FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chen, Hsiao Ting	Kidney urothelial carcinoma	25 May 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1631801-01

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 urothelial carcinoma
NAME Chen, Hsiao Ting
DATE OF BIRTH 20 January 1981
SEX Female
MEDICAL RECORD # 49487516

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

SPECIMEN
SPECIMEN SITE Kidney
SPECIMEN ID S112-20568 A (PF23056)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 08 May 2023
SPECIMEN RECEIVED 17 May 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.

ARID1A E966*
TP53 Y220C
EMSY (C11orf30) amplification
KMT2D (MLL2) K3630*

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

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Avelumab** (p. 7), **Pembrolizumab** (p. 9), **Nivolumab** (p. 8), **Atezolizumab** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 13)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***KMT2D (MLL2)*** K3630* (p. 6)

BIOMARKER FINDINGS

Tumor Mutational Burden - 12 Muts/Mb

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

10 Trials see p. 13

Microsatellite status - MS-Stable

No therapies or clinical trials. See Biomarker Findings section

GENOMIC FINDINGS

ARID1A - E966*

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

10 Trials see p. 15

TP53 - Y220C

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

1 Trial see p. 17

NCCN category

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

KMT2D (MLL2) - K3630* p. 6

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.

EMSY (C11orf30) - amplification p. 6

KMT2D (MLL2) - K3630* 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 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]. Another study for patients with urothelial bladder carcinoma showed that high tumor mutational burden (TMB) was associated with superior OS and disease-specific survival compared with low TMB; the OS benefit of high TMB was driven by the cohort with Stage 3 disease, whereas OS was similar between low and high TMB for patients with Stage 2 or Stage 4 disease[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]. Microsatellite instability (MSI), as determined through loss of MSH2 or MSH6 protein expression, correlated with noninvasive well-differentiated bladder tumors and favorable OS[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].

GENE
ARID1A

ALTERATION
E966*

HGVS VARIANT
NM_006015.4:c.2896G>T (p.E966*)

VARIANT CHROMOSOMAL POSITION
chr1:27092965

VARIANT ALLELE FREQUENCY (% VAF)
83.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[47]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[48]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[49]. In a Phase 1 trial, a patient with metastatic colorectal cancer (CRC) harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[50]. On the basis of limited clinical and preclinical evidence, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[51-52]. A Phase 1 study of EZH2 inhibitor CPI-0209 reported 1 PR for a patient with ARID1A-mutated endometrial cancer[53]. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[54-56]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[57]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[58-59] and to 5-fluorouracil in CRC cell lines[60]. Limited clinical evidence indicates that ARID1A-altered urothelial cancer may be sensitive to pan-HDAC inhibitors; a retrospective analysis reported a CR to belinostat and a PR to panobinostat in patients with ARID1A alterations[61].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2023)[62-70]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[57,71-74], CRC[57,75-77], and gastric cancer[57,78-82]. In the context of urothelial carcinomas, one study reported no association between ARID1A mutation and tumor grade[83], whereas others have reported contradictory associations between ARID1A protein loss and prognosis[84-85].

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[66,81,86-92]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[66,79,87-88,93], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
TP53

ALTERATION
Y220C

HGVS VARIANT
NM_000546.4:c.659A>G (p.Y220C)

VARIANT CHROMOSOMAL POSITION
chr17:7578190

VARIANT ALLELE FREQUENCY (% VAF)
82.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with TP53 Y220C-mutated disease, a Phase 1 study of the Y220C-specific reactivator PC14586 reported an ORR of 32% (8/25) and DCR of 88% (22/25) at higher doses across a variety of solid tumor types[94]. 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[95-98] or p53 gene therapy such as SGT53[99-103]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[104]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[105]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[106]. 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[107]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[108]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[109]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[110]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[103]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[111]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[112].

