PRECIPIO EXPECT MORE
203-787-1717
203-901-1289

NEXT-GEN SEQUENCING

Patient: **John A. Doe**
DOB/Gender: 10/10/44 (74 yrs) - Male
Patient ID/MRN: 123456
Date Collected: 01/02/2024

Case# **XX-00000**
Status: Final

Report Category:
Detected

Provider: Jane Smith, M.D.
Hospital Oncology Center
Tel: 800-123-4567
Fax: 800-765-4321

RESULT SUMMARY:

Peripheral blood:

Significant Genomic Variants Detected

ASXL1 G646fs (Tier 1A)	CBL R149* (Tier 1A)	CUX1 c.757-2A>G (Tier 3)
JAK2 V617F (Tier 1A)	NRAS A59D (Tier 1A)	STAG2 Q590* (Tier 1A)
TET2 S1577fs (Tier 2C)		

Pertinent NEGATIVE Results

ABL1 mut	BCOR mut	BRAF mut
CALR mut	CEBPA mut	CSF3R mut
DNMT3A mut	ETV6 mut	EZH2 mut
FLT3 ITD	FLT3 TKD	GATA2 mut
IDH1 mut	IDH2 mut	IKZF1 mut
KIT D816V	KIT mut	KRAS mut
MPL mut	NPM1 mut	PDGFRA D842V
PDGFRA T674I	PTEN mut	RUNX1 mut
SETBP1 mut	SF3B1 mut	SRSF2 mut
TP53 mut	U2AF1 mut	WT1 mut
ZRSR2 mut		

Prognostic Implications per NCCN

Biomarker	Association Prognosis	Diseases	Note
ASXL1 G646fs	Unfavorable	Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia	ASXL1 nonsense or frameshift mutation is independently associated with a poor prognosis in MDS and CMML.
ASXL1 G646fs	Unfavorable	Systemic Mastocytosis	SRSF2/ASXL1/RUNX1, and/or EZH2 or ASXL1/CBL mutation profile is an adverse prognostic variable in systemic mastocytosis.
ASXL1 G646fs	Unfavorable	Acute Myeloid Leukemia	Mutated ASXL1 is associated with poor/adverse risk in AML, as long as it does not co-occur with favorable-risk AML subtypes.
ASXL1 G646fs	Unfavorable	Myelofibrosis	ASXL1 mutation is associated with inferior OS, leukemia-free survival, and leukemia-free survival following HCT in MF.
CBL R149*	Unfavorable	Systemic Mastocytosis	SRSF2/ASXL1/RUNX1, and/or EZH2 or ASXL1/CBL mutation profile is an adverse prognostic variable in systemic mastocytosis.
CBL R149*	Unfavorable	Myelofibrosis	Mutation in U2AF1, DNMT3A, or CBL is associated with inferior OS following HCT in MF.
JAK2 V617F	Intermediate	Myelofibrosis	JAK2 V617F is associated with intermediate prognosis and higher risk of thrombosis compared to patients with CALR mutation in MF.
JAK2 V617F	Unfavorable	B-Cell Acute Lymphoblastic Leukemia	BCR-ABL1-like (Ph-like) ALL is associated with unfavorable/poor risk.
NRAS A59D	Unfavorable	Myelofibrosis	RAS mutations are associated with inferior OS in MF.
NRAS A59D	Unfavorable	T-Cell Acute Lymphoblastic Leukemia	RAS/PTEN mutation is a high risk feature in T-cell ALL.
STAG2 Q590*	Unfavorable	Acute Myeloid Leukemia	Mutated STAG2 is associated with poor/adverse risk in AML, as long as it does not co-occur with favorable-risk AML subtypes.
STAG2 Q590*	Unfavorable	Myelodysplastic Syndromes	STAG2 nonsense, frameshift, and splice site mutations are associated with a poor prognosis in MDS.
Negative: TP53 Mutation	Favorable	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	Wild-type TP53 is associated with a favorable prognosis in CLL/SLL.

