FOUNDATIONONE®HEME

PATIENT

TUMOR TYPE
B-lymphoblastic leukemia-lymphoma (B-ALL)

REPORT DATE

TRF#

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, sarcomas, and pediatric cancers.

PATIENT

DISEASE B-lymphoblastic leukemia-lymphoma (B-ALL)
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-Low (1 Muts/Mb)

Genomic Findings

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

ABL1 BCR-ABL1 fusion (p210)
RUNX1 R166Q

5 Therapies with Clinical Benefit
0 Therapies with Lack of Response
4 Clinical Trials

BIOMARKER FINDINGS
Microsatellite status - MS-Stable
Tumor Mutational Burden - TMB-Low (1 Muts/Mb)

GENOMIC FINDINGS
***ABL1* -** BCR-ABL1 fusion (p210)
4 Trials *see p. 7*

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)
Dasatinib	Bosutinib
Imatinib	Nilotinib
Ponatinib	

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.

***RUNX1* -** R166Q ..... p. 4

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

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 [6]. MSI at any level has been reported at variable levels in samples from patients with acute lymphoblastic leukemia (ALL), including 12% (3/24) to 38% (6/16) of common ALL [7-8], 4.2% (4/96) to 14% (5/36) of B-cell ALL (B-ALL) [9-10], and 9% (1/11) to 33% (2/6) of T-cell ALL (T-ALL) [10-12]. In pediatric patients with ALL, MSI at any level has been observed in 2.5% (1/40) to 12.5% (4/32) of common ALL [13-14], 10% (1/10) to 33% (3/6) of T-ALL [11,14-15], and 6% (4/63) of B-ALL [9] or absent in B-ALL [11,14]. MSI-H has been reported in 4% (1/24) to 19% (3/16) of ALL [7-8], 8% (3/36) of B-ALL [10], and 9% (1/11) of T-ALL [10]. Several studies have reported an association between increased MSI and relapsed ALL after chemotherapy [13,15-18]; however, one study did not [9].

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 [19]. 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 [19-21]. 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 [22-24]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins [19,21,23-24].

BIOMARKER

Tumor Mutational Burden

CATEGORY

TMB-Low (1 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 [25], anti-PD-L1 [26-29], and anti-PD-1 therapies [4,30-31]; 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)[30]. 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 [4,30-31]. 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 [32] or nivolumab [33], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab [34], 2 pediatric patients with biallelic mismatch repair deficiency-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab [35], 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 [36]. For patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab [25,37] and anti-PD-1/anti-PD-L1 treatments [27]. 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)[26], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival [28]. 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[38].

FREQUENCY & PROGNOSIS

Acute lymphocytic leukemia (ALL) harbors a median TMB of 1.7 mutations per megabase (muts/Mb), and 1.3% of cases have high TMB (>20 muts/Mb)[39]. Reports of high TMB are generally rare in leukemia [39]. In a study of 92 patients with various hematologic malignancies, elevated TMB levels (>10 muts/Mb) were not detected in AML (0/5) or ALL (0/1) cases analyzed[40]. Increased TMB was observed for some patients at relapse in a study of pediatric ALL [41].

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 [42-43] and cigarette smoke in lung cancer [30,44], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes [45-49], and microsatellite instability (MSI) [45,48-49]. This sample harbors a low TMB. Compared to patients with tumors harboring higher TMB levels, patients with tumors harboring low TMB levels have experienced lower rates of clinical benefit from treatment with immune checkpoint inhibitors, including anti-CTLA-4 therapy in melanoma [25], anti-PD-L1 therapy in urothelial carcinoma [26], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer [4,30].

GENE
ABL1

ALTERATION
BCR-ABL1 fusion (p210)

POTENTIAL TREATMENT STRATEGIES

The BCR-ABL fusion protein is the best studied ABL1 alteration and results in an activated ABL kinase; therapies to inhibit activated ABL1 have focused on BCR-ABL-positive hematological malignancies [50-51]. Tyrosine kinase inhibitors such as imatinib, nilotinib, dasatinib, ponatinib, and bosutinib are FDA approved for the treatment of hematological malignancies with BCR-ABL fusions. Treatment with these therapies has been correlated with increased responses for patients with ALL or CML, compared to treatment regimens lacking tyrosine kinase inhibitors [52-56].

