Investigational AML Franchise

Daiichi-Sankyo cancerenterprise

The investigational Acute Myeloid Leukemia (AML) Franchise of the Daiichi Sankyo Cancer Enterprise is pushing the boundaries of science aiming to define a new standard of care for patients with AML, a fast-growing form of leukemia that has the lowest five-year survival rate of all leukemias.[1] Advancements in the understanding of the molecular biology of AML are creating opportunities for our researchers to discover and develop therapies that target the underlying drivers of the disease.

Daiichi Sankyo Approach to AML

For more than 30 years, the standard of care for the treatment of AML went unchanged in part due to the complex biology of AML.[2,3] While a few new treatments have been approved recently, there is still significant unmet need and much work to be done to continue to expand the treatment options available for patients with AML. Our investigational AML Franchise is evaluating a portfolio of therapies that leverage three distinct strategies for the treatment of AML, including quizartinib in phase 3 clinical development, milademetan (DS-3032), DS-3201, and PLX51107 in phase 1 clinical development, and DS-1001 in preclinical development. Our investigational AML Franchise will evaluate combination regimens including these and other compounds for their potential to change the standard of care for patients with AML.

Obligation & Commitment

We are dedicated to transforming science into value for patients, and this sense of obligation informs everything we do. As an anchor in the Daiichi Sankyo Cancer Enterprise, significant investment and resources have been committed to the investigational AML Franchise.

- Formation of the investigational AML Franchise underscores our commitment to understanding AML tumor biology and developing therapies that improve the depth and quality of responses by targeting AML on multiple fronts.
- Combination regimens, which may address the heterogeneity and polyclonality of the disease, may be key to changing the standard of care for AML. With a portfolio of compounds that target different AML drivers, our investigational AML Franchise is an ideal platform in which to study various combination therapies.

Partnerships & Collaborations

Daiichi Sankyo Cancer Enterprise is actively pursuing partnerships and collaborations with experts and academic centers worldwide to help advance the science of AML. A collaboration with MD Anderson Cancer Center, one of the largest integrated leukemia centers worldwide, is focused on accelerating the development of novel therapies for AML.

- Multiple phase 1 and 2 clinical trials, led by MD Anderson, will be launched to evaluate our investigational compounds and multiple agents in combination regimens.
- Incorporation of translational work, including exploration of novel biomarkers, as well as preclinical studies of new agents, is aimed at improving our understanding of mechanisms of resistance to existing and emerging treatments.

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Care. Compassion. Science. It's Our Obligation.

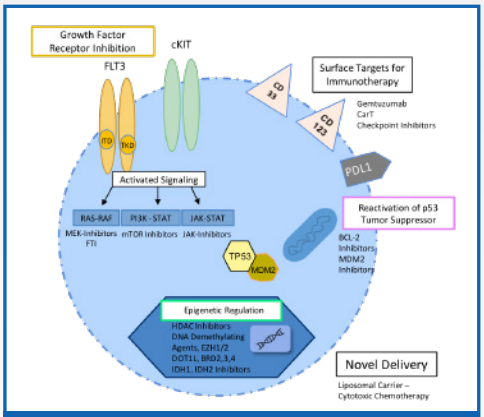
Relentless Focus on Transforming Science

Molecular subtyping (classifying tumors into distinct categories based on molecular features) is creating new scientific opportunities to better understand the science behind AML and improve on current treatment options.[4]

Our investigational AML Franchise is currently developing a portfolio of therapies that leverage three distinct strategies:

- **Growth Factor Receptor Inhibition** with quizartinib, a FLT3 inhibitor in phase 3 clinical development
- **Reactivation of p53 Tumor Suppressor** with milademetan (DS-3032), an MDM2 inhibitor in phase 1 development
- **Epigenetic Regulation** with DS-3201, a dual EZH1/2 inhibitor in phase 1 development; PLX51107, a BRD4 inhibitor in phase 1 development; and DS-1001, a mutant IDH1 inhibitor in preclinical development for AML

Pursuing multiple pathways and studying these investigational compounds in combination with other therapies may potentially enable us to deliver more effective treatment options and expedite development to reach patients sooner.



