



NCI Protocol #: 10323

Patient ID: MD123-0002

Date: 1 Sep 2021

1 of 14

Patient Name: Janis Johnson
Date Collected: 8/24/21
Biopsy Site: Bone Marrow
Sample ID: 10323-AJ54BX97-1
Telephone: 202-555-6789
Tumor Content (%): 50%

Patient DOB: 4/24/1972
Referring Physician: Michael Smith
Primary Diagnosis: Acute Myeloid Leukemia
MoCha ID: OCA-15003
Fax: 202-555-9876

Tumor content assessment performed by:

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Report Highlights

4 Relevant Biomarkers
4 Therapies Available
54 Clinical Trials

Relevant Acute Myeloid Leukemia Findings

| Gene | Finding | Gene | Finding |
|--------|--------------------------|--------|------------------------|
| ABL1 | None detected | MECOM | None detected |
| ASXL1 | None detected | MLLT3 | None detected |
| CEBPA | None detected | MYH11 | None detected |
| CREBBP | None detected | NPM1 | NPM1 W288Cfs*12 |
| FLT3 | FLT3 ITD mutation | NUP214 | None detected |
| IDH1 | None detected | RARA | None detected |
| IDH2 | None detected | RUNX1 | None detected |
| KMT2A | None detected | TP53 | None detected |

Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|--|--------------------|---|--|-----------------|
| IA | FLT3 ITD mutation | gilteritinib ¹ midostaurin + chemotherapy ¹ sorafenib + chemotherapy venetoclax + chemotherapy | None | 45 |
| Prognostic significance: ELN 2017: Favorable to Intermediate | | | | |
| Diagnostic significance: None | | | | |

Public data sources included in relevant therapies: FDA¹, NCCN

Public data sources included in prognostic and diagnostic significance: NCCN

Tier Reference: Li et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017 Jan;19(1):4-23.

Shahanawaz Jiwani, MD, PhD, Laboratory Director | CLIA ID 21D2097127

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.10(002). The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|------|---|---|--|-----------------|
| IA | <i>NPM1 W288Cfs*12</i> Prognostic significance: ELN 2017: Favorable to Intermediate Diagnostic significance: None | None | None | 8 |
| IIC | <i>WT1 R375Gfs*6</i> Prognostic significance: None Diagnostic significance: None | None | None | 3 |
| IIC | <i>TET2 P1723S</i> Prognostic significance: None Diagnostic significance: None | None | None | 2 |

Public data sources included in relevant therapies: FDA1, NCCN

Public data sources included in prognostic and diagnostic significance: NCCN

Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence based on included data sources

*DNMT3A H677Qfs*26*

Variant Details

DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|--------|---|--|------------|----------------|------------------|----------------|-------------------------------------|
| DNMT3A | p.(H677Qfs*26) | c.2031_2037delCCAG . GGG | . | chr2:25464475 | 45.64% | NM_022552.4 | frameshift Deletion |
| TET2 | p.(P1723S) | c.5167C>T | . | chr4:106196834 | 50.15% | NM_001127208.2 | missense |
| NPM1 | p.(W288Cfs*12) | c.863_864insTCTG | COSM17559 | chr5:170837547 | 45.77% | NM_002520.6 | frameshift Insertion |
| WT1 | p.(R375Gfs*6) | c.1122_1122delAinsC . GG | . | chr11:32417945 | 41.98% | NM_024426.6 | frameshift Block Substitution |
| FLT3 | p.(E604_F605insSNEY FYVDFREYEYDLKWE) | c.1812_1813insTCTAA . TGAGTACTTCTACGT TGATTTTCAGAGAATA TGAATATGATCTCAA ATGGGAG | . | chr13:28608243 | 48.00% | NM_004119.2 | nonframeshift Insertion |

Comments:

Shahanawaz Jiwani, MD, PhD, Laboratory Director | CLIA ID 21D2097127

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Signed By: _____

Biomarker Descriptions

DNMT3A (DNA methyltransferase 3 alpha)

Background: The DNMT3A gene encodes the DNA methyltransferase 3 alpha which functions as a de novo methyltransferase (DNMT) with equal methylation efficiency for unmethylated and hemimethylated DNA¹. Methylation of DNA occurs at CpG islands, a region of DNA consisting of sequential cytosine/guanine dinucleotide pairs. CpG island methylation plays an important role in development as well as stem cell regulation. Alterations to global DNA methylation patterns are dependent on DNMTs, which are associated with cancer initiation and progression^{2,3}.

