172

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

FULVESTRANT, PACLITAXEL, ARQ 751

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

NCT02761694

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

GEDATOLISIB, DOCETAXEL, DACOMITINIB, CISPLATIN

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

NCT01920061

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

TRASTUZUMAB, CH 5132799

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

NCT03767335

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

Early Phase 1 clinical trials (1)

PEMBROLIZUMAB

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

NCT02872025

Early Phase 1 clinical trials (1)

Qualifying variant

Gene	Classification	Variant
ERBB2	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: Pathogenic

Treatment options
6 Sensitive
10 Trials

Biomarker summary: ERBB2-amplification is an activating alteration.

Clinical relevance: ERBB2 (also known as HER2/neu) encodes the receptor tyrosine kinase Her2, in the same family as Egfr [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 receptorpositive, 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 PantHER 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 Egfr-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:

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 NSAI 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 (46.7versus 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>T
c.1043T>A
Amino Acid: p.L348*
Allelic Fraction: 56.0% (of 1989 reads)
Classification: Tier 2C
Assessment: Pathogenic

Treatment 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 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, ERRFI1, ERG, ERCC5, ERCC4, ERCC3, ERCC2, ERCC1, ERBB4, ERBB3, ERBB2, EPHB1, EPHA7, EPHA5, EPHA3, EPCAM, EP300, EMSY, EML4, EIF4E, EIF4A2, EIF1AX, EGFR, EGFL7, EED, E2F3, DOT1L, DNMT3B, DNMT3A, DNMT1, DNAJB1, DIS3, MST1R, MST1, MSH6, MSH3, MSH2, MRE11, MPL, MLLT3, KMT2A, MLH1, MITF, MGA, MET, MEN1, MEF2B, MED12, MDM4, MDM2, MDC1, MCL1, MAX, MAPK3, MAPK1, MAP3K4, MAP3K14, MAP3K13, MAP3K1, MAP2K4, MAP2K2, MAP2K1, MALT1, MAGI2, LZTR1, LYN, LRP1B, LMO1, LATS2, LATS1, LAMP1, KRAS, KMT2D, KMT2C, KMT2B, KLHL6, KLF4, KIT, KIF5B, KEL, KEAP1, KDR, KDM6A, KDM5C, KDM5A, KAT6A, JUN, JAK3, JAK2, JAK1, IRS2, IRS1, IRF4, IRF2, INSR, INPP4B, INPP4A, INHBA, INHA, IL7R, IL10, IKZF1, IKBKE, IGF2, IGF1R, IGF1, IFNGR1, IDH2, IDH1, ID3, ICOSLG, HSP90AA1, HSD3B1, HRAS, HOXB13, HNRNPK, HNF1A, HLA-C, HLA-B, HLA-A, H3-4, H3C13, H3C14, H3C15, H3C12, H3C11, H3C10, H3C8, H3C7, H3C6, H3C4, H3C3, H3C2, H3C1, H2BC5, H1-2, HGF, RBM10, RB1, RASA1, RARA, RANBP2, RAF1, RAD54L, RAD52, RAD51D, RAD51C, RAD51B, RAD51, RAD50, RAD21, RAC1, RAB35, QKI, PTPRT, PTPRS, PTPRD, PTPN11, PTEN, PTCH1, PRSS8, PRKDC, PRKCI, PRKAR1A, PREX2, PRDM1, PPP6C, PPP2R2A, PPP2R1A, PPM1D, PPARG, POLE, POLD1, PNRC1, PMS2, PMS1, PMAIP1, PLK2, PLCG2, PIM1, PIK3R3, PIK3R2, PIK3R1, PIK3CG, PIK3CD, PIK3CB, PIK3CA, PIK3C3, PIK3C2G, PIK3C2B, PHOX2B, PHF6, PGR, PDPK1, PDK1, PDGFRB, PDGFRA, PDCD1LG2, PDCD1, PBRM1, PAX8, PAX7, PAX5, PAX3, PARP1, PRKN, PALB2, PAK5, PAK3, PAK1, NUTM1, NUP93, NTRK3, NTRK2, NTRK1, NSD1, NRG1, NRAS, NPM1, NOTCH4, NOTCH3, NOTCH2, NOTCH1, NKX3-1, NKX2-1, NFKBIA, NFE2L2, NF2, NF1, NEGR1, NCOR1, NCOA3, NBN, NAB2, MYOD1, MYD88, MYCN, MYCL, MYC, MYB, MUTYH, MTOR, ZRSR2, ZNF703, ZNF217, ZFHX3, ZBTB7A, ZBTB2, YES1, YAP1, XRCC2, XPO1, XIAP, WT1, CCN6, VTCN1, VHL, VEGFA, U2AF1, TSHR, TSC2, TSC1, TRAF7, TRAF2, TP63, TP53, TOP2A, TOP1, TNFRSF14, TNFAIP3, TMPRSS2, TMEM127, TGFBR2, TGFBR1, TFRC, TFE3, TET2, TET1, TERT, TERC, TCF7L2, TCF3, ELOC, TBX3, TAF1, SYK, SUZ12, SUFU, STK40, STK11, STAT5B, STAT5A, STAT4, STAT3, STAG2, STAG1, SRSF2, SRC, SPTA1, SPOP, SPEN, SOX9, SOX2, SOX17, SOX10, SOCS1, SNCAIP, SMO, SMC3, SMC1A, SMARCD1, SMARCB1, SMARCA4, SMAD4, SMAD3, SMAD2, SLX4, SLIT2, SHQ1, SH2D1A, SH2B3, SF3B1, SETD2, SETBP1, SDHD, SDHC, SDHB, SDHAF2, SDHA, RYBP, RUNX1T1, RUNX1, RPTOR, RPS6KB2, RPS6KB1, RPS6KA4, ROS1, RNF43, RIT1, RICTOR, RHOA, RHEB, COP1, RET, REL, RECQL4

Methods and limitations

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

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (6.0.20200507), 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

SELECTED REFERENCES

1. Ahlin C, Lundgren C, Embretsén-Varro E, Jirström K, Blomqvist C, Fjällskog M- (2017) High expression of cyclin D1 is associated to high proliferation rate and increased risk of mortality in women with ER-positive but not in ER-negative breast cancers. Breast Cancer Res Treat. 2017 Aug;164(3):667-678. Epub 2017 May 20 (PMID: 28528450)
2. Ahmad F, Badwe A, Verma G, Bhatia S, Das BR (2016) Molecular evaluation of PIK3CA gene mutation in breast cancer: determination of frequency, distribution pattern and its association with clinicopathological findings in Indian patients. Med Oncol. 2016 Jul;33(7):74. Epub 2016 Jun 9 (PMID: 27282497)
3. Ahmad S, Hewett PW, Al-Ani B, Sissaoui S, Fujisawa T, Cudmore MJ, Ahmed A (2011) Autocrine activity of soluble Flt-1 controls endothelial cell function and angiogenesis. Vasc Cell. 2011 Jul 13;3(1):15 (PMID: 21752276)
4. Aleskandarany MA, Rakha EA, Ahmed MA, Powe DG, Paish EC, Macmillan RD, Ellis IO, Green AR (2009) PIK3CA expression in invasive breast cancer: a biomarker of poor prognosis. Breast Cancer Res Treat. 2010 Jul;122(1):45-53. Epub 2009 Aug 22 (PMID: 19701705)
5. Allo G, Bernardini MQ, Wu RC, Shih IeM, Kalloger S, Pollett A, Gilks CB, Clarke BA (2013) ARID1A loss correlates with mismatch repair deficiency and intact p53 expression in high-grade endometrial carcinomas. Mod Pathol. 2014 Feb;27(2):255-61. Epub 2013 Jul 26 (PMID: 23887303)
6. Alpi AF, Pace PE, Babu MM, Patel KJ (2008) Mechanistic insight into site-restricted monoubiquitination of FANCD2 by Ube2t, FANCL, and FANCI. Mol Cell. 2008 Dec 26;32(6):767-77 (PMID: 19111657)
7. André T, Kotelevets L, Vaillant JC, Coudray AM, Weber L, Prévot S, Parc R, Gespach C, Chastre E (2000) Vegf, Vegf-B, Vegf-C and their receptors KDR, FLT-1 and FLT-4 during the neoplastic progression of human colonic mucosa. Int J Cancer. 2000 Apr 15;86(2):174-81 (PMID: 10738243)
8. Apostolou P, Fostira F (2013) Hereditary breast cancer: the era of new susceptibility genes. Biomed Res Int. 2013;2013:747318. Epub 2013 Mar 21 (PMID: 23586058)
9. Baldin V, Lukas J, Marcote MJ, Pagano M, Draetta G (1993) Cyclin D1 is a nuclear protein required for cell cycle progression in G1. Genes Dev. 1993 May;7(5):812-21 (PMID: 8491378)
10. Bando H, Weich HA, Brokelmann M, Horiguchi S, Funata N, Ogawa T, Toi M (2005) Association between intratumoral free and total VEGF, soluble VEGFR-1, VEGFR-2 and prognosis in breast cancer. Br J Cancer. 2005 Feb 14;92(3):553-61 (PMID: 15668703)
11. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK, ToGA Trial Investigators (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97. Epub 2010 Aug 19 (PMID: 20728210)
12. Barbareschi M, Cuorvo LV, Girlando S, Bragantini E, Eccher C, Leonardi E, Ferro A, Caldara A, Triolo R, Cantaloni C, Decarli N, Galligioni E, Dalla Palma P (2012) PI3KCA mutations and/or PTEN loss in Her2-positive breast carcinomas treated with trastuzumab are not related to resistance to anti-Her2 therapy. Virchows Arch. 2012 Aug;461(2):129-39. Epub 2012 Jun 29 (PMID: 22744290)
13. Baselga J, Cortés J, Im SA, Clark E, Ross G, Kiermaier A, Swain SM (2014) Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in human epidermal growth factor receptor 2-positive, first-line metastatic breast cancer. J Clin Oncol. 2014 Nov 20;32(33):3753-61. Epub 2014 Oct 20 (PMID: 25332247)
14. Baselga J, Im SA, Iwata H, Cortés J, De Laurentiis M, Jiang Z, Arteaga CL, Jonat W, Clemons M, Ito Y, Awada A, Chia S, Jagiełło-Gruszfeld A, Pistilli B, Tseng LM, Hurvitz S, Masuda N, Takahashi M, Vuylsteke P, Hachemi S, Dharan B, Di Tomaso E, Urban P, Massacesi C, Campone M (2017) Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017 Jul;18(7):904-916. Epub 2017 May 30 (PMID: 28576675)
15. Beroukhim R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, Barretina J, Boehm JS, Dobson J, Urashima M, Mc Henry KT, Pinchback RM, Ligon AH, Cho YJ, Haery L, Greulich H, Reich M, Winckler W, Lawrence MS, Weir BA, Tanaka KE, Chiang DY, Bass AJ, Loo A, Hoffman C, Prensner J, Liefeld T, Gao Q, Yecies D, Signoretti S, Maher E, Kaye FJ, Sasaki H, Tepper JE, Fletcher JA, Tabernero J, Baselga J, Tsao MS, Demichelis F, Rubin MA, Janne PA, Daly MJ, Nucera C, Levine RL, Ebert BL, Gabriel S, Rustgi AK, Antonescu CR, Ladanyi M, Letai A, Garraway LA, Loda M, Beer DG, True LD, Okamoto A, Pomeroy SL, Singer S, Golub TR, Lander ES, Getz G, Sellers WR, Meyerson M (2010) The landscape of somatic copy-number alteration across human cancers. Nature. 2010 Feb 18;463(7283):899-905 (PMID: 20164920)
16. Bitler BG, Aird KM, Garipov A, Li H, Amatangelo M, Kossenkov AV, Schultz DC, Liu Q, Shih IeM, Conejo-Garcia JR, Speicher DW, Zhang R (2015) Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers. Nat Med. 2015 Mar;21(3):231-8. Epub 2015 Feb 16 (PMID: 25686104)
17. Boisvert RA, Howlett NG (2014) The Fanconi anemia ID2 complex: dueling saxes at the crossroads. Cell Cycle. 2014;13(19):2999-3015 (PMID: 25486561)
18. Bowman T, Garcia R, Turkson J, Jove R (2000) STATs in oncogenesis. Oncogene. 2000 May 15;19(21):2474-88 (PMID: 10851046)
19. Brockmann M, Poon E, Berry T, Carstensen A, Deubzer HE, Rycak L, Jamin Y, Thway K, Robinson SP, Roels F, Witt O, Fischer M, Chesler L, Eilers M (2013) Small molecule inhibitors of aurora-a induce proteasomal degradation of N-myc in childhood neuroblastoma. Cancer Cell. 2013 Jul 08;24(1):75-89. Epub 2013 Jun 20 (PMID: 23792191)

