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 cancer (NOS)
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 - 4 Muts/Mb
Microsatellite status - Cannot Be Determined
Tumor Fraction - Cannot Be Determined

Gene Alterations

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

ESR1 Y537S, D538G
PIK3CA E542V, N1044K
CBFB Y85fs*31
DNMT3A splice site 1123-1G>A
INPP4B Y115fs*2
WT1 E258*

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

GENOMIC SIGNATURES

Blood Tumor Mutational Burden - 4 Muts/Mb

Microsatellite status - Cannot Be Determined

Tumor Fraction - Cannot Be Determined

GENE ALTERATIONS		VAF %
ESR1 -	Y537S	0.65%
	D538G	0.67%
10 Trials see p. 16		
PIK3CA -	E542V	3.8%
	N1044K	3.5%
10 Trials see p. 18		

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Genomic Signatures section

Unable to determine Microsatellite status due to insufficient evidence of genomic instability.

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.

THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)		THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
Fulvestrant	1	None
◆ Anastrozole[1]		
◆ Exemestane[1]		
◆ Letrozole[1]		
Alpelisib	1	Temsirolimus
Everolimus	2A	

◆ *1. Patient may be resistant to indicated therapy*

☐ *NCCN category*

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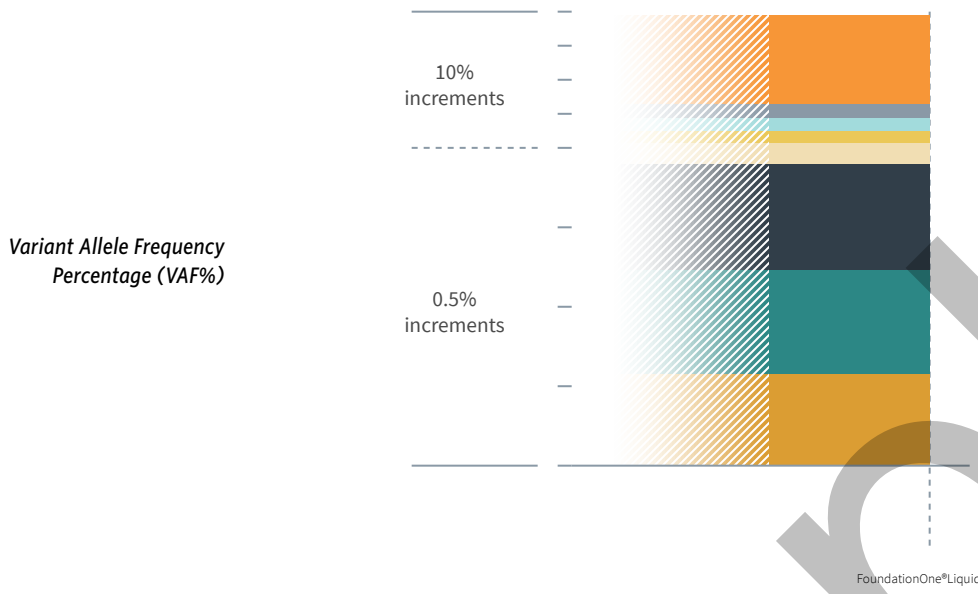
GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

CBFB - Y85fs*31 ..... p. 8
DNMT3A - splice site 1123-1G>A ..... p. 8
INPP4B - Y115fs*2 ..... p. 8
WT1 - E258* ..... p. 9

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		4 Muts/Mb
Microsatellite status		Cannot Be Determined
Tumor Fraction		Cannot Be Determined
ESR1	D538G	0.67%
	Y537S	0.65%
PIK3CA	N1044K	3.5%
	E542V	3.8%
CBFB	Y85fs*31	4.1%
DNMT3A	splice site 1123-1G>A	25.9%
INPP4B	Y115fs*2	1.6%
WT1	E258*	0.58%

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

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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
4 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 below levels that would be predicted to 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
Cannot Be Determined

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]. Tumor fraction estimate is computationally derived from observed aneuploid instability in the sample. However, the tumor fraction estimate in this sample could not be determined with confidence.

