FOUNDATIONONE®HEME

PATIENT
Wang, Kung-Wei

TUMOR TYPE
Diffuse large B-cell lymphoma (NOS)

COUNTRY CODE
TW

REPORT DATE
09 Nov 2021

ORDERED TEST #
ORD-1220222-01

ABOUT THE TEST FoundationOne® Heme is a comprehensive genomic profiling test designed to identify genomic alterations within hundreds of cancer-related genes in hematologic malignancies and sarcomas.

PATIENT

DISEASE Diffuse large B-cell lymphoma (NOS)
NAME Wang, Kung-Wei
DATE OF BIRTH 08 July 1941
SEX Male
MEDICAL RECORD # 2890553

PHYSICIAN

ORDERING PHYSICIAN Yang, Muh-Hwa
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Testis
SPECIMEN ID PF21029
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 28 September 2021
SPECIMEN RECEIVED 25 October 2021

Biomarker Findings

Tumor Mutational Burden - 22 Muts/Mb
Microsatellite status - MS-Stable

Genomic Findings

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

B2M M1?, T24fs*52
CARD11 K215N
CDKN2A/B CDKN2B loss, CDKN2A loss
MLL2 P4961fs*1
MYD88 L265P
PIM1 Q127*, L2F
VHL R200W - subclonal†

† See About the Test in appendix for details.

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

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Tumor Mutational Burden - 22 Muts/Mb	none	none
10 Trials *see p. 9*		
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	

No therapies or clinical trials are associated with the Genomic Findings for this sample.

If you have questions or comments about this result, please contact your Foundation Medicine customer support representative.

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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.

Electronically signed by Lena Stuart, M.D. | 09 November 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
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 Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type.

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.

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BIOMARKER

Tumor Mutational Burden

RESULT
22 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]. As it is unclear whether TMB is associated with efficacy of immune checkpoint inhibitors in hematological malignancies, it is unknown whether this approach would be relevant here.

FREQUENCY & PROGNOSIS

Diffuse large B-cell lymphoma (DLBCL) harbors a median TMB of 10 mutations per megabase (muts/Mb), and 18.4% of cases have high TMB (>20 muts/Mb)[11]. Increased mutation burden has been identified in DLBCL at relapse compared to at diagnosis[12]. In one study, TMB was significantly higher in DLBCL (44% with >10 muts/Mb) as compared to low-grade non-Hodgkin lymphoma (LGNHL; 0% with >10 muts/Mb; p<0.0001); IHC testing in a separate cohort showed higher PD-L1 expression in DLBCL (8/10 PD-L1 positive) as compared to LGNHL (2/10 PD-L1 positive) (p=0.01), thereby suggesting possible benefit of checkpoint inhibitor therapy in DLBCL[13]. Aberrant somatic hypermutation occurs frequently in the primary central nervous system lymphoma (PCNSL) subtype and often targets the IGH, IGK, IGL, MYC, PAX5, BCL2, RhoH, and PIM1 genes[14-18].

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[19-20] and cigarette smoke in lung cancer[21-22], treatment with temozolomide-based chemotherapy in glioma[23-24], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[25-29], and microsatellite instability (MSI)[25,28-29]. Associations of TMB levels with sensitivity to immune checkpoint inhibitors have not been extensively characterized in hematologic malignancies and the effects of TMB on therapeutic outcomes in this context are unclear.

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[30-32], including approved therapies nivolumab and pembrolizumab[33]. 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)[34].

FREQUENCY & PROGNOSIS

High MSI (MSI-H) is generally rare in hematologic malignancies compared with solid tumors. Moreover, reports of MSI in hematologic malignancies in the literature are conflicting and varied due to substantial heterogeneity, lack of consensus on the markers and methods used for MSI assessment, small sample size in most studies, and possible elimination of MSI-positive cells in the bloodstream by immunosurveillance[35]. Several small studies have observed MSI at any level in 12% (3/25) to 33% (5/15) of diffuse large B cell lymphoma (DLBCL)[36-40]. MSI-H has been reported in ~3% of DLBCL cases in general[38,41], in a patient with MALT lymphoma with a DLBCL component[42], and in two patients with hereditary non-polyposis colon cancer (HNPCC) who developed DLBCL[43-44]. However, none (0/48) of the DLBCL cases in a computational analysis of paired tumor and normal cases in the TCGA dataset were MSI-H[45], and another study of 70 DLBCL cases found no instances of MSI[46]. In one study, the incidence of MSI in DLBCL was 7-fold higher compared with lower grade MALT lymphoma (p=0.009), suggesting that MSI frequency was associated with transition from low- to high-grade disease[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[47]. 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[47-49]. 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[50-52]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[47,49,51-52].

