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].

GENE
FANCE

ALTERATION
V311fs*2

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies that directly address alterations in FANCE. However, somatic alterations in Fanconi anemia pathway genes may predict cancer sensitivity to DNA-damaging drugs, such as cisplatin or mitomycin C, and to PARP inhibitors [109-112]. However, there are limited data showing that these inhibitors are effective for patients with FANCE alterations.

FREQUENCY & PROGNOSIS
Somatic mutations in FANCE are infrequently observed in human malignancies (COSMIC, 2018).

FINDING SUMMARY
FANCE encodes a key component of an eight protein (FANCA/B/C/E/F/G/L/M) Fanconi anemia (FA) nuclear E3 ubiquitin ligase complex. This complex is involved in DNA repair and is essential for prevention of chromosome breakage caused by DNA damage[113]. Upon DNA damage or during the S-phase of the cell cycle, the FA complex is activated and recruited to the sites of DNA damage/DNA repair. The complex then activates FANCD2 and FANCI via mono-ubiquitination, leading to their co-localization with FANCD1/BRCA2, BRCA1, RAD51, PCNA and other proteins at the DNA repair foci on chromatin. Germline mutations in FANCE cause Fanconi anemia, a clinically heterogeneous disorder involving various developmental abnormalities as well as predisposition to cancer; underlying these phenotypes are defects in DNA repair [114].

GENE
GNAS

ALTERATION
R201S

POTENTIAL TREATMENT STRATEGIES
There are no therapies targeted to GNAS mutation in cancer.

FREQUENCY & PROGNOSIS
The highest incidences of GNAS mutations have been reported in intraductal papillary mucinous neoplasms (40-66%)[115-116] and appendiceal mucinous neoplasms (50-72%)[117-118] as well as in tumors affecting the pituitary gland (27%), pancreas (16%), and bone (14%) (COSMIC, 2018). Amplification of GNAS has been reported in ovarian epithelial carcinomas (12-30%)[119-121], colorectal adenocarcinoma (9%)[55], stomach adenocarcinoma (7%)[122], lung adenocarcinoma (6.5%)[123], breast invasive carcinoma (6.5%)[124], pancreatic adenocarcinoma (6%)[125], and sarcomas (5.8%)[126]. GNAS mutations are rare in hematological malignancies generally (COSMIC, 2018)[127-128]. Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome [129]. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer [120-121], while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with gastric cancer [130].

FINDING SUMMARY
GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha) [131]. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase [131]. GNAS has been reported to be amplified in cancer [132] and may be biologically relevant in this context [133-134]. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration [135-140] are predicted to be activating. Mutations at R201 specifically are commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with GNAS activating mutations [141-143].

GENE
KDM6A

ALTERATION
Q1304*, splice site 2832+1G>A, E206fs*11

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to address KDM6A alterations in cancer.

FREQUENCY & PROGNOSIS
In the COSMIC database, KDM6A mutations have been reported in 2% of samples analyzed, with the highest incidence in tumors of the urinary tract (16%) and salivary gland (4%) (COSMIC, 2018). KDM6A mutations or copy number alterations have also been identified in medulloblastoma (8.9%)[144], adenoid cystic carcinoma (6.7%) [145], and metastatic prostate cancer (10%) [146]. KDM6A inactivation has been found as a recurrent tumorigenic event in male T-cell acute lymphoblastic leukemia (T-ALL), and loss of KDM6A increased the sensitivity of T-ALL cells to therapies targeting histone H3 lysine 27 methylation in preclinical assays [147]. However, KDM6A overexpression has been noted in breast cancer and renal cell carcinoma, and correlated with inferior prognosis in patients with breast cancer [148-150].

FINDING SUMMARY
KDM6A encodes a histone H3 lysine 27 demethylase UTX, which functions as a transcriptional regulator [151]. A significant number of inactivating KDM6A mutations have been found across multiple tumor types, suggesting a role as a tumor suppressor [151].

GENE
RUNX1

ALTERATION
S303*, P425L - subclonal

POTENTIAL TREATMENT STRATEGIES

There are no therapies available to directly target inactivating alterations in RUNX1. Limited clinical[152-153] and preclinical [154] 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[152,155156-157]. Similarly, on the basis of limited clinical [158] and preclinical [159-161] evidence, RUNX1 rearrangements may predict sensitivity to HDAC inhibitors. However, further studies are required to establish clinical significance.

