FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Breast carcinoma (NOS)

REPORT DATE

COUNTRY CODE
RO

ORDERED TEST #

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 Breast carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY

ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - 5 Muts/Mb

Gene Alterations

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

BRCA1 V1234fs*8
PTEN loss
BAP1 rearrangement intron 13
TP53 T256P

3 Disease relevant genes with no reportable alterations: ***BRCA2, ERBB2, PIK3CA***

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Olaparib** (p. 9), **Talazoparib** (p. 10)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***BRCA1*** **V1234fs*8** (p. 5)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***BRCA1*** **V1234fs*8** (p. 5)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Genomic Signatures section
Tumor Mutational Burden - 5 Muts/Mb	**No therapies or clinical trials.** see Genomic Signatures section

GENE ALTERATIONS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA1 **-** V1234fs*8	Olaparib [1]	Niraparib
10 Trials *see p. 12*	Talazoparib [1]	Rucaparib
PTEN **-** loss	none	none
10 Trials *see p. 14*		

[ ] *NCCN category*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

BRCA1 **-** V1234fs*8 ..... p. 5

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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GENE ALTERATIONS 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 Alterations section.

BAP1 - rearrangement intron 13 ..... p. 7

TP53 - T256P ..... p. 8

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 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 and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

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GENOMIC SIGNATURE

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 is extremely rare in breast cancer, reported in 0-1% of cases across studies[6-11]. The incidence of MSI is increased in triple-negative breast cancer[9-11] and in tumors with homologous recombination defects, such as mutations in BRCA1/2[9,11]. Notably, in Lynch syndrome–related breast cancer, MSI has been reported in 51-85% of cases[12-17]. A prospective study of 123 patients with breast cancer treated with chemotherapy reported an increase in the incidence of MSI-H following chemotherapy treatment (from 0% pre-treatment to 19% post-treatment) and a significant association between MSI and tumor recurrence[18].

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[19]. 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[19-21]. 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[22-24]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19,21,23-24].

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GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT
5 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[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-34]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[25-28,35-39]. 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[35]; similar findings were observed in the KEYNOTE 028 and 012 trials[28]. 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)[39]. 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[40]. 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[38]. 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[41] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[26].

FREQUENCY & PROGNOSIS

A study of 3,969 patients with breast cancer reported a median TMB of 2.63 mutations per megabase (Muts/Mb), with 5% of cases harboring TMB ≥10 Muts/Mb; median TMB was significantly higher in hormone receptor (HR)-negative and HER2-negative tumors than HR-positive or HER2-positive tumors[42]. The Breast Invasive Carcinoma TCGA analysis reported an average (non-silent) mutation load of 0.84 Muts/Mb for luminal A tumors, 1.38 Muts/Mb for luminal B tumors, 2.05 Muts/Mb for HER2-enriched tumors, and 1.68 Muts/Mb for basal-like tumors[43]. In breast cancer, TMB is significantly higher in recurrent versus primary tumors, metastatic versus localized cancers, triple-negative versus HR-positive tumors, and CDH1-mutated versus CDH1-wildtype tumors[42,44-45]. Among metastatic tumors, TMB-high samples have been reported more frequently in invasive lobular carcinoma (9-17% of cases, depending on the TMB cutoff to designate TMB-high) than in invasive ductal carcinoma (2-8% of cases, depending on the cutoff), and TMB-high (at either cutoff) has not been observed in papillary carcinoma[42,44-45]. Breast carcinoma harbors a median TMB of 3.8 muts/Mb, and 3.1% of cases have high TMB (>20 muts/Mb)[46]. In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors[42]. 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[45]. 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[47].

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[48-49] and cigarette smoke in lung cancer[50-51], treatment with temozolomide-based chemotherapy in glioma[52-53], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[54-58], and microsatellite instability (MSI)[54,57-58]. 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[26-27,35].

