

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

<sup>†</sup> See About the Test in appendix for details.

4 Therapies with Clinical Benefit  
0 Therapies with Lack of Response

15 Clinical Trials

**BIOMARKER FINDINGS**

**Microsatellite status - MS-Stable**

**Tumor Mutational Burden - TMB-Low (4 Muts/Mb)**

**GENOMIC FINDINGS**

**IDH2** - R140Q - subclonal

10 Trials *see p. 10*

**TET2** - S1494\* - subclonal

10 Trials *see p. 13*

**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)
Azacitidine	none
Decitabine	
Enasidenib	
Venetoclax	
Azacitidine	none
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.*

<b>FANCE</b> - V311fs*2 ..... p. 5	<b>RUNX1</b> - S303*, P425L - subclonal ..... p. 6
<b>GNAS</b> - R201S ..... p. 5	<b>SF3B1</b> - K700E ..... p. 6
<b>KDM6A</b> - Q1304*, splice site 2832+1G>A, E206fs*11 ..... p. 5	

**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.

TRF#

BIOMARKER FINDINGS

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<sup>1-3</sup>, including approved therapies nivolumab and pembrolizumab<sup>4</sup>. 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)<sup>5</sup>.

FREQUENCY & PROGNOSIS

In studies of acute myeloid leukemia (AML), MSI at any level has been reported at incidences from 6-56%<sup>6-13</sup>; however, contradicting studies reported an absence of MSI in AML<sup>14-15</sup>. Similarly, MSI-H has been observed with incidences of 3-32%<sup>8,10-11,13</sup> or reported as absent in AML<sup>6,14</sup>. 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<sup>16</sup>. 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<sup>17</sup>. In addition, a small number of studies have not found a significant correlation of MSI with relapsed AML<sup>10</sup>, nor with progression from MDS to AML<sup>18</sup>, and other publications have reported a high incidence (20-32%) of MSI in de novo AML/MDS<sup>11-13,19</sup>. In contrast, other studies have reported increased incidences of MSI in relapsed or therapy-related AML/MDS compared to de novo disease<sup>9,13,19-24</sup>, and a cell lineage analysis of AML/CML progression found increased MSI associated with relapsed disease after chemotherapy in 3/6 patients<sup>25</sup>. 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<sup>26</sup>.

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<sup>27</sup>. 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<sup>27-29</sup>. 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<sup>30-32</sup>. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins<sup>27,29,31-32</sup>.

SAMPLE

TRF#

BIOMARKER FINDINGS

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<sup>33</sup>, anti-PD-L1<sup>34-37</sup>, and anti-PD-1 therapies<sup>4,38-39</sup>; 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)<sup>38</sup>. 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<sup>4,38-39</sup>. 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<sup>40</sup> or nivolumab<sup>41</sup>, a patient with hypermutant glioblastoma who obtained clinical benefit from pembrolizumab<sup>42</sup>, 2 pediatric patients with biallelic mismatch repair deficiency-associated ultrahypermutant glioblastoma who experienced clinically and radiologically significant responses to nivolumab<sup>43</sup>, 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<sup>44</sup>. For patients with melanoma, mutational load was associated with long-term clinical benefit from ipilimumab<sup>33,45</sup> and anti-PD-1/anti-PD-L1 treatments<sup>35</sup>. For patients with metastatic urothelial carcinoma (mUC), those who responded to atezolizumab treatment had a significantly increased mutational load (12.4 mutations [mut] per megabase [Mb]) compared to nonresponders (6.4 muts/Mb)<sup>34</sup>, and mutational load of 16 muts/Mb or higher was associated with significantly longer overall survival<sup>36</sup>. 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<sup>46</sup>.

FREQUENCY & PROGNOSIS

Acute myeloid leukemia (AML) harbors a median TMB of 1.7 mutations per megabase (mut/Mb), and 0% of cases have high TMB

(>20 muts/Mb)<sup>47</sup>. Reports of high TMB are generally rare in leukemia<sup>47</sup>. 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<sup>48</sup>. 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<sup>49-50</sup> and cigarette smoke in lung cancer<sup>38,51</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>52-56</sup>, and microsatellite instability (MSI)<sup>52,55-56</sup>. 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<sup>33</sup>, anti-PD-L1 therapy in urothelial carcinoma<sup>34</sup>, and anti-PD-1 therapy in non-small cell lung cancer and colorectal cancer<sup>4,38</sup>.

SAMPLE

TRF#

GENOMIC FINDINGS

**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<sup>57-59</sup>, BCL-2 inhibitors such as venetoclax<sup>60-62</sup>, DNA methyltransferase inhibitors such as azacitidine and decitabine<sup>63-68</sup>, or combination of enasidenib and azacitidine<sup>69</sup>. 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<sup>57</sup>. In preclinical studies, enasidenib induced differentiation in human AML cell lines and ex vivo cultures<sup>58</sup>, a phenotype also observed clinically<sup>57,59</sup>.

**FREQUENCY & PROGNOSIS**

In the TCGA dataset, IDH2 mutation was observed in 10% of acute myeloid leukemia (AML) cases<sup>70</sup>. 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<sup>71-73</sup>, although this may not hold true for all treatment regimens, such as cytarabine and idarubicin<sup>74</sup>.

**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<sup>75</sup>. Amino acids 140 and 172 are hotspots for cancer-related mutations in IDH2<sup>76</sup>. 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)<sup>75-80</sup>. This leads to downstream effects that are associated with tumorigenesis<sup>78,81</sup>, and research suggests that hotspot IDH gene mutations could be early stage events in specific cancers<sup>81-82</sup>.

**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<sup>68,83-84</sup>. In other clinical studies, patients with TET2-mutated angioimmunoblastic T-cell lymphoma (AITL)

were reported to achieve complete responses to azacitidine<sup>85-87</sup>.

**FREQUENCY & PROGNOSIS**

TET2 mutations have been reported in 8-27% of acute myeloid leukemia (AML) cases<sup>70,72,88-93</sup>. Although in some studies TET2 mutation correlated with poor prognosis in favorable-risk cytogenetically normal AML<sup>88,93</sup>, biallelic CEBPA-mutated AML<sup>94</sup>, and AML with intermediate-risk cytogenetics<sup>89-90</sup>, other studies have found no association between TET2 mutation and survival<sup>91-92</sup>. 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<sup>95</sup>. 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<sup>96</sup>.

**FINDING SUMMARY**

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation<sup>97-98</sup>. 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<sup>99-103</sup>. DNMT3A/TET2/ASXL1 mutations have been associated with clonal hematopoiesis of indeterminate potential (CHIP) in hematologic malignancies<sup>104-108</sup>.

TRF#

GENOMIC FINDINGS

**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<sup>109-112</sup>. 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<sup>113</sup>. 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<sup>114</sup>.

**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%)<sup>115-116</sup> and appendiceal mucinous neoplasms (50-72%)<sup>117-118</sup> 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%)<sup>119-121</sup>, colorectal adenocarcinoma (9%)<sup>122</sup>, stomach adenocarcinoma (7%)<sup>122</sup>, lung adenocarcinoma (6.5%)<sup>123</sup>, breast invasive carcinoma (6.5%)<sup>124</sup>, pancreatic adenocarcinoma (6%)<sup>125</sup>, and sarcomas (5.8%)<sup>126</sup>. GNAS mutations are rare in hematological malignancies generally (COSMIC, 2018)<sup>127-128</sup>. Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome<sup>129</sup>. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer<sup>120-121</sup>, while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with gastric cancer<sup>130</sup>.

**FINDING SUMMARY**

GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha)<sup>131</sup>. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase<sup>131</sup>. GNAS has been reported to be amplified in cancer<sup>132</sup> and may be biologically relevant in this context<sup>133-134</sup>. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration<sup>135-140</sup> 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<sup>141-143</sup>.

**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%)<sup>144</sup>, adenoid cystic carcinoma (6.7%)<sup>145</sup>, and metastatic prostate cancer (10%)<sup>146</sup>. 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<sup>147</sup>.

However, KDM6A overexpression has been noted in breast cancer and renal cell carcinoma, and correlated with inferior prognosis in patients with breast cancer<sup>148-150</sup>.

**FINDING SUMMARY**

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

TRF#

GENOMIC FINDINGS

**GENE**  
**RUNX1**

**ALTERATION**  
S303\*, P425L - subclonal

**POTENTIAL TREATMENT STRATEGIES**

There are no therapies available to directly target inactivating alterations in RUNX1. Limited clinical<sup>152-153</sup> and preclinical<sup>154</sup> 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<sup>152,155,156-157</sup>. Similarly, on the basis of limited clinical<sup>158</sup> and preclinical<sup>159-161</sup> 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<sup>162-166</sup>. RUNX1 mutations have been associated with progression to AML and with reduced platelet counts in patients with CMML<sup>167-168</sup>. RUNX1 mutations have been significantly associated with worse prognosis in patients with MDS or AML<sup>162,169-170</sup>.