Alterations and prevalence: DNMT3A mutations are observed in approximately 25% of all acute myeloid leukemia (AML) including 29-34% of AML with normal karyotype (NK-AML)^{4,5,6,7,8,9,10}. Mutations in DNMT3A are also reported in 12-18% of myelodysplastic syndromes (MDS) as well as 4-6% of melanoma, lung adenocarcinoma, and uterine cancer^{9,11}. The majority of mutations in DNMT3A are missense however, frameshift, nonsense, and splice site mutations have also been reported^{4,9}. Missense mutations at R882 are most prevalent and are observed to coexist with NPM1 and FLT3 mutations^{12,13}. The R882 mutations occur at the dimer/tetramer interface within the catalytic domain, which leads to disruption of DNMT3A tetramerization and loss of CpG methylation^{14,15}. However, DNMT3A mutations observed in AML at positions other than R882 also contribute to pathogenesis by mechanisms that do not involve methyltransferase activity¹⁶.

Potential relevance: DNMT3A mutations confer shorter overall survival (OS) in patients with AML including those with NK-AML^{4,7,8,13}. DNMT3A mutations are a useful in the diagnosis of angioimmunoblastic T-cell lymphoma (AITCL) when trying to differentiate from other peripheral T-cell lymphomas (PTCL)¹⁷.

FLT3 (fms related receptor tyrosine kinase 3)

Background: The FLT3 gene encodes the fms related tyrosine kinase 3, a tyrosine kinase receptor that is a member of the class III receptor tyrosine kinase family that also includes PDGFR, FMS, and KIT¹⁸. FLT3 is highly expressed in hematopoietic progenitor cells¹⁹. Genomic alterations in FLT3 activate downstream oncogenic pathways including PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways which promote cellular proliferation, survival, and inhibition of differentiation¹⁸.

Alterations and prevalence: Somatic mutations occur in approximately 30% of acute myeloid leukemia (AML), 7-10% of melanoma, and up to 8% of uterine cancer^{9,20,21,22}. The most common activating FLT3 mutations are internal tandem duplications (ITD) that range from 3 to 400 base pairs in length within exons 14 and 15 in the juxtamembrane (JM) domain²³. The second most frequent mutations are point mutations in exon 20 within the tyrosine kinase domain (TKD)²⁴. FLT3 is amplified in up to 8% of colorectal cancer, 3% of stomach cancer, and is commonly overexpressed in AML^{9,22,25}.

Potential relevance: The presence of FLT3-ITD confers poor prognosis in myelodysplastic syndrome (MDS) and AML^{10,11}. Similarly, the FLT3 TKD mutation D835 confers poor prognosis in MDS¹¹. Midostaurin²⁶ (2017) and gilteritinib²⁷ (2018) are kinase inhibitors approved for AML patients with FLT3-ITD and TKD mutations including D835 and I836 mutations. The FDA granted fast track designations in 2017 to crenolanib²⁸ for FLT3 mutation-positive relapsed or refractory AML and in 2018 to quizartinib²⁹ for AML with FLT3-ITD. A phase II trial testing crenolanib in 34 patients with FLT3-ITD and TKD mutated relapsed/refractory AML, reported that FLT3 inhibitor naïve patients demonstrated a longer overall survival (OS) and event free survival (EFS) in comparison to previously treated patients (median OS: 55 weeks vs 13 weeks; median EFS: 13 weeks vs 7 weeks)³⁰. Another phase II trial of crenolanib with chemotherapy in newly diagnosed FLT3 mutated AML reported complete remission in 24/29 (83%) patients³¹. Several multi-targeted tyrosine kinase inhibitors such as sorafenib (2005), sunitinib (2006), cabozantinib (2012), and ponatinib (2012) are FDA approved and include FLT3 as a target. Sorafenib is recommended in combination with chemotherapy in FLT3-ITD mutated AML¹⁰.