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GENE
BRCA1

ALTERATION
V1234fs*8

TRANSCRIPT ID
NM_007294

CODING SEQUENCE EFFECT
3700_3704delGTAAA

VARIANT ALLELE FREQUENCY (% VAF)
59.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[59-76] or ATR inhibitors[77-79]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[60,65,68,75-76] and for patients with platinum-resistant or -refractory disease[59,64,71,74]. 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[62,80]. In the Phase 3 BROCADE3 study for patients with HER2-negative breast cancer harboring deleterious germline BRCA mutations, the addition of veliparib to platinum chemotherapy, which was continued as a monotherapy if chemotherapy was discontinued, improved median PFS compared with placebo plus platinum chemotherapy (14.5 vs. 12.6 months; HR=0.71)[81]. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and platinum-refractory ovarian carcinoma experienced a PR or prolonged SD[77]. 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[78]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[82]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[83]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[84], ovarian carcinoma[85], and TNBC[86] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. The WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments[87]. In a Phase 1 monotherapy trial of 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[88].

— Nontargeted Approaches —

Germline BRCA mutations are associated with benefit from platinum chemotherapeutic agents (NCCN Breast Cancer Guidelines, v2.2022). Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin[89-98].

FREQUENCY & PROGNOSIS

In the Breast Invasive Carcinoma TCGA datasets, BRCA1 mutations have been reported in 2-4% of cases[43,99]. A study of patients with sporadic breast cancer identified BRCA1 mutation in 9.3% (4/43) of cases[100]. BRCA1 mutations account for approximately 4.6-7% of breast cancer cases in patients with a family history of breast cancer[101-102]. A study reported decreased nuclear BRCA1 protein expression in breast carcinoma samples (n=22), as compared to normal breast tissue[103]. For BRCA1 and BRCA2 mutation carriers, the risk of developing breast cancer by the age of 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[104-106]. One study reported that the presence of germline BRCA2 mutations was significantly associated with inferior PFS for patients with breast cancer treated with first-line CDK4/6 inhibitors plus endocrine combination therapy[107].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[108]. Alterations such as seen here may disrupt BRCA1 function or expression[109-111].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the BRCA1 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) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Mar 2022)[112]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[113-114], 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[115]. 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%[116]. 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[115,117-122]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

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GENE
PTEN

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[123-126]. Patients with PTEN-mutated HR+ HER2- breast cancer benefited from the addition of fulvestrant to the AKT inhibitor capivasertib in a Phase 2 study (mPFS 9.5 vs. 5.2 months, not significant), and patients who were HR+ experienced an ORR of 21% (for those exposed to fulvestrant) and 8% (for those who were fulvestrant-naive) on the combination in a Phase 1 trial[127-128]. In a Phase 2 study of capivasertib monotherapy for patients with PTEN- or AKT1-mutated breast cancer (ER+ or ER-), the ORR was 18% (2/11)[129]. The Phase 3 IPATunity130 trial for patients with AKT1-, PTEN-, or PIK3CA-mutated HR+ HER2- breast cancer reported no significant PFS improvement with the first-line AKT inhibitor ipatasertib in combination with paclitaxel relative to paclitaxel alone (9.3 vs. 9.3 months)[130], despite Phase 1 results showing a potential benefit[131]. In a Phase 2 study of the PIK3CA inhibitor buparlisib for patients with PTEN-negative HR+ HER2- breast cancer, the mPFS was 2.5 months (n=3)[132]. Clinical studies in breast cancer have not observed an association between PTEN deficiency and response to the mTOR inhibitors everolimus or temsirolimus[133-138], although exploratory analysis of Phase 3 studies suggests that patients with HER2+ metastatic breast cancer and PTEN loss derived significant benefit from everolimus added to trastuzumab plus chemotherapy[139]. One PR has been observed in a patient with breast cancer harboring PTEN and STK11 alterations following treatment with the mTORC1/2 inhibitor sapanisertib combined with metformin[140]. A Phase 2 trial of the ATKi inhibitor capivasertib with paclitaxel versus paclitaxel alone showed a median OS benefit (19.1 vs. 13.5 months) both for patients with AKT1-, PTEN-, or PIK3CA-mutated triple-negative breast cancer (TNBC) (HR=0.58, 95% CI 0.2-1.6) and for patients with TNBC without PI3K-pathway mutations (HR=0.74, 95% CI 0.47-1.18)[141]. Despite promising initial results in earlier trials, the Phase 3 IPATunity130 trial for patients with AKT1-, PTEN-, or PIK3CA-mutated TNBC failed to show improved PFS for the first-line AKT inhibitor ipatasertib in combination with paclitaxel relative to paclitaxel alone (7.4 vs. 6.1 months)[142-143]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[144-148], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[149], ovarian cancer[150], uterine leiomyosarcoma[151], and endometrial cancer[148] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[64,152].