20. Broderick DK, Di C, Parrett TJ, Samuels YR, Cummins JM, McLendon RE, Fults DW, Velculescu VE, Bigner DD, Yan H (2004) Mutations of PIK3CA in anaplastic oligodendrogliomas, high-grade astrocytomas, and medulloblastomas. Cancer Res. 2004 Aug 01;64(15):5048-50 (PMID: 15289301)

21. Brodeur GM, Seeger RC, Schwab M, Varmus HE, Bishop JM (1984) Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. Science. 1984 Jun 08;224(4653):1121-4 (PMID: 6719137)

22. Brown CJ, Lain S, Verma CS, Fersht AR, Lane DP (2009) Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer. 2009 Dec;9(12): 862-73 (PMID: 19935675)

23. Castillo A, Paul A, Sun B, Huang TH, Wang Y, Yazinski SA, Tyler J, Li L, You MJ, Zou L, Yao J, Wang B (2014) The BRCA1-interacting protein Abraxas is required for genomic stability and tumor suppression. Cell Rep. 2014 Aug 07;8(3):807-17. Epub 2014 Jul 24 (PMID: 25066119)

24. Cha JD, Kim HJ, Cha IH (2011) Genetic alterations in oral squamous cell carcinoma progression detected by combining array-based comparative genomic hybridization and multiplex ligation-dependent probe amplification. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011 May;111(5): 594-607. Epub 2011 Feb 22 (PMID: 21334929)

25. Chou A, Toon CW, Clarkson A, Sioson L, Houang M, Watson N, DeSilva K, Gill AJ (2014) Loss of ARID1A expression in colorectal carcinoma is strongly associated with mismatch repair deficiency. Hum Pathol. 2014 Aug;45(8):1697-703. Epub 2014 Apr 24 (PMID: 24925223)

26. Cordon-Cardo C, Latres E, Drobnjak M, Oliva MR, Pollack D, Woodruff JM, Marechal V, Chen J, Brennan MF, Levine AJ (1994) Molecular abnormalities of mdm2 and p53 genes in adult soft tissue sarcomas. Cancer Res. 1994 Feb 01;54(3):794-9 (PMID: 8306343)

27. Cornen S, Adelaide J, Bertucci F, Finetti P, Guille A, Birnbaum DJ, Birnbaum D, Chaffanet M (2012) Mutations and deletions of ARID1A in breast tumors. Oncogene. 2012 Sep 20;31(38):4255-6. Epub 2012 Jan 16 (PMID: 22249247)

28. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DiPersio J, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Müller MC, Gambacorti-Passerini C, Wong S, Lustgarten S, Rivera VM, Clackson T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes T, Goldman JM, Shah NP, Kantarjian H, PACE Investigators (2013) A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013 Nov 07;369(19):1783-96. Epub 2013 Nov 1 (PMID: 24180494)

29. Crafter C, Vincent JP, Tang E, Dudley P, James NH, Klinowska T, Davies BR (2015) Combining AZD8931, a novel EGFR/HER2/HER3 signalling inhibitor, with AZD5363 limits AKT inhibitor induced feedback and enhances antitumour efficacy in HER2-amplified breast cancer models. Int J Oncol. 2015 Aug;47(2):446-54. Epub 2015 Jun 22 (PMID: 26095475)

30. Cristofanilli M, Krishnamurthy S, Guerra L, Broglio K, Arun B, Booser DJ, Menander K, Van Wart Hood J, Valero V, Hortobagyi GN (2006) A nonreplicating adenoviral vector that contains the wild-type p53 transgene combined with chemotherapy for primary breast cancer: safety, efficacy, and biologic activity of a novel gene-therapy approach. Cancer. 2006 Sep 01;107(5):935-44 (PMID: 16874816)

31. Dang CV, O'Donnell KA, Zeller KI, Nguyen T, Osthus RC, Li F (2006) The c-Myc target gene network. Semin Cancer Biol. 2006 Aug;16(4):253-64. Epub 2006 Jul 25 (PMID: 16904903)

32. Danovi D, Meulmeester E, Pasini D, Migliorini D, Capra M, Frenk R, de Graaf P, Francoz S, Gasparini P, Gobbi A, Helin K, Pelicci PG, Jochemsen AG, Marine JC (2004) Amplification of Mdmx (or Mdm4) directly contributes to tumor formation by inhibiting p53 tumor suppressor activity. Mol Cell Biol. 2004 Jul;24(13):5835-43 (PMID: 15199139)

33. Davies BR, Greenwood H, Dudley P, Crafter C, Yu DH, Zhang J, Li J, Gao B, Ji Q, Maynard J, Ricketts SA, Cross D, Cosulich S, Chresta CC, Page K, Yates J, Lane C, Watson R, Luke R, Ogilvie D, Pass M (2012) Preclinical pharmacology of AZD5363, an inhibitor of AKT: pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. Mol Cancer Ther. 2012 Apr;11(4):873-87. Epub 2012 Jan 31 (PMID: 22294718)

34. De Vita S, Mulligan C, McElwaine S, Dagna-Bricarelli F, Spinelli M, Basso G, Nizetic D, Groet J (2007) Loss-of-function JAK3 mutations in TMD and AMKL of Down syndrome. Br J Haematol. 2007 May;137(4):337-41 (PMID: 17456055)

35. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG, GRID study investigators (2012) Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan 26;381(9863):295-302. Epub 2012 Nov 22 (PMID: 23177515)

36. Di Conza G, Mancini F, Buttarelli M, Pontecorvi A, Trimarchi F, Moretti F (2012) MDM4 enhances p53 stability by promoting an active conformation of the protein upon DNA damage. Cell Cycle. 2012 Feb 15;11(4):749-60 (PMID: 22374672)

37. Diamond JR, Eckhardt SG, Pitts TM, van Bokhoven A, Aisner D, Gustafson DL, Capasso A, Sams S, Kabos P, Zolman K, Colvin T, Elias AD, Storniolo AM, Schneider BP, Gao D, Tentler JJ, Borges VF, Miller KD (2018) A phase II clinical trial of the Aurora and angiogenic kinase inhibitor ENMD-2076 for previously treated, advanced, or metastatic triple-negative breast cancer. Breast Cancer Res. 2018 Aug 02;20(1):82. Epub 2018 Aug 2 (PMID: 30071865)

38. Dienstmann R, Rodon J, Serra V, Tabernero J (2014) Picking the point of inhibition: a comparative review of PI3K/AKT/mTOR pathway inhibitors. Mol Cancer Ther. 2014 May;13(5):1021-31. Epub 2014 Apr 18 (PMID: 24748656)

39. Do K, Wilsker D, Ji J, Zlott J, Freshwater T, Kinders RJ, Collins J, Chen AP, Doroshow JH, Kummar S (2015) Phase I Study of Single-Agent AZD1775 (MK-1775), a Wee1 Kinase Inhibitor, in Patients With Refractory Solid Tumors. J Clin Oncol. 2015 Oct 20;33(30):3409-15. Epub 2015 May 11 (PMID: 25964244)

40. Dorsman JC, Levitus M, Rockx D, Rooimans MA, Oostra AB, Haitjema A, Bakker ST, Steltenpool J, Schuler D, Mohan S, Schindler D, Arwert F, Pals G, Mathew CG, Waisfisz Q, de Winter JP, Joenje H (2007) Identification of the Fanconi anemia complementation group I gene, FANCI. Cell Oncol. 2007;29(3):211-8 (PMID: 17452773)

41. Dragoj M, Milosevic Z, Bankovic J, Dinic J, Pesic M, Tanic N, Stankovic T (2015) Association of CCND1 overexpression with KRAS and PTEN alterations in specific subtypes of non-small cell lung carcinoma and its influence on patients' outcome. Tumour Biol. 2015 Nov;36(11):8773-80. Epub 2015 Jun 9 (PMID: 26055143)

42. Du M, Thompson J, Fisher H, Zhang P, Huang CC, Wang L (2018) Genomic alterations of plasma cell-free DNAs in small cell lung cancer and their clinical relevance. Lung Cancer. 2018 Jun;120:113-121. Epub 2018 Apr 12 (PMID: 29748005)

43. Ellingson MS, Hart SN, Kalari KR, Suman V, Schahl KA, Dockter TJ, Felten SJ, Sinnwell JP, Thompson KJ, Tang X, Vedell PT, Barman P, Sicotte H, Eckel-Passow JE, Northfelt DW, Gray RJ, McLaughlin SA, Moreno-Aspitia A, Ingle JN, Moyer AM, Visscher DW, Jones K, Conners A, McDonough M, Wieben ED, Wang L, Weinshilboum R, Boughey JC, Goetz MP (2015) Exome sequencing reveals frequent deleterious germline variants in cancer susceptibility genes in women with invasive breast cancer undergoing neoadjuvant chemotherapy. Breast Cancer Res Treat. 2015 Sep;153(2): 435-43. Epub 2015 Aug 22 (PMID: 26296701)

44. Elliott NE, Cleveland SM, Grann V, Janik J, Waldmann TA, Davé UP (2011) FERM domain mutations induce gain of function in JAK3 in adult T-cell leukemia/lymphoma. Blood. 2011 Oct 06;118(14):3911-21. Epub 2011 Aug 5 (PMID: 21821710)

45. Elsheikh S, Green AR, Aleskandarany MA, Grainge M, Paish CE, Lambros MB, Reis-Filho JS, Ellis IO (2007) CCND1 amplification and cyclin D1 expression in breast cancer and their relation with proteomic subgroups and patient outcome. Breast Cancer Res Treat. 2008 May;109(2):325-35. Epub 2007 Jul 26 (PMID: 17653856)

