FOUNDATIONONE®CDx

PATIENT
RU

TUMOR TYPE
Salivary gland adenoid cystic carcinoma

COUNTRY CODE
RU

REPORT DATE
24 Jul 2020

ORDERED TEST #

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

PATIENT

DISEASE Salivary gland adenoid cystic carcinoma
NAME
DATE OF BIRTH 1962
SEX
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE Salivary Gland
SPECIMEN ID
SPECIMEN TYPE Block
DATE OF COLLECTION 13 August 2019
SPECIMEN RECEIVED 13 July 2020

Genomic Signatures

Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Gene Alterations

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

HRAS Q61R

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

GENOMIC SIGNATURES

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

GENE ALTERATIONS

***HRAS* -** Q61R

7 Trials *see p. 6*

ACTIONABILITY

No therapies or clinical trials. see Genomic Signatures section	
No therapies or clinical trials. see Genomic Signatures section	
THERAPIES APPROVED IN THE EU (IN PATIENT'S TUMOR TYPE)	THERAPIES APPROVED IN THE EU (IN OTHER TUMOR TYPE)
none	Binimetinib
	Cobimetinib
	Trametinib

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
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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

FREQUENCY & PROGNOSIS

A small study of salivary gland carcinomas detected MSI in 50% (2/4) of cases; however, two larger studies reported no MSI in 58 total salivary gland tumors[6-8]. A study of oral cancer reported microsatellite instability in the single case of adenoid cystic carcinoma (ACC) analyzed[9], but there are no larger studies assessing MSI in ACC (PubMed, Jan 2020). Published data investigating the prognostic implications of MSI in adenoid cystic carcinomas are limited (PubMed, Aug 2019).

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[10]. 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[10-12]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER

Tumor Mutational Burden

RESULT
0 Muts/Mb

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[16-18] and anti-PD-1 therapies[16-19]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[16-19]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[16]. 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[20] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[17]. 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[19]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Adenoid cystic carcinomas harbor a median TMB of 1-2 mutations per megabase (muts/Mb), and less than 2% of cases have high TMB (>20 muts/Mb)[21]. The prognostic significance of TMB in adenoid cystic carcinoma has not been extensively studied (PubMed, Jan 2020).

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[22-23] and cigarette smoke in lung cancer[24-25], treatment with temozolomide-based chemotherapy in glioma[26-27], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[28-32], and microsatellite instability (MSI)[28,31-32]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[17-18].

GENE
HRAS

ALTERATION
Q61R

TRANSCRIPT NUMBER
NM_005343

CODING SEQUENCE EFFECT
182A>G

POTENTIAL TREATMENT STRATEGIES

On the basis of significant clinical benefit for 1 patient each with cholangiocarcinoma[33] and salivary gland carcinoma[34] treated with trametinib, as well as strong preclinical data[35-39], HRAS activating alterations may predict sensitivity to MEK inhibitors, such as binimetinib, cobimetinib, trametinib, and selumetinib. The reovirus Reolysin targets cells with activated RAS signaling[40-42] and has demonstrated mixed clinical efficacy, with the highest rate of response reported for head and neck cancer[43-51]. HRAS activating mutations may also predict sensitivity to farnesyl transferase inhibitors based on Phase 2 studies of tipifarnib in head and neck squamous cell carcinoma (HNSCC) with HRAS-mutated allele frequency ≥20% (ORR of 50.0% [9/18], mDOR of 14.7 months, mPFS of 5.9 months, and mOS of 15.4 months), HRAS-mutated salivary gland cancer (8.3% [1/12] PRs, 58.3% [7/12] SDs, mPFS of 7.0 months), and HRAS-mutated metastatic urothelial carcinoma (ORR of 41.7% [5/12], mPFS of 5.1 months)[52], as well as preclinical evidence in various cancer types[53-55]. HRAS mutations have been associated with secondary tumors, particularly cutaneous SCCs, occurring after treatment of primary tumors with RAF inhibitors[56-58]. Preclinical studies have also reported that activating HRAS mutations are associated with resistance to EGFR inhibitors[59-61].

