FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Breast invasive ductal carcinoma (IDC)

COUNTRY CODE
LT

REPORT DATE

ORDERED TEST #

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT

DISEASE Breast invasive ductal carcinoma (IDC)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

Blood Tumor Mutational Burden - 23 Muts/Mb
Microsatellite status - Cannot Be Determined
Tumor Fraction - 22%

Gene Alterations

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

BRCA1 complex rearrangement, E1660fs*17
CHEK2 splice site 320-18_323del22
CDH1 D221H
TP53 W91*

4 Therapies Approved in the EU
0 Therapies with Lack of Response
19 Clinical Trials

GENOMIC SIGNATURES	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Blood Tumor Mutational Burden - 23 Muts/Mb	None	None
10 Trials see p. 10		
Microsatellite status - Cannot Be Determined	Unable to determine Microsatellite status due to insufficient evidence of genomic instability.	
Tumor Fraction - 22%	Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.	

GENE ALTERATIONS		VAF %	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
BRCA1 -	complex rearrangement	19.4%	Olaparib [1]	Niraparib
	E1660fs*17	20.2%	Talazoparib [1]	Rucaparib
10 Trials see p. 12				
CHEK2 -	splice site 320-18_323del22	14.9%	None	None
10 Trials see p. 14				

[ ] *NCCN category*

Electronically signed by Douglas Lin, M.D. |
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

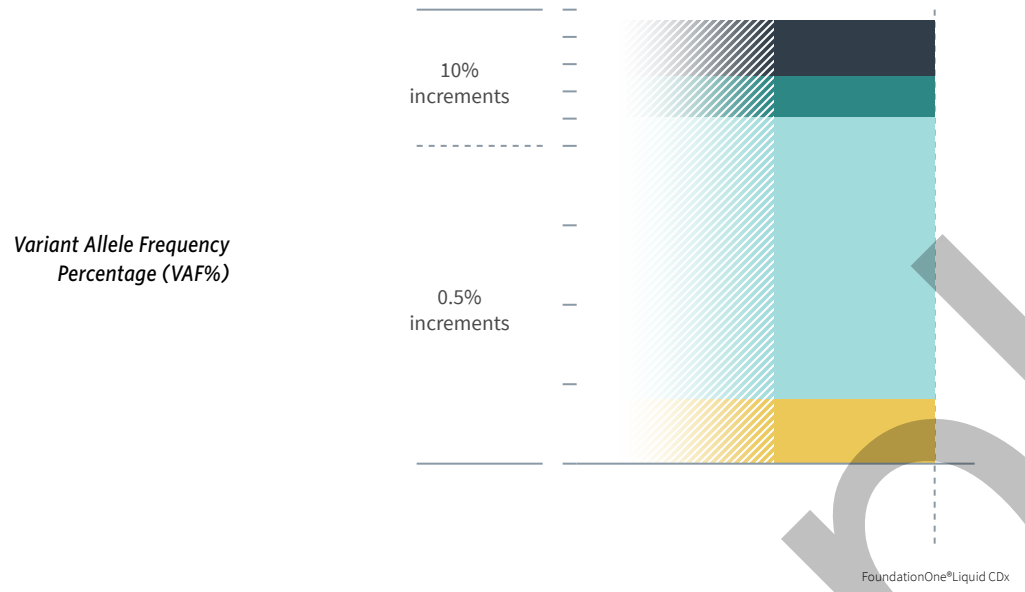
GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

CDH1 - D221H ..... p. 6 *TP53* - W91* ..... p. 7

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies 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/or exhaustive. Neither the therapies 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 through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally in some EU Member States but may not be available in your Member State: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, and Triptorelin. The Summary of Product Characteristics of EU-approved therapies are available at https://www.ema.europa.eu/en/medicines. The information available on EMA's website is updated in regular intervals but may not reflect the current status at any time. In the appropriate clinical context, germline testing of *APC*, *BRCA1*, *BRCA2*, *BRIP1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		VAF%
Blood Tumor Mutational Burden		23 Muts/Mb
Microsatellite status		Cannot Be Determined
Tumor Fraction		22%
BRCA1	● E1660fs*17	20.2%
	complex rearrangement	19.4%
CHEK2	● splice site 320-18_323del22	14.9%
CDH1	● D221H	0.41%
TP53	● W91*	12.4%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

GENOMIC SIGNATURE

Blood Tumor Mutational Burden

RESULT
23 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2020)[5-7]. Published data investigating the prognostic implications of bTMB levels in breast cancer are limited (PubMed, Jul 2020). In a study of 3,969 patients with breast cancer, median TMB was significantly higher in hormone receptor (HR)-negative and HER2-negative tumors than HR-positive or HER2-positive tumors; hypermutation was more frequently observed in metastatic tumors than in primary tumors[8]. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb[9]. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (>mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data[10].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[11-12] and cigarette smoke in lung cancer[13-14], treatment with temozolomide-based chemotherapy in glioma[15-16], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17-21], and microsatellite instability (MSI)[17,20-21]. This sample harbors a bTMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3].

GENOMIC SIGNATURE

Tumor Fraction

RESULT
22%

POTENTIAL TREATMENT STRATEGIES

There are currently no targeted approaches to address specific tumor fraction levels; however, on the basis of emerging clinical evidence, changes in tumor fraction may correlate with treatment duration and clinical response and may be a useful indicator for cancer management[22-27].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels has been reported in a variety of tumor types, with higher tumor fraction levels reported in patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[28]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[29], Ewing sarcoma and osteosarcoma[30], prostate cancer[25], breast cancer[31], leiomyosarcoma[32], esophageal cancer[33], colorectal cancer[34], and gastrointestinal cancer[35].

FINDING SUMMARY

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. Tumor cells in most advanced solid tumor types may shed ctDNA through the process of apoptosis or necrosis[28,36-37]. Tumor fraction has been proposed to be a noninvasive surrogate biomarker of disease burden dynamics. Elevated tumor fraction levels have been associated with inferior prognosis, and therapeutic resistance to treatment in certain tumor types[25,31,34], whereas reduced levels have been correlated with tumor shrinkage and improved clinical outcome in patients with non-small cell lung cancer, urothelial cancer, and melanoma treated with immunotherapy[23,27,38]. The tumor fraction estimate, shown here, is computationally derived from observed aneuploid instability in the sample.

