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Consulting physician		Patient		Sample	
Provider	General Hospital	Name	Michelle Doe	Accession Number	D19-03598
Physician	Dr. E Smith	Age	65	Collection site	Bone marrow
Pathologist	Dr. R Jones	Gender	Female	Type	Biopsy
Report Date	Feb 18, 2022	Diagnosis	Acute myeloid leukemia	Collection date	Feb 18, 2022

Panel Analysis: Hematological Malignancies

Comprehensive genomic next generation sequencing test that targets variants in key genes known to be involved in myeloid malignancies such as AML, MDS, MPN, CML, CMML, and JMML.

Overall comment

NPM1 mutations in the presence of FLT3-ITD have been associated with an intermediate prognosis. WT1 mutations have been associated with reduced relapse-free, event-free, and overall survival in studies of AML, particularly in CN-AML patients.

Patient specific comment

This is a sample report and content and layout are customizable.

Analysis results: Positive

3 Variants of strong clinical significance, Tier 1	Approved treatments	Other findings
FLT3: p.Y597_E598insDYVDFREY, Pathogenic	Gilteritinib Midostaurin	Trials: 1 Phase 3 1 Phase 2 7 Phase 1/Phase 2 1 Phase 1
NPM1: p.W259fs*?, Pathogenic	-	Trials: 3 Phase 1/Phase 2 1 Phase 1
WT1: p.R385fs*69, Pathogenic	-	Trials: 1 Phase 1/Phase 2
1 Variant of potential clinical significance, Tier 2	**Approved treatments**	**Other findings**
RAD21 †: p.L183fs*7, Likely Pathogenic	-	-
	3 Variants of uncertain significance, Tier 3	

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

Interactions

Clinically relevant co-occurring variants are reported in the "interactions" section starting on page 2.

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 2.

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GUIDELINES

The NCCN Guidelines (v.1.2022), which cite the 2017 ELN recommendations, place non-APL AML patients with wild-type NPM1 plus a high allelic ratio of FLT3-ITD (greater than or equal to 0.5) in the poor/adverse risk category, while patients with mutant NPM1 plus a high allelic ratio of FLT3-ITD, as well as patients with wild-type NPM1 plus a low allelic ratio of FLT3-ITD (less than 0.5), are placed in the intermediate risk category. Additionally, patients with mutant NPM1 and a low allelic ratio of FLT3 are placed in the favorable risk category [35]. These guidelines additionally state that midostaurin plus standard chemotherapy may be considered for both induction and maintenance therapy in AML patients with FLT3/ITD/TKD with intermediate/poor risk cytogenetics. Gilteritinib (category 1) or sorafenib plus hypomethylating agents (category 2A) may be considered as a therapeutic option in relapsed or refractory disease, depending on the physician's evaluation of the individual patient (NCCN Guidelines v.1.2022). AML with mutant NPM1 is recognized as a subtype of AML with recurrent genetic abnormalities in the WHO classification of myeloid neoplasms and acute leukemia [4]. The NCCN Guidelines (v. 1.2022), which cite the 2017 ELN recommendations, place AML patients harboring NPM1 mutation in the absence of FLT3-ITD or with a low allelic ratio of FLT3-ITD in the category of favorable risk.

INTERACTIONS

NPM1 mutations in the presence of FLT3-ITD, as reported here, have been associated with intermediate prognosis in the case of a high allelic ratio of FLT3-ITD, and with favorable prognosis in the case of a low allelic ratio of FLT3-ITD in AML [35, 57, 118, 151].

TREATMENT OPTIONS

Therapies with potential clinical benefit (2)

GILTERITINIB

Gilteritinib, a kinase inhibitor, is FDA- and EMA-approved for treating adult patients with relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.

Sensitive

Gene	Classification	Variant
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA

MIDOSTAURIN

Midostaurin, a kinase inhibitor, is FDA- and EMA-approved for treating adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL); midostaurin is FDA-approved for treating adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation (midostaurin is not indicated as a single-agent induction therapy for the treatment of patients with AML); midostaurin is EMA-approved for treating adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive, in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy.