Biomarker Descriptions (continued)

NPM1 (nucleophosmin 1)

Background: The NPM1 gene encodes the nucleophosmin protein, a histone chaperone of the nucleophosmin/nucleoplasmin family, which also includes NPM2 and NPM3³². NPM1 functions as an oncogene and tumor suppressor, and is important in maintaining genomic stability, DNA repair, and apoptosis^{32,33}. NPM1 has a highly conserved N-terminal region which constitutes the core domain responsible for oligomerization, an acidic domain, a nuclear localization signal, and a disorganized C-terminal region which is required for nucleolar localization³². Oligomerization of NPM1 localizes the protein in the nucleus of proliferating cells where it binds to Akt in response to growth factor stimulation and escapes proteolytic degradation by caspase activity, thereby promoting cell survival^{32,33}. NPM1 is one of the most frequently altered genes in hematological cancers³⁴. Most NPM1 mutations occur in the C-terminus, impacting protein folding or the nucleolar localization signal, and result in the localization of NPM1 to the cytoplasm (NPMc) instead of to the nucleus³².

Alterations and prevalence: NPM1 mutations are observed in 45-60% of AML with a normal karyotype (NK-AML), 28-35% of de novo acute myeloid leukemia (AML) and are frequently co-mutated with DNMT3A and/or FLT3-ITD^{10,35,36}. NPM1 fusions are associated with distinct partner genes in acute promyelocytic leukemia (APL), anaplastic large-cell lymphoma (ALCL), AML, and myelodysplasia³⁴. Specifically, NPM1-ALK fusion is found in 30% of all ALCL and this specific fusion is observed in 85% of ALK-positive ALCL³². The t(5;17)(q35;q21) translocation that results in NPM1-RARA fusion is observed in APL³⁷.

Potential relevance: NPM1 mutated AML is recognized as a distinct diagnostic disease entity by the World Health Organization (WHO)³⁸. NPM1 mutations are associated with better outcomes, increased complete remission, and improved overall survival in AML^{10,36}. NPM1 without FLT3-ITD mutations or with <0.5 allelic ratio FLT3-ITD mutations are associated with favorable risk in AML, whereas wild-type NPM1 confers poor/adverse risk¹⁰. Concurrent NPM1 and with >0.5 allelic ratio FLT3-ITD mutations confer intermediate risk in AML¹⁰. The NPM1 frameshift mutation W288fs*12 is associated with poor prognosis in myelodysplastic syndrome (MDS)¹¹. The ALK-NPM1 fusion, and translocation t(2;5)(p23;q35) which leads to an ALK-NPM1 fusion, is diagnostic of cutaneous and non-cutaneous anaplastic large cell lymphoma^{17,39}.

TET2 (tet methylcytosine dioxygenase 2)

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to a family of ten-eleven translocation (TET) proteins that also includes TET1 and TET3⁴⁰. TET2 is involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine^{41,42}. The TET proteins contain a C-terminal core catalytic domain that contains a cysteine-rich domain and a double stranded β -helix domain (DSBH)⁴³. TET2 is a tumor suppressor gene. Loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies^{40,41,42}.

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40%-60% chronic myelomonocytic leukemia (CMML)¹¹. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies^{41,44}. TET2 mutations are also observed in 9% of uterine, 8% of melanoma and acute myeloid leukemia (AML), as well as 6% of diffuse large B-cell lymphoma (DLBCL).

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations^{38,45}. TET2 mutations are associated with poor prognosis in PMF and increased rate of transformation to leukemia^{45,46}.

WT1 (WT1 transcription factor)

Background: The WT1 gene encodes the Wilms tumor 1 homolog, a zinc-finger transcriptional regulator that plays an important role in cellular growth and metabolism^{47,48}. WT1 is endogenously expressed in embryonic kidney cells as well as hematopoietic stem cells and regulates the process of filtration of blood through the kidneys⁴⁹. WT1 protein contains N-terminal proline-glutamine rich regions that are involved in RNA and protein interaction while the C-terminal domain contains Kruppel link cysteine histidine zinc fingers that are involved in DNA binding⁴⁷. WT1 interacts with various genes including TP53, STAT3, and epigenetic modifiers such as TET2 and TET3^{47,50}. WT1 is primarily characterized as a tumor suppressor gene involved in the development of renal Wilm's tumor (WT), a rare pediatric kidney cancer^{47,51}. Loss of function mutations observed in WT1, including large deletions and intragenic mutations, can impact the zinc finger domain, thereby decreasing the DNA binding activity⁴⁷. WT1 overexpression is observed in acute myeloid leukemia (AML) and lymphoid cancers^{47,52}.

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations of WT1 occur in 7% of AML, 5% of melanoma, and 1% of mesothelioma²². WT1 overexpression is observed in AML, acute lymphoblastic lymphoma (ALL), and myelodysplastic syndrome (MDS)⁴⁷

Potential relevance: Somatic mutations in WT1, including nonsense, frameshift, and splice-site mutations, are associated with poor prognosis in MDS¹¹. Overexpression of WT1 in MDS is associated with a higher risk of progression to AML. WT1 overexpression is also associated with poor prognosis, resistance to chemotherapy, and poor overall survival in AML⁵⁰.

