FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chao, Ching	Unknown primary adenocarcinoma	15 Sep 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1450681-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Unknown primary adenocarcinoma
NAME Chao, Ching
DATE OF BIRTH 04 March 1985
SEX Female
MEDICAL RECORD # 48800722

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S111-30912A (PF22102)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 11 August 2022
SPECIMEN RECEIVED 07 September 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ERBB2 amplification
CTNNB1 S45P
CDKN2A/B CDKN2A loss, CDKN2B loss
FANCC Q485fs*2
FH A273T
MAP2K4 Q327*
TP53 G244V
VEGFA amplification - equivocal†

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Ado-trastuzumab emtansine** (p. 10), **Afatinib** (p. 10), **Dacomitinib** (p. 11), **Fam-trastuzumab deruxtecan** (p. 11), **Lapatinib** (p. 12), **Margetuximab** (p. 12), **Neratinib** (p. 13), **Trastuzumab** (p. 14), **Trastuzumab + Pertuzumab** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

Electronically signed by Erik Williams, M.D. | 15 September 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ERBB2 **-** amplification	none	Ado-trastuzumab emtansine
		Afatinib
		Dacomitinib
		Fam-trastuzumab deruxtecan
		Lapatinib
		Margetuximab
		Neratinib
		Trastuzumab
		Trastuzumab + Pertuzumab
10 Trials see p. 16		
CTNNB1 **-** S45P	none	none
4 Trials see p. 15		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been observed at high frequency in endometrial cancers (14-33%)[6-13], colorectal cancers (CRCs; 10-15%)[3,14-17], and gastric cancers (12-35%)[18-21] and at lower frequencies in many other tumor types, including esophageal[22], small bowel[23-27], hepatobiliary[28-34], prostate[35-37], and urinary tract carcinomas[38-40]. In one study, MSI-H status was associated with a positive prognostic effect in patients with gastric cancer treated with surgery alone and a negative predictive effect in patients treated with chemotherapy[41]. Data regarding the role of MSI-H on prognosis and survival in endometrial cancer are conflicting[6,9-10,12,42-44]. However, studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[8,11,13,43], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16,45-46]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[15,47-48]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15-16,46,48].

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BIOMARKER

Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[49-51], anti-PD-1 therapies[49-52], and combination nivolumab and ipilimumab[53-58]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[49-52,59-63]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[59]; similar findings were observed in the KEYNOTE 028 and 012 trials[52]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[63]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[64]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[62]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[65] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[50].

FREQUENCY & PROGNOSIS

Carcinomas that have been reported to harbor the highest frequencies of elevated TMB include colorectal (CRC) (8-25%)[17,66], endometrial (7-24%)[67], intestinal type gastric (20%)[68], and non-small cell lung carcinoma (NSCLC; 8-13%)[69-70] . In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[71], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)[69]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[71-72], several other large studies did find a strong link[73-76]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[17,66] and with microsatellite instability (MSI)[66], which in turn has been reported to correlate with better prognosis[14,77-83]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[67,84-86] and bladder cancer[87], it is also linked with improved prognosis in patients with these tumor types[67].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[88-89] and cigarette smoke in lung cancer[90-91], treatment with temozolomide-based chemotherapy in glioma[92-93], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17,67,94-96], and microsatellite instability (MSI)[17,67,96]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[50-51,59].

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GENE
ERBB2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive clinical evidence, ERBB2 amplification or activating mutation may predict sensitivity to therapies targeting HER2, including antibodies such as trastuzumab[97-102], pertuzumab in combination with trastuzumab[99,103-105], and zanidatamab (ZW25)[106], as well as antibody-directed conjugates such as ado-trastuzumab emtansine (T-DM1)[107] and fam-trastuzumab deruxtecan (T-DXd)[108-110], HER2 kinase inhibitors such as tucatinib[111-114], and dual EGFR/HER2 kinase inhibitors such as lapatinib[115-123], afatinib[102,124-133], neratinib[134-137], dacomitinib[138], and pyrotinib[139-140] . A Phase 1 basket trial of pyrotinib demonstrated an ORR of 17% (4/23) for ERBB2-altered solid tumors, with PRs for 1 patient each with HER2-positive salivary, biliary, ovarian, or endometrial cancers[141]. Patients with ERBB2-mutated non-small cell lung cancer (NSCLC) have also benefited from pyrotinib (30-53% ORR)[142].

FREQUENCY & PROGNOSIS

ERBB2 amplification has been reported in a wide range of cancers in the scientific literature[143] and in the TCGA datasets, with highest prevalence in esophageal carcinoma (15%), breast invasive carcinoma (13-14%)[144-145], stomach adenocarcinoma (13%)[146], pancreatic adenocarcinoma (11%)[147], and uterine carcinosarcoma (11%, 6/56) (cBioPortal, Oct 2021)[148-149]. HER2 is predicted to be overexpressed (as assessed by FISH, CNV analysis, or immunohistochemistry) in 12-25% of breast cancers[143,150-151]. Phosphorylated HER2 was expressed in 62.5% (55/88) of HER2-positive breast cancers[152]. Reports on the correlation of ERBB2 amplification or HER2 overexpression with prognosis have been mixed for most diseases, including gastric, esophageal, gastroesophageal[153-155], bladder urothelial[156], colorectal[157-159]. HER2 overexpression in pancreatic carcinoma has been correlated with inferior prognosis[160-163], but ERBB2 amplification was not correlated with prognosis in two studies[163-164]. ERBB2 amplification or expression have been associated with higher tumor grade and shorter survival in patients with endometrial adenocarcinoma[165-167] and prostate cancer[168-169].

FINDING SUMMARY

ERBB2 (also known as HER2) encodes a receptor tyrosine kinase which is in the same family as EGFR. Amplification or overexpression of ERBB2 can lead to excessive proliferation and tumor formation[170].

GENE
CTNNB1

ALTERATION
S45P

TRANSCRIPT ID
NM_001904

CODING SEQUENCE EFFECT
133T>C

VARIANT ALLELE FREQUENCY (% VAF)
25.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[171-173]. Small studies have reported clinical benefit following treatment of everolimus combined with other targeted agents for patients with CTNNB1-mutated hepatocellular carcinoma[174-175] or endometrial carcinoma[176]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[177-179]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a PR rate in 2 out of 4 patients and SD rate of in 1 out of 4 patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[180]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[181-184]. Phase 1 and 2 clinical trials of gamma-secretase inhibitor PF-03084014 have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[185-186], suggesting CTNNB1-mutated tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutated cells, clinical data supporting this therapeutic approach are lacking[172,187-189].

FREQUENCY & PROGNOSIS

CTNNB1 mutations are common in various solid tumors and are often seen in endometrial (14%), hepatobiliary (11%), melanoma (4.7%), prostate (3.4%), and non-small cell lung (2.9%) cancer (NSCLC)[190]. Aberrant beta-catenin expression has been associated with poor prognosis in lung adenocarcinoma and other non-small cell lung carcinomas[191-193]. Low membrane expression of beta-catenin has been associated with poor prognosis in ovarian endometrioid and endometrial carcinomas[194-195]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[196].

FINDING SUMMARY

CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[197]. CTNNB1 exon 3 mutations, such as observed here, lead to increased beta-catenin protein stability and activation of the WNT pathway, and are considered to be activating[198-216].

GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[217-220]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[221] and palbociclib treatment[222-223]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[224-230]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[231-232], the clinical relevance of p14ARF as a predictive biomarker is not clear. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[225,227-228,233-235].

FREQUENCY & PROGNOSIS

In the TCGA datasets, concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in several tumor types, with the highest incidences in glioblastoma multiforme (54%), mesothelioma (45%), esophageal adenocarcinoma (39%), bladder urothelial carcinoma (31%), melanoma (31%), and HNSCC (30%) cases (cBioPortal, Mar 2022)[148-149]. In addition, mutation of CDKN2A has been reported in 45% of cutaneous SCC[236], 21% of HNSCC[237], 17% of lung SCC[238], and 3-4.5% of esophageal SCC[239-240] cases. Loss of p16INK4a expression has been reported in 67-80% of pancreatic ductal adenocarcinomas[241-242] and in 59% of NSCLCs[243]. Inactivation of CDKN2A and/or CDKN2B and loss of p16INK4a and/or p15INK4b protein expression have been correlated with poor patient prognosis in several tumor types, including pancreatic ductal adenocarcinoma, gastric cancer, and lung cancer[241,244-250].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[251-252]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[253-254]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[255-256]. One or more alterations observed here are predicted to result in p16INK4a loss of function[257-278]. One or more alterations seen here are predicted to result in p14ARF loss of function[261,278-281]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[282].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[283]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[284-285]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[286-288]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[289-291]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
FANCC

ALTERATION
Q485fs*2

TRANSCRIPT ID
NM_000136

CODING SEQUENCE EFFECT
1453delC

VARIANT ALLELE FREQUENCY (% VAF)
18.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address loss of FANCC activity. However, limited preclinical evidence[292-293] and clinical evidence in sarcoma[294] suggest that FANCC alterations may predict sensitivity to PARP inhibitors.

