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 Lymph node lymphoma follicular lymphoma
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - TMB-Intermediate (16 Muts/Mb)

Genomic Findings

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

IGH IGH-BCL2 rearrangement
BCL2 P59S - subclonal, R129H, E13D†
BTG1 Q42fs*38
CREBBP Q1491K
MLL2 W268*, R5432W
TNFAIP3 splice site 1906+2T>A
ZMYM3 G49fs*13

† See About the Test in appendix for details.

1 Therapies with Clinical Benefit
0 Therapies with Lack of Response
8 Clinical Trials

BIOMARKER FINDINGS
Microsatellite status - MS-Stable
Tumor Mutational Burden - TMB-Intermediate (16 Muts/Mb)
GENOMIC FINDINGS
***IGH* -** IGH-BCL2 rearrangement
8 Trials *see p. 9*

ACTIONABILITY
No therapies or clinical trials. see Biomarker Findings section
No therapies or clinical trials. see Biomarker Findings section

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

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain 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.

BIOMARKER
Microsatellite status

CATEGORY
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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 [1-3], including approved therapies nivolumab and pembrolizumab [4]. 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)[5].

FREQUENCY & PROGNOSIS

In studies of follicular lymphoma, MSI at any level has been observed in 6% (2/17) to 63% (5/8) of cases [6-9]; MSI-H has been observed with an incidence of 5% (2/40) to 13% (1/8) [7,9] or reported as absent [6,8,10]. 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 [11]. The prognostic significance of MSI in follicular lymphoma has not been extensively studied (PubMed, Nov 2018).

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 [12]. 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 [12-14]. 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 [15-17]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins [12,14,16-17].

BIOMARKER
Tumor Mutational Burden

CATEGORY
TMB-Intermediate (16 Muts/Mb)

POTENTIAL TREATMENT STRATEGIES

On the basis of emerging clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-CTLA-4 [18], anti-PD-L1 [19-22], and anti-PD-1 therapies [4,23-24]; FDA-approved agents include ipilimumab, atezolizumab, avelumab, durvalumab, pembrolizumab, and nivolumab. In multiple solid tumor types, higher mutational burden has corresponded with response and improved prognosis. Pembrolizumab improved progression-free survival (14.5 vs. 3.4-3.7 months) for patients with non-small cell lung cancer (NSCLC) and higher mutational load (greater than 200 nonsynonymous mutations; hazard ratio = 0.19)[23]. In studies of patients with either NSCLC or colorectal cancer (CRC), patients whose tumors harbored elevated mutational burden reported higher overall response rates to pembrolizumab [4,23-24]. Anti-PD-1 therapies have achieved clinical benefit for certain patients with high mutational burden, including 3 patients with endometrial adenocarcinoma who reported sustained partial responses (PRs) following treatment with pembrolizumab [25] or nivolumab [26], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab [27], 2 pediatric patients with biallelic mismatch repair deficiency-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab [28], and 2 patients with microsatellite-stable rectal cancers, 1 who achieved an ongoing PR to pembrolizumab and the other an ongoing complete response to nivolumab [29]. For patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab [18,30] and anti-PD-1/anti-PD-L1 treatments [20]. For patients with metastatic urothelial carcinoma (mUC), those who responded to atezolizumab treatment had a significantly increased mutational load (12.4 mutations [muts] per megabase [Mb]) compared to nonresponders (6.4 muts/Mb)[19], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival [21]. In a retrospective analysis of 17 solid tumor types (comprised of 47% NSCLC, 40% mUC, and 13% encompassing 15 other solid tumors), a TMB of ≥16 muts/Mb associated with an objective response rate to atezolizumab of 30% vs. 14% for chemotherapy alone[31].

