FOUNDATIONONE®LIQUID CDx

PATIENT
Tsao, Wei-Chih

TUMOR TYPE
Unknown primary urothelial carcinoma

COUNTRY CODE
TW

REPORT DATE
21 March 2023

ORDERED TEST #
ORD-1587799-01

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT
DISEASE Unknown primary urothelial carcinoma
NAME Tsao, Wei-Chih
DATE OF BIRTH 18 February 1980
SEX Male
MEDICAL RECORD # 46146514

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

SPECIMEN
SPECIMEN ID W-CT 18Feb1980
SPECIMEN TYPE Blood
DATE OF COLLECTION 10 March 2023
SPECIMEN RECEIVED 16 March 2023

Biomarker Findings

Blood Tumor Mutational Burden - 3 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction

Genomic Findings

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

FGFR3 V555L, FGFR3-TACC3 fusion
NF2 splice site 1122+1G>T
TP53 R273H, Q192*

Report Highlights

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

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. There is higher sensitivity for identifying genomic alterations and a lower risk of false negative results in specimens with elevated tumor fraction; the positive percent agreement observed between liquid and tissue for defined short variants is ≥ 90% (Li et al., 2021; AACR Abstract 2231) (see Biomarker Findings section).**

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FGFR3 -	V555L	7.9%	Erdafitinib 2A	Infigratinib
	FGFR3-TACC3 fusion	13.7%		Pemigatinib
10 Trials see p. 12				
NF2 -	splice site 1122+1G>T	43.1%	None	Everolimus
				Temsirolimus
8 Trials see p. 14				

2A *NCCN category*

Electronically signed by Douglas A. Mata, MD, MPH | 21 March 2023
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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

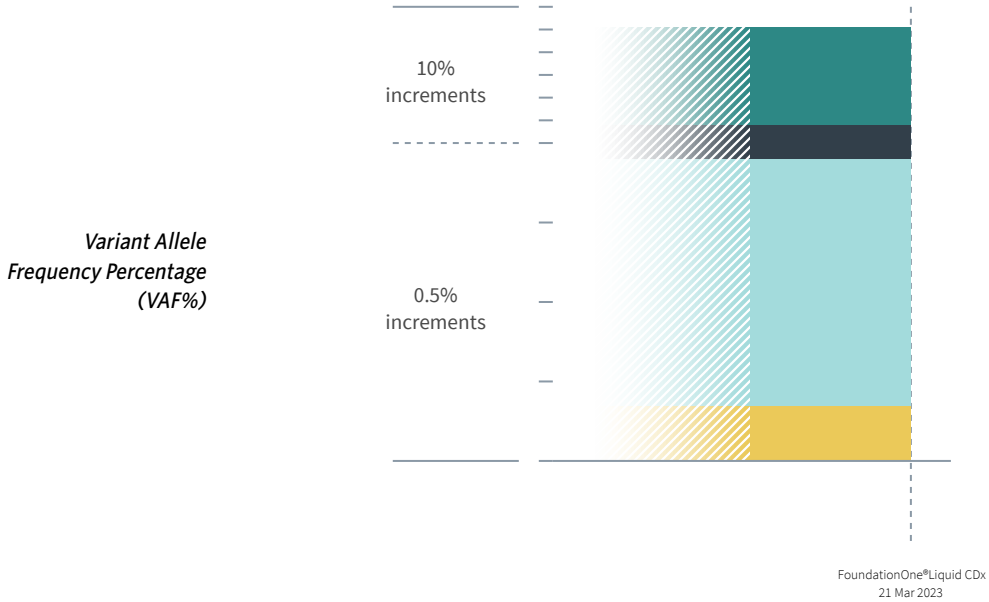
GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

TP53 - R273H, Q192* p. 8

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies 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/or exhaustive. Neither the therapies 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 or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF1*, *NF2*, *PALB2*, *PMS2*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.



HISTORIC PATIENT FINDINGS		ORD-1587799-01 VAF%
Blood Tumor Mutational Burden		3 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		44%
FGFR3	● V555L	7.9%
	FGFR3-TACC3 fusion	13.7%
NF2	● splice site 1122+1G>T	43.1%
TP53	● Q192*	0.35%
	● R273H	1.6%

IMPORTANT NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx or FoundationOne®CDx tests. Up to five previous tests may be shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable or reportable variants may become VUS.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

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Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

Please note that other aspects of this table may have changed from the previous version to reflect the most up-to-date reporting information.