FREQUENCY & PROGNOSIS

Somatic mutations in FANCC are very infrequently observed in human malignancies (COSMIC, Jan 2022)[295].

FINDING SUMMARY

FANCC encodes a key component of an eight protein (FANCA/B/C/E/F/G/L/M) Fanconi anemia (FA) nuclear E3 ubiquitin ligase complex. This complex is involved in DNA repair and is essential for prevention of chromosome breakage caused by DNA damage[296]. Upon DNA damage or during the S-phase of the cell cycle, the FA complex is activated and recruited to the sites of DNA damage/DNA repair. The complex then activates FANCD2 and FANCL via monoubiquitination, leading to their co-localization with FANCD1/BRCA2, BRCA1, RAD51, PCNA, and other proteins at the DNA repair foci on chromatin. Germline mutations in FANCC cause Fanconi anemia, a clinically heterogeneous disorder involving various developmental abnormalities as well as predisposition to cancer; underlying these phenotypes are defects in DNA repair[297].

GENE
FH

ALTERATION
A273T

TRANSCRIPT ID
NM_000143

CODING SEQUENCE EFFECT
817G>A

VARIANT ALLELE FREQUENCY (% VAF)
48.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A preclinical study showed that FH-deficient renal cancer cells are dependent on ABL1 activity and sensitive to the multikinase inhibitor vandetanib; treatment with vandetanib inhibited the growth and tumorigenicity of these cells in vitro and in vivo[298]. Tumors with FH loss or inactivation may therefore be sensitive to vandetanib, which is approved to treat medullary thyroid cancer and is in clinical trials in solid tumors. A Phase 2 trial of bevacizumab and erlotinib reported overall response rate in 60% (12/20) of patients with hereditary leiomyomatosis and renal cell cancer, and 29% (6/21) of patients with sporadic papillary renal cell carcinoma[299].

FREQUENCY & PROGNOSIS

FH mutations have been detected in several tumor types, with the highest incidences reported in tumors of the endometrium (2.6%), skin (2.3%), liver (1.7%), stomach (1.5%), and lung (1.4%)(COSMIC, Jan 2022)[295]. FH-deficient renal cell carcinoma (RCC) arises in about 20% of families affected by hereditary leiomyomatosis and renal cell cancer (HLRCC) and is associated with aggressive disease and poor prognosis[300-302].

FINDING SUMMARY

FH encodes fumarate hydratase, an enzymatic component of the Krebs cycle. FH has been identified as a possible hypoxia inducible factor activating gene[303]. Loss-of-function germline mutations in FH are associated with hereditary leiomyomatosis and renal cell cancer (HLRCC); tumors arising in FH mutation carriers often demonstrate FH biallelic inactivation[300,302,304-305].

POTENTIAL GERMLINE IMPLICATIONS

FH germline inactivating alterations are associated with FH tumor predisposition syndrome, also known as hereditary leiomyomatosis and renal cell cancer (HLRCC), an autosomal-dominant syndrome characterized by cutaneous leiomyomata, uterine fibroids, and aggressive renal cell carcinoma (RCC)[305]. Pheochromocytoma and paraganglioma have also been described at lower frequency[306-307]. Whereas cutaneous leiomyomata appear at a mean age of 30 years, increasing in size and number with age, the age at diagnosis of uterine fibroids ranges from 18 to 53 years[307-308]. HLRCC has been associated with a 21% lifetime risk of RCC[309]. In the appropriate clinical context, germline testing of FH is recommended.

GENE
MAP2K4

ALTERATION
Q327*

TRANSCRIPT ID
NM_003010

CODING SEQUENCE EFFECT
979C>T

VARIANT ALLELE FREQUENCY (% VAF)
56.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to target MAP2K4 loss or inactivation. However, a preclinical study reported that inactivation of MAP2K4 may confer sensitivity to MEK inhibitors[310].

FREQUENCY & PROGNOSIS

MAP2K4 mutations have been reported at highest frequencies in liver (4.3%), endometrial (3.8%), breast (3.7%), pancreatic (3.5%), biliary tract (3.5%), and gastric (3.3%) carcinomas (COSMIC, Feb 2022)[295]. MAP2K4 homozygous deletion has been observed in multiple tumor types, including stomach adenocarcinoma (3.4%), ovarian serous cystadenocarcinoma (2.6%), breast invasive carcinoma (2.3%), pancreatic adenocarcinoma (2.2%), and colorectal adenocarcinoma (1.9%)(cBioPortal, Feb 2022)[148-149]. Loss of MKK4 expression has been linked to tumor cell invasion, metastasis, and poor prognosis in some cancer types[311-314].

FINDING SUMMARY

MAP2K4 encodes the protein kinase MKK4, a member of a MAPK signaling cascade that leads to apoptosis in response to cellular stress[315]. MAP2K4 has been proposed to act as a tumor suppressor in several cancer types, including pancreatic cancer, but has also been suggested to act as an oncogene in certain situations[311-312,315-319]. Alterations such as seen here may disrupt MAP2K4 function or expression[311,316,320-321].

GENE
TP53

ALTERATION
G244V

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
731G>T

VARIANT ALLELE FREQUENCY (% VAF)
51.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[322-325], or p53 gene therapy and immunotherapeutics such as SGT-53[326-330] and ALT-801[331]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[332]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[333]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[334]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[335]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[336]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[337]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[338]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[330]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[339-341]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[342]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[343-344]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[345-346]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

Pan-cancer analysis of the TCGA datasets across 12 cancer types identified TP53 as the most frequently mutated gene, with 42% of more than 3,000 tumors harboring a TP53 mutation; in this study TP53 mutation occurred most frequently in ovarian serous carcinoma (95%), lung squamous cell carcinoma (SCC) (79%), head and neck SCC (70%), colorectal adenocarcinoma (59%), lung adenocarcinoma (52%), and bladder urothelial carcinoma (50%)[347]. TP53 loss of heterozygosity (LOH) is frequently seen in tumors and often occurs when one copy of TP53 harbors a mutation; in some tumors, LOH is correlated with progression[348-351]. While the prognostic significance of TP53 alteration or dysregulation varies according to tumor type, studies have shown an association with poor prognosis for patients with breast cancer[352-354], endometrial cancer[355-356], HNSCC[357-359], or urothelial cancer[360-361]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[362]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[363].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[364]. Alterations such as seen here may disrupt TP53 function or expression[365-369].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[370-372], including sarcomas[373-374]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[375] to 1:20,000[374]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[376]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[377-382]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[377-378]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[383]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[381,384-385]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
VEGFA

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The approved VEGFA-targeted agents bevacizumab and ziv-aflibercept have demonstrated efficacy in multiple tumor types; however, expression or amplification of VEGFA has not been established as a reliable biomarker of response to these therapies[386-417]. Preclinical hepatocellular carcinoma (HCC) models with VEGFA amplification showed increased sensitivity to sorafenib, and a small retrospective study reported significantly increased OS for 7 patients with VEGFA-amplified HCC treated with sorafenib[418]. However, a prospective biomarker study showed that VEGFA amplification detected by circulating cell-free DNA was not significantly associated with DCR, time to progression, or median OS for patients with HCC treated with first-line sorafenib[419]. It is currently not known if VEGFA amplification predicts response to other inhibitors targeting VEGFRs.

FREQUENCY & PROGNOSIS

In the TCGA datasets, VEGFA amplification was observed in 13% of esophageal carcinoma, 7% of stomach adenocarcinoma, 3% of lung adenocarcinoma, 2% of pancreatic adenocarcinoma, and 1% of colorectal adenocarcinoma (CRC) cases[17,146,420]. Amplification of the 6p12 locus, where VEGFA is located, has been observed in 3% of CRC cases[421]. Increased plasma VEGF-A levels have been associated with decreased overall survival in patients with non-small cell lung cancer (NSCLC)[390,401] and with worse prognosis in patients with cervical cancer[422], and VEGF expression was reported to be correlated with higher stage in hypopharyngeal SCC[423]. There have been conflicting reports regarding the value of serum VEGF-A levels as a prognostic indicator in patients with gastric cancer[386,424], gastroesophageal junction cancer[424], non-small cell lung cancer (NSCLC)[390,401], pancreatic ductal adenocarcinoma[425-427]; furthermore, it has not been shown that VEGFA amplification or expression in tumor cells results in increased plasma levels of VEGF-A[401].