FREQUENCY & PROGNOSIS

In the context of follicular lymphoma (FL), a tumor mutation burden (TMB) of 8.3 mutations per megabase (muts/Mb) was reported, with 3.7% of cases having high TMB (>20 muts/Mb)[32]. Another study reported tumor mutation burden (TMB) of >15 muts/Mb in 8.8% (19/216), ≥6.6 muts/Mb and ≤15 muts/Mb in 39% (85/216), and <6.6 muts/Mb in 52% (112/216) of patients. A lower mutation burden (<1 muts/Mb) has been reported for pediatric-type FL [33]. One study observed a similar somatic mutation load in low-grade and transformed FL cases and found that mutations due to aberrant somatic hypermutation were less frequent in transformed FL than previously reported for de novo diffuse large B-cell lymphoma (DLBCL)[34]. Patients with high-TMB follicular lymphoma (FL) exhibited an increased incidence of the T-cell activation signature and improved progression-free survival compared to patients with lower TMB FL[35]. Patients with low-TMB FL derived significant benefit from rituximab maintenance therapy [hazard ratio (HR)=0.29]; however, there was no significant association for patients with intermediate (HR=0.81) or high (HR=0.29) TMB, although the sample size of high-TMB cases was small[35]. Increased mutation burden has been identified in DLBCL at relapse compared to at diagnosis[36].

FINDING SUMMARY

Tumor mutational 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 [37-38] and cigarette smoke in lung cancer [23,39], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes [40-44], and microsatellite instability (MSI) [40,43-44]. This sample harbors an intermediate TMB. This level of TMB is high enough that it may be associated with sensitivity to immune checkpoint inhibitors in some tumor types, including anti-PD-1 therapy in non-small cell lung cancer [23], anti-PD-L1 therapy in bladder cancer [19], and anti-CTLA-4 therapy in melanoma [18], potentially due to expression of immune-reactive neo-antigens in these tumors [23]. However, in other studies of checkpoint inhibitors, including anti-PD-1 therapy in colorectal cancer [4], patients with tumors harboring intermediate TMB levels experienced lower rates of clinical benefit than those with high TMB.

GENE
IGH

ALTERATION
IGH-BCL2 rearrangement

POTENTIAL TREATMENT STRATEGIES

BET bromodomain-containing proteins, in particular BRD4, have been reported to bind to and regulate the IGH transcriptional enhancer [45]. BET domain inhibitors have been reported to block IGH-mediated transcriptional activation for an IGH-MYC rearrangement in a MM cell line [46] and may be effective in negating IGH-driven transcriptional deregulation here. Preliminary results from the Phase I trial of BET inhibitor OTX015 in patients with hematological malignancies reported clinical activity in AML and lymphoma patients[47-48] . On the basis of clinical evidence[49-50] as well as extensive preclinical evidence [51-54], alterations leading to BCL2 overexpression may predict sensitivity to therapies targeting BCL2, such as venetoclax. BCL2 inhibitors have shown clinical activity in patients with chronic lymphocytic leukemia (CLL)[55-56], non-Hodgkin lymphoma (NHL)[57] and multiple myeloma (MM)[50,58] . Several preclinical studies suggest that concurrent expression of BCL-XL or MCL-1 may confer resistance to BCL2 inhibitors, and combination therapies targeting MCL-1 or BCL-XL may be required to overcome resistance in tumor cells [52,59-60].

FREQUENCY & PROGNOSIS

IGH-BCL2 rearrangement is considered a hallmark molecular alteration in follicular lymphoma (FL), cited in more than 90% of cases in some studies [61-63] and thought to be an early genetic event in FL tumorigenesis [64-65]. BCL2 protein expression was detected in 23/29 FL and 20/22 MZL samples in one study [66]. Co-occurring mutations in BCL2 are frequently observed in patients with the IGH-BCL2 rearrangement, likely as a result of somatic hypermutation normally occurring at the IGH locus [67]. BCL2 abnormalities have not been reported to have high prognostic impact in patients with FL [68-70], although one study reported inferior prognosis in patients with FL harboring a BCL2 abnormality than those without [71]. Translocations involving the IGH locus have been observed to have a relatively favorable prognosis in the context of gastric DLBCL [72].

FINDING SUMMARY

IGH (immunoglobulin heavy) is a gene that codes for the heavy-chain component of antibodies [73]. During antibody diversification, the IGH locus undergoes recombination and somatic hypermutation, remodeling events that are susceptible to aberrant rearrangement with other parts of the genome [74-76]. Because the IGH locus contains multiple strong transcriptional enhancers, IGH-involving rearrangements frequently result in aberrant upregulation of gene expression within rearranged regions [77]. A chromosomal translocation, t(14;18), that fuses the BCL2 gene into the immunoglobulin heavy chain locus, as observed here, results in dysregulation of BCL2 expression [78-81], and is a hallmark of follicular lymphoma [82]. IGH-BCL2 has been shown to alter the transcriptional activation of BCL2 as well as lead to abnormal post-transcriptional regulation of BCL2 mRNA [83]. BCL2 encodes the B-cell CLL/lymphoma 2 (BCL2) protein, which is an integral outer mitochondrial membrane protein that blocks apoptotic cell death [84]. BCL2 acts as a proto-oncogene in B-cell neoplasms, where its expression is frequently dysregulated due to gene translocation or amplification [78,85]. Increased BCL2 protein expression correlates with both BCL2 gene amplification and translocation [86-87].

