FOUNDATIONONE®CDx

PATIENT
Yeh, Chen-Yu

TUMOR TYPE
Bladder urothelial (transitional cell) carcinoma

COUNTRY CODE
TW

REPORT DATE
20 Oct 2021

ORDERED TEST #
ORD-1213873-01

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 Bladder urothelial (transitional cell) carcinoma
NAME Yeh, Chen-Yu
DATE OF BIRTH 24 January 1980
SEX Female
MEDICAL RECORD # 40170556

PHYSICIAN

ORDERING PHYSICIAN Mu-Hsin Chang, Peter
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Pelvis
SPECIMEN ID S110-26284 A
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 08 September 2021
SPECIMEN RECEIVED 14 October 2021

Biomarker Findings

Tumor Mutational Burden - 13 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

NF2 splice site 1575-1G>C
TERT promoter -124C>T
TP53 splice site 994-1G>A

2 Disease relevant genes with no reportable alterations: ***FGFR2, FGFR3***

10 Therapies with Clinical Benefit
0 Therapies with Resistance
20 Clinical Trials

BIOMARKER FINDINGS

Tumor Mutational Burden - 13 Muts/Mb

10 Trials *see p. 14*

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

Microsatellite status - MS-Stable

No therapies or clinical trials. see Biomarker Findings section

GENOMIC FINDINGS

NF2 - splice site 1575-1G>C

10 Trials *see p. 16*

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
none	Everolimus
	Temsirolimus

☐ *NCCN category*

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.

TERT - promoter -124C>T ..... p. 4
TP53 - splice site 994-1G>A ..... p. 5

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

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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.

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BIOMARKER

Tumor Mutational Burden

RESULT
13 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 studies of immune checkpoint inhibitors in urothelial carcinoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-L1[1,11-15] and anti-PD-1 immunotherapeutic agents[16-17] . For patients with metastatic urothelial carcinoma treated with the PD-L1 inhibitor atezolizumab, those with a significantly increased mutational load (9.7 Muts/Mb or greater by this assay or others) were associated with response and longer OS compared with those with lower TMB[1,11-13]. Similarly, in a study of pembrolizumab in muscle invasive bladder cancer, the median TMB in responders was 12.3 Muts/Mb, versus 7.0 Muts/Mb in nonresponding patients[17]. The PD-1 inhibitor nivolumab led to increased ORR, PFS, and OS for patients with a TMB of 167 missense mutations/tumor or higher (~ equivalency = 9 Muts/Mb or higher as measured by this assay) compared with those harboring lower TMB in a study of metastatic urothelial cancer[16].

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, the median somatic mutation burden was 5.5 mutations per megabase (muts/Mb)[18]. One study reported that the number of somatic mutations positively correlates with increased tumor stage and grade of bladder cancers[19]. For patients with metastatic urothelial carcinoma receiving atezolizumab, however, higher median mutation load has been reported to be significantly associated with improved PFS and OS[11-12,20].

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[21-22] and cigarette smoke in lung cancer[23-24], treatment with temozolomide-based chemotherapy in glioma[25-26], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[27-31], and microsatellite instability (MSI)[27,30-31]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in urothelial carcinoma[1,11-15,32].

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[33-35], including approved therapies nivolumab and pembrolizumab[36]. 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)[37].

FREQUENCY & PROGNOSIS

MSI has been detected in 26-49% of urothelial carcinomas[38-39]; MSI-H has also been reported in multiple case studies of upper urinary tract urothelial carcinoma[40]. MSI, as determined through loss of MSH2 or MSH6 protein expression, correlated with non-invasive, well-differentiated bladder tumors and favorable overall survival[38].

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
splice site 1575-1G>C

TRANSCRIPT ID
NM_000268

CODING SEQUENCE EFFECT
1575-1G>C

VARIANT ALLELE FREQUENCY (% VAF)
20.7%

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 mutation has been observed in 0-3% of urothelial carcinomas[67-70]. Published data investigating the prognostic implications of NF2 alterations in urothelial carcinoma are limited (PubMed, Jan 2021).