Diagnostic Implications per WHO

Biomarker	Diseases	Note
ASXL1 G646fs	Histiocytic and Dendritic Cell Neoplasm	Among histiocytic and dendritic cell neoplasms, ASXL1 mutations have been observed in 28-46% of blastic plasmacytoid dendritic cell neoplasm (BPDCN) cases. In mixed lineage neoplasms, ASXL1 mutations are observed in acute leukemia of ambiguous lineage.
ASXL1 G646fs	Myeloid Neoplasm	Among myeloid neoplasms, ASXL1 mutations have been identified in myelodysplastic/myeloproliferative neoplasm, chronic myeloid leukemia, mastocytosis, acute myeloid leukemia. Nearly all chronic neutrophilic leukemia cases exhibit mutation in ASXL1 (70-80%). In mixed lineage neoplasms, ASXL1 mutations are observed in acute leukemia of ambiguous lineage.
CBL R149*	Histiocytic and Dendritic Cell Neoplasm	Among histiocytic and dendritic cell neoplasms, CBL mutations or CBL rearrangements like CBL-USP2 have been identified in ALK-positive histiocytosis and interdigitating dendritic cell sarcoma, respectively.
CBL R149*	Myeloid Neoplasm	Among myeloid neoplasms, CBL mutations have been identified in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, and myeloproliferative neoplasms like primary myelofibrosis (PMF) and juvenile myelomonocytic leukemia (JMML). Germline CBL mutations predispose carriers to JMML or a JMML-like disorder.
CUX1 c.757-2A>G	Myeloid Neoplasm	CUX1 mutations have been identified in myeloid neoplasms.
JAK2 V617F	Myeloid Neoplasm	Among myeloid neoplasms, JAK2 mutations and rearrangements have been identified in myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS). JAK2 p.V617F and JAK2 exon 12 mutations have been strongly associated with patients with MPN. The presence of a driver mutation in JAK2 supports the diagnosis of an MPN. Patients diagnosed with MDS-SF3B1 who acquire JAK2 p.V617F or equivalent mutations with resultant thrombocytosis may be regarded as having developed MDS/MPN-SF3B1-T through clonal evolution. JAK2 p.V617F and JAK2 exon 13 indels are each seen in 1-4% of cases with hypereosinophilia (PMID:26017288; PMID:30656986; PMID:30573779; PMID:31697804).
JAK2 V617F	Lymphocytic Neoplasm	Among lymphocytic neoplasms, JAK2 mutations have been identified in B-cell lymphoblastic leukemia/lymphoma, plasmablastic lymphoma, anaplastic large cell lymphoma (ALCL), mature T-cell and NK-cell non-Hodgkin lymphoma, and chronic myelomonocytic leukemia. In primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (PCAETL), upregulation JAK2 signaling is observed in virtually all cases often due to rearrangements. In cases without JAK2 rearrangements, gain of function mutations in JAK2 can be observed (PMID:33792220). In chronic myelomonocytic leukemia (CMML), there is a high frequency of JAK2 p.V617F. JAK2 mutation (most commonly codon R683) leads to constitutive JAK/STAT activation downstream of CRLF2. JAK2 gene fusions occur in ~7% of B-cell acute lymphoblastic leukemia (PMID:26859458). STAT3-JAK2 rearrangements are recurrent in indolent T-cell non-Hodgkin lymphoma (PMID:29592893; PMID:31558678). PAX5-JAK2 rearrangement also occurs in B-cell lymphoblastic leukemia/lymphoma (PMID:30643249).