Relevant Therapy Summary

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ No evidence

FLT3 ITD mutation

| Relevant Therapy | FDA | NCCN | Clinical Trials* |
|---|-------------------------------------|-------------------------------------|---|
| gilteritinib | <input checked="" type="radio"/> | <input checked="" type="radio"/> | <input checked="" type="radio"/> (I/II) |
| midostaurin + cytarabine + daunorubicin | <input checked="" type="radio"/> | <input checked="" type="radio"/> | <input checked="" type="checkbox"/> |
| midostaurin + cytarabine | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> | <input checked="" type="checkbox"/> |
| sorafenib + azacitidine | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> | <input checked="" type="checkbox"/> |
| sorafenib + decitabine | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> | <input checked="" type="checkbox"/> |
| venetoclax + azacitidine | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> | <input checked="" type="checkbox"/> |
| venetoclax + cytarabine | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> | <input checked="" type="checkbox"/> |
| venetoclax + decitabine | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> | <input checked="" type="checkbox"/> |
| sorafenib | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (IV) |
| chemotherapy, midostaurin | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (III) |
| crenolanib, chemotherapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (III) |
| crenolanib, midostaurin, chemotherapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (III) |
| gemtuzumab ozogamicin, chemotherapy, gilteritinib | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (III) |
| gilteritinib, midostaurin, chemotherapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (III) |
| chemotherapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (II/III) |
| ibrutinib, sorafenib, chemotherapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (II/III) |
| alemtuzumab, chemotherapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (II) |
| allogeneic stem cells, chemotherapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (II) |
| chemotherapy, radiation therapy | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> | <input checked="" type="radio"/> (II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ No evidence

FLT3 ITD mutation (continued)

| Relevant Therapy | FDA | NCCN | Clinical Trials* |
|--|-----|------|------------------|
| chemotherapy, stem cell therapy, radiation therapy | × | × | ● (II) |
| gilteritinib, chemotherapy | × | × | ● (II) |
| natural killer cell therapy, stem cell therapy | × | × | ● (II) |
| ponatinib | × | × | ● (II) |
| quizartinib, chemotherapy | × | × | ● (II) |
| SKLB1028 | × | × | ● (II) |
| sorafenib, chemotherapy, cytokine, stem cell therapy | × | × | ● (II) |
| venetoclax, chemotherapy | × | × | ● (II) |
| CA 4948 | × | × | ● (I/II) |
| CART-FLT3 | × | × | ● (I/II) |
| CC-90009, gilteritinib | × | × | ● (I/II) |
| chemotherapy, sorafenib | × | × | ● (I/II) |
| dubermatinib, chemotherapy | × | × | ● (I/II) |
| KRT-232, TL-895 | × | × | ● (I/II) |
| NMS-P948 | × | × | ● (I/II) |
| ponatinib, chemotherapy | × | × | ● (I/II) |
| stem cell therapy | × | × | ● (I/II) |
| venetoclax, gilteritinib, chemotherapy | × | × | ● (I/II) |
| venetoclax, quizartinib | × | × | ● (I/II) |
| allogeneic double negative T cells | × | × | ● (I) |
| clifutinib | × | × | ● (I) |
| LNK01002 | × | × | ● (I) |
| nintedanib, chemotherapy | × | × | ● (I) |
| PHI-101 | × | × | ● (I) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Summary (continued)

☒ In this cancer type
 ☐ In other cancer type
 ☒ In this cancer type and other cancer types
 ☒ No evidence

NPM1 W288Cfs*12

| Relevant Therapy | FDA | NCCN | Clinical Trials* |
|--|-----|------|------------------|
| chemotherapy | × | × | ● (II) |
| pembrolizumab, chemotherapy | × | × | ● (II) |
| chemotherapy, supplement | × | × | ● (I/II) |
| KO-539 | × | × | ● (I/II) |
| SNDX-5613 | × | × | ● (I/II) |
| venetoclax, pevonedistat, chemotherapy | × | × | ● (I/II) |
| JNJ-75276617 | × | × | ● (I) |