BIOMARKER

Blood Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1[3-4], anti-PD-1/CTLA4 therapies[5-6] , anti-PD-L1/CTLA4 therapies[7-10]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[5]. In non-small cell lung cancer (NSCLC), multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single-agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 Muts/Mb-16 Muts/Mb[1,8-10]. In head and neck squamous cell carcinoma (HNSCC), a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[11]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[7].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2023). Published data investigating the prognostic implications of bTMB levels in bladder cancer are limited (PubMed, Jul 2022). One study reported that the number of somatic mutations positively correlates with increased tumor stage and grade of bladder cancers[12]. 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[13-14]. 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[15].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[16-17] and cigarette smoke in lung cancer[18-19], treatment with temozolomide-based chemotherapy in glioma[20-21], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[22-26], and microsatellite instability (MSI)[22,25-26]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-2,4]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[27-32].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[33]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[34], Ewing sarcoma and osteosarcoma[35], prostate cancer[30], breast cancer[36], leiomyosarcoma[37], esophageal cancer[38], colorectal cancer[39], and gastrointestinal cancer[40].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[41], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[42-43].

GENE
FGFR3

ALTERATION
V555L, FGFR3-TACC3 fusion

TRANSCRIPT ID
NM_000142.3

CODING SEQUENCE EFFECT
1663G>C

VARIANT CHROMOSOMAL POSITION
chr4:1807494

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR3 may predict sensitivity to selective FGFR kinase inhibitors, including erdafitinib[44-46], pemigatinib[47], infigratinib[48-49], rogaratinib[50], Debio 1347[51-52], and derazantinib[53]; multikinase inhibitors such as pazopanib[54-55] and ponatinib[56-57]; and vofatamab, an antibody targeting FGFR3[58-60] . A study of the tumor immune microenvironment in urothelial bladder cancer found enhanced FGFR3 pathway activation in non-T-cell-inflamed tumors compared with T-cell-inflamed tumors, suggesting that FGFR3-altered tumors may be resistant to immunotherapy[61]. However, clinical data from the IMvigor-210/211, CheckMate-275, and PURE-01 studies have not reported statistically significant associations between FGFR3 status and response to PD-1/PD-L1 inhibition[62-63]. Phase 2 studies have shown activity of erdafitinib, pemigatinib, and infigratinib in FGFR3-altered urothelial carcinoma, with ORRs ranging from 25-40%[44,47-49]. Early analysis of the Phase 2 FIERCE-21 study for patients with pretreated urothelial carcinoma harboring FGFR3 mutations or fusions showed better median PFS when vofatamab was combined with docetaxel relative to vofatamab alone (not reached vs. 4 months)[59]. Interim analysis of the Phase 2 FIERCE-22 trial evaluating vofatamab combined with pembrolizumab for patients with pretreated urothelial cancer reported an ORR of 36% (8/22), with responses observed for 33% (5/15) and 43% (3/7) of patients with wildtype or mutated and/or rearranged FGFR3, respectively[60]. In a Phase 1 study, rogaratinib elicited an ORR of 24% (12/51, 1 CR) and a DCR of 73% (37/51) in advanced urothelial carcinoma with FGFR1, FGFR2, or FGFR3 mRNA overexpression[50].

FREQUENCY & PROGNOSIS

FGFR3 mutation and amplification have been reported in 26-59% and 18% of bladder urothelial carcinoma cases, respectively[64-67]. FGFR3 mutations are detected more frequently in upper tract urothelial carcinoma (26-40%) compared to bladder urothelial carcinoma (19-26%)[68-70]. S249C has been reported to be the most frequent FGFR3 mutation in urothelial tumors, with similar incidences of 62% and 58% in bladder tumors and upper urothelial tract tumors, respectively[64]. FGFR3 and TP53 have been reported to be the most frequently mutated genes in bladder cancer, and it has been suggested that urothelial carcinomas develop through at least two molecular pathways: one related to FGFR3, typically in less invasive tumors, and one related to TP53, characterized by higher grade invasive tumors[71]. FGFR3 expression has been found in 70% of bladder urothelial carcinomas, with high expression in 36% and 22% of low-grade and high-grade samples, respectively[65]. FGFR3 mutation has been associated by univariate analysis with low tumor stage in bladder tumors and with a lower risk of death for patients with bladder tumors; in multivariate analysis, FGFR3 mutations were associated with lower risk only in ureter tumors[64]. For patients with non-muscle-invasive bladder cancer, a meta-analysis of 62 studies reported that FGFR3 mutation was associated with worse recurrence-free survival but better PFS[72]. In another study of metastatic urothelial cancer cases, FGFR2 or FGFR3 mutations or fusions were associated with significantly worse OS outcomes (n=77)[73]. For muscle-invasive bladder cancer, a study of samples across multiple datasets reported that FGFR3 pathway activation was associated with luminal-papillary subtypes and with better OS outcomes than other subtypes[74]; a second meta-analysis also associated muscle-invasive bladder and upper urinary tract tumors with better prognosis[72].

