FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chiu, Mei Lun	Unknown primary urothelial carcinoma	10 Jan 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1532151-01

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 Unknown primary urothelial carcinoma
NAME Chiu, Mei Lun
DATE OF BIRTH 07 July 1951
SEX Female
MEDICAL RECORD # 48552734 PF22148

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 Omentum
SPECIMEN ID S111-19325A (PF22148)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 11 May 2022
SPECIMEN RECEIVED 24 December 2022

Sample qualified for detection of a genomic signal from a second source. This most commonly occurs due to contamination, which may occur at sample procurement, at the originating laboratory, or during molecular testing. Secondary genomic signals unrelated to contamination may also be seen in patients with prior allogeneic transplant. Although there is high confidence in the reported alterations, sensitivity for detecting additional genomic alterations and signatures may be reduced and TMB may be underreported.

Biomarker Findings

Tumor Mutational Burden - 12 Muts/Mb
Microsatellite status - Cannot Be Determined [α]

Genomic Findings

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

CCND1 amplification
FGF19 amplification
FGF3 amplification
FGF4 amplification
HRAS amplification
IGF1R amplification
MLL2 splice site 4237-2A>T, splice site 14644-2A>T
MUTYH splice site 892-2A>G
STAG2 splice site 894-2A>T
TP53 K132*

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

α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Avelumab** (p. 11), **Pembrolizumab** (p. 13), **Nivolumab** (p. 12), **Atezolizumab** (p. 14)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 18)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***MUTYH* splice site 892-2A>G** (p. 8)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***MLL2* splice site 14644-2A>T, splice site 4237-2A>T** (p. 8)

Electronically signed by Erik Williams, M.D. | 10 January 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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

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BIOMARKER FINDINGS

Tumor Mutational Burden - 12 Muts/Mb

10 Trials see p. 18

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	

Microsatellite status - Cannot Be Determined

No therapies or clinical trials. See Biomarker Findings section

GENOMIC FINDINGS

CCND1 - amplification

5 Trials see p. 20

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

NCCN category

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VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

MUTYH - splice site 892-2A>G p. 8

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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.

MLL2 - splice site 4237-2A>T, splice site 14644-2A>T p. 8

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.

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].

— Potential Resistance —

CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses[18-19]; in these studies, CCND1 amplification was associated with significantly decreased response rate[19] and OS (HR=1.6-2.0)[18-19] across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)[18-19].

FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, the median somatic mutation burden was 5.5 mutations per megabase (muts/Mb)[20]. One study reported that the number of somatic mutations positively correlates with increased tumor stage and grade of bladder cancers[21]. 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[22].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[23-24] and cigarette smoke in lung cancer[25-26], treatment with temozolomide-based chemotherapy in glioma[27-28], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[29-33], and microsatellite instability (MSI)[29,32-33]. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in urothelial carcinoma[1,11-15,34].

BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[35-36] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab[26,37-42], as well as PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[43-45] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI has been detected in 26-49% of urothelial carcinomas[46-47]; MSI-H has also been reported in multiple case studies of upper urinary tract urothelial carcinoma[48]. MSI, as determined through loss of MSH2 or MSH6 protein expression, correlated with non-invasive, well-differentiated bladder tumors and favorable overall survival[46].

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[49]. 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[49-51]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

GENE
CCND1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[52-57], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[56,58]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[59]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[59]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[60].

— Potential Resistance —

CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses[18-19]; in these studies, CCND1 amplification was associated with significantly decreased response rate[19] and OS (HR=1.6-2.0)[18-19] across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)[18-19].

