KDDF
Korea Drug Development Fund

Asset #42
Weill Cornell Medicine

6-Ethylthioinosine for the Treatment of Cancers that Overexpress Adenosine Kinase (ADK)

Therapeutic Area	Oncology	**Indications**	NSCLC, Colorectal/Pancreatic Cancer
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

- The γ-herpesvirus KSHV, also called HHV-8, is the etiological agent of Kaposi's sarcoma (KS), multicentric Castleman's disease, and primary effusion lymphoma (PEL).
- KS, the most common malignancy in AIDS patients, is often treatable by antiviral therapy and radiation or chemotherapy.
- PEL is a rare HIV-associated non-Hodgkin's lymphoma (NHL) that is largely a highly aggressive and intractable disease, with rapid progression to death.
- Unmet Need: Specific and effective therapeutics for diseases caused by KSHV

Technology Advantages

- Precision medicine approach
- Applicable to multiple tumor types
- Demonstrated efficacy in PEL and MM xenograft models
- Overcomes treatment resistance to gemcitabine and erlotinib in pancreatic and NSCLC cancer

Key Data

Mechanistic Insights of 6-ETI: Mutations, Binding, and Cancer Therapy Potential

A

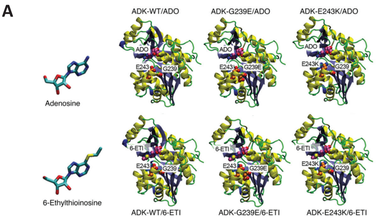
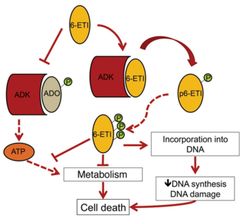


Figure indicates locations of independent recurrent mutations G239E and E243K on ADK, discovered by SNP calling on RNA-Seq data from 6-ETI–resistant clones. Schrödinger's Maestro: ADK binding to adenosine (top panel), and postulated binding to 6-ETI (bottom panel).

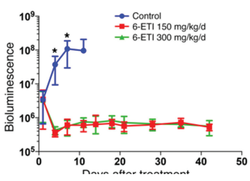
B



6-ETI competes with adenosine and other nucleosides, inhibiting ATP-dependent processes via ADK binding. It's also phosphorylated by ADK, leading to DNA synthesis inhibition, damage response, and cell death.

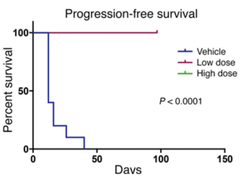
6-ETI is effective in vivo in a PEL xenograft mouse model

C



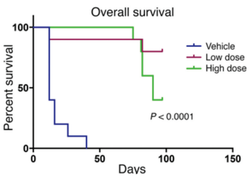
Statistical analysis was performed using 1-way ANOVA (P = 0.0032 at day 11 after treatment). Statistical analysis: Unpaired t-test (*P ≤ 0.05) for vehicle vs. low and high dose-treated mice at specific time points.

D



In the progression-free survival curve, as by day 100 all live mice were tumor free, and none had died of tumor. The difference in survival curves was analyzed by log-rank (Mantel-Cox) test (P < 0.0001).

E



The overall survival was performed, and the results are color-coded by treatment group. The difference in survival curves was analyzed by log-rank (Mantel-Cox) test (P < 0.0001).

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-US2017-027590 (2017.04.14)

Patent Family
PCT, US

Publication(s)

- Nayar at al. (2017). Identification of a nucleoside analog active against adenosine kinase–expressing plasma cell malignancies. Journal of Clinical Investigation