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
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
47.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches are under development, including immunotherapies utilizing TERT as a tumor-associated antigen, antisense oligonucleotide- or peptide-based therapies, and TERT promoter-directed cytotoxic molecules.

FREQUENCY & PROGNOSIS

TERT promoter mutations have been observed in a variety of solid tumors, including bladder cancer[82-90]. One study reported TERT promoter mutations in 67% (14/21) of high-grade and 56% (34/61) of low-grade bladder carcinomas[82], while another study demonstrated that 85% (44/52) of all bladder cancer samples and 88% (7/8) of bladder cancer cell lines exhibited TERT promoter alteration[89]. TERT promoter mutations correlated with increased TERT mRNA expression in urothelial cancer cells[91]. In patients with bladder urothelial carcinoma, both TERT promoter mutations and increased TERT expression associate with poor prognosis, although carrying an additional germline alteration at -245 (rs2853669) may confer a better prognosis[85,91-92].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[93]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[94-96]. 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)[82-83,97], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[97].

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GENE
TP53

ALTERATION
splice site 994-1G>A

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
994-1G>A

VARIANT ALLELE FREQUENCY (% VAF)
20.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[98-101], or p53 gene therapy and immunotherapeutics such as SGT-53[102-106] and ALT-801[107]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[108]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[109]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[110]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[111]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[112]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[113]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[106]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[114]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[115-116]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[117-118]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutation has been reported in 49–54% of bladder urothelial carcinoma (UC)[18,119], 33% of renal pelvis UC[120], and 25% (22/71) of ureter UC samples[121]. Expression of p53 has been correlated with TP53 mutation, and reported in 52–84% of bladder cancers[122-127], 48% (24/50) bladder SCCs[128], 36–53% of upper urinary tract UCs (UTUC)[129-131], and in 4/4 urethral clear cell carcinomas[132]. TP53 mutations in both bladder and renal pelvis urothelial carcinoma (UC) are more common in invasive tumors[120,127,133-134], and have been associated with inferior survival in patients with renal pelvis UC[120] or upper tract UC (UTUC)[135]. Alterations to the p53 pathway are correlated with aggressive disease and poor prognosis in bladder cancer[136-138], and p53 overexpression has been linked to poor progression-free survival in UTUC[135,139], disease progression in UC of the renal pelvis and ureter[140], and higher tumor grade in bladder squamous cell carcinoma[141-143].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[144]. Alterations such as seen here may disrupt TP53 function or expression[145-149].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[150-152], including sarcomas[153-154]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[155] to 1:20,000[154]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[156]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[157-162]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[157-158]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[163]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[161,164-165]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Atezolizumab

Assay findings association

Tumor Mutational Burden
13 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) and urothelial carcinoma, 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[2-4,166-167] , 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 IMvigor130 study, patients with metastatic urothelial carcinoma harboring TMB-high (>10 muts/Mb) and PD-L1 expression >5% experienced improved OS with atezolizumab monotherapy compared to platinum-based chemotherapy (HR=0.22)[168]. As second-line therapy for advanced urothelial carcinoma in the Phase 3 IMvigor211 study, atezolizumab compared with chemotherapy did not significantly improve median OS (11.1 vs. 10.6 months, HR=0.87) for patients with PD-L1 expression on 5% or more of tumor-infiltrating immune cells[13]. The ORRs (23% vs. 22%) and median PFSs (HR=1.01) were similar between the treatment arms, but atezolizumab was associated with a numerically longer median duration of response (15.9 vs. 8.3 months)[13] The Phase 3 IMvigor130 study for patients with treatment-naive urothelial carcinoma found that the addition of atezolizumab to platinum-based chemotherapy improved median PFS (8.2 vs. 6.3 months, HR=0.82) and numerically improved median OS (16.0 vs. 13.4 months, HR=0.83) compared to placebo, with similar ORRs (47.4% vs. 43.8%) but a higher CR rate (12.5% vs. 6.8%)[169]. In a Phase 2 study, patients with metastatic urothelial carcinoma treated with atezolizumab as first-line therapy experienced an ORR of 23%, a CR rate of 9%, and a clinical benefit rate of 30%[12]. Another Phase 2 trial of atezolizumab as second-line therapy reported an ORR of 15%, with 80% (37/46) of the responses ongoing at the median follow-up of 14.4 months; the median PFS was 2.11 months, and the 12-month OS rate was 37%[11,170] . Long-term follow-up of a Phase 1 expansion cohort reported a 3-year OS rate of 27% on second-line atezolizumab[171]. Multiple studies have reported superior ORR and OS outcomes with atezolizumab monotherapy for patients with higher tumor mutational burden (TMB) or PD-L1 expression compared to those with lower TMB or PD-L1 expression[11-13,168] .