FREQUENCY & PROGNOSIS

Mutations in RUNX1 have been identified in 8-16% of myelodysplastic syndrome (MDS), 6-28% of acute myeloid leukemia (AML), and 11-23% of chronic myelomonocytic leukemia (CMML) samples [162-166]. RUNX1 mutations have been associated with progression to AML and with reduced platelet counts in patients with CMML [167-168]. RUNX1 mutations have been significantly associated with worse prognosis in patients with MDS or AML [162,169-170].

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 [171-172]. 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 [173]. RUNX1 alterations that result in loss or disruption of the RUNT domain (amino acids 50–178) or C-terminal transactivation domain (amino acids 291–371), including alterations at residues R107 (also known as R80), K110 (K83), L144 (L117), R162 (R135), D198 (D171), R201 (R174), or R204 (R177)[174-180], as observed here, are predicted to be inactivating. Although alterations such as also 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
SF3B1

ALTERATION
K700E

POTENTIAL TREATMENT STRATEGIES

Preclinical studies of various leukemia cell lines and preclinical models suggest that mutations in genes encoding spliceosome components, including SF3B1, may confer sensitivity to spliceosome inhibitors [181-184]. Small-molecule inhibitors of the spliceosome, including those that inhibit SF3B1, are being clinically investigated [183].

FREQUENCY & PROGNOSIS

SF3B1 has been primarily studied in the context of hematologic malignancies and most extensively in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and chronic lymphocytic leukemia (CLL).

Alterations in SF3B1 have been reported in <2% of AML samples but at higher frequencies in cases of AML-associated MDS (5.8%), CLL (4-29%), MDS (5-39%), MDS characterized with ring sideroblasts (RS; 33-87%), and most frequently in refractory anemia associated with RS and marked thrombocytopenia (RARS-T; 87%)[185-205]. SF3B1 mutation strongly correlates with the presence of RS [188,193,206]. SF3B1 mutation has been reported to co-occur with JAK2 V617F in up to 64% of patients with RARS-T [187,189,193,198,207], which correlates with a greater percentage of RS than for either mutation alone. Co-occurrence of these mutations has been implicated as a molecular classifier for RARS-T, potentially a distinct entity from either MDS or MPN [193,198]. SF3B1 mutations are associated with better overall survival and lower risk of transformation to AML in patients with MDS [185,188-190,194,196,198]. In contrast, SF3B1 alterations were associated with disease progression, resistance to fludarabine, and adverse survival outcomes (10-year survival of 34-48% vs. 60-73% for matched general population) in patients with CLL [200-205]. SF3B1 mutations have been reported to occur as part of age-related clonal hematopoiesis, which commonly occurs in people over 70 years of age and is associated with increased risk of hematologic cancers [104-106].

FINDING SUMMARY

SF3B1 encodes a subunit of the spliceosome, the complex that is responsible for the splicing of pre-mRNA molecules to create mature messenger RNA [188,200,202,208]. SF3B1 mutations predominantly occur in HEAT domains 5-7 at codons 625, 662, 666, and 700 [190,201,209-212], which result in neomorphic activity that upregulates aberrant mRNA splicing [213-216]. The consequences of SF3B1 alterations outside of these sites have not been extensively characterized.

Azacitidine

Assay findings association

IDH2
R140Q - subclonal

TET2
S1494* - subclonal

AREAS OF THERAPEUTIC USE

Azacitidine is an injectable nucleoside analog that acts as a DNA methyltransferase inhibitor. It is FDA approved for the treatment of patients with myelodysplastic syndrome (MDS). It is also approved in combination with Venetoclax for the treatment of patients 75 years of age or older with newly diagnosed acute myeloid leukemia (AML) or comorbidities that preclude use of intensive induction chemotherapy.

GENE ASSOCIATION

IDH mutations may predict sensitivity to DNA methyltransferase (DNMT) inhibitors. Patients with acute myeloid leukemia (AML) harboring a mutation in IDH1 or IDH2 were reported to achieve a better rate of response to the DNMT inhibitors azacitidine or decitabine[65], although the trend to higher response rates for patients with mutant IDH was not significant in other studies[67-68 66,217]. On the basis of clinical studies in angioimmunoblastic T-cell lymphoma (AITL)[85-86 87] and MDS[68,83 84], inactivating mutations in TET2 may predict sensitivity to DNA methyltransferase (DNMT) inhibitors.