FREQUENCY & PROGNOSIS

TP53 mutation has been reported in 49–54% of bladder urothelial carcinoma (UC)[18,113], 33% of renal pelvis UC[114], and 25% (22/71) of ureter UC samples[115]. Expression of p53 has been correlated with TP53 mutation, and reported in 52–84% of bladder cancers[116-121], 48% (24/50) bladder SCCs[122], 36–53% of upper urinary tract UCs (UTUC)[123-125], and in 4/4 urethral clear cell carcinomas[126]. TP53 mutations in both bladder and renal pelvis urothelial carcinoma (UC) are more common in invasive tumors[114,121,127-128], and have been associated with inferior survival in patients with renal pelvis UC[114] or upper tract UC (UTUC)[129]. Alterations to the p53 pathway are correlated with aggressive disease and poor prognosis in bladder cancer[130-132], and p53 overexpression has been linked to poor progression-free survival in UTUC[129,133], disease progression in UC of the renal pelvis and ureter[134], and higher tumor grade in bladder squamous cell carcinoma[135-137].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[138]. Alterations such as seen here may disrupt TP53 function or expression[139-143]. TP53 Y220C is targetable by mutation-specific inhibitors such as PC14586[94].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Apr 2023)[144]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[145-147], including sarcomas[148-149]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[150] to 1:20,000[149]. 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[151]. 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[152-157]. 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[152-153]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[158]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[156,159-160]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
EMSY (C11orf30)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

EMSY overexpression in breast cancer cell lines has been reported to mimic the effects of inactivating BRCA2 mutations[161]. Unlike BRCA2 inactivation, which predicts sensitivity to DNA-repair-associated inhibitors, such as the PARP inhibitor olaparib[162-163], EMSY amplification in breast cancer lines was not associated with enhanced sensitivity to this drug in 1 preclinical study[164]. In a preclinical study of KEAP1-mutated lung cancer, loss of KEAP1 induced EMSY accumulation and sensitization to PARP inhibitors and stimulator of interferon genes protein agonists[165]. In clinical studies of high-grade serous ovarian cancer, high EMSY expression was associated with greater rates of response to platinum-based chemotherapy and improved clinical outcomes[166-168], although EMSY copy number was found to be a poor predictor of EMSY overexpression[166]. There are no therapies that target EMSY alterations.

FREQUENCY & PROGNOSIS

In the TCGA datasets, EMSY amplification has been most frequently observed in ovarian carcinoma (8%)[169], breast invasive carcinoma (6%)[170], esophageal carcinoma (5%)(cBioPortal, 2023), and head and neck squamous cell carcinoma (3.5%)[63-64,171]. EMSY overexpression has been primarily reported in breast and high-grade ovarian cancers, where it is implicated in BRCA2 inactivation and correlates with poor prognosis or advanced disease[164,172-178]. The consequences of EMSY alterations in other solid tumors or hematologic malignancies have not been studied in detail in the scientific literature (PubMed, Jan 2023).

FINDING SUMMARY

EMSY, also known as C11orf30, encodes a BRCA2-interacting protein with roles in transcriptional regulation[178-179]. Preclinical studies have suggested that EMSY binds to and suppresses the function of BRCA2, and EMSY overexpression may therefore mimic BRCA2 inactivation[161,178]. Amplification of the EMSY gene correlates with increased mRNA expression[164,180], although conflicting data have been reported[181]. The functional consequences of other EMSY alterations have not been extensively studied (PubMed, Jan 2023).

GENE
KMT2D (MLL2)

ALTERATION
K3630*

HGVS VARIANT
NM_003482.4:c.10888A>T (p.K3630*)

VARIANT CHROMOSOMAL POSITION
chr12:49427600

VARIANT ALLELE FREQUENCY (% VAF)
46.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS

MLL2 alterations are observed in a number of solid tumor contexts[182], and are especially prevalent in lung squamous cell carcinoma (SCC)[183] and small cell lung carcinoma (SCLC)[184]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[185]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[186]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[187].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[188]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[189]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[190].