FREQUENCY & PROGNOSIS

HRAS mutation was detected in ~6% (4/70) of salivary gland adenoid cystic carcinomas (ACCs)[62]. HRAS mutation has been observed in 1.5% of adenoid cystic carcinomas[63]. In patients with salivary gland ACC, mutations in either KRAS or HRAS correlated with a reduction in disease-free and overall survival[62]. Published data investigating the prognostic implications of HRAS alterations in adenoid cystic carcinoma are limited (PubMed, Feb 2020).

FINDING SUMMARY

HRAS encodes a member of the RAS family of membrane proteins that bind GDP/GTP and possess GTPase activity. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[64]. HRAS alterations affecting amino acids G12, G13, Q61 and K117, as well as mutations A59T, A146T, and A146V have been characterized to be activating and oncogenic[64-75].

Binimetinib

Assay findings association

HRAS
Q61R

AREAS OF THERAPEUTIC USE

Binimetinib is a MEK inhibitor that is available in the EU in combination with encorafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of limited clinical data[33-34] and strong preclinical data[35-39] , HRAS activating alterations may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of binimetinib for the treatment of adenoid cystic carcinoma are limited (PubMed, May 2020). Patients with various solid tumors have benefited from binimetinib as a monotherapy or in combination with other agents. In the Phase 3 COLUMBUS trial, patients with BRAF V600-mutated melanoma achieved superior benefit from addition of binimetinib to the BRAF inhibitor encorafenib (ORR 64%, PFS 14.9 months, OS 33.6 months) compared with encorafenib alone (ORR 52%, PFS 9.6 months, OS 23.5 months)[76-77] . The Phase 3 NEMO trial for patients with NRAS-mutated melanoma reported marginally increased ORR and PFS with no significant OS benefit for binimetinib monotherapy (ORR 15%, PFS 3 months, OS 11 months) compared with dacarbazine (ORR 7%, PFS 1.8 months, OS 10.1 months)[78]. Single-arm and retrospective studies have suggested intracranial activity of binimetinib alone or combined with encorafenib for NRAS- or BRAF-mutated metastatic melanoma[79-80] . The Phase 3 BEACON study for patients with BRAF V600E-mutated colorectal cancer showed that triplet therapy of binimetinib with encorafenib and the EGFR-targeting antibody cetuximab significantly improved median OS (9.0 vs. 5.4 months, HR=0.52) and ORR (26% vs. 2%) relative to the standard irinotecan and cetuximab therapy[81]. For patients with low-grade serous ovarian carcinoma, the Phase 3 MILO study of binimetinib versus physician's choice chemotherapy reported no significant improvement in median PFS (9.1 vs. 10.6 months) and did not meet its primary end point[82]. Although single-agent binimetinib has had limited efficacy in biliary tract cancer[83-84] , Phase 1/2 studies have evaluated binimetinib combined with gemcitabine and cisplatin in previously untreated patients (ORR 36%, DCR 74%, PFS 6.0 months, OS 13.3 months)[85] or binimetinib combined with capecitabine in patients with progression on gemcitabine (ORR 21%, DCR 76%, PFS 4.1 months, OS 7.8 months)[86]. In early phase studies, objective responses have been reported for patients with various KRAS-, NRAS-, or BRAF-mutated solid tumor types, including lung, thyroid, uterine, and ovarian cancer, who were treated with binimetinib as a single agent[87-88] or in combination with other therapies[89-92] .