— Potential Resistance —

A multivariate analysis showed that patients with metastatic triple negative breast cancer (TNBC) harboring PTEN alterations were more likely to progress and experience shorter PFS and OS when treated with anti-PD-1/L1 therapies compared with patients with wildtype PTEN[153]. Clinical and preclinical evidence suggests that PTEN loss or mutation may predict resistance to PI3K inhibitors[154-156], and to CDK inhibitors such as palbociclib, ribociclib, and abemaciclib[154,157].

FREQUENCY & PROGNOSIS

In the TCGA dataset, PTEN mutation has been reported in 4% of breast invasive carcinomas, while putative homozygous deletion of PTEN has been reported in 2% of cases[43]. PTEN mutation has also been observed in 5.3% (1/19) of metaplastic breast cancers[158] and 2% of invasive lobular carcinoma tumors analyzed[159]. PTEN mutations are associated more frequently with triple-negative breast cancer than with HER2- or hormone-positive breast cancer[160-161]. Loss or reduction of PTEN expression has been observed in 28% of invasive ductal breast carcinomas and has been correlated with metastasis and poor patient prognosis, including decreased 2-year disease-free survival[162-164].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[124]. Alterations such as seen here may disrupt PTEN function or expression[165-206].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[207-208]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[207,209]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[207]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

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GENE
BAP1

ALTERATION
rearrangement intron 13

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical[210] and preclinical[211] evidence in the context of mesothelioma suggests that tumors with BAP1 inactivation may be sensitive to EZH2 inhibitors such as tazemetostat. Preclinical studies suggest that BAP1 is involved in the DNA damage response[212-215], and BAP1 inactivation might be associated with sensitivity to PARP inhibitors[213-214]. One preclinical study suggests that HDAC inhibitors may be beneficial in BAP1-mutated uveal melanoma; however, it is unclear if these inhibitors are effective in other BAP1-mutated cancers[216].

— Potential Resistance —

One preclinical study suggests that BAP1 inactivation in breast cancer may be associated with resistance to tamoxifen[217].

FREQUENCY & PROGNOSIS

BAP1 somatic mutations are reported to be rare in breast cancer[218], and have been reported in 0.4-2% of breast invasive carcinoma cases[43,99,219-220]. BAP1 has been suggested to play a tumor suppressive role in breast cancer cells by regulating genomic stability; high BAP1 expression was significantly associated with improved overall survival in patients with breast cancer, and with prolonged progression-free survival in patients with basal or luminal breast cancer[221].

FINDING SUMMARY

BAP1 (BRCA1 associated protein-1) encodes a ubiquitin hydrolase, a protein involved in regulating the availability of target proteins for the ubiquitin-proteasome protein degradation pathway; BAP1 is located on chromosome 3p21.3, in a region of frequent loss of heterozygosity (LOH) in breast and lung cancer, and has been postulated to be a tumor suppressor[222-223]. Alterations such as seen here may disrupt BAP1 function or expression[223-232].

POTENTIAL GERMLINE IMPLICATIONS

BAP1 germline inactivating alterations, including mutations and deletions, are associated with BAP1 tumor predisposition syndrome (BAP1-TPDS), an autosomal-dominant syndrome characterized by early onset of benign melanocytic skin tumors[226,233-234]. An estimated 2% of patients with BAP1-inactivated melanocytic tumors display germline BAP1 mutations[235]. Later in life, patients have an increased risk of cancers such as uveal melanoma, mesothelioma, clear cell renal cell carcinoma, basal cell carcinoma, and meningioma[225-229,236]. In small studies, the prevalence of pathogenic germline BAP1 mutation has been reported as 22% in familial uveal melanoma and 4.4% in mesothelioma[237-238]. In the appropriate clinical context, germline testing of BAP1 is recommended.