46. Emoto M, Oshima K, Ishiguro M, Iwasaki H, Kawarabayashi T, Kikuchi M (1999) Establishment and characterization of a serous papillary adenocarcinoma cell line of the human ovary in a serum-free culture. Pathol Res Pract. 1999;195(4):237-42 (PMID: 10337661)

47. Engelman JA (2009) Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nat Rev Cancer. 2009 Aug;9(8):550-62 (PMID: 19629070)

48. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M, Shparyk Y, Thummala AR, Voytko NL, Fowst C, Huang X, Kim ST, Randolph S, Slamon DJ (2014) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35. Epub 2014 Dec 16 (PMID: 25524798)

49. Fodde R, Kuipers J, Rosenberg C, Smits R, Kielman M, Gaspar C, van Es JH, Breukel C, Wiegant J, Giles RH, Clevers H (2001) Mutations in the APC tumour suppressor gene cause chromosomal instability. Nat Cell Biol. 2001 Apr;3(4):433-8 (PMID: 11283620)

50. Fong GH, Rossant J, Gertsenstein M, Breitman ML (1995) Role of the Flt-1 receptor tyrosine kinase in regulating the assembly of vascular endothelium. Nature. 1995 Jul 06;376(6535):66-70 (PMID: 7596436)

51. Fountzilas G, Giannoulatou E, Alexopoulou Z, Zagouri F, Timotheadou E, Papadopoulou K, Lakis S, Bobos M, Poulios C, Sotiropoulou M, Lyberopoulou A, Gogas H, Pentheroudakis G, Pectasides D, Koutras A, Christodoulou C, Papandreou C, Samantas E, Papakostas P, Kosmidis P, Bafaloukos D, Karanikiotis C, Dimopoulos MA, Kotoula V (2016) TP53 mutations and protein immunopositivity may predict for poor outcome but also for trastuzumab benefit in patients with early breast cancer treated in the adjuvant setting. Oncotarget. 2016 May 31;7(22):32731-53 (PMID: 27129168)

52. Francavilla C, Rigbolt KT, Emdal KB, Carraro G, Vernet E, Bekker-Jensen DB, Streicher W, Wikström M, Sundström M, Bellusci S, Cavallaro U, Blagoev B, Olsen JV (2013) Functional proteomics defines the molecular switch underlying FGF receptor trafficking and cellular outputs. Mol Cell. 2013 Sep 26;51(6):707-22. Epub 2013 Sep 5 (PMID: 24011590)

53. Fu Y, Zheng S, An N, Athanasopoulos T, Popplewell L, Liang A, Li K, Hu C, Zhu Y (2011) β-catenin as a potential key target for tumor suppression. Int J Cancer. 2011 Oct 01;129(7):1541-51. Epub 2011 Jun 21 (PMID: 21455986)

54. Fumarola C, Bonelli MA, Petronini PG, Alfieri RR (2014) Targeting PI3K/AKT/mTOR pathway in non small cell lung cancer. Biochem Pharmacol. 2014 Aug 01;90(3):197-207. Epub 2014 May 24 (PMID: 24863259)

55. Ghanem MA, van Steenbrugge GJ, Sudaryo MK, Mathoera RB, Nijman JM, van der Kwast TH (2003) Expression and prognostic relevance of vascular endothelial growth factor (VEGF) and its receptor (FLT-1) in nephroblastoma. J Clin Pathol. 2003 Feb;56(2):107-13 (PMID: 12560388)

56. Giles RH, van Es JH, Clevers H (2003) Caught up in a Wnt storm: Wnt signaling in cancer. Biochim Biophys Acta. 2003 Jun 05;1653(1):1-24 (PMID: 12781368)

57. Giron-Michel J, Azzi S, Khawam K, Mortier E, Caignard A, Devocelle A, Ferrini S, Croce M, François H, Lecru L, Charpentier B, Chouaib S, Azzarone B, Eid P (2012) Interleukin-15 plays a central role in human kidney physiology and cancer through the γc signaling pathway. PLoS One. 2012;7(2): e31624. Epub 2012 Feb 21 (PMID: 22363690)

58. Goel S, Wang Q, Watt AC, Tolaney SM, Dillon DA, Li W, Ramm S, Palmer AC, Yuzugullu H, Varadan V, Tuck D, Harris LN, Wong KK, Liu XS, Sicinski P, Winer EP, Krop IE, Zhao JJ (2016) Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors. Cancer Cell. 2016 Mar 14;29(3):255-269 (PMID: 26977878)

59. Goh G, Schmid R, Guiver K, Arpornwirat W, Chitapanarux I, Ganju V, Im SA, Kim SB, Dechaphunkul A, Maneechavakajorn J, Spector N, Yau T, Afrit M, Ahmed SB, Johnston SR, Gibson N, Uttenreuther-Fischer M, Herrero J, Swanton C (2016) Clonal Evolutionary Analysis during HER2 Blockade in HER2-Positive Inflammatory Breast Cancer: A Phase II Open-Label Clinical Trial of Afatinib +/- Vinorelbine. PLoS Med. 2016 Dec;13(12):e1002136. Epub 2016 Dec 6 (PMID: 27923043)

60. Gong X, Litchfield LM, Webster Y, Chio LC, Wong SS, Stewart TR, Dowless M, Dempsey J, Zeng Y, Torres R, Boehnke K, Mur C, Marugán C, Baquero C, Yu C, Bray SM, Wulur IH, Bi C, Chu S, Qian HR, Iversen PW, Merzoug FF, Ye XS, Reinhard C, De Dios A, Du J, Caldwell CW, Lallena MJ, Beckmann RP, Buchanan SG (2017) Genomic Aberrations that Activate D-type Cyclins Are Associated with Enhanced Sensitivity to the CDK4 and CDK6 Inhibitor Abemaciclib. Cancer Cell. 2017 Dec 11;32(6):761-776.e6 (PMID: 29232554)

61. Green RA, Kaplan KB (2003) Chromosome instability in colorectal tumor cells is associated with defects in microtubule plus-end attachments caused by a dominant mutation in APC. J Cell Biol. 2003 Dec 08;163(5):949-61 (PMID: 14662741)

62. Guan B, Gao M, Wu CH, Wang TL, Shih IeM (2012) Functional analysis of in-frame indel ARID1A mutations reveals new regulatory mechanisms of its tumor suppressor functions. Neoplasia. 2012 Oct;14(10):986-93 (PMID: 23097632)

63. Guan B, Wang TL, Shih IeM (2011) ARID1A, a factor that promotes formation of SWI/SNF-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. Cancer Res. 2011 Nov 01;71(21):6718-27. Epub 2011 Sep 7 (PMID: 21900401)

64. Hamdi Y, Soucy P, Adoue V, Michailidou K, Canisius S, Lemaçon A, Droit A, Andrulis IL, Anton-Culver H, Arndt V, Baynes C, Blomqvist C, Bogdanova NV, Bojesen SE, Bolla MK, Bonanni B, Borresen-Dale AL, Brand JS, Brauch H, Brenner H, Broeks A, Burwinkel B, Chang-Claude J, NBCS Collaborators, Couch FJ, Cox A, Cross SS, Czene K, Darabi H, Dennis J, Devilee P, Dörk T, Dos-Santos-Silva I, Eriksson M, Fasching PA, Figueroa J, Flyger H, García-Closas M, Giles GG, Goldberg MS, González-Neira A, Grenaker-Alnæs G, Guénel P, Haeberle L, Haiman CA, Hamann U, Hallberg E, Hooning MJ, Hopper JL, Jakubowska A, Jones M, Kabisch M, Kataja V, Lambrechts D, Le Marchand L, Lindblom A, Lubinski J, Mannermaa A, Maranian M, Margolin S, Marme F, Milne RL, Neuhausen SL, Nevanlinna H, Neven P, Olswold C, Peto J, Plaseska-Karanfilska D, Pylkäs K, Radice P, Rudolph A, Sawyer EJ, Schmidt MK, Shu XO, Southey MC, Swerdlow A, Tollenaar RA, Tomlinson I, Torres D, Truong T, Vachon C, Van Den Ouweland AM, Wang Q, Winqvist R, kConFab/AOCS Investigators, Zheng W, Benitez J, Chenevix-Trench G, Dunning AM, Pharoah PD, Kristensen V, Hall P, Easton DF, Pastinen T, Nord S, Simard J (2016) Association of breast cancer risk with genetic variants showing differential allelic expression: Identification of a novel breast cancer susceptibility locus at 4q21. Oncotarget. 2016 Dec 06;7(49):80140-80163 (PMID: 27792995)

65. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell. 2000 Jan 07;100(1):57-70 (PMID: 10647931)

66. Haricharan S, Brown P (2015) TLR4 has a TP53-dependent dual role in regulating breast cancer cell growth. Proc Natl Acad Sci U S A. 2015 Jun 23; 112(25):E3216-25. Epub 2015 Jun 10 (PMID: 26063617)

67. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F (2003) Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J. 2003 Aug 15;374(Pt 1):1-20 (PMID: 12773095)

68. Henkels KM, Farkaly T, Mahankali M, Segall JE, Gomez-Cambronero J (2011) Cell invasion of highly metastatic MTLn3 cancer cells is dependent on phospholipase D2 (PLD2) and Janus kinase 3 (JAK3). J Mol Biol. 2011 May 20;408(5):850-62. Epub 2011 Mar 22 (PMID: 21414324)

69. Herter-Sprie GS, Greulich H, Wong KK (2013) Activating Mutations in ERBB2 and Their Impact on Diagnostics and Treatment. Front Oncol. 2013;3: 86. Epub 2013 Apr 23 (PMID: 23630663)

70. Higgins MJ, Baselga J (2011) Targeted therapies for breast cancer. J Clin Invest. 2011 Oct;121(10):3797-803. Epub 2011 Oct 3 (PMID: 21965336)

71. Hiratsuka S, Maru Y, Okada A, Seiki M, Noda T, Shibuya M (2001) Involvement of Flt-1 tyrosine kinase (vascular endothelial growth factor receptor-1) in pathological angiogenesis. Cancer Res. 2001 Feb 01;61(3):1207-13 (PMID: 11221852)

72. Hiratsuka S, Minowa O, Kuno J, Noda T, Shibuya M (1998) Flt-1 lacking the tyrosine kinase domain is sufficient for normal development and angiogenesis in mice. Proc Natl Acad Sci U S A. 1998 Aug 04;95(16):9349-54 (PMID: 9689083)

73. Hisamuddin IM, Yang VW (2006) Molecular Genetics of Colorectal Cancer: An Overview. Curr Colorectal Cancer Rep. 2006 Apr;2(2):53-59 (PMID: 19079560)

74. Holzmann K, Kohlhammer H, Schwaenen C, Wessendorf S, Kestler HA, Schwoerer A, Rau B, Radlwimmer B, Döhner H, Lichter P, Gress T, Bentz M (2004) Genomic DNA-chip hybridization reveals a higher incidence of genomic amplifications in pancreatic cancer than conventional comparative genomic hybridization and leads to the identification of novel candidate genes. Cancer Res. 2004 Jul 01;64(13):4428-33 (PMID: 15231651)

