CytoCell

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A Sysmex Group Company

KMT2A Breakapart FISH Probe Kit PDx

CytoCell

FDA-Authorized Companion Diagnostic

Benefits:

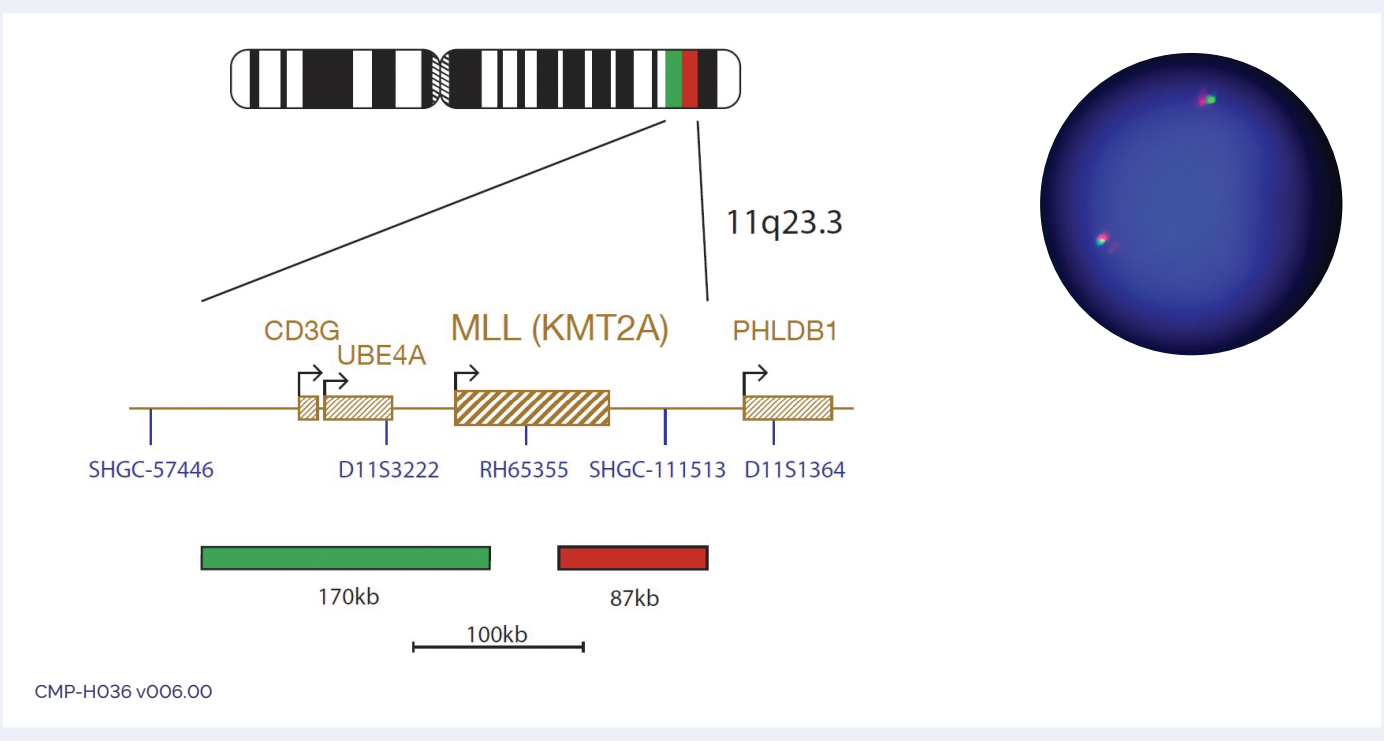
- Reliable detection of *KMT2A* rearrangements in acute leukemia
- Facilitates identification of patients who may be eligible for Syndax's menin-inhibitor
- High-intensity signals with excellent contrast—reduce retest rates
- Easy-to-use, pre-mixed probes—simplify processing and minimize chance for error

CytoCell KMT2A Breakapart FISH Probe Kit PDx

Cat. No. **CDA-LPH013** (10 tests)

The *KMT2A* (lysine methyltransferase 2A) gene at 11q23.3 is commonly rearranged in acute leukemias, especially in infant leukemia. *KMT2A* rearrangements can be detected in approximately 70%-80% of infants with acute lymphoblastic leukemia (ALL) and in 5-10% of pediatric and adult ALLs[1,2]. They can also be found in more than 50% of infants with acute myeloid leukemia (AML) and is also seen in 10% of adolescents and 2-3% of adults with AML. *KMT2A* rearrangements are also seen in mixed-phenotype acute leukemia, a rare type of acute leukemia more common in infants and children than adults[2].

