EO-4426

Drug Class: "Dual" DNA Pol α & RNR Inhibitor

A First-in-Class Orally Bioavailable, Brain Penetrant - Dual Inhibitor of DNA Polymerase Alpha (Pol α) and Ribonucleotide Reductase (RNR) for the Treatment of Cancer

Overview:
EO-4426 (tezacitabine) is an orally bioavailable, brain penetrating, small molecule anticancer drug that targets both DNA polymerase alpha **(Pol α)** and ribonucleotide reductase **(RNR)**, two essential and complementary enzymes involved in DNA replication and repair. This dual-targeting mechanism represents a novel therapeutic strategy to exploit the vulnerabilities of cancer cells, particularly their dependence on rapid and efficient DNA replication.

Mechanism of Action:

- **Pol α Inhibition**: **Pol α** is a critical component of the primase complex and is responsible for initiating DNA synthesis during replication. Inhibition of **Pol α** disrupts replication initiation, halting the progression of DNA replication forks.
- **RNR Inhibition**: **RNR** is essential for the de novo synthesis of deoxyribonucleotide triphosphates (dNTPs), the building blocks of DNA. Inhibiting **RNR** depletes intracellular dNTP pools, further impairing DNA synthesis and repair.

The simultaneous inhibition of **Pol α** and **RNR** induces severe replication stress, leading to replication fork collapse, DNA damage accumulation, and ultimately, cancer cell death.

Scientific and Clinical Rationale:

- **Unmet Need and Novelty**: While several **RNR** inhibitors (e.g., hydroxyurea, gemcitabine, clofarabine) are FDA-approved for cancer treatment, there are currently no approved or clinical-stage oral and brain penetrant therapies specifically targeting DNA polymerase alpha.
- **Targeting a Central Node in Replication**: **Pol α** plays a foundational role in initiating DNA replication, making it a compelling target in rapidly dividing cancer cells. Compared to other polymerases like Pol θ, which is more involved in DNA repair and synthetic lethality approaches, **Pol α** offers broader and potentially more impactful therapeutic reach.
- **CNS Penetration: EO-4426** crosses the blood brain barrier and has demonstrated anti-cancer activity in preclinical brain tumor models providing an opportunity for the treatment of brain metastases and primary brain tumors
- **Broad Antitumor Potential**: **EO-4426** has demonstrated clinical activity across a wide range of tumor types, including lung, breast, colon, prostate, brain tumors, and leukemia, suggesting its utility across diverse cancer indications.

- **Gemcitabine Resistance: EO-4426** dual mechanism of action supports the potential for activity gemcitabine-resistant cancers where *Cytidine Deaminase (CDA)* overexpression is a mechanism of resistance. *CDA Biomarker Testing* can be used to identify gemcitabine resistant patients, a major clinical challenge especially in the treatment of Pancreatic, NSCLC, Breast, and Bladder cancer.

Clinical Development History:

EO-4426 has been studied in over 400 patients across multiple Phase 1 and Phase 2 clinical trials, both as a single agent and in combination with chemotherapeutics such as 5-FU and cisplatin. It has been evaluated in both intravenous and oral formulations.

- **Safety Profile**: In four Phase 1 studies, intravenous **EO-4426** was well tolerated. The dose-limiting toxicity was neutropenia, which was transient and reversible.
- **Efficacy Signals**: Clinical activity was observed in multiple cancer types, supporting its continued development and potential for broad applicability.

Pre-clinical activity

EO-4426 demonstrated promising activity against several cancers including brain tumors in pre-clinical models

Preclinical Tumor Models	Outcome
D45 Brain Tumor	Median Survival: EO4426: 46.5d control: 20d
SK-N-C brain tumor	90d Survival: EO4426: 90% carmustine: 26% untreated: 23%
MDA-MB-231 breast cancer	90-100% cure (CR)
L1210 leukemia	80% cure (CR)
Lewis lung carcinoma	80% cure (CR)

Future Clinical Development:

EO-4426 is especially well-suited for treating cancers that exhibit CDA overexpression and have recurred following treatment with RNR inhibitors such as gemcitabine or hydroxyurea

Given its unique mechanism and favorable clinical profile, **EO-4426** represents a promising first-in-class oral therapeutic candidate capable of addressing high unmet needs in oncology.