QCI Precision Insights for Europe

Provide patient-specific reports to your oncologists in a fraction of the time and with greater confidence

1 Identify clinically significant variants with respect to potential treatments.

2 Highlight variants with evidence of prognostic and diagnostic value.

3 Include variants with potential clinical significance and associated therapies.

4 Ensure a consistent report format that clearly conveys the degree of importance with professional guideline levels of evidence for variant classification (ELN, ESMO, WHO, etc.).

5 Help minimize risk by identifying biomarkers with potential interactions, such as drug sensitivity, resistance, or other implications.

Patient ID: N-of-One Sample AML for EU **Report ID:** N-of-One Sample AML for EU
Report Date: Dec 18, 2019 **Disease:** Acute myelocytic leukemia (AML)

1. Summary

CLINICALLY RELEVANT ALTERATIONS

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TIER 1: VARIANTS OF STRONG CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
FLT3	F594_D600dup	Midostaurin (A)	Sorafenib (B/C), Ponatinib (C.2), Sunitinib (C/D), Cabozantinib (D)	None	Yes

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Prognostic and Diagnostic Variants

Marker	Alteration	Prognostic Level of Evidence	Diagnostic Level of Evidence
FLT3	F594_D600dup	A	None found
NPM1	W288fs	A	A

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TIER 2: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
PTPN11	G503A	None	Binimetinib (D), Trametinib (D), Cobimetinib (D)	None	Yes
BCOR	splice site 4326+1G>A	None	None	None	No

Prognostic and Diagnostic Variants: None

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GUIDELINES

Marker-Alteration	Summary
FLT3-F594_D600dup	The 2017 ELN recommendations for AML note that screening for mutations in NPM1, CEBPA, RUNX1, FLT3 (for ITD and TKD alterations as well as mutant-to-wild-type ratio), TP53, and ASXL1 may be useful for diagnosis, risk assessment, prognostication, and treatment (Döhner et al., 2017; 27895058). The 2017 ELN recommendations place AML patients with wild-type NPM1 plus a high allelic ratio of FLT3-ITD (greater than or equal to 0.5) in the adverse risk category, while patients with mutated 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.; AML patients with mutated NPM1 and a low allelic ratio of FLT3 are placed in the favorable risk category (Döhner et al., 2017; 27895058). These guidelines additionally state that midostaurin plus standard chemotherapy may be considered for both induction and consolidation therapy in AML patients aged 18-60 years with an activating FLT3 mutation (Döhner et al., 2017; 27895058).

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INTERACTIONS

Marker-Alteration	Summary	Resistant Therapies	Synergistic Therapies	Diagnostic Level of Evidence	Prognostic Level of Evidence
FLT3-F594_D600dup NPM1-W288fs	NPM1 mutations in the presence of FLT3-ITD have been associated with an intermediate prognosis (Schnittger et al., 2005; 16076867, Schlenk et al., 2008; 18450602, Thiede et al., 2006; 16455956, Metzeler et al., 2016; 27288520, Tsai et al., 2016; 27055875).	None	None	None found	A

*This is a sample report that has been edited to illustrate key components. To view a full report, contact bioinformaticssales@qiagen.com

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2.1.2 BIOLOGICAL RELEVANCE of FLT3-F594_D600dup

FLT3 alterations in Acute myelocytic leukemia (AML)	
Molecular function	The alteration reported here results in the tandem duplication of seven amino acids within exon 14, within the juxtamembrane domain of the Flt3 protein (Integrative Genomics Viewer, v.2.6). FLT3 internal tandem duplications (ITD) occurring within the juxtamembrane domain of the Flt3 protein have been reported to result in ligand-independent dimerization and constitutive activation of Flt3 (Meshinchi and Appelbaum, 2009; 19549778, Brandts et al., 2005; 16266983, Kiyoi and Naoe, 2002; 12400596). FLT3-ITD alterations have also been shown to lead to activation of several signaling pathways, including those of Akt and Stat5, and have oncogenic effects (Brandts et al., 2005; 16266983, Kiyoi and Naoe, 2002; 12400596, Kelly et al., 2002; 11756186).