GENE
BRCA1

ALTERATION
complex rearrangement, E1660fs*17

TRANSCRIPT ID
NM_007294

CODING SEQUENCE EFFECT
4978_4981GAAG>AAA

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[39-56] or to ATR inhibitors[57-58]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[40,45,48,55-56] and for patients with platinum-resistant or -refractory disease[39,44,51,54]. In a Phase 1 monotherapy trial of the WEE1 inhibitor adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression[59]. The PARP inhibitors talazoparib and olaparib have shown significant clinical efficacy for patients with HER2-negative advanced breast cancer and a germline BRCA mutation in Phase 3 studies[42,60]. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and either platinum-refractory peritoneal or ovarian carcinoma experienced a PR or prolonged SD[61]. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan[57]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[62]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[63]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[64], ovarian carcinoma[65], and TNBC[66] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin[67-76].

FREQUENCY & PROGNOSIS

In the Breast Invasive Carcinoma TCGA datasets, BRCA1 mutations have been reported in 2-4% of cases[77-78]. A study of patients with sporadic breast cancer identified BRCA1 mutation in 9.3% (4/43) of cases[79]. BRCA1 mutations account for approximately 4.6-7% of breast cancer cases in patients with a family history of breast cancer[80-81]. A study reported decreased nuclear BRCA1 protein expression in breast carcinoma samples (n=22), as compared to normal breast tissue[82]. For BRCA1 and BRCA2 mutation carriers, the risk of developing breast cancer by age 70 has been found to be approximately 57-65% and 39-49%, respectively, and a lifetime risk of up to 90% has also been reported[83-85].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[86]. BRCA1 alterations that disrupt the ring-type zinc finger domain (amino acids 24-65) or BRCT domains (aa 1642-1855), such as observed here, are predicted to result in a loss of function[87-89]. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[90-91], and the lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[92]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[93]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[92,94-99]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

GENE
CHEK2

ALTERATION
splice site 320-18_323del22

TRANSCRIPT ID
NM_007194

CODING SEQUENCE EFFECT
320-18_323del22

POTENTIAL TREATMENT STRATEGIES

Limited clinical data indicate that CHEK2 inactivation may predict sensitivity to PARP inhibitors. Patients with CHEK2-altered prostate cancer have experienced clinical responses to PARP inhibitors[40,100-101]. Clinical benefit has been observed for patients with ovarian[45] and testicular[102] cancers treated with PARP inhibitors. One study of patients with breast cancer reported that carriers of the CHEK2 H371Y mutation have a higher likelihood of response to neoadjuvant chemotherapy[103], whereas another study found that CHEK2 mutation carriers have a lower frequency of objective clinical responses to neoadjuvant therapy[104]. A third study reported that the CHEK2 1100delC mutation is not associated with differential efficacy of chemotherapy and endocrine therapy in patients with metastatic breast cancer[105].

FREQUENCY & PROGNOSIS

CHEK2 mutations have been reported in 4.4% of glioblastoma (GBM) samples and in carcinomas of the urinary tract (3%), ovary (3%), endometrium (1.2%), and large intestine (1.9%), as well as in a variety of solid and hematologic cancer types at low frequency (COSMIC, 2020). Some CHEK2 alterations, including T367fs*15 (also known as 1100delC) and S428F, have been reported as germline variants in low penetrance susceptibility to certain cancers, including breast and ovarian[106-110]. Germline mutations in CHEK2 have been associated with uterine serous carcinoma cases and with an increased risk of breast, colorectal, and thyroid cancer, as well as non-Hodgkin lymphoma[111-118]. In breast cancer, certain CHEK2 mutations are associated with higher grade and larger tumors as well as bilateral disease[119]. A study reported that a polymorphism in CHEK2 was associated with worse survival of patients with GBM, but this association lost significance after adjusting for other prognostic factors[120-121]. Another study in prostate cancer reported that CHEK2 expression is decreased in higher grade tumors and that CHEK2 is a tumor suppressor that decreases the growth of prostate cancer cells and regulates androgen receptor signaling[122]. 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[123-128]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[127,129-130]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

CHEK2 encodes the protein checkpoint kinase 2, a serine/threonine kinase that plays an important role in the DNA-damage response; it is a putative tumor suppressor[131-134]. CHEK2 alterations that disrupt or remove the SQ/TQ cluster domain (SCD; amino acids 19–69), forkhead-associated domain (FHA; amino acids 115–175), and/or the kinase domain (amino acids 220–486) are predicted to be inactivating[106,135-144].

GENE
CDH1

ALTERATION
D221H

TRANSCRIPT ID
NM_004360

CODING SEQUENCE EFFECT
661G>C

POTENTIAL TREATMENT STRATEGIES

There are no available therapies to compensate directly for CDH1 mutation or loss or E-cadherin inactivation.

FREQUENCY & PROGNOSIS

In the TCGA datasets, CDH1 mutation has been most frequently observed in breast invasive carcinoma (13.4%)[77], stomach adenocarcinoma (10%)[145], and endometrial carcinoma (5.2%)[17]. Truncating somatic alterations in the CDH1 gene have also been reported in 84% (26/31) of plasmacytoid bladder cancer cases but not in any cases with non-plasmacytoid histology (0/56)[146]. CDH1 homozygous deletion has been reported at the highest incidence in prostate adenocarcinoma (4.5%)[147] and ovarian serous cystadenocarcinoma (2.5%)[148]. Loss of heterozygosity (LOH) of the CDH1 locus was found in gallbladder cancer[149], gastric cancer[150], endometrial carcinoma[151], and meningioma[152]. CDH1 inactivation, through mutations, reduced or lost expression, or promoter hypermethylation, has been associated with more advanced tumor stage, poor prognosis or reduced overall survival in a number of solid tumors, including breast cancer[153-155], endometrial cancer[156-157], gastric cancer[150], non-small cell lung carcinoma[158], ovarian carcinoma[159], pancreatic adenocarcinoma[160], colon cancer[161-162], cervical squamous cell carcinoma[163], cholangiocarcinoma[164-165], head and neck cancer squamous cell carcinoma (HNSCC)[166-167], and early stage esophageal squamous cell carcinoma[168].