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GENE
B2M

ALTERATION
M1?, T24fs*52

TRANSCRIPT ID
NM_004048, NM_004048

CODING SEQUENCE EFFECT
-30_59del89,
58_59insCTATCCAGCGTGAGTCTCTCCTACCCTCCCGCTCTG
GTCCTTCCTCTCCCGCTCTGCA

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical studies in melanoma, lung cancer, and colorectal cancer (CRC) suggest that B2M mutation or loss may be a mechanism of tumor escape from immune recognition[53-58] and a resistance mechanism to immune checkpoint inhibitor (ICI) therapies[59-63]. However, the effect of B2M inactivation on ICI outcomes may be context dependent, as a pan-cancer meta-analysis did not find B2M mutations to be a significantly associated with clinical response to ICIs overall but observed notable effects on ICI outcomes in select tumor type cohorts (melanoma, head and neck squamous cell carcinoma, and non-small cell lung cancer)[64]. Furthermore, patients with B2M-mutated CRC experienced clinical benefit (clinical benefit rate of 85% [11/13] overall and 91% [10/11] in MSI-H CRC) on ICI therapies[65].

FREQUENCY & PROGNOSIS

In hematologic malignancies, B2M alterations have been primarily reported in both germinal center B-cell like and activated B-cell diffuse large B-cell lymphoma (DLBCL), with mutations and deletions present in 13% and 25% of DLBCL cases, respectively, and biallelic loss due to mutation or deletion in 13% of cases[66-67]. Inactivating B2M mutations have also been reported in classical Hodgkin lymphoma[68]. In one study of classical Hodgkin lymphoma, B2M mutations were closely associated with loss of beta-2-microglobulin protein expression, and reduced beta-2-microglobulin expression was significantly associated with improved prognosis and the nodular sclerosis histologic subtype rather than the mixed cellularity subtype[68]. High serum levels of beta-2-microglobulin have been correlated with poor prognosis in hematologic malignancies such as Hodgkin and non-Hodgkin lymphoma[69-73], including follicular lymphoma[74-76], DLBCL[77], mantle cell lymphoma[78], and NK/T-cell lymphoma[79-80], as well as in multiple myeloma[81-88], myelodysplastic syndrome[89-90], acute myeloid leukemia[91], acute lymphocytic leukemia[92], chronic lymphocytic leukemia[93], and Waldenstrom macroglobulinemia[94].

FINDING SUMMARY

B2M encodes beta-2-microglobulin, a component of the MHC complex that presents antigen peptides to the immune system and binds the inhibitory receptor LILRB1 on macrophages. Alterations in B2M that lead to loss, truncation, destabilization, or aberrant expression of beta-2-microglobulin can promote tumor evasion of immunosurveillance through loss of MHC presentation[66,68,95-96].

GENE
CARD11

ALTERATION
K215N

TRANSCRIPT ID
NM_032415

CODING SEQUENCE EFFECT
645G>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Although there are no therapies targeting CARD11 alterations, a number of drugs that block NF-kB activation are under investigation[97-99]. Preclinical evidence from models of mantle cell lymphoma suggests that tumors with CARD11 mutations may exhibit reduced sensitivity to inhibitors of BCR/NF-kB signaling including ibrutinib and lenalidomide[100-101]. CARD11 mutations have also been correlated with reduced sensitivity to sotrastaurin (protein kinase C inhibitor) in preclinical models of DLBCL[102].

FREQUENCY & PROGNOSIS

CARD11 alterations have been most frequently reported in B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL; 11-23%)[103-105], follicular lymphoma (21-25%)[106], primary central nervous system lymphoma (16-30%)[107-108], splenic marginal zone lymphoma (7-9%)[109-110], and mantle cell lymphoma (6%)[100]. CARD11 mutations have also been detected in T-cell lymphomas, specifically in angioimmunoblastic T-cell lymphomas (AITLs), peripheral T-cell lymphomas (PTCLs), and cases of Sezary syndrome[111-113]. Copy number gains and consequent CARD11 overexpression have been reported in 71% (12/17) of patients with aggressive AITL and in 41% (30/73) of patients with PTCL[114-115]. Increased CARD11 expression has also been observed in T-ALL[116]. CARD11 amplification in DLBCL and increased CARD11 protein expression in AITL or PTCL is associated with reduced overall survival[103,115]. Although CARD11 mutations have been detected in a variety of solid tumors[117-122], the prognostic implications of CARD11 alterations in non-hematological malignancies are unclear.