Sensitive

Gene	Classification	Variant
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA

AVAILABLE CLINICAL TRIALS

Phase 3 clinical trials (1)

IODINE I 131 APAMISTAMAB, FLUDARABINE PHOSPHATE

A Multicenter, Pivotal Phase 3 Study of Iomab-B Prior to Allogeneic Hematopoietic Cell Transplant Versus Conventional Care in Older Subjects With Active, Relapsed or Refractory Acute Myeloid Leukemia (AML)
NCT02665065

Qualifying variant			Contact
Gene	Classification	Variant	United States: AZ, CT, DC, FL, IA, IL, KS, MN, MO, NC, NE, NY, OH, OR, TX, WA, WI
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA	Vijay Reddy, MD; vreddy@actiniumpharma.com;

Phase 2 clinical trials (1)

GILTERITINIB, VENETOCLAX, IDARUBICIN, MIDOSTAURIN, CLADRIBINE, CYTARABINE

Phase II Study of Cladribine Plus Idarubicin Plus Cytarabine (ARAC) in Patients With AML, HR MDS, or Myeloid Blast Phase of CML
NCT02115295

Qualifying variant	Contact

Phase 2 clinical trials (1)

Gene	Classification	Variant	United States: TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTT CAGAGAATATGA	Tapan Kadia; tkadia@mdanderson.org; 713-792-7305;

Phase 1/Phase 2 clinical trials (10)

GILTERITINIB, VENETOCLAX, DECITABINE, CEDAZURIDINE

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
NCT05010122

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTT CAGAGAATATGA	Farhad Ravandi-Kashani;

CA-4948

A Phase 1/2A, 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
NCT04278768

Qualifying variant			Contact
Gene	Classification	Variant	United States: FL, MA, NC, NE, NY, TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTT CAGAGAATATGA	Reinhard von Roemeling, MD; clinicaltrials@curis.com; 617-503-6500;

GILTERITINIB, 5-AZACYTIDINE, VENETOCLAX

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
NCT04140487

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTT CAGAGAATATGA	Nicholas Short; nshort@mdanderson.org; 713-563-4485;

QUIZARTINIB, VENETOCLAX

A Phase Ib/II Study of Venetoclax in Combination With Quizartinib in FLT3-Mutated Acute Myelogenous Leukemia (AML)
NCT03735875

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTT CAGAGAATATGA	Naval Daver; ndaver@mdanderson.org; 713-794-4392;

QUIZARTINIB, VENETOCLAX, DECITABINE

A Phase I/II Study of Quizartinib in Combination With Decitabine and Venetoclax for the Treatment of Patients With Acute Myeloid Leukemia (AML)
NCT03661307

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTT CAGAGAATATGA	Musa Yilmaz; myilmaz@mdanderson.org; 713-745-9945;

GILTERITINIB, VENETOCLAX, DECITABINE

A Master Protocol for Biomarker-Based Treatment of AML (The Beat AML Trial)
NCT03013998

Phase 1/Phase 2 clinical trials (10)

Qualifying variants			Contact
Gene	Classification	Variant	United States: CA, FL, GA, IL, KS, MD, MN, NC, NY, OH, OR, PA, TX, UT
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA	Spencer Kalk; spencer.kalk@syneoshealth.com; 919-227-5843;
WT1	Tier 1A Pathogenic	p.R385fs*69 c.1152delA	

QUIZARTINIB, 5-AZACYTIDINE, CYTARABINE

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)
NCT01892371

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA	Yesid Alvarado, MD; yalvarad@mdanderson.org; 713-794-4364;

VINCRISTINE, METHOTREXATE, DEXAMETHASONE, PREDNISONE, 5-AZACYTIDINE, VENETOCLAX, LEUCOVORIN, CYCLOPHOSPHAMIDE, 2-MERCAPTOETHANESULFONIC ACID, CYTARABINE, RITUXIMAB, DS-1594B

An Open-Label Phase 1/2 Multi-Arm Study of DS-1594b as a Single-Agent and in Combination With Azacitidine and Venetoclax or Mini-HCVD for the Treatment of Patients With Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL)
NCT04752163