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[152-157]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[156,159-160]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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[2-4,191-192] , 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 dose expansion phase of the Phase 1b/2 JAVELIN PARP Medley combining talazoparib with avelumab for solid tumors, patients with genomically unselected urothelial carcinoma experienced an ORR of 15% (6/40, 1 CR), and of those with DNA damage repair alterations (n=15), an ORR of 13%[193]. The Phase 3 JAVELIN Bladder 100 trial of maintenance avelumab for patients with advanced or metastatic urothelial cancer reported longer median OS (mOS) for avelumab plus best supportive care (BSC) compared with BSC in the randomized population (29.7 vs. 20.5 months, HR=0.69)[194-195] . Biomarker analysis of JAVELIN Bladder 100 showed further survival benefit with the addition of avelumab to BSC for patients with elevated TMB (HR=0.48) relative to those with TMB at or below the median (HR=0.88) and for patients with high PD-L1 expression (HR=0.35) relative to those with low PD-L1 expression (HR=0.79)[196]. A Phase 2 trial of first-line avelumab for patients with metastatic or advanced urothelial cancer with PD-L1-positive disease who were ineligible for cisplatin treatment reported an ORR of 23% (16/71), a median PFS (mPFS) of 2 months, and mOS of 10 months[197]. In a Phase 2 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[198].

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[2-4,191-192] , 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, Feb 2023). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[199-201] . 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[199,202] .

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[2-4,191-192], 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

Exploratory analysis of the CheckMate-274 trial suggests that adjuvant nivolumab may provide less benefit for patients with upper tract high-risk muscle-invasive urothelial carcinoma (estimated disease-free survival HR of 1.23 and 1.56 for patients with renal pelvis and ureteral primary tumors, respectively)[203]. Phase 1/2 and Phase 2 studies evaluating nivolumab for patients with platinum-refractory metastatic urothelial carcinoma (UC) reported ORRs of 21-26%, PFS of 1.9-2.8 months, and OS of 8.6-9.9 months[204-207]. 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 (mDFS) for the intent-to-treat population (22.0 vs. 10.9 months, HR=0.71) as well as for patients with PD-L1+ tumors (tumor cell score ≥1%: 52.6 vs. 8.4 months, HR=0.52; combined positive score ≥1%: 24.6 vs. 9.4 months, HR=0.62)[203,208-209]. A Phase 2 study of nivolumab plus chemotherapy for patients with muscle-invasive bladder cancer reported a complete clinical response (cCR) rate of 43% (33/76); an exploratory biomarker analysis of this study found an association between cCR and tumor mutational burden ≥10 Muts/Mb[210]. Combining the multikinase inhibitor cabozantinib with nivolumab or with nivolumab plus ipilimumab demonstrated activity for patients with chemotherapy-refractory metastatic UC who were immunotherapy-naive (ORR of 50% [6/12] and 22% [2/9], respectively; median PFS of 24 and 10 months, respectively); cabozantinib combined with nivolumab also benefited patients who were immunotherapy-refractory (ORR of 29% [2/7])[211], and responses to these combination treatments were observed for patients with bladder squamous cell carcinoma (SCC) or bladder adenocarcinoma[212]. Addition of the IDO1 inhibitor BMS986205 to nivolumab in previously treated advanced UC elicited ORRs for 37% (3/27 CRs, 7/27 PRs) of patients who were immunotherapy-naive but no responses for 3 patients who had prior immunotherapy[213]. 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 patients who were PD-L1+ and 45% (5/11) of patients who were PD-L1-responding[214].