FINDING SUMMARY

VEGFA (vascular endothelial growth factor A) encodes a ligand that promotes angiogenesis through the receptor tyrosine kinases VEGFR1 and VEGFR2[428]. VEGFA promotes tumor growth by activating both autocrine VEGFR signaling in tumor cells and paracrine signaling to fibroblasts and immune cells in the tumor microenvironment[428]. VEGFA has been reported to be amplified in cancer[149], and is associated with response to sorafenib[418].

Ado-trastuzumab emtansine

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface, which inhibits HER2 signaling; it also releases the cytotoxic therapy DM1 into cells, leading to cell death. T-DM1 is FDA approved to treat patients with HER2-positive (HER2+) metastatic breast cancer and disease progression on prior therapy as well as patients with HER2+ early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ERBB2 amplification or activating mutations may predict sensitivity to T-DM1[107,429-444] .

SUPPORTING DATA

The vast majority of data on the therapeutic use of T-DM1 have been collected in the context of breast cancer, although clinical trials investigating T-DM1 are underway in several tumor types, primarily in HER2+ cancers. Phase 2 basket trials for HER2-amplified cancers have reported ORR of 8-28% with T-DM1, including responses in salivary gland, lung, endometrial, biliary tract, and ovarian cancers[430,437]. A Phase 3 trial in 602 patients with HER2+ breast cancer reported that those who received T-DM1 showed an improved progression-free survival (PFS) and a lower rate of adverse events than patients who received the physician's choice of therapy[433]. A second Phase 3 trial in 991 patients with HER2+ breast cancer reported that T-DM1 brought about significantly longer overall survival (OS) and PFS, as compared with lapatinib plus capecitabine, in patients previously treated with trastuzumab plus a taxane[107,434] . Two separate Phase 2 trials reported robust activity for single-agent T-DM1 as a treatment for HER2+ metastatic breast cancer in patients previously treated with standard HER2-directed therapies or HER2-directed therapies plus chemotherapy, with objective response rates of 34.5% and 25.9%, respectively, and PFS of 6.9 months and 4.9 months, respectively[435-436] .

Afatinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Clinical and preclinical data support sensitivity of ERBB2 amplification[125,445-447] , or HER2 overexpression[124,448-450] , to afatinib.

SUPPORTING DATA

Afatinib has been primarily evaluated for the treatment of EGFR-mutant NSCLC, in which treatment with afatinib exhibited significant improvement in progression free survival (PFS) vs. chemotherapy treatments[451-452] . A Phase 2 trial of afatinib in patients with either EGFR or ERBB2 amplification and esophagogastric, biliary tract, urothelial tract, or gynecologic cancer reported a 5% (1/20) objective response rate, with complete response achieved in one patient and stable disease (SD) achieved in 8 patients; the authors concluded that afatinib activity as a single agent was encouraging[447]. A Phase 1 trial of afatinib in advanced cancer reported SD in 14/31 patients[453]. A Phase 1 study of afatinib combined with pemetrexed in patients with advanced solid tumors reported confirmed partial response in 3% (1/30) of patients and SD in 33% (10/30) of patients[454]. Outcomes of partial response and/or stable disease have been reported in various clinical trials involving multiple cancer types, including HER2-positive breast cancer, NSCLC, colorectal cancer, and esophageal cancer[127,451-452,455-456] .

Dacomitinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Prospective early-phase single-arm clinical trials report anti-tumor activity of dacomitinib in advanced solid tumors with ERBB2 activating mutations[138,457] , ERBB2 amplification[458-459] , or HER2 overexpression[460].

SUPPORTING DATA

Investigations into the efficacy of dacomitinib have primarily been in the context of non-small cell lung cancer (NSCLC). Patients with EGFR-mutant NSCLC treated with dacomitinib exhibited significant improvement in OS compared with gefitinib treatment (median OS, 34.1 vs. 26.8 months)[461-462] . A Phase 2 study of dacomitinib in patients with advanced penile squamous cell carcinoma (SCC) reported an ORR of 32% (1 CR, 8 PR), including a 100% DCR (1 CR, 1 PR, 2 SD) in four patients with EGFR amplification[463-464]. A Phase 2 study of dacomitinib in patients with recurrent or metastatic head and neck SCC reported clinical benefit (defined as PFS>4 months) in 13/31 (42%) of patients[458]. Studies of dacomitinib in esophageal[465] and cutaneous[466] SCC reported RRs of 12.5% (6/48) and 28.6% (12/42), respectively, but high DCRs of 73% and 86%, respectively. In contrast, trials of dacomitinib in heavily pretreated patients with HER2+ gastric cancer[460] and patients with EGFR-amplified glioblastoma[467] found RRs of fewer than 10% and DCRs of fewer than 50%: 11/27 (41%) DCR in HER2+ gastric cancer[460] and 15/49 (31%) in EGFR-amplified glioblastoma[467].

Fam-trastuzumab deruxtecan

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Fam-trastuzumab deruxtecan is an antibody-drug conjugate that targets the protein ERBB2/HER2 on the cell surface and delivers the cytotoxic payload DXd, which inhibits DNA topoisomerase I to induce DNA damage. Fam-trastuzumab deruxtecan is FDA approved to treat patients with HER2-positive breast cancer and gastric or gastroesophageal junction adenocarcinoma who have received prior HER2-targeted therapy. It is also approved for patients with HER2-low advanced breast cancer who have previously been treated with chemotherapy, as well as for patients with advanced ERBB2-mutated non-small cell lung cancer (NSCLC) who have received systemic therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data in solid cancers, including breast[108,468] , gastric[109,469] , non-small cell lung[470-471] , and colon[472] cancers, ERBB2 amplification may predict sensitivity to fam-trastuzumab deruxtecan.

SUPPORTING DATA

Fam-trastuzumab deruxtecan has demonstrated activity in multiple ERBB2-positive cancer types. In the Phase 2 DESTINY trials, clinical benefit was observed for patients treated with fam-trastuzumab deruxtecan monotherapy who had previously treated, HER2-expressing breast (61% ORR, median PFS 16.4 months)[108], colorectal (45% ORR, median PFS 6.9 months)[473], or gastric or gastroesophageal cancer (43% ORR, median PFS 5.6 months)[109], as well as HER2-mutated lung cancer (62% ORR, median PFS 14.0 months)[474]. Benefit was also observed in a Phase 2 trial for ERBB2-expressing biliary tract cancer (30% ORR)[475]. In a Phase 1 study evaluating single-agent fam-trastuzumab deruxtecan for the treatment of patients with ERBB2-mutated solid tumors or ERBB2-expressing solid tumors other than breast or gastric cancer, the median PFS was 7.2 months and the ORR was 28% (17/60), with responses reported for patients with non-small cell lung carcinoma (NSCLC), breast cancer, colorectal cancer (CRC), salivary gland carcinoma, cholangiocarcinoma, and endometrial cancer[476].

Lapatinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Lapatinib is a tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and to a lesser degree, ERBB4. It is FDA approved in combination with capecitabine to treat patients with HER2-overexpressing (HER2+) metastatic breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation or amplification of ERBB2 may predict sensitivity to lapatinib[115-123] .

SUPPORTING DATA

Clinical data on the efficacy of lapatinib have primarily been in the context of breast cancer[107,116-117,477-481] . Phase 3 and Phase 2 studies have reported clinical activity of lapatinib plus chemotherapy combinations for HER2+ advanced gastric[482], gastroesophageal[483-484] , and upper gastrointestinal tract[485] cancer. Additionally, Phase 1 studies evaluating lapatinib alone or in combination with chemotherapy agents reported PRs in patients with various solid tumors and 1 CR in a patient with EGFR-overexpressing head and neck squamous cell carcinoma[486-489] . In a Phase 1 trial of lapatinib plus pazopanib, one patient with a salivary gland tumor experienced a PR[490].

Margetuximab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Margetuximab is an Fc-engineered antibody targeting ERBB2/HER2 that was designed to enhance the anti-tumor immune response. Margetuximab is FDA approved for the treatment of patients with HER2-positive breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification may predict sensitivity to margetuximab[491-494] .