FINDING SUMMARY

FGFR3 (Fibroblast growth factor receptor 3) encodes a receptor tyrosine kinase that typically promotes cell cycle progression and angiogenesis via activation of downstream signaling pathways, including RAS-MAPK and AKT; gain of function mutations in FGFRs have been reported in several cancer types[75-77]. FGFR3 fusions that retain the kinase domain (exons 11-17) have been shown to be activating and oncogenic[51,78]. Additionally, fusions that disrupt a binding site of the regulatory microRNA miR-99a in the FGFR3 3' UTR have been demonstrated to increase FGFR3 expression[79]. Rearrangements that include the N-terminal portion of FGFR3 (exons 1-17), such as observed here, are predicted to be activating and oncogenic. FGFR3 V555L has been shown to reduce sensitivity to infigratinib in a preclinical study; however, V555L has not been fully characterized and therefore the effects of this mutation on FGFR3 activity are unclear[80].

GENE
NF2

ALTERATION
splice site 1122+1G>T

TRANSCRIPT ID
NM_000268.3

CODING SEQUENCE EFFECT
1122+1G>T

VARIANT CHROMOSOMAL POSITION
chr22:30067938

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

NF2 inactivating alterations may indicate sensitivity to mTOR inhibitors[81-84]. Two case studies reported clinical benefit for patients with NF2-mutated cancers, including urothelial carcinoma[85] and metaplastic breast cancer[86-87] treated with everolimus and temsirolimus, respectively. Loss or inactivation of NF2 may also predict sensitivity to FAK inhibitors based on clinical data in mesothelioma[88] and meningioma[89] and strong preclinical data[90-92]. Limited preclinical and clinical evidence in vestibular schwannoma suggests possible sensitivity of NF2-deficient tumors to the pan-ERBB inhibitor lapatinib[93-94]. Similarly, on the basis of limited clinical[95] and preclinical[96-98] evidence, NF2 inactivation may predict sensitivity to MEK inhibitors, such as approved agents trametinib and cobimetinib. These and other relevant compounds are being investigated in clinical trials. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[99], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[100]. 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

NF2 mutation has been observed in 0-3% of urothelial carcinomas[70,101-103]. Published data investigating the prognostic implications of NF2 alterations in urothelial carcinoma are limited (PubMed, Mar 2023).

FINDING SUMMARY

Merlin, encoded by NF2, coordinates cell contact with growth signals; the inactivation of Merlin disrupts this mechanism and can lead to unrestrained growth despite cell contact[104]. 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.

POTENTIAL GERMLINE IMPLICATIONS

Heterozygous germline NF2 loss or inactivation is associated with neurofibromatosis type 2, which results in the development of vestibular schwannomas, meningiomas, ependymomas, and ocular disturbances[105-107]. Prevalence for this disorder in the general population is estimated to be 1:25,000[107]. In the appropriate clinical context, germline testing of NF2 is recommended.

GENE
TP53

ALTERATION
R273H, Q192*

TRANSCRIPT ID
NM_000546.4, NM_000546.4

CODING SEQUENCE EFFECT
818G>A, 574C>T

VARIANT CHROMOSOMAL POSITION
chr17:7577120, chr17:7578275

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[108-111] or p53 gene therapy such as SGT53[112-116]. 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[117]. 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[118]. 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[119]. 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[120]. 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[121]. 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[122]. 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[123]. 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[116]. 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[124]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[125].