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-high (≥10 Muts/Mb), microsatellite instability-high (MSI-H), or MMR-deficient (dMMR) solid tumors; as monotherapy for PD-L1-positive 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 non-small cell lung cancer (NSCLC), melanoma, HNSCC, urothelial carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, MSI-H or dMMR endometrial carcinoma, 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, urothelial carcinoma, 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[2-4,191-192] , 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[215]. 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[215]. The Phase 3 KEYNOTE-045 trial for patients with platinum-refractory advanced urothelial carcinoma (UC) found second-line pembrolizumab superior to chemotherapy (median OS [mOS] 10.1 vs. 7.2 months, HR=0.71; 4-year OS rate 17% vs. 10%)[216-217] . For cisplatin-ineligible patients with advanced UC, first-line pembrolizumab monotherapy achieved an ORR of 29% and mOS of 11.3 months, with improved clinical benefit observed for patients with a PD-L1 combined positive score (CPS) ≥10 compared with patients with PD-L1 CPS <10 (mOS 18.5 vs. 9.7 months, ORR 47% vs. 21%)[216]; pembrolizumab combined with the Nectin 4-directed antibody drug conjugate enfortumab vedotin has benefited patients in this setting irrespective of PD-L1 expression (ORR 65-73%, mOS 26.1 months)[218-219] . The EV-103/KEYNOTE-869 trial reported an ORR of 65% (49/76) for cisplatin-ineligible patients, including 61% (27/44) for patients with PD-L1 expression of CPS <10[218]. The Phase 3 KEYNOTE-361 study investigating first-line pembrolizumab for advanced UC reported similar mOS for patients treated with single-agent pembrolizumab versus platinum-containing chemotherapy (15.6 vs. 14.3 months, HR=0.92) irrespective of PD-L1 CPS ≥10 (16.1 vs. 15.2 months, HR=1.01) and found that the addition of pembrolizumab to chemotherapy was not superior to chemotherapy (mOS 17.0 vs. 14.3 months, HR=0.86)[220]. A post-hoc analysis of first-line pembrolizumab monotherapy efficacy reported that patients with a CR or PR at 9 weeks of pembrolizumab therapy achieved better mOS outcomes (50.7 months) than patients with SD (17.5 months) or PD (5.3 months) as best response[221]. A Phase 2 study investigated neoadjuvant pembrolizumab followed by radical cystectomy in muscle-invasive urothelial bladder carcinoma (MIBC) and reported pathologic CRs for 42% (21/50) of patients[222]. Three-year event-free survival rates of 60%, 77%, and 90% were reported for cohorts with PD-L1 low, medium, and high CPS, respectively[223]. The Phase 2 KEYNOTE-057 trial evaluating pembrolizumab for patients with high-risk non-MIBC unresponsive to the Bacillus Calmette-Guerin vaccine reported clinical benefit for patients with carcinoma in situ (CIS) with and without papillary tumors (cohort A)[224] and non-CIS papillary tumors (cohort B)[225].

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[2-4,191-192] , 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)[226]. As second-line therapy for advanced urothelial carcinoma in the Phase 3 IMvigor211 study, atezolizumab did not significantly improve median OS (mOS) compared with chemotherapy (11.1 vs. 10.6 months, HR=0.87) but was associated with a numerically longer median duration of response (15.9 vs. 8.3 months) for patients with PD-L1 expression on 5% or more of tumor-infiltrating immune cells[13] and improved 2-year OS rate (23% vs. 13%, HR=0.82) irrespective of PD-L1 status[227]. The Phase 3 IMvigor130 study for patients with treatment-naive metastatic 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 mOS (16.1 vs. 13.4 months, HR=0.85)[228-229] , while atezolizumab monotherapy compared with chemotherapy did not significantly improve mOS (15.2 vs. 13.3 months, HR=0.98)[230]. 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 8.9%, and a clinical benefit rate of 30%[12]. 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 with those with lower TMB or PD-L1 expression[11-13,226,230] . A neoadjuvant trial for patients with muscle-invasive bladder cancer added atezolizumab to gemcitabine plus cisplatin and met its primary endpoint (non-muscle-invasive downstaging rate of 27/39)[231]. In the COSMIC-021 trial, patients with urothelial carcinoma (UC) post-platinum chemotherapy treated with the combination of atezolizumab with cabozantinib experienced an ORR of 27%, a DCR of 64%, and a median PFS (mPFS) of 5.4 months (n=30)[232]. The trial also reported benefit for patients with locally advanced or metastatic UC (mUC) receiving the combination in the first line, whether cisplatin-eligible (ORR: 30% [9/30]) or ineligible (ORR: 20% [6/30])[233]. For patients who had previously received an immune-checkpoint inhibitor (ICI), the ORR was 10% (3/31)[233].

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[2-4,191-192] , 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, Feb 2023). 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[234]. 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[235-236] . 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[237].

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[2-4,191-192] , 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 neoadjuvant setting, a Phase 2 study of durvalumab and olaparib yielded an ORR of 14% (4/29) for patients with muscle-invasive bladder carcinoma[238]. 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 (mOS) for patients with PD-L1-high tumor status compared with chemotherapy (14.4 vs. 12.1 months, HR=0.89, p=0.30)[239-240] . 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)[241]. 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 a 70% (14/20) DCR; median PFS was 18.5 months and mOS was not reached, but 1- and 2-year OS probabilities were 84% and 77%, respectively[242]. 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)[243]. Combining durvalumab with matched targeted therapies (FGFR, PARP, or mTOR inhibitors) did not improve PFS or OS for patients with platinum-refractory advanced urothelial cancer in the Phase 2 BISCAY study[244].