SUPPORTING DATA

The Phase 3 SOPHIA trial of margetuximab for HER2+ metastatic breast cancer reported improved median PFS (5.8 vs. 4.9 months, HR=0.76) and ORR (22% vs. 16%) when combining margetuximab with chemotherapy, compared with trastuzumab and chemotherapy, for patients who had progressed on ≥2 prior HER2-directed therapies[491]; however, median OS was not statistically different between the 2 treatment arms (21.6 vs. 21.9 months, HR=0.62)[495]. In a Phase 1 trial for HER2-overexpressing solid tumors, 12% (7/60) of patients, including 4 with breast, 2 with gastroesophageal, and 1 with lacrimal gland cancers, experienced PRs, and a further 52% (31/60) of the cohort experienced SD[492]. In a study of margetuximab for HER2+ cancers, a patient with salivary gland cancer reported a PR[493].

Neratinib

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Neratinib is an irreversible tyrosine kinase inhibitor that targets EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the extended adjuvant treatment of early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab. Neratinib is also approved in combination with capecitabine to treat patients with advanced or metastatic HER2+ breast cancer who have been previously treated with 2 or more anti-HER2 regimens. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[134-137,496-498] and preclinical[499-503] evidence, ERBB2 amplification or activating mutations may confer sensitivity to neratinib.

SUPPORTING DATA

Neratinib has been largely evaluated in the context of breast cancer and non-small cell lung cancer (NSCLC). For patients with advanced HER2-positive breast cancer, neratinib treatment resulted in PFS of 22.3 weeks for patients with prior trastuzumab treatment and 39.6 weeks for those with no prior trastuzumab treatment[504]. In patients with HER2-positive breast cancer with brain metastases, neratinib elicited a CNS ORR of 8% (3/40)[505]. In a Phase 3 study of patients with HER2-positive, early stage breast cancer previously treated with trastuzumab, neratinib significantly improved the 2-year invasive disease-free survival compared to placebo (HR=0.67, p=0.0091)[497]. In Phase 2 trials of single-agent neratinib for patients with ERBB2-mutated, non-amplified metastatic breast cancer, clinical benefit rates of 31-40% and median PFS of 3.5-4 months have been achieved[135-137] . Neratinib in combination with various other agents has also shown significant clinical activity against breast cancer[498,506-511] . In patients with ERBB2-mutated NSCLC, where the majority of cases harbor inhibitor-resistant exon 20 insertions, neratinib monotherapy has resulted in ORRs of 0-4%[136,496,512-513] . However, clinical outcomes have been improved by combination of neratinib with other targeted agents, such as temsirolimus or trastuzumab[496,512-513] . Trials of neratinib have shown high ORRs (up to 44%) in ERBB2-mutated cervical cancer[136,514] but very low ORRs in colorectal and bladder cancer[136].

Trastuzumab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets the protein ERBB2/HER2. It is FDA approved as monotherapy and in combination with chemotherapy for HER2+ metastatic gastric or gastroesophageal adenocarcinoma. Trastuzumab biosimilars are also FDA approved for these indications. Please see the drug label(s) for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification, overexpression, or activating mutations may confer sensitivity to trastuzumab[97-98,102,119,515-519] .

SUPPORTING DATA

The majority of data investigating the therapeutic use of trastuzumab has been in the context of breast cancer. Trastuzumab was approved for breast cancer on the basis of a Phase 3 randomized clinical trial comparing treatment with trastuzumab and chemotherapy to treatment with chemotherapy alone. The addition of trastuzumab was associated with significant improvements in time to progression, objective response rate, response duration, and overall survival[97]. A subsequent Phase 3 study of patients with HER2-positive (HER2+) breast cancer reported 5-year event-free survival in 58% of patients treated with trastuzumab plus neoadjuvant therapy, compared to 43% in patients treated with neoadjuvant therapy alone[515]. Long-term follow-up Phase 2 analysis reported a 5-year distant disease-free survival rate of 92% in patients with HER2+ breast cancer treated with dose-dense chemotherapy and trastuzumab and 89% in patients treated with lapatinib and dose-sense chemotherapy[516]. A Phase 3 trial of patients with HER2+ breast cancer treated with lapatinib, trastuzumab, or a combination of the two, reported event-free survival rates of 78%, 76%, and 84%, and overall survival of 93%, 90%, and 95%, respectively[520]. In a Phase 2 study of 14 patients with salivary gland carcinoma with overexpressed HER2 protein, trastuzumab had low activity, with a median time to progression of 4.2 months[521]. A retrospective study of patients with HER2-positive salivary duct carcinoma reported that 62% (5/8) of patients who received adjuvant therapy including chemotherapy with paclitaxel, carboplatin, and trastuzumab (TCH) exhibited no evidence of disease after more than 24 months and 100% (5/5) of patients with metastatic disease exhibited response to TCH[522]. Trastuzumab was approved in combination with cisplatin and 5-fluorouracil or capecitabine for (HER2+) metastatic gastric or gastroesophageal junction adenocarcinoma in the first line treatment setting based upon improvement in survival observed in the ToGA trial[98]. A Phase 1/2 trial of trastuzumab in patients with HER2+ esophageal adenocarcinoma and co-treated with cisplatin, paclitaxel and radiotherapy reported a median survival of 24 months with a two-year survival rate of 50%[523].

Trastuzumab + Pertuzumab

Assay findings association

ERBB2
amplification

AREAS OF THERAPEUTIC USE

Trastuzumab is a monoclonal antibody that targets ERBB2/HER2, and pertuzumab is a monoclonal antibody that interferes with the interaction between HER2 and ERBB3. These therapies are FDA approved in combination for the treatment of patients with HER2-positive (HER2+) metastatic breast cancer who have not received prior chemotherapy or HER2-targeted therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical studies in multiple tumor types, ERBB2 amplification or activating mutations may predict sensitivity to trastuzumab in combination with pertuzumab[104,517,524-528] .

SUPPORTING DATA

The Phase 2 MyPathway basket trial for patients with HER2-positive solid tumors treated with trastuzumab plus pertuzumab reported a 23% ORR (60/258), a 45% DCR (115/258), a 7.9 month median duration of response, 2.8 months mPFS, and 10.9 months mOS; clinical responses were observed across multiple tumor types, including CRC, lung, urothelial, biliary, and ovarian[105,493,529] .

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
CTNNB1

ALTERATION
S45P

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

GENE
ERBB2

ALTERATION
amplification

RATIONALE
ERBB2 amplification or activating mutation may confer sensitivity to HER2-targeted and dual EGFR/HER2-directed therapies, and may enhance efficacy of HSP90 inhibitors.

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Chongqing (China), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Warszawa (Poland), Gdynia (Poland), Grzepnica (Poland), Budapest (Hungary)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT03498521

PHASE 2

A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site

TARGETS
ALK, RET, SMO, AKTs, PARP, PD-L1, EGFR, VEGFA, MEK, BRAF, ERBB2, TRKB, TRKC, ROS1, TRKA

LOCATIONS: Fukuoka (Japan), Ehime (Japan), Seoul (Korea, Republic of), Aichi (Japan), Tokyo (Japan), Chiba (Japan), Bangkok (Thailand), South Brisbane (Australia), Bedford Park (Australia), Blacktown (Australia)

NCT04579380

PHASE 2

Basket Study of Tucatinib and Trastuzumab in Solid Tumors With HER2 Alterations

TARGETS
ERBB2, ER

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Osakasayama (Japan), Nagoya-shi (Japan), Kawasaki-shi (Japan), Chuo-Ku (Japan), Tokyo (Japan), Kashiwa-shi (Japan), Poznan (Poland), Amsterdam (Netherlands)

NCT04162327

PHASE 1

A Phase Ia/Ib Study of IBI315 in Patients With HER2-expressing Advanced Solid Tumor

TARGETS
ERBB2, PD-1

LOCATIONS: Beijing (China)

NCT04040699

PHASE 1

KN026 Combined With KN046 in Subjects With HER2 Positive Solid Tumor

TARGETS
ERBB2, CTLA-4, PD-L1

LOCATIONS: Beijing (China)

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
ALK, ROS1, AXL, TRKA, MET, TRKC, CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, EGFR, ERBB4

LOCATIONS: Hawaii, Washington, Oregon, California

NCT04983238

PHASE 1/2

Evaluation of Safety and Efficacy of Sodium Thiosulfate (BYON5667) Eye Drops to Reduce Ocular Toxicity in Cancer Patients Treated With SYD985

TARGETS
ERBB2

LOCATIONS: Antwerp (Belgium), Leuven (Belgium), Lille (France), Paris (France), Bordeaux (France), Barcelona (Spain), L'Hospitalet De Llobregat (Spain), Lleida (Spain), Madrid (Spain)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ATM H42R	***BAP1*** A321T	***CDK12*** amplification	***ERBB4*** M322K
FANCC I80T	***LYN*** rearrangement	***RNF43*** R145Q	***STAG2*** R760C

