FOUNDATIONONE®CDx

| PATIENT | TUMOR TYPE | REPORT DATE |
|---|---|---|
| Chen, Chien Cheng | Kidney renal cell carcinoma (NOS) | 25 Jan 2023 |
| | COUNTRY CODE | ORDERED TEST # |
| | TW | ORD-1541546-01 |

**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** Chen, Chien Cheng
**DATE OF BIRTH** 20 March 1955
**SEX** Male
**MEDICAL RECORD #** 27477196

**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** Bone
**SPECIMEN ID** S111-55042 A (PF23005)
**SPECIMEN TYPE** Slide Deck
**DATE OF COLLECTION** 28 December 2022
**SPECIMEN RECEIVED** 12 January 2023

## Biomarker Findings

**Tumor Mutational Burden** - 12 Muts/Mb
**Microsatellite status** - MS-Stable

## Genomic Findings

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

***NF2*** loss exons 3-9
***CDC73*** splice site 1560-2A>T
***CDKN2A/B*** CDKN2B loss, CDKN2A loss
***NOTCH3*** K603*
***TERT*** promoter -124C>T

## Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Nivolumab** (p. 8), **Nivolumab + Ipilimumab** (p. 8), **Pembrolizumab** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)

## BIOMARKER FINDINGS

### Tumor Mutational Burden - 12 Muts/Mb

**10 Trials** see p. 12

| THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|
| Nivolumab | 1 | Atezolizumab |
| Nivolumab + Ipilimumab | 1 | Cemiplimab |
| Pembrolizumab | 2A | Durvalumab |
| Avelumab | | |
| Dostarlimab | | |

### Microsatellite status - MS-Stable

**No therapies or clinical trials.** See Biomarker Findings section

## GENOMIC FINDINGS

### *NF2* - loss exons 3-9

**10 Trials** see p. 14

| THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|
| none | none |

NCCN category



Electronically signed by Erik Williams, M.D. | 25 January 2023
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**Post-Sequencing Analysis:** 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

## GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

***CDC73*** - splice site 1560-2A>T ..... p. 4
***CDKN2A/B*** - CDKN2B loss, CDKN2A loss ..... p. 5
***NOTCH3*** - K603* ..... p. 6
***TERT*** - promoter -124C>T ..... p. 6

**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.

BIOMARKER

# Tumor Mutational Burden

**RESULT**
12 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[1-3], anti-PD-1 therapies[1-4], and combination nivolumab and ipilimumab[5-10]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[1-4,11-15]. 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[11]; similar findings were observed in the KEYNOTE 028 and 012 trials[4]. 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)[15]. 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[16]. 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[14]. 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[17] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[2].

## 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)[18-19]. 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[20-21]. For patients with ccRCC, increased TMB is associated with poor survival outcomes, higher tumor grade, and advanced pathological stage[22].

## 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[23-24] and cigarette smoke in lung cancer[25-26], treatment with temozolomide-based chemotherapy in glioma[27-28], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[29-33], and microsatellite instability (MSI)[29,32-33]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[2-4,11].

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[34-36], including approved therapies nivolumab and pembrolizumab[37]. 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)[38].

## FREQUENCY & PROGNOSIS

MSI-high and MSI-low were each reported in 1% of cases in a study of 152 renal cell carcinomas (RCC)[39]. Another study reported that fewer than 1% of RCC cases had MSI-H status[40]. Published data investigating the prognostic implications of MSI in RCC are limited (PubMed, Jan 2023).

## 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[41]. 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[41-43]. 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[44-46]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[41,43,45-46].



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GENE
## *NF2*

**ALTERATION**
loss exons 3-9

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

NF2 inactivating alterations may indicate sensitivity to mTOR inhibitors[47-50]. Two case studies reported clinical benefit for patients with NF2-mutated cancers, including urothelial carcinoma[51] and metaplastic breast cancer[52-53] treated with everolimus and temsirolimus, respectively. Loss or inactivation of NF2 may also predict sensitivity to FAK inhibitors based on clinical data in mesothelioma[54] and meningioma[55] and strong preclinical data[56-58]. Limited preclinical and clinical evidence in vestibular schwannoma suggests possible sensitivity of NF2-deficient tumors to the pan-ERBB inhibitor lapatinib[59-60]. Similarly, on the basis of limited clinical[61] and preclinical[62-64] evidence, NF2 inactivation may predict sensitivity to MEK inhibitors, such as approved agents trametinib and cobimetinib. These and other relevant compounds are being investigated in clinical trials. 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[65], 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[66].

