FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Huang, Chien Chang	Bladder carcinoma (NOS)	27 Feb 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1570859-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Bladder carcinoma (NOS)
NAME Huang, Chien Chang
DATE OF BIRTH 20 August 1961
SEX Male
MEDICAL RECORD # 38460321

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

SPECIMEN
SPECIMEN SITE Bone
SPECIMEN ID S112-02810 A (PF23015)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 30 January 2023
SPECIMEN RECEIVED 20 February 2023

Sample qualified for suboptimal assessment of copy-number alterations. Sensitivity for detecting gene amplifications and losses may be reduced.

Biomarker Findings

Tumor Mutational Burden - 28 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

FANCA A778fs*45
FBXW7 E471G
CREBBP Q104*
KDM6A A516fs*17
RB1 S576*
STAG2 M1I
TERT promoter -124C>T
TP53 loss exons 8-9

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. 9), **Pembrolizumab** (p. 11), **Nivolumab** (p. 10), **Atezolizumab** (p. 12)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 15)

BIOMARKER FINDINGS

Tumor Mutational Burden - 28 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	

10 Trials see p. 15

Microsatellite status - MS-Stable

No therapies or clinical trials. See Biomarker Findings section

GENOMIC FINDINGS

FANCA - A778fs*45

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

10 Trials see p. 17

NCCN category

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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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PATIENT
Huang, Chien Chang

TUMOR TYPE
Bladder carcinoma (NOS)

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TW

REPORT DATE
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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FBXW7 **-** E471G	none	none
8 Trials see p. 19		

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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.

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BIOMARKER

Tumor Mutational Burden

RESULT
28 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
FANCA

ALTERATION
A778fs*45

TRANSCRIPT ID
NM_000135.2

CODING SEQUENCE EFFECT
2332delG

VARIANT CHROMOSOMAL POSITION
chr16:89836416-89836417

VARIANT ALLELE FREQUENCY (% VAF)
14.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies that directly target defects in the FA complex. Clinical evidence in prostate[47-49], breast[50], and ovarian cancers[51], including multiple patient responses, indicates that FANCA inactivation may confer sensitivity to PARP inhibitors.

— Nontargeted Approaches —

Inactivation of the FA/BRCA pathway sensitizes cells to mitomycin C and cisplatin[52-55] and results in increased sensitivity of glioma cells to alkylating agents such as temozolomide[56].

FREQUENCY & PROGNOSIS

FANCA mutations and deletion have been reported at low frequencies (<2.5%) across solid tumors[57-58]. In some patient populations, germline polymorphisms specifically in FANCA have been linked to an increased risk of esophageal, breast, cervical, and bladder cancer[59-62]. A single nucleotide polymorphism (SNP) in FANCA has been correlated with inferior PFS and OS for patients with melanoma[63], whereas methylation of FANCA correlated with inferior prognosis in high-grade serous ovarian carcinoma[64]. However, the link between FANCA expression and function has either not been explored, or not correlated with outcome, in these studies and other studies have failed to link FANCA polymorphisms with the risk of breast or cervical cancer[65-66]. Low expression of FANCA has been correlated with inferior prognosis in univariate but not multivariate analysis in breast cancer[67]. FANCA has been reported to be downregulated in higher versus lower grade ovarian cancer, but FANCA expression did not impact OS or PFS[68]. Gain of 16q, associated with increased copy number of FANCA, correlated with decreased PFS[69]. Inactivation of the FA/BRCA pathway sensitizes cells to mitomycin C and cisplatin[52-55] and results in increased sensitivity of glioma cells to alkylating agents such as temozolomide[56].

FINDING SUMMARY

FANCA encodes a key component of the multi-protein Fanconi anemia (FA) complex, a nuclear E3 ubiquitin ligase that is essential for preventing chromosome breakage caused by DNA damage[70-71]. Germline mutations or deletions affecting FANCA have been reported in 26-65% of patients with Fanconi anemia (FA), a rare autosomal recessive disorder characterized by congenital abnormalities, bone marrow failure, hypersensitivity to DNA crosslinking agents, and predisposition to a subset of cancers, including acute myeloid leukemia, myelodysplastic syndrome, gynecological malignancies, and head and neck tumors[56,72-78]. Frequency estimates suggest an incidence of 3:1,000,000 individuals in Europe and the US, and a heterozygote carrier frequency of 1:181 to 1:300 in the US and Europe, respectively, with slightly higher rates for some populations, such as the Ashkenazi Jewish population (1:89)[75,79]. Alterations such as seen here may disrupt FANCA function or expression[80-93].