**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<sup>171-172</sup>. 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<sup>173</sup>. 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)<sup>174-180</sup>, 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<sup>181-184</sup>. Small-molecule inhibitors of the spliceosome, including those that inhibit SF3B1, are being clinically investigated<sup>183</sup>.

**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 (4-20%), 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%)<sup>185-205</sup>. SF3B1 mutation strongly correlates with the presence of RS<sup>188,193,206</sup>. SF3B1 mutation has been reported to co-occur with JAK2 V617F in up to 64% of patients with RARS-T<sup>187,189,193,198,207</sup>, 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<sup>193,198</sup>. SF3B1 mutations are associated with better overall survival and lower risk of transformation to AML in patients with MDS<sup>185,188-190,194,196,198</sup>. 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<sup>200-205</sup>. 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<sup>104-106</sup>.

**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<sup>188,200,202,208</sup>. SF3B1 mutations predominantly occur in HEAT domains 5-7 at codons 625, 662, 666, and 700<sup>190,201,209-212</sup>, which result in neomorphic activity that upregulates aberrant mRNA splicing<sup>213-216</sup>. The consequences of SF3B1 alterations outside of these sites have not been extensively characterized.

TRF#

THERAPIES WITH CLINICAL BENEFIT

IN PATIENT'S TUMOR TYPE

## 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<sup>65</sup>, although the trend to higher response rates for patients with mutant IDH was not significant in other studies<sup>67-68 66,217</sup>. On the basis of clinical studies in angioimmunoblastic T-cell lymphoma (AITL)<sup>85-86 87</sup> and MDS<sup>68,83 84</sup>, 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-naïve 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)<sup>218</sup>. Favorable trends for azacitidine were observed in all subgroups, including patients with poor-risk cytogenetics<sup>218</sup>, 20-30% of bone marrow blasts (24.5 vs. 16.0 months)<sup>219-220</sup>, 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<sup>221</sup>. 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)<sup>222</sup>. Interim analysis of the Phase 3 Flugaza trial for untreated patients with AML, comparing single-agent azacitidine to flutabine plus cytarabine and fligrastrim (FLUGA chemotherapy), reported similar efficacies for the two regimens [overall response rates (ORR) of 62% vs. 57%<sup>223</sup>. 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<sup>224-225 226</sup>, whereas for patients with R/R AML, a median OS of 7.4 months was attained<sup>227</sup>. As combination therapy in the frontline setting, the NAE inhibitor pevonedistat plus azacitidine achieved an ORR of 60%<sup>228</sup>. 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<sup>229</sup> or vorinostat<sup>230</sup> led to response rates (RRs) of 40-42%; the latter combination enabled 2 patients to proceed to allogeneic hematopoietic stem cell transplant (allo-HSCT)<sup>230</sup>. Addition of midostaurin to azacitidine resulted in a RR of 26% for patients with these malignancies<sup>231</sup>. In the setting exclusively of R/R AML, combining azacitidine with sorafenib resulted in a RR of 46%<sup>232</sup> and with bortezomib<sup>233</sup> or everolimus<sup>234</sup>, 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<sup>235</sup>. The combination of azacitidine with the anti-KIR antibody lirilumab led to 1/21 CR, 1/21 CRI, and 2/21 HIs<sup>236</sup>. 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<sup>237</sup>. As salvage therapy for patients who relapsed after allo-HSCT, combining azacitidine with sorafenib led to a RR of 50% for those with AML<sup>238</sup> and with donor lymphocyte infusions, a RR of 30% for those with AML and MDS<sup>239</sup>.

TRF#

THERAPIES WITH CLINICAL BENEFIT

IN PATIENT'S TUMOR TYPE

## 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<sup>65</sup>, although the trend to higher response rates for patients with mutant IDH was not significant in other studies<sup>67-68 66,217</sup>. On the basis of clinical studies in angioimmunoblastic T-cell lymphoma (AITL)<sup>85-86 87</sup> and MDS<sup>68,83 84</sup>, 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<sup>240</sup>. 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<sup>241-242 243</sup>. 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%<sup>244</sup>. 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<sup>245</sup>. 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<sup>246-247 248-249</sup>. 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<sup>250</sup>. 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)]<sup>251</sup>. Addition of arsenic trioxide to decitabine increased median OS for patients with MDS or CMML in a small Phase 2 study<sup>252</sup>. Decitabine has also been evaluated as a bridge to allogeneic transplant for patients with good performance status<sup>253-254</sup>; as maintenance therapy for younger patients in first remission<sup>255</sup>; and in combination with various agents<sup>256-257 258-259 260-261 262-263 264-265</sup>.

## 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<sup>266-267 57</sup> and preclinical data<sup>58-59</sup>, 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<sup>57</sup>. For patients with AML who attained complete remission (n= 34; 19.3%), median OS was 19.7 months<sup>57</sup>. Additionally, 11% of patients proceeded to transplant. Similar ORRs were reported for patients with IDH2 R140 (35.4%) and R172 (53.3%) mutations<sup>57</sup>.



TRF#

THERAPIES WITH CLINICAL BENEFIT IN PATIENT'S TUMOR TYPE

## 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<sup>60</sup>.

#### 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<sup>268-269</sup>. NPM1 mutation status was significantly and independently associated with better outcomes in this trial (ORR of 91% [21/23], median OS not reached)<sup>268</sup>. 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)<sup>270</sup>. 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<sup>271</sup>. 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%)<sup>272</sup>. 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<sup>60-61</sup>.

**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.

SAMPLE

TRF#

**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](https://www.foundationmedicine.com/genomic-testing#support-services). 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), Nyíregyháza (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)

TRF#

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  $\geq$  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)

TRF#

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

SAMPLE

TRF#

CLINICAL TRIALS

GENE  
**TET2**

**RATIONALE**  
One strategy under investigation to address mutation or loss of TET2 in human cancer

involves DNA methyltransferase (DNMT) inhibitors.

ALTERATION  
S1494\* - subclonal

**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), Nyíregyháza (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

TRF#

**CLINICAL TRIALS**

<b>NCT02073838</b>	<b>PHASE 2</b>
A Phase II, Multi-center, Open Label, Randomized Study of Ribavirin and Hedgehog Inhibitor With or Without Decitabine in Acute Myeloid Leukemia (AML)	<b>TARGETS</b> DNMT, SMO
.....	
<b>LOCATIONS:</b> Montreal (Canada)	
<b>NCT03404193</b>	<b>PHASE 2</b>
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	<b>TARGETS</b> BCL2, DNMT
.....	
<b>LOCATIONS:</b> Texas	
<b>NCT01515527</b>	<b>PHASE 2</b>
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)	<b>TARGETS</b> DNMT
.....	
<b>LOCATIONS:</b> Texas	
<b>NCT02257138</b>	<b>PHASE 1/2</b>
Phase I/II Study of Ruxolitinib Plus Decitabine in Patients With Post Myeloproliferative Neoplasm - Acute Myeloid Leukemia (AML)	<b>TARGETS</b> JAK2, JAK1, DNMT
.....	
<b>LOCATIONS:</b> Texas	
<b>NCT01892371</b>	<b>PHASE 1/2</b>
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)	<b>TARGETS</b> FLT3, KIT, PDGFRs, RET, DNMT
.....	
<b>LOCATIONS:</b> Texas	
<b>NCT02397720</b>	<b>PHASE 2</b>
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	<b>TARGETS</b> DNMT, CTLA-4, PD-1
.....	
<b>LOCATIONS:</b> Texas	