### FREQUENCY & PROGNOSIS

NF2 alterations have been reported in 1.4% of renal non-clear cell carcinoma and 0.9% of kidney renal clear cell carcinoma[67-68]. Truncating mutations in NF2 have been reported in ccRCC, with one study reporting NF2 truncating mutations in 4% of samples[69-70]. Published data investigating the prognostic implications of NF2 alterations in renal cell carcinoma are limited (PubMed, Jul 2022).

### FINDING SUMMARY

Merlin, encoded by NF2, coordinates cell contact with growth signals; the inactivation of Merlin disrupts this mechanism and can lead to unrestrained growth despite cell contact[71]. Alterations such as seen here may disrupt NF2 function or expression[72-78].

### POTENTIAL GERMLINE IMPLICATIONS

Heterozygous germline NF2 loss or inactivation is associated with neurofibromatosis type 2, which results in the development of vestibular schwannomas, meningiomas, ependymomas, and ocular disturbances[79-81]. Prevalence for this disorder in the general population is estimated to be 1:25,000[81]. In the appropriate clinical context, germline testing of NF2 is recommended.

GENE
## *CDC73*

**ALTERATION**
splice site 1560-2A>T

**TRANSCRIPT ID**
NM_024529.4

**CODING SEQUENCE EFFECT**
1560-2A>T

**VARIANT CHROMOSOMAL POSITION**
chr1:193219804

**VARIANT ALLELE FREQUENCY (% VAF)**
15.2%

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no targeted therapies available to address genomic alterations in CDC73.

### FREQUENCY & PROGNOSIS

Loss of parafibromin expression and to some extent CDC73 mutation has been correlated with higher incidence of metastasis, disease recurrence, and in some cases decreased overall survival in patients with PC[82-83]. CDC73 down-regulation has also been observed in oral squamous cell carcinomas (OSCC), and knockdown of CDC73 results in increased cell viability and proliferation in preclinical OSCC models[84-85].

### FINDING SUMMARY

CDC73 encodes parafibromin, a component of the PAF protein complex[86]. PAF complexes with BCL9, PYGO, and beta-catenin to assemble a nuclear WNT signaling complex[87]. Parafibromin has been reported to inhibit MYC and CCND1[88-92], as well as cell proliferation[84-85,92-93]. It can also activate or inhibit beta-catenin signaling, depending on context[87,94-95]. Inactivating germline mutations in CDC73 are causal in hyperparathyroidism-jaw tumor syndrome[96], and frequent somatic mutation has been documented in parathyroid carcinoma (PC); however, CDC73 mutation is rare in benign parathyroid adenoma[97]. Heterozygous germline inactivation of CDC73 has additionally been suggested to be a predisposing factor for PC[98].

GENE
## *CDKN2A/B*

**ALTERATION**
CDKN2B loss, CDKN2A loss

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[99-102]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[103] and palbociclib treatment[104-105]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[106-112]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[113-114], the clinical relevance of p14ARF as a predictive biomarker is not clear. The p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, and although concomitant loss of CDKN2A and CDKN2B may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[109-110,115-116], direct supporting data for CDKN2B alteration as a predictive biomarker for these therapies are limited[117-118].