75. Hon WC, Berndt A, Williams RL (2011) Regulation of lipid binding underlies the activation mechanism of class IA PI3-kinases. Oncogene. 2012 Aug 09;31(32):3655-66. Epub 2011 Nov 28 (PMID: 22120714)

76. Hortobagyi GN, Chen D, Piccart M, Rugo HS, Burris HA, Pritchard KI, Campone M, Noguchi S, Perez AT, Deleu I, Shtivelband M, Masuda N, Dakhil S, Anderson I, Robinson DM, He W, Garg A, McDonald ER, Bitter H, Huang A, Taran T, Bachelot T, Lebrun F, Lebwohl D, Baselga J (2015) Correlative Analysis of Genetic Alterations and Everolimus Benefit in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From BOLERO-2. J Clin Oncol. 2016 Feb 10;34(5):419-26. Epub 2015 Oct 26 (PMID: 26503204)

77. Houben R, Hesbacher S, Schmid CP, Kauczok CS, Flohr U, Haferkamp S, Müller CS, Schrama D, Wischhusen J, Becker JC (2011) High-level expression of wild-type p53 in melanoma cells is frequently associated with inactivity in p53 reporter gene assays. PLoS One. 2011;6(7):e22096. Epub 2011 Jul 8 (PMID: 21760960)

78. Hu X, Kim JA, Castillo A, Huang M, Liu J, Wang B (2011) NBA1/MERIT40 and BRE interaction is required for the integrity of two distinct deubiquitinating enzyme BRCC36-containing complexes. J Biol Chem. 2011 Apr 01;286(13):11734-45. Epub 2011 Jan 31 (PMID: 21282113)

79. Hudis C, Swanton C, Janjigian YY, Lee R, Sutherland S, Lehman R, Chandarlapaty S, Hamilton N, Gajria D, Knowles J, Shah J, Shannon K, Tetteh E, Sullivan DM, Moreno C, Yan L, Han HS (2013) A phase 1 study evaluating the combination of an allosteric AKT inhibitor (MK-2206) and trastuzumab in patients with HER2-positive solid tumors. Breast Cancer Res. 2013 Nov 19;15(6):R110 (PMID: 24252402)

80. Isakoff SJ, Engelman JA, Irie HY, Luo J, Brachmann SM, Pearline RV, Cantley LC, Brugge JS (2005) Breast cancer-associated PIK3CA mutations are oncogenic in mammary epithelial cells. Cancer Res. 2005 Dec 01;65(23):10992-1000 (PMID: 16322248)

81. Janku F, Lee JJ, Tsimberidou AM, Hong DS, Naing A, Falchook GS, Fu S, Luthra R, Garrido-Laguna I, Kurzrock R (2011) PIK3CA mutations frequently coexist with RAS and BRAF mutations in patients with advanced cancers. PLoS One. 2011;6(7):e22769. Epub 2011 Jul 29 (PMID: 21829508)

82. Javle M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, Ramanathan RK, Goyal L, Sadeghi S, Macarulla T, El-Khoueiry A, Kelley RK, Borbath I, Choo SP, Oh DY, Philip PA, Chen LT, Reungwetwattana T, Van Cutsem E, Yeh KH, Ciombor K, Finn RS, Patel A, Sen S, Porter D, Isaacs R, Zhu AX, Abou-Alfa GK, Bekaii-Saab T (2017) Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. J Clin Oncol. 2018 Jan 20;36(3):276-282. Epub 2017 Nov 28 (PMID: 29182496)

83. Javle M, Rashid A, Churi C, Kar S, Zuo M, Eterovic AK, Nogueras-Gonzalez GM, Janku F, Shroff RT, Aloia TA, Vauthey JN, Curley S, Mills G, Roa I (2013) Molecular characterization of gallbladder cancer using somatic mutation profiling. Hum Pathol. 2014 Apr;45(4):701-8. Epub 2013 Nov 12 (PMID: 24508317)

84. Jensen JD, Knoop A, Laenkholm AV, Grauslund M, Jensen MB, Santoni-Rugiu E, Andersson M, Ewertz M (2011) PIK3CA mutations, PTEN, and pHER2 expression and impact on outcome in HER2-positive early-stage breast cancer patients treated with adjuvant chemotherapy and trastuzumab. Ann Oncol. 2012 Aug;23(8):2034-42. Epub 2011 Dec 15 (PMID: 22172323)

85. Jeong EG, Kim MS, Nam HK, Min CK, Lee S, Chung YJ, Yoo NJ, Lee SH (2008) Somatic mutations of JAK1 and JAK3 in acute leukemias and solid cancers. Clin Cancer Res. 2008 Jun 15;14(12):3716-21 (PMID: 18559588)

86. Jones S, Li M, Parsons DW, Zhang X, Wesseling J, Kristel P, Schmidt MK, Markowitz S, Yan H, Bigner D, Hruban RH, Eshleman JR, Iacobuzio-Donahue CA, Goggins M, Maitra A, Malek SN, Powell S, Vogelstein B, Kinzler KW, Velculescu VE, Papadopoulos N (2011) Somatic mutations in the chromatin remodeling gene ARID1A occur in several tumor types. Hum Mutat. 2012 Jan;33(1):100-3. Epub 2011 Nov 23 (PMID: 22009941)

87. Jones S, Wang TL, Shih IeM, Mao TL, Nakayama K, Roden R, Glas R, Slamon D, Diaz LA, Vogelstein B, Kinzler KW, Velculescu VE, Papadopoulos N (2010) Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. Science. 2010 Oct 08;330(6001):228-31. Epub 2010 Sep 8 (PMID: 20826764)

88. Kamada R, Nomura T, Anderson CW, Sakaguchi K (2010) Cancer-associated p53 tetramerization domain mutants: quantitative analysis reveals a low threshold for tumor suppressor inactivation. J Biol Chem. 2011 Jan 07;286(1):252-8. Epub 2010 Oct 26 (PMID: 20978130)

89. Kaminagakura E, Werneck da Cunha I, Soares FA, Nishimoto IN, Kowalski LP (2011) CCND1 amplification and protein overexpression in oral squamous cell carcinoma of young patients. Head Neck. 2011 Oct;33(10):1413-9. Epub 2011 Jan 20 (PMID: 21254295)

90. Kang S, Bader AG, Vogt PK (2005) Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. Proc Natl Acad Sci U S A. 2005 Jan 18;102(3):802-7. Epub 2005 Jan 12 (PMID: 15647370)

91. Kaplan KB, Burds AA, Swedlow JR, Bekir SS, Sorger PK, Näthke IS (2001) A role for the Adenomatous Polyposis Coli protein in chromosome segregation. Nat Cell Biol. 2001 Apr;3(4):429-32 (PMID: 11283619)

92. Karakas B, Colak D, Kaya N, Ghebeh H, Al-Qasem A, Hendrayani F, Toulimat M, Al-Tweigeri T, Park BH, Aboussekhra A (2013) Prevalence of PIK3CA mutations and the SNP rs17849079 in Arab breast cancer patients. Cancer Biol Ther. 2013 Oct 01;14(10):888-96. Epub 2013 Aug 12 (PMID: 23982433)

93. Karlsson A, Helou K, Walentinsson A, Hedrich HJ, Szpirer C, Levan G (2001) Amplification of Mycn, Ddx1, Rrm2, and Odc1 in rat uterine endometrial carcinomas. Genes Chromosomes Cancer. 2001 Aug;31(4):345-56 (PMID: 11433525)

94. Katayama H, Sen S (2011) Functional significance of Aurora kinase A regulatory interactions with p53-ERα complex in human breast cancer cells. Horm Cancer. 2011 Apr;2(2):117-24 (PMID: 21761334)

95. Kato JY, Matsuoka M, Polyak K, Massagué J, Sherr CJ (1994) Cyclic AMP-induced G1 phase arrest mediated by an inhibitor (p27Kip1) of cyclin-dependent kinase 4 activation. Cell. 1994 Nov 04;79(3):487-96 (PMID: 7954814)

96. Kato S, Han SY, Liu W, Otsuka K, Shibata H, Kanamaru R, Ishioka C (2003) Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc Natl Acad Sci U S A. 2003 Jul 08;100(14):8424-9. Epub 2003 Jun 25 (PMID: 12826609)

97. Katoh M (2008) Cancer genomics and genetics of FGFR2 (Review). Int J Oncol. 2008 Aug;33(2):233-7 (PMID: 18636142)

98. Kendall RL, Thomas KA (1993) Inhibition of vascular endothelial cell growth factor activity by an endogenously encoded soluble receptor. Proc Natl Acad Sci U S A. 1993 Nov 15;90(22):10705-9 (PMID: 8248162)

99. Kikuchi A (2000) Regulation of beta-catenin signaling in the Wnt pathway. Biochem Biophys Res Commun. 2000 Feb 16;268(2):243-8 (PMID: 10679188)

100. Kim H, Kim K, Choi J, Heo K, Baek HJ, Roeder RG, An W (2011) p53 requires an intact C-terminal domain for DNA binding and transactivation. J Mol Biol. 2012 Feb 03;415(5):843-54. Epub 2011 Dec 9 (PMID: 22178617)

101. Kim SB, Wildiers H, Krop IE, Smitt M, Yu R, Lysbet de Haas S, Gonzalez-Martin A (2016) Relationship between tumor biomarkers and efficacy in TH3RESA, a phase III study of trastuzumab emtansine (T-DM1) vs. treatment of physician's choice in previously treated HER2-positive advanced breast cancer. Int J Cancer. 2016 Nov 15;139(10):2336-42. Epub 2016 Jul 26 (PMID: 27428671)

102. Knutson SK, Kawano S, Minoshima Y, Warholic NM, Huang KC, Xiao Y, Kadowaki T, Uesugi M, Kuznetsov G, Kumar N, Wigle TJ, Klaus CR, Allain CJ, Raimondi A, Waters NJ, Smith JJ, Porter-Scott M, Chesworth R, Moyer MP, Copeland RA, Richon VM, Uenaka T, Pollock RM, Kuntz KW, Yokoi A, Keilhack H (2014) Selective inhibition of EZH2 by EPZ-6438 leads to potent antitumor activity in EZH2-mutant non-Hodgkin lymphoma. Mol Cancer Ther. 2014 Apr;13(4):842-54. Epub 2014 Feb 21 (PMID: 24563539)

103. Koga T, Hashimoto S, Sugio K, Yoshino I, Nakagawa K, Yonemitsu Y, Sugimachi K, Sueishi K (2001) Heterogeneous distribution of P53 immunoreactivity in human lung adenocarcinoma correlates with MDM2 protein expression, rather than with P53 gene mutation. Int J Cancer. 2001 Jul 20;95(4):232-9 (PMID: 11400116)

104. Koo GC, Tan SY, Tang T, Poon SL, Allen GE, Tan L, Chong SC, Ong WS, Tay K, Tao M, Quek R, Loong S, Yeoh KW, Yap SP, Lee KA, Lim LC, Tan D, Goh C, Cutcutache I, Yu W, Ng CC, Rajasegaran V, Heng HL, Gan A, Ong CK, Rozen S, Tan P, Teh BT, Lim ST (2012) Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. Cancer Discov. 2012 Jul;2(7):591-7. Epub 2012 Jun 15 (PMID: 22705984)