FINDING SUMMARY

CARD11 (also known as CARMA1) is a scaffold protein critical for B- and T-cell receptor-mediated NF-kappaB (NF-kB) activation[123-125]. Activating CARD11 mutations, often occurring within the CARD (aa 18-110) or coiled-coil (aa 130-499) domains, can facilitate constitutive NF-kB signaling, proliferation, and cell survival in lymphomas[104,111,113,125-132]. Preclinical evidence suggests that activating CARD11 mutations may reduce sensitivity to ibrutinib, lenalidomide, and sotrastaurin in lymphoma[100-102]. Some germline CARD11 mutations have been found to underlie B-cell expansion with NF-kB and T-cell anergy (BENTA), a disorder characterized by congenital B-cell lymphocytosis[125,128,133].

GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[134-137]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[138-139], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[140-146]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[147-148], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[141,143-144,149-151].

FREQUENCY & PROGNOSIS

Deletion of the CDKN2A/B locus on chromosome 9p21 is relatively common in B-cell lymphoma, reported primarily in diffuse large B-cell lymphoma (DLBCL), in which it is seen in 32% of cases[152], as well as in 13% of follicular lymphoma (FL) cases[153]. CDKN2A inactivation has been reported in 21-36% of DLBCL cases[152,154-157] and in 6-13% of FL cases, particularly in higher grade FL cases, and in 33% of FL cases transformed to DLBCL[153,158-162]. CDKN2A/B loss via deletion or methylation has been associated with reduced mRNA expression and higher grade malignancy in B-cell and T-cell lymphomas[152,163] and is also correlated with poor prognosis in FL patients (HR=3.6, p=0.0352), although many of these patients were treated prior to rituximab becoming a widely used therapy[153]. Deletion of CDKN2A/B is not mutually exclusive with TP53 or MDM2 alterations and may be associated with the transformation of FL to DLBCL[153,159-162]. An array comparative genome hybridization (aCGH) study identified loss of the CDKN2A/B locus as a candidate marker for chemoresistance in B-cell lymphoma[164].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[165-166]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[167-168]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[169-170]. One or more alterations observed here are predicted to result in p16INK4a loss of function[171-192]. One or more alterations seen here are predicted to result in p14ARF loss of function[175,192-195]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[196].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[197]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[198-199]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[200-202]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[203-205]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
MLL2

ALTERATION
P4961fs*1

TRANSCRIPT ID
NM_003482

CODING SEQUENCE EFFECT
14880_15016>CTGAATC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

Somatic alterations of MLL2 are frequently observed in lymphoma, including in the majority of follicular lymphomas, where the observed pattern of genomic alterations suggests a tumor suppressor function[106]. High protein expression of MLL2 has been correlated with higher clinical stage, and poorer overall survival in patients >60 years of age with gastrointestinal diffuse large B cell lymphoma (PGI-DLBCL)[206].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[207]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[208]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[209].

GENE
MYD88

ALTERATION
L265P

TRANSCRIPT ID
NM_002468

CODING SEQUENCE EFFECT
794T>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available therapies that directly target MYD88. In preclinical studies, inhibitors of IRAK1/4 or BTK kinases exhibited antiproliferative effects on cells with an MYD88 activating mutation[210]. BTK inhibitors showed antitumor activity for patients with MYD88-mutated diffuse large B-cell lymphoma, but only in the presence of a concurrent CD79B activating alteration (4/5 responses to ibrutinib for patients with concurrent MYD88 and CD79B mutations versus 0/7 for patients with MYD88 mutations and wildtype CD79B)[211-212]. Multiple studies demonstrated numerically higher efficacy of zanubrutinib for patients with MYD88 L265P-mutated Waldenstrom macroglobulinemia (WM) than those with unmutated MYD88, although the studies were not powered to statistically compare the efficacy between the 2 groups[213-215]. A Phase 1/2 study evaluating pirtobrutinib to treat B-cell malignancies reported ORRs for patients with WM of 68% (13/19, with responses ongoing for 10/13), including for patients who had progressed on prior covalent BTK inhibitors[216]. In a Phase 1b/2 trial of the noncovalent BTK inhibitor vecabrutinib, no responses were observed for any of the 9 treated patients with hematologic malignancies (chronic lymphocytic leukemia [CLL], n=6; mantle cell lymphoma, n=3; WM, n=1), although these patients were only treated with a low dose (25-50 mg) as part of the dose escalation cohort[217]. The effect of MYD88 L265P on the efficacy of ibrutinib for patients with CLL is not yet clear[218]. CXCR4 inhibitors such as plerixafor[219] may be a suitable combination therapy with ibrutinib for patients with CXCR4 activation in addition to MYD88 activating mutations[220-221].