### FREQUENCY & PROGNOSIS

In the Kidney Renal Clear Cell Carcinoma (ccRCC) and Kidney Renal Papillary Cell Carcinoma TCGA datasets, putative homozygous deletion of both the CDKN2A and CDKN2B genes has been reported in 4.5% and 3% of cases, respectively (cBioPortal, Jul 2022)[119-120]. CDKN2A/B deletion has been reported to be one of the most significant copy number alterations in ccRCC[121]. In a study of sarcomatoid renal cell carcinoma (RCC), CDKN2A alterations were reported in 27% (7/26) of cases, with CDKN2B also altered in 15% (4/26) of these samples[122]. One study has reported loss of heterozygosity (LOH) on 9p21, which includes the region that encodes CDKN2A and CDKN2B, in 25% of papillary renal cell carcinoma tumors[123]. Loss due to deletion or hypermethylation of chromosome 9p, which includes the CDKN2A and CDKN2B loci, has been reported at frequencies ranging from 13% to 80% of renal cell carcinoma samples, including ccRCC and papillary subtypes, and has been associated with poor prognosis[124-128]. In addition, loss of chromosome 9p has been associated with advanced tumor grade, disease progression, and overall poor prognosis in both ccRCC and papillary renal cell carcinoma[125-126,129].

### FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[130-131]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[132-133]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[134-135]. One or more alterations observed here are predicted to result in p16INK4a loss of function[136-157]. One or more alterations seen here are predicted to result in p14ARF loss of function[140,157-160]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[161].

### POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[162]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[163-164]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[165-167]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[168-170]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
## *NOTCH3*

**ALTERATION**
K603*

**TRANSCRIPT ID**
NM_000435.2

**CODING SEQUENCE EFFECT**
1807A>T

**VARIANT CHROMOSOMAL POSITION**
chr19:15297949

**VARIANT ALLELE FREQUENCY (% VAF)**
19.9%

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[171], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI)[172-174]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[175]. Phase 2 studies have evaluated the efficacy of tarextumab in combination with chemotherapy in metastatic pancreatic cancer or extensive-stage small cell lung cancer, though NOTCH3 expression was not found to be a predictor of OS or PFS in either study[176]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

### FREQUENCY & PROGNOSIS

NOTCH3 mutation was observed in <1% of clear cell carcinoma, 2.0% (3/148) of kidney chromophobe carcinoma, and 2.6% of renal papillary carcinoma samples analyzed in COSMIC (Jan 2023)[177]. In 1 study of 473 samples of renal cell carcinoma, NOTCH3 overexpression was observed in 51.5% of clear cell renal cell carcinoma (CCRCC) samples[178]. The frequency of NOTCH3 rearrangements in kidney cancer has not been evaluated (cBioPortal, COSMIC, Jan 2023)[119-120,177]. Published data investigating the prognostic implications of NOTCH3 alterations in kidney carcinoma are limited (PubMed, Jan 2023), although overexpression of NOTCH signaling pathway members in clear cell renal carcinoma has been correlated with better overall survival for patients in 1 study[178].

### FINDING SUMMARY

NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[179-180]. Alterations that disrupt or remove the transmembrane domain (amino acids 1644-1664), RAM domain (amino acids 1665-1837), and/or ANK repeats region (amino acids 1838-2000), which are necessary for the transcriptional activity of NOTCH family proteins, as well as internal deletions that remove EGF repeats (7-10 and 21-22), have been shown in vitro to negatively affect ligand binding and reduce NOTCH3 transcriptional activity and are predicted to be inactivating[180-184].

GENE
## *TERT*

**ALTERATION**
promoter -124C>T

**TRANSCRIPT ID**
NM_198253.2

**CODING SEQUENCE EFFECT**
-124C>T

**VARIANT CHROMOSOMAL POSITION**
chr5:1295228

**VARIANT ALLELE FREQUENCY (% VAF)**
29.6%

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[185]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[186]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[187].

### FREQUENCY & PROGNOSIS

TERT mutations have been reported in <3% of papillary renal cell carcinomas (RCCs), clear cell RCCs and chromophobe RCCs[177,188-189]. In one study, TERT promoter mutations were detected in 9% (9/96) of clear cell RCC tumors and in 13% (1/8) of chromophobe RCC tumors[190]. TERT promoter mutations in RCC have been significantly associated with poor prognosis in survival in a retrospective study[191], and one study reported TERT promoter mutations correlating with advanced grade, metastasis, and higher TERT expression[190].

### FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[192]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[193-195]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[196-198], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[196].