Avelumab

Assay findings association

Tumor Mutational Burden
13 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[2-4,166-167] , 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 Phase 3 JAVELIN Bladder 100 trial of maintenance avelumab for patients with advanced or metastatic urothelial cancer reported longer median PFS (mPFS; 3.7 vs. 2.0 months, HR=0.62), higher ORR (9.7% vs. 1.4%), and longer median OS (mOS; 21.4 vs. 14.3 months, HR=0.69) for avelumab plus best supportive care (BSC) as compared with BSC in the randomized population; longer mPFS (5.7 vs. 2.1 months, HR=0.56), higher ORR (13.8% vs. 1.2%), and longer mOS (not reached vs. 17.1 months, HR=0.56) were also reported for the PD-L1-positive population[172]. In the Phase 2 JAVELIN Medley VEGF study, avelumab plus axitinib yielded an ORR of 10% (2/20) and mPFS of 2.3 months for patients with treatment-naive, cisplatin-ineligible urothelial carcinoma[173].

Dostarlimab

Assay findings association

Tumor Mutational Burden
13 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[2-4,166-167], 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

Clinical data on the efficacy of dostarlimab for the treatment of urothelial carcinoma are limited (PubMed, May 2021). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[174-176]. 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[174,177].

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Nivolumab

Assay findings association

Tumor Mutational Burden
13 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 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, classical Hodgkin lymphoma (cHL), gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma or squamous cell carcinoma (ESCC). Furthermore, nivolumab is approved to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,166-167] , 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 Phase 2 CheckMate 275 and Phase 1/2 CheckMate 032 studies evaluating nivolumab for patients with platinum-refractory metastatic urothelial carcinoma (UC) reported ORRs of 20% (6.3% CR) and 26% (10.3% CR), PFS of 1.9 and 2.8 months, and OS of 8.6 and 9.9 months, respectively[178-180] . CheckMate 032 additionally reported a 38% ORR, 4.9 month median PFS (mPFS), and 15.3 month median OS for patients treated with nivolumab and ipilimumab; a 58% ORR was observed for patients with ≥1% tumor PD-L1 expression[178]. In a Phase 3 trial of neoadjuvant nivolumab and ipilimumab for patients with high-risk advanced UC, 60% (9/15) of patients with a combined positive PD-L1 score ≥10 experienced a pathologic CR compared with 22% (2/9) of patients with lower PD-L1 expression[181]. A Phase 2 study of ipilimumab and nivolumab for patients with platinum-refractory metastatic UC who progressed on nivolumab monotherapy observed PRs for 23% (5/22) of patients[182]. The Phase 3 CheckMate-274 study of adjuvant nivolumab versus placebo following radical surgery for patients with high-risk muscle-invasive UC reported an improved median disease-free survival (20.8 vs. 10.8 months) with 75% of patients treated with nivolumab alive and disease-free at 6 months versus 60% with placebo (HR=0.70); the percentages were 75% and 56%, respectively, for patients with PD-L1 expression ≥1% (HR=0.55); in an exploratory subgroup analysis, the DFS HR was 0.82 for patients with PD-L1-negative tumors[183]. A Phase 2 study of nivolumab plus chemotherapy for patients with muscle-invasive bladder cancer reported a complete clinical response (cCR) rate of 48% (31/64)[184]. An exploratory biomarker analysis of this study found an association between cCR and TMB ≥ 10 Muts/Mb (p=0.02) or ERCC2 mutation (p=0.02)[184]. Combining the multikinase inhibitor cabozantinib with nivolumab or with nivolumab plus ipilimumab demonstrated activity for immunotherapy-naive patients with chemotherapy-refractory metastatic UC (ORR of 50% [6/12] and 22% [2/9], respectively; mPFS of 24 and 10 months, respectively); cabozantinib combined with nivolumab also benefited immunotherapy-refractory patients (ORR of 29% [2/7])[185] and responses to these combination treatments were observed for patients with bladder squamous cell carcinoma or bladder adenocarcinoma[186]. Addition of the IDO1 inhibitor BMS986205 to nivolumab in previously treated advanced UC elicited ORRs for 37% (3/27 CRs, 7/27 PRs) of immunotherapy-naive patients but no responses for 3 patients who had prior immunotherapy[187]. As first-line therapy for advanced UC, nivolumab combined with the immunostimulatory therapy bempegaldesleukin achieved an ORR of 48% (13/27; 5/27 CRs), with 50% (6/12) of PD-L1-positive and 45% (5/11) of PD-L1-negative patients responding[188].