FINDING SUMMARY

CDH1 encodes the transmembrane protein E-cadherin, a tumor suppressor that plays an important role in epithelial cell-cell adhesion and tissue morphogenesis[169]. Loss of E-cadherin expression leads to decreased cellular adhesion and results in cell migration and cancer metastasis[170-173]. CDH1 alterations that remove or disrupt critical domains of E-cadherin, including the extracellular cadherin (amino acids 155-709), juxtamembrane (amino acids 734-783), and catenin binding (amino acids 811-882) domains, are predicted to be inactivating[174-178]. Germline CDH1 mutations, including truncations, splice site mutations, and missense mutations, have been reported in patients with hereditary diffuse gastric cancer[179] and infiltrating lobular breast cancer[180-181].

GENE
TP53

ALTERATION
W91*

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
272G>A

POTENTIAL TREATMENT STRATEGIES

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[182-185], or p53 gene therapy and immunotherapeutics such as SGT-53[186-190] and ALT-801[191]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[192]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[193]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[194]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[195]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[196]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[197]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[190]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[198]. 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[199-200]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[201-202]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in breast cancer; mutations in this gene have been identified in 27-37% of breast carcinoma samples[77,203-207]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[205,208-209]. TP53 mutation is also implicated in breast cancer susceptibility, as TP53 mutation carriers have an 18-60 fold increased risk for early onset breast cancer[108,210-211]. Variants seen in this gene have been reported to occur in clonal hematopoiesis of indeterminate potential (CHIP), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[123-128]. CHIP is associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[123-124]. Clinical management of patients with CHIP may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[212]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CHIP[127,129-130]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CHIP.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[213]. Alterations that have been functionally characterized as inactivating and/or result in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, are thought to dysregulate the transactivation of p53-dependent genes and are predicted to promote tumorigenesis[214-218]. One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with Li-Fraumeni syndrome (ClinVar, Mar 2020)[219]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[220-222], including sarcomas[223-224]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[225] to 1:20,000[224]. 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[226]. In the appropriate clinical context, germline testing of TP53 is recommended.

Olaparib

Assay findings association

BRCA1
complex rearrangement, E1660fs*17

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is available in the EU as a monotherapy to treat patients with BRCA-mutated and/or platinum-sensitive high-grade serous epithelial ovarian, Fallopian tube, or peritoneal cancer. It is also approved as a monotherapy for patients with HER2-negative germline BRCA-mutated breast cancer, and germline BRCA-mutated pancreatic adenocarcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in ovarian cancer[49-53] as well as strong clinical evidence in multiple other cancer types[39-41,49,52,56,227] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

SUPPORTING DATA

A Phase 3 study of olaparib monotherapy for patients with germline BRCA1/2 (gBRCA1/2) mutated HER2-negative metastatic breast cancer reported a significantly longer median PFS (7.0 vs. 4.2 months, HR=0.58) and a higher ORR (59.9% vs. 28.8%) compared to standard chemotherapy[42]. Phase 2 studies of olaparib monotherapy for patients with BRCA-mutated advanced breast cancer reported median PFS of 3.7 to 5.7 months and high clinical benefit rates (60%–85%)[39,41,52] . The Phase 2 MEDIOLA trial of olaparib with durvalumab for patients with gBRCA1/2-mutated metastatic breast cancer reported an ORR of 63.3% and a median PFS of 8.2 months[228]. A Phase 1 trial of olaparib with the PI3K inhibitor buparlisib reported an ORR of 33.3% (4/12) for patients with gBRCA1/2-mutated breast cancer[229]. A Phase 1 trial of olaparib plus carboplatin for patients with gBRCA1/2-mutated breast cancer reported an ORR of 87.5% (7/8)[230]. Patients with HER2-negative metastatic breast cancer and germline BRCA mutation achieved significantly longer median PFS (7.0 vs. 4.2 months, HR=0.58) and a higher ORR (59.9% vs. 28.8%) on olaparib compared with standard chemotherapy (capecitabine, eribulin, or vinorelbine) in a Phase 3 study[42]. Phase 1 trials of olaparib plus chemotherapy for patients with triple-negative breast cancer (TNBC) reported ORRs of 37% to 38%[231-232] . A small Phase 1 trial reported a 20% ORR (1/5) for patients with breast cancer and wild-type germline BRCA status following combination treatment with olaparib and buparlisib[229]. A Phase 2 study comparing durvalumab in combination with olaparib and paclitaxel (DOP) to chemotherapy alone reported pathologic complete response (pCR) for 37% versus 22% of patients with HER2-negative breast cancer, 47% versus 27% of patients with TNBC, and 28% versus 14% of patients with HR-positive HER2-negative breast cancer[233].

Talazoparib

Assay findings association

BRCA1
complex rearrangement, E1660fs*17

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is available in the EU as monotherapy to treat patients with HER2-negative locally advanced or metastatic breast cancer with germline BRCA mutations, who have been previously treated with, or are not considered candidates for, available therapies. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data in breast cancer[60,234-235] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[236-239] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

In the Phase 3 EMBRACA trial, patients with HER2-negative advanced breast cancer and germline BRCA mutations achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)[60,235] . Clinical benefit with talazoparib was observed for patients with triple-negative breast cancer, hormone-receptor positive breast cancer, and those with CNS metastases[60]. Additionally, interim OS analysis demonstrated a trend toward longer survival with talazoparib compared with chemotherapy (22.3 vs. 19.5 months, HR=0.76)[60]. The efficacy of single-agent talazoparib against BRCA-mutated advanced breast cancer was also demonstrated in earlier-phase studies, which reported ORRs of 21% to 50%[234,237]. As neoadjuvant treatment for BRCA-mutated, HER2-negative breast cancer, talazoparib led to a pathologic complete response (pCR) in 53% (10/19) of patients[240]. In the Phase 2 I-SPY2 trial, talazoparib with synergy-dosed irinotecan (TI) for the treatment of patients with early stage, high-risk HER2-negative breast cancer reported fewer Grade 3/4 adverse events compared with the chemotherapy control arm (paclitaxel with doxorubicin and cyclophosphamide [AC]), although a similar pCR rate was observed[241]. Notably, 6/10 patients with germline BRCA mutations achieved a pCR with TI treatment[241]. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, patients with HER2-negative advanced breast cancer experienced an ORR of 31% (4/13 PRs), with responses observed for 3 patients with germline PALB2 mutations and 1 patient with germline CHEK2 and FANCA mutations as well as somatic PTEN mutation; 3 additional patients with germline PALB2 or somatic ATR or PTEN alterations had SD ≥ 6 months[102].