# Avelumab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

### AREAS OF THERAPEUTIC USE

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 in order to enhance antitumor immune responses. It is FDA approved to treat patients 12 years and older with Merkel cell carcinoma, or for urothelial carcinoma in various treatment settings. The combination of avelumab and axitinib is FDA approved for patients with renal cell carcinoma (RCC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,17,199], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

### SUPPORTING DATA

A Phase 3 trial for patients with advanced renal cell carcinoma (RCC) reported a longer median PFS (13.3 vs. 8.0 months, HR=0.69) and a higher ORR (52.5% vs. 27.3%) for first-line combination of avelumab and axitinib compared with single-agent sunitinib; clinical benefit was observed regardless of PD-L1 status[200]. A trial of the combination in the neoadjuvant setting reported PR as best response for 30% (12/40) of patients prior to resection; for these patients, the DFS rate was 92% at median follow up of 23.5 months[201]. A Phase 2 trial of avelumab with talazoparib for VHL-deficient clear cell RCC reported a best response of SD (7/10); the efficacy threshold was not met for this population[202].

# Dostarlimab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

### 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 clinical data across solid tumors[2-4,17,199], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

### 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[203]. Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[203-205]. 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[203,206].

## Nivolumab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

### 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 clinical data across solid tumors[2-4,17,199] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

### SUPPORTING DATA

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[207-208] . 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[209-210] . 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[211], with benefit observed across risk status and PD-L1 expression subgroups[212-213] . 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[214]. Clinical benefit has also been reported from nivolumab in combination with other agents in Phase 1 trials, including sunitinib, pazopanib, axitinib, and bempegaldesleukin[215-217] .

## Nivolumab + Ipilimumab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

### 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, and ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. The combination is FDA approved in various treatment settings for patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), pleural mesothelioma, and esophageal squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data across solid tumors[5-6,218] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

### SUPPORTING DATA

In the Phase 3 CheckMate 214 study for treatment-naive patients with advanced clear cell renal cell carcinoma (RCC), first-line nivolumab plus ipilimumab elicited improved median OS (mOS; not reached vs. 38.4 months, HR=0.66) compared with sunitinib monotherapy; benefit from combination nivolumab plus ipilimumab over sunitinib was seen in patients with intermediate/poor-risk disease (median PFS [mPFS] 11.2 vs. 8.3 months, HR=0.74; mOS 48.1 vs. 26.6 months, HR=0.65) but not in the favorable risk population (mPFS 12.4 vs. 28.9 months; mOS not reached in either arm)[219-221] . For patients with localized RCC at high risk of relapse following nephrectomy, the Phase 3 CheckMate 914 study showed that adjuvant nivolumab plus ipilimumab did not improve median disease-free survival relative to placebo (HR=0.92)[222]. The Phase 3 COSMIC-313 study for treatment-naïve patients with intermediate and poor risk advanced clear cell RCC reported improved mPFS for patients treated with cobimetinib plus nivolumab plus ipilimumab compared with patients treated with placebo plus nivolumab and ipilimumab (not reached vs. 11.3 months, HR=0.73); the ORR for the triplet combination was 43% compared to 36% for the placebo combination[223].

# Pembrolizumab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

## 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 clinical data across solid tumors[2-4,17,199], TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3].

## SUPPORTING DATA

In the Phase 2 KEYNOTE 158 multi-solid tumor trial, treatment with the PD-1 inhibitor pembrolizumab led to improved ORR for patients with TMB of 10 Muts/Mb or higher compared those with TMB <10 Muts/Mb (28.3% [34/120] vs. 6.5% [41/635])[11]. In the KEYNOTE 028/012 pan-solid tumor trials, a similar improvement in ORR was reported for patients with >103 non-synonymous mutations/exome (~ equivalency >8 Muts/Mb as measured by this assay) compared to those with <103 non-synonymous mutations/exome (30.6% [11/36] vs. 6.5% [5/77])[4]. 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[224-225]. 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[226]. 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[227-228], 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[229-230]. 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[231]. 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)[232]. 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[233]. 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[234-236].