Diagnostic Implications per WHO

Biomarker	Diseases	Note
NRAS A59D	Histiocytic and Dendritic Cell Neoplasm	Among histiocytic and dendritic cell neoplasms, NRAS mutations have been frequently identified in blastic plasmacytoid dendritic cell neoplasm, histiocytic sarcoma, langerhans cell histiocytosis, Rosai-Dorfman disease, and juvenile xanthogranuloma (PMID:25115387; PMID:30157397; PMID:28752840; PMID:31768065; PMID:26566875; PMID:26922062; PMID:28597077; PMID:28664935; PMID:29236635; PMID:32601132; PMID:32929178; PMID:33904632).
NRAS A59D	Lymphocytic Neoplasm	Among lymphocytic neoplasms, NRAS mutations are frequently identified in B-cell lymphoblastic leukemia/lymphoma with hyperdiploidy and high-grade B-cell lymphoma with MYC and BCL2 rearrangements.
NRAS A59D	Myeloid Neoplasm	Among myeloid neoplasms, NRAS mutations have been identified in myelodysplastic/myelo proliferative neoplasm (MPN/MDS) and acute myeloid leukemia (AML). The presence of a NRAS mutation may be helpful in the diagnosis of juvenile myelomonocytic leukemia (JMML).
STAG2 Q590*	Myeloid Neoplasm	Among myeloid neoplasms, STAG2 mutations have been identified in acute myeloid leukemia, chronic neutrophilic leukemia, myelodysplastic/myeloproliferative meoplasms, and primary myelofibrosis.
TET2 S1577fs	Histiocytic and Dendritic Cell Neoplasm	TET2 mutations have been identified in histiocytic and dendritic cell neoplasms. TET2 mutations have frequently been identified in blastic plasmacytoid dendritic cell neoplasm (BPDCN) cases (21%-70% of cases).
TET2 S1577fs	Lymphocytic Neoplasm	Among lymphocytic neoplasms, TET2 mutations have been identified in nodular lymphocyte-predominant Hodgkin lymphoma, marginal zone lymphoma (MZL), enteropathy-associated T-cell lymphoma (EATL), and mature T-cell and NK-cell neoplasm. Extranodal MZL affecting the thyroid are characterized by highly frequent and concurrent inactivating mutations in TET2. 25% to 30% of NK-cell large granular lymphocyte leukemia (NK-LGLL) have mutations in TET2. Peripheral T-cell lymphoma with higher expression of TBX2 is mainly characterized by TET2 mutation. In patients from Asia, the most commonly mutated gene in EBV+ nodal T- and NK-cell lymphoma is TET2 (64%).
TET2 S1577fs	Myeloid Neoplasm	TET2 mutation has been identified in various myeloid neoplasms: myeloproliferative neoplasm (MPN), systemic mastocytosis (SM), myelodysplastic/myeloproliferative neoplasm (MDS/MPN), and acute myeloid leukemia (AML). TET2 is found in 10-15% of MPN patients. TET2 mutations present in up to 91.8% of chronic myelomonocytic leukemia (CMML) patients and appear to persist in patients who respond to therapy with hypomethylating agents. Patients with the TET2 gene have an increased risk of development of a myeloid neoplasm if exposed to a cytotoxic therapy. The TET2 mutation is noted as common in elderly AML patients.

ACTIONABILITY SUMMARY

FDA / NCCN Therapies for the Patient's Tumor Type (Tier 1A)

Biomarker	Therapies	Setting	Source(s)
JAK2 V617F	ruxolitinib		NCCN
JAK2 V617F	ruxolitinib + chemotherapy	Induction/consolidation	NCCN
NRAS A59D	binimetinib,cobimetinib,selumetinib,trametinib		NCCN
Negative: KIT D816V	imatinib		FDA (Approved),NCCN

FDA / NCCN Therapies with Resistance / Decreased Response (Tier 1A)

None

FDA / NCCN Therapies for Other Tumor Types (Tier 2C)

None

Clinical Trials Summary

ASXL1 G646fs: 8 trials
CBL R149*: 2 trials
JAK2 V617F: 5 trials
NRAS A59D: 6 trials
STAG2 Q590*: 5 trials
TET2 S1577fs: 2 trials

ALTERATION DETAILS

Mutations

Alteration	Type	VAF(%)	Location	Transcript	ClinVar*	Pathway	Effect via JAX- CKB**
ASXL1 G646fs c.1934dupG	Insertion - Frameshift	34.5	Exon 12	NM_015338.5	Pathogenic/Likely pathogenic	Chromatin remodeling/DNA methylation	gain of function - predicted; gain of function
CBL R149* c.445C>T	Substitution - Nonsense	2.4	Exon 3	NM_005188.3	Uncertain significance	Receptor tyrosine kinase/growth factor signaling	-
CUX1 c.757-2A>G	Splice Acceptor Site	2.6	Intron 9	NM_001913.3			-
JAK2 V617F c.1849G>T	Substitution - Missense	9.0	Exon 14	NM_004972.3	Pathogenic/Likely pathogenic	JAK-STAT signaling	gain of function
NRAS A59D c.176C>A	Substitution - Missense	12.6	Exon 3	NM_002524.4	Likely pathogenic	MAP kinase signaling	-
STAG2 Q590* c.1768C>T	Substitution - Nonsense	2.3	Exon 19	NM_001042749.1		DNA damage/repair	-
TET2 S1577fs c.4728delT	Deletion - Frameshift	43.3	Exon 11	NM_001127208.2		Chromatin remodeling/DNA methylation	-