TRF#

**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

SAMPLE

TRF#

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
BAP1	BARD1	BCL10	BCL11B	BCL2	BCL2L2	BCL6	BCL7A
BCORL1	BIRC3	BLM	BRAF	BRCA1	BRCA2	BRD4	BRIP1
BTG2	BTK	BTLA	C11orf30 (EMSY)	CAD	CALR*	CARD11	CBFB
CCND1	CCND2	CCND3	CCNE1	CCT6B	CD22	CD274 (PD-L1)	CD36
CD70	CD79A	CD79B	CDC73	CDH1	CDH12	CDK4	CDK6
CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHD2	CHEK1	CHEK2
CIITA	CKS1B	CPS1	CREBBP	CRKL	CRLF2	CSF1R	CSF3R
CTNNA1	CTNNB1	CUX1	CXCR4	DAXX	DDR2	DDX3X	DNM2
DOT1L	DTX1	DUSP2	DUSP9	EBF1	ECT2L	EED	EGFR
EP300	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4
ESR1	ETS1	ETV6	EXOSC6	EZH2	FAF1	FAM46C	FANCA
FANCD2	FANCE	FANCF	FANCG	FANCL	FAS (TNFRSF6)	FBXO11	FBXO31
FGF10	FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1
FGFR3	FGFR4	FHIT	FLCN	FLT1	FLT3	FLT4	FLYWCH1
FOXO1	FOXO3	FOXP1	FRS2	GADD45B	GATA1	GATA2	GATA3
GNA11	GNA12	GNA13	GNAQ	GNAS	GPR124	GRIN2A	GSK3B
HDAC1	HDAC4	HDAC7	HGF	HIST1H1C	HIST1H1D	HIST1H1E	HIST1H2AC
HIST1H2AL	HIST1H2AM	HIST1H2BC	HIST1H2BJ	HIST1H2BK	HIST1H2BO	HIST1H3B	HNF1A
HSP90AA1	ICK	ID3	IDH1	IDH2	IGF1R	IKBKE	IKZF1
IKZF3	IL7R	INHBA	INPP4B	INPP5D (SHIP)	IRF1	IRF4	IRF8
JAK1	JAK2	JAK3	JARID2	JUN	KAT6A (MYST3)	KDM2B	KDM4C
KDM5C	KDM6A	KDR	KEAP1	KIT	KLHL6	KMT2A (MLL)	KMT2C (MLL3)
KRAS	LEF1	LRP1B	LRRK2	MAF	MAFB	MAGED1	MALT1
MAP2K2	MAP2K4	MAP3K1	MAP3K14	MAP3K6	MAP3K7	MAPK1	MCL1
MDM4	MED12	MEF2B	MEF2C	MEN1	MET	MIB1	MITF
MLH1	MPL	MRE11A	MSH2	MSH3	MSH6	MTOR	MUTYH
MYCL (MYCL1)	MYCN	MYD88	MYO18A	NCOR2	NCSTN	NF1	NF2
NFKBIA	NKX2-1	NOD1	NOTCH1	NOTCH2	NPM1	NRAS	NTSC2
NTRK2	NTRK3	NUP93	NUP98	P2RY8	PAG1	PAK3	PALB2
PAX5	PBRM1	PC	PCBP1	PCLO	PDCD1	PDCD11	PDCD1LG2 (PD-L2)
PDGFRB	PDK1	PHF6	PIK3CA	PIK3CG	PIK3R1	PIK3R2	PIM1
POT1	PPP2R1A	PRDM1	PRKARIA	PRKDC	PRSS8	PTCH1	PTEN
PTPN2	PTPN6 (SHP-1)	PTPRO	RAD21	RAD50	RAD51	RAF1	RARA
RB1	RELN	RET	RHOA	RICTOR	RNF43	ROS1	RPTOR
SIPR2	SDHA	SDHB	SDHC	SDHD	SERP2	SETBP1	SETD2
SGK1	SMAD2	SMAD4	SMARCA1	SMARCA4	SMARCB1	SMC1A	SMC3
SOCS1	SOCS2	SOCS3	SOX10	SOX2	SPEN	SPOP	SRC
STAG2	STAT3	STAT4	STAT5A	STAT5B	STAT6	STK11	SUFU
TAF1	TBL1XR1	TCF3 (E2A)	TCL1A (TCL1)	TET2	TGFBR2	TLL2	TMEM30A
TMSB4XP8 (TMSL3)		TNFAIP3	TNFRSF11A	TNFRSF14	TNFRSF17	TOP1	TP53
TRAF2	TRAF3	TRAF5	TSC1	TSC2	TSHR	TUSC3	TYK2
U2AF2	VHL	WDR90	WHSC1 (MMSET or NSD2)	WISP3	WISP3	WT1	XBP1
YY1AP1	ZMYM3	ZNF217	ZNF24 (ZSCAN3)	ZNF703	ZRSR2		XPO1

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



TRF#

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
FGFR10P	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)

TRF#

**APPENDIX**

**Performance Specifications**

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.

TRF#

APPENDIX

About FoundationOne®Heme

**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.



TRF#

APPENDIX

About FoundationOne®Heme

**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

SAMPLE

TRF#

**APPENDIX**

References

- 1 Gatalica Z, Snyder C, Maney T, et al. (2014) Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. *Cancer Epidemiol. Biomarkers Prev.* ePub Dec 2014
- 2 Kroemer G, Galluzzi L, Zitvogel L, et al. (2015) Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy? *Oncoimmunology* 4 (7):e1058597
- 3 Lal N, Beggs AD, Willcox BE, et al. (2015) An immunogenomic stratification of colorectal cancer: Implications for development of targeted immunotherapy. *Oncoimmunology* 4 (3):e976052
- 4 Le DT, Uram JN, Wang H, et al. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N. Engl. J. Med.* ePub Jun 2015
- 5 ASCO-SITC 2016; Abstract P60
- 6 Pabst T, Schwaller J, Bellomo MJ, et al. (1996) Frequent clonal loss of heterozygosity but scarcity of microsatellite instability at chromosomal breakpoint cluster regions in adult leukemias. *Blood* 88 (3):1026-34
- 7 Ribeiro EM, Rodriguez JM, Cósér VM, et al. (2002) Microsatellite instability and cytogenetic survey in myeloid leukemias. *Braz. J. Med. Biol. Res.* 35 (2):153-9
- 8 Indraccolo S, Minuzzo S, Nicoletti L, et al. (1999) Mutator phenotype in human hematopoietic neoplasms and its association with deletions disabling DNA repair genes and bcl-2 rearrangements. *Blood* 94 (7):2424-32
- 9 Das-Gupta EP, Seedhouse CH, Russell NH (2001) Microsatellite instability occurs in defined subsets of patients with acute myeloblastic leukaemia. *Br. J. Haematol.* 114 (2):307-12
- 10 Krsková-Honzátková L, Cermák J, Sajdová J, et al. (2002) Microsatellite instability in hematological malignancies. *Leuk. Lymphoma* 43 (10):1979-86
- 11 Nomdedéu JF, Perea G, Estivill C, et al. (2005) Microsatellite instability is not an uncommon finding in adult de novo acute myeloid leukemia. *Ann. Hematol.* 84 (6):368-75
- 12 Seedhouse CH, Das-Gupta EP, Russell NH (2003) Methylation of the hMLH1 promoter and its association with microsatellite instability in acute myeloid leukemia. *Leukemia* 17 (1):83-8
- 13 Herzog G, Lu-Hesselmann J, Zimmermann Y, et al. (2005) Microsatellite instability and p53 mutations are characteristic of subgroups of acute myeloid leukemia but independent events. *Haematologica* ePub May 2005
- 14 Bonneville R, Krook MA, Kautto EA, et al. (2017) Landscape of Microsatellite Instability Across 39 Cancer Types. *JCO Precis Oncol* 2017
- 15 Rimsza LM, Kopecky KJ, Ruschulte J, et al. (2000) Microsatellite instability is not a defining genetic feature of acute myeloid leukemogenesis in adults: results of a retrospective study of 132 patients and review of the literature. *Leukemia* 14 (6):1044-51