FREQUENCY & PROGNOSIS

TP53 mutation has been reported in 49–54% of bladder urothelial carcinoma (UC)[67,126], 33% of renal pelvis UC[127], and 25% (22/71) of ureter UC samples[128]. Expression of p53 has been correlated with TP53 mutation, and reported in 52–84% of bladder cancers[129-134], 48% (24/50) bladder SCCs[135], 36–53% of upper urinary tract UCs (UTUC)[136-138], and in 4/4 urethral clear cell carcinomas[139]. TP53 mutations in both bladder and renal pelvis urothelial carcinoma (UC) are more common in invasive tumors[127,134,140-141], and have been associated with inferior survival in patients with renal pelvis UC[127] or upper tract UC (UTUC)[142]. Alterations to the p53 pathway are correlated with aggressive disease and poor prognosis in bladder cancer[143-145], and p53 overexpression has been linked to poor progression-free survival in UTUC[142,146], disease progression in UC of the renal pelvis and ureter[147], and higher tumor grade in bladder squamous cell carcinoma[148-150].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[151]. Alterations such as seen here may disrupt TP53 function or expression[152-156].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[157]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[158-160], including sarcomas[161-162]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[163] to 1:20,000[162]. 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[164]. 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[165-170]. 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[165-166]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[171]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[169,172-173]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Erdafitinib

Assay findings association

FGFR3
V555L, FGFR3-TACC3 fusion

AREAS OF THERAPEUTIC USE

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor. It is FDA approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have FGFR2 or FGFR3 alterations and have progressed after prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence, FGFR3 fusions[45,174-176] and activating mutations[44-45,175] may confer sensitivity to erdafitinib.

SUPPORTING DATA

A Phase 2 study evaluating erdafitinib to treat patients with unresectable or metastatic urothelial carcinoma (UC) previously treated with chemotherapy and harboring FGFR2/3 fusions or FGFR3 activating mutations reported an overall ORR of 40% (4 CRs) and a DCR of 80%[177]. Patients with only FGFR2/3 fusions achieved a median PFS (mPFS) of 2.8 months and a median OS (mOS) of 10 months, and patients with only FGFR3 mutations had an mPFS of 5.6 months and an mOS of 12 months[177]. Patients with prior immunotherapy experienced an ORR of 59% (13/22)[44], mPFS of 5.7 months, and mOS of 11 months in this trial[177]. A Phase 1 study reported a similar ORR (43%, 10/23) for patients with advanced UC and FGFR alterations treated with erdafitinib[45,178] . The Phase 2 NORSE study evaluating erdafitinib alone or in combination with the PD-1 antibody cetrelimab to treat patients with metastatic or locally advanced UC harboring FGFR mutations or fusions reported ORRs of 33% (6/18, 1 CR) and 68% (13/19, 4 CRs) and DCRs of 100% (18/18) and 94% (17/18) for the single-agent and combination-agent arms, respectively[179].

Everolimus

Assay findings association

NF2
splice site 1122+1G>T

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on individual responses for patients with NF2-mutated metaplastic breast cancer[86-87] and urothelial carcinoma[85] treated with temsirolimus and everolimus, respectively, as well as preclinical evidence[81-84] , NF2 inactivation may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study of everolimus in metastatic urothelial carcinoma did not meet its primary endpoint; however, 2 PRs, 1 near-CR, and 12 minor regressions were observed (n=45)[180]; an additional Phase 2 study of everolimus in urothelial carcinoma reported 2 patients with PRs and 8 patients with SD (n=37)[181]. A Phase 2 study for patients with advanced urothelial carcinoma reported improved PFS and OS for patients treated with first-line everolimus plus paclitaxel (5.9 months and 10.9 months, respectively) compared to everolimus alone (2.3 months and 4.5 months), although the trial was discontinued due to adverse events for patients in both cohorts[182]; a Phase 2 study of second-line everolimus plus paclitaxel for patients with urothelial cancer reported an ORR of 12.5% and 3 patients achieved PRs; median PFS and OS were 2.9 months and 5.6 months, respectively[183]. A Phase 1 study of everolimus with pazopanib for patients with metastatic urothelial carcinoma reported an ORR of 21% (n=19; 1 CR, 3PRs)[54]. Two case studies of patients with bladder carcinoma harboring inactivating NF2 mutations reported exceptional responses to therapy regimens involving the mTOR inhibitor everolimus[84-85] . Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[99], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[100].