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ASXL1: ASXL1, additional sex combs like 1, transcriptional regulator, is involved in epigenetic regulation of gene expression and forms complexes with several proteins to regulate transcription (PMID: 23736028). Mutations in ASXL1 are frequent in chronic myelomonocytic leukemia (PMID: 26771811, PMID: 23736028), and have been identified in a number of different tumor types including acute myeloid leukemia and liver cancer (PMID: 23736028).

ASXL1 G646fs c.1934dupG: ASXL1 G646Wfs*12 indicates a shift in the reading frame starting at amino acid 646 and terminating 12 residues downstream causing a premature truncation of the 1541 amino acid Asxl1 protein (UniProt.org). G646Wfs*12 results in increased activity of the Asxl1-Bap1 complex as demonstrated by the loss of H2AK119 ubiquitination, decreased H3K27me3 levels, and impaired myeloid differentiation compared to wild-type in cultured cells (PMID: 26095772), and therefore, leads to a gain of Asxl1 protein function.

CBL: CBL, Cbl proto-oncogene, is an E3 ubiquitin-protein ligase involved in cell signaling and ubiquitination of tyrosine kinases (PMID: 23085373). CBL mutations, often resulting in a loss of function, have been identified primarily in myeloid neoplasms, including myelodysplastic syndrome, acute myeloid leukemia, chronic myeloid leukemia, myelofibrosis, and juvenile myelomonocytic leukemia (PMID: 25477533).

CUX1: CUX1, cut like homeobox 1, is a transcription factor, that may act as a transcriptional repressor or an activator (PMID: 32547943), is required for cell motility (PMID: 22306263), and plays a role in cell cycle progression, cell proliferation, and DNA repair (PMID: 28147323). CUX1 fusions with BRAF have been observed in solid tumors (PMID: 25190083, PMID: 26314551), with FGFR1 in hematological tumors (PMID: 21330321), and with ALK in NSCLC (PMID: 30010043), and altered Cux1 expression may play a role in castrate resistant prostate cancer (PMID: 32180898).

JAK2: JAK2, Janus kinase 2, is a non-receptor protein tyrosine kinase that binds cytokine receptors to activate the interferon-alpha/beta/gamma pathway and is a member of the JAK/STAT signaling pathway (PMID: 15575979, PMID: 30092288). JAK2 mutations are observed in a variety of tumor types, including myeloproliferative neoplasms (PMID: 30074114), lymphoma (PMID: 29984752), leukemia (PMID: 29979407), and cervical cancer (PMID: 30003068).

JAK2 V617F c.1849G>T: JAK2 V617F lies within the protein kinase domain 1 of the Jak2 protein (UniProt.org). V617F results in constitutive activation of Jak2 and downstream Stat5 and Erk, is transforming in cell culture, and leads to development of erythrocytosis in mouse models (PMID: 15858187, PMID: 15837627, PMID: 15793561, PMID: 28473624).

NRAS: NRAS, NRAS proto-oncogene, GTPase, is a member of the family of small GTPase that when activated by growth factors, stimulates multiple effector pathways such as RAF and PI3K to promote cell proliferation and survival (PMID: 29524560). NRAS mutations have been observed in a variety of cancers including melanoma, thyroid, breast, ovary cancer, and leukemia (PMID: 29524560, PMID: 30154648, PMID: 28860801).

STAG2: STAG2, cohesin subunit SA-2, functions as part of the cohesin complex to regulate spindle formation and sister chromatid association in mitosis (PMID: 12034751, PMID: 24854081, PMID: 29175904). Somatic STAG2 mutations have been reported in glioblastoma, Ewing's sarcoma, bladder cancer, and melanoma, and loss of Stag2 expression has been demonstrated in a variety of other tumor types, including bladder cancer (PMID: 22668012, PMID: 28627627, PMID: 27207471, PMID: 29954776).