- 16 Maletzki C, Stier S, Linnebacher M (2013) Microsatellite instability in hematological malignancies: Hypermutation vs. immune control-who is challenging who? *Oncoimmunology* 2 (8):e25419
- 17 Walker CJ, Eisfeld AK, Genutis LK, et al. (2017) No evidence for microsatellite instability in acute myeloid leukemia. *Leukemia* ePub 06 2017
- 18 Mori N, Morosetti R, Hoflehner E, et al. (2000) Allelic loss in the progression of myelodysplastic syndrome. *Cancer Res.* 60 (11):3039-42
- 19 Sheikha MH, Tobal K, Liu Yin JA (2002) High level of microsatellite instability but not hypermethylation of mismatch repair genes in therapy-related and secondary acute myeloid leukaemia and myelodysplastic syndrome. *Br. J. Haematol.* 117 (2):359-65
- 20 Olipitz W, Hopfinger G, Aguiar RC, et al. (2002) Defective DNA-mismatch repair: a potential mediator of leukemogenic susceptibility in therapy-related myelodysplasia and leukemia. *Genes Chromosomes Cancer* 34 (2):243-8
- 21 Casorelli I, Offman J, Mele L, et al. (2003) Drug treatment in the development of mismatch repair defective acute leukemia and myelodysplastic syndrome. *DNA Repair (Amst.)* 2 (5):547-59
- 22 Ben-Yehuda D, Krichevsky S, Caspi O, et al. (1996) Microsatellite instability and p53 mutations in therapy-related leukemia suggest mutator phenotype. *Blood* 88 (11):4296-303
- 23 Tasaka T, Lee S, Spira S, et al. (1997) Microsatellite instability during the progression of acute myelocytic leukaemia. *Br. J. Haematol.* 98 (1):219-21
- 24 Offman J, Gascoigne K, Bristow F, et al. (2005) Repeated sequences in CASPASE-5 and FANCD2 but not NF1 are targets for mutation in microsatellite-unstable acute leukemia/myelodysplastic syndrome. *Mol. Cancer Res.* 3 (5):251-60
- 25 Shlush LI, Chapal-Ilani N, Adar R, et al. (2012) Cell lineage analysis of acute leukemia relapse uncovers the role of replication-rate heterogeneity and microsatellite instability. *Blood* ePub Jul 2012
- 26 Offman J, Opelz G, Doeblner B, et al. (2004) Defective DNA mismatch repair in acute myeloid leukemia/myelodysplastic syndrome after organ transplantation. *Blood* 104 (3):822-8
- 27 Kocarnik JM, Shiovitz S, Phipps AI (2015) Molecular phenotypes of colorectal cancer and potential clinical applications. *Gastroenterol Rep (Oxf)* 3 (4):269-76
- 28 You JF, Buhard O, Ligtenberg MJ, et al. (2010) Tumours with loss of MSH6 expression are MSI-H when screened with a pentaplex of five mononucleotide repeats. *Br. J. Cancer* ePub Dec 2010
- 29 Bairwa NK, Saha A, Gochhait S, et al. (2014) Microsatellite instability: an indirect assay to detect defects in the cellular mismatch repair machinery. *Methods Mol. Biol.* ePub 2014
- 30 Boland CR, Thibodeau SN, Hamilton SR, et al. (1998) A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 58 (22):5248-57
- 31 Pawlik TM, Raut CP, Rodriguez-Bigas MA (2004) Colorectal carcinogenesis: MSI-H versus MSI-L. *Dis. Markers* 20 (4-5):199-206
- 32 Boland CR, Goel A (2010) Microsatellite instability in colorectal cancer. *Gastroenterology* ePub Jun 2010
- 33 Snyder A, Makarov V, Merghoub T, et al. (2014) Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N. Engl. J. Med.* ePub Dec 2014
- 34 Rosenberg JE, Hoffman-Censits J, Powles T, et al. (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* ePub May 2016
- 35 Johnson DB, Frampton GM, Rioth MJ, et al. (2016) Targeted Next Generation Sequencing Identifies Markers of Response to PD-1 Blockade. *Cancer Immunol Res* ePub Nov 2016
- 36 Balar AV, Galsky MD, Rosenberg JE, et al. (2017) Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet* ePub 01 2017
- 37 Miao D, Margolis CA, Vokes NI, et al. (2018) Genomic correlates of response to immune checkpoint blockade in microsatellite-stable solid tumors. *Nat. Genet.* ePub Sep 2018
- 38 Rizvi NA, Hellmann MD, Snyder A, et al. (2015) Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* ePub Apr 2015
- 39 Dong ZY, Zhong WZ, Zhang XC, et al. (2017) Clin. Cancer Res. 23 (12):3012-3024
- 40 Mehnert JM, Panda A, Zhong H, et al. (2016) Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. *J. Clin. Invest.* ePub Jun 2016
- 41 Santin AD, Bellone S, Buza N, et al. (2016) Regression of Chemotherapy-Resistant Polymerase ε (POLE) Ultra-Mutated and MSH6 Hyper-Mutated Endometrial Tumors with Nivolumab. *Clin. Cancer Res.* 22 (23):5682-5687
- 42 Johanns TM, Miller CA, Dorward IG, et al. (2016) Immunogenomics of Hypermutated Glioblastoma: A Patient with Germline POLE Deficiency Treated with Checkpoint Blockade Immunotherapy. *Cancer Discov* ePub 11 2016
- 43 Bouffet E, Larouche V, Campbell BB, et al. (2016) Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency. *J. Clin. Oncol.* ePub Jul 2016
- 44 Fabrizio DA, George TJ, Dunne RF, et al. (2018) Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition. *J Gastrointest Oncol* 9 (4):610-617
- 45 Van Allen EM, Miao D, Schilling B, et al. (2015) Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science* ePub Oct 2015
- 46 Legrand et al., 2018; ASCO Abstract 12000
- 47 Chalmers ZR, Connelly CF, Fabrizio D, et al. (2017) Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med* ePub 04 2017
- 48 Karim et al., 2017; AACR Abstract 3724
- 49 Pfeifer GP, You YH, Besaratinia A (2005) Mutations induced by ultraviolet light. *Mutat. Res.* 571 (1-2):19-31