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GENE
TP53

ALTERATION
T256P

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
766A>C

VARIANT ALLELE FREQUENCY (% VAF)
29.6%

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[239-242], or p53 gene therapy and immunotherapeutics such as SGT-53[243-247] and ALT-801[248]. 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[249]. 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[250]. 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[251]. 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[252]. 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[253]. 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[254]. 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[255]. 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[247]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[256-258]. 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[259]. 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[260-261]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[262-263]. 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[43,219,264-267]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[265,268-269]. 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[270-272].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[273]. Alterations such as seen here may disrupt TP53 function or expression[274-278].

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[279-281], including sarcomas[282-283]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[284] to 1:20,000[283]. 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[285]. 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[286-291]. 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[286-287]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[292]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[290,293-294]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Olaparib

Assay findings association

BRCA1
V1234fs*8

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is available in the EU as a monotherapy to treat patients with BRCA-mutated high-grade epithelial ovarian, Fallopian tube, or peritoneal cancer. It is also available in combination with bevacizumab for patients with HRD-positive high-grade epithelial ovarian, Fallopian tube, or peritoneal cancer. It is additionally available as a monotherapy for patients with HER2-negative germline BRCA-mutated breast cancer, BRCA-mutated castration-resistant prostate 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[69-73] as well as strong clinical evidence in multiple other cancer types[59-61,69,72,76,295] , 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–metastatic breast cancer reported a significantly longer median PFS (7.0 vs. 4.2 months, HR=0.58) and a higher ORR (60% vs. 29%) compared with standard chemotherapy[62]. The Phase 3 OlympiA trial of adjuvant olaparib for patients with gBRCA1/2-mutated breast cancer reported significantly increased invasive disease-free survival (IDFS) (HR=0.63), distant DFS (DDFS) (HR=0.61), and OS (HR=0.68; p=0.0091) compared with placebo; 4-year rates of IDFS, DDFS, and OS comparing olaparib with placebo were 83% versus 75%, 87% versus 79%, and 90% versus 86%, respectively[296]. 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%)[59,61,72] . The Phase 2 MEDIOLA trial of olaparib with durvalumab for patients with gBRCA1/2-mutated metastatic breast cancer reported an ORR of 63%, median PFS of 8.2 months, and median OS of 21.5 months[297]. A Phase 1 trial of olaparib with the PI3K inhibitor buparlisib reported an ORR of 33% (4/12) for patients with gBRCA1/2-mutated breast cancer[298]. A Phase 1 trial of olaparib plus carboplatin for patients with gBRCA1/2-mutated breast cancer reported an ORR of 88% (7/8)[299]. In a Phase 2 study of olaparib plus pembrolizumab for advanced solid tumors, patients with BRCA1 or BRCA2 mutations achieved an ORR of 29% (6/21), whereas patients with mutations in other homologous recombination repair genes achieved an ORR of 6.3% (2/32)[300]. Phase 1 trials of olaparib plus chemotherapy for patients with triple-negative breast cancer (TNBC) reported ORRs of 37-38%[301-302] . 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[298]. A Phase 2 study comparing durvalumab in combination with olaparib and paclitaxel 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[303].