FREQUENCY & PROGNOSIS

MYD88 mutations have been reported in activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL, 30% of cases)[210,222], 6% of marginal zone lymphoma, 5% of Burkitt lymphoma, 5% of MALT lymphoma, and 2% of follicular lymphoma cases[109,155,223-224]. Somatic alteration of MYD88 is most frequently observed in Waldenstrom macroglobulinemia (WM)/lymphoplasmacytic lymphoma (70-100% of cases)[225-229]. Although MYD88 L265P has been associated with increased bone marrow involvement and serum IgM levels in WM, particularly in the presence of a concurrent CXCR4 mutation, the MYD88 L265P mutation had a positive impact on overall survival compared to wild-type MYD88[220,229]. In another study, high levels of MYD88 expression correlated with decreased disease-free progression in patients with DLBCL (p=0.025)[222].

FINDING SUMMARY

MYD88 encodes a myeloid differentiation factor[230], which functions as an adaptor protein in Toll-like receptor (TLR) signaling, a central component of the innate immune response[231]. L265P is the most prevalent MYD88 mutation[210,228]; this mutation activates NFkB signaling[210,232] and is frequently observed in patients with Waldenstrom's macroglobulinemia (WM)[228] or activated B-cell-like subtype diffuse large B-cell lymphoma (ABC-DLBCL)[210]. MYD88 activating mutations have been shown to predict response to ibrutinib in patients with WM, and clinical responses have been observed in patients with L265P or S243N mutations[233-234].

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GENE
PIM1

ALTERATION
Q127*, L2F

TRANSCRIPT ID
NM_002648, NM_002648

CODING SEQUENCE EFFECT
379C>T, 4C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target PIM1 alterations, although PIM kinase inhibitors are in clinical development, primarily in hematologic malignancies[235-237]. In preclinical studies, expression PIM1 or other PIM kinases has been reported to activate the mTOR pathway[238-239]. Although some preclinical studies have reported that PIM activation confers resistance to inhibitors of the PI3K-Akt-mTOR pathway[240-241], others have found that PIM-overexpressing cells are sensitive to mTOR inhibition[238,242]. However, studies have consistently shown synergistic anti-proliferative effects of PIM inhibitors in combination with PI3K-Akt-mTOR pathway inhibitors[238,242-243], and such approaches may be relevant for tumors with PIM1 activation.

FREQUENCY & PROGNOSIS

Mutations in PIM1 have been reported in 1/9 of classic Hodgkin lymphoma (HL) and in 3/8 of nodular lymphocyte predominant HL (NLPHL) samples[244] but have been more frequently reported in non-Hodgkin lymphoma (NHL), including 19-65% diffuse large B-cell lymphoma (DLBCL), 19-100% primary central nervous system lymphoma (PCNSL), 16% (5/32) of follicular lymphoma (FL), 35% (9/26) of FL transformed to DLBCL samples, 61.5% (8/13) of mucosa-associated lymphoid tissue-type (MALT) lymphomas, 9.5% (2/21) of nodal marginal zone B-cell lymphomas and in 1/11 primary cutaneous marginal zone B-cell lymphomas (PCMZL)[14,16,106,108,156,245-250]. PIM1 kinase is predicted to be constitutively active, regulated primarily at the level of expression[251-254]. PIM1 expression has been reported in MCL, DLBCL, acute myeloid leukemia (AML) and B-cell acute lymphocytic leukemia (B-ALL) samples[254-260] and high expression has been reported to predict poor outcome in MCL and DLBCL[253,255,258]. Expression of PIM1 and/or PIM2 was also associated with poor prognosis in FL[261].