SUPPORTING DATA

Azacitidine has provided clinical benefit, both when used as a single agent and as part of combination regimens, for patients with AML who are treatment-naive or who have progressed with relapsed or refractory (R/R) disease. For patients with newly diagnosed AML, single-agent azacitidine was compared with conventional care regimens (CCRs) in the Phase 3 AZA-AML-001 trial; median overall survival (OS) was increased by azacitidine (10.4 vs. 6.5 months), although the primary endpoint was not met (HR 0.85, p=0.101)[218]. Favorable trends for azacitidine were observed in all subgroups, including patients with poor-risk cytogenetics[218], 20-30% of bone marrow blasts (24.5 vs. 16.0 months)[219-220], and MDS-related changes (65-74 years, 14.2 vs. 7.3 months, HR 0.64; ≥ 74 years, 5.9 vs. 3.8 months, HR = 0.77); greater survival was seen for patients <75 years[221]. In a biomarker analysis of this trial, FLT3 mutations associated with shorter OS compared to wild-type during azacitidine treatment (5.4 vs. 12 months; p=0.017); this trend was less evident during CCRs (5.6 vs. 6.4 months, p=0.17)[222]. Interim analysis of the Phase 3 Flugaza trial for untreated patients with AML, comparing single-agent azacitidine to flutarabine plus cytarabine and fligrastim (FLUGA chemotherapy), reported similar efficacies for the two regimens [overall response rates (ORR) of 62% vs. 57%[223]. For patients with AML who were unfit to receive intensive chemotherapy, azacitidine as frontline monotherapy led to a median OS of 9.4-9.6 months[224-225 226], whereas for patients with R/R AML, a median OS of 7.4 months was attained[227]. As combination therapy in the frontline setting, the NAE inhibitor pevonedistat plus azacitidine achieved an ORR of 60%[228]. Also as frontline combination approaches, for patients with AML and MDS unable to receive induction chemotherapy or to enter standard clinical trials, azacitidine plus the histone deacetylase inhibitors pracinostat[229] or vorinostat[230] led to response rates (RRs) of 40-42%; the latter combination enabled 2 patients to proceed to allogeneic hematopoietic stem cell transplant (allo-HSCT)[230]. Addition of midostaurin to azacitidine resulted in a RR of 26% for patients with these malignancies[231]. In the setting exclusively of R/R AML, combining azacitidine with sorafenib resulted in a RR of 46%[232] and with bortezomib[233] or everolimus[234], 22%. Addition of nivolumab led to CR + CR with incomplete recovery (CRi) for 18% and hematologic improvement (HI) for 15% of patients; none achieving these responses had relapsed at the time of reporting[235]. The combination of azacitidine with the anti-KIR antibody lirilumab led to 1/21 CR, 1/21 CRi, and 2/21 HIs[236]. As maintenance therapy for patients with AML in first and second complete remission, lenalidomide plus azacitidine achieved median relapse-free survival of 12 and 11 months, respectively[237]. As salvage therapy for patients who relapsed after allo-HSCT, combining azacitidine with sorafenib led to a RR of 50% for those with AML[238] and with donor lymphocyte infusions, a RR of 30% for those with AML and MDS[239].

Decitabine

Assay findings association

IDH2
R140Q - subclonal

TET2
S1494* - subclonal

AREAS OF THERAPEUTIC USE

Decitabine is an injectable nucleoside analog that acts as a DNA methyltransferase inhibitor. It has been approved by the FDA for the treatment of patients with myelodysplastic syndrome (MDS). It is also approved in combination with Venetoclax for the treatment of patients 75 years of age or older with newly diagnosed acute myeloid leukemia (AML) or comorbidities that preclude use of intensive induction chemotherapy.

GENE ASSOCIATION

IDH mutations may predict sensitivity to DNA methyltransferase (DNMT) inhibitors. Patients with acute myeloid leukemia (AML) harboring a mutation in IDH1 or IDH2 were reported to achieve a better rate of response to the DNMT inhibitors azacitidine or decitabine[65], although the trend to higher response rates for patients with mutant IDH was not significant in other studies[67-68 66,217]. On the basis of clinical studies in angioimmunoblastic T-cell lymphoma (AITL)[85-86 87] and MDS[68,83 84], inactivating mutations in TET2 may predict sensitivity to DNA methyltransferase (DNMT) inhibitors.