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[5-6,245] , a TMB score of ≥10 Muts/Mb (as measured by this assay) may predict sensitivity to combination nivolumab and ipilimumab treatment.

SUPPORTING DATA

In a Phase 3 trial of neoadjuvant nivolumab and ipilimumab for patients with high-risk advanced urothelial carcinoma (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[246]. 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[247]. The Phase 1/2 CheckMate 032 trial 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[205]. A Phase 2 study of nivolumab in combination with ipilimumab for patients with advanced bladder cancers reported 1 CR for a patient with plasmacytoid carcinoma and 2 PRs for patients with small cell carcinoma[248]. A Phase 1 trial of nivolumab plus ipilimumab and cabozantinib for patients with refractory metastatic UC and other genitourinary cancers reported a 42% ORR among patients with metastatic UC and bladder squamous cell carcinoma (SCC)[249]. In the Phase 1 NABUCCO study of neoadjuvant ipilimumab plus nivolumab for patients with advanced urothelial cancer, 96% (23/24) of patients underwent resection within 12 weeks and 46% (11/24) had a pathological CR[250].

Retifanlimab

Assay findings association

Tumor Mutational Burden
12 Muts/Mb

AREAS OF THERAPEUTIC USE

Retifanlimab 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 Merkel cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,191-192] , 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 POD1UM-203 trial of retifanlimab for patients with cisplatin-ineligible locally advanced or metastatic urothelial carcinoma with PD-L1 expression (combined positive score ≥10%) reported an ORR of 38% (11/29; 1 CR, 10 PRs), median PFS of 5.7 months, and median OS of 15.2 months[251].

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.

ORDERED TEST # ORD-1631801-01

CLINICAL TRIALS

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.

NCT04237649

PHASE NULL

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

TARGETS
ADORA2A, CD73, PD-1

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

NCT03682068

PHASE 3

Study of Durvalumab Given With Chemotherapy, Durvalumab in Combination With Tremelimumab Given With Chemotherapy, or Chemotherapy in Patients With Unresectable Urothelial Cancer

TARGETS
PD-L1, CTLA-4

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Xiamen (China), Hangzhou (China), Shanghai (China), Nanchang (China), Suzhou (China), Nanjing (China), Guangzhou (China), Beijing (China)

NCT03869190

PHASE 1/2

A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-based Treatment Combinations in Patients With Locally Advanced or Metastatic Urothelial Carcinoma After Failure With Platinum-Containing Chemotherapy

TARGETS
CD38, PARP, CD47, PD-L1, Nectin-4, IL-6R

LOCATIONS: Taipei City (Taiwan), Huwei Township (Taiwan), Tainan (Taiwan), Kaohsiung City (Taiwan), Seoul (Korea, Republic of), Athens (Greece), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Caen (France)

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: Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Seongnam-si (Korea, Republic of), Xi'an (China)

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), Busan (Korea, Republic of), Shatin (Hong Kong), High West (Hong Kong), Chungbuk (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Bangkok (Thailand), Nedlands (Australia)

NCT04047862

PHASE 1

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

TARGETS
PD-1, TIGIT

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

NCT03530397

PHASE 1

A Study to Evaluate MEDI5752 in Subjects With Advanced Solid Tumors

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

LOCATIONS: Taipei (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), Meldola (Italy)

NCT03967977

PHASE 3

Study of Tislelizumab in Combination With Chemotherapy Compared to Chemotherapy Alone for Participants With Urothelial Carcinoma

TARGETS
PD-1

LOCATIONS: Fuzhou (China), Quanzhou (China), Wenzhou (China), Xiamen (China), Ningbo (China), Hangzhou (China), Shanghai (China), Nanchang (China), Nanjing (China), Hefei (China)