FINDING SUMMARY

PIM1 encodes a serine/threonine kinase that regulates cell survival and proliferation and cooperates with the MYC oncogene to promote lymphomagenesis[251-254,262-264]. The PIM1 locus is subject to somatic hypermutation in lymphoid malignancies, including diffuse large B-cell lymphoma (DLBCL)[156,265-266]. PIM1 mutations also may contribute to the transformation of FL or chronic lymphocytic leukemia (CLL) to DLBCL[246,267]. Although a few mutations have been characterized in vitro as having an effect on PIM1 kinase activity[252], direct experimental evidence for any selectable advantage for somatically mutated PIM1 variants in lymphoma cells is lacking.

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GENE
VHL

ALTERATION
R200W - subclonal

TRANSCRIPT ID
NM_000551

CODING SEQUENCE EFFECT
598C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Various strategies are under clinical investigation to block pathways downstream of inactivated VHL, including HIF, VEGF, and mTOR. The multikinase inhibitor sunitinib, which has activity against VEGFRs and other targets, is approved to treat several tumor types and has shown strong efficacy in patients with VHL disease[268-272]. Several clinical trials found response rates up to 64% and disease control rates up to 90%[273-274]. However, multiple clinical studies of sunitinib in patients with renal cell carcinoma reported that mutation or inactivation of the VHL gene is not significantly associated with therapeutic response or survival[275-277]. Other agents that inhibit VEGFRs, including the multikinase inhibitors sorafenib, axitinib, pazopanib, regorafenib, cabozantinib, and vandetanib; the anti-VEGFR2 antibody ramucirumab; and the mTOR inhibitors everolimus and temsirolimus, are also approved in multiple tumor types. However, studies have similarly shown that VHL mutation or inactivation does not correlate with responses to these agents[276,278-279]. Therefore, it is unclear whether these therapeutic strategies would be beneficial in this case. The HIF2a inhibitor belzutifan achieved an ORR of 36% in a clinical trial for VHL disease-associated clear cell renal cell carcinoma[280]. Responses were also seen in other VHL mutation-associated tumor types, including CNS hemangioblastomas and pancreatic neuroendocrine tumors; however, it was not determined whether VHL inactivation was significantly associated with these responses[280].

FREQUENCY & PROGNOSIS

VHL mutations are extremely rare in leukemias and lymphomas. VHL mutations were reported in <0.5% of hematological and lymphoid malignancies in COSMIC (Jan 2021). Reduced expression of VHL, mediated by promoter hypermethylation or targeting by microRNAs, has been reported in chronic lymphoid leukemia and associated with poor prognosis[281-282]. Similarly, hypermethylation of VHL has been associated with reduced survival and disease-free survival in one study of diffuse large B-cell lymphoma[283], although the functional relevance of this is unclear[284].

FINDING SUMMARY

VHL encodes the protein pVHL (von Hippel-Lindau tumor suppressor), which is frequently inactivated, either via mutation or hypermethylation, in clear cell renal cell carcinoma (ccRCC) and plays an important role in its pathogenesis[285]. Inactivating mutations in VHL lead to dysregulation of critical downstream growth regulators, especially members of the HIF family and VEGF[286-287]. Alterations such as seen here may disrupt VHL function or expression[288-326].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the VHL 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 von Hippel-Lindau syndrome (ClinVar, Sep 2021)[327]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in VHL underlie von Hippel-Lindau syndrome, a rare but highly penetrant autosomal dominant syndrome occurring in 1/36,000 live births that predisposes to the development of several types of cancer, including clear cell renal cell carcinomas and pancreatic neuroendocrine tumors, as well as retinal and central nervous system hemangioblastomas[328-330]. In the appropriate clinical context, germline testing of VHL is recommended.

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

22 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. As it is unclear whether TMB is associated with efficacy in hematological malignancies, it is not known whether these therapeutic strategies would be relevant here.