WT1 R375Gfs*6

| Relevant Therapy | FDA | NCCN | Clinical Trials* |
|--|-----|------|------------------|
| chemotherapy | × | × | ● (II) |
| sorafenib, chemotherapy, cytokine, stem cell therapy | × | × | ● (II) |
| BI-836858 + chemotherapy | × | × | ● (I/II) |

TET2 P1723S

| Relevant Therapy | FDA | NCCN | Clinical Trials* |
|--|-----|------|------------------|
| BI-836858 + chemotherapy | × | × | ● (I/II) |
| nonengraftment donor lymphocyte infusion | × | × | ● (I/II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Clinical Trials Summary

FLT3 ITD mutation + WT1 R375Gfs*6

| NCT ID | Title | Phase |
|-------------|--|-------|
| NCT03164057 | A Phase II Trial of Epigenetic Priming in Patients With Newly Diagnosed Acute Myeloid Leukemia | II |

Clinical Trials Summary (continued)

FLT3 ITD mutation

| NCT ID | Title | Phase |
|-------------|---|--------|
| NCT02156297 | Sorafenib to Treat AML Patients With FLT3-ITD Mutation: a Non-interventional Cohort Study | IV |
| NCT04174612 | A Phase III, Prospective, Randomized Multi-center Intervention Trial of Early Intensification in AML Patients Bearing FLT3 Mutations Based on Peripheral Blast Clearance: A MYNERVA-GIMEMA Study | III |
| NCT03250338 | Phase III Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy of the Addition of Crenolanib to Salvage Chemotherapy Versus Salvage Chemotherapy Alone in Subjects < or = 75 Years of Age With Relapsed/Refractory FLT3 Mutated Acute Myeloid Leukemia | III |
| NCT03258931 | Phase III Randomized Study of Crenolanib Versus Midostaurin Administered Following Induction Chemotherapy and Consolidation Therapy in Newly Diagnosed Subjects With FLT3 Mutated Acute Myeloid Leukemia | III |
| NCT04293562 | A Phase III Randomized Trial for Patients With De Novo AML Comparing Standard Therapy Including Gemtuzumab Ozogamicin (GO) to CPX-351 With GO, and the Addition of the FLT3 Inhibitor Gilteritinib for Patients With FLT3 Mutations | III |
| NCT04027309 | A Phase III, Multicenter, Open-label, Randomized, Study of Gilteritinib Versus Midostaurin in Combination With Induction and Consolidation Therapy Followed by One-year Maintenance in Patients With Newly Diagnosed Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes With Excess Blasts-2 (MDS-EB2) With FLT3 Mutations Eligible for Intensive Chemotherapy (HOVON 156 AML / AMLSG 28-18) | III |
| NCT03256071 | Low Dose Decitabine + Modified BUCY Conditioning Regimen for High Risk Acute Myeloid Leukemia Undergoing Allo-HSCT | II/III |
| NCT03642236 | Combination of Brutons Tyrosine Kinase (BTK) Inhibitor Overcomes Drug-resistance in Refractory/ Relapsed FLT3 Mutant Acute Myeloid Leukemia (AML) | II/III |
| NCT02626715 | A Phase II Study of Myeloablative and Reduced-Intensity Conditioning Regimens for Children and Young Adults With Acute Myeloid Leukemia or Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Stem Cell Transplantation. | II |
| NCT01760655 | A Two Step Approach to Reduced Intensity Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Hematologic Malignancies | II |
| NCT03121014 | A Phase II Study of Intensity Modulated Total Marrow Irradiation (IM-TMI) in Addition to Fludarabine/ Busulfan Conditioning for Allogeneic Transplantation in High Risk AML and Myelodysplastic Syndromes | II |
| NCT03333486 | A Phase II Trial of Haploidentical Allogeneic Stem Cell Transplantation Utilizing Mobilized Peripheral Blood Stem Cells | II |
| NCT03836209 | Randomized Trial of Gilteritinib vs Midostaurin in FLT3 Mutated Acute Myeloid Leukemia (AML) | II |
| NCT03690115 | Phase II Study of Ponatinib (Iclusig) for Prevention of Relapse After Allogeneic Stem Cell Transplantation (Allo-SCT) in FLT3-ITD AML Patients: the PONALLO Trial." | II |
| NCT03989713 | Quizartinib and High-dose Ara-C Plus Mitoxantrone in Relapsed/Refractory AML With FLT3-ITD | II |
| NCT04278768 | A Phase I/IIA, Open Label Dose Escalation and Expansion Study of Orally Administered CA-4948 as a Monotherapy in Patients With Acute Myelogenous Leukemia or Myelodysplastic Syndrome and in Combination With Azacitidine or Venetoclax | I/II |