SUPPORTING DATA

Two Phase 3 trials compared decitabine with best supportive care for patients with high-risk MDS. The first study reported a significantly higher overall response rate (ORR; 17% vs. 0%) and a trend toward a longer median time to AML progression or death (12.1 vs. 7.8 months) with decitabine[240]. These data supported the FDA approval of decitabine for MDS. The second study for patients aged 60 or older who are ineligible for intensive chemotherapy observed a nonsignificant prolongation of median overall survival (OS; 10.1 vs. 8.5 months) and a significant improvement of progression-free survival (6.6 vs. 3.0 months) with decitabine[241-242 243]. In a Phase 3 trial for patients with MDS in China, decitabine resulted in an ORR of 26.5% and a 2-year OS rate of 48.9%[244]. For patients aged 65 or older with newly diagnosed AML and higher risk cytogenetics, decitabine significantly improved the complete remission rate (17.8% vs. 7.8%) and prolonged the median OS (7.7 vs. 5.0 months) compared with treatment choice[245]. This Phase 3 study led the European Medicines Agency (EMA) to approve decitabine as first-line treatment for AML in patients who are not candidates for standard induction therapy. The activity of first-line decitabine for older patients with AML has been established in Phase 2 studies that report ORRs of 25-64% and a median OS of 5.5-12.7 months[246-247 248-249]. Decitabine alternating with clofarabine and low-dose cytarabine was associated with an ORR of 68% and median OS of 11.1 months in this setting[250]. In a prospective biomarker trial for AML or transfusion-dependent MDS, the ORR after 10-day cycles of decitabine was 46% and was higher for patients with poor-risk cytogenetics [67% (29/43)] or with TP53 mutations [100% (21/21)][251]. Addition of arsenic trioxide to decitabine increased median OS for patients with MDS or CMML in a small Phase 2 study[252]. Decitabine has also been evaluated as a bridge to allogeneic transplant for patients with good performance status[253-254]; as maintenance therapy for younger patients in first remission[255]; and in combination with various agents[256-257 258-259260-261 262-263 264-265].

Enasidenib

Assay findings association

IDH2
R140Q - subclonal

AREAS OF THERAPEUTIC USE

Enasidenib is an inhibitor of isocitrate dehydrogenase-2 (IDH2) mutations with neomorphic activity. It is FDA approved to treat adult patients with relapsed or refractory acute myeloid leukemia (AML) whose malignancies are positive for mutated IDH2.

GENE ASSOCIATION

On the basis of a prospective clinical study[266-267 57] and preclinical data[58-59], IDH2 R140 and R172 mutations may predict sensitivity to enasidenib.

SUPPORTING DATA

In a Phase 1/2 study of single-agent enasidenib for patients with IDH2-mutated advanced myeloid malignancies, those with relapsed or refractory acute myeloid leukemia (AML; n= 176) experienced an ORR of 40.3%, with median response duration of 5.8 months and median OS of 9.3 months[57]. For patients with AML who attained complete remission (n= 34; 19.3%), median OS was 19.7 months[57]. Additionally, 11% of patients proceeded to transplant. Similar ORRs were reported for patients with IDH2 R140 (35.4%) and R172 (53.3%) mutations[57].

Venetoclax

Assay findings association

IDH2
R140Q - subclonal

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

Preclinical data suggest that mutations in IDH2 leading to 2-HG production may predict sensitivity to BCL-2 inhibitors such as venetoclax. Out of five patients with acute myelogenous leukemia treated with venetoclax who experienced a significant clinical response, three had an IDH mutation[60].

SUPPORTING DATA

A Phase 1b trial of patients age 65 or older with treatment-naive AML treated with venetoclax in combination with either azacitidine or decitabine reported an ORR of 67% (97/145; complete response (CR) or CR with incomplete marrow recovery (CRi), median duration of response of 11.3 months, and median OS of 17.5 months[268-269]. NPM1 mutation status was significantly and independently associated with better outcomes in this trial (ORR of 91% [21/23], median OS not reached)[268]. Biomarker analysis from patients from this study revealed IDH1/2 mutations predicted longer responses (HR=0.119, P=0.042), while PTPN11 and other RAS pathway mutations predicted shorter responses (HR=10.22; P=0.0019)[270]. For patients age 65 or older with AML, low-dose cytarabine (LDAC) combined with venetoclax resulted in 62% of patients achieving a CR/CRi, including 7/7 patients with NPM1 mutations and 7/10 patients with IDH1/2 mutations, and a reported median OS of 11.4 months[271]. In a biomarker analysis of patients with AML treated with venetoclax combined with either hypomethylating agents or LDAC, a higher percentage of BCL2-positive blasts isolated from peripheral blood at baseline were observed for those who achieved a response compared to patients who have not yet achieved a response (78% vs. 64%)[272]. A Phase 2 study in patients with acute myelogenous leukemia (AML) treated with venetoclax reported an ORR of 19% (6/32) (2 achieved CR, and 4 achieved Cri); three patients who experienced a response also had an IDH mutation[60-61].