Qualifying variant			Contact
Gene	Classification	Variant	United States: TX
NPM1	Tier 1A Pathogenic	p.W259fs*? c.773_776dupTCTG	Naval G Daver;

KO-539

A Phase 1/2A First in Human Study of the Menin-MLL(KMT2A) Inhibitor KO-539 in Patients With Relapsed or Refractory Acute Myeloid Leukemia
NCT04067336

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, FL, IL, IN, MA, MD, MI, MN, NC, NY, PA, TN, TX, WA
NPM1	Tier 1A Pathogenic	p.W259fs*? c.773_776dupTCTG	Mary Pevear; mpevear@kuraoncology.com; 781-346-9905;

SNDX-5613, COBICISTAT

AUGMENT-101: A Phase 1/2, 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
NCT04065399

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, FL, GA, IL, MA, MO, NY, TX
NPM1	Tier 1A Pathogenic	p.W259fs*? c.773_776dupTCTG	Sue Fischer; sfischer@syndax.com; 781-795-9419;

Phase 1 clinical trials (2)

RETIFANLIMAB, INCB081776

A Phase 1a/1b Study Exploring the Safety and Tolerability of INCB081776 in Participants With Advanced Malignancies
NCT03522142

Qualifying variant			Contact
Gene	Classification	Variant	United States: CT, MA, PA, TN, TX
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA	Incyte Corporation Call Center (US); medinfo@incyte.com; 1.855.463.3463;

JNJ-75276617

A First in Human Study of the Menin-KMT2A (MLL1) Inhibitor JNJ-75276617 in Participants With Acute Leukemia
NCT04811560

Phase 1 clinical trials (2)

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, KY, MA, NY, TX
NPM1	Tier 1A Pathogenic	p.W259fs*? c.773_776dupTCTG	Study Contact; JNJ.CT@sylogent.com; 844-434-4210;

VARIANT DETAILS

Variants of strong clinical significance (3)

FLT3 Y597_E598insDYVDFREY

Gene: FLT3
Exon: 14
Nucleotide: NM_004119.3: g.28608262_28608263insTCATATTCTCTGAAATCAACGTAG c.1770_1793dupCTACGTTGATTTCAGAGAATATGA
Amino Acid: p.Y597_E598insDYVDFREY
Allelic Fraction: 31.0% (of 13551 reads)
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
2 Sensitive
10 Trials

Biomarker summary: FLT3-Y597_E598insDYVDFREY is predicted to be an activating mutation.

Clinical relevance: Activating FLT3 alterations have been reported to promote proliferation, inhibit apoptosis, and result in oncogenic transformation [56, 85, 162, 84, 99]. Activating alterations in FLT3 may predict sensitivity to small molecule multi-tyrosine kinase inhibitors, several of which have been approved by numerous agencies for certain indications [23, 41, 127, 123, 176, 91]. Midostaurin and gilteritinib have specifically been approved by the FDA and EMA for acute myeloid leukemia (AML) patients harboring FLT3 internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutations [137, 112]. Additional second-generation inhibitors with greater specificity for Flt3 are also in clinical development [154, 28, 50].

Disease summary: Constitutive activation of Flt3 by internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutations has been reported to result in the activation of several signaling pathways, including those of Akt and Stat5, and has been reported to promote proliferation, survival, and transformation of myeloid cells [22, 69, 10, 114, 70, 89]. FLT3 mutations have been associated with elevated white blood cell and bone marrow blast counts in studies of acute myeloid leukemia (AML), and have been reported most commonly in patients with normal cytogenetics [135, 49, 76, 7]. FLT3-ITD mutations in normal karyotype AML have been associated with poor prognosis in numerous scientific studies [116, 135, 153, 49, 76, 80]. However, recent studies have suggested that AML patients with a low allelic ratio of FLT3-ITD (generally defined as a mutant-to-wild-type ratio of lower than 0.5 as determined by quantitative DNA fragment length analysis) and concurrent NPM1 mutations have a favorable prognosis; patients with wild-type NPM1 and a low allelic ratio of FLT3-ITD or mutant NPM1 and a high allelic ratio of FLT3-ITD (greater than or equal to 0.5) have an intermediate prognosis; and patients with wild-type NPM1 and a high allelic ratio of FLT3-ITD have a poor prognosis [35, 57, 118, 151, 133].

