FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Cheng, Yi Hsin	Kidney renal cell carcinoma (NOS)	19 Dec 2022
	COUNTRY CODE: TW	ORDERED TEST #: ORD-1521384-01

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 Kidney renal cell carcinoma (NOS)
NAME Cheng, Yi Hsin
DATE OF BIRTH 07 March 1964
SEX Male
MEDICAL RECORD # 40164203 (PF22139)

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Kidney
SPECIMEN ID S111-46660F
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 11 November 2022
SPECIMEN RECEIVED 10 December 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

PBRM1 E1364*
VHL S65fs*1

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***VHL* S65fs*1** (p. 4)
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Nivolumab** (p. 6), **Belzutifan** (p. 5), **Pembrolizumab** (p. 7)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***PBRM1* -** E1364*	Nivolumab	1	Cemiplimab
	Pembrolizumab	2A	
10 Trials see p. 9	Dostarlimab		
***VHL* -** S65fs*1	Belzutifan	2A	none
9 Trials see p. 11			

NCCN category

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 by the US FDA.

Electronically signed by Erik Williams, M.D. | 19 December 2022
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

MSI-high and MSI-low were each reported in 1% of cases in a study of 152 renal cell carcinomas (RCC)[6]. Another study reported that fewer than 1% of RCC cases had MSI-H status[7]. Published data investigating the prognostic implications of MSI in RCC are limited (PubMed, Jan 2022).

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[8]. 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[8-10]. 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[11-13]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[8,10,12-13].

BIOMARKER

Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[14-16], anti-PD-1 therapies[14-17], and combination nivolumab and ipilimumab[18-23]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[14-17,24-28]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[24]; similar findings were observed in the KEYNOTE 028 and 012 trials[17]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[28]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[29]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[27]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[30] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[15].

FREQUENCY & PROGNOSIS

Kidney carcinoma, including renal clear cell carcinoma, renal papillary carcinoma, and renal sarcomatoid carcinoma subtypes, harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 0-2% of cases have been reported to harbor high TMB (>20 muts/Mb)[31-32]. Renal cell carcinomas harbor an average TMB among solid tumors, with a median of approximately 1-2 non-synonymous somatic mutations per megabase in kidney clear-cell or papillary carcinoma[33-34]. For patients with ccRCC, increased TMB is associated with poor survival outcomes, higher tumor grade, and advanced pathological stage[35].

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[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. 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[15-16,24].

GENE
PBRM1

ALTERATION
E1364*

TRANSCRIPT ID
NM_018313.4

CODING SEQUENCE EFFECT
4090G>T

VARIANT CHROMOSOMAL POSITION
chr3:52595825

VARIANT ALLELE FREQUENCY (% VAF)
15.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of significant clinical data from prospective studies, PBRM1 inactivation may predict benefit from PD-1-targeting immune checkpoint inhibitors, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, for patients with clear cell renal cell carcinoma (ccRCC) and prior anti-angiogenic therapy[47-49]. Post hoc analysis of the Phase 3 CheckMate 025 study for metastatic ccRCC with progression on anti-angiogenics demonstrated improved median PFS (5.6 vs. 2.9 months, HR=0.67) and OS (27.9 vs. 20.9 months, HR=0.65) with nivolumab for patients harboring PBRM1 inactivating mutations[47]. Similarly, the Phase 2 real-world NIVOREN study reported improved nivolumab 1-year OS rates (84% vs. 74%, HR=0.59) for previously treated patients with ccRCC and PBRM1 protein loss by immunohistochemistry[50]. Although patients with PBRM1-mutated ccRCC have also benefited from nivolumab in combination with the anti-CTLA-4 immunotherapy ipilimumab or from the anti-PD-L1 immunotherapy atezolizumab[49,51], PBRM1 mutation status was not associated with survival outcomes for combination nivolumab and ipilimumab in the Phase 3 CheckMate 214 study[52] or for single-agent atezolizumab in the Phase 2 IMmotion150 study[53-54] for treatment-naive advanced or metastatic ccRCC.