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Talazoparib

Assay findings association

BRCA1
V1234fs*8

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[80,304-305] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[306-309] , 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 (63% vs. 27%), and improved quality of life on talazoparib compared with standard chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)[80,305] . Clinical benefit from talazoparib was observed for patients with either triple-negative or hormone receptor-positive (HR+) breast cancer, and for those with CNS metastases[80]. Final OS analysis showed that talazoparib did not significantly improve OS compared with chemotherapy (median OS [mOS] 19.3 vs. 19.5 months, HR=0.85) but did significantly delay definitive clinically meaningful deterioration in global health status/quality of life[310]. Retrospective genomic analysis showed that MYC amplification was associated with significantly shorter mOS for patients with triple-negative cancer treated with talazoparib, but not for those treated with chemotherapy; in contrast, for patients with HR+ cancer, MYC amplification was associated with shorter mOS for the chemotherapy treatment group, but not for the talazoparib treatment group[311]. The efficacy of single-agent talazoparib for the treatment of BRCA-mutated advanced breast cancer was also demonstrated in earlier-phase studies, which reported ORRs of 21%-50%[304,307]. As neoadjuvant treatment for BRCA-mutated HER2-negative breast cancer, talazoparib led to a pathologic complete response (pCR) for 53% (10/19) of patients[312]. In the Phase 2 I-SPY2 trial, talazoparib with synergy-dosed irinotecan (TI) for 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[313]. Notably, 6/10 patients with germline BRCA mutations achieved a pCR with TI treatment[313]. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, those 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 for 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[314].

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Niraparib

Assay findings association

BRCA1
V1234fs*8

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is available in the EU as a monotherapy to treat patients with epithelial high-grade ovarian, Fallopian tube, or peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian and breast cancers[63-64,315] , 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[64]. 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[316].

Rucaparib

Assay findings association

BRCA1
V1234fs*8

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[65-66,250] , as well as clinical data in other cancer types[66,317-318] , 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[66]. However, 39% (9/23) of evaluable patients with breast cancer achieved stable disease lasting 12 weeks or more[66]. 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[317].

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 listed in this report may not be complete and exhaustive and the therapeutic agents 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.

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CLINICAL TRIALS

NOTE Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 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. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

GENE
BRCA1

ALTERATION
V1234fs*8

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

NCT04915755

PHASE 3

Efficacy and Safety Comparison of Niraparib to Placebo in Participants With Either Human Epidermal Growth Factor 2 Negative (HER2-) Breast Cancer Susceptibility Gene Mutation (BRCAmut) or Triple-Negative Breast Cancer (TNBC) With Molecular Disease

TARGETS
PARP

LOCATIONS: Rzeszow (Poland), Krakow (Poland), Brindisi (Italy), Warszawa (Poland), Wroclaw (Poland), Napoli (Italy), Poznan (Poland), Meldola (FC) (Italy), Padova (Italy), Bologna (Italy)

NCT04768296

PHASE 2

Berzosertib + Topotecan in Relapsed Platinum-Resistant Small-Cell Lung Cancer (DDRiver SCLC 250)

TARGETS
TOP1, ATR

LOCATIONS: Meldola (Italy), Rome (Italy), Roma (Italy), Pisa (Italy), Milano (Italy), Strasbourg (France), Arlon (Belgium), Yvoir (Belgium), Brussels (Belgium), Gent (Belgium)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), London (United Kingdom), Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Massachusetts, Rhode Island, New York, Toronto (Canada), North Carolina, Illinois

NCT03127215

PHASE 2

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

TARGETS
FUS-DDIT3, PARP

LOCATIONS: Dresden (Germany), München (Germany), Stuttgart (Germany), Tuebingen (Germany), Heidelberg (Germany), Frankfurt (Germany), Freiburg (Germany), Mainz (Germany), Essen (Germany)

NCT04095273

PHASE 1

Study to Test How Well Patients With Advanced Solid Tumors Respond to Treatment With the ATR Inhibitor BAY1895344 in Combination With Pembrolizumab, to Find the Optimal Dose for Patients, How the Drug is Tolerated and the Way the Body Absorbs, Distributes and Discharges the Drug

TARGETS
ATR, PD-1

LOCATIONS: St. Gallen (Switzerland), Bellinzona (Switzerland), Tübingen (Germany), Heidelberg (Germany), Sutton (United Kingdom), Newcastle Upon Tyne (United Kingdom), Madrid (Spain), Massachusetts, Connecticut, New York

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NCT02810743

PHASE 3

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

TARGETS
PARP

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

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), Cambridge (United Kingdom), Sutton (United Kingdom), Bordeaux (France), Oxford (United Kingdom), Coventry (United Kingdom), Manchester (United Kingdom), Withington (United Kingdom), Massachusetts, New York

