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 NAME Thyroid papillary carcinoma
DATE OF BIRTH 1944
SEX Male
MEDICAL RECORD

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE Thyroid
SPECIMEN ID 1
SPECIMEN TYPE Block
DATE OF COLLECTION
SPECIMEN RECEIVED

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

Genomic Signatures

Microsatellite status - Cannot Be Determined
Tumor Mutational Burden - Cannot Be Determined

Gene Alterations

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

NTRK1 TPM3-NTRK1 fusion
CHEK2 I157T
TET2 P587fs*14

1 Disease relevant genes with no reportable alterations: ***RET***

3 Therapies approved in the EU
0 Therapies with Lack of Response
15 Clinical Trials

GENOMIC SIGNATURES	ACTIONABILITY
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** see Genomic Signatures section
Tumor Mutational Burden - Cannot Be Determined	**No therapies or clinical trials.** see Genomic Signatures section

GENE ALTERATIONS	THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
***NTRK1* -** TPM3-NTRK1 fusion	Entrectinib 2A	Crizotinib
5 Trials *see p. 10*	Larotrectinib 2A	
***CHEK2* -** I157T	none	none
10 Trials *see p. 8*		

☐ *NCCN category*

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 Genomic Alterations section.

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

Therapies contained in this report may have been approved 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.

BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden[1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[2-6], including the approved therapies nivolumab (alone or in combination with ipilimumab)[7-9], pembrolizumab[10-11], atezolizumab, avelumab, and durvalumab[3-5] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI has been reported in 17-65% (n = 17-76) of thyroid cancer cases[12-15]. One study reported MSI positivity in 84% (59/70) of papillary thyroid carcinoma (PTC) cases, with 64% (38/59) being MSI-H and 46% (21/59) being MSI-low (MSI-L), and MSI positivity in 92% (11/12) of follicular thyroid carcinoma (FTC) cases, with 82% (9/11) being MSI-H and 18% (2/11) being MSI-L; MSI-H was not observed in benign thyroid samples[16]. MSI was significantly associated with low risk characteristics in patients with malignant thyroid tumors[15], and MSI positivity at one or more marker sites was significantly associated with improved survival in patients with thyroid cancer[14]. One study reported an increased incidence of MSI in pediatric and adult patients with radiation-associated thyroid cancer, as compared with spontaneous thyroid carcinomas without radiation history[17].

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[18]. 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[18-20]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered. While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[18], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[21]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[21-23] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[24-26]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[27-29], anti-PD-1 therapies[27-30], and combination nivolumab and ipilimumab[31-35]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[27-30,36]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[27]. 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[37] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[28]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[30,36]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. As the TMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

Median TMB is relatively low in thyroid carcinomas, with 1.8 mutations per megabase (muts/Mb) reported in papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and medullary thyroid carcinoma (MTC) and 2.5 muts/Mb reported in anaplastic thyroid carcinoma (ATC)[38]. High TMB (>20 muts/Mb) has been reported in 1% of MTCs and 1.4% of ATCs, but not in any of the PTCs or FTCs analyzed[38]. A whole exome study of 39 follicular thyroid carcinoma tissue samples reported a worse prognosis for those with higher mutational burden (hazard ration 1.4, p=0.02), independent of histopathological classification[39].

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[40-41] and cigarette smoke in lung cancer[11,42], treatment with temozolomide-based chemotherapy in glioma[43-44], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[45-49], and microsatellite instability (MSI)[45,48-49]. Elevated TMB has been reported to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[28-30,36]. However, the TMB level in this sample could not be determined with confidence.