FREQUENCY & PROGNOSIS

Somatic mutations in PBRM1 are common in clear cell renal cell carcinomas (ccRCC) (41%)[55]. The PBRM1/ARID1A/SMARCA4 network of SWI/SNF chromatin remodeling complex components is a frequently mutated subnetwork of genes that may define a molecular subtype of ccRCC[56]. A case study reported loss of Brg1 expression in a rhabdoid RCC that may have arisen from a ccRCC[57]. Preclinical studies have shown that loss of PBRM1 increases the proliferation of ccRCC cell lines[55]. PBRM1 protein loss or mutation is correlated with late tumor stage, low differentiation grade, and/or poor patient prognosis in ccRCC[58-60]; however, one ccRCC study reported no correlation between PBRM1 mutation and cancer-specific survival[61]. In ccRCC, PBRM1 alterations are generally observed to be mutually exclusive with BAP1 alterations[55,62]; a retrospective analysis of 145 primary ccRCCs found a decreased median overall survival for patients with mutations in both BAP1 and PBRM1 compared with patients having either mutated gene alone[63].

FINDING SUMMARY

PBRM1 (Polybromo-1), also known as BAF180, encodes a subunit of ATP-dependent chromatin-remodeling complexes and a required cofactor for ligand-dependent transactivation by nuclear hormone receptors[64]. Mutation, loss, or inactivation of PBRM1 has been reported in several cancers, suggesting PBRM1 is a tumor suppressor[55,65-66]. Alterations such as seen here may disrupt PBRM1 function or expression[67-72].

GENE
VHL

ALTERATION
S65fs*1

TRANSCRIPT ID
NM_000551.3

CODING SEQUENCE EFFECT
192_195delCTCG

VARIANT CHROMOSOMAL POSITION
chr3:10183720-10183724

VARIANT ALLELE FREQUENCY (% VAF)
13.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Various strategies are under clinical investigation to block pathways downstream of inactivated VHL, including HIF, VEGF, and mTOR. The multikinase inhibitor sunitinib, which has activity against VEGFRs and other targets, is approved to treat several tumor types and has shown strong efficacy in patients with VHL disease[73-77]. Several clinical trials found response rates up to 64% and DCRs up to 90%[78-79]. However, multiple clinical studies of sunitinib in patients with renal cell carcinoma reported that mutation or inactivation of the VHL gene is not significantly associated with therapeutic response or survival[80-82]. Other agents that inhibit VEGFRs, including the multikinase inhibitors sorafenib, axitinib, pazopanib, regorafenib, cabozantinib, and vandetanib; the anti-VEGFR2 antibody ramucirumab; and the mTOR inhibitors everolimus and temsirolimus, are also approved in multiple tumor types. However, studies have similarly shown that VHL mutation or inactivation does not correlate with responses to these agents[81,83-84]. Therefore, it is unclear whether these therapeutic strategies would be beneficial in this case. The HIF2a inhibitor belzutifan achieved an ORR of 64% in a clinical trial for VHL disease-associated clear cell renal cell carcinoma[85]. Responses were also seen in other VHL mutation-associated tumor types, including CNS hemangioblastomas and pancreatic neuroendocrine tumors; however, it was not determined whether VHL inactivation was significantly associated with these responses[86].

FREQUENCY & PROGNOSIS

VHL mutations and VHL promoter methylation have been reported to occur frequently in renal carcinoma (RCC), particularly in clear cell renal carcinoma (ccRCC)[87-89], and are early events in RCC tumorigenesis[90-91]. VHL mutations have been reported in 52% ccRCC, 4.3% of chromophobe RCC, and 2.0% of papillary RCC (COSMIC, Jan 2022)[92]. Studies exploring the prognostic value of VHL mutation in RCC have given mixed results[93].

FINDING SUMMARY

VHL encodes the protein pVHL (von Hippel-Lindau tumor suppressor), which is frequently inactivated, either via mutation or hypermethylation, in clear cell renal cell carcinoma (ccRCC) and plays an important role in its pathogenesis[94]. Inactivating mutations in VHL lead to dysregulation of critical downstream growth regulators, especially members of the HIF family and VEGF[95-96]. Alterations such as seen here may disrupt VHL function or expression[97-137].

POTENTIAL DIAGNOSTIC IMPLICATIONS

Inactivating VHL mutations are characteristic of the clear cell subtype of renal cell carcinoma (RCC) (NCCN Kidney Cancer Guidelines, v1.2023)[138-139].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in VHL underlie von Hippel-Lindau syndrome, a rare but highly penetrant autosomal dominant syndrome occurring in 1/36,000 live births that predisposes to the development of several types of cancer, including clear cell renal cell carcinomas and pancreatic neuroendocrine tumors, as well as retinal and central nervous system hemangioblastomas[140-142]. In the appropriate clinical context, germline testing of VHL is recommended.