GENE
ESR1

ALTERATION
Y537S, D538G

TRANSCRIPT ID
NM_000125

CODING SEQUENCE EFFECT
1610A>C, 1613A>G

POTENTIAL TREATMENT STRATEGIES

Therapies that directly target ER-alpha, such as selective ER modulators (SERMs) and the selective ER degrader (SERD) fulvestrant, as well as aromatase inhibitors (AIs) that inhibit estrogen production, are approved to treat ER-positive (ER+) and/or hormone receptor-positive (HR+) breast cancer (NCCN Guidelines v1.2019). AI treatment has also been reported to provide clinical benefit in a subset of HR+ gynecologic malignancies[39-43]. Clinical data suggest that ESR1 mutations may confer sensitivity to the first-generation SERD fulvestrant in breast cancer[44-45]. A retrospective analysis of ESR1 mutations in gynecologic malignancies reported clinical benefit for patients with ESR1 mutations and fulvestrant treatment as a monotherapy or in combination, including 1 patient with peritoneal serous carcinoma and an ESR1 Y537N mutation who experienced prolonged clinical benefit (48+ months) from fulvestrant monotherapy[46]. The therapeutic utility of SERMs, including toremifene[47], raloxifene[48], and tamoxifen[49], for ESR1 mutation-positive breast cancer is unclear. Although ESR1 mutations have been reported in patients who progressed on tamoxifen[47,50-51], a retrospective analysis of primary breast tumors reported that patients with non-emergent ESR1 mutations experienced improved (Y537N) or similar (Y537S or D538G) median progression-free survival (PFS) relative to those lacking ESR1 mutation[49]. Preclinical studies suggest that certain ESR1 mutations (Y537S and D538G) may be less sensitive to clinical concentrations of antiestrogens, and higher doses or more potent antiestrogens may be required to inhibit tumors with these mutations[49,52-54]. Clinical data suggest that ESR1 mutations may confer sensitivity to the first-generation SERD fulvestrant[44-45]. In a study of patients with breast cancer treated with fulvestrant as monotherapy or in combination with palbociclib, ESR1 Y537S was the most commonly acquired mutation, suggesting that Y537S may decrease fulvestrant sensitivity[55]. Next-generation selective estrogen receptor degraders (SERDs), including elacestrant, GDC-0927, GDC-9545, SAR439859, AZD9833, and LSZ102, have demonstrated efficacy in ER+ breast cancer. Two Phase 1 studies of elacestrant for the treatment of patients with ER+, HER2– breast cancer reported ORRs of 19.4% (6/31) and 12.5% (2/16), with 50.9% (29/57) and 56.3% (9/16) of patients harboring ESR1 mutations, respectively[56-57] . A Phase 1 study of GDC-0927 for the treatment of ER+, HER2– metastatic breast cancer reported an unconfirmed ORR of 12.5% (3/24), with 2 patients harboring an ESR1 mutation; a patient with ESR1 D538G had SD in the study for over 490 days[58]. A Phase 1/2 study of SAR439859 observed a numerically lower ORR (3.6% [1/28] vs. 10% [3/30]) for heavily pretreated patients with ESR1 mutations compared with those without[59]; a Phase 1 study of AZD9833 showed a higher ORR (27.3% [6/22] vs. 4.8% [1/21]) for patients with ESR1 mutations[60]. In a Phase 1 study for the treatment of HR+ breast cancer, single-agent LSZ102 reported a PR for 1.8% (1/57) and SD for 29.8% (17/57) of cases[61], while LSZ102 plus ribociclib led to a PR for 11.3% (8/71) and SD for 39.4% (28/71) of cases[62]. A Phase 1b study for patients with ER+, HER2– metastatic breast cancer reported ORRs of 12.9% (4/31) for GDC-9545 alone and 33.3% (15/45) for GDC-9545 plus palbociclib, with clinical benefit observed for patients with detectable ESR1 mutations[63].

FREQUENCY & PROGNOSIS

The most frequent ESR1 mutations include D538G, Y537S, Y537N, and E380Q, with concurrent ESR1 mutations detected in up to 40% of ER+ breast cancer samples harboring an ESR1 alteration[45,52,64-65]. In the TCGA breast invasive carcinoma datasets, ESR1 amplification was observed in 2 to 3% of cases and ESR1 mutation was observed in fewer than 1% of cases[66-67]. Rarely identified in patients with localized disease, ESR1 mutations are more frequently detected in metastatic breast cancers (11–54%)[51,64,68-69], predominantly during progression on hormonal therapy[44,50,64,68,70-73]. ESR1 mutation is associated with shorter median PFS and OS in patients with advanced breast cancer[44,73]. The prevalence, significance, and correlation with protein expression of ESR1 amplification in breast cancer remains controversial[74-82].

FINDING SUMMARY

ESR1 encodes estrogen receptor alpha (ER-alpha), one of the major estrogen receptor isoforms in humans. Along with co-activator proteins, the ER complex promotes transcription of genes involved in cell cycle progression and survival[83]. Alterations that occur within the ligand binding domain of ER-alpha, as seen here, result in ligand-independent activation[68,70-71,84-90]. Emerging clinical[44-45,47,50,68,73,91] and preclinical[45,52,70-71] evidence suggests that these alterations confer resistance to aromatase inhibitors including anastrozole, letrozole, and exemestane.

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GENE
PIK3CA

ALTERATION
E542V, N1044K

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
1625A>T, 3132T>G

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K or AKT[92-93]. On the basis of clinical benefit for patients with PIK3CA mutations and preclinical evidence, PIK3CA-mutated tumors may also respond to mTOR inhibitors, including everolimus and temsirolimus[94-99]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control at the recommended Phase 2 dose (3/14 PRs, 8/14 SDs)[100]. The addition of everolimus to exemestane for the treatment of hormone-receptor-positive (HR+)/HER2-negative advanced breast cancer has shown clinical benefit regardless of PIK3CA status[101]. In the BELLE-2 trial for patients with endocrine-resistant HR+ breast cancer, the combination of the pan-PI3K inhibitor buparlisib with fulvestrant resulted in increased PFS (7.0 vs. 3.2 months) and ORR (18% vs. 4%) compared to placebo with fulvestrant in patients with PIK3CA mutation; no significant improvement in PFS or ORR was observed in patients without PIK3CA mutation[102]. In a Phase 1 study, the addition of GDC-0077, a p110α-selective inhibitor, to fulvestrant reported 2 confirmed PRs (2/14) in PIK3CA-mutated HR+/HER- breast cancer[103]. A patient with previously treated HER2-negative metastatic breast cancer harboring a PIK3CA H1047R alteration achieved an exceptional response with the pan-class I PI3K inhibitor copanlisib[104]. However, studies of copanlisib and the pan-class I PI3K inhibitor buparlisib have demonstrated limited efficacy against PIK3CA-mutated tumors[105-111]. PI3K-alpha-selective inhibitors such as alpelisib or PI3K-beta-sparing inhibitors such as taselisib may have bigger therapeutic windows than pan-PI3K inhibitors[93]. In PIK3CA-mutated advanced solid tumors, alpelisib and taselisib have achieved low ORRs (0% [0/55] to 6% [7/111]) but a high DCR (55% [36/55] to 58% [64/111])[112]. In the Phase 3 SOLAR-1 study, the addition of alpelisib to fulvestrant improved PFS (11.0 vs. 5.7 months, HR=0.65) and ORR (26.6% vs. 12.8%) in PIK3CA-mutated HR+/HER2– breast cancer compared with placebo with fulvestrant[92] but not in PIK3CA-wild-type HR+/HER2– breast cancer. In the Phase 3 SANDPIPER study, the addition of taselisib to fulvestrant improved PFS (7.4 vs. 5.4 months, HR=0.70) and ORR (27.3% vs. 11.9%) in PIK3CA-mutated HR+/HER2– breast cancer compared with placebo with fulvestrant[113]; additionally, patients with multiple PIK3CA mutations achieved a higher ORR following treatment with taselisib (30.2%, n=43) as compared with those treated with placebo (8.7%, n=23) or with patients with single PIK3CA-mutated tumors treated with either taselisib (18.1%, n=193) or placebo (10.0%, n=80)[114]. AKT inhibitors ipatasertib and capivasertib have also been tested in breast cancer. Two Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR = 0.44) or capivasertib (9.3 vs. 3.7 months, HR = 0.30) to paclitaxel in metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations, compared with paclitaxel and placebo[115]. Responses to capivasertib were also reported in 20% (3/15) of patients with PIK3CA-mutated breast cancer in an earlier study[116]. However, a Phase 1 trial reported no PFS benefit for patients with PIK3CA-mutated, ER+/HER2- metastatic breast cancer from the addition of capivasertib to paclitaxel compared with paclitaxel plus placebo (10.9 vs. 10.8 months)[117]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[118-122].