TET2: TET2, methylcytosine dioxygenase TET2, is a member of the ten-eleven-translocation family of genes that plays a role in DNA methylation and is involved in hematopoesis (PMID: 26099018, PMID: 25510268, PMID: 27848178). TET2 has been identified as a tumor suppressor in hematological malignancies, and mutations in TET2 are common in hematological cancers including myelodysplastic syndrome, chronic myelomoncytic leukemia, and atypical CML (PMID: 26099018, PMID: 22240200, PMID: 30138727) and epigenetic dysregulation has been observed in glioblastoma (PMID: 29899831).

Variants of Unknown Significance (Tier 3)		
PHF6 L228R	RUNX1 L112P	TP53 P27S

INVESTIGATIONAL THERAPIES

See Appendix for descriptions of investigational drugs.

ASXL1 G646fs

Therapies	Clinical Trial	Location / Contact
allogeneic hematopoietic stem cell transplantation + busulfan + decitabine + fludarabine + venetoclax	**NCT06337331**: (Phase 2) Adding Venetoclax to the High-dose Chemotherapy Regimen Prior to Mismatche Allogeneic Stem Cell Transplant	Atlanta, Georgia Northside Hospital, Inc. ssolomon@bmtga.com
sirolimus + cyclophosphamide + fludarabine + melphalan + mycophenolate mofetil	**NCT05436418**: (Phase 1/Phase 2) The Lowest Effective Dose of Post-Transplantation Cyclophosphamide in Combination With Sirolimus and Mycophenolate Mofetil as Graft-Versus-Host Disease Prophylaxis After Reduced Intensity Conditioning and Peripheral Blood Stem Cell Transplantation	Bethesda, Maryland National Cancer Institute (NCI) amy.chai@nih.gov

ASXL1 G646fs + CBL R149* + NRAS A59D + STAG2 Q590*

Therapies	Clinical Trial	Location / Contact
allogeneic hematopoietic stem cell transplantation + azacitidine + busulfan + cedazuridine + decitabine + fludarabine + venetoclax	**NCT03613532**: (Phase 1) Venetoclax Added to Fludarabine + Busulfan Prior to Transplant and to Maintenance Therapy for AML, MDS, and MDS/MPN	Boston, Massachusetts Jacqueline Garcia, MD Jacqueline_garcia@dfci.harvard.edu

ASXL1 G646fs + NRAS A59D

Therapies	Clinical Trial	Location / Contact
seclidemstat + azacitidine	**NCT04734990**: (Phase 1/Phase 2) Seclidemstat and Azacitidine for the Treatment of Myelodysplastic Syndrome or Chronic Myelomonocytic Leukemia	Houston, Texas M.D. Anderson Cancer Center gmontalban1@mdanderson.org
sirolimus + busulfan + cyclophosphamide + fludarabine + mycophenolate mofetil	**NCT03983850**: (Phase 1/Phase 2) Optimizing PTCy Dose and Timing	Bethesda, Maryland National Cancer Institute (NCI) ashley.devries@nih.gov

ASXL1 G646fs + STAG2 Q590*

Therapies	Clinical Trial	Location / Contact
Iadademstat + azacitidine + venetoclax	**NCT06357182**: (Phase 1) Iadademstat in Combination With Azacitidine and Venetoclax in Treating Newly Diagnosed Acute Myeloid Leukemia	Portland, Oregon OHSU Knight Cancer Institute
TRGFT-201 + tacrolimus + fludarabine + melphalan + total-body irradiation +/- thiotepa	**NCT06195891**: (Phase 1) Orca-T Following Chemotherapy and Total Marrow and Lymphoid Irradiation for the Treatment of Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia or Myelodysplastic Syndrome	Duarte, California City of Hope Medical Center
allogeneic natural killer cells + azacitidine + venetoclax	**NCT05834244**: (Phase 1) A Phase Ib Trial of Azacitidine, Venetoclax and Allogeneic NK Cells for Acute Myeloid Leukemia (ADVENT-AML)	Houston, Texas M.D. Anderson Cancer Center amaiti@mdanderson.org