NCT03821935

PHASE 1

Study to Determine the Safety, Tolerability, Pharmacokinetics and Recommended Phase 2 Dose (RP2D) of ABBV-151 as a Single Agent and in Combination With ABBV-181 in Participants With Locally Advanced or Metastatic Solid Tumors

TARGETS
PD-1, GARP

LOCATIONS: Taichung City (Taiwan), Taipei City (Taiwan), Seoul (Korea, Republic of), Chuo-ku (Japan), Kashiwa-shi (Japan), South Brisbane (Australia), Camperdown (Australia), Ramat Gan (Israel), Tel Aviv-Yafo (Israel), Haifa (Israel)

GENE
ARID1A

ALTERATION
E966*

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

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)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT05320640

PHASE 1/2

Study of Chidamide, Decitabine and Immune Checkpoint Inhibitors in R/R NHL and Advanced Solid Tumors

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

LOCATIONS: Beijing (China)

NCT04802174

PHASE 1/2

Lurbinectedin With Berzosertib, an ATR Kinase Inhibitor in Small Cell Cancers and High-Grade Neuroendocrine Cancers

TARGETS
ATR

LOCATIONS: Maryland

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Colorado, Oklahoma, Texas, Pennsylvania, Tennessee, Florida

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
TOP1, ATR

LOCATIONS: California, Arizona, Minnesota, Oklahoma, Missouri, Pennsylvania, Connecticut, New York

NCT05053971

PHASE 1/2

Testing A New Anti-cancer Drug Combination, Entinostat and ZEN003694, for Advanced and Refractory Solid Tumors and Lymphomas

TARGETS
BRD3, BRD4, BRD2, BRDT, HDAC

LOCATIONS: Oklahoma, Connecticut, Florida

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

NCT01543763

PHASE 1

Phase I Tolerability, Efficacy, and Safety Study of Pazopanib in Combination With PCI-24781 in Patients With Metastatic Solid Tumors

TARGETS
HDAC, FGFR3, KIT, FGFR1, VEGFRs, FGFR2

LOCATIONS: California

NCT04491942

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to the Usual Chemotherapy Treatment (Cisplatin, or Cisplatin and Gemcitabine) for Advanced Solid Tumors With Emphasis on Urothelial Cancer

TARGETS
ATR

LOCATIONS: California, Wisconsin, Toronto (Canada), Ohio, Pennsylvania, Maryland

GENE
TP53

ALTERATION
Y220C

RATIONALE
Clinical evidence suggests patients with TP53 Y220C mutations may benefit from Y220C-specific reactivators of TP53.

NCT04585750

PHASE 1/2

The Evaluation of PC14586 in Patients With Advanced Solid Tumors Harboring a p53 Y220C Mutation

TARGETS
TP53

LOCATIONS: Washington, Oregon, California, Ohio, Massachusetts, Connecticut, New York, Texas, Tennessee

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.

AR
NM_000044.2: c.528C>A
(p.S176R)
chrX:66765516

AXIN1
NM_003502.3: c.2545G>A
(p.V849I)
chr16:338166

CHEK2
NM_007194.3: c.1387G>T
(p.V463F)
chr22:29090094

CSF3R
NM_156039.3: c.616G>C
(p.E206Q)
chr1:36939093

ERBB4
NM_005235.2: c.1717-2A>T
(p.?)
chr2:212530204

FGFR4
NM_213647.3: c.2126A>G
(p.D709G)
chr5:176523715

JAK1
NM_002227.2: c.205C>T
(p.R69C)
chr1:65348960

KLHL6
amplification

KMT2D (MLL2)
NM_003482.4: c.14747C>T
(p.P4916L)
chr12:49421002

MST1R
rearrangement

PDGFRA
NM_006206.4: c.2624T>A
(p.L875Q)
chr4:55153658

ROS1
NM_002944.2: c.4081T>A
(p.W1361R)
chr6:117677852

SRC
NM_005417.3: c.236C>T
(p.A79V)
chr20:36012792

TENT5C (FAM46C)
NM_017709.3: c.643A>T
(p.M215L)
chr1:118166133

ZNF703
NM_025069.1: c.1183A>T
(p.S395C)
chr8:37555602

ORDERED TEST # ORD-1631801-01

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 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) 7.9.0

The median exon coverage for this sample is 470x

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