Belzutifan

Assay findings association

VHL
S65fs*1

AREAS OF THERAPEUTIC USE

Belzutifan is a HIF2a inhibitor. It is FDA approved to treat adult patients with von Hippel-Lindau (VHL)-associated renal cell carcinoma, central nervous system (CNS) hemangioblastomas, and pancreatic neuroendocrine tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in von Hippel-Lindau (VHL) disease-associated renal cell carcinoma, hemangioblastoma, and pancreatic neuroendocrine tumors, VHL inactivation may predict sensitivity to the HIF2a inhibitor belzutifan[143].

SUPPORTING DATA

A Phase 2 study of belzutifan for the treatment of clear cell renal cell carcinoma (RCC) achieved an ORR of 64% (39/61; 4 CRs, 35 PRs)[85] and a 24-month PFS of 96%[86]. A Phase 1/2 clinical trial of 55 patients with advanced clear cell RCC achieved an ORR of 25% (14 PRs), a DCR of 80%, and a median PFS of 15 months[144-145] . In a Phase 2 study of belzutifan plus cabozantinib for patients with advanced clear cell RCC previously treated with immunotherapy, the ORR was 22% (9 PRs) with a DCR of 90% and a median PFS of 17 months; at the time of data cutoff, all responses were ongoing[146]. In the cohort of this Phase 2 study that assessed treatment-naive patients with advanced clear cell RCC, belzutifan plus cabozantinib was associated with an ORR of 57% (2 CRs, 18 PRs), median PFS of 30.3 months, median DOR of 28.6 months, and estimated 12-month OS rate of 96%[147].

Dostarlimab

Assay findings association

PBRM1
E1364*

AREAS OF THERAPEUTIC USE

Dostarlimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor response. It is FDA approved to treat patients with mismatch repair deficient recurrent or advanced endometrial cancer or solid tumors. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of significant clinical evidence, PBRM1 inactivation may predict benefit from PD-1-targeting immunotherapies, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, in patients with clear cell renal cell carcinoma and progression on prior anti-angiogenic therapy[47-50] .

SUPPORTING DATA

The GARNET Phase 1 basket trial of dostarlimab in mismatch repair-deficient (dMMR) cancers included 1 patient with renal cell carcinoma who experienced an SD[148]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[148-150] . In the Phase 1 GARNET trial, single-agent dostarlimab elicited an ORR of 39% (41/106) and an immune-related ORR of 46% (50/110) for patients with non-endometrial dMMR solid tumors[148,151] .

Nivolumab

Assay findings association

PBRM1
E1364*

AREAS OF THERAPEUTIC USE

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, reducing inhibition of the antitumor immune response. It is FDA approved as a monotherapy in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, colorectal cancer (CRC), classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma or squamous cell carcinoma (ESCC). It is also approved in combination with chemotherapy to treat ESCC, in combination with cabozantinib to treat RCC, and in combination with relatlimab to treat melanoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of significant clinical evidence, PBRM1 inactivation may predict benefit from PD-1-targeting immunotherapies, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, in patients with clear cell renal cell carcinoma and progression on prior anti-angiogenic therapy[47-50] .

SUPPORTING DATA

Post hoc analysis of the Phase 3 CheckMate 025 study demonstrated improved ORR (39% vs. 22%), median PFS (5.6 vs. 2.9 months, HR=0.67), and median OS (27.9 vs. 20.9 months, HR=0.65) on treatment with nivolumab for patients with previously treated advanced clear cell renal cell carcinoma (ccRCC) harboring PBRM1 inactivating mutations compared with those with PBRM1-wildtype tumors[47]. Similarly, the Phase 2 real-world NIVOREN study reported improved 1-year OS rates on nivolumab (84% vs. 74%, HR=0.59) for previously treated ccRCC with PBRM1 protein loss by immunohistochemistry[50]. In the Phase 3 CheckMate 025 study for patients with advanced clear cell renal cell carcinoma (ccRCC) and previous antiangiogenic therapy, nivolumab monotherapy elicited improved median OS (mOS; 25.8 vs. 19.7 months, HR=0.73) and ORR (23% vs. 4%) compared with everolimus; baseline tumor PD-L1 expression was not associated with OS benefit[152-153] . Single-agent nivolumab achieved a mOS of 21.8 months for previously treated ccRCC and 16.3 months for previously treated non-ccRCC in CheckMate 374[154-155] . For treatment-naive patients with advanced ccRCC, the Phase 3 CheckMate 9ER study reported improved mOS (37.7 vs 34.3 months, HR=0.70), mPFS (16.6 vs. 8.3 months, HR=0.56), and ORR (56% vs. 28%, CR 12% vs 5.2%) for the combination of nivolumab and the multikinase inhibitor cabozantinib over sunitinib monotherapy[156], with benefit observed across risk status and PD-L1 expression subgroups[157-158] . In a Phase 2 study, objective responses have been observed in treatment-naive patients with metastatic ccRCC treated with nivolumab or nivolumab in combination with ipilimumab[159]. Clinical benefit has also been reported from nivolumab in combination with other agents in Phase 1 trials, including sunitinib, pazopanib, axitinib, and bempegaldesleukin[160-162] .