FREQUENCY & PROGNOSIS

Mutations in PIK3CA have been reported in 25-40% of breast cancer cases[66,123-127]. In the randomized Phase 2 SAFIR02 trial, PIK3CA mutations were associated with reduced OS in patients with hormone-receptor-positive (HR+)/HER2 negative (HER-) metastatic breast cancer but with improved OS in patients with mTNBC compared to patients with PIK3CA wildtype status[127]. Although double PIK3CA mutations were frequently observed in HR+/HER2- breast cancers, as compared with other receptor subtypes (15.4% vs. 5.4%, p=0.004), this did not impact invasive disease-free survival or OS for patients when compared with single PIK3CA mutations by univariate and multivariate analysis in 1 retrospective study[114]. Mutations in coding exon 20 (H1047R) of PIK3CA have been associated with a better prognosis in breast carcinoma than mutations occurring in coding exon 9 (E542K)[128].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[129-130]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[131-149].

GENE
CBFB

ALTERATION
Y85fs*31

TRANSCRIPT ID
NM_022845

CODING SEQUENCE EFFECT
253_254insT

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in CBFB.

FREQUENCY & PROGNOSIS
A significant frequency of CBFB mutation has been documented in breast cancer[150-151], while elevated CBFB expression has been characterized as enabling RUNX2-mediated invasive phenotypes in in vitro models of breast cancer cell growth and proliferation[152].

FINDING SUMMARY
CBFB encodes the regulatory beta subunit of core binding factor. It complexes with any one of the RUNX proteins (1, 2, or 3) to produce a family of transcription factors required for normal hematopoiesis and osteogenesis[153]. Many cases of acute myeloid leukemia (AML) are characterized by a pericentric inversion of chromosome 16, which creates a fusion gene combining N-terminal CBFB with the C-terminus of MYH11[154]. The resulting fusion protein is hypothesized to contribute to leukemogenesis via dominant-negative inhibition of RUNX1-mediated transcriptional activity[155], although additional, RUNX1-independent mechanisms have also been proposed[156].

GENE
DNMT3A

ALTERATION
splice site 1123-1G>A

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
1123-1G>A

POTENTIAL TREATMENT STRATEGIES
While DNA methyltransferase (DNMT) inhibitors such as azacitidine and decitabine have shown clinical benefit in hematological malignancies, clinical utility in solid tumors has not been demonstrated.

FREQUENCY & PROGNOSIS
DNMT3A mutations have been reported in 13% of hematopoietic and lymphoid malignancies and at lower frequencies in solid tumors, including those of the peritoneum (3%), skin (3%), urinary tract (3%), large intestine (3%), small intestine (3%), and lung (2%) (COSMIC, 2020). The role of DNMT3A alterations in solid tumors is unclear. Multivariate analysis showed strong DNMT3A protein expression to be an independent prognostic marker for improved survival in patients with lung adenocarcinoma[157]. 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[158-163]. CHIP is associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[158-159]. Clinical management of patients with CHIP may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[164]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CHIP[162,165-166]. 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
The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[167-168]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[169-174]. Alterations that result in loss or disruption of the C-terminal catalytic domain (amino acids 627-912), such as observed here, are expected to be inactivating[175-178].

GENE
INPP4B

ALTERATION
Y115fs*2

TRANSCRIPT ID
NM_003866

CODING SEQUENCE EFFECT
343_344insT

POTENTIAL TREATMENT STRATEGIES
There are no approved drugs targeting INPP4B loss or mutation. Multiple preclinical studies have shown that loss or inactivation of INPP4B leads to activation of the PI3K-AKT pathway[179-181]. However, sensitivity of tumors harboring INPP4B alterations to inhibitors of this pathway has not been tested clinically or preclinically.

FREQUENCY & PROGNOSIS
INPP4B mutations have been reported in 5% of cancers across all subtypes, with highest prevalence in carcinomas of the liver (19%), pancreas (13%), prostate (12%), breast (8%), and esophagus (8%) (COSMIC, 2020). Loss of heterozygosity at the INPP4B locus in basal-like breast cancer is correlated with reduced overall survival[179-180]. Reduced expression of INPP4B is also observed in lung cancer, prostate cancer, and acute lymphoblastic leukemia (ALL) in children with Down syndrome[182-184], and has been associated with reduced time to recurrence in prostate cancer[183]. Collectively, these data suggest a tumor suppressor role for INPP4B.