# Atezolizumab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

### AREAS OF THERAPEUTIC USE

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC) as well as adult and pediatric patients 2 years and older with alveolar soft part sarcoma, depending on treatment setting. Atezolizumab is also approved in combination with other therapies to treat patients with non-squamous NSCLC lacking EGFR or ALK alterations, small cell lung cancer, hepatocellular carcinoma, and BRAF V600-positive melanoma. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,17,199] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

### SUPPORTING DATA

In the prospective Phase 2a MyPathway basket study evaluating atezolizumab for patients with TMB-High solid tumors, patients with TMB ≥16 Muts/Mb achieved improved ORR (38% [16/42] vs. 2.1% [1/48]), DCR (62% [26/42] vs. 23% [11/48]), mPFS (5.7 vs. 1.8 months, HR 0.34), and mOS (19.8 vs. 11.4, HR 0.53) as compared to those with TMB ≥10 and <16 Muts/Mb[14]. In a retrospective analysis of patients with 17 solid tumor types (comprised of 47% NSCLC, 40% urothelial carcinoma, and 13% encompassing 15 other solid tumors), TMB of 16 Muts/Mb or greater was reported to be associated with an improved ORR to atezolizumab compared to chemotherapy (30% vs. 14%)[17]. Atezolizumab as a second-line treatment for patients with clear cell renal cell carcinoma (RCC) resulted in an ORR of 15% (9/62), a median PFS of 5.6 months, and a median OS of 28.9 months[237]. A Phase 3 trial of metastatic RCC with sarcomatoid histology comparing atezolizumab plus bevacizumab compared with sunitinib as first-line treatment reported improved median PFS (8.3 vs. 5.3 months) and median OS (21.7 vs. 15.4 months) in the atezolizumab plus bevacizumab cohort compared with sunitinib, regardless of PD-L1 status[238]. Patients with >20% sarcomatoid composition in the atezolizumab plus bevacizumab cohort reported improved ORR (44% vs. 4%) and CR (7% vs. 0%) rates compared with sunitinib[238]. As first-line treatment of metastatic RCC, a prospective Phase 2 trial reported non-significant improvements in median PFS for patients in the stratified intention-to-treat and PD-L1-positive cohorts, respectively, from atezolizumab plus bevacizumab (11.7 and 14.7 months) compared with sunitinib (8.4 and 7.8 months) or atezolizumab monotherapy (6.1 and 5.5 months)[239]. A Phase 1 study of atezolizumab in combination with the multikinase inhibitor cabozantinib for untreated clear cell RCC reported ORRs of 53–58% with median PFS of 15.1–19.5 months across cohorts; PD-L1 positivity and CD8+ T-cell status were associated with response and tumor size reduction[240].

# Cemiplimab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

### 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 clinical data across solid tumors[2-4,17,199] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

### 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[241]. 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[242]. 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[243-244] . 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[245].

# Durvalumab

*Assay findings association*

***Tumor Mutational Burden***
12 Muts/Mb

## AREAS OF THERAPEUTIC USE

Durvalumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1 to enhance antitumor immune responses. It is FDA approved to treat patients with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and biliary tract cancer. Please see the drug label for full prescribing information.

## GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,17,199] , TMB of ≥10 Muts/Mb (based on this assay or others) may predict sensitivity to immune checkpoint inhibitors targeting PD-1 or PD-L1. An association between higher TMB and improved OS, median PFS, and ORR has been observed in large pan-solid tumor studies for patients treated with immune checkpoint inhibitors[2-3] .

## SUPPORTING DATA

A randomized Phase 2 study of durvalumab alone (D), in combination with the anti-CTLA4 antibody tremelimumab (D+T), or with the MET inhibitor savolitinib (D+S) for patients with VEGF-refractory advanced clear cell renal cancer (RCC) reported that the addition of tremelimumab or savolitinib did not significantly improve efficacy with 12-month PFS rates of 26% (10/39) in the D arm, 33% (13/39) in the D+T arm, and 18% (7/39) in the D+S arm[246].