GENE
NTRK1

ALTERATION
TPM3-NTRK1 fusion

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data indicate that NTRK fusions predict sensitivity to TRK inhibitors such as larotrectinib, entrectinib, AZD7451, belizatinib, and PLX7486[50-60]. Durable clinical responses have also been reported in patients with NTRK1 fusion-positive tumors treated with the mutikinase inhibitor crizotinib[51,54-55,61-63]. Larotrectinib is approved to treat patients with NTRK-fusion-positive solid tumors based on ORR and duration of response. Analysis of combined data from several larotrectinib studies reported an ORR of 80.7% (88/109) for adult and pediatric patients with various solid tumors harboring NTRK fusions treated with larotrectinib; the responses were durable, and CRs were observed for 17% of patients[59]. In a Phase 1/2 study for patients with NTRK fusions, larotrectinib showed clinical efficacy for patients with intracranial disease; disease control was observed for all evaluable patients (1 PR, 7 SDs) with primary central nervous system (CNS) tumors[64]. Pooled analysis of 3 Phase 1/2 trials of entrectinib for adult patients with NTRK-fusion-positive solid tumors reported an ORR of 57.4% (31/54), median PFS of 11.2 months, and median OS of 20.9 months[65-66] . Similar activity was observed for patients with NTRK1 fusions (ORR of 59.1% [13/22]) and NTRK3 fusions (ORR of 58.1% [18/31]); however, 1 patient with NTRK2 fusion did not respond[65]. Subgroup analysis of patients with NSCLC reported an ORR of 70%, with intracranial response seen for 4 of 6 patients[66]. A Phase 1/1b trial of entrectinib for children and adolescents with recurrent or refractory solid tumors reported a CR for a patient with high-grade glioma (HGG) and an NTRK3 fusion, 2 PRs for patients with HGG and NTRK1 and NTRK2 fusions, 2 PRs for patients with infantile fibrosarcoma (IFS) and NTRK3 fusions, and 1 PR for a patient with melanoma and an NTRK3 fusion[67]. Acquired resistance to larotrectinib and entrectinib due to the emergence of kinase domain mutations in NTRK fusions has been reported for some patients[58-59,68-69]. Next-generation TRK inhibitors such as selitrectinib (LOXO-195) and repotrectinib have shown preclinical and clinical activity against acquired NTRK resistance mutations[68,70-71]. For patients with NTRK-fusion-positive cancers previously treated with at least 1 TRK inhibitor, treatment with selitrectinib achieved an ORR of 34.5% (10/29), with an ORR of 45% (9/20) for patients harboring a TRK kinase mutation[72]. In a Phase 1 study, a PR was reported for a patient with NTRK1-fusion-positive papillary thyroid cancer treated with taletrectinib[73]. Analysis of paired pre- and post-treatment samples from patients with NTRK1 or NTRK3 fusions treated with various first or next generation TRK inhibitors, identified emerging mutations in the MAPK or upstream RTK pathway (BRAF, KRAS, MET, MAP2K1) in 6/8 patients who developed acquired resistance[74]. Limited clinical and preclinical data suggest upfront combination TRK and MEK inhibitor treatment may be more effective than sequential treatment[74].

FREQUENCY & PROGNOSIS

NTRK1 activating fusions have been reported in papillary thyroid cancer (PTC) at frequencies ranging from 0-16%[75-82]. However, NTRK1 amplification was only found in 1/507 PTC samples in a large-scale study, with NTRK1 deletion also found in 1 sample[83]. NTRK1 alterations have not been reported in medullary thyroid cancer (MTC) or follicular thyroid carcinoma (COSMIC, Apr 2020)[84]. Two studies reported that NTRK1 rearrangements are associated with more aggressive disease and worse prognosis in PTC patients, compared to subtypes of PTC driven by other oncogenic events[77,81]. However, another study found no significant difference in tumor-specific survival in patients with PTC harboring NTRK1 or RET fusions compared to those with fusion-negative PTC[79]. Clinical benefit, specifically resolution of pulmonary metastases, was reported in a pediatric patient with PTC harboring a TPM3-NTRK1 fusion treated with larotrectinib[85]. The prognostic implications of NTRK1 alterations in MTC have not been an area of significant focus in the literature (PubMed, Nov 2020).

FINDING SUMMARY

NTRK1 encodes the receptor tyrosine kinase TRKA, which plays a role in the development of the nervous system by regulating cell proliferation, differentiation, and survival of neurons. TRKA is activated upon binding of its ligand NGF to promote several downstream signaling pathways including GRB2-RAS-MAPK, NF-Kappa-B, and RAS-PI3K-AKT1[86-89]. NTRK1 fusions that include an N-terminal oligomerization-promoting partner gene linked to the kinase domain of TRKA (aa 510-781), as seen here, have been characterized as activating, exhibiting constitutive kinase activity and tyrosine phosphorylation[51-52,75,77,90-93]. Patients with NTRK1 fusions have experienced clinical benefit from TRK inhibitors such as larotrectinib[59-60] and entrectinib[58] and from crizotinib[51,54,61].