FINDING SUMMARY
INPP4B encodes an enzyme that negatively regulates the PI3K-AKT pathway and behaves as a tumor suppressor[179-181,185-186].

GENE
WT1

ALTERATION
E258*

TRANSCRIPT ID
NM_024426

CODING SEQUENCE EFFECT
772G>T

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies that target WT1 mutation. Preclinical studies in acute myeloid leukemia (AML) have shown that WT1 loss may disrupt interactions with the TET2 enzyme[187-189] and, based on one clinical study, may confer sensitivity to the DNA methyltransferase (DNMT) inhibitor azacitidine in AML and myelodysplastic syndrome patients[190]. However, it is not known if this approach would be beneficial for solid tumors or in the context of WT1 mutation. WT1 peptide-based vaccines are being investigated in hematopoietic malignancies and solid cancers, although their relevance to WT1 mutation is unknown[191-195].

FREQUENCY & PROGNOSIS

WT1 alterations have been reported in Wilms tumors at frequencies ranging from 9% to 81%, with higher rates in bilateral Wilms tumors[196-200], and at lower frequencies (<8%) in various other solid tumors (COSMIC, 2020). Reduced expression or aberrant methylation of WT1 has been reported in a variety of cancers including breast cancer, colorectal cancer, testicular germ cell tumors, and non-small cell lung carcinoma (NSCLC)[201-205], and low expression of WT1 in NSCLC was predictive of poor patient prognosis in one study[206]. However, the majority of solid tumors examined have been reported to overexpress WT1[207-214]. In several tumor types, overexpression of WT1 has been associated with poor prognosis[214-216].

FINDING SUMMARY

The WT1 gene encodes a zinc finger transcription factor, which has been described as both a tumor suppressor and oncogene in a variety of cancers, including Wilms tumor (nephroblastoma), a malignant tumor of the kidney found most commonly in children[217]. WT1 alterations that disrupt the N-terminal region (amino acids 74–244, also 6–180 in alternate transcripts) and/or zinc finger domain (amino acids 391–506, also 323–438 in alternate transcripts) are predicted to be inactivating[218-222]. Missense mutations at codons 404, 462, and 464 (336, 394, and 396 in alternate transcripts) have been observed in patients with T-cell acute lymphoblastic leukemia (T-ALL)[223], acute myeloid leukemia (AML) post myelodysplastic syndrome[224-225], Wilms tumor or the disorder Denys-Drash syndrome[222-223,226-228]. Germline mutations in WT1 are associated with several rare genitourinary developmental and cancer syndromes, including Wilms tumor, WAGR syndrome, Denys-Drash syndrome, Frasier syndrome, nephrotic syndrome type 4, and Meacham syndrome[229-234]. Wilms tumor, the most common of these, occurs in approximately 1:10,000 children and accounts for 7–8% of childhood cancers[229-230,235], and in the appropriate clinical context, germline testing of WT1 is recommended.

Alpelisib

Assay findings association

PIK3CA
E542V, N1044K

AREAS OF THERAPEUTIC USE

Alpelisib inhibits phosphatidylinositol 3-kinase (PI3K) with selective activity against the alpha isoform (PI3K-alpha), which is encoded by the PIK3CA gene. It is available in the EU in combination with fulvestrant for men and postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of prospective clinical data, PIK3CA mutations including C420R, E542K, E545A, E545G, E545K, E545D, Q546E, Q546R, H1047L, H1047Y, and H1047R are associated with sensitivity to alpelisib. In ER+/HER2– breast cancer, PFS benefit from the addition of alpelisib to fulvestrant was specifically observed for patients with PIK3CA mutations (11.0 vs. 5.7 months, HR=0.65), including patients with PIK3CA exon 9 or exon 20 mutations[92]. Objective responses have also been achieved by patients with several other solid tumor types harboring PIK3CA mutation[112,236] .

SUPPORTING DATA

The Phase 3 SOLAR-1 study in HR+/HER2– endocrine therapy-resistant advanced breast cancer reported that the addition of alpelisib to fulvestrant improved median PFS (11.0 vs. 5.7 months, HR=0.65), ORR (26.6% vs. 12.8%), and clinical benefit rate (61.5% vs. 45.3%) for patients with PIK3CA mutation; benefit was observed for patients with PIK3CA exon 9 and exon 20 mutations[92]. For PIK3CA-wild-type patients, addition of alpelisib to fulvestrant did not significantly improve median PFS (7.4 vs. 5.6 months, HR=0.85)[92]. A Phase 2 study reported a 17.4% ORR, 50.4% 6-month PFS rate, and median PFS of 7.3 months with alpelisib plus fulvestrant for patients with PIK3CA-mutated HR+/HER2– advanced breast cancer previously treated with a CDK4/6 inhibitor in combination with an aromatase inhibitor[237]. As neoadjuvant therapy for postmenopausal women with HR+/HER2– early breast cancer, alpelisib added to letrozole did not increase ORR for patients with (45% vs. 43%) or without (61% vs. 63%) PIK3CA mutation in a placebo-controlled Phase 2 trial[238]. In combination with letrozole and the CDK4/6 inhibitor ribociclib, alpelisib resulted in objective responses for 7.4% (2/27) and unconfirmed PRs for 15% (4/27) of patients with HR+/HER2– advanced breast cancer[239]. A Phase 1/2 study of alpelisib and nab-paclitaxel in patients with HER2– metastatic breast cancer previously treated with chemotherapy reported a 57% ORR (24/42, 2 CR) and a median PFS of 9 months, with improved median PFS in patients with PIK3CA pathway activation (13 vs. 7 months, HR=0.39)[240]. For patients with HER2+ advanced breast cancer who progressed on trastuzumab and/or a taxane, alpelisib combined with ado-trastuzumab emtansine yielded a 43% ORR (6/14, 1 CR), including responses for patients with high AKT expression or PTEN loss[241].