Molecular function: The FLT3 alteration reported here results in the insertion of a single amino acid followed by the tandem duplication of seven amino acids within exon 14, corresponding to the juxtamembrane domain of the Flt3 protein (Integrative Genomics Viewer, v.2.12). FLT3-ITD alterations similar to the one reported here have been found to result in ligand-independent dimerization, constitutive Flt3 kinase activity, activation of downstream signaling pathways, and oncogenic transformation [97, 22, 70, 71, 69]. Therefore, although this alteration has not been functionally characterized, is predicted to be activating.

Incidence: FLT3 mutations have been reported in 23% (16452/70942) of Acute myeloid leukemia (AML) samples analyzed in COSMIC (Nov 2021). FLT3 mutations have been reported in 6.7-30% of Acute myeloid leukemia (AML) samples (cBioPortal for Cancer Genomics, Nov 2021). FLT3 mutations have been reported as the most common alteration in AML, with FLT3 internal tandem duplication (FLT3-ITD) and tyrosine kinase domain (FLT3-TKD) mutations cited in 12-35% and 4-10% of cases, respectively, and found to occur more frequently in AML with a normal karyotype [17, 39, 170, 95, 111, 126, 67, 30, 155, 101, 144, 7, 8, 70, 33].

NPM1 W259fs*?

Gene: NPM1
Exon: 10
Nucleotide: NM_199185.4: g.170837543_170837544insTCTG c.773_776dupTCTG
Amino Acid: p.W259fs*?
Allelic Fraction: 40.0% (of 3453 reads)
Classification: Tier 1A
Assessment: Pathogenic

Biomarker summary: NPM1-W288fs exhibits altered function compared to wild-type.

Clinical relevance: NPM1 encodes nucleophosmin (Npm1), a multifunctional protein that regulates the ARF /p53 pathway and enhances Myc oncogenic activities [53, 88, 68, 90]. NPM1 mutations, particularly C-terminal truncations, have been reported frequently in myeloid malignancies, and although mutation has not been commonly found in solid tumors, overexpression of the Npm1 protein has been reported [48, 143, 46, 68, 113, 65]. There are currently no approved drugs targeting NPM1 alterations or changes in Npm1 protein expression, however, several strategies are being investigated in preclinical and clinical studies in acute leukemia, including disruption of the menin/MLL interaction and proteasome degradation of Npm1 with arsenic trioxide and all-trans retinoic acid [66, 119, 164, 94, 40, 172, 74, 82].

Disease summary: NPM1 mutation in AML has been shown to result in the aberrant cytoplasmic localization of Npm1, in contrast to its normal nucleolar localization, and has been reported to play a role in the development of AML through the mislocalization and inhibition of Npm1 binding partners, including the tumor suppressor ARF [43, 44, 175, 27, 46]. NPM1 mutations in AML have been associated with M4 and M5

Variants of strong clinical significance (3)

Treatment options
4 Trials

morphology, increased leukocyte and bone marrow blast counts, female sex, and decreased expression of CD34; NPM1 mutations have been reported more frequently in cytogenetically normal AML (CN-AML) and often occur in combination with FLT3, IDH1/2, NRAS, and DNMT3A mutations [36, 130, 143, 150, 110, 108, 125]. AML with mutant NPM1 is recognized as a subtype of AML with recurrent genetic abnormalities in the WHO classification of myeloid neoplasms and acute leukemia [4]. NPM1 mutations in the absence of FLT3-ITD have been associated with favorable outcomes in AML, especially in cytogenetically normal AML (CN-AML), while NPM1 mutations in the presence of FLT3-ITD have been associated with an intermediate prognosis [130, 128, 143, 98, 149]. Additionally, monitoring of mutant NPM1 transcript levels has been reported to be useful in the detection of minimal residual disease (MRD) and prediction of disease relapse [129, 79, 131, 61, 64].