Pembrolizumab

Assay findings association

Tumor Mutational Burden
13 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 a single agent for PD-L1-positive non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), cervical cancer, or gastric, esophageal, or gastroesophageal junction (GEJ) 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 a single agent for patients with melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, classical Hodgkin lymphoma, or primary mediastinal large B-cell lymphoma, and in combination with chemotherapy or targeted therapy for NSCLC, HNSCC, esophageal or GEJ 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[2-4,166-167], 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 PURE-01 study of neoadjuvant pembrolizumab for muscle-invasive bladder urothelial carcinoma, TMB was significantly associated with the probability of pathologic CR (pCR) but was not an independent marker of pCR probability[189]. For TMB ≤11 Muts/Mb, the probability of pCR was not dependent on the PD-L1 combined positive score (CPS); however, increased CPS was associated with increased pCR probability for TMB >11 Muts/Mb[189]. The Phase 3 KEYNOTE-045 trial for patients with advanced urothelial carcinoma found second-line pembrolizumab superior to chemotherapy for median OS (10.1 vs. 7.3 months, HR=0.74) and ORR (21% vs. 11%), but not PFS (2.1 vs. 3.3 months, HR=0.96)[190]; a 2-year follow-up revealed PFS rates were higher for patients who received pembrolizumab (12% vs. 3.0%)[191]. First-line pembrolizumab therapy for cisplatin-ineligible patients with advanced urothelial carcinoma achieved a confirmed ORR of 29%, median DOR of 33.4 months, and median OS of 11.3 months after 5 years of follow-up in the Phase 2 KEYNOTE-052 trial. Improved median OS (18.5 months), ORR (47%, n=110, 21% CR), and median DOR (not yet reached at the 5-year mark) were observed for the subset of patients with a PD-L1 combined positive score (CPS) ≥10, compared with a median OS of 9.7 months, an ORR of 21% (n= 251, 4% CR), and a DOR of 21.2 months for the subset of patients with a PD-L1 CPS <10[192]. The Phase 2 PURE-01 study investigated neoadjuvant pembrolizumab followed by radical cystectomy in muscle-invasive urothelial bladder carcinoma (MIBC) and reported pathologic CRs for 40% (17/43) of patients; there was a significant association between CR rate and PBRM1 mutation (p=0.0024)[193]. For patients with high-risk non-MIBC unresponsive to the Bacillus Calmette-Guerin vaccine, follow-up analysis from the Phase 2 KEYNOTE-057 trial reported a 3-month CR rate of 40% (41/102) for patients treated with pembrolizumab, 75% and 53% of whom experienced a CR duration of at least 6 months and 12 months, respectively[194]. In a Phase 1b/2 trial, treatment of patients with advanced urothelial cancer with combination pembrolizumab and lenvatinib elicited an ORR of 25% (5/20, 1 CR) and median PFS of 5.4 months[195].