Pembrolizumab

Assay findings association

PBRM1
E1364*

AREAS OF THERAPEUTIC USE

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved for patients with tumor mutational burden (TMB)-high (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or mismatch repair-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), cervical cancer, or esophageal cancer; and in combination with chemotherapy for PD-L1-positive triple-negative breast cancer (TNBC) or cervical cancer. It is also approved in various treatment settings as monotherapy for patients with melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, endometrial carcinoma that is MSI-H or dMMR, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma; and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or gastroesophageal junction cancer, renal cell carcinoma, TNBC, or endometrial carcinoma that is not MSI-H or dMMR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of significant clinical evidence, PBRM1 inactivation may predict benefit from PD-1-targeting immunotherapies, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, in patients with clear cell renal cell carcinoma and progression on prior anti-angiogenic therapy[47-50] .

SUPPORTING DATA

In the KEYNOTE-427 Phase 2 study, first-line pembrolizumab elicited a 36% ORR, 58% DCR, and 7.1-month median PFS (mPFS) for patients with advanced clear cell renal cell carcinoma (ccRCC) and a 27% ORR, 43% DCR, and 4.2-month mPFS for patients with advanced non-clear cell RCC. Anti-tumor activity was seen for favorable- and intermediate- and/or poor-risk groups, PD-L1-positive and -negative groups, and patients with sarcomatoid histology[163-164] . In the adjuvant setting for treatment-naive ccRCC, single-agent pembrolizumab improved disease-free survival compared with placebo (HR=0.68) in interim analysis of KEYNOTE-564[165]. In Phase 3 studies, the combination of pembrolizumab with multi-TKIs such as lenvatinib or axitinib has significantly improved outcomes for patients with previously untreated ccRCC as compared with sunitinib monotherapy; CLEAR demonstrated an ORR of 71% vs 36% and improved mPFS (23.3 vs. 9.2 months, HR=0.42) and median OS (mOS; not reached for either arm, HR=0.72) for pembrolizumab plus lenvatinib[166-167] , and KEYNOTE-426 showed improved mPFS (15.4 vs. 11.1 months, HR=0.71) and mOS (not reached vs. 35.7 months, HR=0.68) for pembrolizumab plus axitinib[168-169] . The KEYNOTE-146 Phase 1b/2 study of lenvatinib combined with pembrolizumab also demonstrated an ORR of 77% (17/22) for treatment-naive patients with metastatic RCC compared with 41% (7/17) for patients previously treated with non-immune checkpoint inhibitor (ICI) therapies and 56% (58/104) for patients who had relapsed on prior treatment with an ICI[170]. For patients with non-clear cell RCC, the Phase 2 KEYNOTE-B61 study of frontline pembrolizumab plus lenvatinib preliminarily reported an ORR of 48% (39/82) and a DCR of 79% (65/82)[171]. Although anti-tumor activity was also reported for frontline pembrolizumab with the multi-TKI pazopanib in a Phase 1/2 trial for advanced ccRCC, due to significant hepatotoxicity the combination was not recommended for further clinical investigation[172]. Early phase trials have reported activity of pembrolizumab in combination with the CTLA-4-targeting immune checkpoint inhibitor ipilimumab, pegylated interferon alfa 2b, or the IL-10-targeting monoclonal antibody pegilodecakin in previously treated RCC[173-175] .

Cemiplimab

Assay findings association

PBRM1
E1364*

AREAS OF THERAPEUTIC USE

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC), cutaneous squamous cell carcinoma, or basal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of significant clinical evidence, PBRM1 inactivation may predict benefit from PD-1-targeting immunotherapies, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, in patients with clear cell renal cell carcinoma and progression on prior anti-angiogenic therapy[47-50] .