GENE
BCL2

ALTERATION
P59S - subclonal, R129H, E13D

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence[49-50] as well as extensive preclinical evidence [51-54], alterations leading to BCL-2 overexpression may predict sensitivity to therapies targeting BCL-2, such as venetoclax. BCL-2 inhibitors have shown clinical activity in patients with chronic lymphocytic leukemia (CLL)[56,88-89], non-Hodgkin lymphoma (NHL)[57] and multiple myeloma[50,58] . Several preclinical studies suggest that concurrent expression of BCL-XL or MCL-1 may confer resistance to BCL-2 inhibitors, and combination therapies targeting MCL-1 or BCL-XL may be required to overcome resistance in tumor cells [52,59-60]. 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

Mutations in BCL2 have been detected in 3% of hematopoietic malignancies, including in 23% of diffuse large B-cell lymphoma (DLBCL) and 45% (28/62) of follicular lymphoma (FL) cases (COSMIC, Dec 2018). In the literature, BCL2 mutations have been reported in 9% of DLBCL cases [90], and occur more frequently in germinal center B-cell like DLBCL [90].

BCL2 protein expression was detected in 23/29 FL and 20/22 MZL samples in one study [66]. Co-occurring mutations in BCL2 are frequently observed in patients with the IGH-BCL2 rearrangement, likely as a result of somatic hypermutation normally occurring at the IGH locus [67]. BCL2 abnormalities have not been reported to have high prognostic impact in patients with FL [68-70], although one study reported inferior prognosis in patients with FL harboring a BCL2 abnormality than those without [71]. Expression of BCL2 mRNA is a strong predictor of shorter overall survival in patients with DLBCL, particularly among patients with the activated B-cell form of DLBCL [86,91].

FINDING SUMMARY

BCL2 encodes the B-cell CLL/lymphoma 2 protein, which is an integral outer mitochondrial membrane protein that blocks apoptotic cell death [84]. BCL2 acts as a proto-oncogene in B-cell neoplasms, where its expression is frequently deregulated due to gene translocation or amplification [78,85]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
BTG1

ALTERATION
Q42fs*38

POTENTIAL TREATMENT STRATEGIES

There are no therapies to directly address BTG1 alterations. In preclinical studies, downregulation of BTG1 has been reported to sensitize cells to radiation [92] but to reduce sensitivity to BCL2 inhibitors [93]. In preclinical studies, loss of BTG1 expression has also been implicated in loss of responsiveness to glucocorticoids in leukemic cells [94].

FREQUENCY & PROGNOSIS

BTG1 was originally identified in the context of chronic lymphocytic leukemia (CLL) as part of a t(8;12)(q24;q22) rearrangement that resulted in MYC overexpression [95]. BTG1 missense mutations are rare in cancer, with the highest frequency reported in 15/55 (27%) diffuse large B-cell lymphoma (DLBCL) samples in one study [67]. However, BTG1 deletions and loss have been frequently reported in B-cell malignancies, including Waldenström macroglobulinemia (WM; 87%) [96], chronic myeloid leukemia (CML-BC; 2/6) [97], and several subtypes of acute lymphocytic leukemia (ALL): BCR-ABL-positive ALL (31.8%)[97], Down syndrome-associated ALL (6.9-29%) [98-100], t(12;21) TEL-AML1 ALL (25%) [101], pediatric ALL (12%)[102], B-cell precursor ALL (BCP-ALL)(9-31%) [97,103], adolescent and adult ALL (9%) [104], and mixed-phenotype acute leukemia (MPAL; 4/18 combined from two studies) [97,105]. Although clonal analysis of BTG1 alterations suggested that BTG1 may be a driver mutation in leukemia [103], BTG1 alterations were not prognostic in multiple ALL subtypes [97-99,104]. BTG1 has been proposed as a biomarker of the treatment response in AML as BTG1 is detected at higher levels in normal samples and in samples from patients who are undergoing complete remission, but not in samples from individuals in non-remission state [106]. In the context of solid tumors, downregulation of BTG1 expression in tumor compared to normal tissue has been reported in breast [107-109], gastric [110], kidney [111], ovarian [112], nasopharyngeal [113], and thyroid [114] cancers, as well as NSCLC [115], esophageal squamous cell carcinoma (SCC)[116], and hepatocellular carcinoma (HCC) [117-118]. This downregulation correlated with inferior survival and/or adverse clinicopathologic features in these cancers [107,110-118]. Consistent with its role as a tumor suppressor, overexpression of BTG1 in a variety of cell types has been shown to inhibit proliferation and migration and induce apoptosis [101,108-109,111,113-114,116-117,119].