FREQUENCY & PROGNOSIS

The p210 BCR-ABL fusion has been predominantly reported in CML patients, as opposed to p190 present in ALL patients, and has been associated with higher BCR-ABL transcript expression than p190 and with transformation of CML to blast crisis; however, p210 Ph+ ALL cases have also been reported [57-61]. The Philadelphia chromosome (Ph+) is present in 95% of chronic myeloid leukemia (CML) patients, as well as patients with acute lymphoblastic leukemia (ALL) and <5% of acute myelogenous leukemia (AML) cases; Ph+ ALL accounts for 2-5% of pediatric patients, 20-40% of adults, and >50% of individuals over the age of 50 [58-59,62-69]. Clinical studies have failed to detect consistent difference in responses of ALL patients with p190 versus p210 to imatinib or allogeneic transplantation [60,66,70-74], although residual p190 transcript level has been associated with higher risk of relapse after transplantation than residual p210 [75-76].

FINDING SUMMARY

ABL1 encodes the Abelson protein tyrosine kinase, which is involved in cell growth and survival [77]. Activating alterations in ABL1 kinase have been reported in leukemia, including the BCR-ABL1 translocation carried on the Philadelphia chromosome in chronic myelogenous leukemia (CML) [51,78]. The fusion reported here is similar to the oncogenic p210 BCR-ABL fusion that is found in 64% of patients with CML [79-81].

GENE
RUNX1

ALTERATION
R166Q

POTENTIAL TREATMENT STRATEGIES

There are no therapies available to directly target inactivating alterations in RUNX1. Limited clinical[82-83] and preclinical [84] data suggest that RUNX1 alterations, rearrangements in particular, may be associated with sensitivity to DNMT inhibitors, such as the approved agents azacitidine and decitabine. However, multiple clinical studies have reported that RUNX1 is not a significant biomarker for efficacy of these therapies[82,85-87]. Similarly, on the basis of limited clinical [88] and preclinical [89-91] evidence, RUNX1 rearrangements may predict sensitivity to HDAC inhibitors. However, further studies are required to establish clinical significance.

FREQUENCY & PROGNOSIS

RUNX1 mutations have been reported in 3% of all acute lymphoblastic leukemias (ALLs) analyzed in COSMIC; they were detected in 1.5% of B-cell ALL cases and in 6% of T-cell ALL cases (COSMIC, Sep 2018). In one study of 90 adult patients with T-cell ALL, RUNX1 mutations were reported in 15.5% of cases [92]. In patients with T-cell ALL, RUNX1 mutations have been associated with poorer overall survival [92].

FINDING SUMMARY

RUNX1 encodes a transcription factor that is involved in developmental gene expression programs and hematopoiesis. It is a frequent site of translocation and mutation in myeloid cancers, and it functions as a tumor suppressor in this context [93-94]. Reports of RUNX1 translocations and mutations in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are common. RUNX1 plays a context-dependent role in epithelial cells and has been implicated as both a tumor suppressor and oncogene in different types of solid tumors [95]. Mutations at R166, more frequently described as R139 based on an alternative transcript, including R139Q and R139G, have been characterized as inactivating, and R139Q has been reported as a germline mutation in familial myeloid leukemia predisposition syndromes [96-100]. Other changes at this position are predicted to be inactivating as well.

Dasatinib

Assay findings association

ABL1
BCR-ABL1 fusion (p210)

AREAS OF THERAPEUTIC USE

Dasatinib is a kinase inhibitor that targets the BCR-ABL fusion protein, SRC family kinase receptors, KIT, EPHA2, and PDGFR-beta. It is FDA approved for the treatment of certain subtypes of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL).

GENE ASSOCIATION

Activating ABL1 fusions may predict sensitivity to dasatinib.

SUPPORTING DATA

Dasatinib is approved for Ph+ ALL based on a Phase 2 study that demonstrated major hematologic responses (MaHRs) for 42% (15/36) of imatinib-resistant or -intolerant patients[62,101] . As first-line therapy for Ph+ ALL, dasatinib combined with HCVAD (alternating hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and high-dose cytarabine and methotrexate) followed by maintenance therapy achieved a complete remission rate (CRR) of 96% (69/72), median disease-free survival of 31 months, and median OS of 47 months[102-103] . Analysis of Phase 2 data for patients with newly diagnosed Ph+ ALL suggests that ponatinib plus HCVAD may result in superior outcomes, including longer OS, compared to dasatinib plus HCVAD[104]. Patients with relapsed Ph+ ALL or blast-phase CML experienced a 3-year OS rate of 26% and 70%, respectively, and a combined CRR of 71% (24/34) on dasatinib plus HCVAD[105]. In the Children's Oncology Group (COG) trial AALL0622, newly diagnosed pediatric patients with Ph+ ALL treated with a combination of dasatinib and intensive chemotherapy exhibited 5-year OS and event-free survival (EFS) rates of 86% and 60%, respectively; patients with IKZF1 deletion experienced inferior OS (80% vs. 100%; p= 0.04) and EFS (52% vs. 82%; p=0.04)[106]. Five-year OS did not significantly differ between patients with Ph+ ALL receiving chemotherapy in conjunction with dasatinib in COG trial AALL0622 (86%)[106] or imatinib in COG trial AALL0031 (81%)[107]. Post-transplant maintenance therapy with tyrosine kinase inhibitors, including dasatinib, is associated with improved outcomes for patients with Ph+ ALL in retrospective studies[108-109] . For elderly patients with newly diagnosed Ph+ ALL, dasatinib plus low-intensity chemotherapy achieved a CRR of 96% and a 5-year OS rate of 36%[110-111] . A Phase 1 trial of dasatinib for pediatric patients with relapsed or refractory leukemia observed MaHRs for 47% (8/17) of cases with advanced-phase CML or Ph+ ALL and a median MaHR duration of 4.4 months[112]. Case reports describe pediatric or young adult patients with ABL1-positive T-cell ALL (ABL1 amplification or NUP214-ABL1 fusion) who achieved remissions on dasatinib alone or combined with chemotherapy[113-114] .