Molecular function: NPM1 W288fs is expected to effectively truncate the Npm1 protein at amino acid 288 of 294 (UniProt). This truncation results in the loss of two tryptophan residues, W288 and W290, that are critical for nucleolar localization of Npm1 [104, 45]. In addition, the resulting protein would also lack a lysine residue at position 292, one of six lysines that undergo acetylation, which enhances the interaction of Npm1 with acetylated histones and is required for the enhancement of chromatin transcription [140]. Several C-terminal NPM1 W288 truncating and frameshift alterations have been reported to result in mislocalization of Npm1, as well as a gain in oncogenic function through deregulation of downstream pathways [27, 45, 46, 21, 121, 44]. The most common NPM1 W288fs alteration, type A, is the result of the insertion/duplication of a TCGT tetranucleotide, but many similar alterations resulting in W288fs have been reported [3, 6]. Therefore, although this alteration results in loss of the nucleolar localization domain, it is predicted to be associated with promotion of tumorigenesis.

Incidence: NPM1 mutations have been reported in 31% (6394/20758) of Acute myeloid leukemia (AML) samples analyzed in COSMIC (Nov 2021). NPM1 mutations have been reported in 0.7-27% of Acute myeloid leukemia (AML) samples (cBioPortal for Cancer Genomics, Nov 2021). NPM1 mutations, predominately resulting in C-terminal truncations, have been reported in 14-37% of AML samples and in 30-53% of cytogenetically normal AML (CN-AML) samples analyzed in scientific studies [169, 16, 158, 155, 156, 81, 143, 128, 130, 150, 110]. In addition, one study analyzing the TAGET dataset has reported NPM1 mutations in 7.6% (66/869) of pediatric AML cases [160].

WT1 R385fs*69

Gene: WT1
Exon: 7
Nucleotide:
NM_024426.6:
g.32417915delT
c.1152delA
Amino Acid: p.R385fs*69
Allelic Fraction: 20.0% (of 13829 reads)
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
1 Trial

Biomarker summary: WT1-R385fs is an inactivating mutation.

Clinical relevance: WT1 encodes the Wilms tumor 1 protein (Wt1). Wt1 has been reported to have both tumor suppressive and tumorigenic properties [62, 138]. There are no approved targeted therapies for WT1 mutations or expression. Wt1 vaccines are in clinical trials for Wt1-expressing hematologic and solid tumor cancers, including renal cell carcinoma, biliary tract cancers, and non-small cell lung cancer [138, 105, 142, 141]. In the case of an inactivating alteration, as reported here, Wt1 vaccines are not expected to be relevant.

Disease summary: In studies of AML, both overexpression of WT1 mRNA and inactivating mutations of WT1 have been reported [120]. WT1 mRNA transcript levels have been reported to be elevated in the blood and bone marrow of leukemia patients and have been reported to serve in minimal residual disease monitoring [54, 122, 83, 115, 78]. WT1 mRNA expression has been positively associated with relapse and poor overall survival in several studies of AML [173, 54, 52, 132, 117, 168, 60, 103, 165]. WT1 mutations, predominately resulting in protein truncation, have been associated with younger patient age, cytogenetically normal (CN) AML, and the presence of FLT3 internal tandem duplication (ITD) mutations [20, 124, 60, 59, 14]. WT1 mutations have also been associated with reduced relapse-free, event-free, and overall survival in studies of AML, particularly in CN-AML patients [63, 124, 152, 60, 109, 59, 77, 37].

Molecular function: WT1 R385 in NM_024426 corresponds to R168 in NM_001198551 (Integrative Genomics Viewer, v.2.12). The WT1 frameshift alteration reported here is expected to effectively truncate the Wt1 protein before or within the zinc finger region, resulting in disruption of this region (UniProt). The zinc finger domains of Wt1 have been reported to be necessary for DNA binding and proper nuclear localization of the protein [24, 55, 42, 11]. Therefore, this alteration is expected to be inactivating.