FREQUENCY & PROGNOSIS

CCND1 amplification has been reported in 12-15% of bladder urothelial carcinomas[20,61-62]. The expression of cyclin D1, as detected by immunohistochemistry, has been reported in 64-83% of urothelial carcinomas[63-67]. The evidence linking CCND1 amplification and expression with prognosis in patients with urothelial carcinoma is mixed[62-64,68-71]. CCND1 amplification was associated with tumor progression and worse patient survival in patients with bladder cancer[62]. In another study involving patients with surgically treated lymph node-positive bladder urothelial carcinoma, CCND1 amplification correlated with shorter survival, although high nuclear cyclin D1 in metastases predicted a favorable response to adjuvant chemotherapy[69]. Cyclin D1 expression was reported to be higher in lower stage urothelial tumors and increased expression in advanced tumors was associated with improved survival[63-64]. Similarly, a study of non-muscle-invasive bladder cancer correlated high cyclin D1 expression with increased PFS[68]. However, in patients with bilharzial-related bladder cancer, cyclin D1 expression was associated with invasion and higher tumor grade[71]. Another study reported no significant association of CCND1 protein expression and prognosis in patients with urothelial carcinoma[70].

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[72] and may lead to excessive proliferation[73-74].

GENE
FGF19

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with advanced hepatocellular carcinoma (HCC) reported a 17% ORR (11/66, 1 CR, ongoing for >1.5 years) and 3.3-month PFS for FGF19 IHC–positive patients; patients with negative or unknown FGF19 IHC scores experienced poorer outcomes (0% ORR, 2.3-month PFS)[75]. A Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, demonstrated an ORR of 7.5% (4/53) and SD rate of 53% (28/53) for patients with HCC[76]. A Phase 1 study of the FGFR4 inhibitor H3B-6527 reported a 17% ORR (OS of 10.3 months, 46% clinical benefit rate) among patients with HCC; enrollment of patients with intrahepatic cholangiocarcinoma (ICC) was suspended due to efficacy[77]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[78], though another retrospective study found patients with higher pretreatment serum levels of FGF19 experienced reduced benefit from sorafenib compared with those with lower serum FGF19 (PFS of 86 vs. 139 days, OS of 353 vs. 494 days); no difference was observed for lenvatinib[79]. A patient with head and neck squamous cell carcinoma (HNSCC) with 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) amplification experienced a CR lasting 9 months from a pan-FGFR inhibitor[80].

FREQUENCY & PROGNOSIS

For patients with solid tumors, FGF19 amplification has been reported most frequently in breast cancer (17%), head and neck cancer (12%), lung squamous cell carcinoma (SCC; 12%), and urothelial carcinoma cancer (11%)[81-83]. FGF19 mutations are rare in solid tumors[81]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[84-85], and in prostate cancer following radical prostatectomy[86]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[87] and lung SCC[88].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[89-90]. FGF19 lies in a region of chromosome 11q13 that also contains FGF3, FGF4, and CCND1; this region is frequently amplified in a diverse range of malignancies[91]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[92], lung squamous cell carcinoma[88,93], and head and neck squamous cell carcinoma (HNSCC)[87], but was not observed in other cancers[79,94].

GENE
FGF3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[95].

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[73].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[96].

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[97-98] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[97]. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[95].

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[73] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, Jan 2023)[99-100].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[101] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[102]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[62,73,97,103-105] and may confer sensitivity to the multi-kinase inhibitor sorafenib[97].

GENE
HRAS

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of significant clinical benefit for 1 patient each with cholangiocarcinoma[106] and salivary gland carcinoma[107] treated with trametinib, as well as strong preclinical data[108-112], HRAS activating alterations may predict sensitivity to MEK inhibitors, such as binimetinib, cobimetinib, trametinib, and selumetinib. The reovirus Reolysin targets cells with activated RAS signaling[113-115] and has demonstrated mixed clinical efficacy, with the highest rate of response reported for head and neck cancer[116-124]. HRAS activating mutations may also predict sensitivity to farnesyl transferase inhibitors based on Phase 2 studies of tipifarnib in head and neck squamous cell carcinoma (HNSCC) with HRAS-mutated allele frequency ≥20% (ORR of 50.0% [9/18], mDOR of 14.7 months, mPFS of 5.9 months, and mOS of 15.4 months), HRAS-mutated salivary gland cancer (8.3% [1/12] PRs, 58.3% [7/12] SDs, mPFS of 7.0 months), and HRAS-mutated metastatic urothelial carcinoma (ORR of 41.7% [5/12], mPFS of 5.1 months)[125], as well as preclinical evidence in various cancer types[126-128]. HRAS mutations have been associated with secondary tumors, particularly cutaneous SCCs, occurring after treatment of primary tumors with RAF inhibitors[129-131]. Preclinical studies have also reported that activating HRAS mutations are associated with resistance to EGFR inhibitors[132-134].