Cemiplimab

Assay findings association

Tumor Mutational Burden
13 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 NSCLC with high PD-L1 expression (TPS ≥ 50%), cutaneous squamous cell carcinoma (CSCC), or basal cell carcinoma (BCC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,166-167] , 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

Clinical data on the efficacy of cemiplimab for the treatment of urothelial carcinoma are limited (PubMed, Jun 2021). 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[196]. 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[197-198] . 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[199].

Durvalumab

Assay findings association

Tumor Mutational Burden
13 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) and small cell lung cancer (SCLC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,166-167] , 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

Biomarker analysis of the Phase 3 DANUBE trial for patients with locally advanced or metastatic urothelial carcinoma reported that a blood TMB (bTMB) score ≥24 Muts/Mb (approximately 12 Muts/Mb as measured by this assay) or tissue TMB (tTMB) score ≥10 Muts/Mb was associated with improved survival following combination treatment of durvalumab with the CTLA-4 inhibitor tremelimumab compared with chemotherapy; neither bTMB nor tTMB was associated with better outcomes following treatment with durvalumab alone[200]. In the first-line setting for locally advanced or metastatic urothelial carcinoma, the randomized, controlled, Phase 3 DANUBE study showed that durvalumab monotherapy did not significantly improve median OS for patients with PD-L1 high tumor status compared with chemotherapy (14.4 vs. 12.1 months, HR=0.89, p=0.30); durvalumab plus tremelimumab also did not improve median OS in the intention-to-treat population (15.1 vs. 12.1 months, HR=0.85, p=0.075)[201-202] . For chemotherapy-pretreated patients with advanced urinary tract carcinoma, the Phase 3b STRONG study of durvalumab reported an ORR of 18% and mOS of 7.0 months, with longer mOS observed for patients with high PD-L1 expression (9.3 vs. 6.5 months)[203]. The Phase 2 DUART study of concurrent durvalumab and radiation therapy followed by adjuvant durvalumab for patients with locally advanced bladder urothelial carcinoma reported a 65% (13/20) ORR and 70% (14/20) DCR; median PFS was 18.5 months and median OS was not reached, but 1- and 2- year OS probabilities were 84% and 77%, respectively[204]. In a Phase 1 study of durvalumab with tremelimumab in a cohort of patients with platinum-refractory metastatic urothelial cancer, an ORR of 21% (35/168, 4 CRs), a median PFS of 1.9 months, and an OS of 9.5 months were reported[205]. For patients with localized muscle-invasive bladder cancer, the Phase 2 IMMUNOPRESERVE-SOGUG study of durvalumab plus tremelimumab with concurrent radiotherapy reported a CR rate of 81% (26/32), 12-month DFS rate of 76%, 12-month bladder intact DFS rate of 73%, and 12-month OS rate of 87%[206]. Interim results from the Phase 2 ARCADIA study evaluating the combination of durvalumab and cabozantinib to treat patients with advanced urothelial carcinoma following progression on platinum chemotherapy reported an ORR of 38% (6/16, 2 CRs)[207]. Combining durvalumab with matched targeted therapies (FGFRi, PARP, or mTOR inhibitors) did not improve PFS or OS for patients with platinum-refractory advanced urothelial cancer in the Phase 2 BISCAY study[208]. In the neoadjuvant setting, a Phase 2 study of durvalumab and olaparib yielded an ORR of 14% (4/29) for patients with muscle-invasive bladder carcinoma[209].

Everolimus

Assay findings association

NF2
splice site 1575-1G>C

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on individual responses for patients with NF2-mutated metaplastic breast cancer[52-53] and urothelial carcinoma[51] treated with temsirolimus and everolimus, respectively, as well as preclinical evidence[47-50] , NF2 inactivation may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus.