FINDING SUMMARY

B-cell translocation gene 1 (BTG1) encodes a tumor suppressor that interacts with a variety of transcriptional regulators, affecting cell proliferation, migration, invasion and survival [109,120-125]. Both the N-terminal and C-terminal regions of BTG1 are required for its tumor suppressor activities [120,126].

GENE
CREBBP

ALTERATION
Q1491K

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies available to directly address genomic alterations in CREBBP, but the use of histone deacetylase inhibitors has been proposed as one rational therapeutic strategy in the context of CREBBP mutations [127-128], and mutations in EP300 and/or CREBBP have been shown to increase the sensitivity of DLBCL and ALL cells to the HDAC inhibitor vorinostat [128-129]. HDAC inhibitors have been reported to induce apoptosis in glucocorticoid-resistant leukemic cells [130]. HDAC inhibitors, such as belinostat, romidepsin, and vorinostat are approved for the use in peripheral T-cell lymphoma (PTCL) patients and are in clinical trials for several cancer types, including myeloma [131]. A Phase 1 trial of vorinostat in combination with bortezomib reported that 27% of patients achieved a partial response and 59% had disease stabilization [132]. 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

Somatic mutations affecting CREBBP are most commonly reported in a subset of hematopoietic malignancies, including follicular lymphoma (FL), lymphoblastic leukemia, and up to 40% of diffuse large B-cell lymphoma (DLBCL) cases [90]. Transformed FLs, duodenal-type FLs, limited-stage typical FLs, and advanced-stage typical FL display CREBBP mutations in 54% (19/35), 68% (21/31), 82% (14/17), and 71% (171/241) of cases [133]. Another study similarly reported CREBBP mutation in 83% (15/18) of limited-stage FL cases, while in contrast, patients with pediatric-type nodal FL rarely harbored such alterations (1/26 cases) [134-135]. CREBBP was mutated in the majority of double-hit (DH) or triple hit (TH) lymphomas (80%; 16/20 case) assessed in one genomic analysis, being found in all TH lymphomas but only in DH lymphomas harboring rearrangements of MYC and BCL2 [136]. Patients with primary breast DLBCL harbored CREBBP mutations in 11% (2/18) of cases [137], while mutation was seen in 26% (5/26) of cases of primary cutaneous DLBCL [138] and 83% (5/6) of t(14;18)-negative DLBCLs [139]. In preclinical studies, CREBBP has been implicated as a tumor suppressor that disrupts B-cell development and promotes B-cell lymphomagenesis [140-142]. CREBBP mutation has been associated with worse overall survival, progression-free survival and event-free survival in DLBCL [143]. An increased frequency of CREBBP mutation was observed for patients with DLBCL who relapsed or were refractory to R-CHOP, relative to those with primary DLBCL who were treatment-naive (42% vs. 31%) [144]. CREBBP deletion was reported to significantly associate with shorter OS for patients with FL; however, deletion of a >1 Mb region on chromosome 16pm harboring the CREBBP locus associated with improved PFS and OS for patients treated with CHOP-RIT versus CHOP-R [145]. For treatment-naïve patients with FL, CREBBP mutation significantly associated with shorter PFS (HR=2.68) [146].

FINDING SUMMARY

CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase (HAT) activity. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE
MLL2

ALTERATION
W268*, R5432W

POTENTIAL TREATMENT STRATEGIES

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 [147]. MLL2 alterations are also observed in a number of solid tumor contexts (COSMIC, 2019), being especially prevalent in squamous cell lung carcinoma [148] and small cell lung carcinoma [149].