Infigratinib

Assay findings association

FGFR3
V555L, FGFR3-TACC3 fusion

AREAS OF THERAPEUTIC USE

Infigratinib is a TKI that inhibits FGFR1, FGFR2, and FGFR3. It is FDA approved for the treatment of patients with unresectable locally advanced or metastatic cholangiocarcinoma who have FGFR2 rearrangements or fusions and have progressed after prior therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on clinical activity in FGFR3-mutated urothelial carcinoma treated with infigratinib[48-49,184-185] , FGFR3 mutations may predict sensitivity to the FGFR inhibitors pemigatinib or infigratinib. Based on clinical activity in cholangiocarcinoma treated with infigratinib[186], FGFR3 fusions or rearrangements may confer sensitivity to the FGFR inhibitors pemigatinib or infigratinib.

SUPPORTING DATA

Following a Phase 1 study that showed activity of infigratinib for patients with FGFR3-mutated urothelial carcinoma[184], a Phase 2 study of infigratinib for patients with urothelial carcinoma harboring either FGFR3 mutations or rearrangements and ineligible for platinum chemotherapy reported an ORR of 25% (17/67) and DCR of 64% (43/67); median PFS and OS were estimated to be 3.75 and 7.75 months, respectively[48]. In this Phase 2 study, most responses were reported for patients with FGFR3-mutated tumors; however, a CR was reported for a patient with urothelial carcinoma harboring an FGFR3 rearrangement[48]. Additional analysis of this Phase 2 study showed improved ORR (50% [4/8] vs. 22% [13/59]) and survival for patients with upper tract urothelial carcinoma relative to those with bladder urothelial carcinoma[49]. Responses to infigratinib have been reported for multiple patients with non-muscle invasive bladder cancer, including CR in 1 patient with an FGFR3-rearranged tumor and 2 patients with FGFR3-mutated tumors[185].

Pemigatinib

Assay findings association

FGFR3
V555L, FGFR3-TACC3 fusion

AREAS OF THERAPEUTIC USE

Pemigatinib is a small molecule inhibitor of FGFR kinases. It is FDA approved to treat patients with advanced or metastatic cholangiocarcinoma who have FGFR2 rearrangements or fusions and have progressed after prior chemotherapy, as well as for treating patients with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangements. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on clinical activity in FGFR3-mutated urothelial carcinoma treated with infigratinib[48-49,184-185] , FGFR3 mutations may predict sensitivity to the FGFR inhibitors pemigatinib or infigratinib. Based on clinical activity in cholangiocarcinoma treated with infigratinib[186], FGFR3 fusions or rearrangements may confer sensitivity to the FGFR inhibitors pemigatinib or infigratinib.

SUPPORTING DATA

A patient with bladder carcinoma harboring an FGFR3-TACC3 fusion experienced a CR[187], and 1 patient with FGFR3-mutated urothelial carcinoma (n=3) experienced a PR[47] to pemigatinib treatment. Pemigatinib has been primarily studied in the treatment of FGFR2-rearranged cholangiocarcinoma. The Phase 2 FIGHT-202 study of pemigatinib for previously treated patients with FGFR2-rearranged advanced cholangiocarcinoma reported a longer median OS (21.1 vs. 6.7 vs. 4.0 months), longer median PFS (6.9 vs. 2.1 vs. 1.7 months), and a higher ORR (36% [3 CRs] vs. 0% vs. 0%) than those with or without FGF/FGFR alterations[188-191] . A Phase 1/2 study of pemigatinib for patients with FGFR-altered tumors reported 12 PRs for patients with cholangiocarcinoma (n=5), urothelial carcinoma, recurrent pilocytic astrocytoma, and head and neck, pancreatic, gallbladder, uterine, and non-small-cell lung cancer (NSCLC; each n=1); the ORR was 25% (n=5) and 23% (n=3) for patients with tumors harboring FGFR fusions and/or rearrangements and FGFR mutations, respectively[47].

Temsirolimus

Assay findings association

NF2
splice site 1122+1G>T

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Based on individual responses for patients with NF2-mutated metaplastic breast cancer[86-87] and urothelial carcinoma[85] treated with temsirolimus and everolimus, respectively, as well as preclinical evidence[81-84] , NF2 inactivation may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study investigating temsirolimus in 15 patients with metastatic urothelial cancer reported minimal activity, with no responses, although 4 patients experienced SD[192]. An additional clinical study of temsirolimus in patients with recurrent or metastatic bladder cancer who had already received first-line chemotherapy reported PRs in 3 patients and SD in 19 patients, out of the 45 evaluable patients included in the study[193].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

IMPORTANT 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. There may also be compassionate use or early access programs available, which are not listed in this report. 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 are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. 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. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
FGFR3

ALTERATION
V555L, FGFR3-TACC3 fusion

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR3. Preclinical data suggest reduced sensitivity of the FGFR3 V555M mutation to erdafitinib and AZD4547, although it retains sensitivity to dovitinib. Additionally, both this and other V555 mutations may reduce sensitivity to infigratinib.