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
IDH2

ALTERATION
R140Q - subclonal

RATIONALE
IDH2 mutations may predict sensitivity to IDH2 inhibitors. In the context of hematologic diseases, IDH2 mutation may predict sensitivity to DNA methyltransferase (DNMT) inhibitors, including azacitidine and decitabine. The BCL-2 inhibitor venetoclax has also shown efficacy in IDH2-mutant AML.

NCT02993523

PHASE 3

A Randomized, Double-Blind, Placebo Controlled Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy

TARGETS
BCL2, DNMT

LOCATIONS: Nagoya-shi (Japan), Nordbyhagen (Norway), Calgary (Canada), Vancouver (Canada), Woluwe-Saint-Lambert (Belgium), Budapest IX (Hungary), Drammen (Norway), California, Wrocław (Poland), Bologna (Italy), Fuzhou (China), Yoshida-gun (Japan), Fukuoka-shi (Japan), Pretoria (South Africa), Georgia, Zagreb (Croatia), Guangzhou (China), Maebashi-shi (Japan), Bergen (Norway), Wuhan, Hubei (China), Higashi Ibaraki-gun (Japan), Hitachi-shi (Japan), Illinois, Indiana, Nanjing (China), Changchun (China), Kansas, Kemerovo (Russian Federation), Kentucky, Kyoto-shi (Japan), Milan (Italy), Maine, Cracow (Poland), Ancona (Italy), Maryland, Massachusetts, Michigan, Sendai-shi (Japan), Nagasaki-shi (Japan), New York, St. Pölten (Austria), Nizhnij Novgorod (Russian Federation), Aalborg (Denmark), North Carolina, Linz (Austria), Okayama-shi (Japan), Hamilton (Canada), Ottawa (Canada), Toronto (Canada), Gent (Belgium), Osaka-shi (Japan), Osakasayama-shi (Japan), Osijek (Croatia), Pennsylvania, Penza (Russian Federation), Tampere (Finland), Plzeň 23 (Czechia), Lecce (Italy), Woolloongabba (Australia), Porto Alegre (Brazil), Rome (Italy), Ryazan (Russian Federation), Ribeirão Preto (Brazil), São Paulo (Brazil), Saratov (Russian Federation), Seoul (Korea, Republic of), Shanghai (China), Chengdu (China), Adelaide (Australia), Taichung City (Taiwan), Taipei City (Taiwan), Petakh Tikva (Israel), Tennessee, Texas, Ulm (Germany), Tianjin (China), Bunkyo-ku (Japan), Komae-shi (Japan), Shinagawa-ku (Japan), Uppsala (Sweden), Utah, Helsinki (Finland), Uddevalla (Sweden), Vermont, Fitzroy (Australia), Parkville (Australia), Prahran (Australia), Kiev (Ukraine), Brugge (Belgium), Nedlands (Australia), Shenton Park (Australia), Yamagata-shi (Japan), Hangzhou (China), Graz (Austria), Salzburg (Austria), Wien (Austria), Jette, Brussels (Belgium), Beijing (China), Jinan (China), Shijiazhuang (China), Wuhan (China), Zhengzhou, Henan (China), Brno (Czechia), Hradec Kralove (Czechia), Ostrava (Czechia), Turku (Finland), Angers (France), Paris (France), Pessac Cedex (France), Toulouse (France), Frankfurt (Germany), Halle (Germany), Hamburg (Germany), Hannover (Germany), Muenster (Germany), Budapest (Hungary), Debrecen (Hungary), Kaposvar (Hungary), Nyíregyhaza (Hungary), Szeged (Hungary), Be'er Ya'akov (Israel), Haifa (Israel), Jerusalem (Israel), Ramat Gan (Israel), Tel-aviv (Israel), Bergamo (Italy), Genoa (Italy), Napoli (Italy), Reggio Calabria (Italy), Hidaka (Japan), Tokyo (Japan), Gralum (Norway), Chorzow (Poland), Braga (Portugal), Porto (Portugal), San Juan (Puerto Rico), Moscow (Russian Federation), Samara (Russian Federation), Barcelona (Spain), Madrid (Spain), Malaga (Spain), Pamplona (Spain), Valencia (Spain), Lund (Sweden), Stockholm (Sweden), Changhua County (Taiwan), Kaohsiung (Taiwan), Ankara (Turkey), Samsun (Turkey), Dnipropetrovsk (Ukraine), Kyiv (Ukraine), Poltava (Ukraine)

NCT03069352

PHASE 3

A Randomized, Double-Blind, Placebo Controlled Study of Venetoclax Co-Administered With Low Dose Cytarabine Versus Low Dose Cytarabine in Treatment Naïve Patients With Acute Myeloid Leukemia Who Are Ineligible for Intensive Chemotherapy