Everolimus

Assay findings association

PIK3CA
E542V, N1044K

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor. It is available in the EU to treat advanced renal cell carcinoma (RCC) following antiangiogenic therapy; unresectable or metastatic, well- or moderately-differentiated, progressive pancreatic neuroendocrine tumors; unresectable or metastatic, well-differentiated non-functional, progressive neuroendocrine tumors of the lung or gastrointestinal tract; and, in association with tuberous sclerosis complex (TSC), renal angiomyolipoma and subependymal giant cell astrocytoma. Everolimus is also available in combination with exemestane to treat postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer following prior therapy with a nonsteroidal aromatase inhibitor. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[94-95,98] and preclinical[99] evidence in multiple tumor types, PIK3CA activation may predict sensitivity to mTOR inhibitors such as everolimus.

SUPPORTING DATA

In an exploratory cohort of the BOLERO-2 Phase 3 study, the addition of everolimus to exemestane in the first line for hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer improve the median PFS compared to exemestane alone (11.5 vs. 4.1 months, HR = 0.39)[242]. Everolimus combined with exemestane as second-line therapy in the same setting also improved the median PFS compared with exemestane in BOLERO-2 (7.8 vs. 3.2 months, HR = 0.45)[243-245] , and modestly improved the median PFS compared with everolimus alone in BOLERO-6 (8.4 vs. 6.8 months, HR = 0.74)[246]. Patients with HR+, HER2- breast cancer also benefited from everolimus combined with other antiestrogen therapies, including letrozole, tamoxifen, and anastrozole[247-249] . For patients with HR+, HER- breast cancer who progressed on antiestrogen therapies, addition of everolimus to the most recent endocrine therapy showed efficacy with 8% ORR and median PFS of 6.6 months[250]. For patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median PFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo), but increased PFS in the HR-negative subpopulation (20.3 vs. 13.1 months)[251]. For patients with trastuzumab-resistant HER2+ breast cancer, the addition of everolimus to trastuzumab plus vinorelbine prolonged median PFS (7.0 vs. 5.8 months)[252]. Patients with metastatic triple-negative breast cancer treated with everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/25)[253]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[254], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[255].

Fulvestrant

Assay findings association

ESR1
Y537S, D538G

AREAS OF THERAPEUTIC USE

Fulvestrant is an estrogen receptor (ER) antagonist and selective estrogen receptor degrader (SERD). It is available in the EU in combination with palbociclib to treat women with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer following prior endocrine therapy. It is also available for the treatment of postmenopausal women with ER-positive advanced breast cancer who have not previously been treated with endocrine therapy or who have disease relapse on or after adjuvant antiestrogen therapy or disease progression on antiestrogen therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of a prospective-retrospective clinical study[44], activating mutations in ESR1 may predict relative benefit from selective estrogen receptor degraders, such as fulvestrant[45]. Patients with ESR1 mutations experienced an increased median progression-free survival (PFS) on fulvestrant compared to exemestane and greater benefit when palbociclib was added to fulvestrant[44].

SUPPORTING DATA

In an exploratory subgroup analysis for patients with ESR1 mutations treated with fulvestrant (35.6 vs. 24.6 months, HR=0.69), statistical significance was not reached for the overall population (34.9 vs. 28.0 months; HR=0.81, p=0.09)[256]. Prospective-retrospective analysis of ESR1 mutational status of 2 Phase 3 studies showed increased median PFS for patients with ESR1 mutations on fulvestrant compared with exemestane [5.7 vs. 2.6 months, HR=0.52, p=0.02] and greater benefit when palbociclib was added to fulvestrant (9.4 vs. 3.6 months)[44]. In the PALOMA Phase 3 study, fulvestrant combined with palbociclib to treat patients with HR+, HER2– breast cancer who progressed on endocrine therapy reported improved median PFS (11.2 vs. 4.6 months) and ORR (25% vs. 11%) compared with placebo with fulvestrant[256-258] ; the combination treatment significantly improved OS relative to the comparator for patients with prior sensitivity to endocrine therapy (39.7 vs. 29.7 months, HR=0.72). The PARSIFAL Phase 2 trial reported similar efficacy for addition of fulvestrant versus letrozole to palbociclib as first-line treatment of HR+, HER2– breast cancer[259]. A global Phase 3 MONARCH2 study of fulvestrant with the addition of abemaciclib for women with HR+, HER2– advanced breast cancer who had progressed after endocrine therapy showed significantly improved median PFS (16.4 vs. 9.3 months, HR=0.55) and ORR (48% vs. 21%) compared with placebo plus fulvestrant[260], with similar results in the interim analysis of Phase 3 MONARCHplus study of a predominantly Chinese population[261]. A Phase 3 trial of ribociclib in combination with fulvestrant in patients with HR+, HER2– breast cancer previously treated with up to 1 line of endocrine therapy improved median PFS (20.5 vs. 12.8 months, HR=0.59 and 33.6 vs. 19.2, HR=0.55 in first-line setting), ORR (41 vs. 29% in patients with measurable disease), and OS (not reached vs. 45.1 months, HR=0.73 as first line and 40.2 vs. 32.5 months, HR=0.73 as second line) as compared with placebo with fulvestrant[262-263] . For endocrine-therapy naive patients with HR+ advanced or metastatic breast cancer, the FALCON Phase 3 study demonstrated superior median PFS (16.6 vs. 13.8 months) with single-agent fulvestrant compared with anastrozole[264]. A Phase 3 study of fulvestrant in combination with anastrozole to treat patients with HR+ advanced or metastatic breast cancer reported improved median PFS (15.0 vs. 13.5 months, HR=0.80, p=0.007) and median OS (49.8 vs. 42.0 months, HR=0.82, p=0.03) relative to anastrozole alone[265-266] and a greater median OS benefit from the combination in patients who had not been previously treated with adjuvant hormonal therapy (52.2 vs. 40.3, HR=0.73) than in those who had been (48.2 vs. 43.5, HR=0.97)[266]. Phase 2 trials have reported increased median PFS and clinical benefit when fulvestrant is combined with everolimus or palbociclib, pertuzumab, and trastuzumab (in neoadjuvant setting) in patients with AI-resistant or treatment naive breast cancer, respectively[267-268] .