TRF#

**APPENDIX**
**References**

- 50 Hill VK, Gartner JJ, Samuels Y, et al. (2013) The genetics of melanoma: recent advances. *Annu Rev Genomics Hum Genet* ePub 2013
- 51 Pfeifer GP, Denissenko MF, Olivier M, et al. (2002) Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. *Oncogene* 21 (48):7435-51
- 52 Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. (2013) Integrated genomic characterization of endometrial carcinoma. *Nature* ePub May 2013
- 53 Briggs S, Tomlinson I (2013) Germline and somatic polymerase  $\epsilon$  and  $\delta$  mutations define a new class of hypermutated colorectal and endometrial cancers. *J. Pathol.* ePub Jun 2013
- 54 Heitzer E, Tomlinson I (2014) Replicative DNA polymerase mutations in cancer. *Curr. Opin. Genet. Dev.* ePub Feb 2014
- 55 (2012) Comprehensive molecular characterization of human colon and rectal cancer. *Nature* ePub Jul 2012
- 56 Roberts SA, Gordenin DA (2014) Hypermutation in human cancer genomes: footprints and mechanisms. *Nat. Rev. Cancer* ePub 12 2014
- 57 Stein EM, DiNardo CD, Pollyea DA, et al. (2017) *Blood* ePub 08 2017
- 58 Yen K, Travins J, Wang F, et al. (2017) *Cancer Discov* ePub 05 2017
- 59 Amatangelo MD, Quek L, Shih A, et al. (2017) Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. *Blood* ePub 08 2017
- 60 Konopleva et al., 2014; ASH Abstract 118
- 61 Konopleva M, Pollyea DA, Potluri J, et al. (2016) Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia. *Cancer Discov* ePub 10 2016
- 62 Chan SM, Thomas D, Corces-Zimmerman MR, et al. (2015) Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia. *Nat. Med.* ePub Feb 2015
- 63 Figueroa ME, Abdel-Wahab O, Lu C, et al. (2010) Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell* ePub Dec 2010
- 64 Turcan S, Rohle D, Goenka A, et al. (2012) IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature* ePub Feb 2012
- 65 Emadi A, Faramand R, Carter-Cooper B, et al. (2015) Presence of isocitrate dehydrogenase mutations may predict clinical response to hypomethylating agents in patients with acute myeloid leukemia. *Am. J. Hematol.* ePub May 2015
- 66 DiNardo CD, Patel KP, Garcia-Manero G, et al. (2014) Lack of association of IDH1, IDH2 and DNMT3A mutations with outcome in older patients with acute myeloid leukemia treated with hypomethylating agents. *Leuk. Lymphoma* ePub Aug 2014
- 67 Metzeler KH, Walker A, Geyer S, et al. (2012) DNMT3A mutations and response to the hypomethylating agent decitabine in acute myeloid leukemia. *Leukemia* ePub May 2012
- 68 Traina F, Visconte V, Elson P, et al. (2014) Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. *Leukemia* ePub Jan 2014
- 69 DiNardo et al., 2017; ASH Abstract 639
- 70 Cancer Genome Atlas Research Network, Ley TJ, Miller C, et al. (2013) Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N. Engl. J. Med.* ePub 05 2013
- 71 Green CL, Evans CM, Zhao L, et al. (2011) The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. *Blood* ePub Jul 2011
- 72 Patel JP, Gönen M, Figueroa ME, et al. (2012) Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N. Engl. J. Med.* ePub Mar 2012
- 73 Boissel N, Nibourel O, Renneville A, et al. (2011) Differential prognosis impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. *Blood* ePub Mar 2011
- 74 Ravandi F, Patel K, Luthra R, et al. (2012) Prognostic significance of alterations in IDH enzyme isoforms in patients with AML treated with high-dose cytarabine and idarubicin. *Cancer* ePub May 2012
- 75 Reitman ZJ, Yan H (2010) Isocitrate dehydrogenase 1 and 2 mutations in cancer: alterations at a crossroads of cellular metabolism. *J. Natl. Cancer Inst.* ePub Jul 2010
- 76 Jin G, Reitman ZJ, Spasojevic I, et al. (2011) 2-hydroxyglutarate production, but not dominant negative function, is conferred by glioma-derived NADP-dependent isocitrate dehydrogenase mutations. *PLoS ONE* ePub Feb 2011
- 77 Kranendijk M, Salomons GS, Gibson KM, et al. (2011) A lymphoblast model for IDH2 gain-of-function activity in d-2-hydroxyglutaric aciduria type II: novel avenues for biochemical and therapeutic studies. *Biochim. Biophys. Acta* 1812 (11):1380-4
- 78 Gross S, Cairns RA, Minden MD, et al. (2010) Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J. Exp. Med.* ePub Feb 2010
- 79 Ward PS, Patel J, Wise DR, et al. (2010) The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell* ePub Mar 2010
- 80 Dang L, Jin S, Su SM (2010) IDH mutations in glioma and acute myeloid leukemia. *Trends Mol Med* ePub Sep 2010
- 81 Amary MF, Bacsi K, Maggiani F, et al. (2011) IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. *J. Pathol.* ePub Jul 2011
- 82 Cardaci S, Ciriolo MR (2012) TCA Cycle Defects and Cancer: When Metabolism Tunes Redox State. *Int J Cell Biol* ePub 2012
- 83 Itzykson R, Kosmider O, Cluzeau T, et al. (2011) Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. *Leukemia* ePub Jul 2011
- 84 Bejar R, Lord A, Stevenson K, et al. (2014) TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. *Blood* ePub Oct 2014
- 85 Delarue et al., 2016; ASH Abstract 4164
- 86 Cheminant M, Bruneau J, Kosmider O, et al. (2015) Efficacy of 5-azacytidine in a TET2 mutated angioimmunoblastic T cell lymphoma. *Br. J. Haematol.* ePub Mar 2015
- 87 Saillard C, Guermouche H, Derriueux C, et al. (2017) Response to 5-azacytidine in a patient with TET2-mutated angioimmunoblastic T-cell lymphoma and chronic myelomonocytic leukaemia preceded by an EBV-positive large B-cell lymphoma. *Hematol Oncol* ePub Dec 2017
- 88 Metzeler KH, Maharry K, Radmacher MD, et al. (2011) TET2 mutations improve the new European LeukemiaNet risk classification of acute myeloid leukemia: a Cancer and Leukemia Group B study. *J. Clin. Oncol.* ePub Apr 2011
- 89 Lin PH, Li HY, Fan SC, et al. (2017) A targeted next-generation sequencing in the molecular risk stratification of adult acute myeloid leukemia: implications for clinical practice. *Cancer Med* ePub 02 2017
- 90 Chou WC, Chou SC, Liu CY, et al. (2011) TET2 mutation is an unfavorable prognostic factor in acute myeloid leukemia patients with intermediate-risk cytogenetics. *Blood* ePub Oct 2011
- 91 Shen Y, Zhu YM, Fan X, et al. (2011) Gene mutation patterns and their prognostic impact in a cohort of 1185 patients with acute myeloid leukemia. *Blood* ePub Nov 2011
- 92 Gaidzik VI, Paschka P, Späth D, et al. (2012) TET2 mutations in acute myeloid leukemia (AML): results from a comprehensive genetic and clinical analysis of the AML study group. *J. Clin. Oncol.* ePub Apr 2012
- 93 Weissmann S, Alpermann T, Grossmann V, et al. (2012) Landscape of TET2 mutations in acute myeloid leukemia. *Leukemia* ePub May 2012
- 94 Grossmann V, Haferlach C, Naderajah N, et al. (2013) CEBPA double-mutated acute myeloid leukaemia harbours concomitant molecular mutations in 76-8% of cases with TET2 and GATA2 alterations impacting prognosis. *Br. J. Haematol.* ePub Jun 2013
- 95 Ceraulo et al., 2016; ASH Abstract 3952
- 96 Mohamed AM, Balsat M, Koering C, et al. (2017) TET2 exon 2 skipping is an independent favorable prognostic factor for cytogenetically normal acute myelogenous leukemia (AML): TET2 exon 2 skipping in AML. *Leuk. Res.* ePub 05 2017
- 97 Ito S, D'Alessio AC, Taranova OV, et al. (2010) Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. *Nature* ePub Aug 2010
- 98 Guo JU, Su Y, Zhong C, et al. (2011) Hydroxylation of 5-methylcytosine by TET1 promotes active DNA demethylation in the adult brain. *Cell* ePub Apr 2011
- 99 Iyer LM, Tahilian M, Rao A, et al. (2009) Prediction of novel families of enzymes involved in oxidative and other complex modifications of bases in nucleic acids. *Cell Cycle* ePub Jun 2009
- 100 Ko M, Huang Y, Jankowska AM, et al. (2010) Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. *Nature* ePub Dec 2010