FREQUENCY & PROGNOSIS

HRAS amplification has not been detected in published datasets of bladder and upper tract urothelial carcinoma[135-137]. Activating HRAS mutations have been shown to play a role in the early development and progression of urothelial carcinomas[138-141]. Among upper tract urothelial carcinomas, HRAS mutation was detected in 8 of 60 high-grade cases but not in any of the 23 low-grade cases[142]. In one study, HRAS was reported to be a driving oncogene of the low-grade, non-invasive papillary subtype of urothelial carcinoma[143].

FINDING SUMMARY

HRAS encodes a member of the RAS family of membrane proteins that bind GDP/GTP and possess GTPase activity. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[144]. HRAS has been reported to be amplified in cancer[100] and may be biologically relevant in this context[145-146].

GENE
IGF1R

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IGF1R-based therapies including monoclonal antibodies (mAbs; dalotuzumab, figitumumab, cixutumumab, ganitumab, R1508, and AVE1642), tyrosine kinase inhibitors targeting IGF1R (linsitinib), and mAbs against IGF1R ligands (MEDI-573 and BI836845) are in preclinical and clinical development[147-149]. Phase 2 studies evaluating single-agent IGF1R mAbs in patients with sarcoma reported stable disease (SD) in 16-40% of cases, partial responses (PRs) in 2-12% of cases, and complete responses in 2/2 patients with Ewing sarcoma[147,150-152]. Clinical benefit was also reported for patients with thymic malignancies treated with cixutumumab monotherapy in a Phase 2 study, with a disease control rate of 89% (33/37), including 5 PRs, for patients with thymomas and SD in 42% (5/12) of patients with thymic carcinoma[153]. Limited clinical efficacy has been reported for single-agent ganitumab in genomically unstratified patients with neuroendocrine tumors[154], ganitumab plus hormonal therapy in previously treated breast cancer[155], and single-agent linsitinib in adrenocortical carcinoma[156]. Because IGF1R signaling is upstream of critical signaling pathways, combination therapies with IGF1R inhibitors and mTOR inhibitors may be beneficial[157-159]. It is unclear if the combination of IGFR1 mAb with mTOR inhibitors is superior to IGF1R mAb alone for the treatment of sarcomas[147]. Phase 1 studies evaluating the combination of IGF1R mAbs with mTOR inhibitors in breast cancer have been mixed[160-161]. Although the combination of linsitinib with everolimus to treat colorectal cancer did not lead to clinical benefit[162], clinical activity was reported in a Phase 1 study evaluating the combination of linsitinib and erlotinib in patients with various solid tumors[163]. Preclinical studies indicate that IGF1R kinase inhibitors synergize with CDK4 inhibitors to suppress the growth of cancers that depend on CDK4[164-165].

FREQUENCY & PROGNOSIS

In bladder urothelial carcinoma, IGF1R mutations have been reported in 3.9% of samples analyzed in the TCGA dataset, while putative high-level IGF1R amplification has been reported in fewer than 1% of cases[20]. In another study, IGF1R amplification was not found in any of 97 bladder urothelial carcinoma samples[166]. Increased expression of IGF1R has been reported in 62-74% of invasive bladder cancer tissues, including in invasive bladder urothelial carcinomas[167-169]. Elevated IGF1R expression in bladder cancer has been correlated with increased tumor grade and tumor stage, recurrence, and poor prognosis[169-170].

FINDING SUMMARY

IGF1R encodes insulin-like growth factor-1 receptor, a receptor tyrosine kinase that is activated by IGF-1 and IGF-2 and mediates anti-apoptotic signals[171]. Overexpression or activation of IGF-1R may lead to tumor formation[172]. IGF1R has been reported to be amplified in cancer[100] and may be biologically relevant in this context[145-146].