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: London (United Kingdom), Newcastle upon Tyne (United Kingdom), Connecticut, Texas

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)

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Pennsylvania, Tennessee, Florida, Colorado, Oklahoma

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GENE
PTEN

ALTERATION
loss

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT03997123

PHASE 3

Capivasertib+Paclitaxel as First Line Treatment for Patients With Locally Advanced or Metastatic TNBC

TARGETS
AKTs

LOCATIONS: Košice (Slovakia), Prešov (Slovakia), Ankara (Turkey), Zilina (Slovakia), Bratislava (Slovakia), Heraklion (Greece), Guimarães (Portugal), Chengdu (China), Xi'an (China), Beijing (China)

NCT04915755

PHASE 3

Efficacy and Safety Comparison of Niraparib to Placebo in Participants With Either Human Epidermal Growth Factor 2 Negative (HER2-) Breast Cancer Susceptibility Gene Mutation (BRCAmut) or Triple-Negative Breast Cancer (TNBC) With Molecular Disease

TARGETS
PARP

LOCATIONS: Rzeszow (Poland), Krakow (Poland), Brindisi (Italy), Warszawa (Poland), Wroclaw (Poland), Napoli (Italy), Poznan (Poland), Meldola (FC) (Italy), Padova (Italy), Bologna (Italy)

NCT04862663

PHASE 3

Capivasertib + Palbociclib + Fulvestrant for HR+/HER2- Advanced Breast Cancer (CAPItello-292).

TARGETS
AKTs, CDK6, ER, CDK4

LOCATIONS: Kraków (Poland), Warszawa (Poland), Bydgoszcz (Poland), Odense C (Denmark), Solna (Sweden), Leuven (Belgium), Villejuif (France), Chicoutimi (Canada), St Herblain (France), Tennessee

NCT04770246

PHASE 2

TAS-117 in Patients With Advanced Solid Tumors Harboring Germline PTEN Mutations

TARGETS
AKT2, AKT1, AKT3

LOCATIONS: Vienna (Austria), Villejuif (France), London (United Kingdom), Pennsylvania, Ohio, Texas, California

NCT04802759

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Participants With Breast Cancer

TARGETS
ER, CDK4, CDK6, AKTs, PI3K-alpha, mTOR

LOCATIONS: Tel Aviv (Israel), Petach Tikva (Israel), Ramat Gan (Israel), Jerusalem (Israel), Barcelona (Spain), Valencia (Spain), Madrid (Spain), Massachusetts, Goyang-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), London (United Kingdom), Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Massachusetts, Rhode Island, New York, Toronto (Canada), North Carolina, Illinois

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CLINICAL TRIALS

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), Cambridge (United Kingdom), Sutton (United Kingdom), Bordeaux (France), Oxford (United Kingdom), Coventry (United Kingdom), Manchester (United Kingdom), Withington (United Kingdom), Massachusetts, New York

NCT04464174

PHASE 2

Ipatasertib Plus Non-Taxane Chemotherapy for Advanced or Metastatic Triple-Negative Breast Cancer

TARGETS
AKTs

LOCATIONS: Barcelona (Spain), Lleida (Spain), Castellón De La Plana (Spain), Zaragoza (Spain), Valencia (Spain), Alicante (Spain), El Palmar (Spain), Madrid (Spain), Málaga (Spain), Cáceres (Spain)

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: London (United Kingdom), Newcastle upon Tyne (United Kingdom), Connecticut, Texas

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)

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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.

EPHA3 D344V	***ESR1*** S118P	***MLL2*** Q3745_H3746insQ	***NF2*** rearrangement
POLE R2165C	***PRDM1*** amplification	***RAD51D*** I311N	***STAG2*** H774N

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APPENDIX Genes Assayed in FoundationOne®CDx

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*	*ETV1*
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 GENOMIC SIGNATURES

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

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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 PRINCIPLES

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: 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).

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

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. 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. 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.
4. 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.
5. 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.
6. 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

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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 6.2.0

The median exon coverage for this sample is 1,247x

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