CBL R149* + NRAS A59D

Therapies	Clinical Trial	Location / Contact
ASTX029+ASTX029 + decitabine/cedazuridine	**NCT06284460**: (Phase 1/Phase 2) Phase I/II Study of a Combination of Decitabine and Cedazuridine (ASTX727) and ASTX029, an ERK Inhibitor, for Patients With RAS Pathway Mutant Myelodysplastic Syndromes and Myelodysplastic/Myeloproliferative Neoplasms	Houston, Texas M.D. Anderson Cancer Center gmontalban1@mdanderson.org

JAK2 V617F

Therapies	Clinical Trial	Location / Contact
VAC85135 + ipilimumab	**NCT05444530**: (Phase 1) A Study of VAC85135, a Neoantigen Vaccine Regimen, Concurrently Administered With Ipilimumab for the Treatment of Myeloproliferative Neoplasms	Tampa, Florida Janssen Research & Development, LLC Participate-In-This-Study@its.jnj.com
allogeneic hematopoietic stem cell transplantation	**NCT04959903**: (Phase 1/Phase 2) Safety and Efficacy of SMART101 in Pediatric and Adult Patients With Hematological Malignancies After T Cell Depleted Allo-HSCT	New York, New York Smart Immune SAS frederic.lehmann@smart-immune.com
blinatumomab + brexucabtagene autoleucel + inotuzumab ozogamicin + lymphodepletion therapy + (hyperCVAD regimen or mini-hyper-CVD regimen)	**NCT06287229**: (Phase 1/Phase 2) Phase Ib/II Study Assessing the Clinical Activity and Safety of Brexucabtagene Autoleucel as a Consolidation in Patients With Relapsed/Refractory (R/R) and Newly Diagnosed B-cell Acute Lymphocytic Leukemia (ALL) Post Cytoreduction With Mini-HCVD-inotuzumab-blinatumomab/HCVAD-inotuzumab-blinatumomab	Houston, Texas M.D. Anderson Cancer Center ejabbour@mdanderson.org
elotuzumab	**NCT04517851**: (Phase 2) Elotuzumab for the Treatment of JAK2-Mutated Myelofibrosis	Houston, Texas M.D. Anderson Cancer Center pbose@mdanderson.org
givinostat	**NCT06093672**: (Phase 3) Study on Efficacy and Safety of Givinostat Versus Hydroxyurea in Patients With Polycythemia Vera	Houston, Texas Italfarmaco patientadvocacy@italfarmacogroup.com

NRAS A59D

Therapies	Clinical Trial	Location / Contact
BDTX-4933	**NCT05786924**: (Phase 1) A Study of BDTX-4933 in Patients With KRAS, BRAF and Select RAS/MAPK Mutation-Positive Cancers	Fairfax, Virginia Black Diamond Therapeutics, Inc. blackdiamondtx@careboxhealth.com
cobimetinib + ixazomib + dexamethasone + pomalidomide	**NCT03732703**: (Phase 1/Phase 2) Myeloma-Developing Regimens Using Genomics (MyDRUG)	Atlanta, Georgia Multiple Myeloma Research Consortium patientnavigator@themmrf.org

STAG2 Q590*

Therapies	Clinical Trial	Location / Contact
talazoparib+talazoparib + decitabine	**NCT03974217**: (Phase 1) Talazoparib for Cohesin-Mutated AML and MDS With Excess Blasts	Boston, Massachusetts Dana-Farber Cancer Institute Jacqueline_garcia@dfci.harvard.edu

TET2 S1577fs

Therapies	Clinical Trial	Location / Contact
ascorbic acid+ascorbic acid + decitabine	**NCT03418038**: (Phase 2) Ascorbic Acid and Chemotherapy for the Treatment of Relapsed or Refractory Lymphoma, CCUS, and Chronic Myelomonocytic Leukemia	Jacksonville, Florida Mayo Clinic
membrane-bound interleukin-21-expanded haploidentical natural killer cells + decitabine + fludarabine	**NCT04220684**: (Phase 1) Trial Testing Safety of IL-21 NK Cells for Induction of R/R AML	Columbus, Ohio Sumithira Vasu OSUCCCClinicaltrials@osumc.edu

Relevant negatives: ABL1

Therapies	Clinical Trial	Location / Contact
asciminib+asciminib	**NCT05384587**: (Phase 2) Asciminib Monotherapy, With Dose Escalation, for 2nd and 1st Line Chronic Myelogenous Leukemia	Stuart, Florida Novartis Pharmaceuticals john.sabo@novartis.com