Anastrozole

Patient may be resistant to Anastrozole

Assay findings association

ESR1
Y537S, D538G

AREAS OF THERAPEUTIC USE

Anastrozole is a selective nonsteroidal aromatase inhibitor. It is available in the EU for the adjuvant treatment of postmenopausal women with hormone-receptor-positive (HR+) early invasive breast carcinoma either as first-line treatment or after 2 to 3 years of adjuvant tamoxifen, or for the treatment of postmenopausal women with advanced HR+ breast cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on randomized-controlled trials, retrospective studies and case reports, aromatase inhibitors may provide clinical benefit for hormone receptor positive (HR+) breast and gynecologic malignancies[39-43,269-271]. Based on prospective and retrospective studies in breast carcinoma, ESR1 ligand-independent activating alterations, such as seen here, confer resistance of aromatase inhibitors (AIs), particularly for patients who have already received AI treatment[44-45,50,68,91,272-274].

SUPPORTING DATA

A long-term follow-up of the ATAC Phase 3 clinical trial reported significant improved disease-free survival [hazard ratio (HR) = 0.91, p=0.04], time to recurrence, and time to distant recurrence in postmenopausal women with early stage breast cancer treated with anastrozole as adjuvant therapy compared to tamoxifen[270]; however, patients in the ATAC cohort had not received prior treatment with aromatase inhibitors (AI), and ESR1 mutations are infrequently acquired in the adjuvant setting[73,91,275]. In another study, patients with ESR1 mutations had a substantially shorter progression-free survival on subsequent AI-based therapy compared to patients with wild-type ESR1 (HR = 3.1)[73].

Exemestane

Patient may be resistant to Exemestane

Assay findings association

ESR1
Y537S, D538G

AREAS OF THERAPEUTIC USE

Exemestane is a steroidal irreversible aromatase inhibitor that is available in the EU for the adjuvant treatment of estrogen receptor-positive (ER+), invasive, early breast cancer in postmenopausal women who have previously received 2 or 3 years of adjuvant tamoxifen. Exemestane is also available to treat women with advanced breast cancer and natural or induced postmenopause who have progressed following antiestrogen therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on randomized-controlled trials, retrospective studies and case reports, aromatase inhibitors may provide clinical benefit for hormone receptor positive (HR+) breast and gynecologic malignancies[39-43,269-271]. Based on prospective and retrospective studies in breast carcinoma, ESR1 ligand-independent activating alterations, such as seen here, confer resistance of aromatase inhibitors (AIs), particularly for patients who have already received AI treatment[44-45,50,68,91,272-274].

SUPPORTING DATA

Retrospective mutational analyses of the Phase 3 SoFEA study demonstrated significantly reduced median progression-free survival [PFS, 2.6 vs. 8.0 months; hazard ratio (HR) = 2.12; p=0.01] and a trend toward decreased overall survival (OS; 12.8 vs. 22.8 months) for patients with hormone receptor-positive (HR+) breast cancer who harbored ESR1 mutations and were treated with exemestane, relative to those with wild-type ESR1 treated similarly[44]. Further, median PFS was significantly shorter for patients harboring ESR1 mutations treated with exemestane than for those treated with a regimen containing the selective ER degrader fulvestrant (2.4 vs. 5.7 months; HR = 0.52; p=0.02); a significant difference between the regimens was not observed among patients with wild-type ESR1 (3.0 vs. 5.4 months, HR = 1.07, p=0.77)[44]. In retrospective mutational analyses of the intent-to-treat cohort of the Phase 3 BOLERO-2 study, both the exemestane plus placebo and exemestane plus everolimus arms demonstrated significantly decreased median OS for patients with HR+ breast cancer harboring ESR1 D538G (25.99 vs. 32.1 months, p=0.03) or Y537S (19.98 vs. 32.1 months, p=0.003), relative to those lacking these mutations[91]. Among the patients with advanced breast cancer in the BOLERO-2 study who were treated with exemestane and placebo, those harboring ESR1 D538G exhibited reduced median PFS relative to those lacking either ESR1 D538G or Y537S (2.69 vs. 3.94 months, HR = 1.71, p=0.02), whereas those harboring ESR1 Y537S did not show a significant difference relative to the Y537S/D538G-negative population (4.14 vs. 3.94 months, HR = 0.95, p=0.86); however, this control population was not analyzed for other ESR1 alterations that may have been present following previous treatment with nonsteroidal aromatase inhibitors[91].

Letrozole

Patient may be resistant to Letrozole

Assay findings association

ESR1
Y537S, D538G

AREAS OF THERAPEUTIC USE

Letrozole is a selective nonsteroidal aromatase inhibitor. It is available in the EU for the extended adjuvant treatment of postmenopausal women with hormone-dependent invasive breast cancer who have received prior tamoxifen therapy for 5 years, as first-line therapy for postmenopausal women with hormone-dependent advanced breast cancer, and for treatment of advanced breast cancer after relapse or progression in women who are in either natural or induced postmenopausal endocrine status and have previously received antiestrogen therapy. Letrozole is also available as neoadjuvant therapy for postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer who are not eligible for chemotherapy and for whom an immediate surgical intervention is not indicated. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on randomized-controlled trials, retrospective studies and case reports, aromatase inhibitors may provide clinical benefit for hormone receptor positive (HR+) breast and gynecologic malignancies[39-43,269-271]. Based on prospective and retrospective studies in breast carcinoma, ESR1 ligand-independent activating alterations, such as seen here, confer resistance of aromatase inhibitors (AIs), particularly for patients who have already received AI treatment[44-45,50,68,91,272-274].