NCT03674567

PHASE 1/2

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

TARGETS
PD-1, CCR4

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

NCT03207867

PHASE 2

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

TARGETS
PD-1, ADORA2A

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

NCT04261439

PHASE 1

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

TARGETS
PD-1

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

NCT04476459

PHASE 1/2

Camrelizumab in Combination With Apatinib in Refractory and Relapsed DLBCL

TARGETS
RET, VEGFR2, PD-1

LOCATIONS: Guangzhou (China)

NCT02500407

PHASE 1/2

A Safety and Pharmacokinetic Study of BTCT4465A, With or Without Single-dose Obinutuzumab Pretreatment, in Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL)

TARGETS
PD-L1, CD20, CD3

LOCATIONS: Seoul (Korea, Republic of), Nedlands (Australia), South Brisbane (Australia), Woolloongabba (Australia), Adelaide (Australia), Darlinghurst (Australia), Fitzroy (Australia), Melbourne (Australia), Clayton (Australia), Hobart (Australia)

NCT03005782

PHASE 1

Study of REGN3767 (Anti-LAG-3) With or Without REGN2810 (Anti-PD1) in Advanced Cancers

TARGETS
PD-1, LAG-3

LOCATIONS: Seoul (Korea, Republic of), Perth (Australia), Brisbane (Australia), Melbourne (Australia), London (United Kingdom), Headington (United Kingdom), Dublin (Ireland), California

NCT04070040

PHASE 2

Camrelizumab for Patients With Recurrent Primary Central Nervous System Lymphoma (PCNSL)

TARGETS
PD-1

LOCATIONS: Beijing (China)

NCT01703949

PHASE NULL

Brentuximab Vedotin in Treating Patients With Relapsed or Refractory CD30+ Lymphoma

TARGETS
PD-1, CD30

LOCATIONS: Washington

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)

NCT03244176

PHASE NULL

Feasibility Study of Induction and Maintenance Avelumab Plus R-CHOP in Patients With Diffuse DLBCL: The AvR-CHOP Study

TARGETS
PD-L1, CD20

LOCATIONS: Ballarat (Australia), Heidelberg (Australia), Box Hill (Australia)

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.

BCL11B
A586V

BIRC3
F176V

DUSP2
L67F

ERBB3
R1309H

ETS1
T10I

FANCC
T367K

FANCE
G175D

FGF19
R61H

GPR124
C1196Y and D1313V

IDH1
R20Q

IKBKE
A346V

KDM4C
G799V

MDM4
N281S

PIM1
A10V, E70*, G102D, G137V, G28D, L177F, L184F, P81S, R57G, S312N and T204fs*31

PRKDC
T1375S

RAD51
R97H

TBL1XR1
W316S

Electronically signed by Lena Stuart, M.D. | 09 November 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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APPENDIX Genes Assayed in FoundationOne®Heme

FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies and sarcomas 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 utilizes DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACTB*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	*APC*
APH1A	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*	*ARID1A*	*ARID2*	*ASMTL*
ASXL1	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*
B2M	*BAP1*	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*
BCL7A	*BCOR*	*BCORL1*	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*
BRD4	*BRIP1*	*BRSK1*	*BTG2*	*BTK*	*BTLA*	*C11orf30 (EMSY)*	*CAD*
*CALR**	*CARD11*	*CBFB*	*CBL*	*CCND1*	*CCND2*	*CCND3*	*CCNE1*
CCT6B	*CD22*	*CD274 (PD-L1)*	*CD36*	*CD58*	*CD70*	*CD79A*	*CD79B*
CDC73	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1B*	*CDKN2A*
CDKN2B	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*	*CIC*	*CIITA*
CKS1B	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*
DNMT3A	*DOT1L*	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*
EGFR	*ELP2*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*
ERBB3	*ERBB4*	*ERG*	*ESR1*	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*
FAF1	*FAM46C*	*FANCA*	*FANCC*	*FANCD2*	*FANCE*	*FANCF*	*FANCG*
FANCL	*FAS (TNFRSF6)*	*FBXO11*	*FBXO31*	*FBXW7*	*FGF10*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FHIT	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*	*FOXL2*	*FOXO1*
FOXO3	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*	*GID4 (C17orf39)*
GNA11	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GPR124*	*GRIN2A*	*GSK3B*
GTSE1	*HDAC1*	*HDAC4*	*HDAC7*	*HGF*	*HIST1H1C*	*HIST1H1D*	*HIST1H1E*
HIST1H2AC	*HIST1H2AG*	*HIST1H2AL*	*HIST1H2AM*	*HIST1H2BC*	*HIST1H2BJ*	*HIST1H2BK*	*HIST1H2BO*
HIST1H3B	*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*	*IDH1*	*IDH2*
IGF1R	*IKBKE*	*IKZF1*	*IKZF2*	*IKZF3*	*IL7R*	*INHBA*	*INPP4B*
INPP5D (SHIP)	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*
KDR	*KEAP1*	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*
LEF1	*LRP1B*	*LRRK2*	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*
MAP2K2	*MAP2K4*	*MAP3K1*	*MAP3K14*	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*
MDM2	*MDM4*	*MED12*	*MEF2B*	*MEF2C*	*MEN1*	*MET*	*MIB1*
MITF	*MKI67*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*	*MSH6*
MTOR	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*	*MYO18A*	*NCOR2*
NCSTN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*	*NOTCH1*
NOTCH2	*NPM1*	*NRAS*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*NUP93*
NUP98	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*	*PAX5*	*PBRM1*
PC	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*	*PDGFRA*	*PDGFRB*
PDK1	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*
PTPN11	*PTPN2*	*PTPN6 (SHP-1)*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*
RARA	*RASGEF1A*	*RB1*	*RELN*	*RET*	*RHOA*	*RICTOR*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*S1PR2*	*SDHA*	*SDHB*	*SDHC*	*SDHD*
SERP2	*SETBP1*	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA1*
SMARCA4	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*	*SOCS1*	*SOCS2*	*SOCS3*
SOX10	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*	*STAG2*	*STAT3*
STAT4	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*	*TAF1*
TBL1XR1	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*	*TMSB4XP8 (TMSL3)*
TNFAIP3	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*	*TRAF2*
TRAF3	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*
U2AF2	*VHL*	*WDR90*	*WHSC1 (MMSET or NSD2)*	*WISP3*	*WT1*	*XBP1*	*XPO1*
YY1AP1	*ZMYM3*	*ZNF217*	*ZNF24 (ZSCAN3)*	*ZNF703*	*ZRSR2*		