Cobimetinib

Assay findings association

HRAS
Q61R

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor. It is available in the EU in combination with vemurafenib to treat unresectable or metastatic melanoma with a BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of limited clinical data[33-34] and strong preclinical data[35-39] , HRAS activating alterations may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Of 2 patients with adenoid cystic carcinoma, 1 achieved stable disease for 7 months in response to treatment with cobimetinib[93]. Cobimetinib has been investigated primarily in combination with vemurafenib for the treatment of patients with BRAF V600-mutated melanoma. In the Phase 3 coBRIM study, patients with V600-mutated melanoma treated with the BRAF inhibitor vemurafenib plus cobimetinib reported improved ORR (67.6% vs. 44.7%), median OS (22.3 months vs. 17.4 months; HR=0.70), and median PFS (9.9 months vs. 6.2 months; HR=0.51) compared with vemurafenib alone[94-95] . Single-agent cobimetinib has shown clinical activity in the context of histiocytosis (ORR of 64.3%, 9/14)[96]. The Phase 2 COLET study comparing first-line cobimetinib in combination with paclitaxel to paclitaxel alone for the treatment of patients with advanced triple-negative breast cancer reported numerically higher ORR (38.3% [18/47] vs. 20.9% [9/43]) and improved median PFS (5.5 vs. 3.8 months, HR=0.73)[97]. Additional cohorts from the COLET study treated with triple combinations of cobimetinib, atezolizumab, and either paclitaxel or nab-paclitaxel showed ORRs of 34.4% (11/32) or 29.0% (9/31), respectively, with numerically higher ORRs and PFS reported for patients with PD-L1 expression[98]. A Phase 1b study evaluating atezolizumab in combination with cobimetinib for advanced solid tumors reported an ORR of 8.3% (7/84) for patients with CRC, 40.9% (9/22) for patients with melanoma, 17.9% (5/28) for patients with NSCLC, and 18.8% (3/16) for patients with other tumors (ovarian cancer, clear cell sarcoma, and renal cell carcinoma); there was no association between BRAF or KRAS mutation status and response rate in any disease setting[99-100] . In a Phase 1b study of cobimetinib and the AKT inhibitor ipatasertib, 3/47 patients with KRAS-mutated ovarian, mesonephric cervical, or endometrial carcinoma had a PR[101].

Trametinib

Assay findings association

HRAS
Q61R

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is available in the EU as monotherapy or in combination with dabrafenib to treat unresectable or metastatic melanoma with a BRAF V600 mutation as well as in combination with dabrafenib as adjuvant treatment for completely resected advanced BRAF V600-mutated melanoma. It is also available in combination with dabrafenib to treat patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of limited clinical data[33-34] and strong preclinical data[35-39] , HRAS activating alterations may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Clinical data on the efficacy of trametinib for the treatment of adenoid cystic carcinoma are limited (PubMed, Feb 2020). A Phase 1 trial of trametinib in 206 patients with solid tumors reported 21 (10%) objective responses[102]. Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown significant response rates in patients with melanoma, including those with BRAF and NRAS mutations, but very low response rates in patients with other solid tumors, including those with KRAS mutations[103-104] . A Phase 1b trial of trametinib in combination with gemcitabine in patients with solid tumors showed a complete response in a patient with breast cancer, as well as partial responses in pancreatic and salivary gland cancer[105]. A Phase 1b trial of combination treatment with the MEK inhibitor binimetinib and the PI3K-alpha inhibitor alpelisib reported disease control (partial responses or stable disease) in 47% (21/45) of patients, including partial responses in 2 of 3 patients with KRAS-mutant ovarian cancer and 1 of 3 patients with NRAS-mutant melanoma; a 43% rate of stable disease was observed in patients with KRAS-mutant colorectal cancer, with responses independent of PIK3CA mutation status[106]. 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[107], 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[108].

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
HRAS

ALTERATION
Q61R

RATIONALE
HRAS activating alterations may predict sensitivity to MEK or farnesyl transferase inhibitors.

NCT03745989

PHASE 1

Study of MK-8353 + Selumetinib in Advanced/Metastatic Solid Tumors (MK-8353-014)

TARGETS
ERK1, ERK2, MEK

LOCATIONS: Bellinzona (Switzerland), Toronto (Canada), Vancouver (Canada), Florida, Texas

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Massachusetts, Pennsylvania, Maryland, Michigan, Virginia, Wisconsin, Ohio, North Carolina, Tennessee, Oregon

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Melbourne (Australia), Blacktown (Australia), Randwick (Australia)

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada), Florida, Texas

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Seoul (Korea, Republic of)

NCT03833427

PHASE 1

Study of Selumetinib (MK-5618) in Combination With Pembrolizumab (MK-3475) in Participants With Advanced/Metastatic Solid Tumors (MK-5618-001)

TARGETS
PD-1, MEK

LOCATIONS: Quebec (Canada), Toronto (Canada), New Jersey, Michigan, Texas, California

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

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.

BRIP1
R264W

EP300
N2209_Q2213>K

MET
I333R

MLL2
P4175Q

RNF43
R657Q

WHSC1 (MMSET)
L639V

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 defined based on counting the total number of all synonymous and nonsynonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit rounded to the nearest integer. The clinical validity of TMB defined by this panel has not been established.
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.

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

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The median exon coverage for this sample is 801x

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