TARGETS
BCL2

LOCATIONS: Edmonton (Canada), Edegem (Belgium), Athens (Greece), Villingen-Schwenningen (Germany), Woluwe-Saint-Lambert (Belgium), Budapest IX (Hungary), Busan (Korea, Republic of), Ciudad de México (Mexico), Jung-gu (Korea, Republic of), Dublin 8 (Ireland), Florida, Fuzhou (China), Yoshida-gun (Japan), Fukuoka-shi (Japan), Pretoria (South Africa), Guangzhou (China), Maebashi-shi (Japan), Bergen (Norway), Higashi Ibaraki-gun (Japan), Nanjing (China), Changchun (China), Kemerovo (Russian Federation), Kentucky, Kyoto-shi (Japan), Morelia (Mexico), Sendai-shi (Japan), Nagasaki-shi (Japan), Waratah (Australia), Westmead (Australia), Nizhnij Novgorod (Russian Federation), Monterrey (Mexico), Osaka-shi (Japan), Osakasayama-shi (Japan), Pécs (Hungary), Pennsylvania, Greenfield Park (Canada), Montreal (Canada), Pierre Benite CEDEX (France), Ryazan (Russian Federation), Florianopolis (Brazil), Le Mans CEDEX 9 (France), Seoul (Korea, Republic of), Shanghai (China), Chengdu (China), Taipei City (Taiwan), Texas, Tianjin (China), Bunkyo-ku (Japan), Komae-shi (Japan), Shinagawa-ku (Japan), Valencia (Spain), Melbourne (Australia), Washington, Wisconsin, Yamagata-shi (Japan), Hangzhou (China), Buenos Aires (Argentina), Cordoba (Argentina), Porto Alegre (Brazil), Sao Paulo (Brazil), Jinan (China), Wuhan (China), Zhengzhou, Henan (China), Brno (Czechia), Ostrava (Czechia), Prague (Czechia), Bayonne (France), Pessac (France), Vandoeuvre Les Nancy Cedex (France), Berlin (Germany), Hamburg (Germany), Alexandroupolis (Greece), Patras (Greece), Thessaloniki (Greece), Budapest (Hungary), Debrecen (Hungary), Gyor (Hungary), Kaposvar (Hungary), Kecskemét (Hungary), Dublin (Ireland), Galway (Ireland), Limerick (Ireland), Akita (Japan), Hidaka (Japan), Nagoya (Japan), Shimotsuga (Japan), Tokyo (Japan), Auckland (New Zealand), Gralum (Norway), San Juan (Puerto Rico), Moscow (Russian Federation), Samara (Russian Federation), Sankt-peterburg (Russian Federation), Saratov (Russian Federation), St. Petersburg (Russian Federation), Yaroslavl (Russian Federation), Madrid (Spain), Kaohsiung (Taiwan), Birmingham (United Kingdom), Cardiff (United Kingdom), Harrow (United Kingdom)

CLINICAL TRIALS

NCT02670044

PHASE 1/2

A Phase IB/II Multi-Arm Study With Venetoclax in Combination With Cobimetinib and Venetoclax in Combination With Idasanutlin in Patients Aged >/= 60 Years With Relapsed or Refractory Acute Myeloid Leukemia Who Are Not Eligible for Cytotoxic Therapy

TARGETS
MEK, BCL2, MDM2

LOCATIONS: Edmonton (Canada), California, Colorado, Bologna (Italy), Pesaro (Italy), Roma (Italy), Massachusetts, New York, North Carolina, Toronto (Canada), Montreal (Canada), Texas, Bobigny (France), Marseille (France), Pessac (France)

NCT02878785

PHASE 1/2

Multicenter Phase 1/2 Study of Combination Therapy w/ DNA Methyltransferase Inhibitor Decitabine & Poly ADP Ribose Polymerase Inhibitor Talazoparib for Untreated AML in Adults Unfit for Cytotoxic Chemotherapy or R/R AML

TARGETS
PARP, DNMT

LOCATIONS: Maryland

NCT02494258

PHASE 2

A Phase 2, Open-Label, Single-Arm Rollover Study to Evaluate Long-Term Safety in Subjects Who Participated in Other Celgene Sponsored CC-486 (Oral Azacitidine) Clinical Trials in Solid Tumors and Hematological Disorders

TARGETS
DNMT

LOCATIONS: Florida, Maryland, Texas, Virginia

NCT02190695

PHASE 2

Leukemia SPORE Phase II Randomized Study of Decitabine Versus Decitabine and Carboplatin Versus Decitabine and Arsenic in Relapsed, Refractory, and Elderly Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