FINDING SUMMARY

MLL2 encodes an H_3K_4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling [150]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder [151].

GENE
TNFAIP3

ALTERATION
splice site 1906+2T>A

POTENTIAL TREATMENT STRATEGIES

There are no therapies that address the loss of TNFAIP3. A20 has multiple functions and is subject to a wide range of genomic lesions, thereby making it challenging to develop a unified therapeutic approach. Potential avenues targeting dysregulation of ubiquitination pathways include anti-CD20 therapies, such as rituximab, and proteasome inhibitors, such as bortezomib [152]. RNAi-mediated downregulation of TNFAIP3 has been reported to sensitize multiple myeloma cells to bortezomib [153].

FREQUENCY & PROGNOSIS

Monoallelic or biallelic deletion of TNFAIP3 has been reported in 46% (6/13) of Sézary syndrome cases [154], 11-50% of diffuse large B-cell lymphomas (DLBCLs) [155-156], 17-44% of mantle cell lymphomas (MCLs) [155], 11-32% of Hodgkin lymphomas (HLs)[157], 26% of follicular lymphomas (FLs) [155], 22% of non-HLs (NHLs)[155], and 17% of MALT lymphomas [155]. Genomic loss of TNFAIP3 occurs more frequently in activated B-cell like (ABC-) DLBCL than in germinal center B-cell like (GCB-) DLBCL [155] and has not been detected in DLBCL transformed from chronic lymphocytic leukemia (Richter syndrome) [158]. Loss of chromosome 6q23, containing the TNFAIP3 locus, was reported in 53% (10/19) of primary central nervous system lymphomas [159]. TNFAIP3 mutations, which are predominantly truncating or inactivating, have been reported in 3.7% of hematopoietic and lymphoid malignancies in COSMIC (2018) and in the scientific literature in 36-61% of primary mediastinal B-cell lymphomas (PMBLs) [160-161], 54% (15/28) of DLBCLs [155], 44% (16/36) of HLs [160], 17% (3/18) of MCLs [155], and 11% of FLs [162]. In one study, TNFAIP3 mutations were associated with poorer overall and progression-free survival in patients with ABC-DLBCL who were treated with R-CHOP [161], whereas another reported no prognostic significance of TNFAIP3 mutation in ABC-DLBCL in a cohort primarily treated with CHOP alone [163]. Loss of A20 expression was reported in 27% of DLBCLs, 24% of HLs, 19% of FLs, 13% of MCLs, and 8% of PMBLs [164]; restoring A20 expression into either HL or NHL cell lines induced apoptosis in preclinical studies [155,160]. In ocular adnexal MALT lymphomas, TNFAIP3 mutation or loss was found to be mutually exclusive from MALT1- or IGH-involving rearrangements [165].

FINDING SUMMARY

TNFAIP3 encodes tumor necrosis factor alpha-induced protein 3, also known as A20, a regulator of NF-kB signaling and apoptosis [166] that has both ubiquitin ligase and deubiquitinase activities [167-168] and whose loss or inactivation may be tumorigenic [155]. TNFAIP3 is frequently deleted or mutated in lymphoma, where it functions as a tumor suppressor [155], but its expression and function are context dependent in solid tumors [166,169-172], leukemia [173-175], and multiple myeloma [176-177]. TNFAIP3 mutations that disrupt the A20p37 chain (amino acids 371–790), which mediates ubiquitin ligase activity and interaction with the cIAP1/TRAF2 complex [167,178], are predicted to be inactivating. In T-cells, cleavage of A20 codon R439 by MALT1 has been shown to upregulate NFkB signaling; R439A has been shown to block MALT1-mediated NF-kB activation [179]; however, the function of R439 mutations outside of the context of T-cell lymphoma has not been reported.

GENE
ZMYM3

ALTERATION
G49fs*13

POTENTIAL TREATMENT STRATEGIES

There are no targeted therapies to address genomic alterations in ZMYM3.

FREQUENCY & PROGNOSIS

ZMYM3 mutations are rare in solid tumors and hematological cancers, being most frequently reported in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) (2-4.3% of cases) [180].