GENE
FBXW7

ALTERATION
E471G

TRANSCRIPT ID
NM_033632.3

CODING SEQUENCE EFFECT
1412A>G

VARIANT CHROMOSOMAL POSITION
chr4:153249366

VARIANT ALLELE FREQUENCY (% VAF)
37.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[94-95]. Case series reported objective responses for 2 patients with FBXW7-mutated cervical squamous cell carcinoma treated with everolimus[96]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

In the bladder urothelial carcinoma TCGA dataset, FBXW7 mutations were detected in 8.7% of cases[18]. Another study identified FBXW7 mutation in 4.3% (2/47) of bladder urothelial carcinomas and in 13% (2/16) of non-bladder urothelial carcinomas[97]. Published data investigating the prognostic implications of FBXW7 alterations in urothelial carcinoma are limited (PubMed, Jul 2022). Reduced FBXW7 expression has been associated with poor prognosis in some cancers such as colorectal cancer, gastric cancer, esophageal SCC, cervical SCC, melanoma, and non-small cell lung carcinoma[98-105].

FINDING SUMMARY

FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[106]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[106-107]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
CREBBP

ALTERATION
Q104*

TRANSCRIPT ID
NM_004380.2

CODING SEQUENCE EFFECT
310C>T

VARIANT CHROMOSOMAL POSITION
chr16:3900786

VARIANT ALLELE FREQUENCY (% VAF)
36.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CREBBP. The use of histone deacetylase (HDAC) inhibitors are being investigated in clinical trials that are recruiting patients with either lymphoma or urothelial carcinoma harboring CREBBP alterations. However, it has been reported that there is no correlation between CREBBP mutation status and response to HDAC inhibitors in DLBCL[108].

FREQUENCY & PROGNOSIS

CREBBP mutations have been observed at high frequency in follicular lymphoma (FL, 26%) and diffuse large B-cell lymphoma (DLBCL, 16%), and at lower frequency in acute lymphoblastic leukemia (ALL, 7%), and tumors of the urinary tract (15%), skin (12%), liver (8.7%), endometrium (8.5%), and stomach (8.2%)(COSMIC, 2023)[109]. These mutations include missense substitutions clustered in the CREBBP histone acetyltransferase domain and truncating mutations throughout the gene sequence, suggesting a role for CREBBP inactivation in these diseases. CREBBP mutations have been reported to occur in the transition from prostate acinar carcinoma to squamous cell carcinoma (SCC)[110], which may indicate significance for CREBBP in SCC. In two cases of relapsed pediatric B-cell ALL, CREBBP mutation conferred resistance to glucocorticoid therapy[111]. Reports have found CREBBP mutation in 62-68% of patients with FL[112-113], which was associated with immune evasion[112]. AML with MYST3/CREBBP fusion was reported to occur in 60-80% of cases 9-72 months after adjuvant chemotherapy for breast cancer and was associated with a poor prognosis[114-115].

FINDING SUMMARY

CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase activity. Inherited microdeletions and truncating point mutations in CREBBP are reported to be causal in approximately 20% of cases of Rubinstein-Taybi syndrome[116]. The chromosomal rearrangement t(8;16)(p11;p13) is characteristic of the M4/M5 subtype of acute myeloid leukemia (AML) and results in a chimeric gene fusing MYST3/MOZ (a gene essential for the development of the hematopoietic system and maintenance of hematopoietic stem cells) to CREBBP[117]. CREBBP-BCORL1 fusion has been reported in patients with ossifying fibromyxoid tumors[118-119].