Niraparib

Assay findings association

BRCA1
complex rearrangement, E1660fs*17

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is available in the EU for the maintenance treatment of patients with relapsed high grade serous epithelial ovarian, Fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian and breast cancers[43-44,242] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with solid tumors, 2/4 patients with breast cancer and BRCA1/2 mutations experienced a PR[44]. An open label study combining PD-1 inhibitor pembrolizumab with niraparib for patients with TNBC reported an ORR of 21% and DCR of 49%; ORR and DCR for patients with BRCA alterations were 47% and 80%, respectively, with 2 CRs, 5 PRs, 5 SDs and mPFS of 8.3 months[243].

Rucaparib

Assay findings association

BRCA1
complex rearrangement, E1660fs*17

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is available in the EU to treat patients with platinum-sensitive relapsed or progressive BRCA mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more prior lines of platinum-based chemotherapy and who are unable to tolerate further platinum-based chemotherapy. Rucaparib is also available for the maintenance treatment of patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence in ovarian cancer[45-46,193] , as well as clinical data in other cancer types[46,244-245] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and BRCA1/2 mutations, no objective responses were reported in breast cancer patients[46]. However, 39% (9/23) of evaluable patients with breast cancer achieved stable disease lasting 12 weeks or more[46]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 1 patient with breast cancer and a BRCA mutation given the recommended Phase 2 dose reported an objective response[244].

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. Therapies listed in this report may not be complete and/or exhaustive. In particular, the listed therapies are limited to EMA or nationally approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be EMA or nationally approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by EMA or an EU Member State nationally. There may also be other treatment modalities available than pharmaceutical drug products.

CLINICAL TRIALS

IMPORTANT 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. There may also be compassionate use or early access programs available, which are not listed in this report. 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 are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. 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. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENOMIC SIGNATURE

Blood Tumor Mutational Burden

RATIONALE
Increased tumor mutational burden may predict response to anti-PD-1 or anti-PD-L1 immune checkpoint inhibitors.

RESULT
23 Muts/Mb

NCT04177108

PHASE 3

A Study Of Ipatasertib in Combination With Atezolizumab and Paclitaxel as a Treatment for Participants With Locally Advanced or Metastatic Triple-Negative Breast Cancer.

TARGETS
PD-L1, AKTs

LOCATIONS: Bialystok (Poland), Warszawa (Poland), Lublin (Poland), Łódź (Poland), Poznan (Poland), Kraków (Poland), Gliwice (Poland), Ivano-Frankivsk (Ukraine), Uzhhorod (Ukraine), Chernigiv (Ukraine)

NCT03725059

PHASE 3

Study of Pembrolizumab (MK-3475) Versus Placebo in Combination With Neoadjuvant Chemotherapy & Adjuvant Endocrine Therapy in the Treatment of Early-Stage Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (ER+/HER2-) Breast Cancer (MK-3475-756/ KEYNOTE-756)

TARGETS
PD-1

LOCATIONS: Bialystok (Poland), Ostroleka (Poland), Wieliszew (Poland), Warszawa (Poland), Gdansk (Poland), Gdynia (Poland), Bydgoszcz (Poland), Lodz (Poland), Gliwice (Poland), Wrocław (Poland)

NCT03498716

PHASE 3

A Study Comparing Atezolizumab (Anti PD-L1 Antibody) In Combination With Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone In Patients With Operable Triple-Negative Breast Cancer

TARGETS
PD-L1

LOCATIONS: Warszawa (Poland), Gdańsk (Poland), Łódź (Poland), Lutsk (Ukraine), Poznan (Poland), Lviv (Ukraine), Uzhgorod (Ukraine), Chernigiv (Ukraine), Olomouc (Czechia), Zlin (Czechia)

NCT04109066

PHASE 3

Study of Nivolumab Versus Placebo in Participants With High-Risk Breast Cancer

TARGETS
PD-1

LOCATIONS: Warszawa (Poland), Koszalin (Poland), Berlin (Germany), Kobenhavn O (Denmark), Helsinki (Finland), Dresden (Germany), Rostock (Germany), Wien (Austria), Tampere (Finland), Salzburg (Austria)

NCT03371017

PHASE 3

A Study of the Efficacy and Safety of Atezolizumab Plus Chemotherapy for Patients With Early Relapsing Recurrent Triple-Negative Breast Cancer

TARGETS
PD-L1

LOCATIONS: Warszawa (Poland), Turku (Finland), Halle (Germany), Saint-Petersburg (Russian Federation), Tampere (Finland), Moscow (Russian Federation), Sremska Kamenica (Serbia), München (Germany), Belgrade (Serbia), Frankfurt (Germany)

NCT04191135

PHASE 2/3

Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction With First-Line Chemotherapy Plus Pembrolizumab in Triple Negative Breast Cancer (TNBC) (MK-7339-009/KEYLYNK-009)

TARGETS
PD-1, PARP

LOCATIONS: Warszawa (Poland), Gdynia (Poland), Pleszew (Poland), Krakow (Poland), Gliwice (Poland), Swidnica (Poland), Zhytomyr (Ukraine), Ivano-Frankivsk (Ukraine), Kyiv (Ukraine), Dresden (Germany)

NCT04181788

PHASE 2

Sasanlimab (PF-06801591, PD-1 Inhibitor) in Participants With Advanced Malignancies

TARGETS
PD-1

LOCATIONS: Kaliningrad (Russian Federation), Ivano-Frankivsk (Ukraine), Uzhgorod (Ukraine), Kyiv (Ukraine), Khodosivka (Ukraine), Pushkin (Russian Federation), Saint-Petersburg (Russian Federation), Saint Petersburg (Russian Federation), Sumy (Ukraine), Yaroslavl (Russian Federation)

NCT03742102

PHASE 1/2

A Study of Novel Anti-cancer Agents in Patients With Metastatic Triple Negative Breast Cancer.