Source: Adapted from Dohner H, et al. New Engl J Med. 2015;373:1136-1152. Thol F, et al. Blood. 2015;126:319-327. Khan I, et al. Clin Can Res. 2012;18(19):5163-5171. Ramos N, et al. J Clin Med. 2015; 4:665-695. Isidori A, et al. Can Res Frontiers. 2016;2:226-251.

These are investigational agents and have not been approved by the FDA or any other regulatory agency worldwide as a treatment for any indication. Safety and efficacy have not been established.

Growth Factor Receptor Inhibition

Growth factors bind to receptors on the surface of cells and initiate chemical reactions that result in cell growth and proliferation. Mutations in the receptor can lead to constitutive activation of the receptor even in the absence of the ligand (growth factor). This constitutive activation drives abnormal signaling, cell proliferation and cell survival in AML. Growth factor receptor inhibitors block the signaling processes of dysregulated signaling genes that may trigger cancer cells to divide and grow.[5]

COMPOUND	TUMOR TYPE	RELEVANT PATHWAY	PHASE OF DEVELOPMENT (REGION)
Quizartinib (AC220)	Newly-Diagnosed AML (QuANTUM-First)	FLT3	Phase 3 (US, EU, Asia)
	Relapsed/Refractory AML (QuANTUM-R) *FDA Fast Track Designation* *Orphan Drug Designation in US and EU*		Phase 3 (US, EU, Asia)
	Relapsed/Refractory AML		Phase 2 (Japan)

Reactivation of p53 Tumor Suppressor

The tumor suppressor gene p53 involved in the regulation of several biologic activities including apoptosis, cell cycle arrest and senescence can be inactivated by MDM2 through cellular protein interactions. Overexpression of MDM2 can lead to the inactivation of the p53 tumor suppressor function, which may result in inhibition of apoptosis, uncontrolled cellular proliferation and tumor development. Reactivating p53 tumor suppressor function aims to restore normal activity to potentially control cancer cell growth.[6]

COMPOUND	TUMOR TYPE	RELEVANT PATHWAY	PHASE OF DEVELOPMENT (REGION)
Milademetan (DS-3032)	AML, Acute Lymphocytic Leukemia (ALL), Chronic Myeloid Leukemia (CML), Myelodysplastic Syndrome (MDS)	MDM2	Phase 1 (US)
	Solid Tumors, Lymphoma		Phase 1 (US)
	Solid Tumors, Lymphoma		Phase 1 (Japan)
Milademetan (DS-3032) + Quizartinib	Relapsed/Refractory AML, Newly-Diagnosed AML	FLT3 MDM2	Phase 1 preparation (US)

Epigenetic Regulation

Epigenetic regulation is the process by which enzymes (known as epigenetic regulators) help control and coordinate cell-specific gene expression.[7] Novel mutations in genes that are involved in epigenetic control of the genome have been found in a significant proportion of AML patients and have been implicated early in the clonal evolution of AML.[8] Aberrant epigenetic changes are heritable changes in gene expression that do not alter the underlying DNA sequence and may lead to the development and progression of cancer.[7] Targeting epigenetic regulation aims to reverse these changes that contribute to cancer cell growth and to maintain normal gene expression.[7]

COMPOUND	TUMOR TYPE	RELEVANT PATHWAY	DEVELOPMENT (REGION)
DS-3201	AML, ALL	EZH1/2	Phase 1 (US)
	Non-Hodgkin's Lymphoma		Phase 1 (Japan)
PLX51107	AML, MDS, Solid Tumors, Lymphoma	BRD4	Phase 1 (US)
DS-1001	AML	IDH1	Preclinical

References
1. Leukemia & Lymphoma Society. Facts 2015-2016. 2016. | **2.** Krug U, et al. Leukemia. 2016;30:1230-1236. | **3.** Dohner H, et al. N Engl J Med. 2015; 373(12):1136-1152. | **4.** Dohner H, et al. Blood. 2010;115(3):453-474. | **5.** Masson K, et al. Cell Signal. 2009;21:1717-1726. | **6.** Duffy M, et al. Cancer Treat Rev. 2014;40:1153-1160. | **7.** Wee S, et al. Ann NY Acad Sci. 2014;1309:30-36. | **8.** O'Brien E, et al. Adv in Hematol. 2014;2014:103175.

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