To date, more than 90 partners have been identified with the most common partner genes being *AFF1* (4q21), *MLLT3* (9p22) and *MLLT1* (19p13.3)[2]. The *KMT2A* rearrangements lead to the expression of *KMT2A* fusion proteins that interact with the nuclear protein menin. This *KMT2A* fusion protein – menin interaction leads to aberrant expression of *HOX* genes and *MEIS1*, causing a hematopoietic transformation block and leukemic transformation[3,4,5].



References

1. Van der Burg M, *et al. Leukemia* 2004;18(5):895–908
2. WHO Classification of Tumours Editorial Board. Haematolymphoid tumours, Lyon ,France, 5th edition, IARC, 2024 https://tumourclassification.iarc.who.int/chapters/63
3. Kuhn MWM & Armstrong SA. *Cancer Cell* 2015;27:431-432
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Indications for Use

The CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx is a fluorescence *in situ* hybridization (FISH) test used to detect rearrangement of the *KMT2A* region on chromosome 11 at location 11q23.3 in 3:1 methanol/glacial acetic acid fixed bone marrow specimens from patients with acute leukemia with *KMT2A* rearrangement.

The assay is indicated for detecting the presence of rearrangements involving the *KMT2A* region as a companion diagnostic to aid in identifying those patients for whom treatment with REVUFORJ® (revumenib) is indicated in accordance with the approved therapeutic product labeling. The CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx is not intended for monitoring of residual disease.

Analytical Performance

Analytical Specificity

The analytical specificity of the CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx was established by analyzing a total of 200 target loci from metaphase chromosomes prepared from five normal male peripheral blood samples.

The analytical specificity was calculated as the number of FISH signals that hybridized to the correct locus divided by the total number of FISH signals hybridized. The result was then multiplied by 100, to give a percentage, and is given with a 95% confidence interval. The analytical specificity of the KMT2A Breakapart FISH Probe Kit PDx was 100%, as shown in Table 1.

Probe Name	Target	Number of metaphase chromosomes hybridized	Number of correctly hybridized loci	Analytical Specificity (%)	95% Confidence Interval (%)
KMT2A, Red	11q23.3	200	200	100	98.12 - 100
KMT2A, Green	11q23.3	200	200	100	98.12 - 100

Table 1 - Analytical Specificity for the CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx

Analytical Performance (cont.)

Analytical Sensitivity

The sensitivity of the CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx was evaluated using interphase nuclei from karyotypically normal bone marrow samples, representative of the intended population. Each sample was analyzed by two independent analysts, with each analyst scoring 100 nuclei per sample (200 nuclei per sample in total), resulting in 5,000 scorable nuclei evaluated across 25 samples for each study. The sensitivity, as shown in Table 2, was calculated as the percentage of cells with the expected signal pattern, and the result is reported with a 95% confidence interval.

Study	No. of cells with expected signal patterns	Total number of cells with scoreable signals	Analytical Sensitivity (%)	95% Confidence interval (%)
Study 1	4965	5000	99.30	99.04, 99.54
Study 2	4955	5000	99.10	98.81, 99.35

Table 2 - Analytical Sensitivity for the CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx

Characterization of Normal Cut-off Values

The normal cut-off for the CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx, shown in Table 3, was established using data from 1,600 AML and 25 ALL bone marrow samples negative for the rearrangement. Two independent analysts each analyzed 100 interphase nuclei per sample. For the '1F1R1G' signal pattern, the normal cut-off value was calculated to be 3.8% for AML and 3.1% for ALL. Analytical validation demonstrating performance is limited to 1F1R1G signal pattern. Other signal patterns that are considered positive for *KMT2A* rearrangement have not been validated.

Disease	Abnormal signal pattern	No. samples analyzed to generate cut-off	No. nuclei evaluated per sample	Max. no false positive signal patterns	Normal cut-off value (%)
AML	1F1R1G	1600	200	3	3.8
ALL	1F1R1G	25	200	2	3.1

Table 3 - Characterization of Normal Cut-off Values for the CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx

For further information please consult the Package Insert.