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Homologous Recombination status
Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.1.0

The median exon coverage for this sample is 796x

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Zighelboim I, et al. J. Clin. Oncol. (2007) pmid: 17513808
7. Hampel H, et al. Cancer Res. (2006) pmid: 16885385
8. Stelloo E, et al. Clin. Cancer Res. (2016) pmid: 27006490
9. Kanopienė D, et al. Medicina (Kaunas) (2014) pmid: 25458958
10. Black D, et al. J. Clin. Oncol. (2006) pmid: 16549821
11. Nout RA, et al. Gynecol. Oncol. (2012) pmid: 22609107
12. Steinbakk A, et al. Cell Oncol (Dordr) (2011) pmid: 21547578
13. Bilbao C, et al. Int. J. Radiat. Oncol. Biol. Phys. (2010) pmid: 20005452
14. Guastadisegni C, et al. Eur. J. Cancer (2010) pmid: 20627535
15. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
16. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
17. Nature (2012) pmid: 22810696
18. Hiyama T, et al. J. Gastroenterol. Hepatol. (2004) pmid: 15209621
19. Wu MS, et al. Cancer Res. (1998) pmid: 9537253
20. dos Santos NR, et al. Gastroenterology (1996) pmid: 8536886
21. Fang WL, et al. Biomed Res Int (2013) pmid: 23555086
22. Farris AB, et al. Am. J. Surg. Pathol. (2011) pmid: 21422910
23. Agaram NP, et al. Am. J. Clin. Pathol. (2010) pmid: 20395525
24. Ruemmele P, et al. Am. J. Surg. Pathol. (2009) pmid: 19252434
25. Planck M, et al. Cancer (2003) pmid: 12627520
26. Hibi K, et al. Jpn. J. Cancer Res. (1995) pmid: 7775257
27. Muneyuki T, et al. Dig. Dis. Sci. (2000) pmid: 11117578
28. Zhang SH, et al. World J. Gastroenterol. (2005) pmid: 15918185
29. Chiappini F, et al. Carcinogenesis (2004) pmid: 14656944
30. Suto T, et al. J Surg Oncol (2001) pmid: 11223838
31. Momoi H, et al. J. Hepatol. (2001) pmid: 11580146
32. Liengswangwong U, et al. Int. J. Cancer (2003) pmid: 14506736
33. Moy AP, et al. Virchows Arch. (2015) pmid: 25680569
34. Yoshida T, et al. J. Gastroenterol. (2000) pmid: 11063221
35. Pritchard CC, et al. Nat Commun (2014) pmid: 25255306
36. Azzouzi AR, et al. BJU Int. (2007) pmid: 17233803
37. Burger M, et al. J. Mol. Med. (2006) pmid: 16924473
38. Bai S, et al. Am. J. Clin. Pathol. (2013) pmid: 23690119
39. Giedl J, et al. Am. J. Clin. Pathol. (2014) pmid: 25319978
40. Yamamoto Y, et al. Clin. Cancer Res. (2006) pmid: 16675567
41. Smyth et al., 2015; ASCO Gastrointestinal Cancers Symposium Abstract 62
42. Bilbao-Sieyro C, et al. Oncotarget (2014) pmid: 25026289
43. Mackay HJ, et al. Eur. J. Cancer (2010) pmid: 20304627
44. Arabi H, et al. Gynecol. Oncol. (2009) pmid: 19275958
45. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
46. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
47. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
48. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
49. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
50. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
51. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
52. Cristescu R, et al. Science (2018) pmid: 30309915
53. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
54. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
55. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
56. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
57. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
58. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
59. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
60. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
61. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
62. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
63. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
64. Schenker et al., 2022; AACR Abstract 7845
65. Legrand et al., 2018; ASCO Abstract 12000
66. Stadler ZK, et al. J. Clin. Oncol. (2016) pmid: 27022117
67. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
68. Frampton et al., 2016; ASCO Abstract 11558
69. Spigel et al., 2016; ASCO Abstract 9017
70. Jiang et al., 2016; ASCO Abstract e23128
71. Xiao D, et al. Oncotarget (2016) pmid: 27009843
72. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
73. Govindan R, et al. Cell (2012) pmid: 22980976
74. Ding L, et al. Nature (2008) pmid: 18948947
75. Imielinski M, et al. Cell (2012) pmid: 22980975
76. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
77. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11535541
78. Elsaleh H, et al. Clin Colorectal Cancer (2001) pmid: 12445368
79. Brueckl WM, et al. Anticancer Res. () pmid: 12820457
80. Guidoboni M, et al. Am. J. Pathol. (2001) pmid: 11438476
81. Gryfe R, et al. N. Engl. J. Med. (2000) pmid: 10631274
82. Sinicrope FA, et al. Gastroenterology (2006) pmid: 16952542
83. Laghi L, et al. Dig Dis (2012) pmid: 22722556
84. Mehnert JM, et al. J. Clin. Invest. (2016) pmid: 27159395
85. Hussein YR, et al. Mod. Pathol. (2015) pmid: 25394778
86. Church DN, et al. Hum. Mol. Genet. (2013) pmid: 23528559
87. Cazier JB, et al. Nat Commun (2014) pmid: 24777035
88. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
89. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
90. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
91. Rizvi NA, et al. Science (2015) pmid: 25765070
92. Johnson BE, et al. Science (2014) pmid: 24336570
93. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
94. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
95. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
96. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
97. Slamon DJ, et al. N. Engl. J. Med. (2001) pmid: 11248153
98. Bang YJ, et al. Lancet (2010) pmid: 20728210
99. Chumsri S, et al. J Natl Compr Canc Netw (2015) pmid: 26358791
100. Cappuzzo F, et al. N. Engl. J. Med. (2006) pmid: 16775247
101. Falchook GS, et al. J Thorac Oncol (2013) pmid: 23328556
102. Mazières J, et al. J. Clin. Oncol. (2013) pmid: 23610105
103. Baselga J, et al. N. Engl. J. Med. (2012) pmid: 22149875
104. Swain SM, et al. N. Engl. J. Med. (2015) pmid: 25693012
105. Meric-Bernstam F, et al. Lancet Oncol. (2019) pmid: 30857956
106. Meric-Bernstam et al., 2019; ESMO Abstract 453PD
107. Verma S, et al. N. Engl. J. Med. (2012) pmid: 23020162
108. Modi S, et al. N. Engl. J. Med. (2019) pmid: 31825192
109. Shitara K, et al. N. Engl. J. Med. (2020) pmid: 32469182
110. Li BT, et al. N Engl J Med (2021) pmid: 34534430
111. Murthy RK, et al. N. Engl. J. Med. (2020) pmid: 31825569
112. Borges VF, et al. JAMA Oncol (2018) pmid: 29955792
113. Murthy R, et al. Lancet Oncol. (2018) pmid: 29804905
114. Moulder SL, et al. Clin. Cancer Res. (2017) pmid: 28053022
115. Fan Y, et al. Mol Oncol (2020) pmid: 32478891
116. Cameron D, et al. Oncologist (2010) pmid: 20736298
117. Geyer CE, et al. N. Engl. J. Med. (2006) pmid: 17192538
118. Serra V, et al. Cancer Discov (2013) pmid: 23950206
119. Ali SM, et al. J. Clin. Oncol. (2014) pmid: 24516025
120. Grellety T, et al. Ann. Oncol. (2016) pmid: 26487584
121. Vornicova O, et al. Oncologist (2014) pmid: 25085898
122. Ronellenfitsch MW, et al. J Clin Invest (2020) pmid: 32017710
123. Hou JY, et al. Gynecol Oncol Rep (2020) pmid: 32405522
124. Lin NU, et al. Breast Cancer Res. Treat. (2012) pmid: 22418700
125. Schwab CL, et al. Br. J. Cancer (2014) pmid: 25268372
126. De Grève J, et al. Lung Cancer (2015) pmid: 25682316
127. De Grève J, et al. Lung Cancer (2012) pmid: 22325357
128. Li BT, et al. Lung Cancer (2015) pmid: 26559459
129. Dziadziuszko R, et al. J Thorac Oncol (2019) pmid: 30825613
130. Lai WV, et al. Eur. J. Cancer (2019) pmid: 30685684
131. Liu Z, et al. Onco Targets Ther (2018) pmid: 30425522
132. Fang W, et al. Oncologist (2019) pmid: 31748336
133. Yuan B, et al. Front Oncol (2020) pmid: 32477948
134. Ben-Baruch NE, et al. J Natl Compr Canc Netw (2015) pmid: 26358790
135. Ma CX, et al. Clin. Cancer Res. (2017) pmid: 28679771
136. Hyman DM, et al. Nature (2018) pmid: 29420467
137. Smyth LM, et al. Cancer Discov (2019) pmid: 31806627
138. Kris MG, et al. Ann. Oncol. (2015) pmid: 25899785
139. Jiang et al., 2019; ASCO Abstract 1001
140. Xu et al., 2020; ASCO Abstract 1003
141. Li et al., 2020; ASCO Abstract 3510
142. Wang Y, et al. Ann. Oncol. (2019) pmid: 30596880
143. Chmielecki J, et al. Oncologist (2015) pmid: 25480824
144. Nature (2012) pmid: 23000897
145. Ciriello G, et al. Cell (2015) pmid: 26451490
146. Nature (2014) pmid: 25079317
147. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
148. Cerami E, et al. Cancer Discov (2012) pmid: 22588877