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*Note: the assay was updated on 11/8/2016 to include the detection of alterations in CALR

HEMATOLOGICAL MALIGNANCY DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*	*EPOR*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FGFR2*	*IGH*	*IGK*	*IGL*
JAK1	*JAK2*	*KMT2A (MLL)*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*	*RARA*
RET	*ROS1*	*TMPRSS2*	*TRG*					

HEMATOLOGICAL MALIGNANCY RNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFF1*	*AFF4*	*ALK*	*ARHGAP26 (GRAF)*	
ARHGEF12	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*	*BCL10*	*BCL11A*
BCL11B	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*	*BCR*	*BIRC3*
BRAF	*BTG1*	*CAMTA1*	*CARS*	*CBFA2T3*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CD274 (PD-L1)*	*CDK6*	*CDX2*	*CHIC2*	*CHN1*	*CIC*	*CIITA*	*CLP1*
CLTC	*CLTCL1*	*CNTRL (CEP110)*	*COL1A1*	*CREB3L1*	*CREB3L2*	*CREBBP*	*CRLF2*	*CSF1*
CTNNB1	*DDIT3*	*DDX10*	*DDX6*	*DEK*	*DUSP22*	*EGFR*	*EIF4A2*	*ELF4*
ELL	*ELN*	*EML4*	*EP300*	*EPOR*	*EPS15*	*ERBB2*	*ERG*	*ETS1*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*	*FCRL4*	*FEV*	*FGFR1*
FGFR1OP	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*	*FOXO4*	*FOXP1*
FSTL3	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*HERPUD1*	*HEY1*	*HIP1*
HIST1H4I	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*	*HOXA3*	*HOXA9*	*HOXC11*
HOXC13	*HOXD11*	*HOXD13*	*HSP90AA1*	*HSP90AB1*	*IGH*	*IGK*	*IGL*	*IKZF1*
IL21R	*IL3*	*IRF4*	*ITK*	*JAK1*	*JAK2*	*JAK3*	*JAZF1*	*KAT6A (MYST3)*
KDSR	*KIF5B*	*KMT2A (MLL)*	*LASP1*	*LCP1*	*LMO1*	*LMO2*	*LPP*	*LYL1*
MAF	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MKL1*	*MLF1*	*MLLT1 (ENL)*	*MLLT10 (AF10)*
MLLT3	*MLLT4 (AF6)*	*MLLT6*	*MN1*	*MNX1*	*MSI2*	*MSN*	*MUC1*	*MYB*
MYC	*MYH11*	*MYH9*	*NACA*	*NBEAP1 (BCL8)*	*NCOA2*	*NDRG1*	*NF1*	*NF2*
NFKB2	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NTRK1*	*NTRK2*	*NTRK3*
NUMA1	*NUP214*	*NUP98*	*NUTM2A*	*OMD*	*P2RY8*	*PAFAH1B2*	*PAX3*	*PAX5*
PAX7	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2 (PD-L2)*	*PDE4DIP*	*PDGFB*	*PDGFRA*	*PDGFRB*
PER1	*PHF1*	*PICALM*	*PIM1*	*PLAG1*	*PML*	*POU2AF1*	*PPP1CB*	*PRDM1*
PRDM16	*PRRX1*	*PSIP1*	*PTCH1*	*PTK7*	*RABEP1*	*RAF1*	*RALGDS*	*RAP1GDS1*
RARA	*RBM15*	*RET*	*RHOH*	*RNF213*	*ROS1*	*RPL22*	*RPN1*	*RUNX1*
RUNX1T1 (ETO)	*RUNX2*	*SEC31A*	*SEPT5*	*SEPT6*	*SEPT9*	*SET*	*SH3GL1*	*SLC1A2*
SNX29 (RUNDC2A)	*SRSF3*	*SS18*	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*STL*	*SYK*
TAF15	*TAL1*	*TAL2*	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TEC*	*TET1*	*TFE3*
TFG	*TFPT*	*TFRC*	*TLX1*	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*
TPM3	*TPM4*	*TRIM24*	*TRIP11*	*TTL*	*TYK2*	*USP6*	*WHSC1 (MMSET or NSD2)*	
WHSC1L1	*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*	*ZNF521*			