GENE
CHEK2

ALTERATION
I157T

TRANSCRIPT ID
NM_007194

CODING SEQUENCE EFFECT
470T>C

VARIANT ALLELE FREQUENCY (% VAF)
49.03%

POTENTIAL TREATMENT STRATEGIES

Limited clinical data indicate that CHEK2 inactivation may predict sensitivity to PARP inhibitors. Patients with CHEK2-altered prostate cancer have experienced clinical responses to PARP inhibitors[94-96]. Clinical benefit has been observed for patients with ovarian[97] and testicular[98] cancers treated with PARP inhibitors. One study of patients with breast cancer reported that carriers of the CHEK2 H371Y mutation have a higher likelihood of response to neoadjuvant chemotherapy[99], whereas another study found that CHEK2 mutation carriers have a lower frequency of objective clinical responses to neoadjuvant therapy[100]. A third study reported that the CHEK2 1100delC mutation is not associated with differential efficacy of chemotherapy and endocrine therapy in patients with metastatic breast cancer[101].

FREQUENCY & PROGNOSIS

CHEK2 mutations have been reported in 4.4% of glioblastoma (GBM) samples and in carcinomas of the urinary tract (3%), ovary (3%), endometrium (1.2%), and large intestine (1.9%), and at low frequency in a variety of solid and hematologic cancer types (COSMIC, 2020). In breast cancer, certain CHEK2 mutations are associated with higher grade and larger tumors as well as bilateral disease[102]. A study reported that a polymorphism in CHEK2 was associated with worse survival of patients with GBM, but this association lost significance after adjusting for other prognostic factors[103-104]. Another study in prostate cancer reported that CHEK2 expression is decreased in higher grade tumors and that CHEK2 is a tumor suppressor that decreases the growth of prostate cancer cells and regulates androgen receptor signaling[105]. 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[106-111]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[110,112-113]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

CHEK2 encodes the protein checkpoint kinase 2, a serine/threonine kinase that plays an important role in the DNA-damage response; it is a putative tumor suppressor[114-117]. CHEK2 alterations that disrupt or remove the SQ/TQ cluster domain (SCD; amino acids 19–69), forkhead-associated domain (FHA; amino acids 115–175), and/or the kinase domain (amino acids 220–486) are predicted to be inactivating[118-128]. Germline CHEK2 mutation has been associated with cancer susceptibility of low to moderate penetrance, especially in hereditary breast cancer[129]. CHEK2 germline mutation has been identified in approximately 2.5% of familial or high-risk breast cancer cases[130-131]. Although heterozygous germline CHEK2 mutation increases breast cancer risk two- to three-fold, it is not associated with younger age at diagnosis[131-132]. In the appropriate clinical context, germline testing of CHEK2 is recommended.

GENE
TET2

ALTERATION
P587fs*14

TRANSCRIPT ID
NM_001127208

CODING SEQUENCE EFFECT
1758delG

VARIANT ALLELE FREQUENCY (% VAF)
7.21%

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors, including 1-3% of lung cancer (including lung adenocarcinomas and lung squamous cell carcinomas)[133-135], 3% of melanomas[136], 2% of colorectal adenocarcinomas[137], 2% of hepatocellular carcinomas[138], and 0.4-2% of breast invasive carcinomas[139-141]. Reduced TET2 expression has been reported in a number of solid tumors, including melanoma[142], cervical squamous cell carcinoma[143], hepatocellular carcinoma[144-145], breast cancer[145-146], prostate cancer[147], epithelial ovarian cancer[148], and oral squamous cell carcinoma[149]. Reduced expression of TET2 has been associated with advanced stage in prostate cancer[147] and ovarian cancer[148], as well as disease progression in melanoma[142,150]. 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[106-111]. CHIP is associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[106-107]. Clinical management of patients with CHIP may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[151]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CHIP[110,112-113]. 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

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[152-153]. TET2 alterations that impact critical residues or result in the disruption or loss of the catalytic domain (amino acids 1129-1936), such as seen here, are predicted to impair the tumor suppressor activity of TET2[145,154-157].

Entrectinib

Assay findings association

NTRK1
TPM3-NTRK1 fusion

AREAS OF THERAPEUTIC USE

Entrectinib is a TKI that targets TRKA/B/C (NTRK1/2/3), ROS1, and ALK. It is available in the EU to treat patients with ROS1-positive non-small cell lung cancer (NSCLC) and patients with NTRK fusion-positive solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical evidence in various solid tumor types[58,65,67,158] , NTRK fusions may predict sensitivity to entrectinib.