Relevant negatives: TP53

Therapies	Clinical Trial	Location / Contact
nemtabrutinib	**NCT05624554**: (Phase 3) A Study of Nemtabrutinib vs Chemoimmunotherapy for Participants With Previously Untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Without TP53 Aberrations (MK-1026-008, BELLWAVE-008)	Clermont, Florida Merck Sharp & Dohme LLC Trialsites@merck.com

TIER 1A THERAPY DETAILS

JAK2 V617F

Therapies	Approval / Guideline Summary	Underlying Evidence
ruxolitinib	NCCN recommended for aCML, BCR-ABL1 negative with CSF3R or JAK2 mutations (Category 2A).	The NCCN guideline for ruxolitinib was supported by data from a case study (PMID: 27899359). The case study demonstrated that 4 mo. treatment with ruxolitinib eliminated splenomegaly and markedly improved symptom burden in a patient with aCML and CSF3R T618I. In addition, the patient's WBC count decreased and their platelet count improved.
ruxolitinib + chemotherapy	NCCN recommended for pediatric patients with Ph-like B-cell ALL with JAK-STAT pathway activation (Category 2A/Other recommended intervention).	The NCCN guideline for ruxolitinib was supported by data from one case study (PMID: 29773603). The case study demonstrated that ruxolitinib and consolidation chemotherapy resulted in a clinical response and undetectable transcript levels at day 57, but MRD >= 0.01% remained for one pediatric patient with chemoresistant B-ALL harboring a GOLGA5-JAK2 fusion.

NRAS A59D

Therapies	Approval / Guideline Summary	Underlying Evidence
binimetinib	NCCN recommended for Langerhans cell histiocytosis with MAP kinase pathway mutation, if cobimetinib or trametinib are not tolerated (Category 2A/Other recommended intervention).	The NCCN guideline for binimetinib was supported by a clinical study that demonstrated that trametinib had an ORR of 31% (5/16; PR = 4, CR = 1) in patients with non-Langerhans cell histiocytosis with a MAP kinase pathway mutation.
cobimetinib	NCCN recommended for Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease with MAP kinase pathway mutation (Category 2A/Preferred intervention).	The NCCN guideline for cobimetinib was supported by data from an open-label, phase-II trial (NCT02649972, PMID: 30867592). The trial demonstrated that cobimetinib had an ORR of 89% (CR = 13%, PR = 3%, SR = 1%) in patients with Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease with MAP kinase pathway mutation.
selumetinib	NCCN recommended for Langerhans cell histiocytosis with MAP kinase pathway mutation, if cobimetinib or trametinib are not tolerated (Category 2A/Other recommended intervention).	The NCCN guideline for selumetinib was supported by a clinical study that demonstrated that trametinib had an ORR of 31% (5/16; PR = 4, CR = 1) in patients with non-Langerhans cell histiocytosis with a MAP kinase pathway mutation.
trametinib	NCCN recommended for Langerhans cell histiocytosis, Erdheim-Chester disease, and Rosai-Dorfman disease with MAP kinase pathway mutation (Category 2A/Other recommended intervention).	The NCCN guideline for trametinib was supported by a study that demonstrated that trametinib had an ORR of 31% (PR = 25%, CR = 6%) in patients with non-Langerhans cell histiocytosis with a MAP kinase pathway mutation.

Negative: KIT D816V

Therapies	Approval / Guideline Summary	Underlying Evidence
imatinib	FDA approved for adults with aggressive systemic mastocytosis without the D816V c-Kit mutation. NCCN recommended as Category 2A/Useful in certain circumstances.	The FDA approval for imatinib was supported by data from an open-label, phase-II study (PMID:18451237). The study demonstrated that KIT D816V, compared with wild-type aggressive systemic mastocytosis, was associated with resistance to imatinib (PR: 0% vs. 40%). An additional open-label, single arm, phase-IV EudraCT study (NCT01297777; PMID:28978170) demonstrated that imatinib improved ORR in patients with systemic mastocytosis lacking KIT D816V.

INVESTIGATIONAL DRUG DESCRIPTIONS

allogeneic natural killer cells: Limited information is currently available on this drug

ASTX029: ASTX029 is an ERK1/2 inhibitor that prevents MAPK/ERK pathway activation, which may result in growth inhibition and tumor regression (PMID: 34330842).