SUPPORTING DATA

A Phase 1b trial evaluating combination cemiplimab with an oncolytic vaccinia virus for patients with metastatic or unresectable clear cell RCC observed 1 CR, 5 PRs, and reduction of tumor burden in 75% (12/16) of patients[176]. Cemiplimab has been studied primarily in advanced cutaneous squamous cell carcinoma (CSCC), where it elicited a combined ORR of 48% (41/85) in Phase 1 and 2 studies[177]. A Phase 2 trial of cemiplimab in patients with basal cell carcinoma (BCC) reported ORRs of 31% (5 CRs and 21 PRs) in patients with locally advanced BCC and 21% (6 PRs) in patients with metastatic BCC[178-179] . The Phase 3 EMPOWER-Lung 1 trial for advanced non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50% reported that cemiplimab is associated with improved PFS (8.2 vs. 5.7 months), OS (not reached vs. 14.2 months), and ORR (37% vs. 21%) compared with chemotherapy[180].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

NOTE 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. 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 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. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
PBRM1

ALTERATION
E1364*

RATIONALE
PBRM1 inactivation may predict benefit from PD-1-targeting immune checkpoint inhibitors.

NCT04237649

PHASE NULL

KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Shatin, New Territories (Hong Kong), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Toronto (Canada), Missouri

NCT04736706

PHASE 3

A Study of Pembrolizumab (MK-3475) in Combination With Belzutifan (MK-6482) and Lenvatinib (MK-7902), or Pembrolizumab/Quavonlimab (MK-1308A) in Combination With Lenvatinib, Versus Pembrolizumab and Lenvatinib, for Treatment of Advanced Clear Cell Renal Cell Carcinoma (MK-6482-012)

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, CTLA-4, HIF2a, PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Xiamen (China), Ningbo (China), Hangzhou (China), Jiaxing (China)

NCT05166577

PHASE 1/2

Nanatinostat Plus Valganciclovir in Patients With Advanced EBV+ Solid Tumors, and in Combination With Pembrolizumab in EBV+ RM-NPC

TARGETS
HDAC, PD-1

LOCATIONS: Taipei City (Taiwan), Taipei (Taiwan), Taoyuan City (Taiwan), Sha Tin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Kuching (Malaysia), Kuala Lumpur (Malaysia), Singapore (Singapore), Blacktown (Australia)

NCT04152018

PHASE 1

Study of PF-06940434 in Patients With Advanced or Metastatic Solid Tumors.

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Liverpool (Australia), Wollongong (Australia), Poprad (Slovakia), Bratislava (Slovakia), Washington, California, Arizona

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

TARGETS
PD-L1, PD-1, CTLA-4

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Melbourne (Australia), Amsterdam (Netherlands), Ravenna (Italy)

NCT04261439

PHASE 1

A Phase I/Ib Study of NIZ985 Alone and in Combination With Spartalizumab

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Chuo ku (Japan), Essen (Germany), Napoli (Italy), Barcelona (Spain), Madrid (Spain), California, Texas

NCT04047862

PHASE 1

Study of BGB-A1217 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIGIT

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Hualien City (Taiwan), Taichung (Taiwan), Fujian (China), Hangzhou (China), Shanghai (China), Guangdong (China), Changsha (China), Wuhan (China)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China)

NCT05102006

PHASE 1/2

Phase Ib/II Clinical Study of LBL-007 in Treatment of Advanced Malignant Tumors

TARGETS
LAG3, PD-1

LOCATIONS: Nanchang (China), Changzhou (China), Guangzhou (China), Changsha (China), Wuhan (China), Bengbu (China), Linyi (China), Zhengzhou (China), Jinan (China), Chongqing (China)

NCT03744468

PHASE 1/2

Study of BGB-A425 in Combination With Tislelizumab in Advanced Solid Tumors

TARGETS
PD-1, TIM-3

LOCATIONS: Busan (Korea, Republic of), Ulsan (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Perth (Australia), Hervey Bay (Australia), Birtinya (Australia), Adelaide (Australia), Melbourne (Australia)

GENE
VHL

RATIONALE
Clinical evidence suggests that inactivation of VHL may predict sensitivity to HIF2a inhibitors.