105. Kung PP, Bingham P, Brooun A, Collins M, Deng YL, Dinh D, Fan C, Gajiwala KS, Grantner R, Gukasyan HJ, Hu W, Huang B, Kania R, Kephart SE, Krivacic C, Kumpf RA, Khamphavong P, Kraus M, Liu W, Maegley KA, Nguyen L, Ren S, Richter D, Rollins RA, Sach N, Sharma S, Sherrill J, Spangler J, Stewart AE, Sutton S, Uryu S, Verhelle D, Wang H, Wang S, Wythes M, Xin S, Yamazaki S, Zhu H, Zhu J, Zehnder L, Edwards M (2017)

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)

106. Kyrieleis OJP, McIntosh PB, Webb SR, Calder LJ, Lloyd J, Patel NA, Martin SR, Robinson CV, Rosenthal PB, Smerdon SJ (2016) Three-Dimensional Architecture of the Human BRCA1-A Histone Deubiquitinase Core Complex. Cell Rep. 2016 Dec 20;17(12):3099-3106 (PMID: 28009280)

107. Lapenna S, Giordano A (2009) Cell cycle kinases as therapeutic targets for cancer. Nat Rev Drug Discov. 2009 Jul;8(7):547-66 (PMID: 19568282)

108. Lentz O, Urlacher V, Schmid RD (2004) Substrate specificity of native and mutated cytochrome P450 (CYP102A3) from Bacillus subtilis. J Biotechnol. 2004 Feb 19;108(1):41-9 (PMID: 14741768)

109. Levine AJ (1997) p53, the cellular gatekeeper for growth and division. Cell. 1997 Feb 07;88(3):323-31 (PMID: 9039259)

110. Li L, Tan Y, Chen X, Xu Z, Yang S, Ren F, Guo H, Wang X, Chen Y, Li G, Wang H (2014) MDM4 overexpressed in acute myeloid leukemia patients with complex karyotype and wild-type TP53. PLoS One. 2014;9(11):e113088. Epub 2014 Nov 18 (PMID: 25405759)

111. Li Z, Sun Y, Chen X, Squires J, Nowroozizadeh B, Liang C, Huang J (2014) p53 Mutation Directs AURKA Overexpression via miR-25 and FBXW7 in Prostatic Small Cell Neuroendocrine Carcinoma. Mol Cancer Res. 2015 Mar;13(3):584-91. Epub 2014 Dec 15 (PMID: 25512615)

112. Lin PH, Kuo WH, Huang AC, Lu YS, Lin CH, Kuo SH, Wang MY, Liu CY, Cheng FT, Yeh MH, Li HY, Yang YH, Hsu YH, Fan SC, Li LY, Yu SL, Chang KJ, Chen PL, Ni YH, Huang CS (2016) Multiple gene sequencing for risk assessment in patients with early-onset or familial breast cancer. Oncotarget. 2016 Feb 16;7(7):8310-20 (PMID: 26824983)

113. Liu P, Cheng H, Santiago S, Raeder M, Zhang F, Isabella A, Yang J, Semaan DJ, Chen C, Fox EA, Gray NS, Monahan J, Schlegel R, Beroukhim R, Mills GB, Zhao JJ (2011) Oncogenic PIK3CA-driven mammary tumors frequently recur via PI3K pathway-dependent and PI3K pathway-independent mechanisms. Nat Med. 2011 Aug 07;17(9):1116-20. Epub 2011 Aug 7 (PMID: 21822287)

114. Liu T, Tee AE, Porro A, Smith SA, Dwarte T, Liu PY, Iraci N, Sekyere E, Haber M, Norris MD, Diolaiti D, Della Valle G, Perini G, Marshall GM (2007) Activation of tissue transglutaminase transcription by histone deacetylase inhibition as a therapeutic approach for Myc oncogenesis. Proc Natl Acad Sci U S A. 2007 Nov 20;104(47):18682-7. Epub 2007 Nov 14 (PMID: 18003922)

115. Logan CY, Nusse R (2004) The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004;20:781-810 (PMID: 15473860)

116. Luttun A, Tjwa M, Moons L, Wu Y, Angelillo-Scherrer A, Liao F, Nagy JA, Hooper A, Priller J, De Klerck B, Compernolle V, Daci E, Bohlen P, Dewerchin M, Herbert JM, Fava R, Matthys P, Carmeliet G, Collen D, Dvorak HF, Hicklin DJ, Carmeliet P (2002) Revascularization of ischemic tissues by PlGF treatment, and inhibition of tumor angiogenesis, arthritis and atherosclerosis by anti-Flt1. Nat Med. 2002 Aug;8(8):831-40. Epub 2002 Jul 1 (PMID: 12091877)

117. Ma CX, Sanchez C, Gao F, Crowder R, Naughton M, Pluard T, Creekmore A, Guo Z, Hoog J, Lockhart AC, Doyle A, Erlichman C, Ellis MJ (2016) A Phase I Study of the AKT Inhibitor MK-2206 in Combination with Hormonal Therapy in Postmenopausal Women with Estrogen Receptor-Positive Metastatic Breast Cancer. Clin Cancer Res. 2016 Jun 01;22(11):2650-8. Epub 2016 Jan 18 (PMID: 26783290)

118. Mackay HJ, Eisenhauer EA, Kamel-Reid S, Tsao M, Clarke B, Karakasis K, Werner HM, Trovik J, Akslen LA, Salvesen HB, Tu D, Oza AM (2013) Molecular determinants of outcome with mammalian target of rapamycin inhibition in endometrial cancer. Cancer. 2014 Feb 15;120(4):603-10. Epub 2013 Oct 25 (PMID: 24166148)

119. Malinge S, Ragu C, Della-Valle V, Pisani D, Constantinescu SN, Perez C, Villeval JL, Reinhardt D, Landman-Parker J, Michaux L, Dastugue N, Baruchel A, Vainchenker W, Bourquin JP, Penard-Lacronique V, Bernard OA (2008) Activating mutations in human acute megakaryoblastic leukemia. Blood. 2008 Nov 15;112(10):4220-6. Epub 2008 Aug 28 (PMID: 18755984)

120. Malkin D, Li FP, Strong LC, Fraumeni JF, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ, Tainsky MA, et al. (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science. 1990 Nov 30;250(4985):1233-8 (PMID: 1978757)

121. Mamo A, Cavallone L, Tuzmen S, Chabot C, Ferrario C, Hassan S, Edgren H, Kallioniemi O, Aleynikova O, Przybytkowski E, Malcolm K, Mousses S, Tonin PN, Basik M (2011) An integrated genomic approach identifies ARID1A as a candidate tumor-suppressor gene in breast cancer. Oncogene. 2012 Apr 19;31(16):2090-100. Epub 2011 Sep 5 (PMID: 21892209)

122. Mantere T, Haanpää M, Hanenberg H, Schleutker J, Kallioniemi A, Kähkönen M, Parto K, Avela K, Aittomäki K, von Koskull H, Hartikainen JM, Kosma VM, Laasanen SL, Mannermaa A, Pylkäs K, Winqvist R (2014) Finnish Fanconi anemia mutations and hereditary predisposition to breast and prostate cancer. Clin Genet. 2015 Jul;88(1):68-73. Epub 2014 Jul 30 (PMID: 24989076)

123. Mertz JA, Conery AR, Bryant BM, Sandy P, Balasubramanian S, Mele DA, Bergeron L, Sims RJ (2011) Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci U S A. 2011 Oct 04;108(40):16669-74. Epub 2011 Sep 26 (PMID: 21949397)

124. Miller KR, Kelley K, Tuttle R, Berberich SJ (2010) HdmX overexpression inhibits oncogene induced cellular senescence. Cell Cycle. 2010 Aug 15;9 (16):3376-82. Epub 2010 Aug 23 (PMID: 20724842)

125. Miller TW (2012) Initiating breast cancer by PIK3CA mutation. Breast Cancer Res. 2012 Feb 07;14(1):301. Epub 2012 Feb 7 (PMID: 22315990)

126. Minami Y, Shimamura T, Shah K, LaFramboise T, Glatt KA, Liniker E, Borgman CL, Haringsma HJ, Feng W, Weir BA, Lowell AM, Lee JC, Wolf J, Shapiro GI, Wong KK, Meyerson M, Thomas RK (2007) The major lung cancer-derived mutants of ERBB2 are oncogenic and are associated with sensitivity to the irreversible EGFR/ERBB2 inhibitor HKI-272. Oncogene. 2007 Jul 26;26(34):5023-7. Epub 2007 Feb 19 (PMID: 17311002)

127. Miyasaka A, Oda K, Ikeda Y, Sone K, Fukuda T, Inaba K, Makii C, Enomoto A, Hosoya N, Tanikawa M, Uehara Y, Arimoto T, Kuramoto H, Wada-Hiraike O, Miyagawa K, Yano T, Kawana K, Osuga Y, Fujii T (2015) PI3K/mTOR pathway inhibition overcomes radioresistance via suppression of the HIF1-α/VEGF pathway in endometrial cancer. Gynecol Oncol. 2015 Jul;138(1):174-80. Epub 2015 Apr 22 (PMID: 25913131)

128. Mizukami Y, Nonomura A, Takizawa T, Noguchi M, Michigishi T, Nakamura S, Ishizaki T (1995) N-myc protein expression in human breast carcinoma: prognostic implications. Anticancer Res. 1995 Nov-Dec;15(6B):2899-905 (PMID: 8669886)

129. Mohamed AM, Elwakil TF, Taher IM, Elbarbary MM, Kayed HF, Hussein HA, Eid OM (2009) Cyclin D1 gene amplification in proliferating haemangioma. Cell Tissue Res. 2009 Oct;338(1):107-15. Epub 2009 Sep 9 (PMID: 19823825)

130. Mosquera JM, Beltran H, Park K, MacDonald TY, Robinson BD, Tagawa ST, Perner S, Bismar TA, Erbersdobler A, Dhir R, Nelson JB, Nanus DM, Rubin MA (2013) Concurrent AURKA and MYCN gene amplifications are harbingers of lethal treatment-related neuroendocrine prostate cancer. Neoplasia. 2013 Jan;15(1):1-10 (PMID: 23358695)

131. Moynahan ME, Chen D, He W, Sung P, Samoila A, You D, Bhatt T, Patel P, Ringeisen F, Hortobagyi GN, Baselga J, Chandarlapaty S (2017) Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR+, HER2- advanced breast cancer: results from BOLERO-2. Br J Cancer. 2017 Mar 14;116(6):726-730. Epub 2017 Feb 9 (PMID: 28183140)

132. Mu K, Li L, Yang Q, Zhang T, Gao P, Meng B, Liu Z, Wang Y, Zhou G (2011) Detection of CHK1 and CCND1 gene copy number changes in breast cancer with dual-colour fluorescence in-situ hybridization. Histopathology. 2011 Mar;58(4):601-7. Epub 2011 Mar 14 (PMID: 21401699)

133. Nessling M, Solinas-Toldo S, Wilgenbus KK, Borchard F, Lichter P (1998) Mapping of chromosomal imbalances in gastric adenocarcinoma revealed amplified protooncogenes MYCN, MET, WNT2, and ERBB2. Genes Chromosomes Cancer. 1998 Dec;23(4):307-16 (PMID: 9824203)

