FOUNDATIONONE®HEME

PATIENT

TUMOR TYPE
Acute myeloid leukemia (AML) (NOS)

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 Acute myeloid leukemia (AML) (NOS)
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 (4 Muts/Mb)

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

IDH2 R140Q - subclonal†
TET2 S1494* - subclonal†
FANCE V311fs*2
GNAS R201S
KDM6A Q1304*, splice site 2832+1G>A, E206fs*11
RUNX1 S303*, P425L - subclonal†
SF3B1 K700E

† See About the Test in appendix for details.

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

BIOMARKER FINDINGS	ACTIONABILITY	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - TMB-Low (4 Muts/Mb)	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)**
IDH2 - R140Q - subclonal	Azacitidine	none
	Decitabine	
	Enasidenib	
10 Trials *see p. 10*	Venetoclax	
TET2 - S1494* - subclonal	Azacitidine	none
10 Trials *see p. 13*	Decitabine	

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 acute myeloid leukemia (AML), MSI at any level has been reported at incidences from 6-56% [6-13]; however, contradicting studies reported an absence of MSI in AML [14-15]. Similarly, MSI-H has been observed with incidences of 3–32% [8,10-11,13] or reported as absent in AML [6,14]. 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 [16]. In a large study of 1,394 patients with de novo or therapy-related AML, MSI-H was not observed; however, 4.8% of cases demonstrated instability at one microsatellite locus [17]. In addition, a small number of studies have not found a significant correlation of MSI with relapsed AML [10], nor with progression from MDS to AML [18], and other publications have reported a high incidence (20–32%) of MSI in de novo AML/MDS [11-13,19]. In contrast, other studies have reported increased incidences of MSI in relapsed or therapy-related AML/MDS compared to de novo disease [9,13,19-24], and a cell lineage analysis of AML/CML progression found increased MSI associated with relapsed disease after chemotherapy in 3/6 patients [25]. Therefore, the role of MSI in MDS/AML progression and resistance to chemotherapy is unclear. One study has suggested that organ transplant patients are at higher risk of developing AML/MDS as a result of prolonged immunosuppression, and reported all 7 such patients analyzed exhibited MSI, with 6/7 being MSI-H [26].

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 [27]. 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 [27-29]. 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 [30-32]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins [27,29,31-32].

BIOMARKER
Tumor Mutational Burden

CATEGORY
TMB-Low (4 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 [33], anti-PD-L1 [34-37], and anti-PD-1 therapies [4,38-39]; 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)[38]. 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 [4,38-39]. 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 [40] or nivolumab [41], a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab [42], 2 pediatric patients with biallelic mismatch repair deficiency-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab [43], 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 [44]. For patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab [33,45] and anti-PD-1/anti-PD-L1 treatments [35]. 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)[34], and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival [36]. 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[46].

FREQUENCY & PROGNOSIS

Acute myeloid leukemia (AML) harbors a median TMB of 1.7 mutations per megabase (muts/Mb), and 0% of cases have high TMB (>20 muts/Mb)[47]. Reports of high TMB are generally rare in leukemia [47]. 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[48]. Published data investigating the prognostic implications of TMB in AML are limited (PubMed, Oct 2018).

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 [49-50] and cigarette smoke in lung cancer [38,51], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes [52-56], and microsatellite instability (MSI) [52,55-56]. 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 [33], anti-PD-L1 therapy in urothelial carcinoma [34], and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer [4,38].

GENE
IDH2

ALTERATION
R140Q - subclonal

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical responses in patients with AML and preclinical data, IDH2 mutations may predict response to mutant-selective IDH2 inhibitors such as enasidenib [57-59], BCL-2 inhibitors such as venetoclax[60-62], DNA methyltransferase inhibitors such as azacitidine and decitabine [63-68], or combination of enasidenib and azacitidine[69]. In Phase 1/2 studies of enasidenib for patients with IDH2-mutated advanced hematological malignancies, overall response rates of 40.3% and 53% were achieved for patients with relapsed/refractory AML and myelodysplastic syndrome (MDS), respectively [57]. In preclinical studies, enasidenib induced differentiation in human AML cell lines and ex vivo cultures [58], a phenotype also observed clinically [57,59].

FREQUENCY & PROGNOSIS

In the TCGA dataset, IDH2 mutation was observed in 10% of acute myeloid leukemia (AML) cases [70]. Compared with other IDH2 or IDH1 mutations, R140Q is associated with a more favorable prognosis for AML patients, particularly in the absence of FLT3 mutations [71-73], although this may not hold true for all treatment regimens, such as cytarabine and idarubicin [74].

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis [75]. Amino acids 140 and 172 are hotspots for cancer-related mutations in IDH2 [76]. Functional studies have reported that mutation of R140 or R172, such as observed here, alters IDH2 enzymatic activity, resulting in gain-of-function activity and the production of the potential oncometabolite, D-2-hydroxyglutarate (2-HG)[75-80]. This leads to downstream effects that are associated with tumorigenesis [78,81], and research suggests that hotspot IDH gene mutations could be early stage events in specific cancers [81-82].

GENE
TET2

ALTERATION
S1494* - subclonal

POTENTIAL TREATMENT STRATEGIES

TET2 loss or inactivating mutations may lead to increased DNA methylation and may predict sensitivity to DNA methyltransferase (DNMT) inhibitors such as the FDA-approved therapies azacitidine and decitabine. TET2 mutation status in myelodysplastic syndrome (MDS) was significantly associated with better response rates to the DNMT inhibitors azacitidine and/or decitabine [68,83-84]. In other clinical studies, patients with TET2-mutated angioimmunoblastic T-cell lymphoma (AITL) were reported to achieve complete responses to azacitidine[85-87].

FREQUENCY & PROGNOSIS

TET2 mutations have been reported in 8-27% of acute myeloid leukemia (AML) cases [70,72,88-93]. Although in some studies TET2 mutation correlated with poor prognosis in favorable-risk cytogenetically normal AML [88,93], biallelic CEBPA-mutated AML [94], and AML with intermediate-risk cytogenetics [89-90], other studies have found no association between TET2 mutation and survival [91-92]. In pediatric patients with AML treated with intensive chemotherapy, lower TET2 expression was associated with shorter overall survival, event-free survival, and disease-free survival, whereas TET2 expression had no significant effect on outcome in adult patients[95]. TET2 exon 2 skipping has been associated with a favorable outcome in adult patients with AML treated with intensive chemotherapy but with unfavorable outcome in adult patients treated with intensive chemotherapy plus gemtuzumab ozogamicin and in pediatric patients [96].

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation [97-98]. TET2 alterations that impact critical residues or result in the disruption or loss of the catalytic domain (amino acids 1129-1936), such as seen here, are predicted to impair the tumor suppressor activity of TET2 [99-103]. DNMT3A/TET2/ASXL1 mutations have been associated with clonal hematopoiesis of indeterminate potential (CHIP) in hematologic malignancies [104-108].