Incidence: WT1 mutations have been reported in 8.4% (596/7113) of Acute myeloid leukemia (AML) samples analyzed in COSMIC (Nov 2021). WT1 mutations have been reported in 3.3-9.0% of Acute myeloid leukemia (AML) samples (cBioPortal for Cancer Genomics, Nov 2021). WT1 mutations, predominately resulting in protein truncation, have been reported in 4-7% of AML cases overall, with higher frequency of 7-13% observed in cytogenetically normal AML (CN-AML) and in pediatric AML cases [58, 20, 173, 38, 2, 77, 152, 60, 174, 148].

Variant of potential clinical significance (1)

RAD21 L183fs*7

Variant of potential clinical significance (1)

Gene: RAD21
Exon: 6
Nucleotide: NM_006265.3: g.117869645_117869646delTA c.548_549delTA
Amino Acid: p.L183fs*7
Allelic Fraction: 44.0% (of 6364 reads)
Classification: Tier 2C
Assessment: Likely Pathogenic

Biomarker summary: RAD21-L183fs*7 is an inactivating mutation.

Clinical relevance: RAD21 encodes the Rad21 protein, a key component of the cohesin complex which maintains fidelity in chromosome segregation [75, 161, 12, 13]. At present, there are no therapies that directly address loss of Rad21 activity; however, inactivation of Rad21 and other cohesin complex components has been associated with enhanced sensitivity to PARP inhibitors in preclinical models [96, 9]. Although Rad21 has been implicated as a tumor suppressor in some contexts, it has also been described as activated or essential for cell proliferation and survival in various cancer cell line lineages [93, 5, 32, 171, 163]. Therefore, the potential relevance of any targeted therapies must be carefully considered in each situation.

Disease summary: RAD21 mutation has been significantly associated with increased sensitivity to venetoclax in AML patients; depletion or mutation of RAD21 in AML cell line models mimicked this effect [18].

Molecular function: The RAD21 frameshift alteration reported here is expected to effectively truncate the 631-amino acid Rad21 protein prior to or within the C-terminal Smc1-binding domain (UniProt, Interpro) [159, 31]. The interaction between Rad21 and Smc1 is required for the formation of the cohesin complex [147, 15]. In addition, one study has reported RAD21 truncation alterations (including I621fs) in myeloid malignancies and that the alterations correlated with low RAD21 expression [146]. Therefore, this alteration is predicted to be inactivating.

Incidence: RAD21 mutations have been reported in 3.3% (171/5232) of Acute myeloid leukemia (AML) samples analyzed in COSMIC (Nov 2021). RAD21 mutations have been reported in 0.7-3.0% of Acute myeloid leukemia (AML) samples (cBioPortal for Cancer Genomics, Nov 2021). Literature studies have reported RAD21 mutations in 2-17% of AML samples [106, 146, 145, 34].

Variants of uncertain significance (3)

Gene	Variant	Allelic fraction	Classification
BCORL1	c.1123G>C p.A375P	13.0% (of 2140 reads)	Tier 3, Uncertain Significance
BCORL1	c.3073G>A p.V1025M	44.0% (of 5452 reads)	Tier 3, Uncertain Significance
STAG2	c.1580G>T p.C527F	20.0% (of 825 reads)	Tier 3, Uncertain Significance

REPORT INFORMATION

Genes tested

Methods and limitations

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (8.1.20220121), Ingenuity Knowledge Base (F-release), CADD (v1.6), NCBI Gene (2021-02-19), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2021-02-19), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2022-01-23 11:45:51.283), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (F-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2.2.2 (HumVar)), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Jan 10 09:32 iva-1.0.2063.jar), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 37), CentoMD (5.3), dbVar (2021_04), OMIM (September 21, 2021), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2021-09-08), DGV (2016-05-15), COSMIC (v94), HGMD (2021.4), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 154, GRCh38 154), SIFT4G (2016-02-23)

Clinical significance of variants based on AMP / ASCO / CAP guidelines*

Strong clinical significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential clinical significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial

		Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain clinical significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

*Adapted from PMID:27993330 jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf

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