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

149. Gao J, et al. Sci Signal (2013) pmid: 23550210
150. Sci Transl Med (2012) pmid: 22461643
151. Jones KL, et al. Lancet Oncol. (2009) pmid: 19959074
152. Ramić S, et al. Anticancer Res. (2013) pmid: 23749902
153. Polkowski W, et al. Ann. Surg. Oncol. () pmid: 10340889
154. Haas M, et al. Virchows Arch. (2011) pmid: 21359545
155. Maresch J, et al. Crit. Rev. Oncol. Hematol. (2012) pmid: 21783379
156. Tsai YS, et al. Adv Urol (2012) pmid: 22991510
157. Martin V, et al. Br. J. Cancer (2013) pmid: 23348520
158. Seo AN, et al. PLoS ONE (2014) pmid: 24879338
159. Sclafani F, et al. Ann. Oncol. (2013) pmid: 24146218
160. Harder J, et al. Br. J. Cancer (2012) pmid: 22374460
161. Komoto M, et al. Cancer Sci. (2009) pmid: 19432892
162. Safran H, et al. Am. J. Clin. Oncol. (2001) pmid: 11586103
163. Tsiambas E, et al. JOP (2006) pmid: 16685109
164. Sharif S, et al. Dig. Dis. Sci. (2008) pmid: 18463983
165. Peiró G, et al. Mod. Pathol. (2004) pmid: 14752523
166. Saffari B, et al. Cancer Res. (1995) pmid: 7585656
167. Kudela M, et al. Eur. J. Gynaecol. Oncol. (2012) pmid: 22611955
168. Zhang YF, et al. Chin. Med. J. (2011) pmid: 22340411
169. Minner S, et al. Clin. Cancer Res. (2010) pmid: 20179235
170. Higgins MJ, et al. J. Clin. Invest. (2011) pmid: 21965336
171. Tanwar PS, et al. Biol. Reprod. (2009) pmid: 19403928
172. Tanwar PS, et al. PLoS ONE (2011) pmid: 21695255
173. Fujishita T, et al. Proc. Natl. Acad. Sci. U.S.A. (2008) pmid: 18768809
174. Bhoori S, et al. J. Hepatol. (2010) pmid: 20347502
175. Janku F, et al. Oncotarget (2014) pmid: 24931142
176. Slomovitz BM, et al. J. Clin. Oncol. (2015) pmid: 25624430
177. Niida A, et al. Oncogene (2004) pmid: 15378020
178. Chamorro MN, et al. EMBO J. (2005) pmid: 15592430
179. Kagey MH, et al. Br. J. Pharmacol. (2017) pmid: 28574171
180. Kagey et al., 2017; AACR Abstract 369
181. Kwon C, et al. Nat. Cell Biol. (2011) pmid: 21841793
182. Arcaroli JJ, et al. Br. J. Cancer (2013) pmid: 23868008
183. Shang H, et al. Cancer (2015) pmid: 26349011
184. Kode A, et al. Nature (2014) pmid: 24429522
185. Kummar et al., 2015; ASCO Abstract 10563
186. Messersmith WA, et al. Clin. Cancer Res. (2015) pmid: 25231399
187. Zhu J, et al. Carcinogenesis (2012) pmid: 22964660
188. Kogan Y, et al. Biochem. J. (2012) pmid: 22356261
189. Lachenmayer A, et al. Clin. Cancer Res. (2012) pmid: 22811581
190. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
191. Nozawa N, et al. Pathol. Res. Pract. (2006) pmid: 16843618
192. Chiu CG, et al. Am. J. Surg. (2012) pmid: 22402266
193. Kim H, et al. Korean J Pathol (2013) pmid: 23483484
194. Rosen DG, et al. Mod. Pathol. (2010) pmid: 19820688
195. Athanassiadou P, et al. Int. J. Gynecol. Cancer () pmid: 17504383
196. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
197. Biochem. Biophys. Res. Commun. (2000) pmid: 10679188
198. Anastas JN, et al. Nat. Rev. Cancer (2013) pmid: 23258168
199. Fukuchi T, et al. Cancer Res. (1998) pmid: 9721853
200. Cancer Sci. (2003) pmid: 12824913
201. Takahashi Y, et al. Virchows Arch. (2006) pmid: 16523258
202. Tanaka Y, et al. Cancer Res. (2001) pmid: 11731417
203. Abraham SC, et al. Am. J. Pathol. (2002) pmid: 11943721
204. Austinat M, et al. Mol. Cancer (2008) pmid: 18282277
205. Wu G, et al. Mol. Cell (2003) pmid: 12820959
206. Provost E, et al. Oncogene (2005) pmid: 15829978
207. Curr. Opin. Genet. Dev. (1999) pmid: 10072352
208. Segditsas S, et al. Oncogene (2006) pmid: 17143297
209. Barth AI, et al. J. Cell Biol. (1997) pmid: 9024698
210. Harada N, et al. EMBO J. (1999) pmid: 10545105
211. Hsu SC, et al. Mol. Cell. Biol. (1998) pmid: 9671490
212. Breuhahn K, et al. J. Pathol. (2008) pmid: 18491352
213. Soon PS, et al. Oncologist (2008) pmid: 18515740
214. Tacon LJ, et al. Oncologist (2011) pmid: 21212436
215. Simon DP, et al. Mol. Cell. Endocrinol. (2012) pmid: 22266195
216. Hirotsu Y, et al. Hepatol. Res. (2016) pmid: 26850916
217. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
218. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
219. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
220. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
221. Fennell DA, et al. Lancet Oncol (2022) pmid: 35157829
222. Elvin JA, et al. Oncologist (2017) pmid: 28283584
223. Gao J, et al. Curr Oncol (2015) pmid: 26715889
224. Gopalan et al., 2014; ASCO Abstract 8077
225. Peguero et al., 2016; ASCO Abstract 2528
226. Konecny et al., 2016; ASCO Abstract 5557
227. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
228. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
229. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
230. Johnson DB, et al. Oncologist (2014) pmid: 24797823
231. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
232. Gamble LD, et al. Oncogene (2012) pmid: 21725357
233. Shapiro et al., 2013; ASCO Abstract 2500
234. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
235. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
236. Li YY, et al. Clin. Cancer Res. (2015) pmid: 25589618
237. Nature (2015) pmid: 25631445
238. Nature (2012) pmid: 22960745
239. Song Y, et al. Nature (2014) pmid: 24670651
240. Lin DC, et al. Nat. Genet. (2014) pmid: 24686850
241. Oshima M, et al. Ann. Surg. (2013) pmid: 23470568
242. Tsiambas E, et al. J BUON () pmid: 17600882
243. Yanagawa N, et al. Lung Cancer (2013) pmid: 23254264
244. Chang DT, et al. Cancer (2010) pmid: 20665497
245. Lee TL, et al. Clin. Cancer Res. (2002) pmid: 12060614
246. Hu SL, et al. Tumori () pmid: 21302620
247. Shi J, et al. Am J Cancer Res (2012) pmid: 22206050
248. Bradly DP, et al. Diagn. Mol. Pathol. (2012) pmid: 23111194
249. Lou-Qian Z, et al. PLoS ONE (2013) pmid: 23372805
250. Tan S, et al. Exp. Lung Res. () pmid: 23614702
251. Quelle DE, et al. Cell (1995) pmid: 8521522
252. Mutat. Res. (2005) pmid: 15878778
253. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
254. Oncogene (1999) pmid: 10498883
255. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
256. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
257. Ruas M, et al. Oncogene (1999) pmid: 10498896
258. Jones R, et al. Cancer Res. (2007) pmid: 17909018
259. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
260. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
261. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
262. Gombart AF, et al. Leukemia (1997) pmid: 9324288
263. Yang R, et al. Cancer Res. (1995) pmid: 7780957
264. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
265. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
266. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
267. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
268. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
269. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
270. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
271. Koh J, et al. Nature (1995) pmid: 7777061
272. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
273. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
274. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
275. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
276. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
277. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
278. Rutter JL, et al. Oncogene (2003) pmid: 12853981
279. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
280. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
281. Zhang Y, et al. Cell (1998) pmid: 9529249
282. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
283. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
284. Adv Exp Med Biol (2010) pmid: 20687502
285. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
286. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
287. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
288. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
289. Kaufman DK, et al. Neurology (1993) pmid: 8414022
290. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
291. Chan AK, et al. Clin Neuropathol () pmid: 28699883
292. Ghosh S, et al. Am. J. Pathol. (2014) pmid: 24200853
293. Lombardi AJ, et al. Clin. Cancer Res. (2015) pmid: 25609062
294. Piha-Paul et al., 2018; AACR-NCI-EORTC Abstract A096
295. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
296. Moldovan GL, et al. Annu. Rev. Genet. (2009) pmid: 19686080
297. Deakyne JS, et al. Biochemistry Mosc. (2011) pmid: 21568838
298. Sourbier C, et al. Cancer Cell (2014) pmid: 25490448
299. Srinivasan et al., 2014; EORTC-NCI-AACR Abstract 5
300. Schmidt C, et al. Semin Cell Dev Biol (2020) pmid: 31085323
301. Lau HD, et al. Am J Surg Pathol (2020) pmid: 31524643
302. Gardie B, et al. J Med Genet (2011) pmid: 21398687
303. Morris MR, et al. J. Clin. Pathol. (2004) pmid: 15220362
304. Lehtonen HJ, et al. J Med Genet (2006) pmid: 16155190
305. Tomlinson IP, et al. Nat. Genet. (2002) pmid: 11865300
306. Castro-Vega LJ, et al. Hum Mol Genet (2014) pmid: 24334767
307. Muller M, et al. Clin Genet (2017) pmid: 28300276
308. Fam Cancer (2011) pmid: 21404119
309. Forde C, et al. Eur Urol Oncol (2019) pmid: 31831373