TARGETS
PD-L1, STAT3, CD73, AKTs

LOCATIONS: Warszawa (Poland), Gdańsk (Poland), Lublin (Poland), Łódź (Poland), Kraków (Poland), London (United Kingdom), Manchester (United Kingdom), Greenfield Park (Canada), Pennsylvania, London (Canada)

NCT03179436

PHASE 1/2

Safety, Pharmacokinetics (PK), and Efficacy of MK-1308 in Combination With Pembrolizumab in Advanced Solid Tumors (MK-1308-001)

TARGETS
CTLA-4, PD-1

LOCATIONS: Warszawa (Poland), Poznan (Poland), Lund (Sweden), Padova (Italy), Lille (France), Siena (Italy), Villejuif (France), Pierre Benite (France), Marseille (France), Athens (Greece)

NCT03668119

PHASE 2

A Study of Nivolumab Combined With Ipilimumab and Nivolumab Alone in Patients With Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)

TARGETS
PD-1, CTLA-4

LOCATIONS: Warszawa (Poland), Gdansk (Poland), Copenhagen (Denmark), Herlev (Denmark), Amsterdam (Netherlands), Rotterdam (Netherlands), Leuven (Belgium), Bruxelles (Belgium), Brussels (Belgium), Milano (Italy)

GENE
BRCA1

RATIONALE
BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors or ATR inhibitors.

ALTERATION
complex rearrangement, E1660fs*17

NCT04191135

PHASE 2/3

Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction With First-Line Chemotherapy Plus Pembrolizumab in Triple Negative Breast Cancer (TNBC) (MK-7339-009/KEYLYNK-009)

TARGETS
PD-1, PARP

LOCATIONS: Warszawa (Poland), Gdynia (Poland), Pleszew (Poland), Krakow (Poland), Gliwice (Poland), Swidnica (Poland), Zhytomyr (Ukraine), Ivano-Frankivsk (Ukraine), Kyiv (Ukraine), Dresden (Germany)

NCT03330847

PHASE 2

To Assess Safety and Efficacy of Agents Targeting DNA Damage Repair With Olaparib Versus Olaparib Monotherapy.

TARGETS
ATR, WEE1, PARP

LOCATIONS: Olsztyn (Poland), Warszawa (Poland), Lodz (Poland), Poznań (Poland), Kraków (Poland), Wroclaw (Poland), Grzepnica (Poland), Olomouc (Czechia), Brno (Czechia), Praha 10 (Czechia)

NCT03562832

PHASE 2

Investigation of Anti-tumour Effect and Tolerability of the PARP Inhibitor 2X-121 in Patients With Metastatic Breast Cancer Selected by the 2X-121 DRP

TARGETS
PARP, Tankyrase

LOCATIONS: Herlev (Denmark)

NCT02810743

PHASE 3

Substantially Improving the Cure Rate of High-risk BRCA1-like Breast Cancer

TARGETS
PARP

LOCATIONS: Groningen (Netherlands), Enschede (Netherlands), NIjmegen (Netherlands), Utrecht (Netherlands), Amsterdam (Netherlands), Maastricht (Netherlands), Leiden (Netherlands), Rotterdam (Netherlands)

NCT02826512

PHASE 2

A Feasibility Study of Niraparib for Advanced, BRCA1-like, HER2-negative Breast Cancer Patients

TARGETS
PARP

LOCATIONS: Amsterdam (Netherlands)

NCT03840200

PHASE 1/2

A Study Evaluating the Safety, Pharmacokinetics and Efficacy of Ipatasertib Administered in Combination With Rucaparib in Participants With Advanced Breast, Ovarian Cancer, and Prostate Cancer.

TARGETS
PARP, AKTs

LOCATIONS: Padova (Italy), Milano (Italy), Terni (Italy), Roma (Italy), Barcelona (Spain), Pamplona (Spain), Malaga (Spain), New Jersey, Pennsylvania, Seoul (Korea, Republic of)

CLINICAL TRIALS

NCT03901469

PHASE 2

A Study of ZEN003694 and Talazoparib in Patients With Triple Negative Breast Cancer

TARGETS
BRD2, BRD3, BRD4, BRDT, PARP

LOCATIONS: Leuven (Belgium), Brussels (Belgium), Barcelona (Spain), Madrid (Spain), New York, Pennsylvania, Tennessee, Kansas, Texas, Arizona

NCT03150576

PHASE 2/3

Platinum and Polyadenosine 5'Diphosphoribose Polymerisation (PARP) Inhibitor for Neoadjuvant Treatment of Triple Negative Breast Cancer (TNBC) and/or Germline BRCA (gBRCA) Positive Breast Cancer

TARGETS
PARP

LOCATIONS: Cambridge (United Kingdom)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Villejuif (France), London (United Kingdom), Sutton (United Kingdom), Withington (United Kingdom), Saint Herblain (France), Massachusetts, New York, Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), California

NCT03127215

PHASE 2

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

TARGETS
FUS-DDIT3, PARP

LOCATIONS: Heidelberg (Germany)

GENE
CHEK2

ALTERATION
splice site 320-18_323del22

RATIONALE
On the basis of clinical evidence in prostate and other solid cancers, CHEK2 loss or inactivation may confer sensitivity to PARP inhibitors.

NCT04191135

PHASE 2/3

Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction With First-Line Chemotherapy Plus Pembrolizumab in Triple Negative Breast Cancer (TNBC) (MK-7339-009/KEYLYNK-009)

TARGETS
PD-1, PARP

LOCATIONS: Warszawa (Poland), Gdynia (Poland), Pleszew (Poland), Krakow (Poland), Gliwice (Poland), Swidnica (Poland), Zhytomyr (Ukraine), Ivano-Frankivsk (Ukraine), Kyiv (Ukraine), Dresden (Germany)

NCT03330847

PHASE 2

To Assess Safety and Efficacy of Agents Targeting DNA Damage Repair With Olaparib Versus Olaparib Monotherapy.