Clinical Trials Summary (continued)

FLT3 ITD mutation (continued)

| NCT ID | Title | Phase |
|-------------|--|-------|
| NCT04336982 | An Exploratory Phase I/II Open-Label Multi-Arm Trial to Evaluate the Safety and Efficacy of CC-90009 Combinations in Subjects With Acute Myeloid Leukemia | I/II |
| NCT04518345 | A Phase Ib/II Study of TP-0903 in Patients With Acute Myeloid Leukemia and FLT3 Mutations | I/II |
| NCT03013998 | A Master Protocol for Biomarker-Based Treatment of AML (The Beat AML Trial) | I/II |
| NCT04240002 | A Phase I/II, Multicenter, Open-Label, Single Arm, Dose Escalation and Expansion Study of Gilteritinib (ASP2215) Combined With Chemotherapy in Children, Adolescents and Young Adults With FMS-like Tyrosine Kinase 3 (FLT3)/Internal Tandem Duplication (ITD) Positive Relapsed or Refractory Acute Myeloid Leukemia (AML) | I/II |
| NCT04669067 | An Open-Label, Multicenter, Phase Ib/II Study of the Safety and Efficacy of TL-895 Combined With KRT-232 in Patients With Relapsed/Refractory (R/R) FLT3+ Acute Myeloid Leukemia (AML) | I/II |
| NCT03922100 | A Phase I/II Study of NMS-03592088, a FLT3, KIT and CSF1R Inhibitor, in Patients With Relapsed or Refractory AML or CMML | I/II |
| NCT02829840 | Phase I/II, Dose-Escalation Study of Ponatinib, a FLT3 Inhibitor, With and Without Combination of 5-Azacytidine, in Patients With FLT3-Mutated Acute Myeloid Leukemia (AML) | I/II |
| NCT01892371 | 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) | I/II |
| NCT03793478 | A Phase I/II, Multicenter, Dose-Escalating Study To Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy Of Quizartinib Administered in Combination with Re-Induction Chemotherapy, and as a Single-Agent Continuation Therapy, in Pediatric Relapsed/Refractory AML Subjects Aged 1 Month to <18 Years (and Young Adults Aged up to 21 Years) with FLT3-ITD mutations. | I/II |
| NCT01203722 | Reduced Intensity, Partially HLA Mismatched Allogeneic BMT for Hematologic Malignancies Using Donors Other Than First-degree Relatives | I/II |
| NCT04140487 | A Phase I/II Study of Azacitidine, Venetoclax, and Gilteritinib for Patients With Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome With an Activating FLT3 Mutation | I/II |
| NCT05010122 | A Phase I/II Study of ASTX727, Venetoclax, and Gilteritinib for Patients With Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome With an Activating FLT3 Mutation | I/II |
| NCT03735875 | A Phase Ib/II Study of Venetoclax in Combination With Quizartinib in FLT3-Mutated Acute Myelogenous Leukemia (AML) | I/II |
| No NCT ID | Safety and Effective of Prophylactic Infusion of DNT cells in Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Myeloid Malignancies: A Single Center Clinical Research | I |
| No NCT ID | A Phase I Study to Assess the Safety of Micro-dose Lenalidomide as Maintenance Therapy Post-allogeneic Haematopoietic Cell Transplantation for Patients with Acute Myeloid Leukaemia or Myelodysplastic Syndromes, at High Risk of Relapse | I |
| NCT04827069 | A Phase I, Multi-center, Open,Single Arm, Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Clifutinib Besylate(HEC73543) in Relapsed or Refractory Acute Myeloid Leukemia (AML) | I |

Clinical Trials Summary (continued)

FLT3 ITD mutation (continued)