SUPPORTING DATA

Analysis of combined data from 3 Phase 1/2 trials of entrectinib (ALKA-372-001, STARTRK-1, and STARTRK-2) for adult patients with various NTRK fusion-positive solid tumors reported an ORR of 57.4% (31/54, 4 CRs), median PFS of 11.2 months, and median OS of 21 months; intracranial ORR was 54.5% (6/11)[159]. Additionally, 80.0% (8/10) of evaluable pediatric patients with high-grade glioma (n=4), CNS embryonal tumor (n=1), melanoma (n=1), or infantile fibrosarcoma (n=2) with NTRK fusions responded to entrectinib; 1 non-responder was observed to have an out-of-frame NTRK fusion[160]. Clinical benefit with entrectinib monotherapy has been achieved for adult and pediatric patients with various solid tumors with and without CNS metastases and with NTRK, ROS1, or ALK fusions[58,67,158,161-163] , and preclinical sensitivity has been observed in NTRK fusion-positive AML cell lines[164]. In a Phase 1 trial, responses were restricted to patients harboring NTRK, ROS1, or ALK rearrangements, with the exception of ALK-mutant neuroblastoma, and were observed for patients with ALK or ROS1 rearrangements who had not received prior ALK TKI or crizotinib, respectively[58].

Larotrectinib

Assay findings association

NTRK1
TPM3-NTRK1 fusion

AREAS OF THERAPEUTIC USE

Larotrectinib is a TKI that targets NTRK1, NTRK2, and NTRK3. It is available in the EU to treat adult and pediatric patients with NTRK fusion-positive solid tumors that are locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on extensive clinical evidence in various solid tumors[59-60,165] , NTRK fusions may predict sensitivity to larotrectinib.

SUPPORTING DATA

Combined data from Phase 1 and Phase 2 larotrectinib trials reported an ORR of 79.2% (19/24) for patients with NTRK-fusion-positive thyroid cancer[59,166] . In addition, 2 patients with NTRK1- or NTRK3-fusion-positive papillary thyroid cancer but no measurable disease showed no disease progression for >7 months when treated with larotrectinib[60].

Crizotinib

Assay findings association

NTRK1
TPM3-NTRK1 fusion

AREAS OF THERAPEUTIC USE

Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is available in the EU to treat patients with advanced non-small cell lung cancer (NSCLC) whose tumors are positive for ALK either as first-line or following previous treatment. It is also available to treat patients with ROS1-positive advanced NSCLC. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Alterations that activate NTRK1 may predict sensitivity to crizotinib. Clinical benefit with crizotinib treatment has been achieved in patients NTRK1-fusion-positive tumors including infantile fibrosarcoma[54-55,61] , lung adenocarcinoma[51,167] , and undifferentiated pleomorphic sarcoma[62].

SUPPORTING DATA

Although a Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies reported a lower ORR in patients with various solid tumors relative to those with either lymphoma or IMT, a partial response was reported in a patient with medullary thyroid cancer[168]. Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements[169-173] , ROS1 rearrangements[174-178] , an NTRK1 fusion[51], or MET activation[179-195] . Crizotinib has also benefited patients with MET-mutated renal cell carcinoma[196] and patients with MET-amplified gastroesophageal cancer, glioblastoma, and carcinoma of unknown primary[197-199] . While a Phase 1b study evaluating crizotinib for the treatment of patients with ALK-positive malignancies, reported ORR of 52.9% (9/17) and 66.7% (6/9) in patients with lymphoma and inflammatory myofibroblastic tumors (IMT), respectively, an ORR of 11.8% (2/17) was reported for patients with other types of tumors[168]. Whereas median PFS and median OS were not reached for patients with lymphoma or IMT, median PFS was 1.3 months and median OS was 8.3 months for patients with other tumor types, and the median duration of treatment was ~1 month relative to 1-3 years for patients with lymphoma or IMT[168]. A Phase 1 clinical trial of crizotinib in pediatric solid tumors reported objective responses in 14/79 patients, including nine CRs and five PRs; response was enriched in patients with activating alterations in ALK[200].

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.