BDTX-4933: BDTX-4933 inhibits BRAF mutations, including class 1, 2 and 3 mutations, and active RAF dimers, which potentially decreases tumor growth (Cancer Res 2023;83(7_Suppl):Abstract nr 3415).

givinostat: Givinostat (ITF2357) is a pan-HDAC inhibitor, which promotes cell-cycle arrest and apoptosis of tumor cells (PMID: 24648290, PMID: 32047238, PMID: 31346710).

Iadademstat: ORY-1001 (iadademstat) binds to and inhibits KDM1A (LSD1), leading to increased H3K4 dimethylation and potentially resulting in increased differentiation and decreased growth of tumor cells (PMID: 29502954, PMID: 32191225).

membrane-bound interleukin-21-expanded haploidentical natural killer cells: Limited information is currently available on this drug

nemtabrutinib: ARQ 531 is an ATP-competitive BTK inhibitor with activity against wild-type BTK and BTK C481S, which may inhibit migration and viability of tumor cells (PMID: 30093506, PMID: 31992353).

seclidemstat: Seclidemstat (SP-2577) is a reversible LSD1 (KDM1A) inhibitor that inhibits transcriptional function of EWS/ETS fusions, leading to anti-tumor activity (AACR Annual Meeting 2019, Abstract CT-109, PMID: 32649682).

sirolimus: Rapamune (sirolimus) binds to the FKBP-12 to generate an immunosuppressive complex that binds and allosterically inhibits mTOR (PMID: 25261369). Rapamune (sirolimus) is FDA approved for the prevention of renal transplant rejection and for patients with lymphangioleiomyomatosis (FDA.gov).

tacrolimus: Tacrolimus binds to FKBP-12 and inhibits calcineurin activity, resulting in immunosuppression (NCI Drug Dictionary).

TRGFT-201: Limited information is currently available on this drug

VAC85135: VAC85135 is a cancer vaccine comprising a viral vector expressing neoantigens, which may result in the induction of a cytotoxic T-lymphocyte (CTL) response against neoantigen-expressing tumor cells (NCI Drug Dictionary).

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TEST DETAILS

NGS Hematologic Malignancies Panel

DNA sequencing: 58 genes

ABL1	ANKRD26	ASXL1	ATRX	BCOR	BCORL1	BRAF	CALR	CBL	CBLB
CBLC	CDKN2A	CEBPA	CSF3R	CUX1	DDX41	DNMT3A	ETNK1	ETV6	EZH2
FLT3	GATA1	GATA2	GNAS	HRAS	IDH1	IDH2	IKZF1	JAK2	JAK3
KDM6A	KIT	KMT2A	KRAS	MPL	NF1	NPM1	NRAS	PDGFRA	PHF6
PIGA	PPM1D	PTEN	PTPN11	RAD21	RUNX1	SETBP1	SF3B1	SMC1A	SMC3
SRSF2	STAG1	STAG2	TET2	TP53	U2AF1	WT1	ZRSR2		

Electronically Signed By: Jason S. Willis, MD (01/09/2024 15:44)

Disclaimer: The adequacy of staining is verified by the appropriate positive and negative controls. The reagents used for these assays (flow cytometry, cytogenetics, molecular, IHC & histology) are analyte specific reagents (ASR) or research use only (RUO). Their performance characteristics have been validated by Precipio, Inc., in its locations (New Haven, CT & Omaha, NE). They have not been reviewed by the FDA. The FDA has deemed that such approval is unwarranted. These assays are for clinical use and should not be viewed as experimental or "research use only". This laboratory is CLIA & CAP certified to perform high complexity clinical testing. Images that may be included within this report are representative of the patient but not all testing in its entirety and should not be used to render a result. For BM biopsy, IHC provides additional information for diagnosis that is not provided by Flow Cytometry and the samples for each procedure are derived from different specimens (biopsy and aspirate, respectively).

All detected mutations have been filtered to identify those of pathogenic significance, utilizing NCCN, WHO (V5.0), and ACMG guidelines. However, if there is a suspicion of a germline (inherited) variant based on the VAF or the clinical scenario, then consulting a genetic counselor may be advisable to determine if further clinical testing is warranted.