TRF#

**APPENDIX**
**References**

- 101 Yang H, Liu Y, Bai F, et al. (2013) Tumor development is associated with decrease of TET gene expression and 5-methylcytosine hydroxylation. *Oncogene* ePub Jan 2013
- 102 Hu L, Li Z, Cheng J, et al. (2013) Crystal structure of TET2-DNA complex: insight into TET-mediated 5mC oxidation. *Cell* ePub Dec 2013
- 103 Wang Y, Xiao M, Chen X, et al. (2015) WT1 recruits TET2 to regulate its target gene expression and suppress leukemia cell proliferation. *Mol. Cell* ePub Feb 2015
- 104 Xie M, Lu C, Wang J, et al. (2014) Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nat. Med.* ePub Dec 2014
- 105 Jaiswal S, Fontanillas P, Flannick J, et al. (2014) Age-related clonal hematopoiesis associated with adverse outcomes. *N. Engl. J. Med.* ePub Dec 2014
- 106 Genovese G, Köhler AK, Handsaker RE, et al. (2014) Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N. Engl. J. Med.* ePub Dec 2014
- 107 Steensma DP, Bejar R, Jaiswal S, et al. (2015) Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* ePub Jul 2015
- 108 Link DC, Walter MJ (2016) 'CHIP'ping away at clonal hematopoiesis. *Leukemia* ePub 08 2016
- 109 Rios J, Puhalla S (2011) PARP inhibitors in breast cancer: BRCA and beyond. *Oncology (Williston Park, N.Y.)* 25 (11):1014-25
- 110 Jacquemont C, Simon JA, D'Andrea AD, et al. (2012) Non-specific chemical inhibition of the Fanconi anemia pathway sensitizes cancer cells to cisplatin. *Mol. Cancer* ePub Apr 2012
- 111 Kratz K, Schöpf B, Kaden S, et al. (2010) Deficiency of FANCD2-associated nuclease KIAA1018/FAN1 sensitizes cells to interstrand crosslinking agents. *Cell* ePub Jul 2010
- 112 Lombardi AJ, Hoskins EE, Foglesong GD, et al. (2015) Acquisition of Relative Interstrand Crosslinker Resistance and PARP Inhibitor Sensitivity in Fanconi Anemia Head and Neck Cancers. *Clin. Cancer Res.* 21 (8):1962-72
- 113 Moldovan and D'Andrea 2009; 19686080
- 114 Deakynne JS, Mazin AV (2011) Fanconi anemia: at the crossroads of DNA repair. *Biochemistry Mosc.* ePub Jan 2011
- 115 Furukawa T, Kuboki Y, Tanji E, et al. (2011) Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. *Sci Rep* ePub 2011
- 116 Wu J, Matthaei H, Maitra A, et al. (2011) Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. *Sci Transl Med* ePub Jul 2011
- 117 Nishikawa G, Sekine S, Ogawa R, et al. (2013) Frequent GNAS mutations in low-grade appendiceal mucinous neoplasms. *Br. J. Cancer* ePub Mar 2013
- 118 Singhi AD, Davison JM, Choudry HA, et al. (2014) GNAS is frequently mutated in both low-grade and high-grade disseminated appendiceal mucinous neoplasms but does not affect survival. *Hum. Pathol.* ePub Aug 2014
- 119 (2011) Integrated genomic analyses of ovarian carcinoma. *Nature* ePub Jun 2011
- 120 Kan Z, Jaiswal BS, Stinson J, et al. (2010) Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature* ePub Aug 2010
- 121 Tominaga E, Tsuda H, Arai T, et al. (2010) Amplification of GNAS may be an independent, qualitative, and reproducible biomarker to predict progression-free survival in epithelial ovarian cancer. *Gynecol. Oncol.* ePub Aug 2010
- 122 (2014) Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* ePub Sep 2014
- 123 (2014) Comprehensive molecular profiling of lung adenocarcinoma. *Nature* ePub Jul 2014
- 124 (2012) Comprehensive molecular portraits of human breast tumours. *Nature* ePub Oct 2012
- 125 Witkiewicz AK, McMillan EA, Balaji U, et al. (2015) Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. *Nat Commun* ePub Apr 2015
- 126 Barretina J, Taylor BS, Banerji S, et al. (2010) Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. *Nat. Genet.* ePub Aug 2010
- 127 Lohr JG, Stojanov P, Carter SL, et al. (2014) Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell* ePub Jan 2014
- 128 Chapman MA, Lawrence MS, Keats JJ, et al. (2011) Initial genome sequencing and analysis of multiple myeloma. *Nature* ePub Mar 2011
- 129 Zacharin M, Bajpai A, Chow CW, et al. (2011) Gastrointestinal polypos in McCune Albright syndrome. *J. Med. Genet.* ePub Jul 2011
- 130 Alakus H, Mönig SP, Warnecke-Eberz U, et al. (2009) Association of the GNAS1 T393C polymorphism with tumor stage and survival in gastric cancer. *World J. Gastroenterol.* ePub Dec 2009
- 131 Hayward BE, Moran V, Strain L, et al. (1998) Bidirectional imprinting of a single gene: GNAS1 encodes maternally, paternally, and biallelically derived proteins. *Proc. Natl. Acad. Sci. U.S.A.* 95 (26):15475-80
- 132 Gao J, Aksoy BA, Dogrusoz U, et al. (2013) Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci Signal* ePub Apr 2013
- 133 Zack TI, Schumacher SE, Carter SL, et al. (2013) Pan-cancer patterns of somatic copy number alteration. *Nat. Genet.* ePub Oct 2013
- 134 Beroukhim R, Mermel CH, Porter D, et al. (2010) The landscape of somatic copy-number alteration across human cancers. *Nature* ePub Feb 2010
- 135 Masters SB, Miller RT, Chi MH, et al. (1989) Mutations in the GTP-binding site of GS alpha alter stimulation of adenylyl cyclase. *J. Biol. Chem.* 264 (26):15467-74
- 136 Graziano MP, Gilman AG (1989) Synthesis in Escherichia coli of GTPase-deficient mutants of Gs alpha. *J. Biol. Chem.* 264 (26):15475-82
- 137 Jang IS, Juhn YS (2001) Adaptation of cAMP signaling system in SH-SY5Y neuroblastoma cells following expression of a constitutively active stimulatory G protein alpha, Q227L Galpha. *Exp. Mol. Med.* 33 (1):37-45
- 138 Landis CA, Masters SB, Spada A, et al. (1989) GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. *Nature* 340 (6236):692-6
- 139 Tobar-Rubin R, Sultan D, Janevska D, et al. (2013) Intragenic suppression of a constitutively active allele of Gs $\alpha$  associated with McCune-Albright syndrome. *J. Mol. Endocrinol.* ePub Apr 2013
- 140 Mariot V, Wu JY, Aydin C, et al. (2011) Potent constitutive cyclic AMP-generating activity of XL $\alpha$ s implicates this imprinted GNAS product in the pathogenesis of McCune-Albright syndrome and fibrous dysplasia of bone. *Bone* ePub Feb 2011
- 141 Weinstein LS, Shenker A, Gejman PV, et al. (1991) Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N. Engl. J. Med.* 325 (24):1688-95
- 142 Collins MT, Sarlis NJ, Merino MJ, et al. (2003) Thyroid carcinoma in the McCune-Albright syndrome: contributory role of activating Gs alpha mutations. *J. Clin. Endocrinol. Metab.* 88 (9):4413-7
- 143 Nault JC, Fabre M, Couchy G, et al. (2012) GNAS-activating mutations define a rare subgroup of inflammatory liver tumors characterized by STAT3 activation. *J. Hepatol.* ePub Jan 2012
- 144 Robinson G, Parker M, Kranenburg TA, et al. (2012) Novel mutations target distinct subgroups of medulloblastoma. *Nature* ePub Aug 2012
- 145 Ho AS, Kannan K, Roy DM, et al. (2013) The mutational landscape of adenoid cystic carcinoma. *Nat. Genet.* ePub Jul 2013
- 146 Grasso CS, Wu YM, Robinson DR, et al. (2012) The mutational landscape of lethal castration-resistant prostate cancer. *Nature* ePub Jul 2012
- 147 Van der Meulen J, Sanghvi V, Mavrakis K, et al. (2015) The H3K27me3 demethylase UTX is a gender-specific tumor suppressor in T-cell acute lymphoblastic leukemia. *Blood* ePub Jan 2015
- 148 Wang L, Chang J, Varghese D, et al. (2013) A small molecule modulates Jumonji histone demethylase activity and selectively inhibits cancer growth. *Nat Commun* ePub 2013
- 149 Kim JH, Sharma A, Dhar SS, et al. (2014) UTX and MLL4 coordinately regulate transcriptional programs for cell proliferation and invasiveness in breast cancer cells. *Cancer Res.* ePub Mar 2014
- 150 Shen Y, Guo X, Wang Y, et al. (2012) Expression and significance of histone H3K27 demethylases in renal cell carcinoma. *BMC Cancer* ePub Oct 2012
- 151 van Haaften G, Dalgliesh GL, Davies H, et al. (2009) Somatic mutations of the histone H3K27 demethylase gene UTX in human cancer. *Nat. Genet.* ePub May 2009
- 152 Kuendgen et al., 2013; ASH Abstract 2757
- 153 Inoue A, Kawakami C, Takitani K, et al. (2014) Azacitidine in the treatment of pediatric therapy-related myelodysplastic syndrome after allogeneic hematopoietic stem cell transplantation. *J. Pediatr. Hematol. Oncol.* ePub Jul 2014
- 154 Buchi F, Masala E, Rossi A, et al. (2014) Redistribution of H3K27me3 and acetylated histone H4 upon exposure to azacitidine and decitabine results in de-repression of the AML1/ETO target gene IL3. *Epigenetics* ePub Mar 2014