GENE
MLL2

ALTERATION
splice site 4237-2A>T, splice site 14644-2A>T

TRANSCRIPT ID
NM_003482.4, NM_003482.4

CODING SEQUENCE EFFECT
4237-2A>T, 14644-2A>T

VARIANT CHROMOSOMAL POSITION
chr12:49440575, chr12:49421107

VARIANT ALLELE FREQUENCY (% VAF)
32.2%, 33.0%

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[81], and are especially prevalent in lung squamous cell carcinoma (SCC)[82] and small cell lung carcinoma (SCLC)[173]. 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[174]. 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])[175]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[176].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[177]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[178]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[179].

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[180-185]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[184,186-187]. 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
MUTYH

ALTERATION
splice site 892-2A>G

TRANSCRIPT ID
NM_001048171.1

CODING SEQUENCE EFFECT
892-2A>G

VARIANT CHROMOSOMAL POSITION
chr1:45797760

VARIANT ALLELE FREQUENCY (% VAF)
38.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2023)[188]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[189-190]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[191-193]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[194].

FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[195]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[189-190,196-198]. Numerous other MUTYH mutations have also been shown to result in loss of function[196-199].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH 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 MUTYH-associated polyposis (ClinVar, Sep 2022)[200]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[189,201-203]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[189]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[204-208]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[190]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

GENE
STAG2

ALTERATION
splice site 894-2A>T

TRANSCRIPT ID
NM_006603.4

CODING SEQUENCE EFFECT
894-2A>T

VARIANT CHROMOSOMAL POSITION
chrX:123184034

VARIANT ALLELE FREQUENCY (% VAF)
29.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that directly target STAG2. However, in preclinical studies, STAG2 inactivation by mutation or knockdown resulted in increased sensitivity to PARP inhibitors[209] or oxaliplatin[210].

FREQUENCY & PROGNOSIS

STAG2 mutations have been observed most frequently in urothelial bladder carcinoma (16-35%)[20,211-214], Ewing sarcoma (13-22%)[215-216], upper urinary tract urothelial carcinoma (11%)[217], myeloid malignancies (6%)[218-219], and glioblastoma (6%)[220]. STAG2 truncation mutations are associated with loss of protein expression[211-212,214,216]. In patients with Ewing sarcoma, STAG2 and TP53 mutations often co-occur and are associated with decreased overall survival, although mutation of either STAG2 or TP53 alone was not demonstrated to affect survival[215-216]. STAG2 mutation in patients with myelodysplastic syndrome is associated with decreased overall survival and has also been associated with increased response to treatment with azacitidine or decitabine in patients with myeloid malignancies[218]. The data on the prognostic significance of STAG2 mutation or loss of STAG2 protein expression in the context of urothelial bladder carcinoma are conflicting[211-214]. In patients with pancreatic ductal adenocarcinoma, loss of STAG2 staining was significantly associated with decreased overall survival, but was also associated with survival benefit from adjuvant chemotherapy[210]. An inactivating STAG2 mutation was identified in a patient with melanoma that acquired resistance to vemurafenib and preclinical evidence suggests that loss of STAG2 expression decreases the sensitivity of BRAF V600E-positive melanoma cells to vemurafenib, dabrafenib, and trametinib[221].

FINDING SUMMARY

STAG2 encodes a subunit of the cohesin complex, which maintains sister chromatid cohesion. The cohesin complex includes four subunits: SMC1A, SMC3, RAD21, and either STAG1 or STAG2[222]. Cohesin is also involved in transcriptional regulation, DNA replication and DNA repair[222]. STAG2 mutations, which are mostly truncating, or loss of STAG2 protein expression have been reported in multiple cancer types[222-223]. STAG2 deletion has been shown to promote tumorigenesis in preclinical studies[210], and STAG2 inactivation has been proposed to promote tumorigenesis via a mechanism that involves increased aneuploidy[211,213,220] or altered transcriptional regulation[212,214,218-219].

GENE
TP53

ALTERATION
K132*

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
394A>T

VARIANT CHROMOSOMAL POSITION
chr17:7578536

VARIANT ALLELE FREQUENCY (% VAF)
53.1%

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[224-227] or p53 gene therapy such as SGT53[228-232]. 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[233]. 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[234]. 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[235]. 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[236]. 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[237]. 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[238]. 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[239]. 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[232]. 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[240]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[241].