310. Xue Z, et al. Cell Res (2018) pmid: 29795445
311. Ahn YH, et al. Mol. Cell. Biol. (2011) pmid: 21896780
312. Davis SJ, et al. BMC Cancer (2011) pmid: 21575258
313. Ishikawa M, et al. Oncology (2010) pmid: 21372598
314. Hickson JA, et al. Cancer Res. (2006) pmid: 16489030
315. Curtis C, et al. Nature (2012) pmid: 22522925
316. Teng DH, et al. Cancer Res. (1997) pmid: 9331070
317. Lee HY, et al. Clin. Cancer Res. (2005) pmid: 16115952
318. Lee HY, et al. J. Biol. Chem. (2003) pmid: 12714585
319. Cunningham SC, et al. Cancer Res. (2006) pmid: 16740690
320. Kan Z, et al. Nature (2010) pmid: 20668451
321. Takekawa M, et al. Mol. Cell (2005) pmid: 15866172
322. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
323. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
324. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
325. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
326. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
327. Xu L, et al. Mol. Med. (2001) pmid: 11713371
328. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
329. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
330. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
331. Hajdenberg et al., 2012; ASCO Abstract e15010
332. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
333. Moore et al., 2019; ASCO Abstract 5513
334. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
335. Oza et al., 2015; ASCO Abstract 5506
336. Lee J, et al. Cancer Discov (2019) pmid: 31315834
337. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
338. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
339. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
340. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
341. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
342. Gourley et al., 2016; ASCO Abstract 5571
343. Kwok M, et al. Blood (2016) pmid: 26563132
344. Boudny M, et al. Haematologica (2019) pmid: 30975914
345. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
346. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
347. Kandoth C, et al. Nature (2013) pmid: 24132290
348. Wongsurawat VJ, et al. Cancer Epidemiol. Biomarkers Prev. (2006) pmid: 16537709
349. Brosh R, et al. Nat. Rev. Cancer (2009) pmid: 19693097
350. Baker SJ, et al. Science (1989) pmid: 2649981
351. Calcagno DQ, et al. BMC Gastroenterol (2013) pmid: 24053468
352. Alsner J, et al. Acta Oncol (2008) pmid: 18465328
353. Olivier M, et al. Clin. Cancer Res. (2006) pmid: 16489069
354. Végran F, et al. PLoS ONE (2013) pmid: 23359294
355. Wild PJ, et al. EMBO Mol Med (2012) pmid: 22678923
356. Lee EJ, et al. Gynecol. Oncol. (2010) pmid: 20006376
357. Ganci F, et al. Ann. Oncol. (2013) pmid: 24107801
358. Lindenbergh-van der Plas M, et al. Clin. Cancer Res. (2011) pmid: 21467160
359. Peltonen JK, et al. Head Neck Oncol (2011) pmid: 21513535
360. Bringuier PP, et al. Int. J. Cancer (1998) pmid: 9761125
361. Feng C, et al. Sci Rep (2014) pmid: 24500328
362. Dong ZY, et al. Clin. Cancer Res. (2017) pmid: 28039262
363. Russo A, et al. J. Clin. Oncol. (2005) pmid: 16172461
364. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
365. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
366. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
367. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
368. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
369. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
370. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
371. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
372. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
373. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
374. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
375. Lalloo F, et al. Lancet (2003) pmid: 12672316
376. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
377. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
378. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
379. Xie M, et al. Nat. Med. (2014) pmid: 25326804
380. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
381. Severson EA, et al. Blood (2018) pmid: 29678827
382. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
383. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
384. Chabon JJ, et al. Nature (2020) pmid: 32269342
385. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
386. Van Cutsem E, et al. J. Clin. Oncol. (2012) pmid: 22565005
387. Miles DW, et al. Br. J. Cancer (2013) pmid: 23422754
388. Gianni L, et al. J. Clin. Oncol. (2013) pmid: 23569311
389. Cameron D, et al. Lancet Oncol. (2013) pmid: 23932548
390. Hegde PS, et al. Clin. Cancer Res. (2013) pmid: 23169435
391. Schneider BP, et al. Clin. Cancer Res. (2013) pmid: 23340303
392. Baumgarten P, et al. Neuro-oncology (2016) pmid: 26627848
393. Sathornsumetee S, et al. J. Clin. Oncol. (2008) pmid: 18182667
394. Olafson LR, et al. J Clin Neurosci (2019) pmid: 31582283
395. Duda DG, et al. Oncologist (2010) pmid: 20484123
396. Stremitzer S, et al. Mol. Cancer Ther. (2016) pmid: 27535973
397. Weickhardt AJ, et al. Br. J. Cancer (2015) pmid: 26125443
398. Kopetz S, et al. J. Clin. Oncol. (2010) pmid: 20008624
399. Fountzilas G, et al. Anticancer Res. (2011) pmid: 21868552
400. Sánchez-Rovira P, et al. Clin Transl Oncol (2013) pmid: 23397155
401. Mok T, et al. J Thorac Oncol (2014) pmid: 24807156
402. An SJ, et al. Cancer Gene Ther. (2014) pmid: 24577128
403. Bais C, et al. J. Natl. Cancer Inst. (2017) pmid: 29059426
404. Xu L, et al. Cancer Res. (2009) pmid: 19826039
405. Hasselbalch B, et al. APMIS (2010) pmid: 20666740
406. Marisi G, et al. Sci Rep (2017) pmid: 28465540
407. Jubb AM, et al. J. Clin. Oncol. (2006) pmid: 16365183
408. Goede V, et al. Br. J. Cancer (2010) pmid: 20924372
409. Bruhn MA, et al. Int. J. Cancer (2014) pmid: 24374727
410. Escudier B, et al. Lancet (2007) pmid: 18156031
411. Yang JC, et al. N. Engl. J. Med. (2003) pmid: 12890841
412. Burstein HJ, et al. Clin. Cancer Res. (2008) pmid: 19047116
413. Jubb AM, et al. Clin. Cancer Res. (2011) pmid: 21224365
414. Miles D, et al. Eur. J. Cancer (2017) pmid: 27817944
415. Dowlati A, et al. Clin. Cancer Res. (2008) pmid: 18316562
416. Horn L, et al. J. Clin. Oncol. (2009) pmid: 19826110
417. Blakeley JO, et al. J. Clin. Oncol. (2016) pmid: 26976425
418. Horwitz E, et al. Cancer Discov (2014) pmid: 24687604
419. Oh CR, et al. BMC Cancer (2019) pmid: 30935424
420. Nature (2014) pmid: 25079552
421. Vlajnic T, et al. Mod. Pathol. (2011) pmid: 21743435
422. Du K, et al. Asian Pac. J. Cancer Prev. (2014) pmid: 25374209
423. Hong YM, et al. Genet. Mol. Res. (2014) pmid: 25158264
424. Park DJ, et al. Ann. Surg. Oncol. (2014) pmid: 24370903
425. Chang YT, et al. Pancreas (2008) pmid: 18665074
426. Georgiadou D, et al. Eur J Surg Oncol (2014) pmid: 24480377
427. Rahbari NN, et al. BMC Cancer (2011) pmid: 21729304
428. Goel HL, et al. Nat. Rev. Cancer (2013) pmid: 24263190
429. Jhaveri KL, et al. Ann. Oncol. (2019) pmid: 31504139
430. Li et al., 2018; ASCO Abstract 2502
431. Li BT, et al. Cancer Discov (2020) pmid: 32213539
432. Hotta K, et al. J Thorac Oncol (2018) pmid: 29313813
433. Krop IE, et al. Lancet Oncol. (2014) pmid: 24793816
434. Welslau M, et al. Cancer (2014) pmid: 24222194
435. Krop IE, et al. J. Clin. Oncol. (2012) pmid: 22649126
436. Burris HA, et al. J. Clin. Oncol. (2011) pmid: 21172893
437. Jhaveri et al., 2018; ASCO Abstract 100
438. Baselga J, et al. Clin. Cancer Res. (2016) pmid: 26920887
439. Perez EA, et al. J. Clin. Oncol. (2017) pmid: 28056202
440. Hurvitz SA, et al. J. Clin. Oncol. (2013) pmid: 23382472
441. von Minckwitz G, et al. N. Engl. J. Med. (2019) pmid: 30516102
442. Hurvitz SA, et al. J. Clin. Oncol. (2019) pmid: 31157583
443. Martin M, et al. Ann. Oncol. (2016) pmid: 27052654
444. Mondaca S, et al. JCO Precis Oncol (2019) pmid: 32923849
445. Talwar S, et al. Gynecol Oncol Case Rep (2012) pmid: 24371631
446. Choudhury NJ, et al. J. Clin. Oncol. (2016) pmid: 27044931
447. Kwak EL, et al. Cancer (2013) pmid: 23775486
448. Rimawi MF, et al. Clin. Breast Cancer (2015) pmid: 25537159
449. Gunzer K, et al. Springerplus (2016) pmid: 26835225
450. Janjigian YY, et al. J. Nucl. Med. (2013) pmid: 23578997
451. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
452. Katakami N, et al. J. Clin. Oncol. (2013) pmid: 23816963
453. Marshall J, et al. Future Oncol (2013) pmid: 23414476
454. Chu et al., 2013; ASCO Abstract 2523
455. Yap TA, et al. J. Clin. Oncol. (2010) pmid: 20679611
456. Eskens FA, et al. Br. J. Cancer (2008) pmid: 18026190
457. Jänne PA, et al. Clin. Cancer Res. (2011) pmid: 21220471
458. Kim HS, et al. Clin. Cancer Res. (2015) pmid: 25424851
459. Reckamp KL, et al. Cancer (2014) pmid: 24501009
460. Oh DY, et al. Gastric Cancer (2016) pmid: 26581547
461. Opsomer RJ, et al. Acta Urol Belg (1985) pmid: 2986437
462. Wu YL, et al. Lancet Oncol. (2017) pmid: 28958502
463. Necchi et al., 2018; ASCO Abstract 399
464. Necchi A, et al. BJU Int. (2018) pmid: 28921872
465. Kim HS, et al. Oncotarget (2015) pmid: 26462025
466. Cavalieri S, et al. Eur. J. Cancer (2018) pmid: 29734047

