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.