FREQUENCY & PROGNOSIS

TP53 mutation has been reported in 49–54% of bladder urothelial carcinoma (UC)[20,61], 33% of renal pelvis UC[242], and 25% (22/71) of ureter UC samples[243]. Expression of p53 has been correlated with TP53 mutation, and reported in 52–84% of bladder cancers[244-249], 48% (24/50) bladder SCCs[250], 36–53% of upper urinary tract UCs (UTUC)[251-253], and in 4/4 urethral clear cell carcinomas[254]. TP53 mutations in both bladder and renal pelvis urothelial carcinoma (UC) are more common in invasive tumors[242,249,255-256], and have been associated with inferior survival in patients with renal pelvis UC[242] or upper tract UC (UTUC)[257]. Alterations to the p53 pathway are correlated with aggressive disease and poor prognosis in bladder cancer[258-260], and p53 overexpression has been linked to poor progression-free survival in UTUC[257,261], disease progression in UC of the renal pelvis and ureter[262], and higher tumor grade in bladder squamous cell carcinoma[263-265].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[266]. Alterations such as seen here may disrupt TP53 function or expression[267-271].

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[272-274], including sarcomas[275-276]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[277] to 1:20,000[276]. 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[278]. 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[180-185]. 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[180-181]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[279]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[184,186-187]. 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[2-4,280-281] , 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) 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[282]. The Phase 2 ARIES trial of first-line avelumab for patients with metastatic or advanced urothelial cancer with PD-L1-positive disease and who were ineligible for cisplatin treatment reported an ORR of 23% (16/71), mPFS of 2 months, and mOS of 10 months[283]. 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[284].

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[2-4,280-281] , 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, Sep 2022). Dostarlimab has been studied primarily in recurrent and advanced mismatch repair-deficient (dMMR) endometrial and non-endometrial cancers[42,285-286] . 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[285,287] .

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[2-4,280-281] , 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[288-290] . 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[288]. 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[291]. 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[292]. 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[293]. 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)[294]. 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)[294]. 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])[295] and responses to these combination treatments were observed for patients with bladder squamous cell carcinoma or bladder adenocarcinoma[296]. 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[297]. 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[298].

Pembrolizumab

Assay findings association

Tumor Mutational Burden
12 Muts/Mb

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

On the basis of clinical data across solid tumors[2-4,280-281], 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[299]. 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[299]. The Phase 3 KEYNOTE-045 trial for patients with advanced urothelial carcinoma (UC) found second-line pembrolizumab superior to chemotherapy for median OS (mOS) (10.1 vs. 7.3 months, HR=0.74)[300] and 2-year PFS rates (12% vs. 3.0%)[301]. First-line pembrolizumab therapy for cisplatin-ineligible patients with advanced UC achieved a confirmed ORR of 29%, median duration of response (mDOR) of 33.4 months, and mOS of 11.3 months after 5 years of follow-up in a Phase 2 trial; improved clinical benefit was 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%)[302]. However, the Phase 3 KEYNOTE-361 study investigating pembrolizumab in first-line settings for advanced UC reported similar mOS for patients treated with single-agent pembrolizumab versus chemotherapy (15.6 vs. 14.3 months, HR=0.92) irrespective of high 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)[303]. A post-hoc analysis of pembrolizumab monotherapy efficacy in KEYNOTE-361 and KEYNOTE-052 reported that patients with a CR or PR response 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[304]. The Phase 3 LEAP-011 trial for advanced UC reported that the addition of lenvatinib to first-line pembrolizumab was similar to pembrolizumab monotherapy, with a median PFS of 4.2 versus 4.0 months (HR=0.91), an mOS of 11.2 versus 13.8 months (HR=1.25), and an ORR of 31.2% versus 26.5%[305]. 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; 54% (19/35) of patients experiencing CR had a PD-L1 CPS ≥10[306]. For patients with high-risk non-MIBC carcinoma in situ unresponsive to the Bacillus Calmette-Guerin vaccine, follow-up analysis from a Phase 2 trial reported a 3-month CR rate of 40% for patients treated with pembrolizumab, 75% and 53% of whom experienced a CR duration of at least 6 months and 12 months, respectively[307].