467. Sepúlveda-Sánchez JM, et al. Neuro-oncology (2017) pmid: 28575464
468. Tamura K, et al. Lancet Oncol. (2019) pmid: 31047803
469. Shitara K, et al. Lancet Oncol. (2019) pmid: 31047804
470. Tsurutani et al., 2018; IASLC WCLC Abstract OA02.07
471. Nakagawa et al., 2021; WCLC Abstract OA04.05
472. Yoshino et al., 2018; ESMO Abstract 563P
473. Siena et al., 2020; ASCO Abstract 4000
474. Smit et al., 2020; ASCO Abstract 9504
475. Ohba et al., 2020; ASCO Abstract 4006
476. Tsurutani J, et al. Cancer Discov (2020) pmid: 32213540
477. Bian L, et al. Tumour Biol. (2013) pmid: 23729232
478. Baselga J, et al. Lancet (2012) pmid: 22257673
479. Robidoux A, et al. Lancet Oncol. (2013) pmid: 24095300
480. Alba E, et al. Br. J. Cancer (2014) pmid: 24457911
481. Gelmon KA, et al. J. Clin. Oncol. (2015) pmid: 25779558
482. Satoh T, et al. J. Clin. Oncol. (2014) pmid: 24868024
483. Lorenzen S, et al. Eur. J. Cancer (2015) pmid: 25694417
484. Galsky MD, et al. Invest New Drugs (2012) pmid: 20857170
485. Hecht JR, et al. J. Clin. Oncol. (2016) pmid: 26628478
486. Burris HA, et al. Clin. Cancer Res. (2009) pmid: 19825948
487. Chu QS, et al. J. Clin. Oncol. (2007) pmid: 17704424
488. Chew HK, et al. Ann. Oncol. (2012) pmid: 21778300
489. Siegel-Lakhai WS, et al. Clin. Cancer Res. (2007) pmid: 17671135
490. Tan AR, et al. Br. J. Cancer (2014) pmid: 24800949
491. Rugo et al., 2019; ASCO Abstract 1000
492. Bang YJ, et al. Ann. Oncol. (2017) pmid: 28119295
493. Burris et al., 2013; ASCO Abstract 3004
494. Catenacci et al., 2019; ESMO Abstract 2812
495. Rugo et al., 2021; SABCS Abstract PD8-01
496. Li et al., 2020; WCLC Abstract FP14.15
497. Chan A, et al. Lancet Oncol. (2016) pmid: 26874901
498. Park JW, et al. N. Engl. J. Med. (2016) pmid: 27406346
499. Schwab CL, et al. Gynecol. Oncol. (2015) pmid: 26260909
500. Menderes G, et al. Med. Oncol. (2017) pmid: 28397106
501. Hu Z, et al. Oncotarget (2015) pmid: 26375550
502. Kavuri SM, et al. Cancer Discov (2015) pmid: 26243863
503. Bose R, et al. Cancer Discov (2013) pmid: 23220880
504. Burstein HJ, et al. J. Clin. Oncol. (2010) pmid: 20142587
505. Freedman RA, et al. J. Clin. Oncol. (2016) pmid: 26834058
506. Hyman et al., 2016; SABCS Abstract PD2-08
507. Saura C, et al. J. Clin. Oncol. (2014) pmid: 25287822
508. Awada A, et al. Ann. Oncol. (2013) pmid: 22967996
509. Martin M, et al. Eur. J. Cancer (2013) pmid: 23953056
510. Chow LW, et al. Br. J. Cancer (2013) pmid: 23632474
511. Awada A, et al. JAMA Oncol (2016) pmid: 27078022
512. Gandhi et al. 2017; WCLC Abstract MA04.02
513. Gandhi L, et al. J. Clin. Oncol. (2014) pmid: 24323026
514. D'Souza et al., 2019; SGO Abstract 18
515. Gianni L, et al. Lancet Oncol. (2014) pmid: 24657003
516. Morris PG, et al. Cancer (2013) pmid: 24037735
517. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
518. Wang K, et al. Clin. Cancer Res. (2016) pmid: 27334835
519. Nishikawa K, et al. Int. J. Cancer (2017) pmid: 27521503
520. de Azambuja E, et al. Lancet Oncol. (2014) pmid: 25130998
521. Haddad R, et al. Oral Oncol. (2003) pmid: 12907212
522. Limaye SA, et al. Oncologist (2013) pmid: 23429737
523. Safran H, et al. Int. J. Radiat. Oncol. Biol. Phys. (2007) pmid: 17097832
524. Hurvitz SA, et al. Lancet Oncol. (2018) pmid: 29175149
525. von Minckwitz G, et al. N. Engl. J. Med. (2017) pmid: 28581356
526. Swain SM, et al. Ann Oncol (2018) pmid: 29253081
527. Gianni L, et al. Lancet Oncol. (2016) pmid: 27179402
528. Shao Z, et al. JAMA Oncol (2020) pmid: 31647503
529. Hempstead RW, et al. Am J Dermatopathol (1985) pmid: 2932031