GENE
KDM6A

ALTERATION
A516fs*17

TRANSCRIPT ID
NM_021140.2

CODING SEQUENCE EFFECT
1547_1592del46

VARIANT CHROMOSOMAL POSITION
chrX:44922685-44922731

VARIANT ALLELE FREQUENCY (% VAF)
11.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to address KDM6A alterations in cancer.

FREQUENCY & PROGNOSIS

KDM6A mutations have been reported in 3.9% of samples analyzed, with the highest incidence in tumors of the urinary tract (31%), liver (7.3%), endometrium (6.7%), salivary gland (6.0%), and pancreas (5.1%) (COSMIC, Jan 2023)[109]. KDM6A mutations or copy number alterations have also been identified in medulloblastoma (8.9%)[120], adenoid cystic carcinoma (6.7%)[121], and metastatic prostate cancer (10%)[122]. KDM6A inactivation has been found as a recurrent tumorigenic event in male T-cell acute lymphoblastic leukemia (T-ALL), and loss of KDM6A increased the sensitivity of T-ALL cells to therapies targeting histone H3 lysine 27 methylation in preclinical assays[123]. However, KDM6A overexpression has been noted in breast cancer and renal cell carcinoma, and correlated with inferior prognosis in patients with breast cancer[124-126].

FINDING SUMMARY

KDM6A encodes a histone H3 lysine 27 demethylase UTX, which functions as a transcriptional regulator[127]. A significant number of inactivating KDM6A mutations have been found across multiple tumor types, suggesting a role as a tumor suppressor[127].

GENE
RB1

ALTERATION
S576*

TRANSCRIPT ID
NM_000321.2

CODING SEQUENCE EFFECT
1727C>G

VARIANT CHROMOSOMAL POSITION
chr13:49027160

VARIANT ALLELE FREQUENCY (% VAF)
20.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data[128] and strong preclinical data[129-132], RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer (SCLC). A clinical study evaluating the Aurora kinase A inhibitor alisertib for patients with prostate cancer did not find an association between RB1 deletion and clinical benefit[133]. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members[134] and activation of the NOTCH pathway[135].

— Nontargeted Approaches —

Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer[136-137].

FREQUENCY & PROGNOSIS

RB1 mutations have been reported in 80% (49/61) of bladder small cell carcinomas[138]. RB1 mutations have been detected in 10-20% of bladder urothelial carcinomas, including transitional cell carcinomas[18,139-140] and in up to 5.4% (2/37) of upper tract urothelial carcinomas[141-143]. Recurrent focal genomic deletion of RB1 has been reported in urothelial carcinomas[144]. Expression of Rb has been reported in 47-52% of bladder urothelial carcinomas in one study, and was found to correlate with RB1 alteration[145]. Published data investigating the prognostic implications of RB1 alterations in bladder neuroendocrine carcinomas are limited (PubMed, Nov 2022). Loss of Rb expression has been suggested to play a role in the progression of urothelial cancers, and has been associated with advanced tumor stage and poor patient survival[146-148].

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle[137,149]. Alterations such as seen here may disrupt RB1 function or expression[150-156].

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year[157]. Germline mutations in RB1 account for approximately 40% of RB tumors[158] and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma[159-160]. In the appropriate clinical context, germline testing of RB1 is recommended.

GENE
STAG2

ALTERATION
M1I

TRANSCRIPT ID
NM_006603.4

CODING SEQUENCE EFFECT
3G>A

VARIANT CHROMOSOMAL POSITION
chrX:123156480

VARIANT ALLELE FREQUENCY (% VAF)
29.2%

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[161] or oxaliplatin[162].

FREQUENCY & PROGNOSIS

STAG2 mutations have been observed most frequently in urothelial bladder carcinoma (16-35%)[18,139,163-165], Ewing sarcoma (13-22%)[166-167], upper urinary tract urothelial carcinoma (11%)[168], myeloid malignancies (6%)[169-170], and glioblastoma (6%)[171]. STAG2 truncation mutations are associated with loss of protein expression[163-165,167]. In patients with Ewing sarcoma, STAG2 and TP53 mutations often co-occur and are associated with decreased OS, although mutation of either STAG2 or TP53 alone was not demonstrated to affect survival[166-167]. STAG2 mutation in patients with myelodysplastic syndrome is associated with decreased OS and has also been associated with increased response to treatment with azacitidine or decitabine in patients with myeloid malignancies[169]. The data on the prognostic significance of STAG2 mutation or loss of STAG2 protein expression in the context of urothelial bladder carcinoma are conflicting[139,163-165]. In patients with pancreatic ductal adenocarcinoma, loss of STAG2 staining was significantly associated with decreased OS but was also associated with survival benefit from adjuvant chemotherapy[162]. 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[172].