FINDING SUMMARY

ZMYM3, also known as ZNF261, is a zinc-finger containing protein capable of binding to methylated histones [181]. ZMYM3 is a component of multi-protein complexes containing histone deacetylase activity that function to silence gene expression by modifying chromatin structure [182-183]. However, the role of ZMYM3 in cancer is not clear. Disruptions at the ZMYM3 locus have been linked to intellectual disability [184-185].

Venetoclax

Assay findings association

IGH
IGH-BCL2 rearrangement

AREAS OF THERAPEUTIC USE

Venetoclax is a small-molecule BCL-2 inhibitor. It is FDA approved for the treatment of patients with chronic lymphocytic leukemia (CLL) whose tumors harbor chromosome 17p deletion and who have received at least one prior therapy. It is also approved in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of patients 75 years of age or older with newly diagnosed acute myeloid leukemia (AML), or who have comorbidities that preclude use of intensive induction chemotherapy.

GENE ASSOCIATION

Based on clinical and preclinical data in non-Hodgkin lymphoma[49,51] , multiple myeloma[50], and chronic lymphocytic leukemia[51], BCL2 alterations that lead to increased expression of BCL-2 may predict sensitivity to BCL-2 inhibitors such as venetoclax.

SUPPORTING DATA

A Phase 1 study of patients with non-Hodgkin lymphoma (NHL) treated with venetoclax monotherapy reported an ORR of 44% (47/106), median progression-free survival of 6 months, and 12-month overall survival rate of 70%; ORR was 100% (4/4) in Waldenstrom macroglobulinemias, 75% (21/28) in mantle cell lymphoma (MCL), 67% (2/3) in marginal zone lymphoma (MZL), 38% (11/29) in follicular lymphoma (FL), and 18% (6/34) in diffuse large B-cell lymphomas (DLBCL); ORR was similar with low (n=5) and high (n=41) BCL-2 expression (n=41)[186]. Early report of a Phase 1/1b study examining a combination of venetoclax and ibrutinib for patients with relapsed or refractory MCL reported responses in 3/3 patients with one complete response[187]. A Phase 1 trial of venetoclax in combination with bendamustine and rituximab to treat patients with relapsed or refractory NHL reported an ORR of 73% (29/40), including 87% (20/23) in FL, 75% (3/4) in MZL, and 46% (6/13) in DLBCL[188]; objective responses were observed in 2 (1 CR and 1 PR) of 3 MYC/BCL-2 double-positive tumors[189]. Interim data release from a Phase 2 study for the treatment of patients with relapsed or refractory FL reported a 33% ORR for venetoclax in combination with rituximab (64% among non-refractory patients), 56-68% ORR for venetoclax in combination with rituximab and bendamustine and a 64% ORR for a combination of rituximab and bendamustine; increased toxicity was noted in the venetoclax+rituximab+bendamustine arm[190].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however the agents listed in this report may have little or no evidence in the patient's tumor type.

CLINICAL TRIALS

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. 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.

GENE
IGH

ALTERATION
IGH-BCL2 rearrangement

RATIONALE
Based on preclinical evidence, BET domain inhibitors have been reported to inhibit IGH-mediated transcriptional activation and may therefore be beneficial here. Several strategies are under investigation to address amplification or overexpression of BCL2 in human cancer. One such strategy involves targeting BCL-2 directly. Another is to indirectly increase the expression of proteins that antagonize the anti-apoptotic activity of BCL-2.

NCT01943851

PHASE 1

A Dose Escalation Study to Investigate the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD) and Clinical Activity of GSK525762 in Subjects With Relapsed, Refractory Hematologic Malignancies

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Colorado, New York, Texas, East Melbourne (Australia), Seoul (Korea, Republic of), Barcelona (Spain), Madrid (Spain), Málaga (Spain), Cambridge (United Kingdom), London (United Kingdom)

NCT02543879

PHASE 1

Study of a Novel BET Inhibitor FT-1101 in Patients With Relapsed or Refractory Hematologic Malignancies

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: California, Florida, Illinois, Maryland, North Carolina, Tennessee, Texas

NCT02611323

PHASE 1/2

A Study of Obinutuzumab, Rituximab, Polatuzumab Vedotin, and Venetoclax in Relapsed or Refractory Follicular Lymphoma (FL) or Diffuse Large B-Cell Lymphoma (DLBCL)