ALTERATION
S65fs*1

NCT04736706

PHASE 3

A Study of Pembrolizumab (MK-3475) in Combination With Belzutifan (MK-6482) and Lenvatinib (MK-7902), or Pembrolizumab/Quavonlimab (MK-1308A) in Combination With Lenvatinib, Versus Pembrolizumab and Lenvatinib, for Treatment of Advanced Clear Cell Renal Cell Carcinoma (MK-6482-012)

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, CTLA-4, HIF2a, PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Xiamen (China), Ningbo (China), Hangzhou (China), Jiaxing (China)

NCT05030506

PHASE 1

A Study of Belzutifan (MK-6482) as Monotherapy and in Combination With Lenvatinib (E7080/MK-7902) With or Without Pembrolizumab (MK-3475) in China Participants With Advanced Renal Cell Carcinoma (MK-6482-010)

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, HIF2a

LOCATIONS: Hangzhou (China), Nanjing (China), Guangzhou (China), Tianjin (China), Beijing (China)

NCT04586231

PHASE 3

A Study of MK-6482 in Combination With Lenvatinib Versus Cabozantinib for Treatment of Renal Cell Carcinoma (MK-6482-011)

TARGETS
HIF2a, MET, ROS1, RET, VEGFRs, FGFRs, PDGFRA, KIT

LOCATIONS: Hwasun (Korea, Republic of), Fukuoka (Japan), Seoul (Korea, Republic of), Osakasayama (Japan), Suita (Japan), Kashihara (Japan), Toyoake (Japan), Hamamatsu (Japan), Yokohama (Japan), Tokyo (Japan)

NCT04626479

PHASE 1/2

Substudy 03A: A Study of Immune and Targeted Combination Therapies in Participants With First Line (1L) Renal Cell Carcinoma (MK-3475-03A)

TARGETS
PD-1, HIF2a, LAG-3, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Songpagu (Korea, Republic of), Seoul (Korea, Republic of), Herston (Australia), Blacktown (Australia), Kogarah (Australia), Heidelberg (Australia), Haifa (Israel), Jerusalem (Israel), Petah Tiqwa (Israel), Ramat Gan (Israel)

NCT04626518

PHASE 1/2

Substudy 03B: A Study of Immune and Targeted Combination Therapies in Participants With Second Line Plus (2L+) Renal Cell Carcinoma (MK-3475-03B)

TARGETS
HIF2a, CTLA-4, FGFRs, RET, PDGFRA, VEGFRs, KIT, ITL4, LAG-3, PD-1

LOCATIONS: Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Herston (Australia), Blacktown (Australia), Kogarah (Australia), Melbourne (Australia), Jerusalem (Israel), Petah Tiqwa (Israel), Ramat Gan (Israel), Tel Aviv (Israel)

NCT04895748

PHASE 1

DFF332 as a Single Agent and in Combination With Everolimus & Immuno-Oncology Agents in Advanced/Relapsed Renal Cancer & Other Malignancies

TARGETS
mTOR, HIF2a, ADORA2A, PD-1

LOCATIONS: Koto ku (Japan), Singapore (Singapore), Brno (Czechia), Milano (Italy), Villejuif Cedex (France), Barcelona (Spain), California, Missouri, Massachusetts, New York

NCT03634540

PHASE 2

A Trial of PT2977 in Combination With Cabozantinib in Patients With Clear Cell Renal Cell Carcinoma (ccRCC)

TARGETS
MET, ROS1, RET, VEGFRs, HIF2a

LOCATIONS: Washington, California, Michigan, Massachusetts, Tennessee, Florida

NCT04627064

PHASE 1

ABEMA Alone or in COMBO With MK-6482

TARGETS
CDK4, CDK6, HIF2a

LOCATIONS: Massachusetts

NCT04846920

PHASE 1

A Study of Belzutifan (MK-6482) in Participants With Advanced Clear Cell Renal Cell Carcinoma (MK-6482-018)

TARGETS
HIF2a

LOCATIONS: Michigan, Massachusetts, Tennessee, 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.

BRCA2 L1829F	***CARD11*** A687V	***IKBKE*** G660E	***MST1R*** V670G
MYC K172Q	***ROS1*** D2213E and Y1353S	***SOCS1*** T57I	***TET2*** P555L

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*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 BIOMARKERS

Homologous Recombination status
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 PRINCIPLE

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: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings 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 biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. 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.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2*, and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.4.0

The median exon coverage for this sample is 934x

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
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