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[173]. Cohesin is also involved in transcriptional regulation, DNA replication and DNA repair[173]. STAG2 mutations, which are mostly truncating, or loss of STAG2 protein expression have been reported in multiple cancer types[173-174]. STAG2 deletion has been shown to promote tumorigenesis in preclinical studies[162], and STAG2 inactivation has been proposed to promote tumorigenesis via a mechanism that involves increased aneuploidy[139,163,171] or altered transcriptional regulation[164-165,169-170].

GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253.2

CODING SEQUENCE EFFECT
-124C>T

VARIANT CHROMOSOMAL POSITION
chr5:1295228

VARIANT ALLELE FREQUENCY (% VAF)
47.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[175]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[176]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[177].

FREQUENCY & PROGNOSIS

In 1 study, TERT promoter mutations were reported in all 11 urinary bladder small cell cancers analyzed[178]. One study reported TERT promoter mutations in 67% (14/21) of high-grade and in 56% (34/61) of low-grade bladder carcinomas[179]. Another study reported that 85% (44/52) of all bladder cancer samples harbored a TERT promoter mutation[180]. For patients with bladder urothelial carcinoma, both TERT promoter mutations and increased TERT expression associate with poor prognosis, although carrying an additional germline alteration at -245 (rs2853669) may confer a better prognosis[181-183]. In urothelial cancer, the prognostic significance of TERT promoter mutation in clinical benefit from immune checkpoint inhibitors (ICI) is unclear; 1 study reported an association between TERT promoter mutations and improved median OS from ICIs (n=78)[184], but another study observed no such relationship (n=166)[185].

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[186]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[187-189]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[179,190-191], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[190].

GENE
TP53

ALTERATION
loss exons 8-9

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[192-195] or p53 gene therapy such as SGT53[196-200]. 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[201]. 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[202]. 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[203]. 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[204]. 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[205]. 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[206]. 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[207]. 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[200].

FREQUENCY & PROGNOSIS

TP53 mutation was detected in 90% (55/61) of small cell carcinoma of the bladder in a study[138]. Similarly, in one genomic analysis of 132 bladder cancer specimens that harbored a small cell component, TP53 mutations were identified in 92% of samples[208]. TP53 mutation has been reported in 49–54% of bladder urothelial carcinoma (UC)[18,209], 33% of renal pelvis UC[210], and 25% (22/71) of ureter UC samples[211]. Expression of p53 has been correlated with TP53 mutation, and reported in 52–84% of bladder cancers[140,145,212-215], 48% (24/50) bladder SCCs[216], 36–53% of upper urinary tract UCs (UTUC)[217-219], and in 4/4 urethral clear cell carcinomas[220]. TP53 mutations in both bladder and renal pelvis urothelial carcinoma (UC) are more common in invasive tumors[140,144,210,221], and have been associated with inferior survival in patients with renal pelvis UC[210] or upper tract UC (UTUC)[222]. Alterations to the p53 pathway are correlated with aggressive disease and poor prognosis in bladder cancer[223-225], and p53 overexpression has been linked to poor progression-free survival in UTUC[222,226], disease progression in UC of the renal pelvis and ureter[227], and higher tumor grade in bladder squamous cell carcinoma[228-230].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[231]. Alterations such as seen here may disrupt TP53 function or expression[232-236].

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[237-239], including sarcomas[240-241]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[242] to 1:20,000[241]. 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[243]. In the appropriate clinical context, germline testing of TP53 is recommended.