SUPPORTING DATA

Follow-up analysis from the Phase 3 Breast International Group (BIG) 1-98 study reported significantly improved intention-to-treat disease-free survival (HR = 0.86), and OS (HR = 0.87) in postmenopausal women with early stage breast cancer treated with letrozole monotherapy compared to tamoxifen monotherapy; sequential treatments involving tamoxifen and letrozole did not improve outcome compared with letrozole monotherapy[269]. For postmenopausal patients with newly diagnosed metastatic estrogen receptor-positive (ER+)/HER2- breast cancer, Phase 2 and 3 studies reported significant clinical benefit from letrozole combined with palbociclib[276-278], with an improved ORR (42% vs. 35%) and median PFS (24.8 vs. 14.5 months) compared with letrozole plus placebo in the Phase 3 PALOMA-2 trial[276,279]. However, patients with ESR1 mutations had a substantially shorter PFS on subsequent AI-based therapy compared to patients with wild-type ESR1 (HR = 3.1)[73], including in the presence of palbociclib (PFS = 3.3 months vs. 9.0 months, p = 0.038)[280].

Temsirolimus

Assay findings association

PIK3CA
E542V, N1044K

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor. It is available in the EU to treat advanced renal cell carcinoma (RCC) and relapsed or refractory mantle cell lymphoma (MCL). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical[96-97,281] and preclinical[99] evidence, PIK3CA activation may predict sensitivity to mTOR inhibitors such as temsirolimus. In two studies of temsirolimus-containing treatment regimens in a variety of cancer types, response rates of 4/16 (25%)[96] and 7/23 (30%)[281] were reported in patients with PIK3CA-mutant tumors.

SUPPORTING DATA

A Phase 1 trial examining the combination of temsirolimus, liposomal doxorubicin, and bevacizumab in 74 patients with breast and gynecological malignancies reported that 37.9% of patients experienced either a CR (1.4%), PR (18.9%), or SD (17.6%); among 25 patients with PIK3CA mutation or PTEN loss, 52% experienced a CR, PR (36%), or SD (16%)[282]. Another Phase 1 trial including patients with several types of cancer reported a 42% incidence of complete or partial responses in patients with metastatic breast cancer[283]. However, a Phase 2 study of temsirolimus in pretreated patients with metastatic breast cancer reported minimal clinical activity and no association with PTEN protein or PIK3CA mutation status[284]. A Phase 3 placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer was terminated at the second interim since the addition of temsirolimus to letrozole did not improve PFS as a first-line therapy[285]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[97].

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.

GENE
ESR1

ALTERATION
Y537S, D538G

RATIONALE
Tumors with ESR1 activating mutations may be sensitive to selective estrogen receptor degraders (SERDs). Clinical evidence suggests that ESR1 ligand-independent activating alterations reduce the efficacy of AI-containing regimens in breast carcinoma, particularly for patients who have already received AI treatment.

NCT03778931

PHASE 3

Phase 3 Trial of Elacestrant vs. Standard of Care for the Treatment of Patients With ER+/HER2- Advanced Breast Cancer

TARGETS
Aromatase, ER

LOCATIONS: Leoben (Austria), Wels (Austria), Budapest (Hungary), Pécs (Hungary), Debrecen (Hungary), Udine (Italy), Szolnok (Hungary), Innsbruck (Austria), Nyiregyhaza (Hungary), Bologna (Italy)

NCT03284957

PHASE 1/2

Phase 1 / 2 Study of SAR439859 Single Agent and in Combination With Palbociclib in Postmenopausal Women With Estrogen Receptor Positive Advanced Breast Cancer

TARGETS
ER, CDK4, CDK6

LOCATIONS: Brno (Czechia), Hradec Kralove (Czechia), Praha 4 (Czechia), Praha 2 (Czechia), Negrar (Italy), Warsaw (Poland), Szczecin (Poland), Milano (Italy), Gdynia (Poland), Napoli (Italy)

NCT04214288

PHASE 2

A Comparative Study of AZD9833 Versus Fulvestrant in Women With Advanced ER-Positive HER2-Negative Breast Cancer

TARGETS
ER

LOCATIONS: Kecskemét (Hungary), Ohio, Alabama

NCT04305496

PHASE 3

Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2– Breast Cancer

TARGETS
ER, AKTs

LOCATIONS: Szolnok (Hungary), Krakow (Poland), Pringy (France), Namur (Belgium), Charleroi (Belgium), Bruxelles (Belgium), Edegem (Belgium), Wilrijk (Belgium), Catanzaro (Italy), Rouen (France)

NCT03220178

PHASE 4

Impact of eHealth-support on Quality of Life in Metastatic Breast Cancer Patients Treated With Palbociclib and Endocrine Therapy

TARGETS
ER, Aromatase, CDK4, CDK6

LOCATIONS: Mainz (Germany)

CLINICAL TRIALS

NCT03227328

PHASE 2

CDK4/6-inhibitor or Chemotherapy, in Combination With ENDOcrine Therapy, for Advanced Breast Cancer / KENDO

TARGETS
CDK6, CDK4, ER

LOCATIONS: Ravenna (Italy), Rimini (Italy), Meldola (Italy)

NCT03809988

PHASE 2

PALbociclib Rechallenge in horMone Receptor-posItive/HER2- Negative Advanced Breast Cancer (PALMIRA)

TARGETS
CDK4, CDK6, Aromatase, ER

LOCATIONS: Strasbourg (France), Dijon (France), Paris (France), Maidstone (United Kingdom), Girona (Spain), La Roche-sur-Yon (France), Terrassa (Spain), Barcelona (Spain), Badalona (Spain), Manchester (United Kingdom)

NCT03099174

PHASE 1

This Study in Patients With Different Types of Cancer (Solid Tumours) Aims to Find a Safe Dose of Xentuzumab in Combination With Abemaciclib With or Without Hormonal Therapies. The Study Also Tests How Effective These Medicines Are in Patients With Lung and Breast Cancer.