TRF#

**APPENDIX**
**References**

- 155 Guadagnuolo et al., 2014; ASH Abstract 1030
- 156 Braun T, Itzykson R, Renneville A, et al. (2011) Molecular predictors of response to decitabine in advanced chronic myelomonocytic leukemia: a phase 2 trial. *Blood* ePub Oct 2011
- 157 Tobiasson M, McLornan DP, Karimi M, et al. (2016) Mutations in histone modulators are associated with prolonged survival during azacitidine therapy. *Oncotarget* ePub Apr 2016
- 158 Odenike OM, Alkan S, Sher D, et al. (2008) Histone deacetylase inhibitor romidepsin has differential activity in core binding factor acute myeloid leukemia. *Clin. Cancer Res.* 14 (21):7095-101
- 159 Barbetti V, Gozzini A, Rovida E, et al. (2008) Selective anti-leukaemic activity of low-dose histone deacetylase inhibitor ITF2357 on AML1/ETO-positive cells. *Oncogene* ePub Mar 2008
- 160 Hu Z, Gu X, Baraoidan K, et al. (2011) RUNX1 regulates corepressor interactions of PU.1. *Blood* ePub Jun 2011
- 161 Bots M, Verbrugge I, Martin BP, et al. (2014) Differentiation therapy for the treatment of t(8;21) acute myeloid leukemia using histone deacetylase inhibitors. *Blood* ePub Feb 2014
- 162 Bejar R, Stevenson K, Abdel-Wahab O, et al. (2011) Clinical effect of point mutations in myelodysplastic syndromes. *N. Engl. J. Med.* ePub Jun 2011
- 163 Papaemmanuil E, Gerstung M, Malcovati L, et al. (2013) Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* ePub Nov 2013
- 164 Gaidzik VI, Bullinger L, Schlenk RF, et al. (2011) RUNX1 mutations in acute myeloid leukemia: results from a comprehensive genetic and clinical analysis from the AML study group. *J. Clin. Oncol.* ePub Apr 2011
- 165 Schlegelberger B, Göhring G, Thol F, et al. (2012) Update on cytogenetic and molecular changes in myelodysplastic syndromes. *Leuk. Lymphoma* ePub Apr 2012
- 166 Bacher U, Haferlach T, Schnittger S, et al. (2011) Recent advances in diagnosis, molecular pathology and therapy of chronic myelomonocytic leukaemia. *Br. J. Haematol.* ePub Apr 2011
- 167 Kuo MC, Liang DC, Huang CF, et al. (2009) RUNX1 mutations are frequent in chronic myelomonocytic leukemia and mutations at the C-terminal region might predict acute myeloid leukemia transformation. *Leukemia* ePub Aug 2009
- 168 Itzykson R, Kosmider O, Renneville A, et al. (2013) Prognostic score including gene mutations in chronic myelomonocytic leukemia. *J. Clin. Oncol.* ePub Jul 2013
- 169 Schnittger S, Dicker F, Kern W, et al. (2011) RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis. *Blood* ePub Feb 2011
- 170 Harada H, Harada Y, Kimura A (2006) Implications of somatic mutations in the AML1/RUNX1 gene in myelodysplastic syndrome (MDS): future molecular therapeutic directions for MDS. *Curr Cancer Drug Targets* ePub Sep 2006
- 171 Rio-Machín A, Menezes J, Maiques-Díaz A, et al. (2012) Abrogation of RUNX1 gene expression in de novo myelodysplastic syndrome with t(4;21)(q21;q22). *Haematologica* ePub Apr 2012
- 172 Silva FP, Morolli B, Storlazzi CT, et al. (2003) Identification of RUNX1/AML1 as a classical tumor suppressor gene. *Oncogene* 22 (4):538-47
- 173 Scheitz CJ, Tumber T (2013) New insights into the role of Runx1 in epithelial stem cell biology and pathology. *J. Cell. Biochem.* ePub May 2013
- 174 Bravo J, Li Z, Speck NA, et al. (2001) The leukemia-associated AML1 (Runx1)--CBF beta complex functions as a DNA-induced molecular clamp. *Nat. Struct. Biol.* 8 (4):371-8
- 175 Matheny CJ, Speck ME, Cushing PR, et al. (2007) Disease mutations in RUNX1 and RUNX2 create nonfunctional, dominant-negative, or hypomorphic alleles. *EMBO J.* 26 (4):1163-75
- 176 Zhao LJ, Wang YY, Li G, et al. (2012) Functional features of RUNX1 mutants in acute transformation of chronic myeloid leukemia and their contribution to inducing murine full-blown leukemia. *Blood* ePub Mar 2012
- 177 Yamamoto K, Tsuzuki S, Minami Y, et al. (2013) Functionally deregulated AML1/RUNX1 cooperates with BCR-ABL to induce a blastic phase-like phenotype of chronic myelogenous leukemia in mice. *PLoS ONE* ePub 2013
- 178 Cammenga J, Niebuhr B, Horn S, et al. (2007) RUNX1 DNA-binding mutants, associated with minimally differentiated acute myelogenous leukemia, disrupt myeloid differentiation. *Cancer Res.* 67 (2):537-45
- 179 Michaud J, Wu F, Osato M, et al. (2002) In vitro analyses of known and novel RUNX1/AML1 mutations in dominant familial platelet disorder with predisposition to acute myelogenous leukemia: implications for mechanisms of pathogenesis. *Blood* 99 (4):1364-72
- 180 Li Z, Yan J, Matheny CJ, et al. (2003) Energetic contribution of residues in the Runx1 Runt domain to DNA binding. *J. Biol. Chem.* 278 (35):33088-96
- 181 Obeng EA, Chappell RJ, Seiler M, et al. (2016) Physiologic Expression of Sf3b1(K700E) Causes Impaired Erythropoiesis, Aberrant Splicing, and Sensitivity to Therapeutic Spliceosome Modulation. *Cancer Cell* ePub 09 2016
- 182 Lee SC, Dvinge H, Kim E, et al. (2016) Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal proteins. *Nat. Med.* ePub 06 2016
- 183 Yoshimi A, Abdel-Wahab O (2017) Molecular Pathways: Understanding and Targeting Mutant Spliceosomal Proteins. *Clin. Cancer Res.* 23 (2):336-341
- 184 Lee SC, Abdel-Wahab O (2016) Therapeutic targeting of splicing in cancer. *Nat. Med.* ePub 09 2016
- 185 Papaemmanuil E, Cazzola M, Boultonwood J, et al. (2011) Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N. Engl. J. Med.* ePub Oct 2011
- 186 Yoshida K, Sanada M, Shiraishi Y, et al. (2011) Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature* ePub Sep 2011
- 187 Visconte V, Makishima H, Jankowska A, et al. (2012) SF3B1, a splicing factor is frequently mutated in refractory anemia with ring sideroblasts. *Leukemia* ePub Mar 2012
- 188 Visconte V, Rogers HJ, Singh J, et al. (2012) SF3B1 haploinsufficiency leads to formation of ring sideroblasts in myelodysplastic syndromes. *Blood* ePub Oct 2012
- 189 Malcovati L, Papaemmanuil E, Bowen DT, et al. (2011) Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. *Blood* ePub Dec 2011
- 190 Patnaik MM, Lasho TL, Hodnefield JM, et al. (2012) SF3B1 mutations are prevalent in myelodysplastic syndromes with ring sideroblasts but do not hold independent prognostic value. *Blood* ePub Jan 2012
- 191 Thol F, Kade S, Schlarmann C, et al. (2012) Frequency and prognostic impact of mutations in SRSF2, UZF1, and ZRSR2 in patients with myelodysplastic syndromes. *Blood* ePub Apr 2012
- 192 Damm F, Kosmider O, Gelsi-Boyer V, et al. (2012) Mutations affecting mRNA splicing define distinct clinical phenotypes and correlate with patient outcome in myelodysplastic syndromes. *Blood* ePub Apr 2012
- 193 Jeromin S, Haferlach T, Grossmann V, et al. (2013) High frequencies of SF3B1 and JAK2 mutations in refractory anemia with ring sideroblasts associated with marked thrombocytosis strengthen the assignment to the category of myelodysplastic/myeloproliferative neoplasms. *Haematologica* ePub Feb 2013
- 194 Makishima H, Visconte V, Sakaguchi H, et al. (2012) Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. *Blood* ePub Apr 2012
- 195 Bejar R, Stevenson KE, Caughey BA, et al. (2012) Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. *J. Clin. Oncol.* ePub Sep 2012
- 196 Cui R, Gale RP, Xu Z, et al. (2012) Clinical importance of SF3B1 mutations in Chinese with myelodysplastic syndromes with ring sideroblasts. *Leuk. Res.* ePub Nov 2012
- 197 Yang J, Qian J, Yao DM, et al. (2013) SF3B1 mutation is a rare event in Chinese patients with acute and chronic myeloid leukemia. *Clin. Biochem.* ePub May 2013
- 198 Broséus J, Alpermann T, Wulfert M, et al. (2013) Age, JAK2(V617F) and SF3B1 mutations are the main predicting factors for survival in refractory anaemia with ring sideroblasts and marked thrombocytosis. *Leukemia* ePub Sep 2013
- 199 Malcovati L, Karimi M, Papaemmanuil E, et al. (2015) SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. *Blood* ePub Jul 2015
- 200 Quesada V, Conde L, Villamor N, et al. (2011) Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. *Nat. Genet.* ePub Dec 2011
- 201 Rossi D, Brusca G, Spina V, et al. (2011) Mutations of the SF3B1 splicing factor in chronic lymphocytic leukemia: association with progression and fludarabine-refractoriness. *Blood* ePub Dec 2011
- 202 Wang L, Lawrence MS, Wan Y, et al. (2011) SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N. Engl. J. Med.* ePub Dec 2011