| NCT ID | Title | Phase |
|-------------|--|-------|
| NCT05024552 | A Phase I Study of Vyxeos Plus Gilteritinib in Relapsed or Refractory, FLT3-Mutated Acute Myeloid Leukemia | I |
| NCT04896112 | An Open-Label, Multicenter, Phase I Study to Evaluate the Safety, Pharmacokinetics and Preliminary Efficacy of LNK01002 in Patients With Malignant Myeloid Hematologic Neoplasms | I |
| NCT03513484 | Phase Ib, Open Label, Combination Study of Nintedanib With 5-Azacitidine in Acute Myeloid Leukemia Characterized by HOX Gene Overexpression, That Are Not Candidates of Intensive Chemotherapy | I |
| NCT04842370 | A Prospective, Phase Ia/Ib, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the FLT3 Inhibitor, PHI 101, Alone in Subjects With Relapsed or Refractory Acute Myeloid Leukemia (AML) | I |
| NCT02126553 | Phase II Study of Lenalidomide Maintenance in Patients With High Risk AML in Remission | II |
| No NCT ID | Open-Label, Multicenter, Prospective Intervention Trial Of Sequential MEC (Mitoxantrone / Etoposide / Cytarabine) And Gilteritinib In Patients With Relapsed Or Refractory FLT3 Mutation-Positive Acute Myeloid Leukemia | II |
| NCT02727803 | Personalized NK Cell Therapy in Cord Blood Transplantation | II |
| NCT04015024 | Phase IIa Clinical Study of SKLB1028 Capsule in the Treatment of FLT3 Mutation Recurrence / Refractory AML Patients | II |
| NCT04062266 | Phase II Study of 5-Azacitidine (AZA) + Venetoclax as Maintenance Therapy in Patients With High Risk AML in Remission | II |
| NCT05023707 | Pilot Study of the Safety and Efficacy of Anti-FLT3 Chimeric Antigen Receptor Engineered T-Cells in the Treatment of Relapsed or Refractory Acute Myeloid Leukemia (AML) | I/II |
| NCT03247088 | Phase I/II Study Of Sorafenib Added To Busulfan And Fludarabine Conditioning Regimen In Patients With Relapsed/Refractory AML Undergoing Stem Cell Transplantation | I/II |
| NCT02272998 | Phase II Study Of Ponatinib For Advanced Cancers With Genomic Alterations In Fibroblastic Growth Factor Receptor (FGFR) And Other Genomic Targets (KIT, Pdgfra, RET FLT3, ABL1) | II |

NPM1 W288Cfs*12

| NCT ID | Title | Phase |
|-------------|---|-------|
| No NCT ID | International Multicenter, Open-Label, Phase II Study to Treat Molecular Relapse of Pediatric Acute Myeloid Leukemia With Azacitidine | II |
| NCT04689815 | Measurable-residual Disease (MRD) Monitoring of Nucleophosmin 1 (NPM1)-Mutated Acute Myeloid Leukaemia (AML) and Pre-emptive Therapy With Oral Arsenic Trioxide-based Regimen | II |
| NCT03769532 | MRD-guided Treatment With Pembrolizumab and Azacitidine in NPM1mut AML Patients With an Imminent Hematological Relapse | II |
| NCT03031249 | Efficacy and Safety of ATO Plus ATRA in Nucleophosmin-1 Mutated Acute Myeloid Leukemia | I/II |
| NCT04067336 | A Phase I/IIA First in Human Study of the Menin-MLL(KMT2A) Inhibitor KO 539 in Patients With Relapsed or Refractory Acute Myeloid Leukemia. | I/II |

Clinical Trials Summary (continued)

NPM1 W288Cfs*12 (continued)

| NCT ID | Title | Phase |
|-------------|--|-------|
| NCT04065399 | AUGMENT-101: A Phase I/II, Open-label, Dose-Escalation and Dose-Expansion Cohort Study of SNDX 5613 in Patients With Relapsed/Refractory Leukemias, Including Those Harboring an MLL/KMT2A Gene Rearrangement or Nucleophosmin 1 (NPM1) Mutation | I/II |
| NCT03862157 | A Phase I/II Study of Azacitidine, Venetoclax and Pevonedistat in Adults With Newly Diagnosed Secondary or Therapy-Related AML | I/II |
| NCT04811560 | A First in Human Study of the Menin-KMT2A (MLL1) Inhibitor JNJ-75276617 in Participants With Acute Leukemia | I |

WT1 R375Gfs*6

| NCT ID | Title | Phase |
|-------------|---|-------|
| NCT03013998 | A Master Protocol for Biomarker-Based Treatment of AML (The Beat AML Trial) | I/II |
| No NCT ID | International Multicenter, Open-Label, Phase II Study to Treat Molecular Relapse of Pediatric Acute Myeloid Leukemia With Azacitidine | II |

TET2 P1723S

| NCT ID | Title | Phase |
|-------------|---|-------|
| NCT03013998 | A Master Protocol for Biomarker-Based Treatment of AML (The Beat AML Trial) | I/II |
| NCT04620681 | CD8 Depleted, Non-Engrafting, HLA Mismatched Unrelated Donor Lymphocyte Infusion in Patients With MDA and Secondary AML | I/II |