134. Nik-Zainal S, Davies H, Staaf J, Ramakrishna M, Glodzik D, Zou X, Martincorena I, Alexandrov LB, Martin S, Wedge DC, Van Loo P, Ju YS, Smid M, Brinkman AB, Morganella S, Aure MR, Lingjærde OC, Langerød A, Ringnér M, Ahn SM, Boyault S, Brock JE, Broeks A, Butler A, Desmedt C, Dirix L, Dronov S, Fatima A, Foekens JA, Gerstung M, Hooijer GK, Jang SJ, Jones DR, Kim HY, King TA, Krishnamurthy S, Lee HJ, Lee JY, Li Y, McLaren S, Menzies A, Mustonen V, O'Meara S, Pauporté I, Pivot X, Purdie CA, Raine K, Ramakrishnan K, Rodríguez-González FG, Romieu G, Sieuwerts AM, Simpson PT, Shepherd R, Stebbings L, Stefansson OA, Teague J, Tommasi S, Treilleux I, Van den Eynden GG, Vermeulen P, Vincent-Salomon A, Yates L, Caldas C, van't Veer L, Tutt A, Knappskog S, Tan BK, Jonkers J, Borg Å, Ueno NT, Sotiriou C, Viari A, Futreal PA, Campbell PJ, Span PN, Van Laere S, Lakhani SR, Eyfjord JE, Thompson AM, Birney E, Stunnenberg HG, van de Vijver MJ, Martens JW, Børresen-Dale AL, Richardson AL, Kong G, Thomas G, Stratton MR (2016) Landscape of somatic mutations in 560 breast cancer whole-genome sequences. Nature. 2016 Jun 02;534(7605):47-54. Epub 2016 May 2 (PMID: 27135926)

135. Nogova L, Sequist LV, Perez Garcia JM, Andre F, Delord JP, Hidalgo M, Schellens JH, Cassier PA, Camidge DR, Schuler M, Vaishampayan U, Burris H, Tian GG, Campone M, Wainberg ZA, Lim WT, LoRusso P, Shapiro GI, Parker K, Chen X, Choudhury S, Ringeisen F, Graus-Porta D, Porter D, Isaacs R, Buettner R, Wolf J (2016) Evaluation of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Kinase Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in Fibroblast Growth Factor Receptors: Results of a Global Phase I, Dose-Escalation and Dose-Expansion Study. J Clin Oncol. 2017 Jan 10;35(2):157-165. Epub 2016 Nov 21 (PMID: 27870574)

136. Nord H, Segersten U, Sandgren J, Wester K, Busch C, Menzel U, Komorowski J, Dumanski JP, Malmström PU, Díaz de Ståhl T (2010) Focal amplifications are associated with high grade and recurrences in stage Ta bladder carcinoma. Int J Cancer. 2010 Mar 15;126(6):1390-402 (PMID: 19821490)

137. O'Brien NA, Browne BC, Chow L, Wang Y, Ginther C, Arboleda J, Duffy MJ, Crown J, O'Donovan N, Slamon DJ (2010) Activated phosphoinositide 3-kinase/AKT signaling confers resistance to trastuzumab but not lapatinib. Mol Cancer Ther. 2010 Jun;9(6):1489-502. Epub 2010 May 25 (PMID: 20501798)

138. Olivier M, Petitjean A, Marcel V, Pétré A, Mounawar M, Plymoth A, de Fromentel CC, Hainaut P (2008) Recent advances in p53 research: an interdisciplinary perspective. Cancer Gene Ther. 2009 Jan;16(1):1-12. Epub 2008 Sep 19 (PMID: 18802452)

139. Ooi A, Oyama T, Nakamura R, Tajiri R, Ikeda H, Fushida S, Nakamura H, Dobashi Y (2015) Semi-comprehensive analysis of gene amplification in gastric cancers using multiplex ligation-dependent probe amplification and fluorescence in situ hybridization. Mod Pathol. 2015 Jun;28(6):861-71. Epub 2015 Mar 6 (PMID: 25743022)

140. Ornitz DM, Xu J, Colvin JS, McEwen DG, MacArthur CA, Coulier F, Gao G, Goldfarb M (1996) Receptor specificity of the fibroblast growth factor family. J Biol Chem. 1996 Jun 21;271(25):15292-7 (PMID: 8663044)

141. Owens MA, Horten BC, Da Silva MM (2004) HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer. 2004 Apr;5(1):63-9 (PMID: 15140287)

142. Pagano M, Theodoras AM, Tam SW, Draetta GF (1994) Cyclin D1-mediated inhibition of repair and replicative DNA synthesis in human fibroblasts. Genes Dev. 1994 Jul 15;8(14):1627-39 (PMID: 7958844)

143. Pearson HB, Li J, Meniel VS, Fennell CM, Waring P, Montgomery KG, Rebello RJ, Macpherson AA, Koushyar S, Furic L, Cullinane C, Clarkson RW, Smalley MJ, Simpson KJ, Phesse TJ, Shepherd PR, Humbert PO, Sansom OJ, Phillips WA (2018) Identification of Pik3ca Mutation as a Genetic Driver of Prostate Cancer That Cooperates with Pten Loss to Accelerate Progression and Castration-Resistant Growth. Cancer Discov. 2018 Jun;8(6):764-779. Epub 2018 Mar 26 (PMID: 29581176)

144. Pereira B, Chin SF, Rueda OM, Vollan HK, Provenzano E, Bardwell HA, Pugh M, Jones L, Russell R, Sammut SJ, Tsui DW, Liu B, Dawson SJ, Abraham J, Northen H, Peden JF, Mukherjee A, Turashvili G, Green AR, McKinney S, Oloumi A, Shah S, Rosenfeld N, Murphy L, Bentley DR, Ellis IO, Purushotham A, Pinder SE, Børresen-Dale AL, Earl HM, Pharoah PD, Ross MT, Aparicio S, Caldas C (2016) The somatic mutation profiles of 2,433 breast cancers refines their genomic and transcriptomic landscapes. Nat Commun. 2016 May 10;7:11479 (PMID: 27161491)

145. Peurala E, Koivunen P, Haapasaari KM, Bloigu R, Jukkola-Vuorinen A (2013) The prognostic significance and value of cyclin D1, CDK4 and p16 in human breast cancer. Breast Cancer Res. 2013 Jan 21;15(1):R5 (PMID: 23336272)

146. Pezo RC, Chen TW, Berman HK, Mulligan AM, Razak AA, Siu LL, Cescon DW, Amir E, Elser C, Warr DG, Sridhar SS, Yu C, Wang L, Stockley TL, Kamel-Reid S, Bedard PL (2017) Impact of multi-gene mutational profiling on clinical trial outcomes in metastatic breast cancer. Breast Cancer Res Treat. 2018 Feb;168(1):159-168. Epub 2017 Nov 24 (PMID: 29177603)

147. Planchard D, Loriot Y, André F, Gobert A, Auger N, Lacroix L, Soria JC (2015) EGFR-independent mechanisms of acquired resistance to AZD9291 in EGFR T790M-positive NSCLC patients. Ann Oncol. 2015 Oct;26(10):2073-8. Epub 2015 Aug 12 (PMID: 26269204)

148. Plate KH, Breier G, Weich HA, Mennel HD, Risau W (1994) Vascular endothelial growth factor and glioma angiogenesis: coordinate induction of VEGF receptors, distribution of VEGF protein and possible in vivo regulatory mechanisms. Int J Cancer. 1994 Nov 15;59(4):520-9 (PMID: 7525492)

149. Prosperi JR, Goss KH (2010) A Wnt-ow of opportunity: targeting the Wnt/beta-catenin pathway in breast cancer. Curr Drug Targets. 2010 Sep;11(9): 1074-88 (PMID: 20545611)

150. Quintayo MA, Munro AF, Thomas J, Kunkler IH, Jack W, Kerr GR, Dixon JM, Chetty U, Bartlett JM (2012) GSK3β and cyclin D1 expression predicts outcome in early breast cancer patients. Breast Cancer Res Treat. 2012 Nov;136(1):161-8. Epub 2012 Sep 14 (PMID: 22976805)

151. Quintás-Cardama A, Manshouri T, Estrov Z, Harris D, Zhang Y, Gaikwad A, Kantarjian HM, Verstovsek S (2010) Preclinical characterization of atiprimod, a novel JAK2 AND JAK3 inhibitor. Invest New Drugs. 2011 Oct;29(5):818-26. Epub 2010 Apr 7 (PMID: 20372971)

152. Razis E, Bobos M, Kotoula V, Eleftheraki AG, Kalofonos HP, Pavlakis K, Papakostas P, Aravantinos G, Rigakos G, Efstratiou I, Petraki K, Bafaloukos D, Kostopoulos I, Pectasides D, Kalogeras KT, Skarlos D, Fountzilas G (2011) Evaluation of the association of PIK3CA mutations and PTEN loss with efficacy of trastuzumab therapy in metastatic breast cancer. Breast Cancer Res Treat. 2011 Jul;128(2):447-56. Epub 2011 May 19 (PMID: 21594665)

153. Rebbeck TR, Mitra N, Domchek SM, Wan F, Friebel TM, Tran TV, Singer CF, Tea MK, Blum JL, Tung N, Olopade OI, Weitzel JN, Lynch HT, Snyder CL, Garber JE, Antoniou AC, Peock S, Evans DG, Paterson J, Kennedy MJ, Donaldson A, Dorkins H, Easton DF, Epidemiological Study of BRCA1 and BRCA2 Mutation Carriers (EMBRACE), Rubinstein WS, Daly MB, Isaacs C, Nevanlinna H, Couch FJ, Andrulis IL, Freidman E, Laitman Y, Ganz PA, Tomlinson GE, Neuhausen SL, Narod SA, Phelan CM, Greenberg R, Nathanson KL (2011) Modification of BRCA1-Associated Breast and Ovarian Cancer Risk by BRCA1-Interacting Genes. Cancer Res. 2011 Sep 01;71(17):5792-805. Epub 2011 Jul 28 (PMID: 21799032)

154. Rizzolo P, Navazio AS, Silvestri V, Valentini V, Zelli V, Zanna I, Masala G, Bianchi S, Scarnò M, Tommasi S, Palli D, Ottini L (2016) Somatic alterations of targetable oncogenes are frequently observed in BRCA1/2 mutation negative male breast cancers. Oncotarget. 2016 Nov 08;7(45): 74097-74106 (PMID: 27765917)

155. Rosa-Rosa JM, Caniego-Casas T, Leskela S, Cristobal E, González-Martínez S, Moreno-Moreno E, López-Miranda E, Holgado E, Pérez-Mies B, Garrido P, Palacios J (2019) High Frequency of ERBB2 Activating Mutations in Invasive Lobular Breast Carcinoma with Pleomorphic Features. Cancers (Basel). 2019 Jan 11;11(1) (PMID: 30641862)

156. Rosenberg PS, Alter BP, Ebell W (2008) Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. Haematologica. 2008 Apr;93(4):511-7. Epub 2008 Mar 5 (PMID: 18322251)