TARGETS
ATR, WEE1, PARP

LOCATIONS: Olsztyn (Poland), Warszawa (Poland), Lodz (Poland), Poznań (Poland), Kraków (Poland), Wroclaw (Poland), Grzepnica (Poland), Olomouc (Czechia), Brno (Czechia), Praha 10 (Czechia)

NCT03562832

PHASE 2

Investigation of Anti-tumour Effect and Tolerability of the PARP Inhibitor 2X-121 in Patients With Metastatic Breast Cancer Selected by the 2X-121 DRP

TARGETS
PARP, Tankyrase

LOCATIONS: Herlev (Denmark)

NCT02810743

PHASE 3

Substantially Improving the Cure Rate of High-risk BRCA1-like Breast Cancer

TARGETS
PARP

LOCATIONS: Groningen (Netherlands), Enschede (Netherlands), NIjmegen (Netherlands), Utrecht (Netherlands), Amsterdam (Netherlands), Maastricht (Netherlands), Leiden (Netherlands), Rotterdam (Netherlands)

NCT02826512

PHASE 2

A Feasibility Study of Niraparib for Advanced, BRCA1-like, HER2-negative Breast Cancer Patients

TARGETS
PARP

LOCATIONS: Amsterdam (Netherlands)

NCT03840200

PHASE 1/2

A Study Evaluating the Safety, Pharmacokinetics and Efficacy of Ipatasertib Administered in Combination With Rucaparib in Participants With Advanced Breast, Ovarian Cancer, and Prostate Cancer.

TARGETS
PARP, AKTs

LOCATIONS: Padova (Italy), Milano (Italy), Terni (Italy), Roma (Italy), Barcelona (Spain), Pamplona (Spain), Malaga (Spain), New Jersey, Pennsylvania, Seoul (Korea, Republic of)

CLINICAL TRIALS

NCT03901469

PHASE 2

A Study of ZEN003694 and Talazoparib in Patients With Triple Negative Breast Cancer

TARGETS
BRD2, BRD3, BRD4, BRDT, PARP

LOCATIONS: Leuven (Belgium), Brussels (Belgium), Barcelona (Spain), Madrid (Spain), New York, Pennsylvania, Tennessee, Kansas, Texas, Arizona

NCT03150576

PHASE 2/3

Platinum and Polyadenosine 5'Diphosphoribose Polymerisation (PARP) Inhibitor for Neoadjuvant Treatment of Triple Negative Breast Cancer (TNBC) and/or Germline BRCA (gBRCA) Positive Breast Cancer

TARGETS
PARP

LOCATIONS: Cambridge (United Kingdom)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Villejuif (France), London (United Kingdom), Sutton (United Kingdom), Withington (United Kingdom), Saint Herblain (France), Massachusetts, New York, Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), California

NCT03127215

PHASE 2

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

TARGETS
FUS-DDIT3, PARP

LOCATIONS: Heidelberg (Germany)

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.

ARID1A
D1050N

ATM
S333F

BCL6
rearrangement

BRCA1
D1574N, E384D, H1686Y and L1605F

CUL4A
V174I

DIS3
C36R

FGF4
*207Wext*36

IRF2
I175F

KDM6A
Y116N

MPL
S258I

NF1
M840I

SETD2
C2485F and E2034K

TIPARP
L147F

TP53
D42N

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, **Intron 7**	*KMT2D* (MLL2)
KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *); 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11A*	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*
MTAP	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*
NF1	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**
NRAS **Exons 2, 3**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**
PDGFRB **Exons 12-21, 23**	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*WTI*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

FoundationOne Liquid 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 IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid 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.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx 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 malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also detects select genomic rearrangements, select copy number alterations, tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

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. *Note:* The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

RANKING OF ALTERATIONS AND THERAPIES

Genomic Signatures and Gene Alterations
Therapies are ranked based on the following criteria: Therapies approved in the EU in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies approved in the EU in another tumor type (ranked alphabetically within each NCCN category).

Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation in the patient's tumor.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from observed aneuploid instability in the sample.
9. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Genomic signatures and gene alterations 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 genomic signature or gene alteration. 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. 2020. All rights reserved. To view the most recent and complete version of the guideline, 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.

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 Liquid CDx.

TREATMENT DECISIONS ARE THE 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 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, 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