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[2-4,280-281] , 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)[308]. As second-line therapy for advanced urothelial carcinoma in the Phase 3 IMvigor211 study, atezolizumab compared with chemotherapy did not significantly improve median OS (mOS) (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 (mPFS) (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 2-year OS rate was 23% with atezolizumab versus 13% with chemotherapy in an exploratory analysis of the overall trial population irrespective of PD-L1 status[309]. The Phase 3 IMvigor130 study for patients with treatment-naive metastatic urothelial carcinoma found that the addition of atezolizumab to platinum-based chemotherapy improved mPFS (8.2 vs. 6.3 months, HR=0.82) and numerically improved mOS (16.0 vs. 13.4 months, HR=0.83) compared with placebo, with similar ORRs (47% vs. 44%)[310]. A second interim analysis of mOS in the IMvigor130 trial showed a favorable trend for atezolizumab monotherapy compared with platinum-based chemotherapy (15.2 vs. 13.1 months, OS HR=0.99) but did not reach statistical significance, and exploratory analysis observed the greatest benefit for patients who were cisplatin-ineligible with tumor portion score (TPS) of ≥5% (OS HR=0.60)[311]. 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[11-13,308] . 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)[312]. 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)[313]. 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])[314]. For patients who had previously received an immune-checkpoint inhibitor (ICI), the ORR was 10% (3/31)[314].

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[2-4,280-281], 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, Sep 2022). 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[315]. 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[316-317]. 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[318].

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[2-4,280-281] , 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[319]. 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)[320-321] . 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)[322]. 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[323]. 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[324]. 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%[325]. 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)[326]. 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[327]. 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[328].

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[5-6,329] , 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[292]. 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[288]. 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[330]. 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[331]. 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[332].

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

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or, visit https://www.foundationmedicine.com/genomic-testing#support-services.

BIOMARKER

Tumor Mutational Burden

RESULT

12 Muts/Mb

RATIONALE

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

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)

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), Taichung (Taiwan), Tainan City (Taiwan), Nagasaki (Japan), Daejeon (Korea, Republic of), Seongnam-si (Korea, Republic of), Songpagu (Korea, Republic of), Seoul (Korea, Republic of), Gyeonggi-do (Korea, Republic of), Takatsuki (Japan)

NCT04700124

PHASE 3

Perioperative Enfortumab Vedotin (EV) Plus Pembrolizumab (MK-3475) Versus Neoadjuvant Chemotherapy for Cisplatin-eligible Muscle Invasive Bladder Cancer (MIBC) (MK-3475-B15/ KEYNOTE-B15 / EV-304)

TARGETS
PD-1, Nectin-4

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Shanghai (China), Nantong (China), Nanjing (China), Guangzhou (China), Changsha (China), Nagasaki (Japan), Jeollanam-do (Korea, Republic of), Seoul (Korea, Republic of)

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), Tainan (Taiwan), Kaohsiung City (Taiwan), Seoul (Korea, Republic of), Athens (Greece), London (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Caen (France), Montpellier (France)

NCT05166577

PHASE 1/2

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

TARGETS
HDAC, PD-1

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

NCT04589845

PHASE 2

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

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

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

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)

NCT04152018

PHASE 1

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

TARGETS
PD-1

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

NCT04261439

PHASE 1

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

TARGETS
PD-1

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

GENE
CCND1

ALTERATION
amplification

RATIONALE
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to single-agent CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts, New York, Virginia, Texas, Florida

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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.

ACVR1B
E240V

APC
K1938I

AURKB
splice site 862-1G>A

BCORL1
R1698Q

CD22
D50N

JAK1
K696*

MEN1
G508D

NF1
R2517Q

PIK3C2G
D8Y

RET
P384A

RICTOR
P27R

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLE

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

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

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
5. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
6. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.4.0

The median exon coverage for this sample is 708x

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