TARGETS
DNMT, RARA

LOCATIONS: Pennsylvania, Texas

NCT02391480

PHASE 1

A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABBV-075 in Subjects With Advanced Cancer

TARGETS
BRD2, BRD3, BRD4, BRDT, BCL2

LOCATIONS: Arizona, California, Connecticut, Illinois, Indiana, North Carolina, Texas

NCT02073838

PHASE 2

A Phase II, Multi-center, Open Label, Randomized Study of Ribavirin and Hedgehog Inhibitor With or Without Decitabine in Acute Myeloid Leukemia (AML)

TARGETS
DNMT, SMO

LOCATIONS: Montreal (Canada)

NCT03484520

PHASE 1

Phase 1b Study of Venetoclax and Dinaciclib (MK7965) in Patients With Relapsed/Refractory Acute Myeloid Leukemia

TARGETS
CDK1, CDK2, CDK5, CDK9, BCL2

LOCATIONS: Arizona, Arkansas, California, Illinois, Maryland, North Carolina, Ohio, Southport (Australia), Hobart (Australia), Texas, Valencia (Spain), Melbourne (Australia), Madrid (Spain), Salamanca (Spain)

CLINICAL TRIALS

NCT03613532

PHASE 1

A Phase 1 Study of Venetoclax Added to Busulfan and Fludarabine Reduced Intensity Conditioning Regimen for AML, MDS, and MDS/MPN Overlap Syndromes

TARGETS
BCL2

LOCATIONS: Massachusetts

CLINICAL TRIALS

GENE
TET2

ALTERATION
S1494* - subclonal

RATIONALE
One strategy under investigation to address mutation or loss of TET2 in human cancer involves DNA methyltransferase (DNMT) inhibitors.

NCT02993523

PHASE 3

A Randomized, Double-Blind, Placebo Controlled Study of Venetoclax in Combination With Azacitidine Versus Azacitidine in Treatment Naïve Subjects With Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy

TARGETS
BCL2, DNMT

LOCATIONS: Nagoya-shi (Japan), Nordbyhagen (Norway), Calgary (Canada), Vancouver (Canada), Woluwe-Saint-Lambert (Belgium), Budapest IX (Hungary), Drammen (Norway), California, Wrocław (Poland), Bologna (Italy), Fuzhou (China), Yoshida-gun (Japan), Fukuoka-shi (Japan), Pretoria (South Africa), Georgia, Zagreb (Croatia), Guangzhou (China), Maebashi-shi (Japan), Bergen (Norway), Wuhan, Hubei (China), Higashi Ibaraki-gun (Japan), Hitachi-shi (Japan), Illinois, Indiana, Nanjing (China), Changchun (China), Kansas, Kemerovo (Russian Federation), Kentucky, Kyoto-shi (Japan), Milan (Italy), Maine, Cracow (Poland), Ancona (Italy), Maryland, Massachusetts, Michigan, Sendai-shi (Japan), Nagasaki-shi (Japan), New York, St. Pölten (Austria), Nizhnij Novgorod (Russian Federation), Aalborg (Denmark), North Carolina, Linz (Austria), Okayama-shi (Japan), Hamilton (Canada), Ottawa (Canada), Toronto (Canada), Gent (Belgium), Osaka-shi (Japan), Osakasayama-shi (Japan), Osijek (Croatia), Pennsylvania, Penza (Russian Federation), Tampere (Finland), Plzeň 23 (Czechia), Lecce (Italy), Woolloongabba (Australia), Porto Alegre (Brazil), Rome (Italy), Ryazan (Russian Federation), Ribeirão Preto (Brazil), São Paulo (Brazil), Saratov (Russian Federation), Seoul (Korea, Republic of), Shanghai (China), Chengdu (China), Adelaide (Australia), Taichung City (Taiwan), Taipei City (Taiwan), Petakh Tikva (Israel), Tennessee, Texas, Ulm (Germany), Tianjin (China), Bunkyo-ku (Japan), Komae-shi (Japan), Shinagawa-ku (Japan), Uppsala (Sweden), Utah, Helsinki (Finland), Uddevalla (Sweden), Vermont, Fitzroy (Australia), Parkville (Australia), Prahran (Australia), Kiev (Ukraine), Brugge (Belgium), Nedlands (Australia), Shenton Park (Australia), Yamagata-shi (Japan), Hangzhou (China), Graz (Austria), Salzburg (Austria), Wien (Austria), Jette, Brussels (Belgium), Beijing (China), Jinan (China), Shijiazhuang (China), Wuhan (China), Zhengzhou, Henan (China), Brno (Czechia), Hradec Kralove (Czechia), Ostrava (Czechia), Turku (Finland), Angers (France), Paris (France), Pessac Cedex (France), Toulouse (France), Frankfurt (Germany), Halle (Germany), Hamburg (Germany), Hannover (Germany), Muenster (Germany), Budapest (Hungary), Debrecen (Hungary), Kaposvar (Hungary), Nyíregyhaza (Hungary), Szeged (Hungary), Be'er Ya'akov (Israel), Haifa (Israel), Jerusalem (Israel), Ramat Gan (Israel), Tel-aviv (Israel), Bergamo (Italy), Genoa (Italy), Napoli (Italy), Reggio Calabria (Italy), Hidaka (Japan), Tokyo (Japan), Gralum (Norway), Chorzow (Poland), Braga (Portugal), Porto (Portugal), San Juan (Puerto Rico), Moscow (Russian Federation), Samara (Russian Federation), Barcelona (Spain), Madrid (Spain), Malaga (Spain), Pamplona (Spain), Valencia (Spain), Lund (Sweden), Stockholm (Sweden), Changhua County (Taiwan), Kaohsiung (Taiwan), Ankara (Turkey), Samsun (Turkey), Dnipropetrovsk (Ukraine), Kyiv (Ukraine), Poltava (Ukraine)