Assay Information

Methodology, Scope, and Application: The NCI Myeloid Assay (NMA) is a next-generation sequencing (NGS) assay which identifies pre-defined and novel genomic variants covering 40 DNA genes and 29 fusion drivers that are categorized into 4 mutation types: single nucleotide variants (SNVs), small insertions/deletions (Indels), large (>3 bases) insertions/deletions (Large Indels) including FLT3 internal tandem duplications (ITDs), and gene fusions. The assay utilizes Thermo Fisher Scientific's Oncomine® Myeloid Assay GX, a next-generation sequencing (NGS) assay that utilizes a multiplex polymerase chain reaction (PCR) with DNA and RNA extracted from blood and bone marrow mononuclear cells for sequencing on the Ion Torrent Genexus Integrated Sequencer and analyzed by the current version of the Ion Torrent Genexus pipeline. The NMA currently can reliably identify the presence or absence of >1600 known mutations and polymorphisms compared to the Human Reference Genome hg19, including the genes listed below. The NMA is a laboratory developed test designed to find gene mutations for major myeloid disorders.

Analytical Sensitivity and Specificity: The NMA has been determined to be suitably analytically sensitive and specific for the various types of abnormalities within its reportable range, demonstrating XX.XX% sensitivity compared with orthogonal assay results and 100.00% specificity for the 4 mutation types reported. XX.XX% or greater reproducibility has been demonstrated. All quality measures for this assay were within defined assay parameters.

Hereditary and Germline Mutations: This assay examines cancer cells only and does not examine normal (non-cancer) cells. Mutations detected by the assay may be present only in the cancer cells, or in every cell of the body (including non-cancer cells). This test also cannot tell whether a potential germline mutation causes or will cause a hereditary cancer syndrome. If the patient's history includes

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Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2021.10(002).

any one or combination of features suggestive of a possible hereditary cancer predisposition (such as, cancer arising at a young age, especially a cancer of a type unusual in younger patients; a personal history of multiple different types of cancers; or a significant cancer history among blood relatives, especially but not exclusively of the same type as the patient's) it is recommended that the physician arrange for the patient to meet with a genetic counselor and, if warranted, undergo the appropriate genetic test on normal (i.e. non-cancer) tissue (blood or cells brushed from the oral surface of the cheek) to check for a germline abnormality, regardless of the results of this research study.

Report Content: Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in the generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on the current version of OncoPrint Reporter. The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of this version. NCCN information was sourced from www.nccn.org and reflects its current version. Clinical Trials information reflects the current version. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other Identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials identified in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

Genes assayed for hotspot mutations:

ABL1, BRAF, CBL, CSF3R, DNMT3A, FLT3, GATA2, HRAS, IDH1, IDH2, JAK2, KIT, KRAS, MPL, MYD88, NPM1, NRAS, PTPN11, SETBP1, SF3B1, SRSF2, U2AF1, WT1

Genes assayed with full exon coverage:

ASXL1, BCOR, CALR, CEBPA, ETV6, EZH2, IKZF1, NF1, PHF6, PRPF8, RB1, RUNX1, SH2B3, STAG2, TET2, TP53, ZRSR2

Genes assayed for detection of fusions:

ABL1, ALK, BCL2, BRAF, CCND1, CREBBP, EGFR, ETV6, FGFR1, FGFR2, FUS, HMGA2, JAK2, KMT2A (MLL), MECOM, MET, MLLT10, MLLT3, MYBL1, MYH11, NTRK3, NUP214, PDGFRA, PDGFRB, RARA, RBM15, RUNX1, TCF3, TFE3

DISCLAIMER

This assay can detect indels, including FLT3-ITDs up to 120bps. Sensitivity for larger indels may be reduced and variant allele frequencies may be reported lower than expected.

This assay is not sensitive enough to detect mutations in the CEBPA gene

This assay is considered a Laboratory Developed Test (LDT). Its performance characteristics have been determined through extensive testing although it has not been cleared by the US Food and Drug Administration and such approval is not required for clinical implementation. Furthermore, any comments included in the report are strictly interpretive and the opinion of the reviewer. This laboratory is certified under the Clinical Laboratory Improvements Amendments (CLIA) for the performance of high-complexity testing for clinical purposes. The correlative data presented is a result of the curation of published data sources, but may not be exhaustive. The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

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