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2.1.5 SAMPLE RELEVANT THERAPIES

Therapies targeting FLT3

Drug	Trade Name	Level of Evidence	Target/Rationale	Highest Level of Clinical Development
Midostaurin	Rydapt	A	PKCa/VEGFR-2/Kit/Pdgfr/Flt3 multi-kinase inhibitor.	Phase 3 (Acute myelocytic leukemia (AML)) EMA Approved (Mastocytosis, FLT3-positive AML)
Gilteritinib	Xospata	A	Flt3/Axl inhibitor.	Phase 3 (Acute myelocytic leukemia (AML)) Phase 3 (FLT3-positive AML)
Sorafenib	Nexavar	B/C	Raf kinase inhibitor, also inhibits VEGFR-2/Pdgfr-beta/Kit.	Phase 3 (Acute myelocytic leukemia (AML)) EMA Approved (Hepatocellular carcinoma (HCC), Renal cell carcinoma, Thyroid carcinoma)
Ponatinib	Iclusig	C.2	Bcr-Abl/VEGFR-1,2,3/Fgfrs/Kit/Tie-2/Flt3 kinase inhibitor.	Phase 2 (Acute myelocytic leukemia (AML)) EMA Approved (Chronic myelocytic leukemia (CML), Acute lymphocytic leukemia (ALL))
Crenolanib		C.2	Small molecule kinase inhibitor of Flt3, Pdgfr-alpha, and Pdgfr-beta.	Phase 3 (Acute myelocytic leukemia (AML)) Phase 3 (GIST (Gastrointestinal stromal tumor))
Quizartinib		C.2	Flt3/CSF-1R/Kit/Pdgfr small molecule kinase inhibitor.	Phase 3 (Acute myelocytic leukemia (AML)) Phase 3 (Myelodysplastic Syndrome (MDS), FLT3-positive AML)

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2.1.6 BIOMARKER-MATCHED CLINICAL TRIALS

Trials Prioritized By Clinical Specificity*

	Markers	Trial ID	Title	Phase	Targets	Locations/contact
1	FLT3	NCT02997202	A Trial of the FMS-like Tyrosine Kinase 3 (FLT3) Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients With FLT3/Internal Tandem Duplication (ITD) Acute Myeloid Leukemia (AML)	Phase 3	ALK, AXL, FLT3	•Overall contact: Astellas Pharma Global Development,astellas.registration@astellas.com,800-888-7704 •AL (1), AZ (2), CA (2), CT (1), FL (3), GA (3), IL (3), IN (1), KS (1), MA (5), MD (2), MI (1), MN (2), MO (1), NC (3), NE (1), NY (2), OH (4), OR (1), PA (2), TN (1), TX (1), UT (2), VA (2), WA (1), WI (2), WV (1), Australia (3), Belgium (4), Canada (3), Denmark (1), Germany (7), Japan (20), K, New Zealand (6), Taiwan (
2	FLT3	NCT02624570	Midostaurin Access Program for Newly Diagnosed FLT3 (ITD or TKD) Mutated AML Adult Patients Eligible for Standard Induction and Consolidation Chemotherapy		CSF1R, FLT3, KDR, KIT, PRKCB	•Overall conta Pharmaceuti vartis.com,1- •AZ (1), CA (4 (1), IL (2), IN (1), MI (2), M NY (2), OR ((2), TX (4), U WY (1)

6 Provide detailed information on biomarker molecular function and incidence in disease for richer report context.

7 List molecularly targeted therapies specific to your country for each clinically significant biomarker with the type and level of evidence supporting the selection.

8 Simplify treatment selection by listing clinical trials by relevance and country.

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Chief Medical Officer, Guardant Health, Inc.

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