NCT02878785

PHASE 1/2

Multicenter Phase 1/2 Study of Combination Therapy w/ DNA Methyltransferase Inhibitor Decitabine & Poly ADP Ribose Polymerase Inhibitor Talazoparib for Untreated AML in Adults Unfit for Cytotoxic Chemotherapy or R/R AML

TARGETS
PARP, DNMT

LOCATIONS: Maryland

NCT02494258

PHASE 2

A Phase 2, Open-Label, Single-Arm Rollover Study to Evaluate Long-Term Safety in Subjects Who Participated in Other Celgene Sponsored CC-486 (Oral Azacitidine) Clinical Trials in Solid Tumors and Hematological Disorders

TARGETS
DNMT

LOCATIONS: Florida, Maryland, Texas, Virginia

NCT02190695

PHASE 2

Leukemia SPORE Phase II Randomized Study of Decitabine Versus Decitabine and Carboplatin Versus Decitabine and Arsenic in Relapsed, Refractory, and Elderly Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

TARGETS
DNMT, RARA

LOCATIONS: Pennsylvania, Texas

CLINICAL TRIALS

NCT02073838

PHASE 2

A Phase II, Multi-center, Open Label, Randomized Study of Ribavirin and Hedgehog Inhibitor With or Without Decitabine in Acute Myeloid Leukemia (AML)

TARGETS
DNMT, SMO

LOCATIONS: Montreal (Canada)

NCT03404193

PHASE 2

A Phase II Study of Venetoclax in Combination With 10-Day Decitabine in Newly Diagnosed Elderly or Relapsed/Refractory Acute Myeloid Leukemia and Relapsed High-risk Myelodysplastic Syndrome

TARGETS
BCL2, DNMT

LOCATIONS: Texas

NCT01515527

PHASE 2

Phase II Study of Cladribine Plus Low Dose Cytarabine (LDAC) Induction Followed By Consolidation With Cladribine Plus LDAC Alternating With Decitabine in Patients With Untreated Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS)

TARGETS
DNMT

LOCATIONS: Texas

NCT02257138

PHASE 1/2

Phase I/II Study of Ruxolitinib Plus Decitabine in Patients With Post Myeloproliferative Neoplasm - Acute Myeloid Leukemia (AML)

TARGETS
JAK2, JAK1, DNMT

LOCATIONS: Texas

NCT01892371

PHASE 1/2

Phase I/II Study of the Combination of Quizartinib (AC220) With 5-Azacytidine or Low-Dose Cytarabine for the Treatment of Patients With Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

TARGETS
FLT3, KIT, PDGFRs, RET, DNMT

LOCATIONS: Texas

NCT02397720

PHASE 2

An Open-label Phase II Study of Nivolumab (BMS-936558) in Combination With 5-azacytidine (Vidaza) for the Treatment of Patients With Refractory/ Relapsed Acute Myeloid Leukemia and Newly Diagnosed Older Acute Myeloid Leukemia (AML) (>65 Years) Patients

TARGETS
DNMT, CTLA-4, PD-1

LOCATIONS: Texas

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.

EPHA7
A625T

LRRK2
G2412E

PBRM1
E486K

PRKDC
K1422E

SRC
I217V

YY1AP1
C46_R48del

ZNF217
E278A

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*	*NTSC2*	*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 852x

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 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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