Electronically signed by Erik Williams, M.D. | 27 February 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Avelumab

Assay findings association

Tumor Mutational Burden
28 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[2-4,244-245] , 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 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[246]. 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)[247]. A Phase 2 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), median PFS of 2 months, and mOS of 10 months[248]. 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[249].

Dostarlimab

Assay findings association

Tumor Mutational Burden
28 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[2-4,244-245] , 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[250-252] . 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[250,253] .

Nivolumab

Assay findings association

Tumor Mutational Burden
28 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[2-4,244-245] , 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[254-256] . 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[254]. 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[257]. 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[258]. 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[259]. 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)[260]. 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)[260]. 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])[261] and responses to these combination treatments were observed for patients with bladder squamous cell carcinoma or bladder adenocarcinoma[262]. 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[263]. 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[264].

Pembrolizumab

Assay findings association

Tumor Mutational Burden
28 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 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, 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[2-4,244-245], 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[265]. 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[265]. The Phase 3 KEYNOTE-045 trial for patients with advanced urothelial carcinoma (UC) found second-line pembrolizumab superior to chemotherapy for median OS (mOS) (10.3 vs. 7.4 months, HR=0.74)[266] and 4-year PFS (9.5% vs. 2.7%) and OS (17% vs. 10%) rates[267]. 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%)[267]. 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 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)[268]. 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[269]. 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%[270]. 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[271]. 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[272].

Atezolizumab

Assay findings association

Tumor Mutational Burden
28 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[2-4,244-245] , 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)[273]. 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[274]. 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%)[275]. 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)[276]. 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[11-13,273] . 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)[277]. 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)[278]. 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])[279]. For patients who had previously received an immune-checkpoint inhibitor (ICI), the ORR was 10% (3/31)[279].

Cemiplimab

Assay findings association

Tumor Mutational Burden
28 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[2-4,244-245] , 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[280]. 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[281-282] . 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[283].

Durvalumab

Assay findings association

Tumor Mutational Burden
28 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[2-4,244-245] , 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 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)[284-285] . 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)[286]. 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[287]. 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)[288]. 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[289]. 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[290].

Nivolumab + Ipilimumab

Assay findings association

Tumor Mutational Burden
28 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[5-6,291] , 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[258]. 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[254]. 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[292]. 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[293]. 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[294].

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.

Electronically signed by Erik Williams, M.D. | 27 February 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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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

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

28 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)

NCT04960709

PHASE 3

Treatment Combination of Durvalumab, Tremelimumab and Enfortumab Vedotin or Durvalumab and Enfortumab Vedotin in Patients With Muscle Invasive Bladder Cancer Ineligible to Cisplatin

TARGETS
PD-L1, Nectin-4, CTLA-4

LOCATIONS: Taipei (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Busan (Korea, Republic of), Shatin (Hong Kong), Miyazaki-shi (Japan), Kumamoto-shi (Japan), Fukuoka-shi (Japan), Matsuyama-shi (Japan), Incheon (Korea, Republic of)

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), 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), Xi'an (China), Tianjin (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)

GENE
FANCA

ALTERATION
A778fs*45

RATIONALE
FANCA alterations may predict sensitivity to PARP inhibitors.

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)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

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)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

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)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Illinois, Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

GENE
FBXW7

ALTERATION
E471G

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05125523

PHASE 1

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

TARGETS
mTOR

LOCATIONS: Tianjin (China)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03203525

PHASE 1

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

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

NCT01582191

PHASE 1

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

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

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.

ARID1A
S334L

ATR
D2331V

BCL6
K534N

BRD4
V228I

CCND1
E66K

CCNE1
G21S

CD79A
W66C

EPHB1
Y471N

ERBB4
R95H

FGFR3
V553M

GATA6
Y569C

JAK2
E173K

JAK3
R214W

KEL
G480A

LTK
E187K

MERTK
H424Q

MSH6
K1358fs*2, T118K and T1225M

MST1R
V199M

NTRK1
E275A

RET
R749T

RICTOR
S1042L

SMO
G720L

SNCAIP
E831G

TEK
S123F

TP53
rearrangement

ZNF703
S229F

ORDERED TEST # ORD-1570859-01

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) 7.6.0

The median exon coverage for this sample is 924x

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