NCT03390504
PHASE 3

A Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Participants With Advanced Urothelial Cancer and Selected Fibroblast Growth Factor Receptor (FGFR) Gene Aberrations

TARGETS
PD-1, FGFRs

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Niao-Sung Hsiang (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Hangzhou (China), ShangHai (China), Shanghai (China)

NCT04083976
PHASE 2

A Study of Erdafitinib in Participants With Advanced Solid Tumors and Fibroblast Growth Factor Receptor (FGFR) Gene Alterations

TARGETS
FGFRs

LOCATIONS: Hangzhou (China), Shanghai (China), Guangzhou (China), Matsuyama (Japan), Hiroshima-shi (Japan), Chongqing (China), Beijing (China), Chengdu (China), Toyoake (Japan), Chuo-Ku (Japan)

NCT05024214
PHASE 1/2

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

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

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

NCT04492293
PHASE 2

An Efficacy and Safety Study of ICP-192 in Subjects With Bladder Urothelial Cancer

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Hangzhou (China), Shanghai (China), Suzhou (China), Hefei (China), Changsha (China), Wuhan (China), Jinan (China), Chongqing (China), Tianjin (China), Taiyuan (China)

NCT05086666
PHASE 1/2

A Phase 1b/2 Clinical Study to Evaluate the Safety and Tolerability and Efficacy of AZD4547

TARGETS
FGFRs

LOCATIONS: Shanghai (China)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

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

LOCATIONS: Shanghai (China)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Changchun (China), Brisbane (Australia), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland)

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)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

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

LOCATIONS: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of), North Carolina

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Seodaemun (Korea, Republic of), Osakasayama (Japan), Nagoya (Japan), Kawasaki (Japan), Chuo-Ku (Japan), Koto-ku (Japan), Chiba (Japan), Kashiwa (Japan)

GENE
NF2

ALTERATION
splice site 1122+1G>T

RATIONALE
Inactivation or loss of NF2 results in the dysregulation of mTOR and FAK pathway signaling. Therefore, mTOR and/or FAK inhibitors may be relevant for patients with NF2 inactivating mutations. 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), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

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

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

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.

BRCA1 K223N	***CARD11*** S694L	***ERBB2*** M1042fs*19	***GATA3*** P425S
IKZF1 P420L	***KRAS*** D132N	***MET*** P1322fs*31	***MLL2*** A3541S
NOTCH1 R2263Q	***PARP1*** V511F	***PDGFRA*** R374S	***PTPN11*** G158E

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B or WTX)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	***CCND1***	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*	***CD274*** **(PD-L1)**	*CDC73*
CDH1	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*	***CDKN2A***	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2 **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15, **24-27**	*EMSY* (C11orf30)	*EP300*	*EPHA3*
EPHB1	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***	***ESR1*** **Exons 4-8**
*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FANCA*	*FANCC*	*FANCG*
FANCL	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*	*FGF23*	*FGF3*
FGF4	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*	*FLCN*	*FLT1*
FLT3 **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*	*GID4* (C17orf39)	***GNA11*** **Exons 4, 5**
GNA13	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3-3A* (H3F3A)	*HDAC1*	*HGF*	*HNF1A*
HRAS **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*	*INPP4B*
IRF2	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*	*KDM5C*
KDM6A	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)	***KRAS***

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

LTK	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*	*MAPK1*
MCL1	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***	*MITF*
MKNK1	*MLH1*	***MPL*** **Exon 10**	*MRE11* (MRE11A)	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*	*MTAP*
MTOR **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*	***NF1***
NF2	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**	***NRAS*** **Exons 2, 3**
NSD2 (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**	***PDGFRB*** **Exons 12-21, 23**
PDK1	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*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*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C* (FAM46C)	*TERC** ncRNA	***TERT**** **Promoter**
TET2	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*
TYRO3	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

FoundationOne Liquid 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. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid 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.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx 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 malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

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. *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.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

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.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

KMT2D (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

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.

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 >30%, 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, ATM, CBL, CHEK2, 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.

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.

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 Liquid CDx.

TREATMENT DECISIONS ARE THE 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, 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

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