Clinical Summary

A single-site retrospective bridging study evaluated the CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx as a companion diagnostic (CDx) for revumenib, an oral menin inhibitor for the treatment of relapsed or refractory acute leukemia with a *KMT2A* rearrangement in adult and pediatric patients 1 year and older.

The study used blinded, randomized, de-identified 3:1 methanol/acetic acid-fixed bone marrow samples from patients enrolled in Syndax's Phase 1/2 trial (SNDX-5613-0700) and additional procured samples. Clinical performance was assessed by bridging CDx results to the Clinical Trial Assay (CTA), with primary efficacy defined by CR/CRh rates in CDx-positive patients.

Of 139 trial patients identified as *KMT2A*-rearrangement positive, 63 samples were available for CDx testing. An additional 102 negative samples were tested, which together with the 63 available positive samples comprised the CDx-evaluable cohort.

The study required ≥95% concordance between CDx and local diagnostic results for positive, negative, and overall agreement. All acceptance criteria were met.

Measure of agreement	CDx (CTA as reference)	
	Percent agreement (%) [n/N]	95% CI (exact Clopper-Pearson)
PPA	95.2 (60/63)	86.7, 99.0
NPA	100.0 (102/102)	96.4, 100.0
OPA	98.2 (162/165)	94.8, 99.6

Data includes all CDx-evaluable patients in Phase 1/2 of SNDX-5613-0700.
PPA = Positive percent agreement, NPA = Negative percent agreement, OPA = Overall percent agreement.

Table 4 - Concordance between CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx and clinical trial assay (CTA)

Efficacy was estimated from the CDx-evaluable population for patients enrolled into the SNDX-5613-0700 trial and tested positive using the CDx, as the proportion achieving complete remission (CR) or CR with partial hematologic recovery (CRh). Response rate is detailed in Table 5 below.

Best Response	Count(N=60)	Percentage (95% CI) (exact Clopper-Pearson)
CR/CRh	15	25.0 [14.7, 37.9]
CR – Complete Remission	10	16.7 [8.3, 28.5]
CRh – CR with partial hematologic recovery	5	8.3 [2.8, 18.4]
Other response*	45	75.0 [62.1, 85.3]

Includes best response data for all CDx-evaluable patients in Phase 1/2 of SNDX-5613-0700.
Other responses to therapy include: CRi – CR with incomplete hematologic recovery, CRp – CR with incomplete platelet recovery, MLFS – Morphologic leukemia free state, No response, PD – Progressive disease, PR – Partial remission, Response missing, and Unknown.

Table 5 - CR/CRh for CDA-LPH013 KMT2A Breakapart FISH Probe Kit PDx positive patients

For further information please consult the Package Insert.

Limitations

This device is designed to detect rearrangements with breakpoints in the region bounded by the red and green clones in this probe set, which includes the *KMT2A* gene. Breakpoints outside of this region, or variant rearrangements wholly contained within this region, may not be detected with this device.

This device is not intended for monitoring of residual disease or for use as prenatal test, or population-based screening test.

This device has not been validated for sample types, disease types, or purposes outside of those stated in the indications for use.

Reporting and interpretation of FISH results should be performed by a qualified pathologist or cytogeneticist.

Reporting and interpretation of FISH results should be consistent with professional standards of practice and should take into consideration other clinical and diagnostic information. Failure to adhere to the protocol may affect the performance and lead to false results.

The reproducibility of the test in samples with positivity ranging between 3.1–6.2% for ALL and 3.8–7.6% for AML are 65.3% and 75%, respectively. Therefore, use caution when interpreting results within this range.

Analytical validation demonstrating performance is limited to 1F1R1G signal pattern. Other signal patterns that are considered positive for *KMT2A* rearrangement have not been validated.

This device is intended for *in vitro* diagnostic use only.

For prescription use only.

Probe Name	Supported Disease	Cat. No.*	Package Insert
KMT2A Breakapart FISH Probe Kit PDx	Acute Leukemia	CDA-LPH013	DS083/CDA

*Kit includes FISH probe and DAPI. For sale in the US only. This product has not been licensed in accordance with Canadian law.

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