PDF Service Version 2.16.1

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
6. Gao J, et al. Sci Signal (2013) pmid: 23550210
7. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
8. Barroso-Sousa R, et al. Ann. Oncol. (2020) pmid: 32067680
9. Chumsri S, et al. J Natl Compr Canc Netw (2020) pmid: 32380464
10. Haricharan S, et al. Breast Cancer Res. Treat. (2014) pmid: 24839032
11. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
12. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
13. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
14. Rizvi NA, et al. Science (2015) pmid: 25765070
15. Johnson BE, et al. Science (2014) pmid: 24336570
16. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
17. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
18. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
19. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
20. Nature (2012) pmid: 22810696
21. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
22. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
23. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
24. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
25. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
26. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
27. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
28. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
29. Lapin M, et al. J Transl Med (2018) pmid: 30400802
30. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
31. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
32. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
33. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
34. Fan G, et al. PLoS ONE (2017) pmid: 28187169
35. Vu et al., 2020; DOI: 10.1200/PO.19.00204
36. Snyder MW, et al. Cell (2016) pmid: 26771485
37. Stroun M, et al. Clin. Chim. Acta (2001) pmid: 11694251
38. Lipson EJ, et al. J Immunother Cancer (2014) pmid: 25516806
39. Kaufman B, et al. J. Clin. Oncol. (2015) pmid: 25366685
40. Mateo J, et al. N. Engl. J. Med. (2015) pmid: 26510020
41. Tutt A, et al. Lancet (2010) pmid: 20609467
42. Robson M, et al. N. Engl. J. Med. (2017) pmid: 28578601
43. Mirza MR, et al. N. Engl. J. Med. (2016) pmid: 27717299
44. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
45. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
46. Drew Y, et al. Br. J. Cancer (2016) pmid: 27002934
47. Pujade-Lauraine E, et al. Lancet Oncol. (2017) pmid: 28754483
48. Ledermann JA, et al. Lancet Oncol. (2016) pmid: 27617661
49. Fong PC, et al. N. Engl. J. Med. (2009) pmid: 19553641
50. Audeh MW, et al. Lancet (2010) pmid: 20609468
51. Fong PC, et al. J. Clin. Oncol. (2010) pmid: 20406929
52. Gelmon KA, et al. Lancet Oncol. (2011) pmid: 21862407
53. Kaye SB, et al. J. Clin. Oncol. (2012) pmid: 22203755
54. Domchek SM, et al. Gynecol. Oncol. (2016) pmid: 26723501
55. Moore K, et al. N. Engl. J. Med. (2018) pmid: 30345884
56. Golan T, et al. N. Engl. J. Med. (2019) pmid: 31157963
57. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
58. Saito YD, et al. Cancer Treat Res Commun (2018) pmid: 31299005
59. Do K, et al. J. Clin. Oncol. (2015) pmid: 25964244
60. Litton JK, et al. N. Engl. J. Med. (2018) pmid: 30110579
61. De Bono et al., 2019; ASCO Abstract 3007
62. O'Carrigan et al., 2016; ASCO Abstract 2504
63. Yap et al., 2016; AACR-NCI-EORTC Abstract 1LBA
64. Pouliot GP, et al. PLoS ONE (2019) pmid: 31721781
65. Kim H, et al. Clin. Cancer Res. (2017) pmid: 27993965
66. Jin J, et al. Neoplasia (2018) pmid: 29605721
67. Cruz C, et al. J. Clin. Oncol. (2018) pmid: 30240327
68. Poveda A, et al. Ann. Oncol. (2017) pmid: 28368437
69. García MJ, et al. Mol. Cancer Ther. (2013) pmid: 23364677
70. Schöffski P, et al. Eur. J. Cancer (2011) pmid: 21376569
71. Italiano A, et al. Cancer (2011) pmid: 21287534
72. Laroche-Clary A, et al. Br. J. Cancer (2015) pmid: 25602962
73. Ghouadni A, et al. Breast (2017) pmid: 28467918
74. Monk BJ, et al. Ann. Oncol. (2015) pmid: 25722380
75. Monk BJ, et al. Gynecol. Oncol. (2020) pmid: 31924332
76. Yasui H, et al. J Chemother (2016) pmid: 27077926
77. Nature (2012) pmid: 23000897
78. Ciriello G, et al. Cell (2015) pmid: 26451490
79. Al-Moundhri MS, et al. Gulf J Oncolog (2013) pmid: 23996866
80. Ghadirian P, et al. Clin. Genet. (2014) pmid: 23621881
81. Huzarski T, et al. J. Clin. Oncol. (2013) pmid: 23940229
82. Tulchin N, et al. Cancer Cell Int. (2013) pmid: 23855721
83. Gage M, et al. J Surg Oncol (2012) pmid: 22441895
84. Melchor L, et al. Hum. Genet. (2013) pmid: 23552954
85. Oncol Nurs Forum (2013) pmid: 23615136
86. O'Donovan PJ, et al. Carcinogenesis (2010) pmid: 20400477
87. Nelson AC, et al. Radiat. Res. (2010) pmid: 20681793
88. Silver DP, et al. Cancer Discov (2012) pmid: 22843421
89. Ludwig T, et al. Genes Dev. (2001) pmid: 11358863
90. Miki Y, et al. Science (1994) pmid: 7545954
91. Wooster R, et al. Nature () pmid: 8524414
92. Ford D, et al. Lancet (1994) pmid: 7907678
93. MedGenMed (2005) pmid: 16369438
94. Whittemore AS, et al. Am. J. Hum. Genet. (1997) pmid: 9042908
95. Claus EB, et al. Cancer (1996) pmid: 8635102
96. Struewing JP, et al. N. Engl. J. Med. (1997) pmid: 9145676
97. Oddoux C, et al. Nat. Genet. (1996) pmid: 8841192
98. King MC, et al. Science (2003) pmid: 14576434
99. Hall MJ, et al. Cancer (2009) pmid: 19241424
100. Abida W, et al. Clin. Cancer Res. (2020) pmid: 32086346
101. Mateo J, et al. Lancet Oncol. (2019) pmid: 31806540
102. Gruber et al., 2019; ASCO Abstract 3006
103. Liu Y, et al. BMC Cancer (2015) pmid: 25884806
104. Pfeifer W, et al. Breast Cancer Res. Treat. (2014) pmid: 25414026
105. Kriege M, et al. J. Cancer Res. Clin. Oncol. (2015) pmid: 25958056
106. Lee SB, et al. Cancer Res. (2001) pmid: 11719428
107. Maxwell KN, et al. Am. J. Hum. Genet. (2016) pmid: 27153395
108. Walsh T, et al. JAMA (2006) pmid: 16551709
109. Shaag A, et al. Hum. Mol. Genet. (2005) pmid: 15649950
110. Southey MC, et al. J. Med. Genet. (2016) pmid: 27595995
111. Pennington KP, et al. Cancer (2013) pmid: 22811390
112. Angelova SG, et al. Neoplasma (2012) pmid: 22862163
113. Walsh T, et al. Cancer Cell (2007) pmid: 17292821
114. Domagala P, et al. Breast Cancer Res. Treat. (2012) pmid: 21701879
115. Ma X, et al. Gut (2014) pmid: 23946381
116. Havranek O, et al. PLoS ONE (2015) pmid: 26506619
117. Wójcicka A, et al. Genes Chromosomes Cancer (2014) pmid: 24599715
118. Siołek M, et al. Int. J. Cancer (2015) pmid: 25583358
119. Kilpivaara O, et al. Int. J. Cancer (2005) pmid: 15472904
120. Simon M, et al. Neurosurgery (2006) pmid: 17016233
121. Dong YS, et al. Tumour Biol. (2014) pmid: 24532427
122. Ta HQ, et al. Cancer Res. (2015) pmid: 26573794
123. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
124. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
125. Xie M, et al. Nat. Med. (2014) pmid: 25326804
126. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
127. Severson EA, et al. Blood (2018) pmid: 29678827
128. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
129. Chabon JJ, et al. Nature (2020) pmid: 32269342
130. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
131. Tomlinson IP, et al. Mutagenesis (2012) pmid: 22294770
132. Xu HP, et al. Nucleic Acids Res. (1990) pmid: 2205842
133. van der Groep P, et al. Cell Oncol (Dordr) (2011) pmid: 21336636
134. Schutte M, et al. Am. J. Hum. Genet. (2003) pmid: 12610780
135. Xu X, et al. Mol. Cell. Biol. (2002) pmid: 12024051
136. Lee CH, et al. J. Biol. Chem. (2001) pmid: 11390408
137. Schwarz JK, et al. Mol. Cancer Res. (2003) pmid: 12805407
138. Ng CP, et al. J. Biol. Chem. (2004) pmid: 14681223
139. Matsuoka S, et al. Proc. Natl. Acad. Sci. U.S.A. (2000) pmid: 10973490
140. Zhou BB, et al. J. Biol. Chem. (2000) pmid: 10744722
141. Ahn JY, et al. Cancer Res. (2000) pmid: 11085506
142. Melchionna R, et al. Nat. Cell Biol. (2000) pmid: 11025670
143. Yoda A, et al. J. Biol. Chem. (2006) pmid: 16798742
144. Chehab NH, et al. Genes Dev. (2000) pmid: 10673500
145. Nature (2014) pmid: 25079317
146. Al-Ahmadie HA, et al. Nat. Genet. (2016) pmid: 26901067
147. Cell (2015) pmid: 26544944
148. Nature (2011) pmid: 21720365
149. Priya TP, et al. Virchows Arch. (2010) pmid: 20376482
150. Corso G, et al. J. Clin. Oncol. (2013) pmid: 23341533
151. Moreno-Bueno G, et al. J. Pathol. (2003) pmid: 12635138
152. Nikuseva-Martić T, et al. Pathol. Res. Pract. (2007) pmid: 17905526
153. Liu J, et al. Oncol Lett (2016) pmid: 27073531
154. Tang D, et al. Med. Oncol. (2012) pmid: 21519872
155. Kashiwagi S, et al. Br. J. Cancer (2010) pmid: 20551954
156. Mell LK, et al. Clin. Cancer Res. (2004) pmid: 15328195
157. Kim YT, et al. Yonsei Med. J. (2002) pmid: 12497652
158. Nakata S, et al. Cancer (2006) pmid: 16598757
159. Faleiro-Rodrigues C, et al. Ann. Oncol. (2004) pmid: 15367415
160. Hong SM, et al. Mod. Pathol. (2011) pmid: 21552209
161. Matsuoka T, et al. J Surg Oncol (2011) pmid: 21360533
162. Karamitopoulou E, et al. Pathology (2011) pmid:

21233674
163. Li B, et al. PLoS ONE (2016) pmid: 27223886
164. Yao X, et al. Onco Targets Ther (2012) pmid: 23091390
165. Nitta T, et al. Br. J. Cancer (2014) pmid: 25077440
166. Misawa K, et al. Oncotarget (2016) pmid: 27027429
167. Fujii R, et al. J. Exp. Clin. Cancer Res. (2014) pmid: 24887090
168. Lee EJ, et al. Int. J. Cancer (2008) pmid: 18697202
169. Nat. Rev. Mol. Cell Biol. (2005) pmid: 16025097
170. Wong AS, et al. J. Cell Biol. (2003) pmid: 12810698
171. Sarrió D, et al. Int. J. Cancer (2003) pmid: 12800196
172. Mastracci TL, et al. Mod. Pathol. (2005) pmid: 15696125
173. Berx G, et al. Cold Spring Harb Perspect Biol (2009) pmid: 20457567
174. Shapiro L, et al. Cold Spring Harb Perspect Biol (2009) pmid: 20066110
175. Shiraishi K, et al. J. Immunol. (2005) pmid: 16002701
176. Nat. Rev. Cancer (2014) pmid: 24442140
177. Ishiyama N, et al. Cell (2010) pmid: 20371349
178. Brooks-Wilson AR, et al. J. Med. Genet. (2004) pmid: 15235021
179. Hansford S, et al. JAMA Oncol (2015) pmid: 26182300
180. Desmedt C, et al. J. Clin. Oncol. (2016) pmid: 26926684
181. Christgen M, et al. Pathol. Res. Pract. (2016) pmid: 27233940
182. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
183. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
184. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
185. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
186. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
187. Xu L, et al. Mol. Med. (2001) pmid: 11713371
188. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
189. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
190. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
191. Hajdenberg et al., 2012; ASCO Abstract e15010
192. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
193. Moore et al., 2019; ASCO Abstract 5513
194. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
195. Oza et al., 2015; ASCO Abstract 5506
196. Lee J, et al. Cancer Discov (2019) pmid: 31315834
197. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
198. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
199. Kwok M, et al. Blood (2016) pmid: 26563132
200. Boudny M, et al. Haematologica (2019) pmid: 30975914
201. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
202. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
203. Banerji S, et al. Nature (2012) pmid: 22722202
204. Stephens PJ, et al. Nature (2012) pmid: 22722201
205. Alsner J, et al. Acta Oncol (2008) pmid: 18465328
206. Alkam Y, et al. Histopathology (2013) pmid: 24004112
207. Uji K, et al. Cancer Lett. (2014) pmid: 23973262
208. Olivier M, et al. Clin. Cancer Res. (2006) pmid: 16489069
209. Végran F, et al. PLoS ONE (2013) pmid: 23359294
210. Garber JE, et al. J. Clin. Oncol. (2005) pmid: 15637391
211. Apostolou P, et al. Biomed Res Int (2013) pmid: 23586058
212. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
213. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
214. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
215. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
216. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
217. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
218. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
219. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
220. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
221. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
222. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
223. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
224. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
225. Lalloo F, et al. Lancet (2003) pmid: 12672316
226. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
227. Del Conte G, et al. Br. J. Cancer (2014) pmid: 25025963
228. Domchek et al., 2019; ESMO Abstract 1191O
229. Matulonis UA, et al. Ann. Oncol. (2017) pmid: 27993796
230. Lee JM, et al. J. Natl. Cancer Inst. (2014) pmid: 24842883
231. Takahashi et al., 2016; ASCO Abstract 1080
232. Dent RA, et al. Breast Cancer Res. (2013) pmid: 24063698
233. Pusztai et al., 2020; AACR Abstract CT011
234. Turner et al., 2017; ASCO Abstract 1007
235. Ettl J, et al. Ann. Oncol. (2018) pmid: 30124753
236. Meehan et al., 2017; AACR Abstract 4687
237. de Bono J, et al. Cancer Discov (2017) pmid: 28242752
238. Lu E, et al. J Natl Compr Canc Netw (2018) pmid: 30099369
239. De Bono et al., 2020; ASCO Abstract 5566
240. Litton JK, et al. J. Clin. Oncol. (2019) pmid: 31461380
241. Schwab et al., 2019; AACR Abstract CT123/2
242. Konstantinopolous et al., 2018; ASCO Abstract 106
243. Vinayak S, et al. JAMA Oncol (2019) pmid: 31194225
244. Kristeleit et al., 2014; ASCO Abstract 2573
245. Domcheck et al., 2016; ASCO Abstract 4110