Imatinib

Assay findings association

ABL1
BCR-ABL1 fusion (p210)

AREAS OF THERAPEUTIC USE

Imatinib targets the BCR-ABL fusion protein, PDGFR, and KIT. It is FDA approved for the treatment of KIT-positive gastrointestinal stromal tumors (GIST), Ph+ chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL), myelodysplastic syndrome/myeloproliferative syndrome (MDS/MPS), aggressive systemic mastocytosis without a D816V KIT mutation, hypereosinophilic syndrome and/or chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans.

GENE ASSOCIATION

Activating ABL1 fusions may predict sensitivity to imatinib.

SUPPORTING DATA

In clinical studies, patients with multiple stages of CML or BCR-ABL-positive ALL were able to achieve hematological and sometimes cytological remission following imatinib treatment[52,115-116] . Responses to imatinib have also been reported in ALL patients harboring ETV6-ABL1 or NUP214-ABL1 fusions[117-118] .

Ponatinib

Assay findings association

ABL1
BCR-ABL1 fusion (p210)

AREAS OF THERAPEUTIC USE

Ponatinib is a multikinase inhibitor targeting BCR-ABL, RET, KIT, FLT-3, PDGFRs, VEGFRs, FGFRs, and other tyrosine kinases. It is FDA approved for the treatment of advanced, T315I-mutated chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), as well as for CML and Ph+ ALL patients for whom no other tyrosine kinase inhibitor is indicated.

GENE ASSOCIATION

Activating fusions in ABL1 may predict sensitivity to ponatinib.

SUPPORTING DATA

A Phase 2 study reported major hematologic and cytogenetic responses in 41% (13/32) and 47% (15/32), respectively, of patients with Ph+ ALL[119]. In particular, among the 22 Ph+ ALL patients with the T315I mutation treated with ponatinib, 36% had a major hematologic response, 41% had a major cytogenetic response, and 32% had a complete cytogenetic response[119]. In a Phase 2 study of ponatinib in combination with chemotherapy (HCVAD, high-dose MTX/Ara-C) as first-line therapy for patients with Ph+ ALL, the 3-year complete response duration and overall survival rate were 79% and 82%, respectively; at the time of reporting, 96% (50/52) of patients had achieved minimum residual disease[120].

Bosutinib

Assay findings association

ABL1
BCR-ABL1 fusion (p210)

AREAS OF THERAPEUTIC USE

Bosutinib is a third-generation tyrosine kinase inhibitor that targets both ABL and SRC kinases. It is FDA approved to treat newly diagnosed chronic phase Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) or chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy.

GENE ASSOCIATION

Activating ABL1 fusions may predict sensitivity to bosutinib.

SUPPORTING DATA

For patients with acute lymphoblastic leukemia (ALL) treated with bosutinib, 9% (2/22) had a hematologic response[121]. In a Phase 1 trial combining the CD22 antibody inotuzumab ozogamicin and bosutinib for Ph+, T315I-negative ALL or lymphoid blast phase CML, 11/14 patients achieved a complete response (CR) or CR with incomplete blood count recovery (CRi); of the 11 responders, 10 (91%) achieved complete cytogenetic remission (CCyR), and 6 (55%) had undetectable BCR-ABL[122]. A retrospective analysis reported that a heavily pretreated patient with Ph+ ALL and an ABL1 V299L mutation achieved a CR and eventual minimal residual disease (MRD) negativity from the combination of bosutinib and the CD3/CD19 bispecific antibody blinatumomab[123]. Bosutinib facilitated remissions in clinical studies of CML, including a 73% response rate for those who had failed prior imatinib or nilotinib therapies[124-127] . Two Phase 3 studies for patients with newly diagnosed, chronic phase CML (CP-CML) reported significantly higher rates of major molecular response (MMR) at 12 months following treatment with bosutinib versus imatinib (BELA, 41% vs. 27%; and BFORE, 47.2% and 36.9%)[128-129] . An elderly patient whose CML transformed to B-ALL achieved a complete hematologic response after 14 months of fourth-line bosutinib treatment[130].

