TRIAZOLES & CANCER
TRIAZOLE DERIVATIVES TO FIGHT MYELODYSPLASTIC SYNDROMES AND ACUTE MYELOID LEUKEMIA

BACKGROUND

Myelodysplastic syndromes (MDS) are estimated to occur at a rate between 4 and 5 for every 100,000 people in the world. Approximately 13,000 people in the United States and 2,500 in France are diagnosed each year.

40% of MDS patients have an innate resistance to azacitidine, the standard treatment for severe MDS, and even 100% become resistant during treatment. 33% of MDS evolve in acute myeloid leukemia (AML). The median survival of patients with AML is 4 months.

HOW IT WORKS

A scientific team demonstrated that two new classes of triazole derivatives:

- Kill cancerous cells by autophagy via the mTOR signaling pathway;
- Are active with caspase and apoptosis independent effects and did not induce cell cycle arrest;
- Demonstrate interesting in vitro activities on chronic myeloid leukemia (K562 cell line), acute monocytic leukemia (MOLM-13, MOLM-14, OCI-AML2, and OCI-AML3 cell lines), and myelodysplastic syndromes (SKM1-R, an azacitidine-resistant cell line, and SKM1-S).

The clinical positioning of these triazole derivatives should be on MDS patients resistant to azacitidine and/or evolving into AML.

KEY BENEFITS vs. STATE OF THE ART

Reference MDS treatments are azacitidine (Vidaza®), decitabine (Dacogen®), lenalidomide (Revlimid®) and imatinib (Gleevec®) but new therapeutic options are always required:

- A family of innovative and patentable triazole derivatives active on azacitidine resistant and sensible cell lines
- Some triazole derivatives have demonstrated superior activities (in vitro and in vivo) to the reference treatments
- Caspase and apoptosis independent cell death mechanisms should reduce the development of resistance
- Could be candidate for orphan designation

DEVELOPMENT STATUS

In vitro results: molecules of this family demonstrated in vitro submicromolar IC_{50} (200-900nM) on various MDS and AML cell lines,

In vivo results: other molecules of this family demonstrated in vivo activities (5-10 mg/kg, i.p.) in various mouse models of cancer (MDS, AML, CML...),

Ongoing lead optimization, and preclinical validation on MDS/AML mouse models.

APPLICATIONS

Myelodysplastic syndromes with resistance to azacitidine
Myelodysplastic syndromes evolving into acute myeloid leukemia
Acute myeloid leukemia and Chronic myeloid leukemia