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

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The median exon coverage for this sample is 842x

ACCURACY		
Sensitivity: Base Substitutions	At ≥5% Minor Allele Frequency	>99.0%
Sensitivity: Insertions/Deletions (1-40bp)	At ≥10% Minor Allele Frequency	98.0%
Sensitivity: Focal Copy Number Alterations (Homozygous Deletions or Amplifications)	At ≥8 copies	>95.0%
Sensitivity: Microsatellite Instability-High (MSI-H) status	Positive Predictive Agreement (PPA)	100.0% (87.54%-100.00%)*
Sensitivity: Microsatellite Stable (MSS) status	Positive Predictive Agreement (PPA)	89.66% (81.50%, 94.46%)*
Sensitivity: Known Gene Fusions	>95.0%	
Specificity: Base Substitutions, Insertions/Deletions, and Focal Copy Number Alterations	Positive Predictive Value (PPV)	>99.0%
Specificity: Known Gene Fusions	Positive Predictive Value (PPV)	>95.0%
Specificity: Microsatellite Instability-High (MSI-H) status	Negative Predictive Agreement (NPA)	97.44% (91.12%-99.29%)*
Specificity: Microsatellite Stable (MSS) status	Negative Predictive Agreement (NPA)	94.44% (86.57%, 97.82%)*
Accuracy: Tumor Mutation Burden	At ≥20% tumor nuclei	>90.0%
Reproducibility (average concordance between replicates)	97.0% inter-batch precision 97.0% intra-batch precision 95.0% microsatellite status precision 96.0% tumor mutation burden precision	

*95% Confidence Interval

Assay specifications were determined for pical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne, please refer to the article, Frampton, GM. et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, Nat Biotechnol (2013 Oct. 20).

In the fractional-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 FoundationOne Heme 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 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.

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne Heme test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne Heme samples and is reported as the number of mutations per megabase (Muts/Mb). Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

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ABOUT FOUNDATIONONE HEME

FoundationOne®Heme is a comprehensive genomic profiling test for hematologic malignancies and sarcomas. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials, and quantitative markers that may support immunotherapy clinical trial enrollment. FoundationOne Heme is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across more than 250 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas.

FoundationOne Heme was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

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.

Diagnostic Significance

FoundationOne Heme 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 FoundationOne Heme 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 Heme for identifying a copy number amplification is five (5) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that FoundationOne Heme data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that FoundationOne Heme analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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 Heme.

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. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne Heme is performed using DNA and RNA derived from tumor, and as such germline events may not be reported.

The following targets typically have low coverage resulting in a reduction in sensitivity: SDHD exon 4, TNFRSF11A exon1, and TP53 exon 1.

FoundationOne Heme 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

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, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, 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.

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

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Electronically signed by Lena Stuart, M.D. | 09 November 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309
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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Electronically signed by Lena Stuart, M.D. | 09 November 2021
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Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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