Nilotinib

Assay findings association

ABL1
BCR-ABL1 fusion (p210)

AREAS OF THERAPEUTIC USE

Nilotinib targets tyrosine kinases such as ABL (including BCR-ABL), PDGFRs, KIT, CSF1R, DDR1, and DDR2. It is FDA approved to treat newly diagnosed pediatric or adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, adults with Ph+ CML in chronic or accelerated phase with resistance or intolerance to prior therapy including imatinib, and pediatric patients with Ph+ CML in chronic phase with resistance or intolerance to prior tyrosine-kinase inhibitor therapy.

GENE ASSOCIATION

Activating fusions in ABL1 may predict sensitivity to nilotinib.

SUPPORTING DATA

In a Phase 2 study of the effects of nilotinib combined with chemotherapy in patients with Ph+ acute lymphoblastic leukemia (ALL), 91% of patients achieved complete hematologic remission (HCR); the 2-year hematologic relapse-free survival (HRFS) rate was 72% for 82 patients that achieved HCR, and the 2-year overall survival rate was 72%[131]. Nilotinib combined with chemotherapy was well tolerated and highly effective with a 97% complete response (CR) in elderly patients with newly diagnosed Ph+ ALL in another Phase 2 trial[132]. In a Phase 1 study of nilotinib in patients with imatinib-resistant Ph+ CML or ALL, 15.4% (2/13) patients with Ph+ ALL responded to nilotinib[133].

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
ABL1

ALTERATION
BCR-ABL1 fusion (p210)

RATIONALE
Therapies that inhibit the kinase activity of ABL may be appropriate for a patient with an activating ABL1 fusion.

NCT02081378

PHASE 1

A Phase I, Multicenter, Open-label Study of Oral ABL001 in Patients With Chronic Myelogenous Leukemia (CML) or Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia (Ph+ ALL)

TARGETS
ABL, BCR-ABL, KIT, PDGFRs, DDR2, SRC

LOCATIONS: Paris Cedex 10 (France), Kobe-shi (Japan), Massachusetts, Michigan, New York, Oregon, Roma (Italy), Seoul (Korea, Republic of), Adelaide (Australia), Texas, Utah, Bordeaux (France), Berlin (Germany), Frankfurt (Germany), Jena (Germany), Amsterdam (Netherlands), Singapore (Singapore), Madrid (Spain)

NCT03263572

PHASE 2

Phase II Study of the Combination of Blinatumomab and Ponatinib in Patients With Philadelphia Chromosome (Ph)-Positive and/or BCR-ABL Positive Acute Lymphoblastic Leukemia (ALL)

TARGETS
ABL, FGFRs, FLT3, KIT, PDGFRs, RET, VEGFRs

LOCATIONS: Texas

NCT02420717

PHASE 2

A Phase II Study of the Combination of Ruxolitinib or Dasatinib With Chemotherapy in Patients With Philadelphia Chromosome (Ph)-Like Acute Lymphoblastic Leukemia (ALL)

TARGETS
CD20, JAK2, JAK1, ABL, DDR2, KIT, PDGFRs, SRC

LOCATIONS: Texas

NCT01424982

PHASE 2

Phase II Study of Combination of Hyper-CVAD and Ponatinib in Patients With Philadelphia (PH) Chromosome Positive and/or BCR-ABL Positive Acute Lymphoblastic Leukemia (ALL)

TARGETS
ABL, FGFRs, FLT3, KIT, PDGFRs, RET, VEGFRs

LOCATIONS: Texas

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

BRCA2 A2351G	***CIITA*** P699L and V642I	***CREBBP*** F1358S	***ETS1*** V13L
GPR124 C1196Y	***IKZF3*** T190M	***IRS2*** A512T	***KMT2C (MLL3)*** S4300P
MSH6 K1358fs*2	***NSD1*** S822C	***NUP98*** P1085L	***PDGFRB*** A366T
PTCH1 K838T	***PTPRO*** R480W	***STAT4*** L307F	***YY1AP1*** C46_R48del

APPENDIX Genes Assayed in FoundationOne®Heme

FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies, sarcomas, and pediatric cancers 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 883x

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, sarcomas and pediatric cancers. 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, pediatric cancers.

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, Cipalstraat 3, 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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