TRF#

**APPENDIX**
**References**

- 203 Rossi D, Rasi S, Spina V, et al. (2012) Different impact of NOTCH1 and SF3B1 mutations on the risk of chronic lymphocytic leukemia transformation to Richter syndrome. *Br. J. Haematol.* ePub Aug 2012
- 204 Mansouri L, Cahill N, Gunnarsson R, et al. (2013) NOTCH1 and SF3B1 mutations can be added to the hierarchical prognostic classification in chronic lymphocytic leukemia. *Leukemia* ePub Feb 2013
- 205 Cazzola M, Rossi M, Malcovati L, et al. (2013) Biologic and clinical significance of somatic mutations of SF3B1 in myeloid and lymphoid neoplasms. *Blood* ePub Jan 2013
- 206 Della Porta MG, Travaglino E, Boveri E, et al. (2015) Minimal morphological criteria for defining bone marrow dysplasia: a basis for clinical implementation of WHO classification of myelodysplastic syndromes. *Leukemia* ePub Jan 2015
- 207 Jeromin S, Haferlach T, Weissmann S, et al. (2015) Refractory anemia with ring sideroblasts and marked thrombocytosis cases harbor mutations in SF3B1 or other spliceosome genes accompanied by JAK2V617F and ASXL1 mutations. *Haematologica* ePub Apr 2015
- 208 Wang C, Chua K, Seghezzi W, et al. (1998) Phosphorylation of spliceosomal protein SAP 155 coupled with splicing catalysis. *Genes Dev.* 12 (10):1409-14
- 209 Hahn CN, Scott HS (2011) Spliceosome mutations in hematopoietic malignancies. *Nat. Genet.* ePub Dec 2011
- 210 Yang J, Qian J, Lin J, et al. (2013) Development of a high-resolution melting analysis for the detection of the SF3B1 mutations. *Genet Test Mol Biomarkers* ePub Apr 2013
- 211 Maguire SL, Leonidou A, Wai P, et al. (2015) SF3B1 mutations constitute a novel therapeutic target in breast cancer. *J. Pathol.* ePub Mar 2015
- 212 Wan Y, Wu CJ (2013) SF3B1 mutations in chronic lymphocytic leukemia. *Blood* ePub Jun 2013
- 213 Gentien D, Kosmider O, Nguyen-Khac F, et al. (2014) A common alternative splicing signature is associated with SF3B1 mutations in malignancies from different cell lineages. *Leukemia* ePub Jun 2014
- 214 Schmidt M, Epstein S, Maruta K, et al. (1989) Modulation of arachidonic acid metabolism has limited effects on the development of type I diabetes in animal models. *Diabetes Res.* 12 (4):161-4
- 215 Darman RB, Seiler M, Agrawal AA, et al. (2015) Cancer-Associated SF3B1 Hotspot Mutations Induce Cryptic 3' Splice Site Selection through Use of a Different Branch Point. *Cell Rep* ePub Nov 2015
- 216 Alsafadi S, Houy A, Battistella A, et al. (2016) Cancer-associated SF3B1 mutations affect alternative splicing by promoting alternative branchpoint usage. *Nat Commun* ePub Feb 2016
- 217 Willekens et al., 2017; ASH Meeting Abstract 1313
- 218 Dombret H, Seymour JF, Butrym A, et al. (2015) International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* ePub Jul 2015
- 219 Mozessohn et al., 2016; ASH Abstract 4338
- 220 Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. (2010) Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J. Clin. Oncol.* ePub Feb 2010
- 221 Seymour et al., 2016; ASH Abstract 2818
- 222 Tang et al., 2016; ASH Abstract 2859
- 223 Montesinos et al., 2016; ASH Abstract 4036
- 224 Thépot S, Itzykson R, Seegers V, et al. (2014) Azacitidine in untreated acute myeloid leukemia: a report on 149 patients. *Am. J. Hematol.* ePub Apr 2014
- 225 Ramos F, Thépot S, Pleyer L, et al. (2015) Azacitidine frontline therapy for unfit acute myeloid leukemia patients: clinical use and outcome prediction. *Leuk. Res.* ePub Mar 2015
- 226 Pleyer L, Stauder R, Burgstaller S, et al. (2013) Azacitidine in patients with WHO-defined AML - results of 155 patients from the Austrian Azacitidine Registry of the AGMT-Study Group. *J Hematol Oncol* ePub Apr 2013
- 227 Stahl et al., 2016; ASH Abstract 1063
- 228 Swords et al., 2016; ASH Abstract 98
- 229 Garcia-Manero et al., 2016; ASH Abstract 100
- 230 Montalban-Bravo G, Huang X, Naqvi K, et al. (2017) A clinical trial for patients with acute myeloid leukemia or myelodysplastic syndromes not eligible for standard clinical trials. *Leukemia* ePub Q2 2017
- 231 Strati P, Kantarjian H, Ravandi F, et al. (2015) Phase I/II trial of the combination of midostaurin (PKC412) and 5-azacytidine for patients with acute myeloid leukemia and myelodysplastic syndrome. *Am. J. Hematol.* ePub Apr 2015
- 232 Ravandi F, Alattar ML, Grunwald MR, et al. (2013) Phase 2 study of azacitidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood* ePub Jun 2013
- 233 Walker AR, Klisovic RB, Garzon R, et al. (2014) Phase I study of azacitidine and bortezomib in adults with relapsed or refractory acute myeloid leukemia. *Leuk. Lymphoma* ePub Jun 2014
- 234 Tan P, Tiong IS, Fleming S, et al. (2017) The mTOR inhibitor everolimus in combination with azacitidine in patients with relapsed/refractory acute myeloid leukemia: a phase Ib/II study. *Oncotarget* ePub Aug 2017
- 235 Daver et al., 2016; ASH Abstract 763
- 236 Daver et al., 2016; ASH Abstract 1641
- 237 Wei A, Tan P, Perruzza S, et al. (2015) Maintenance lenalidomide in combination with 5-azacitidine as post-remission therapy for acute myeloid leukaemia. *Br. J. Haematol.* ePub Apr 2015
- 238 Rautenberg C, Nachtkamp K, Dienst A, et al. (2017) Sorafenib and azacitidine as salvage therapy for relapse of FLT3-ITD mutated AML after allo-SCT. *Eur. J. Haematol.* ePub Apr 2017
- 239 Schroeder T, Czibere A, Platzbecker U, et al. (2013) Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation. *Leukemia* ePub Jun 2013
- 240 Kantarjian H, Issa JP, Rosenfeld CS, et al. (2006) Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer* 106 (8):1794-803
- 241 Lübbert M, Suciú S, Baila L, et al. (2011) Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *J. Clin. Oncol.* ePub May 2011
- 242 Becker H, Suciú S, Rüter BH, et al. (2015) Decitabine versus best supportive care in older patients with refractory anemia with excess blasts in transformation (RAEBt) - results of a subgroup analysis of the randomized phase III study 06011 of the EORTC Leukemia Cooperative Group and German MDS Study Group (GMDSSG). *Ann. Hematol.* ePub Dec 2015
- 243 Lübbert M, Suciú S, Hagemeyer A, et al. (2016) Decitabine improves progression-free survival in older high-risk MDS patients with multiple autosomal monosomies: results of a subgroup analysis of the randomized phase III study 06011 of the EORTC Leukemia Cooperative Group and German MDS Study Group. *Ann. Hematol.* ePub Jan 2016
- 244 Wu D, Du X, Jin J, et al. (2015) Decitabine for Treatment of Myelodysplastic Syndromes in Chinese Patients: An Open-Label, Phase-3b Study. *Adv Ther* ePub Nov 2015
- 245 Kantarjian HM, Thomas XG, Dmoszynska A, et al. (2012) Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J. Clin. Oncol.* ePub Jul 2012
- 246 Cashen AF, Schiller GJ, O'Donnell MR, et al. (2010) Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J. Clin. Oncol.* ePub Feb 2010
- 247 Blum W, Garzon R, Klisovic RB, et al. (2010) Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc. Natl. Acad. Sci. U.S.A.* ePub Apr 2010
- 248 Lübbert M, Rüter BH, Claus R, et al. (2012) A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy. *Haematologica* ePub Mar 2012
- 249 Ritchie EK, Feldman EJ, Christos PJ, et al. (2013) Decitabine in patients with newly diagnosed and relapsed acute myeloid leukemia. *Leuk. Lymphoma* ePub Sep 2013
- 250 Kadia TM, Faderl S, Ravandi F, et al. (2015) Final results of a phase 2 trial of clofarabine and low-dose cytarabine alternating with decitabine in older patients with newly diagnosed acute myeloid leukemia. *Cancer* ePub Jul 2015
- 251 Welch JS, Petti AA, Miller CA, et al. (2016) TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. *N. Engl. J. Med.* ePub 11 2016
- 252 Kropf et al., 2016; ASH Abstract 3170

TRF#

APPENDIX

References

- 253 Lübbert M, Bertz H, Müller MJ, et al. (2013) When azanucleoside treatment can be curative: nonintensive bridging strategy before allografting in older patients with myelodysplastic syndrome/acute myeloid leukemia. *J. Clin. Oncol.* ePub Feb 2013
- 254 Lübbert M, Bertz H, Rüter B, et al. (2009) Non-intensive treatment with low-dose 5-aza-2'-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. *Bone Marrow Transplant.* ePub Nov 2009
- 255 Blum W, Sanford BL, Klisovic R, et al. (2017) Maintenance therapy with decitabine in younger adults with acute myeloid leukemia in first remission: a phase 2 Cancer and Leukemia Group B Study (CALGB 10503). *Leukemia* ePub 01 2017
- 256 Lübbert et al., 2016; ASH Abstract 589
- 257 Fathi et al., 2016; ASH Abstract 591
- 258 Halpern et al., 2016; ASH Abstract 1064
- 259 Mims et al., 2016; ASH Abstract 900
- 260 Issa JP, Garcia-Manero G, Huang X, et al. (2015) Results of phase 2 randomized study of low-dose decitabine with or without valproic acid in patients with myelodysplastic syndrome and acute myelogenous leukemia. *Cancer* ePub Feb 2015
- 261 Kirschbaum M, Gojo I, Goldberg SL, et al. (2014) A phase 1 clinical trial of vorinostat in combination with decitabine in patients with acute myeloid leukaemia or myelodysplastic syndrome. *Br. J. Haematol.* ePub Oct 2014
- 262 Welch JS, Niu H, Uy GL, et al. (2014) A phase I dose escalation study of oral bexarotene in combination with intravenous decitabine in patients with AML. *Am. J. Hematol.* ePub Aug 2014
- 263 Liesveld JL, O'Dwyer K, Walker A, et al. (2013) A phase I study of decitabine and rapamycin in relapsed/refractory AML. *Leuk. Res.* ePub Dec 2013
- 264 Mawad R, Becker PS, Hendrie P, et al. (2016) Phase II study of tosedostat with cytarabine or decitabine in newly diagnosed older patients with acute myeloid leukaemia or high-risk MDS. *Br. J. Haematol.* ePub Jan 2016
- 265 Daver N, Kantarjian H, Ravandi F, et al. (2016) A phase II study of decitabine and gemtuzumab ozogamicin in newly diagnosed and relapsed acute myeloid leukemia and high-risk myelodysplastic syndrome. *Leukemia* ePub Feb 2016
- 266 Stein et al., 2016; ASH Abstract 343
- 267 Stein et al., 2014; ASH Abstract 115
- 268 DiNardo CD, Pratz K, Pullarkat V, et al. (2018) Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood* ePub Oct 2018
- 269 DiNardo CD, Pratz KW, Letai A, et al. (2018) Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol.* ePub Feb 2018
- 270 Pollyea DA, Stevens BM, Jones CL, et al. (2018) Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. *Nat. Med.* ePub Dec 2018
- 271 Wei et al., 2017; ASH Abstract 890
- 272 Chyla et al., 2016; ASH Abstract 1709

SAMPLE