TARGETS
CD20, BCL2, CD79B

LOCATIONS: Arizona, Connecticut, Bergamo (Italy), Meldola (Italy), Ravenna (Italy), Rimini (Italy), Florida, Georgia, Kentucky, Milano (Italy), Michigan, New Jersey, St. Leonards (Australia), Waratah (Australia), Pennsylvania, Torino (Italy), Woolloongabba (Australia), Adelaide (Australia), Hobart (Australia), Texas, Melbourne (Australia)

NCT03205176

PHASE 1

AZD5153 in Patients With Relapsed or Refractory Solid Tumors, Including Lymphomas

TARGETS
BRD4

LOCATIONS: Florida, Oklahoma, Tennessee

NCT02992522

PHASE 1

Obinutuzumab, Venetoclax, and Lenalidomide in Treating Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma

TARGETS
CD20, BCL2

LOCATIONS: Ohio

NCT02956382

PHASE 1/2

Ibrutinib and Venetoclax in Relapsed and Refractory Follicular Lymphoma

TARGETS
BCL2, BTK

LOCATIONS: District of Columbia, New Jersey

CLINICAL TRIALS

NCT03135262

PHASE 1/2

A Study of Obinutuzumab in Combination With Idasanutlin and Venetoclax in Participants With Relapsed or Refractory (R/R) Follicular Lymphoma (FL) or Rituximab in Combination With Idasanutlin and Venetoclax in Participants With R/R Diffuse Large B-Cell Lymphoma (DLBCL)

TARGETS
CD20, BCL2, MDM2

LOCATIONS: Nedlands (Australia), Würzburg (Germany), Gyeonggi-do (Korea, Republic of), Seoul (Korea, Republic of), Christchurch (New Zealand)

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Barcelona (Spain), Madrid (Spain)

APPENDIX Variants of Unknown Significance

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.

BCL2
E165D, G194D, G197S, N192H, and P90S

BRCA2
T3249S

CBL
E138fs*14 and G413D

CUX1
Q321H

EPHA7
R426Q

ETS1
I14N

FGFR3
A281T

GPR124
L1280P

HIST1H2BO
V119fs*?

KDM5A
N379S

MSH3
A60_A62del

PIK3CG
K1045I

PIM1
V155M

RELN
V2065I

SETBP1
W532*

TYK2
Y604F

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*			

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

APPENDIX Genes Assayed in FoundationOne®Heme

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)

The median exon coverage for this sample is 797x

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 status	At ≥20% tumor nuclei	97.0%
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 status	Positive Predictive Value (PPV)	>95.0%
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	

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).

Microsatellite status, which is a measure of microsatellite instability (MSI), is determined by assessing indel characteristics at 114 homopolymer repeat loci in or near the targeted gene regions of the FoundationOne Heme test. Microsatellite status is assayed for all FoundationOne Heme samples and may be reported as "MSI-High", "MSI-Intermediate", "MS-Stable", or "Cannot Be Determined". Microsatellite status is reported as "Cannot Be Determined" if the sample is not of sufficient quality to be confidently determined.

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne and FoundationOne Heme tests and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne and FoundationOne Heme samples and may be reported as “TMB-High”, “TMB-Intermediate”, “TMB-Low”, or “Cannot Be Determined”. TMB results, which are rounded to the nearest integer, are determined as follows: TMB-High corresponds to greater than or equal to 20 mutations per megabase (Muts/Mb); TMB-Intermediate corresponds to 6-19 Muts/Mb; TMB-Low corresponds to fewer than or equal to 5 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.

For additional information specific to the performance of this specimen, please contact Foundation Medicine, Inc. at 1-888-988-3639.

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 Alterations and Therapies

Biomarker Findings

Appear at the top of the report, but are not ranked higher than Genomic Findings.

Genomic Findings

Therapies with Clinical Benefit In Patient's Tumor Type → Therapies with Clinical Benefit in Other Tumor Type → Clinical Trial Options → No Known Options (If multiple findings exist within any of these categories, the results are listed alphabetically by gene name.)

Therapies

Sensitizing therapies → Resistant therapies. (If multiple therapies exist within any of these categories, they are listed alphabetically by therapy name.)

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

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 complies with all European Union (EU) requirements of the IVD Directive 98/79EC. As such, the FoundationOne Heme Assay has been registered for CE mark by our EU Authorized Representative, Qarad b.v.b.a, Pas 257, B-2440 Geel, Belgium.

CE

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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