TARGETS
CDK4, CDK6, IGF-1, IGF-2, Aromatase, ER

LOCATIONS: Besançon (France), København Ø (Denmark), Herlev (Denmark), Paris (France), Marseille (France), Barcelona (Spain), L'Hospitalet de Llobregat (Spain), Plerin Sur Mer (France), Turku (Finland), Helsinki (Finland)

NCT03322215

PHASE 2

HR+/HER2- Advanced Breast Cancer and Endocrine Resistance

TARGETS
CDK4, CDK6, ER

LOCATIONS: Malmö (Sweden), Göteborg (Sweden), Stockholm (Sweden), Uppsala (Sweden)

NCT03363893

PHASE 1/2

Modular Study to Evaluate CT7001 Alone in Cancer Patients With Advanced Malignancies

TARGETS
ER

LOCATIONS: Brighton (United Kingdom), London (United Kingdom), Oxford (United Kingdom), Manchester (United Kingdom), Liverpool (United Kingdom), Ohio, Virginia, Florida, Texas

GENE
PIK3CA

ALTERATION
E542V, N1044K

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

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: Wien (Austria), Brno (Czechia), Linz (Austria), Olomouc (Czechia), Tatabánya (Hungary), Salzburg (Austria), Budapest (Hungary), Gliwice (Poland), Pécs (Hungary), Udine (Italy)

NCT03997123

PHASE 3

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

TARGETS
AKTs

LOCATIONS: Jihlava (Czechia), Praha 4 (Czechia), Praha 10 (Czechia), Horovice (Czechia), Chomutov (Czechia), Wroclaw (Poland), Tomaszów Mazowiecki (Poland), Poznan (Poland), Konin (Poland), Radom (Poland)

NCT04305496

PHASE 3

Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2− Breast Cancer

TARGETS
ER, AKTs

LOCATIONS: Szolnok (Hungary), Krakow (Poland), Pringy (France), Namur (Belgium), Charleroi (Belgium), Bruxelles (Belgium), Edegem (Belgium), Wilrijk (Belgium), Catanzaro (Italy), Rouen (France)

NCT04191499

PHASE 2/3

A Study Evaluating the Efficacy and Safety of GDC-0077 + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer

TARGETS
PI3K-alpha, ER, CDK4, CDK6

LOCATIONS: Paderborn (Germany), Novgorod Veliky (Russian Federation), Saint Petersburg (Russian Federation), Moscow (Russian Federation), Yaroslavl (Russian Federation), Volgograd (Russian Federation), Quebec City (Canada), Connecticut, New York, Toronto (Canada)

NCT03056755

PHASE 2

Efficacy and Safety of Treatment With Alpelisib Plus Endocrine Therapy in Patients With HR+, HER2-negative aBC, With PIK3CA Mutations, Whose Disease Has Progressed on or After CDK 4/6 Treatment With an Aromatase Inhibitor (AI) or Fulvestrant

TARGETS
ER, PI3K-alpha, Aromatase

LOCATIONS: Dresden (Germany), Augsburg (Germany), Erlangen (Germany), Ulm (Germany), Berlin (Germany), Tübingen (Germany), Heidelberg (Germany), Bologna (Italy), Ancona (Italy), Bergamo (Italy)

NCT03424005

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Metastatic Triple-Negative Breast Cancer (Morpheus-TNBC)

TARGETS
PD-L1, AKTs, MEK, VEGFA

LOCATIONS: Erlangen (Germany), Essen (Germany), Lyon (France), Villejuif CEDEX (France), London (United Kingdom), Toulouse (France), Barcelona (Spain), Glasgow (United Kingdom), Madrid (Spain), Petach Tikva (Israel)

CLINICAL TRIALS

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)

NCT03337724

PHASE 2/3

A Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Participants With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor-Positive, HER2-Negative Breast Cancer

TARGETS
AKTs

LOCATIONS: Stoke on Trent (United Kingdom), Zaragoza (Spain), Diyarbakir (Turkey), Kumamoto (Japan), Hyogo (Japan)

NCT04060862

PHASE 3

A Study of Ipatasertib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Hormone Receptor Positive and HER2 Negative Locally Advanced Unresectable or Metastatic Breast Cancer

TARGETS
AKTs, CDK4, CDK6, ER

LOCATIONS: Sutton (United Kingdom), London (United Kingdom), Barcelona (Spain), Manchester (United Kingdom), New Jersey, Hamilton (Canada), Georgia, Calgary (Canada), Porto Alegre (Brazil), Malvern (Australia)

NCT03800836

PHASE 1

A Study to Evaluate the Safety and Efficacy of Ipatasertib in Combination With Atezolizumab and Paclitaxel or Nab-Paclitaxel in Participants With Locally Advanced or Metastatic Triple-Negative Breast Cancer

TARGETS
AKTs, PD-L1

LOCATIONS: Dijon (France), Villejuif CEDEX (France), Paris (France), London (United Kingdom), Angers (France), Nottingham (United Kingdom), Bordeaux (France), Barcelona (Spain), Madrid (Spain), Sevilla (Spain)

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.

ALK
I795T

BCORL1
S501C

BRIP1
N716D

CHEK2
I160T

DNMT3A
P904A

ERRFI1
R148W

MED12
R438G

MSH3
A62_P63insAAAPAA

RET
L56M

WHSC1 (MMSET)
H528N

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.

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*

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

APPENDIX Genes assayed in FoundationOne®Liquid CDx

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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

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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

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