SUPPORTING DATA

A single-arm, non-randomized Phase 2 study of everolimus in metastatic urothelial carcinoma did not meet its primary endpoint; however, two PRs, one near-CR, and twelve minor regressions were observed[210]. A Phase 2 study of everolimus in urothelial carcinoma reported two patients with PRs and eight patients with SD, out of 37 patients treated in the study[211]. Preclinical studies have suggested that the use of everolimus in combination with cisplatin may be an effective therapeutic strategy for the treatment of urothelial bladder cancer[212]. Two case studies of patients with bladder carcinoma harboring inactivating NF2 mutations reported exceptional responses to therapy regimens involving the mTOR inhibitor everolimus[50-51] . 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].

Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
13 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), and pleural mesothelioma. Furthermore, nivolumab is approved in combination with ipilimumab to treat patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (CRC) that has progressed on fluoropyrimidine, oxaliplatin, and irinotecan. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[5-6,213] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

A Phase 2 study of ipilimumab and nivolumab for patients with platinum-refractory metastatic UC who progressed on nivolumab monotherapy observed PRs for 23% (5/22) of patients[182]. The Phase 1/2 CheckMate 032 reported a 38% ORR, a 4.9 month median PFS, and a 15.3 month median OS for patients with locally advanced or metastatic UC treated with nivolumab and ipilimumab; a 58% ORR was observed for patients with ≥1% tumor PD-L1 expression[178]. A Phase 2 study of nivolumab in combination with ipilimumab for patients with advanced bladder cancers reported 1 CR in a patient with plasmacytoid carcinoma and 2 PRs in patients with small cell carcinoma[214]. A Phase 1 trial of nivolumab plus ipilimumab and cabozantinib in patients with refractory metastatic UC and other genitourinary cancers reported a 42% ORR among patients with metastatic UC and bladder squamous cell carcinoma[215]. In the Phase 1 NABUCCO study of neoadjuvant ipilimumab plus nivolumab for patients with advanced urothelial cancer, 93% (23/24) of patients underwent resection within 12 weeks and 46% (11/24) had a pathological CR[216].

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Temsirolimus

Assay findings association

NF2
splice site 1575-1G>C

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on individual responses for patients with NF2-mutated metaplastic breast cancer[52-53] and urothelial carcinoma[51] treated with temsirolimus and everolimus, respectively, as well as preclinical evidence[47-50] , NF2 inactivation may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus.

SUPPORTING DATA

A Phase 2 study investigating temsirolimus in 15 patients with metastatic urothelial cancer reported minimal activity, with no responses, although 4 patients experienced SD[217]. An additional clinical study of temsirolimus in patients with recurrent or metastatic bladder cancer who had already received first-line chemotherapy reported PRs in 2 patients and SD in 16 patients, out of the 36 evaluable patients included in the study[218].

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.

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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

13 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.

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

LOCATIONS: Taipei (Taiwan), Sunto Gun (Japan), Singapore (Singapore), Milano (Italy), Barcelona (Spain), California, Illinois, Missouri, Connecticut, Texas

NCT03898180

PHASE 3

Study of First-line Pembrolizumab (MK-3475) With Lenvatinib (MK-7902/E7080) in Urothelial Carcinoma Cisplatin-ineligible Participants Whose Tumors Express Programmed Cell Death-Ligand 1 and in Participants Ineligible for Platinum-containing Chemotherapy (MK-7902-011/E7080-G000-317/LEAP-011)

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

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Kaoshiung (Taiwan), Xiamen (China), Hangzhou (China), Shanghai (China), Guangdong (China), Nanjing (China)

NCT03661320

PHASE 3

A Study of Chemo Only Versus Chemo Plus Nivo With or Without BMS-986205, Followed by Post-Surgery Therapy With Nivo or Nivo and BMS-986205 in Patients With MIBC

TARGETS
IDO1, PD-1

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taichung (Taiwan), Kaohsiung (Taiwan), Fukuoka (Japan), Gyeongsangnam-do (Korea, Republic of), Daegu (Korea, Republic of), Seongnam-si (Korea, Republic of), Seongnam-si, (Korea, Republic of), Seoul (Korea, Republic of)