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
CHEK2

ALTERATION
I157T

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

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Moscow (Russian Federation), Ryazan (Russian Federation), Saint-Petersburg (Russian Federation), St.Petersburg (Russian Federation), Kazan (Russian Federation), Samara (Russian Federation), Arkhangelsk (Russian Federation), Saint Petersburg (Russian Federation), Cluj Napoca (Romania), Comuna Floresti (Romania)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Kharkiv (Ukraine), Daugavpils (Latvia), Kyiv (Ukraine), Cherkasy (Ukraine), Dnipro (Ukraine), Riga (Latvia), Zhytomyr (Ukraine), Kropyvnytsky (Ukraine), Zaporizhzhia (Ukraine), Vinnytsia (Ukraine)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04276376

PHASE 2

Efficacy and Safety of the Combination of Rucaparib (PARP Inhibitor) and Atezolizumab (Anti-PD-L1 Antibody) in Patients With DNA Repair-deficient or Platinum-sensitive Solid Tumors

TARGETS
PD-L1, PARP

LOCATIONS: Villejuif (France)

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

CLINICAL TRIALS

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, BRAF, MEK, SMO

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

NCT03875313

PHASE 1/2

Study of CB-839 (Telaglenastat) in Combination With Talazoparib in Patients With Solid Tumors

TARGETS
GLS, PARP

LOCATIONS: Massachusetts, New York, Wisconsin, Iowa, Georgia, Alabama, Utah, Texas

NCT04267939

PHASE 1

ATR Inhibitor BAY 1895344 Plus Niraparib Phase 1b Study in Advanced Solid Tumors and Ovarian Cancer

TARGETS
ATR, PARP

LOCATIONS: Massachusetts, New York, Texas

NCT03842228

PHASE 1

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TARGETS
PI3K, PD-L1, PARP

LOCATIONS: Massachusetts, Texas

NCT03992131

PHASE 1/2

A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)

TARGETS
PARP, FGFRs, VEGFRs, TOP1

LOCATIONS: Massachusetts, Tennessee, Texas

GENE
NTRK1

RATIONALE
NTRK1 activating fusions may predict sensitivity to TRK inhibitors or crizotinib.

ALTERATION
TPM3-NTRK1 fusion

NCT03093116

PHASE 1/2

A Study of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Lublin (Poland), Gdańsk (Poland), Poznan (Poland), Szczecin (Poland), Berlin (Germany), Dresden (Germany), Groningen (Netherlands), Aviano (Italy), Heidelberg (Germany), Cologne (Germany)

NCT02568267

PHASE 2

Basket Study of Entrectinib (RXDX-101) for the Treatment of Patients With Solid Tumors Harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK Gene Rearrangements (Fusions)

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Warszawa (Poland), Gdańsk (Poland), Poznań (Poland), Gliwice (Poland), Berlin (Germany), Dresden (Germany), Göttingen (Germany), Heidelberg (Germany), Köln (Germany), Padova (Italy)

NCT02576431

PHASE 2

Study of LOXO-101 in Subjects With NTRK Fusion Positive Solid Tumors (NAVIGATE)

TARGETS
TRKA, TRKB, TRKC

LOCATIONS: Copenhagen (Denmark), Berlin (Germany), London (United Kingdom), Southampton (United Kingdom), Dublin (Ireland), Bordeaux Cedex (France), Barcelona (Spain), Santander (Spain), Valencia (Spain), Madrid (Spain)

NCT03215511

PHASE 1/2

Phase 1/2 Study of LOXO-195 in Patients With Previously Treated NTRK Fusions or Non-fusion NTRK Cancers

TARGETS
TRKC, TRKA, TRKB

LOCATIONS: Copenhagen (Denmark), Milano (Italy), Paris (France), Villejuif (France), Dublin (Ireland), Barcelona (Spain), Massachusetts, New York, Pennsylvania, Michigan

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Alaska, Vermont, New Hampshire, Massachusetts, New York, Connecticut

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.

BRAF
I463T

FLT1
S733del

MAP3K1
S939C

MET
H888D

NOTCH3
I470T

SPEN
G3464A

TSC2
A583T

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)*	*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	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*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*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*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*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*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*	*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*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*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*	*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*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST 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 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.

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.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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.

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*

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

MR Suite Version 1.0.0

The median exon coverage for this sample is N/A

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