157. Ross JS, Gay LM, Wang K, Ali SM, Chumsri S, Elvin JA, Bose R, Vergilio JA, Suh J, Yelensky R, Lipson D, Chmielecki J, Waintraub S, Leyland-Jones B, Miller VA, Stephens PJ (2016) Nonamplification ERBB2 genomic alterations in 5605 cases of recurrent and metastatic breast cancer: An emerging opportunity for anti-HER2 targeted therapies. Cancer. 2016 Sep 01;122(17):2654-62. Epub 2016 Jun 10 (PMID: 27284958)

158. Roy PG, Pratt N, Purdie CA, Baker L, Ashfield A, Quinlan P, Thompson AM (2010) High CCND1 amplification identifies a group of poor prognosis women with estrogen receptor positive breast cancer. Int J Cancer. 2010 Jul 15;127(2):355-60 (PMID: 19904758)

159. Roy-Chowdhuri S, de Melo Gagliato D, Routbort MJ, Patel KP, Singh RR, Broaddus R, Lazar AJ, Sahin A, Alvarez RH, Moulder S, Wheler JJ, Janku F, Gonzalez-Angulo AM, Chavez-MacGregor M, Valero V, Ueno NT, Mills G, Mendelsohn J, Yao H, Aldape K, Luthra R, Meric-Bernstam F (2015) Multigene clinical mutational profiling of breast carcinoma using next-generation sequencing. Am J Clin Pathol. 2015 Nov;144(5):713-21 (PMID: 26486734)

160. Rubie H, Hartmann O, Michon J, Frappaz D, Coze C, Chastagner P, Baranzelli MC, Plantaz D, Avet-Loiseau H, Bénard J, Delattre O, Favrot M, Peyroulet MC, Thyss A, Perel Y, Bergeron C, Courbon-Collet B, Vannier JP, Lemerle J, Sommelet D (1997) N-Myc gene amplification is a major prognostic factor in localized neuroblastoma: results of the French NBL 90 study. Neuroblastoma Study Group of the Société Francaise d'Oncologie Pédiatrique. J Clin Oncol. 1997 Mar;15(3):1171-82 (PMID: 9060561)

161. Sakre N, Wildey G, Behtaj M, Kresak A, Yang M, Fu P, Dowlati A (2017) RICTOR amplification identifies a subgroup in small cell lung cancer and predicts response to drugs targeting mTOR. Oncotarget. 2017 Jan 24;8(4):5992-6002 (PMID: 27863413)

162. Samuels Y, Diaz LA, Schmidt-Kittler O, Cummins JM, Delong L, Cheong I, Rago C, Huso DL, Lengauer C, Kinzler KW, Vogelstein B, Velculescu VE (2005) Mutant PIK3CA promotes cell growth and invasion of human cancer cells. Cancer Cell. 2005 Jun;7(6):561-73 (PMID: 15950905)

163. Samuels Y, Wang Z, Bardelli A, Silliman N, Ptak J, Szabo S, Yan H, Gazdar A, Powell SM, Riggins GJ, Willson JK, Markowitz S, Kinzler KW, Vogelstein B, Velculescu VE (2004) High frequency of mutations of the PIK3CA gene in human cancers. Science. 2004 Apr 23;304(5670):554. Epub 2004 Mar 11 (PMID: 15016963)

164. Santarpia L, Iwamoto T, Di Leo A, Hayashi N, Bottai G, Stampfer M, André F, Turner NC, Symmans WF, Hortobágyi GN, Pusztai L, Bianchini G (2013) DNA repair gene patterns as prognostic and predictive factors in molecular breast cancer subtypes. Oncologist. 2013;18(10):1063-73. Epub 2013 Sep 26 (PMID: 24072219)

165. Santibáñez-Koref MF, Birch JM, Hartley AL, Jones PH, Craft AW, Eden T, Crowther D, Kelsey AM, Harris M (1991) p53 germline mutations in Li-Fraumeni syndrome. Lancet. 1991 Dec 14;338(8781):1490-1 (PMID: 1683921)

166. Santra MK, Wajapeyee N, Green MR (2009) F-box protein FBXO31 mediates cyclin D1 degradation to induce G1 arrest after DNA damage. Nature. 2009 Jun 04;459(7247):722-5. Epub 2009 May 3 (PMID: 19412162)

167. Savino M, Annibali D, Carucci N, Favuzzi E, Cole MD, Evan GI, Soucek L, Nasi S (2011) The action mechanism of the Myc inhibitor termed Omomyc may give clues on how to target Myc for cancer therapy. PLoS One. 2011;6(7):e22284. Epub 2011 Jul 21 (PMID: 21811581)

168. Schuler PJ, Harasymczuk M, Visus C, Deleo A, Trivedi S, Lei Y, Argiris A, Gooding W, Butterfield LH, Whiteside TL, Ferris RL (2014) Phase I dendritic cell p53 peptide vaccine for head and neck cancer. Clin Cancer Res. 2014 May 01;20(9):2433-44. Epub 2014 Feb 28 (PMID: 24583792)

169. Sela S, Itin A, Natanson-Yaron S, Greenfield C, Goldman-Wohl D, Yagel S, Keshet E (2008) A novel human-specific soluble vascular endothelial growth factor receptor 1: cell-type-specific splicing and implications to vascular endothelial growth factor homeostasis and preeclampsia. Circ Res. 2008 Jun 20;102(12):1566-74. Epub 2008 May 30 (PMID: 18515749)

170. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013 Sep 20;31(27):3327-34. Epub 2013 Jul 1 (PMID: 23816960)

171. Seto T, Higashiyama M, Funai H, Imamura F, Uematsu K, Seki N, Eguchi K, Yamanaka T, Ichinose Y (2006) Prognostic value of expression of vascular endothelial growth factor and its flt-1 and KDR receptors in stage I non-small-cell lung cancer. Lung Cancer. 2006 Jul;53(1):91-6. Epub 2006 May 11 (PMID: 16697074)

172. Shao W, Li S, Li L, Lin K, Liu X, Wang H, Wang H, Wang D (2018) Chemical genomics reveals inhibition of breast cancer lung metastasis by Ponatinib via c-Jun. Protein Cell. 2019 Mar;10(3):161-177. Epub 2018 Apr 17 (PMID: 29667003)

173. Shen J, Ju Z, Zhao W, Wang L, Peng Y, Ge Z, Nagel ZD, Zou J, Wang C, Kapoor P, Ma X, Ma D, Liang J, Song S, Liu J, Samson LD, Ajani JA, Li GM, Liang H, Shen X, Mills GB, Peng G (2018) ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. Nat Med. 2018 May;24(5):556-562. Epub 2018 May 7 (PMID: 29736026)

174. Shen J, Peng Y, Wei L, Zhang W, Yang L, Lan L, Kapoor P, Ju Z, Mo Q, Shih IeM, Uray IP, Wu X, Brown PH, Shen X, Mills GB, Peng G (2015) ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors. Cancer Discov. 2015 Jul;5(7):752-67. Epub 2015 Jun 11 (PMID: 26069190)

175. Shvarts A, Steegenga WT, Riteco N, van Laar T, Dekker P, Bazuine M, van Ham RC, van der Houven van Oordt W, Hateboer G, van der Eb AJ, Jochemsen AG (1996) MDMX: a novel p53-binding protein with some functional properties of MDM2. EMBO J. 1996 Oct 01;15(19):5349-57 (PMID: 8895579)

176. Silwal-Pandit L, Vollan HK, Chin SF, Rueda OM, McKinney S, Osako T, Quigley DA, Kristensen VN, Aparicio S, Børresen-Dale AL, Caldas C, Langerød A (2014) TP53 mutation spectrum in breast cancer is subtype specific and has distinct prognostic relevance. Clin Cancer Res. 2014 Jul 01;20(13):3569-80. Epub 2014 May 6 (PMID: 24803582)

177. Sims AE, Spiteri E, Sims RJ, Arita AG, Lach FP, Landers T, Wurm M, Freund M, Neveling K, Hanenberg H, Auerbach AD, Huang TT (2007) FANCI is a second monoubiquitinated member of the Fanconi anemia pathway. Nat Struct Mol Biol. 2007 Jun;14(6):564-7. Epub 2007 Apr 25 (PMID: 17460694)

178. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar 15;344(11):783-92 (PMID: 11248153)

179. Smogorzewska A, Matsuoka S, Vinciguerra P, McDonald ER, Hurov KE, Luo J, Ballif BA, Gygi SP, Hofmann K, D'Andrea AD, Elledge SJ (2007) Identification of the FANCI protein, a monoubiquitinated FANCD2 paralog required for DNA repair. Cell. 2007 Apr 20;129(2):289-301. Epub 2007 Apr 5 (PMID: 17412408)

180. Solyom S, Aressy B, Pylkäs K, Patterson-Fortin J, Hartikainen JM, Kallioniemi A, Kauppila S, Nikkilä J, Kosma VM, Mannermaa A, Greenberg RA, Winqvist R (2012) Breast cancer-associated Abraxas mutation disrupts nuclear localization and DNA damage response functions. Sci Transl Med. 2012 Feb 22;4(122):122ra23 (PMID: 22357538)

181. Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, Göker E, Georgoulias V, Li W, Isla D, Guclu SZ, Morabito A, Min YJ, Ardizzoni A, Gadgeel SM, Wang B, Chand VK, Goss GD, LUX-Lung 8 Investigators (2015) Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2015 Aug;16(8):897-907. Epub 2015 Jul 5 (PMID: 26156651)

182. Sridhar J, Akula N, Pattabiraman N (2006) Selectivity and potency of cyclin-dependent kinase inhibitors. AAPS J. 2006 Mar 24;8(1):E204-21 (PMID: 16584130)

183. Srivastava S, Zou ZQ, Pirollo K, Blattner W, Chang EH (1990) Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. Nature. 1990 Dec 20-27;348(6303):747-9 (PMID: 2259385)

184. Sun Q, Lin P, Zhang J, Li X, Yang L, Huang J, Zhou Z, Liu P, Liu N (2015) Expression of Fibroblast Growth Factor 10 Is Correlated with Poor Prognosis in Gastric Adenocarcinoma. Tohoku J Exp Med. 2015 Aug;236(4):311-8 (PMID: 26268776)

185. Tabernero J, Bahleda R, Dienstmann R, Infante JR, Mita A, Italiano A, Calvo E, Moreno V, Adamo B, Gazzah A, Zhong B, Platero SJ, Smit JW, Stuyckens K, Chatterjee-Kishore M, Rodon J, Peddareddigari V, Luo FR, Soria JC (2015) Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors. J Clin Oncol. 2015 Oct 20;33(30):3401-8. Epub 2015 Aug 31 (PMID: 26324363)

186. Takahashi T, Boku N, Murakami H, Naito T, Tsuya A, Nakamura Y, Ono A, Machida N, Yamazaki K, Watanabe J, Ruiz-Garcia A, Imai K, Ohki E, Yamamoto N (2012) Phase I and pharmacokinetic study of dacomitinib (PF-00299804), an oral irreversible, small molecule inhibitor of human epidermal growth factor receptor-1, -2, and -4 tyrosine kinases, in Japanese patients with advanced solid tumors. Invest New Drugs. 2012 Dec;30(6):2352-63. Epub 2012 Jan 17 (PMID: 22249430)