NCT03732677

PHASE 3

Durvalumab+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC

TARGETS
PD-L1

LOCATIONS: Taipei (Taiwan), Taipei City (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Baguio City (Philippines), Quezon City (Philippines), Manila (Philippines), Nagasaki-shi (Japan)

NCT04223856

PHASE 3

Enfortumab Vedotin and Pembrolizumab, With or Without Chemotherapy, vs. Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer

TARGETS
PD-1, Nectin-4

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Hwasun (Korea, Republic of), Daejeon (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Okayama (Japan), Toyama (Japan), Kawasaki-shi (Japan)

NCT04241185

PHASE 3

Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Chemoradiotherapy (CRT) Versus CRT Alone in Muscle-invasive Bladder Cancer (MIBC) (MK-3475-992/KEYNOTE-992)

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Nagasaki (Japan), Daejeon (Korea, Republic of), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Takatsuki (Japan), Tokyo (Japan)

NCT03674567

PHASE 1/2

Dose Escalation and Expansion Study of FLX475 Monotherapy and in Combination With Pembrolizumab

TARGETS
PD-1, CCR4

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Shatin (Hong Kong), High West (Hong Kong), Ulsan (Korea, Republic of), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia), Heidelberg (Australia)

NCT04181788

PHASE 1/2

Sasanlimab (PF-06801591, PD-1 Inhibitor) in Participants With Advanced Malignancies

TARGETS
PD-1

LOCATIONS: Taipei (Taiwan), Kaohsiung (Taiwan), Shanghai (China), Nanjing (China), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Chongqing (China), Beijing (China), Chuo-ku (Japan), Kopeysk (Russian Federation)

NCT02829723

PHASE 1/2

Phase I/II Study of BLZ945 Single Agent or BLZ945 in Combination With PDR001 in Advanced Solid Tumors

TARGETS
PD-1, CSF1R

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Nagoya (Japan), Koto ku (Japan), Singapore (Singapore), Tel Aviv (Israel), Zurich (Switzerland), Rozzano (Italy), Barcelona (Spain), Hospitalet de LLobregat (Spain)

NCT03207867

PHASE 2

A Phase 2 Study of NIR178 in Combination With PDR001 in Patients With Solid Tumors and Non-Hodgkin Lymphoma

TARGETS
PD-1, ADORA2A

LOCATIONS: Taipei (Taiwan), Koto ku (Japan), Singapore (Singapore), Brno (Czechia), Salzburg (Austria), Essen (Germany), Koeln (Germany), St. Gallen (Switzerland), Rotterdam (Netherlands), Liege (Belgium)

GENE
NF2

ALTERATION
splice site 1575-1G>C

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, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, 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, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT02758587

PHASE 1/2

Study of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition in Advanced Solid Malignancies (FAK-PD1)

TARGETS
FAK, PD-1

LOCATIONS: Edinburgh (United Kingdom), Glasgow (United Kingdom), Leicester (United Kingdom), Belfast (United Kingdom), Southampton (United Kingdom)

NCT03190174

PHASE 1/2

Nivolumab (Opdivo®) Plus ABI-009 (Nab-rapamycin) for Advanced Sarcoma

TARGETS
mTOR, PD-1

LOCATIONS: California

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

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, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

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.

ATM
amplification

BCOR
S1633L

BRAF
A27T

DAXX
E457del

EED
amplification

EPHB1
R767C

MAP2K2 (MEK2)
P298L

MRE11A
amplification

MTOR
E751Q, H1744Y and Q752H

NF2
E564Q and L549F

PDGFRB
R370C

PTCH1
E44G and S827G

RAD52
R55H

TSC1
A84T

TYRO3
E371K

Electronically signed by Erik Williams, M.D. | 20 October 2021
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APPENDIX Genes Assayed in FoundationOne®CDx

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: 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. 2021. 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. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics

of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. 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.
5. 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.
6. 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%.

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

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physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

The median exon coverage for this sample is 370x

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