**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.

**BIOMARKER**

# Tumor Mutational Burden

**RESULT**

12 Muts/Mb

**RATIONALE**

Increased tumor mutational burden may predict response to anti-PD-1 (alone or in combination with anti-CTLA-4) or anti-PD-L1 immune checkpoint inhibitors.

## 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)

## NCT04589845

**PHASE 2**

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

**TARGETS**
TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha, RAFs, NRAS

**LOCATIONS:** Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China)

## 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

## NCT03829501

**PHASE 1/2**

Safety and Efficacy of KY1044 and Atezolizumab in Advanced Cancer

**TARGETS**
ICOS, PD-L1

**LOCATIONS:** Taipei (Taiwan), Napoli (Italy), Milano (Italy), Manchester (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Tennessee, Florida

## 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)

## NCT04282018

**PHASE 1/2**

Brief Title: Study of BGB-10188 as Monotherapy, and in Combination With Zanubrutinib, and Tislelizumab

**TARGETS**
PI3K-delta, PD-1, BTK

**LOCATIONS:** Fuzhou (China), Zhejiang (China), Shanghai (China), Suzhou (China), Changsha (China), Jining (China), Chengdu (China), West Perth (Australia), Adelaide (Australia), Blacktown (Australia)

## 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)

## NCT05024214

**PHASE 1/2**

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

**TARGETS**
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

**LOCATIONS:** Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

## NCT04892498

**PHASE 2**

Hypofractionated Radiotherapy Combined With PD-1 Inhibitor Sequential GM-CSF and IL-2 for the Treatment of Advanced Refractory Solid Tumors (PRaG2.0)

**TARGETS**
PD-1

**LOCATIONS:** Hangzhou (China), Suzhou (China), Wuxi (China), Hefei (China), Xuzhou (China)

**GENE**
*NF2*

**ALTERATION**
loss exons 3-9

**RATIONALE**
Inactivation or loss of NF2 results in the dysregulation of mTOR and FAK pathway signaling. Therefore, mTOR and/or FAK inhibitors may be relevant for patients with NF2 inactivating mutations.

## NCT03239015

**PHASE 2**

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

**TARGETS**
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

**LOCATIONS:** Shanghai (China)

## NCT04337463

**PHASE NULL**

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

**TARGETS**
mTORC1, mTORC2, PD-1

**LOCATIONS:** Chongqing (China), Chengdu (China)

## NCT04803318

**PHASE 2**

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

**TARGETS**
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

**LOCATIONS:** Guangzhou (China)

## NCT05125523

**PHASE 1**

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

**TARGETS**
mTOR

**LOCATIONS:** Tianjin (China)

## 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

## NCT03297606

**PHASE 2**

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

## NCT04203901

**PHASE 2**

Dendritic Cell Immunotherapy Plus Standard Treatment of Advanced Renal Cell Carcinoma

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

**LOCATIONS:** Minnesota, New York, Pennsylvania, West Virginia, Texas, Georgia, Florida

## NCT01582191

**PHASE 1**

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

**TARGETS**
mTOR, EGFR, SRC, RET, VEGFRs

**LOCATIONS:** Texas

## NCT03203525

**PHASE 1**

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

**TARGETS**
VEGFA, mTOR

**LOCATIONS:** Texas

## NCT05012371

**PHASE 2**

Lenvatinib With Everolimus Versus Cabozantinib for Second-Line or Third-Line Treatment of Metastatic Renal Cell Cancer

**TARGETS**
MET, ROS1, RET, VEGFRs, KIT, FGFRs, PDGFRA, mTOR

**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.

***CD22***
Y170N

***CDH1***
V202I

***CDK12***
Y1468H

***CSF1R***
S67C and T75I

***EGFR***
T6_A21del

***FGF6***
S51L

***GATA3***
C267S

***GNAS***
G370R and M1L

***IRS2***
R558P

***JAK1***
S262A

***MERTK***
I162L and R584W

***MST1R***
V670G

***MYC***
T93I

***MYD88***
rearrangement

***NTRK1***
E275A

***TYRO3***
Q157L

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. 2023. 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) 7.5.0



The median exon coverage for this sample is 905x

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