187. Takezawa K, Pirazzoli V, Arcila ME, Nebhan CA, Song X, de Stanchina E, Ohashi K, Janjigian YY, Spitzler PJ, Melnick MA, Riely GJ, Kris MG, Miller VA, Ladanyi M, Politi K, Pao W (2012) HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. Cancer Discov. 2012 Oct;2(10):922-33. Epub 2012 Sep 5 (PMID: 22956644)

188. Tan BX, Khoo KH, Lim TM, Lane DP (2014) High Mdm4 levels suppress p53 activity and enhance its half-life in acute myeloid leukaemia. Oncotarget. 2014 Feb 28;5(4):933-43 (PMID: 24659749)

189. Tanioka M, Sakai K, Sudo T, Sakuma T, Kajimoto K, Hirokaga K, Takao S, Negoro S, Minami H, Nakagawa K, Nishio K (2014) Transcriptional CCND1 expression as a predictor of poor response to neoadjuvant chemotherapy with trastuzumab in HER2-positive/ER-positive breast cancer. Breast Cancer Res Treat. 2014 Oct;147(3):513-25. Epub 2014 Sep 9 (PMID: 25200445)

190. Tentler JJ, Ionkina AA, Tan AC, Newton TP, Pitts TM, Glogowska MJ, Kabos P, Sartorius CA, Sullivan KD, Espinosa JM, Eckhardt SG, Diamond JR (2015) p53 Family Members Regulate Phenotypic Response to Aurora Kinase A Inhibition in Triple-Negative Breast Cancer. Mol Cancer Ther. 2015 May;14(5):1117-29. Epub 2015 Mar 10 (PMID: 25758253)

191. Thakur R, Mishra DP (2013) Pharmacological modulation of beta-catenin and its applications in cancer therapy. J Cell Mol Med. 2013 Apr;17(4):449-56. Epub 2013 Mar 14 (PMID: 23490077)

192. Theodorou V, Boer M, Weigelt B, Jonkers J, van der Valk M, Hilkens J (2004) Fgf10 is an oncogene activated by MMTV insertional mutagenesis in mouse mammary tumors and overexpressed in a subset of human breast carcinomas. Oncogene. 2004 Aug 12;23(36):6047-55 (PMID: 15208658)

193. Tomizawa K, Suda K, Onozato R, Kosaka T, Endoh H, Sekido Y, Shigematsu H, Kuwano H, Yatabe Y, Mitsudomi T (2011) Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. Lung Cancer. 2011 Oct;74(1):139-44. Epub 2011 Feb 25 (PMID: 21353324)

194. Van Allen EM, Wagle N, Sucker A, Treacy DJ, Johannessen CM, Goetz EM, Place CS, Taylor-Weiner A, Whittaker S, Kryukov GV, Hodis E, Rosenberg M, McKenna A, Cibulskis K, Farlow D, Zimmer L, Hillen U, Gutzmer R, Goldinger SM, Ugurel S, Gogas HJ, Egberts F, Berking C, Trefzer U, Loquai C, Weide B, Hassel JC, Gabriel SB, Carter SL, Getz G, Garraway LA, Schadendorf D, Dermatologic Cooperative Oncology Group of Germany (DeCOG) (2013) The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discov. 2014 Jan;4(1):94-109. Epub 2013 Nov 21 (PMID: 24265153)

195. Wade M, Li YC, Wahl GM (2013) MDM2, MDMX and p53 in oncogenesis and cancer therapy. Nat Rev Cancer. 2013 Feb;13(2):83-96. Epub 2013 Jan 10 (PMID: 23303139)

196. Wade M, Wahl GM (2009) Targeting Mdm2 and Mdmx in cancer therapy: better living through medicinal chemistry? Mol Cancer Res. 2009 Jan;7(1):1-11 (PMID: 19147532)

197. Walsh T, Casadei S, Coats KH, Swisher E, Stray SM, Higgins J, Roach KC, Mandell J, Lee MK, Ciernikova S, Foretova L, Soucek P, King MC (2006) Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA. 2006 Mar 22;295(12):1379-88 (PMID: 16551709)

198. Wang B, Elledge SJ (2007) Ubc13/Rnf8 ubiquitin ligases control foci formation of the Rap80/Abraxas/Brca1/Brcc36 complex in response to DNA damage. Proc Natl Acad Sci U S A. 2007 Dec 26;104(52):20759-63. Epub 2007 Dec 5 (PMID: 18077395)

199. Wang B, Hurov K, Hofmann K, Elledge SJ (2009) NBA1, a new player in the Brca1 A complex, is required for DNA damage resistance and checkpoint control. Genes Dev. 2009 Mar 15;23(6):729-39. Epub 2009 Mar 4 (PMID: 19261749)

200. Wang B, Matsuoka S, Ballif BA, Zhang D, Smogorzewska A, Gygi SP, Elledge SJ (2007) Abraxas and RAP80 form a BRCA1 protein complex required for the DNA damage response. Science. 2007 May 25;316(5828):1194-8 (PMID: 17525340)

201. Wang K, Kan J, Yuen ST, Shi ST, Chu KM, Law S, Chan TL, Kan Z, Chan AS, Tsui WY, Lee SP, Ho SL, Chan AK, Cheng GH, Roberts PC, Rejto PA, Gibson NW, Pocalyko DJ, Mao M, Xu J, Leung SY (2011) Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. Nat Genet. 2011 Oct 30;43(12):1219-23 (PMID: 22037554)

202. Wang L, Zhang Q, Zhang J, Sun S, Guo H, Jia Z, Wang B, Shao Z, Wang Z, Hu X (2011) PI3K pathway activation results in low efficacy of both trastuzumab and lapatinib. BMC Cancer. 2011 Jun 15;11:248 (PMID: 21676217)

203. Wang YC, Lin RK, Tan YH, Chen JT, Chen CY, Wang YC (2005) Wild-type p53 overexpression and its correlation with MDM2 and p14ARF alterations: an alternative pathway to non-small-cell lung cancer. J Clin Oncol. 2005 Jan 01;23(1):154-64 (PMID: 15625370)

204. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, Fereday S, Tam A, Galletta L, Tonin PN, Provencher D, Miller D, Jones SJ, Moore RA, Morin GB, Oloumi A, Boyd N, Aparicio SA, Shih IeM, Mes-Masson AM, Bowtell DD, Hirst M, Gilks B, Marra MA, Huntsman DG (2010) ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med. 2010 Oct 14;363(16):1532-43. Epub 2010 Sep 8 (PMID: 20942669)

205. Wu W, Sun XH (2011) Janus kinase 3: the controller and the controlled. Acta Biochim Biophys Sin (Shanghai). 2012 Mar;44(3):187-96. Epub 2011 Nov 29 (PMID: 22130498)

206. Xiong S, Pant V, Suh YA, Van Pelt CS, Wang Y, Valentin-Vega YA, Post SM, Lozano G (2010) Spontaneous tumorigenesis in mice overexpressing the p53-negative regulator Mdm4. Cancer Res. 2010 Sep 15;70(18):7148-54. Epub 2010 Aug 24 (PMID: 20736370)

207. Yamamoto H, Shigematsu H, Nomura M, Lockwood WW, Sato M, Okumura N, Soh J, Suzuki M, Wistuba II, Fong KM, Lee H, Toyooka S, Date H, Lam WL, Minna JD, Gazdar AF (2008) PIK3CA mutations and copy number gains in human lung cancers. Cancer Res. 2008 Sep 01;68(17):6913-21 (PMID: 18757405)

208. Yang D, Liu H, Goga A, Kim S, Yuneva M, Bishop JM (2010) Therapeutic potential of a synthetic lethal interaction between the MYC proto-oncogene and inhibition of aurora-B kinase. Proc Natl Acad Sci U S A. 2010 Aug 03;107(31):13836-41. Epub 2010 Jul 19 (PMID: 20643922)

209. Ye Q, Kantonen S, Henkels KM, Gomez-Cambronero J (2013) A new signaling pathway (JAK-Fes-phospholipase D) that is enhanced in highly proliferative breast cancer cells. J Biol Chem. 2013 Apr 05;288(14):9881-91. Epub 2013 Feb 12 (PMID: 23404507)

210. Yonesaka K, Zejnullahu K, Okamoto I, Satoh T, Cappuzzo F, Souglakos J, Ercan D, Rogers A, Roncalli M, Takeda M, Fujisaka Y, Philips J, Shimizu T, Maenishi O, Cho Y, Sun J, Destro A, Taira K, Takeda K, Okabe T, Swanson J, Itoh H, Takada M, Lifshits E, Okuno K, Engelman JA, Shivdasani RA, Nishio K, Fukuoka M, Varella-Garcia M, Nakagawa K, Jänne PA (2011) Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. Sci Transl Med. 2011 Sep 07;3(99):99ra86 (PMID: 21900593)

211. Young CD, Zimmerman LJ, Hoshino D, Formisano L, Hanker AB, Gatza ML, Morrison MM, Moore PD, Whitwell CA, Dave B, Stricker T, Bhola NE, Silva GO, Patel P, Brantley-Sieders DM, Levin M, Horiates M, Palma NA, Wang K, Stephens PJ, Perou CM, Weaver AM, O'Shaughnessy JA, Chang JC, Park BH, Liebler DC, Cook RS, Arteaga CL (2015) Activating PIK3CA Mutations Induce an Epidermal Growth Factor Receptor (EGFR) /Extracellular Signal-regulated Kinase (ERK) Paracrine Signaling Axis in Basal-like Breast Cancer. Mol Cell Proteomics. 2015 Jul;14(7):1959-76. Epub 2015 May 7 (PMID: 25953087)

212. Yu H, Kortylewski M, Pardoll D (2007) Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol. 2007 Jan;7(1):41-51 (PMID: 17186030)

213. Yu H, Pardoll D, Jove R (2009) STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer. 2009 Nov;9(11):798-809 (PMID: 19851315)

214. Yuan H, Chen J, Liu Y, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, Xie Y (2015) Association of PIK3CA Mutation Status before and after Neoadjuvant Chemotherapy with Response to Chemotherapy in Women with Breast Cancer. Clin Cancer Res. 2015 Oct 01;21(19):4365-72. Epub 2015 May 15 (PMID: 25979484)

215. Zhang X, Ibrahimi OA, Olsen SK, Umemori H, Mohammadi M, Ornitz DM (2006) Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. J Biol Chem. 2006 Jun 09;281(23):15694-700. Epub 2006 Apr 4 (PMID: 16597617)

216. de Vries C, Escobedo JA, Ueno H, Houck K, Ferrara N, Williams LT (1992) The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor. Science. 1992 Feb 21;255(5047):989-91 (PMID: 1312256)

217. U.S. Food and Drug Administration https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf

218. U.S. Food and Drug Administration. Alpelisib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212526s000lbl.pdf

219. U.S. Food and Drug Administration. Lapatinib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022059s024lbl.pdf

220. U.S. Food and Drug Administration. Neratinib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208051s005s006lbl.pdf

221. U.S. Food and Drug Administration. Trastuzumab emtansine. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125427s105lbl.pdf

222. U.S. Food and Drug Administration. Trastuzumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761100s000lbl.pdf

223. (2018) Breast Cancer NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer V.3.2019 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

224. (2019) B-Cell Lymphomas NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for B-Cell Lymphomas V.5.2019 https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf